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CASE BASED REVIEW

Eosinophilic granulomatosis with polyangiitis presenting with myositis: case based review

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Abstract

Eosinophilic granulomatosis with polyangitis (EGPA) is a systemic necrotizing small-vessel vasculitis that presents heterogeneously as a multi-organ disease. EGPA evolves through three phases: (1) prodromic phase with asthma, atopy and sinusitis, (2) eosinophilic phase characterized by peripheral eosinophilia and eosinophilic infiltration without necrosis, and (3) vasculitic phase involving organ damage. EGPA often presents with asthma, mononeuritis multiplex, lung infiltrates, sinusitis and constitutional symptoms. Although myalgias are common, EGPA rarely presents with true weakness with elevated creatinine kinase (CK). We describe a rare case of a patient presenting with eosinophilic myositis, who subsequently developed fulminant EGPA. The patient's diagnosis was supported by an initial clinical presentation of weakness and elevated CK, followed by fleeting pulmonary infiltrates and mononeuritis multiplex, peripheral eosinophilia, and strongly positive myeloperoxidase anti-cytoplasmic antibody (MPO-ANCA). Muscle biopsy revealed eosinophilic myositis. The patient responded well to high-dose glucocorticoids and cyclophosphamide with improved symptoms and biochemical markers. Based on our literature review, there are only seven similar cases reported of EGPA presenting with myositis and confirmatory muscle biopsies. There is significant heterogeneity in their clinical findings, histopathology and treatments that were used. Our case report and literature review highlights the importance of recognizing myositis as an initial presenting symptom of EGPA, providing an opportunity for early diagnosis and treatment to reduce risk of further disease progression and morbidity.

Keywords Eosinophilic granulomatosis with polyangiitis (EGPA) · ANCA vasculitis · MPO vasculitis · Myositis · Eosinophilic myositis

Introduction

Eosinophilic granulomatosis with polyangiitis (EGPA) is a systemic necrotizing vasculitis that affects small- to medium-sized vessels. Both vessel inflammation and eosinophilic infiltration are thought to contribute to organ damage, resulting in heterogeneous clinical presentations. The respective roles of hypereosinophilia and vasculitis are not well understood [1].

EGPA has been described as evolving through three disease phases. The first is a prodromic phase characterized by asthma, atopic disease, and rhinosinusitis. Next is an eosinophilic phase characterized by peripheral eosinophilia and subclinical eosinophilic tissue infiltration without necrosis. The final phase is a vasculitic phase with clinical manifestations due to small-vessel vasculitis, which is where patients are usually diagnosed [1, 2]. However, not all patients go through these phases in a linear trajectory. Clinical manifestations in EGPA can be divided into two major subsets,

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vasculitic and eosinophilic manifestations. Antineutrophilic cytoplasmic antibody (ANCA) positivity appears to be associated with glomerulonephritis, upper respiratory tract involvement, alveolar hemorrhage, purpura, and peripheral neuropathy. The absence of ANCA is associated with lung infiltrates, myocardial involvement, and gastrointestinal involvement [3–6]. The cause of this dichotomy is unclear but may relate to different pathophysiological mechanisms [7, 8].

In a large systematic retrospective study, the most common EGPA manifestations at time of diagnosis were asthma (91.1%), weight loss (49.3%), mononeuritis multiplex (46%), sinusitis or polyposis (41.8%), skin lesions (39.7%), and lung infiltrates (38.6%) [4].

Myalgias are often a common symptom of EGPA, seen predominantly in the prodromal phase, and have been observed in 37–57% of cases [8]. However, it is rarely the main presenting symptom and typically not associated with weakness [3]. Although rare, there are reports of EGPA presenting with myositis. Creatine kinase (CK) levels have not been routinely reported in EGPA case series previously. Muscle biopsies from EGPA patients with muscle involvement are rarely reported and mostly reveal vasculitic changes [8].

We describe a case of a patient presenting with eosinophilic myositis, who subsequently developed fulminant clinical EGPA manifestations. A literature review of similar cases was completed and summarized.

Case presentation

An 82-year-old Caucasian female presented to the rheumatology clinic complaining of progressive pain and weakness over her shoulders and thighs, progressive dysphagia, and weight loss of six pounds over 1 month. Her history was negative for rhinorrhea, asthma, polyposis, chronic nasal obstruction, hemoptysis, rashes, or neurological symptoms such as paresthesias or peripheral neuropathy. She had a longstanding history of stable bronchiectasis with mycobacterium avium complex (MAC) colonization monitored by a respirologist.

