Recalcitrant generalized pustular eruption after diltiazem

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ABSTRACT

Generalized pustular eruptions may occasionally present challenges both for diagnosis and treatment. A 55-year-old male was hospitalized with fever and a severe generalized pustular eruption after recent intake of diltiazem. A careful interpretation of history, clinical course and investigation findings and an active treatment intervention proved the key to management of the case.

Key words: Diltiazem, generalized pustular eruption

INTRODUCTION

Generalized pustular eruptions may occasionally present a diagnostic dilemma, prompting a careful analysis of history, clinical course and investigation findings. Difficulty may also be encountered during treatment. Herein we report a case of generalized pustular eruption that posed both a diagnostic and a therapeutic challenge.

CASE REPORT

A 55-year-old male with localized plaque psoriasis since 8 years was hospitalized with fever and a severe generalized pustular eruption of 3 days duration. He was receiving supervised topical corticosteroids and emollients for his psoriasis. He was also on losartan, atorvastatin and clopidogrel since 1 year for hypertension and ischemic heart disease. One week prior, diltiazem 120 mg/day was added by the cardiologist. The patient did not offer a history of similar eruptions in the past, or any drug allergies.

On examination, he was febrile (103°F), with a blood pressure of 90/50 mmHg. He had nonfollicular pustules over his entire body that coalesced into lakes at several places [Figure 1]. Erosions were noted over the palpebral conjunctiva and glans penis [Figure 2]. Plaque lesions of psoriasis were evident over the elbow prominences and abdomen [Figure 1].

Generalized pustular psoriasis (GPP) and acute generalized exanthematosus pustulosis (AGEP) following diltiazem intake were considered as differential diagnoses and the patient was investigated.

The total WBC count was 19600/cumm with 68% neutrophils and 5% eosinophils. Erythrocyte sedimentation rate was 54 mm/hr and C reactive protein was 18mg/dL. Absolute eosinophil count was 520/cumm. Serum calcium was 8.1 mg/dl. Serology for hepatotrophic viruses and HIV was negative. ASO titre was 148 IU/ml and bacteriological examination of the pustules was negative. Tzanck smear was negative for any acantholytic cells or multinucleated giant cells. Skin biopsy revealed orthokeratosis, mild acanthosis with spongiosis and a superficial dermal lymphocytic infiltrate [Figure 3].

Based on a history of recent diltiazem intake, examination findings, negative bacteriological study, peripheral eosinophilia and spongiotic dermatitis on histopathology, a diagnosis of AGEP was made and the suspected drug diltiazem withdrawn. Dexamethasone 100 mg was administered as an IV infusion on three consecutive days with supportive topical measures. The patient turned afebrile within 24 hrs. Pustules cleared over 72 hours and leucocytosis returned to normal after 5 days. However, pustules reappeared on the seventh day, encircling the erstwhile plaque lesions of psoriasis [Figure 4]. A second skin biopsy revealed parakeratosis, acanthosis, spongiform
neutrophilic abscesses, papillomatosis and a patchy lymphomononuclear infiltrate in the superficial dermis, confirming pustular psoriasis [Figure 5].

Methotrexate 15 mg/week was started and upgraded to 22.5 mg/week over 3 weeks. Pustules and fever continued, hence acitretin 25 mg/day was added and the dose increased to 50 mg/day over 4 weeks. Adjunctive narrow-band UVB phototherapy 200 mJ thrice a week was administered. As the patient’s pustules were not controlled with the combination therapy, etanercept 50 mg subcutaneously twice a week was added. Tuberculin skin testing prior to etanercept revealed an

Figure 1: Generalized pustular eruption coalescing into lakes at several places

Figure 2: Conjunctival and genital mucosal involvement

Figure 3: Orthokeratosis, acanthosis with spongiosis and a superficial dermal lymphocytic infiltrate (H and E, ×40)

Figure 4: Reappearance of pustules encircling erstwhile plaques of psoriasis

Figure 5: Second biopsy showing parakeratosis, acanthosis, spongiform neutrophilic abscesses, papillomatosis and a patchy lymphomononuclear infiltrate in the superficial dermis (H and E, ×10, ×100)

Figure 6: Clearance of pustular lesions after adding etanercept to ongoing methotrexate, acitretin and NB UVB
induration of 12 mm, hence the patient was given oral rifampicin and isoniazid chemoprophylaxis for 3 months. The patient turned afebrile after two doses of etanercept, with complete clearance of the pustular eruption after 1 week [Figure 6]. Etanercept was continued for a total duration of 6 weeks. The patient was discharged on methotrexate 15 mg/week and acitretin 25 mg/day. Acitretin and methotrexate were tapered over 4 months.

DISCUSSION

While it has been alleged that AGEP is a variant of GPP,[1,4] other studies[2,3] have found them to be distinct entities. Nonetheless, differentiation between AGEP and GPP both on clinical and histopathological grounds can be difficult.[3] Fever with generalized pustular rash, mucous membrane involvement, leucocytosis and hypocalcemia that were seen in this case have been reported to occur both in AGEP and GPP.[1,3] Further, AGEP has been reported to occur more frequently in patients with psoriasis.[1,3] Reappearance of pustules (encircling erstwhile plaques of psoriasis) during corticosteroid withdrawal prompted us to consider pustular psoriasis that was confirmed by the presence of spongiform neutrophilic abscesses on histopathology.

GPP commonly occurs as complication of plaque psoriasis due to infection, withdrawal of corticosteroids or antipsoriatic therapy, drugs, hypocalcemia or severe stress.[2] Our patient was on prescription topical corticosteroids (betamethasone-salicylic acid ointment 15 g per month over <2% body surface area) and liquid paraffin for localized plaque psoriasis. He denied the application of any new topical agents. Although pustular psoriasis following clopidogrel has been reported,[4] our patient was on the drug for 1 year before, during and after the pustular episode, indicating low probability as a trigger. Other than recent the exposure to diltiazem, no definitive infectious, metabolic or plausible drug-induced trigger for pustular psoriasis could be identified. The Naranjo adverse drug reaction probability scale score[5] indicated a probable association between diltiazem intake and GPP. Although psoriasiform plaques have been described to occur after prolonged intake of calcium channel blockers,[6] there are no reports of GPP occurring after diltiazem. Hypocalcemic tetany after intravenous administration[7] and hypocalcemia after oral intake of diltiazem have been reported.[8] At presentation, our patient had serum calcium of 8.1 mg/dl. We speculate that diltiazem may have induced hypocalcemia in our patient, precipitating GPP.

In our case, after the initial transient improvement with dexamethasone, GPP failed to respond to a combination of methotrexate, acitretin and NB-UVB phototherapy. Hypertension and heart disease precluded the use of cyclosporine. GPP was eventually controlled by the addition of etanercept, a recombinant fusion receptor protein that competitively binds tumour necrosis factor-alpha (TNF-α), a key cytokine in psoriasis.[9] At 1-year follow up, the patient remains asymptomatic and medication-free for psoriasis. Although experience with etanercept in plaque and arthropathic forms of psoriasis has been expanding, there are few reports of its use in GPP.[9,10]

Diltiazem-associated GPP has not been reported so far in the literature. Quelling the disease in our case ultimately demanded the synergy of four treatment modalities, emphasising the at times-recalcitrant nature of GPP.

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Cite this article as: Jandhyala S, Manu V. Recalcitrant generalized pustular eruption after diltiazem. Indian Dermatol Online J 2012;3:42-4.

Source of Support: Nil, Conflict of Interest: None declared.