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Case Report

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Eosinophilic Cellulitis (Well's Syndrome) and Eosinophilic Granulomatosis with Poly angiitis (Churgg-Strauss Syndrome); Different Clinical Entities, or a Single Spectrum of Disease? A Case Study, Discussion and Literature Review

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Abstract

This case study represents an unusual presentation female in her seventies who presented with a chronic eosinophilic rash without systemic involvement on a background of psoriatic arthritis (pSA) and Sjogren's Syndrome (sSS). Biopsy of the lesions identified flame figures. The differentials for such lesions are wide, however this case discusses three of the most likely differentials including Eiosinophilic Cellulitis (Well's Syndrome), Eosionophilic Granlomatosis with Polyangiitis (Churgg Strauss Syndrome) and Granulomatous Dermatitis (GD). A common aberrant eiosinophilic response is dicussed and a review of the literature identifies the possibility that these diagnoses represent a single spectrum of disease, rather than separate clinical entities. Whilst the provoking incident was not able to be established in this case, the possibility of covid-19 vaccination contributing to the development of lesions is discussed. This case highlights the importance of conducting skin biopsies of unusual lesions that do not follow an expected clinical course and that skin biopsies might need to be performed opportunistically by emergency departments especially in rural areas where dermatology services are lacking. A lack of knowledge of various complex systemic diseases that present with unusual skin lesions often results in missed diagnosis and delayed patient care. Education of primary care physicians and healthcare professionals working in emergency departments is required to ensure timely biopsy and appropriate serology with screening for underlying systemic diseases including malignancy is required to prevent missed diagnosis and delayed care.

Keywords: Dermatopathology, Psoriatic Arthritis (pSA), Sjogren's Syndrome (sSS), Granulomatous Dermatitis, Covid-19 Vaccination Wells Syndrome, EGPA

Introduction

This paper will discuss a case study involving a patient who presented with inflammatory skin lesions, the results of biopsy findings of flame figures and differential diagnosis. A review of the literature demonstrates the range of differentials in this case appear to have overlapping complex eosinophilic patterns raising a question about the relationship between these disease entities. In particular, such findings can occur in eosinophilic cellulitis and granulomatous dermatitis both of which can be features of eosinophilic granulomatosis with polyangiitis (Churgg Strauss Syndrome) (EGPA).

This case highlights challenges patients in rural Australia face in accessing care for complex cases of dermatopathology. The discussion and literature review draw a number of conclusions including eosinophilic cellulitis, eosinophilic granulomatosis with polyangiitis (EGPA) and some forms of granulomatous dermatitis might be a single spectrum of disease involving an abnormal eosinophilic response. Covid-19 vaccinations can trigger such a response. As complex dermatologic lesions are virtually impossible to diagnose visually, patients in rural areas should received timely biopsies, with serology screening for underlying systemic disease including malignancy.

Case Study

A female of South Asian descent in her mid seventies presented to her general practitioner for a painful, pruritic umbilicated lesion with an associated bullae on her right lower leg (See Figure 1). She was systemically well at the time of presentation, with no other associated symptoms. The patient reported the lesion started after working in the garden the previous week. She denied any insect bites, or working with new plants and reported being an avid gardener of over five decades. She denied similar symptoms in the past. The patient denied commencing any new medications and had not recently ceased any medications, however had received a Covid -19 vaccination 4 weeks prior to the development of the

lesion. The patient had no contacts with anyone who had scabies infections. She owned no pets.

The patient's past medical history included:

Patent ductus arteriosus requiring surgical repair as an adult
Allergic rhinitis
Chronic sinusitus
Adult-onset asthma
Eczema
Cellulitis
Skeeter syndrome
Severe hyperemesis gravidarum
De Quervain's Thyroiditis
Paroxysmal atrial fibrillation
Psoriatic arthritis (PsA)
Secondary Sjogren's Syndrome (sSS)
Calcium pyrophosphate deposition disease (CPPD)
Osteoarthritis (OA)
Varicose veins
Peripheral sensory neuropathy of hands and feet

The patient's only regular medication was rivaroxaban 20mg PO daily. She reported anaphylaxis to penicillins.

The patient commenced a course of oral cephalexin, but despite completing this, the lesion progressed and began oozing serous discharge. An additional lesion adjacent to the first lesion developed. Compression bandaging performed by the patient at home failed to reduce the serous ooze and oedema.

As the lesions had not responded to the first course of antibiotic treatment, the patient commenced a course of oral clindamycin and received once dose of ivermectin to cover a possible scabies infection. Despite this her lower right leg continued to become more oedematous and she presented to the local emergency department for management. During this presentation an Infectious Diseases opinion was sought, however no investigations were performed. The patient was discharged back to her General Practioner (GP) for management of cellulitis. Her GP prescribed a course of oral Bactrim and ordered basic serology. FBC, U&E, LFT and CRP was unremarkable. No additional investigations including malignancy screening were performed.

