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Atopik Dermatit Güncel Patofizyolojisi

Current Patophsigology of Atopic Dermatitis

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ÖZET

Atopik dermatit (AD); en sık görülen kronik, kaşıntılı, inflamatuar deri hastalığıdır. Genetik ve çevresel faktörlerin etkisiyle deride meydana gelen hastalık, genellikle bebeklik döneminden itibaren bulgu vermeye başlar. Egzema , enfeksiyonlar, kaşıntı, kaşıntıya bağlı ortaya çıkan uyku bozuklukları hastaların hayat kalitesini doğrudan ve olumsuz etkilemektedir. AD tanı ve tedavisi eşlik eden/edebilecek komorbiditeler nedeniyle multidisipliner bir yaklaşımla ele alınmalıdır. Bu yazıda AD patofizyolojisini güncel çalışmalarla ve son verilerle ortaya koyarak tartışmayı amaçlıyoruz.

Anahtar Kelimeler: *Atopik, dermatit, patofizyoloji*

ABSTRACT

Atopic dermatitis (AD); is the most common chronic, itchy, inflammatory skin disease. The disease that occurs on the skin under the influence of genetic and environmental factors, usually begins to show symptoms from infancy. Eczema, itching, infections and sleep disorders caused by itching directly and negatively affect the quality of life of patients. Diagnosis and treatment of AD should be handled with a multidisciplinary approach. We aim to discuss the pathophysiology of AD by presenting current studies and latest data.

Keywords: *Atopic, dermatitis, pathophysiology*

GİRİŞ

Atopik dermatit (AD), en sık görülen kronik, kaşıntılı, inflamatuar deri hastalığıdır (1). Genetik ve çevresel faktörlerin etkisiyle ortaya çıkar. Genellikle bebeklik döneminden itibaren bulgu vermeye başlar. Egzema, enfeksiyonlar, kaşıntı, kaşıntıya bağlı ortaya çıkan uyku bozuklukları; atopik yürüyüş içerisindeki diğer alerjik hastalıklar kişinin hayat kalitesini doğrudan ve olumsuz etkilemektedir. Epidermal bariyerdeki fonksiyon bozukluğu, oluşan ve derinleşen inflamasyon ağı kuruluk-kaşıntı kısır döngüsü oluşturur.

Dermatoloji, alerji-immünoloji, pediatri ve dahiliye gibi birçok branşı ilgilendiren atopik dermatit; son yıllarda daha sık karşılaştığımız kronik bir rahatsızlıktır. Eşlik edebilen diğer alerjik rahatsızlıklar ve enfeksiyonlar birlikte düşünüldüğünde hasta yönetiminin multidisipliner bir yaklaşımla ele alınması gerekmektedir.

AD prevalansı; yüksek gelir düzeyi olan ülkelerde çocukların yaklaşık %20'sini, erişkinlerin %10'unu etkilemektedir (2). Farklı coğrafyalarda prevalans %0,2 ile %36 arasında değişmektedir. Amerika'da AD hastalarının yaklaşık %50'si ilk basamakta tedavi edilmektedir, bu yüzden birinci basamak sağlık hizmeti sunan yerlerde prevalans daha yüksek olabilmektedir. Yapılan kapsamlı bir anket çalışması; Amerika'da AD prevalansının küresel verilerle uyumlu olarak %9-18 olduğunu göstermiştir (3). AD'li çocukların %60'ında semptomlar yaşamın ilk yılında ortaya çıkmaktadır ve pediatrik vakalarda hafif kız cinsiyet hakimiyeti olduğu bulunmuştur (3,4).

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Patogenez

AD patogenezindeki temel nokta epidermal bariyerdeki disfonksiyondur. Deri bariyerinin bozulması; derinin hızlıca kurumasına, oluşan kuruluk da kaşıntıya yol açmaktadır. Kaşınan deri daha da kurur ve tekrarlayan kaşıntıya yol açar, bu sebeple hastalarda kuruluk-kaşıntı-kuruluk kısır döngüsü oluşur. Bu kısır döngünün kırılmasında temelde iki nokta vardır: Cildin nem tutma kapasitesini artırmak ve epidermisteki inflamasyonu azaltmak (5,6).

Günümüzdeki kronik hastalıkların birçoğunda olduğu gibi AD patogenezinde de genetik ve çevresel faktörler birlikte rol oynar. Genetik temel, şarjörü doldurur; çevresel faktörler tetiği çeker ve semptomlar ortaya çıkar.

Genetik Faktörler

Aile öyküsü AD genetik risk faktörleri arasında en güçlü risk faktörüdür. Bir ebeveynde AD öyküsünün olması riski 2-3 kat, iki ebeveynde AD öyküsü olması riski 3-5 kat artırmaktadır (7,8).

21.000'den fazla vakayı ve 95.000 kontrol grubunu içeren 26 genomik ilişkilendirme çalışmasının meta-analizi; filaggrin (FLG) proteininin AD'de önemli rol oynadığını göstermiştir (9). Ancak, FLG (kromozom 1q23.3) ile birlikte AD'de rolü olabilecek otuz dört gen bölgesi daha keşfedilmiştir. İlişkili genler çoğunlukla, kişinin doğal bağışıklık sisteminin ve T hücre fonksiyonlarının düzenlenmesinde görev almaktadır. Kromozom 1q21.3'teki genler, 5q31.1'de yer alan sitokin kümesi genleri ve kromozom 11q13.5 üzerinde EMSY ve LRRC32 gen bölgeleri arasında kalan alan; AD semptomlarının ortaya çıkmasında özellikle rol oynuyor gibi görünmektedir. D vitamini gen polimorfizmleri ve D vitamini reseptörü ile ilgili CYP27A1 genleri de AD ile ilişkili bulunmuştur (2,9).

FLG genindeki mutasyonların AD patogenezinde temel rol oynadığı gösterilmiştir, AD hastalarının %20-40'ında FLG fonksiyon kaybı mutasyonu mevcuttur (1-3,9). FLG geni deride 5 temel görev üstlenir:

1) Cildin nem tutma kapasitesinin artırılması
2) Keratinosit farklılaşması
3) Epidermal korneositlerin kohezyonu ve adezyonu
4) Ciltteki lipid bileşiminin dengede tutulması
5) Hücreler arasındaki sıkı bağlantıların (tight junction) korunması

FLG genindeki mutasyonlar ve atipik varyasyonlar ise; bozulmuş korneosit kohezyonuna, derideki lipid içeriğinin değişmesine, keratinosit farklılaşmasının bozulmasına, deri mikrobiyotasının değişerek infeksiyonlara yatkınlık oluşmasına sebep olmaktadır (7,9,10).

FLG geni tarafından üretilen profilaggrin proteini, fosforilasyona uğrayarak keratohyalin granüllerinde depolanır. Ardından defosforilasyona uğrayarak monomerlerine ayrılır. Oluşan monomerlerin ileri degredasyonu, deride doğal nemlendirici faktörün (NMF) ortaya çıkmasını sağlar. NMF; içeriğindeki aminoasitler, üre, gliserol, hyalüronik asit gibi moleküllerin ve sodyum başta olmak üzere çeşitli iyonların etkisiyle epidermiste suyu tutar ve cildin kurumasını engeller. Gendeki fonksiyon bozukluğu ise cildin nem tutma kapasitesini sınırlayarak suyun hızlıca kaybedilmesine sebep olur (11,12).

FLG homozigot mutasyonları; erken başlangıç yaşı, uzun hastalık süresi ve enfeksiyonlarla şiddetli AD semptomları ile ilişkilidir (1,7). FLG, AD hastalarının hem lezyonlu hem de lezyonsuz derisinde sağlıklı kontrollere kıyasla daha az eksprese edilmektedir. FLG parçalanma ürünleri yaşamın ilk yılında dirseklere ve burun ucuna kıyasla en az yanaklarda bulunmuştur ve olgun FLG haline en geç yanaklarda ulaşmıştır (1,7,12). Bu sonuçlar, atopik bünyeye sahip bebeklerde egzemanın neden genellikle önce yanaklarda başladığını kanıtlar niteliktedir.

Çevresel Faktörler

AD patogenezinde yer alan temel yolaklar, kişinin yaşam tarzı ve tüm çevresel faktörlerin birlikte etkisiyle oluşan ekspozomlar ile altta yatan inflamasyonun artmasına yol açabilir. Artan inflamasyon ve tetikleyicilerin varlığında semptomlar ilk kez ortaya çıkabilir ya da var olan semptomlar daha da şiddetlenebilir. Söz konusu alerjenler ve tetikleyiciler genellikle şunlardır:

- Tahriş edici kumaşlar (örneğin yün),
- Havadaki tahriş edici maddeler ve aeroalerjenler (örneğin; ev tozu akarları, tütün dumanı, hava kirliliği, küfler, tozlar, hayvan tüyleri)
- Kokulu sabunlar, deterjanlar, yumuşatıcılar,
- Dar kıyafetler,
- Belirli yiyecekler (yer fıstığı, soya, yumurta, inek sütü, besin katkı maddeleri, tatlandırıcılar),
- Sıcaklık ve nem koşullarında aşırılıklar, ortam neminin ve sıcaklığının hızlı değişimi,
- Kontakt dermatite neden olabilecek kimyasal maruziyeti ve ellerin sürekli ıslak kalması (13).

Besin alerjilerinin özellikle topikal tedavilere yanıt vermeyen, 5 yaşından küçük, orta ve şiddetli atopik dermatit vakalarında daha yaygın olduğu bulunmuştur (14).

Hijyen Hipotezi

AD vakalarının özellikle gelişmiş Batı ülkelerinde ve ABD'de daha fazla görülmesi, yüksek sosyokültürel seviyelere sahip ailelerde AD insidansının fazla, erken yaşta çiftlik yaşamıyla tanışan topluluklarda insidansın daha düşük olması; hijyen koşulları ile atopik dermatit arasında doğru orantılı bir ilişki olduğunu göstermektedir (15).

Patofizyolojik Mekanizmalar

Atopik dermatit, birbirini etkileyen ve birbirinin etkisini güçlendiren 3 faktörle ortaya çıkar:

1) Bozulmuş cilt bariyeri
2) Derideki antimikrobiyal aktivitenin azalması
3) Alerjenlere karşı artmış proinflamatuar atopik yanıt

Bozulmuş cilt bariyeri, immün disregülasyon ve inflamasyon etkisi ile oluşur.
Toll like reseptörlerin (TLR) doku hasarı ve mikrobiyal ajanlarla uyarılması, alarminlerin salınmasına yol açar. Alarminler; antimikrobiyal peptitleri (AMP), IL-1A, timik stromal lenfopoietin (TSLP), IL-25 ve IL-33 gibi sitokinleri; proteazları (kallikreinler, katepsinler) ve periostin gibi hücre dışı matriks (ECM) proteinlerini içeren kompleks bir gruptur. Derideki AMP'ler Th2 sitokinleri tarafından inhibe edilir ve S.aureus kolonizasyonuyla ilişkilidir (1,16).

Alarminlerin salınması:
- İnflamatuar epidermal dendritik hücreler,
- Dermal dendritik hücreler
- T helper 2 (Th2) hücreleri,
- Ciltte yerleşik grup 2 doğal lenfoid hücreler (ILC2'ler), Doğal öldürücü hücreler (NK)
- Mast hücreleri
- Bazofiller
- Langerhans hücreleri dahil olmak üzere tip 2 bağışıklık hücrelerini aktive eder (2,17). Aktive olmuş Th2 hücreleri, enflamasyonun yanı sıra B hücresi IgE sınıf değişimini destekleyen IL-4 ve IL-13'ü serbest bırakır.

Th2 aktivasyonu ve artan IL-4,13; FLG ekspresyonunda azalmaya sebep olur. Ayrıca IL-31,33, Sinyal dönüştürücü ve transkripsiyon aktivatörü (STAT) 6, TSLP ve TSLP reseptörleri (IL-7R ve TSLPR), interferon düzenleyici faktör 2, FcERI alfa AD ile ilişkili diğer immün sistem proteinleridir. TSLP, AD hastalarının epidermisinde daha fazla eksprese edilmekte ve bu durum alerjenlerle, mikroorganizmalarla artmaktadır. Koredeki bir çalışmada 2 ya-şındaki bebeklerin vücudunda klinik AD lezyonları oluş-madan 2 ay önce deri TSLP düzeylerinin yüksek çıktığı gösterilmiştir (1,17).

ILC2, IL-5 ve 13 üretir. AD hastalarının lezyonlu derisinde daha yüksek bulunmuştur. ILC2; IL-25,33 ve TSLP ile aktive, E-kaderin ile inhibe edilmektedir. E-kaderin gibi korneodesmosinler (CNDS) de keratinositler arasındaki sıkı bağlantılarda işlev gören bir proteindir ve IL-4,13,22,25,31 tarafından ekspresyonu azaltılır. CNDS eksikliği olan deriye vaccinia virüs penetrasyonunun kolaylaştığı bildirilmiştir (1,3,11,17) (Resim 1).

AD'de akut dönemde Th2 ve Th22, kronik dönemde Th1 yanıtı daha baskın bulunmuştur. Pediatrik vakalarda; Th2,9,17 oranları deri lezyonlarında daha fazla bulunmuş ve aynı hastaların serum örneklerinde Th2 ile Th17 belirteçleri daha yüksek çıkmıştır (3,16).

Fosfodiesteraz 4 (PDE4), sitokin üretimini düzenleyen bir enzimdir. PDE4 inhibisyonu; inflamatuar kaskatta tümör nekroze edici faktör (TNF), IL-2,5,8,12,22 azalışı ile korele bulunmuştur (2,18).

AD vakalarında lezyonlu deride CD4 baskın inflamasyon; langerhans hücreleri, deride yerleşik dendritik hücreler ve ILC2 hücrelerin de etken olduğu karmaşık bir hücre ağı mevcuttur. AD'de lezyonlu deride aktifleşmiş NK hücrelerinin bulunması, periferik kanda NK hücre konsantrasyonunun azalması ve bileşiminin değişmiş olması tip 2 inflamasyona karşı düzenleyici bir tepki olarak kabul edilebilir (2,16-18).

İnflamatuar hücrelerdeki bu uyarım hücre içi sinyal iletim yolaklarından janus kinaz/sinyal iletimi transkripsiyon aktivatörü (JAK-STAT) yolağını aktifleştirir. JAK-STAT fosforilasyonu ve artan nükleer transkripsiyon ile inflamatuar yanıt derinleşir. Artan JAK aktivitesi; Th1 hücrelerinden IFN gama, Th17 hücrelerinden IL-17 ve 22, Th22 hücrelerinden IL-22 salınımını artırarak keratinosit hiperplazisine yol açar. B hücreleri, mast hücreleri, eozinofil ve bazofillerin inflamasyon kaskadına katılmaları ile IgE üretimi uyarılır (17). Bunların sonucunda; proteaz-antiproteaz dengesi bozulur. Stratum granülozumdaki sıkı bağlantılar işlevini yitirir, doğal nemlendirici faktörün oluşması engellenir, nem tutan makromoleküllerin degredasyonu artar (18,19). Korneositler arasındaki kohezyon kaybolur. Transepidermal su kaybı (TEWL) artar.

Derideki AMP'lerin azalması, FLG genindeki mutasyonlarla ve artan inflamasyon yanıtı ile meydana gelir. AMP'lerin azalması ve deri pH'ının artması ile atopik deride enfeksiyonlara yatkınlık oluşur, deri mikrobiyomu değişir. AD'li bireylerin lezyon olmayan deri bölgelerinde, azalmış klaudin-1 ekspresyonu ve sıkı bağlantı işlevinde bozulma tespit edilmiştir (20). Mikrobiyal kolonizasyon ve artan IL-4, IL-5, IL-13, IL-17A, IL-22, IL-25, IL-31 gibi proinflamatuar sitokinler epidermal bariyer bozukluğunu artırarak ciltteki mikrobiyomun değişmesine yol açar. AD'de deri mikrobiyomunun değişmesi ve deri pH'ının artmasıyla, S.aureus kolonizasyonu ve sekonder bakteriyel enfeksiyon riski artar (1,16,17,21). Derideki lipid bileşimi değişir. Seramid, kolesterol ve uzun zincirli yağ asidi oranının azalması; kısa zincirli yağ asidi oranının artması, bunlara bağlı olarak deri pH'ının artması bariyer disfonksiyonunu artırır (21,22). Seramidler kornifiye zarf prote-inlerine kovalent bağlanır ve her bir korneositin yüzeyini kaplar. Th2 sitokinleri ve TAT-6 sinyal iletim yolağı ile deride uzun zincirli serbest yağ asitleri ve seramidler azalır. S.aureus ile kolonize deride seramidler daha az tespit edilmiştir ve TEWL ile seramid seviyeleri arasında negatif korelasyon vardır. Normal flora elemanı olarak da görülebilen S.aureus AD hastalarının

%90'ına kadarında kolonize bulunmuştur. Deri florasında şiddetli AD hastalarında S.aureus, hafif AD hastalarında *S.epidermidis* fazlalığı göze çarpmaktadır (1,19,21). Bakteri türlerinin belirlenmesinde çok spesifik bir belirteç olan 16s rRNA dizilim çalışmaları göstermiştir ki;

- Alevlenmeler sırasında Streptococcus, Corynebacterium ve Propionibacterium cinslerinde azalma,
- Cilt mikrobiyal çeşitliliğinde çarpıcı bir düşüş,
- S.aureus yoğunluğunda artış,
- Tedaviden sonra derideki mikrobiyom çeşitliliğinde normale dönüş izlenmektedir (2,21).

S.aureus bakterisinin sahip olduğu; Toksik şok sendromu toksin-1 (TT-1), stafilokokal enterotoksin serotipleri EA, EB, EC, ED, EE veya EG, antijen sunan hücre yüzeyindeki MHC II moleküllerine bağlanan süper antijenlerdir. Süperantijenlerin varlığı aşırı T hücre sitokinlerinin üretimi ile sonuçlanır. Süperantijenler aynı zamanda, bir IgE yanıtı ortaya çıkarabilen ve mast hücre degranülasyonunu tetikleyebilen alerjenlerdir. .aureus bakteriyel enfeksiyonları tedaviyi güçleştirmekte ve egzematize alanların artmasına, hastalık şiddetinin alevlenmesine neden olmaktadır (23).

Yapılan başka bir çalışmada; derideki Corynebacterium ve Propionibacterium cinsleri ile 20-24 karbonlu uzun zincirli yağ asitleri arasında pozitif korelasyon saptanmıştır (20). AD hastalarının bağırsak mikrobiyotasında sağlıklı kontrollere kıyasla; Bifidobacterium türlerinin daha az, staphylococcus türlerinin d aha fazla olduğu bulunmuştur (22). Lipit karışımı ve seramid içeren nemlendiricilerin kullanımının AD hastalarında, bakteriyel kolonizasyonu ve topikal kortikosteroid ihtiyacını azalttığı bilinmektedir. Nemlendiricilerdeki vazelin içerikleri deride AMP seviyelerini ve FLG protein üretimini artırmakta bu da TEWL miktarını kontrol etmeye yardımcı olmaktadır (1,22,23). Bu çalışmalar da göstermiştir ki, deri lipid bileşiminin ve mikrobiyotasının değişimi AD hastalarında bariyer fonksiyon bozukluğunu artırmaktadır.

S.hominis ve S.epidermidis otolog deri mikrobiyom transplantasyonunun, derideki .aureus kolonizasyonunu azalttığı gösterilmiştir. Ayrıca yüksek IgE, düzenleyici T hücresi ve transforme edici büyüme faktörü beta seviyelerine sahip hastaların probiyotiklere yanıtı daha fazla olmuştur (1). S.aureus ve Malessesia kolonizasyonunun AD semptomlarını şiddetlendirdiği kanıtlanmıştır. AD hastalarında, özellikle geçmeyen baş-boyun dermatitlerinde deri Malessesia antijenlerine karşı IgE hiperreaktivitesi gösterir. Bu hastalar topikal-sistemik antifungal tedaviden fayda görebilirler (1,2,17,23).