Examination revealed normal vital signs and she was afebrile. Her cardiac and respiratory examinations were unremarkable. Strength testing using the Medical Research Council (MRC) scale [9] showed 3/5 weakness with bilateral hip flexion, 4 + /5 bilateral knee flexion, 4 + /5 bilateral deltoids, and 4 + /5 bilateral biceps. Strength testing in all other muscle groups, including neck flexors, was otherwise 5/5. Sensation, tone and reflexes were normal. There were no skin rashes, nail changes or nailfold abnormalities. She was admitted to hospital for further investigation.

Laboratory values revealed leukocytosis, 18.4×10^9/L ($N = 4.0–11.0 \times 10^9$/L); marked eosinophilia, 8.8×10^9/L ($N = 0.00–0.70 \times 10^9$/L); hyperCKemia, 2627 U/L ($N < 170$ U/L); increased C-reactive protein, 65 mg/L ($N = 0–5$ mg/L); slightly increased rheumatoid factor, 44 IU/mL ($N < 20$); and increased alanine transaminase, 81 U/L (normal < 31 U/L). Antinuclear antigen (ANA) was negative and complement C3 and C4 were normal. Anti-cytoplasmic antibody was positive on immunofluoresence for P-ANCA with ELISA showing strongly positive anti-myeloperoxidase antibody (MPO-ANCA) at > 200. Serum protein electrophoresis showed a non-specific reactive pattern. Infectious workup including blood, stool and urine cultures, and testing for human immunodeficiency virus, hepatitis-B virus, hepatitis-C virus, Epstein–Barr virus, and cytomegalovirus, and parasites were negative. A purified protein derivative (PPD) skin test was also non-reactive for latent tuberculosis.

Chest X-ray at presentation was normal, but interestingly a CT chest done 1 week prior to presentation due to dyspnea showed fleeting opacities. Abdominal and pelvic ultrasound did not show abnormalities suggestive of malignancy. Electrocardiogram was normal and a transthoracic echocardiogram showed no cardiac abnormalities.

Magnetic resonance imaging (MRI) of the lower extremity muscles showed diffusely abnormal T2 signal intensity throughout the musculature of the pelvis, buttocks, hips and thighs with minimal muscle atrophy. Muscle biopsy of the right vastus lateralis revealed predominantly eosinophilic inflammatory cell infiltrate. There was minimal endomysial infiltrate surrounding the blood vessels, but not involving the vessel walls. No granulomas were seen. Electromicroscopy showed no tubular reticular inclusions. The overall findings were in keeping with eosinophilic myositis.

During the patient's hospital admission, she developed numbness over the left foot dorsum and sole associated with left ankle dorsiflexion weakness manifesting with a partial foot drop. Neurological assessment with electrophysiological testing was consistent with mononeuritis multiplex. Given the clinical presentation of peripheral eosinophilia, eosinophilic myositis, transient pulmonary opacities, mononeuritis multiplex, and strongly positive MPO-ANCA, the patient was diagnosed with EGPA. The broad differential diagnosis of eosinophilic myositis was considered, especially eosinophilic polymyositis due to the biopsy results and hypereosinophilic syndrome (HES) due to the systemic manifestations. However, eosinophilic polymyositis would not explain all her other clinical manifestations and strongly positive serology. The HES diagnostic criteria rely on ruling out other major causes for hypereosinophilia and organ damage. Since EGPA explains the clinical presentation and serology well, the hematologist did not pursue a bone marrow biopsy as HES cannot be technically diagnosed as there is a better explanation.

After ruling out infectious and malignant etiologies, she was initially pulsed with IV methylprednisolone 500 mg daily for 3 days due to new onset foot drop. She then received high-dose oral prednisone at 1 mg/kg daily. With steroids, there was notable improvement in her muscle strength, dyspnea and dysphagia. There was a dramatic decline in her CK and eosinophil count. Her neurological symptoms persisted despite high-dose corticosteroids. Treatment with intravenous cyclophosphamide was then initiated.

