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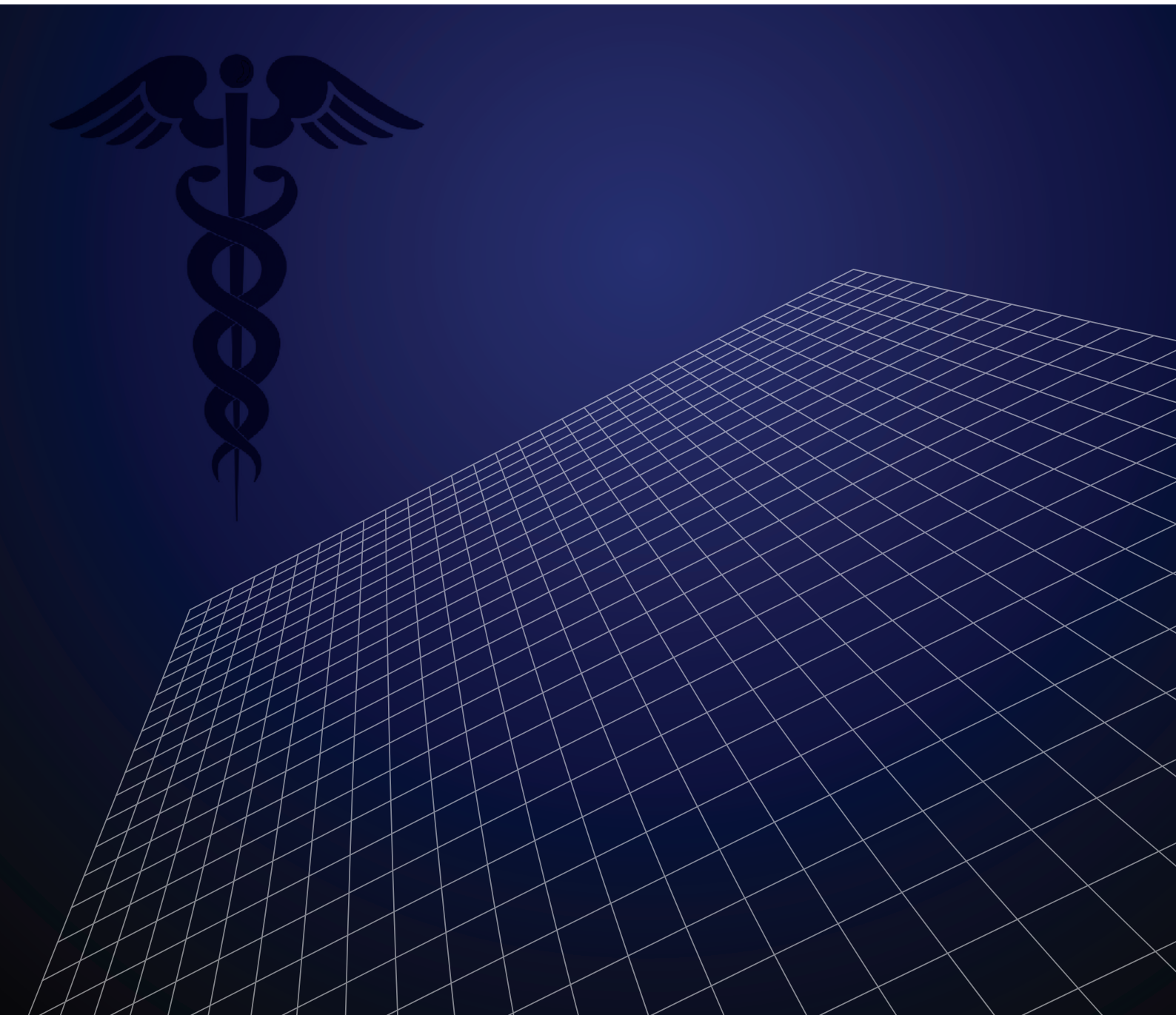

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Original Makale

Çeşitli örneklerden izole edilen Candidaların tür dağılımı ve antifungal direnç oranları

Distribution of Candida species isolated from various sample and antifungal resistance ratio

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ÖZ

Amaç: Bu çalışmada Bozok Üniversitesi Araştırma ve Uygulama Hastanesi'ne başvuran hastalara ait çeşitli klinik örneklerden izole edilen Candidaların tür dağılımları ve antifungal duyarlılık oranlarının belirlenmesi amaçlanmıştır.

Gereç ve Yöntemler: Ekim 2014-Ocak 2016 tarihleri arasında Candida türleri izole edilen 42 adet klinik örnek retrospektif olarak değerlendirildi. İzolatların tanımlanmasında germ tüp testi ile ticari VITEK 2 Compact® (Biomerieux, France) maya identifikasyon sistemi kullanıldı. İzolatların antifungal duyarlılıkları flukonazol, vorikonazol, kaspofungin, mikafungin, amfoterisin B ve flusitozin antifungallerini içeren disposable VITEK 2 AST YS02 test kartları kullanılarak belirlendi.

Bulgular: Çeşitli klinik örneklerden toplam 42 Candida türü izole edildi. C. albicans % 66,7 ile en sık soyutlanan tür olurken, non-albicans türler %33,3 oranında saptandı. C.albicans'ı sırasıyla C.glabrata (%11,9), C.kefyr (%7,1), C.tropicalis (%4,8), C.famata (%2,4), C.krusei (%2,4), C.lusitaniae (%2,4) ve C.spherica (%2,4) izledi.

Tüm izolatların antifungal direnç oranları sırasıyla; flukonazol %14, flusitozin %3, vorikonazol %6, amfoterisin-B %5, kaspofungin %6, mikafungin %3 oranları belirlendi. C.albicans izolatlarında flukonazol direnç oranı %11 olarak saptandı. C.kefyr, C.lusitaniae ve C.tropicalis izolatlarında mevcut antifungallere direnç görülmedi. C.glabrata'nın antifungal direnç oranı diğer Candida türlerine göre daha yüksekti.

Sonuçlar: Çalışmamızda en sık izole edilen C.albican'tan sonra gelen C.glabrata izolatlarının diğer Candida türlerine göre antifungal direncinin daha yüksek olduğu saptanmıştır. Son yıllarda non-albicans türlerin ve antifungal direnç oranlarının artması sebebiyle Candidaların tür düzeyinde tanımlanması ve antifungal duyarlılık testlerinin yapılmasının gerekliliği düşünülmektedir.

Anahtar Kelimeler: Candida, antifungal direnç, non-albicans

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ABSTRACT

Aim: In this study was aimed to determine the antifungal susceptibility and the distribution of Candida species isolated from different clinical samples of patients admitted to the Bozok University Research and Application Hospital.

Material and Methods: In our study, forty-two Candida species isolated from clinical samples between the October 2014 and January 2016 dates were evaluated retrospectively. For the identification of isolates; germ tube test and commercial VITEK 2 Compact® (Biomerieux, France) was used the yeast identification system. Antifungal susceptibility of isolates was detected by using VITEK 2 AST YS02 disposable test cards containing fluconazole, voriconazole, caspofungin, micafungin, amphotericin-B and flucytosine for use with VITEK® 2 instruments.

Results: A total of 42 Candida species were isolated from various clinical specimens. C. albicans was the most frequently isolated species with 66.7% while non-albicans species were detected in 33.3%. Other Candida species were as follows; C. glabrata (11.9%), C.kefy is (7.1%), C.tropicalis (4.8%), C.famata (2.4%), C.kruse (2.4%), C.lusitania (2.4%) and C.spherica (2.4%), respectively.

In all isolates, the rates of antifungal resistance were found 14% for fluconazole, 6% for voriconazole, 5% for amphotericin-B, 6% for caspofungin and 3% for micofungin. Fluconazole resistance rate was found as 11% in C. albicans isolates. In the isolates of C.kefyr, C.lusitania and C.tropicalis was not saw resistance to existing antifungals. Antifungal resistance ratio of C. glabrata was higher than the other Candida species.

Conclusion: In our study the isolates of C. glabrata following the most frequently isolated C. albicans were found to have higher antifungal resistance than the other Candida species. In recent years, due to the increase of non-albicans species and antifungal resistance rates, it has been thought that identification of Candida species and antifungal susceptibility tests should be done.

Keywords: Candida, antifungal resistance, non-albicans

Giriş

Son yıllarda modern tedavi yöntemlerinin gelişmesi, çeşitli nedenlerle kemoterapi, immunsupresif tedavi sayısında ve transplantasyon imkanlarında artış, yoğun bakım ünitesinde yatan hasta sayısının artması, parenteral beslenme, geniş spektrumlu yada kombine antibiyotik kullanımında artış, tanı veya tedavi amaçlı invazif işlemlerin uygulanması Candida enfeksiyonlarının sıklığında artışa yol açmıştır [1-3]. Bu hastalar risk grubu olarak değerlendirilir ve bu hasta grubunda gelişen fırsatçı mantar enfeksiyonlarının çoğunluğunda Candida türlerine ait patojenler izole edilmektedir [1,4].

Kandidemi ve kandidüri dışında invazif Candida enfeksiyonlarında tanı koymak oldukça zordur. Bu nedenle hasta yönetim ve tedavisinde kandidiyazis risk faktörleri göz önünde bulundurulmalıdır [5]. Candida türleri nozokomiyal kan dolaşımı enfeksiyonlarına neden olan patojenler arasında dördüncü sırada yer almaktadır [6,7]. Hastane mantar enfeksiyonlarının büyük bir kısmından (%80) Candida türleri sorumludur. Nozokomiyal enfeksiyonlara en sık neden olan Candida türü Candida albicans'tır [7-9]. Son 15 yıldır non-albicans Candida türlerinin neden olduğu enfeksiyonların sıklığı hızla artmıştır. Çeşitli araştırmalarda fungemi ataklarının yarıdan fazlasında non-albicans Candidaların sorumlu olduğu görülmüştür. Azollerin yaygın kullanımı epidemiyolojinin değişmesinde en önemli faktör olarak öne sürülmüştür [10].

Mantar enfeksiyonlarının sıklığının artışı, mortalite ve morbiditede oranlarında artışa neden olmakta ve antifungallerin ampirik kullanımını yaygınlaştırmaktadır. Antifungallerin ampirik tedavide daha yaygın kullanılması, dirençli mantar izolatların oluşumunu kolaylaştırmakta ve dirençli izolat oranlarında artışa sebep olmaktadır. Antifungallere direnç gelişimini azaltmak, etkili antifungal tedavi uygulamak için in vitro olarak duyarlılık testlerinin yapılması gerekmektedir [11].

Bu çalışmada, hastanemizde 16 aylık süre içerisinde çeşitli örneklerden izole edilen Candida türlerinin fenotipik identifikasyonu ve antifungal duyarlılık profilinin ortaya konulması amaçlanmıştır.

Gereç ve Yöntemler

Ekim 2014-Ocak 2016 tarihleri arasında mikrobiyoloji laboratuarına gelen 14 vajen sürüntüsü, 13 idrar, 7 bronkoalveolar lavaj, 7 balgam ve 1 yara olmak üzere toplam 42 klinik örnekte izole edilen Candida türleri retrosektif olarak değerlendirildi. Çalışma Helsinki Deklarasyonuna uyumlu

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şekilde yürütülmüştür. Koyun kanlı agar besiyerinde üreyen kolonilerin gram boyamasında maya hücreleri görülen örnekler, 2 adet sabouraud dekstroz agar besiyerine pasaj alınarak, besiyerlerinden birisi 37°C, diğeri 25°C de 24 saat inkübe edildi.

İzolatların tanımlanmasında germ tüp testi ile ticari VITEK 2 Compact® (Biomerieux, France) maya tanımlama sistemi kullanıldı. İzolatların antifungallere karşı duyarlılıkları flukonazol, vorikonazol, kaspofungin, mikafungin, amfoterisin-B ve flusitozin antifungallerini içeren disposable VITEK 2 AST YS02 test kartları kullanılarak belirlendi. Bahsedilen antifungal duyarlılık testleri Clinical and Laboratory Standards Institute (CLSI) tavsiyeleri gözönüne alınarak yapıldı.

Kullanılan antifungaller için MIC değerleri; amfoterisin-B için ≤ 0,25µg/mL, kaspofungin için ≤ 0,25µg/mL, flukonazol için ≤ 1µg/mL, flusitozin için ≤ 1µg/mL, mikafungin için ≤ 0,06 µg/mL ve vorikonazol için ≤ 0,12 µg/mL dir. Gruplar arası sayıların dağılımının karşılaştırılmasında Ki-Kare Testi kullanıldı. Sonuçlar sayı ve yüzde (n,%) olarak verildi.

Bulgular

Hastaların %50'si (21) erkek, %50'si (21) kadındı. Hastaların yaşları 2 ile 92 arasında değişiyordu. 42 izolatın 16 tanesi (%38) kadın doğum polikliniği, 8 tanesi (%19) yoğun bakım servisi, 15 tanesi (%36) dahili birimler (iç hastalıkları, enfeksiyon hastalıkları, göğüs hastalıkları, nöroloji, pediatri ve gastroenteroloji servisleri) ve 3 tanesi (%7) cerrahi birimlerde (üroloji ve göğüs cerrahi servisleri) tedavi gören hastalardan izole edildi.

C.albicans %66,7 oranıyla en sık, C.glabrata %11,9 oranıyla ikinci sıklıkta izole edilen Candida türleriydi (Tablo 1).

Tablo 1. İzole edilen Candida türlerinin dağılımı

Candida türü	Sayı(%)
C.albicans	28(66,7)
C.glabrata	5(11,9)
C.kefyr	3(7,1)
C.tropicalis	2(4,8)
C.krusei	1(2,4)
C.lusitaniae	1(2,4)
C.spherica	1(2,4)
C.famata	1(2,4)
Toplam	42(100)

C.albicans bütün yaş gruplarında en sık görülen Candida türüydü. Diğer Candida türlerine 20 yaş ve altında rastlanmadı. Yirmi yaş ve altında izole edilen tek türün C.albicans olduğu görüldü. Bununla birlikte Ki-Kare testi ile yapılan karşılaştırmada türlerin yaş gruplarına göre dağılımında anlamlı bir farklılık bulunamadı (X2=5.4, p=0.979) (Tablo 2).

Tablo 2. İzole edilen Candida türlerinin yaş gruplarına göre dağılımı

Türler	≤20 Yaş	21 - 60 Yaş	≥61 Yaş
	n(%)	n(%)	n(%)
C.albicans	2(7,1)	13(46,4)	13(46,4)
C.glabrata	0(0,0)	3(60,0)	2(40,0)
C.kefyr	0(0,0)	2(66,7)	1(33,3)
C.tropicalis	0(0,0)	1(50,0)	1(50,0)
C.krusei	0(0,0)	1(100,0)	0(0,0)
C.lusitaniae	0(0,0)	0(0,0)	1(100,0)
C.spherica	0(0,0)	1(100,0)	0(0,0)
C.famata	0(0,0)	1(100,0)	0(0,0)
Toplam	2(4,8)	22(52,4)	18(42,9)

Tüm izolatlarda flukonazol direnç oranı %14, C.albicans izolatlarında %11 olarak saptandı. Mikafungine tüm izolatlar duyarlıydı. C.albicans izolatı dışındaki tüm izolatlar kaspofungin ve amfoterisin-B ye duyarlı olarak saptandı. C.glabrata dışında flusitozin direnci görülmedi. C.kefyr, C.lusitaniae ve C.tropicalis izolatları tüm antifungallere duyarlıydı. C.glabrata ise diğer türlere göre daha dirençliydi. C.famata ve C.spherica'nın duyarlılık testleri çalışılamadı. C.krusei izolatları intrinsik dirençli olduğu flukonazol dışındaki diğer antifungallere duyarlı olarak saptandı (Tablo 3). Candida izolatlarının klinik örneklere göre dağılımı Tablo 4'de gösterilmiştir.

Tablo 3. İzole edilen *Candida* suşlarının türlere göre antifungal duyarlılık oranları

	FLS	FLK	VOR	AMP-B	CAS	MİKA
	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)
C.albicans(n=28)	28(100)	25(89)	27(96)	27(96)	27(96)	28(100)
C.glabrata(n=5)	4(80)	3(60)	3(60)	5(100)	5(100)	5(100)
C.kefyr(n=3)	3(100)	3(100)	3(100)	3(100)	3(100)	3(100)
C.tropicalis(n=2)	2(100)	2(100)	2(100)	2(100)	2(100)	2(100)
C.krusei(n=1)	1(100)	0(0)	1(100)	1(100)	1(100)	1(100)
C.lusitaniae(n=1)	1(100)	1(100)	1(100)	1(100)	1(100)	1(100)

Kısaltmalar; FLK: Flukonazol, AMP-B:Amfoterisin-B, FLS: Flusitozin
VOR: Vorikonazol,
CAS: Kaspofungin; MİKA: Mikafungin

Tablo 4. İzole edilen *Candida* suşlarının klinik örneklere göre dağılımı

Candida türü	BAL	Balgam	İdrar	Vajen	Yara
C.albicans	5	5	9	8	1
C.glabrata	1	0	1	3	0
C.kefyr	0	1	0	2	0
C.tropicalis	1	0	1	0	0
C.krusei	0	1	0	0	0
C.lusitaniae	0	0	1	0	0
C.spherica	0	0	0	1	0
C.famata	0	0	1	0	0
Toplam n(%)	7(16,7)	7(16,7)	13(30,1)	14(33,3)	1(2,4)

Kısaltmalar; BAL: Bronkoalveolar lavaj

Tartışma

Zamanımızda tıp biliminde gelişmelerin sonucu, fungal enfeksiyonların etkilediği risk grupları genişlemektedir. Candida türleri nozokomiyal mantar enfeksiyonlarının %80'den daha fazlasından sorumlu olmakla birlikte, nozokomiyal kan dolaşımı enfeksiyon etkenleri arasında ilk sıralarda yer almaktadır. Son zamanlarda, albicans dışı Candida izolatlarının neden olduğu enfeksiyonların giderek arttığı görülmektedir. En sık saptanan tür olan C.albicans dahil olmak üzere C.parapsilosis, C.tropicalis, C.glabrata ve C.krusei türleri, insanlarda hastalık etkeni olan 17 Candida türünün %95'ini kapsamaktadır [12].

Günümüzde hospitalize vakalara eşlik eden akciğer ve renal hastalıklar, malignensiler gibi durumların görülme sıklığının artması, yaşam süresinde artış gibi etkenler ile hospitalize vakalarda Candida enfeksiyon sıklığı gün geçtikçe artmaktadır. Günümüzde antifungal ilaçlar ile tedavi süreci erken başlamasına karşın, Candida enfeksiyonlarının mortalite ve morbidite seviyesi oldukça yüksek seyretmektedir [13]. Araştırmamızda Candida türleri geniş yaş grubu aralığında (2-92 yaş) izole edildi. Yaş artışı ile doğru orantılı olarak malignensi ve kronik hastalık prevelansının artması, aynı zamanda yaşlı bireylerde immün sistemde zayıflama gibi etkenler gözününe alındığında, bilhassa hospitalize olgularda Candida enfeksiyonlarının takip ve tedavilerinde daha dikkatli olunması gerekmektedir.

İspanya'da yedi yıl boyunca yoğun bakım ünitelerinde invaziv Candida enfeksiyonları takip edilen bir çalışmada, kandidemi gelişen hastalarda antifungal tedavi başlanmasına rağmen mortalite oranı %39 olarak bildirildi. [14]. Hastanemiz yoğun bakım ünitesinde Candida izole edilen sekiz hastadan beşi ex oldu (Mortalite oranı %63). Ex olan hastaların yaşları 60 ile 88 arasında değişmekteydi.

Ülkemizde Candida türlerinin dağılımları ile ilgili yapılan çalışmalarda çoğunlukla C. albicans ilk sırada yer almaktadır. Sav ve ark. [15] 1122 Candida izolatından; C. albicans 848 (%75,6), C. glabrata 143 (%12,8), C.parapsilosis 40 (%3,57), C. krusei 33 (%2,94), C. kefyr 33 (%2,94) ve C. Tropicalis 19 (%1,7); Temiz ve ark. [16] 69 Candida izolatından; C. albicans 49 (%71,0), C. tropicalis 6 (%8,7), C. glabrata 6 (%8,7), C. Parapisilosis 5 (%7,3), C. dubliniensis 2 (%2,9), C. guilliermondii 1 (%1,4) oranlarında bildirmişlerdir. Diğer çalışmalarda da [17-19] C. albicans çoğunlukla en sık izole edilen Candida türü olarak bildirildi.

Son zamanlarda yapılan çalışmalarda non-albicans türlerinde artış bildirildi. Etiz ve ark. [12] izole ettikleri 280 Candida suşundan en sık C.parapsilosis (%33,9), Şahiner ve ark. [21] tarafından kan kültürlerinden izole edilen Candida türleri sırasıyla; C.parapsilosis (%38,5), C.tropicalis (%30,8), C.albicans (%26,9) olarak bildirilmiştir.

Değişik ülkelerde yapılan çalışmalarda da C. albicans çoğunlukla en sık izole edilen tür olmuştur. Bailly ve ark [22] 2403 Candida suşundan sırasıyla; C. albicans %53, C. glabrata %16, C.parapsilosis %8, C.tropicalis %8 oranlarında ve C.parapsilosis izolasyon oranının 2004 yılında %5,7'den 2013 yılında %8,4'e yükseldiğini bildirmişlerdir. İspanya'da 1357 Candida enfeksiyonlu hastanın değerlendirildiği bir çalışmada en sık izole edilen C. albicans'ı, C. parapsilosis takip etmiştir [23]. Phaller ve ark. [24] en sık C. albicans, ardından C. glabrata, Jung ve ark. [25] C.albicans %38, C.parapsilosis %26 ve C.tropicalis %20 oranlarında tür dağılımları bildirmişlerdir.

Bizim çalışmamızda çeşitli klinik örneklerden izole edilen 42 Candida suşunda C. albicans %66,7 oranında en sık soyutlanan tür olurken, non-albicans türler %33,3 oranında izole edilmiştir. C.albicans'ı sırasıyla C.glabrata (%11,9), C.kefyr (%7,1), C.tropicalis (%4,8), C.famata (%2,4), C.krusei (%2,4), C.lusitaniae (%2,4) ve C.spherica (%2,4) izlemiştir.

Candida türlerindeki dağılım coğrafi bölge farklılıkları ile birlikte hasta gruplarına göre değişiklikler göstermektedir [26]. Günümüzde Candida enfeksiyonları ile karşılaşma sıklığının artması, özellikle yoğun bakım ünitelerinde profilaktik antifungal kullanımını artırmakta, bunun sonucunda antifungallere duyarlılığı azalmış veya dirençli suşların oluşmasına sebep olmaktadır [27].

Etkin bir triazol olan flukonazol, maliyetinin de düşük olması gibi nedenler sonucu, maya kaynaklı enfeksiyonların tedavisinde en sık kullanılan antifungallerdendir. C. krusei flukonazole karşı doğal dirençlidir ve flukonazolün C. glabrata'ya karşı etkisi oldukça sınırlıdır [28]. Candida suşlarında flukonazol direncini Çekin ve ark. [29] %4,5, Temiz ve ark. [16] C.albicans için %4, C.glabrata için %5 ve C.tropicalis için %5 olarak bildirmişlerdir. Ülkemizde flukonazol direnci % 0-38 arasında değişmekte olup, direnç giderek artmakta ve bölgelere göre değişmektedir [16]. Hastanın öyküsünde flukonazol tedavisi almış olması kandidemi gelişme olasılığını artırmaktadır [30]. Çalışmamızda tüm izolatlarda flukonazol direnç oranı %14, C.albicans izolatlarında flukonazol direnç oranı %11 olarak saptanmıştır. En yüksek flukonazol direncine sahip Candida türü C.glabrata olmuştur (%40).

Amfoterisin-B en eski poliyen grubu ilaçlardan olan, invaziff fungal enfeksiyon tedavilerinde kullanılan onaylanmış antifungal bir ilaçtır [31]. Farklı merkezlerde yapılan çalışmalarda amfoterisin-B'ye karşı direnç gelişiminin oldukça düşük olduğu bildirilmiştir [12,16,17,32-34]. Çalışmamızda sadece bir C.albicans izolatında amfoterisin-B direnci saptanmıştır.

Vorikonazol flukonazolden türetilen triazol grubu, sentetik, geniş spekturumlu yeni bir antifungal ilaçtır. Flukonazolün etkisinin sınırlı olduğu C. krusei ve C. glabra türleri başta olmak üzere diğer Candida türlerine de etkilidir [16]. Erdem ve ark. [18] ile Çalışkan ve ark. [27] yaptıkları çalışmalarda Candida türlerinde vorikonazol direnci saptanmazken, Özbek ve ark. [35] % 3,63, Hancı ve ark. [36] %22,5 oranında direnç bildirmişlerdir. Çalışmamızda bir C.albicans, iki C.glabrata izolatında vorikonazol direnci saptanmıştır.

Günümüzde çeşitli mikozların tedavisinde onay alan anidulafungin, kaspofungin ve mikafungin ekinokandin türevleridir. Flukonazole dirençli Candida türlerine karşı ekinokandinlerin etkinliği mükemmeldir. Candidanın klinik izolatları arasında ekinokandin direnci oldukça nadirdir [37]. Pfaller ve ark. [38] çok merkezli çalışmalarında kan örneklerinden izole edilen C.krusei izolatlarında %12,5, Etiz ve ark. [12] Candida suşlarında kaspofungine %11 oranında direnç bildirmişlerdir. Özkaya ve ark. [32] ise 93 adet Candida suşunda kaspofungin direncine rastlamamışlardır. Çalışmamızda tüm Candida izolatları mikafungine duyarlı iken, kaspofungin direnci bir C.albicans izolatında görülmüştür.

Flusitozin toksisitesi yüksek bir antifungal olmasından dolayı kullanımı oldukça sınırlıdır. Çalışkan ve ark. [27] ile Pelit ve ark [17] flusitozin direncine rastlamamışlardır. Bayram ve ark. [19] %4, Erdem ve ark. [18] %1,7 oranında flusitozin direnci bildirmişlerdir. Uluslararası SENTRY Antimikrobiyal Sürveyans Programı kapsamında kan kültüründen izole edilen 1201 adet Candida izolatının flusitozin direnç oranı %4,5 olarak bildirilmiştir [39]. Çalışmamızda bir C.glabrata izolatı dışında tüm Candida türleri flusitozine duyarlıdır. Hastanemizde flusitozin direncinin düşük olması, flusitozinin tedavide sınırlı oranda kullanılmasından kaynaklanabilir.

Sonuç olarak çalışmamızda, identifiye ettiğimiz Candida türlerinde çeşitliliğin arttığı ve özellikle C.glabrata izolatlarının diğer Candida türlerine göre antifungal direncinin daha yüksek olduğu görülmüştür. Son yıllarda non-albicans türlerin ve antifungal direnç oranlarının da artması göz önüne alınarak Candidaların tür düzeyinde tanımlanması ve antifungal duyarlılık testlerinin yapılması, hem hastanemiz hem de ülke genelinde Candida enfeksiyonlarının tedavi protokollerine katkı sağlayacağı düşüncesindeyiz.

Maddi Destek ve Çıkar İlişkisi

Çalışmayı maddi olarak destekleyen kişi/kuruluş yoktur ve yazarların çıkara dayalı bir ilişkisi yoktur.

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Original Article

Platelet-to-lymphocyte ratio predicts contrast-induced nephropathy in acute myocardial infarction

Akut miyokard infarktüsünde trombosit/lenfosit oranı kontrast nefropatisini öngörür

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ABSTRACT

Aim: Contrast-induced nephropathy (CIN) is responsible for an increased mortality rate and correlates with increases in hospital stays and the risk of cardiovascular complications. The platelet to lymphocyte ratio (PLR) was introduced as a potential marker to determine the balance between thrombosis and inflammation and was associated with increased cardiovascular morbidity and mortality. We investigated whether PLR on admission is an independent risk factor that predicts the development of CIN in patients with ST-segment elevation myocardial infarction (STEMI) underwent primary percutaneous coronary intervention (pPCI).

