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Drug-Induced Hypersensitivity Syndrome with Elevated Inflammatory Parameters Thought to be Triggered by Amphotericin B

Amfoterisin B'nin Tetiklediği Düşünülen Yüksek İnflamatuvar Parametrelere Sahip İlaca Bağlı Aşırı Duyarlılık Sendromu

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ABSTRACT

Although it is known that inflammatory markers may elevate for various reasons, they are almost always considered indicators of infectious disease in clinical practice. Drug-induced hypersensitivity syndrome is a rare and life-threatening adverse drug reaction. Elevations in inflammatory parameters also may be observed during the course of hypersensitivity reactions. This paper presents a case of a young adult diabetic patient who was receiving broad-spectrum antibacterial treatment for orbital cellulitis and developed drug-induced hypersensitivity syndrome upon initiation of antifungal therapy. The condition resembled an exacerbated infection due to high fever and increased inflammatory parameters. Clinicians should be aware that elevations in inflammatory biomarkers, such as C-reactive protein and procalcitonin, occur not only in infections but also have diagnostic value in allergic reactions. Furthermore, clinical findings should be more decisive than laboratory results for antimicrobial necessity. This awareness will contribute to managing the increasing challenge of antibiotic resistance.

Key Words: *Drug-induced hypersensitivity syndrome; Inflammatory biomarkers; Dress syndrome; Hypersensitivity reaction; Orbital cellulitis*

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ÖZ

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İnflamatuvar belirteçlerin başka nedenlerle de arttığı bilinmesine rağmen bu belirteçler klinik uygulamada neredeyse her zaman bulaşıcı bir hastalığın göstergesi olarak kabul edilmektedir. İlaç kaynaklı hipersensitivite sendromu, nadir görülen ve yaşamı tehdit eden bir advers ilaç reaksiyonudur. İnflamatuvar parametrelerde artışlar, hipersensitivite reaksiyonları sırasında da gözlemlenebilir. Bu çalışmada, orbital selülit tanısıyla geniş spektrumlu antibakteriyel tedavi gören, antifungal tedaviye başlandıktan sonra ilaç kaynaklı hipersensitivite sendromu gelişen ve yüksek ateş ile artan inflamatuvar parametreler nedeniyle infeksiyonun alevlendiği düşünülen diyabetli genç bir yetişkin hasta sunulmaktadır. Klinisyenler, C-reaktif protein ve prokalsitonin gibi inflamatuvar biyobelirteçlerdeki artışın yalnızca infeksiyonlarda değil, aynı zamanda alerjik reaksiyonların tanısında da anlamlı olabileceğini göz önünde bulundurmalıdır. Ayrıca, antimikrobiyal tedavi gerekliliğinin belirlenmesinde laboratuvar sonuçlarından ziyade klinik bulgular ön planda değerlendirilmelidir. Bu yaklaşım, artan antibiyotik direncinin kontrol altına alınmasına katkı sağlayacaktır.

Anahtar Kelimeler: *İlaç kaynaklı hipersensitivite sendromu; İnflamatuvar biyobelirteçler; Dress sendromu; Hipersensitivite reaksiyonu; Orbital selülit*

INTRODUCTION

Drug-induced hypersensitivity syndrome (DIHS) also known as drug reaction with eosinophilia and systemic symptoms (DRESS) is a potentially fatal acute hypersensitivity reaction to drugs[1]. A wide variety of drugs have been reported to cause this condition[2-5]. Although the exact etiopathogenesis is unknown, genetic, immunological, and metabolic factors likely contribute to DIHS[5]. In addition, the reactivation of herpes viruses, including human herpes virus (HHV) 6, HHV-7, Epstein-Barr virus (EBV), and cytomegalovirus (CMV), is considered to play a role in its pathogenesis, with HHV-6 reactivation specifically implicated in triggering recurrence and exacerbation[6]. DIHS and DRESS are defined by different criteria established by the Japanese Committee for the Study of Severe Cutaneous Adverse Events (J SCAR) and the RegiSCAR group and are presented together in Table 1[7-9]. However, both