Within 2 weeks of treatment, laboratory testing showed white blood cell count 13.30×10^9/L; eosinophil count 0.010×10^9/L; creatine kinase (CK) 259 U/L; and alanine transaminase (ALT), 217 U/L. Within 6 weeks of therapy, the patient was symptom-free with normalization of muscle strength and resolution of partial left foot drop.

Search strategy

Data sources and searches

A comprehensive literature review was performed using electronic search platforms and databases including PubMed, Medline, EMBASE, and Scopus from inception to December 20, 2019 to look for cases of EGPA with myositis. The following keywords and MeSH headings were used alone or in combination; "eosinophilic granulomatosis with polyangitis", "Churg-Strauss syndrome", "myositis", "eosinophilia", and "eosinophilic myositis." Given the specificity of the topic, no additional restrictions were provided. Abstracts from relevant studies were reviewed and appropriate articles were retrieved. A manual search was also performed scrutinizing reference lists of the included studies to identify additional references. Figure 1 shows the flow diagram depicting the study selection process.

Study selection

Two authors (SK, GA) independently reviewed abstracts and retrieved any relevant articles for inclusion based on the following criteria: (1) cases of EGPA with myositis, elevated CK and muscle biopsy and (2) published in a peer-reviewed journal. Grey literature and any study lacking clinical, biochemical and pathology data for individual patients were excluded. Articles were included if both reviewers agreed on their relevance and any disagreements were resolved by consensus. The search was not restricted by language and one non-English study was translated in full for inclusion.

Data extraction and quality assessment

Two authors (SK, GA) independently extracted the following data from the studies using a standard form: title, author, publication year, patient demographics, clinical presentation and diagnosis, laboratory findings, imaging results, electromyography results, muscle pathology findings, treatments, and follow-up.

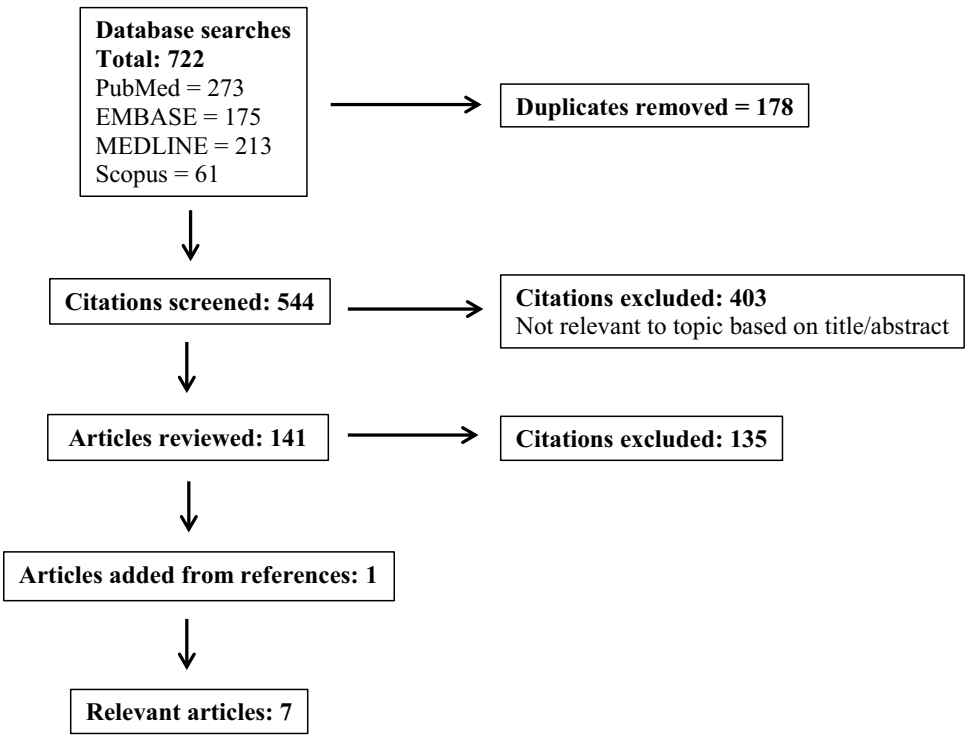

Fig. 1 Flow diagram illustrating selection process of articles

Literature review and discussion

EGPA often presents a diagnostic challenge due to its heterogenous clinical manifestations. The most common manifestations are constitutional symptoms, asthma, polyposis, lung infiltrates, mononeuritis multiplex, and peripheral eosinophilia [4, 10]. Although myalgia is commonly seen in EGPA, it is rarely the main presenting symptom and does not typically present with weakness and elevated CK, which would suggest myositis [3]. There is paucity of reported data on muscle biopsies in patients presenting with EGPA and myositis.

