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RESEARCH ARTICLE

Clinicopathological Features and Treatment Outcomes of Gestational Trophoblastic Disease: A Retrospective Study From A Tertiary Care Center in Türkiye

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Abstract

Introductıon: This research aimed to evaluate the clinical features, treatment modalities, and outcomes in patients with gestational trophoblastic disease (GTD).

Methods: A retrospective study was performed on 27 patients diagnosed with GTD. Data were collected from hospital records, including demographic details, clinical presentations, FIGO staging, and chemotherapy regimens. Treatment outcomes were assessed based on complete remission (CR) rates, treatment duration, and resistance to therapy.

Results: The median age of the patients was 27 (18–53) years, and the majority were FIGO stage I (77.8%). Chemotherapy regimens included weekly methotrexate in 11 patients (40.7%), five-day methotrexate (14.8%) in four patients, and etoposide,methotrexate and dactinomycin (EMA) / cyclophosphamide and vincristine (CO) in six patients (22.2%), while six (22.2%) patients achieved spontaneous remission without chemotherapy. CR rates were high across all regimens, with 81.8% for weekly methotrexate, 75% for five-day methotrexate, and 83.3% for EMA-CO. Resistant disease was observed in four (14.8%) patients. The median duration to CR varied by regimen, ranging from 5 to 10 weeks.

Conclusion: GTD is a highly chemotherapy-sensitive disease with excellent CR rates in both low- and high-risk patients. Accurate risk stratification and individualized treatment remain key to optimizing outcomes. Further studies are needed to address challenges in resistant cases and explore emerging therapies.

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Introduction

Gestational trophoblastic disease (GTD) encompasses a category of neoplasia that can be classified as either benign or malignant, originating from atypical trophoblastic tissue proliferation. Hydatidiform mole (HM), the most common form of GTD, is considered a benign, premalignant disease. HM is characterized by trophoblastic proliferation and increased human chorionic gonadotropin (HCG) levels. HM has two histological subtypes: complete mole and partial mole. In complete mole, HCG levels may rise above 100,000 IU/L, whereas in partial mole, HCG levels are relatively low because trophoblastic proliferation is less.[1,2] The incidence of HM varies among countries in the world, with an incidence of 1-2 per 1000 pregnancies in developed countries [3] and it develops most frequently in people under 15 and over 45 years of age, and the risk is higher in people over 45 years of age.[1,4] Endometrial curettage is the initial treatment for HMs in women who want to preserve fertility.[5,6] For women who have completed childbearing, hysterectomy serves as another treatment option.

As stated above, HM is a premalignant disease and it may transform into a malignant form called gestational trophoblastic disease (GTN). There are different types of GTN including invasive mole, choriocarcinoma, epithelioid trophoblastic tumor (ETT), and placental-site trophoblastic tumor (PSTT). GTN is usually diagnosed by HCG surveillance. The most common GTN after a normal pregnancy is choriocarcinoma. It can progress very rapidly to metastatic disease and is considered the most aggressive GTN subtype. Its incidence varies by country, but it is seen in approximately 3 per 100,000 births in Europe and North America.[3,7] PSTT and ETT are relatively rare compared to other GTN subtypes.[3,8,9] While endometrial curettage and hysterectomy are the mainstays of management for HM, GTN mostly requires chemotherapy.[10]

Gestational trophoblastic neoplasia (GTN) is classified into low-risk and high-risk categories based on the International Federation of Gynecology and Obstetrics (FIGO) staging and the modified WHO prognostic scoring system. According to this system, patients with FIGO stage I–III disease and a WHO risk score of less than 7 are considered to have low-risk GTN, which is associated with an excellent prognosis and nearly 100% cure rates.[11,12] These patients are typically managed with single-agent chemotherapy, such as methotrexate or actinomycin D.[13] In contrast, high-risk GTN is defined as a WHO prognostic score of 7 or higher, or any disease classified as FIGO stage IV.[11,12] These cases carry a greater risk of resistance to single-agent therapy and are therefore treated with multiagent chemotherapy, most commonly the etoposide,methotrexate and dactinomycin (EMA) / cyclophosphamide and vincristine (CO) regimen (etoposide, methotrexate, actinomycin D, cyclophosphamide, and vincristine).[13] Accurate risk stratification is essential for guiding treatment decisions and optimizing outcomes.

Despite its rarity, GTD remains a significant clinical challenge, particularly in cases involving high-risk disease or resistance to treatment. We conducted a retrospective analysis of clinical characteristics, therapeutic strategies, and outcomes in GTD patients treated at a tertiary healthcare institution in Turkey. By evaluating real-world data, we aim to provide insights into the effectiveness of different chemotherapy regimens and identify factors associated with treatment response and resistance in this population.

Material and Methods

This retrospective study was performed at Ankara City Hospital, Turkey, and included patients diagnosed with GTD. Demographic and clinical data were collected from hospital records, including age, gravida, parity, antecedent pregnancy type, presenting symptoms, serum β-hCG levels, tumor characteristics such as size, metastasis, FIGO stage, and chemotherapy regimens received by patients. The study was approved by the local ethics committee under the approval number TABED-1-25-1023.

The chemotherapy regimens applied to the patients were recorded, including weekly methotrexate (MTX), five-day MTX, and EMA-CO. Weekly MTX was administered as a single-agent therapy at a dose of 50 mg/m² intravenously, given once per week. Five-day MTX involved administering MTX at a dose of 0.4 mg/kg daily for five consecutive days, repeated every two weeks. EMA-CO, a combination chemotherapy regimen, consisted of etoposide (100 mg/m²), MTX (100 mg/m² intravenously, followed by 200 mg/m² over 12 hours), and actinomycin-D (0.5 mg) on days 1 and 2, combined with cyclophosphamide (600 mg/m²) and vincristine (1.0 mg/m²) on day 8. This regimen was typically administered in 14-day cycles. These regimens were selected based on disease severity, FIGO risk score, and clinical judgment to

ensure optimal therapeutic efficacy.

Treatment outcomes were assessed based on complete remission (CR), defined as normalization of serum β-hCG levels over three consecutive weekly measure. Patients with resistant disease were identified based on failure to achieve CR or recurrence.

Comprehensive descriptive statistical analysis of all patient demographic and clinical characteristics was performed using the IBM SPSS 25.0 software package. Summary statistics were calculated either as mean with standard deviation or as median with interquartile range, depending on how the data were distributed.

Results

This study included a total of 27 participants. Table 1 provides an overview of the patients' baseline characteristics. The participants' median age was 27 years (range: 18–53). Regarding antecedent pregnancy outcomes, nine patients (33.3%) had a complete mole, two patients (7.4%) had a partial mole, 12 patients (44.4%) had a term pregnancy, and four patients (14.8%) experienced an abortion. Among the presenting symptoms, vaginal bleeding was the most frequent, observed in 18 patients (66.7%), followed by abdominal pain in 7 patients (25.9%). Backache and incidental findings on imaging were each reported in 1 patient (3.7%) (Table 1).

The histopathological subtypes of GTD included complete mole in 12 patients (44.4%), partial mole in 5 patients (18.5%), invasive mole in 9 patients (33.3%), and choriocarcinoma in 1 patient (3.7%). Metastases were identified in 6 patients (22.2%), most commonly in the lungs (4 patients, 14.8%) and liver (2 patients, 7.4%). The number of metastatic lesions varied from 1–4 in 2 patients (7.4%), 5–8 in 1 patient (3.7%), and >8 in 3 patients (11.1%) (Table 1).

Most patients were classified as FIGO stage I (21 patients, 77.8%), with four patients (14.8%) in stage III and two patients (7.4%) in stage IV. Based on the FIGO risk scoring system, 20 patients (74.1%) were categorized as low risk (scores 0–6), while seven patients (25.9%) were classified as high risk (scores ≥7). Resistant disease was observed in 4 patients (14.8%) (Table 1).

Table 1. Baseline characteristics of patients with gestational trophoblastic disease

	n=27
Variables	**Medium (Minimum-Maximum)**
Age (years)	**27 (18-53)**
Gravida	**3 (1-8)**
Parity	**1 (0-5)**
Variables	**n (%)**
Antecedent pregnancy	
Complete mole	9 (33.3)
Partial mole	2 (7.4)
Term	12 (44.4)
Abortion	4 (14.8)
Presenting symptom	
Bleeding	18 (66.7)
Abdominal pain	7 (25.9)
Backache	1 (3.7)
On imaging for another condition	1 (3.7)
Serum β-hCG at diagnosis (mIU/mL)	
$<10^3$	4 (14.8)
10^3 -10^4	3 (11.1)
10^4 -10^5	11 (40.7)
$>10^5$	9 (33.3)
Subtype of GTD	
Complete mole	12 (44.4)
Partial mole	5 (18.5)
Invasive mole	9 (33.3)
Choriocarcinoma	1 (3.7)
Largest tumor size	
<4 cm	11 (40.7)
4-8 cm	9 (33.3)
>8 cm	7 (25.9)
Site of metastases	
Lung	4 (14.8)
Liver	2 (7.4)
Number of metastases	
1-4	2 (7.4)
5-8	1 (3.7)
>8	3 (11.1)
FIGO stage	
I	21 (77.8)
II	0 (0)
III	4 (14.8)
IV	2 (7.4)
Pretreatment serum β-hCG (mIU/mL)	
$<10^3$	6 (22.2)
10^3 -10^4	8 (29.6)
10^4 -10^5	9 (33.3)
$>10^5$	4 (14.8)
FIGO risk score, number	
0-6	20 (74.1)
≥7	7 (25.9)
Resistant disease, number	4 (14.8)

Table 2 summarizes treatment modalities, chemotherapy regimens, and resistant disease for hydatidiform moles and low-risk (FIGO score <7) and high-risk (FIGO score ≥7 or stage 4) GTD patients. Chemotherapy after uterine evacuation was applied to 15 (75%) patients diagnosed with hydatidiform mole or classified as having low-risk disease and five (71.4%) patients with high-risk disease. Hysterectomy alone was performed in two (10%) patients with hydatidiform mole or low-risk disease and one patient (14.3%) with high-risk disease. Uterine evacuation without additional treatment was observed in three (15%) patients with hydatidiform mole or low-risk disease, while it was not used in high-risk cases. Chemotherapy alone was applied to one (14.3%) patient with high-risk disease but not in hydatidiform mole or low-risk cases. Regarding chemotherapy regimens, 5-day MTX was used in four (20%) patients with hydatidiform mole or low-risk disease, while weekly MTX was given to 11 patients (55%) with hydatidiform mole or low-risk disease. EMA-CO was administered to six (85.7%) patients with high-risk disease but was not used in hydatidiform mole or low-risk cases. No chemotherapy was received by five (25%) patients with hydatidiform mole or low-risk disease and one (14.3%) patient with high-risk disease. In terms of disease resistance, three (15%) patients with hydatidiform mole or low-risk disease and one (14.3%) patient with high-risk disease exhibited resistance. One patient diagnosed with high-risk GTD died before receiving chemotherapy due to pulmonary embolism at the time of diagnosis.

