

APLAR GRAND ROUND CASE

Catastrophic subarachnoid hemorrhage in eosinophilic granulomatosis with polyangiitis without asthma

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Abstract

Eosinophilic granulomatosis with polyangiitis (EGPA) is characterized by eosinophilic vasculitis. Patients rarely present without asthma. Cases developing subarachnoid hemorrhage from central nervous system vasculitis are rarely reported. We report a 48-year-old woman with rapidly evolving and progressive multi-system eosinophilic vasculitis in the absence of asthma. Tissue eosinophilia was apparent in a breast lump biopsy. Prior otitis media and prominent lymphoid tissue in the postnasal spaces hinted at otolaryngological disease. She had rapid disease progression with mononeuritis multiplex and eventually succumbed to complications of intracranial hemorrhage secondary to central nervous system vasculitis. This case demonstrates the diagnostic dilemma and treatment considerations in EGPA without asthma. It also raises the question if a reliable biomarker can aid diagnosis in atypical presentations of disease.

Key words: breast mass, eosinophilic granulomatosis with polyangiitis, subarachnoid hemorrhage.

INTRODUCTION

Asthma is a cardinal feature of eosinophilic granulomatosis with polyangiitis (EGPA). Few cases of EGPA presenting with intracranial hemorrhage secondary to vasculitis have been described. We report on a patient with rapidly progressing EGPA affecting multiple organ systems who developed spontaneous subarachnoid hemorrhage (SAH) despite aggressive treatment.

CASE REPORT

A previously healthy 48-year-old Malay woman presented with a fortnight's history of leg cramps, myalgia, fever and 6 kg weight loss. She had recurrent otitis media without asthma or allergic rhinitis. One year ago, magnetic resonance imaging (MRI) of the posterior

nasal space for non-resolving otitis media with effusion, revealed left otomastoiditis and a small enhancing focus in the left fossa of Rosenmüller. Clinical examination was unremarkable. Significant peripheral blood eosinophilia of $1553/\text{mm}^3$ was noted. Symptoms and eosinophilia persisted despite empirical treatment with albendazole and ivermectin for possible parasitic infection.

Antinuclear antibody titer was 1 : 320 and anti-myeloperoxidase was 31 U/mL (positive ≥ 20 U/mL). Urine microscopy was unremarkable with no proteinuria. Creatine kinase was elevated at 2326 U/L suggesting myositis. Due to evolving paraesthesia in the right leg, nerve conduction study was performed, which was normal. Electromyography showed no denervation and normal recruitment patterns. Pulmonary function tests failed to demonstrate bronchodilator reversibility of subclinical asthma. Computed tomography (CT) thorax showed no occult pulmonary infiltrates. Mammogram and ultrasound revealed an area of altered echotexture in the left breast measuring $2.3 \times 1.1 \times 0.4$ cm. Core biopsy yielded changes compatible with fibroadenoma,

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with a large number of eosinophils in the mammary stroma (Fig. 1). There was no vasculitis or granulomatous inflammation. Investigations to rule out underlying malignancy were undertaken. Repeat MRI of neck and posterior nasal space showed stable mucosal/sub-mucosal changes in the left fossa of Rosenmuller. Bone marrow aspirate and trephine was negative for lymphocytic or myeloproliferative forms of hypereosinophilic syndrome (HES). There was no clonality on flow cytometric analysis of T cells and eosinophils. In addition, peripheral blood analysis for *FIP1L1/PDGFR*A mutation was negative. In the interim, she developed worsening numbness over the right ulnar distribution. Repeat nerve conduction study revealed decreased sensory nerve action potential amplitude in the right superficial peroneal nerve but she refused nerve biopsy.

A 3-day course of pulse intravenous (i.v.) methylprednisolone 500 mg daily was administered, followed by prednisolone 50 mg daily. The patient was discharged when fever resolved and eosinophil counts dropped from 7920/mm³ to zero. The need for cyclophosphamide therapy was discussed in the outpatient setting, but was declined. Twenty days later, she was re-admitted for new numbness over the left ulnar nerve distribution and recrudescence of eosinophilia to 1220/mm³ on prednisolone 40 mg daily. Left sural nerve biopsy showed moderate reduction in myelinated and

unmyelinated nerve fibers but no tissue eosinophilia, vasculitis or granulomatous inflammation.

