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İÇİNDEKİLER

KLİNİK ARAŞTIRMA
ORIGINAL ARTICLE

Malnütrisyonun ve Polifarmasinin Demans Hastalarında Düşme Riski Üzerindeki Etkileri

Effects of Malnutrition and Polypharmacy on Fall Risk in Dementia Patients

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ÖZET

Amaç: Demans hastalarında morbidite ve mortalitenin önemli nedenlerinden biri olan "düşme riski" üzerine beslenme yetersizliği ve çoklu ilaç kullanımının etkilerini değerlendirilmesi amaçlanmıştır.

Materyal ve Metodlar: Bu kesitsel çalışma, demans polikliniğinde en az bir yıldır takip edilen erken evre demans hastalarını kapsamaktadır. Polifarmasi ölçütü olarak beşten fazla ilaç kullanımı seçilmiş ve ilaç tipleri alt gruplara ayrılmıştır. Hastalara Morse Düşme Ölçeği ve Mini Nutrisyonel Değerlendirme Ölçeği uygulandı.

Bulgular: Çalışmaya toplamda 240 demans hastası (150 kadın): Alzheimer Demans, Frontotemporal Demans, Lewy Cisimcikli Demans ve Vasküler Demans randomize olarak dahil edilmiştir. Malnütrisyon ve polifarmasinin düşme riskini artırdığı gözlemlenmiş, en yüksek risk psikotrop ilaç grubunda bulunmuştur. Tek antipsikotik kullanımının antipsikotik ve antidepresan birlikteliğine göre düşme riskini daha çok arttırdığı gözlenmiş olup, bu durum yüksek antipsikotik ilaç dozları ile ilişkilendirilmiştir.

Sonuç: Malnütrisyon, özellikle psikopolifarmasi ile bir araya geldiğinde düşme ve buna bağlı morbidite ve mortaliteyi ciddi oranda arttırmaktadır. Sık aralıklarla malnütrisyon takibinin yapılması ve olabildiğince az miktarda, kısa sürelerde ve kısıtlı endikasyonlarda psikotropik ilaçların kullanılması gereklidir.

Anahtar Kelimeler: Beslenme, demans, düşme, kognitif bozukluk, , polifarmasi

SUMMARY

Aim: It is aimed to evaluate the effects of malnutrition and polypharmacy on the risk of falling, which is an important cause of morbidity and mortality in patients with dementia.

Material and Methods: This cross-sectional study includes early stage dementia patients who were followed for at least one year in the dementia outpatient clinic. As a criterion for polypharmacy, patients using more than five drugs were determined and drug types were divided into subgroups. The patients' Morse Fall Scale and Mini Nutritional Assessment Scale were filled in.

Results: A total of 240 dementia patients (150 women) were included in the study. Patients with Alzheimer's Dementia, Frontotemporal Dementia, Dementia with Lewy Bodies and Vascular Dementia were ramdomly enrolled to study. It has been observed that malnutrition and polypharmacy increase the risk of falling, and the highest risk was found in the psychotropic drug group. It has been observed that the use of a single antipsychotic increases the risk of falling more than the combination of antipsychotics and antidepressants, and this is associated with high doses of antipsychotics.

Conclusion: When malnutrition is combined with polypharmacy and especially psychopolypharmacy, it significantly increases the risk of falls and related morbidity and mortality. It is necessary to monitor malnutrition at frequent intervals and use psychotropic drugs at the lowest dose, for the shortest period of time and for limited indications.

Keywords: Cognitive impairment, dementia, fall, nutrition, polypharmacy

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GİRİŞ

Demans, birden fazla bilişsel fonksiyonun işlevsellik kaybına yol açacak şekilde bozulduğu nörodejeneratif hastalıkların ana başlığıdır. Yaşlı nüfusun artmasına bağlı olarak önemi giderek artan bir halk sağlığı sorunudur. Yaşın ve beslenme yetersizliğinin düşme üzerine etkisi olduğu gibi, demansın da düşme riski arttırıcı etkileri vardır (1). Geriatrik populasyonda kronik hastalıkların artmasıyla polifarmasi sık karşılaşılan bir durum haline gelmiştir. Polifarmasi yani çoklu ilaç kullanımı Dünya Sağlık Örgütü (DSÖ) tarafından aynı anda çok sayıda (beş veya daha fazla) ilaç kullanımı; psikotropik polifarmasi ise aynı hastada 2 veya daha fazla psikiyatrik ilacın kullanılması olarak tanımlanmıştır. Polifarmasi, ileri yaşta ve demans hastalarında düşmeyi artırıcı nedenlerden bir tanesidir (2).

Çalışmamızda demans hastalarının düşme riski üzerinde; malnütrisyon ve polifarmasinin özellikle de psikotrop polifarmasinin etkilerini saptamayı amaçladık.

Literatürde düşme riski, daha çok düşen hastalara ait bilgilerin geriye dönük sorgulanması ile elde edilmiştir (3). Çalışmamızda ise henüz morbidite ile sonuçlanmış düşme öyküsü olmayan hastalarda malnütrisyon ve polifarmasi risk grupları oluşturularak düşme gerçekleşmeden, düşmeyi yordayıcı bilgilere ulaşılması amaçlanmıştır.

MATERYAL ve METODLAR

Düşme riskini ölçmek üzere Türkçe geçerliliği olan ve objektif bilgi veren Morse Düşme Riski Tanılama Ölçeği (MDÖ) kullanıldı. Malnütrisyonu göstermek için MNA uygulandı. Çalışma kesitsel olarak planlandı ve etik kurul onayı alındı. Hastalık evresi Klinik Demans Derecelendirme ölçeğine göre Evre I ve II olan ve sakatlık ile sonuçlanmış düşme öyküsü olmayan hastalar randomize bir şekilde alındı. Yaş sınırı uygulanmadı. Eğitim şartı aranmadı. Hastanın genel durumunu etkileyecek kontrolsüz metabolik hastalığı olanlar çalışmaya dahil edilmedi. Yürümeyi ve dengeyi bozacak ileri düzeyde kifoz, gonartroz gibi ortopedik problemi olan hastalar çalışmaya dahil edilmedi. Tüm hastalar başlangıçta çalışmanın yapısı hakkında bilgilendirildi. Hasta veya yasal vasisinden onam alındı. Polifarmasi için beş ve fazlası ilaç kullanan hastalar alındı. İlaç tipleri psikotrop ve nonpsikotrop olarak ikiye ayrılıp psikotrop ilaçlar da kendi arasında antidepresan ve antipsikotik olarak ikiye ayrıldı. Demografik veriler kayıtlandı.

Hasta Seçimi

Çalışmaya, Alzheimer Demans (AD) hastaları için National Institute on Aging and the Alzheimer's Association (NIA-AA) (4); Frontotemporal demans (FTD) hastaları için the 'International Behavioral Variant FTD Criteria Consortium (FTDC)'(5); vasküler demans hastaları için Uluslararası Vasküler Davranışsal ve Bilişsel Bozukluklar Derneği'nin vasküler demans kriterleri (6) ve Lewy Cisimcikli Demans (LBD) hastaları için McKeith ve arkadaşlarının revize edilmiş 2017 Revised criteria for the clinical diagnosis of dementia with Lewy bodies (DLB) (7) tanı kriterleri kullanılarak teşhis edilen, 2023 Temmuz-2024 Temmuz tarihleri arasında takip edilen 240 hasta dâhil edildi.

Ölçüm Araçları

Morse Düşme Riski Tanılama Ölçeği (MDÖ): Ölçek Janice M. Morse tarafından 1985 yılında geliştirilmiştir. Bu ölçekte 6 risk faktörü düşme riskini tanımlamaktadır. Bu risk faktörleri düşme öyküsü, ek hastalık tanısı, mobilizasyon yardımı, intravenöz tedavi veya heparin kullanımı, yürüyüş/transfer ve mental durum değerlendirmelerini içerir (8). Ölçek düşme eğilimini kazalardan bağımsız olarak öngörebilir. Ölçeğin dilimize geçerlik güvenirlik çalışması Demir ve İntepeler tarafından 2012 yılında yapılmıştır (9). Mini Nutrisyonel Değerlendirme Ölçeği Kısa Formu (MNA-SF): MNA-SF 2001'de Rubenstein ve arkadaşları tarafından geliştirilmiş, Kaiser ve arkadaşları tarafından 2009'da revize edilmiştir (10)(11). MNA-SF altı maddeden oluşur; hastanın iştah durumunda değişiklik olup olmadığı, son 3 ayda kilo kaybı olup olmadığı, mobilitesi, son 3 ayda psikolojik stres veya akut hastalık geçirip geçirmediği, nöropsikolojik problem varlığı ve vücut kitle indeksi (VKİ) hesaplanarak puanlama yapılır. Ölçeğin puanlaması; normal beslenme (12-14 arası), malnütrisyon riski altında olma durumu (7-11 arasında) veya belirgin malnütrisyon durumunun (<7) varlığı şeklinde yapılır (11). Polifarmasi: Aynı anda çok sayıda (beş veya daha fazla) ilaç kullanımı olarak tanımlanmıştır (12). Psikotrop Polifarmasi: Aynı hastada 2 veya daha fazla psikiyatrik ilacın aynı anda kullanılmasıdır (13).

İstatistiksel Analiz

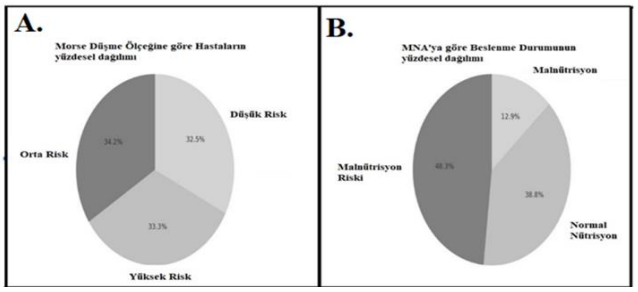
MDÖ ve MNA-SF gibi sayısal değerler için tanımlayıcı istatistikler: ortalama, standart sapma (SD), medyan, minimum ve maksimum değerleri içeriyordu. İki grup arasındaki ortalamaları karşılaştırmak için t-testleri kullanıldı. Polifarmasi ve polifarmasi olmayan grupların yanı sıra psikotropik ve psikotropik olmayan polifarmasi grupları arasındaki MDÖ puanlarını karşılaştırmak için tek yönlü ANOVA kullanıldı. Hangi spesifik grupların anlamlı farklılıklara sahip olduğunu belirlemek için ANOVA'dan sonra Tukey'nin post-hoc testi kullanıldı.