The patient self-initiated oral fexofenadine which partially reduced pruritic symptoms.

Despite a course of Bactrim additional lesions then developed on the patient's right hand, fingers and wrists (see Figure 3).

At this point the primary author became involved with the case as the patient had presented three times to her primary health care provider and once to the emergency department and despite the ongoing progression of her lesions, no biopsy had been performed, no dermatology referral had been made, no autoimmune serology had been ordered and no malignancy screening had been performed.

The patient had developed additional symptoms of mild intermittent headaches and mild abdominal pain.

At this point examination findings revealed a systemically well elderly female with a normal respiratory, cardiac and abdominal examination.

Two coalescing lesions on the patient's right lower leg of erythematous to violaceous oedematous umbilicated annular plaques with bullae and epithelial breakdown of the distal medial lesion were observed (see Figure 2).

The primary author sought dermatology advice by phone. Due to long waiting lists, the patient was not able to be seen in clinic. On dermatology advice the patient was commenced on 50mg oral prednisolone for 5 days and referred back to her primary care provider for a biopsy.

Oedema resolved over a 5 day period. As the lesions healed, they developed a scaley plaque (See Figure 3).

Three weeks later an additional lesion developed on the patient's lower left calf. The patient initiated a second course of oral steroids and presented to her GP who performed a biopsy. Viral and bacterial swabs of the lesions were sent for PCR and MC&S respectively. A urinalysis was not performed.

Once the patient stopped taking prednisolone the lesions reappeared on the patient's right foot, Right Ear and Face (See Figure 3). The patient self-initiated a further course of prednisolone at 5mg PO for a further 2 weeks.

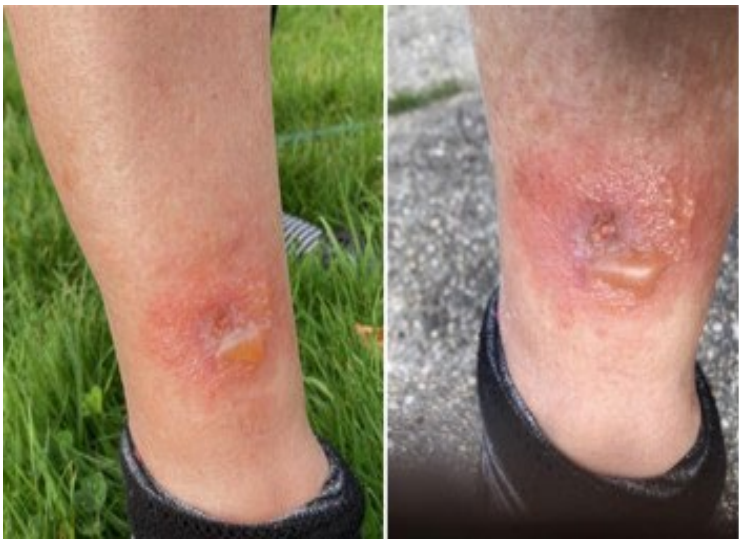

Figure 1: Initial Lesion on Patient's Lower Right Calf.

