A Case with Acute Generalized Exanthematous Pustulosis Due to Iopromide: Differential Diagnosis

Iopromide'e Bağlı Gelişen Akut Jeneralize Ekzantematöz Püstülozlu Bir Olgu

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ABSTRACT Acute generalized exanthematous pustulosis is a rare cutaneous reaction characterized by generalised non-follicular, pinhead-sized, sterile pustules on an erythematous background. The eruption is usually related to drug administration and appears suddenly 7-10 days after the medication is started. Although many medications can cause acute generalized exanthematous pustulosis, the most common group is antibiotics, especially ß-lactams and macrolids. The acute onset of disease is accompanied by typical histological changes, fever greater than 38 °C, raised neutrophil count (> 7x109 /L), and spontaneous and rapid resolution in less than 15 days. Histopathology shows subcorneal pustules with a background of dermal edema and spongiosis, leukocytoclastic vasculitis, perivascular eosinophils, or focal necrosis of keratinocytes. We present a case of acute generalized exanthematous pustulosis due to Ultravist® (Iopromide) use for thoracic computerized tomography, and review the published literature.

Key Words: Iopromide; drug eruptions

ÖZET Akut jeneralize ekzantematöz püstüloz, non-foliküler, eritematöz zeminli, toplu iğne başı büyüklüğünde yaygın steril püstüllerle karakterize nadir bir cilt reaksiyonudur. Erüpsiyon genellikle ilaç kullanımı ile ilgilidir ve ilacın başlanmasından 7-10 gün sonra ani olarak başlar. Her ne kadar pek çok ilaç akut jeneralize ekzantematöz püstüloza neden olabilirse de, en yaygın grup antibiyotikler, özellikle de β-laktamlar ve makrolidlerdir. Hastalığın akut başlangıcına tipik histolojik değişiklikler, 38 °C'den yüksek ateş, artmış nötrofil sayısı (> 7x109 /L) ve 15 günden kısa bir sürede kendiliğinden hızlı iyileşme eşlik eder. Histopatolojide geri planda deride ödem ve spongiosis, lökositoklastik vaskülit, perivasküler eozinofiller, fokal keratinosit nekrozu izlenen subkorneal püstüller görülür. Biz göğüs bilgisayarlı tomografi çekimi için kullanılan Ultravist® (Iopromide)'e bağlı bir akut jeneralize ekzantematöz püstüloz vakasını sunmakta ve yayınlanan literatürü gözden geçirmekteyiz.

Anahtar Kelimeler: İopromid; ilaç erüpsiyonu

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Acute generalized exanthematous pustulosis (AGEP) is a rare skin eruption, characterized by acute generalized non-follicular, pinhead-sized, sterile pustules on an erythematous background. Over 90% of cases of AGEP are induced by systemic drug treatment, mainly antibiotics such as β-lactams and non-steroidal anti-inflammatory agents.[1] In this article, we report a case of AGEP in a 50 year old man who was administered Ultravist® (Iopromide) for thoracic computerized tomography. To

our knowledge there are no reports of AGEP caused by Ultravist® use in the literature.

CASE REPORT

A 50-year-old man was admitted to our hospital with an abrupt and sudden onset of itchy generalized pustular rash. One week prior to presentation, the patient was given Ultravist® (Iopromide) for thoracic computer tomography. Two days after iopromide administration he developed severe generalized pustules on his trunk and extremities. The patient had no previous history of hypersensitivity reactions, psoriasis or other associated diseases. On physical examination, he had multiple non-follicular superficial pustules and underlying erythema affecting the abdomen, inguinal region and extremities (Figure 1) and a fever of 38.5 °C. There was no mucosal involvement. A skin biopsy was obtained from one of the lesions and the histopathological features included spongiform subcorneal pustules and diffuse dermal infiltrate of lymphocytes and eosinophils (Figure 2). Laboratory investigations showed a white blood cell count of 13,500 /μL with 70% neutrophils and 10% eosinophils. Blood and pustule cultures were negative. The mycological examination of a pustule was negative. In the light of the clinical and histopathological findings, we considered that the patient as AGEP related to Ultravist® (Iopromide) administration. The patient was treated with oral prednisone. He was educated to avoid this medication in the future.