BULGULAR

Çalışmaya toplam 240 (90 erkek/150 kadın) hasta dahil edildi. Çalışma grubunda AD 156 kişi (toplam grubun %65'i 63 erkek/93 kadın), FTD 24 kişi (toplam grubun %10'u 14 erkek/10 kadın), LCD 24 kişi (toplam grubun %10'u 18 erkek/6 kadın), VD 36 kişi (toplam grubun %15'i 20 erkek/16 kadın) mevcut idi. Tüm grubun yaş ortalaması 72.01±7.50 yıldır.

Polifarmasi saptanan hasta sayısı 190 (%76,3), polifarmasi

saptanmayan hasta sayısı ise 50 (%23.7)'dir. MNA ve Morse Düşme Riski açısından hastaların yüzdesel dağılımı Şekil 1'de gösterilmektedir.



Şekil 1. Morse Düşme Ölçeği (MDÖ)'ne göre düşme risklerinin (A) ve Mini Nutrisyonel Değerlendirme (MNA)'ye göre malnütrisyon riskinin yüzdesel dağılımı (B).

Hastaların toplam 26 (%10.83)'sında malnütrisyon ve polifarmasi birlikteliği görüldü. Polifarmasi saptanan hastalarda kullanılan ilaçların dağılımı sırasıyla %33,3 antidepresan, %8,7 antipsikotik ilaç ve %34.2 oranında ise her iki grup ilacı aynı anda kullandığı saptandı (psikotropik polifarmasi).

Korelasyon analizi, MDÖ ile MNA puanları arasında anlamlı negatif bir korelasyon göstermiştir (r (238) = -0,45, p <0,01). MDÖ ile polifarmasi arasında ise anlamlı pozitif bir korelasyon tespit edildi (r (238) = 0,30, p <0,05), MNA puanları ile polifarmasi arasında da anlamlı bir negatif korelasyon bulundu (r(238) = -0,35, p < 0,05).

Yaş ile MDÖ puanları arasında anlamlı pozitif korelasyon saptanmış (r (238) = 0,25, p <0,05) olmasına rağmen yaş ile MNA puanları arasında anlamlı korelasyon saptanmamıştır (p>0,05).

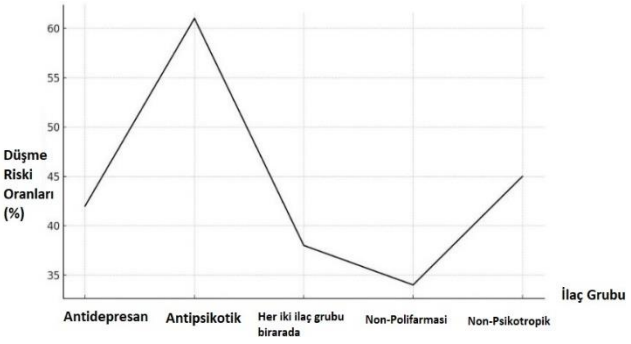
Tek yönlü ANOVA'da malnütrisyonlu hastaların düşme riski puanları (65.8±15.4), malnütrisyon riski olan hastalara (55.2±14.1) ve normal beslenmeye sahip olanlara (38,3, ±13,8) göre anlamlı derecede yüksek bulundu (p <0,05).

Polifarmasi saptanan hasta grubunda, düşme riski puanları (60,8, ± 18,3), polifarmasi saptanmayan hastalara göre (42.7. ±14,5) anlamlı derecede yüksek bulundu (p <0,05).

'Psikotropik polifarmasi' saptanan hastaların düşme riski puanları (62.4 ± 16,7), sadece polifarmasisi olan hastalardan (54.3± 15.2) anlamlı derecede daha yüksek bulundu (p <0,05).

Polifarmasi grupları içindeki düşme riski oranları Şekil 2'te gösterilmektedir. Düşme riski antipsikotik kullananlarda en yüksek, polifarmasi saptanmayan hastalarda ise en düşük oranlarda saptanmıştır.

Hem malnütrisyon hem de polifarmasi olan hastaların düşme riski puanları (70.2± 14.8) yalnızca malnütrisyon (58.6 ± 13,5) ve yalnızca polifarmasi (54.7 ±15.1) olan hastalara göre anlamlı derecede yüksek bulunmuştur.



Şekil 2. Polifarmasi grupları arasında düşme riskini karşılaştırılması

TARTIŞMA

Demansın dünya çapında prevalansı yaklaşık %5-7 civarındadır. Bu oran yaşla birlikte artar ve 85 yaş üstü popülasyonda %30'lara kadar çıkabilir (14). Demans hastalarında düşme, morbidite ve mortaliteyi arttırır. Bu artış, yüksek mali yüke sebebiyet verir ve bakım veren yükünü artırır. Bu nedenle iyi dökümante edilmesi gereken durumdur. Düşmeye nörodejenerasyona bağlı denge merkezlerinin etkilenmesi, algılama güçlükleri, ekstrapiramidal sistem bulguları, postüral instabilite, gezinme ve ajitasyon, otonom bozukluklar, polifarmasi, ileri yaş, görme bozuklukları sebep olmaktadır (15-18). Kognitif bozukluğu olan kişilerde tekrarlayan düşmeler, engelliliğe sebep olabilecek ciddiyette düşme oranlarını yükseltir (19).

Yaş malnütrisyon için bir risk faktörüdür (20). Yaş artışı ve demansa bağlı yeme güçlüklerinin nedenleri arasında tat ve koku almada azalma, diş sağlığında bozulma, görsel işitsel sorunlar ve alet kullanmada güçlük nedeni ile yemek hazırlama yeteneğinde bozulma ortaya çıkar. Ayrıca ilaç yan etkisine bağlı ağız tat değişiklikleri iştahsızlığa yol açar. İlerleyen evrelerde ise disfaji gelişmesi beslenme zorluklarının ana nedenlerindendir (21-23). Çalışmamızda da yaşın artışı ile malnütrisyon arasında ilişki saptanmamışken, düşme riski ile arasında pozitif ilişki ortaya konmuştur. Bu durum çalışma grubumuzun hastalık evresi ve demans tipleri açısından farklı olgulardan oluşmasıyla açıklanmıştır.

Demans hastalarının BOS ve plazmalarında proinflamatuar sitokinlerin arttığına dair çalışmalar mevcuttur ve bunların iştahsızlık ve kilo kaybı ile ilişkili olabileceği düşünülmektedir (24). Kilo kaybı hastalık teşhisinden önce dahi olabilir. Evre ilerledikçe malnütrisyon riski artar. Hafif evrede malnütrisyon gösterilmesinin evre ilerlemesinde öngörücü olabileceği düşünülmektedir (25). Bunun bir sebebi de beyinin yüksek enerji ihtiyacının karşılanamaması ve nörotransmitterler için gerekli yapıtaşlarının beslenme ile sağlanamamasıdır. Kilo kaybı gelişene kadar beslenme yetersizliği fark edilmeyebilir.

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Malnütrisyon mortalite ve morbiditeyi artırarak yaşam kalitesini bozar ve bakıcı yükünü artırır (26). İleri evre demans hastalarında kilo kaybı bağımsız bir mortalite göstergesidir (27).

Çalışmamızda MDÖ ile MNA puanları arasında anlamlı negatif bir korelasyon bulunmuştur. Vücut ağırlık kaybı ileri yaşta kastan kayıp olarak gözlemlenir ve kırılganlığı artırarak düşmede artışa sebebiyet verir (28-29). Bu da beslenme durumu kötüleştikçe düşme riskinin arttığını göstermektedir. Araştırmamızda MDÖ ile polifarmasi arasında anlamlı pozitif bir korelasyon tespit edildi. Bu durum polifarmasisinin düşme riskini artırdığını işaret etmektedir. Kullanılan ilaç sayısının artması morbidite ve mortalitenin bir göstergesi olmakla birlikte düşme riskini de artırmaktadır (16). Çalışmalar psikotroplar dışında diüretikler başta olmak üzere en az bir ilaç dahi fazla kullanımının düşme riskini 2 kat artırdığını göstermiştir (16-17). İlaç sayısı 10 üzerine çıktığında düşme sıklığında %50 artış görülmüştür (30). İlaç-ilaç etkileşimlerinin de düşme riskini artırdığı çalışmalarda gözlenmiştir (31-32).

Çalışmamızın en önemli kısıtlaması sağlıklı kontrol grubunun olmamasıdır. Gelecekte sayıca daha fazla hasta ve kontrol içeren prospektif çalışmalara ihtiyaç vardır.

Çalışmamızda MNA puanları ile polifarmasi arasında da anlamlı bir negatif korelasyon bulundu bu da polifarmasi hastalarında beslenme durumunun daha kötü olduğuna işaret eder. Bu durumun nedenleri arasında en sık ilaçların iştah kapatıcı özellikleri suçlanmaktadır (33).

SONUÇ

Çalışmamızda literatüre benzer şekilde psikotrop ilaç kullanımı ile düşme riski arasında anlamlı bir ilişki saptadık. Ancak ikili araştırmalarda tek antipsikotik kullanan hastalarda antidepresan ve antipsikotik kullanan hastalara göre düşme riski daha yüksek bulduk. Bunun sebebi sayılarının görece az olmasında ya da antidepresan alanlarda antipsikotik dozunun daha düşük tutulması nedeniyle olabilir. Çalışma sonucunda önerimiz maddi manevi yükü fazla olan düşme riskini azaltmak adına daha geniş çalışmalar yapılarak, önleme stratejilerinin geliştirilmesini sağlamak uygun olacaktır. Malnütrisyonu belirlemede kilo tek ölçüt olmamalıdır, düzenli beslenme sorgulaması rutin muayenenin içine eklenmelidir. Olabildiğince polifarmasiden kaçınılmalı, gereği halinde başlanan psikotrop ilaçlar için gereklilik kalktığında kesilme planı yapılmalıdır.