Allerjenlere karşı artmış proinflmatuar atopik yanıt, ilk dönemlerde özellikle Th2 hücreleri tarafından gerçekleştirilir. Th2 sitokinleri olan IL-4, IL-13, IL-22, IL-31 kuruluğu ve kaşıntıyı ortaya çıkaran en önemli medyatörlerdir. Bu sitokinler deride;

- İnflamasyon yanıtı oluştururlar.
- Terminal keratinosit farklılaşma genlerinin (örneğin, FLG, loricrin, involukrin) ve AMP'lerin üretimini inhibe ederler.
- Epidermal hiperplaziyi uyarırlar (24).

Nöroimmün etkileşimler

Fare modellerinde; cildi innerve eden duyusal nöronların IL-4, IL-13, IL-31 reseptörlerini içerdiği bulunmuştur (25). AD vakalarında özellikle IL-31'in kaşıntıyı tetikleyebileceği gösterilmiştir. IL-31 duyusal sinir uzamasını ve dallanmasını sağlar, bu da STAT-3'ün minimal uyarılara duyarlılığını artırır. Spinal kolon dorsal boynuz astrositlerindeki STAT-3 aktivasyonu lipokalin-2 üretimini artırarak kronik kaşıntıya sebep olur (1,25,26). IL-4'ün ise kaşıntıyı doğrudan uyarmadığı; ancak dorsal kök gangliyonlarının pruritojen maddelere olan duyarlılığını artırarak kaşıntıya sebep olduğu düşünülmektedir. Kaşıntının, anti IL4/13 ajan Dupilumab ve JAK inhibitörleriyle daha ilk günlerden itibaren gerilemesi de bunu kanıtlar niteliktedir (26,27).

IL-31, AD vakalarında hem lezyonlu deride hem de serumda yüksek bulunmuştur. IL-31 düzeyi ile hastalık şiddetinin paralellik gösterdiği ortaya konulmuştur. IL-31 gen polimorfizmlerinin özellikle atopik ve non-atopik egzema ile ilişkili olduğu gösterilmiştir (27-31).

IL-17; FLG ve involukrin ekspresyonunu azaltmaktadır. Normal IgE seviyelerine sahip intrinsik AD'de daha yüksek bulunmuştur (1,32). Pediatrik vakalarda Th17 sinyalizasyonunun erişkin AD'li bireylere göre daha baskın olduğu bulunmuştur (3,16,32). Psöriasiste inflamasyonda baskın olan Th17, Asya ırkında ve pediatrik AD vakalarında daha az olarak rol oynamaktadır; ancak Avrupa-Amerika bölgesindeki AD vakalarında Th17 yanıtı ve Th17'ye bağlı sitokin fırtınası inflamasyonda belirgin rol almamıştır (31). Asyalı AD, pediatrik AD, intrinsik AD ve yeni başlangıçlı AD vakalarında Th17 ve Th22 yanıtı birlikte görülmüştür. Bu vakalarda deri örneklerinin histopatolojik incelemesinde kısmi parakeratoz ve nötrofil infiltrasyonu mevcutken, Avrupalı-Amerikalı AD vakalarında bu yanıtla karşılaşılmamıştır. Günümüzde; psöriasiste olduğu gibi spesifik hücre/sitokin inhibisyonları, Th1 ve Th17 inhibisyonu AD için etkili bir terapötik hedef gibi görünmemektedir; çünkü AD'de T hücre birikimleri poliklonaldir ve antijen özgüllüğü yeterince anlaşılamamıştır (1-3,32).

IL-4 ve IL-13, Th2 yanıtının oluşmasında ve ilerlemesinde anahtar medyatörlerdir (32,33). Aynı zamanda farklılaşmamış T hücrelerinin Th2'ye dönüşümünde de rol oynayarak inflamasyon yanıtının daha da derinleşmesine neden olurlar. Mast hücrelerinin ve eozinofillerin göçünü uyararak alerjik mediatörlerinin salınmasına yol açarlar,

ayrıca IgM'nin sınıf değişimini uyarıp IgE sentezinin artmasına neden olarak da yine alerjik semptomların oluşmasına neden olurlar. IL-13 ayrıca, matriks metalloproteinaz 9 aracılığı ile deri bariyer proteinlerinin ve lipidlerinin ekspresyonunu azaltır (16,30,33,34) (Resim 2).

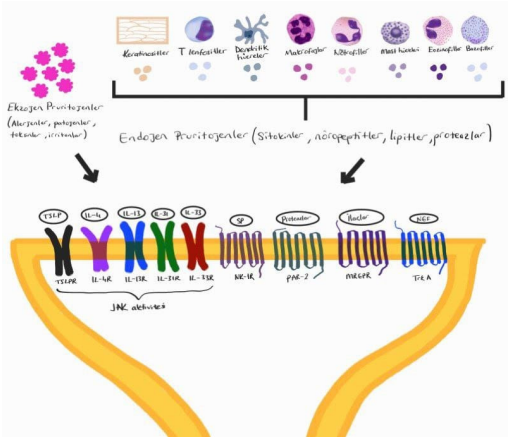
IL-22 epidermal hiperplazide ve kaşıntıda rolü olan bir sitokindir, anti IL-22 monoklonal antikoru olan fezakinumabın devam eden faz çalışmalarında kaşıntı ve yaşam kalite skorlarında anlamlı bir iyileşme sağladığı gösterilmiştir (35).

IL-31'in kaşıntıdaki ve nöroimmün etkileşimlerdeki rolü yukarıda anlatılmıştır. Anti IL-31 monoklonal antikoru nemolizumabın AD'de ve prurigo nodülariste etkili olduğu bulunmuştur (36). Kaşıntı skorlarında azalma ve uyku kalitesinde iyileşme plaseboya göre istatistiksel olarak anlamlı oranda yüksek çıkmıştır (37).

Aktive T hücrelerinde, uyarım sağlayan reseptör OX40'ın inhibisyonu AD hastalarında inflamasyonu azaltabilir. Bu amaçla faz 2B çalışmaları devam eden anti-OX40 ajanlar telazorlimab ve rocatinlimab umut vaat eden sonuçlar vermektedir (38). Ayrıca anti-OX40L inhibitörü amlitelimab ile ilgili de faz 2A çalışmaları devam etmektedir (39). PDE4 inhibisyonu psöriasiste olduğu gibi AD vakalarında da inflamasyonu azaltmakta ve semptomların kontrol altına alınmasına yardımcı olmaktadır. Topikal krizaborolün AD vakalarında etkili olduğu gösterilmiştir (40,41). Roflumilast ve difamilast çalışmaları devam eden diğer topikal PDE4 inhibitörü ilaçlardır (42,43).

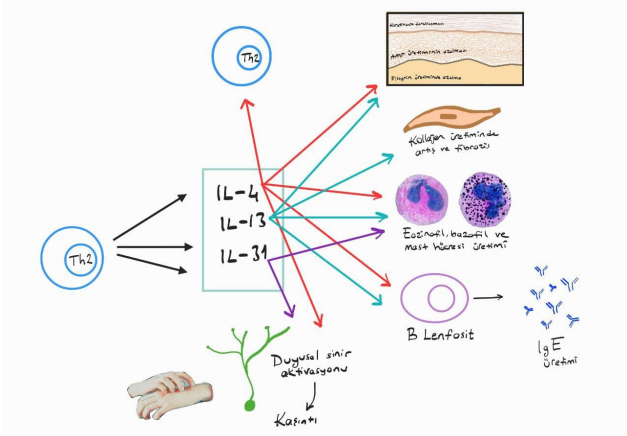
Sonuç

AD, klinik bir tanıdır. Hastanın kuruluk ve kaşıntı semptomları, olası cilt enfeksiyonları, eşlik eden alerjik ve psikiyatrik hastalıklar yaşam kalitesini düşürmektedir. Kişinin iş-okul yaşamını, sosyal yaşamını, beslenme ve giyim alışkanlıklarını doğrudan etkilemektedir. Özellikle IL-22'nin, IL-31'in, IL-33'ün patogenezdeki rollerinin daha iyi aydınlatılmış olması yeni tedavilerin bulunmasında ve araştırmaların yönlendirilmesinde önem arz etmektedir. FLG geni dışında da kırka yakın gen bölgesinin AD patofizyolojisindeki rolleri gösterilmiştir. Bu genler; immünolojik sistemin hem doğal bağışıklık kolunda hem de hücresel bağışıklık kolunda fonksiyonların düzenlenmesinde görevli genlerdir. Pediatrik, yeni başlangıçlı ve Asyalı AD vakalarında daha belirgin olan Th17 yanıtının Avrupa-Amerikalı ve kronik AD vakalarında görülmemesi, bu vakalar arasında histopatolojik olarak farklılıkların bulunması AD'de kişiselleştirilmiş tedavilerin daha çok önem kazanacağını göstermektedir. Tedavide; topikal tedavilerden sistemik yeni biyolojik ajanlara kadar değişen geniş bir ilaç yelpazesi bulunmaktadır. Spesifik hücre/sitokin inhibisyonu hastalığın doğası ve karmaşık, poliklonal inflamasyon ağı sebebiyle şu an için AD vakalarında etkin bir yaklaşım olarak görünmemektedir. Devam eden patofizyolojiye yönelik çalışmalar ve yeni tedavi hedeflerinin araştırılması ileride AD tedavisi için farklı uygulamalar sağlayabilir. Ancak unutulmamalıdır ki; atopik dermatitte farmakolojik olmayan tedavi ve hasta eğitimi en az farmakolojik tedavi kadar önemlidir. Tanı koymada, kişiselleştirilmiş tedavilerin seçiminde ve uygulanmasında, hasta takibi ve sürecin yönetilmesinde patofizyolojiyi iyi bilmek, neyin neden nasıl olduğunun farkına varmak biz hekimleri daha iyi bir noktaya taşıyacaktır.



TSLP: *Timik Stromal Lenfopoietin,* ***NK-1:*** *Nörokinin 1,* ***PAR-2:*** *Proteaz Aktive Reseptör 2,* ***MRGPR:*** *Mas İlişkili G Protein Reseptörü,* ***SP:*** *Serin Proteaz,* ***NGF:*** *Nöronal Büyüme Faktörü,* ***Trk A:*** *Tirozin Kinaz A,* ***JAK:*** *Janus Kinaz*

Resim 1. Mikroçevre ve ekspozomların hücre yüzey reseptörleri ile ilişkisi.



Resim 2. Th2 aktivasyonu ve görevli temel sitokinlerin etkileri.

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RESEARCH ARTICLE

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Evaluation of Photodynamic Therapy-Combined Intravitreal Bevacizumab in Age-Related Macular Degeneration

Yaşa Bağlı Makula Dejenerasyonunda Fotodinamik Tedavi ile Kombine İntravitreal Bevacizumabın Değerlendirilmesi

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ABSTRACT

Aim: *It was aimed to compare treatment results of photodynamic therapy (PDT) and PDT-combined intravitreal bevacizumab injection (PDT+IVB) in patients with age-related macular degeneration (AMD).*

Materials and Methods: *63 eyes of 55 patients with neovascular AMD were included. Group 1 consisted of 40 eyes of 35, Group 2 consisted of 23 eyes of 20 patients. Visual acuity (VA), intraocular pressure measurement and fundus examination were performed. Pattern Electroretinography P50 amplitude and edema map values (EMV) were mea-sured with Heidelberg Retina Tomograph (HRTII).*

Results: *VA increased in 14 (35%), remained unchanged in 17 (42.5%), and decreased in 9 (22.5%) eyes in Group 1 (PDT). The PERG P50 amplitudes were compared with values of pre-treatment, and found to increased at 10.6%, 11.98%, and 8.46% and HRTII EMV were 5.86%, 4.88%, and 11.22% at 1st, 3rd, and 6th months, respectively. In Group 2 (PDT+IVB), VA improved in 9 (39.13%), remained unchanged in 8 (34.78%), and decreased in 6 (34.78%) eyes. PERG P50 amplitudes were reduced to 10.15%, 5.8%, and 0.1% and HRTII EMV were reduced to 13.07%, 12.17%, and 14.87% at 1st, 3rd, and 6th months, respectively.*

Conclusion: *Verteporfin and PDT are effective and safe methods that preserve VA in subfoveal choroidal neovascular membranes due to neovascular AMD.*

Keywords: *Age-related macular degeneration, photodynamic therapy, intravitreal injection, bevacizumab, vascular endothelial growth factor, early diagnosis*

ÖZET

Amaç: *Yaşa bağlı makula dejenerasyonu (AMD) olan hastalarda fotodinamik tedavi (PDT) ve PDT ile kombine intravitreal bevacizumab enjeksiyonu (PDT+IVB) tedavi sonuçlarının karşılaştırılması amaçlandı.*

Gereç ve Yöntemler: *Neovasküler YBMD'li 55 hastanın 63 gözü dahil edildi. Grup 1 35 hastanın 40 gözü, Grup 2, 20 hastanın 23 gözü içermekteydi. Görme keskinliği (VA), göz içi basıncı ölçümü ve göz dibi muayenesi yapıldı. Patern Elektroretinografi P50 genliği ve ödem haritası değerleri (EMV) Heidelberg Retina Tomografi (HRTII) ile ölçüldü.*

Bulgular: *Grup 1'de (PDT) 14 (%35) gözde VA arttı, 17 (%42.5)'sinde değişmedi, 9 (%22.5)'unda azaldı. PERG P50 amplitüdleri tedavi öncesi değerlerle karşılaştırıldı ve 1., 3. ve 6. aylarda sırasıyla %10.6, %11.98 ve %8.46 artmış ve HRTII EMV %5.86, %4.88 ve %11.22 bulundu. Grup 2'de (PDT+IVB) 9 (%39.13)'unda VA düzeldi, 8 (% 34.78)'inde değişmedi, 6 (%34.78)'sında azaldı. PERG P50 amplitüdleri 1., 3. ve 6. aylarda sırasıyla %10.15, %5.8 ve %0.1, HR-TII EMV %13.07, %12.17 ve %14.87 azaldı.*

Sonuç: *Verteporfin ve PDT, neovasküler AMD'ye bağlı subfoveal koroidal neovasküler membranlarda VA'yı koruyan etkili ve güvenli yöntemlerdir.*

Anahtar Kelimeler: *Yaşa bağlı makula dejenerasyonu, fotodinamik tedavi, intravitreal enjeksiyon, bevacizumab, vasküler endotelyal büyüme faktörü, erken tanı*

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INTRODUCTION

Age-related macular degeneration (AMD) has been defined as a progressive decrease in central visual acuity (VA) and described as a macular neurodegenerative disease (1). In developed countries, it is the most common cause of central vision loss in patients 65 and over age (2).

AMD is divided into 2 groups (3). Exudative/neovascular AMD constitutes ~10% of cases characterized by the formation of new vessels developing from choroid. Atrophic/non-exudative AMD constitutes ~90% of cases characterized by a slight decrease in vision over many years, photoreceptor loss and geographic atrophy (3). It is hypothesized that abnormal enzymatic activity of senescent retinal pigment epithelium (RPE) cells causes accumulation of metabolic products. Swelling of RPE cells disrupts their normal cell metabolism, causing them to secrete extracellularly (4). Tears in Bruch's membrane are thought to be responsible for neovascularization from choriocapillaris (5).

Vascular endothelial growth factor (VEGF) is specific to vascular endothelial cells. In the retina, the primer sources are RPE, muller cells, ganglion cells, and pericytes (6). Bevacizumab blocks all biologically active isoforms of VEGF (7).

Photodynamic therapy (PDT) is based on the principle of selective vasoocclusion of neovascular membrane by stimulating it with light following intravenous verteporfin, a synthetic photosensitizer (8).

This study aimed to compare treatment results of PDT and PDT combined with intravitreal bevacizumab injection (PDT+IVB) in patients with AMD.

MATERIALS and METHODS

Ethical Considerations

This prospective study was performed in the Ophthalmology Clinic of Erciyes University Faculty of Medicine. Approval for our research was granted by the Ethics Committee of Erciyes University (approval number: 2009-01/94). Informed consent was obtained from the participants. The principles of the Declaration of Helsinki were observed throughout the research.

Study Design

63 eyes of 55 newly diagnosed neovascular AMD patients treated between 2006 and 2009 were included. Cases with choroidal neovascular membrane due to ocular diseases other than AMD (pathological myopia, angioid streaks, central serous retinopathy, etc), uncontrolled systemic hypertension, impaired bleeding profile, renal dysfunction, thromboembolic history, hyperlipidemia, active diabetic retinopathy, myocardial infarction within 6 months, history of cerebrovascular disease were not included.

Patients were divided into two groups: Group 1 treated with PDT; Group 2 treated with PDT+intravitreal bevacizumab. The largest lesion diameter was determined according to FFA.

The laser spot diameter was calculated using the PDT application method. After verteporfin infusion laser biomicroscope was used. The application was made with a 689 nm diode laser using 50 J/cm² energy and 600 mW/cm² power for 83 seconds. Intravitreal bevacizumab was injected and intraocular pressure was measured. Cases were called for ophthalmological control (VA, intraocular pressure value, slit-lamp, fundus examinations, PERG, HRT and FFA) at 1st, 3rd and 6th months. Recordings were taken with the PERG Primus 2.5 Tomey Primus electrophysiology device. Adjustments were made according to the standards of the International Society of Ocular Clinical Electrophysiology (ISCEV: International Society of Electrophysiology of Vision). Macular edema analysis was performed using the HRT II macular edema module. The edema map value (EMV) was obtained by adapting these measurements to all points, and using them to evaluate in the evaluation of macular edema.

Statistical Analysis

IBM SPSS Statistics version 17.0 was used for statistical analysis. Data of normal distribution was checked. Distribution was defined as mean ± SD. Student's t test was used for age and PDT diameter; the Pearson chi-square test was used for FFA, gender and lesion type; The Mann-Whitney U test was used for HRTII EMV, VA values, and PERG P50 amplitudes. Statistical significance was shown as $p<0.05$.

RESULTS

31 cases were male (56.36%), 24 cases were female (43.64%). Their mean age was 63.85 years (range 53-85 years). Group 1 consisted of cases treated with PDT. 40 eyes of 35 cases were included. 23 (57.5%) cases were male, 12 cases (42.5%) were female. Their mean age was 72.7±8.6 years (range 53-83 years). 23 (67.6%) patients had classically dominant, 14 patients (53.8%) had occult, and 3 patients (7.5%) had minimally dominant lesions. The mean PDT diameter was 4828.75 ± 1255 (2000-7900) microns. Standard PDT was applied according to FFA. VA values, PERG P50 value, and mean EMV were shown in Table 1.

There were no statistically significant differences between mean VA values, PERG P50 value and HRTII EMV detected in pre-treatment and post-treatment controls (for each, $p>0.05$). According to baseline value, mean EMVs after treatment were 5.86% at 1st, 4.88% at 3rd, and 11.22% at 6th month. No statistically significant differences were found between EMVs ($p>0.05$). Maximum reduction in EMV was observed at the 3rd month. There was no significant increase between VA values after treatment and changes in PERG P50 amplitudes. When PERG P50 values were compared with pre-treatment value, we found a rate of 10.6% at 1st, 11.98% at 3rd, and 8.46% at 6th month.

These values were compared with baseline value (p> 0.05). In Group 1, VA improved in 14 (35%), did not change in 17 (42.5%), and decreased in 9 (22.5%) eyes after treatment. Scar development was observed at the rate of 82.9% in FFA and the leakage was 39.3% at 3rd month, while these rates were 80.5% and 31.8% in 6th month, respectively. The differences were statistically significant (p< 0.05).

