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CASE REPORT

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A case report of recurrent Well's syndrome masquerading as cellulitis

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ABSTRACT

Eosinophilic cellulitis (Well's syndrome) is a rare relapsing inflammatory disorder characterized by infiltration of eosinophils into the dermis. Although rare, WS should be considered in patients with a history of asthma and skin lesions that are resistant to antibiotic therapy. We report a case of recurrent WS. A 67-year-old woman with a history of asthma presented with a longstanding left pretibial ulcer with surrounding erythema, pain, and serous drainage, which had failed treatment with oral and parenteral antibiotics. Skin biopsy revealed eosinophilic cellulitis. Rapid improvement occurred with systemic steroid treatment; however, recurrent disease in the perineum developed as corticosteroids were tapered.

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KEYWORDS
Well's syndrome; prednisone; cellulitis

1. Introduction

Eosinophilic cellulitis (Well's syndrome) is a rare relapsing inflammatory disorder with an unknown etiology. It is characterized by infiltration of eosinophils into the dermis [1]. More than 150 cases have been reported to require treatment with systemic corticosteroids and steroid-sparing agents. The etiology and pathogenesis of Well's Syndrome are unknown, but the triggering factors are reported to include insect bites, medications, and infections [2]. However, in 50% of the cases, the inciting culprit remains unknown. Peak incidence is seen in the second and third decades of life. We report a case of Well's syndrome that was initially thought to be a skin and soft tissue infection resulting from a dog scratch.

2. Case description

A 67-year-old female with a past medical history of asthma and hemorrhoids presented with complaints of a left pretibial ulcer following a scratch from her dog, with surrounding erythema, pain and serous drainage. She was from East Coast of the U.S. and denies any travel; insect bite; or a history of pulmonary nodules, sinusitis, or hives. She was allergic to latex and cephalosporins. She was on fluticasone and, as needed, albuterol inhalers for asthma. She denies any recent new medication use except that she received several courses of oral and intravenous antibiotics with no significant improvement in ulcer. She reported significant pain in the affected area, which interfered with sleep. On examination, a 4 cm × 3.5 cm ragged moist ulcer with surrounding erythema, edema, tenderness, and significant serous drainage was noticed on the left distal pretibial leg. (Figure 1—photo of leg dated 3/10/2020) The differential diagnosis for this refractory ulcer was broad, including infectious causes (bacterial, fungal, and non-tuberculous mycobacterial) and non-infectious conditions such as vasculitis, pyoderma gangrenosum, and squamous cell carcinoma. Her vital signs were stable, and her wound and blood cultures were negative. Serum inflammatory markers (ESR and CRP) were normal. A radiograph of the leg did not demonstrate osteomyelitis. Ultrasound was negative for deep venous thrombus. Biopsy of the ulcer's edge revealed superficial and deep perivascular and interstitial chronic inflammation with numerous eosinophils that was initially read as consistent with an insect bite. However, after we contacted the dermatopathologist and explained the unique clinical history, the diagnosis of eosinophilic cellulitis was determined. Treatment with prednisone 60 mg daily resulted in a rapid and dramatic improvement in pain and in the appearance of the skin lesion. Prednisone was tapered, and after 18 days of treatment, on a dose of 5 mg of prednisone, the ulcer, pain, and most of the redness had completely resolved.

One week later, she reported new severe pain and itch in the perianal area, which had kept her awake for five nights. She also noted excessive serosanguinous drainage. She endorsed the use of many topical agents including witch hazel and sitz baths. Examination revealed extremely large and inflamed external hemorrhoids and a sharply defined 30 cm x 30 cm circular patch of skin centering around the anus, extending to the perineum, inguinal creases,