Table 2. Treatment modalities for GTD groups

		Hydatidiform mole or low-risk GTN	High-risk GTN
		n (%)	
		20 (74.1)	n (%)
		7 (25.9)	
Treatment modality	Chemotherapy after uterine evacuation	15 (75)	5 (71.4)
	Hysterectomy only	2 (10)	1 (14.3)
	Uterine evacuation only	3 (15)	0 (0)
	Chemotherapy only	0 (0)	1 (14.3)
Chemotherapy regimen	5-day MTX	4 (20)	0 (0)
	Weekly methotrexate	11 (55)	0 (0)
	EMA-CO	0 (0)	6 (85.7)
	No chemotherapy	5 (25)	1 (14.3)
Resistant disease	Yes	3 (15)	1 (14.3)
	No	17 (85)	6 (85.7)

The median duration of treatment to achieve complete remission (CR) varied by regimen. Weekly MTX required a median of 7 weeks (5-10), while five-day MTX achieved CR in a median of 5 (4–13) weeks. For EMA-CO, the median duration was 10 (7–24) weeks, and for patients who did not receive chemotherapy, CR was reached in a median of 10 (6–20) weeks (Table 3).

CR rates were high across all groups, with the highest observed in the no-chemotherapy group (100%, 6/6 patients). The CR rates for weekly MTX, five-day MTX, and EMA-CO were 81.8% (9/11), 75% (3/4), and 83.3% (5/6), respectively. The median number of chemotherapy cycles administered was comparable between weekly MTX and EMA-CO, both requiring a median of 6 cycles (range: 1–9 for weekly MTX and 1–10 for EMA-CO). Patients treated with five-day MTX required a median of 4 (1–8) cycles (Table 3).

Table 3. Comparison of treatment regimens

	MTX Weekly	Five-day MTX	EMA-CO	No chemotherapy
n (%)	11 (40.7)	4 (14.8)	6 (22.2)	6 (22.2)
The duration of treatment to CR (weeks), Median (Min-Max)	7 (5-10)	5 (4-13)	10 (7-24)	10 (6-20)
CR rates (%)	81.8 (9/11)	75 (3/4)	83.3 (5/6)	100 (6/6)
Number of total cycles, Median (Minimum-Maximum)	6 (1-9)	4 (1-8)	6 (1-10)	-

Discussion

This retrospective analysis of patients with GTD highlights the diverse clinical presentations and treatment outcomes of this rare malignancy. While the study demonstrates the effectiveness of tailored chemotherapy regimens, it also underscores the importance of individualized management strategies based on patient risk profiles.

In this study, the median age of the GTD patients was 27 (18-53) years, which aligns with values reported in the literature. Anuj Gupta et al.[14] reported a median age of 28 years (20–51), while another study conducted in China found a median age of 32 years (22–49 years).[15] This demographic similarity underscores the need for fertility-preserving strategies in treatment planning. The most frequent presenting symptom was vaginal bleeding, observed in 66.7% of patients, followed by abdominal pain (25.9%), backache (3.7%), and incidental findings during imaging for another condition (3.7%). These symptoms are typical of GTD presentations, and patients have reported vaginal bleeding as the most common symptom in the literature.[16] In this study, metastatic sites included the lungs (14.8%) and liver (7.4%), with the number

of metastases being 1–4 in 7.4% of patients, 5–8 in 3.7%, and more than 8 in 11.1%. In a meta-analysis, the most common metastasis site was reported as the lungs, which is consistent with our study.[17]

The incidence of high-risk GTN in our study was 25.9%. The incidence of high-risk GTN varies across studies. A study conducted in India reported the high risk-disease incidence of 65.1% [14], while another epidemiologic study conducted in Japan reported a high-risk disease incidence of 16.6%.[18] These variations may reflect variations in healthcare access, referral patterns, and differences in early detection rates. For instance, regions with more advanced screening programs and specialized centers may detect and treat GTD earlier, potentially reducing the proportion of high-risk cases. Additionally, referral bias in tertiary care centers may lead to a higher proportion of severe cases being reported.

Patients with low-risk GTN commonly receive single-agent chemotherapy as the first-line approach.[19] Besides low-risk GTN, some patients with HM in our study also received chemotherapy. Prophylactic chemotherapy after uterine evacuation in HM is controversial.[20] Research indicates that prophylactic chemotherapy (MTX or dactinomycin) can be administered to patients who are deemed to be at high risk for gestational trophoblastic neoplasia (GTN) following a hydatidiform mole (HM). Factors that may categorize patients as high risk include being over the age of 40, having human chorionic gonadotropin (hCG) levels exceeding 100,000 mIU/mL, exhibiting abnormal uterine growth, and/or having theca lutein cysts exceeding 6 cm.[1,16,20,21] In our study, 15 (75%) (4 patients 5-day MTX, 11 patients weekly MTX) of the hydatidiform mole or low-risk GTN patients received chemotherapy after uterine evacuation, 3 (15%) underwent only uterine evacuation, and 2 (10%) underwent only hysterectomy. Methotrexate or dactinomycin may be given as chemotherapy agents for low-risk GTN.[19] There are numerous studies comparing these agents, but a clear comparison cannot be made because of differences in patient characteristics, drug doses, and schedules.[5,22-25] One analysis showed that dactinomycin was more effective than MTX; however, this analysis showed that the majority of patients received weekly intramuscular MTX, which is known to be less effective than 5- or 8-day MTX regimens.[25] The reason why weekly MTX administration was more common in our patients was that this application was used more commonly in the past.

EMA-CO regiment is used most frequently for high-risk GTN.[26] EMA-EP (etoposide, methotrexate, and etoposide alternating with dactinomycin and cisplatin) regimen is also included in the first-line treatment of high-risk GTD.[27,28] However, EMA-CO is preferred over EMA-EP due to its high toxicity and inability to provide adequate salvage chemotherapy in recurrence.[22,29] In our study, all high-risk patients receiving chemotherapy received EMA-CO. Five (71.4%) patients with high-risk disease received chemotherapy after uterine evacuation, and one (14.3%) patient underwent hysterectomy and died immediately after diagnosis due to pulmonary embolism without receiving chemotherapy. In one case of high-risk GTD, uterine evacuation was not performed because of the risk of uterine perforation. This patient initially received EMA-CO. Complete remission was achieved only after 24 weeks in this patient. This highlights the critical role of uterine evacuation in the treatment of GTD, as it can significantly accelerate β-hCG normalization and reduce the need for long-term chemotherapy in appropriate cases.

In our study, complete remission (CR) rates were notably high in the non-chemotherapy group. However, these patients predominantly had HM that requires no treatment unless it harbors any risk factors for transforming into GTN, as mentioned above. CR rates were 81.8% and %75, with weekly and five-day MTX regimens, respectively. Our findings were consistent with the literature since approximately %75 of patients with low-risk GTN achieve complete marker remission following first-line treatment.[25] Despite the generally favorable outcomes associated with single-agent MTX in low-risk patients, one case in our study developed severe toxicity, manifesting as pancytopenia. This case underscores that, while MTX is often considered a safe and effective option for low-risk disease, it is not without risks. Clinicians should remain vigilant for potential toxicities and carefully weigh the benefits against the risks, even in seemingly straightforward cases.

Resistant disease was observed in a small subset of all patients (%15 for hydatidiform mole or low-risk GTN and %14.3 for high-risk GTN). This finding was aligned with the expected rates since a study conducted among 877 patients with GTD reported 17.4% of patients with resistant disease.[30] These cases often necessitate multi-agent regimens such as EMA-CO, which, although effective, require close monitoring for cumulative toxicity. Additionally, the potential role of emerging therapies, including targeted treat-

ments, warrants further exploration to address these challenges.

The limitations of the study were its retrospective nature and small sample size. Nonetheless, it contributes to the growing evidence supporting risk-adapted treatment strategies in GTD and highlights the importance of considering both efficacy and safety in patient management.

Conclusion

The successful management of gestational trophoblastic disease requires a patient-centered approach that balances treatment efficacy with safety considerations. Our findings emphasize the importance of individualized risk assessment in guiding therapeutic decisions. While single-agent chemotherapy remains the cornerstone for low-risk GTN, multi-agent regimens such as EMA-CO play a crucial role in high-risk cases. Additionally, uterine evacuation has been shown to facilitate treatment response by shortening chemotherapy duration and improving remission rates. Despite the generally high success rates, clinicians must remain vigilant for treatment resistance and potential toxicities, reinforcing the need for close monitoring and timely intervention. Looking ahead, optimizing existing protocols and integrating novel treatment modalities will be essential to further improving patient outcomes. Continued research and interdisciplinary collaboration are vital for refining therapeutic strategies and addressing the challenges associated with complex or high-risk cases.

Statements & Declarations

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Declaration of Conflict Interests

No author has any financial or personal relationships that could inappropriately influence this work.

Ethics approval

Approval for the study was granted by the Clinical Research Ethics Committee of Ankara City Hospital (decision no: TABED-1-25-1023), and the research was performed according to the the principles of the Declaration of Helsinki.