Yazar Katkıları: Çalışma Konsepti/Tasarımı: ÖT, MT, MBÜ, SS, Veri Toplama: ÖT, MBÜ, Veri Analizi/Yorumlama: ÖT, SS, Yazı Taslağı: ÖT, İçeriğin Eleştirel İncelemesi: ÖT, MT, ENS, MBÜ, SS, Son Onay ve Sorumluluk: ÖT, SS, Malzeme ve Teknik Destek: MBÜ, Süpervizyon: ÖT, SS

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ORIGINAL ARTICLE
KLİNİK ARAŞTIRMA

Relationship Between ISX Gene Expression and Cancer Stem Cell Markers in Hepatocellular Carcinoma Cells Exposed to Microenvironmental Changes

Mikroçevre değişimlerine maruz kalan hepatosellüler karsinom hücrelerinde ISX gen ekspresyonu ile kanser kök hücre belirteçleri arasındaki ilişki

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SUMMARY

Aim: This study aimed to demonstrate the homeobox (ISX) protein, which is a newly identified proto-oncogene and known to be associated with hypervitaminosis A disease at the level of ISX gene expression by culturing hepatocellular carcinoma (HCC) cell line in different extracellular matrix media and to show the effect of culture media differences on cancer stem cell markers.

Material and Methods: HepG2 cells were cultured in type I collagen and matrigel culture media, and the expression of the ISX gene was investigated using real-time PCR, and changes in the cellular amounts and localizations of alpha-fetoprotein (AFP), stem cell markers OV-6 and Nanog proteins were investigated using a confocal microscope.

Results: ISX expression was detected 4-fold higher in the Matrigel and 2-fold higher in the type I collagen culture than the control group. The Oct-4 antibody is significantly higher in the type I collagen culture ($p<0.05$) and the Nanog antibody showed a significant decrease in the Matrigel culture than the control group cells ($p<0.05$). Ov-6 and AFP antibodies are the highest type I collagen but there are no statistical significance was found ($p>0.05$).

Conclusion: It is thought that the results obtained from this study may help further studies on the mechanisms of liver cancer and the development of treatment options that will affect the behavior of cancer stem cells.

Keywords: Hepatocellular carcinoma, Vitamin A, ISX gene, Type 1 collagen, Matrigel

ÖZET

Amaç: Bu çalışmada yeni tanımlanan bir proto-onkogen olan ve vücutta çok fazla A vitamini birikmesiyle ortaya çıkan hipervitaminoz A hastalığıyla ilişkili olduğu bilinen homeobox (ISX) proteininin, Hepatoselüler karsinom (HCC) hücre hattının farklı ekstrasellüler matriks ortamlarda kültüre edilmesiyle, ISX gen ekspresyonu düzeyinde gösterilmesi, ayrıca kültür ortam faklılıklarının kanser kök hücre belirteçleri üzerindeki etkisinin değerlendirmesi amaçlanmıştır.

Materyal ve Metodlar: Karaciğer karsinom hücre hattı olan HepG2 hücreler tip I kollajen ve matrigel kültür ortamlarda kültüre edilerek, ISX geninin ekspresyonu real time PCR kullanılarak, alfa-fetoprotein (AFP), kök hücre belirteçleri olan OV-6 ve Nanog proteinlerinin hücresel miktarları ve lokalizasyonlarındaki değişiklikler konfokal mikroskop ile araştırılmıştır.

Bulgular: ISX gen ekspresyonu, kontrol grubuna göre Matrigel kültür ortamda 4 kat, tip I kolajen kültürde ise 2 kat daha fazla tespit edilmiştir. Oct-4 antikorunun ekspresyonu tip I kollajen kültür ortamında kontrol grubuna göre istatistiksel olarak anlamlı derecede yüksektir ($p<0,05$). Nanog antikoru, kontrol grubuna göre Matrigel ortamda HepG2 hücrelerinde anlamlı bir azalma gösterirken ($p<0,05$), Ov-6 ve AFP ekspresyonu en yüksek tip I kollajen ortamda görülmüş ancak istatistiksel olarak anlamlı bir fark bulunmamıştır ($p>0,05$).

Sonuç: Bu çalışmadan elde edilen sonuçların karaciğer kanseri mekanizmaları ve kanser kök hücrelerinin davranışını etkileyecek tedavi seçeneklerinin geliştirilmesi konusunda yapılacak ileri çalışmalara yardımcı olabileceği düşünülmektedir.

Anahtar kelimeler: Hepatoselüler karsinom, A vitamini, ISX geni, Tip1 kollajen, Matrigel

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INTRODUCTION

Hepatocellular carcinoma (HCC) is a liver cancer that has been highly associated with chronic inflammation triggered by environmental toxins or viruses such as HBV/HCV (1) and genetic changes are among the important risk factors for HCC (2).

Vitamin A mostly comes from animal sources (retinoids) and vitamin A precursors (carotenes) in vegetables. Vitamin A is effective in vision, immunity, erythropoiesis, embryogenesis, growth, and development at the same time it is an important antioxidant. In this way, it can increase the activity of detoxifying enzymes that successfully struggle with reactive oxygen species (3). Vitamin A deficiency can occur because of weak dietary intake of fat malabsorption. It has been observed that vitamin A decreases in infections in children. Vitamin A deficiency can cause night blindness, keratinization, and epithelial metaplasia. It is known that the epithelial tissue of the upper respiratory and urinary tracts transforms into keratinous squamous cells in vitamin A deficiency. Hypervitaminosis A disease is seen in vitamin A excess. Excessive accumulation of this vitamin, which can be stored in the body thanks to its fat-soluble, leads to toxic effects (4).

Intestine-specific homeobox (ISX) protein, which is a newly identified proto-oncogene, is known to be associated with hypervitaminosis A disease, which occurs with too much vitamin A accumulation in the body. Homeobox genes have an important role in the growth, differentiation, and morphogenesis of cells in the early embryonic period. As the rearrangement of these genes increases cell survival and proliferation and inhibits cell differentiation, studies have found that homeobox genes are abnormally expressed in a wide variety of human tumor masses. The association of the ISX gene with HCC was proven HCC diagnosed patients who were infected with HBV and/or HCV between 2004 and 2009 (4). Since homeobox genes have been identified in various stages of hepatocellular carcinoma in recent years, it is thought that they may be an important therapeutic target in diagnosing the disease before it progresses (4).

Alpha-feto protein (AFP) is an oncofetal protein synthesized by cells in hepatocellular carcinoma (5), and is the most widely used serum biomarker in the treatment of HCC (6). Studies have shown that when the AFP level in the blood is above 200 ng/ml, the probability of HCC shows a high risk of 90%, and it is understood that high AFP level is a biomarker with high diagnostic value for HCC (5). Ov-6 is one of the important surface markers characterized in many subtypes of liver cancer, especially hepatocellular carcinoma (7). A recent study has shown that HCC cells that are OV6 positive (OV6+) not only have a stronger capacity to form spheroids, but also exhibit stronger tumorigenic and metastatic properties (8).

Nanog is a major transcription factor related to cellular multipotency that plays critical roles in the development of tumor cells (9) and Octamer-binding transcription factor 4 (OCT4), one of the stem cell factors that are essential in embryogenesis and pluripotency (10).

Tumor cells have a highly complex and heterogeneous microenvironment. Type 1 collagen is the most abundant type of collagen in our body and forms an important part of our bones; It is found in blood vessels, cornea, sclera, tendon, ligament, and skin structure. In addition to its structural role, it has a significant growth factor binding capacity, so it plays a role in the homeostasis of the cell by binding to more than one protein. Dysregulation of type 1 collagen in solid tumors affects the behavior of cancer cells. It is known that type 1 collagen also affects metastasis and increases the invasive effect of tumor masses (11).

Matrigel, a basement membrane extracellular matrix, supports the differentiation of many different cell types and the growth of differentiated cells from tissue explants. Cells on or in this matrix associate with each other usually in three dimensions and then form structures similar to those in the tissue of origin (12).

In our study, we aim to show the effect of type 1 collagen associated with HCC on the expression of the ISX gene responsible for vitamin A metabolism by molecular analyses. We also aim to show the changes in the cellular amounts and localization of the oncofetal protein, alpha-fetoprotein (AFP) and the stem cell marker OV-6 and Nanog proteins by confocal microscope.

MATERIAL AND METHODS

Cell Culture and Study Design

The human hepatocellular carcinoma cell line HepG2 which obtained from ATCC (American Type Culture Collection, USA), was used. Cells were cultured in Dulbecco's Modified Eagle's Medium (DMEM) supplemented with 10% fetal bovine serum (FBS) and 1% antibiotics (penicillin streptomycin). Cells that reached 60-70% confluency were treated with trypsin and removed from the culture container, and after cell counting, they were divided into three main culture: Classic culture (control group), type 1 collagen culture and matrigel culture.

In the classic culture, classic HepG2 cell culture was performed, $4x10^5$ cells/well were planted in 6-well culture dishes and $7.5x10^5$ cells/well in 24-well culture dishes with round coverslips.

In the type 1 collagen culture, HepG2 cells were

planted in 6-well plates and 24-well culture dishes with round coverslips, which were coated with 6% diluted Type 1 collagen (Corning brand Collagen Type I) for at least 4 hours before and kept in incubators with 37°C, 5% carbon dioxide. The analyses in the study were carried out in the cells cultured in Type 1 collagen-coated 2-dimensional culture medium.

In the Matrigel culture, Matrigel (Corning-356234) was diluted with DMEM (1/100) at the appropriate concentration (3mg/mL) according to the manufacturer's recommendation, and then pipetted into culture containers on ice using cold pipette tips. Before cell transplantation, the gel was kept in a 37 °C incubator for 30 minutes to allow the gel to solidify. Then, HepG2 cells were cultured by seeding the appropriate number of cells according to the culture dishes (6 and 24-well plates).

The analysis of all of the three groups were carried out in the study when they covered the culture surface by 60-80% (pre-confluent).

Assessment of Morphological Changes

Microscopic Analysis: Three different cell groups, as mentioned above, were seeded on 6 well plates. Live cell images were examined and photographed at 200 and 400 magnifications under an inverted phase microscope (Zeiss-PrimoVert) at 24, 48 and 72 hours. Changes in the live images of HepG2 cells in the culture medium coated with classical, Type 1 collagen and Matrigel were analyzed with an inverted phase microscope and compared with the control group with HepG2 cells in the classical culture medium.

H&E staining: The cells in three separate culture media were seeded on 24-well plate and round coverslips were fixed with the appropriate fixative when they were 60-80% confluent, and after fixation, the cells were stained with Hematoxylin-Eosin dye for morphological examinations. Nucleus structure, acidic, and basic changes of the cytoplasm of cells were evaluated after this staining. According to the cultural environment differences; Nuclear and cytoplasmic changes in cells were demonstrated by staining method. The stained samples were examined and photographed under a light microscope (Zeiss- Primo Star) at 400 magnifications.

Live-cell images were recorded under an inverted phase microscope (Primovert, Zeiss) for the mutual evaluation of microenvironment temperature and CO2 changes for the death and morphology of HepG2 cells at mentioned above time.

