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Journal
Dermatology Online Journal, 23(1)

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Publication Date
2017

DOI
10.5070/D3231033675

Volume 23 Number 1 | January 2017
DOJ 23 (1): 7

First report of mesalamine (5-aminosalicylic acid) as the causative agent in a case of acute generalized exanthamous pustulosis

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Abstract

Acute generalized exanthamous pustulosis (AGEP) is a rare eruption of non-follicular sterile pustules on a diffuse background of erythema and edema, commonly associated with fever and leukocytosis. Antibiotics are implicated in most cases; however, other drugs have been reported to cause AGEP. We report a case of a 73-year-old man with a history of ulcerative colitis who presented with a diffuse pustular rash, renal failure, elevated liver function tests, and leukocytosis with neutrophilia. A week prior to admission, the patient was started on mesalamine to treat colitis. Upon admission, a workup including a skin biopsy was performed and was consistent with AGEP. Mesalamine was discontinued, and the patient's skin eruption, renal function, liver function tests, and leukocytosis subsequently improved. Mesalamine has an unknown mechanism of action. However, it is thought to be an anti-inflammatory agent that blocks the production of leukotrienes and prostaglandins and is an immunosuppressant that increases the release of adenosine, which interferes with leukocyte function. The decrease in prostaglandin synthesis or deregulation of leukocyte function caused by mesalamine may be the etiology in this case. Discontinuation of the offending agent leads to resolution of AGEP, as it did in this patient.

Keywords: acute generalized exanthamous pustulosis, mesalamine, ulcerative colitis

Background

Acute generalized exanthamous pustulosis (AGEP) is a rare eruption of non-follicular sterile pustules on a diffuse background of erythema and edema, often associated with fever and leukocytosis. The incidence of AGEP is one to five per million cases per year [1]. The onset is acute and 87% of cases are preceded by medication usage, most commonly antibiotics such as the beta lactams and macrolides [2]. The exact pathophysiology of AGEP is unknown; however, studies suggest it is owing to a type IV hypersensitivity reaction [4]. AGEP generally appears within 3 weeks after starting the offending medication. The time to onset depends on whether the patient was previously sensitized to the drug, with a shorter onset time seen in patients who are rechallenged with a drug that previously caused AGEP and those with a known contact sensitivity to the offending drug [5]. Patch testing for the offending drug is usually positive and can show a pustular reaction [5]. On histology there are subcorneal and/or intraepidermal pustules, edema of the papillary dermis, and eosinophils. Most cases of AGEP only require supportive therapy and resolve spontaneously within two weeks after medication discontinuation [1, 6].

Case Synopsis

A 73-year-old man with a one-year history of ulcerative colitis (UC) was admitted for a diffuse skin eruption, renal failure, elevated liver function tests, and leukocytosis. The patient first noticed a pruritic rash on his lower extremities three days prior to hospitalization. The skin lesions generalized and eventually involved his trunk and extremities. Topical triamcinolone cream was used prior to admission

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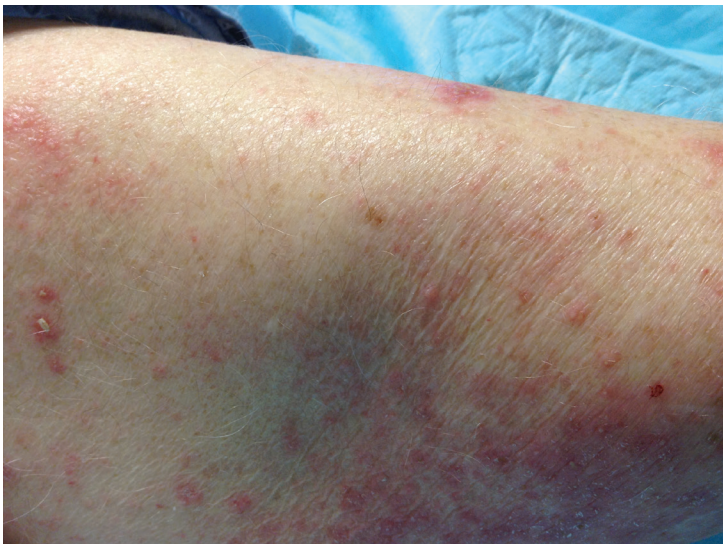

Figure 1. *Well-demarcated, erythematous papules on a diffuse background of erythema and edema.*