We identified only seven existing reports of EGPA presenting with myositis and confirmatory muscle biopsies (Table 1). Two of those patients had new onset asthma [11, 12], which is commonly noted in EGPA. Three patients had longstanding asthma or rhinosinusitis [13–15]. Our patient did not have a history of asthma or rhinosinusitis, but she did have a preceding CT chest with fleeting infiltrates that in retrospect might have represented eosinophilic pneumonia. This, and accompanying mild dyspnea, was resolved with steroid therapy. Only one reported patient with EGPA and myositis had neurological symptoms at presentation (paresthesias) [13]. Our patient developed partial foot drop with sensory disturbances and nerve conduction studies confirmed mononeuritis multiplex. Out of the seven previously reported cases, only one had negative ANCA [8], while four were strongly positive for MPO-ANCA [11, 13–15]. Five cases had predominantly vasculitic changes and necrosis on muscle biopsy [8, 11–14], while two cases reported histologic findings consistent with an inflammatory myopathy but did not specify whether it was eosinophilic [15, 16].

EGPA presenting with myositis is rare and there are no established guidelines or recommendations for treatment in this subset of patients [17]. Generally, high-dose glucocorticoids in combination with an immunosuppressant, especially cyclophosphamide, is most commonly recommended to induce remission with major organ involvement. Methotrexate, azathioprine or mycophenolate mofetil is an option for patients with non-organ threatening disease and for maintenance of remission, although there is no clear consensus on an appropriate immunosuppressive for non-severe disease [18, 19]. As a result, there remains significant variability in reported treatments across the identified cases based on overall clinical presentation. All of the patients were treated with high-dose corticosteroids. Two patients received steroids alone. Three cases used a second immunosuppressive agent including either methotrexate, azathioprine, or mycophenolate mofetil. Intravenous immunoglobulin (IVIG) was used in two cases in addition to glucocorticoids and other immunosuppressives (methotrexate and mycophenolate) with good response. IVIG has been shown to have clinical benefit in ANCA-associated vasculitis as adjunctive therapy with an acceptable safety profile, particularly in relapsing or refractory disease [20]. Our patient received high-dose steroid and intravenous cyclophosphamide due to development of new mononeuritis multiplex, while on high-dose oral prednisone. The overall prognosis was excellent in the reported cases, with treatment response within 4–6 weeks in all patients and remission reported at 6 months to 1 year. Our patient similarly had responded well, with no documented relapses during the course of treatment so far.

The pathophysiology underlying development of myositis in EGPA is not well understood. Overall, it has been suggested that a precipitating factor in a genetically predisposed host results in ongoing activation of eosinophils followed by release of cytotoxic granule proteins that causes local muscle injury. Cationic proteins, enzymes and cytokines, specifically IL-5, seem to be involved in the pathologic process. T-cell activation and expansion has also been described in eosinophilic myositis, but the role is not clear [21, 22]. Eosinophilic myositis is recognized as a specific entity within the spectrum of inflammatory myopathies [23, 24]. Characteristic findings include proximal muscle weakness and usually absence of cutaneous manifestations. CK levels are typically elevated and peripheral eosinophilia ($>0.5\times10^9$/L) is often found. Systemic organ involvement of the lung, gut, and heart is not uncommon [24, 25]. Most patients respond well to corticosteroids [24].

There is heterogeneity of the histopathological features in muscle tissue between idiopathic inflammatory myositidies (IIM), eosinophilic myositis, and small-vessel vasculitis [26]. The histopathological features in dermatomyositis include loss of capillaries, deposits of C5b–C9 on capillaries, and presence of endothelial microtubular inclusions but no frank vasculitis. There is associated perifascicular atrophy with MHC class 1 staining, necrotic myofibres and foci of perivascular lymphocytic infiltrates [27]. In comparison, eosinophilic myositis has hallmark features of myonecrosis and eosinophilic-predominant inflammatory infiltrate, mainly affecting the endomysium [27–29]. In systemic small-vessel vasculitis affecting muscle, an alteration of muscular perfusion and vascular/perivascular infiltrates may occur with endothelial damage due to vasculitis. Extravascular granulomas may be present in ANCA-associated vasculitis [29].