Table 1. Diagnostic criteria for drug-induced hypersensitivity syndrome[7-9]

Japanese Consensus Group[a]	RegiSCAR[b]
Maculopapular rash developing >3 weeks after starting with a limited number of drugs	Hospitalization
Prolonged clinical symptoms two weeks after discontinuation of the causative drug	Acute skin rash
Fever (>38 °C)	Fever (>38 °C)
Liver abnormalities (alanine aminotransferase >100 U·L –1)[c]	Lymph node enlargement at two or more sites
Leukocyte abnormalities (at least one present) Leukocytosis (>11 × 10^9 L –1) Atypical lymphocytosis (>5%) Eosinophilia (>1.5 × 10^9 L –1)	Lymphocytes above or below the laboratory limits Eosinophils above the laboratory limits Platelets below the laboratory limits
Lymphadenopathy	Involvement of at least one internal organ
Human herpesvirus six reactivation	

[a] Diagnosis is confirmed by the presence of the following seven criteria (typical DIHS) or five criteria (atypical DIHS).
[b] Diagnosis is confirmed if three or more criteria are met, excluding hospitalization.
[c] This can be replaced by other organ involvement, such as renal involvement.

syndromes likely represent the same condition[9]. Specifically, HHV-6 reactivation has been included as one of the diagnostic criteria for DIHS but not for DRESS, and typical DIHS considered a severe form of DRESS[9,10].

DIHS/DRESS is characterized by a delayed onset, typically occurring days to weeks after the initiation of treatment with the causative drug, and the inflammatory response persists after discontinuation of the causative treatment[7,8]. This delayed presentation makes diagnosis challenging and may lead to delayed diagnosis[9].

Amphotericin B (AmB) is a key agent in the management of serious systemic fungal infections. Its acute adverse effects are primarily limited by infusion-related toxicity, which is postulated to result from proinflammatory cytokine production by innate immune cells[11]. Because AmB is a microbial product, it has been hypothesized that it stimulates immune cells via toll-like receptors in mammalian cells[12].

In this case, we present a diabetic young adult patient who received broad-spectrum antibacterial therapy for orbital cellulitis and developed DIHS upon initiation of antifungal therapy, which resembled an exacerbated infection due to high fever and increased inflammatory parameters.

Case Presentation

A 33-years-old male patient was admitted to the healthcare facility with complaints of pain in the right eye and maxillary region approximately 20 days prior. He was prescribed eye drops containing tobramycin and oral cefixime. Paranasal sinus tomography revealed findings consistent with right maxillary and frontal sinusitis, and parenteral cefuroxime treatment was initiated.

On the third day of parenteral treatment, the patient developed swelling in the right eye and was referred to our outpatient clinic. On physical examination, right eye movements were restricted in all directions, and the right eyelid was swollen and edematous. Orbital magnetic resonance imaging findings were consistent with orbital cellulitis, and the patient was hospitalized in the infectious disease unit. Empirical piperacillin-tazobactam and vancomycin treatment were initiated.

The laboratory values at the time of hospitalization were as follows: white blood cell (WBC)= 13200/mm^3 [69% polymorphonuclear leukocytes (PNL)], platelet count (PLT)= 226000/mm^3, creatinine= 0.74 mg/dL, aspartate aminotransferase (AST)= 21 U/L, alanine aminotransferase (ALT)= 54 U/L, C-reactive protein (CRP)= 32 mg/L, procalcitonin= 0.049 ng/mL, HbA1c= 14.2%. Paranasal samples were obtained for microbiological and pathological examination. Gram staining of the samples was unremarkable, and the cultures were negative for growth.

On the 11^{th} day of hospitalization, the pathology report indicated mucormycosis, leading to the initiation of liposomal AmB therapy. However, at this point, the swelling in the eye had significantly decreased, eye movements had returned to normal and inflammatory parameters in the blood were improving with the current treatment. Furthermore, endoscopic nasal examination and radiological findings were not consistent with mucormycosis. Nevertheless, due to the patient's insulin-dependent type 1 diabetes and the serious concern for mucormycosis, additional paranasal samples were obtained, and liposomal AmB was added to the treatment regimen.