Reverse transcription-quantitative polymerase chain reaction (RT-qPCR)

Expression patterns of ISX gene was determined with the LightCycler® 96 System (Roche Life Science). Total RNA was extracted using RNeasy Mini Kit (Qiagen) according to the manufacturer's instructions and quantified by using a Take3 micro-volume plate in a BioTek microplate reader (USA). 500 ng high-quality total RNA was then reverse transcribed using the RT² First Strand Kit (Qiagen). The cDNA was mixed with RT2 SYBR Green Mastermix (Qiagen). RT-PCR experiment was performed under standardized conditions. PCR primers for human IXS, 5'-GATGCGCTGAAGGGATCCTG-3' and 5'-GGCTCAGCCCTTACCAGTTT-3', and for GAPDH, 5'-CGAGGGGGGAGCCAAAAGGG-3' and 5'-GAAACTGCGACCCCGACCGT-3'. Delta delta Ct ($2^{-\Delta\Delta CT}$) relative quantitation method was used for quantitation of qPCR products. All data were normalized to an average of housekeeping gene, GAPDH which showed minimal variation among samples. Bar graph was generated by using GraphPad Prism V.8.0.2 (USA).

Immunocytochemistry Analysis

To show the effect of environmental differences on the expression of stem cell markers Oct-4, Nanog, OV6 and AFP in HepG2 cells cultured in 4 different microenvironments; 7.5x 〖10〗 ^4 cells per well were planted on sterile, round glass coverslips placed in 24-well culture dishes, and when the cells covered the culture surface by 60-80%, they were fixed with 4% paraformaldehyde. Anti Oct-4 antibody (Abcam-Ab19857), anti-Nanog antibody (Abcam-Ab21624), anti OV6 antibody (Abcam- MAB2020) and anti-AFP antibody (BioCare-CP028A) and then labeled with appropriate secondary antibodies (Thermo). The location and changes in expression rate of the relevant antibodies in the cells viewed three-dimensionally under a confocal microscope (Zeiss LSM700) were obtained using the Zen analysis program and the results were evaluated statistically. When starting the staining process for 4 antibodies, the coverslips in the fixative were first washed for 3x5 minutes with Cello-IF solution brought to 37 degrees. Primary antibodies were prepared separately as a 1/50 dilution with Cello-IF solution and treated with the cells and incubated at 37 degrees. Then, the cells were washed with Cello-IF solution brought to 37 degrees for 3x5 minutes. Secondary antibodies specific to the primary antibody were diluted 1/100 with cello-IF solution and incubated in an oven at 37 degrees. After incubation, cells were washed with warm PBS for 3x5 minutes. Covering was performed with Hoescht nuclei dye (Sigma-33258). The preparations were stored in the dark and at +4 degrees until examined under a confocal microscope.

Statistical Analysis

All data are expressed as the mean ± standard deviation. Statistical evaluation was performed by one-way ANOVA test using GraphPad Prism V.8.0.2, and

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one-way analysis of variance and Dunnett's multiple comparative statistical analysis was used for comparison between groups. p<0.05 was considered significant.

RESULTS

Morphological Analysis Results

It is understood that the cells in the classical culture medium in Figure 1 tend to be confluent. It has been determinated that cells in type 1 collagen medium have cytoplasmic extensions, unlike other culture mediums. Thus, it was observed that the cells in the type 1 collagen culture had a spindle structure. It was determined that the morphological structure of the cells in matrigel culture was more oval compared to other culture media.

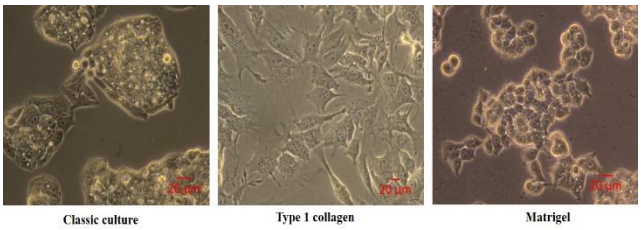

Figure 1. Live images of HepG2 cells in different culture media under an inverted microscope.

HepG2 cells with higher hematoxylin-eosin staining and prominent cell nuclei are observed in the classic culture. When the type 1 collagen culture is examined, it is seen that there is an increase in the cytoplasm/nucleus ratio of HepG2 cells and that the cells have a spindle-like morphological structure considering their cytoplasmic extensions. In Matrigel culture, it is observed that the cytoplasm of HepG2 cells enlarges, eosin staining increases compared to classic culture, and the cells have a morphologically reticulated structure (Figure 2).

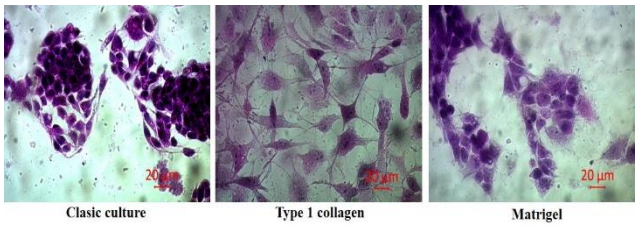

Figure 2. H&E staining images of HepG2 cells in different culture media.

PCR Results

Real-time polymerase chain reaction RT-PCR analysis was performed to show the effect of type I collagen and matrigel culture on ISX gene expression in HepG2 cells compared to the control group HepG2 cells. Compared to the control group, the ISX gene CT values of the cells in our experimental groups with Type I collagen and matrigel were placed into the relative deltadeltaCT (ΔΔCt) formula to determine the increasing or decreasing change., ISX gene expression is 4-fold higher in the culture medium containing Matrigel than in the classic culture (p=0.0394), which is the control group, and 2-fold higher expression of the ISX gene in the type I collagen culture than in the control group (p=0.0042) (Figure 3). The one-way ANOVA, Dunnett's multiple comparisons test, was used for comparison between groups.

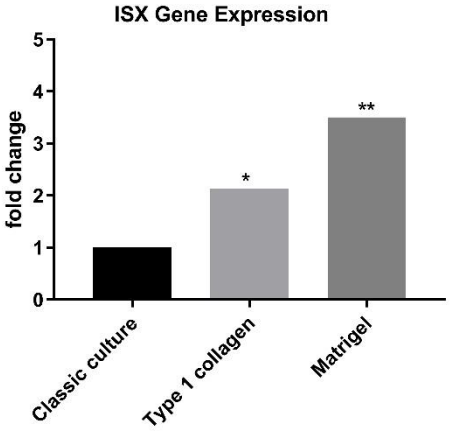

Figure 3. Confocal microscope images of Oct-4 and Nanog proteins in different culture environments of HepG2 cells.

Immunocytochemistry Analysis Results

By immunohistochemical methods, the expression of Oct-4, Nanog, OV6 and AFP in HepG2 cells was performed by examining the preparations prepared according to the above-mentioned protocol under a laser scanning confocal microscope. The localization of the relevant proteins within the cell and the change in their amount were evaluated. The expression of Oct-4 antibody is statistically significantly higher in type I collagen culture medium than in the control group, which is the classical culture medium (p<0.05), and is also higher than in Matrigel medium. Nanog antibody showed a significant decrease in HepG2 cells in Matrigel culture medium compared to control group cells (p<0.05). The expression of OV-6, another stem cell marker, in HepG2 cells was seen in HepG2 cells in the culture medium containing the highest type I collagen. No statistical significance was found (p>0.05). The expression of AFP, a liver cancer marker, is highest in HepG2 cells with type I collagen (p>0.05) (Figure 4). Expression results of four antibodies were analyzed using ANOVA, one-way analysis of variance and Dunnett's multiple comparative statistical analysis on at least two controlled results. Microscopic images of the four antibodies showing their expression in HepG2 cells under a confocal microscope are shown in Figure 5, Figure 6 and Figure 7.

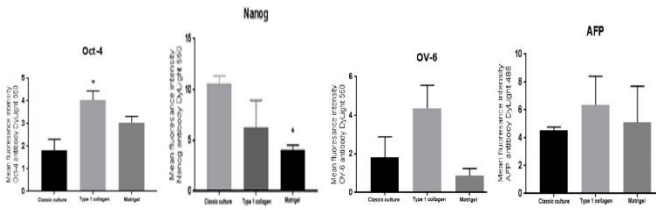

Figure 4. Statistical analysis result according to the results of antibodies measurement in HepG2 cells in different environments.

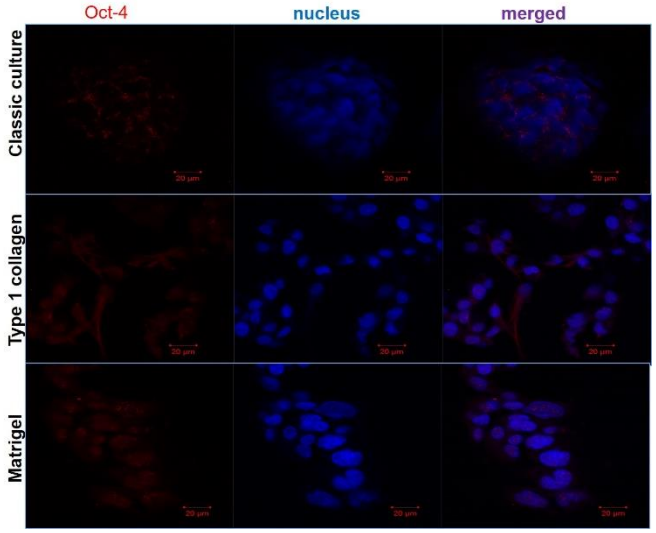

Figure 5. Confocal microscope images of Oct-4 proteins of HepG2 cells in different culture media.

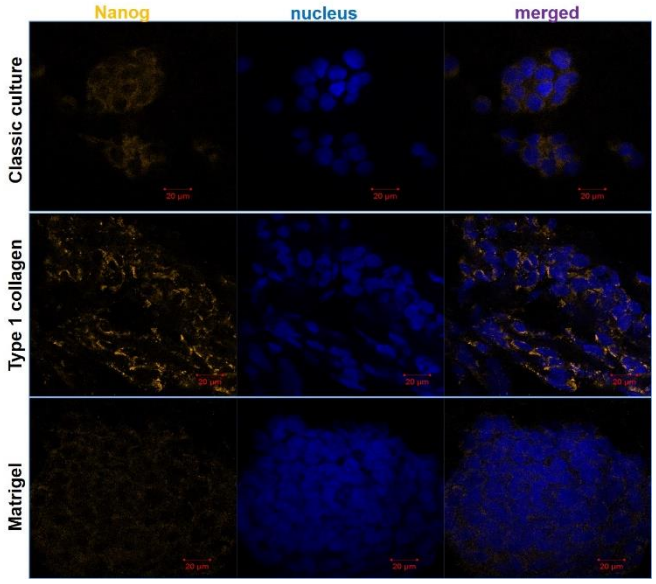

Figure 6. Confocal microscope images of Nanog proteins of HepG2 cells in different culture media.