Author Contribution

Ugur Ozberk: Data Curation and Analysis, Investigation, Writing—original draft. Selin Akturk Esen, Ismet Seven and Burak Bilgin: Data Curation and Analysis. Oznur Bal, Efnan Algın and Dogan Uncu: Conceptualization, Methodology, Supervision, Writing—review & editing

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RESEARCH ARTICLE

From Inflammation to Frailty: Investigating the Systemic Immunity-Inflammation Index in Older Patient

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Abstract

Introductıon: Chronic inflammation is increasingly recognized as a crucial contributor to frailty pathogenesis, but accurate diagnosis remains a challenge. Aim Our study aims to investigate the relationship between frailty and the Systemic Immunity-Inflammation Index (SII, SIRI), a comprehensive indicator of inflammation.

Methods: This cross-sectional study enrolled 200 patients. All participants underwent a comprehensive geriatric assessment. Frailty was assessed using the clinical frailty scale, (≥ 4; frail, <4 robust). 99 patients were included in the study as frail (Group 1) and 101 patients as robust (Group 2). To determine the SII, we used the formula: Platelet count×Neutrophil / Lymphocyte count. The calculation formula for SIRI is neutrophil count × monocyte count/Lymphocyte count.

Results: The average age of the participants was 75.15 ± 8,8, and 55% (n=110) were female. Patients were grouped frail and robust. The frail group had 99 patients, while the robust group comprised 101 patients. Frail patients showed higher median SII and SIRI scores than the robust group($p < 0.001$). Bınary logistic regression analysis revealed that the SII and SIRI scores were significantly and independently associated with frailty even after adjusting for potential confounding factors respectively (r =1.52, 95% CI= 1.189–1.964, $p < 0.001$, r=1.004, 95% CI=0.585-1.724, p=0.987). The ROC analysis identified the optimal cut-off for SII in predicting sarcopenia as > 596. At this threshold, the negative predictive values were determined to be 83.8%, with a specificity of 86%, cut-off for SIRI in predicting sarcopenia as > 1.1 .

Conclusion: The results of this cross-sectional study indicate a positive correlation between systemic inflammatory biomarkers (SII, SIRI) and frailty.

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Introduction

Frailty is a complex condition that can significantly reduce survival rates at any age and is associated with progressive impairments across multiple physiological systems due to aging.[1]

Blood inflammatory markers are readily available and reasonably priced biomarkers. Systemic Immunity-Inflammation Index(SII) is a reliable and consistent measure that integrates three different types of inflammatory cells (lymphocytes, neutrophils, and platelets) and can be used as indications of both systemic inflammation and local immune response.[2,3] The SII can predict the prognosis of patients with a variety of malignancies, acute ischemic stroke, coronary artery disease, and acute renal injury, according to multiple research studies.[4] Systemic ınflammatory Response Index(SIRI) is a more complete measure of chronic inflammation since it comprises neutrophils, monocytes, and lymphocytes.[5] Furthermore, prior studies have discovered a link between frailty and interleukin-6 and C-reactive protein.[6] Several studies have linked systemic inflammatory biomarkers to the likelihood of frailty.[7] Pathophysiological changes occurring in several systems, including the cardiovascular, endocrine, immunological, and musculoskeletal systems, contribute to the development of frailty syndrome.[8]

This study specifically focused on geriatric assessment and aims to evaluate the relationship between frailty in older adults and the SII and the SIRI

Material and Methods

Study design

Features of the population, BMI, multimorbidities(≥1 medical condition), smoking status, and biochemical results were recorded. Patients under 65, current smokers, and those with alcohol or drug addiction were excluded. Between January 2025 and February 2025, 200 patients aged 65 and over were retrospectively scanned and geriatric evaluations and CBC scans were performed. Education level was categorized as 0 = 0–5 years, 1 = 6–12 years, and 2 = >12 years.

Comprehensive geriatric evaluation

The Lawton-Brody Instrumental Activities of Daily Living (IADL) and Katz Activities of Daily Living (ADL) were used to assess the functional condition of the subjects. Katz's ADL assessment consisted of six questions on how independently the patient performed basic care and everyday duties. The score dropped as independence increased.[9] The IADL evaluates individuals' capacity to do complicated everyday tasks, and the rating is determined by adding up to eight points.[10] The Mini-Nutritional Assessment Short Form (MNA-SF) was used to assess the individual's nutritional status and malnutrition was indicated by ≤7 points.[11] Additionally, the number of drugs was noted, and using more than five was deemed to be polypharmacy.[12]

Frailty assessment

The same experienced doctor evaluated patients' frailty state using the Clinical Frailty Scale (CFS). Clinical frailty is defined by CFS using a scoring system that ranges from 1 (extremely fit) to 9 (terminally ill), live with frailty (CFS ≥4), and being non-frail/robust (CFS < 4).[13,14]

Systemic inflammatory biomarkers

All participants underwent a comprehensive blood analysis after an overnight fast on the same day as theirs. This analysis included a complete blood count (CBC), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) measurement. CBC was performed with a Beckman Coulter automated analyzer. SII was assessed according to the formula: Platelet count(109/mm3)×Neutrophil count (109/mm3) / Lymphocyte count (109/mm3).[15] The calculation formula for SIRI is Neutrophil count × Monocyte count/Lymphocyte count.[16]

Statistical analyses

Version 23 of the SPSS software was used to perform the statistical analysis. The variables were examined visually and analytically to see if they were regularly distributed. Descriptive analyses were presented as percentages for categorical variables, mean ± SD for normally distributed variables, and median [interquartile range (IQR)] for non-normally distributed variables. The Chi-square test was employed to compare the category variables. The continuous variables were compared using the Mann-Whitney U test. Using two-sided tests, all reported p-values were computed and compared to a 5% significance level. ROC analysis was performed to determine the cut-offs of the available indices and analyzed by logistic binary regression to exclude confounding factors.

Results

A total of 200 individuals aged 65 years and older were included in this cross-sectional study. The mean age of the participants was 75.15 ± 8.8 years, and 55% were female.The cohort was separated into

two groups according to frailty state, with 99 patients (45%) defined as frail (Group-1) and 101 patients (50.5%) as robust (Group-2). Table 1 shows that patients living with frailty have a considerably higher mean age (79.75 ± 3.43 years) than the robust group (72.71 ± 5.8 years, p < 0.001).

Table 1. The baseline characteristics of the patients are frail and robust.

	Frail (n=99)	Robust (n=101)	p
Age, years	79.75±3.43	72.71.±5.8	<0.001
Marital status, Married	81(63.8)	30(53.6)	0.170
Sex, Female	46(46)	61 (61)	0.037
Education level			0.585
0	55(55)	49 (50)	
1	33 (33)	28 (29)	
2	18(18)	19 (20)	
Height, cm	165 [14]	159 [9.5]	0.129
Polypharmacy, n (%)	80(80)	53(53)	0.001
Weight, kg	65[15]	74 [15.4]	0.50
BMI, kg/m2	24.5±5.2	28.9±5.9	0.443
Katz Activities of Daily Living	4(0-6)	6(0-6)	0.001
Lawton Instrumental Activities of Daily Living	5(0-8)	7(0-8)	0.001
SII	942 (137-9710)	250 (190-440)	<0.001
SIRI	1.5(0.11-14)	0.99(0.6-1.5)	<0.001

*Variables are presented as n (%), mean±SD or median [IQR]
BMI, Body mass index; cm, centimeter; kg, Kilogram; kg/m2., Kilogram/square meters; SII, Systemic Immunity-Inflammation Index; SIRI, Systemic Inflammation Response Index

Frail individuals had a higher prevalence of polypharmacy (80% vs. 53% in robust patients, p < 0.001) and scored significantly lower on both Katz Activities of Daily Living (ADL) and Lawton Instrumental Activities of Daily Living (IADL) assessments (p < 0.001). The frail group had significantly higher Systemic Immunity-Inflammation Index (SII) and Systemic Inflammatory Response Index (SIRI) scores than the robust group (SII: p < 0.001; SIRI: p < 0.001).

After correcting for relevant confounders, binary logistic regression analysis showed that SII and SIRI were independently linked with frailty (OR=1.52; 95% CI, 1.189-1.964; p < 0.001; OR=1.004; 95% CI, 0.585-1.724; p=0.987) (Table 3). ROC analysis revealed the appropriate cut-off values for predicting frailty; The SII demonstrated excellent discriminatory ability, with an AUC of 0.895 (95% CI: 0.851–0.940, p < 0.001), suggesting a high level of accuracy in distinguishing between affected and non-affected individuals. The optimal cut-off value for SII was 596, yielding a sensitivity of 83.8% and a specificity of 86.1%, indicating robust diagnostic performance.

Table 3. Association of SII and SIRI with Frailty: Binary Logistic Regression Results

	Odds Ratio	95 % CI	p
Unadjusted Model			
SII	1.005	1.003-1.006	<0.001
Model 1			
SII	1.52	1.189-1.964	<0.001
SIRI	1.004	0.585-1.724	0.987
Age, years	1.111	1.075-1.273	<0.001
BMI (kg/m2)	0.826	0.721-0.945	0.006

BMI, Body mass index; SII, Systemic Immunity-Inflammation Index; SIRI, Systemic Inflammation Response Index; CI: Confidence Interval; kg/m2., Kilogram/square meters

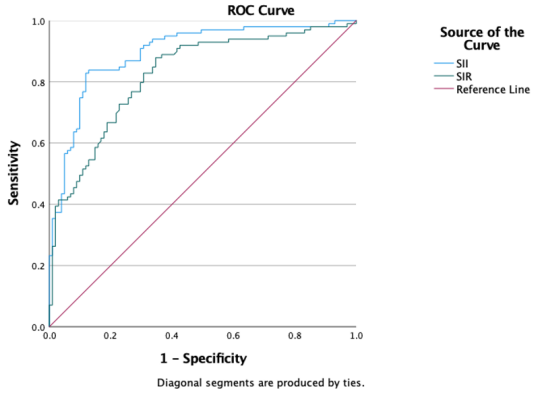
Similarly, the SIRI exhibited strong predictive power, with an AUC of 0.823 (95% CI: 0.765–0.881, p < 0.001). The best cut-off value for SIRI was 1.1, with a sensitivity of 84.7% and specificity of 85.3% (Table 2, Figure-1).