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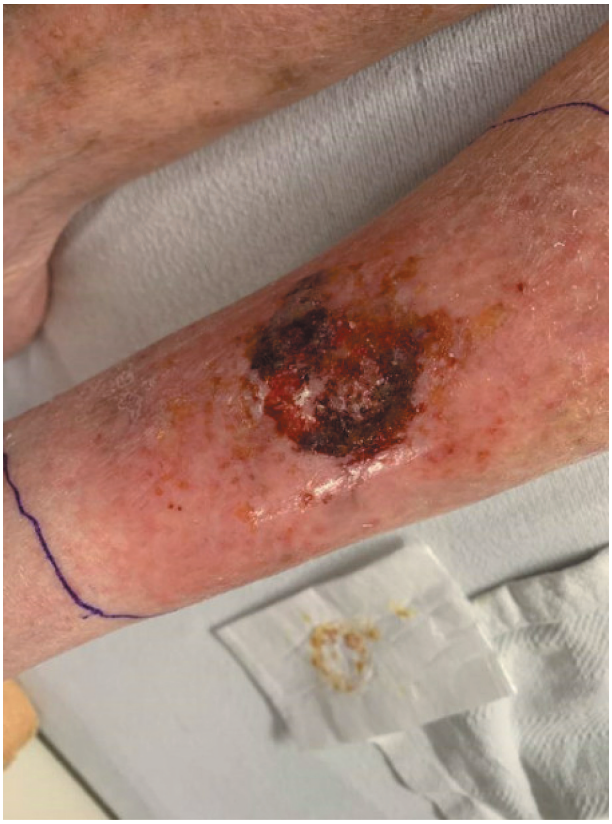

Figure 1. Large ragged painful ulcer with significant surrounding erythema on the left pretibial area.

medial buttocks, and labia majorae with maceration and significant serous drainage from the immediate perianal area (Figure 2) (4/21/2020). CT scan did not reveal perianal or perirectal abscess or fistula. The colorectal surgery consultant felt that the degree of pain and the atypical skin findings could not simply be explained by hemorrhoids. She was admitted for further evaluation, management and pain control. Diagnostic considerations included irritant or allergic contact dermatitis from topical agents, perianal streptococcal cellulitis, or recurrent eosinophilic cellulitis in a very unusual anatomic location. Despite application of topical agents including topical hydrocortisone, petroleum and zinc ointments, hydroxyzine, and narcotic analgesics, the pain, itch and rash persisted and severe dysuria and urethral pain had developed. A 4 mm punch biopsy was taken from the inner buttock, which revealed that eosinophilic predominant infiltrates comprised of perivascular inflammatory cuffs with a lymphohistiocytic component in addition to numerous eosinophils. There were also diffuse interstitial eosinophilic infiltrates in the mid and lower dermis [Figure 3(a–c)].

A diagnosis of recurrent eosinophilic cellulitis of the perineal area was made. Treatment was instituted with solumedrol 40 mg twice daily for twodays. The skin dramatically improved within twodays with improvement of pain and erythema in the area. Solumedrol was replaced with prednisone 60 mg for 3 days followed by a 6-week taper. For breakthrough perianal pain, she was given clobetasol 0.05% cream twice daily for twoweeks and discharged on a tapering steroid dose. Minocycline was started as a steroid-sparing agent, but its use was limited by vertigo. Significant perineal itch continued, unresponsive to hydroxyzine, topical steroids, and topical lidocaine.

Two weeks after completing glucocorticoid therapy, she returned to the emergency department with complaints of severe back pain as well as recurrent cellulitis (lower extremities, groin, and perianal) with lower extremity edema. Significant laboratory findings included eosinophilia (11%). ANA, immunoglobulin panels, inflammatory markers, chemistries, and flow cytometry were normal. Serum protein electrophoresis revealed an elevated alpha-2 globulin fraction, but no monoclonality. She was again treated with parenteral then oral corticosteroids. Back pain was attributed to a musculoskeletal cause. Hematology and rheumatology consultants found no underlying abnormalities that could be associated with Well's syndrome. Prednisone was again tapered over weeks, and she declined additional possible steroid sparing agents. She was free of active disease for fivemonths. Five months, later she had trauma to the left arm that led to severe arm redness, bruising and skin tear [Figure 4(a)] that initially healed, but later, she developed severe pain, redness at the site of injury (Figure 4(b)) and her symptoms were similar to the previous WS flare; she was treated with steroid and symptoms improved significantly and successfully tapered off steroids in fourweeks.