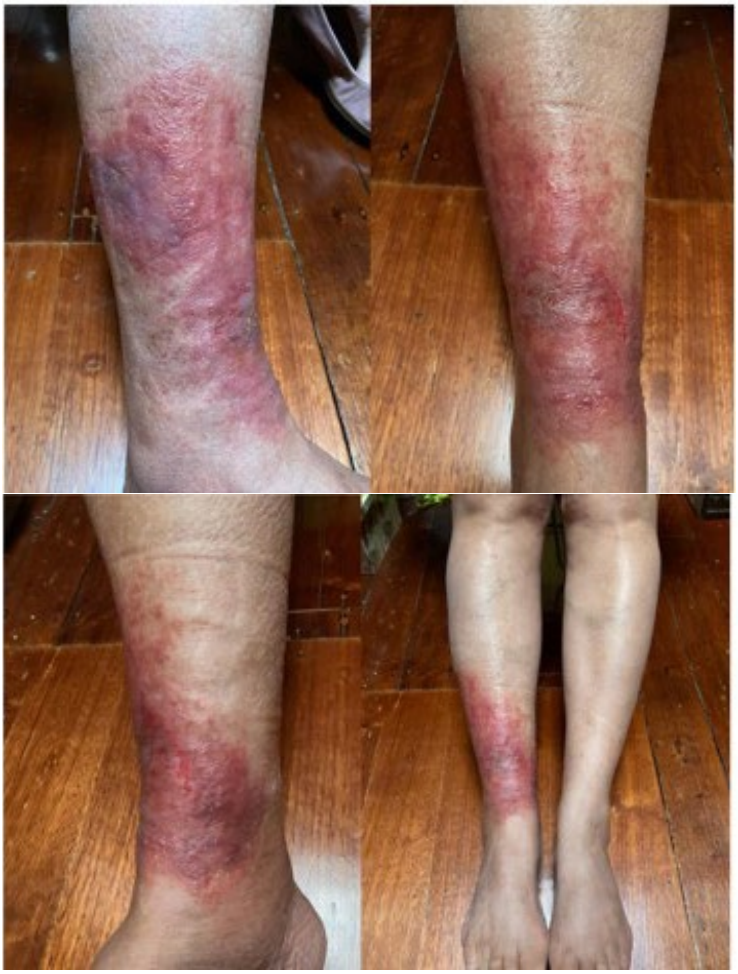

Figure 2: Progression of Lesions Over a 3 Week Period.

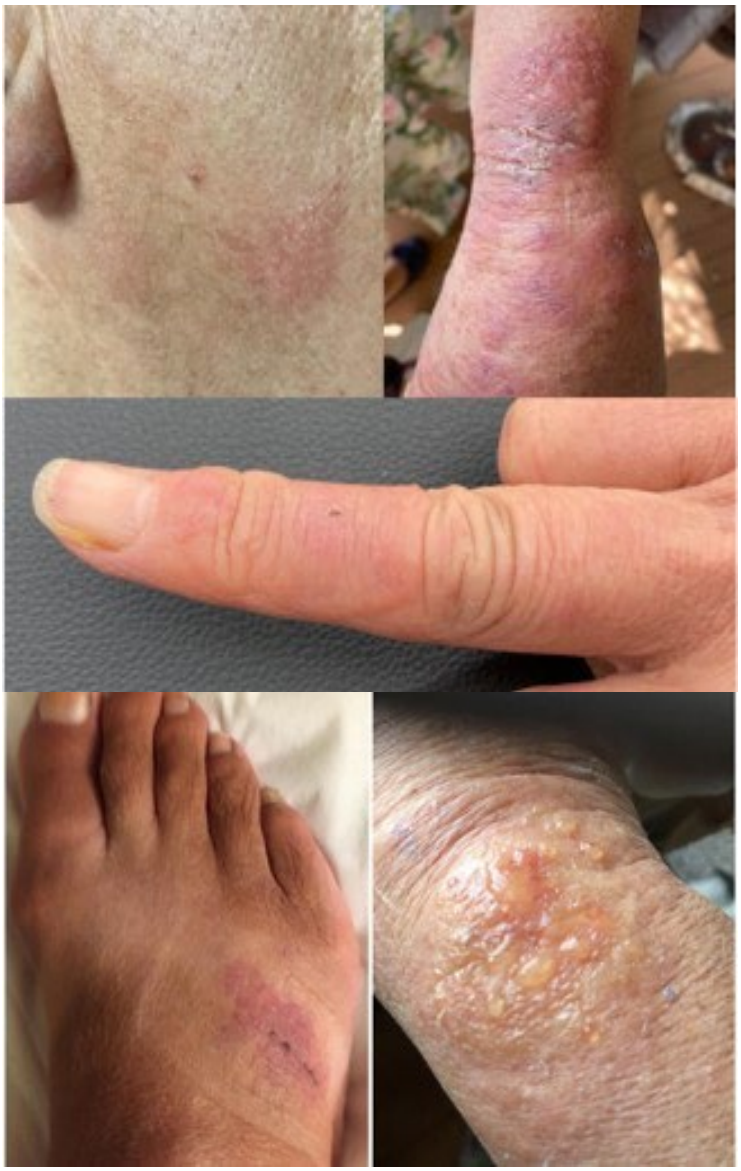

Figure 3: Subsequent Development and Healing of Lesions; Right Wrist, Hand, Fingers, Left Foot, Right Ear and Face Over a 3 Month Period.

Swab Results

Swabs for HSV 1, 2, varicella zoster were negative.
MC&S was negative for bacterial growth.

Biopsy Results

Right Lower Shin

Sections show overlying basketweave hyperkeratosis with mild spongiosis. There is a moderate chronic inflammatory infiltrate within the superficial to deep dermis and extending to subcutis predominantly consisting of eosinophils with some lymphocytes and histiocytes. Inflammatory infiltrate is associated with some endothelial swelling and extravasated red blood cells. However, definitive vasculitis is not seen. No subepidermal blister is seen in multiple levels to suggest bullous pemphigoid.

Focally within the dermis there is a palisade of histiocytes and multinucleated giant cells around eosinophilic collagen bundles reminiscent of flame figures. No fungal or parasitic organisms are identified on PAS stain. There is no evidence of malignancy.

Immunofluorescence studies for IgG, IgM, IgA and C3 are negative.

Swab Results

Swabs for HSV 1, 2, varicella zoster were negative.
MC&S was negative for bacterial growth.