Table 2. Diagnostic Performance of SII and SIRI in Predicting Frailty: ROC Curve Analysis

	Cut-off	AUC	Sensitivity	Specificity	95% CI	p
SII	596	0.895	83.8%	86.1%	0.851-0.940	<0.001
SIRI	1.1	0.823	84.7%	85.3%	0.765-0.881	<0.001

ROC, Receiver Operating Characteristic Curve; AUC, Area Under the Curve; CI, Confidence Interval; SII, Systemic Immunity-Inflammation Index; SIRI, Systemic Inflammation Response Index

Figure-1 The ROC Curve of the Systemic Immunity -Inflammation IndexS



SII, Systemic Immunity-Inflammation Index; SIRI, Systemic Inflammation Response Index; ROC, Receiver Operating Characteristic Curve

Discussion

This study provides strong evidence linking systemic inflammatory biomarkers, particularly the SII and the SIRI, to frailty in older adults. Our findings reinforce the expanding literature suggesting that chronic low-grade inflammation plays a central role in the development of frailty. Notably, frail individuals exhibited significantly higher levels of SII and SIRI compared to their robust counterparts, highlighting the potential of these markers as objective indicators of frailty risk. These results align with previous research indicating that systemic inflammatory markers, such as IL-6 and CRP, are associated with frailty and negative health outcomes in aging populations. The inflammatory load in frail individuals appears to be a key determinant of increased vulnerability, reinforcing the need for targeted therapeutic approaches.[17]

Frailty is a complex geriatric syndrome characterized by increased vulnerability to external stressors due to physiological dysregulation.[18]

Our results indicate that heightened systemic inflammation may contribute to functional decline, as reflected in lower ADL and IADL scores among frail participants. This aligns with prior findings that inflammation-driven muscle catabolism, immune senescence, and metabolic alterations lead to declines in physical and cognitive function, further exacerbating frailty. A recent systematic review confirmed that inflammatory cytokines such as IL-6 and tumor necrosis factor-alpha negatively impact muscle strength and mobility, directly influencing frailty progression.[19] Additionally, the higher prevalence of polypharmacy among frail individuals in our study corresponds with evidence suggesting that polypharmacy is both a consequence and a risk factor for frailty.

Given that polypharmacy may induce adverse drug reactions and exacerbate inflammatory responses, future research should explore interventions aimed at optimizing medication use in frail populations.[20]

One of the key contributions of our study is the identification of clinically meaningful cut-off values for SII and SIRI. These findings are in agreement with prior research that has established SII and SIRI as predictive markers of inflammation-driven diseases, including cardiovascular disease, cancer, and metabolic disorders.[21]

The ability of these indices to predict frailty further supports their clinical utility as cost-effective, widely available biomarkers that could enhance risk assessment in geriatric practice.[22] In line with our findings, a recent study by Alhalwani found that elevated SII levels correlated with disease severity in type 2 diabetes mellitus, another condition associated with frailty.[23] These findings highlight the potential of systemic inflammation indices in risk stratification and disease monitoring across different aging-related conditions.

Interestingly, while both SII and SIRI were initially associated with frailty in unadjusted analyses, binary logistic regression revealed that only SII maintained statistical significance after controlling for confounding variables. This suggests that SII may be a more robust predictor of frailty than SIRI, warranting further investigation. Prior studies have highlighted the role of platelets in aging and frailty, suggesting that platelet-mediated inflammation may play a more significant role in frailty pathogenesis than monocyte-driven responses, which could explain our findings Moreover, a study) demonstrated that SII is linked to increased urinary albumin excretion, reinforcing the systemic impact of chronic inflammation in aging individuals.[24,25]

Future longitudinal studies should investigate whether reductions in inflammatory markers over time correspond with decreased frailty risk, offering further insights into causality.

These findings have important clinical implications. Given the modifiable nature of inflammation, future research should explore targeted interventions aimed at mitigating inflammatory burden in older adults. Studies have shown that lifestyle modifications, including regular physical activity, anti-inflammatory dietary patterns, and pharmacological interventions (e.g., statins and metformin), may help reduce systemic inflammation and delay frailty onset.[26,27]

Additionally, incorporating SII and SIRI into routine geriatric assessments could provide valuable prognostic information, enabling early identification of high-risk individuals and facilitating timely interventions. The integration of systemic inflammatory indices in clinical practice may allow for the implementation of personalized medicine approaches, optimizing patient care and outcomes in aging populations.

Conclusion

Our study highlights the pivotal role of systemic inflammation in frailty pathophysiology and positions SII and SIRI as valuable biomarkers in geriatric assessments. These findings add to the growing evidence supporting the use of inflammatory indices in predicting frailty and suggest that inflammation-targeted strategies may help improve health outcomes in aging populations. Future research should focus on validating these findings in larger, diverse cohorts and exploring novel therapeutic approaches aimed at modulating systemic inflammation to promote healthy aging. Given the increasing global burden of frailty, the identification of reliable, cost-effective biomarkers such as SII and SIRI represents a crucial step forward in geriatric medicine, offering potential avenues for early intervention and improved patient outcomes.

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Ethics Statement: The study protocol, ID: TABED-2-25-1072, was approved by XXX Hospital's Ethics Committee. Since this was a retrospective cross-sectional study, written informed consent was waived. The study adhered to the principles of the Declaration of Helsinki.

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RESEARCH ARTICLE

Diagnostic Value of Presepsin, CRP and Procalcitonin as Markers of Infection in Children with Community-Acquired Pneumonia

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Abstract

Introductıon: Community-acquired pneumonia (CAP) is a common pediatric infection desaese.Biomarkers such as C-reactive protein (CRP) and procalcitonin are frequently used for diagnosis and disease monitoring. Presepsin, has emerged as a novel marker involved in the early immune response to bacterial infections. This study aimed to evaluate the diagnostic value of CRP, procalcitonin, and presepsin in children with CAP.

Methods: A total of 61 children aged 1 month to 17 years were included in this prospective observational study conducted between December 5, 2018, and December 5, 2019. Thirty-seven patients with clinically and radiologically confirmed CAP who were admitted to the Pediatric Outpatient Clinics and Pediatric Emergency Department of Mersin University Faculty of Medicine Hospital, and 24 healthy age-matched children without chronic diseases were enrolled. Detailed demographic, clinical, laboratory, and radiological data were collected. Biomarker levels were measured at the time of diagnosis.

Results: The mean age of patients was 4.3±4.7 years, and 51% were female; the control group had a mean age of 9.6±4.1 years. The most common symptoms were cough (94.6%), fever (75.7%), and wheezing (32.4%). Chest radiography showed lobar pneumonia in 29.7% and interstitial/bronchial pneumonia in 70.3% of cases. CRP, procalcitonin, and presepsin levels were significantly higher in the CAP group than in controls ($p<0.001$, $p<0.001$, $p=0.001$).

Conclusion:CRP and procalcitonin remain valuable markers in diagnosing and managing pediatric CAP. Although presepsin demonstrated high specificity, its lower sensitivity limits its role as a primary diagnostic marker.It may, however, serve as a supportive tool in select clinical settings.

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Introduction

Community-acquired pneumonia (CAP) is one of the leading causes of childhood morbidity and mortality.[1] Early diagnosis and appropriate management are critical to improving outcomes. Biomarkers such as C-reactive protein (CRP) and procalcitonin (PCT) are widely used for diagnosing bacterial infections[2,3] However, their specificity is limited. Presepsin, a soluble CD14 subtype, has been proposed as a more specific biomarker for bacterial infections and sepsis.[4,5] This study evaluates the diagnostic value of presepsin in comparison with CRP and PCT in pediatric CAP cases.

Material and Methods

Research population

Our study is a prospective, observational and analytical case-control study. The study population consisted of a total of 61 participants (37 patients aged between 1 month and 18 years and 24 healthy controls) who were admitted to Mersin University Faculty of Medicine Hospital Pediatric Outpatient Clinics and Pediatric Emergency Department between 05.12.2018-05.12.2019 with complaints of fever, respiratory distress (tachypnea, retraction, cyanosis), and findings compatible with pneumonia in lung listening and chest radiography examinations. Out of a total of 51,711 patients admitted to Mersin University Faculty of Medicine Hospital Pediatric Outpatient Clinics and Pediatric Emergency Department, 246 patients were diagnosed with CAP. 47 of these patients were excluded from the study because they had chronic diseases and 16 patients refused to participate in the study. The remaining 183 participants were randomly selected.

Patients were selected based on clinical symptoms (fever, respiratory distress) and radiological findings, while those with chronic illnesses or recent hospitalization were excluded. Among the participants who met the inclusion criteria, 5 ml of blood was collected in two serum tubes before treatment and on the third day of treatment from patients diagnosed with CAP in the first evaluation. Sera of the patients were stored in a deep freezer at -80°C until the day of analysis. Serum presepsin level was determined by ELISA method using presepsin-ELISA kit (Thermo Multiscan Go Thermo Fisher Scientific Multiscan Go, Finland) according to the manufacturer's instructions. Serum CRP and PCT levels were determined on a Roche-Cobas

6000 device according to the manufacturer's instructions. The reference range was 0.01-0.50 mg/dl for CRP and 0-0.5 ng/ml for procalcitonin.[6] Sociodemographic and routine examination data were obtained from the hospital information management system. Chest radiographs were interpreted by the same clinician.

Statistical Analysis

Statistical analysis and interpretation were performed by Mersin University Department of Biostatistics Laboratory using IBM SPSS 21 program. Shapiro-Wilk test assessed whether data were normally distributed. Mann-Whitney U test compared non-normally distributed continuous variables between groups. Chi-square test was used for categorical variables, with post-hoc analysis for significant results. Wilcoxon Rank Sum test compared paired measurements (day 1 vs. day 3). Spearman correlation analyzed the relationship between biomarkers and clinical findings. ROC curve analysis assessed the diagnostic performance of CRP, PCT, and presepsin, calculating their AUC, sensitivity, and specificity. $p<0.05$ was considered statistically significant.ROC analysis was performed with MedCalc v.10.3.

Ethics

This study was conducted following the amended Helsinki Declaration and approved by our center's clinical research ethics committee (Mersin University Clinical Research Ethics Committee on 20.12.2018 with the number 923913). Informed consent was obtained from the patients and their relatives who participated in the study.