Material and Methods: 1348 consecutive patients with acute STMI who were admitted to our institution and underwent pPCI were retrospectively evaluated. Data obtained from hospital files and computer records. CIN development was accepted as the endpoint.

Results: A total of 127 (9.4%) patients experienced CIN. 16 patients underwent renal replacement theraphy. In-hospital mortality rate was found 2.7% (n = 37). Patients were divided into two groups based on development of CIN. Age (P = 0.001), baseline GFR (P < 0.001), grade 3 and more chronic kidney disease (P < 0.001), baseline creatinin (P < 0.001), EF (P < 0.001), presence of DM (P < 0.001) were different between groups. In multivariate analyses, PLR (odds ratio [OR] 1.012, 95% confidence interval [CI] 1.006-1.017, P < 0.001) was independently predicted CIN development.

Conclusion: PLR is easily available, widely used, and relatively cheap biomarker, and is an independent predictor of CIN development in patients with STEMI undergoing pPCI.

Keywords: platelet/lymphocyte ratio, ST-segment elevation acute myocardial infarction, contrast-induced nephropathy

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ÖZ

Amaç: Kontrast madde nefropatisi (CIN) uzamış hastanede yatış süresi, artmıs kardiyovasküler komplikasyonlar ve mortalite ile ilişkilidir. Trombosit/lenfosit oranı (PLR) tromboz ve inflamasyon arasındaki dengeyi gösteren potansiyel bir belirteç olarak tanımlanmış ve artan kardiyovasküler morbidite ve mortalite ile ilişkili bulunmuştur. Biz bu çalışmada PLR'nin primer perkütan koroner girişim (pPCI) yapılan ST yükselmeli miyokard infarktüsü (STEMI) hastalarda CIN gelişimini tahmin etmede bağımsız bir risk faktörü olup olmadığı araştırdık.

Gereç ve Yöntemler: Kurumumuza akut STEMI ile başvuran ve pPCI yapılan 1348 hasta geriye dönük olarak değerlendirildi. Hastane dosya ve bilgisayar kayıtlarından veriler elde edildi. CIN gelişimi sonlanım noktası olarak kabul edildi.

Bulgular: 127 (%9.4) hastada CIN gelişmişti. 16 hastaya renal replasman tedavisi uygulandı. Hastane içi mortalite oranı %2,7(n = 37) bulunmuştur. Hastalar CIN gelişimine göre iki gruba ayrıldı. Yaş (P = 0,001), bazal GFR (P < 0,001), grade 3 ve üzeri kronik böbrek hastalığı (P < 0,001), bazal kreatinin (P < 0,001), EF (P < 0,001), DM varlığı (P < 0,001) gruplar arasında farklı idi. Çok değişkenli analizlerde, PLR (odds ratio [OR] 1.012, %95 güven aralığı [CI] 1,006-1,017, P < 0,001) CIN gelişimini bağımsız olarak öngördü.

Sonuçlar: PLR, kolay ulaşılabilir yaygın olarak kullanılan ve nispeten ucuz biyomarkerdir ve STEMI nedeniyle pPCI uygulanan hastalarda CIN gelişiminin bağımsız bir belirleyicisidir.

Anahtar Kelimeler: trombosit/lenfosit oranı, ST yükselmeli miyokard infarktüsü, kontrast madde nefropatisi

Introduction

Contrast-induced nephropathy (CIN) is the third most common cause of renal insufficiency in hospitalized patients. CIN is responsible for an increased mortality rate of 14% and, for most patients, correlates with increases in hospital stays and the risk of cardiovascular complications [1]. The risk of CIN is even higher in patients referred for primary coronary angioplasty in the context of acute coronary syndromes. While it seems that intraarterial administration of contrast medium is associated with a higher risk of CIN than intravenous infusion primary coronary angioplasty appears to be a particularly high-risk procedure, as it affects a population at greater risk of CIN (i.e. older patients with co-morbidities, such as diabetes, heart failure and chronic renal failure). The main pit- fall is that renal function is often unknown at the time of contrast exposure because primary coronary angioplasty has to be performed without delay, leaving no time for renal function assessment. Moreover, the short delay between patient admission and primary coronary angioplasty significantly limits the use of pedigree renal protection measures, such as intravenous hydration (at least prior to the procedure) [2]. Identifying patients at high risk of CIN before PCI is of utmost clinical importance to make timely pre-procedural decisions regarding the therapeutic intervention to minimizing the risk.

The platelet to lymphocyte ratio (PLR) was introduced as a potential marker to determine the balance between thrombosis and inflammation, oncologic and cardiac disorders. Increased platelet and decreased lymphocyte counts in the circulation have been associated with increased cardiovascular morbidity and mortality [3]. Because of the potential role of inflammation in the development of CIN.

In the present study, we investigated whether PLR on admission is an independent risk factor that predicts the development of CIN in patients with ST-segment elevation myocardial infarction (STEMI) underwent primary percutaneous coronary intervention (pPCI).

Material and methods

The study population consisted of 1348 consecutive patients with acute STEMI who were admitted to our institution and underwent p-PCI within 12 h of the onset of symptoms between January 2013 and March 2015. This retrospective study was conducted in accordance with the principles of The Declaration of Helsinki. Inclusion criteria were presence of typical ongoing chest pain lasting for >30 minutes and ST elevation of at least ≥2 mm in at least 2 contiguous leads or new-onset complete left bundle-branch block. The baseline demographic, clinical and angiographic features, in-hospital

outcomes, admission laboratory test results were obtained from hospital files and computer records. Exclusion criteria were acute renal failure or end-stage renal failure requiring dialysis, known malignant or chronic inflammatory disease, recipient of transplanted organs, contrast dye exposure within the last 10 days, and chronic treatment with steroid or nonsteroidal anti-inflammatory drugs.

All of pPCI procedures were performed either femoral or radial approach with a 6F guiding catheter. 300 mg chewable aspirin and 600 mg loading dose of clopidogrel on admission, and 70 U/kg intravenous standard heparin were administered to all patients. Non-ionic, iso-osmolar or non-ionic, low-osmolar contrast media (CM) were used. The use of glycoprotein IIb/IIIa receptor blocker (tirofiban) was left to the primary operator's discretion. Occlusion of the infarct related artery was crossed by using a guidewire, direct stenting was implanted whenever possible; in the remaining cases, manual thrombus aspiration and/or balloon predilatation were carried out. The type of stent used was left to the operator's judgment. If the lesion anatomy was not suitable for stenting, only balloon dilatation was performed. After the procedure all patients were transferred to coronary intensive care unit and guideline-based cardiac medications were administered at the maximum tolerated doses. A successful intervention was described as a reduction in the stenosis or obstruction to less than 50% with Thrombolysis in Myocardial Infarction (TIMI) grade 2 or 3 flow after p-PCI. If could not achieved, it was deemed unsuccessful.

Hypertension was defined as use of blood pressure lowering drugs at admission, systolic pressure >140 mm Hg, or diastolic pressure >90 mm Hg in measurements. Anemia was defined as baseline hemoglobin levels <13 g/dL in males and <12 g/dL in females. Estimated glomerular filtration rate was calculated by using the Modification of Diet in Renal Disease Formula [4]. Patients were considered to have hyperlipidemia if they were being treated with lipid-lowering drugs at the time of admission or had abnormal fasting lipid test results according to guidelines [5]. Patients being treated with glucose-lowering drugs or had a fasting plasma glucose concentration >7 mmol/L or a nonfasting plasma glucose concentration >11.1 mmol/L were considered to have diabetes. CIN was defined as either an increase in serum creatinine greater than 25% or an absolute raise in serum creatinine of 0.5 mg/dL within 72 hours of administration of radiocontrast [6].

Multivessel disease was described as the presence of >50% stenosis in at least two or more major epicardial arteries. Cardiogenic shock was defined as marked and persistent (>30 minutes) hypotension with systolic arterial pressure being < 90 mmHg nonresponsive to fluid replacement, or the need of inotropes or intra-aortic balloon pumping to maintain blood pressure >90 mmHg due to left ventricular dysfunction, right ventricular infarction, and mechanical complications.

Echocardiography was performed in all patients and the left ventricular ejection fraction was calculated by using the modified biplane Simpson's method. In-hospital heart failure was recognised in the presence of Framingham criteria for the diagnosis of heart failure and left ventricular systolic and/or diastolic dysfunction on echocardiography. In-hospital cardiovascular mortality defined as unexplained sudden death, death from acute MI, heart failure, and arrhythmia. CIN development was accepted as the endpoint.

Statistical analysis

All analyses were performed using SPSS for Windows version 20.0 (IBM Corporation). Continuous variables are presented as mean+standard deviation and categorical variables are presented as percentages. Group means for continuous variables were compared using either the unpaired Student's t test or the Mann-Whitney U test according to normality. Categorical variables were compared by the Chi-square test. Pearson test was used for correlation analysis. Receiver-operating characteristic (ROC) analyses were used to detect the cut-off value of PLR in the prediction of CIN. To determine the independent predictors of CIN, parameters that were found to be significant in the univariate analysis were evaluated by stepwise forward logistic regression analysis. Two-sided P values <0.5 were considered significant.

Results

The mean age of the patients studied was 57.3±11years and 32.3% of the patients were women. A total of 127 (9.4%) patients experienced CIN. 16 patients underwent renal replacement therapy. In-hospital mortality rate was found 2.7% (n = 37). Patients were divided into two groups based on development of CIN. The baseline demographic, angiographic and clinic characteristics of the patient groups are shown in Table 1.

Table 1. Baseline demographic, angiographic, and clinical characteristics of patient groups based on development of CIN.

	CIN (+) group n=127	CIN (-) group n=1221	P value
Age (years)	64±12	56±11	<0.001
Sex (male), n (%)	93 (73.2)	820 (67.2)	0.97
GFR ≤ 60, n (%)	58 (45.7)	147 (7.9)	<0.001
Anterior infarction, n (%)	60 (47.6)	485 (39.7)	0.05
Suspected vessel,n (%)			
LAD	65 (51.2)	528 (43.2)	
CX	13 (10.2)	187 (15.3)	0.26
RCA	45 (35.4)	478 (39.1)	
Others	4 (3.2)	28 (2.4)	
DM,n (%)	76(59.8)	227(19.4)	<0.001
HT,n (%)	51 (32.3)	402(32.9)	0.48
HL,n (%)	24(18.9)	251 (20.6)	0.37
Smoking,n (%)	23 (18.1)	261 (21.4)	0.23
PCI history,n (%)	21(16.5)	150(12.3)	0.11
By-pass history,n (%)	6(4.7)	25(2.0)	0.64
Anemia, n (%)	50(39.4)	353(28.9)	0.11
Unsuccesful intervention, n (%)	22(17.3)	84(6.9)	<0.001
Multivessel disease, n (%)	19(15)	256 (21)	0.66
Shock on admission, n (%)	8(6.3)	24(2.0)	0.07
Predilatation, n (%)	107 (84.3)	873(71.5)	0.02
Stent lenght ,mm	23.1±6.8	21.5±6.4	0.04
Trofiban usage,n(%)	63 (49.6)	594(48.6)	0.83
In-hospital mortality, n(%)	19(15)	18(1.5)	<0.001
GFR (mL/min/1,73m2)	67.6±45.6	99±30.6	<0.001
EF (%)	40.4±8.7	50.2±1.3	<0.001
WBC (103/µL)	14±7	12±4.6	0.004
Hemoglobin (g/dl)	12.9±2.1	13.6±1.7	0.001
Neutrophil (103/ µL)	11.5±6.5	9.1±3.8	<0.001
Lymphocyte (103/ µL)	1.711±0.94	2.057±0.48	0.004
Platelet (103/ µL)	241.2±42.3	179.5±51.8	<0.001
Total cholesterol (mg/dl)	178.5±32.4	178.9±43.4	0.74
LDL (mg/dl)	105±35.1	108.9±37.2	0.51
HDL (mg/dl)	37.4±10.2	38.2±9.8	0.44
TG (mg/dl)	153±76.1	158.9±96.7	0.94
Contrast volume (ml)	172.5±95.3	144.7±85.1	0.001
Basal creatinin (mg/dl)	1.18±0.43	0.87±0.26	<0.001
Peak troponin (ng/mL)	37.8±16.8	32.4±18.4	<0.001
CRP (mg/L)	11.6±4.1	3.5±0.4	<0.001
Platelet to lymphocyte ratio	187.1±141.6	114.1±67.4	<0.001

CIN, contrast-induced nephropathy; CRP; C reactive protein; CX, circumflex artery ;DM, diabetes mellitus; EF, left ventricular ejection fraction; GFR, glomerular filtration rate; HT, hypertension; HL, hyperlipidemia;; HDL, high-density lipoprotein; LAD, left anterior descending artery; LDL, low-density lipoprotein; PCI, percutaneous coronary intervention; RCA, right coronary artery ;TG, triglyceride;WBC, white blood cell.

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Age (P = 0.001), baseline GFR (P < 0.001), grade 3 and more chronic kidney disease (P < 0.001), baseline creatinine (P < 0.001), EF (P < 0.001), presence of DM (P < 0.001) were different between groups. Patients who developed CIN (group 1) had more unsuccessful intervention (P < 0.001) than group 2.

Predilatation was done more often in group 1 (P = 0.02). Longer stents were implanted in group1 (23.1 ± 6.8 cm, P = 0.04). The PLR was significantly higher in the CIN group than in the non-CIN group (187.1 ± 141.6 vs 114.1 ± 67.4, P < 0.001). Amount of contrast media (172.5 ± 95.3 vs 144.7 ± 85.1 mL, P < 0.001) was higher in the CIN than non-CIN group. Patients in group 1 had higher CRP values (P < 0.001) In-hospital mortality was higher in group 1 (P < 0.001). PLR was significantly correlated with CRP in our study (r = 0.224, P < 0.001) Independent predictors of CIN development are presented in Table 2.

Table 2. The predictors of the development of CIN in the multivariable logistic regression analyses.

Parameters	OR (%95 CI)	P value
Age	1.081(1.031-1.134)	0.011
GFR <60	0.057(0.009-0.367)	0.003
DM	0.350 (0.129-0.950)	0.039
Multivessel disease	0.228 (0.076-0.690)	0.009
EF	1.061 (1.010-1.114)	0.018
CRP	1.403 (1.286-1.531)	<0.01

CIN, contrast-induced nephropathy; CRP; C reactive protein; DM, diabetes mellitus; EF, left ventricular ejection fraction; GFR, glomerular filtration rate.

In multivariate analyses, PLR (odds ratio [OR] 1.012, 95% confidence interval [CI] 1.006-1.017, P < 0.001) was independently predicted CIN development.

The area under the ROC curve for PLR was 0.74, and a PLR of >119.2 predicted CIN with sensitivity of 72% and specificity of 63% (0.735, 95% CI 0.691-0.779, P < 0.001; Figure 1).

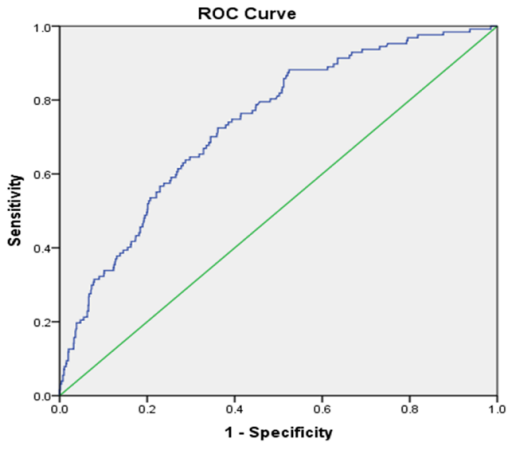

Figure 1. Receiver operating characteristic curve of PLR for predicting CIN development

Discussion

Our study findings showed that PLR, a readily accessible parameter, is an independent risk factor for CIN in patients with STEMI. The incidence of CIN in this study (9.4%) was in agreement with previous reports [7]. Previous studies indicated that a higher PLR value emerged as a significant independent predictor of long-term survival in patients who presented with STEMI. Among the factors we identified for the prediction of CIN development, impaired renal function (GFR <60mL/min/1.73m2), EF, CRP and DM were in line with the literature [8]. Moreover, patients having greater extent of atherosclerosis revealed by multivessel affection and increased size of tents used were also significant predictors of CIN in our study population. It may be related to decreased ventricular function, remote ischemia and intraprocedural hemodynamic impairments that result in renal hypoperfusion. We also identified shock on admission as a predictor of CIN but its role should be discussed since shock implies potential kidney failure. It is more a predictor of multifactorial acute renal failure rather than CIN. But, decreased renal perfusion pressure whatever the cause aggravates CIN development. PLR was found to be a predictor of CIN development after angiography in patients without ST elevation myocardial infarction [9]. However, different from our population there was enough time to evaluate renal function and to take adequate renal protective measures since interventions were planned but not urgently done. Additionally, in STEMI patients the renal function could not be accurately evaluated because acute hemodynamic changes and the contrast medium dose have to be governed primarily by the complexity of lesions that need to be opened, not by renal function. Also, we did not exclude patients with impaired renal function or patients in shock or patients with depressed left ventricular function and analysed blood test results droven at emergency department on admission. Our study population is a homogeneous group of unselected patients with STEMI undergoing pPCI which is directly relevant to most patients undergoing pPCI in the general population.

CIN is considered an intrinsic acute kidney injury, usually with conserved diuresis, but in severe cases acute tubular necrosis and even end-stage renal disease may develop. However, irreversible renal function losses occur in rare cases. The physiopathology of CIN is multifactorial and is still incompletely understood. Direct toxicity of contrast media, contrast induced modification in renal microvascular haemodynamics (increase vasoconstriction and decrease vasodilatation in the renal medulla), oxidative stress reperfusion injury, tubular obstruction and inflammation are suggested mechanisms contribute to its pathogenesis [10,11].

Infarcted heart activates damage-associated signaling pathways and triggers an intense sterile inflammatory response. Remote organ inflammation is evidenced by upregulation of VCAM-1 in renal glomeruli and by the recruitment and infiltration

of inflammatory cells throughout the kidney 24 h following myocardial infarction [12]. Unlike neutrophils, a lower lymphocyte count has been observed in acute myocardial infarction and lower lymphocyte count were found to be related to more cardiovascular events during the follow up [13]. Moreover, activated platelets recognised as inflammatory cells release inflammatory and mitogenic substances and promote the recruitment of more platelets and leukocytes. Formation of neutrophil-platelet aggregates plugs the microcirculation and cause reperfusion-related injury. Platelet activation in STMI is associated with increased generation of circulating microparticles acknowledged as intercellular communicators and links between inflammation and thrombosis [14]. PLR reflects both hyperactive coagulation and inflammatory pathways, and both of them are the suspected underlying mechanisms of CIN.

We found that the volume of contrast medium was significantly higher in patients experienced CIN but was not an independent predictor of CIN development. However, Nymann et al. proved that an adjustment of contrast amount to the GFR allows a reduction of the incidence of CIN in STMI [15]. Evolution of clinical practice and progress in contrast agent development, more usage of low or iso-osmolar agents may be explanations. Pre-exisiting renal dysfunction is another independent predictor of CIN development in our cohort. A greater incidence of baseline chronic kidney disease was observed in those patients who eventually developed postprocedural CIN. PLR has role in the evaluation of inflammation in end stage renal disease and it can predict inflammation and albuminuria in patients with diabetic nephropathy [16].

The present study has some limitations. It is cross-sectional retrospective and reflects single center experience. Complete follow-up data is not adequate. We measured PLR only once at admission and without correction for potential variability in PLR levels. To reflect the inflammatory status of patients we assessed CRP values but more sensitive markers could be evaluated.

As a conclusion the present study results demonstrated that PLR is easily available, widely used, and relatively cheap biomarker, and is an independent predictor of CIN development in patients with STEMI undergoing pPCI. It may also allow risk stratification and selection of a treatment strategy in patients with STEMI prior to or during coronary interventional procedures.

Declaration of conflicting interests

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Original Article

Monocyte count to high-density lipoprotein ratio predicts occlusion of the infarct-related artery in STEMI

Monosit sayısı /yüksek yoğunluklu lipoprotein oranı, STEMI'de enfarktla ilişkili arterin oklüzyonunu öngörür

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ABSTRACT

Aim: Patency of infarct-related artery (IRA) in patients with ST-segment elevation myocardial infarction (STEMI) before primary percutaneous coronary intervention (pPCI) is associated with better clinical outcomes. However, there were limited data regarding the predictors of IRA patency before pPCI in the setting of STEMI. We intended to evaluate the association of monocyte count to high-density lipoprotein ratio (MHR) with IRA patency in STEMI.

Material and Methods: A total of 726 patients were recruited. IRA patency was determined by the thrombolysis in myocardial infarction (TIMI) flow grade. According TIMI flow grade in the IRA before PCI, the study population was divided into two groups as TIMI 0,1 or 2 group (occluded IRA, n=624) and TIMI 3 group (patent IRA, n=102). Blood samples were collected on admission to calculate MHR. Of all patients, 92 (20.4%) patients revealed pre-pPCI TIMI 3 flow in IRA.

Results: The MHR was significantly higher in occluded IRA group (22.4 ± 5.4 vs 17.8 ± 6.9, $P < 0.001$). Glucose, troponin I, and platelet to lymphocyte ratio (PLR) levels were also higher in occluded IRA group ($P < 0.05$). Multivariate regression analysis demonstrated the MHR on admission (odds ratio [OR]: 1.191; 95% confidence interval [CI]: 1.116-1.272, $P < 0.001$) and pre-hospital use of prasugrel or ticagrelor (OR: 7.045; CI: 1.687-29.414, $P = 0.007$) as independent predictors of IRA patency.

Conclusion: IRA patency is more frequently found in patients having received fast acting antiplatelet therapy before pPCI and a higher MHR value independently predicts it.

Keywords: monocyte count to high-density lipoprotein ratio, ST-segment elevation myocardial infarction, infarct-related artery patency

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ÖZ

Amaç: ST segment yükselmeli miyokard enfarktüsü (STEMI) olan hastalarda, primer perkütan koroner girişim (pPKI) öncesi enfarktüs ilişkili arter acıklığı daha iyi klinik sonuçlar ile ilişkilidir. Bununla birlikte, STEMI ortamında pPKI öncesinde IRA açıklığının öngördürücüleri ile ilgili sınırlı veri vardır. STEMI'de monosit sayısı /yüksek yoğunluklu lipoprotein oranı (MHR) ile enfarktla ilişkili arterin acıklığı arasındaki ilişkiyi değerlendirmek istedik.

Gereç ve Yöntemler: Toplam 726 hasta çalışmaya alındı. IRA açıklığı, miyokard enfarktüsünde tromboliz (TIMI) akım sınıflaması ile belirlendi. PKI öncesi IRA'da TIMI akım derecesine göre çalışma popülasyonu, TIMI 0,1 veya 2 grup (tıkalı IRA, n=624) ve TIMI 3 grubu (patent IRA, n=102) olmak üzere iki gruba ayrıldı. MHR hesaplamak için basvuruda kan örnekleri toplandı. Tüm hastaların 92'sinde (%20,4) IRA'da pre-pPKI TIMI 3 akımı vardı.

Bulgular: MHR, tıkanan IRA grubunda anlamlı derecede yüksekti (22,4 ± 5,4'e karşılık 17,8 ± 6,9, P < ,001). Tıkalı IRA grubunda, glikoz, troponin İ ve trombosit/lenfosit oranı (PLR) düzeyleri de yüksekti (P < 0.05). Çok değişkenli regresyon analizinde, başvuru sırasındaki MHR değeri (odds oranı [1,391]; %95 güven aralığı [CI]: 1,116-1,272, P < 0,001) ve prasugrel veya tikagrelorun hastane öncesi kullanımı (OR: 7,045; CI:1,687-29,414, P = 0,007) IRA açıklığının bağımsız öngördürücüleri olarak bulundu.

Sonuçlar: IRA açıklığı, pPKI öncesi hızlı etkili antitrombosit tedavi alan hastalarda daha sık görülmektedir ve daha düşük bir MHR değeri IRA açıklığını bağımsız bir şekilde tahmin eder.

Anahtar Kelimeler: monosit sayısı /yüksek yoğunluklu lipoprotein oranı, ST segment yükselmesi miyokard enfarktüsü, infarktla ilişkili arter açıklığı

Introduction

Immediate reperfusion of ischemic myocardium is crucial for restoring normal cardiac function in ST-segment elevation myocardial infarction (STEMI). Infarct-related artery (IRA) patency prior to mechanical reperfusion is associated with better clinical outcomes in patients with STEMI [1]. Early reperfusion of the culprit artery before the procedure also improves post procedural success and maintenance of ventricular function [2]. Thus, factors related to pre-procedural IRA patency may yield additional prognostic information.

Monocytes are involved in evolvement of vulnerable plaques in STEMI [3]. On the other hand, low high-density lipoprotein (HDL) levels were associated with increased in-hospital mortality after myocardial infarction [4]. Monocyte counts to HDL ratio (MHR) is a novel parameter independently and significantly predicting short-term and long-term mortality in STEMI [5]. Moreover, MHR serves as a simple assessment tool for inflammatory status and represents atherosclerotic burden [6].

However, there were no data about its predictive value for spontaneous recanalization of blood flow in the IRA. In this study, we aimed to investigate the relationship between on admission MHR and IRA patency in patients with STEMI.

Material and methods

We retrospectively enrolled 726 consecutive patients who underwent coronary angiography with a diagnosis of STEMI between February 2015 and May 2016 in our tertiary center. The study was conducted in accordance with the principles of the Declaration of Helsinki. The STEMI was defined as symptoms of acute myocardial infarction lasting ≥ 30 minutes with the presence of new or presumed new >1 mm ST-segment elevation in ≥ 2 contiguous leads or left bundle branch block [7]. Diagnosis was later confirmed by subsequent increase in Troponin I level. Patients with clinical evidence of severe valvular heart disease, active cancer, hematological proliferative disorders, active hepatobiliary diseases, chronic antihyperlipidemic treatment, active infection, chronic inflammatory disease, receiving steroid therapy for autoimmune disease, and patients without a recorded measurement of admission laboratory parameters including cholesterol levels before coronary angiography were excluded from this study. Previous history of MI either STEMI or non-STEMI was also accepted as an exclusion criteria. The study was confirmed by the local ethics committee.

The baseline demographic, cilinical and angiographic features, admission laboratory test results were obtained from hospital

files and computer records. Lipid parameters were measured on emergency admission. Troponin I levels were measured with a Beckman Image 800 analyzer. Monocyte count was calculated using the data elicited from the complete blood count differential analysis. The reference value for monocyte in our laboratory is 2% to 10%. Monocyte to HDL ratio was calculated by dividing monocyte count (103/μL) to HDL level (mg/dL) and reported as 106/mg.

Hypertension was defined as use of blood pressure lowering drugs at admission, systolic pressure >140 mm Hg, or diastolic pressure >90 mm Hg in measurements. Patients being treated with glucose-lowering drugs or had a fasting plasma glucose concentration >7 mmol/l or a nonfasting plasma glucose concentration >11.1 mmol/L were considered to have diabetes. Echocardiography was performed in all patients and the left ventricular ejection fraction (EF) was calculated by using the modified biplane Simpson's method.

Coronary angiography was performed using either femoral or radial approach. Each coronary artery were displayed in at least 2 different plane images. The infarct-related artery was graded according to the Thrombolysis in Myocardial Infarction (TIMI) classification [8].

Angiograms and the TIMI scale were assessed by at least 2 experienced interventional cardiologists who did not have knowledge of the clinical data. Before coronary intervention, TIMI flow grade was documented for each patient. Patients were divided into 2 groups according to the TIMI scale. Non-patent flow was defined as TIMI grade 0, 1, and 2 flows and patent flow was defined as TIMI 3 flow.

