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LETTERS TO THE EDITOR

Acute Generalized Exanthematous Pustulosis Simulating Toxic Epidermal Necrolysis: Overlapping Processes☆

Pustulosis exantemática generalizada aguda simulando necrólisis epidérmica tóxica: forma combinada

To the Editor:

We read with interest the report by Horcajada-Reales et al.[1] of 2 cases with overlapping clinical characteristics involving acute generalized exanthematous pustulosis (AGEP) and toxic epidermal necrolysis (TEN). We would like to share a similar case we encountered in our practice.

AGEP and TEN are well-established, distinct entities belonging to the group of severe cutaneous drug reactions. They both have characteristic clinical presentations and differ in pathogenesis, prognosis, and treatment. It is, however, sometimes hard to distinguish between the 2 conditions and this difficulty can lead to an erroneous clinical diagnosis.

AGEP is a skin condition generally associated with a good prognosis. It typically presents as a rapidly evolving pustular eruption accompanied by fever and leukocytosis with neutrophilia. A skin biopsy reveals a subcorneal pustule.

TEN, on the other hand, often affects the mucous membranes and is accompanied by fever and generalized discomfort, which precedes the appearance of eythematous-violaceous exanthema and epidermal detachment. Histological findings include epidermal necrosis and apoptotic keratinocytes.

Our patient was an 82-year-old woman with no known allergies. She was admitted to hospital because of a 39 °C fever and a violaceous exanthema mainly affecting the trunk. The eruption was characterized by skin detachment in some areas and a positive Nikolski sign (Figs. 1A and 1B). Laboratory testing revealed elevated transaminase levels: gamma glutamyl-transferase (GGT), 494 U/L; fatty acid (FA), 364 U/L; glutamic-oxalacetic transaminase (GOT), 91 U/L; and glutamic-pyruvic transaminase (GPT), 99 U/L.

Two weeks before admission she had been diagnosed with acute self-limited gastroenteritis and treated with trimethoprim sulfamethoxazole. The only personal medical history of interest was dyslipidemia.

Piperacillin-tazobactam was prescribed for a suspected biliary tract infection and cholangio-magnetic resonance imaging revealed a small extrahepatic bile duct ectasia. The results of blood cultures were negative. *Enterococcus faecalis* was isolated in a urine culture. Serology was negative for hepatitis A, B and C and HIV.

Given the suspected diagnosis of TEN secondary to sulfamethoxazole or cotrimoxazole, corticosteroids (prednisone 60 mg/d for 5 days) and intravenous immunoglobulins (1 g/kg/d for 2 days) were prescribed and achieved an excellent clinical response (complete resolution of the condition within 8 days).

Histological study revealed subcorneal pustules with abundant neutrophils, both findings consistent with a diagnosis of generalized exanthematous pustulosis (Fig 1C).

The possibility of different severe adverse drug reactions overlapping is a subject of some debate. Although they are distinct entities, the clinical features can be similar and have certain pathophysiologic mechanisms in common.

AGEP, for instance, can present with vesicular-bullous lesions that mimic the clinical appearance of TEN.[2] There are also forms of TEN that manifest as pustules or blisters.

Cases have been reported of patients who, after initially presenting with AGEP, subsequently developed TEN.[1] In other cases, such as the one described here, the patient presents the clinical features of TEN with histological findings consistent with AGEP.

There are 17 published cases of overlapping forms, most of which are associated with antibiotic use.[1]

The main differences between AGEP and TEN are shown in Table 1.[3]

In terms of pathogenesis, it seems clear that both conditions are type 4 hypersensitivity reactions (HSR) and that the difference between them lies in the type of T-cell activated in each case.[4] In both cases, the initial stage is characterized by keratinocyte cytolysis caused by CD8+ T cells. Subsequently, the two conditions diverge and the pathway differs in each one. In AGEP, activated CD4+ T cells produce interleukin (IL) 8, IL-17 and IL-36, which recruit neutrophils and lead to the formation of pustules (type 4d HSR).[5]