Financial disclosure

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Results

The study population consisted of two groups, 37 patients diagnosed with CAP and 24 healthy controls, totaly 61 patients. The mean age of the CAP group was 4.3±4.7 years, while the control group had a mean age of 9.6±4.1 years. (Table-1). Fever (76%), cough (95%), and wheezing (32%) were the most common symptoms. Chest radiography showed lobar pneumonia in 29.7% and interstitial/bronchial pneumonia in 70.3%. The chest radiographs of the patient group are mentioned in Table-2.

Table-1. Demographic data of patient and control groups

	Patient	Control	p
Age (n (mean±sd))	37 (4.29±4.74)	24 (9.6±4.07)	<0.001
Gender			
Girl	19 (51.4%)	8 (33.3%)	0.166
Male	18 (48.6%)	16 (66.7%)	

Table-2. Findings of the patients according to chest radiography findings

Infiltration	Number	Percentage
Infiltration	31	83,8
Infiltration + ARDS	1	2,7
Infiltration + atelectasis	4	10,8
Infiltration + effusion	1	2,7
Total	37	100,0

*ARDS: Acute respiratory distress syndrome

CRP, PCT, and presepsin levels were significantly higher in CAP patients than in controls ($p<0.001$, $p<0.001$, $p=0.001$, respectively). CRP levels correlated with fever ($p=0.003$) and lobar pneumonia ($p=0.001$). CRP, procalcitonin and presepsin values were significantly higher in the patient group compared to the control group (Table-3).

Diagnostic accuracy for CAP differentiation :
-CRP: AUC=0.979, sensitivity=97.3%, specificity =91.67%
-PCT: AUC=0.834, sensitivity=97.3%, specificity =70.83%
-Presepsin: AUC=0.759, sensitivity=59.46%, specificity =91.67%

Table-3: The relationship between infection marker levels of the patient group and control groups

Token	Patient Group (n=37) Median[25P.-75P.]	Control Group (n=24) Median [25P.-75P.]	p
CRP (mg/dL)	3,54 [1,11-11,07]	0,03 [0,01-0,15]	<0,001
Procalcitonin (ng/mL)	0,31 [0,08-2,03]	0,05 [0,03-0,09]	<0,001
Presepsin (ng/mL)	1,43 [0,56-6,12]	0,69 [0,28-0,88]	0,001

Discussion and Conclusion

Pneumonia is an important cause of morbidity in children. In the follow-up process of cases, infection markers can be used for early diagnosis, evaluation of infection severity, and evaluation of response to treatment. The sensitivity of the markers varies according to the severity of the infection and whether it is systemic, local or invasive.[7-9] In our study, the variables affecting CRP, procalcitonin and presepsin levels, which are used as infection markers in children diagnosed with pneumonia, in the diagnosis and treatment follow-up of community-acquired pneumonia were examined and the relationship between each other was evaluated.

In our study, CRP, which is used in many infections; procalcitonin, which is elevated in serious infections and sepsis as well as noninfectious conditions such as infarction and aspiration pneumonia; and presepsin, which is prominent in septic shock and community-acquired pneumonia, were examined.[10-12] The mean CRP, procalcitonin and presepsin levels of the patient group were higher than those of the control group. Lee et al. found that elevated procalcitonin and CRP levels were significant in lobar pneumonia. However, they reported that elevated procalcitonin levels were more reliable in diagnosing lobar pneumonia than elevated CRP levels.[13] In our study, CRP was found to be similarly elevated in lobar pneumonia.

Noh et al. reported that procalcitonin and CRP were correlated with body temperature and an increase in body temperature may be associated with the severity of sepsis.[14] It is thought that the increase in presepsin level is also associated with an increase in body temperature.[15] In our study, it was observed that the presence/absence of fever significantly affected the difference in CRP level only on the first day.

Agnello et al. reported that CRP was more predictive than procalcitonin in children with lobar consolidation and pleural effusion and may be useful in predicting the severity of the disease and in the management of pneumonia in a study of 119 children aged 1-14 years with community-acquired pneumonia.[16] This finding is consistent with the difference in day 3 CRP levels in our study. After statistical analysis, it was observed that only the presence/absence of lobar involvement significantly affected the difference in the third day CRP level. From these findings, it was thought that CRP level among the markers of infection in patients with fever on the first day would be more useful for the follow-up of patients with a definitive diagnosis. However, presepsin and procalcitonin levels did not change according to the presen-

ce or absence of fever on the first day and remained high in all patients. Interpretation based only on CRP level on the first day of admission may result in the omission of patients who do not show symptoms. Therefore, according to the results of our study, taking presepsin and procalcitonin levels into consideration during the evaluation of patients for the diagnosis of community-acquired pneumonia may help to prevent subclinical diseases. For further clarification of this situation, it may be recommended to evaluate these markers together with other diagnostic criteria for pneumonia.

Studies have reported that presepsin levels are significantly elevated in the presence of infection. However, the elevation in presepsin levels is mostly in the first 24 hours of infection.[17] It was observed that the median presepsin level of the participants on the first day was higher than the median presepsin level of the patients on the third day. However, in some patients, day three presepsin levels were higher than day one. This may be due to increased severity of infection. The same was true for CRP and procalcitonin levels. Infection markers of all participants were evaluated on the first day and only the patient group was evaluated on the third day. In this way, it was aimed to ensure that all participants sampled on the first day were representative of the population and the second group was representative of the patient group followed up. It was thought that CRP and procalcitonin levels would give more meaningful results in the long term during pneumonia follow-up. However, considering that presepsin measurement may increase the accuracy of other infection markers and may be valuable in bacterial infections, it is thought that these markers should be evaluated together.12 In a study of 144 adult intensive care unit patients, high presepsin levels predicted progression to severe CAP and increased the diagnostic accuracy of other markers. Similarly, in our study, very high presepsin levels were found in a case of pneumonia progressing to ARDS.[18]

Using symptoms, examination and radiological imaging methods, the markers of patients diagnosed with pneumonia were examined and then the reliability of infection markers in differentiating patients from healthy patients was tested. Povoa et al. reported that CRP had 93.4% sensitivity and 86.1% specificity at the cut-off point of 8.7mg/dL in pneumonia patients.[19] Vugt et al. found that a CRP level of 3 mg/dL was the optimal cut-off point for differentiating patients and healthy individuals in community-acquired pneumonia.[20] Holm et al. found that procalcitonin was 70% sensitive at a cut-off point of 0.06 ng/ml and CRP was 73% sensitive at a cut-off point of 2 mg/dL in pneumonia.[21] Morgenthaler et al. reported the optimal cut-off point of procalcitonin as 0.05 ng/ml with 77.8% sensitivity and 98.5% specificity.[22] In a study of 300 febrile patients, 46 of whom had LRTI, Liaudat et al. found the sensitivity and specificity of procalcitonin to be 56% and 92%, respectively, and 83% and 43%, respectively, at the cut-off points of 0.5 and 0.2 ng/ml for the diagnosis of bacteremia.[23] In our study, the sensitivity, and specificity of CRP were found to be high in differentiating sick and healthy individuals. Procalcitonin had relatively lower sensitivity, and specificity at the optimal cut-off point. Presepsin, on the other hand, has a low sensitivity at the optimal cut-off point, and is insufficient to differentiate sick individuals, while its specificity is the same as CRP with 91.67%.

Liu et al. reported that the elevated presepsin levels of patients with severe community-acquired pneumonia and the presepsin levels of patients with mild and moderate community-acquired pneumonia were statistically significant. They also found that presepsin was an independent predictor of 28-day mortality in community-acquired pneumonia.[24] In our study, presepsin failed to differentiate community-acquired pneumonia compared to CRP and procalcitonin. This may be attributed to the low number of patients diagnosed with severe pneumonia. Again, in correlation with our study, Halıcı et al. reported that presepsin was useful in detecting pneumonia in adult patients presenting with COPD exacerbation, but its diagnostic accuracy was not higher than CRP and procalcitonin.[25]

This study has certain limitations. The control group consisted of generally healthy pediatric outpatients, and despite the absence of clinical symptoms, subclinical infections could not be completely ruled out, which may have influenced biomarker levels. A more thorough assessment of infection presence in controls could improve the accuracy of comparisons. Additionally, some patients presented after 3-4 days of symptoms, leading to variability in biomarker levels. Since presepsin is known to peak early in infection, delayed sampling may have influenced its diagnostic performance.

Standardizing the timing of sample collection in future studies could yield more precise results. The sample size was limited due to the high cost of presepsin testing, restricting broader applicability. Larger multicenter studies are needed to validate presepsin's role in pediatric CAP diagnosis and follow-up.

CRP is the most reliable marker for early CAP detection and disease monitoring. PCT provides additional value but is not superior to CRP. Presepsin may help identify subclinical infections, but its low sensitivity limits its standalone diagnostic use. Further large-scale studies are needed to explore the clinical utility of presepsin in pediatric infections. Combining presepsin with CRP and PCT may improve diagnostic accuracy, especially in differentiating bacterial and viral pneumonia.

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CASE REPORT

A Rare Case in a Pediatric Patient: Dyke-Davidoff-Masson Syndrome

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Abstract

Dyke-Davidoff-Masson syndrome (DDMS) is a clinical condition characterized by epilepsy, hemiplegia or hemiparesis, mental retardation, facial asymmetry, psychiatric disorders, sensorineural hearing loss, cerebral atrophy on neuroimaging, excessive enlargement and air increase in the paranasal sinuses, and unilateral skull thickening. In this paper, a 16-year-old male patient who was followed up with diagnoses of epilepsy, intellectual disability, and left hemiparesis, and who was diagnosed with DDMS upon the detection of right cerebral atrophy, thickening in the right hemiclavarial bone structures, and increased aeration of the frontal sinuses on neuroimaging, is presented. DDMS, a rare case in the literature, is emphasized for consideration in the differential diagnosis of cerebral hemiatrophy.