Statistical analysis

The analyses were carried out using the SPSS version 22.0 statistical package program (IBM SPSS Statistics for Windows, Armonk, NY, USA). Kolmogorov-Smirnov test was used to assess normality of distribution. All data were presented as a mean ± SD for parametric variables and as percentages for categorical variables. The comparisons between the two groups were performed with Student's t-test for continuous variables and with the chi-squared test for the categorical variables. The correlation between IRA patency and clinical variables and laboratory parameters was assessed by the Pearson correlation test. Multivariate logistic regression analysis was performed to detect the independent predictors of IRA patency. The parameters that were significant in univariate analysis were included. For all analyses, a p value <0.05 was considered significant.

Results

A total of 726 patients with STEMI who had been treated with primary PCI were included. On the admission angiography, infarct-related artery was LAD in 290 (39%) patients, Cx in 96 (13%) patients, RCA in 334 (46%) patients and graft in 2 (0.2%) patients. According to TIMI flow grade, patients divided into two groups as infarct related artery occluded group and infarct related artery patent group. 624 (85%) patients had TIMI 0,1 or 2 flow grade (occluded IRA group) and 102 (15%) patients had TIMI 3 flow grade (patent IRA group) in the IRA. Baseline and angiographic characteristics, and prehospital medications of the study groups are demonstrated in Table 1.

There were no significant differences in terms of age, male gender, rate of hypertension, diabetes mellitus, smoking, hyperlipidemia, systolic blood pressure, heart rate and having history of myocardial infarction, previous PCI or coronary bypass operation.. Admission EF was significantly higher in the patent IRA group (47±12 versus 44±13, p=0.02). Significant difference wasn't detected between pre-hospital medications, except superior use of prasugrel or tikagrelor in the occluded IRA group as compared to the patent IRA group (12 % versus 2%, P < 0.01). The laboratory parameters are also shown in Table 2.

Platelet count, monocyte count, serum glucose, troponin I, platelet to lymphocyte ratio and monocyte to HDL ratio (MHR) were significantly higher in the occluded IRA group as compared to the patent IRA group (251.2 ± 75.4 versus 231.3 ± 59.4, P = 0.01; 792 ± 230 versus 586 ± 196, P < 0.001; 163 ± 90 versus 134 ± 36, P = 0.002; 2.3 ± 2.1 versus 1.7 ± 1.8, P = 0.008; 189.9 ± 144.7 versus 138.8 ± 123.7, P < 0.001; 22.4 ± 5.4 versus 17.8 ± 6.9, P < 0.001). Lymphocyte count was significantly higher in the patent IRA group (2.3 ± 1.4 versus 1.7 ± 0.9 P < 0.001).

When univariate logistic regression analysis was performed to define possible independent predictors of IRA patency; platelet, lymphocyte and monocyte counts, serum glucose, troponin I, platelet to lymphocyte ratio and monocyte to HDL ratio remained significant and were included in the multivariate analysis. In the multivariate logistic regression analysis; serum glucose, monocyte to HDL ratio and pre-hospital use of prasugrel or tikagrelor remained as independent predictors of IRA patency (Table 3).

Multivariate regression analysis demonstrated the MHR on admission (odds ratio [OR]: 1.191; 95% confidence interval [CI]: 1.116-1.272, P < 0.001) and pre-hospital use of prasugrel or ticagrelor (OR: 7.045; CI: 1.687-29.414, P = 0.007) as independent predictors of IRA patency.

Table 1. Baseline and angiographic characteristics of patients

Parameters	Infarct related artery occluded group (n=624)	Infarct related artery patent group (n=102)	P value
Clinical variables			
Age , years	63±11	62±12	0.50
Male, n (%)	449(72)	67(65)	0.17
Hypertension , n (%)	197(31)	35(34)	0.60
Diabetes mellitus, n (%)	186(30)	23(22)	0.12
Smoking, n (%)	178(28)	23 (22)	0.20
Hyperlipidemia, n (%)	142(22)	17(16)	0.16
Systolic blood pressure (mmHg)	133(49)	130(17)	0.64
Heart rate (bpm)	88±30	82±12	0.07
Previous myocardial infarction, n (%)	82(13)	9(8)	0.21
Previous percutaneous coronary intervention, n (%)	105(160	14(13)	0.42
Previous coronary artery bypass grafting, n (%)	20(3)	2(2)	0.49
Admission LVEF, mean ± SD (%)	44±13	47±12	0.02
Pre-hospital medications , n (%)			
Aspirin	307(49)	58(56)	0.16
Clopidogrel	255(41)	36(35)	0.27
Prasugrel or Ticagrelor	13(12)	13(2)	<0.01
Beta-blockers	7(1)	3(2)	0.14
Statins	4(0.6)	2(2)	0.17
ACE-inhibitors or ARB	116(18)	21(20)	0.64
Infarct-related artery, n (%)			
LAD	250(40)	40(39)	0.88
CX	82(13)	14(14)	
RCA	287(45)	47(46)	
GRAFT	2(0.3)	1(0.9)	
TIMI flow in IRA, n (%)			
0	501(81)	-	
1	69(11)	-	
2	51(8)	-	
3	-	102(100)	

ACE= angiotensin-converting enzyme; ARB = angiotensin-receptor blocker; CX=circumflex artery; IRA=infarct-related artery; LVEF = left ventricular ejection fraction; LAD= left anterior descending artery; RCA=right coronary artery.

Table 2. Laboratory parameters of patients			
Parameters	Infarct related artery occluded group (n=624)	Infarct related artery patent group (n=102)	P value
Hemoglobin, g/dL	13±1.9	13.2±2.1	0.21
Platelet, 103/mm3	251.2±75.4	231.3±59.4	0.01
Mean platelet volume, fL	8.8±3	8.2±1.2	0.07
White blood cell,103/mm3	11.2±5.1	10.4±3.2	0.11
Neutrophil,103/mm3	9.2±3.5	8.6±2.2	0.10
Lymphocyte,103/mm3	1.7±0.9	2.3±1.4	<0.001
Monocyte, 109/L	792±230	586±196	<0.001
Serum glucose, mg/dL	163±90	134±36	0.002
Serum creatinine, mg/dL	0.96±0.4	0.92±0.3	0.22
Total cholesterol, mg/dL	172.1±43.5	164±36.2	0.14
HDL-cholesterol, mg/dL	36.7±9.2	37.2±8.8	0.68
LDL-cholesterol, mg/dL	105.7±38.4	101.7±31.6	0.42
Triglyceride, mg/dL	145.1±92.8	136.7±59.8	0.36
Troponin I, ng/mL	2.3±2.1	1.7±1.8	0.008
Platelet to lymphocyte ratio	189.9±144.7	138.8±123.7	<0.001
Monocyte to HDL ratio	22.4±5.4	17.8±6.9	<0.001
Data are given as mean±SD. HDL=high-density lipoprotein; LDL=low-density lipoprotein.			

Table 3. Multivariate Logistic Regression Analysis Showing the Predictors for the Patency in Infarct-Related Artery.			
Variables	OR	95% CI	P
Mean platelet volume	1.236	0.992-1.541	0.05
Platelet to lymphocyte ratio	1.004	1.000-1.007	0.03
Serum glucose	1.008	1.001-1.014	0.01
Troponin I	1.129	0.967-1.318	0.12
LVEF	0.993	0.976-1.010	0.41
Monocyte to HDL ratio	1.191	1.116-1.272	<0.001
Pre-hospital use of prasugrel or ticagrelor	7.045	1.687-29.414	0.007
CI=confidence interval; HDL=high-density lipoprotein; LVEF = left ventricular ejection fraction; OR, odds ratio.			

Discussion

In the present study, we investigated the relationship between MHR and IRA patency in patients with STEMI, and our data demonstrated that (i) MHR was significantly increased in patients with STEMI who had an occluded IRA before primary PCI; (ii) also MHR was found as an independent predictor of IRA patency in patients with STEMI. We also showed that patients with pre-PCI patent IRA had decreased value of admission troponin I levels and increased EF compared with patients with pre-PCI impaired IRA flow.

Primary PCI is the most effective reperfusion strategy for STEMI. Rapid attainment of a patent infarct artery is crucial for survival and improved short and long term outcomes. Even if the excellent prognosis is generally obtained after successful primary PCI, it may be further enhanced if TIMI-3 flow is restored before angioplasty. Some IRAs are completely occluded in patients with STEMI and some are not. Although these patients come with similar clinical presentations, Stone et al proved that early reperfusion with initial TIMI-3 flow before PCI was a powerful and independent predictor of in-hospital and late survival in patients undergoing a mechanical reperfusion strategy [1]. Patency status of IRA after coronary occlusion is associated with spontaneous and pre-PCI medication-mediated lysis of intracoronary thrombin. Patients who spontaneously achieve TIMI 3 flow may have different fibrinolytic properties related to their balance between coagulation, inflammation, thrombosis, and atherosclerosis.

Inflammation is accused for both initiation and progression of atherosclerosis, and contributes to acute rupture of atherosclerotic plaques with superimposed thrombus formation. Platelets, leukocytes, and endothelial cells are the active players of this process. Monocyte activation and macrophages (their mature form) have pivotal role both in the development and exacerbation of atherosclerotic process, a lipid driven inflammatory disease [9]. Blood monocytes are recruited into the intima and sub-intimal layers of the vessel wall, differentiate into the foam cells by taking up oxidized LDL and other lipids via the scavenger receptors. These migratory properties of monocytes are shown to be accelerated in patients with hypercholesterolemia [10]. Foam cells secrete pro-inflammatory cytokines, matrix metalloproteinases and tissue factor into the local vessel wall. While metalloproteinases digest the internal elastic lamina and cause plaque rupture, released tissue factor comes in contact with circulating blood and yields thrombus formation [11].

HDL cholesterol exhibits anti-inflammatory and anti-thrombotic effect on human monocytes by counteracting the activation and migration of them. Activted monocytes can also be reversed by HDL and its major protein component apolipoprotein A-1. Moreover, it inhibits LDL oxidation and removes cholesterol from those cells [12]. As the blood HDL cholesterol levels decrease, monocyte chemoattractant protein -1 (potent chemotactic factor for monocytes) levels increase [13]. Reddy et al. demonstrated that lower levels of HDL cholesterol, theoretically related to inadequate limitation of inflammatory response, were associated with increased in-hospital mortality following acute myocardial infarction [4].

MHR has been accepted as a vascular inflammatory marker and is a good predictor for atherosclerosis development, progression and cardiovascular outcomes. Its value in acute STMI been investigated some previous clinical studies. Karatas et al showed that admissionMHR values are found to be independently correlated with inhospital major adverse cardiovascular events and mortality after primary PCI [14]. Likewise, Cicek et al have recently found that rates of in-hospital mortality, major adverse cardiovascular events, late mortality, target vessel revascularization, stroke, and reinfarct were higher in the higher MHR group compared with the other MHR groups. They conclude that admission MHR is associated independently and significantly with short-term and long-term mortality in STEMI [5]. Cetin et al documented that MHR was a novel marker of inflammation seemed to be an independent predictor of stent thrombosis in STEMI patients [15]. Finally, Balta et al have recently investigated the relation between MHR and no-reflow phenomenon in patients with STEMI [16]. No-reflow was defined as post intervention TIMI flow grades 0-2 and reflow was defined as TIMI 3 flow grade. They found no-reflow more comon in higher MHR group and suggested MHR as an independent predictor of non-TIMI 3 flow after intervention in STEMI. Likewise, we found higher MHR levels in IRA occluded group and suggested MHR as an independent predictor of non-TIMI 3 flow before intervention in STEMI. It was also proven that pre-PCI IRA flow rate is closely related topost-PCI coronary flow rate and TIMI flow rate after primary PCI is closely related to worse outcomes in patients with STEMI [17].

Similiarly to literature, we found platelet to lymphocyte ratio (PLR) (another inflammatory indicator) was significantly higher in patients with a pre-PCI occluded IRA [18]. It is accepted as a indirect measure of inflammatory and thrombotic

pathways since both platelets and lymphocytes contribute STEMI pathophysiology. MHR is more like a inflammatory and oxidative stress marker.

In our study, pre-hospital administration of anti-platelet agents of rapid onset of action (prasugrel and ticagrelor) were associated with higher rates of pre PCI TIMI 3 flow. Our findings parallel to the guidelines support the idea to give potent anti-platelet agents as early as possible after first medical contact in patients with STEMI who referred for PCI [19].

Study limitations: Our study has some limitations. First, it was a retrospectively designed single center study and cardiovascular end points were not evaluated. Therefore we cannot make any conclusions on the role of MHR in cardiovascular morbidity and mortality. Second, study population is relatively small. Using only admission laboratory values rather than values at a time interval is the another limitation. We did not evaluate other cytokines or inflammatory markers such as C-reactive protein and fibrinogen, NLR. Lastly, we did not measure others markers of myocardial damage such as CK-MB.

As a conclusion our study findings demonstrated that MHR was an independent negative predictor of IRA patency in patients with STEMI undergoing PCI. Higher MHR was associated with lower TIMI flow grade on admission coronary angiogram. MHR may play a role in the pathogenesis of pre-PCI IRA patency as well as no-reflow phenomenon pathogenesis. MHR can be easily derived from complete blood count and might be used as an indicator of IRA patency in daily practice.

Declaration of conflicting interests

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Original Article

The relationship between acute exacerbation of chronic obstructive pulmonary disease and neutrophile-to-lymphocyte ratio, serum uric acid and gamma-glutamyl transferase levels

Kronik obstrüktif akciğer hastalığının akut alevlenmesi ile nötrofil-lenfosit oranı ve serum ürik asit düzeyleri arasındaki ilişki

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ABSTRACT

Aim: Chronic inflammation plays a pathogenic role in chronic obstructive pulmonary disease. Increase in the ratio of circulating neutrophil to lymphocyte ratio (NLR), serum uric acid and gamma-glutamyl transferase (GGT) levels may serve as a marker of systemic inflammation. The aim of this study is to evaluate the potential predictive value of blood neutrophil-to- lymphocyte NLR and possible role of serum uric acid and gamma-glutamyl transferase levels as biomarkers in chronic obstructive pulmonary disease patients.

Material and Methods: The sample was derived from a population of 276 patients admitted for acute exacerbation of chronic obstructive pulmonary disease to our respiratory medicine department.

Results: Higher N/L ratios, uric acid and GGT levels were detected in chronic obstructive pulmonary disease patients than in the controls ($P < 0.001$). Positive correlations between smoking (pack-years) and NLR, serum GGT, uric acid, and C-reactive protein levels were found ($P < 0.001$; $r = 0.339$, $P < 0.001$; $r = 0.224$, $P < 0.001$; $r = 0.242$, and $P < 0.001$; $r = 0.563$, respectively).

Conclusion: Our study demonstrated that NLR, serum GGT and uric acid levels are significantly higher in patients with chronic obstructive pulmonary disease. With regard to the associations between chronic obstructive pulmonary disease and these parameters, they can be used to determine disease burden besides other risk factors in routine clinical practice.

Keywords: chronic obstructive pulmonary disease, neutrophil to lymphocyte ratio, uric acid, gamma-glutamyl transferase, C- reactive protein, inflammation

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ÖZ

Amaç: Kronik inflamasyon, kronik obstrüktif akciğer hastalığında (KOAH) patojenik bir rol oynamaktadır. Dolaşımdaki nötrofil-lenfosit oranı (N / L oranı), serum ürik asit ve gama-glutamil transferaz (GGT) düzeylerindeki artış, sistemik bir iltihabın göstergesi olabilir.

Bu çalışmanın amaı KOAH'lı hastalarda biyolojik belirteç olarak kan nötrofil-lenfosit (N / L) oranı ile serum ürik asit ve gama-glutamil transferaz (GGT) düzeylerinin muhtemel rolü üzerindeki olası değerini değerlendirmektir.

Gereç ve Yöntemler: Retrospektif bir çalışma.Gereç ve Yöntem: Örneklem, KOAH'ın stabil ve akut alevlenmesi için göğüs hastalıkları bölümümüze başvuran 260 hastadan (stabil KOAH, n = 68, KOAH'ın akut alevlenişi, n = 192) oluşturuldu.

Bulgular: KOAH hastalarının akut alevlenmesinde yüksek N / L oranları ve serum ürik asit seviyeleri tespit edildi (p <0.01). Sigara (paket-yıllar) ile N / L oranı ve C-reaktif protein düzeyleri arasında pozitif korelasyon bulundu (sırasıyla P = 0.014; r = 0.153 ve P = 0.001; r = 0.252).

Sonuçlar: Çalışmamız, akut KOAH alevlenmesi olan hastalarda N / L oranı ve serum ürik asit düzeylerinin belirgin olarak daha yüksek olduğunu göstermiştir. Kronik obstrüktif akciğer hastalığı ile bu parametreler arasındaki ilişkilerle ilgili olarak, rutin klinik uygulamada diğer risk faktörlerinin yanında hastalık yükünü belirlemek için kullanılabilirler.

Anahtar Kelimeler: kronik obstriktif akciğer hastalığı, nötrofil lenfosit oranı inflamasyon, C reaktif protein, serum ürik asit, inflamasyon

Introduction

Chronic obstructive pulmonary disease (COPD), is a type of obstructive lung disease characterized by chronically poor airflow. Acute exacerbation of COPD was defined as " a sustained worsening of the patient' s condition, from the stable state and beyond normal day-to- day variations, and necessitates a change in regular medication [1]. Exacerbations of respiratory symptoms are important because of their profound and long – lasting adverse effects on patients [2]. During the acute episode, levels of circulating acute phase proteins and inflammatory cells are elevated [3]. Biomarkers are any clinical features, imaging quantification or laboratory-based test markers that characterize disease activity, which are useful for diagnosing and monitoring disease processes and response to therapy [4]. Providing reliable evidence to validate biomarkers remains an important challenge to be addressed include the accuracy and reliability of clinical utility and cost- effectiveness [5].

Blood neutrophil to lymphocyte ratio (NLR) is a simple marker of subclinical inflammation that can be easily obtained from the record of a patient's blood cells. Also, serum uric acid (sUA) and gamma-glutamyl transferase (GGT) levels have been associated with increased levels of inflammatory markers that may be important in the outcomes of COPD patients [6,7]. The aim of the study was to evaluate the predictive value of the NLR and possible roles of sUAand GGT as biomarkers in COPD patients.

Material and Methods

The sample was derived from a population of 357 consecutive patients admitted for acute exacerbation of chronic obstructive pulmonary disease (AECOPD) to the respiratory medicine department of Ufuk University Faculty of Medicine (Ankara, Turkey) between December 2012 and September 2015. The study was conducted in accordance with the principles of The Declaration of Helsinki. In total, 81 of them were excluded because they met the exclusion criteria (n = 56) and did not fulfill the inclusion criteria (n = 25). Finally, 276 patients were enrolled, including 135 male (48.9%) and 141 female subjects (51.1%). All subjects were current or ex-smokers (35.76 ± 30.19 pack - years). The inclusion criteria were age above 40 years, current smoker or ex-smoker, a spirometry clear enough to enable evaluation of the respiratory function, and the patient's consent. The exclusion criteria were current bronchial asthma, bronchiectasis, pregnancy, cardiomyopathy, coronary artery disease, congestive heart failure, history of any inflammatory disease (infection, malignancy, rheumatic disorders etc.), gout disease, and any hepatobiliary disorders. Blood samples were collected for complete blood count (CBC), CRP, GGT and sUA. The tubes containing EDTA were used for automatic blood count; the others were measured using conventional methods. Spirometry was performed using a VMAX Encore system (Germany). Staging of airflow limitation

was made according to GOLD guidelines (GOLD stage I [FEV1 ≥ 80%], Stage II [50 ≤ FEV1 < 80], Stage III [30% ≤ FEV1 < 50%] and Stage IV [FEV1 < 30%] [8]. Also, severity of dispnea was evaluated with the COPD Assessment Test (CAT) [9]. The case definition of an exacerbation was a functional one, based on the decision by a patient's primary clinician or by study personnel to prescribe antibiotics or systemic corticosteroids, alone or in combination.

Statistical Analysis

The data were analyzed with the IBM SPSS Statistics 21 for Windows. The normal distribution of variables was verified with the Kolmogorov-Smirnov test. Degrees of association between continuous variables were evaluated by Spearman's Rank Correlation analyses. Comparisons between the groups were made with the Kruskal Wallis test and Mann-Whitney U test. When needed, binary comparisons among the groups were made using the Conover-Inman test ($p<0.05$ was considered statistically significant). A chi square (X2) test was used to investigate whether distributions of categorical variables differed within groups. Optimal cut-off values to predict the severe COPD by sUA and GGT were determined by receiver operating characteristics (ROC) analysis, and area under the curve (AUC) values were determined. To determine the independent risk factors (age, sex, smoking, and NLR) for the presence of COPD, binary logistic regression analysis was performed. The data were shown as mean ± SD for continuous variables and absolute numbers (%) for dichotomous variables. All analyses were stratified by presence of COPD. A P value less than 0.05 was considered statistically significant.

Results

The mean age of the study population was 65.9 ± 11.7 years and 48.9 % of them were male. Baseline characteristics and biochemical examinations are shown in Table 1.

Table 1. Baseline Characteristics of the Individuals

	Control Group	AECOPD Group	p value
Age (years)	59.33±10.28	70.99±10.14	<0.001
Smoking (pack-years)	0.50±5.47	35.76±30.19	<0.001
Uric acid (mg/dL)	5.23±1.65	8.80±28.92	<0.001
GGT (U/L)	26.76±16.81	46.95±51.15	<0.001
LDL (mg/dL)	126.21±34.67	100.90±36.29	<0.001
HDL (mg/dL)	47.03±13.17	43.35±13.81	0.024
TC (mg/dL)	195.71±41.15	176.08±49.10	<0.001
Triglyceride (mg/dL)	138.62±71.34	120.14±56.02	0.038
TC/HDL	4.40±1.32	4.38±1.68	0.433
Hemoglobin (g/dL)	13.50±1.72	13.47±2.18	0.698
MPV (fL)	8.43±1.03	7.94±1.45	<0.001
Platelet count (x103/µL)	262.25±71.49	234.84±91.87	0.006
Creatinine (mg/dL)	0.80±0.38	1.09±1.13	<0.001
Neutrophil (x103/mm3)	4.76±1.81	7.25±3.53	<0.001
Lymphocyte (x103/mm3)	1.88±0.62	1.55±0.74	<0.001
NLR	2.82±1.66	6.37±7.09	<0.001
CRP (mg/L)	5.77±11.27	93.00±87.25	<0.001

Of the 276 patients, 56.5% had COPD, 23.6% had diabetes mellitus, 51.4% had hypertension, 41.3% had hyperlipidemia, and 42.4% had history of smoking. Mean NLR were 2.8 ± 1.7 and 6.4 ± 7.1in the control and COPD groups, respectively ($P < 0.001$).

There are positive correlations between CRP and GGT, NLR ($P = 0.001$; $r = 0.213$, $P < 0.001$; $r = 0.403$, respectively). There are negative correlations between CRP and FEV1, FEV1 / FVC. ($P < 0.001$; $r = -0.286$, $P = 0.002$; $r = -0.241$, respectively) Also, negative correlations between smoking (pack-years) and FEV1, FEV1 / FVC, and HDL levels were found ($P = 0.017$; $r = -0.183$, $P < 0.001$; $r = -0.274$, and $P < 0.001$; $r = -0.245$, respectively). Differently, positive correlations between smoking (pack-years) and NLR, Cr levels, hemoglobin, GGT, sUA and CRP levels were found ($P < 0.001$; $r = 0.339$, $P < 0.001$; $r = 0.216$, $P = 0.039$; $r = 0.125$, $P < 0.001$; $r = 0.224$, $P < 0.001$; $r = 0.242$,and $P < 0.001$; $r = 0.563$, respectively). CATS and MPV, sUA, serum creatinine levels showed statistically significant positive correlations ($P = 0.001$; $r = 0.291$, $P = 0.032$; $r = 0.190$, $P = 0.004$; $r = 0.240$) (Figure 1).

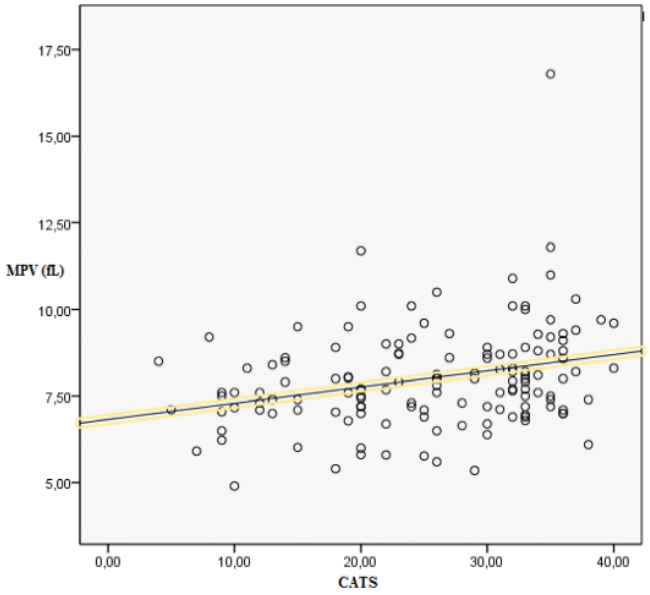

Figure 1. There is a positive correlation between MPV and CATS (P = 0.001; r = 0.291)

Higher levels of NLR were found in the AECOPD patients than in the controls (P < 0.001) (Figure 2).

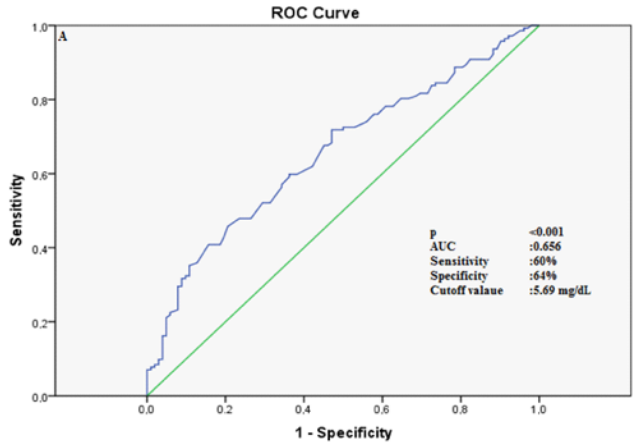

Figure 2. NLR were higher in the COPD patients than in the controls (P < 0.001)

Also, higher levels of GGT and sUA levels were detected in AECOPD group (Table 1) After adjustment for age, sex, and smoking status, the relationship of AECOPD to NLR maintained its significance [P < 0.001; adjusted OR = 1.418 (95 % CI, 1.177 - 1.708)]. Cut off values of sUA (A) and GGT (B) levels for predicting the AECOPD are shown in Figure 3.

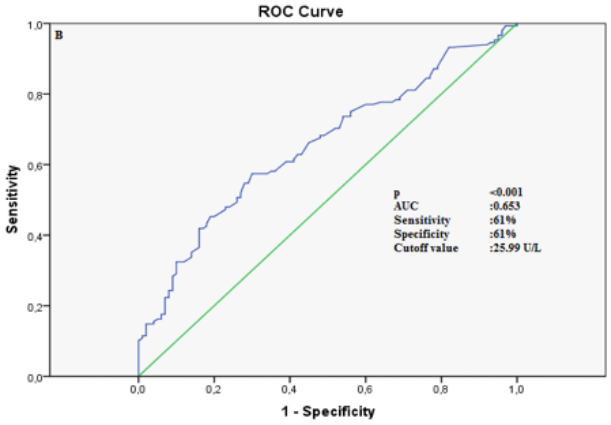

Figure 3. Cut-off values of uric acid (A) and GGT (B) for predicting the AECOPD. AUC, area under the curve; COPD, chronic obstructive pulmonary disease; GGT, gamma-glutamyl transferase; ROC, receiver-operating characteristic.