Group 2 consisted of 23 eyes of 20 subjects. 12 (60%) cases were male, 8 (40%) were female. Their mean age was 76±7.11 years (range 56-81 years). 11 (32.4%) had classically dominant and 12 (46.2%) had occult lesions. There were no classical type in this group. Their mean PDT diameter was 5219±1517 (2500-7900) microns. IVB 1.25/0.05 mg/ml was administered after standard PDT. Mean VA value, PERG P50 value, and HRTII EMVs were shown in Table 1. The difference wasn't statistically significant between mean VA and PERG P50 values of 1st, 3rd, and 6th month controls before and after treatment (p> 0.05). However, difference between HRTII EMVs was statistically significant (p<0.05). According to baseline value, mean EMVs after treatment were 13.07% in1st, 12.17% int 3rd and 14.87% in 6th month. Decreased values were seen in 1st and 3rd months. The difference was statistically significant between 1st and 3rd month EMVs p<0.05). The differences between values of before and after treatment in terms of VA, PERG P50 amplitude and HRTII EMV weren't statistically significant. Compared to pre-treatment value, we found a decrease of 10.15% in 1st, 5.8% in 3rd and 0.1% in 6th month in PERG P50 values. But differences were not statistically significant (p> 0.05).

Table 1. Visual acuity (VA), PERG P50 amplitudes and HRT II EMV of Group 1 and Group 2 before treatment (BT) and at 1st months 3rd months 6th months after treatment (AT). * Shows groups that differ

	BT (mean ± SD)	1.month AT (mean ± SD)	3. month AT (mean ± SD)	6. month AT (mean ± SD)	p
Group 1 (n=40) VA	1.45 ± 0.93	1.45 ± 0.87	1.36 ± 0.74	1.29 ± 0.74	0.47
PERG P50 amplitudes	1.42 ± 0.86	1.27 ± 0.73	1.25 ± 0.76	1.30 ± 1.04	0.28
HRT II EMV	2.05 ± 0.76	1.93 ± 0.65	1.95 ± 0.75	1.82 ± 0.60	0.17
Group 2 (n=23) VA	1.37 ± 0.82	1.29 ± 0.73	1.35 ± 0.78	1.19 ± 0.59	0.46
PERG P50 amplitudes	1.38 ± 0.62	1.24 ± 0.67	1.30 ± 0.56	1.40 ± 0.91	0.59
HRT II EMV	2.22 ± 0.75	1.93 ± 0.54*	1.95 ± 0.56*	1.89 ± 0.63*	0.03*

PERG: *Pattern Electroretinogram,* ***HRT:*** *Heidelberg Retina Tomography* ***EMV:*** *Edema Map Value,* ***BT:*** *Before Treatment,* ***AT:*** *After Treatment,* ***VA:*** *Visual Acuity*

After PDT+IVB, VA values were increased in 9 (39.13%), did not change in 8 (34.78%), and decreased in 6 (26.08%) eyes. Scar development in FFA was 17.1% in 3rd and 19.5% in 6th month (p< 0.05). In this group, leakage in FFA was 60.7% in 3th and 68.2% in 6th month. The difference was statistically significant between these values (p< 0.05).

The differences weren't statistically significant between groups in terms of age, gender, PDT diameter and lesion type. But importantly, when groups were evaluated in terms of scar development and leakage in FFA in 3th and 6th months we saw statistically significant differences (p<0.05). The alterations in VA values after treatments were presented in Table 2.

Table 2. The alterations in visual acuity (VA) after treatment.

	Number of Eyes	Increased VA	Steady VA	Decreased VA
Group 1	40	14 (35%)	17 (42.5%)	9 (22.5%)
Group 2	23	9 (39.13%)	8 (34.38%)	6 (26.08%)

VA: Visual Acuity

VA, PERG values and HRT values of group 1 and 2 before treatment and 1st, 3rd, 6th months after treatment were shown in Figure 1, 2 and 3.

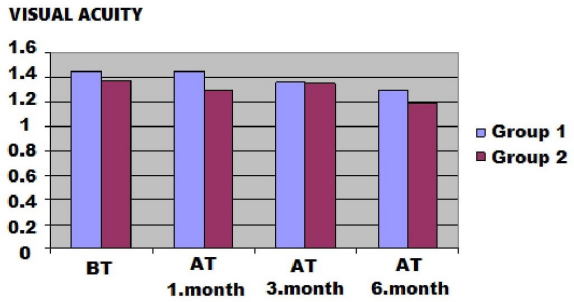

Figure 1. Visual acuity of group 1 and group 2 before treatment (BT) and at lst 3rd 6th months after treatment (AT).

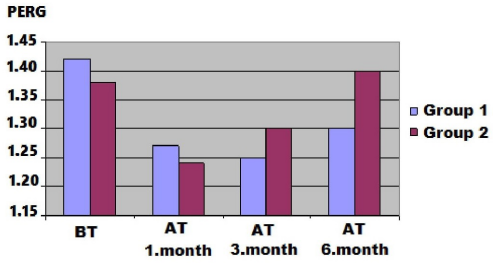

Figure 2. PERG values of group 1 and group 2 before treatment (BT) and at lst 3rd 6th months after treatment (AT).

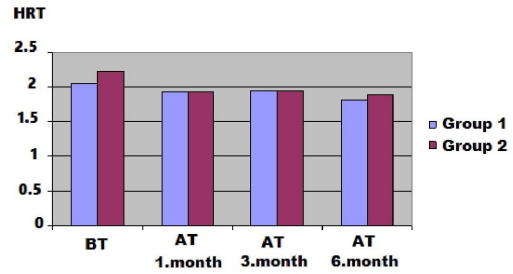

Figure 3. HRT values of group 1 and group 2 before treatment (BT) and at lst 3rd 6th months after treatment (AT).

DISCUSSION

Hemodynamic changes in choroidal circulation play a role in AMD pathophysiology (9). Simultaneous degeneration of elastin and collagen causes calcification and fragmentation of the Bruch membrane (10). Angiogenetic stimulation and VEGF levels increase due to the triggering of relative choroidal ischemia. This cycle ultimately initiates the formation of new vessels from choriocapillaris along the calcified and ruptured Bruch membrane (10).

Vitreous VEGF levels are higher in patients with AMD (11,12). In hypoxia, the release of VEGF increases exaggeratedly and regulates the adhesion of leukocytes to endothelium. Macrophages also facilitate the migration of choroidal capillaries by eroding already thinned bruch membrane with proteolytic enzymes (13). In AMD, increased VEGF was demonstrated in RPE cells (14). VEGF has functions in paracrine signal transmission between RPE and choriocapillaris and in the continuation of fenestrated structure of choriocapillaris (15).

VEGF blockade is provided by intravitreal bevacizumab administration, although there is no significant regression in vessels of the advanced choroidal neovascular membrane (CNVM). Withdrawal of intraretinal, subretinal and subRPE fluid shows that antipermeability effect of the drug is more prominent than the antineovascular effect (16).

Argon laser photocoagulation and PDT are two treatment options for neovascular AMD. PDT is a tissue selective local treatment with superficial action and strong damage effects on microvascular tissues (17). PDT with verteporfin is an essential advance in the treatment of neovascular AMD. It provides a short-lived but potent antiangiogenic effect on CNVM. Verteporfin binds to plasma lipoproteins and accumulates particularly at sites of neovascularization. The laser beam causes an activation, resulting in the release of short-lived singlet oxygen and reactive oxygen radicals that damage to endothelial cells of newly formed vessels and cause the release of procoagulant and vasoactive substances via leukotriene-cyclooxygenase pathway. Then, vascular occlusion occurs (17). Results from clinical studies showed that PDT was effective and safe in reducing vision loss and didn't permanently damage neurosensory retina on the membrane (18).

Chen et al. (19) reported that combined intravitreal ranibizumab with PDT can improve visual acuity, decrease CMT, and reduce the area of macular degeneration of wet AMD patients compared to intravitreal ranibizumab alone. Saviano et al. (20) reported that PDT combined with intravitreal bevacizumab injection is superior to bevacizumab monotherapy in treating macular CNV. Potter et al. (21) performed two doses of PDT in neovascular AMD. The first group received bevacizumab combined with 25J/cm² of PDT (25J/cm²), the second group received bevacizumab combined with 12 J/cm² of PDT, and the third group received bevacizumab monotherapy. The 6th-month results of the study showed that the patients needed 2.8, 2.5, and 5.1 times of bevacizumab injection on average in group I, group II, and group III, respectively, so it can be observed that the frequency of bevacizumab injection decreased with PDT (21).

Although short-term successful results of PDT have been reported, in the Treatment of Age-related Macular Degeneration with Photodynamic Therapy (TAP) trial, there was consistent evidence at both 1 and 2 years that PDT results in less deterioration in visual acuity in the randomized eye than placebo

We applied standard PDT to 63 eyes/55 patients. 23 (67.6%) of 40 eyes/35 patients were dominant classical, 14 of them (53.8%) were occult, 3 of them (7.5%) were minimal classical type. 11 (32.4%) eyes were dominant classical and 12 (46.2%) eyes were occult type in group 2.

We evaluate our cases according to lesion types. Our patients with occult lesions seem to respond better to treatment: VA increased 30.43% in dominant classical lesions and 42.85% in occult lesions.

The point to be considered was the size of the lesion. PDT was recommended in lesion seizes less than four macular photocoagulation study-disk area (MPS-DA), while follow-up was more appropriate for large lesions. PDT was applied again to 8 eyes (20%) in 3rd month. Herein, PDT was applied once to 32 (80%) eyes and twice to 8 (20%) eyes.

Follow-up of lesion size is essential in the evaluation of the amount of progression. In the TAP study, progression of dominant classical lesions was observed. In the 24-month follow-up, lesion size was smaller than 6 MPS-DA in 55% of patients in verteporfin group, while this rate was 25% in placebo group (19). VIP study, the progression of the classical component of the lesion was 45% less in the verteporfin group than in the placebo group in the 24-month follow-up. The rate of being above 9 MPS-DA in pure occult lesion size was 2 times higher in placebo group (22). In TAP and VIP reports, initial lesion size affected visual results of PDT rather than membrane properties of CNVM (22). Their results were worse in lesions with a DA greater than 4 MPS in predominant classical CNVMs.

Angiographic findings provide an independent and objective assessment of outcomes. In our cases, the difference between groups regarding scar development in FFA of 3rd and 6th month measurements were statistically significant ($p<0.05$). Patients with predominant classical CNVM and lesion diameter greater than 4 MPS-DA were

worse in our cases. The most common ocular side effect is transient decrease in VA due to foveal inflammation in first days. In VIP study the frequency decreased after the first two treatments (22). VA loss of more than 4 rows in first 7 days after treatment was reported in 3 patients in TAP study and in 10 patients in VIP study. In our cases, 2 patients had low back pain during infusion, and 2 patients had nausea and vomiting. None of other side effects were observed.

Although short-term successful results of PDT have been reported, the use of PDT was dramatically reduced after the recent anti-VEGF agent in the management of patients with neovascular AMD. Recently, PDT has been performed for specific situations, including the combination treatment of anti-VEGF agents and PDT (23, 24), in patients with a contraindication to the use of intravitreal anti-VEGF agents, and in patients with polypoidal choroidal vasculopathy (25, 26).

Ideal treatment should prevent the formation of new CNV by reducing inflammation and reducing VEGF secretion, as well as eliminating existing CNV. Targeting both vascular and extravascular component of CNV would be the most appropriate treatment. However, it seems difficult for single treatments to provide this process and reliability. Moreover, the need for more than one treatment and inability to obtain sufficient results in studies with monotherapies revealed the need for combination therapy. Verteporfin and PDT damage endothelial cells of newly formed vessels and cause vessel occlusion. With the addition of anti-VEGF therapy, it is planned to prevent the effects of VEGF, which occurs during the pathogenesis of CNV and is induced by PDT with verteporfin.

In our study; there was no statistically significant differences in VA, PERG P50 amplitude and HRT II EMVs during 6-month follow-up period between groups. This can be explained by;1) diameters of PDT performed due to the large lesion diameters of group 2 were also large, 2) VA levels were lower than those in group 1, 3) patients presented at a very late stage.

PDT with verteporfin is an effective treatment modality for preserving current VA in patients with neovascular AMD with progressively declining VA. Early diagnosis of disease is important. There is a correlation between initial and final VA of cases diagnosed early and it reflects positively on treatment results. Bevacizumab is one of the most effective, safe and cost-effective treatment options in the treatment of neovascular AMD.

Ethics Committee Approval: The Ethics Committee of Erciyes University approved the study protocol (approval number: 2009-01/94).
Conflict of Interest: The authors disclosed no conflict of interest during the preparation or publication of this manuscript.
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RESEARCH ARTICLE

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Diagnostic Performance and Reproducibility of the Radiological Society of North America Expert Consensus Statement on COVID-19 Pneumonia

COVID-19 Pnömonisine İlişkin Kuzey Amerika Radyoloji Derneği Uzman Konsensusunun Tanısal Performansı

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ABSTRACT

Aim: *To investigate the interobserver and intraobserver agreement and performance of the Radiological Society of North America Expert agreement declaration in assessing chest computed tomography (CT) findings related to new COVID-19 pneumonia.*

Materials and Methods: *In this retrospective study, conducted from March 15 to April 1, 2020, 113 patients with suspected COVID-19 infection were enrolled. All patients underwent investigation using real-time reverse transcription polymerase chain reaction (RT-PCR) and chest CT scans. Chest CT features were categorized by three radiologists following the North American Consensus Statement. Characteristic and indeterminate features were considered as Group A, while atypical and negative features were considered as Group B. The interobserver and intraobserver agreement of the imaging features were evaluated, along with the sensitivity and specificity of the consensus statement.*

Results: *The study population comprised 113 consecutive patients. Out of the 113 patients, 61 tested positive for RT-PCR. Group A (categories 3 and 4) consisted of 89 patients, while Group B (categories 1 and 2) included 24 patients. The ICC score for intraobserver and interobserver agreement was 0.996 (95% CI) and 0.971 (95% CI), respectively. Using RT-PCR as a reference standard, the sensitivity, specificity, negative predictive value, and positive predictive value of CT findings (group A, B) for COVID-19 pneumonia were 82%, 25%, 56.1%, and 54.1%, respectively.*

Conclusion: *The expert agreement declaration on reporting new COVID-19 pneumonia tomography findings is a well-designed, reliable, and reproducible standardized CT reporting language. It demonstrates excellent intra- and interobserver agreement.*

Keywords: *Computed tomography, coronavirus disease-2019, diagnosis, pneumonia, real-time reverse transcription polymerase chain reaction*

ÖZET

Amaç: *COVID-19 pnömonisinde gözlenen toraks bilgisayarlı tomografi (BT) bulgularının değerlendirilmesinde Kuzey Amerika Radyoloji Derneği Uzman Anlaşması beyanının gözlemciler arası ve gözlemci içi uyumunu ve performansını araştırmayı amaçladık.*

Gereç ve Yöntemler*: 15 Mart - 1 Nisan 2020 tarihleri arasında yürütülen bu retrospektif çalışmaya COVID-19 enfeksiyonu şüphesi olan 113 hasta dahil edildi. Tüm hastalara real time reverse transkriptaz polimeraz zincir reaksiyonu (RT-PCR) ve toraks BT incelemesi yapıldı. Toraks BT özellikleri Kuzey Amerika Uzlaşı Beyannamesine göre üç radyolog tarafından kategorize edildi. Karakteristik ve intermediate özellikler A grubu olarak kabul edildi. Atipik ve negatif özellikler B grubu olarak kabul edildi. Görüntüleme özelliklerinin gözlemciler arası ve gözlemci içi uyumu konsensüs ifadesinin duyarlılığı ve özgüllüğü ile birlikte değerlendirildi.*

Bulgular: *Çalışma popülasyonu 113 ardışık hastadan oluşmaktadır. 113 hastanın 61'i RT-PCR pozitifti. Grup A (kategori 3 +4) 89 hastadan ve grup B (kategori 1+2) 24 hastadan oluşuyordu. Gözlemci içi ve gözlemciler arası uyum için skoru sırasıyla 0.996 (%95 CI) ve 0.971 (%95 CI) idi. Referans standart olarak RT-PCR kullanıldığında, BT bulgularının (grup A, B) COVID-19 pnömonisi için duyarlılık, özgüllük, negatif ve pozitif prediktif değerleri sırasıyla %82, %25, %56.1 ve %54.1 idi.*

Sonuç: *Yeni COVID-19 pnömonisi tomografi bulgularının raporlanmasına ilişkin uzman anlaşması beyanı, iyi tasarlanmış, güvenilir ve tekrarlanabilir standart raporlama dilidir ve gözlemciler arası ve gözlemci içi mükemmel bir uyum gösterir.*

Anahtar Kelimeler: *Bilgisayarlı tomografi, koronavirüs hastalığı-2019, pnömoni, polimeraz zincir reaksiyonu, tanı*

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INTRODUCTION

Many studies have been carried out on COVID-19 infection, such as the symptoms, diagnosis and clinical approach of the disease, during the pandemic period declared in early 2020, and today, studies on the sequelae of this infection continue. During this pandemic stage, chest computed tomography (CT) has shown great importance for the rapid and accurate diagnosis and plays a pivotal role in assisting the clinical management of patients with uncertain clinical scenarios. Performing imaging, especially thorax CT, is a forced situation because serologic testing results have some drawbacks such as the long turnaround time and false-negative results (1). Suggestions for performing CT have increased through expert opinions (1). The value of structured reporting of COVID-19– related CT exams is paramount because of the need for rapid clinical acts such as patient care, treatment management, isolation of the patient, and filiation.

Several recent studies characterized CT imaging features of COVID-19 and reported the performance of radiologists in discriminating COVID-19 pneumonias from other viral etiologies (2-4). The described typical imaging patterns were bilateral, multifocal, and predominantly peripheral ground-glass opacities (GGO) associated with sub-segmental and mostly subpleural patchy consolidations, predominantly involving the lower lung lobes and posterior segments (2-4).

The purpose of this retrospective study was to measure the performance and interobserver and intraobserver variability of this recently published expert agreement statement in tomography findings of COVID-19 pneumonia.

MATERIALS and METHODS

Patients

This retrospective study was approved by our Institutional Ethics Committee (Decision number: 39-2020). Our retrospective study comprised 113 caucasion patients (67 males and 46 females) who were enrolled from March 15th through April 1st, 2020. Inclusion criteria were patients with suspected COVID-19 pneumonia, thorax CT examination and RT-PCR testing. Exclusion criteria were accepted as non-diagnostic thorax CT examination and no RT-PCR test. Patients who were found suspicious of having COVID-19 pneumonia, were sent to the radiology department to perform thorax CT. All patients were investigated using real-time reverse transcription polymerase chain reaction (RT-PCR) testing. After PCR testing, CT imaging was employed in all patients. COVID-19 pneumonia was confirmed through positive PCR test results. A total of 61 patients were verified as having COVID-19 on the basis of positive results for respiratory samples tested using RT-PCR. The diagnosis of 'not COVID-19' for 52 patients was called after 2 negative RT-PCR tests. Time interval between 2 tests was 2 days. There were no follow up CT scans in our study.

CT Scanning Protocol

CT data were acquired using a 128 detector CT scanner (PHILIPS Ingenuity, Netherlands). The parameters of the CT scan were as follows: the patient was in the supine position and end inspiratory acquisition; tube current–exposure time product, 200–300 mAS; tube voltage, 120 kV and section thickness after reconstruction, 1.25 mm. CT scans were obtained without contrast material administration.

Imaging Analysis

CT images were retrospectively evaluated by three radiologists with 6-, 15- and 18- years' experience in general radiology. All CT features were categorized as typical, indeterminate, atypical and negative features in accordance with Radiological Society of North America (RSNA) Expert Consensus Statement on reporting chest CT findings related to COVID-19 published on March 25th (5). The typical features are based upon available literature and more specific and commonly observed and reported imaging properties of this pandemic virus pneumonia.