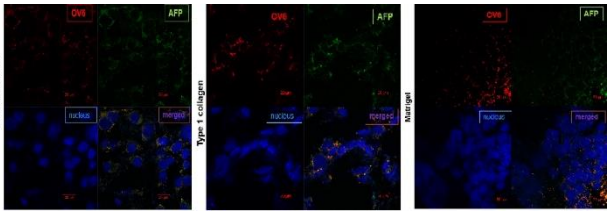

Figure 7. Confocal microscope images of OV6 and AFP proteins of HepG2 cells in different culture media.

DISCUSSION

Intestine-specific homeobox (ISX) proto-oncogene, which is the member of the homeobox gene family, shows a gut-specific expression pattern in both the adult and fetal intestines and it is a newly identified proto-oncogene. It is known to be associated with hypervitaminosis A disease that occurs with too much vitamin A accumulation in the body (4). Since homeobox genes have been identified in various stages of hepatocellular carcinoma in recent years, it is thought that they may be an important therapeutic target in diagnosing the disease before it progresses (13). Tumor cells have a highly complex and heterogeneous microenvironment and cancer-associated fibroblasts are responsible for the formation of this microenvironment (11). Type 1 collagen is the most abundant type of collagen in our body and forms an important part of our bones; It is found in blood vessels, cornea, sclera, tendon, ligament and skin structure. In addition to its structural role, it has a significant growth factor binding capacity, so it plays a role in the homeostasis of the cell by binding to more than one protein. Dysregulation of type 1 collagen in solid tumors affects the behavior of cancer cells. It is known that type 1 collagen also affects metastasis and increases the invasive effect of tumor masses. A study with mice, it was observed that the proliferative property of cells located near type 1 collagen in tumor tissues increased (8). Similarly, the effect of type 1 collagen has been observed in the development of hepatocellular carcinoma due to non-alcoholic fatty liver disease (14). In our study has observed that ISX gene expression both increased in both type 1 collagen culture and matrigel culture. AFP, is an oncofetal protein synthesized by cells in hepatocellular carcinoma (6). Since its discovery, AFP is the most widely used serum biomarker in the treatment of hepatocellular carcinoma (15). In studies, it has been determined that when the level of AFP in the blood is above 200 ng/mL, the probability of HCC is as high as 90% (6). Based on this connection, it is understood that a high AFP level in the blood is a biomarker with high diagnostic value for HCC. In our study has observed that AFP positive cancer stem cell number increased in type 1 collagen culture but decreased in matrigel culture. Another marker, OV-6, has been identified as a surface marker for liver cancer stem cells. It is one of the

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important surface markers characterized in many subtypes of liver cancer, especially hepatocellular carcinoma (8). A recent study showed that HCC cells that are OV6 positive (OV6+) not only have a stronger capacity to form spheroids, but also exhibit stronger tumorigenic and metastatic properties. As a result of this study, it was emphasized that OV6+ HCC cells have high self-renewal and tumor formation abilities (5). As observed in AFP stem cell marker, OV6 positive cancer stem cell number increased in type 1 collagen culture however decreased in matrigel culture dramatically. In our study has shown that ISX expression increased both type1 collagen and matrigel cultures. Nanog is a major transcription factor related to cellular multipotency that plays critical roles in the development of tumor cells, drug resistance, metastasis, it is a very important potantial to therapeutic target for various malignancies incluiding breast, colon, gastric ovarian and liver cancer (5,16-18). Nanog positive cell number effected negativly in both type 1 collagen and matrigel cell culture media. OCT4, one of the stem cell factors that are essential in embryogenesis and pluripotency. OCT4 is overexpressed in CSCs of various cancers. It is very crucial to tumor chemoresistance and prognosis (10). A recent study suggests that OCT4 expression is important for prognostic factors in prostate cancer (19). Also, another study showed that increased expression of OCT4 is associated with low differentiation and significantly correlated with tumor recurrence (20). OCT4 positive cell number both increased in type one collagen culture and matrigel culture.

In summary, our study has shown for the first time the comparative effect of two different extracellular matrix environments on 4 different liver cancer stem cell markers. Changes in ISX gene expression were also observed, but there was no significant relationship between increased ISX expression and increased cancer stem cell expression. Understanding these mechanisms with further studies may help develop treatment options that will affect the behavior of cancer stem cells, which are known to affect cancer prognosis and spread.

CONCLUSION

Our study showed that the behavior of liver cancer cells can be affected by extracellular matrix components. In addition to enhancing the effect of extracellular matrix on ISX gene expression, it was determined that type I collagen also significantly affects the expression of stem cell proteins. These results obtained from this study may help further studies on liver cancer mechanisms and the development of treatment options that will affect the behavior of cancer stem cells.

Author Contributions: Working Concept/Design: HS, ZG, ZA, Data Collection: HS, ZG, GD, ZA, Data Analysis / Interpretation: GD, ZA, Text Draft: HS, ZG, Critical Review of Content: HS, Last Proof and Responsibility: ZA, Supervision: ZA.
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ORIGINAL ARTICLE
KLİNİK ARAŞTIRMA

Intracardiac masses in our routine practice: Evaluation with the literature

Rutin patoloji pratiğinde sık karşılaşılan intrakardiyak kitleler: Literatür eşliğinde değerlendirme

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SUMMARY

Aim: Cardiac masses are rare and may be either neoplastic or non-neoplastic. This study aims to provide a comprehensive overview of cardiac masses and to evaluate their clinicopathological features.

Material and Methods: We retrospectively analyzed 35 cases of cardiac surgery performed at our institution between 2014 and 2022 for the presence of a cardiac mass.

Results: The patients' ages ranged from 7 months to 79 years (mean: 46.2 years), with a female-to-male ratio of 25:10. Primary benign cardiac tumors comprised the majority of cases. Myxoma was the most frequently observed tumor, followed by papillary fibroelastoma, fibroma, rhabdomyoma, and glomus tumor. Two cases of metastatic carcinoma were also identified. Non-neoplastic lesions were also common and included thrombus, calcified cardiac pseudotumor, and infective endocarditis, listed in decreasing order of frequency.

Conclusion: This study presents the clinical distribution and pathological characteristics of various cardiac masses observed in our institution, based on a relatively large case series.

Keywords: Cardiac masses, neoplastic, non-neoplastic lesions

ÖZET

Amaç: Kardiyak kitleler nadirdir, neoplastik ve non-neoplastik olarak ayrılmaktadır. Bu makalenin amacı kardiyak kitlelere genel bir bakış sağlamak ve klinikopatolojik özelliklerini gözden geçirmektir

Materyal ve Metodlar: Merkezimizde 2014-2022 yılları arasında kardiyak kitle nedeniyle opere edilen 35 vakayı retrospektif olarak inceledik.

Bulgular: Vakaların yaşları 7 ay ile 79 yıl arasında değişmektedir (ortalama yaş 46,2 yıl) ve 25'i kadındır. Serimizin büyük bir kısmını primer benign kalp tümörleri oluşturmaktadır ve en sık görülen tümöral lezyon miksoma olup, bunu sırasıyla fibroelastom, fibroma, rabdomyom ve glomus tümör izlemektedir. İki vaka metastatik karsinom tanılıdır. Non-neoplastik kitle lezyonları da çoğunlukta olup insidansına göre trombüs, kalsifiye kardiyak psödotümör ve infektif endokardit olarak sıralanmaktadır.

Sonuç: Bu çalışmada, çeşitli kardiak kitlelerin klinikopatolojik bulgularının bir arada değerlendirildiği geniş bir vaka serisi sunulmaktadır.

Anahtar kelimeler: Kardiak kitleler, tümörler, tümör dışı lezyonlar

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INTRODUCTION

Cardiac masses are uncommon, but they are significant causes of morbidity and mortality, as any intracardiac mass may lead to considerable hemodynamic or electrical disturbances (1). The clinical presentation is highly variable, generally depending on the location and size of the mass, and some lesions may also produce systemic symptoms (2). The main symptoms include sudden death, chest pain, heart failure, superior vena cava syndrome, valvular abnormalities, arrhythmias, and dyspnea. However, many cardiac tumors remain asymptomatic and are incidentally discovered (3).

Cardiac masses are broadly classified as neoplastic or non-neoplastic. Non-neoplastic lesions include thrombi, vegetations, calcific lesions, and rarer entities such as pericardial cysts. Neoplastic lesions are further divided into primary (benign or malignant) and metastatic tumors (4). Although myxoma was historically the most common primary benign cardiac tumor, papillary fibroelastoma (PFE) has become more frequently diagnosed in recent years, likely due to advancements in high-resolution imaging techniques (5). The most common primary malignant cardiac tumors are angiosarcoma, undifferentiated pleomorphic sarcoma, myxofibrosarcoma, and leiomyosarcoma. Unlike primary malignant tumors, metastatic involvement of the heart is relatively frequent (6).

Some non-neoplastic lesions—such as thrombi and infective endocarditis—can closely mimic true neoplasms, particularly myxomas (7). Given the rarity of both neoplastic and non-neoplastic cardiac masses, their evaluation often presents a diagnostic challenge. In this study, we aimed to retrospectively review the clinical, demographic, and pathological characteristics of cardiac masses encountered in our department.

MATERIAL AND METHODS

Cases with a preoperative diagnosis of cardiac mass that were surgically excised between 2014 and 2022 and subsequently diagnosed in our department were identified through archival review. Demographic and clinical data of the patients were retrieved from the hospital information system.

All specimens were fixed in formalin, routinely processed, and stained with hematoxylin and eosin. While some cases were diagnosed based solely on light microscopic evaluation, histochemical stains (such as Periodic acid-Schiff, Alcian Blue, and Masson Trichrome) and immunohistochemical studies were performed when necessary for diagnostic clarification.

This study was approved by the Ethics Committee of Istanbul Medipol University (Decision date: 16.03.2023, Decision No: E-10840098-772.02-1984) and conducted in accordance with the principles of the Declaration of Helsinki.

RESULTS

Over an 8-year period, a total of 35 cases were identified. Of these, 25 patients were female and 10 were male. The ages ranged from 7 months to 79 years, with a mean age of 46.2 years. The most common presenting symptom was dyspnea, while chest pain, syncope, fatigue, palpitations, fever, nausea, and vomiting were observed less frequently.