Steroid dose was increased (i.v. methylprednisolone 1 g for 2 days, followed by oral prednisolone 80 mg daily). Epigastric pain and fever recurred. Treatment was changed to i.v. hydrocortisone 100 mg 6-hourly. Intravenous cyclophosphamide was held off due to concerns for infection. Multiple aerobic and anaerobic blood cultures and urine culture yielded nothing significant. As there was low clinical suspicion for tuberculosis and opportunistic infections, these were not screened for. CT abdomen and pelvis, to elucidate the cause of epigastric pain did not reveal gastric or bowel wall thickening, mesenteric changes or abscess to suggest intra-abdominal infection or gastrointestinal involvement from EGPA. Intravenous cyclophosphamide 800 mg (0.6 g/m²) was then administered.

Two days later, the patient developed neck stiffness, vomiting and drowsiness with neurological findings of right-sided hemiparesis, right gaze deviation and nuchal rigidity. Urgent CT brain showed extra-axial hematomas posterior to both cerebellar hemispheres and subarachnoid hemorrhage (SAH) involving infratentorial cerebrospinal spaces, extending into the intra-ventricular space (Fig. 2). Emergent posterior fossa decompressive craniectomy was performed with insertion of an external ventricular drain (EVD) at right Keen's point.

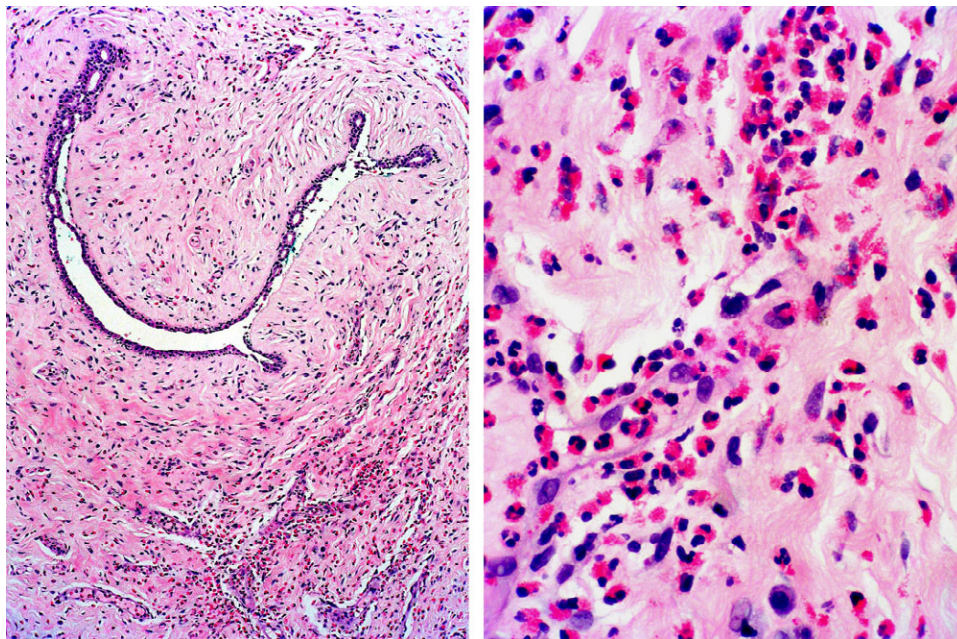


Figure 1 Fibroepithelial lesion with large number of eosinophils in the mammary stroma. Hemotoxylin and eosin stained, under 100× (left) and 400× (right) magnification.