New agreement declaration of imaging features was described as follows:

I. Typical features (Category 4):
II. Indeterminate features (Category 3, Figs. 1a and 1b):
III. Atypical features (Category 2):
IV. Negative features (Category 1);

The only pre-test preparation for all three radiologists is to read RSNA Expert Consensus Statement on reporting chest CT findings related to COVID-19 (4). They implemented RSNA Expert Consensus imaging features as mentioned above and newly categorized. Typical features were categorized as 4, indeterminate features as 3, atypical features as 2, and negative for pneumonia was 1. Three radiologists evaluated CT imaging features without any knowledge about the RT-PCR test results. They evaluated CT scans individually. For intraobserver agreement evaluation, one of three radiologists evaluated the scans again after 3 weeks to avoid case memory. Categories 4+3 (typical and indeterminate features) were allocated to group A, and categories 2+1 (atypical and negative features) were assigned as group B. Group A stands for likely COVID-19 findings. Group B is for unlikely

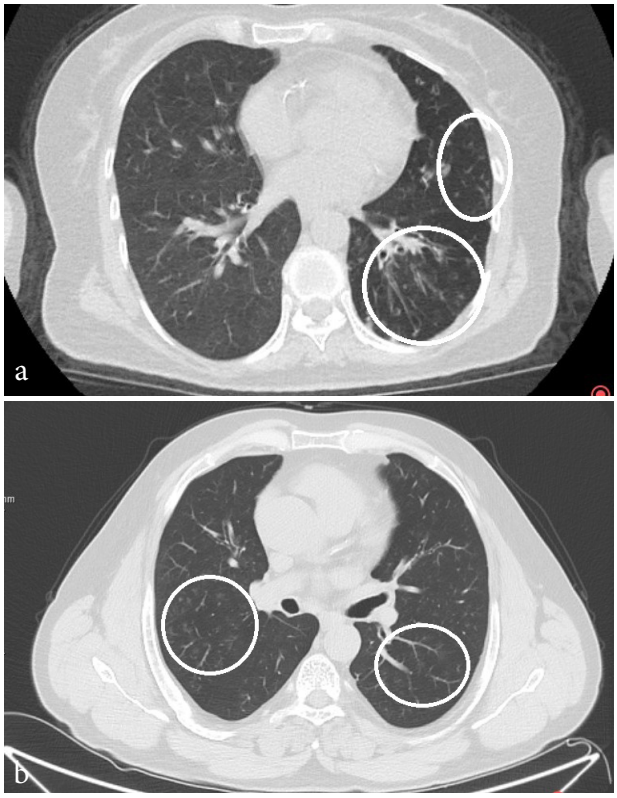

Figure 1. 45 year-old woman with suspected COVID-19 infection and PCR (-) test result. Axial CT scans (a,b) indicated a focal ground -glass opacities and tree-in-bud sign in lingual segment of the left lung (a) and left lower lobe (b) (white circles). The CT imaging score was evaluated as score 2 (atypical features for COVID-19).

COVID-19 findings. These groups were created in order to maintain more definitive radiologic results so that evaluation of suspected COVID-19 patients can be less complicated in clinical practice.

Statistical Analysis

Statistical analyses were performed using the Number Cruncher Statistical System (NCSS) 2007 (Kaysville, UT) software. The interobserver and intraobserver agreement of the imaging features were examined using the interclass coefficient (ICC) with confidence intervals of 95%. Agreement values are interpreted as follows: values less than 0.5 are indicative of poor reliability, values between 0.5 and 0.75 indicate moderate reliability, values between 0.75 and 0.9 indicate good reliability, and values higher than 0.90 indicate excellent reliability. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated in order to test the performance of the agreement statement for patients with COVID-19.

RESULTS

The study population comprised 113 consecutive patients (67 males and 46 females). The mean age of the patients was 51±14 (range, 20-88) years.

Of the 113 patients, 61 were RT-PCR-positive and 52 were RT-PCR negative (Table 1). Group A (categories 3 +4) was constituted by 89 patients and group B (categories 1+2) included 24 patients (Table 1). The ICC score for intraobserver agreement was 0.996 (95% CI), and the ICC score for interobserver agreement was 0.971 (95% CI). Using RT-PCR as a reference standard, the sensitivity, specificity and positive and negative predictive values of CT findings (group A, B) for COVID-19 pneumonia were 81,97%, 25%, 56.18%, and 54.17%, respectively.

DISCUSSION

Several research papers have been recently published for the description of characteristic CT imaging features and the temporal evaluation of imaging findings in patients with COVID-19 (2-4). In these studies, chest CT was strongly suggested in suspected COVID-19 patients for both the initial evaluation and follow-up (6).

Li et al. mentioned that CT imaging had high accuracy in suggesting COVID-19 and might be beneficial as a standard method for the diagnosis of COVID-19 pneumonia (7). Similarly, Ai et al. reported about the complementary role of chest CT in cases with false-negative RT-PCR test results, stating that the sensitivity of chest CT imaging was 97% in RT-PCR-confirmed cases (8). In a meta-analysis, the pooled positive rate of chest CT imaging was reported as 89.76% among subjects suspected of having COVID-19 (9). These findings emphasize the importance of CT imaging, especially in clinically suspected patients with negative test results. Owing to the strong infectivity of COVID-19, accurate and rapid identification tools are promptly required to recognize and to clinically manage these patients appropriately as soon as possible. This approach can reduce mortality ratios and spread of the pandemic virus.

The existence of the many different studies and the identification of the many characteristic imaging findings related to COVID-19 pneumonia as a result of these studies have created the necessity of reaching a concensus in reporting.

There is a wide range of CT manifestations of viral pneumonia and most cases have similar presentations on imaging. However, some CT imaging features that are not characteristic for COVID-19 pneumonia, like centrilobular and tree-in-bud nodules, bronchial mucus plug and bronchial wall thickening could be noted during reporting. On March 25th, 2020, the RSNA published a consensus on reporting chest CT findings based upon available literature and more specifically observed CT imaging findings in COVID-19 pneumonia (5). The goal of the expert consensus was to serve as a guide to radiologists while evaluating chest tomographic imaging features probably related to COVID-19 pneumonia. Some atypical imaging features could be confusing for radiolo-

Table 1. Details of the total numbers of Group A (categories 3+4) and group B (categories 1+2) patients with positive and negative RT-PCR test results.

		RT-PCR Test Results		
CT Imaging Score		Positive	Negative	Total
Group A	Positive	50	39	89
Group B	Negative	11	13	24
	Total	61	52	113

RT-PCR: *Real-Time Reverse Transcriptase-polymerase chain reaction*

gists and can complicate interpretations while addressing the probability of COVID-19 infections. Furthermore, the frequency of incidental lung lesions detected, which could be attributed to COVID-19, may increase. Structured reporting has the advantage of reducing miscommunication problems with referring physicians, thereby assisting in the medical management of patients during this epidemic stage. Additionally, this will reduce uncertainty in CT reporting findings and enhance physicians' comprehension of documentation, thereby enabling improved and more efficient clinical management.

Our study demonstrates excellent inter- and intra-observer agreement in utilizing the RSNA Consensus Statement for reporting chest CT findings, with high ICC scores. This high agreement score implies a high level of reliability and reproducibility of this reporting language. We have demonstrated that this standardized reporting language can be widely utilized, providing guidance and boosting confidence for radiologists by reducing reporting variability. Furthermore, this consensus enhances the diagnostic performance of radiologists in evaluating COVID-19 pneumonia imaging. Facilitating the universal collection of data for future COVID-19 studies could be another potential benefit of structured reporting (categories like 1 to 4).

The diagnostic performance of chest CT remains widely unknown. In the literature, the reported sensitivities and specificities of chest tomography for detecting new pandemic virus pneumonia vary widely (ranging from 60% to 98% and 25% to 53%, respectively) (8,10-13). The RSNA associated these differences with the retrospective structure of the published papers and the lack of rigorous diagnostic criteria for CT imaging (5). In our study, the sensitivity and specificity of the new expert agreement declaration for pandemic pneumonia were 82% and 25%, respectively, which is consistent with the current literature. Also, Bryne et al. conducted a similar study and reported that North America Expert Consensus Statement showed significant to almost perfect agreement among expert thoracic radiologists in patients with suspected COVID-19 pneumonia, which is consistent with our study (13). They reported high ICC scores for negative (0.962), typical (0.815), and atypical (0.806) COVID-19 CT findings, and a significant score (0.636) for indeterminate COVID-19 CT findings. In our study, we also demonstrated high interobserver and intraobserver agreement among radiologists who were not experts in thoracic radiology. Our results showed that the RSNA Expert Consensus Statement can be widely utilized by general radiologists with excellent consistency. In addition, the relatively high sensitivity value suggests that the RSNA Consensus Statement is a reliable CT reporting language for identifying patients with COVID-19. However, its low specificity reduces its effectiveness in diagnosing non-COVID-19 cases.

In the literature, the positive and negative predictive values of chest CT in indicating COVID-19 were reported as 65% to 92% and 42% to 83%, respectively (8,10). In our study, the PPV and NPV of the RSNA Expert Consensus Statement were 56.18% and 54.17%, respectively. Our NPV result is consistent with the literature. By contrast, the PPV is not compatible (56.82% vs. nearly 90% in the literature). Several reasons might explain the incompatible result. Our local RT-PCR testing results may not demonstrate the same level of sensitivity and specificity as RT-PCR tests conducted in other studies. There may be sampling errors. One other possible explanation could be the potential high prevalence of other non-COVID-related viral pneumonias.

Limitations

There are some limitations in the current study. First, the number of cases is relatively small because the number of tests available at that time was low. Second, patients who were CT-positive but RT-PCR-negative were not tested for other etiological agents such as influenza, which may have affected our relatively low positive predictive value (PPV).

Conclusion

The North America Agreement Declaration on reporting CT features of new pandemic virus pneumonia is a well-designed, reliable, and reproducible standardized CT reporting language that demonstrates excellent intra- and inter-observer agreement. This reporting language can reduce variability in reporting, eliminate uncertainty among radiologists, and improve clinical management during similar pandemic stages.

Ethics Committee Approval: The study was approved by the ethics committee board of Istanbul Haseki Training and Research Hospital (Decision number: 39-2020).

Conflict of Interest: The authors declare no conflict of interest in this study.

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RESEARCH ARTICLE

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Evaluation of Basic and Advanced Cardiac Life Support Knowledge of Resident Doctors at Kayseri Training and Research Hospital

Kayseri Eğitim ve Araştırma Hastanesi Asistan Doktorların Temel ve İleri Kardiyak Yaşam Desteği Bilgilerinin Değerlendirilmesi

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ABSTRACT

Aim*: Cardiopulmonary resuscitation (CPR), which includes Basic Life Support (BLS), Advanced Cardiac Life Support (ACLS), and Post Resuscitation Care (PRC), has become an important medical topic that is kept current with constantly changing and updated guidelines. The aim of this study was to evaluate whether medical residents (MRs) at Kayseri Training and Research Hospital (KTRH) can recognize cardiac arrest, their knowledge and skill level of BLS and ACLS.*

Materials and Methods: *This study was conducted between 30.12.2015-01.05.2016, as a descriptive questionnaire study to evaluate the approaches and knowledge levels of MRs working in 11 different clinics at KTRH. The questi-onnaire consisted of a personal information form as well as questions assessing BLS and ACLS, CPR training and CPR application history. The questionnaires were administered face-to-face by the researchers. SPSS Statistics 22.0 (SPSS Inc. ®, Chicago, USA) program was used for statistical analysis.*

Results: *There were 163 participants in the study. The mean number of correct responses to the knowledge assessment questions was significantly ($p<0.05$) higher among those who felt CPR training in medical school was adequate and who followed ALCS and CPR guidelines than among those who felt CPR training was inadequate and who did not follow CPR guidelines. There was a significant ($p<0.05$) positive correlation between age and length of practice and the correct rate of BLS knowledge scores. There was a significant ($p<0.05$) positive correlation between age and years of practice and BLS knowledge scores. In addition, the mean ACLS knowledge level correct response rate was significantly ($p<0.01$) higher in surgical specialties than in medical specialties.*

Conclusion : *In order to increase the chances of survival in cases of reversible sudden cardiac arrest, BLS and ACLS training should be renewed and updated on a global and national level, starting with the health care professionals.*

Keywords: *Advanced cardiac life support, basic life support, emergency medicine, resident doctors*

ÖZET

Amaç: *Temel Yaşam Desteği (TYD), İleri Kardiyak Yaşam Desteği (İKYD) ve Resüsitasyon Sonrası Bakımı (RSB) içeren kardiyopulmoner resüsitasyon (KPR), sürekli değişen ve güncellenen kılavuzlarla güncel tutulan önemli bir tıbbi konu haline gelmiştir. Bu çalışmanın amacı, Kayseri Eğitim ve Araştırma Hastanesi'ndeki (KEAH) asistan hekimlerin (AH) kardiyak arresti tanıyıp tanımadıklarını, TYD ve İKYD konusundaki bilgi ve beceri düzeylerini değerlendirmektir.*

Gereç ve Yöntemler*: Bu çalışma 30.12.2015-01.05.2016 tarihleri arasında KEAH'de 11 farklı klinikte çalışan AH'ların yaklaşımlarını ve bilgi düzeylerini değerlendirmek amacıyla tanımlayıcı anket çalışması olarak yapılmıştır. Anket, kişisel bilgi formunun yanı sıra TYD ve İKYD, KPR eğitimi ve KPR uygulama geçmişini değerlendiren sorular-*

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dan oluşuyordu. Anketler araştırmacılar tarafından yüz yüze uygulanmıştır. İstatistiksel analiz için SPSS İstatistik 22.0 (SPSS Inc.®, Chicago, ABD) programı kullanıldı.
***Bulgular:** Araştırmaya 163 katılımcı katıldı. Bilgi değerlendirme sorularına verilen ortalama doğru yanıt sayısı, tıp fakültesinde KPR eğitiminin yeterli olduğunu hisseden ve İKYD ve KPR kılavuzlarını takip edenler arasında anlamlı derecede ($p<0,05$) daha yüksekti. Yaş ve uygulama süresi ile TYD bilgi puanlarının doğruluk oranı arasında pozitif yönde anlamlı ($p<0,05$) bir ilişki vardı. Bunun yanında yaş ve çalışma yılı ile TYD bilgi puanları arasında pozitif yönde ($p<0,05$) anlamlı bir ilişki vardı. Ek olarak, ortalama İKYD bilgi düzeyi doğru yanıt oranı, cerrahi uzmanlıklarda tıbbi uzmanlıklara göre anlamlı derecede ($p<0.01$) daha yüksekti.*
***Sonuç :** Ani kalp durması vakalarında hayatta kalma şansını arttırmak için sağlık çalışanlarından başlayarak kü-resel ve ulusal düzeyde TYD ve İKYD eğitimlerinin yenilenmesi ve güncellenmesi gerekmektedir.*

***Keywords:** Acil tıp, ileri kardiyak yaşam desteği, temel yaşam desteği, tıpta uzmanlık öğrencisi.*

INTRODUCTION

The unexpected cessation of circulation and/or spontaneous respiration is called cardiopulmonary arrest (CPA). When cardiac and/or pulmonary arrest occurs, all of the procedures performed urgently to provide circulatory and respiratory support are called Cardiopulmonary Resuscitation (CPR) (1). Ninety percent of sudden deaths are due to heart disease and 10% are due to non-cardiac causes. There is a vital and important relationship between the heart, lungs and brain. Therefore, if one of these three organs stops functioning, the other two will also stop functioning within a short period of time (2,3). When the patient stops breathing, even if the heart continues to pump for a few minutes, the blood supply to the brain decreases dramatically in terms of oxygen.

As a result, the brain tissue eventually dies from lack of oxygen (2). The most common reversible cause of CPA is ventricular fibrillation. These patients should be defibrillated as soon as possible to increase the success of CPR. This should be considered a public health practice, and efforts are being made by the World Health Organization (WHO) to develop global guidelines for the training of personnel and the provision of physical conditions for defibrillation.

Resuscitation is a skill that requires ongoing training. However, it is important to provide practical as well as theoretical training (4). CPR, consisting of Basic Life Support (BLS), Advanced Cardiac Life Support (ACLS), and post-resuscitation care, is a significant medical topic that stays current with frequently updated guidelines. Thus, healthcare professionals' knowledge and practices in managing arrested patients must be periodically reviewed and refreshed.

Because BLS is the initial stage of cardiac arrest treatment, healthcare professionals, such as physicians and nurses, in high-risk areas should possess adequate BLS skills before initiating ACLS (5). According to published guidelines, BLS and ACLS are revised approximately every 5 years. Quick and precise patient management is crucial for patient survival and prevention of neurological complications (6). Approaches to cardiopulmonary arrest by medical residents, who will take responsibility as specialists in various hospitals and clinics after their specialty training, are of special importance within the framework of this responsibility as well as the framework of their clinical duties during their specialty training.

The study aimed to assess the ability of medical residents (MRs) at Kayseri Training and Research Hospital (KTRH) to recognize cardiac arrest, apply and sustain BLS and ACLS, and their knowledge level on these topics. In addition, the study explored the factors that influence MRs' performance, their interest in recent advancements, and the potential benefits of related training opportunities.

MATERIALS and METHODS

Study Design

This descriptive survey assesses the methods and knowledge levels of medical residents at the Kayseri Training and Research Hospital concerning cardiopulmonary resuscitation practices in children and adults between 30 December 2015 and 1 May 2016.

Permission was obtained from both the Erciyes University Clinical Research Ethics Committee (Decision number: 96681246/195, Meeting date: 18 December 2015) and the KTRH Education Planning Coordination Board prior to the study's commencement. In addition, the research adhered to the "World Medical Association Declaration of Helsinki Ethical Principles."

Inclusion and Exclusion Criteria

Medical residents currently working in 11 different clinics at KTRH and who consented to participate in the study were eligible for inclusion. Individuals who were not graduates of the Faculty of Medicine, those who were on leave during the study period, those who declined to participate, and those who provided assistance in the study were not eligible for the study.

Formation of Study Groups

The medical residents involved in the study were categorized based on the departments they were working in - either internal medicine or surgical sciences. Furthermore, a comparison was made between the knowledge levels of medical residents working in departments with intensive care, such as internal medicine, cardiology, general surgery, and pediatrics, and those working in departments without intensive care.

Questionnaire Design and Data Collection

The survey comprised 46 questions consisting of both multiple-choice and Likert scale questions. The first 16 questions in the questionnaire consisted of questions assessing the medical resident's age, gender, year of graduation (duration in the medical profession), department, year of medical residency training, previous CPR training, and CPR application history. All responses to the aforementioned questions were single-answer or based on a 3-point Likert scale. The following 30 questions were composed of BLS and ACLS topics referencing cardiopulmonary resuscitation guidelines published by the American Heart Association in Circulation magazine in October 2010, in accordance with relevant literature reviews and expert opinions (7). Of these, 15 questions addressed BLS and 15 questions addressed ACLS. All questions were designed as multiple-choice questions with 5 options. The answers were evaluated using CPR guidelines as the basis. The researchers conducted the surveys in person and recorded the data on a computerized form for statistical analysis.

Data Analysis and Statistical Methods

Continuous variables were expressed as arithmetic mean ± standard deviation or median, minimum and maximum values while categorical variables as numbers and percentages according to their distributional structure. The compatibility of the data with normal distribution was evaluated by Kolmogorov Smirnov test and nonparametric statistical methods were utilized for cases that did not show normal distribution. The Mann-Whitney U test was used for two independent groups while Kruskal-Wallis test was used for more than two independent groups. The relationships between categorical variables were analyzed by Chi-square analysis. SPSS Statistics 22.0 (SPSS Inc. ®, Chicago, USA) program was used for data analysis. Results were considered significant when $p<0.05$ at a 95% significance level.

RESULTS

At the beginning of the study on December 30, 2015; 113 (63.3%) of a total of 163 MRs in the CTRH staff agreed to participate in the study and responded to the questions. Among the research assistants who participated in this study, 80 (70.8%) were male and 33 (29.2%) were female. Their ages ranged from 25 to 38 years old, with an average of 28.9±2.6 years and a median of 28 years. Upon analyzing the years of graduation from medical school, the study revealed that the oldest graduate finished in 2001. The newest graduate obtained their degree in 2015. The graduates of 2010 (64 people; 56.6%) had the highest participation frequency in the survey based on graduation year. Upon analyzing the MR periods, the median duration was found to be 3 years. There was a higher percentage of individuals in their first year of MR (29.1%) compared to others. Of all the research assistants that participated in the study, 26.5% worked at the internal medicine clinic, 21.2% at the pediatrics clinic, and 13.3% at the emergency medicine clinic.