In our series, 24 cases were classified as neoplastic and 11 as non-neoplastic. Myxoma was the most frequently encountered neoplastic mass, whereas thrombus was the most common non-neoplastic lesion. Other neoplastic masses included papillary fibroelastoma (PFE), fibroma, rhabdomyoma, and glomus tumor. Additional non-neoplastic lesions were calcified amorphous pseudotumor (CAPT) and infective endocarditis (IE). Two patients were diagnosed with secondary (metastatic) cardiac tumors.

The distribution of diagnoses, clinical features, and basic histopathological findings is summarized in Table 1.

Myxomas were predominantly located in the left atrium; only one female patient had a tumor in the right atrium. Clinically, this patient did not exhibit any symptoms different from those seen in other myxoma cases. No familial myxoma cases were identified in our series. Histologically, all myxomas showed fusiform and polygonal cells embedded in an amorphous myxoid stroma (Figure 1).

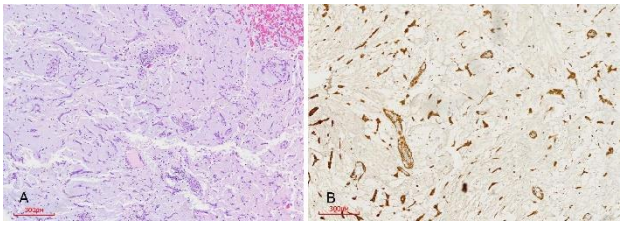

Figure 1. Myxoma; A) Myxoma cells in cord structure or around blood vessels. B) Calretinin positivity

Five cases were diagnosed as papillary fibroelastoma (PFE). In one patient, the mass was discovered during the evaluation of cardiac etiology following a cerebrovascular event. Histological sections of all cases revealed papillary structures with acellular, avascular stroma, covered by a single layer of endocardial cells (Figure 2).

Only one case of rhabdomyoma was detected. A baby girl was delivered via cesarean section after a cardiac mass was identified during the prenatal period. She was admitted to our hospital 20 hours after birth. Histopathological

Table 1. Distribution of diagnosis and clinicopathologic features.

	Number (%)	Age range	Gender F/M	Symptoms	Diameter of the mass	Localisation	Basic morphologic findings
Non-neoplastic	11 (33.4%)						
Thrombus	7 (21.2%)	4-74 (34.6)	5/2	Dyspnea, chest pain, weakness	Varying between 1.5 cm and 5 cm	Right atrium (6 case) Left atrium (1 case)	Hemorrhagic areas, fibrin accumulations
Calcified amorf pseudotumor	2 (6.1%)	66 and 79	2/0	Fainting	1 cm and 3.5 cm	Right ventricle and right atrium	Nodular calcification, eosinophilic amorphous material
Infective endocardit	2 (6.1%)	7 months and 51 years	1/1	Fever	2 cm and 3 cm	Right atrium and tricuspid valve	Numerous bacterial colonies and neutrophils enmeshed in fibrin
Neoplastic	24 (68.6%)						
Primary benign tumors	22 (62.8%)						
Myxoma	13 (37.2%)	38-74 (55.1)	11/2	Dyspnea, palpitations, dizziness, fatigue	Varying between 3 cm and 6 cm	Left atrium (12 case) Right atrium (1 case)	Stellate, ovoid, or spindle-shaped cells in abundant matrix. Hemosiderin-laden macrophages, hemorrhage, fibrinoid necrosis and inflammatury cells in the stroma
Papillary fibroelastoma	5 (14.3%)	35-57 (45)	3/2	Dyspnea, chest pain	Varying between 0.6 cm and 2 cm	Left artium (1 case) Tricuspit valve (1 case) Mitral valve (3 case)	Numerous branching papillary fronds, each fronds composed of an avascular core of hyalinized hypocellular stroma with elastic fibers
Fibroma	2 (5.7%)	1 and 10 months	1/1	murmur and echocardiography abnormality	2.5 cm and 4.8 cm	Right ventricle and right atrium	Spindle cells in a collagenous background
Rabdomyoma	1 (2.8%)	1 months	1/0	Detected in the intrauterine period	4 cm	Right ventricle	Large vacuolated cells with abundant glycogen so called spider cells
Glomus tumour	1 (2.8%)	57	1/0	chest pain	3.5 cm	Right ventricle	composed of 3 components: glomus cells, vasculature, and smooth muscle cells
Secondary tumors (metastasis)	2 (5.7%)						
Metastatic carcinoma	2 (5.7%)	65 and 78 years	0/2	Detected during scanning	4.5 cm and 3.5 cm	Right atrium and right ventricle	malignant epithelial tumor with glandular differentiation or mucin production
Total	35 (100%)		25/10				

examination showed large, polygonal, clear cells containing glycogen vacuoles. No mitotic figures were observed. Immunohistochemically, the tumor cells were positive for smooth muscle actin (SMA) and desmin. Histochemically, intracytoplasmic positivity with periodic acid-Schiff (PAS) was also noted (Figure 3). Unfortunately, the patient died 10 days postoperatively due to sepsis.

Two cases of fibroma were identified in infants. One was a 10-month-old infant who presented with vomiting. A cardiac murmur was detected during examination, and echocardiography revealed a 2.5 × 2.5 cm mass in the right atrium. The other was a 34-day-old infant with a 4.8 × 4.4 cm mass originating from the right ventricular wall, as shown on echocardiography. In both cases, microscopic examination confirmed fibroma, composed of spindle cells in a collagenous stroma. Immunohistochemically, smooth muscle actin (SMA) showed a tram-track pattern of

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positivity. Masson's trichrome staining demonstrated a clear boundary between the fibroma (blue) and the adjacent normal myocardium (red) (Figure 4).

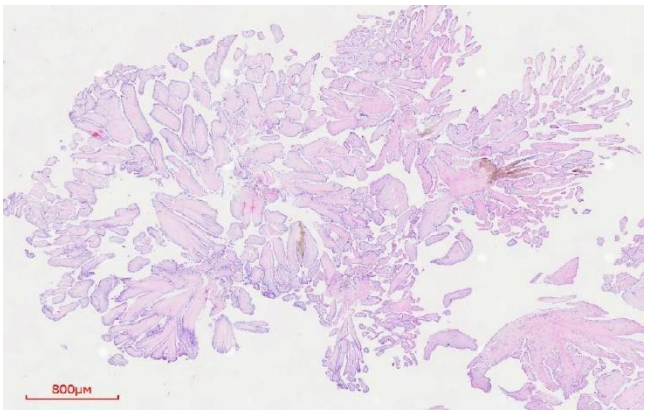

Figure 2. Papillary fibroelastoma; Avascular tumor fronds growing into a cardiac chamber.

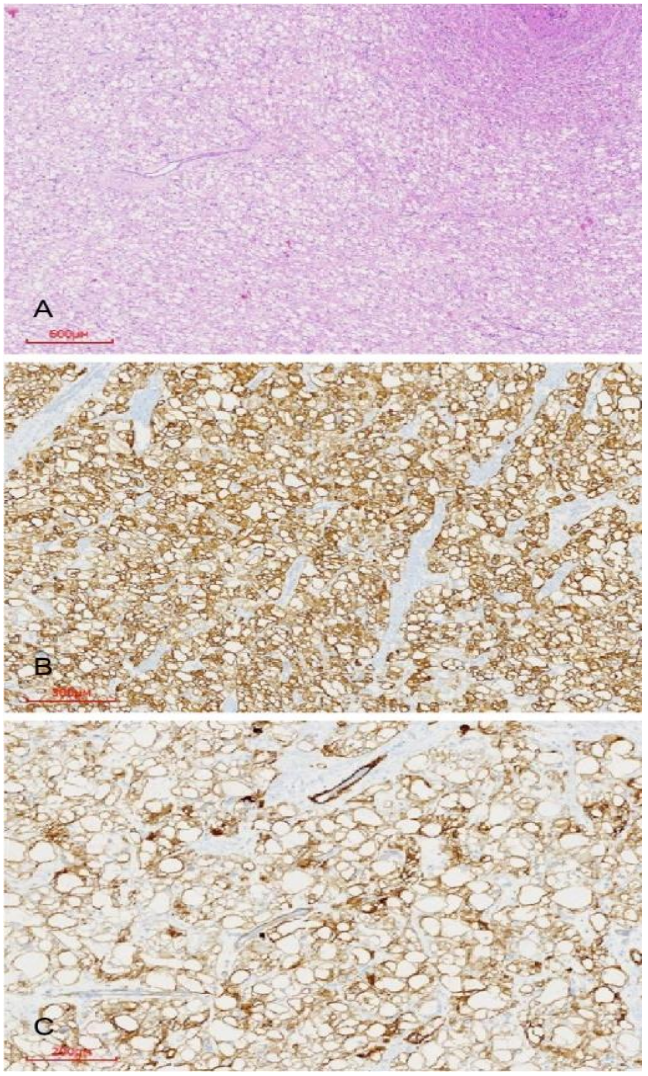

Figure 3. Rhabdomyoma; A) The tumor is composed of a uniform population of round and polygonal cells with focal cytoplasmic vacuolization. B) SMA C) Desmin.

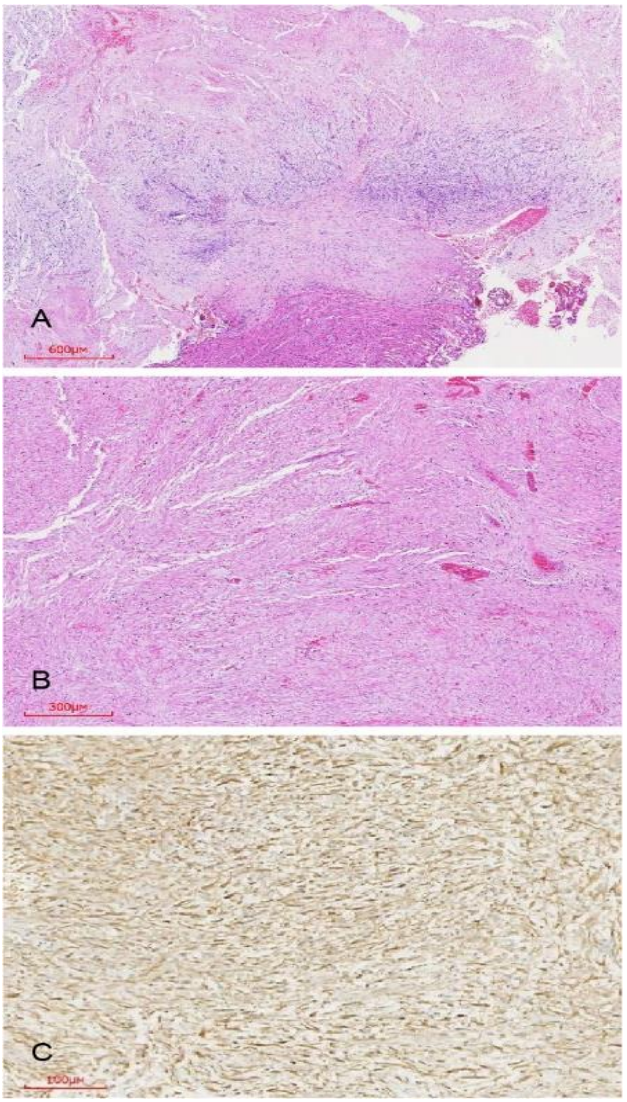

Figure 4. Fibroma; A-B) Cardiac fibromas are composed of bland fibroblastic cells in a dense collagenous stroma. C) Immunohistochemical SMA positivity in the tumor.

