CASE REPORT

A Case of Eosinophilic Granulomatosis with Polyangiitis Mimicking Cutaneous Tuberculosis and Tuberculous Lymphadenitis

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Summary
Eosinophilic granulomatosis with polyangiitis (EGPA), or Churg-Strauss Syndrome (CSS) is a rare granulomatous necrotizing vasculitic disease characterized by the presence of asthma, sinusitis, and hypereosinophilia. We describe a patient who was initially diagnosed with tuberculous lymphadenitis and later diagnosed with EGPA.

Key Words: *Churg-Strauss syndrome, Eosinophilic Granulomatosis with Polyangiitis, Tuberculous lymphadenitis, Rituximab*

Introduction
Eosinophilic granulomatosis with polyangiitis (EGPA), or Churg-Strauss syndrome (CSS) is a rare granulomatous necrotizing vasculitic disease characterized by the presence of asthma, sinusitis, and hypereosinophilia.[1-3] EGPA causes vasculitis of small-to-medium blood vessels that affects many organ systems such as the cardiovascular, pulmonary, renal, nervous and vascular systems.[4] Vasculitis of extrapulmonary organs is a major cause of morbidity and mortality in this disease.[3] Corticosteroids are considered the first-line of treatment for EGPA patients to achieve remission.[4] Rituximab is an anti-CD20 monoclonal antibody that is approved for use in the treatment of lymphoid malignancies, rheumatoid arthritis, and granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA).[5] We report a challenging case of active severe EGPA mimicking cutaneous tuberculosis and tuberculous lymphadenitis who initially responded to intravenous (IV) pulse corticosteroid and Rituximab, relapsed and retreated, but succumbed to Coronavirus disease 2019 (COVID-19) infection.

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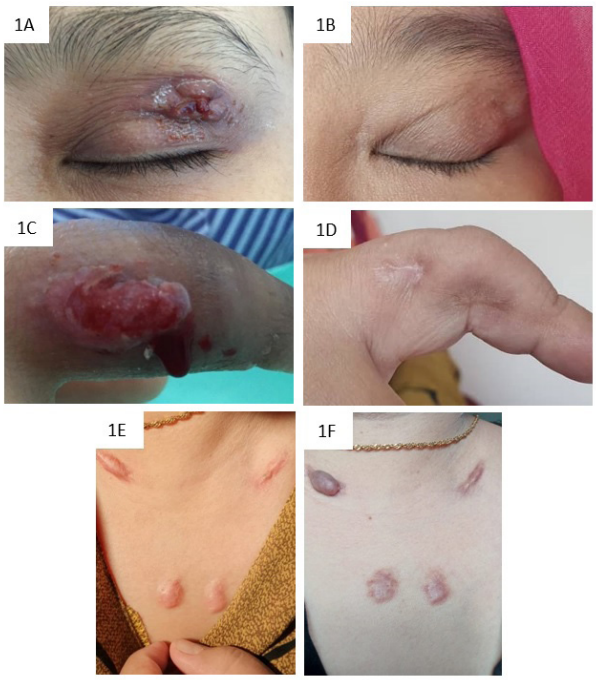
Case Report

A 38-year-old female with underlying bronchial asthma and rhinosinusitis presented to the dermatology clinic with multiple erythematous papules, plaques and ulcerated nodules on her left eye lid (Figure 1A), dorsum of the right index finger (Figure 1C), forearms, and chest (Figure 1E) with intermittent fever for 6 months. Systemic review was otherwise unremarkable. She had been empirically treated for smear-negative tuberculous lymphadenitis by the treating physician for a year but showed no improvement.

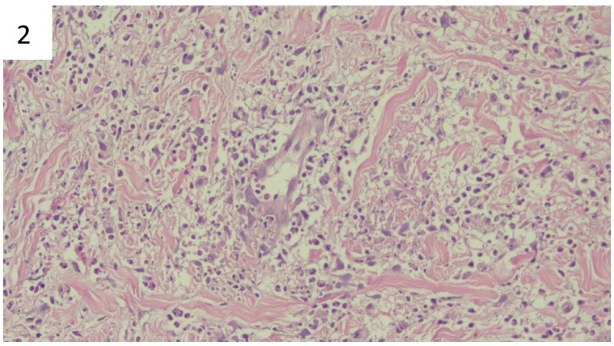
Figure 1. Churg-Strauss syndrome. (A) Erythematous multilobulated plaque with ulcerated haemorrhagic crust on left eye lid; (B) Eye lid post-treatment, resolved lesion; (C) Erythematous juicy ulcerated nodule with contact bleeding on right dorsal index finger; (D) Index finger post-treatment, resolved lesion; (E) Multiple pink elongated papules over anterior chest; (F) Chest post-treatment, resolved lesions with keloid scars.