3. Discussion

Well's syndrome (WS) is a very rare dermatological condition. It was first reported in 1971 as recurrent granulomatous dermatitis with eosinophilia [3]. Patients with WS often develop other eosinophilic diseases including Churg Strauss syndrome and cutaneous eosinophilic vasculitis. Well's syndrome should be considered when patients with a history of asthma and present with skin lesions that are resistant to antibiotic therapy. Conditions that can mimic WS are listed in Table 1. Patients with WS are often misdiagnosed with bacterial cellulitis but do not improve with antibiotics, which should prompt clinicians to consider non-bacterial causes. The diagnosis is made with skin biopsy, generally demonstrating an eosinophilic dermal infiltration [4]. WS may present as tender urticarial plaques, vesicles, bullae or nodules. Skin symptoms are associated with peripheral eosinophilia in some, but not all patients.

Low dose prednisone is recommended for patients with recurrent episodes [5]. Unfortunately, our patient's disease relapsed on several occasions. Senio et al. reported a case

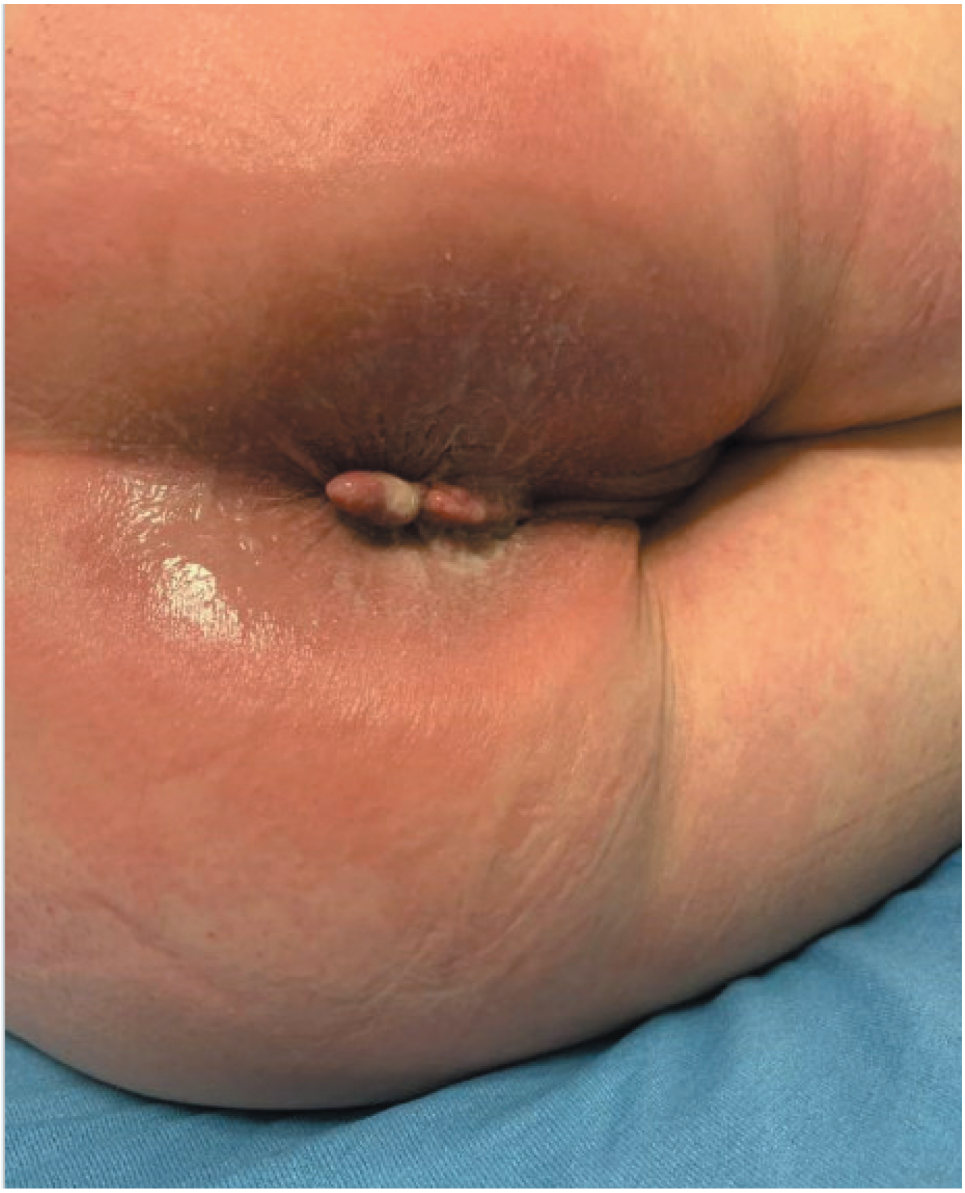

Figure 2. A 30 cm × 30 cm well- defined painful bright pink circular patch centered around the anus.