When the first dose of AmB was administered, the patient experienced widespread pain in the body, and flushing. Consequently, he was premedicated with paracetamol and antihistamines for subsequent doses, and these symptoms did not recur. On the fifth day of AmB treatment, the patient developed two episodes of high fever, peaking at 39.2 °C, accompanied by chills and shivering. Physical examination did not reveal lymphadenopathy. However, the patient's laboratory values showed significant abnormalities: WBC= 1000/mm^3 (12% PNL, 0.9% eosinophils), Hb= 10 g/dL, PLT= 39000/mm^3, creatinine= 1.64 mg/dL, AST= 176 U/L, ALT= 196 U/L, CRP= 204 mg/L, procalcitonin= 4.23 ng/mL, and D-dimer= 67076 ng/mL.

Mild erythema developed in the neck region, but eosinophilia was not present. The patient received a single dose of 20 mg IV prednisolone (prednol) with continued antihistamine therapy.

Antibiotic therapy was switched from piperacillin-tazobactam and vancomycin to meropenem, and antifungal therapy was switched from AmB to posaconazole. Following these changes, the fever resolved promptly. Laboratory values improved, with: CRP= 14 mg/L, procalcitonin= 0.147 ng/mL, and D-dimer= 688 ng/mL.

Leukopenia, thrombocytopenia, and liver and renal function tests also improved.

On the seventh day of meropenem treatment, the patient developed a diffuse maculopapular rash on the torso and bilateral upper extremities, which faded with pressure. Meropenem was discontinued, and a skin biopsy was performed.

On the ninth day of posaconazole treatment, the patient once again developed fever. The laboratory parameters were as follows: creatinine= 1.52 mg/dL, CRP= 303 mg/L, procalcitonin= 1.2 ng/mL, WBC= 5400/mm^3, and PLT= 139000/mm^3.

The laboratory parameters throughout the clinical course are summarized in Table 2. There was no source of infection on examination. A single dose of prednisolone (40 mg/IV) was administered, after which the fever resolved, and the skin lesions improved.

No bacterial or fungal growth was detected in the sinus material sample (second paranasal sample) collected at the initiation of liposomal AmB. Additionally, the pathological examination findings were not consistent with mucormycosis. Consequently, posaconazole treatment was discontinued on the 10th day. The correlations between fever and laboratory values are shown in Figure 1.

After antifungal treatment was discontinued, the patient was discharged with complete recovery of clinical and laboratory findings. HHV-6 serology, requested as part of follow-up testing, was positive. When evaluated using the Japanese Consensus Group criteria, the patient met five criteria (symptoms lasting more than two weeks, fever, liver and renal dysfunction, leukopenia, HHV-6 positivity). This led to a diagnosis of atypical DIHS. The patient met four of the RegiSCAR criteria (fever, rash, thrombocytopenia, involvement of internal organs). Based on these findings, the patient was diagnosed with DIHS.

DISCUSSION

Drug-induced hypersensitivity syndrome, also known as drug reaction with eosinophilia and systemic symptoms, is a rare and life-threatening adverse drug reaction. These conditions are often difficult to differentiate from infectious diseases due to their overlapping symptoms. Clinical findings frequently mimic sepsis, making differential diagnosis challenging, leading to misdiagnosis and unnecessary antibiotic use[9].

Table 2. Laboratory parameters and antimicrobial treatments during the clinical course

	Day of Hospitalization	Day 15	Day 25	Reference Value
WBC	13200	1000	5400	3600-11200 uL
PLT	226000	39000	139000	159000-386000 uL
CRP	32	204	303	0-5 mg/L
Procalcitonin	0.049	4.23	1.2	0-0.05 ng/mL
AST	21	176	8.07	0-31 U/L
ALT	54	196	14.96	0-34 U/L
Creatinine	0.74	1.64	1.52	0.67-1.17 mg/dL
Antimicrobial treatment*	Piperacillin Tazobactam plus Vancomycin	Piperacillin Tazobactam plus Vancomycin plus Amphotericin B	Meropenem plus Posaconazole	

(*) Treatment was switched to meropenem plus posaconazole on the 16th day of antibacterial and fifth day of amphotericin B treatment.
WBC: White blood cell, PLT: Platelets, CRP: C-reactive protein, AST: Aspartate aminotransferase, ALT: Alanin aminotransferase.