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Introduction

Dyke-Davidoff-Masson syndrome (DDMS) was first described by Dyke, Davidoff, and Masson in 1933 and is a clinical condition characterized by epilepsy, hemiplegia or hemiparesis, mental retardation, facial asymmetry, psychiatric disorders, sensorineural hearing loss, cerebral atrophy on neuroimaging, excessive enlargement and air increase in the paranasal sinuses, and unilateral skull thickening.[1-2] In this paper, a 16-year-old male patient diagnosed with DDMS, which is rare in the literature, is presented.

Case

A 16-year-old male patient, followed up for epilepsy, left hemiparesis, and intellectual disability, presented to our clinic with increased irritability and restlessness in recent times. His medical history revealed that he was born at term, did not receive incubator care, and had normal developmental milestones until one year of age. At one year old, he experienced generalized tonic-clonic seizures, for which levetiracetam treatment was initiated. Subsequently, he exhibited developmental delays, spoke his first meaningful word and started walking at 2.5 years of age. As his seizures continued during that period, sodium valproate was added to his treatment. He received special education due to intellectual disability. There was no history of consanguinity between his parents, and no history of epilepsy or other neurological diseases in his family.

On neurological examination, he was conscious, had limited cooperation, aggressive behaviors and stereotypies, facial asymmetry, and left hemiparesis. His cognitive development was observed to be delayed compared to his peers.

Electroencephalography showed focal epileptic abnormalities originating from the right frontocentrotemporal region. Cranial magnetic resonance imaging (MRI) revealed encephalomalacic changes in the right occipital, temporal, and frontal regions, dilatation in the occipital horn of the right lateral ventricle secondary to volume loss, thickening in the right hemiclavarial bone structures, and increased aeration of the frontal sinuses (Figure-1a, b).

Based on the findings of left hemiparesis, facial asymmetry, intellectual disability, epilepsy, and right cerebral hemiatrophy on MRI, the patient was diagnosed with DDMS.

Figure

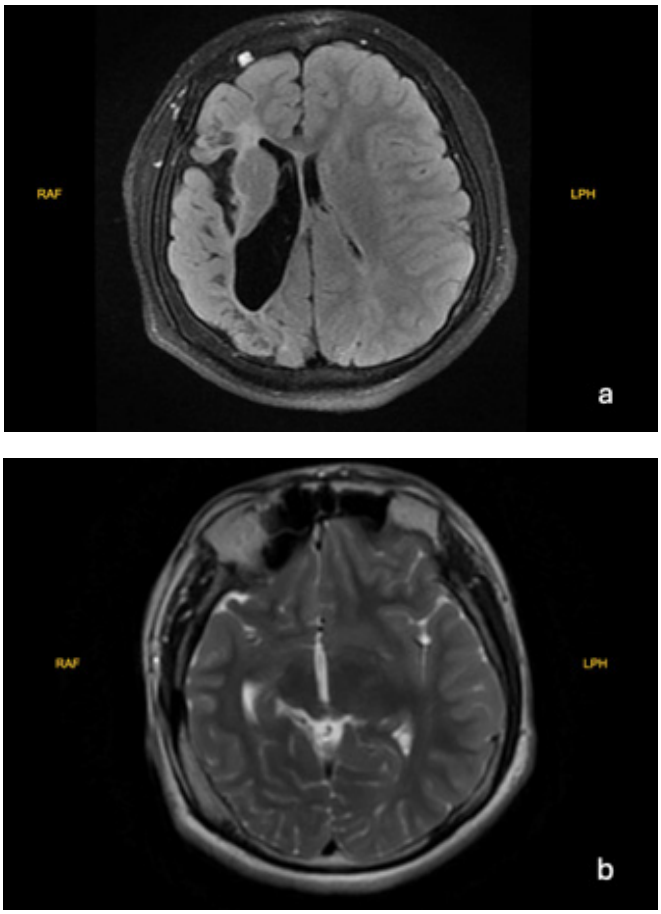

Figure-1 Cranial magnetic resonance imaging shows encephalomalacic changes in the right occipital, temporal, and frontal regions accompanied by thickening in the right hemiclavarial bone structures in a; increased aeration of the frontal sinuses is observed in b.

Discussion

The characteristic symptoms of DDMS were first described by Dyke, Davidoff, and Masson in 1933 in a series of nine cases.[3] According to the literature, it is a rare neurological disorder diagnosed more frequently in pediatric patients. It is characterized by epileptic seizures, contralateral hemiparesis or hemiplegia, intellectual disability, learning problems, facial asymmetry, language and speech disorders, contralateral choreic movements, sensory disturbances, and unsteady gait. In our case, most of the symptoms of DDMS, such as epileptic seizures controlled with antiepileptic treatment, hemiparesis, intellectual disability, and facial asymmetry, were present.

In a literature review by Rondo et al., 70% of cases had contralateral hemiparesis or hemiplegia, 46% had intellectual disability, and 31% had facial asymmetry. In the study, there was a male predomi-

nance of 55.3%, similar to our case.[4]

DDMS has two etiologies: congenital and acquired. The congenital type is generally caused by brain damage occurring in the intrauterine or neonatal period due to vascular causes where maturation is incomplete. In these cases, symptoms may appear perinatally or in infancy. A compatible genetic model has not been identified for the DDMS clinic.[5]
Acquired DDMS causes include infection, intracerebral hemorrhage or ischemia, trauma, neoplasms, and immunological disorders. The onset of the clinical picture in acquired DDMS may extend to late childhood or adolescence, depending on the timing and nature of the etiological factors.[6] In our case, the patient's clinical findings became evident in early childhood.

In neuroimaging of DDMS, unilateral cerebral volume loss, calvarial thickening, hyperpneumatization of the paranasal sinuses and mastoid cells, enlarged sulci, ipsilateral enlargement of the ventricles, and encephalomalacia have been demonstrated. The encephalomalacic changes and increased calvarial thickness detected in our case's imaging support the role of congenital causes in the etiology of the case.[4-7]

The irritability, anger outbursts, and increased psychomotor activity, which were the reasons for our patient's admission to the outpatient clinic, were found to be similar to the literature.[8]

DDMS treatment should be multidisciplinary; seizures should be controlled with antiepileptic drugs, and motor and cognitive rehabilitation support should be provided. In addition, hemispherectomy can be considered as a treatment method for refractory seizures and hemiplegia. In our case, seizures were controlled with a single antiepileptic drug. Special education and physical therapy exercises were given.[9-10]

Differential diagnoses of DDMS include Sturge-Weber syndrome, hemimegalencephaly, linear sebaceous nevus syndrome, Rasmussen encephalitis, and Silver-Russell syndrome, which also show cerebral hemiatrophy.[11]

Neuroimaging should be performed in cases with complaints such as mental retardation, hemiplegia or hemiparesis, and facial asymmetry accompanied by epilepsy, and the detection of findings such as cerebral hemiatrophy and skull thickening in imaging should suggest DDMS. Given that the diagnosis of DDMS is established through radiological imaging in addition to clinical findings, patients with cerebral hemiatrophy should be more carefully evaluated for the syndrome. In patients where DDMS is suspected, the initiation of early motor and cognitive rehabilitation support is crucial for improving quality of life through early diagnosis and rehabilitation interventions.

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CASE REPORT

Modified Thorek Mammoplasty for the Treatment of Idiopathic Gigantomastia

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Abstract

Idiopathic gigantomastia is a rare and severe condition characterized by excessive breast enlargement, which often causes significant physical and psychological distress. Although various surgical techniques have been described for the management of this condition, there is no universally accepted approach. This case report discusses the surgical management of a 29-year-old female patient with idiopathic gigantomastia using a modified Thorek reduction mammoplasty technique. The modified technique involved incorporating a superomedial pedicle to preserve breast volume. The superomedial dermoglandular flap was designed and adapted to the upper margin of the areola, providing autoaugmentation to restore breast volume and prevent post-operative ptosis. This modification allowed for the preservation of the breast's natural projection while achieving a satisfactory aesthetic result. The nipple-areola complex was grafted onto the pedicled flap, avoiding the risks of pedicle-based techniques due to the patient's existing breast anatomy and tissue characteristics. Following the surgery, the patient experienced no complications, and her post-operative appearance was significantly improved, with both physical symptoms and psychological distress alleviated. The total excised tissue weighed 3546 grams from the right breast and 4487 grams from the left, reflecting the extent of the hypertrophy. This report highlights the efficacy of the modified Thorek mammoplasty technique, particularly in cases of severe gigantomastia, and suggests that the incorporation of a superomedial pedicle can be an effective strategy for maintaining breast volume and ensuring an aesthetically pleasing outcome.

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Introduction

Although initially described by Palmuth in 1648, gigantomastia was formally defined in medical literature by Strombeck in 1964.[1,2] Gigantomastia is a rare, benign condition characterized by excessive and rapid breast enlargement, which can result in significant physical discomfort and psychosocial distress. Despite the absence of a universally accepted definition, it is commonly described as the hypertrophy of breast tissue necessitating the excision of at least 1500 grams from a single breast.[3–5] Some authors, however, define it as a condition where one breast exceeds 2500 grams in weight.[6]

Physiological breast enlargement is considered normal during puberty and pregnancy. The etiology of gigantomastia remains unclear, although gestation, hormonal dysregulation, medication use, and autoimmune diseases have been implicated in its pathogenesis.[4,7,8] Idiopathic gigantomastia specifically refers to massive, bilateral or unilateral breast enlargement occurring in adolescent females, in the absence of any identifiable pathological cause.[7] Gigantomastia can be classified into several subtypes, including juvenile, idiopathic, gestational, hormonal, and drug-induced forms.

Various surgical techniques have been described in the literature; however, there remains no standardized approach to the management of this condition.[7] In the present report, we describe the surgical management of a case of idiopathic gigantomastia using a modified Thorek reduction mammoplasty technique incorporating a superomedial pedicle with free nipple-areola grafting.

Case

A 29-year-old G2P2 female patient presented to the plastic surgery clinic with complaints of progressive, massive, bilateral, and asymmetric breast enlargement. Her symptoms included difficulty finding appropriately fitting bras, breast, back, and lumbar pain, as well as occasional ulceration of the breast skin. Medical history revealed that breast enlargement had been present since puberty and had progressively worsened during both pregnancies. The patient had no known systemic disease, was not taking any medications or hormones, and had no family history of gigantomastia or breast cancer. She could not precisely recall the onset of hypertrophy but reported that her breast size had been noticeably larger than her peers' since approximately age 12–13. She had completed her last pregnancy about three years ago. A mammogram performed at an external center two months prior had been reported as BIRADS-2.