series of 32 and estimated the probability of recurrence as 56%. Success rates are 92%, 50% and 25% with systemic steroids, topical corticosteroids and antihistamines respectively [6]. Patients with recurrent episodes should start with steroid-sparing agents.

IL-5 produced by T-helper type 2 lymphocytes stimulates eosinophilic production, maturation, migration, activation and survival. Blockage of IL-5 is therefore a proposed treatment. Various monoclonal antibodies targeting IL-5 have been under review. Specifically, the efficacy of mepolizumab for treatment of Well syndrome has been described by Herout et al. [7] Magdalena et al. [8] mentioned in their case report successful treatment of recalcitrant eosinophilic annular erythema with mepolizumab as well. Unfortunately, there is limited supporting evidence regarding immunomodulating therapy for the treatment of WS [9].

Well's syndrome should be considered in patients with a history of asthma who present with signs and symptoms concerning for cellulitis when antibiotic therapy is not effective. Our case demonstrates Well's syndrome in an unusual anatomic location (the perineum), highlights that extreme pain, itch, drainage and ulceration may be prominent in this condition, and demonstrates that Well's syndrome is very responsive to systemic steroids but may rebound after cessation of therapy. No standardized therapeutic approach has been developed as an alternative to corticosteroids, although a variety of antihistamines and immunosuppressants have been anecdotally noted to provide some benefit.

Disclosure statement

No potential conflict of interest was reported by the author(s).