In TEN, by contrast, CD8+ T cells release perforin and granzyme B, triggering massive keratinocyte apoptosis by activating the Fas-Fas-ligand receptor and tumor necrosis factor alpha (TNF-α) (type 4c HSR). The latest

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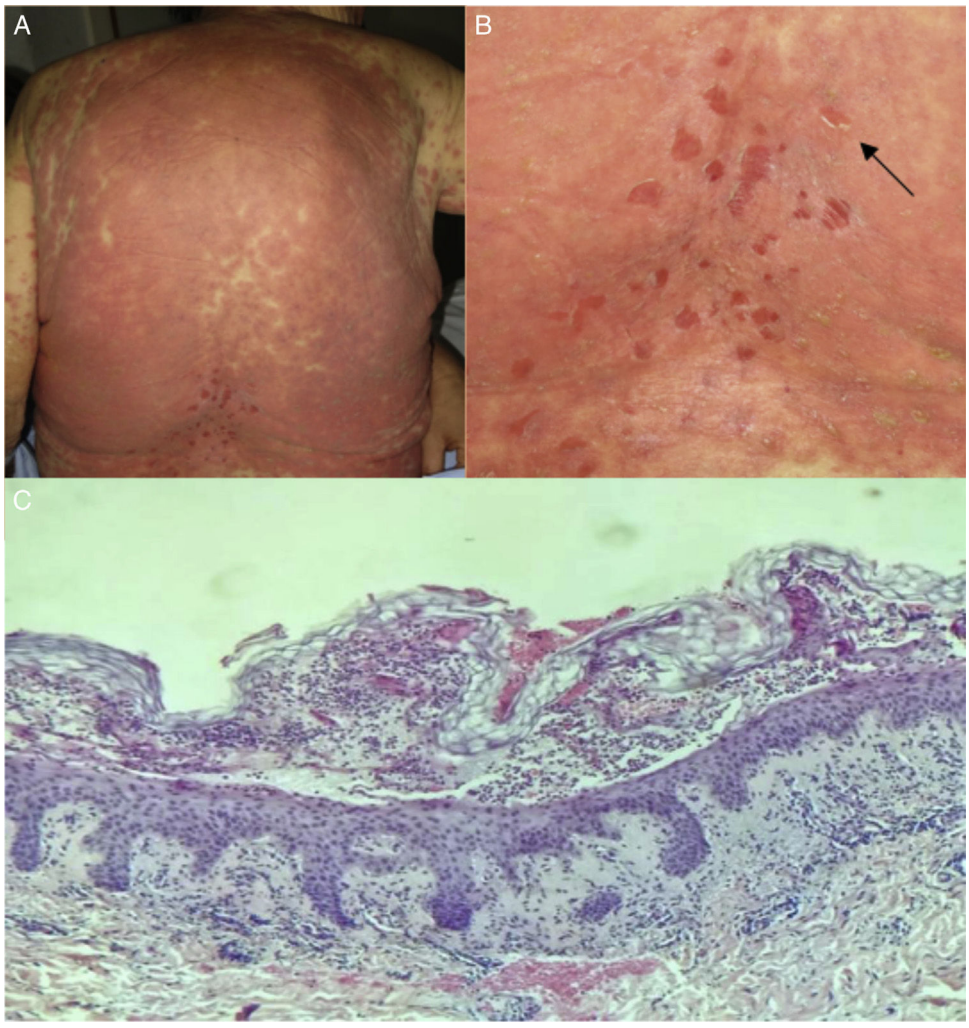

Figures 1A and 1B Erythematous-violaceous areas on the back with positive Nikolski sign (arrow). C, Subcorneal pustule with abundant neutrophils (hematoxylin-eosin x200).

research is focused on the investigation of certain drug-specific human leukocyte antigens (HLA) that predispose individuals to a genetic susceptibility for TEN when an individual with a specific HLA allele is exposed to a specific drug.[5]

Overlapping forms are probably caused by a combined hypersensitivity reaction between such alleles and a specific drug.