Laboratory tests revealed leukocytosis (16820/mm^3) with eosinophilia (1050/mm^3). Perinuclear anti-neutrophil cytoplasmic antibodies (P-ANCA), chest radiograph, echocardiograph and Tuberculosis Quantiferon results were normal. Computed tomography (CT) scan of thorax, abdomen and pelvis revealed multiple non-necrotic cervical, mediastinal, inguinal lymphadenopathy with lung, liver and bone nodules. Positron emission tomography (PET) scan showed avid lytic lesions with rims of sclerosis along vertebra, bilateral ileum and right tibia representing chronic granulomatous bone changes. Magnetic resonance imaging and angiography (MRI/MRA) brain showed multiple supratentorial non enhancing hyperintense foci.

Biopsies taken from the lymph node and skin plaque showed a mixture of neutrophils, eosinophils and histiocytes in aggregates, forming granulomas. Blood vessels showed evidence of vasculitis with eosinophils (Figure 2). Immunohistochemical staining for S100 and CD1a were positive, whereas langerin (CD207) staining was negative. Culture and polymerase chain reaction (PCR) for *Mycobacterium tuberculosis* from skin biopsy were negative. A diagnosis of EGPA was made based on the clinical manifestations, histopathological findings of eosinophilic granulomas as well as small vessel vasculitis.

Figure 2. Dermal small vessel vasculitis in CSS. Histopathologic findings of infiltrated plaque on chest showing dermal eosinophilic vasculitis and focal granuloma. Hematoxylin-eosin stain, magnification X200.



Induction of remission was achieved with combined pulse IV methylprednisolone 500 mg daily for 3 days and IV Rituximab 375 mg/m^2 weekly for 4 doses. Cyclophosphamide was not used due to type 1 hypersensitivity reaction of urticaria eruption. There was significant improvement in clinical signs, eosinophilia and radiological features in our patient following treatment. Remission was achieved for 6 months, with tapering oral corticosteroid and azathioprine (2 mg/kg/day) as maintenance therapy. Her disease relapsed with hip joint

synovitis confirmed by MRI, multiple areas of hypermetabolic disease involving mediastinal nodes, subcutaneous, bones and joints on PET/CT scan, and raised inflammatory markers. Azathioprine was switched to mycophenolate mofetil (2000 g/day), with a subsequent second cycle of IV Methylprednisolone and Rituximab 15 months after the first cycle. Her symptoms improved significantly whilst maintaining on mycophenolate mofetil, with plans for follow-up scans. Unfortunately, she succumbed to COVID-19 with category 5 severity, complicated with organizing pneumonia and pulmonary embolism 10 weeks after the second cycle of IV Rituximab.

Discussion

EGPA is a rare granulomatous necrotizing vasculitis with a very low incidence of 0.5 to 6.8 new cases per million patients every year.[1,4] It affects both men and women equally and the average age at diagnosis is 48 years.[4] The exact cause of EGPA is unknown.[1] Clinical diagnosis of EGPA is based on the American College of Rheumatology (ACR) Criteria which requires any 4 or more of the following clinical criteria to be present: asthma, eosinophilia > 10%, pulmonary infiltrates, paranasal sinus abnormality, neuropathy, or extravascular eosinophils.[4] Our patient fulfilled the ACR Criteria for EGPA, presenting with peripheral eosinophilia, asthma, paranasal sinus abnormalities and biopsy containing a blood vessel with extravascular eosinophils.[6]

The sequence of pathophysiological events in EGPA includes 3 stages.[4] Firstly, the pre-vasculitic phase can be characterized by asthma and other allergies, along with blood and tissue eosinophila.[4,7] Next, infiltration of eosinophils into tissues occurs in organs such as the lungs, gastrointestinal tract, or heart.[4,7] The last stage is when vasculitis occurs, which can be necrotizing or non-necrotizing, and EGPA is diagnosed.[4] However, this sequence of events may vary in different patients, and multiple manifestations may appear at the same time.[7] The most frequently observed clinical manifestations of EGPA are asthma, allergic rhinitis, peripheral nervous system involvement, gastrointestinal symptoms, cardiac involvement, and renal disease.[7-9] Anti-neutrophil cytoplasmic antibodies (ANCA) have been reported in 6–77% of EGPA patients.[6] In our patient, ANCA was not detected.

