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Case presentation

Adult with morbilliform rash and tattoo bullae

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Abstract

A 34-year-old woman was diagnosed with Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), most likely related to a reaction to allopurinol.

The patient presented with a 2-week history of a painful pruritic rash that started on her back and progressed to the rest of her body over a five-day period. The eruption started after several new drugs were started, including allopurinol for hyperuricemia. On physical examination, the patient had a diffuse morbilliform eruption and geometric intact bullae limited to the boundaries of tattoos.

Most presentations of DRESS include a morbilliform eruption. However, DRESS does not commonly present with bullae. There have been no known reported cases of bullae forming in the area of tattoos in cases of DRESS. This unique presentation suggests that a component of the tattoo or tattooing process alters the cutaneous immune response, creating an immunocompromised district. This alteration may promote a greater localized reaction in the setting of widespread skin involvement in DRESS.

Introduction

Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) is a systemic drug hypersensitivity reaction [1]. DRESS is characterized by rash, fever, lymphadenopathy, internal organ involvement, and hematologic abnormalities including eosinophilia. Bullae have been infrequently reported in severe cases of DRESS [2,3]. Tattoos are increasingly popular and associated with a range of skin reactions including eczematous, lichenoid, granulomatous, pseudolymphomatous, and hypersensitivity reactions as well as infection and neoplasms [4]. We describe a unique case of DRESS presenting with diffuse morbilliform rash and bullae directly overlying decorative tattoos.

Case synopsis

A 34-year-old woman with a history of focal segmental glomerulosclerosis (status post renal transplant two years prior), presented with a 2-week history of a painful and pruritic cutaneous eruption that started on the back and progressed to involve the entire body over the next five days. The eruption was accompanied by leg and facial swelling, as well as intermittent fevers.

Two months prior to presentation, the patient was diagnosed with cytomegalovirus (CMV) colitis. She was treated with intravenous ganciclovir and transitioned to oral valganciclovir. In the past month, she was started on allopurinol for hyperuricemia and had completed courses of nitrofurantoin, cephalexin, and levofloxacin for urinary tract infections.

Physical examination revealed diffuse coalescing erythematous, edematous papules and plaques involving the face, trunk, and bilateral upper and lower extremities, with superficial desquamation and erosions on the upper chest and proximal arms bilaterally. Few intact, clear fluid-filled bullae were present on bilateral shins. The bullae were limited to less than 1% of body surface area. Notably, the geometric bullae were confined exactly to the borders of decorative black tattoos were present on bilateral distal shins (Figure 1). The tattoos were placed over ten years prior.

Laboratory data revealed elevated ALT of 119 U/L (reference range 4-45 U/L), an elevated absolute eosinophil count of $3.39 \times 10^3/\mu\text{L}$ (reference range $0.0-0.5 \times 10^3/\mu\text{L}$), and a significantly elevated creatinine of 6.1 mg/dL (reference range 0.5-1.3 mg/dL). CMV polymerase chain reaction assay was negative.

A skin biopsy specimen from an erythematous, edematous plaque on the left upper chest was obtained and histopathologic exam revealed basal cell vacuolization with necrotic keratinocytes, pigmentary incontinence, and a superficial mixed perivascular and interstitial inflammatory infiltrate comprised primarily of lymphocytes but also with scattered eosinophils (Figure 2). Biopsy of bullae overlying tattoo was deferred to preserve integrity of tattoo. Renal core biopsy demonstrated acute interstitial nephritis with eosinophils.



Figure 1. Clinical Image. Clear fluid-filled bullae limited to location of tattoo.