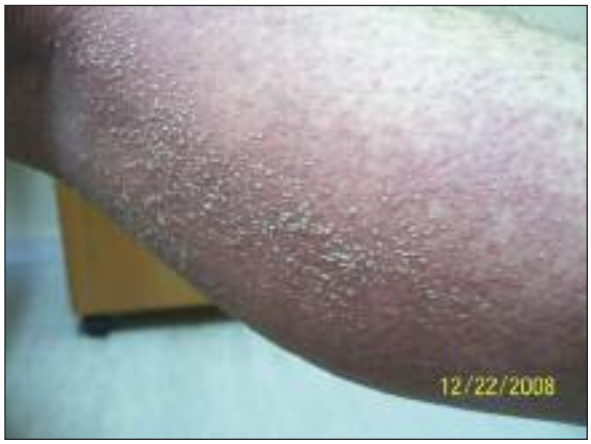

FIGURE 1: Numerous small pinhead-sized, non-follicular pustules arising on the left thigh.

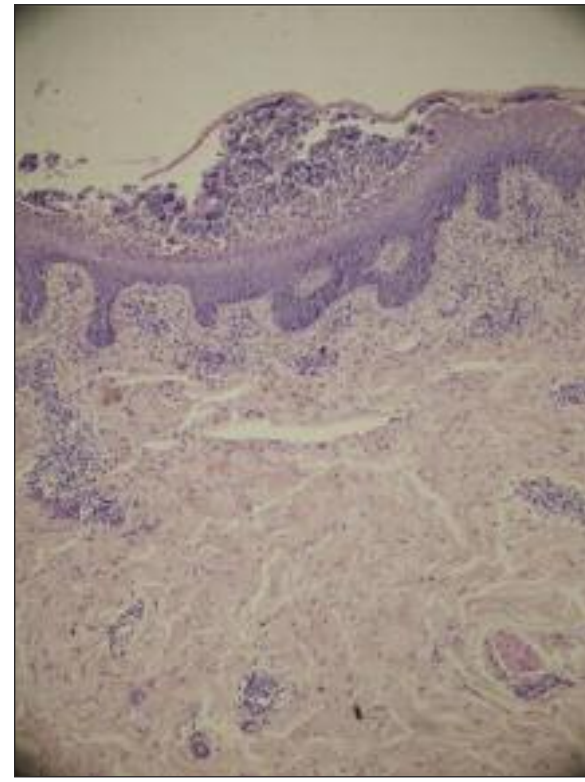

FIGURE 2: Skin biopsy showed spongioform subcorneal pustules with lymphocytes and neutrophils and a mixed cellular infiltrate in the dermis (HEX10).

The skin lesions resolved within 10 days without scarring or pigmentation.

DISCUSSION

Acute generalized exanthematous pustulosis is a self limiting disease with a good prognosis. A typical case of AGEP is characterized by five clinical criteria: (i) multiple small nonfollicular pustules on an erythematous background, (ii) typical histological changes , (iii) fever greater than 38 °C, (iv) raised neutrophil count (> $7x10^9$ /L), and (v) acute evolution with spontaneous resolution in less than 15 days. Histopathology shows subcorneal pustules with a background of dermal edema and spongiosis, leukocytoclastic vasculitis, perivascular eosinophils, or focal necrosis of keratinocytes.[2,3]

The pathophysiological mechanism of AGEP has not been understood yet, but it seems to be an immune reaction. High amounts of neutrophil attracting cytokins such as interleukin -8 (IL-8) pro-

TABLE 1: Drugs associated with acute generalized exanthematous pustulosis.