Discussion

A range of blood biomarkers have been related with severity of airflow limitation. The current study manifested that there was a significant association between GGT, sUA levels and AECOPD. The study also showed that NLR was higher in AECOPD patients than in the control group. All of them were readily available and cost-effective biomarkers.

Exacerbations are associated with the quality of life and disease progression in COPD and therefore early detection of disease activity could significantly reduce the mortality. Elevations of CRP during exacerbation are associated with worsening of COPD [10-12] study from the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) cohort found elevated levels of CRP and fibrinogen and leukocyte count to be associated with the exacerbations in the first year of follow-up in univariate analyses [13]. In our study, we found a negative correlation between CRP and FEV1.

The pathogenesis of COPD is complex. The neutrophil is an important cell in the pathogenesis of COPD [14]. Although the underlying mechanism associated between the NLR and COPD has not been clearly established neutrophils, one of the most important mediators of innate immunity, are professional phagocytes which mount the acute inflammatory response and act as the first line of defense against invading pathogens

[15]. The systemic inflammation is reflected by an increase number of neutrophil granulocytes in the circulation and neutrophil granulocyte count is associated with progression of COPD. Previous epidemiological studies have shown an inverse relationship between circulating neutrophil numbers and the forced expiratory volume in one second (FEV1) [16,17]. Activation may be even more pronounced in neutrophils which are sequestered in the pulmonary microcirculation in smokers and in patients with COPD [18]. Smoking induces oxidative stress and lung inflammation in COPD [19]. As a result of damage to lung tissues induced by oxidants and inflammation, pulmonary function declines with long-term exposure to smoke [8,20]. Likewise, we found a positive correlation between NLR and smoking in our study.

NLR also has been examined as a measure of inflammation in different groups of patients such as those with chronic kidney disease [21,22] cardiovascular disease [23,24], or ulcerative colitis [25]. Previous studies have shown that NLR associated with disease severity and exacerbation in COPD patients that can be used as a new inflammatory marker. This ratio has also been useful to evaluate the adverse clinical outcomes and mortality in various cancer types [26,27]. Previous studies have shown that NLR associated with disease severity and exacerbation in COPD patients that can be used as a new inflammatory marker [28-30]. Gürol et al. [31] found NLR to have higher sensitivity than CRP and WBC. This marker showed a significant increase not only exacerbation but also in stabil COPD patients [32]. In our study, the NLR level was higher in patients with exacerbated COPD than control group. Therefore, NLR may be useful as a diagnostic tool like CRP to show the inflammation and confirm exacerbation COPD and identify patients with the severity of AECOPD.

Oxidative stress appears to be a key component of many reactions associated with chronic inflammation. Gamma-glutamyl transferase (GGT) is a clinical marker of biliary disease, but is also of importance in anti-oxidant metabolic pathways and, consequently, is a potential biomarker of oxidative stress which increases in inflammation because of leukotriene-induced inflammation in COPD [33]. It is imperative for a cell to maintain this level of activate glutathione (GSH) for normal functioning. Cells, in particular within the lungs, have evolved elaborate mechanisms that ensure proper balance between the pro-oxidant and antioxidant molecules as a defense against constant oxidative challenge. GSH is the most important non-protein sulphydryl in the cells and plays a key role in the maintenance of the cellular redox status. The redox potential is defined as the ratio of the concentration of oxidizing equivalents to that of reducing equivalents [34]. As the only enzyme of the cycle located on the outer surface of plasma membrane, gamma-glutamyl transpeptidase (GGT) plays key roles in GSH homeostasis by breaking down extracellular GSH and providing cysteine, the rate-limiting substrate, for intracellular de novo synthesis of GSH. GGT also initiates the metabolism of glutathione S-conjugates to mercapturic acids by transferring the gamma-glutamyl moiety to an acceptor amino acid and releasing cysteinylglycine. In Holme's study, GGT correlated with airflow obstruction and, it was independently related to FEV(1), mortality, smoking history and male gender [35] Lim et al [36] examined association between serum GGT and concentrations of serum C-reactive protein (CRP) among 12,110 adult participants. After adjustment for race, sex, age, cigarette smoking, alcohol intake, and body mass index (BMI), serum concentration of GGT across all deciles was positively associated with serum concentrations of CRP. A strong clinical relationship between CRP and GGT was described [37] In our study we also found positive correlation between GGT levels and CRP as Ermiş et al did [7]. GGT levels are also correlated with smoking status.

Tissue hypoxia has been reported to induce the degradation of adenosine. This results in the release of purine intermediates and end products of purine catabolism, such as uric acid [38]. Elevation of sUA levels has been observed in hypoxic subjects, including patients with COPD [39]. Uric acid is the end-product of purine degradation [40] and it is a biomarker of xanthine oxidase activity, which is known to be an important source of reactive oxygen species [41]. High levels of lung oxidative stress and inflammation, circulating UA levels may be elevated as a result of lung tissue damage. Therefore, several investigators have reported that elevated sUA levels were associated with worsening of cardiovascular disease, heart failure and COPD [42,43]. Positive associations were demonstrated between sUA and inflammatory markers such as CRP and interleukin - 6 (IL-6) [44]. A Spanish study reported associations between sUA / creatinine ratio and FEV 1 [37]. Similarly, Kocak et al found [45], both sUA levels and sUA/creatinine ratios were significantly higher in COPD patients than in healthy controls. According to a Japanese study, hypoxia, pulmonary hypertension, oxidative stress and inflammation, which eventually results in impairment of pulmonary function are possible explanations for the association between sUA levels and pulmonary

function [46] Bartziokas et al [6] have shown that patients with increased sUA levels had increased 30-day mortality rates, and increased risk of AECOPD and hospitalization in the 1- year follow up. Similarly we found positive correlation between sUA levels and smoking (pack-years). Multiple logistic analysis revealed that FVC % predicted in females and FEV1 % predicted in both genders were significant predictive for hyperuricemia. In our study, sUA levels were significantly higher in COPD patients than in controls and there were significant associations between spirometric measures, smoking pack / year and sUA levels. It has been suggested that sUA levels increase in the presence of persistent systemic inflammation caused by COPD.

Our study has some limitations. First, the study population was relatively small and our study was retrospective A larger study population would provide a higher statistical power. Another limitation was that neutrophils and lymphocytes count was not determined visually by peripheral blood smear. Large scale prospective studies are needed to obtain further information.

As a conclusion although there is no ideal single serum marker for predicting disease severity, white blood cell count, CRP and ESR are the most commonly used inflammatory indices in routine clinical practice. Our study demonstrates that in patients with AECOPD, NLR, serum GGT and sUA, which are widely and rapidly available, simple, low-cost biomarkers could be used as marker of inflammation in AECOPD. Large scale prospective, randomized clinical trials are needed to see whether the N / L ratio, GGT, and sUA levels obtained during routine testing are of greater value in terms of diagnosis, risk stratification, and treatment evaluation in patients with COPD.

Declaration of conflicting interests

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Original Article

Comparing the value of Pregnancy Associated Plasma Protein A (PAPP-A) and ischemia modified albumin in the patients with chest pain

Göğüs ağrısı olan hastalarda gebelikle ilişkili Plazma Protein A (PAPP-A) ve iskemi modifiye albümin değerinin karşılaştırılması

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ABSTRACT

Aim: To evaluate the diagnostic value of PAPP-A and CK-MB in early diagnosis of ACS.

Material and Methods: It is a single-center, prospective, clinical study. There were totally 152 cases. At the end of the study the levels of troponin-T, CK-MB, PAPP-A and IMA in the different groups were compared.

Results: There were 13 patients with STEMI, 53 patients with NSTEMI/UAP and 80 patients with non-specific ECG findings. When we consider the definitive diagnosis; there were 8 patients with STEMI, 36 patients with NSTEMI, 23 patients with UAP, 17 patients with SAP and 68 patients with non-coroner chest pain. In our study, the most specific parameter at the highest sensitivity for the patients with the chest pain within the first hours (0-2 hour, 2-4 hour) was IMA. (Sensitivity/specificity; 100/30.7, 93.7/52.3 respectively).

Conclusion: According to our results, PAPP-A and IMA cannot be used as an diagnostic tool like troponin-T and CK-MB in ACS. Also IMA cannot be used as an ideal screening test in the diagnosis of ACS during the early period of chest pain. Still, IMA is more useful diagnostic biochemical marker than troponin-T, CK-MB and PAPP-A as a screening test in detecting ACS during the first hours.

Keywords: PAPP-A, IMA, chest pain, acute coronary syndrome

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ÖZ

Amaç: ÇAKS'un erken tanısında PAPP-A ve CK-MB'nin tanısal değerinin belirlenmesidir.

Gereç ve Yöntemler: Tek merkezli, prospektif, klinik bir çalışma 152 vaka incelendi. Çalışmanın sonunda troponin-T, CK-MB, PAPP-A ve IMA'nın farklı gruplardaki düzeyleri kıyaslandı.

Bulgular: 13 hastada STEMI tanısı kondu, 53 hastada NSTEMI/UAP ve 80 hastada non spesifik EKG bulguları mevcuttu. Kesin tanısına göre 8 hastada STEMI, 36 hastada NSTEMI, 23 hastada UAP (unstabil njina pektoris), 17 hastada SAP (stabil anjina pektoris) 68 hastada non koroner göğüs ağrısı mevcuttu. Göğüs ağrısının ilk saatlerinde (0-2 saat, 2-4 saat) en yüksek sensitivitedeki en spesifik parametre IMA idi. (Sensitivite/spesifite; 100/30.7, 93.7/52.3).

Sonuçlar: Sonuçlarımıza göre, PAPP-A ve IMA, AKS'de troponin-T ve CK-MB gibi bir tanı aracı olarak kullanılamaz. Sonuçlarımız, duyarlılık ve özgüllük özellikleriyle ilgili olarak IMA, göğüs ağrısı erken döneminde AKS tanısında ideal bir tarama testi olarak kullanılamaz. Yine de, IMA, ilk saatler boyunca AKS'yi saptamada bir tarama testi olarak troponin-T, CK-MB ve PAPP-A'ya kıyasla daha yararlı diagnostik biyokimyasal belirteçtir. Çalışma sonuçlarımız literatürde benzer bir çok araştırmanın aksine bir sonuç sergilemektedir ve bulguları daha kapsamlı bir dizi çalışma ile değerlendirilmelidir.

Anahtar kelimeler: PAPP-A, IMA, göğüs ağrısı, akut koroner sendromu

Introduction

Chest pain is a frequent cause of presentations to emergency departments [1]. Testing new biochemical markers in comparison with conventional biomarkers for ruling-in or ruling-out ACS is still an unresolved issue. The BACC study has recently evaluated this topic and demonstrated that a high-sensitivity troponin I test showed great accuracy in ruling out MI in patients with chest pain, with triage times reduced to 1 hour, and also showed better positive predictive ability than some other studies [2]. But, the time profile of the rise of troponins in the course of ACS is variable and the best cut-off for troponin assay as well as the other biomarkers are still to be validated.

Conventional tests have now largely been superseded by high-sensitivity cardiac troponin (hs-cTn) measurements. Recent research reports that this is useful in the early diagnosis of suspected acute myocardial infarction (AMI) [3]. However, because of problems with both sensitivity and specificity and delays in their elevations reaching to detectable level in blood, new and more practical biochemical parameters are needed. Several novel biochemical parameters are therefore being evaluated in the literature. pregnancy associated plasma protein A (PAPP-A) and ischemia modified albumin (IMA) are among the are among the potential biochemical parameters being investigated in terms of diagnostic sensitivity and specificity [4-9].

Despite the information obtained from existing studies, no data pool to permit IMA and PAPP-A to enter routine use. The purpose of this study was to compare the diagnostic values of PAPP-A and IMA in the early period of ACS when levels of conventional biochemical parameters have not yet risen.

Material and Methods

Setting

This research, intended to compare the diagnostic values of PAPP-A and IMA in patients with chest pain, is one-center, prospective clinical study performed at an University Hospital following approval from the ethical committee.

Data collection process

Adult age group (>18 years) patients presenting to the ED in the first 8 h after chest pains of typical or atypical character between 01.01.2011 and 01.06.2011 were included in the study. Patients with advanced liver failure, end stage renal disease, decompensated heart failure, a history of major surgery or major trauma in the previous 3 months, known or suspected chronic inflammatory or neoplastic disease, acute mesenteric ischemia, cerebral ischemia or peripheral artery disease, or declining to take part in the study were excluded.

Establishment of the Study Groups

An initial screening examination was performed by the treating emergency physician with appropriate therapeutic measures and diagnostic studies initiated. All consecutive patients presenting to the ED with chest pain and meeting the inclusion criteria were categorized into four time periods on the basis of time of onset of chest pain (0-2 h, 2-4 h, 4-6 h, 6-8 h) by the same treating emergency physician as blind to the results of study markers.

They were then subdivided on the basis of definitive diagnoses. On the basis of definitive diagnosis, five subgroups were established in the light of definitive diagnoses following

additional diagnostic tests such as effort and angiography and measurement of cardiac enzymes based on the diagnostic algorithm established. These were;

a. ST elevation myocardial infarction (STEMI) group,

b. Non STEMI group,

c. Unstable angina pectoris (UAP) group,

d. Stable angina pectoris (SAP) group and

e. Non-coronary causes group.

Appropriate pictures were subsequently established by analyzing these groups' and subgroups' mean troponin-T, CKMB, PAPP-A and IMA levels at the time intervals determined. The biochemical markers of the patients in these groups and subgroups were then compared at the specific time intervals determined.

Age, gender, chest pain characteristics and duration, other accompanying symptoms, physical examination findings, risk factors and clinical and demographic characteristics of the patients included in the study were recorded by the maintenance of a data form from first application to the ED. All patients with chest pain were administered the diagnosis and treatment algorithm developed according to the American Health Association (AHA) guideline given in Figure 1 [10].

Blood specimens were collected at 0-2 h, 2-4 h, 4-6 h and 6-8 h since onset of pain from time of application. Relevant group membership, based on onset of chest pain, was considered in subsequent follow-ups. During this stage, a number of patients were discharged in the early period due to their clinical condition. Blood specimens were taken from these patients only in the time intervals up to discharge.

In collecting blood specimens, it was avoided from hemolysis as much as possible for each sample. Approximately 10 ml blood was placed a separator biochemistry tube, and since CKMB and troponin measurements are part of the routinely applied diagnostic approach, these were analyzed immediately. For PPAP and IMA measurements, specimens were kept at -80 C and analyzed at the same time for all the study groups (duration of storage at -80 C, min:1 day-max:60 days) by a biochemist as blind to patient's group or data.

Troponin measurement

Troponin-T levels were measured on an Elecsys 2010 (Roche Diagnostic, Tokyo, Japan) device and results were expressed as ng/mL. Values below <0.01 ng/mL were regarded as normal.

CK-MB measurement

CK-MB levels were measured on an Elecsys 2010 (Roche Diagnostic, Tokyo, Japan) device and the results were expressed as ng/mL. Normal value range was taken as 0-6.73 ng/mL for men and 0-3.77 ng/mL for women.

IMA measurement

The decrease in albumin-cobalt binding was evaluated using the rapid and colorimetric method described by Bar et al. and the results were expressed as absorbance units (ABSU) [10].

PAPP-A measurement

Serum PAPP-A levels were determined using enzyme-linked immunosorbent assay (ELISA) kits-DRG PAPP-A ELISA EIA:2397 (DRG Instruments GmbH, Marburg, Germany). Specimen absorbance was measured on a VERSA (Molecular Devices Corporation, California, USA) microplate reader at a wavelength of 450 nm. Results were given as µg/mL.

Patients were monitored for complications throughout their periods of hospitalization. Patients of their relatives were contacted by telephone 3 months after discharge, and any complications arising during that 3-month period were recorded.

Data analysis

Data were loaded onto the Statistical Package for the Social Sciences 13.0 program (SPSS Inc., IL, USA). Clinical and demographic characteristics, such as age, gender, risk factors and accompanying symptoms and descriptive statistics were produced. Normal distribution of biochemical measurements was evaluated using the Kolmogorov-Smirnov test. Comparisons among groups of normally distributed data were performed using Bonferroni-corrected one-way ANOVA, while Bonferroni-corrected Kruskal Wallis analysis of variance was used for non-normally distributed data. ROC analysis was performed for determining sensitivity, specificity, NPV and PPV of biochemical measurements for 0-2, 2-4, 4-6 and 6-8 h intervals for data grouped according to time for diagnosis of ACS on the basis of definitive diagnoses. Spearman's correlation analysis was used to determine the relationship between parameters for 0-2, 2-4, 4-6 and 6-8 h intervals. Significance was set at $P < 0.05$.

Results

Seventeen thousand patients applied to the study center during the 5-month study period. During that time, the number of patients presenting to the ED with typical-atypical chest pain was 215 (1.26% of total patient number). Sixty-three of these 215 patients were excluded for meeting at least one of the exclusion criteria.

After evaluation of the exclusion criteria, 152 patients applying with typical or atypical chest pain were enrolled. Clinical and demographic characteristics of the patients included are shown in Table 1.

Patients were monitored with a diagnostic and therapeutic algorithm developed in line with the AHA guideline. At the end of this period, our patients were grouped according to their definitive diagnoses; 8 patients (5.26%) were diagnosed with STEMI, 36 (23.7%) with NSTEMI, 23 (15.1%) with UAP, 17 (11.18%) with SAP and 68 (44.73%) with non-coronary chest pain. Mean and compared troponin, CK-MB, PAPP-A and IMA levels identified as a result of biochemical analyses and groups formed on the basis of definitive diagnoses and initial duration of chest pain are shown in Table 2. According to definitive

Table 1. Clinical and demographic characteristics of the study group	
Age (Mean±SD)	50.66±18.13
Gender	n, (%)
Male	109 (71.7)
Female	43 (28.3)
Chest pain characteristics	n, (%)
Pain at rest lasting more than 20 min	98 (64.5)
New onset and activity restricting pain	45 (29.6)
Chest pain triggered by effort	66 (43.4)
Worsening angina pain	58 (38.2)
Pleurotic chest pain	32 (21.1)
Localizable pain	81 (53.3)
Mechanical-type pain	32 (21.1)
Accompanying symptoms	n, (%)
Cold sweat	23 (15.1)
Nausea	18 (11.8)
Palpitation	33 (21.7)
Syncope	9 (5.9)
Dyspnea	18 (11.8)
Cough	24 (15.8)
Fever	15 (9.9)
Risk factors	n, (%)
Previous history of CAD	41 (27.0)
Hypertension	62 (40.8)
Cigarette use	57 (37.5)
Previous history of MI	35 (23.0)
Diabetes	27 (17.8)
Obesity	29 (19.1)
Hyperlipidemia	26 (17.1)
Family history	35 (23.0)
Sedentary lifestyle	113 (74.3)
Renal disease	2 (1.3)
Systolic blood pressure (mean mm/Hg±SD)	134.5 ± 24.7
Diastolic blood pressure (mean mm/Hg±SD)	77.75 ± 14.3
HDL (mean mg/dl±SD)	50.44 ± 18.3
LDL (mean mg/dl±SD)	11.06 ± 38.7
Total cholesterol (mean mg/dl±SD)	186.85 ± 42.7
Cardiovascular events taking place during hospitalization	n, (%)
Death	1 (0.7)
New non-fatal MI	1 (0.7)
Repeat need for stent	1 (0.7)
Stroke	0 (0.0)
Malign arrhythmia	7 (4.6)
CPR required	7 (4.6)
MV required	14 (9.2)
Cardiovascular events taking place at 3-month follow-up after discharge	n, (%)
Death	0 (0.0)
Stroke	0 (0.0)
New application with chest pain	26 (17.1)
New hospitalization with chest pain	16 (10.5)
Repeat ACS	8 (5.3)
Stent	4 (2.6)
CABG opp	3 (2)
Malign arrhythmia	1 (0.7)
CAD: Coronary artery disease; ACS: Acute coronary syndrome; MV: Mechanical ventilation; CPR: Cardiopulmonary resuscitation; MI: Myocardial infarction; HDL: High density lipoprotein; LDL: Low density lipoprotein; SD: Standard deviation	

Table 2. Troponin-T, CK-MB, PAPP-A and IMA levels of patients grouped according to definitive diagnosis and chest pain

	Patients applying with chest pain at 0-2 h					Patients applying with chest pain at 2-4 h					Patients applying with chest pain at 4-6 h					Patients applying with chest pain at 6-8 h				
	STEMI n=2	NSTEMI n=4	UAP n=4	SAP n=2	Non-cardiac n=25	STEMI n=2	NSTEMI n=8	UAP n=6	SAP n=5	Non-cardiac n=6	STEMI n=2	NSTEMI n=11	UAP n=4	SAP n=5	Non-cardiac n=18	STEMI n=2	NSTEMI n=13	UAP n=9	SAP n=5	Non-cardiac n=19
Troponin-Tng/ml (Ort.± SD)	0.010 ± .00	0.029 ± .025a	0.01 ± 0.00	0.01 ± 0.00	0.01 ± 0.00a	0.1 ± 0.09 b	0.14 ± 0.21c	0.01 ± 0.00	0.01 ± 0.00	0.01 ± 0.00b,c	0.19 ± 0.26	0.18 ± 0.22 h	0.01 ± 0.00	0.0 ± 0.00	0.05 ± 0.18h	10.61 ± 1.88 d,e	1.23 ± 2.71 f,g,i	0.01 ± 0.00 d,f,g	0.01 ± 0.00	0.05 ± 0.2 e,i
CK-MB ng/ml (Ort.± SD)	3.61 ± 0.71	3.47 ± 0.67	3.31 ± 0.54	2.81 ± 0.0	3.42 ± 0.52	7.35 ± 3.74	5.66 ± 2.93l	3.26 ± 0.71	2.74 ± 0.37	3.06± 0.55l	10.1 ± 11.5	16.5 ± 22.1	2.77 ± 0.25	2.8 ± 0.48	5.29 ± 8.34	273.0 ± 8.48	66.7 ± 112 j,k,m	3.15 ± 0.68j	3.11 ± 0.54k	5.42 ± 8.51 m
PAPP-A µg/ml (Ort.± SD)	1.55 ± 0.17	1.47 ± 0.16	1.66 ± 0.13	1.79 ± 0.0	1.60 ± 0.15	1.86 ± 0.07	1.51 ± 0.31	1.27 ± 0.14	1.46 ± 0.24	1.49 ± 0.32	1.31± 0.24	1.53 ± 0.23	1.56 ± 0.31	1.58 ± 0.15	1.51 ± 0.14	2.41 ± 1.19	1.49 ± 0.27	1.71 ± 0.91	1.23 ± 0.21	1.37 ± 0.23
IMA ABSU (Ort.±SD)	0.41 ± 0.03	0.51 ± 0.11	0.48 ± 0.08	0.29 ± 0.0	0.44 ± 0.08	0.54 ± 0.04	0.51 ± 0.19	0.52 ± 0.04	0.43 ± 0.1	0.45 ± 0.12	0.5 ± 0.01	0.5 ± 0.09	0.59 ± 0.08	0.5 ± 0.16	0.49 ± 0.09	0.58 ± 0.0	0.57 ± 0.09	0.59 ± 0.08	0.51 ± 0.16	0.49 ± 0.09

Significant results at comparisons in the same column and similar time intervals are indicated a,b,f,h,i,j,m P < 0.0001; c,e, P = 0.001; d,k, P = 0.002; g, P = 0.003; l, P = 0.005

diagnosis analysis findings (Table 3), which permit a more accurate picture of the diagnostic value of the biochemical parameters, CK-MB and troponin-T levels were more functional compared to IMA and PAPP-A in the differential diagnosis of chest pain.

STEMI and NSTEMI/UAP patients were regarded as ACS and other patients as non-ACS. Sensitivity, specificity, NPV and PPV values from ROC analysis performed for biochemical parameters measured between 0-2, 2-4, 4-6 and 6-8 h from the onset of chest pain are shown in Table 3.

Table 3. Sensitivity, Specificity, NPV and PPV Values from ROC Analysis

		AUC (95%CI)	Optimal cut-off point	Sensitivity (%); (95%CI)	Specificity (%); (95%CI)	NPV (%); (95%CI)	PPV (%); (%95CI)
Troponin-T ng/ml	0-2 h	0.600; (0.426-0.757)	>0.01	20.0; (2.5-55.6)	100.0; (87.2-100.0)	77.1; (59.9-89.6)	100.0; (15.8-100.0)
	2-4 h	0.719; (0.547-0.854)	>0.01	43.7; (19.8-70.1)	100; (83.9-100.0)	70.0; (50.6-85.3)	100.0; (59.0-100.0)
	4-6 h	0.760; (0.599-0.880)	>0.01	58.8; (32.9-81.6)	95.6; (78.1-99.9)	75.9; (56.5-89.7)	90.9; (56.6-99.8)
	6-8 h	0.748; (0.602-0.862)	>0.014	58.3; (36.6-77.9)	91.6; (73.0-99.0)	68.7; (50.0-83.9)	87.5; (61.7-98.4)
CK-MB ng/ml	0-2 h	0.533; (0.359-0.700)	≤3.1	50.0; (18.7-81.3)	76.9; (56.4-91.0)	80.0; (59.3-93.2)	45.5; (15.6-78.0)
	2-4 h	0.807; (0.644-0.917)	>3.1	81.2; (54.4-96.0)	71.4; (47.8-88.7)	83.3; (57.7-96.6)	68.4; (42.7-87.8)
	4-6 h	0.633; (0.466-0.779)	>4.1	52.9; (27.8-77.0)	91.3; (72.0-98.9)	72.4; (52.4-87.5)	81.8; (48.2-97.7)
	6-8 h	0.729; (0.583-0.846)	>3.8	66.6; (44.7-84.4)	80.0; (59.3-93.2)	71.4; (51.3-86.8)	76.2; (52.2-92.1)
PAPP-A µg/ml	0-2 h	0.573; (0.398-0.736)	≤1.38	20.0; (2.5-55.6)	100.0; (86.8-100.0)	76.5; (58.8-89.3)	100.0; (15.8-100.0)
	2-4 h	0.500; (0.332-0.668)	≤1.25	18.7; (4.0-45.6)	100.0; (83.9-100.0)	61.8; (43.6-77.8)	100.0; (29.2-100.0)
	4-6 h	0.504; (0.342-0.666)	≤1.36	35.3; (14.2-61.7)	91.3; (72.0-98.9)	65.6; (46.5-81.7)	75.0; (34.9-96.8)
	6-8 h	0.663; (0.512-0.793)	>1.72	30.4; (13.2-52.9)	100.0; (86.3-100.0)	61.0; (44.3-76.0)	100.0; (59.0-100.0)
IMA ABSU	0-2 h	0.604; (0.428-0.762)	>0.363	100.0; (69.2-100.0)	30.77; (14.3-51.8)	100.0; (63.1-100.0)	35.7; (18.6-55.9)
	2-4 h	0.786; (0.620-0.903)	>0.444	93.7; (69.8-99.8)	52.3; (29.8-74.3)	91.7; (61.5-99.8)	60.0; (38.2-79.2)
	4-6 h	0.577; (0.409-0.734)	>0.501	68.7; (41.3-89.0)	60.8; (38.5-80.3)	73.7; (48.8-90.9)	55.0; (31.5-76.9)
	6-8 h	0.742; (0.592-0.859)	>0.527	76.2; (52.8-91.8)	64.0; (42.5-82.0)	76.2; (52.8-91.8)	64.0; (42.0-82.4)

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In order to determine the ideal screening test so that almost no patient with ACS presenting to hospital with chest pain at 0-2 and 2-4 h intervals should be missed, we investigated the parameters with the highest sensitivity (100%). PAPP-A had 100% sensitivity for ACS at 0-2 h and specificity of 15.4% (4.4%-34.9%). Specificity of IMA value was 30.8% (14.3%-51.8%). At 2-4 h, sensitivity of PAPP-A value for ACS was 100% while specificity was 9.5% (1.2%-30.4%). Specificity of IMA value was 42.9% (21.8%-66.0%). Specificity of Troponin-T and CK-MB values was lower. On the basis of these results, in contrast to biochemical markers (CK-MB and Troponin-T) in standard use and that do not rise in the early stage of chest pain (0-2 and 2-4 h), IMA having higher specificity at values at which it is 100% sensitive for ACS mean it can be used as a more ideal screening test than PAPP-A. IMA and PAPP-A ROC curves for these periods are shown in Figures 1 and 2.