In most cases, the eventual course of the disease will be AGEP. However, in some patients it has led to

Table 1 Main Differences Between Acute Generalized Exanthematous Pustulosis (AGEP) and Toxic Epidermal Necrolysis (TEN).

Variable	AGEP	TEN
Site	Flexural	Generalized
Pustules	Yes	No
Nikolsky+	Rare	Frequent
Mucosal involvement	+ oral mucosa	++++
Fever	Occasionally	Frequent high fever
Blood test results	Neutrophilia	Neutropenia and elevated transaminases
Latency period	Hours or days	2-3 wks
Histopathology	Subcorneal pustules	Epidermal necrosis
Treatment	Withdrawal of the drug	Drug withdrawal and Intravenous immunoglobulins
Recovery	15 d	3-6 wks
Mortality	Rare	30%

extensive skin lesions, multiorgan involvement, and even death.[6]

It is important to recognize these cases because, given their greater severity, they should be managed and treated as TEN.

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Acquired Port-Wine Stain: Not a simple stain!☆

Mancha de vino de Oporto adquirida: ¡no es una simple mancha!

Dear editor,

we read with interest a case series of acquired port wine stain (PWS) in 3 otherwise healthy children (2 females and 1 male) by Millán-Cayetano et al.[1] published in Actas Dermo-Sifiliográficas journal. The authors stated ''acquired capillary malformation may be considered simply to be a late-onset capillary malformation with a variable latency period''. Actually, acquired PWS is not as ''simple'' as considered by the authors. The authors underestimated skin diseases masquerading as PWS.

Linear morphea is a form of morphea that can affect an entire extremity and follow the lines of Blaschko. Children are more likely than adults to have linear morphea on the face.[2] In many cases, the affected skin is initially erythematous and may resemble a PWS. Vascular damage, such as microvascular injury, and T-cell activation, with subsequent abnormal collagen production by fibroblasts, is thought to be involved in its pathomechanism.[3] Nihjawan et al.[4] reported four cases that had presented with erythematous vascular-appearing patches resembling PWS. Three lesions were located on the face and one was on the leg. The initial biopsies of two patients revealed telangiectatic dermal vessels, consistent with PWS. However, further biopsies revealed dermal fibrosis with patchy lymphocytic infiltrate, consistent with morphea. Diagnosis of morphea was made approximately 6 months to 3 years after the onset of the acquired PWS. On the other hand, perineural inflammation has rarely been reported to be an early histopathological feature of morphea.[5] Singh et al.[6] reported 2 cases of morphea with subtle sclerotic changes initially, presented with perineural and intraneural lymphoplasmacytic infiltration. According to Nihjawan et al.,[4] there was prominent perineural inflammation which prompted the diagnosis of early morphea. In other words, early inflammatory morphea can present initially with a vascular, nonindurated patch.[7] Biopsies of these lesions may not reveal the characteristic features of established morphea and the diagnosis has to be considered if perineural inflammation is seen.[4] Nihjawan et al.[4] recommended, in patients with acquired PWS, delaying PDL treatment until a diagnosis of early morphea can be excluded.[4] However, it is difficult to ascertain whether laser therapy to the initial lesions triggered the increase in fibrosis as some of the reported cases did not receive laser treatment.[7] Treatment of PWS using the PDL may reduce the skin erythema, but did not prevent subsequent sclerosis.

To sum up, acquired PWS is not a simple stain. Inflammatory morphea should be considered in the differential diagnosis whenever an acquired PWS has been identified, especially on the face.[2] Early stages of morphea are sometimes difficult to recognize, and histology may not helpful in early cases because there is overlap, leading to misdiagnosis. Clinicopathological correlation is of paramount importance in such cases. Morphea should be considered if perineural inflammation is seen in histopathology. Dermoscopy can assist in the early diagnosis of localized scleroderma (LS), with no need for invasive examinations.[8]

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