In general, when analyzing the correct responses of MRs to questions that determine their BLS and ACLS knowledge level, researchers found that the median correct answer value for BLS questions was 8 (on a scale of 1-12) and the mean rate of correct responses was 51.8 ± 14.8%. The median value of answering ACLS questions correctly was 8 (2-15) and the mean value of the correct answer rate was 53.6 ± 19.2%.

When we evaluated the participants' resuscitation training, we discovered that 40.7% (n=46) of medical residents did not receive resuscitation training after finishing medical school. However, 33.6% (n=38) of them attended MR orientation training. In their professional career, 27.4% (n=31) of MRs faced at least one patient requiring CPR. On the flip side, 68 (60.2%) of the research assistants who took part in the study failed to follow the updates to the CPR guidelines. 27.4% (n=31) performed CPR outside the hospital, whereas the percentage of those who felt skilled in CPR was 58.4% (n=66). Out of the MRs who took part in the research, 73 (64.6%) believed that the CPR lessons taught during their medical studies were insufficient. Additionally, 90 (79.6%) of the MRs agreed that they should receive refresher CPR training. Only 45.1% of participants knew when the most recent resuscitation guideline was released. The findings of the participants regarding CPR training are shown in Table 1.

When comparing the BLS knowledge levels of participants, those who considered themselves competent in CPR had a significantly ($p<0.05$) higher mean of correct answers than those who did not. In addition, those who found CPR training in medical school adequate had a significantly ($p<0.05$) higher mean of correct answers than those who did not find CPR training adequate (Table 2).

Participants who underwent MR orientation training had a significantly higher mean score ($p<0.05$) on the ACLS knowledge level assessment compared to those who did not receive the training. The mean number of correct responses on the ACLS knowledge assessment was significantly higher ($p<0.05$) for those who felt their CPR training in medical school was adequate compared to those who felt it was inadequate. Following CPR guidelines resulted in significantly higher ($p<0.05$) mean correct ACLS knowledge scores than not following guidelines (Table 3).

Table 1. Findings related to MRs' CPR experience and CPR training

Survey Questions	Answers	n	%
Has a basic and advanced life support course been taught at the faculty you graduated from?	Yes	92	81.4
	No	12	10.6
	I do not remember	9	8.0
Have you taken any courses, seminars, congresses or in-service training on basic and advanced life support after graduation?	Yes	61	54
	No	46	40.7
	I do not remember	6	5.3
Did you attend assistant orientation training?	Yes	38	33.6
	No	75	66.4
Did you perform basic life support outside the hospital?	Yes	31	27.4
	No	82	72.6
Do you consider yourself competent in CPR?	Yes	66	58.4
	No	30	26.5
	I do not remember	17	15.0
Do you find the CPR training given in medical schools sufficient?	Yes	33	29.2
	No	73	64.6
	I do not remember	7	6.2
Would you like to repeat CPR training?	Yes	90	79.6
	No	16	14.2
	I have no idea	7	6.2
Are you following the CPR guide?	Yes	45	39.8
	No	68	60.2
When was the last resuscitation guide published?	2005	2	1.8
	2008	1	0.9
	2010	51	45.1
	2012	26	23.0
	2014	33	29.2

CPR: *Cardiopulmonary Resuscitation*

Table 2. Comparison of BLS knowledge levels of the participants according to some characteristics.

Questions	Answers	Basic Life Support Knowledge Correct Rate			p*
		Mean	Median	Min-Max	
Gender	Female	52.5±15.1	53.0	7-80	0.260
	Male	50.1±14.1	47.0	13-80	
Has a basic and advanced life support course been taught at the faculty you graduated from?	(+)	51.7±14.7	53.0	7-80	0.797
	(-)	52.1±15.4	53.0	13-80	
Have you taken any courses, seminars, congresses or in-service training on basic and advanced life support after graduation?	(+)	51.7±14.3	53.0	13-80	0.935
	(-)	51.9±15.4	53.0	7-80	
Did you attend assistant orientation training?	(+)	49.2±16.3	47.0	7-80	0.140
	(-)	51.3±13.9	53.0	13-80	
Did you perform basic life support outside the hospital?	(+)	50.5±17.1	53.0	20-80	0.802
	(-)	52.3±13.9	53.0	7-80	
Do you consider yourself competent in CPR?	(+)	54.1±13.6	53.0	20-80	**0.025**
	(-)	48.6±15.9	47.0	7-80	
Do you find the CPR training given in medical schools sufficient?	(+)	47.9±15.6	47.0	20-80	**0.036**
	(-)	53.4±14.2	53.0	7-80	
Would you like to repeat CPR training?	(+)	52.8±13.6	53.0	13-80	0.129
	(-)	47.8±18.5	47.0	7-80	
Are you following the CPR guide?	(+)	54.0±15.9	53.0	7-80	0.130
	(-)	50.3±13.9	53.0	13-80	

CPR: *Cardiopulmonary Resuscitation,* ***BLS****: Basic Life Support, *:Mann-Whitney u test*

Table 3. Findings related to the ACLS experience and ACLS trainings received by MRs

Questions	Answers	Advance Cardiac Life Support Knowledge Correct Rate			p*
		Mean	Median	Min-Max	
Gender	Female	54.2±19.7	53.0	13-100	0.513
	Male	52.3±18.2	47.0	20-93	
Has a basic and advanced life support course been taught at the faculty you graduated from?	(+)	52.6±18.7	53.0	13-93	0.157
	(-)	58.4±21.2	60.0	20-100	
Have you taken any courses, seminars, congresses or in-service training on basic and advanced life support after graduation?	(+)	52.6±18.4	53.0	20-100	0.456
	(-)	54.8±20.2	53.0	13-93	
Did you attend assistant orientation training?	(+)	55.8±19.0	53.0	20-100	**0.021**
	(-)	49.4±19.2	47.0	13-93	
Did you perform basic life support outside the hospital?	(+)	50.2±20.9	47.0	13-93	0.180
	(-)	55.0±18.5	53.0	20-100	
Do you consider yourself competent in CPR?	(+)	55.1±17.4	53.0	20-100	0.235
	(-)	51.6±21.5	47.0	13-93	
Do you find the CPR training given in medical schools sufficient?	(+)	48.2±16.9	47.0	20-93	**0.035**
	(-)	55.9±19.7	53.0	13-100	
Would you like to repeat CPR training?	(+)	54.9±18.8	53.0	20-100	0.360
	(-)	58.7±20.4	53.0	13-93	
Are you following the CPR guide?	(+)	62.2±19.7	60.0	13-100	**0.000**
	(-)	48.0±16.7	47.0	20-93	

***CPR**: Cardiopulmonary Resuscitation, **ACLS**: Advance Cardiac Life Support, *: Mann-Whitney u test*

By comparing the numerical values with the values of the correct response rates given to the questions evaluating BLS and ACLS knowledge levels; there was a significant ($p<0.05$) positive correlation between age and the correct rate of BLS Knowledge Level, but there was no significant ($p>0.05$) correlation between age and the correct rate of ACLS Knowledge Level. There was a significant ($p<0.05$) positive correlation between length of practice and BLS Knowledge Level correct rate, but there was no significant ($p>0.05$) correlation between ACLS Knowledge Level correct rate. In addition, no significant ($p>0.05$) correlation was found between MR duration and BLS and ACLS correct rate (Table 4).

Table 4. Comparison of BLS and ACLS knowledge level accuracy rates of MRs by age, residency and training period.

		BLS Knowledge Correct Rate	ACLS Knowledge Correct Rate
Age	r	0.187	0.068
	p	**0.047**	0.473
Years working as a physician	r	0.289	0.164
	p	**0.002**	0.083
Years working as an assistant physician	r	0.113	0.026
	p	0.234	0.781

*Spearman Correlation, **BLS:** Basic Life Support,**ACLS**: Advance Cardiac Life Support*

In the comparison of BLS knowledge levels according to departments, there was no significant difference ($p=0.122$, $p=0.067$, respectively) in the BLS knowledge level correct rates in internal sciences and surgical departments with and without intensive care unit. The mean ACLS knowledge level correct response rate was significantly ($p<0.01$) higher in surgical departments (63 ±21.3) than in internal departments (48.4±15.7). There was no significant ($p=0.216$) difference in the ACLS knowledge level correct rate between internal and surgical sciences with intensive care units.

DISCUSSION

The study assessed the BLS and ACLS knowledge and status of medical residents at KTRH. When researchers assessed opinions on the CPR training received, they found that about half of the participants did not receive BLS and ACLS training after graduating from medical school. Two-thirds of the participants believed they had adequate CPR skills. Almost two-thirds did not think the CPR training offered in medical schools was sufficient. Over half of the participants did not follow the new CPR guidelines and were unaware of the date of the most recent guideline

publication. Additionally, the overwhelming majority thought that CPR training should be repeated. When evaluating participants' knowledge levels, it was found that those who felt competent in BLS, had satisfactory training in medical schools, participated in resident orientation sessions, and followed the current guidelines had higher knowledge levels.

In a study conducted by Pillow et al. with fourth-year medical faculty students, it was observed that most of the students considered themselves inadequate in resuscitation and CPR and 36.8% of the students avoided resuscitation practice for this reason. They emphasized that BLS and ACLS training should be included in the medical school curriculum (8). In our study, 64.6% of the research assistants who participated in the study thought that they were inadequate in CPR.

In a study conducted by Demirkıran et al. on BLS training with first-year students at Istanbul University Cerrahpaşa Medical Faculty, it was observed that the training given was successful. In their study, it was concluded that since CPR training was important for medical faculty students, it was considered appropriate to start this training in the first year (9). In the following education periods, BLS and ACLS training are given in departments such as emergency medicine, anesthesia, and reanimation, cardiology, and pediatrics. However, the number and qualifications of these trainings are not standardized and may vary between medical faculties. In this study, it was found that 64.6% of the participating medical residents thought that the CPR training given at the undergraduate level in medical faculties was inadequate.
In the study by Kımaz et al. in which they evaluated the knowledge levels of BLS and ACLS with the participation of 53 physicians, it was observed that 33 of the physicians (62.3%) participated in CPR courses after graduation (10). In our study, we found that 61 (54%) of the physicians attended a course, seminar, congress or in-service training on BLS and ACLS after graduation. The high percentage of participation in CPR courses in the study by Kımaz et al. may be attributed to the fact that the participants were physicians working in 112 emergency services, that CPR was relatively predominant in their in-house training, and that their participation rates in training were high.

In 1999, Garcia-Barbaro and Caturla-Such surveyed 168 medical faculties and 202 teaching hospitals from 47 countries in Europe, including 11 universities from Turkey, and found that 167 of these institutions offered CPR, 135 BLS, 136 ACLS and 114 both. It was found that medical school students received an average of 7.7±5.7 hours of theoretical and 6.7±5.3 hours of practical training in BLS and an average of 9.8±7.6 hours of theoretical and 8.7±6.8 hours of practical training in ACLS. It was found that CPR training was given in 11 faculties in Turkey and the mean hours of theoretical and practical life support training in these universities were similar to the total mean (11). In this study, similar to the data in the literature, it was found that more than half of the participants were of the opinion that the CPR training given at the medical faculty was not sufficient and 58.4% of them found themselves sufficient in CPR.

BLS is tried to be simplified even more with each current guideline. It was reported that the level of theoretical knowledge increased significantly by providing BLS training even to non-healthcare professionals such as shopping center employees (12). In a study conducted by Çalışkan et al. in university students in departments other than health sciences, it was shown that the level of BLS awareness and knowledge increased with BLS training (13). In addition, in a study conducted with dentists and pharmacists, who are thought to have higher medical knowledge, it was shown that BLS knowledge levels could be increased with training (14). In addition, in this study, in parallel with the literature, it was shown that participation in CPR BLS trainings such as medical resident orientation training increased the level of knowledge statistically significantly. While the level of knowledge can be increased with training in non-physician medical departments, even in the non-healthcare worker population with low education level, BLS knowledge in physicians can be kept up to date and fresh with practical short and frequent repetitive trainings.

Similar to the results in the literature, it was shown that participation in CPR trainings such as MRs orientation training increased the level of knowledge statistically significantly (15). Resuscitation training should be repeated continuously since the guidelines are updated every five years and the practice of application should not be forgotten. The success of resuscitation is ensured by the prevalence, quality and practical applications of the training provided. Another point identified in our study is that only 45.1% of the MRs knew the year of the most recent resuscitation guideline. When this situation is considered together with the rate of those who do not follow the current guidelines, it may explain the low rate of correct responses to questions prepared according to the current guidelines for BLS and ACLS.

In a survey study conducted by Price et al. on CPR training, knowledge and behaviors of physicians, it was concluded that physicians who received resuscitation training in the last six months were safer in resuscitation practice (16). In our study, the relationship between physicians' thoughts about their own competence in CPR and their level of knowledge was examined. It was found that the knowledge levels of medical residents who considered themselves competent in CPR were higher than the others. This difference was

statistically significant for both BLS and ACLS knowledge levels. It can be said that these participants' high level of knowledge increased their confidence in the BLS and ACLS. However, the majority of medical residents (79.6%) believed that CPR training should be repeated.

Şener et al. reported that the BLS knowledge levels of those working in the Departments of Anesthesia and Reanimation and Emergency Medicine were better than those working in other departments in a study conducted on the BLS knowledge levels of research assistants in Dokuz Eylül University Medical Faculty hospital (17). In this study, BLS knowledge level rates were found to be higher in internal sciences and surgical sciences with intensive care units. This result may be thought to be due to the fact that resuscitation training is included in the training program in Emergency Medicine and branches with intensive care units and that clinical experience is high due to frequent encounters with patients in need of resuscitation.

In a study conducted by Filgueiras Filho et al. on physicians working in the emergency department regarding the care of cardiac arrest patients, no difference was found in the level of theoretical knowledge between non-surgeon clinicians and surgeons (18). In our study, although there was no significant difference between residents in medical and surgical departments, it was found that 50.3% of MRs in medical departments and 54.5% of MRs in surgical departments answered the questions related to CPR correctly. However, it was found that 48.4% of medical residents and 63.3% of surgical residents correctly answered questions about ACLS, and the difference was statistically significant. The reason for this difference may be that some of the acute procedures performed by surgical departments take place in the emergency department.

Limitations

This study was based on the BLS and ACLS guidelines at the time of the study. In addition, the study does not include all physicians since medical residents with ongoing training were included in the study. In this study, the level of resuscitation knowledge was evaluated only theoretically and practical skills were not evaluated. Since the research assistants graduated from different universities in different years, their prior resuscitation training is not clearly known.

Conclusion

BLS and ACLS are basic medical skills, and a physician graduating from medical school is expected to be able to perform these procedures. However, postgraduate medical education should include all physicians. To increase the chances of survival in reversible sudden cardiac arrest, BLS and ACLS training should be emphasized to be renewed and updated on a global and national level, starting with healthcare professionals.

Ethics Committee Approval: This study was approved by the Erciyes University Clinical Research Ethics Committee with decision number 96681246/195 and dated 18 December 2015.

Conflict of Interest: The authors declare no conflict of interest in this study.

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CASE REPORT

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Traumatic Pneumorrhachis: A Case Report

Travmatik Pnömoraşi: Olgu Sunumu

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ABSTRACT

Pneumorrhachis, defined as the presence of air in the spinal canal, is a rare clinical condition. In this article, we aimed to present a patient with significant head trauma who fell from a height and was diagnosed with pneumorrhachis. A 52-year-old male patient was brought to our emergency department by ambulance due to falling from the stairs while picking grapes at a height of 3 meters. The patient had a subarachnoidal hemorrhage, subdural hemorrhage, pneumocephalus, and fractures in the frontal, temporal, and parietal bones. Air densities were detected in the cervical spinal canal. Traumatic pneumorrhachis is essential as an indicator of accompanying severe injury.

Keywords: *Intraspinal air, pneumorrhachis, skull fracture*

ÖZET

Spinal kanal içerisinde hava bulunması olarak tanımlanan pnömoraşi nadir görülen bir klinik durumdur. Bu yazıda yüksekten düşen majör kafa travması olan ve pnömoraşi tespit edilen bir hasta sunmayı amaçladık. 52 yaşında erkek hasta 3 metre yüksekte üzüm toplarken merdivenden düşme nedeniyle ambulans ile acil servisimize getirildi. Hastada subaraknoidal kanama, subdural kanama, pnömosefali ve frontal, temporal ve paryetal kemikte kırık vardı. Servikal spinal kanalda hava dansiteleri tespit edildi. Travmatik pnömoraşi eşlik eden ciddi yaralanması bir göstergesi olması açısından önemlidir.

Anahtar Kelimeler: *İntraspinal hava, kafatası kırığı, pnömoraşi*

INTRODUCTION

Pneumorrhachis (PR) was first reported by Gordon and Hardman (1) as the presence of air in the cervical spine in a trauma patient with multiple skull fractures and took its name in 1987 (2). PR is a rare and specific condition that occurs for different reasons and with other possible entry routes. PR occurs for various reasons, especially traumatic and iatrogenic, and is a rare imaging finding. PR can be classified as intradural (subdural or subarachnoid) and extradural (intraspinal, epidural). Although extradural PR is generally harmless, intradural PR is often associated with severe complications (3,4). In this article, we presented a case of pneumorrhachis, which is an extremely rare complication of trauma.

CASE REPORT

A 52-year-old male patient was brought to our emergency department by ambulance due to falling from the stairs while picking grapes at a height of 3 meters. When paramedics found the patient at the scene of the accident, he was in a comatose state. When the patient arrived at the emergency department, he was unconscious, his Glasgow coma scale was 6 (eye: 1, verbal: 2, motor: 3), and there was scalp laceration and otorrhagia in the left ear. The patient was intubated immediately. Vital signs were arterial blood pressure 110/60 mmHg, pulse 144/min, and oxygen saturation 94%. The patient underwent tomography of the head, spine, chest, abdomen, and pelvis by the trauma protocol. Subarachnoidal hemorrhage, subdural hemorrhage in the right pariteofrontal region, and pneumocephaly were detected in the patient. Additionally, there was a comminuted displaced fracture in the right frontal, temporal, and parietal bones (Figure 1). There were air densities in the cervical spinal canal (Figure 2).

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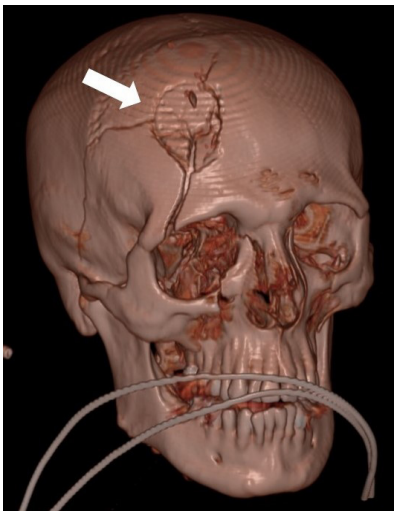

Figure 1. Volume-rendered image shows fractures of the frontotemporoparietal bones (arrow).

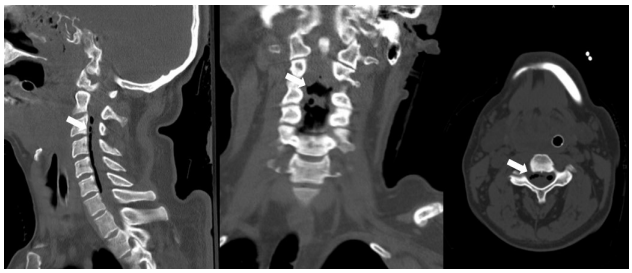

Figure 2. Computed Tomography (CT) scan of cervical pneumorrhachis-sagittal, coronary, and axial view. The white arrows point to the intraspinal air.

There was no pneumothorax, pneumomediastinum, or rib fracture. No pathology was detected in other systems. The patient was admitted to the neurosurgical intensive care unit. In the control tomography taken three days later, the air in the spinal canal had disappeared. However, the patient died on the 22nd day of hospitalization. Due to the patient's unconsciousness, written informed consent was obtained from the patient's family member.