Biopsy Results

Right Lower Shin

Sections show overlying basketweave hyperkeratosis with mild

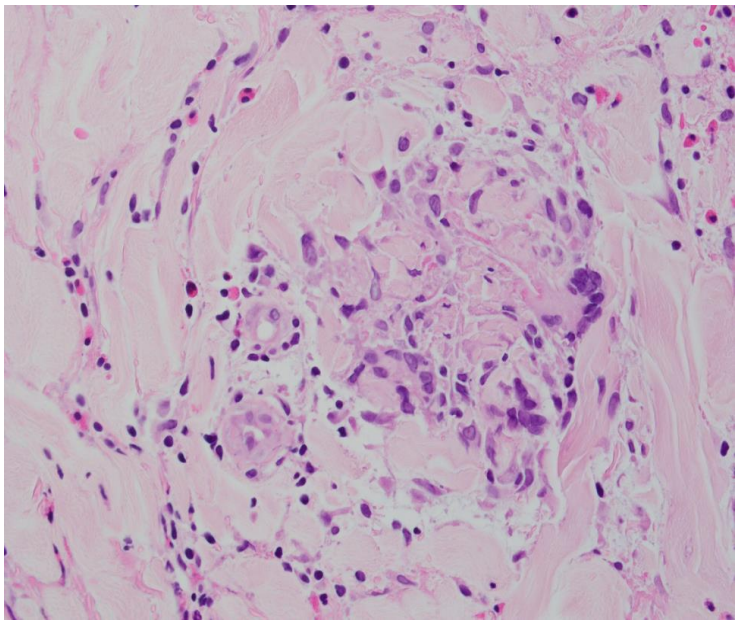

Figure 4: Flame Figure 1 H&E; Reticular Dermis; 400x.

Histiocytes palisade around eosinophilic collagen bundles and small amounts of granular eosinophilc material, reminiscent of a flame figure.

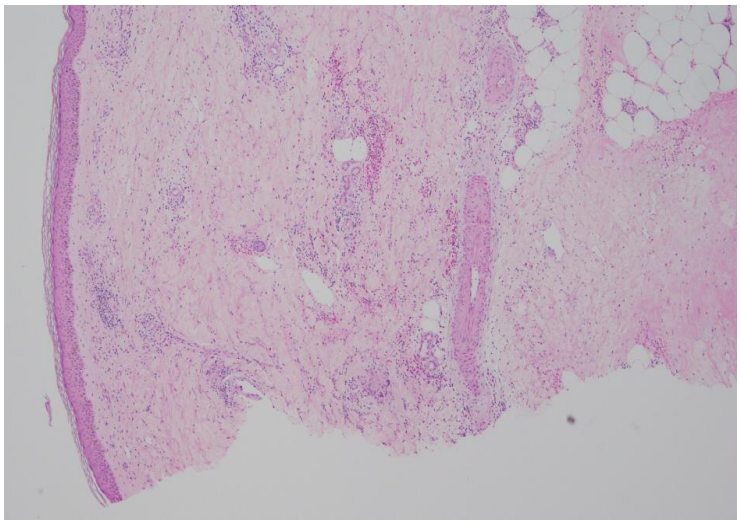

Figure 5: Flame Figure 2 H&E; Skin Punch; 40x.

A mildly spongiotic epidermis overlies a moderate chronic inflammatory infiltrate which contains eosinophils, lymphocytes and some histiocytes.

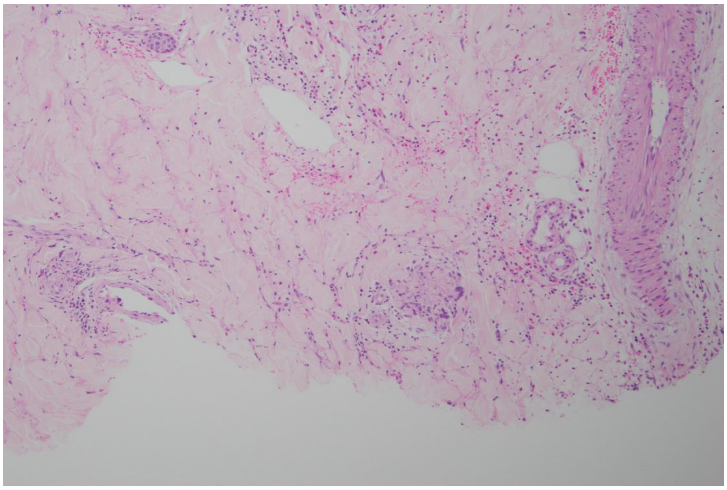

Figure 6: Flame Figures 3 H&E; Reticular Dermis; 100x.