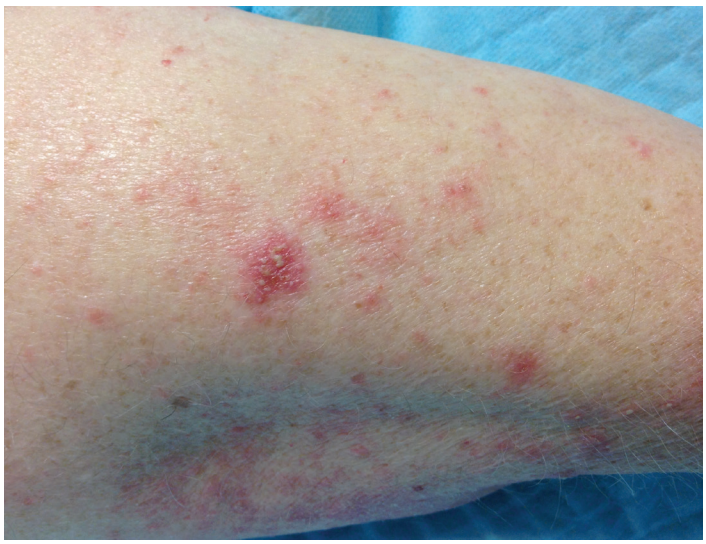

Figure 2. *Scattered small groups of monomorphic, non-follicular white-to-yellow topped pustules.*

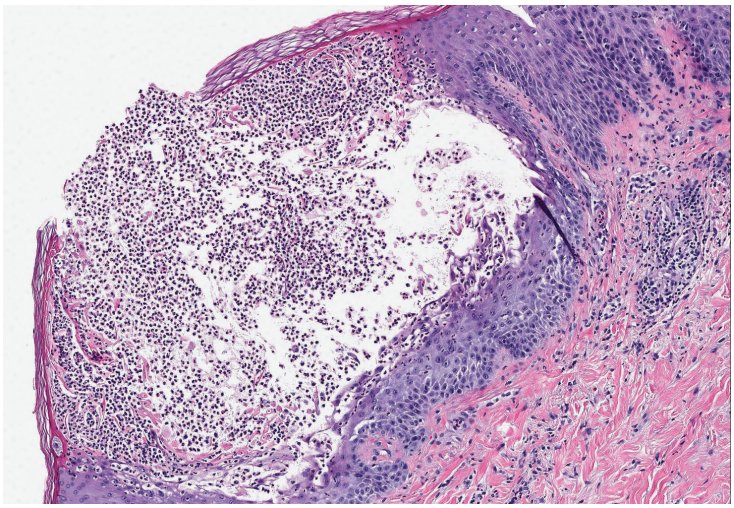

Figure 3. *Subcorneal pustule extended into the epidermis. The underlying dermis has a mixed infiltrate with neutrophils and eosinophils.*

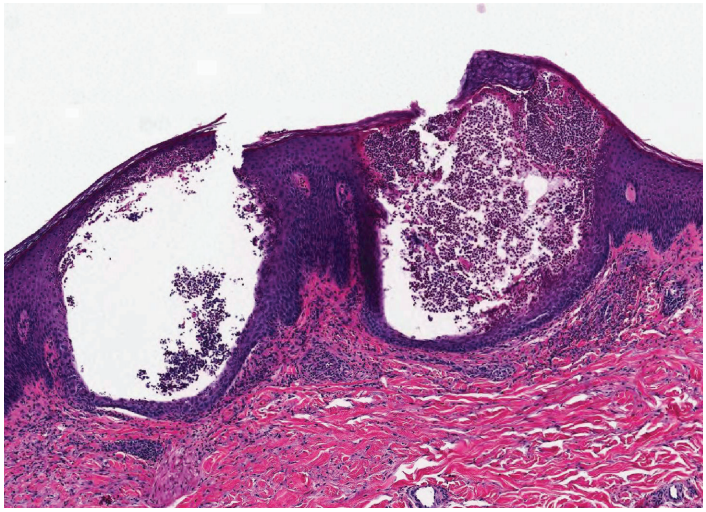

Figure 4. *Intraepidermal pustules with neutrophils and mixed dermal inflammation.*

and helped alleviate the itch but the rash progressed. The patient also noticed the development of mouth sores.

A week prior to admission, the patient was started on mesalamine orally (4.8 grams per day) and mesalamine rectal suppositories (4 grams per day) to treat colitis of his left colon noted during sigmoidoscopy. Prior to admission, the patient had two doses of oral mesalamine and one mesalamine enema. The patient also had a history of contact dermatitis 18 months previously to a mesalamine suppository.

After admission, the dermatology service was consulted. On examination, there were well-demarcated, erythematous plaques and papules with fine scaling and scattered small groups of monomorphic non-follicular white-to-yellow pustules (Figures 1, 2). The lesions blanched with pressure. The oral palate and lower labial mucosa also had scattered erythematous erosions.