Up to 81% of EGPA patients experience cutaneous manifestations, and approximately 14% of cases present such manifestations as a sign of the disease.[7] Palpable purpura of the extremities is the most common cutaneous manifestation, affecting up to 50% of EGPA patients, followed by urticarial lesions and less commonly, livedo reticularis, papules, cutaneous infarctions, Raynaud's phenomenon, vesicles, and pustules.[7,9] The major histopathological features of EGPA include vasculitis, eosinophilic infiltration, and extravascular granuloma.[7]

Our patient was initially treated for smear-negative tuberculous lymphadenitis based on clinical findings of persistent fever, constitutional symptoms and lymphadenopathy. However, there was no clinical improvement upon completion of anti-tuberculosis treatment for a year. Upon suspicion of EGPA, the dermatologist and rheumatologist were consulted, and we proceeded with a skin and lymph node biopsy, culture and PCR, which suggested the diagnosis of EGPA and excluded tuberculosis.

Prior to the use of alkylating agents, survival with this disease was quite poor, current treatment regimens have reversed this poor prognosis, but treatments are still associated with toxicity. Most EGPA patients respond well to immunosuppressive therapy and can achieve long-term remission.[4,9] Generally, corticosteroids act as the first-line therapy for EGPA patients to achieve remission and improve survival.[4] Corticosteroids can either be used alone or in combination with one or more immunosuppressive drugs such as cyclophosphamide or methotrexate, especially in cases where recurrences are more frequent or associated with a severe form of necrotizing

vasculitis in other organs.[4,7] Therapy typically consists of two stages of treatment: remission induction and maintenance of remission.[10]

According to the 2021 American College of Rheumatology/Vasculitis Foundation Guideline for the management of ANCA-associated vasculitis, the recommended treatment for remission induction in patients with active, severe EGPA is pulse glucocorticoids or high-dose oral glucocorticoids with either rituximab or cyclophosphamide.[11] For maintenance, methotrexate, azathioprine, or mycophenolate mofetil or leflunomide is recommended after remission induction.[11]

Our patient had active severe EGPA, she achieved initial clinical remission of 6 months after the first cycle of pulse glucocorticoid steroid and Rituximab, and was maintained with azathioprine. Subsequently, her disease relapsed and required another cycle of pulse glucocorticoid steroid and Rituximab and switching of azathioprine to mycophenolate mofetil, in which she showed improved clinical symptoms. Unfortunately, our patient succumbed to severe COVID-19 infection 10 weeks after the second cycle of Rituximab. Growing evidence has suggested that treatment with anti-CD20 therapy such as Rituximab, increases the risk of developing severe outcomes from COVID-19 (risk ratio: 1.7–5.5).[12] Several studies have demonstrated that humoral immune responses after COVID-19 vaccination are poor in patients receiving anti-CD20 therapy, even after two doses of the vaccine.[12]. Physicians should be aware of such risks and discuss possible alternative treatments with patients who are receiving or would initiate treatment with Rituximab over the remainder of the COVID-19 pandemic.

Conclusion

In summary, we report a case of a patient who was initially treated for tuberculous lymphadenitis and eventually diagnosed with EGPA. In order to establish a diagnosis of EGPA, clinicians must have a high index of suspicion in patients with background of bronchial asthma, rhinosinusitis, persistent eosinophilia and organs involvement that is histologically consistent with an eosinophilic granulomatous reaction. It is essential to diagnose this rare disease early so that effective treatment can be initiated in time to improve the prognosis of EGPA patients. Therapies like Rituximab and other immunosuppressants can be effective in controlling the disease activity. However, the course of the disease and response to therapy is unpredictable. Increased risk of severe COVID-19 infection while on Rituximab may be detrimental, and thus, poses great therapeutic dilemma and challenges to physicians, especially in this era of the COVID-19 pandemic.

Conflict of Interest Declaration

The authors declare that there is no conflict of interest in this work.

Acknowledgement

We would like to thank the Director General of Health Malaysia for his permission to publish this article.

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