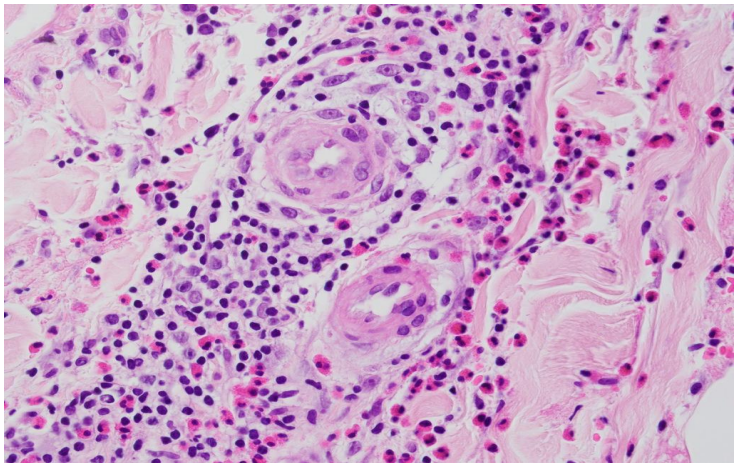

Figure 7: Eosinophils 1 H&E Reticular Dermis; 400x.

An inflammatory infiltrate with prominent eosinophils, lymphocytes and some histiocytes clusters around blood vessels. Definitive vasculitis is not shown.

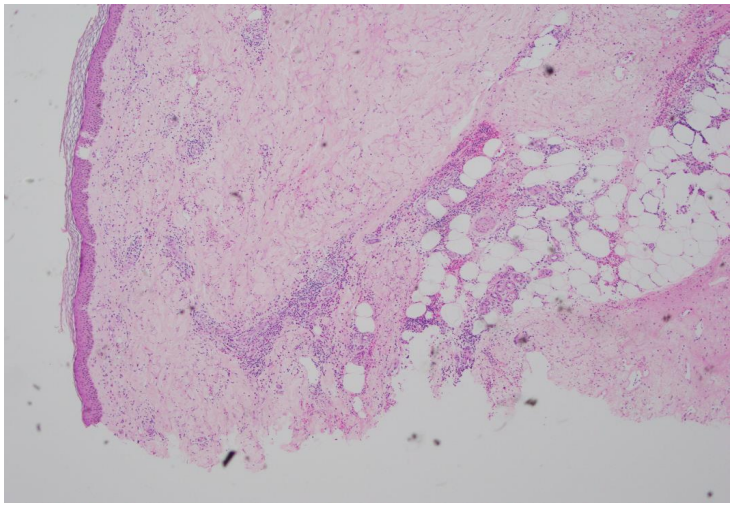

Figure 8: Eosinophils 2 H&E Skin Punch; 40x.

Inflammatory infiltrates are present through to the subcutis.

Discussion

Diagnostic challenges in this case arise from the complexity of the lesions, a delay in biopsy and lack of complete serology work up, making a definitive diagnosis difficult.

Emergency departments do not routinely perform biopsies and this responsibility usually lies with General Practitioners (GPs), however there is currently a national shortage of GPs especially in regional and rural areas with long waiting times, resulting in patients waiting many days, if not weeks to be seen by a GP post discharge from an emergency department presentation, by which stage lesions might no longer be suitable for biopsy.

Serology to exclude autoimmune phenomena and malignancy is recommended at the time of acute presentation according to the literature [1]. However, lack of awareness of the relationship between inflammatory skin lesions and systemic diseases such as autoimmune, lymphoproliferative and malignant processes results in failure to complete autoimmune serology and appropriate malignancy screening in many rural and regional settings where resources are lacking.

When biopsy results are abnormal, dermatology referrals have delays due to long waiting lists as many regional and rural centres have limited dermatology services. All these factors result in delayed diagnosis and present a significant barrier to accessing appropriate care for rural patients.

The differential diagnoses of eosinophilic infiltration in the dermis are numerous and include, but are not limited to the following conditions:

- Eosinophilic cellulitis (Well's Syndrome)
- Palisaded neutrophilic granulomatous dermatitis (PNGD)
- Eosinophilic granulomatosis with polyangiitis (EGPA)
- Interstitial granulomatous dermatitis (IGD)
- Eosinophilic dermatosis of hematologic malignancy
- Necrobiotic papulosis (Granulomatous annulare) (GA)
- Recurrent cutaneous necrotising eosinophilic vasculitis
- Hypereosinophilic syndrome (HES)
- Afebrile neutrophilic dermatosis
- Dermatitis herpetiformis
- Urticarial vasculitis
- Bullous pemphigoid
- Pemphigus vulgaris
- Arthropod bite including scabies
- Parasitic infection
- Drug reaction

More specifically, histologic flame lesions as identified in this patient's biopsy results are associated with a number of conditions including:

- Eosinophilic Cellulitis (Well's Syndrome)
- Palisaded Neutrophilic Granulomatous Dermatitis (PNGD)
- Eosinophilic Granulomatosis with Polyangiitis (EGPA) (Churgg Strauss Syndrome) and other autoimmune rheumatic diseases
- Bullous Pemphigoid [2]
- Parasitic infection and arthropod bites [3]
- Herpetic Dermatitis

These represent the major differential diagnoses for this case which will now be discussed.