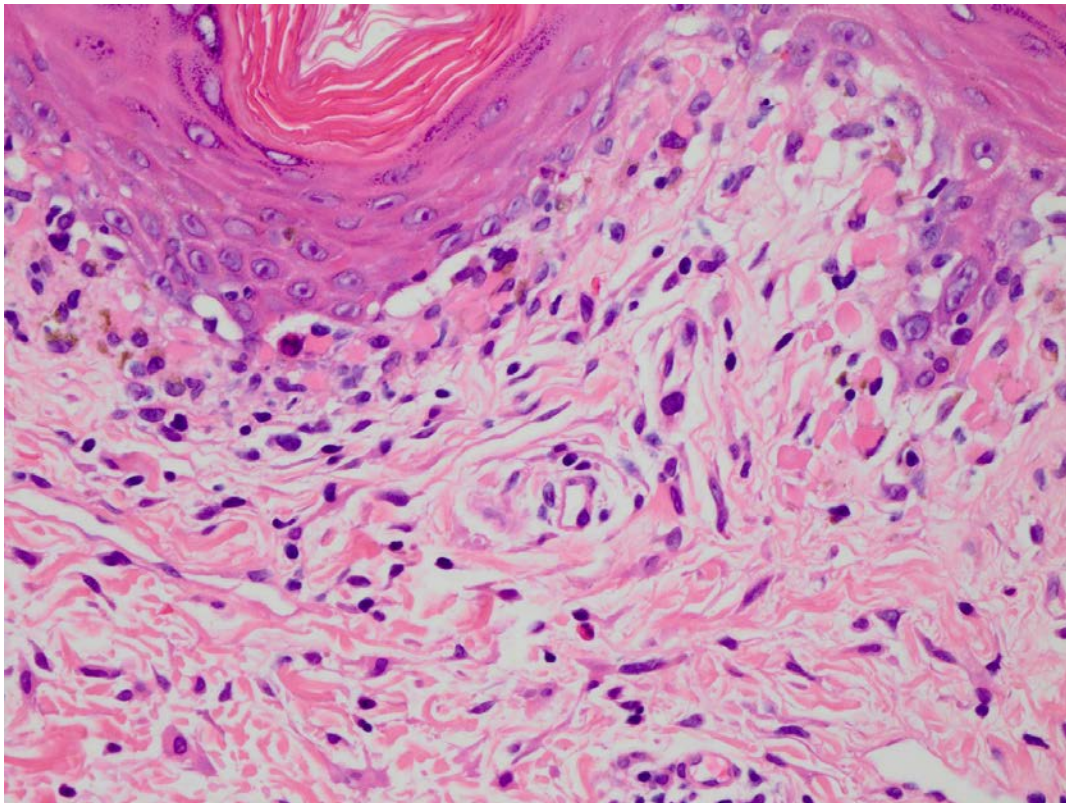


Figure 2. Histopathology Image. Histopathologic analysis demonstrating interface dermatitis and a superficial perivascular mixed inflammatory infiltrate that includes scattered eosinophils (hematoxylin-eosin, original magnification $\times 40$).

Given the findings of the clinical examination, laboratory results and skin and renal biopsies, a diagnosis of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) was rendered and allopurinol was discontinued. She was started on oral prednisone (60 mg daily) and her liver transaminase levels and eosinophil count returned to normal levels during the first week of therapy; her facial edema also significantly improved and her rash began to resolve. Two weeks after diagnosis, withdrawal of allopurinol, and initiation of systemic steroids, no rash was present and her creatinine level had returned to near baseline (3.6 mg/dL, reference range 0.5-1.3 mg/dL), so she was started on a gradual prednisone taper for two months. Her TSH remained within normal limits at 0.79 mIU/mL (reference range 0.3-4.7 mIU/mL) and will be monitored regularly at follow-up.

Discussion

DRESS, also known as drug-induced hypersensitivity syndrome, is a systemic drug hypersensitivity reaction [1]. DRESS typically manifests within eight weeks after initiation of a medication, although in the case of allopurinol, onset may be further delayed [1]. The major clinical features of DRESS are a diffuse morbilliform eruption, facial edema, and systemic symptoms (fever, lymphadenopathy, internal organ involvement). Hepatitis is seen in more than 50% of cases and nephritis in approximately 10% of cases [2]. The most common laboratory findings include eosinophilia, atypical lymphocytosis, and abnormal liver and renal function tests [3]. When DRESS is caused by allopurinol the incidence of renal involvement is much higher, cited at 43% of cases in the French Pharmacovigilance Database study and up to 84% in the literature [5,6].

Allopurinol is a well-known cause of DRESS. In a literature review of 172 reported DRESS cases from 1997 to 2009, allopurinol was associated with 11% of cases [7]. Other culprit drugs that have been reported to commonly cause DRESS include carbamazepine, phenytoin, phenobarbital, lamotrigine, dapsone, sulfasalazine, nevirapine, abacavir, and minocycline [8,9].