Antimicrobials	Anti-inflammatory drugs	Others
Penicillins	Aspirin	Allopurinol
Macrolides	Sulfasalazine	Amoxapine
Cephalosporins	Ibuprofen	Calcium channel blockers
Imipenem	Corticosteroids	Carbamazepine
Quinolones	Celecoxib	Cimetidine
Tetracyclines	Valdecoxib	Clozapine
Chloramphenicol	Diclofenac	Dexamethasone
Gentamicicn	Bufecsemac	Disulfiram
Isoniazid	Bufenin	Enalapril
Metranidazole	Dextropropoxifen	Frusemide
Vancomycin		Lansoprazole
Trimethoprim		Nadoxolol
Fluconazole		Paracetamol
Griseofulvin		Thalidomide
Itraconazole		Acetominofen
Nystatin		Acetozolamide
Terbinafine		Fenitoin
Chloroquine		
Pyrimethamine		

duced by T-cells facilitate the inflamation by accumulation of neutrophils in the lesion sites. CD4+ and CD8+ T cells are responsible for the vesicles. Migration of neutrophils fills the vesicles, and causes sterile pustular eruptions.[2]

Although many medications can cause AGEP, the most common group is antibiotics, especially ß-lactams and macrolids. Among β-lactams, amoxicillin has been most frequently implicated. The drugs associated with AGEP are shown in Table 1.[3] In a study of 55 cases, the median time frame from ingestion of drug to the onset of AGEP was found to be one day.[4] In the minority of cases, viral infections, gingko biloba, insect bites, poison ivy extract and inhaled mercury have also been reported as causative agents of AGEP.[2,3,5]

The differential diagnosis of AGEP includes various other pustular eruptions such as pustular psoriasis, anticonvulsive hypersensitivity syndrome (AHS), acute generalized pustular bacterid (AGPB), subcorneal pustular dermatosis (SPD), erythema multiforme and toxic epidermal necrolysis (TEN).[2,4,5]

As the patient did not have a history of psoriasis, we ruled out the diagnosis of pustular psoriasis. Furthermore, the quite short latency period between administration of the drug and the onset of the eruption was considered typical of AGEP. The distrubution of eruption occurring in the body folds helped us in diagnosis of AGEP.[2-4]

Anticonvulsive hypersensitivity syndrome was excluded because of lack of lymphadenopathy, hepatomegaly, abnormal hepatic function tests and severe visceral involvement (hepatitis, nephritis, pneumonitis, with or without myocarditis).[2]

The presence of fever, leukocytosis, and the appearance of multiple pustules may cause this case to be confused with AGPB, but AGEP is not caused by bacterial pathogens and the contents of the pustules are sterile.[4]

Erythema multiforme and TEN are considered to be important in the differential diagnosis. Significant mucosal involvement, blistering with skin sloughing, having target lesions and positive Nikolsky's sign distinguish these two disorders from AGEP.[4]

Subcorneal pustular dermatosis is another vesiculopustular disease that may clinically and histologically mimic AGEP. The nonannular distribution of pustules favor AGEP. The subcorneal pustular dermatosis seen histologically is consistent with both SPD and AGEP; hovewer, the presence of eosinophils in the infiltrate is only typically seen in AGEP. In addition, SPD shows a sterile pustule with acantolysis, and spongiosis does not typically occur.[2,4]

Acute generalized exanthematous pustulosis can be treated by withdrawing the offending drug and administering systemic corticosteroids. Patch testing may be used to confirm the etiology of AGEP, but it has the potential to trigger the original rash.[3] As the patient's medical history indicated an exposure to iopromide two days prior to his skin eruption and confirmatory histopathology, no patch testing was performed.

We conclude that iopromide may trigger severe allergic adverse cutaneous reactions. Further studies and case reports are needed to add iopromide to the list of causes of AGEP.

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