The lesions found in many of these differential diagnoses are dynamic both clinically and histologically representing a diagnostic challenge, as findings might vary depending on the stage at which biopsy is performed.

The histology report in this case mentioned "palisaded histiocytes and multinucleated giant cells around eosinophilic collagen bundles reminiscent of flame figures". This is a common feature of Granuloma Annulare (GA) [4,5], however a lack of mucin can distinguish GA from PNGD [6,7], and there was no mucin reported in the histopathology of this case. Of note, GA-like lesions are reported in Eosinophilic Granulomatosis with Polyangiitis (EGPA), or Churgg Strauss Syndrome [8,9] which will be discussed further on.

Continuous debate exists in literature over whether some of the differential diagnoses discussed here represent distinct clinical entities versus a continuous spectrum of disease, as is the case with PNGD and IGD [10-12], or IGD with arthtitis (IGDA) as a separate entity from PNGD [13,14] with some authors recommending an overarching term of "granulomatous dermatitis" (GD) be adopted to reflect the overlapping features of these conditions [10,12].

Granulomatous Dermatitis (GD) is a well-recognised cutaneous marker for a number of systemic associations including drug reactions, lymphoproliferative disorders, and autoimmune rheumatic diseases including rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) and EGPA [10,15]. It is most commonly associated with RA [16]. In cases of GD, especially those that do not spontaneously resolve, investigations should be directed toward diagnosis of a causative underlying condition [1]. Where initial investigations do not provide a definitive diagnosis, some tests warrant repeating as a serious systemic disease might reveal itself with the passage of time [1].

As the patient had normal FBC and remained systemically well 12 months after initial presentation, a lymphoproliferative disorder, or occult malignancy is unlikely.

The patient reported a significant history of rheumatic disease and atopy suggestive of immunologic dysregulation making an underlying systemic rheumatic condition more likely.

The patient has previously been investigated for a number of rheumatic diseases which ruled out conditions such as SLE.

EGPA is a possibility. The 2022 American College of Rheumatology/ European Alliance of Associations for Rheumatology Classification Criteria for Eosinophilic Granulomatosis with Polyangiitis [17] is given below:

Clinical Criteria	
Obstructive Airway Disease	+3
Nasal Polyps	+3
Mononeuritis Multiplex	+1
Laboratory and Biopsy Criteria	
Blood eosinophilia > $1x10^9$L	+5
Extravascular eosinophilic-predominant inflammation on biopsy	+2
ANCA positivity (Both C-ANCA and MPO-ANCA)	-3
Haematuria	-1
A score of 6 or greater is considered positive for EGPA.	

Table 1: 2022 ACR/European Alliance of Associations for Rheumatology Classification Criteria for EGPA.

The patient receives a score of 5 for obstructive airway disease and an extravascular inflammation on biopsy. A complete workup for EGPA should include rheumatology referral and investigations as per the 2015 EGPA Consensus Task Force Recommendations for Evaluation and Management [15].

Skin manifestation of EGPA occurs in 50%-81% of cases [16]. The most common location of skin lesions in EGPA is the extensor surface of both lower extremities [16], which is where this patient's lesions first developed. Characteristic histologic findings in EGPA include flame lesions, eosinophilic infiltrates and PNGD has been reported in some cases of EGPA [16]. PNGD can occur in conjunction with leukocytoclastic vasculitis [19].

Other findings might include extravasated red blood cells, leukocytoclastic vasculitis and eosinophilic inflammatory infiltrates around dermis nerve fibres resulting in a mononeurotis multiplex [16,20,]. These findings were absent in the patient's biopsy, however this does not rule out the diagnosis. Approximately 41% of patients with EGPA do not have vasculitis but rather an eosinophilic tissue infiltrate [21].

In the past the patient's rheumatology serology was negative for ANCA. 60% 70% of patients with EGPA have a negative ANCA, meaning a negative result does not exclude the diagnosis. In the 30-40% of patients who test positive, MPO-ANCA is most common and this is associated with vasculitis.

The patient's biopsy was negative for vasculitis, but could still represent a case of EGPA given the nature of the lesions and the history of atopy with adult onset asthma. The patient did not have any pulmonary, or renal involvement during the course of illness.

Of note, the patient had no peripheral eosinophilia, however according to classification criteria in Table 1 it is still possible to achieve a score of 6 in the absence of blood eosinophilia and there are case reports of atypical EGPA without peripheral eosinophilia [22-24].