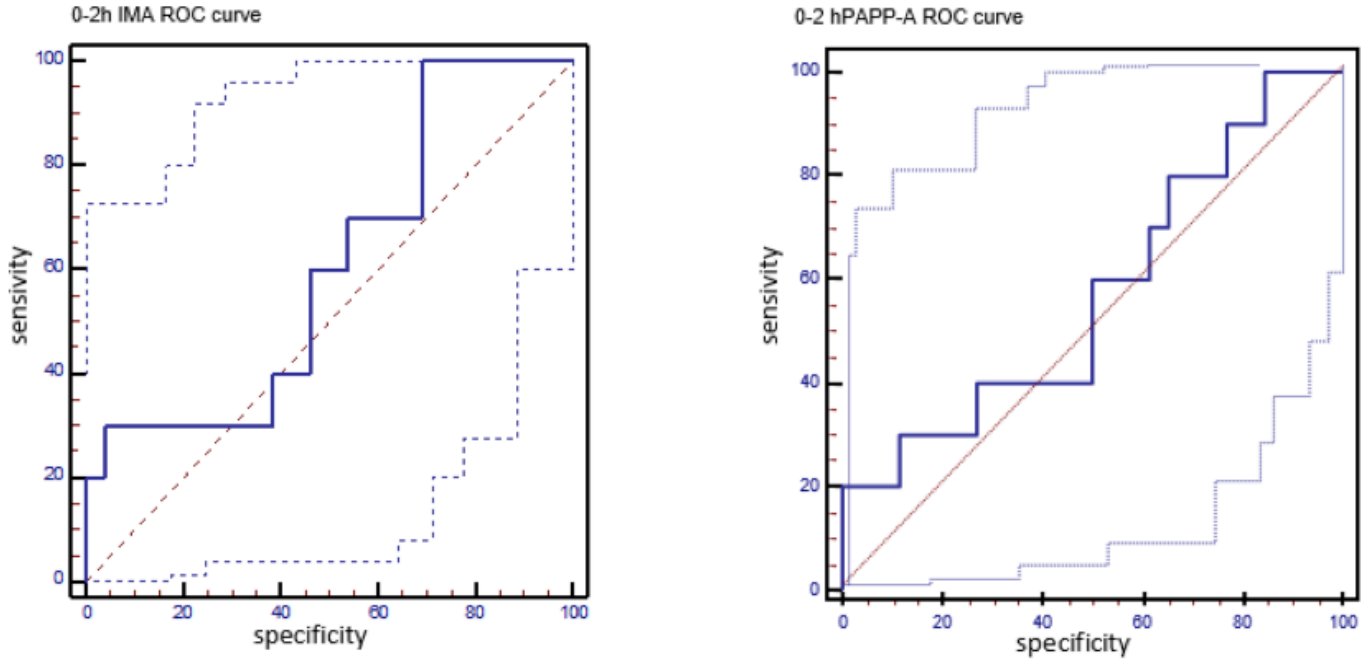

Figure 1. 0-2 h IMA and PAPP-A ROC curves

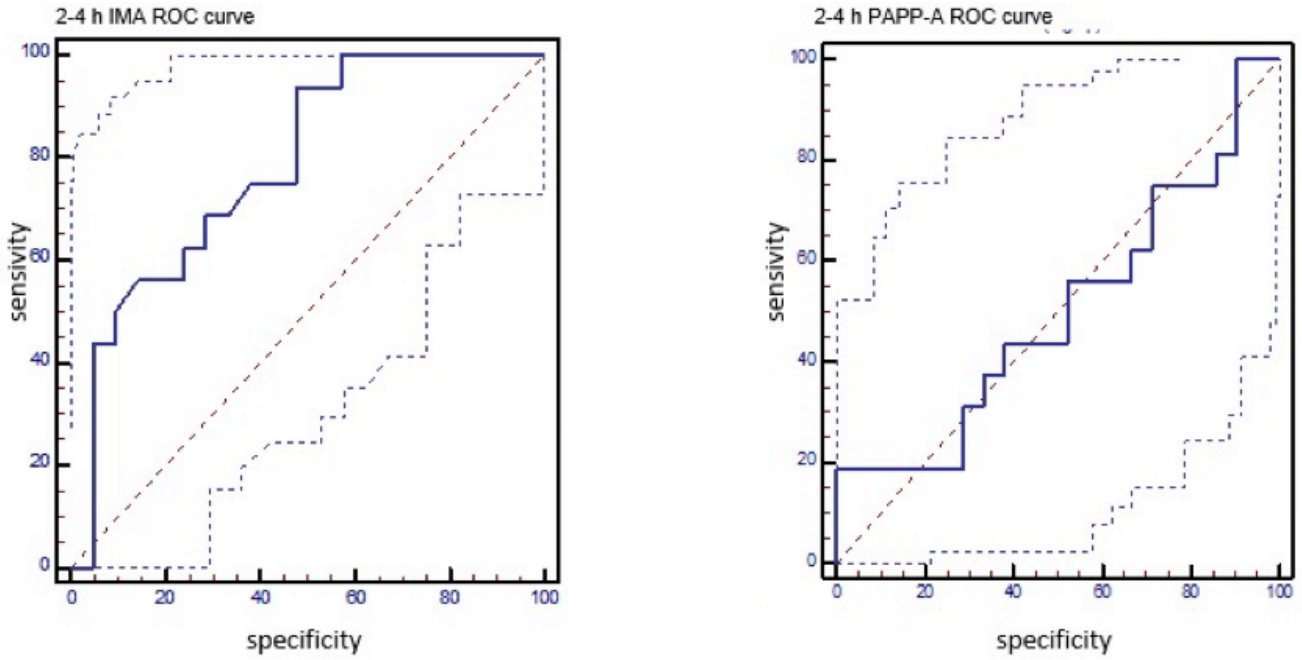

Figure 2. 2-4 h IMA and PAPP-A ROC curves

Spearman's correlation analysis performed for biochemical parameters measured between 1-2, 2-4, 4-6 and 6-8 h from the onset of chest pain. Accordingly, none of the parameters had any significant correlation in the 0-2 h period. For the period of 2-4 hours, there were significant positive correlations between troponin T and IMA, PAPP-A and CK-MB levels ($r = 0.326$, $P = 0.049$; $r = 0.325$, $P = 0.05$; $r = 0.677$, $P < 0.001$; respectively). For the periods of 4-6 and 6-8 hours, there were significant positive correlations only for CK-MB and Troponin-T ($r = 0.648$, $P < 0.001$; $r = 0.716$, $P < 0.001$; respectively).

Discussion

Chest pain is one of the most frequent causes of application to the ED. One of the most important points here, particularly for the emergency physician, is to perform differential diagnosis of the chest pain and make an early and accurate diagnosis. Various biochemical parameters are used in this differentiation. Early diagnosis is very important in terms of prompt and accurate treatment, especially in conditions with high mortality such as ACS. Several invasive and non-invasive techniques are currently used to investigate the etiology of chest pain, and biochemical analyses continue to represent an important diagnostic test assisting the physician with diagnosis.

Several studies have evaluated IMA and PAPP-A levels in patients with ACS. To the best of our knowledge, however, none have evaluated these two biochemical parameters together with standard contemporary cardiac biomarkers. Ours is an original study in that it is the first to compare PAPP-A, IMA, troponin-T and CK-MB values together.

The biochemical markers recommended for use in the diagnosis of ACS are cardiac troponin and CK-MB [11]. These markers show myocardial necrosis and rise in association with necrosis. However, they do not rise in the early period and in UAP. Since they begin to rise 4-6 h after myocardial necrosis and onset of symptoms, a certain period of time needs to pass for them to rise significantly in the blood. This may lead to a delay in diagnosis [12-14]. Therefore, a marker that rises before the development of myocardial necrosis will both improve the effectiveness of treatment and also prevent unnucessary hospitalizations. In particular, since these classic markers are not determined at high elevations, there is a need for a biochemical parameter that can be used in the fist 4 h. Our study evaluated both the classic biochemical markers CK-MB and Troponin-T, and also PAPP-A and IMA, modern parameters recommended for the first 4-h period. In agreement with the literature, CK-MB and Troponin-T exhibited no significant elevation in ACS patients in the first 4 h. In the first diagnostically uncertain 4-h period, the first stage of evaluation of patients with chest pain in the ED and in which classical biochemical prameters have not yet risen, the most important diagnostic tool to guide the emergency physician to a correct diagnosis is still ECG. None of the biochemical parameters we analyzed in patients with suspected ACS on the basis of ECG findings were at diagnostically adequate levels in the first 4 h. However, after the first 4-h period both CK-MB and Troponin-T levels rose significantly in ACS patients in line with ECG findings and guided diagnosis of ACS. PAPP-A and IMA values did not rise sufficiently to act as diagnostic guides in this period.

ECG is an important diagnostic tool in the evaluation of patients with chest pain. However, in order to achieve definitive diagnosis a rather complex algorithm and advanced diagnostic tools (angio, effort, etc.) are required. From that perspective, the most important part of the data we obtained are those based on definitive diagnoses established after following this algorithm and using advanced diagnostic tools. There is exact agreement between the results we obtained from analysis based on definitive diagnosis of patients with chest pain and those obtained from ECG findings at time of application. In other words, the biochemical parameters we examined in the first 4-h period are not differential for ACS patients. Troponin-T and CK-MB levels after the 4th h, and particularly after the 6th h, were determined as biochemical parameters in the diagnosis of ACS patients, as also agreed in the literature. As shown in detail in tables 3 and 4, almost none of the parameters we analyzed had the desired levels of sensitivity and specificity in the first 4 h for diagnosis of ACS. A biochemical marker with the potential to be used as a screening test in the ED, and especially for such a vitally significant disease group as ACS, must have a specificity higher than the highest sensitivity value. From that perspective, CK-MB, Troponin-T and PAPP-A levels are inadequate. However, the sensitivity and specificity values for IMA levels investigated at 0-2 h before onset of chest pain, and particularly at 2-4 h, are relatively more satisfactory (sensitivity and specificity for 0-2 h and 2-4 h, 100/30.7 and 93.7/52.3, respectively)

IMA is a contemporary biochemical parameter. Studies in recent years have shown that serum IMA levels rise in acute ischemic conditions. Albumin's binding to metal capacity in the N-terminus region decreases in acute ischemic conditions and a metabolic protein forms. This change can be measured, and is known as IMA [15]. Measurement of the albumin species that form with the changes in albumin's binding to metal capacity is important and practical in the diagnosis of several ischemic diseases. Bar et al. reported that IMA concentrations in the blood of patients with temporary ischemia established with angiography rose within a few minutes. Blood IMA concentrations then began returning to the levls in insidivudlas with no ischemia approximately 6 h after perfusion with angiography [11]. Vasrious studies have shown elevated IMA levels in acute ischemic events such as pulmonary embolism, peripheral arterial occlusion, deep vein thrombosis, stroke, seziure and acute cardiac arrest. It is

therefore considered suitable as a diagnostic marker [16-19].

IMA measurement is recommended in the early diagnosis of myocardial ischemia in patients with chest pain [20]. Many studies have detertmined IMA to be a very valuable biochemical parameter. In one such study, Sinha et al. examined 208 patients presenting to the ED with chest pain, within 3 h of onset of pain. They determined that IMA had high sensitivity in the early stage of myocardial ischemia (82%), and that sensitivity rose even higher when this was analyzed together with troponin and ECG (95%). That study suggested that IMA can be used as a diagnostic parameter in the early stage of myocardial ischemia [21].

One recent study determined that IMA had a high negative predictive value (NPV) of 90% for excluding acute coronary syndrome, and that when used together with cardiac troponins and non-diagnostic ECG the NPV rose to 97.1% [22]. In a study of patients with retrosternal symptoms in the previous 3 h, typical and atypical findings at ECG but with negative troponin levels, Roy et al. showed that IMA is an independent marker [23]. Another study involved 121 patients with retrosternal chest pain over the previous 20 min. Fifty-eight patients were diagnosed with NSTEMI and 62 with UAP. IMA values were significantly elevated at the normal cutoff point (85 U/ml) in both groups. However, IMA had no diagnostic superiority at comparison of UAP and NSTEMI. In other words, IMA was valuable in the diagnosis of ACS types but inadequate in differentiating between types of ACS [24].

In a study involving diagnosis of ischemic heart disease Dawie J et al. investigated CK-MB, troponin I and IMA levels [25]. Mean IMA values in patients with ACS were significantly higher than those of the healthy control group. In that study, IMA levels were 100% sensitive for ACS patients and 85.3% specific [AUC 0.948 (95% CI 0.914-0.983)]. They evaluated IMA as a rapid and simple method and a biochemical parameter that can be used in myocardial ischemia and infarct.

Other studies in the literature suggest the opposite, however. In one such, Kim JS et al. studied 390 patients with chest pain for the previous 6 h and applying to the ED for that reason. They compared patients with ischemic and non-ischemic chest pain. According to their findings, IMA levels in patients with non-ischemic chest pain and those with ischemic chest pain were significantly different [26]. Similarly, Worster et al. reported that IMA was of no diagnostic value in myocardial ischemia in a study of patients with ischemic-type chest pain synmptoms in the previous 6 h [27].

We determined no significant IMA elevation in either the early or late stages in ACS patients. The fact that other researchers have reported similar results to ours heightens the doubts about the use of IMA in the diagnosis of ACS and reveals the need for further studies before IMA is used routinely as a marker in the early diagnosis of ACS.

Proteins involved in the process of conversion of a stable atherosclerotic plaque into a sensitive plaque are today being intensively studied as potential markers. At autopsies following death from heart diseases, levels of PAPP-A, a matrix metalloprotein, have been reported to be higher in patients with eroded atherosclerotic plaques and a torn fibrous capsule compared to patients with stable plaques [28]. PAPP-A is a biomarker that shows inflammation and plaque instability and that can be detected in the sera of patients with ACS [6, 28]. Contemporary research is taking place into ACS diagnosis and subsequent PAPP-A levels.

In one such study, Bayes-Genis et al. investigated a study group consisting of AMI, UAP, SAP and healthy individuals, and reported higher serum PAPP-A levels in patients with AMI and UAP than in those with SAP and the healthy individuals [28]. Lund et al. showed that PAPP-A measured in troponin-negative patients hospitalized with a diagnosis of UAP is an early marker of ischemic cardiac events [29]. Various other studies involving ACS patients have shown that elevated serum PAPP-A concentrations are a powerful marker for mortality at long- and short-term monitoring. To summarize, since PAPP-A is a marker of plaque instability, not of myocardial damage, high PAPP-A levels are reported to be of use in the determination of future cardiovascular events. Findings from other research suggest that PAPP-A levels are no value in ACS patients, however. Dominguez-Rodriguez et al. compared PAPP-A levels in 80 patients with a diagnosis of acute STEMI and an 80-member control group and determined no difference between the groups [30]. In another study, markers that might be significant in the early diagnosis of and risk evaluation for ACS were investigated, including PAPP-A as well as Troponin T, heart fatty acid binding protein (H-FABP), glycogen phosphorylase-BB, high-sensitivity C-reactive protein, myeloperoxidase, matrix metalloproteinase 9, D-Dimer, Soluble CD40 ligand and N-terminal pro-brain natriuretic peptide (NT-proBNP). In that study, only H-FABP sensitivity was high for patients with ACS in the first 4 h of chest pain. Additionally, in terms of potential risk of death from myocardial infarct within 1 year, in addition to Troponin T, H-FABP and NT-proBNP also emerged as independent markers [31]. In this study, PAPP-A levels determed in UAP, NSTEMI and also acute STEMI patients were no different to those of the SAP and non-coronary patient groups. Similarly to IMA, this increases the doubts about the use of PAPP-A in the diagnosis of ACS. These inconcistent results make it essential for more comprehensive research on the subject to be performed before PAPP-A also enters into routine use.

Limitations of our study; Our comparison of the diagnostic value of two novel biochemical parameters in the diagnosis of ACS was performed in a limited time frame and with a limited number of patients. In addition, although the most up to date

approach for treating patients with suspected ACS at the time the study was performed was adopted, it should be borne in mind that various subsidiary advances have been made on the subject since.

The revised STEMI guidelines now consider high-sensitivity troponin tests to be better than all alternative cardiac markers, such as myoglobin, CK-MB, H-FABP, and conventional troponin assays. However, since high-sensitivity troponin measurement was not possible in the center where the research was performed at the time of the study, all our analyses were based on conventional troponin measurements.

In conclusion, the biochemical parameters we analyzed in the first 4 h period are not reliable for diagnosis of ACS. IMA had the highest sensitivity and specificity in this period, being relatively more than Troponin-T, CK-MB and PAPP-A, but still not satisfactory for an ideal marker.

Declaration of conflicting interests

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Review

Tissue engineering in the treatment of congenital diaphragmatic hernia

Konjenital diyafragma herni tedavisinde doku mühendisliği

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ABSTRACT

Congenital diaphragmatic hernia (CDH) is one of the most common major congenital anomalies and is described as the presence of a diaphragmatic defect that leads the herniation of abdominal organs into the chest. Although advanced treatment strategies are introduced over the recent years, they have not really improved the survival rate which stayed at around 70%. Major determinants of poor outcome in CHD are pulmonary hypoplasia and pulmonary hypertension. Various surgical interventions and novel medical therapies are attempted to improve lung function and survival but remains less than desired. Repair of the diaphragmatic defect with prosthetic materials was found to be associated with high rates of complications and recurrences during follow-up. Therefore, regenerative medicine should be considered as an alternative treatment strategy in CDH both by inducing cellular function in the hypoplastic lungs (stem cell therapy) and by developing a functional myogenic patch (tissue engineering). Nearly 30% of infants who have CDH born with severe pulmonary hypoplasia and hypertension which may lead to respiratory failure and prompt mechanical support, since the survival of these newborns relate to the degree of pulmonary hypoplasia, accurate prenatal evaluation of this degree is of paramount importance. The two main diagnostic tools which could be used for this purpose are prenatal ultrasound (US) and magnetic resonance imaging (MRI). Various prenatal treatment strategies have been tried to cure pulmonary hypoplasia and hypertension in CDH. Vitamin A, corticosteroids, antioxidants such as vitamin C, E, N-acetylcystein, phosphodiesterase inhibitors, glucagon-like peptide 1 agonists and tyrosine kinase inhibitors have all been analyzed in animal studies and demonstrated variable results. Since there are very few human studies, further researches should be performed in humans confirming the clinical benefit of these therapies. Due to the advancements in prenatal screening methods, we, now have the ability to detect most of the major genetic disorders in gestation and have chance to provide optimal treatment strategy in the postnatal period. Results of the animal studies regarding the application of regenerative medicine for treatment of children with CDH are encouraging. Hopefully, with the support of further studies focusing especially on safety and ethical issues, the near future will provide us the evidence necessary for their application in our clinical practice.

Keywords: congenital, diaphragmatic hernia, tissue engineering,

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ÖZ

Doğumsal diyafragmatik herni (CDH), en sık karşılaşılan konjenital anomalilerden biri olup abdominal organların göğsüne herniyasyonuna neden olan diyafram kusurunun varlığı olarak tanımlanmaktadır. Son yıllarda ileri tedavi stratejileri getirilmesine rağmen hayatta kalma oran, % 70 civarında kalmışve geliştirilememiştir. KKH'de kötü sonuçların başlıca belirleyicileri pulmoner hipoplazi ve pulmoner hipertansiyondur. Akciğer fonksiyonlarını ve sağkalımı geliştirmek için çeşitli cerrahi müdahaleler ve yeni tıbbi tedaviler denmektedir, ancak istenilen seviyeden daha az orandadır. Protez materyali ile diyafragma defektinin onarımının, takip sırasında yüksek komplikasyonlar ve rekürrens oranları ile ilişkili olduğu tespit edilmiştir. Bu nedenle, rejeneratif ilaç hem hipoplazi akciğerlerde hücresel fonksiyonu indükleyerek (kök hücre tedavisi) hem de işlevsel bir miyojenik yama (doku mühendisliği) geliştirerek, CDH'de alternatif bir tedavi stratejisi olarak düşünülmektedir.Solunum yetmezliğine sebep olan ciddi pulmoner hipoplazi ve hipertansiyon ile doğan CDH'li yenidoğanların yaklaşık % 30'unun hayatta kalması pulmoner hipoplazi derecesi ile ilişkili olduğundan, bu dereceyi prenatal olarak değerlendirmek büyük önem taşır. Prenatal ultrasonografi (US) ve manyetik rezonans görüntüleme (MRI) iki ana tanı aracıdır. CDH'de pulmoner hipoplazi ve hipertansiyonu iyileştirmek için çeşitli doğum öncesi tedavi stratejileri denendi. Vitamin A, kortikosteroidler, C vitamini, E, N-asetilsistein, fosfodiesteraz inhibitörleri, glukagon benzeri peptit 1 agonistleri ve tirozin kinaz inhibitörleri gibi antioksidanlar hayvan çalışmalarında analiz edildi ve değişken sonuçlar gösterdi. İnsanlar üzerinde çok az çalışma olduğu için, bu terapilerin klinik yararlarını teyit edebilmek için ileri aşama araştırmalar insanlar üzerinde olmalıdır. Doğumdan sonra bebeğe destekleyici tedavisinin yanı sıra solunum yetmezliği durumunda tercihen yüksek frekanslı salınımlı ventilasyon ile solunum desteği de uygulanmalıdır. Eksojen kök hücreler, özellikle AFS hücreleri akciğer gelişimini hem çeşitli pulmoner hücre tiplerine entegre ederek, hem de anti-inflamatuvar ve immünomodülatör etkiler yoluyla parakrin modele göre veya doğal progenitör hücreleri aktive ederek geliştirebilir. Ancak, akciğer hasarının altında yatan mekanizmayı ve kök hücrelerin moleküler tepkisini anlamak için, özellikle de insanlarda yapılacak daha ileri araştırmalara ihtiyaç vardır. Doğum öncesi tarama yöntemlerindeki ilerlemeler sayesinde, artık gebelikteki en büyük genetik bozuklukların çoğunu tespit etme ve postnatal dönemde optimal tedavi stratejisi sunma olanaği bulunmaktadır. CDH'li çocukların tedavisinde rejeneratif tıbbın uygulanmasına ilişkin hayvan çalışmalarının sonuçları gelecek vadetmektedir. Yakın gelecekte özellikle güvenlik ve etik konular çerçevesinde yoğunlaşan daha ileri çalışmaların desteğiyle, klinik olarak uygulanması için gerekli kanıtlar bu çalışmalar ile sağlanacaktır.

Anahtar Kelimeler: doğumsal, diyafragma hernisi, doku mühendisliği

Introduction

Although perinatal care and treatment options progress in the last decades, congenital malformations are still causing major morbidity and mortality [1]. The aim of regenerative medicine is to restore damaged organs by repairing and/or replacing involving cells and tissues. The two main approaches in regenerative medicine are; stem cell therapy, which means stimulating regeneration by injecting functional cells into the damaged site, and tissue engineering defined as formation of new tissues by using biocompatible materials [2].

Congenital diaphragmatic hernia (CDH) is one of the most common major congenital anomalies and is described as the presence of a diaphragmatic defect that leads the herniation of abdominal organs into the chest [3]. Although advanced treatment strategies are introduced over the recent years, they have not really improved the survival rate which stayed at around 70% [4, 5]. Major determinants of poor outcome in CHD are pulmonary hypoplasia and pulmonary hypertension. Various surgical interventions and novel medical therapies are attempted to improve lung function and survival but remains less than desired. In addition, repair of the diaphragmatic defect with prosthetic materials was found to be associated with high rates of complications and recurrences during follow-up [6-8]. Therefore, regenerative medicine should be considered as an alternative treatment strategy in CDH both by inducing cellular function in the hypoplastic lungs [stem cell therapy] and by developing a functional myogenic patch [tissue engineering] [9-12]. We herein review these two popular therapeutic strategies in scope of the latest developments in this topic.

Pulmonary hypoplasia

Nearly 30% of infants who have CDH born with severe pulmonary hypoplasia and hypertension which may lead to respiratory failure and prompt mechanical support [13]. Since the survival of these newborns relate to the degree of pulmonary hypoplasia, accurate prenatal evaluation of this degree is of paramount importance.

Diagnosis

The two main diagnostic tools which could be used for this purpose are prenatal ultrasound (US) and magnetic resonance imaging (MRI). Various US parameters have been identified to foresee the extent of pulmonary hypoplasia such as lung-to-head ratio, total fetal lung volume and the position of the liver and

stomach [14, 15]. Commonly used MRI measurements, that have higher sensitivity and specificity for estimating the degree of pulmonary hypoplasia, include total fetal lung volume, predicted lung volumes and liver herniation percentage [16-18].

Prenatal pharmacologic management

Various prenatal treatment strategies have been tried to cure pulmonary hypoplasia and hypertension in CDH. Vitamin A [19], corticosteroids [20, 21], antioxidants such as vitamin C, E, N-acetylcystein [22], phosphodiesterase inhibitors [23], glucagon-like peptide 1 agonists [24] and tyrosine kinase inhibitors [25] have all been analyzed in animal studies and demonstrated variable results. Since there are very few human studies, further researches should be performed in humans confirming the clinical benefit of these therapies [26, 27].

Postnatal management

Apart from the supportive therapy of the infant after birth, respiratory assistance preferably with high-frequency oscillatory ventilation, should be implemented in case of respiratory failure [3, 28]. Extra-corporeal membrane oxygenation (ECMO) can be considered as an option when the respiratory failure is severe until proper gas exchange is achieved. However, since there is poor evidence regarding the benefits of ECMO in CDH, it should mainly be used in patients for whom lung hypoplasia would cause inadequate gas exchange or severe circulatory failure [3, 29].

Surgical repair of CDH is not advised before cardio-respiratory functions become stable. The herniated abdominal organs are placed back into the abdomen and the diaphragmatic defect is closed either primarily or with a prosthetic patch via a subcostal or transverse abdominal incision [30]. Minimally invasive approaches via thoracoscopy or laparoscopy are alternative options in infants with less severe symptoms [31, 32].

Stem cell therapy

Regeneration of the hypoplastic lungs of the infants with CDH by using stem cell therapy has gained popularity in recent years. The lungs continue to develop during postnatal life and have extensive repair and regeneration capability after destruction [33]. Thus, early intervention with cellular based therapies can induce parenchymal development by increasing the number and size of bronchopulmonary segments in patients with hypoplastic lungs and may restore normal function. Lung development is stimulated by exogenous stem cells through two main mechanisms. They may integrate and differentiate, or induce resident stem cells by paracrine actions [34, 35]. Resident stem cell activation seems to be more successful in regenerating the lung tissue compared to using a single exogenous cell source [36]. Recently, De Coppi and Deprest investigated different kind of stem cells including basal cells, multipotent lung stem cells and multipotent cells which expresses tyrosine kinase c-kit, which all may have the ability to generate different niches in postnatal lung [1]. Among these, the most promising progenitor was found to be multipotent, clonogenic and self-renewing lung stem cells represented by tyrosine kinase c-kit expression as they have the ability to generate bronchiolar, alveolar and pulmonary vessel tissue when injected in mice [35, 37]. Mesenchymal stem cells [MSC] are ideal cells which could be used in pulmonary hypoplasia in CDH due to their immunomodulatory potential [38, 39]. Also, Haaften et al demonstrated in their animal model that MSCs prevent arrested alveolar and vascular growth in part through their paracrine activity [40].