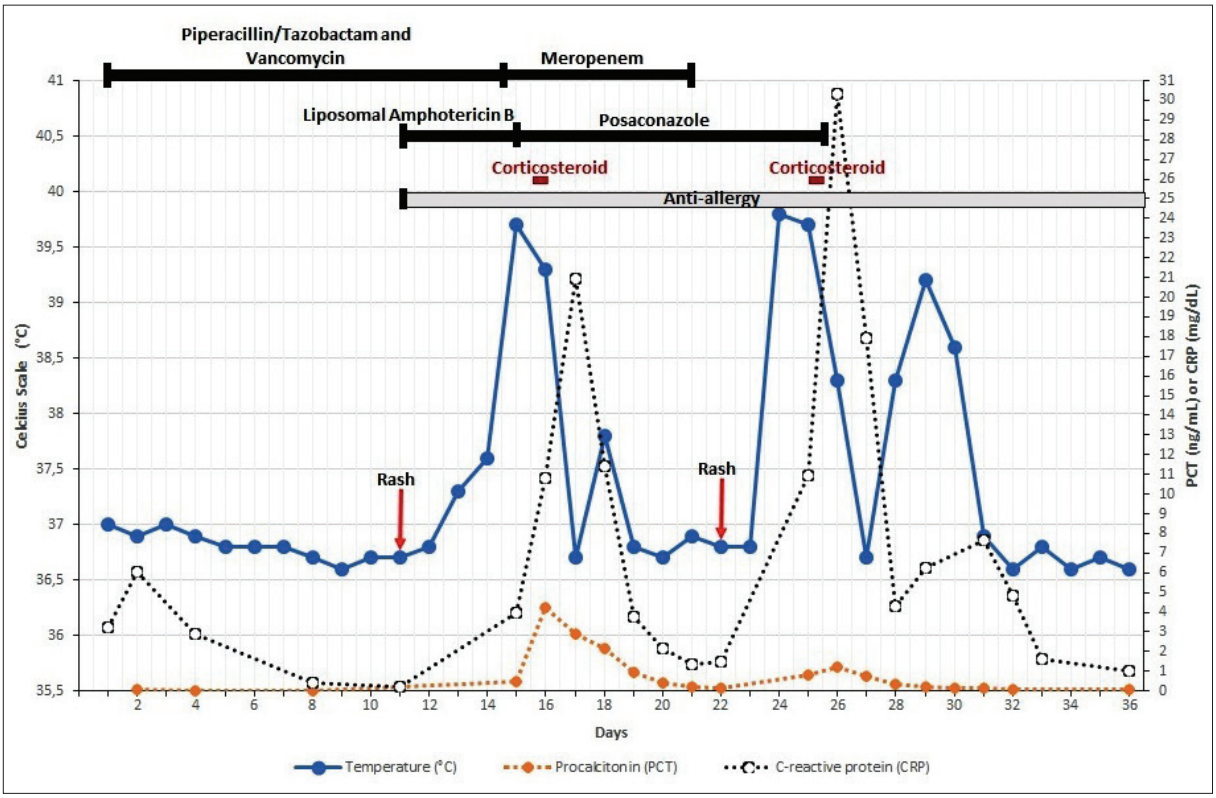

Figure 1. The correlations between fever and laboratory values.

Procalcitonin may help identify infectious or noninfectious sources of systemic inflammatory response syndrome, acute respiratory distress syndrome, pancreatitis, and acute resection[8,9]. Although antibiotic treatment may be initiated when the PCT level is >1.2 ng/mL, even in the absence of a positive blood culture, it has been reported that PCT levels can rise to 10-100 ng/mL or even higher in systemic bacterial, fungal, and parasitic infections[13].