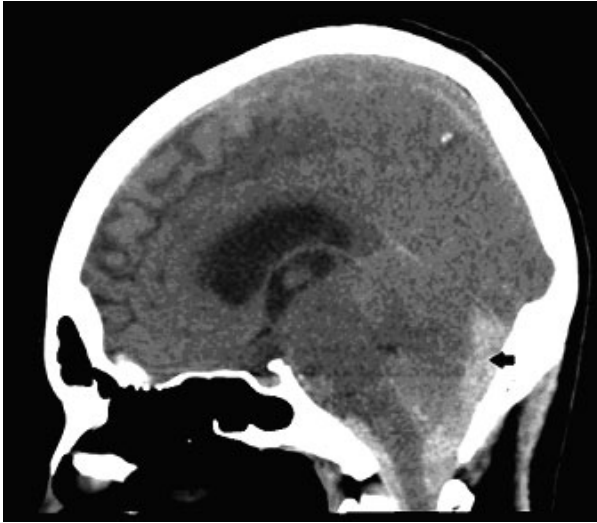


Figure 2 Extensive acute subarachnoid hemorrhage seen in the infra-tentorial cerebrospinal fluid spaces and basal cisterns.

Intra-operatively, blood clots were identified posterior to the origin of the intradural right vertebral artery with no aneurysm. Invasive angiography, on the first post-operative day (POD 1) showed no aneurysm. The right vertebral artery at the level of C2 transverse foramen had a corrugated appearance possibly consistent with vasculitis versus post-operative vasospasm (Fig. 3). She remained on i.v. hydrocortisone 100 mg every 8 h till POD 3. Neurological status improved with Glasgow Coma Scale (GCS) recovery to E4M6 on mechanical ventilation, moving limbs to commands, recognizing relatives and extubation. Upon conversion to oral prednisolone 80 mg daily, fever recurred leading to resumption of i.v. hydrocortisone for refractory vasculitis. Complete blood count did not reveal eosinophilia. In view of neurological recovery, the EVD was removed on POD7. Two hours later, precipitous decline in conscious level prompted urgent CT brain which showed hemorrhage along the tract of the previous EVD, increased intraventricular blood and acute hydrocephalus. Coagulation profile and platelet counts were normal. Bilateral EVDs were inserted at both Kocher's points. Post-operative CT the next day showed interval reduction in ventricular dilation. Following which, recurrent episodes of EVD tube clotting necessitated multiple drain changes but minimal GCS improvement. She succumbed to complications of recurrent intracranial bleeding and infective ventriculitis on day 67 of hospitalization.

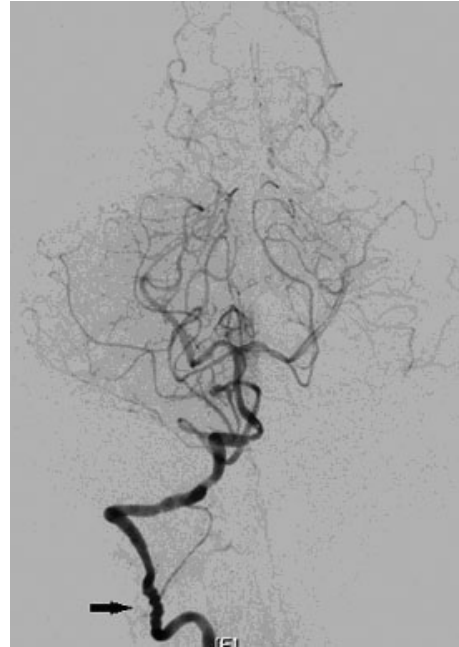


Figure 3 Intracranial angiography demonstrating the corrugated appearance of the right vertebral artery at the level of C2 transverse foramen related to vasculitis.

DISCUSSION

Our patient's rapidly evolving and progressive multi-system eosinophilic syndrome posed diagnostic and therapeutic challenges. Four of the six 1990 American College of Rheumatology (ACR) criteria, asthma, eosinophilia $> 10\%$, neuropathy (mono, or poly), non-fixed pulmonary infiltrates, paranasal sinus abnormality and extravascular eosinophilia, are required for the classification of Churg–Strauss syndrome (former nomenclature for EGPA). This yields a sensitivity of 85% and specificity of 99.7%.¹ The respiratory system is the most commonly involved organ in EGPA.