MSCs can be harvested from placenta, fetal bone marrow, cord blood, adipose tissue and amniotic fluid. Amniotic fluid sampling is routinely considered to detect chromosomal and genetic defects in CDH. Thus, using amniotic fluid-based stem (AFS) cells is more ethical than the obtaining samples from other sources. In addition, harvesting stem cells from the above mentioned alternative sources is more challenging and is associated with higher morbidity [39]. Moreover, AFS cells are less immunogenic, feasible for autologous cell-based therapy and available before birth [41]. Their mechanism of action and the potential pathways which activate the hypoplastic lungs have been investigated in many animal models [42, 43]. Pederiva et al showed that lung growth, bronchial motility, and innervation increased with AFS cell exposure in rats [44]. Recently, Di Bernardo et al showed in a nitrofen model that AFS cells induce fetal rodent lung growth by their paracrine action [45].

In summary, exogenous stem cells, especially AFS cells may improve lung development both by integrating and differentiating into various pulmonary cell types and by a paracrine fashion via anti-inflammatory and immunomodulatory effects or by activating the native progenitor cells. However, further studies, especially in humans, are needed to understand the underlying mechanism of lung damage and the molecular response of stem cells.

Tissue engineering for diaphragmatic repair

Rationale of tissue engineering

Although primary closure of the diaphragmatic defects is associated with low recurrence rate, it can be performed in nearly half of the patients. Defect size is considered to be the most significant surgical predictor of morbidity and mortality in CDH and also associated with longer ventilation duration and hospital stay [46, 47]. Repair of large defects could be performed with various surgical techniques including abdominal or thoracic muscle flaps, free facia lata grafts and different kinds of prosthesis (poly-propylene, poly-tetra-fluoro-ethylene (Teflon), Dacron, and others).

However, most surgeons do not prefer muscle flaps due to the residual defects left in the muscle source, complexity of the procedure and high morbidity [48]. Use of prosthesis for

diaphragmatic repair has been related with higher infection rate, more adhesions, more small bowel obstruction rate and most importantly high recurrence rate, as high as 40-50%, than primary repair [49-51].

The underlying mechanism of hernia recurrence in prosthetic repair is probably the traction and related detachment in the rapidly growing diaphragm of the infant [49]. Therefore, a cell based engineered graft which has the ability of remodeling over time may adapt the rapid growth of the diaphragm and become an ideal alternative for hernia repair.

Cell Sources

Tissue engineering consists of cells, a supportive 3D scaffold and a bioreactor. While, scaffolds consist of bioactive natural materials which does not have mechanical strength, synthetic materials do not have bioactivity, but are mechanically stronger. These two materials can be engineered and with addition of bioactive properties cellular growth can be achieved [52].

The first diaphragmatic repair by using an engineered construct was reported by Fauza and colleagues in 2001. In that animal study they were able to show that, unlike acellular grafts, engineered cellular diaphragmatic constructs are similar to normal muscle in terms of anatomic and histologic structure [53].

Muscular or tendinous constructs can be used for diaphragmatic repairs. Kunisaki et al compared these two options in their study and showed that tendinous grafts lead to improved structural outcomes when compared to alike muscular grafts [54]. The potential reasons of the preference of tendinous constructs are: (i) the residual diaphragm muscle will continue to grow over time; (ii) normally, most of the diaphragm is tendinous and (iii) function of the muscle construct may decline over time due to lack of innervation.

Fetal cells seem to be the best option that could be used for diaphragmatic engineering. Because; fetal cells (i) multiply more rapidly than postnatal cells, (ii) are more resistant to hypoxia, (iii) survive better through the refrigeration and cryopreservation processes, (iv) have ability to grow in vivo due to their angiogenic properties [55, 56]. There are several kind of fetal cell sources such as placenta, amniotic fluid, Wharton's jelly and umbilical cord blood. Among these amniotic fluid considered to be the safest source. AFS cells can be easily obtained during amniocentesis or birth. Throughout gestation MSCs can be obtained from small amounts of amniotic fluid [57-59]. If the need for patch repair can be foreseen via prenatal US or MRI, cells which are obtained by amniocentesis could be engineered to create an autologous muscle or tendon construct and used to repair the diaphragmatic defect in the postnatal period. Recently, Turner at al provided preclinical efficacy by demonstrating in their animal study that diaphragmatic repair by using autologous tendon engineered with amniotic mesenchymal stem cells improved outcomes with no local or systemic adverse effects [60].

In summary, according to the results of various animal models so far, diaphragmatic repair with tissue engineered constructs is safe and associated with better outcomes in comparison to acellular bioprosthesis [60-62].

As a conclusion due to the advancements in prenatal screening methods, we, now have the ability to detect most of the major genetic disorders in gestation and have chance to provide optimal treatment strategy in the postnatal period. Results of the animal studies regarding the application of regenerative medicine for treatment of children with CDH are encouraging. Hopefully, with the support of further studies focusing especially on safety and ethical issues, the near future will provide us the evidence necessary for their application in our clinical practice.

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Olgu Sunumu

Kompozit kolonik adenom-mikrokarsinoid tümör, gerçekten tesadüf mü? Olgu sunumu

Compozite colonic adenoma-microcarcinoid tumor, is really a coincidence? Case report

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ÖZ

Mikst adenonöroendokrin kanserler nadir rastlanan tümörlerdir. Kolonik tübüler adenomlar ile mikrokarsinoid tümörlerin birlikteliği ise literatürde son derece ender bildirilmiştir. Bilindiği üzere, bu tümörlerdeki nöroendokrin bileşen glandüler patern, iğsi hücreli patern, skuamöz-osteoid metaplazi veya pleomorfizm gibi belirgin hitopatolojik değişkenlik gösteren geniş bir yelpaze sergiler. Nadiren çok az farklılaşmış olabilir ve undiferansiye karsinom ya da lenfomaya benzeyebilirler. Bununla beraber, karsinoid veya Zollinger-Ellison gibi birtakım sendromlarla ilişkili karsinoid tümörlerin immünohistokimyasal analizinde, bir amin veya peptit baskın olabileceği gibi çoğunun mültihormonal olduğu gösterilmiştir ve primer tümördeki aminler ve peptidler, üstte bulunan endokrin hücrelerde normal olarak bulunanlarla çoğu zaman eşleşmez. Ayrıca son zamanlarda, neoplastik endokrin ve endokrin dışı epitel hücrelerinin karışımlarını içeren artan sayıda tümör tarif edilmiştir. Dahası, endokrin ve epitel hücresi özelliklerinin aynı hücre içinde gözlendiği farklı tümör türleri de mevcuttur. Bütün bu literatür bilgileri ile benzer olarak, olgumuzda izlenen morfolojik ve immünhistokimyasal bulgular iki neoplastik bileşenin ortak bir öncü hücreden kaynaklandığını göstermektedir.

Anahtar kelimeler: kompozit adenom, mikrokarsinoid, tübüler

ABSTRACT

Mixed adenoneuroendocrine cancers are rare tumors. The association of colonic tubulary adenomas with microcarcinoid tumors has been reported very rarely in the literature. As known, the neuroendocrine component in these tumors display a broad spectrum with marked variability in histopathology properties; such as glandular pattern, spindle cell pattern, squamous-osteoid metaplasia or pleomorphism. Rarely, they may be very poorly differentiated and may resemble undifferentiated carcinoma or lymphoma. In addition, immunohistochemical analysis of carcinoid tumors associated with some syndromes such as Zollinger-Ellison and carcinoid has shown that, most are multihormonal as well as one amine or peptide may predominate and the amines and peptides in the primary tumor do not often match to those normally found in the overlying endocrine cells. However, an increasing number of tumors have recently been described including mixtures of neoplastic endocrine and non-endocrine epithelial cells. Furthermore, there are different types of tumors in which endocrine and epithelial cell characteristics are observed in the same cell. Similar to all this literature information, morphological and immunohistochemical findings in our case show that, the two neoplastic components originate from a common precursor cell.

Key words: compozite adenoma, microcarcinoid, tubulary

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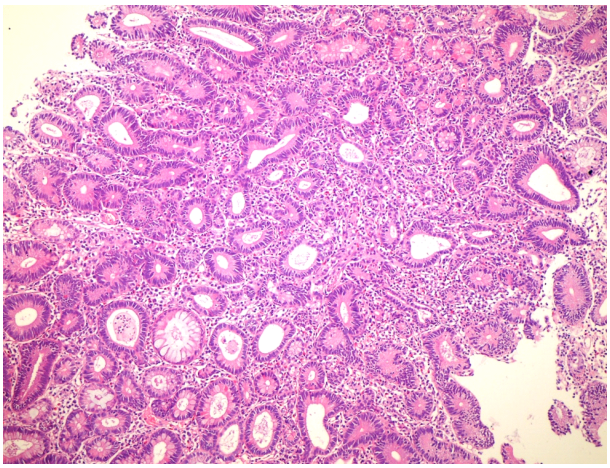
Giriş

Mikst glandüler-nöroendokrin neoplaziler, endokrin ve glandüler komponenti birlikte içeren nadir görülen bir tümör grubunu tanımlar [1]. Bu isimlendirme için her bir komponentin de, difüz ya da lokalize, tümörün en az üçte birini oluşturması gerekmektedir [1]. Dünya Sağlık Örgütü 2010 sınıflamasında, mikst adenonöroendokrin karsinom kategorisinde yer alan bu tümörlerin tanımlamasında, her iki komponent de malign olarak belirtilmiştir [1,2]. Tübüler adenom ve mikrokarsinoid tümör birlikteliği ise literatürde son derece nadir olarak bildirilmiş olup olguların çoğu midede lokalizedir [3,4]. Bu tanımlama hem glandüler hem de nöroendokrin komponentin benign histolojide olduğu tümörleri içermekte olup literatürde kompozit adenom-karsinoid, eğer nöroendokrin komponent çok küçük ya da mikroskobik boyutta ise kompozit adenom-mikrokarsinoid olarak isimlendirilmiştir [4]. Ayrıca çalışmalarda, iki neoplastik bileşenin ortak bir prekürsör hücreden kaynaklandığı da bildirilmektedir [5,6]. Bu yazıda, bir kompozit kolonik adenom-mikrokarsinoid olgusunda iki neoplastik bileşenin ortak bir kök hücreden kaynak aldığını gösteren ilginç histolojik ve immünhistokimyasal görünümler, literatür bilgileri eşliğinde tartışılmıştır.

Olgu Sunumu

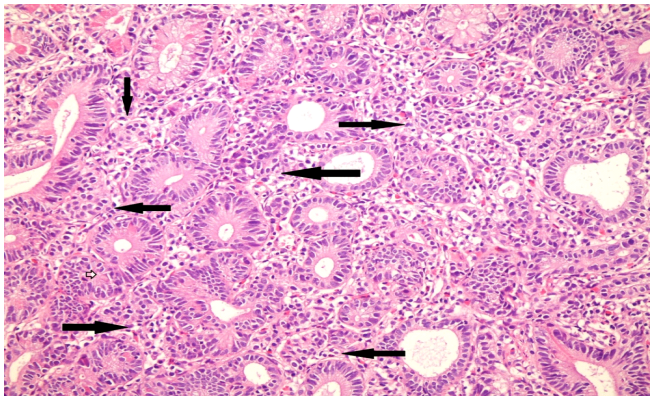
36 yaşında erkek hasta, dışkıda kanama şikayeti ile genel cerrahi polikliniğine başvurmuştur. Anamnez ve laboratuvar tetkiklerinde özellik izlenmeyen hastanın kolonoskopik incelemesinde; kalın barsak yerleşimli en büyüğü 0,8 cm olan 15-20 adet polip tespit edilmiş olup en büyük çaplı 4 adet polip eksize edilmiş ve patoloji bölümüne gönderilmiştir.

Poliplerin histopatolojik incelemesinde 4 adet polipte de düşük dereceli displazi gösteren tübüler adenom varlığı saptanmıştır. Poliplerlerden 0,4 cm boyutundaki birinde ise; tübüler adenom içerisinde 0,2 cm boyutunda, küçük yuva yapıları ve asiner yapılar oluşturan, yuvarlak-oval nükleuslu, ince tanecikli kromatin yapısı gösteren monoton hücrelerden oluşan tümöral infiltrasyon dikkati çekmiştir (Resim 1).



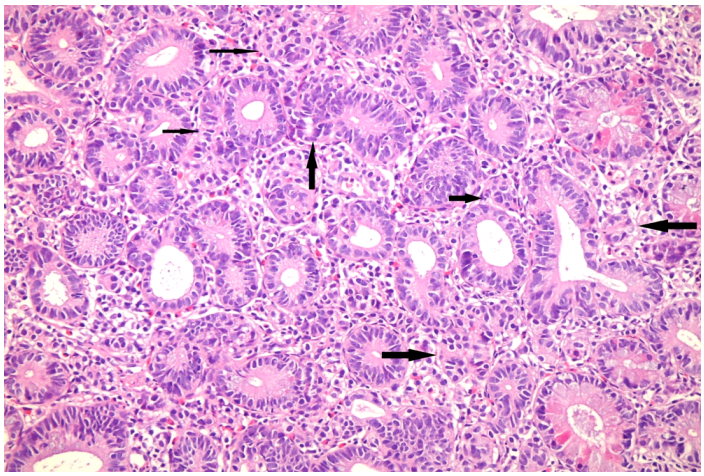
Resim 1. Tübüler adenom içerisinde, küçük asiner yapılar oluşturan tümöral infiltrasyon görülmektedir (40xHE).

Tümörün bazal tabaka altında ve fibröz bir stroma içerisinde yer yer tek hücre şeklinde yerleşim göstermesi yalancı invazyon görünümü vermektedir (Resim 2).

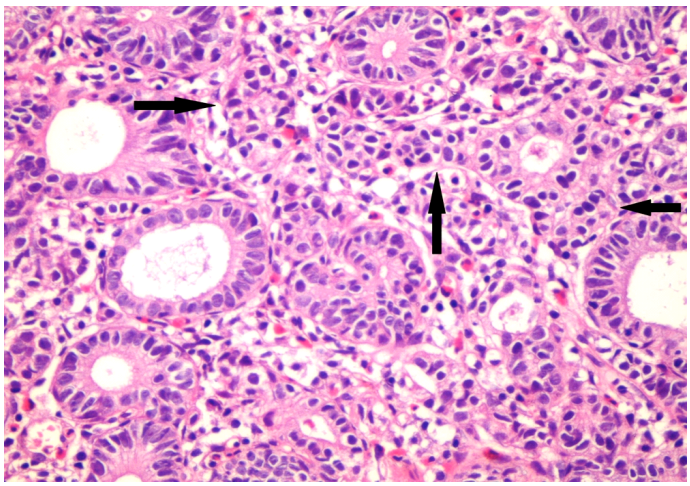


Resim 2. Oklar; küçük yuva-asiner yapılar oluşturan, oval nukleuslu, ince tanecikli kromatin yapısına sahip, monoton hücrelerden oluşan nöroendokrin tümörü göstermektedir (200xHE)

Ayrıca ilginç bir bulgu olarak, nöroendokrin tümörü oluşturan hücrelerin adenomatöz epiteli oluşturan hücrelerle yer yer geçiş göstermekte olduğu dikkati çekmiştir (Resim 3-4).

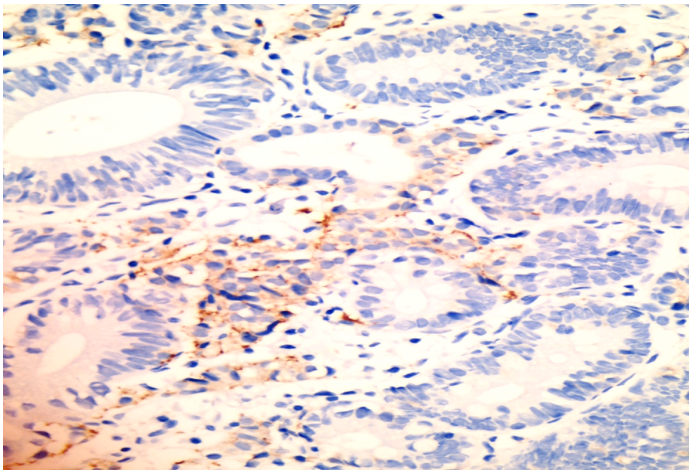


Resim 3. Oklar, nöroendokrin tümörü oluşturan hücrelerin adenomatöz epitelle yer yer geçiş gösterdiğini belirtmektedir (200xHE).



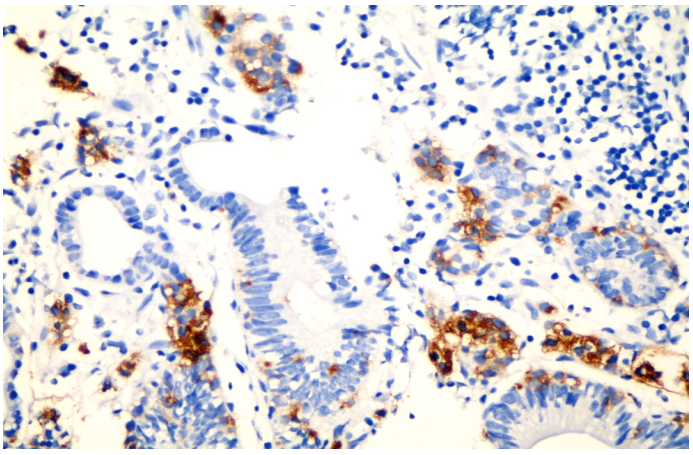
Resim 4. Oklar, nöroendokrin tümörü oluşturan hücrelerin adenomatöz epitelle yer yer geçiş gösterdiğine işaret etmektedir (400xHE).

İmmünhistokimyasal inceleme: İmmünhistokimyasal çalışmada tümöral hücrelerde sinaptofizin (+) (Resim 5), CD 57 (+), PGP 9,5 (+), kromogranin (-) bulunmuştur



Resim 5. Nöroendokrin komponentde immünhistokimyasal olarak sinaptofizin pozitifliği görülmektedir (400xHE).

Mitoz, nekroz, nükleer atipi, nükleer pleomorfizm görülmemiştir. Adenomatöz epitelde Pansitokeratin ve sitokeratin 20 pozitif boyanmıştır. İlginç bir bir bulgu olarak glandüler komponentde tek hücre şeklinde sinaptofizin pozitifliği olduğu, bazı alanlarda ise sinaptofizin pozitif boyanan nöroendokrin komponentin adenomatöz epitel ile geçiş göstediği tespit edilmiştir (Resim 6). Ki-67 proliferasyon indeksi %1'den az olarak saptanmıştır.



Resim 6. Sinaptofizin pozitif boyanan nöroendokrin komponent ile adenomatöz komponentin geçiş göstermesi ve glandüler komponentde tek hücre şeklinde sinaptofizin pozitiflikleri görülmektedir (400xHE).

Olgu bu bulgular eşliğinde kompozit kolonik adenom-mikrokarsinoid tümör olarak rapor edilmiştir. Lezyondaki nöroendokrin komponent 'Nöroendokrin tümör, grade 1' olarak değerlendirilmiştir.

Tartışma

Mikst glandüler-nöroendokrin tümörler; endokrin ve glandüler komponenti birlikte içeren nadir görülen bir tümör grubunu tanımlar [1]. Bu tümörlerde her iki komponent de genellikle malign özellikte olup, her iki komponentin de benign özellikler gösterdiği tübüler adenom ile karsinoid tümör birlikteliği ise son derece nadir [1,2]. Literatürde 'kombine adenom-mikrokarsinoid' olarak isimlendirilen bu tümörler, tübüler adenom ile birlikte küçük bir nöroendokrin komponent içermektedir [2,3]. Olgumuzda izlenen nöroendokrin komponent çok küçük boyutta olup her iki komponent de benign görünümdedir.

Bu tümörler ilk kez Moyana tarafından 1988 yılında tanımlanmıştır [4]. Kolorektal adenomlarda ve adenokarsinomlarda, immünhistokimyasal olarak nöroendokrin hücre ya da hücre grubu tespiti sık rastlanan bir bulgudur [5]. Ayrıca klasik karsinoid tümörlere glandüler komponentin eşlik ettiği olguların da bildirilmesi ve yapılan moleküler ileri çalışmalar, hem glandüler hem de nöroendokrin komponentin aynı multipotenent kök hücreden kaynak aldığını göstermektedir [6,7]. Olgumuzda da izlenen histolojik ve immunhistokimyasal bulgular, her iki komponentin aynı kök hücreden kaynaklandığını desteklemektedir.

Mikrokarsinoidlerin, midede otoimmun atrofik gastirit ve Zollinger-Ellison sendromu ile ilişkisi literatürde birçok yayında tanımlanmıştır [8,9]. Kalın barsakta ise mikrokarsinoid oldukça nadir olup büyük kısmı kronik inflamatuar barsak hastalıkları özellikle de ülseratif kolit hastalarında, multifokal mikroskobik lezyonlar şeklinde rapor edilmiştir [10]. Kronik kolit ile bu yakın ilişki endokrin hücre hiperplazisi gibi mikrokarsinoidlerin de, barsak mukozasının kronik inflamasyona karşı aşırı proliferatif cevabının sonucunda oluştuğunu göstermektedir [10,11]. Olgumuzda ise inflamatuvar barsak hastalığı ile ilişki saptanmamıştır.

İnsidental yakalanması, nöroendokrin hücrelerin etraf stroma ile karışması ve adenomatöz epitelle geçiş göstermesi rutin pratikte bu tümörlerin tanınmasını güç hale getirmektedir [12,13]. Ayrıca bazal lokalizasyon, infiltratif patern, glandüler epitele bitişik pleomorfik şekilli hücresel kümeler şeklinde izlenmesi de yanlış olarak yüksek dereceli displazi ya da invaziv adeokarsinom tanılarına götürebilmektedir [14,15]. Olgumuzda da tarif edilen histolojik tanı tuzakları mevcut olup, immünhistokimyasal çalışma ayırıcı tanıda yararlı olmaktadır.

Literatürde kompozit adenom-karsinoid tümör olarak rapor edilen hastaların klinik takipleri genel olarak benign olarak bildirilmiştir [15,16]. Ancak submukoza invazyonu izlenen bir olguda ise lenf nodu metastazı ve agresif davranış tarif edilmiştir [16]. Olgumuzun postoperatif 36 aylık takibinde

nüks ya da metastaz saptanmamakla beraber, tümörün histolojik görünümünden prognozu tahmin etmek mümkün olmadığından tüm olgular izlenmelidir.

Sonuç olarak olgumuzda izlenen iki neoplastik bileşen arasındaki morfolojik ve immünhistokimyasal yakın benzerlikler, literatürde bildirilen bu tümörlerin ilkel bir öncü hücrenin çok yönlü diferansiyasyonundan kaynaklandığını kavramını güçlendirmiştir. Vaka sayısının arttırılması, bu tümörlerin orijininin anlaşılması ve hedefe yönelik tedaviler için faydalı bilgiler verecektir.

Maddi Destek ve Çıkar İlişkisi

Çalışmayı maddi olarak destekleyen kişi/kuruluş yoktur ve yazarların çıkara dayalı bir ilişkisi yoktur.

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Olgu Sunumu

Hobnail / mikropapiller varyant papiller tiroid karsinomu: Varyant mı, patern mi?

Hobnail / micropapillary variant papillary thyroid carcinoma: Is it a variant or a pattern?

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ÖZ

Papiller tiroid karsinomu, tiroid maligniteleri arasında en sık görülen tiptir ve tüm malignitelerin %1'ini oluşturur. Klasik papiller tiroid karsinomu oldukça iyi prognoza sahip olmakla beraber hastaların %10'unda rekürrens, lenf nodu metastazı, uzak organ metastazı ya da mortalite gelişebilmektedir. Bu agresiv klinik davranış çoğunlukla difüz sklerozan, uzun hücreli ve kolumnar hücreli gibi varyantlarda görülmektedir. Hobnail/mikropapiller varyant papiller tiroid karsinomu, papiller tiroid karsinomunun oldukça nadir görülen, yeni tarif edilen bir varyantıdır. Literatürde benzer şekilde çok az sayıda yayın mevcut olup, genellikle agresiv seyrettiği ve metastaz yapma potansiyelinin klasik papiller tiroid karsinomundan fazla olduğu bildirilmiştir. Ancak sitolojik özellikleri ve moleküler alt yapısı tam olarak anlaşılamamıştır. Bu yazıda; hobnail/mikropapiller varyant papiller tiroid karsinomlu bir hasta sunulmuş olup, tanı problemleri ve malignite kriterleri literatür bilgileri gözden geçirilerek tartışılmıştır.

Anahtar kelimeler: papiller tiroid karsinomu, hobnail, mikropapiller.

ABSTRACT

Papillary thyroid carcinoma is the most common type of thyroid malignancies and constitutes 1% of all malignancies. Classical papillary thyroid carcinoma is very good prognosis; but recurrence, lymph node metastasis, distant organ metastasis or mortality can develop in 10% of patients. This aggressive clinical behavior is more often seen in variants such as diffuse sclerosis, tall cell and columnar cell. Hobnail/micropapillary variant papillary thyroid carcinoma is a relatively rare, newly described variant of papillary thyroid carcinoma. There are very few publications in the literature and it is reported that the aggressive course and metastasizing potential is greater than the classic papillary thyroid carcinoma. However, their cytological properties and molecular backround are not fully understood. In this article; a patient with hobnail/micropapillary variant papillary thyroid carcinoma has been presented, and diagnostic problems and malignancy criteria have been discussed by reviewing the literature.

Key words: papillary thyroid carcinoma, hobnail, micropapillary.

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Giriş

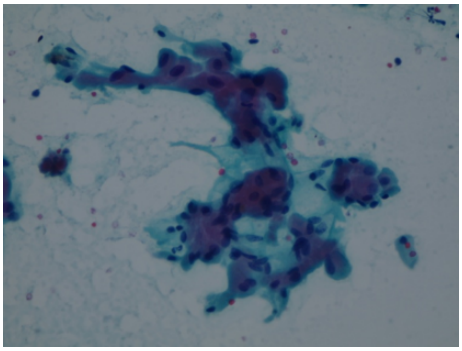
Papiller tiroit karsinomu (PTK); en yaygın rastlanan tiroid kanseri olmanın yanı sıra endokrin maligniteler içerisinde de en sık görülen tümörlerdir [1]. Amerika Birleşik Devletleri'nde, son on yılda, her iki cinsiyette insidansı en hızlı artan tümör olan PTK; 2013 yılında görülen 60.220 yeni vaka ile önemini bir kat daha arttırmıştır [1,2]. Tüm varyantlar dahil olmak üzere, hastaların %90'ında ortalama yaşam beklentisi 10 yıldır [3]. PTK'da hastalığa bağlı mortalite düşük olmakla birlikte, hastaların yaklaşık %15'inde cerrahiyi takiben lokal veya bölgesel nüks ya da uzak organ metastazı görülmektedir [4]. Nüks görülen hastalarda daha kötü sonuçlar izlenmekte olup bu olgular daha agresiv davranmakta, tümör radyoaktif iyot duyarlılığını kaybetmekte ve hastaların %35'i ölmektedir [5].