The pathogenesis of DRESS is unclear, but likely involves complex interacting immunologic and genetic factors. A predisposition to the development of DRESS may be linked with human leukocyte antigen (HLA) subtypes. Specifically, a strong association between HLA-B*58:01 and allopurinol-induced DRESS has been demonstrated in Han Chinese in China and Thai populations. A modest association with HLA-B*58:01 and allopurinol-induced DRESS has also been observed in Korean, Japanese and European populations. The HLA-B molecules on antigen-presenting cells may play a significant role in pathogenesis by binding drug-peptide complexes that are recognized by effector T cells, thus triggering an immune response [10]. Viral reactivation may also contribute to pathogenesis, with human herpesvirus 6 implicated most frequently. Though the exact mechanism of the relationship between viral infection and drug hypersensitivity reactions is unclear, it has been suggested that antiviral T-cells may cross-react with inciting medications and thus contribute to DRESS. Furthermore, the pathogenesis of DRESS may be related to a genetic deficiency in detoxifying enzymes, which leads to increased levels of drug metabolites. These drug metabolites then stimulate drug-specific T-cells and an inflammatory cascade, particularly in cases of anti-epileptic-induced DRESS [11]. Allopurinol-induced DRESS may represent a delayed-type hypersensitivity to the specific metabolite oxypurinol, particularly in patients with HLA-B*58:01 [12]. Oxypurinol is largely excreted by the kidneys [13]. Thus, accumulation of oxypurinol is facilitated by chronic renal insufficiency and by thiazide diuretics [12]. Chung WH, et al. demonstrated that renal impairment was an independent risk factor for allopurinol induced DRESS and that the delayed clearance of oxypurinol in patients with renal impairment is associated with a poorer prognosis [13]. Finally, the mortality rate for DRESS is about 10%, and is higher in allopurinol-associated DRESS, reportedly 20-25% [1].

Although the most characteristic skin finding is a morbilliform eruption, hemorrhagic or bullous involvement has been described [2]. In severe cases of DRESS, bullae may appear on the hands and feet with superficial ulceration owing to the severe edema in the upper dermis, not from epidermal necrosis as in Stevens-Johnson syndrome or toxic epidermal necrolysis [1]. Our patient had an unusual presentation of DRESS, with bilateral bullae clearly confined within tattoos in the setting of a more typical widespread morbilliform rash.

Tattoos have been associated with the development of localized reactions including infection and neoplasms, as well as eczematous, lichenoid, granulomatous, pseudolymphomatous, and hypersensitivity reactions. Many of these tattoo-associated reactions are thought to be secondary to an altered immune environment. As described by Huynh et al., local immune dysregulation likely plays a causal role in cases of verruca within tattoos, not coincidence or direct inoculation [4]. The unique localization of the bullae in this DRESS patient may similarly be the result of the unique immune environment created by the tattoo. This concept, in which a range of infectious, neoplastic, and immune cutaneous disorders can develop in previously injured skin, was first described by Ruocco et al. in 2009 as the immunocompromised cutaneous district [14]. According to Ruocco et al., chronic lymphedema, herpetic infection, radiation dermatitis, burns, amputation, trauma, vaccination, and tattoos are all settings in which the immune balance of affected skin is disrupted and other skin disorders may preferentially develop. The full pathogenic mechanism of the immunocompromised cutaneous district is not yet understood. However, the effect may be

related to disruptions in lymph circulation and subsequent effects on local skin immunity, and/or alterations in cutaneous neuroimmune interactions [14,15]. To our knowledge, there have been no other reported cases of bullae forming within tattoos in cases of DRESS. This unique presentation suggests that the patient's tattoo created an immunocompromised district in which a localized greater drug-induced hypersensitivity reaction caused bullae formation.

We present an unusual clinical presentation of DRESS that highlights a unique adverse tattoo reaction and supports the concept of the tattoo as an immunocompromised district. The case also underscores the importance of a thorough medication history, as well as cautious use of allopurinol, particularly in patients with underlying renal disease.

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