Biopsy showed subcorneal and intraepidermal pustules and a mixed inflammatory infiltrate with eosinophils and neutrophils consistent with AGEP (Figures 3, 4). The mesalamine oral and rectal enemas were discontinued and the eruption improved. Three weeks after discharge, the patient's AGEP was

completely resolved and his renal function tests returned to baseline. For his UC, the patient was started on hydrocortisone enemas and he has had no recurrence of AGEP for the past 18 months.

Discussion

This report illustrates a case of AGEP developing in an UC patient after starting mesalamine (5-aminosalicylic acid). The clinical and histological picture is consistent with AGEP. However, other pustular reactions with systemic features were considered. Drug reaction with eosinophilia and systemic symptoms (DRESS) has been reported as an AGEP-like pustular reaction [7]. However, the time from drug onset to rash development is longer in DRESS (usually >3 weeks) than the time seen in our patient. Also, our patient had a leukocytosis with neutrophilia instead of the characteristic leukocytosis with eosinophilia as seen in DRESS [5, 6]. As is expected with AGEP, the patient's clinical picture resolved after mesalamine discontinuation and the patient had no further issues.

Our patient presented with several non-cutaneous findings in association with AGEP: elevated liver function tests, renal failure, and oral lesions. Even though liver and renal dysfunction is not common in the presentation of AGEP, Hotz et al. reviewed 58 cases of AGEP and found that 10 cases (17%) had associated systemic involvement of one organ system that could not be explained by another medical condition. The liver and kidney were the top two organs affected and those patients showed abnormal liver and renal function tests, respectively. These abnormalities were transient and reversible, improving after AGEP resolution [6]. Our patient's oral lesions were also an interesting finding as mucosal involvement is not typically seen with AGEP. However, Sidoroff et al. found that 20% of patients with AGEP have mucous membrane involvement, most commonly of the oral mucosa [5].

Patch testing can confirm a drug's connection with AGEP. Patients who develop AGEP usually have a pustular reaction when patch tested with the offending drug [5]. Our patient was most likely previously sensitized to mesalamine when a mesalamine suppository was attempted 18 months before the AGEP episode and a contact dermatitis resulted. In retrospect, this contact dermatitis could be considered our patient's positive patch test.

Ulcerative colitis is a chronic relapsing inflammatory disease of the large bowel mucosa and is usually treated with glucocorticoids, aminosalicylates, or immunosuppressive agents. Mesalamine is an aminosalicylate and a first-line treatment in patients with UC. Mesalamine has an unknown mechanism of action. However, it is thought to be anti-inflammatory by blocking the production of leukotrienes and prostaglandins and immunosuppressive by increasing the release of adenosine, which interferes with leukocyte function.

Even though anti-inflammatory drugs like non-steroidal anti-inflammatory drugs (NSAIDs) are not typically thought to cause AGEP, there are cases of this association described in the literature. Bahuguna reported a patient presenting with a pustular skin eruption following aspirin administration. Histology was consistent with AGEP and the lesions resolved soon after aspirin discontinuation [10]. Rastogi et al. and Pakdeethai both presented cases of AGEP secondary to ibuprofen and celecoxib use, respectively [11, 12]. These drugs are common anti-inflammatory drugs that block cyclooxygenase and inhibit prostaglandin synthesis. Although the mechanism of action of mesalamine is unknown, it is thought that it also inhibits prostaglandin synthesis. This connection suggests that AGEP development may be related to decreased prostaglandin levels.

Azathioprine, an immunosuppressive drug, is commonly used to prevent rejection in organ transplant patients. However, it can also be used in steroid-dependent inflammatory bowel disease patients. Azathioprine's active metabolite, 6-mercaptopurine, interferes with purine synthesis and decreases the number of circulating lymphocytes. Avgerinos et al. reported a case of AGEP developing in a patient with UC treated with azathioprine. In this case, biopsy-proven AGEP lesions were found after initiation of azathioprine and resolved soon after stopping the medication [13]. The mechanisms of action of azathioprine and mesalamine are different. However, they both are immunosuppressive and used to treat patients with inflammatory bowel disease.

Although the pathophysiology of AGEP is not entirely clear, many researchers have agreed that it is an immune regulated disease process, most likely a T-cell dominated type IV hypersensitivity reaction [4, 9, 10, 12]. Whether the cause relates to the decrease in prostaglandin synthesis or the deregulation of leukocyte function, mesalamine was the likely causative agent in this patient. The exact connection between AGEP and anti-inflammatory and immunosuppressive drugs is unclear. However, clinicians should be aware of this association, as discontinuation of the drug results in resolution of AGEP.

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