A 57-year-old female patient was diagnosed with a glomus tumor. She presented with chest pain, and a mass was subsequently detected at the outflow tract of the right ventricle. The mass, measuring 3.5 × 2.5 × 1.5 cm, was excised with a preliminary diagnosis of myxoma. Grossly, the tumor appeared semisolid and was encapsulated. Histological examination revealed a well-circumscribed lesion composed of glomus cells, endothelial cells, and smooth muscle cells. Immunohistochemically, endothelial cells were positive for CD34, glomus cells were positive for smooth muscle actin (SMA), while CD31 was negative. Ki-67 staining showed no proliferative activity, and no necrosis was observed. These features were consistent with a diagnosis of glomus tumor (Figure 5).

Thrombus was diagnosed in seven patients. Six of them had right atrial masses, and one had a left atrial mass. Two of these patients had an initial clinical diagnosis of myxoma. All patients had underlying medical conditions,

including chronic renal failure (2 patients), nephrotic syndrome (1 patient), oral contraceptive use (1 patient), congestive heart failure (1 patient), history of atrial septal defect repair (1 patient), and coronary artery stenting (1 patient). Histologically, the thrombi were composed predominantly of fibrin/platelet aggregates, red blood cells, and white blood cells (Figure 6).

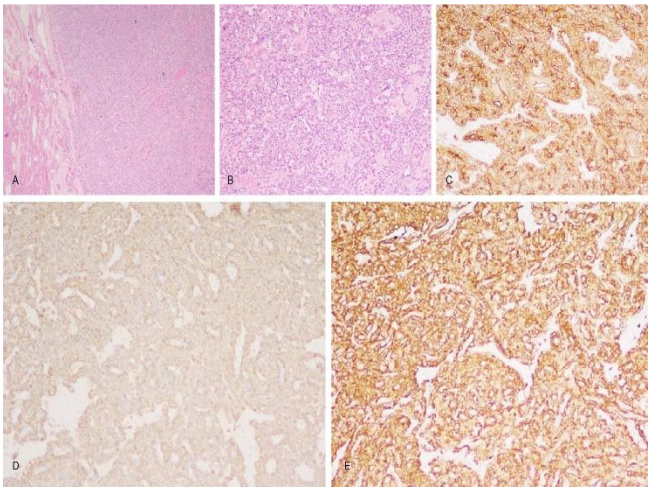

Figure 5. Glomus tumour; A-B) The tumour well circumscribed and show sheets of cells. The tumor cells are round and regular with uniform circular nuclei. C) CD34 (X100), D) SMA (X100) E) CALDESMON (X100).

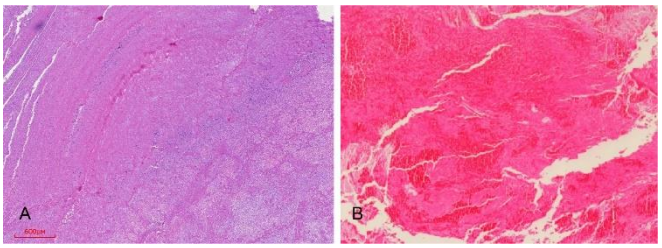

Figure 6. Thrombus; A-B) well-organized thrombus with centrally located red blood cells/hemorrhagic areas (arrows) and surrounding fibrin accumulations (dotted arrows).

Calcified amorphous pseudotumor (CAPT) of the heart was identified in two female patients aged 66 and 79, both of whom presented with syncope. Histopathological examination of the lesions revealed nodular calcium deposits embedded within fibrinous material (Figure 7).

Infective endocarditis was diagnosed in two patients. In the first case, a 7-month-old infant presented with persistent high fever. Imaging revealed an intracardiac mass, and follow-up echocardiography showed an increase in the size of the mass, which began to prolapse through the tricuspid valve. Blood cultures grew coagulase-negative Staphylococcus. Microscopic examination demonstrated bacterial colonies embedded in fibrin, and a diagnosis of acute bacterial endocarditis was made.

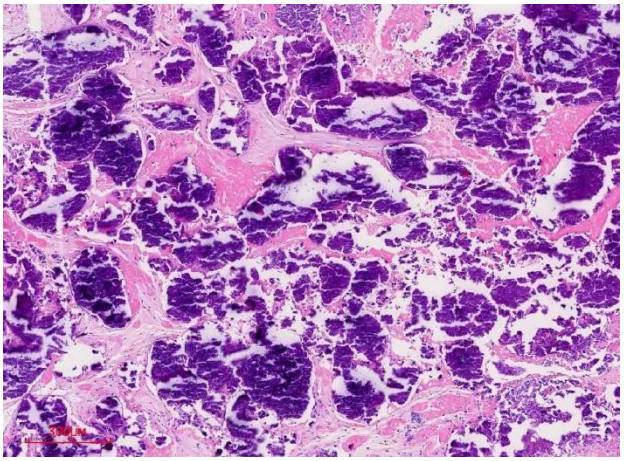

Figure 7. Calcified amorphous tumor; Nodular calcified amorphous debris with admixed degenerated fibrin.

The second case involved a 56-year-old female patient with a history of chronic myeloid leukemia that had transformed into acute myeloid leukemia. During follow-up, a 2 × 2 cm mobile mass was detected on the tricuspid valve. Blood cultures repeatedly yielded Klebsiella species. A diagnosis of infective endocarditis was confirmed based on histopathological findings and positive blood culture results (Figure 8).

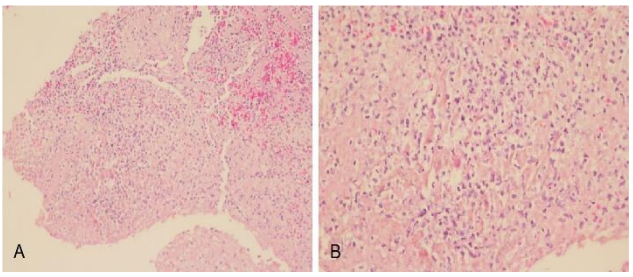

Figure 8. Infective endocardit; A-B) neutrophils, fibrin and bacterial colonies.

Two cases of metastatic carcinoma were identified in this series. The first case involved a 65-year-old male patient with a known diagnosis of colon carcinoma. During follow-up, a mass was detected in the right atrium along with a thrombus in the inferior vena cava. Surgical resection of the right atrial tumor and excision of the inferior vena cava thrombus were performed. Microscopically, the tumor displayed cribriform glands filled with necrotic debris. Immunohistochemically, the tumor was negative for CK7, showed focal positivity for CK20, and was diffusely positive for CDX2, supporting the diagnosis of metastatic colon carcinoma.

The second case was a 78-year-old male patient who presented with sudden loss of consciousness. Imaging revealed masses in both the brain and the lung, as well as a right ventricular mass, which was initially presumed to be a thrombus and surgically excised. Histopathological examination revealed solid adenocarcinoma composed of

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sheets of neoplastic cells containing intracytoplasmic mucin. Immunohistochemically, the tumor was positive for CK7 and negative for CK20 and TTF-1. These findings suggested a pulmonary primary tumor. Notably, in this case, the initial diagnosis of malignancy was established based on the cardiac mass (Figure 9).

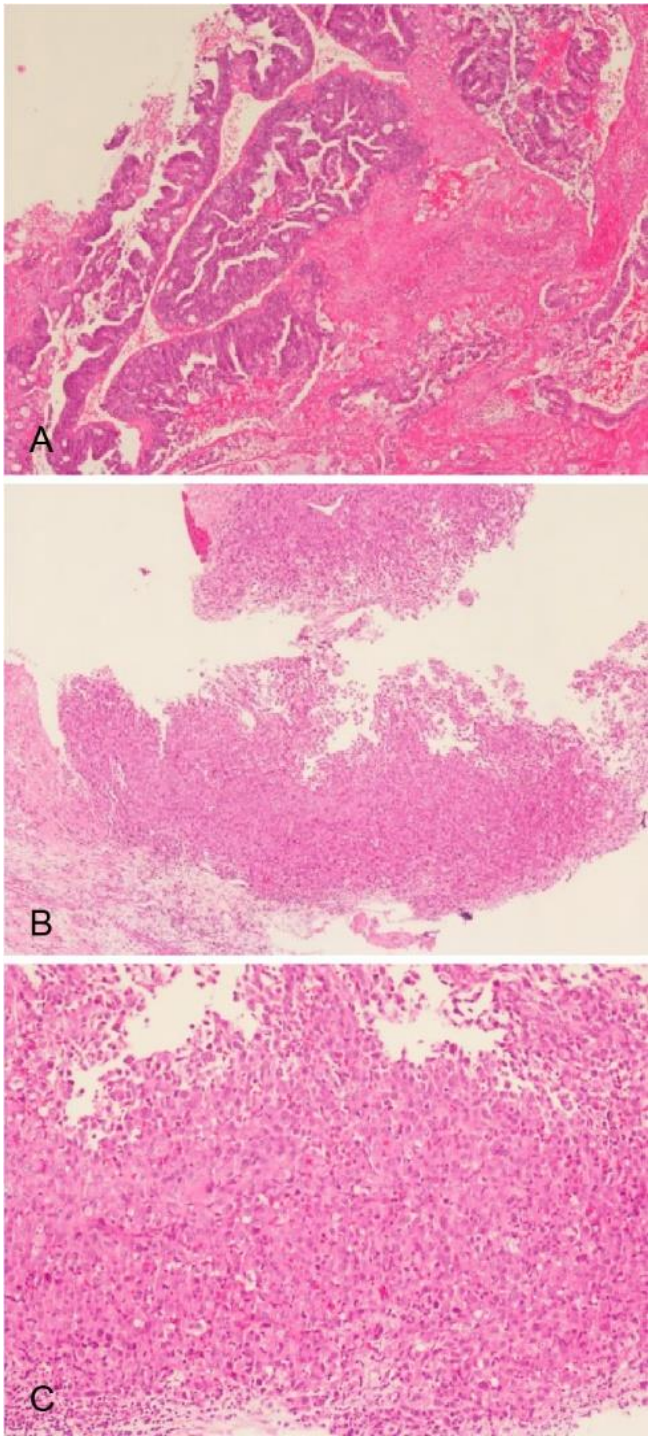

Figure 9. Metastatic carcinoma: A) colorectal cancer is a well-to-moderately differentiated adenocarcinoma consisting of tubuler, anastomosing and branching glands. B-C) Metastatic solid adenocarcinoma.