Amerikan kanser komitesi evreleme sisteminde yer almamakla beraber, histolojik varyantlar prognoz bakımından farklılık göstermektedir [5,6]. Örneğin foliküler varyant PTK daha iyi, uzun hücreli varyant ise klasik PTK'dan daha kötü prognoza sahiptir [5,6]. Histolojik varyantların önemi, Amerikan tiroid birliği rehberinde, artmış risk için bir kriter olarak "agresif histoloji (uzun hücreli, difüz sklerozan, kolumnar hücreli)" başlığı altında kabul edilmiştir [6,7]. Son zamanlarda küçük serilerde, "PTK'nın hobnail/mikropapiller varyantı" adı altında, agresiv hastalık ve kötü prognoz ile giden, PTK'nın yeni bir varyantı tanımlanmıştır [8]. Bu yazıda; PTK'nın hobnail/mikropapiller varyantının özelliklerini gösteren bir olguda tanı problemleri ve malignite kriterleri, literatür bilgileri eşliğinde tartışılmıştır.

Olgu Sunumu

38 yaşında kadın hasta boyunda şişlik şikayeti ile kulak burun boğaz kliniğine başvurdu. Yapılan laboratuvar tetkiklerinde T3, T4 ve TSH normal sınırlarda saptandı. Görüntüleme tetkiklerinde; tiroid US'de sağ lobda 22x15 mm boyutlu, 1 adet hipoekojen solid nodül tesbit edilmesi üzerine İİAB uygulandı. Olgunun yayma preperatının hurthle hücreli neoplazi olarak rapor edilmesi üzerine hastaya bilateral total tiroidektomi uygulandı.

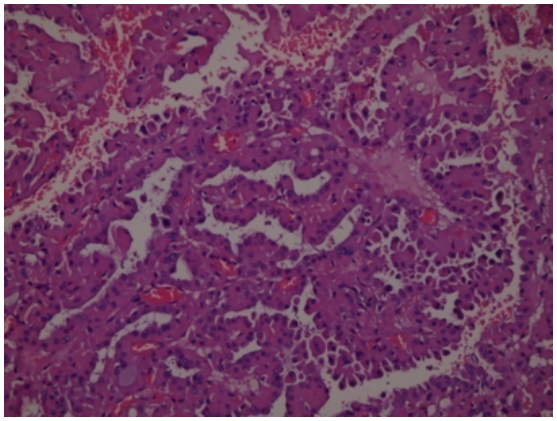
Yayma preperatların incelenmesinde; yer yer papiller yapılar oluşturmuş, geniş eozinofilik sitoplazmalı, iri hiperkromatik nüveli hurthle hücre grupları ve histiositler izlenmiş olup (Resim 1) hurthle hücreli neoplazi olarak rapor edildi.



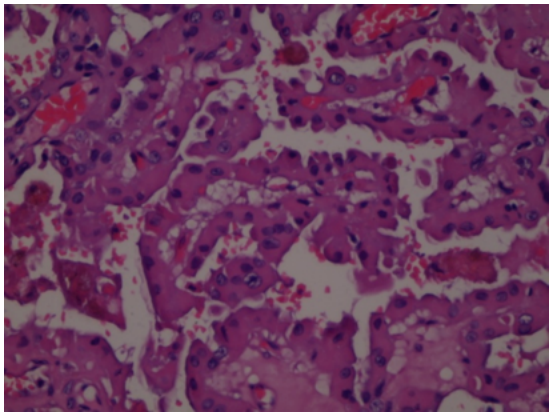
Resim 1. İİAB'de geniş eozinofilik sitoplazmalı, iri hiperkromatik nüveye sahip hobnail / mikropapiller hücreler görülmektedir.

Bunun üzerine hastaya bilateral total tiroidektomi uygulanmış olup, patoloji bölümüne gelen piyeste makroskobik olarak, tiroid sağ lobda 22 mm çapında kahverenkli, kolloidden fakir, kapsüllü, yer yer kanamalı bir adet nodül saptandı. Nodül dışı alanlar ve sol lob diffüz kolloidden zengin görünümde olup ayrı bir nodül yapısı tesbit edilmedi.

Mikroskobik incelemede nodülün tamamı fibröz kapsülle çevrili olup; tümörün hobnail görünümlü iri nüvelere sahip, geniş granüler eozinofilik sitoplazmalı, diskoheziv hücrelerle döşeli papiller yapılardan oluştuğu izlendi (Resim 2-3).



Resim 2. Tümör geniş eozinofilik sitoplazmalı, hobnail görünümlü nüvelere sahip diskohezivhücrelerle döşeli papiller yapılardan oluşmaktadır.



Resim 3. Tümörde papiller yapılar, geniş eozinofilik sitoplazmalı, apikal lokalizasyonlu, hobnail görünümlü hiperkromatik nüvelerle döşelidir.

Tümöral hücrelerde fokal alanlarda berrak sitoplazmik değişiklikler de saptandı. Tümöral nodülün tamamı benzer özellikte hücrelerle döşeli papiller yapılardan oluşmakta idi. Tümör kapsülüne ve tiroid kapsülüne invazyon görülmedi. Anjiolenfatik invazyon, tümör nekrozu, mitoz ve multisentrite saptanmadı. Tümör içinde kolloid fokal alanlarda mevcut olup kanama ve İİAB'ye bağlı olduğu düşünülen fokal enfarkt alanları gözlendi. Psammom body mevcut değildi. Sağ tiroid lobu kapsül çevresinde, reaktif hiperplazi gösteren, 2 mm çaplı iki adet lenf nodu tesbit edildi.

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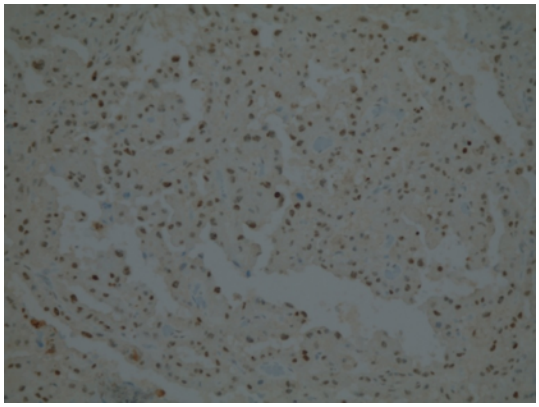
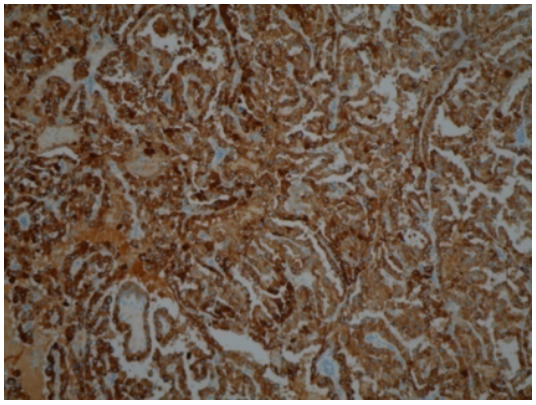
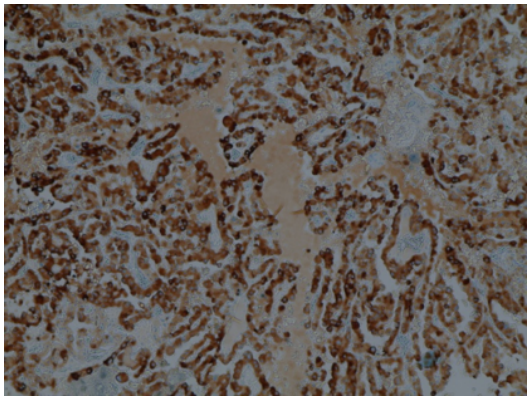
İmmünhistokimyasal incelemede TTF-1 (Resim 4), CK-7 (Resim 5), CK-19 (Resim 6) ile kuvvetli ve yaygın pozitif boyanma, HBME-1 ile zayıf pozitif boyanma saptandı. B-katenin, EMA ve E-kaderin ile membranöz boyanma mevcut idi.



Resim 4. Tümöral hücreler TTF-1 ile nükleer pozitif boyanma göstermektedir.

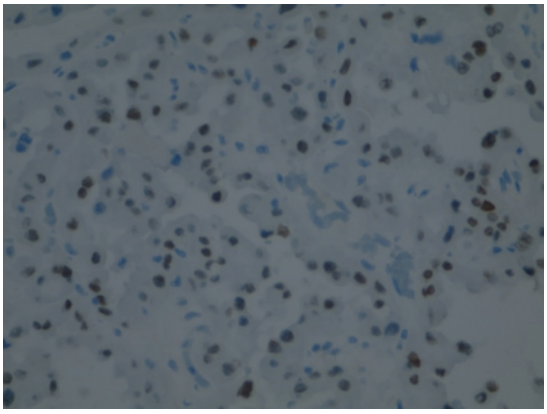


Resim 5. Tümöral hücrelerde CK-7 ile sitoplazmik pozitif boyanma izlenmektedir.



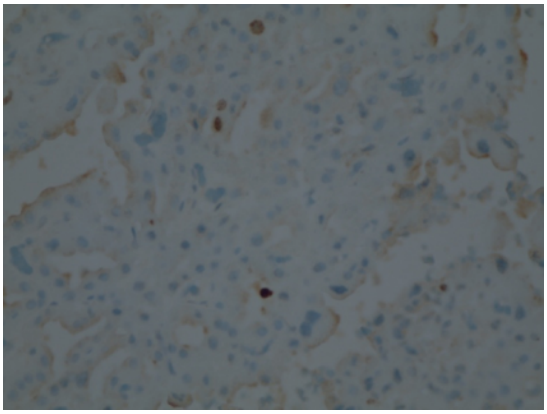
Resim 6. Tümöral hücrelerde CK-19 ile sitoplazmik pozitif boyanma izlenmektedir.

P53 ile neoplastik hücrelerin tamamına yakınında nükleer boyanma görüldü (Resim 7).



Resim 7. Tümöral hücrelerde P53 ile nükleer pozitif boyanma mevcuttur.

Ki-67 proliferasyon indeksi %1 idi (Resim 8).



Resim 8. Tümöral hücrelerde Ki-67 ile seyrek nükleer boyanma izlenmektedir.

Olgu mevcut bulgular eşliğinde "Hobnail/mikropapiller varyant papiller tiroid karsinomu" olarak rapor edildi.

Tartışma

PTK en sık rastlanan endokrin maliginte ve tiroid kanseri olup insidansı kadınlarda %2, erkeklerde ise %0.5'dir [1]. PTK insidansı son otuz yılda artış göstermiş olup, 1973 yılında yüzbinde 3.6 olan insidans, 2002 yılında yüzbinde 8.7'ye yükselmiştir [1,2]. Kanser ölümleri arasında ise sıklığı her 1 milyon kişide yaklaşık 6-8'dir [2,3]. Diğer kanserlerle karşılaştırıldığında yüksek oranda kür, uzun prognoz ve genellikle iyi diferansiye histolojik özellikler gösteren kanserler olarak bilinmektedir [4]. Prognoz; cerrahi veya histolojik parametrelere göre belirgin değişiklikler göstermemekle beraber, kötü prognoz ile ilişkili az sayıda histolojik varyant da mevcuttur [5,6].

Dünya sağlık örgütü PTK'nın birçok farklı tipini tanımlamış olup tanımlanan bu histolojik varyantlar prognoz bakımından farklılık göstermekte ve az sayıda histolojik varyant da (kolumnar hücreli, uzun hücreli, diffüz sklerozan varyant) kötü prognoz ile ilişkilendirilmiştir [5-7]. Son yıllarda; PTK'nın hobnail/mikropapiller varyantı olarak da adlandırılan, nadir fakat çok agresiv bir varyantı tanımlanmıştır [8].

Hobnail/mikropapiller patern, apokrin özellikler ve hücre polaritesinin kaybı ile karakterize, lakünar boşluklarla çevrili küçük papiller kümeler şeklinde tarif edilen bir morfolojiyi ifade etmektedir [9]. Oluşum mekanizmasında hücresel kohezivite ve polarite kaybının etkili olduğu düşünülmektedir [9]. Hobnail/mikropapiller hücreler çeşitli şekil ve boyutta olmakla beraber en belirgin özelliklerinden biri ters polarite olup ve çalışmalar bu özelliği yüksek invaziv potansiyel ile ilişkilendirmiştir [9,10]. Genellikle adenokarsinomalarda rastlanan bir fenotip olmakla beraber, bulunduğu yerden bağımsız olarak lenfovasküler invazyon, lenf nodu metastazı ve düşük prognoz ile ilişkili olduğu kabul edilir [9,10].

Bu hobnail/mikropapiller görünüm ilk olarak akciğer ve overde tanımlanmakla beraber; mesane, akciğer, pankreas ve tükrük bezi gibi faklı organdaki birçok tümörde de tanımlanmıştır [10,11]. Hobnail/mikropapiller karsinom insidansı çeşitli organlarda %5-20 arasında değişmekle beraber bu komponentin tümör içindeki oranı da değişmekte ve genelde %30'dan az olmaktadır ancak saf olarak rapor edilen istisnai vakalar da mevcuttur [12,13]. Literatürde PTK'da benzer morfolojideki tümörler için hobnail, mikropapiller ya da diskoheziv büyüme paterni şeklinde farklı tanımlamalar mevcut olup, bu isimlendirme için tümörün %20-%30 oranında bu morfolojiyi göstermesi gerektiği belirtilmiştir [14]. Olgumuzda tümöral nodülün tamamı geniş eozinofilik granüler sitoplazmalı, hobnail görünümlü diskoheziv hücrelerle döşeli papiller yapılardan oluşmaktadır.

PTK'da hobnail görünüm ilk olarak 2003'de Tang ve arkadaşları tarafından tanımlanmış ve retinoid reseptör ekspresyonu ile ilişkili olduğu belirtilmiştir [14]. Bai ve arkadaşları PTK'da polarite ve kohezivite kaybı gösteren 52 vaka tanımlamış olup, tarif edilen paternin periostin ekspresyonuyla korele olduğnu ve bu paternde mortalitenin daha yüksek olduğunu bildirmiştir [15]. Motosugi ve arkadaşları da hobnail/mikropapiller yapılarla karakterize agresiv davranışlı bir PTK olgusu bildirmiş ve bu görüntünün rekürrens ile ilşkili olduğunu tanımlamıştır [16]. Bellevicine ve arkadaşları da hobnail/mikropapiller özelliklere sahip bir olgu bildirmiş olup bu hücreleri kuyruklu yıldıza benzetmiş ve İİAB ile preoperatif tanınmasının daha kapsamlı boyun cerrahisini garanti edeceğini vurgulamıştır [17]. Asioli ve arkadaşları ise 8 vakalık serisinde 7 vakada rekürrens (%87.5) ve 4 (%50) vakada hastalığa bağlı mortalite geliştiğini bildirmiş olup; PTK'da hobnail/mikropapiller benzeri hücrelerin yüzdesinin artmasının tümörün agresivliğini arttırdığını, %30'un üzerinde ise hasta sağ kalımını önemli ölçüde azalttığını, bu nedenle bu hücrelerin preoperatif olarak tanınmasının klinik yönetim için değerli bilgiler vereceğini belirtmiştir [18].

Hobnail/mikropapiller patern saf olarak görülebileceği gibi, daha sıklıkla diğer agresiv gidişli varyantlar ile bir arada rastlanmaktadır [19]. Uzun hücreli varyant tanısı için tümörü oluşturan hücrelerin, boyu eninin en az iki katı olan hücrelerden oluşması gerekmekte olup neoplastik hücrelerin çekirdek özellikleri klasik PTK ile benzer ve bol eozinofilik sitoplazmalı hücrelerdir. Nekroz, mitotik aktivite ve tiroid dışı yayılım sık olup genellikle yaşlı hastalarda gözükür [19]. Difüz sklerozan varyant ise genelde genç hastalarda gözükür, bir ya da her iki tiroid lobunu difüz tutar, yaygın skuamöz metaplazi, çok sayıda psammom body, yoğun lenfositik infiltrasyon ve stromal fibrozis gösterir [20]. Kolumnar hücreli varyant ise supranükleer ve subnükleer vakuoller içeren pseudostratifiye kolumnar hücrelerden oluşan nadir bir varyanttır. Klasik PTK nükleer özelliklerini yanlızca fokal alanlarda gösterir [21].

Hobnail/mikropapiller varyant PTK'nın ayırıcı tanısında overin seröz karsinomu, peritonun primer seröz karsinomu, akciğer adenokarsinomunun hobnail hücreli tipi gibi metastatik lezyonlarda göz önüne alınmalıdır [22]. Bu ayırımda immünhistokimyasal boyama yararlı olacaktır [22]. Olgumuzda Tiroglobulin ve TTF-1 ile pozitif boyanma saptanmış olup nekroz, mitoz, anjiolenfatik invazyon, multisentrite, tiroid kapsül invazyonu ve tiroid dışı yayılım saptanmamıştır.

PTK'da erken dönemde değişiklikler kromozom yapısında görülmekte olup bu değişiklikler sıklıkla RET protoonkogeninde gözükür. Bu onkogen 10. kromozomda yerleşmiş olup, tirozin kinaz reseptörünü kodlar [23]. Ayrıca PTK'da, diğer sık raslanan bir kromozom bozukluğu olan BRAF mutasyonu ile tümör yayılımı ve nüks arasındaki ilişki birçok çalışmada gösterilmiş olup hobnail/mikropapiller varyant PTK'da da BRAF mutasyonu bildirilmiştir [24,25].

Sonuç olara PTK'da güncel çalışmalar hangi hastanın daha agresiv seyredeceğini tesbit etmek üzere yoğunlaşmış olup tümörlerde izlenen birtakım histolojik paternlerin, prognoz ve hedefe yönelik tedavide yararlı bilgiler verebileceğini düşünmekteyiz. Hobnail/mikropapiller varyant PTK, farklı organlarda izlenen benzer morfolojideki tümörler gibi agresiv davranış göstermesi nedeniyle ayrı bir varyant olarak tanımlanmalıdır. Bu varyantın moleküler alt yapısının aydınlatılması ve diğer agresiv varyantlar ile ilişkisinin ortaya konması için daha ileri çalışmalara ihtiyaç vardır.

Maddi Destek ve Çıkar İlişkisi

Çalışmayı maddi olarak destekleyen kişi/kuruluş yoktur ve yazarların çıkara dayalı bir ilişkisi yoktur.

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Case Report

An atypical presentation of an atypically localized cardiac myxoma

Atipik klinik ile tespit edilen atipik yerleşimli kardiyak miksoma

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ABSTRACT

Atrial myxomas are the most common benign primary cardiac tumors that can lead to many complications as defined in literature. Although the majority occur in the left atrium and attached to interatrial septum, they can arise from any cardiac chamber. Here we report the case of a 55-year-old woman whom was referred to our outpatient clinic for etiological diagnosis of unilateral transient loss of vision. Transesophageal echocardiography revealed a mass that was suspected as cardiac myxoma arising from the posterior wall of the LA in the vicinity of the left superior pulmonary vein. During the surgical procedure cardiac mass was removed totally and the pathological examination confirmed the diagnosis as cardiac myxoma. In patients with transient ischaemic symptoms but without atrial fibrillation echocardiography should be performed to diagnose of potential mass in left atrium.

Keywords: atrial myxoma, cardiac tumor, echocardiography

ÖZ

Atriyal miksomalar, en sık karşılaşılan benign primer kardiyak tümörlerdir. Literatürde tanımlandığı üzere birçok komplikasyona yol açmaktadır. Çoğunlukla solda atriyumda olsa da atriyum ve interatriyal septuma bağlı olarak, herhangi bir kardiyak boşlukta ortaya çıkabilir. Bu olgu raporunda 55 yaşındaki bir kadın hastamızı sunduk. Kardiyoloji polikliniğine tek taraflı geçici görme kaybı etyolojisinin araştırılması amacıyla danışıldı. Transözofageal-ekokardiyografide kardiyak miksoma olarak şüphe edilen bu kitlelenin cerrahi esnasında sol atriyum posteriyor duvar, sol üst pulmoner ven çevresinden kaynaklandığı tespit edildi ve kitle tamamen çıkartıldı. Patolojik inceleme sonucunda tanı kardiyak miksoma olarak doğrulandı. Geçici iskemik semptomları olan ancak atriyal fibrilasyonu olmayan hastalarda sol atriyumda potansiyel kitle tanısını koymak için ekokardiyografi yapılmalıdır.

Anahtar Kelimeler: atriyal miksoma, kardiyak tümör, ekokardiografi

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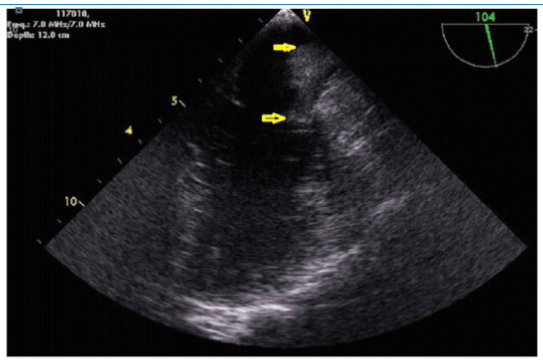
Introduction

Cardiac myxomas are the most frequent benign intra cardiac tumors that can lead to many embolic complications as described in literature [1]. Atrial myxomas are related to systemic embolisation in around 30 to 40 % of cases [2]. Temporary loss of vision caused by intracardiac myxomas embolisation have been observed rare in the literature [3].

Case report

Here we report the case of a 55-year old woman who was referred for etiological diagnosis of unilateral transient loss of vision by an ophthalmologist. She had a history of diabetes mellitus. Physical examination revealed blood pressure 100 / 60 mmHg. Heart rhythm was regular at 66 bpm. The patient had no prior history of heart murmur, syncope, shortness of breath, or chest pain. Further physical examination revealed a soft grade 2/6 systolic murmur at the left sternal border.

Atrial fibrillation was not observed in a 24-hour rhythm holter recording. After a mass was seen in transthoracic echocardiography (TTE), transesophageal echocardiography (TEE) was performed and revealed a 3.8x2.8 cm sized, unclear site of attachment (Figures1a,1b and1c).



Figüre 1a: Traneosephagial echocardiographic findings. A mass with irregular margin in the left atrium and unclear site of attachment (in midesophageal long-axis view showing) Laa left atrial apendicis ,LV left ventricle

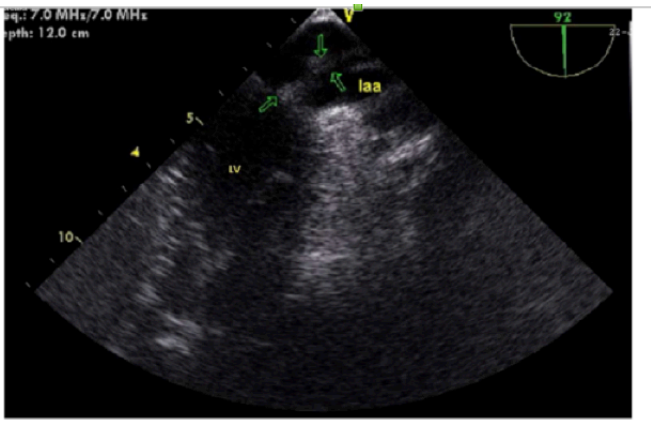


Figure 1b: midesophageal long-axis view (LA left atrium, LV left ventricle,)

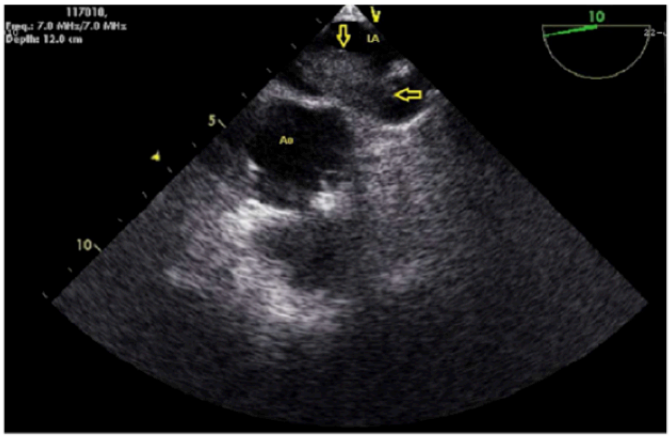


Figure 1c midesophageal short-axis view (LA left atrium, Ao aortic annulus)

It was highly mobile and occasionally extending to the mitral valve area during the diastole. TEE exhibited a large mass with wide base, located at posterior wall of the high left atrium (LA) in the vicinity of left upper pulmonary vein. At first vision was suspected this mass as thrombus causing central retinal artery emboli. So she was treated with the unfractionated heparin and we planned to recheck the size of mass in the left atrium after 7 days. TTE was performed again and we observed no change in the size of the mass.

The patient was referred to surgery. After median sternotomy and dissection of the right atrium, left atrium was explored through transeptal approach, myxomatous large mass with a gelatinous appearance was totally resected during the surgery. The mass was multilobed and a friable with a large pedicle It was attached to the posterior wall of the high left atrium in the vicinity of the left superior pulmonary vein with base of implantation of 5,0 x 3.0 cm diameter.

Macroscopically the lesion was soft, polypoid and lobulated. Microscopic examination revealed a papillary tumor in a myxoid stroma. Tumor was composed of polygonal and stellate cells. There was no mitotic activity, pleomorphism and necrosis in the tissue. (Figures 2a and 2b).

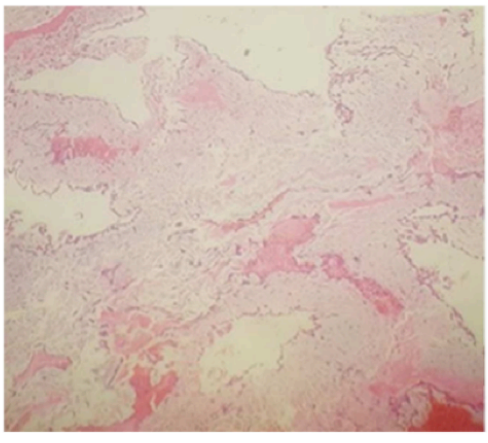


Figure 2a : Cardiac tumor. Microscopic image shows tumors cells aligning on surface surrounded with a myxoid stroma (4X magnification, H&E stained section)

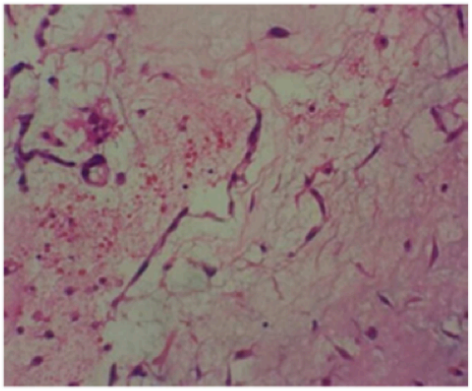


Figure 2b: Medium magnification of tumor. Necrosis and mitotic activity is absent. (40X Magnification, H&E stained section).

Due to the complete atrioventricular (AV) block after surgical procedure, a temporary pacemaker was implanted during the first postoperative day. TTE performed after surgery revealed a mild mitral regurgitation. As the sinus rhythm restored, the pacemaker was removed in the postoperative second day.

Discussion

Atrial myxomas represent approximately 50% of all cardiac tumors and nonfamilial forms occur mainly in the 5th and 6th decade of life [2]. They originate mainly from mesenchymal cells left atrium subendocardial. Although myxomas usually originate in the LA (75%) attached to fossa ovalis, these tumors may also arise from atypical sites such as right atrium (15–20%), posterior or anterior LA walls, atrial appendage, left or right ventricle, and on the valves [4,5]. Myxomas must be at the top of the differential diagnosis list in all intracardiac tumors. Although they are histologically benign, may lead to syncope, systemic embolism or sudden death [6,7].

TTE and TEE have an important role of diagnosis. However, a definitive transthoracic echocardiographic diagnosis of a left atrial myxoma is difficult when the site of origin cannot be clearly identified. According to the literature posterior wall origin of myxomas was identified in 28 cases (including our case report) researches, due to lower incidence of symptoms, posterior wall localized atrial myxomas are diagnosed later than the others [1]. Embolization to the central nervous system may result in transient loss of vision and ischemic attack, stroke, or seizure. Likewise, embolisation to retinal artery may lead to severe irreversible visual impairment, nevertheless it may cause temporary loss of vision as in our case. This is particularly noticeable in patients with diabetes mellitus, high blood pressure and elderly [8]. Any embolic event may be the only symptoms that should lead an early diagnosis [9].