Inspection revealed asymmetric, excessive hypertrophy of the breasts, skin thinning, minimal ulcerations, areas with peau d'orange appearance, significantly enlarged areolae, and dilated superficial veins. Indentation marks from bra straps were observed on both shoulders. Due to excessive weight, the inframammary fold had descended significantly below its anatomical position. On palpation, firm subcutaneous nodules were noted bilaterally, but there was no galactorrhea or axillary lymphadenopathy. The sternal notch–nipple distance was measured as 39 cm on the right and 46 cm on the left. At presentation, the patient weighed 59 kg and was 166 cm tall (BMI: 21,4 kg/m²). All preoperative laboratory results were within normal limits, and the β-HCG test was negative. Given the extensive tissue resection planned, two units of erythrocyte suspension were crossmatched preoperatively (initial hemoglobin: 13.8g/dL). A Thorek reduction mammoplasty under general anesthesia was planned. The patient was thoroughly informed that the nipple would be reconstructed as skin graft and that breastfeeding and lactation would not be possible in the event of a future pregnancy. Written informed consent was obtained regarding this matter. Preoperative clinical photographs are shown in Figure 1.

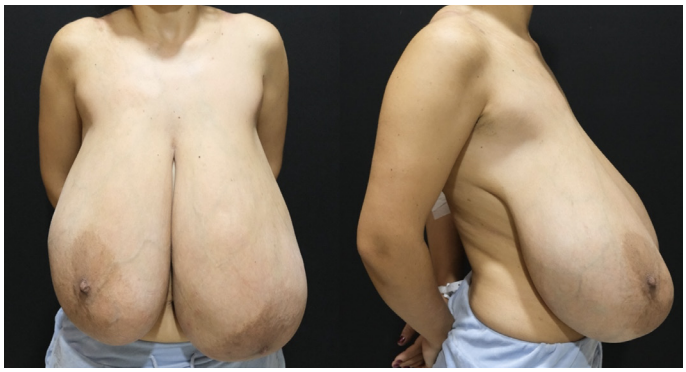

Figure 1. Preoperative appearance of the patient.

Due to the significantly low breast footprint, a superomedial dermoglandular flap resembling a pedicle was planned to preserve breast volume, and the nipple-areola complex was to be grafted onto this flap. The superior border of the areola was marked 19 cm from the sternal notch. A Wise-pattern skin excision design with 6,5 cm lateral limbs was drawn. The planned superomedial dermoglandular flap and surgical markings are shown in Figure 2.

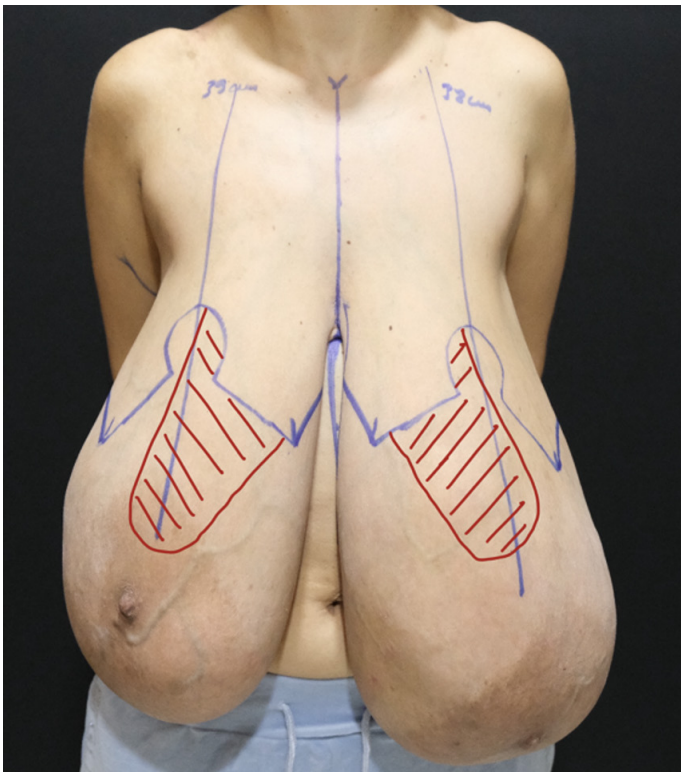

Figure 2. Surgical planning and the superomedial dermoglandular flaps marked for de-epithelialization to restore breast volume.

In the first stage of the operation, the areola was excised as a full-thickness skin graft (FTSG), followed by de-epithelialization of the superomedial tissue. The de-epithelialized flaps were then dissected from the medial, inferior, and lateral breast tissues through incisions extending down to the pectoral fascia. Subsequently, all breast tissue—except for the superomedial dermoglandular flap—was excised at the level of the pectoral fascia in accordance with the preoperative markings. The superomedial dermoglandular flap was then adapted to the site designated for the neo-areola. Thereafter, the medial and lateral breast pillars were approximated and sutured, and the areola graft was inset into its new position. The same procedure was performed bilaterally, resulting in the excision of 3546 grams of breast tissue from the right breast and 4487 grams from the left. After placement of tie-over dressings, one active closed-suction drain was inserted into each breast, and the procedure was completed. The intraoperative view of the patient is presented in Figure 3.

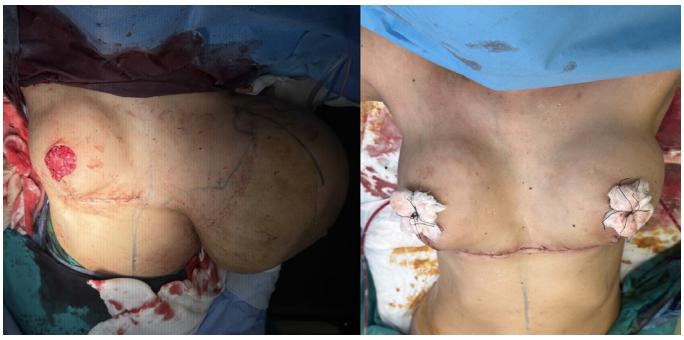

Figure 3. Early and late intraoperative views of the patient.

In the postoperative period, the patient was hospitalized for two days and monitored under intravenous antibiotic therapy and analgesia. As the patient did not exhibit any signs of pallor or tachycardia and her follow-up hemoglobin level was 10.1 g/dL, no blood transfusion was deemed necessary. The patient was discharged on postoperative day 2 with her drains in place.

At the first postoperative follow-up visit on day 7, the drains were removed, and the tie-over dressings were opened. The nipple grafts were observed to have begun to take well, and no wound healing complications were noted. The patient's appearance on postoperative day 7 is shown in Figure 4.

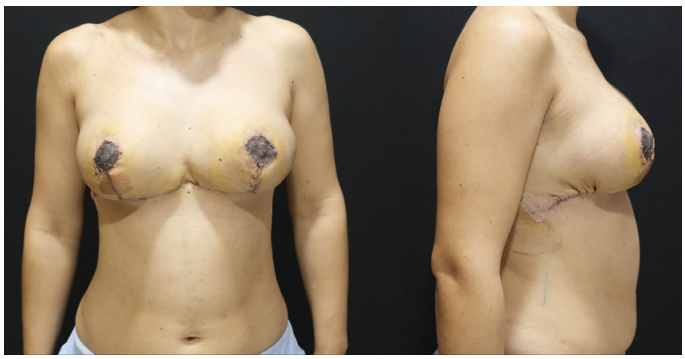

Figure 4. Postoperative appearance of the patient at 1st week.

The pathological examination of the patient's breast tissue reported "Widespread pseudoangiomatous stromal hyperplasia, fibroadenomas, and fibrocystic changes in both breasts." The patient was advised to undergo follow-up with a new mammogram after 6 months. The histopathological appearance of the patient's breast tissue is shown in Figure 5 and the postoperative appearance of the patient at 6th month is shown in Figure 6. No postoperative complications were observed and the peroperative period was uneventful.

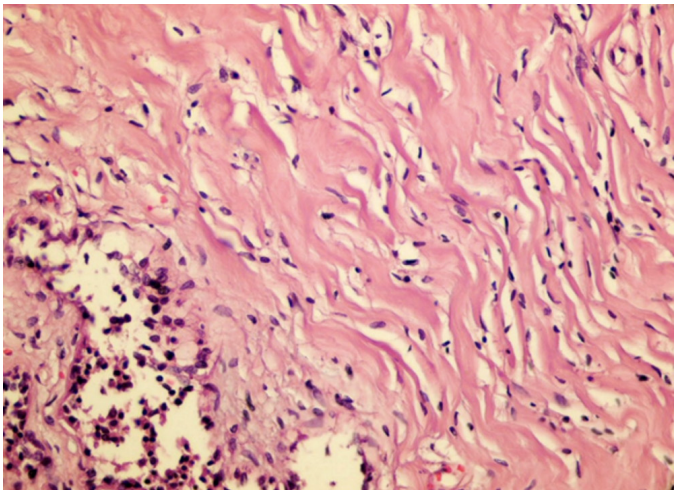

Figure 5: Histopathological appearance of the patient's breast tissue.

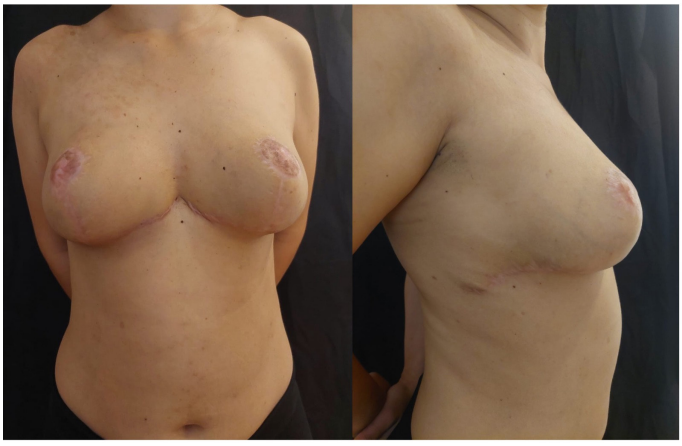

Figure 6: The postoperative appearance of the patient at 6th month.