A recent study of 157 patients with EGPA suggests a revised nomenclature and definition for EGPA proposes a new entity referred to as "hypereosinophilic asthma with systemic (non vasculitic) manifestations" [21]. This reflects a recognition that EGPA might be a disease with a number of phenotypically different presentations, or incomplete forms. In the past the terms the terms "formes-frustes" (incomplete), or "limited" have been used to refer to such cases [25-27]. Changes in nomenclature could better clarify the vastly different range of clinical and atypical presentations found in EGPA.

The patient's history of allergic rhinitis, sinusitis and adult onset asthma would be in keeping with the continuum of disease evolution recognised in EGPA [18,28]. An informal rheumatology opinion was sought during the writing of this case study and it was agreed an incomplete form of EGPA is a possibility in this case.

Eosinophilic Cellulitis (EC) also known as Well's syndrome is a rare condition with only 200 case reports in the literature to date [29]. Generally, there is no systemic involvement [29], but some patients present with fever and fatigue [30]. It should be considered in patients who present with lesions suggestive of cellulitis, but which fail to respond to antibiotic therapy, as with this case [30].

EC is characterised by three distinct phases each with characteristic histopathological findings [29]. In the first stage, burning sensations are followed by development of pruritic plaques, correlating with eosinophilic infiltration on histological examination. Approximately seven days later, the lesions develop becoming tender with associated cutaneous oedema characterised by flame figures on histological examination [29-32]. In the third phase the lesions heal with hyperpigmentation before resolution [29]. The patient's lesions did follow this description of events with corresponding histopathology making it a likely differential diagnosis. Numerous literature reports lesions with features of both Eosinophlic Cellulitis and EGPA suggesting the conditions might represent a single spectrum of disease [29,33-37]. EC reportedly responds to IL-5 inhibitor mepolizumab [38], frequently used to treat EGPA, as well as systemic steroid therapy. The overlap between EC and EGPA further contributes to diagnostic condundrum and is something that requires clarification in future research with a possible revision of current nosology.

As with EGPA, skin involvement is the most common clinical sign in Hypereonsinophilic Syndromes (HES) which include a group of conditions that can be neoplastic primary HES, reactive, or secondary HES, and idiopathic [39]. Multiorgan involvement is common. HES can present with with fever, weight loss, fatigue, and skin lesions in 40-50% of cases [40-42]. Lesions are reported as pruritic erythematous macules, papules, plaques, wheals, and nodules with urticaria being possible in all subtypes [37]. Common histopathologic features in HES include epidermal thickening, intraepidermal eosinophilia, or neutrophilia, karryorhexis, acanthosis and hyperkeratosis [37,39]. Interstitial granulomatous dermatitis (IGD) has been reported in some cases [42]. Vasculitis is usually absent. Although the current diagnostic criteria rely on the exclusion of other disorders, idiopathic HES could potentially be indistinguishable from EGPA without vasculitis as demonstrated in significant overalap especially given both conditions have shown response to steroids and the IL-5 inhibitor mepolizumab [43], however literature generally still considers EGPA as a separate entitiy from idiopathic HES despite shared clinical feature [44]. Treatment of the 2 conditions can vary [44]. Takahashi et al., [45] have proposed a tool for differentiating EGPA from other eosinophilic conditions.

The patient's absence of peripheral eosinophilia makes HES an unlikely diagnosis, although it could present a mild form of disease.

Bullous phemphegoid can present with flame figures [46,47], however the overall clinical picture is not in keeping with the presentation described here.

Dermatitis herpetiformis was considered as it can present with dermal eosinophilic infiltrates around clusters of neutrophils on histology [48], but it was ruled out based on the absence of gluten sensitivity, or coeliac disease in the patient's medical history as well as lack of micro-abscesses, or IgA deposition on immunofluorescence staining which is characteristic of this condition [48,49].

The patient denied any arthropod bite, histology was negative for fungi and parasites, making these very unlikely as a differential diagnosis.

The patient had not commenced, or ceased any new drugs, in the lead up to development of lesions, however had received a 4th Covid-19 vaccination a month prior to the onset of symptoms. The patient went on to received a 5th Covid-19 vaccination seven months post initial development of skin lesions and this had no impact on the course of disease.

Vaccinations are recognised as causing flares of rheumatic diseases and this includes Covid-19 vaccinations [50-52]. Flares of churgg strauss post vaccination

Additionally, there are case reports in the literature of eosinophilic responses occurring post Covid-19 vaccinations [53-56] with one study reporting an incidence of 4.2 in 10,000 vaccinations [54]. One case report described a flare of polyneuropathy in a patient with pre-existing EGPA post Covid-19 vaccination, whilst there are case reports of EGPA occurring post Covid-19 infection as well as covid 19 vaccination [37,57-60].