DISCUSSION

Causes of PR are generally classified as iatrogenic, non-traumatic, and traumatic. Iatrogenic PR may occur during surgical interventions, anesthesia, and as a result of diagnostic examinations. Examples of non-traumatic PR reasons: Conditions such as malignancy, severe cough due to bronchial asthma or acute bronchitis, cardiopulmonary resuscitation, airway obstruction due to foreign body aspiration, physical exertion, use of ecstasy or marijuana, and prolonged and severe vomiting due to diabetic ketoacidosis may be given (5–7).

Traumatic PR is very rare and may occur as a result of isolated head trauma, cervical, thoracic, abdominal, and pelvic injuries, or spinal trauma. Traumatic PR is usually self-limiting and does not require treatment. However, rapid recognition and distinction between epidural and subarachnoid is critical. Although the presence of subarachnoid air is an indicator of underlying severe damage, it may be complicated by tension pneumocephalus or meningitis. Epidural/extradural type traumatic PR is primarily benign. PR, which shows the severity of the trauma, is important because it emphasizes the need for subsequent comprehensive and systemic evaluation (5,6,8). First of all, the diagnosis of PR, which is a radiographic rather than clinical diagnosis, can be made with plain radiography and computed tomography. The primary diagnostic tool of choice for PR is computed tomography (CT). but it may not distinguish between intra- and extradural PR. However, subarachnoid PR located more centrally within the canal than normal anatomy may be considered extradural PR in the presence of corner or peripherally collected air. Magnetic resonance imaging or intrathecal contrast-enhanced CT can distinguish intradural air from extradural air (3,9,10). PR, in our case, was extradural because it was peripherally located and disappeared quickly. Traumatic PR does not require any special treatment other than treating the underlying injury. PR usually disappears with resorption of intra-spinal air within a few days (10). In our case, cervical intraspinal air disappeared in the tomography taken three days later.

Conclusion

Traumatic PR is crucial as it is an indicator of severe injury accompanying it. It is necessary to be skeptical about skull base fractures in patients with PR. The emergency physician should focus on treating the underlying pathology in traumatic PR, and PR usually disappears on its own.

Informed Consent: Due to the patient's unconsciousness, written informed consent was obtained from the patient's family member.

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CASE REPORT

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A Case of Hypertriglyceridemic Pancreatitis Secondary to Tacrolimus and Estradiol Use for In Vitro Fertilization

İn Vitro Fertilization Amaçlı Takrolimus ve Estradiol Kullanımına Sekonder Hipertrigliseridemik Pankreatit Olgusu

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ABSTRACT

Hypertriglyceridemia is a metabolic condition with a multifactorial etiology that may cause life-threatening complications, such as pancreatitis. In pregnant women, hypertriglyceridemia may be secondary to physiological changes during pregnancy or may be exacerbated by medications. The combination of tacrolimus and estradiol is sometimes used in In Vitro fertilization (IVF) for women with a history of recurrent implantation failure. This case report discusses a case of acute pancreatitis caused by hypertriglyceridemia secondary to the use of tacrolimus and estradiol.

Keywords: *Tacrolimus, estradiol, in vitro fertilization, hypertriglyceridemia, pancreatitis*

ÖZET

Hipertrigliseridemi, pankreatit gibi yaşamı tehdit eden komplikasyonlara neden olabilen çoklu etiyolojiye sahip bir metabolik durumdur. Hamile kadınlarda hipertrigliseridemi, gebelik sırasındaki fizyolojik değişikliklere sekonder olabilir veya ilaçlar tarafından kötüleştirilebilir. Tacrolimus ve östradiol kombinasyonu, tekrarlayan implantasyon başarısızlığı öyküsü olan kadınların in vitro fertilizasyon (IVF) tedavisinde kullanılmaktadır. Bu vaka raporu, tacrolimus ve östradiol kullanımına bağlı gelişen hipertrigliseridemiye sekonder akut pankreatit vakasını ele almaktadır.

Anahtar Kelimeler: *Tacrolimus, östradiol, in vitro fertilizasyon, hipertrigliseridemi, pankreatit*

INTRODUCTION

Hypertriglyceridemia during pregnancy may be related to the physiological changes that occur during pregnancy, and this effect may be intensified by the medications administered. Acute pancreatitis due to hypertriglyceridemia is known to pose significant maternal and fetal mortality and morbidity risks in pregnant women (1). In Vitro fertilization (IVF), T helper 1 (Th1) and Th1/Th2 ratios have been found to be elevated in women with a history of recurrent implantation failure (2). Therefore, immunosuppressive agents such as tacrolimus have been increasingly used, as they have been shown to improve implantation rates and pregnancy outcomes, especially in women with an elevated Th1 immune response (2). Additionally, estradiol use has been shown to have a positive impact on pregnancy rates in IVF studies (3). Both tacrolimus and estradiol are known to cause hypertriglyceridemia (4,5). Severe gestational hypertriglyceridemia can lead to acute pancreatitis, with a maternal mortality rate of approximately 20%. Fasting triglycerides >500 mg/dL, despite a strict dietary and lifestyle modifications, should prompt treatment with omega-3-fatty acids and continue a fat-restricted diet (<20g total fat/d or <15% total calories) under the guidance of a registered dietitian. The use of fibrates should be considered as a second-line therapy due to their unclear risk versus benefit and potential teratogenic effects. Plasmapheresis should be considered early in asymptomatic pregnant women with fasting triglyceride

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levels >1000 mg/dL or in pregnant women with clinical signs and symptoms of pancreatitis and triglyceride levels >500 mg/dL despite maximal lifestyle changes and pharmacologic therapy (6). A MEDLINE search (1950-2018) of the English language literature was performed to identify all adult (≥17 years old) human case reports where medication/drug-induced acute pancreatitis was the causative factor. The included case reports were required to provide the name of the drug, and the diagnosis of AP must have been strictly established based on the revised Atlanta Classification criteria. A total of 183 medications were found to be implicated in 577 DIAP cases (7).

This case report presents the first instance of acute pancreatitis caused by hypertriglyceridemia resulting from the combined use of estradiol and tacrolimus in a pregnant woman with recurrent implantation failure.

CASE REPORT

A 32-year-old woman with a known history of polycystic ovary syndrome, hypertension, and nephrolithiasis, who had experienced two previous failed IVF attempts, achieved a 7-week pregnancy with her third IVF attempt.

Due to her previous failures, the patient was administered tacrolimus 1 mg/day, subcutaneous progesterone 225 mg, and estradiol 32 mg/day starting one week before the IVF attempt. Her laboratory results revealed amylase levels of 215 U/L (normal range: 28-100 U/L), lipase levels of 711 U/L (normal range: 13-60 U/L), triglyceride levels of 1228 mg/dL (normal range: 40-160 mg/dL), cholesterol levels of 740 mg/dL (normal range: 70-200 mg/dL), LDL levels of 609 mg/dL (normal range: 100-130 mg/dL), and HDL levels of 18 mg/dL (normal range: 35-55 mg/dL) (Table 1).

Possible causes of hypertriglyceridemia, such as alcohol use, obesity, hypothyroidism, chronic inflammatory disease, and chronic kidney disease, were ruled out. The patient's lipid panel had been within the normal range prior to the IVF attempt. Abdominal ultrasonography revealed normal choledochal and intrahepatic bile ducts, pancreatic edema, peripancreatic fluid collection, and a diagnosis of pancreatitis. Computed tomography was not recommended due to the patient's pregnancy, and magnetic resonance cholangiopancreatography was not advised because she was in her first trimester. Echocardiography was performed to assess coronary artery disease due to the existing hyperlipidemia, revealing an ejection fraction of 60% and left ventricular hypertrophy.

Consultations were obtained from the fields of gastroenterology, gynecology, and endocrinology based on the current findings and complaints.

Due to the presence of pancreatitis, oral intake was discontinued, and the patient was managed with hydration. Tacrolimus and estradiol were discontinued based on the obstetrics and gynecology team's assessment that the pancreatitis was related to drug-induced hyperlipidemia. Apheresis for hyperlipidemia was not considered, as it could potentially result in fetal miscarriage. After discontinuation of tacrolimus and estradiol, the clinical signs of pancreatitis regressed, and amylase and lipase levels returned to normal on the fourth day. A combination of omega-3 fatty acids and fibrates was planned to address hyperlipidemia.

Table 1. Tacrolimus and estradiol treatment cessation-related biochemical parameter alteration.

Parameters:	Day 1	Day 2	Day 3	Day 4	Day 5
Amylase (28-100 U/L)	225	70	46	41	50
Lipase (13-60 U/L)	711	252	190	135	120
Triglyceride (40-160mg/L)	1228	990	989	856	611

DISCUSSION

In both the general population and pregnant women, the most common cause of pancreatitis is of biliary origin (8). Drug use and hypertriglyceridemia are other contributing factors. Tacrolimus, an estradiol and calcineurin inhibitor, has been increasingly used in recent years to enhance implantation success in pregnant women undergoing IVF. Studies have indicated that elevated blood tacrolimus concentrations in the early stages are associated with hyperlipidemia (9). Although the exact impact of tacrolimus on lipid metabolism is not fully understood, it may lead to hypertriglyceridemia through impaired triglyceride clearance due to reduced lipoprotein lipase biosynthesis (10). Additionally, it can elevate triglyceride levels by inducing insulin resistance through beta-cell dysfunction and disruptions in insulin signaling (10). Estrogen contributes to hypertriglyceridemia through various mechanisms. Research has shown that estrogen enhances the secretion of very low-density lipoprotein (VLDL) from the liver while reducing triglyceride catabolism by decreasing levels of hepatic lipase and lipoprotein lipase. Furthermore, in a study conducted on rats, estrogen-induced increase in pancreatic amylase enzyme levels had a direct toxic effect on pancreatic cells (11). In this case, pancreatitis resulted from hypertriglyceridemia, exacerbated by the combined effects of tacrolimus and estradiol, along with the physiologically elevated triglyceride levels during pregnancy. The pancreatitis resolved after discontinuation of both drugs, which were implicated in the etiology. In most cases of hypertriglyceridemia-induced. Acute pancreatitis, conservative management (nothing by mouth, intravenous fluid resuscitation and analgesia) is sufficient to achieve triglyceride levels less than 500 mg/dl. Intravenous insulin and plasmapheresis are sometimes

used, although prospective studies demonstrating clinical benefits, it is still commonly used. Pharmacological management of hypertriglyceridemia (HTG) should start early and target triglyceride levels of less than 500 mg/dL to reduce the risk of recurrent acute pancreatitis. In addition to the currently used fenofibrate and omega-3 fatty acids, several novel agents are being studied for the long-term treatment of HTG (12,13).

Conclusion

For individuals predisposed to hyperlipidemia, close monitoring of lipid profiles and symptoms that may arise due to complications is recommended. It should be noted that the concurrent use of drugs known to cause hyperlipidemia, such as tacrolimus and estradiol, may lead to serious complications such as acute pancreatitis.

Informed Consent: Written informed consent was obtained from the patient for the publication of the study
Conf ict of Interest: No conflict of interest was declared by the authors.
Financial Disclosure: The authors declared that this study has no financial support.

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IMAGE PRESENTATION

Journal of Anatolian Medical Research JAMER 2024;9(1):33-35
DOI:10.55694/jamer.1387428

Idiopathic Granulomatous Mastitis Mimicking Breast Cancer: A Case Report

Meme Kanserini Taklit Eden İdiyopatik Granülomatöz Mastit: Olgu Sunumu

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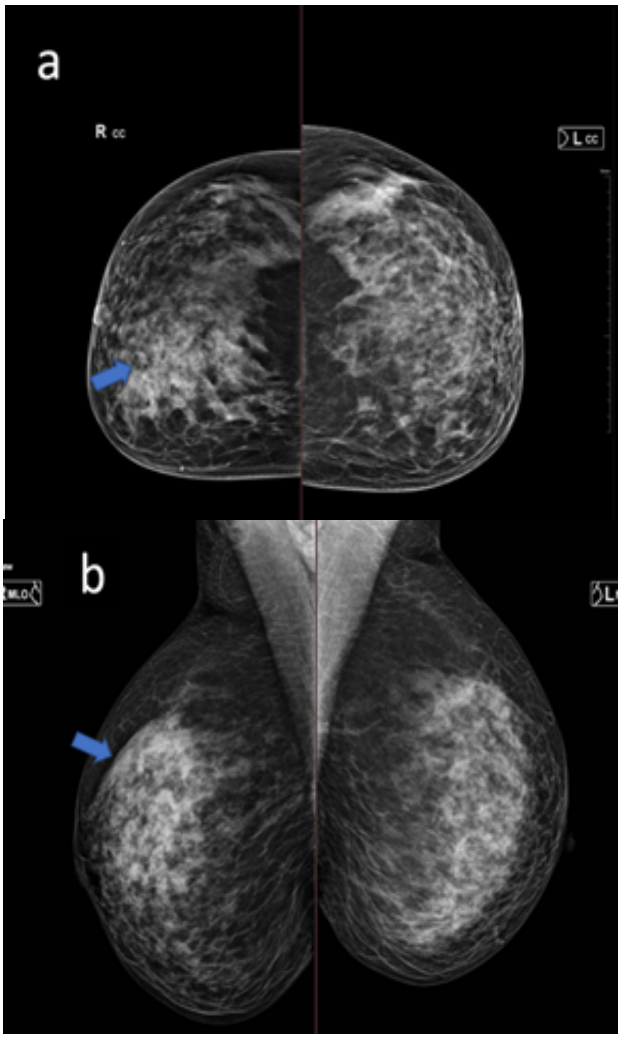

Figure 1. a) CC (craniocaudal) b) MLO (Mediolateral oblique) digital mammograms show an ill-defined asymmetric parenchymal density completely filling the upper inner quadrant of the right breast (arrows). No microcalcifications were observed.

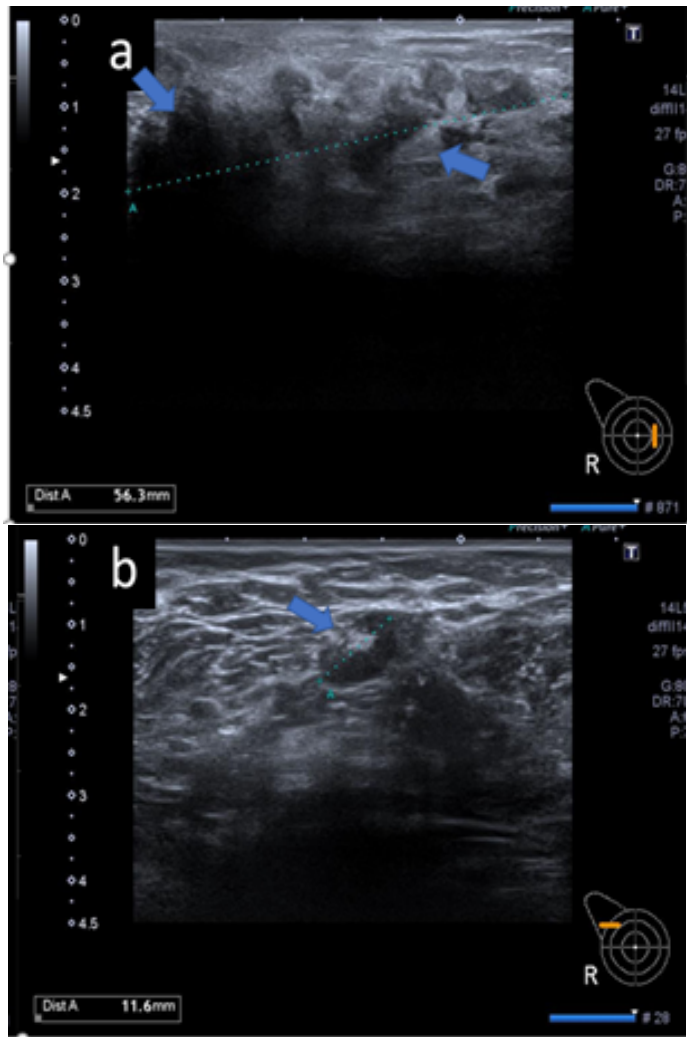

Figure 2. a) Ultrasound (US) image of the inner right shows a shows large non-mass heterogeneous area with distorted containing with atypical dense content (arrows) b) Sonogram shows cortical thickening of the lymph node (arrow).

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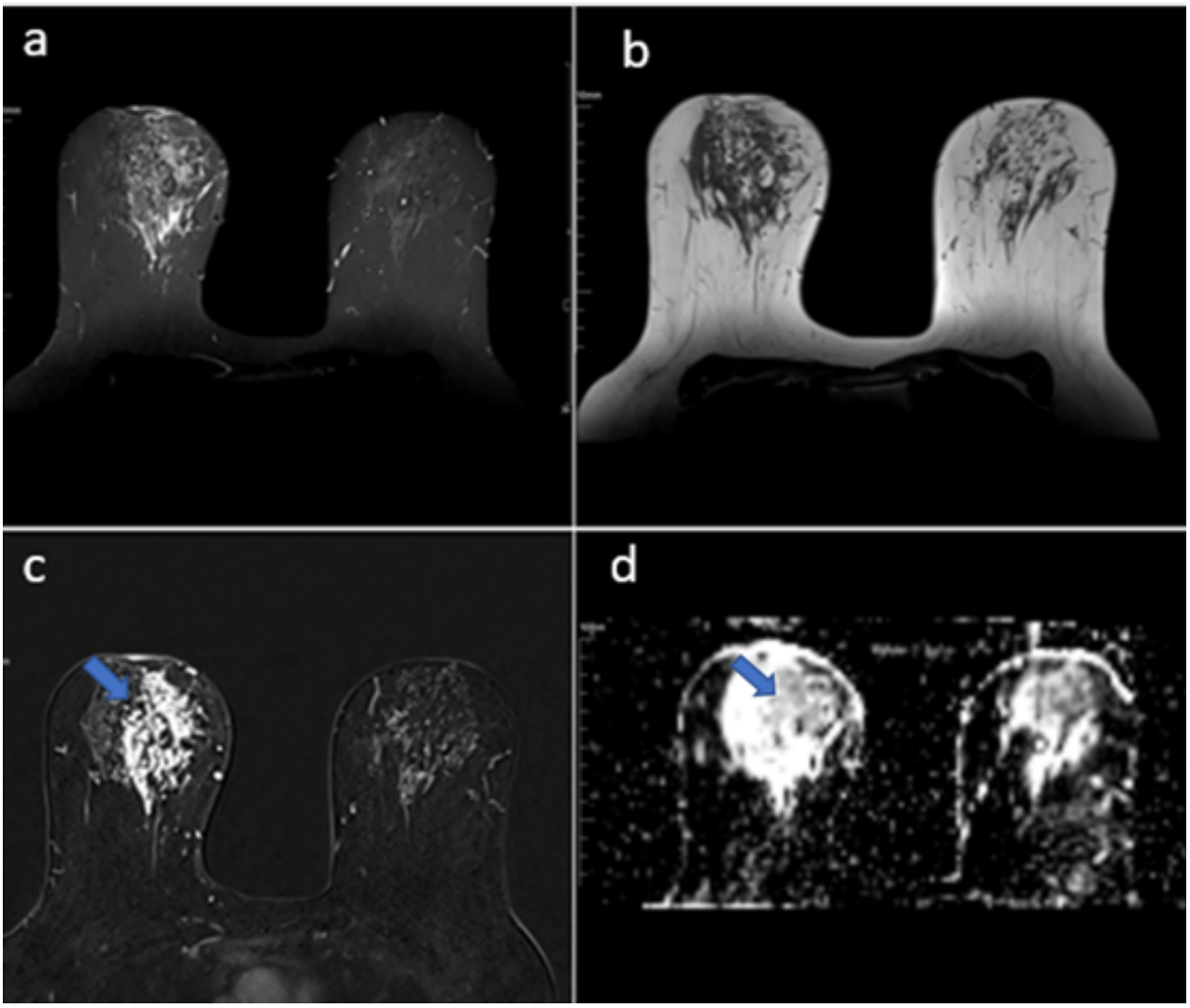

Figure 3. a) STIR axial b) T1-Weighted axial c) Contrast enhanced fat-suppressed T1W axial MR images; blue arrows show heterogeneous clustered intensely enhanced non-mass area filling whole upper inner quadrant of the right breast and retro areolar region. d) Diffusion restriction on diffusion-weighted imaging (arrows).