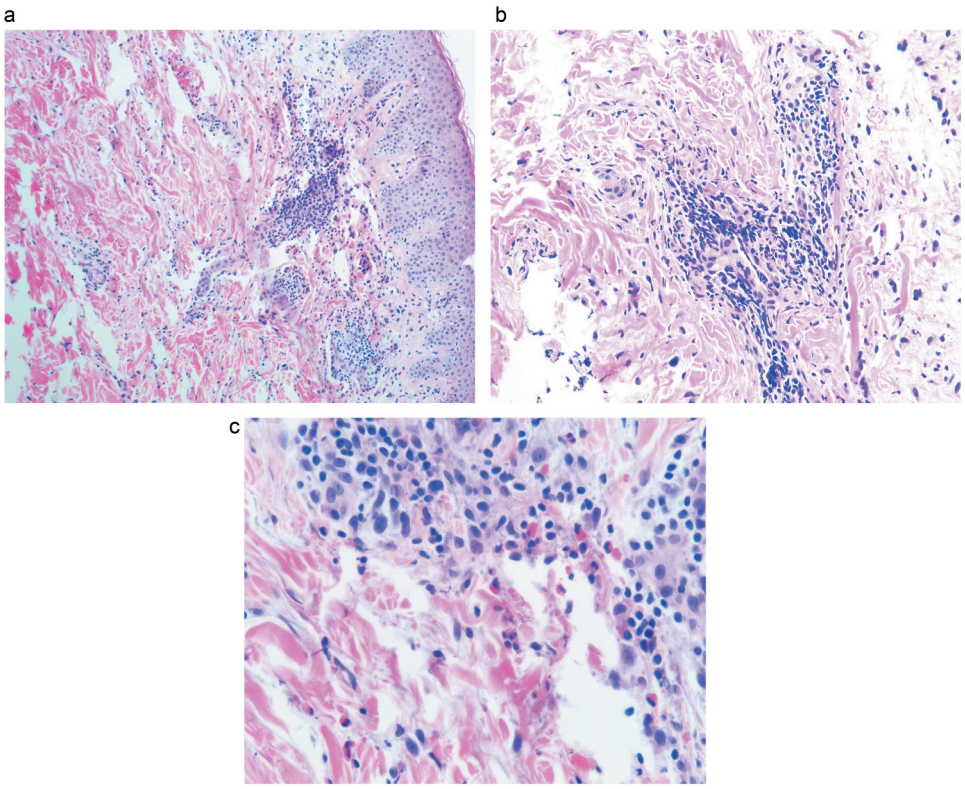

Figure 3. Skin biopsy from the buttock demonstrates that eosinophilic predominant infiltrates comprised of perivascular inflammatory cuffs with a lymphohistiocytic component in addition to numerous eosinophils with diffuse interstitial eosinophilic infiltrates in the mid and lower dermis (4 x) (a). (b) 10x. (c) 40x.

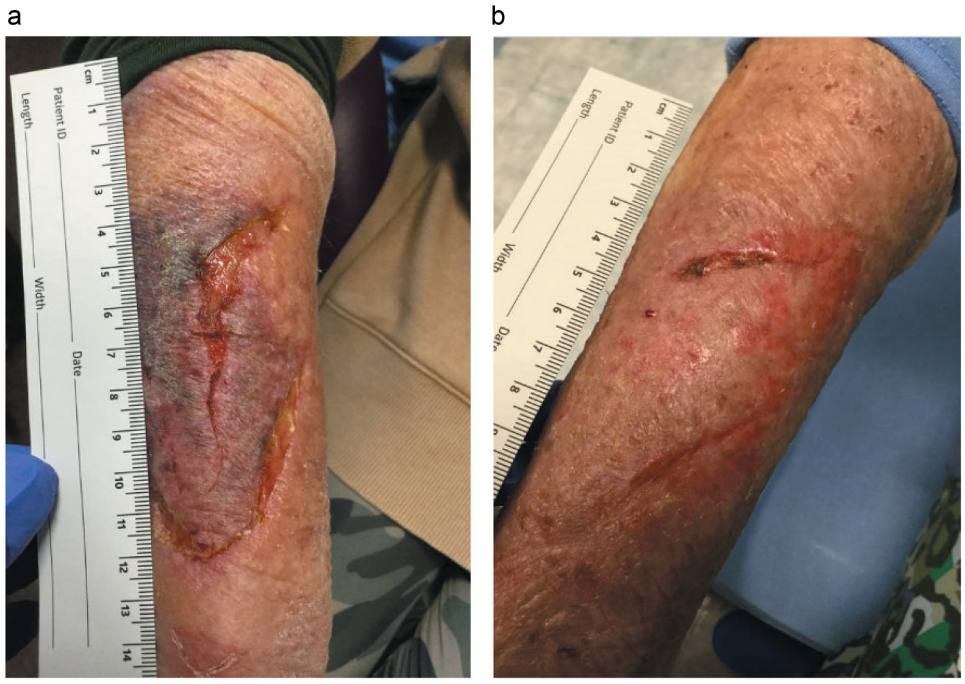

Figure 4. Arm redness, bruising after trauma.

Table 1. Differential diagnosis of eosinophilic cellulitis with recommended diagnostic tests.

Infections	
Bacterial cellulitis	Dermal edema and neutrophilic and lymphocytic infiltrate
Tinea corporis	Segmented hyphae on KOH preparation
Toxocariasis	IgG Antibodies to Toxacara confirmed by ELISA
Scabies	History and physical examination

(*Continued*)

Table 1. (Continued).

Infections	
Erythema migrans	Clinical diagnosis
Insect bite	Clinical diagnosis
Autoimmune	
Bullous pemphigoid	IgG and C3 linear staining on the basement membrane
Pemphigoid sestations	IgG and C3 linear staining on the basement membrane
Drug reaction	
Maculopapular drug eruption	Recent exposure to drugs
DRESS	Clinical diagnosis
Hyper-eosinophilic syndromes	
Eosinophilic fasciitis	Skin biopsy involving fascia and muscles showing edema with infiltrates of plasma cells, histiocytes and eosinophils
Eosinophilic dermatosis of hematological malignancy	Perivascular lymph histiocytic and eosinophilic infiltrate in papillary and mid dermis
Mastocytoma	Skin biopsy

* DRESS—-drug reaction with eosinophilia and systemic symptom.

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