As a conclusion although myxomas originating from the posterior wall of LA are extremely rare, it should be kept in mind for the differential diagnosis of a mass in LA especially in patients with transient ischaemic symptoms but without atrial fibrillation.

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Case Report

Iatrogenic post-intubation tracheal rupture treated surgically with cardiopulmonary bypass support

İyatrojenik post-entübasyon trakea rüptürünün kardiyopulmoner bypass desteği ile cerrahi tedavisi

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ABSTRACT

Iatrogenic tracheobronchial injuries are severe complications of airway access techniques such as endotracheal intubation. The reported incidence is approximately 0.005% for orotracheal intubations. Although conservative methods may also be used, surgical intervention is the treatment of choice for most cases. Herein, we present a 78-year old patient with a post-intubation huge membranous tracheal rupture, which was eventually repaired surgically with cardiopulmonary bypass support.

Keywords: endotracheal intubation, trachea rupture, cardiopulmonary bypass

ÖZ

İatrojenik trakeobronşiyal yaralanmaları, endotrakeal entübasyon gibi hava yolu erişimi tekniklerinin ciddi komplikasyonlarındandır. Orotrakeal entübasyon sonrası görülme sıklığı yaklaşık % 0.005'dir. Zaman zaman koruyucu methodlarla tedavi edilseler de çoğu vaka cerrahi yöntemlerle tedavi edilir. Bu olgu sunumunda, 78 yaşındaki bir hastada, entübasyon sonrası meydana gelen geniş membranöz trakea rüptürünün kardiyopulmoner bypass yardımı ile cerrahi tedavisini sunuyoruz.

Anahtar kelimeler: endotrakeal entübasyon, trakea rupture, kardiyopulmoner bypass

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Introduction

Tracheobronchial injuries are rare but potentially life-threatening complications of endotracheal intubations. The reported incidence is approximately 0.005% for orotracheal intubations [1,2]. The most likely causes of the trachea injury are massive overinflation of the endotracheal tube cuff, the preexisting tracheal wall weakness, steroids, chronic diseases and use of introducer [3]. In most cases surgical cardiopulmonary bypass (CPB) intervention is the treatment of choice, yet conservative methods may also be used [4]. We present a 78-year old patient with post-intubation membranous tracheal rupture, which was eventually repaired surgically with support.

Case report

A 78-year old female was found at home unresponsive with no heartbeats or respiration for almost 10 minutes. Orotracheal intubation was performed by an emergency service member. Cardiopulmonary resuscitation (CPR) was immediately instituted. After 5 minutes of CPR, her rhythm had restored to sinus rhythm and advanced cardiac life support measures were initiated. At arrival in the emergency department (ED) hemodynamic stabilization was established. The Glasgow Coma Scale score was 3, and the pupils were noted to be anisocoric, which gradually became isocoric. Further examination revealed massive subcutaneous emphysema over the neck and the chest wall. Computed tomography (CT) of the chest revealed small volume pneumomediastinum, pneumothorax on the right chest, bilateral non-displaced rib fractures and a large posterior tracheal rupture in the pars membranosa (Figure 1). Cranial CT was reported to be normal. Thus the patient promptly proceeded to surgical repair.

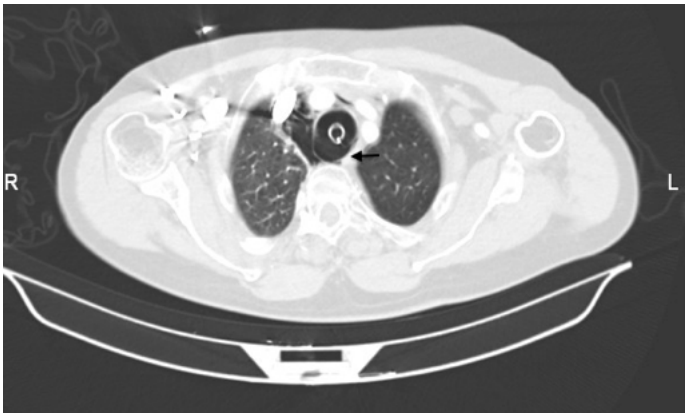

Figure 1. Chest CT scan; CT of the chest showed small volume pneumomediastinum, and a large posterior tracheal rupture in the pars membranosa (black arrow points the large rupture).

Expecting the difficulties of lateral decubitus position for this considerably obese patient and considering the long length of laceration median sternotomy was performed. CPB was initiated with ascending aorta and right atrial cannulation. Large posterior tracheal rupture located in the pars membranosa was confirmed. The lesion was measured nearly 8 cm long and it extended from 1 cm below the level of cricoid cartilage to the carina (Figure 2).

Figure 2. Schematic illustration of the tracheal rupture; A 8 cm long posterior tracheal rupture extends from 1 cm below the level of cricoid cartilage up to the carina.

Endotracheal tube (ETT) was removed. The trachea was transected from the upper level of the rupture allowing clear exposure. The defect was repaired continuously with 5-0 polydioxanone (PDS®) suture up to the level of transection. End to end anastomosis of the transected trachea was performed with 5-0 polydioxanone (PDS®). ETT was inserted, positioned at the level of the carina and the cuff was left deflated. The suture lines were controlled with fiberoptic bronchoscopy. Lung ventilation was then re-instituted and the patient was weaned from CPB. Chest tubes were placed and the incision was closed. During the follow-up in the intensive care unit (ICU) the patient was declared to be hemodynamically stabilised. Sedation was subsequently discontinued. However, there was no response to deep pain stimulation. Pupillary and corneal reflexes were also absent. Neurological consultation revealed probable brain death according to the neurologic criteria. Subcutaneous emphysema and pneumomediastinum resolved and the thoracal drains were removed on the post-operative 2nd day. In the follow-up, the patient's general state detoriated gradually. On the post-operative 5th day the patient had cardiac arrest followed by asystole and cardiopulmonary resuscitation was performed; however, despite all efforts the patient was considered exitus.

Discussion

Iatrogenic tracheobronchial injuries, which occur rarely, are severe complications of airway access techniques such as endotracheal intubation and tracheostomy. The risk of injury seems to increase with difficult or emergency intubations and with multiple vigorous attempts of inexperienced medical staff especially in stressful situations. Obesity, female gender, advanced age, poor medical condition, short stature, chronic obstructive pulmonary disease (COPD), and tracheomalacia are considered to be important risk factors [2,5,6]. Injuries are usually linear and involve the membranous portion of the lower third of the trachea (60-80%). Involvement of the middle trachea is rare [2,7,8]. In this case, we present a 78-year old female who had obesity and history of COPD with a large laceration involving nearly the whole length of trachea.

Persistent air leak around the endotracheal tube, subcutaneous emphysema over the neck and chest, mediastinal emphysema, cyanosis, hemoptysis, and clinical signs of pneumothorax are typical findings [9,10].

Computed tomography (CT) of the thorax is preferred to evaluate mediastinal emphysema and pneumothorax and also allows direct visualization of the tracheal injury in 70% of the cases. Bronchoscopy is considered to be the most effective method for confirming the diagnosis and for determining the exact location and extent of the injury [4,11,12].

The management of iatrogenic tracheobronchial injuries is controversial. Treatment strategy depends on several factors such as clinical presentation and overall condition of the patient, location and extent of the lesion, and the patient's preexisting risk factors.

Iatrogenic tracheobronchial injuries can be treated conservatively in selected cases. The criteria for conservative treatment are considered to be stable vital signs, spontaneous breathing or no difficulty in ventilation while intubated or no respiratory distress after extubation, no evidence of esophageal injury, nonprogressive pneumomediastinum or subcutaneous emphysema and no signs of sepsis [5,13,14]. Carbognani and colleagues chose nonsurgical therapy in small, uncomplicated tears (<2 cm) in stable patients [13]. Gomez-Caro and colleagues also recommended conservative management for patients with no associated esophageal injuries, no rapidly progressive subcutaneous or mediastinal emphysema, and no mediastinitis [15]. Schneider and colleagues advocate conservative treatment in stable patients with a delayed (>24 hours) diagnosis of the tracheobronchial injury [1].

Endoscopic stenting is another therapeutic option. However, few reports exist about acute stenting of tracheal injuries. Madden and colleagues reported two cases of a longitudinal posterior wall perforation after percutaneous tracheostomy treated by tracheal stenting [16]. Shimizu and colleagues successfully inserted a T-silicon stent through a tracheostomy over a laceration [17]. Alternatively, bronchoscopic application of fibrin sealent onto the lesion may ensure tissue regeneration particularly in small tears [18,19]. Aydemir and colleagues reported two patients which were successfully managed with fibrin sealent [20].

The traditional method preferred by most authors for the management of iatrogenic tracheobronchial injury is primary repair. The criteria for surgical repair include the following: lesions >2 cm in length, perforation into the pleural cavity, progressive subcutaneous or mediastinal emphysema and insufficient mechanical ventilation [1,5,14]. In our case the decision was to repair the defect surgically due to the extent and location of the laceration, high possibility of both mediastinitis and expansion of the pneumothorax.

When primary repair is indicated, it is traditionally performed through a right lateral thoracotomy. However, for surgical repair of patients with a laceration of the upper or middle thirds of the trachea transcervical approach can be preferred [21,22]. Considering the length and location of the defect we decided to repair it under CPB support with median sternotomy which would also provide a better exposure for the whole length of the trachea.

In our opinion, CPB support contributes to the exposure of the trachea and provides a safer repair in the surgical management of patients with extended post-intubational tracheal injury.

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TURKISH JOURNAL of CLINICS and LABORATORY

Türk Klinik ve Laboratuvar Dergisi

Turkish Journal of Clinics and Laboratory - Türk Klinik ve Laboratuvar Dergisi

Tıp dergilerine gönderilecek makalelerin standart gereksinmeleri ile ilgili tüm bilgileri www.icmje.org internet adresinde bulabilirsiniz

Amaç ve kapsam: "Turkish Journal of Clinics and Laboratory", hakemli, açık erişimli ve periyodik olarak çıkan, DNT Ortadoğu Yayıncılık A.Ş. ye ait bir dergidir. Hedefimiz uluslararası bir tabanda hastalıkların teşhis ve tedavisinde yenilikler içeren yüksek kalitede bilimsel makaleler yayınlamaktır. Yılda dört kez çıkan bir bilimsel bir tıp dergisidir. Hakemli bir dergi olarak gelen yazılar konsültanlar tarafından, öncelikle, biyomedikal makalelere ait Uluslararası Tıp Dergileri Editörleri Komitesi (www.icmje.org adresinden ulaşılabilir) tarafından tanımlanan standart gereksinimler ile ilgili ortak kurallara uygunluğu açısından değerlendirilir. Tıbbın her dalı ile ilgili retrospektif/prospektif klinik ve laboratuar çalışmalar, ilginç olgu sunumları, davet üzerine yazılan derlemeler, editöre mektuplar, orijinal görüntüler, kısa raporlar ve cerrahi teknik yazılarıları yayımlayan bilimsel, uluslar arası hakemli bir dergidir. Başka bir dergide yayımlanmış veya değerlendirilmek üzere gönderilmiş yazılar veya dergi kurallarına göre hazırlanmamış yazılar değerlendirme için kabul edilmez.

On-line makale gönderimi: Tüm yazışmalar ve yazı gönderimleri dergipark üzerinden http://dergipark.gov.tr/tjcl yapılmalıdır. Yazı gönderimi için detaylı bilgi bu internet adresinden edinilebilir. Gönderilen her yazı için özel bir numara verilecek ve yazının alındığı e-posta yolu ile teyid edilecektir. Makalelerin "full-text" pdf formuna http:/www.dergipark.ulakbim.gov.tr/tjclinlab linkinden ulaşılabilir.

Açık erişim politikası: Turkish Journal of Clinics and Laboratory açık erişimi olan bir dergidir. Kullanıcı lar yazıların tam metnine ulaşabilir, kaynak gösterilerek tüm makaleler bilimsel çalışmalarda kullanılabilir.

Aşağıdaki rehber dergiye gönderilen makalelerde aranan standartları göstermektedir. Bu uluslararası format, makale değerlendirme ve basım aşamalarının hızla yapılmasını sağlayacaktır.

Yazarlara Bilgi: Yazıların tüm bilimsel sorumluluğunu yazar(lar)a aittir. Editör, yardımcı editör ve yayıncı dergide yayınlanan yazılar için herhangi bir sorumluluk kabul etmez.

Dergi adının kısaltması: Turk J Clin Lab

Yazışma adresi: Yazılar e-mail yoluyla sorumlu yazar tarafından, Dergipark ta yer alan Turkish Journal of Clinics and Laboratory linkine girip kayıt olduktan sonra gönderilmelidir.

Makale dili: Makale dili Türkçe ve İngilizcedir. İngilizce makaleler gönderilmeden önce profesyonel bir dil uzmanı tarafından kontrol edilmelidir. Yazıdaki yazım ve gramer hataları içerik değişmeyecek şekilde İngilizce dil danışmanı tarafından düzeltilebilir. Türkçe yazılan yazılarda düzgün bir Türkçe kullanımı önemlidir. Bu amaçla, Türk Dil Kurumu Sözlük ve Yazım Kılavuzu yazım dilinde esas alınmalıdır.

Makalenin başka bir yerde yayımlanmamıştır ibaresi: Her yazar makalenin bir bölümünün veya tamamının başka bir yerde yayımlanmadığını ve aynı anda bir diğer dergide değerlendirilme sürecinde olmadığını, editöre sunum sayfasında belirtmelidirler. 400 kelimeden az özetler kapsam dışıdır. Kongrelerde sunulan sözlü veya poster bildirilerin, başlık sayfasında kongre adı, yer ve tarih verilerek belirtilmesi gereklidir. Dergide yayımlanan yazıların her türlü sorumluluğu (etik, bilimsel, yasal, vb.) yazarlara aittir.

Değerlendirme: Dergiye gönderilen yazılar format ve plagiarism açısından değerlendirilir. Formata uygun olmayan yazılar değerlendirilmeden sorumlu yazara geri gönderilir. Bu tarz bir zaman kaybının olmaması için yazım kuralları gözden geçirilmelidir. Basım için gönderilen tüm yazılar iki veya daha fazla yerli/yabancı hakem tarafından değerlendirilir. Makalelerin değerlendirilmesi, bilimsel önemi, orijinalliği göz önüne alınarak yapılır. Yayıma kabul edilen yazılar editörler kurulu tarafından içerik değiştirilmeden yazarlara haber verilerek yeniden düzenlenebilir. Makalenin dergiye gönderilmesi veya basıma kabul edilmesi sonrası isim sırası değiştirilemez, yazar ismi eklenip çıkartılamaz.

Basıma kabul edilmesi: Editör ve hakemlerin uygunluk vermesi sonrası makalenin gönderim tarihi esas alınarak basım sırasına alınır. Her yazı için bir doi numarası alınır.

Yayın hakları devri: http:/www.dergipark.ulakbim.gov.tr/tjclinlab adresi üzerinden online olarak gönderilmelidir. 1976 Copyright Act'e göre, yayımlanmak üzere kabul edilen yazıların her türlü yayın hakkı yayıncıya aittir.

Makale genel yazım kuralları: Yazılar Microsoft Word programı (7.0 ve üst versiyon) ile çift satır aralıklı ve 12 punto olarak, her sayfanın iki yanında ve alt ve üst kısmında 2,5 cm boşluk bırakılarak yazılmalıdır. Yazı stili Times New roman olmalıdır. "System International" (SI) unitler kullanılmalıdır. Şekil tablo ve grafikler metin içinde refere edilmelidir. Kısaltmalar, kelimenin ilk geçtiği yerde parantez içinde verilmelidir. Türkçe makalelerde %50 bitişik yazılmalı, aynı şekilde İngilizcelerde de 50% bitişik olmalıdır. Türkçede ondalık sayılarda virgül kullanılmalı (55,78) İngilizce yazılarda nokta (55.78) kullanılmalıdır. Derleme 4000, orijinal çalışma 2500, olgu sunumu 1200, editöre mektup 500 kelimeyi geçmemelidir. Özet sayfasından sonraki sayfalar numaralandırılmalıdır.

Yazının bölümleri

1. Sunum sayfası: Yazının Turkish Journal of Clinics and Laboratory 'de yayınlanmak üzere değerlendirilmesi isteğinin belirtildiği, makalenin sorumlu yazarı tarafından dergi editörüne hitaben gönderdiği yazıdır. Bu kısımda makalenin bir bölümünün veya tamamının başka bir yerde yayımlanmadığını ve aynı anda bir diğer dergide değerlendirilme sürecinde olmadığını, maddi destek ve çıkar ilişkisi durumu belirtmelidir.

2. Başlık sayfası: Sayfa başında gönderilen makalenin kategorisi belirtilmedir (Klinik analiz, orijinal çalışma, deneysel çalışma, olgu sunumu vs).

Başlık: Kısa ve net bir başlık olmalıdır. Kısaltma içermemelidir. Türkçe ve İngilizce yazılmalı ve kısa başlık (runing title) Türkçe ve İngilizce olarak eklenmelidir. Tüm yazarların ad ve soyadları yazıldıktan sonra üst simge ile 1'den itibaren numaralandırılıp, unvanları, çalıştıkları kurum, klinik ve şehir yazar isimleri altına eklenmelidir.

Bu sayfada "sorumlu yazar" belirtilmeli isim, açık adres, telefon ve e-posta bilgileri eklenmelidir.

Kongrelerde sunulan sözlü veya poster bildirilerin, başlık sayfasında kongre adı, yer ve tarih verilerek belirtilmesi gereklidir.

3. Makale dosyası: (Yazar ve kurum isimleri bulunmamalıdır)

Başlık: Kısa ve net bir başlık olmalıdır. Kısaltma içermemelidir. Türkçe ve İngilizce yazılmalı ve kısa başlık (runing title) Türkçe ve İngilizce olarak eklenmelidir.

Özet: Türkçe ve İngilizce yazılmalıdır. Orijinal çalışmalarda özetler, Amaç (Aim), Gereç ve Yöntemler (Material and Methods), Bulgular (Results) ve Sonuçlar (Conclusion) bölümlerine ayrılmalı ve 250 sözcüğü geçmemelidir. Olgu sunumları ve benzerlerinde özetler, kısa ve tek paragraflık olmalıdır (150 kelime), Derlemelerde 300 kelimeyi geçmemelidir.

Anahtar kelimeler: Türkçe ve İngilizce özetlerin sonlarında bulunmalıdır. En az 3 en fazla 6 adet yazılmalıdır. Kelimeler birbirlerinden noktalı virgül ile ayrılmalıdır. İngilizce anahtar kelimeler "Medical Subject Headings (MESH)" e uygun olarak verilmelidir. (www.nlm.nih.gov/mesh/MBrowser.html). Türkçe anahtar kelimeler "Türkiye Bilim Terimleri' ne uygun olarak verilmelidir (www.bilimterimleri.com). Bulunamaması durumunda birebir Türkçe tercümesi verilmelidir.

Metin bölümleri: Orijinal makaleler; Giriş, Gereç ve Yöntemler, Bulgular, Tartışma olarak düzenlenmelidir. Olgu sunumları; Giriş, Olgu sunumu, Tartışma olarak düzenlenmelidir. Şekil, fotoğraf, tablo ve grafiklerin metin içinde geçtiği yerler ilgili cümlenin sonunda belirtilmeli metin içine yerleştirilmemelidir. Kullanılan kısaltmalar altındaki açıklamada belirtilmelidir. Daha önce basılmış şekil, resim, tablo ve grafik kullanılmış ise yazılı izin alınmalıdır ve bu izin açıklama olarak şekil, resim, tablo ve grafik açıklamasında belirtilmelidir. Tablolar metin sonuna eklenmelidir. Resimler/fotoğraf kalitesi en az 300dpi olmalıdır.

Etik kurallar: Klinik araştırmaların protokolü etik komitesi tarafından onaylanmış olmalıdır. İnsanlar üzerinde yapılan tüm çalışmalarda, "Yöntem ve Gereçler" bölümünde çalışmanın ilgili komite tarafından onaylandığı veya çalışmanın Helsinki İlkeler Deklerasyonuna (www.wma.net/e/policy/b3.htm) uyularak gerçekleştirildiğine dair bir cümle yer almalıdır. Çalışmaya dahil edilen tüm insanların bilgilendirilmiş onam formunu imzaladığı metin içinde belirtilmelidir. Turkish Journal of Clinics and Laboratory gönderilen yazıların Helsinki Deklarasyonuna uygun olarak yapıldığını, kurumsal etik ve yasal izinlerin alındığını varsayacak ve bu konuda sorumluluk kabul etmeyecektir.

Çalışmada "Hayvan" öğesi kullanılmış ise yazarlar, makalenin Gereç ve Yöntemler bölümünde Guide for the Care and Use of Laboratory Animals (www.nap.edu/catalog/5140.html) prensipleri doğrultusunda çalışmalarında hayvan haklarını koruduklarını ve kurumlarının etik kurullarından onay aldıklarını belirtmek zorundadır.

Teşekkür yazısı: Varsa kaynaklardan sonra yazılmalıdır.

Maddi destek ve çıkar ilişkisi: Makale sonunda varsa çalışmayı maddi olarak destekleyen kişi ve kuruluşlar ve varsa bu kuruluşların yazarlarla olan çıkar ilişkileri belirtilmelidir. (Olmaması durumu da "Çalışmayı maddi olarak destekleyen kişi/kuruluş yoktur ve yazarların herhangi bir çıkar dayalı ilişkisi yoktur" şeklinde yazılmalıdır.

Kaynaklar: Kaynaklar makalede geliş sırasına göre yazılmalıdır. Kaynaktaki yazar sayısı 6 veya daha az ise tüm yazarlar belirtilmeli, 7 veya daha fazla ise ilk 3 isim yazılıp ve ark. ("et al") eklenmelidir. Kaynak yazımı için kullanılan format Index Medicus'ta belirtilen şekilde olmalıdır (www.icmje.org). Kaynak listesinde yalnızca yayınlanmış ya da yayınlanması kabul edilmiş veya DOI numarası almış çalışmalar yer almalıdır. Dergi kısaltmaları "Cumulated Index Medicus" ta kullanılan stile uymalıdır. Kaynak sayısının araştırmalarda 25 ve derlemelerde 60, olgu sunumlarında 10, editöre mektupta 5 ile sınırlandırılmasına özen gösterilmelidir. Kaynaklar metinde cümle sonunda nokta işaretinden hemen önce köşeli parantez kullanılarak belirtilmelidir. Örneğin [4,5]. Kaynakların doğruluğundan yazar(lar) sorumludur. Yerli ve yabancı kaynakların sentezine önem verilmelidir.

Şekil ve tablo başlıkları: Başlıklar kaynaklardan sonra yazılmalıdır.

4. Şekiller: Her biri ayrı bir görüntü dosyası (jpg) olarak gönderilmelidir.

Makalenin basıma kabulünden sonra "Dizginin ilk düzeltme nüshası" sorumlu yazara e-mail yoluyla gönderilecektir. Bu metinde sadece yazım hataları düzeltilecek, ekleme çıkartma yapılmayacaktır. Sorumlu yazar düzeltmeleri 2 gün içinde bir dosya halinde e-mail ile yayın idare merkezine bildirecektir.

Kaynak Yazım Örnekleri

Dergilerden yapılan alıntı;

Özpolat B, Gürpınar ÖA, Ayva EŞ, Gazyağcı S, Niyaz M. The effect of Basic Fibroblast Growth Factor and adipose tissue derived mesenchymal stem cells on wound healing, epithelization and angiogenesis in a tracheal resection and end to end anastomosis rat model. Turk Gogus Kalp Dama 2013; 21: 1010-19.

Kitaptan yapılan alıntı;

Tos M. Cartilage tympanoplasty. 1st ed. Stuttgart-New York: Georg Thieme Verlag; 2009.

Tek yazar ve editörü olan kitaptan alıntı;

Neinstein LS. The office visit, interview techniques, and recommendations to parents. In: Neinstein LS (ed). Adolescent Health Care. A practical guide. 3rd ed. Baltimore: Williams&Wilkins; 1996: 46-60.

Çoklu yazar ve editörü olan kitaptan alıntı;

Schulz JE, Parran T Jr: Principles of identification and intervention. In:Principles of Addicton Medicine, Graham AW. Shultz TK (eds). American Society of Addiction Medicine, 3rd ed. Baltimore: Williams&Wilkins; 1998:1-10.

Eğer editör aynı zamanda kitap içinde bölüm yazarı ise;

Diener HC, Wilkinson M (editors). Drug-induced headache. In: Headache. First ed., New York: Springer-Verlag;1988:45-67.

Doktora/Lisans Tezinden alıntı;

Kılıç C. General Health Survey: A Study of Reliability and Validity. phD Thesis, Hacettepe University Faculty of Medicine, Department of Psychiatrics, Ankara; 1992.

Bir internet sitesinden alıntı;

Sitenin adı, URL adresi, yazar adları, ulaşım tarihi detaylı olarak verilmelidir.

DOI numarası vermek;

Joos S, Musselmann B, Szecsenyi J. Integration of Complementary and Alternative Medicine into Family Practice in Germany: Result of National Survey. Evid Based Complement Alternat Med 2011 (doi: 10.1093/ecam/nep019).

Diğer referans stilleri için "ICMJE Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Sample References" sayfasını ziyaret ediniz.

Bilimsel sorumluluk beyanı: Kabul edilen bir makalenin yayınlanmasından önce her yazar, araştırmaya, içeriğinin sorumluluğunu paylaşmaya yetecek boyutta katıldığını beyan etmelidir. Bu katılım şu konularda olabilir:

a. Deneylerin konsept ve dizaynlarının oluşturulması, veya verilerin toplanması, analizi ya da ifade edilmesi;

b. Makalenin taslağının hazırlanması veya bilimsel içeriğinin gözden geçirilmesi

c. Makalenin basılmaya hazır son halinin onaylanması.

Yazının bir başka yere yayın için gönderilmediğinin beyanı: "Bu çalışmanın içindeki materyalin tamamı ya da bir kısmının daha önce herhangi bir yerde yayınlanmadığını, ve halihazırda da yayın için başka bir yerde değerlendirilmede olmadığını beyan ederim. Bu, 400 kelimeye kadar olan özetler hariç, sempozyumlar, bilgi aktarımları, kitaplar, davet üzerine yazılan makaleler, elektronik formatta gönderimler ve her türden ön bildirileri içerir."

Sponsorluk beyanı: Yazarlar aşağıda belirtilen alanlarda, varsa çalışmaya sponsorluk edenlerin rollerini beyan etmelidirler:

1. Çalışmanın dizaynı

2. Veri toplanması, analizi ve sonuçların yorumlanması

3. Raporun yazılması

Kontrol listesi:

1. Editöre sunum sayfası (Sorumlu yazar tarafından yazılmış olmalıdır)

2. Başlık sayfası (Makale başlığı/kısa başlık Türkçe ve İngilizce, Yazarlar, kurumları, sorumlu yazar posta adresi, tüm yazarların e-mail adresleri, sorumlu yazarın telefon numarası)

3. Makalenin metin sayfası (Makale başlığı/kısa başlık Türkçe ve İngilizce, Özet/anahtar kelimeler, Summary/keywords, makale metni, kaynaklar, tablo ve şekil başlıkları, tablolar, şekiller)

4. Tablo ve grafikler metin içinde olmalıdır.

5. Şekiller (En az 300 dpi çözünürlükte) ayrı bir veya daha fazla dosya halinde gönderilmelidir.

Özel Ortadoğu Hastanesi

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