Discussion

Gigantomastia is a rare condition, predominantly observed in individuals of the white race.[5] The white-to-black ratio has been reported as 9:4.[5] Typically, rapid and sudden breast enlargement occurs unilaterally or bilaterally, in a symmetric or asymmetric manner. There are suggestions that the etiology may involve an increase in the number of prolactin, estrogen, or progesterone receptors in the target organ, or an excessive increase in the sensitivity of these receptors to the hormones at the receptor level.[5,8] The patient's Caucasian background and the bilateral nature of the gigantomastia support the literature.

Tension in the breast skin, tenderness, peau d'orange appearance, and enlargement of the superficial breast veins leading to a varicose appearance may occur.[5] Ulceration and skin loss may be present in the breasts. Literature reports deaths due to infections caused by ulcers and bleeding in breast vessels. The main symptoms of gigantomastia include breast pain, hygiene difficulties, intertriginous lesions in the inframammary folds, neck, back, and lumbar pain, shoulder impressions and indentations from bra straps, orthopnea, skin necrosis, kyphosis, and lumbar lordosis.[9,10,11] In addition, psychological disturbances such as social isolation, peer bullying, and depression or anxiety leading to suicide may occur. The patient discussed in this case presented to us due to the presence of similar physical complaints.

Normal breast development occurs over a period of 3-5 years and involves all tissues that constitute the breast.[7] The breast is composed of three main tissues: fat, stroma, and gland. These tissue types are organized around the alveoli and lobules within the breast. Three dominant hormones regulate breast physiology.[2] These hormones are prolactin, estrogen, and progesterone. The ductal growth of the breast is influenced by anterior pituitary hormones such as luteinizing hormone, growth hormone, and adrenocorticotropic hormone, as well as estrogen, which is the primary stimulator of the breast. Lobuloalveolar growth, on the other hand, is influenced by progesterone and prolactin. Corticosteroids and prolactin are hormones that independently affect breast development.[7] Normal breast development begins with the formation of the mammary ridge from the ectoderm on the 20th day of the embryonic period and is completed towards the end of the fetal period.[7] Looking at the embryology of the breast, it is observed that both ectoderm and mesoderm are responsible for the formation of the breast; the breast tissue originates from the ectoderm, while the skin derives from the mesoderm.[9,10] The nipple and areola arise from the mammary pit and the inward folding of the epidermis, surrounding connective tissue, and mesenchyme.[7]

The primary cause of excessive breast enlargement during or after puberty, without any underlying pathology, remains unknown. Idiopathic gigantomastia is not associated with hormonal disorders.[11] Additionally, chromosomal analysis studies of patients with gigantomastia have shown a normal 46 XX karyotype.[7] Pregnancy-related gravid hypertrophy is usually observed between the ages of 20 and 30, distinguishing it from idiopathic gigantomastia based on the patient's age and pregnancy history. Pseudo-gigantomastia is associated with excessive fat accumulation in the breasts due to obesity.[12]

In this case, given the patient's age, the onset of breast enlargement during adolescence, the absen-

ce of a history of hormone-containing or non-hormone-containing medications such as birth control pills, and no clinical or history findings suggestive of autoimmune diseases like SLE or Graves' disease that could cause gigantomastia led to the conclusion that the patient's condition is idiopathic since by definition, juvenile gigantomastia is characterized by rapid and excessive breast enlargement that occurs during puberty, typically between the ages of 11 and 17, in the absence of any identifiable underlying pathology. Although the patient states that breast enlargement began in adolescence, the hypertrophy worsened significantly during her pregnancies and persisted into adulthood. Thus, the clinical picture does not fulfill the accepted criteria for juvenile gigantomastia.

The diagnosis of idiopathic gigantomastia is made through the exclusion of all other causes.[2] Drug-induced gigantomastia, caused by D-penicillamine, neotetazone, cyclosporine, or protease inhibitors, can be identified by reviewing the medications the patient is taking.[7] D-penicillamine, a chelator that breaks down large protein molecules into smaller molecules and simultaneously increases free estrogen, is one of the riskiest drugs in this regard.[5] Additionally, a physical examination should be conducted to rule out breast enlargement due to trauma-induced panniculitis or palpable masses. At this stage, a pregnancy test must also be performed. To exclude pseudoprecocious puberty, granulosa cell tumors of the ovary, ovarian follicular cysts, and hormonal abnormalities, serum levels of estrogen, progesterone, prolactin, and gonadotropins should be assessed. For adrenal dysfunction, urine 17-ketohydroxysteroid levels should be checked.[7] To exclude pituitary growth disorders, a direct head X-ray or cranial magnetic resonance imaging (MRI) can be used, and any possible enlargement of the sella turcica can be observed.[7]

Pathological examination of gigantomastia excision materials typically reveals some common features. These include ductal and alveolar proliferation, severe hypertrophy and fibrosis of periductal and periacinar stromal tissues, an increased number of lactiferous ducts, their enlargement, and lining by at least two layers of cubic, inactive cells. Usually, lymphocytic infiltration accompanies hyaline connective tissue in the materials.[5,8] In some areas of the breast, necrotic degeneration due to secondary decreased blood supply may result in calcifications.

Another problem related to gigantomastia is its occurrence during the first trimester of pregnancy. Although rare, with an incidence of 1:100,000, this condition can be life-threatening and may require emergency bilateral mastectomy. Deaths due to gravid gigantomastia have been reported in the literature. Infection, ulceration, and hemorrhage are absolute indications for surgery.[8] Therefore, early surgery is recommended before complications such as skin loss, sepsis, or sudden massive bleeding.

Throughout history, various surgical techniques have been applied for gigantomastia, including breast reduction, skin-preserving or total mastectomy with breast-nipple reconstruction, hormonal therapy, or combinations of these approaches.[13] However, there is still no consensus regarding the optimal treatment.[14] A review of the literature reveals a case where a total of 38 kg of breast tissue was excised through mastectomy, followed by late-stage breast reconstruction with implants.[3] Breast reduction with or without hormonal therapy is generally considered the first-line treatment for gigantomastia. Free nipple grafting is also frequently used, depending on the size of the breasts. However, breast reduction surgery does not provide a definitive cure, and recurrence can occur, with advanced pregnancies being a primary cause of recurrence. On the other hand, mastectomy and breast reconstruction are associated with several drawbacks, such as less natural aesthetic results, issues related to breast implants, insufficient lactation, and potential psychological side effects.

Although hormonal manipulation of the breast with tamoxifen, norethindrone, testosterone, progesterone, and stilbestrol has been attempted in treatment, success has not been achieved. Hydrocortisone and prednisone have been beneficial in controlling the inflammatory response but have not reduced breast growth.[2] Diuretics such as hydrochlorothiazide and furosemide have also been tried in the literature, but no benefit was achieved.[2] Bromocriptine has reduced prolactin levels in some cases, but its benefit is limited.[2,8] For all these reasons, the appropriate treatment for gigantomastia remains a subject of debate.

The optimal surgical technique for reduction mammoplasty in the surgical treatment of gigantomastia is still debated. The main reason for this is that each technique has different complications, and none has a clear superiority over the others.[14] The use of the inferior pedicle, considered safer for NAC transposition, has a significant disadvantage over time: the risk of bottoming out. This occurs because the excision is made from the upper part of the breast, and the lower

pole of the breast gradually sags due to gravity.[14] The majority of excisions in gigantomastia are performed from the lower pole, which provides more aesthetic advantages in the long term. Vertical scar techniques have gained significant popularity in recent years, but they can cause the scar to extend along the chest wall, especially when used for very large breasts.[14] The free areola-nipple grafting technique by Thorek, also used in this case, has certain disadvantages. These include a flat, non-erectile, and numb nipple, loss of lactation, color changes in the nipple due to grafting, epidermolysis, graft failure, and the risk of NAC necrosis.[9,14]

In the literature, both superior and central pedicle techniques have been attempted in the surgical treatment of gigantomastia.[9,14] However, due to the presence of varicose veins observed during inspection, which increase the risk of venous insufficiency and NAC (nipple-areola complex) necrosis, pedicle-based breast reduction techniques were avoided in this patient. Additionally, since the excision was planned to be performed from the superolateral area of the breast, which is the highest risk zone for breast cancer, the dermoglandular flap was chosen from the superomedial side.

In the case presented, due to the distance from the sternal notch to the nipple being over 40 cm and the patient not planning any future pregnancies, a Thorek free nipple transfer with reduction mammoplasty was planned. However, because of the excessively large and heavy breasts, the majority of the breast tissue had descended below the current IMF (inframammary fold) level. Therefore, it was believed that sufficient breast volume and projection could not be achieved with a standard Thorek breast reduction. The superomedial pedicle-like dermoglandular flap was adapted to the upper margin of the areola to provide autoaugmentation, and the nipple graft was directly adapted to this flap. Furthermore, to prevent long-term breast ptosis, the superomedial dermoglandular flap was also adapted to the pectoral fascia.

Modifications similar to Thorek mammoplasty have been observed in the literature. Fırat et al. described autoaugmentation-autoprothesis techniques, where the inferior dermoglandular flap was passed under the pectoral muscle to ensure projection, instead of using the superomedial dermoglandular flap as used by us in Thorek mammoplasty.[15] However, as stated above, this modification was considered to minimize tissue retention in the lower pole of the breast.

Conclusion

Gigantomastia is a condition with significant physical and psychological negative effects, and its etiological factors are not fully understood.[8] Although it is thought to result from an altered breast response to normal hormone concentrations, the abnormal relationship between hormone receptors and the target organ remains unclear[5] The choice of surgical approach in treatment is complex and should be tailored to the patient's desires, the specific characteristics of the breasts, and any presence of breast asymmetry.[6] Thorek reduction mammoplasty remains an appropriate option for immediate symptom relief and improved quality of life. However, in cases where the breasts are very heavy and the breast footprint has descended below the IMF level, modifications that provide autoaugmentation should be added to the surgery. Lastly, as there may be blood loss during surgery, adequate preparation for blood and blood products should be ensured.[4]

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