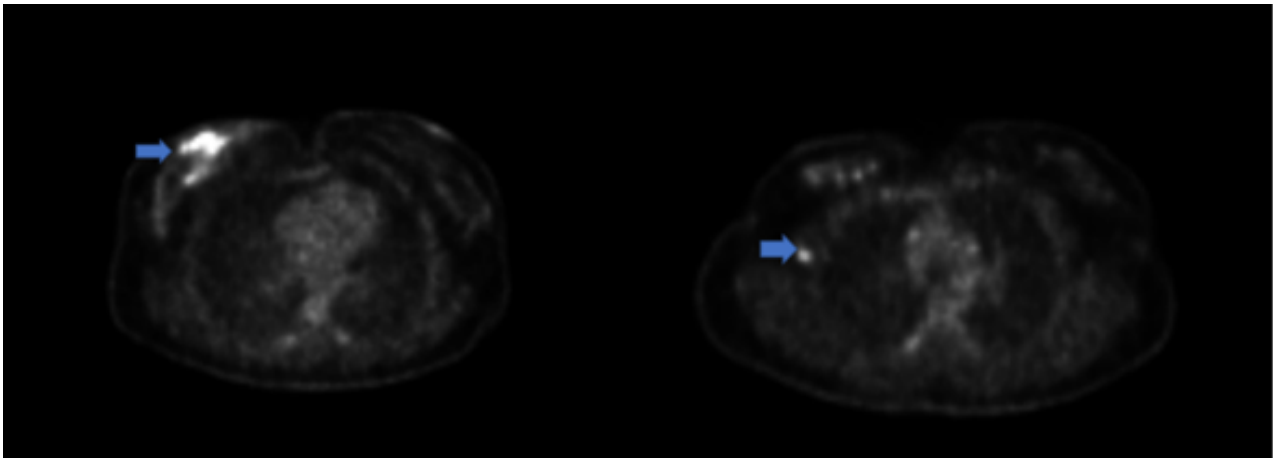

Figure 4. Hypermetabolic nodular area covering the upper middle zone of the right breast on 18F-FDG PET/CT images, with no significant mass formation. Additionally, a hypermetabolic axillary lymph node is observed, which is indicative of a primary malignant breast tumor (arrows).

A 35-year-old female presented with complaints of stiffness and pain in her right breast. She had intermittent, spontaneous, clear nipple discharge. Upon examination, a hard lump was palpated in the upper inner quadrant of the right breast. There were no signs of infection, such as erythema or increased temperature. Given the clinical presentation and imaging findings (mammography: Fig 1 and ultrasonography: Fig 2), malignancy and infectious pathologies were suspected. Ultrasound-guided core needle biopsy was performed. The pathology was reported as chronic granulomatous mastitis, and the fine needle aspiration biopsy on the axilla revealed benign cytology.

Idiopathic Granulomatous Mastitis (IGM) is a rare, chronic inflammatory disease that is resistant and shows a wide range of manifestations on radiological imaging. IGM was first described as a distinct clinical entity by Kessler and Wolloch in 1972. Generally, it affects young women of reproductive age, mostly during the five years following childbirth. Etiology is still unknown; many factors, mainly including hormonal factors, are proposed (1). Histologic criteria for granulomatous mastitis focus on lobules, excluding infections and specific causes. According to the concept of mammary duct–associated inflammatory disease sequence, certain conditions such as pregnancy, breastfeeding, and drug-induced hyperprolactinemia or galactorrhea might be associated with an increased risk of IGM.

A definite diagnosis is through by histopathological evaluation, and radiology has a crucial role for the diagnostic process. Mammography , ultrasonography, and Magnetic resonance imaging are commonly used for diagnosis. However, due to their wide spectrum and low sensitivity, interpreting the findings can be challenging (2). IGM presents similar clinical signs and symptoms to breast carcinoma. Irregular hypoechoic mass with multiple tubular extensions, asymmetry on mammograms, multiple heterogeneous areas with ring-like enhancement, regional heterogeneous non-mass enhancements (NMEs), or enhanced masses are the most common findings. Skin thickening, parenchymal distortion, nipple retraction, and axillary lymphadenopathy may also be observed (3).

Idiopathic Granulomatous Mastitis (IGM) is a rare chronic inflammatory benign disease of the breast with an unknown etiology. The cause may be the autoimmune process, abnormal hormone levels, infection, or lactation. The most common clinical presentation is a unilateral, palpable breast lump, and nipple retraction of the overlying skin.

Radiologically and clinically, it may mimic breast carcinoma. This case report discusses IGM mimicking breast cancer.

Due to all these findings, it is challenging to differentiate malignancy clinically and radiologically (4). In our case, radiological findings were also perplexing. MRI showed a heterogeneous clustered intensely enhanced non-mass area (Fig. 3), which was suspected to be malignant. On PET-CT imaging, a hypermetabolic nodular mass was identified, which was compatible with a primary malignant breast tumor (Fig. 4). After a US-guided biopsy, IGM was confirmed. Then the patient was started on prednisolone treatment and a regression was observed.

Informed Consent: Written informed consent was obtained from the patient for the publication of the study

Conflict of Interest: No conflict of interest was declared by the authors.

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GENEL BİLGİLER

Journal of Anatolian Medical Research (JAMER): Kayseri Şehir Hastanesi'nin tümüyle elektronik ve ücretsiz, senede 3 kez yayımlanan süreli ve bilimsel yayın organıdır. Derginin yazı dili Türkçe ve İngilizcedir. Bütün tıp ve ilgili sağlık alanlarının klinik uygulamaları hakkında orijinal araştırma ve klinik gözlemler yayımlanır. Yeni tekniklerin ve tedavi yöntemlerinin etkinliğini tanımlayan araştırma makalelerine yayın önceliği verilir. JAMER, Araştırma Makalesi, Olgu Sunumu, Derleme, Yorum, Editöre Mektup ve Cevaplarını yayımlar.

· Araştırma Makalesi

Yeni ve önemli temel veya klinik bilgi sunar, önceki çalışmaları genişletir ve ilerletir veya klasik bir konuda yeni bir yaklaşım getirir. Başlık sayfası, Yazarlar ve adresleri, Özet, Anahtar Kelimeler, Giriş, Gereç ve Yöntemler, Etik konular, Bulgular, Tartışma, Sonuç, Teşekkürler (varsa), Çıkar çatışması, Finansal destek, Kaynaklar, Şekiller (en fazla 5 adet), Şekil açıklamaları, Tablolar (en fazla 5 adet) ve Tablo açıklamalarından oluşur. Araştırma makaleleri için ana metin (özet ve kaynaklar hariç) 5000 kelimeyi, kaynakların sayısı ise 40'ı geçmemelidir.

· Olgu Sunumları

İlginç olguları, yeni fikirleri ve teknikleri tanımlar. Olgu sunumu; Başlık, Yazarlar ve adresleri, Özet, Anahtar Kelimeler, Giriş, Olgu sunumu, Tartışma, Sonuç, Teşekkürler (varsa), Hasta onamı, Çıkar çatışması, Finansal destek, Referanslar, Şekiller (en fazla 3 adet), Şekil açıklamaları, Tablolar (en fazla 3 adet) oluşmaktadır. Olgu raporları için ana metin (özet ve kaynaklar hariç) 2000 kelimeyi, kaynakların sayısı ise 20'yi geçmemelidir.

· Derleme

Yayın Kurulu, belirli bir konu hakkında bilgili ve uygun bir şekilde yazmaya yetkin mesleki deneyime sahip bir yazarı davet eder. Derleme; Başlık, Yazarlar ve adresleri, Özet, Anahtar Kelimler, Giriş, Ana Bölümleri, Alt Bölümleri, Sonuç, Teşekkür (varsa), Çıkar çatışması, Finansal destek, Kaynaklar, Şekiller (en fazla 5 adet), Şekil açıklamaları, Tablolar (en fazla 5 adet) ve Tablo açıklamalarından oluşur. Olgu raporları için ana metin (özet ve kaynaklar hariç) 5000 kelimeyi geçmemelidir. Kaynak sayısında bir sınırlama yoktur.

· Editöre mektup

JAMER Editörler Kurulu'nun onayı ile yayımlanır. Mektup, açık ve yorum getirilen makale ile ilişkili olmalıdır. Editöre mektup; 500 kelime, 1 tablo ve 5 kaynak ile sınırlıdır.

· Eleştiri/Yorum

Bir Eleştiri/Yorum, Başlık, Yazarlar, adresleri, Özet, Anahtar Kelimeler, Giriş, Tartışma, Sonuç, Etik Konular, Teşekkürler, Çıkar Çatışması, Referanslar, Şekil Açıklamaları, Şekiller ve Tablolardan oluşur. Yazılar 2000 kelime ile sınırlandırılmalıdır.

MAKALELERİN HAZIRLANMASI

Makaleler, "The Uniform Requirements for Manuscripts Submitted to Biomedical Journals - International Committee of Medical Journal Editors" (www.icmje.org) kurallarına uygun olarak Türkçe veya İngilizce olarak hazırlanmalıdır.
Makaleler ".doc" formatında sunulmalı ve yukarıda belirtilen kelime ve referans sınırlamalarına ve diğer ilgili bilgilere göre hazırlanmalıdır.

· Dil

Makale Türkçe veya İngilizce olarak hazırlanmalıdır.

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· Başlık Sayfası

Başlık sayfası maskeli değerlendirmeye imkan sağlaması için ayrı bir dosya şeklinde gönderilmelidir.
Başlık sayfası şunları içermelidir: (i) Türkçe ve İngilizce olarak hazırlanan makale başlığı özlü fakat bilgilendirici olmalıdır. (ii) Kısa başlık verilmelidir. (iii) Tüm yazarların tam adı, ORCID numarası, mail adresi, bağlı bulundukları kurum veya kuruluşların adı bulunmalıdır. (iv) Makale başlıklarında kısaltmalar, ticari isimler veya ticari markalar kullanılmamalıdır.

· Öz

Tüm makaleler için hem Türkçe, hem de İngilizce özet gönderilmelidir. Özet; çalışmanın amacını, ana bulguları ve ana sonuçlarını içermeli, sözcük sayısı 300'den fazla olmamalıdır. Öz (Abstract); Amaç (Aim), Gereç ve Yöntemler (Material and Methods), Bulgular (Results) ve Sonuç (Conclusion) başlıklarını içermelidir. Olgu çalışmaları ve derlemeler için özetler yapılandırılmamalıdır ve en fazla 250 kelime olmalıdır. Yabancı yazar(lar)ın Türkçe olarak bir yazı göndermesine gerek yoktur, çünkü yazı işleri kurulu bu yazıyı onlara sağlayacaktır.

· Anahtar Kelimeler

Yazarlar; U.S. Ulusal Tıp Kütüphanesi (NLM)'nin Tıbbi Konu Başlıkları'ndan (MeSH) alınan, 3 ile 5 arasında anahtar kelimeyi makalelerinin Öz (Abstract) bölümünden sonra sunmalıdır. Türkçe anahtar kelimeler Türkiye Bilim Terimleri'ne (TBT) göre yazılmalıdır (https://www.bilimterimleri.com/). Kelimeler "virgül (,)" ile birbirinden ayrılmalıdır.

· Ana Metin

Yazar adları ve bağlı bulundukları kurumlar, ana metin içeren dosyada belirtilmemelidir. Çalışmanın yazarlarının tespit edilebileceği diğer tüm bilgiler kaldırılmalıdır. Metin, MS Word programı ile hazırlanmalıdır. Tüm metinler Times New Roman yazı tipinde, 12 punto ve çift aralıklı yazılmalıdır. Makale metni; Giriş (Introduction), Gereç ve Yöntemler (Material and Methods), Bulgular (Results), Tartışma (Discussion) ve Sonuç (Conclusion) başlıklı bölümlere ayrılmalıdır.

(i) Giriş, makalenin amacını belirtmeli ve çalışmanın gerekçesini özetlemelidir. Yalnızca kesin referanslar verilmeli ve bu bölüm yaklaşık bir sayfa ile sınırlandırılmalıdır.

(ii) Gereç ve Yöntemler, gözlemsel veya deneysel konuların seçimini açıkça tanımlamalıdır. İstatistikleri de içeren belirlenmiş yöntemlere referanslar verilmelidir. Etik ile ilgili hususlar bu bölümde verilmelidir. Randomizasyon ile ilgili detaylar verilmelidir. Randomize çalışmaların sonuçlarını bildiren yazılar, hastaların çalışma boyunca ilerlemelerini gösteren CONSORT akış şemasına göre hazırlanmalıdır (http://www.consort-statement.org/). İstatistiksel değerlendirme, Gereç ve Yöntemler bölümünde ayrıntılı olarak açıklanmalıdır.

(iii) Bulgular, özlü bir şekilde verilmeli, şekil ve tabloları içermelidir. Tablo ve şekiller metin içinde tutarlı bir sıraya sahip olmalıdır. Metin içindeki veriler, tablolarda veya şekillerde tekrarlanmamalıdır.

Şekiller ve resimler, Tagged Image File Format (.tiff uzantılı) veya Joint Photographic Experts Group Format (.JPEG uzantılı) olarak ayrı dosyalar halinde sunulmalıdır. Şekillerin çözünürlüğü en az 600 dpi olmalıdır. Metin, tablolar ve şekiller MS Power Point programında hazırlanarak kaydedilmemelidir. Şekil açıklamaları, metne atıfta bulunmadan anlaşılabilecek kadar bilgi içermelidir. Şekiller daha önce başka bir yerde yayınlanmışsa kaynak gösterilmelidir. Şekillerdeki semboller kolaylıkla görünebilmeli ve karakterlerin font büyüklüğü en az 8-10 olmalıdır. Grafiklerdeki apsis ve ordinat isimleri, birimleri ile birlikte verilmelidir. Dergi elektronik ortamda yayınlandığından renkli fotoğraflar kabul edilmektedir. Tablolar resim

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formatında değil, ayrı bir MS Word belgesi olarak sunulmalıdır. Tablolar, metindeki sırasına göre Arap rakamları ile numaralandırılmalıdır. Her bir tablo, tablo numarasıyla birlikte üstte kısa bir açıklayıcı başlığa sahip olmalıdır. P değeri ve kısaltmalara dair açıklamalar tablonun altında dipnot olarak yer almalıdır.

(iv) Tartışma bölümünde çalışmanın yeni ve önemli yönleri vurgulanmalıdır. Bulgular ve gözlemler diğer ilgili çalışmalarla ilişkilendirilmelidir. Tartışmanın kapsamı, metnin diğer bölümleriyle paralel olmalıdır.

(v) Sonuç bölümünde makalenin literatüre katkısına vurgu yapılarak, yazının önemi ortaya konulmalıdır.

- **Açıklama:** Yazarlar, eğer varsa bu bölümde çıkar çatışmasına neden olabilecek her türlü maddi destek veya ilişkiyi beyan etmelidir.
- **Teşekkür:** Varsa katkıda bulunan kişi, kurum ya da kuruluşlar anılır.
- **Hasta onamı:** Olgu raporlarında yer alan hastaların bizzat kendisi veya hukuki vasisi tarafından bilgilendirilmiş yazılı onamı alınmalıdır; matbu bir örneği dergi web sayfasında yer almaktadır.
- **Çıkar çatışması:** Çıkar çatışmasına neden olabilecek her türlü destek ve ilişki beyan edilmelidir.

Finansal destek, maddi destekte bulunan kişi, kurum ya da kuruluşa dair bilgi verilmelidir.

KAYNAKLARIN YAZIMI

Kaynakların metin içindeki gösteriminde Vancouver stili kullanılmalıdır. Kaynakların numaraları metin içinde kullanım sırasına göre verilerek cümle sonunda parantez içinde verilmelidir.

Örnek;

……. gösterilmiştir (1,2,9-11).

Karaçavuş ve arkadaşları (3) ….

Karaçavuş ve ark. (3) …

Dergi isimleri "Index Medicus" a göre kısaltılmalıdır. Index Medicus'ta indekslenmeyen bir dergi kısaltılmadan yazılmalıdır. Kaynakça listesiyle metin içerisindeki sıralama arasında uyumsuzluk bulunmamalıdır. Kaynakların doğruluğundan yazar(lar) sorumludur. Makalede bulunan yazar sayısı 6 veya daha az ise tüm yazarlar belirtilmeli, 7 veya daha fazla ise ilk 6 isim yazılıp sonuna "et al" (Türkçe makaleler için "ve ark.") eklenmelidir.

Kaynak bir dergi ise;

Yazar ya da yazarların soyadları ve isimlerinin başharfleri. Makale ismi. Dergi ismi. Yıl;Cilt(Sayı): İlk ve son sayfa numarası.

Örnek: Bol O, Altuntaş M, Kaynak MF, Koyuncu S, Biçer M, Öner G, Öner U, Doğan Ö, Eryurt SÇ. Uzun Süreli Tatillerin Acil Servis İşleyişine Etkisi. Journal of Anatolian Medical Research. 2019;4(1):13-22.

İsteğe bağlı: Eğer bir derginin bir cilt boyunca sayfa numaraları süreklilik taşıyorsa (birçok tıp dergisinin yaptığı gibi), sayı numarasını atlayın.

Örnek: Halpern SD, Ubel PA, Caplan AL. Solid-organ transplantation in HIV-infected patients. N Engl J Med. 2002;347:284-7.

Kaynak bir dergi eki ise;

Yazar veya yazarların soyadları ve isimlerinin başharfleri. Makalenin başlığı. Derginin ismi. Yıl;Cilt(Suppl. Ek sayısı):İlk sayfa numarası-Son sayfa numarası. Örnek: Shen HM, Zhang QF. Risk assessment of nickel carcinogenicity and occupational lung cancer. Environ Health Perspect 1994;(102 Suppl 1):275-82.

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Yazarlara Bilgi

Kaynak bir kitap ise;
(i) Kişisel yazarlar;
Yazar ya da yazarların soyadları ve isimlerinin baş harfleri. Kitap ismi. Kaçıncı baskı olduğu. Şehir: Yayınevi; Yıl.
Örnek: Murray PR, Rosenthal KS, Kobayashi GS, Pfaller MA. Medical microbiology. 4th ed. St. Louis: Mosby; 2002.
(ii) Yazar ve editörün aynı olduğu kitaplar için;
Örnek: Dionne RA, Phero JC, Becker DE, editors. Management of pain and anxiety in the dental office. Philadelphia: WB Saunders; 2002.
(iii)Yazar (lar) ve editör (ler)in ayrı olduğu kitaplar için;
Örnek: Breedlove GK, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wieczorek RR, editor. White Plains (NY): March of Dimes Education Services; 2001.
(iv) Kitabın bir bölümü için;
Örnek: Meltzer PS, Kallioniemi A, Trent JM. Chromosome alterations in human solid tumors. In: Vogelstein B, Kinzler KW, editors. The genetic basis of human cancer. New York: McGraw-Hill; 2002. p. 93-113.
Not: Türkçe kaynaklarda "p" için "s" ve "editor(s)" "editör(ler)" ifadesi kullanılmalıdır. "In" ifadesi İngilizce kitaplar için geçerlidir, Türkçe kaynaklarda "…… (kitabın adı)" içinde şeklinde yazılmalıdır.
(v) Yazarların organizasyon olduğu kitaplar için;
Örnek: American Occupational Therapy Association, Ad Hoc Committee on Occupational Therapy Manpower. Occupational therapy manpower: a plan for progress. Rockville (MD): The Association; 1985 Apr. 84 p.
Not: Türkçe kaynaklarda "ed" ve "p" sırasıyla "baskı" ve "s" olarak ifade edilmelidir.

Kaynak bir ansiklopedi veya sözlük ise;
Ansiklopedi veya sözlük ismi. Kaçıncı baskı olduğu. Şehir: Basımevi; Yıl. Bölüm; Sayfa numaraları.
Örnek: Dorland's illustrated medical dictionary. 29th ed. Philadelphia: W.B. Saunders; 2000. Filamin; p. 675.
Not: Türkçe kaynaklarda "ed" ve "p" sırasıyla "baskı" ve "s" olarak ifade edilmelidir.