Based on this information, there is the possibility that the Covid-19 vaccination resulted in an eosinophilic response that represents an isolated phenomenon, or that the vaccination unmasked a previously missed diagnosis of incomplete EGPA.

Given the common theme in current literature noting clinical and histopathological overlap between the major differential diagnoses described here, it is possible these clinical entities are different phenotypical presentations of a common underlying abberant eosinophilic process. It is clear from the literature that there are significant gaps in detailed understanding of these diseases clinically, hisopathologically and pathophysiologcially [61]. Therefore, urgent review of the nomenclature, nosology and pathophysiology of these conditions is required [61].

Conceptually these conditions could be considered as overlapping on a single spectrum of inappropriate eosinophilic response as depicted Figure 9.

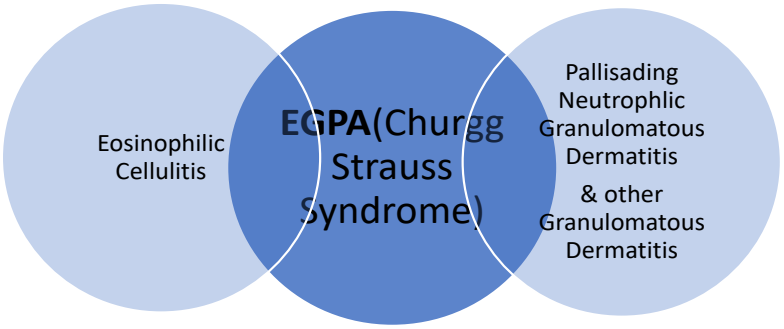

Figure 9: Distinct Clinical Entities, or Overlapping Spectrum of Disease? A Possible Conceptual Model for EGPA, EC, PNGD.

There are no case reports in the literature of PsA nd sSS with development of incomplete EGPA to the best of the primary author's knowledge which would make this an unusual case.

Key Recommendations

- Eosinophilic inflammatory dermatopatholoy represents a broad spectrum of systemic and local eosinophilic pathologies that can be challenging to diagnose due to current controversies over nomenclature and nosology.
- Further research is required to establish relationships between the various eosinophilic pathologies discussed here to identify whether there is an underlying unifying eosinophilic pathologic process representing a single spectrum of disease, rather than distinct clinical entities
- Eosinophilic Granulomatous polyangiitis (EGPA), or Churgg Strauss Syndrome can be a very challenging diagnosis to make given the absence of typical features in many cases as well as varied clinical phenomena depending on the phase of disease at presentation. Evaluation should therefore be conducted in accordance with the 2015 "Eosinophilic granulomatosis with polyangiitis (Churg-Strauss) (EGPA) Consensus Task Force recommendations for evaluation and management" [62-68]
- All patients who present to emergency departments with acute unusual skin lesions should receive a timely biopsy with appropriate serology to avoid diagnostic delays
- All patients whose biopsy results involve eosinophilic infiltrates with flame figures and/or granulomatous lesions should receive comprehensive autoimmune serology with prompt rheumatology/dermatology opinion to rule out autoimmune disorders known to be associated with such dermatopathology
- All patients whose biopsy results report granulomatous dermatitis, or vasculitis should undergo age-appropriate malignancy screening due to the well-established association between such lesions and the possibility of an underlying occult malignancy
- Further education of GPs working in regional and rural areas is required to prevent delays in diagnosis, patient care and unnecessary patient suffering

Conclusion

This case study represents an unusual presentation of a chronic eosinophilic rash without systemic involvement. The differentials for such lesions are wide, but in this case the most likely differentials include Eiosinophilic Cellulitis (Well's Syndrome), EGPA (Churgg Strauss Syndrome) and Granulomatous dermatitis (GA). A discussion of a shared aberrant eiosinophilic response identified the possibility that these diagnoses represent a single spectrum of disease, rather than separate clinical entities. Whilst the provoking incident was not able to be established in this case, the possibility of Covid-19 vaccination contributing to the development of lesion is discussed. This case highlights the importance of conducting skin biopsies of unusual lesions that do not follow an expected clinical course and that skin biopsies might need to be performed opportunistically by emergency departments. A lack of information on various complex systemic diseases that present with unusual skin lesions often results in missed biopsies, delayed diagnosis and patient care. Education of primary care physicians and healthcare professionals working in emergency departments is required to prevent delayed and missed diagnosis, especially in rural areas where dermatology services might be lacking.

Conflict of Interests

The patient is a relative of the primary author. No funding, or financial incentives were received in the authoring, or publishing of this paper.

Patient Consent

The authors obtained patient consent for use of photographs and other information for this case study.

Contributors

The primary author contributed to the conception, design and authored the manuscript including the literature review. The secondary author provided pathology slides with descriptions and contributed to the list of differential diagnoses. Both authors give approval of this work to be published and agree to be accountable for all aspects of the work.

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