DISCUSSION

Cardiac masses include primary benign and malignant tumors, secondary (metastatic) tumors, and tumor-like non-neoplastic lesions (2). Primary cardiac tumors are rare, while metastatic tumors are reported to be 20 to 30 times more common than primary ones (8). The vast majority of primary cardiac tumors are benign. Although myxoma was historically considered the most common primary cardiac tumor, papillary fibroelastoma (PFE) is now recognized as more prevalent due to improved imaging techniques (5). Non-neoplastic lesions—such as thrombi, hamartomas, and reactive proliferations—can mimic neoplastic processes both clinically and pathologically (4).

Cardiac myxomas typically occur in middle-aged women and most commonly originate from the interatrial septum. The most frequent site of involvement is the left atrium, followed by the right atrium and ventricles (2,9). In our study, the number of female patients was five times higher than that of males. The majority of myxomas were located in the left atrium, consistent with the literature, with only one case identified in the right atrium. Left atrial myxomas may cause mitral valve obstruction, leading to symptoms such as dyspnea and orthopnea. In line with this, the main presenting symptom in our series was dyspnea.
In contrast, right atrial myxomas may present with signs of right-sided heart failure (10). Additionally, cardiac myxomas can initially manifest with embolic complications, such as stroke, syncope, chest pain, limb ischemia, or soft tissue masses in the distal extremities (11). In our series, one patient was diagnosed with a 5.5 × 2.5 cm left atrial mass during evaluation for stroke etiology, which was confirmed as a myxoma following surgical excision.

On microscopic examination, cardiac myxomas are characterized by stellate, ovoid, or spindle-shaped cells—referred to as myxoma cells—embedded in a vascular myxoid stroma. These cells may appear singly or in clusters. When clustered, they can form cords, nests, or ring-like structures. This histological feature is considered pathognomonic and is particularly helpful in differentiating myxomas from organizing thrombi. The stroma often shows prominent hemorrhage, hemosiderin-laden macrophages, fibrinoid necrosis, and inflammatory infiltrates. Thick-walled vessels, usually one or two, are commonly seen at the base of the lesion (9).

In our series, ring structures were identified in 41.6% of cases during microscopic evaluation. No mitotic figures were observed; however, the presence of mitosis should raise suspicion for malignancy. Cardiac myxomas can be readily diagnosed based on their typical histopathological features and classical anatomical locations. For confirmation, we used calretinin immunohistochemistry, which is strongly and diffusely positive in myxomas. Calretinin is a valuable marker for differentiating myxomas

from myxosarcomas, which are typically negative (12).

Approximately 90% of cardiac myxomas occur sporadically, while about 10% arise as part of Carney complex—a hereditary syndrome characterized by cardiac and extracardiac myxomas, endocrine abnormalities such as Cushing's syndrome or acromegaly, and spotty skin pigmentation (9). All of our cases were sporadic; no familial or syndromic cases were identified.

Cardiac papillary fibroelastoma (PFE) is now recognized as the most common primary cardiac tumor. There are various theories regarding its etiology, including hypotheses that PFEs may represent true neoplasms, hamartomas, reactive proliferations, organizing thrombi, or posttraumatic lesions. Although PFE was historically considered a tumor-like lesion, recent studies have demonstrated that a subset of PFEs harbour canonical oncogenic driver mutations, particularly in the KRAS gene, supporting their neoplastic nature (13).

PFEs most frequently arise from the valvular endocardium (80–90%), with the aortic valve being the most common site, though they may also originate from other endocardial surfaces within the atria and ventricles (14). In our series, three cases involved the mitral valve, one the aortic valve, and one the tricuspid valve. Three of the patients were female and two were male. The most common presenting symptom was dyspnea; one patient also experienced chest pain.

In two retrospective studies, neurological symptoms—particularly transient ischemic attacks or strokes—were reported as the most frequent clinical presentations, occurring in approximately 30% of patients with PFE (14,15). Similarly, one of our patients presented with syncope and was diagnosed with cerebrovascular disease. Further investigation revealed a 2 × 2 cm mass in the left atrium, which was diagnosed as PFE after surgical resection. In contrast, PFEs may be detected incidentally in up to one-third of patients (4).

Microscopically, PFEs are characterized by multiple branching, leaf-like projections composed of avascular fibroelastic tissue, lined by a single layer of endocardial cells (16). All cases in our series exhibited these typical histological features.

Rhabdomyomas are the most common benign pediatric cardiac tumors, followed by cardiac fibromas (17). Both may occur sporadically or in association with tumor syndromes—particularly tuberous sclerosis for rhabdomyomas and Gorlin syndrome for fibromas (18,19). In our series, there were five pediatric cases, including one rhabdomyoma and two fibromas. None of the patients exhibited features suggestive of an underlying tumor syndrome.

Cardiac rhabdomyomas are composed of large, vacuolated cells rich in glycogen, often referred to as "spider cells." This appearance is due to a centrally located nucleus from which myofibrils radiate toward the cell membrane. These cells are strongly positive with periodic acid–Schiff (PAS) staining due to their glycogen content.

Cardiac fibromas consist of monomorphic fibroblasts exhibiting minimal or no atypia. The tumor margins tend to infiltrate into the adjacent myocardium. Cellular density typically decreases with the patient's age, while the amount of collagen increases. Mitotic activity is generally observed only in tumors occurring during infancy. Additionally, occasional perivascular lymphocytic and histiocytic aggregates or mild chronic inflammation may be present at the interface between the tumor and uninvolved myocardium (20).

Glomus tumors are rare, benign vascular neoplasms of smooth muscle cell origin, most commonly found in the skin. They can be subclassified into solid glomus tumors, glomangiomas, or glomangiomyomas, depending on the proportion and arrangement of vascular structures, smooth muscle cells, and glomus cells (21). When severe cytologic atypia, increased mitotic activity (>5 mitoses per 50 high-power fields), or atypical mitoses are present, the lesion is designated as a malignant glomus tumor (glomangiosarcoma) (22).

To date, only nine cases of cardiac glomus tumors have been reported in the literature. The first case was described by Masson in 1924 (23). Among these, seven were benign and two were malignant (22,24). In one case, multiple foci of cardiac glomus tumors were identified (21). Our case likely represents the tenth reported case of an intracardiac glomus tumor in the literature.

Thrombus is one of the most common types of cardiac masses and may clinically mimic primary cardiac neoplasms such as myxomas (25). It may also coexist with neoplastic cardiac masses (26). Thrombi are composed of variable amounts of erythrocytes, fibrin, and platelets, and can either adhere to the endocardial surface or float freely within the cardiac chambers. They are frequently associated with structural heart disease or the presence of intracardiac devices.

Calcified amorphous pseudotumor (CAPT) of the heart is a rare entity. Histologically, it consists of calcification and eosinophilic amorphous material within a dense collagenous fibrous background. Some reports suggest that CAPT may represent a calcified stage of an organizing thrombus, indicating that these two entities could be part of the same pathological spectrum (4).

In our series, thrombus was the most common non-neoplastic lesion. Seven cases were diagnosed as thrombus, and two as CAPT. Clinical evaluation for thrombus etiology revealed several associated conditions, including nephrotic syndrome, oral contraceptive use,

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congestive heart failure, prior coronary stent placement, and a history of atrial septal defect repair.

Infective endocarditis (IE) is an infection of the endocardial surfaces of the heart and is considered a potentially life-threatening condition. Radiologically, IE can mimic a cardiac mass. It has been reported that IE most commonly resembles cardiac myxoma, and in some cases, myxomas may be misdiagnosed as infective endocarditis. However, histological evaluation allows for a clear distinction between these two entities (27).

Recognized risk factors for IE include a history of prior infective endocarditis, the presence of prosthetic heart valves or intracardiac devices, valvular or congenital heart disease, intravenous drug use, indwelling intravenous lines, immunosuppression, and recent dental or surgical procedures (28).

In our series, two patients were diagnosed with infective endocarditis, one of whom was immunosuppressed due to acute myeloid leukemia.

Metastatic tumors are significantly more common than primary cardiac tumors (29). However, the exact incidence of cardiac metastasis remains uncertain, as it is mostly derived from autopsy studies. This is likely because cardiac metastases often occur in the setting of advanced (stage IV) disease, and many patients die before a cardiac metastasis is clinically diagnosed (30). The most common primary sources of cardiac metastasis are lung carcinomas (35–40%) and breast carcinomas (approximately 10%), followed by hematologic malignancies (10–20%) (31). Colorectal cancer rarely metastasizes to the heart; its prevalence in autopsy series ranges from 1.4% to 2%, and when it does occur, it most commonly involves the pericardium. In our series, two cases of metastatic carcinoma were identified: one was metastatic colon adenocarcinoma, and the other was a poorly differentiated adenocarcinoma, likely of pulmonary origin.

A multicenter study from Turkey reported 40 cases of cardiac masses over a 10-year period, of which 35 were benign (including benign tumors and hydatid cysts), and 5 were malignant (32). In that study, myxoma was the most common benign tumor, but the presence of hydatid cysts was also noteworthy. Among the malignant lesions, there were two cases of lymphoma, one angiosarcoma, one leiomyosarcoma, and one metastatic squamous cell carcinoma.

In the present study, we retrospectively analyzed 35 consecutive cases of cardiac masses. To the best of our knowledge, this constitutes one of the largest single-center series to date that includes such a diverse range of neoplastic and non-neoplastic cardiac lesions.

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