In our patient, on the fifth day of treatment, piperacillin tazobactam, vancomycin, and AmB were discontinued due to a deterioration in laboratory values and the presence of fever. However, antimicrobial treatment could not be completely discontinued because of the severe elevation in inflammatory parameters (CRP= 204 mg/L; procalcitonin= 4.23 ng/mL). Meropenem and posaconazole were initiated. With this treatment, the patient's fever decreased, and laboratory parameters improved.

On the seventh day of treatment, a maculopapular rash developed, followed by an increase in both CRP and PCT levels. Antibacterial treatment was discontinued as there was no growth in any culture, no bacterial infection focus was identified, and the patient responded to steroid treatment. Antifungal treatment was also discontinued when the pathological examination of the sinus material sample taken for the second time revealed no suspicion of mucormycosis.

Only a few cases of procalcitonin elevation in DHIS patients have been reported[14]. In our case, the inflammatory response was attributed to hypersensitivity syndrome, as there was no microbiological evidence. The absence of microbiological growth despite elevated CRP and PCT levels highlights the need for alternative diagnostic approaches, including skin biopsy and histopathological evaluation, to confirm DIHS/DRESS.

The drug reaction in our patient mimicked sepsis syndrome due to leukopenia, thrombocytopenia, and hepatic and renal dysfunction. The patient did not have eosinophilia. However, despite being

a key feature of the syndrome, eosinophilia is not always present, and it is reported that in one third of the cases eosinophil counts remain within normal limits, while lymphocyte counts may be altered[15].

Although no focus of infection could be identified, antimicrobial treatment could not be discontinued. Histomorphological changes observed in the skin biopsy, including spongiosis in the epidermis, edema in the superficial dermis, endothelial swelling in vascular structures, extravasated erythrocytes, and lymphocyte exocytosis, were consistent with DRESS syndrome when considered alongside the clinical findings.

The decision to discontinue antimicrobial therapy was made once biopsy results provided supporting evidence (findings indicative of a drug reaction in skin biopsy samples and the absence of mucormycosis in paranasal biopsy samples). Given that the patient's clinical condition did not deteriorate despite abnormal laboratory values, no signs of systemic inflammation other than fever were detected, and no microbial growth was observed in cultures, drug reactions were suspected as the primary cause of clinical deterioration.

In such cases, with normal eosinophil counts, clinicians may find it difficult to make a diagnosis of the DRESS syndrome. However, a comprehensive evaluation of the clinical picture and an understanding of drug classes with the highest risk of hypersensitivity reactions should guide clinicians toward recognizing this rare but potentially severe adverse drug reaction[15].

The biopsy findings were crucial in ruling out mucormycosis and confirming a drug reaction, emphasizing the importance of histopathological examination before continuing antifungal therapy in ambiguous cases.

Mucorales, which are found in acidic and high-glucose environments, can colonize the mucosal surfaces of diabetic patients due to favorable reproductive conditions in low-pH settings. Granulomatous sinonasal infections caused by mucorales are rare in immunocompetent hosts[16].

In our patient, endoscopic sinus examination findings were not compatible with mucormycosis, and a clinical response was achieved with antibacterial treatment. However, antifungal treatment was initiated based on the pathology results, which triggered an allergic response in the patient. The decision to start antifungal therapy was influenced by the patient's uncontrolled diabetes.

In conclusion, clinicians should be aware that elevations in inflammatory biomarkers, such as CRP and PCT, are not only indicative of infections but also have diagnostic value in allergic reactions, including DIHS/DRESS. Clinical findings should take precedence over laboratory results when determining the necessity of antimicrobial therapy.

CONFLICT of INTEREST

No conflict of interest declared.

AUTHORSHIP CONTRIBUTIONS

Concept and Design: FZA, OÜ

Analysis/Interpretation: All of authors

Data Collection or Processing: FZA, OÜ, EO, FK

Writing: FZA, OÜ, ENT, OK, GRY

Review and Correction: All of authors

Final Approval: All of authors

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