Kaynak bir Tez ise;
Yazarın soyadı ve isminin başharfi. Tez ismi [tez]. Şehir: Üniversite veya Kurum ismi; Yıl.
Örnek: Borkowski MM. Infant sleep and feeding: a telephone survey of Hispanic Americans [dissertation]. Mount Pleasant (MI): Central Michigan University; 2002.
Not: Türkçe kaynaklarda "dissertation" ifadesi için tez kullanılmalıdır.

Kaynak Konferans/Kongre/Sempozyum Bildirisi ise;
Yazar veya yazarların soyadları ve isimlerinin başharfleri. Bildiri ismi. Editör veya editörlerin soyadları ve isimlerinin başharfleri (ed veya eds). Konferans/Kongre/ Sempozyum ismi; Yıl; Şehir. Yayın yeri: Yayınevi; Yıl. Sayfa numaraları.

Bir kitapta yayınlanmış Konferans/Kongre/Sempozyum Bildirisi için;
Örnek: Christensen S, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer; 2002. p. 182-91.
Not: Türkçe kaynaklarda "p" için "s" ve "editor(s)"için "editör(ler)" olarak kullanılmalıdır.

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Yazarlara Bilgi

Bir kitapta yayınlanmamış Konferans/Kongre/Sempozyum Bildirisi için;
Örnek: Harnden P, Joffe JK, Jones WG. Germ cell tumours V. Proceedings of the 5th Germ Cell Tumour Conference; 2001 Sep 13-15; Leeds, UK.

Kaynak bir Web Sitesi ise;
Yazarın soyadı ve isminin başharfi (varsa). Web sitesinin ismi [Internet]. Basım yeri: Yayınevi; İlk Yayın Tarihi [Son güncelleme tarihi: ; Erişim tarihi:]. Erişim adresi: URL.
Örnek:
Cancer-Pain.org [Internet]. New York: Association of Cancer Online Resources, Inc.; c2000-01 [Updated: 2002 May 16; Cited: 2002 Jul 9]. Available from: http://www.cancer-pain.org/.

Diğer kaynak türleri için;
https://www.nlm.nih.gov/bsd/uniform_requirements.html adresine bakılması gerekmektedir.

Etik Hususlar:
Journal of Anatolian Medical Research (JAMER), çalışmaların yayın sürecinde, yazarların, okuyucuların, araştırmacıların, hakemlerin ve editörlerin Araştırma ve Yayın Etik kuralları ile ilgili esaslara uymasını bekler. Söz konusu çalışmalarda ve bilimsel yazılarda, ICMJE (International Committee of Medical Journal Editors) tavsiyeleri ile Committee on Publication Ethics (COPE) tarafından yayınlanan açık erişim rehberlerine göre aşağıda paylaşılan standart, genel ve özel etik kurallara ve sorumluluklara dikkat edilmesi gerekmektedir. Çalışma boyunca Helsinki Deklarasyonu'nun hükümlerine bağlı kalındığı vurgulanmalıdır. Makalenin etik kurul raporu gerekli görülmesi durumunda yazardan istenebilir.
Yapılan araştırmalar için ve etik kurul kararı gerektiren klinik ve deneysel insan ve hayvanlar üzerindeki çalışmalar için ayrı ayrı etik kurul onayı alınmış olmalı, bu onay makalede belirtilmeli ve belgelendirilmelidir.
Etik kurul izni gerektiren çalışmalarda, izinle ilgili bilgiler (kurul adı, tarih ve sayı no) Gereç ve Yöntemler bölümünde ve ayrıca makale ilk/son sayfasında yer verilmelidir. Olgu sunumlarında, bilgilendirilmiş gönüllü olur/onam formunun imzalatıldığına dair bilgiye makalede yer verilmesi gereklidir.
Kullanılan fikir ve sanat eserleri için telif hakları düzenlemelerine riayet edilmesi gerekmektedir.

Etik kurallar ile ilgili dikkat edilmesi gereken hususlar:
I. Bilimsel araştırma ve yayın etiğine aykırı genel eylemler
a) İntihal: Başkalarının fikirlerini, metotlarını, verilerini, uygulamalarını, yazılarını, şekillerini veya eserlerini, bilimsel etik kurallarına uygun biçimde atıf yapmadan kısmen veya tamamen kendi eseriymiş gibi sunmak,
b) Sahtecilik: Araştırmaya dayanmayan veriler üretmek, sunulan veya yayınlanan eseri gerçek olmayan verilere dayandırarak düzenlemek veya değiştirmek, bunları rapor etmek veya yayımlamak, yapılmamış bir araştırmayı yapılmış gibi göstermek,
c) Çarpıtma: Araştırma kayıtları ve elde edilen verileri tahrif etmek, araştırmada kullanılmayan yöntem, cihaz ve materyalleri kullanılmış gibi göstermek, araştırma hipotezine uygun olmayan verileri değerlendirmeye almamak, ilgili teori veya varsayımlara uydurmak için veriler veya sonuçlarla oynamak, destek alınan kişi ve kuruluşların çıkarları doğrultusunda araştırma sonuçlarını tahrif etmek veya şekillendirmek,
ç) Mükerrer yayım: Bir araştırmanın aynı sonuçlarını içeren birden fazla eseri doçentlik sınavı değerlendirmelerinde ve akademik terfilerde ayrı eserler olarak sunmak,
d) Dilimleme: Bir araştırmanın sonuçlarını araştırmanın bütünlüğünü bozacak şekilde, uygun olmayan biçimde parçalara ayırarak ve birbirine atıf yapmadan çok sayıda yayın yaparak belirli sınav değerlendirmelerinde ve akademik teşvik ve terfilerde ayrı eserler olarak sunmak,

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e) Haksız yazarlık: Aktif katkısı olmayan kişileri makale yazarlarına eklemek, aktif katkısı olan kişileri yazarlar arasına dâhil etmemek, yazar sıralamasını gerekçesiz ve uygun olmayan bir biçimde değiştirmek, aktif katkısı olanların isimlerini yayım sırasında veya sonraki baskılarda eserden çıkarmak, aktif katkısı olmadığı halde nüfuzunu kullanarak ismini yazarlar arasına dâhil ettirmek,
f) Diğer etik ihlali türleri: Destek alınarak yürütülen araştırmaların yayınlarında destek veren kişi, kurum veya kuruluşlar ile onların araştırmadaki katkılarını açık bir biçimde belirtmemek, insan ve hayvanlar üzerinde yapılan araştırmalarda etik kurallara uymamak, yayınlarında hasta haklarına saygı göstermemek, hakem olarak incelemek üzere görevlendirildiği bir eserde yer alan bilgileri yayınlanmadan önce başkalarıyla paylaşmak, bilimsel araştırma için sağlanan veya ayrılan kaynakları, mekânları, imkânları ve cihazları amaç dışı kullanmak, tamamen dayanaksız, yersiz ve kasıtlı etik ihlali suçlamasında bulunmak (YÖK Bilimsel Araştırma ve Yayın Etiği Yönergesi, Madde 8)

II. Paydaşların Sorumlulukları

1. Yazarların Sorumlulukları

· Makaledeki tüm verilerin gerçek ve özgün olduğu beyan edilmelidir.
· Ön değerlendirme veya hakem değerlendirme sonucunda gösterilen intihal durumunu, hataları, şupheli durumları ve önerilen düzeltmeleri yapılması zorunludur. Yapılmayacak ise, tutarlı bir şekilde gerekçesi bildirilmelidir.
· Makale veya araştırmanın "Kaynakça"sı eksiksiz ve dergimizin yazım kurallarına uygun olarak hazırlanmalıdır.
· İntihal ve sahte verilerden uzak durulmalıdır.
· Araştırmanın birden fazla dergide yayımlanmasına imkan verilmemelidir.

2. Hakemlerin Sorumlulukları

Dergimiz idaresi, hakemlik sürecinin etik yayıncılık kuralları çerçevesinde başarılı bir şekilde yürütülmesini ve iyileştirilmesini taahhüt eder. Araştırmaların paydaşları ve okuyucularının, JAMER'de yayımlanan incelemelerde gördükleri intihal, mükerrer yayın, yanlışlık, şüpheli içerik veya durumları kayseriseah.dergi@saglik.gov.tr email adresine bildirmeleri memnuniyetle karşılanır. Konu hakkında elde edilen veri sonuçları ilgili taraflara bildirir ve takibini yapar. Hakemlerin aşağıdaki esaslara uymasını temel alır.
· Değerlendirmeler tarafsızca yapılmalıdır.
· Hakemler ile değerlendirme konusu makalenin paydaşları arasında çıkar çatışması olmamalıdır.
· Makale ile ilgili diğer makale, eser, kaynak, atıf, kural ve benzeri eksiklerin tamamlanmasını işaret edilmelidir.
· Çift taraflı kör hakemlik sistemine binaen değerlendirmesi yapılmış makaleler veya hakemleri açıklanmamalıdır.

3. Editörlerin Sorumlulukları

· Editörler, makaleleri kabul etmek ya da reddetmek sorumluluk ve yetkisine sahiptir. Bu sorumluluk ve yetkisini yerinde ve zamanında kullanmak zorundadır.
· Editörler, kabul ya da reddettiği makalelerle ilgili çıkar çatışması içerisinde olmamalıdır.
· Editörler, özgün ve alanına katkı sağlayacak makaleleri kabul etmelidir.
· Editörler, dergi politikası, yayım kuralları ve seviyesine uymayan eksik ve hatalı araştırmaları hiçbir etki altında kalmadan reddetmelidir.
· Editörler, yanlış, eksik ve problemli makalelerin hakem raporu öncesi veya sonrasında geri çekilmesine ya da düzeltildikten sonra yayımlanmasına imkân vermelidir.
· Editörler, en az iki hakem tarafından değerlendirilen makalelerin çift taraflı kör hakemlik sistemine göre değerlendirilmesini sağlar vehakemleri gizli tutar.
Editörler, "Turnitin" intihal programı aracılığıyla makalelerin intihal durumu ve yayımlanmamış özgün araştırmalar olup olmadığını sağlar.

4. İntihal Politikası

Dergimize gelen her çalışma, Turnitin intihal programında taranmaktadır. Editörlerin, hakemlerin ve yazarların, uluslararası yayın etik kurallarına uyması ve makalelerin yazım kurallarına uyumlu olması zorunluluğu vardır.

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Deneysel Araştırmalar Etik Kuralları
Deneysel Araştırmalarda; Destek alınarak yürütülen araştırmaların yayınlarında destek veren kişi, kurum veya kuruluşlar ile onların araştırmadaki katkılarını açık bir biçimde belirtmek, insan ve hayvanlar üzerinde yapılan araştırmalarda etik kurallara uymak, yayınlarında hasta haklarına saygı göstermek Deneysel Araştırma Etik Kuralları bağlamında zorunludur. Deneysel araştırma kapsamında deneylerde ekolojik dengeye ve hayvan sağlığına zarar vermeme dergimizin temel ilkesidir. Bu kapsamda yapılacak çalışmalar için gerekli etik izinler ilgili resmi kuruluşlardan alınarak makalenin dergimize gönderilmesi sürecinde ilgili dosyaya eklenmelidir. Bu konuda bütün sorumluluk yazardadır.

Yazarlığın Kabulü ve Telif Hakkı Sözleşmesinin Devri: Yazının gönderimi sırasında, yazarların "Yazarlığın Kabulü ve Telif Hakkı Sözleşmesinin Devri" formunu doldurup göndermeleri ve yayında adı olan tüm yazarların bilimsel katkı ve sorumlulukları ile herhangi bir çıkar çatışması sorunu olup olmadığını açıkça belirtmeleri gerekir.

Makalenin Değerlendirilmesi: Makaleler yalnızca bu dergide ve yalnızca elektronik ortamda yayımlanmak üzere, başka bir yerde yayımlanmadıklarını (kısmen veya tamamen, başka bir deyişle veya aynı kelimelerle) ve aynı zamanda başka bir yayıncı tarafından eşzamanlı olarak incelenmemeleri gerektiğini kabul ederek alınır ve dergi tarafından reddedilmedikçe başka bir dergiye gönderilmemelidir.

Hakem İncelemesi: Hakemler, değerlendirme, düzenleme ve revizyon işlemlerini tamamen internet üzerinden takip edeceklerdir. Hakemler özel kullanıcı adı ve şifresi ile aşağıdakilerin URL adresini kullanır:
kayserieah.dergipark.gov.tr/jamer

Yayımlanan bir makale, derginin sorumluluğundadır. Düzenleme, revizyon, kabul ve reddetmeyle ilgili süreçler tamamen internet üzerinden editör(ler), ve/veya hakemler tarafından kayserieah.dergipark.gov.tr/jamer sitesi aracılığı ile gerçekleştirilecektir. Düzeltmeler ve dizgi sonrasında tüm yeniden okumalar yazar tarafından internet üzerinden yapılmalı ve belirlenen süre içinde editöre geri gönderilmelidir.

Online makale gönderimi için;
Lütfen kayserieah.dergipark.gov.tr/jamer adresini kullanınız. Herhangi bir sorunla karşılaştığınızda kayseriseah.dergi@saglik.gov.tr ile irtibata geçmekten çekinmeyiniz.

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- **Research Articles**

Present new and important basic and clinical information, extend existing studies, or provide a new approach to a traditional subject. Consists of Title, Authors, their addresses, Abstract, Key Words, Introduction, Material and Methods, , Ethical Considerations, Results, Discussion, Acknowledgements, Conflict of Interest, References, Figure Legends, Figures (up to 5), and Tables (up to 5). For research articles, main text should not exceed 5.000 words and number of references should not exceed 40.

- **Case Reports**

Provide case studies of interest, new ideas, and techniques. A case presentation consists of Title, Authors, their addresses, Abstract, Key Words, Introduction, Patients and Methods, Results, Discussion, Conclusion, Ethical Considerations, Acknowledgements, Conflict of Interest, References, Figure Legends, Figures, and Tables. For case reports, main text should not exceed 1.500 words (3 figure and/or 3 table) and number of references should not exceed 20.

- **Review Articles**

The Editorial Board invites an author who has previous published papers on a specific area to write a review article. A reviewarticle consists of Title, Authors, their addresses, Abstract, Key Words, Introduction, Main Sections under headings written in bold and sentence case, Subsections (if any) under headings written in italic and numbered consecutively with Arabic numerals, Conclusion, Acknowledgements, Conflict of Interest, References, Figure Legends, Figures, and Tables. For the review articles, main text should not exceed 5,000 words. There is no limitation for number of references.

- **Letters to the Editor**

Letters are published at the discretion of the Editorial Board. Letters should be brief and directly related to the published article on which it comments. Letters must be limited to 500 words of text, 1 table, and no more than 5 references.

- **Commentaries**

A commentary consists of Title, Authors, their addresses, Abstract, Key Words, Introduction, Discussion, Conclusion, Ethical Considerations, Acknowledgements, Conflict Of Interest, References, Figure Legends, Figures, and Tables. Manuscripts should be limited to 2000 words of text.

PREPARATION OF MANUSCRIPTS

The manuscript should be prepared in accordance with The Uniform Requirements for Manuscripts Submitted to Biomedical Journals - International Committee of Medical Journal Editors (www.icmje.org).
Manuscripts must be submitted in .doc format, and should be prepared according to the above mentioned word and reference limitations and other related information.

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• **Language**

Manuscripts should be written in clear and concise English or Turkish.

• **Title Page**

Title page must be submitted as a separate file. The title page should contain: (i) the title of the article in Turkish and English, which should be concise but informative, (ii) running title should be written (iii) in the full names of each author, (iv) the institutional affiliation or name of the department (s), (v) the full postal and e-mail address, and telephone numbers of the corresponding author. Do not use abbreviations, commercial names or trademarks in article titles.

• **Abstract**

All articles will have both Turkish and English abstract. The abstract should state the purpose of the study, main findings and the principal conclusions in not more than 250 words with separate headings of Aim, Material and Methods, Results and Conclusion.
Abstracts for Case studies and reviews should be unstructured and not more than 200 words. Foreign author(s) need not submit an abstract in Turkish, as the Editorial board will provide it for them.

• **Key Words**

Authors must include on the title page of their manuscripts 3 to 5 key words from U.S. National Library of Medicine (NLM)'s Medical Subject Headings (MeSH). Key words in Turkish should be given according to Turkey Science Terms (TBT) (https://www.bilimterimleri.com/). The words must be seperated by commas.

• **Main Text**

Names of the authors and their affiliations should not be stated in the file containing main text. Also remove all other information that may identify the authors of the study to the reviewers. Text should be prepared with MS Word document. All text should be written with Times New Roman font type at 12 font size and double spaced. The text of the article should be divided into sections with the headings Introduction, Materials and Methods, Results and Discussion.

(i) The Introduction should state the purpose of the article and summarize the rationale for the study. Give only strictly pertinent references and limit this section approximately to one page.

(ii) The Material and Methods should describe the selection of the observational or experimental subjects clearly. Give references to established methods including statistics. When reporting experiments on human subjects indicate whether the procedures were followed in accordance with the ethical standards. Information about Approval of Ethics Committee should be given in this section. Give details on randomization. Manuscipts reporting the results of randomized trials should prepare according to the CONSORT flow diagram showing the progress of patients throughout the trial (http://www.consort-statement.org/).

Statistical methods should be explained in detail in the Materials and Methods.

(iii) Results must be concise and include figures and tables and in logical sequence in the text, tables and figures/illustrations. Data in the text should not be repeated in the tables or figures/illustrations.

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Figures and images should be submitted as separate files as Tagged Image File Format (with .tiff extension) or Joint Photographic Experts Group Format (with .jpeg extension). Resolution of the figures should be at least 600 dpi. Text, tables, and figures should not be saved as MS Power Point. Figure legends should contain enough information that can be comprehended without referring to the text. If the figure was previously published elsewhere, the reference should be given. Symbols in the figures should be visible at these sizes and font size of the characters should be at least 8-10. In the graphs, names of the abscissa and the ordinate should be given together with their units.
Since the journal is published electronically, colored photographs are accepted. Tables should be submitted as separate MS Word documents, not as pictures. Tables should be numbered consecutively with Arabic numerals in order of appearance in the text. Each table should have a brief explanatory title on top together with the table number. Explanations should be at the bottom of the table as footnotes. Each column in the table should have a precise, explanatory heading.

(iv) Discussion section emphasize the new and important aspects of the study and present your conclusions. Relate the observations to other relevant studies. Extent of the discussion should be parallel to other sections.

(v) Conclusion section the importance of the article should be introduced by emphasizing the contribution of the article to the literature.

- **Disclosure:** Authors should declare any financial support or relationships that may cause conflict of interest in this section, if any.
- **Acknowledgements:** If any, contributors, institutions or organizations are mentioned.
- **Informed consent:** Informed consent of the patients in the case reports must be obtained in person or by their legal guardian; A printed copy is available on the journal's website.
- **Conflict of interest:** Any support and relationship that may cause conflict of interest must be declared. Financial support, financial support person, institution or organization should be given information.

REFERENCES

Vancouver referencing style should be used for all references.
References should be cited numbered in the order of mention in the text and given in parentheses at the end of the sentence.
In the main text of the manuscript, references should be cited using Arabic numbers in parentheses, like this: (1), (2).
A study by Karaçavuş et al. (3),
..... like this (1,2,9-11).

Journal titles should be abbreviated in accordance with the journal abbreviations in Index Medicus/ MEDLINE/PubMed. Abbreviations are not used for journals not in the Index Medicus. There should be no mismatch between the reference list and the order in the text. Authors are responsible for the accuracy of references. When there are six or fewer authors, all authors should be listed. If there are seven or more authors, the first six authors should be listed followed by "et al."

The reference styles for different types of publications are presented in the following examples:

Journal Article Format:
Author(s)– Family name and initials. Title of article. Abbreviated journal title. Publication year;volume(issue): first page number- last page number..
Rose ME, Huerbin MB, Melick J, Marion DW, Palmer AM, Schiding JK, et al. Regulation of interstitial excitatory amino acid concentrations after

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