Asthma is a cardinal clinical feature, present in almost all EGPA patients, usually preceding the vasculitic phase by several years. However, what is unknown is the negative predictive value of absence of asthma history. Diagnosis was delayed due to the absence of asthma, rampant disease course and lack of histological evidence of vasculitis. The positive anti-myeloperoxidase (MPO) of low titer was deemed non-specific for EGPA. She was initially presumed to have idiopathic HES with peripheral neuropathy. HES is defined as blood eosinophilia $\geq 1500/\text{mm}^3$ for longer than 6 months (or death before 6 months associated with signs and symptoms of hypereosinophilic disease), lack

of evidence for parasitic, allergic, or other known causes of eosinophilia, and presumptive signs of organ involvement, such as heart failure, gastrointestinal dysfunction, central nervous system (CNS) abnormalities, fever or weight loss.² Appropriate initial treatment with high-dose systemic glucocorticoid led to drastic normalization of peripheral eosinophilia. In spite of this, the outcome from tissue eosinophilic processes was devastating. In retrospect, undulating fever was a harbinger of systemic vasculitis. Because the diagnosis could not be affirmed, the therapeutic dilemma was timing of cyclophosphamide for induction of remission of EGPA versus vigilance for end-organ dysfunction in idiopathic HES. Recognizing that isolated tissue eosinophilia is the most common and possibly only finding in EGPA,³ cyclophosphamide therapy, although offered early, was declined until further neurological involvement ensued.

Mononeuritis multiplex is the second most common manifestation of EGPA (up to 76%).⁴ Peripheral neuropathies, evident on electrophysiological studies, commonly affect peroneal, median, tibial and ulnar nerves. Nerve conduction study may be insensitive in detecting early neuropathy, as in our patient, with mononeuritis multiplex. Sural nerve biopsy, although showing findings consistent with mononeuritis multiplex, failed to demonstrate vasculitis or eosinophilia, likely due to corticosteroid treatment or sampling error. CNS involvement is uncommon; cerebral hemorrhages or ischemic strokes are rare. SAH in EGPA are associated with high mortality and morbidity. Literature review highlights anecdotal reports of spontaneous SAH in association with EGPA.^{5–7} The proposed mechanism of SAH and unfortunate sequelae of bleeding along the EVD track is intracranial vasculitis associated with EGPA. No clinical parameters could have predicted the presence of cerebral vasculitis; moreover, screening angiogram is not routine practice. Nonetheless, appropriate therapy for CNS vasculitis was instituted before the catastrophic SAH.

This case questions the attribution of prognosis to the baseline Five Factor Score (FFS). The 1996 FFS includes the following parameters associated with higher risk of death: proteinuria > 1 g/day, renal insufficiency, cardiomyopathy, severe gastrointestinal manifestations and CNS involvement.⁸ Our case scores 1 for CNS involvement, corresponding with a 5-year mortality rate of 26%. Revision of the FFS in 2009 resulted in removal of CNS involvement, due to its rarity, affecting statistical significance. The new FFS is scored based on age 65 years and above, renal insufficiency, gastrointestinal

signs, cardiac insufficiency and otolaryngological (ENT) manifestations. All factors were accorded 1 point except for ENT manifestations. Lack of ENT manifestations scores 1 point as their presence correlates with better prognosis. Using the 2009 FFS, our patient scores 0, suggesting mild disease and good prognosis. Therefore, cyclophosphamide would not have been given.⁹ Atypical and rapidly evolving disease course justified individualized treatment using best clinical judgment.

Eotaxin-3 (CCL26), an eotactic chemokine, was found to be significantly higher in EGPA patients compared with other vasculitides, parasitic diseases and HES.¹⁰ High levels, regardless of antineutrophil cytoplasmic antibodies positivity or negativity, reflected active disease, while low levels were measured in quiescent EGPA.¹¹ Thus eotaxin-3 levels may potentially be a biomarker for EGPA, and a possible target for pharmacotherapy. Although it remains a research tool, it will add to the diagnostic armamentarium and warrants validation in clinical practice. Early diagnosis of EGPA may facilitate early treatment, thus preventing the development of irreversible organ damage.

CONCLUSION

Diagnosis of EGPA may be delayed when the hallmark of asthma is absent. In this scenario, a reliable biomarker may aid diagnosis; further studies into chemokines such as eotaxin-3 will shed light. Following high-dose systemic glucocorticoid treatment, aggressive and prompt immunosuppression with cyclophosphamide is warranted in the setting of rapidly progressive organ involvement when EGPA is suspected.

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