Eosinophilic myositis has a broad differential diagnosis. It is important to rule out infectious causes, especially parasites, prior to the administration of glucocorticoids and immunosuppression. Hypereosinophilic syndrome, drugs, muscular dystrophies, malignancy, and systemic vasculitides are other considerations [11, 30, 31]. Detailed

Table 1 EGPA cases presenting with myositis and confirmatory muscle biopsies

Patient (references)	Age/sex	Clinical features	Laboratory findings	MRI	EMG/NCS	Muscle pathology	Initial treatment and outcome
1 [11]	68/F	Fever, new onset asthma, myalgia, UE weakness, cutaneous hemorrhagic bullae	EC: 9160 mm^3 CK: 1076 ANCA: MPO positive (640)	–	Short duration, low amplitude, polyphasic potentials in UE/LE	Small-vessel vasculitis with neutrophilic infiltration. Marked interstitial eosinophilic infiltration. No muscle fiber necrosis, some regeneration	IV methylprednisolone 1 g/d × 3 days followed by prednisolone 50 mg daily Clinical and biochemical improvement within 1 week. Steroids tapered and remission sustained for over 1 year. No other immunosuppressives
2 [13]	81/M	Asthma, nasal polyps, fever, LE weakness, paresthesias in hands/feet	EC: 15.4×10^9/L CK: 538 ANCA: MPO positive (42.1 au/mL)	–	EMG: normal NCS: left median motor and sensory amplitude smaller than right	Predominantly eosinophilic infiltration, macrophages and lymphocytes. Necrosis of vessel wall with fibrinoid exudate. No granulomas. Consistent with vasculitis	Prednisolone, MMF and IVIG Remission achieved (unclear timeline)
3 [12]	58/F	New onset asthma, exercise-induced muscle weakness and pain	–	–	NCS: axonal neuropathy	Necrotizing vasculitis of medium-sized arteries and an extravascular granuloma, both associated with eosinophils. Focal interstitial eosinophilic infiltration with eosinophils. No features of inflammatory myositis	Not provided
4 [8]	74/M	Diffuse weakness, jaw claudication, fevers	EC: 5.07×10^9/L CK: 3708 ANCA: negative	Mild muscular atrophy with diffuse hypersignal in STIR sequence	EMG: increased insertional activity, fibrillation with positive sharp waves, no fasciculations (myopathic recruitment pattern)	Eosinophil-rich necrotizing vasculitis. No granulomas or endomysial eosinophilic infiltrates	Prednisone 80 mg and azathioprine 1 mg/kg daily Tapered prednisone and remission achieved within 6 weeks
5 [16]	–	10 out of 19 patients in single center retrospective study had myalgias. One had biopsy. No other clinical information provided	–	–	–	One patient had biopsy consistent with "myositis" but no further information provided	–

Table 1 (continued)

Patient (references)	Age/sex	Clinical features	Laboratory findings	MRI	EMG/NCS	Muscle pathology	Initial treatment and outcome
6 [14]	71/M	Asthma, nasal polyps, LE pain and weakness, edema	EC: 11.390×10^9/L CK: 2245 ANCA: MPO positive (132)	Normal MRI or LE	EMG: increased insertional activity, low spontaneous activity, membrane hyperexcitability. Motor unit analysis consistent with myopathy NCS: normal	Necrotizing vasculitis of small and medium vessels with large eosinophilic component. Also endomysial and perivascular inflammation consistent with myositis	Prednisone 1 mg/kg/day with taper Clinical and biochemical normalization in 2 weeks
7 [15]	57/M	Chronic bronchitis, rhinosinusitis, diffuse myalgias, paresthesias in arms	EC: 7440 mm3 CK: 4454 ANCA: MPO positive (57.6 U/mL)	–	EMG: signs of muscle 'disfigurement' NCS: inexcitable sensory and motor responses of bilateral median nerve and posterior tibial nerve. No conduction blocks	Muscle atrophy, lymphocytic infiltration and granulocytes of small caliber vessels	Cortisone (1.5 mg/kg/day with taper, IVIG×5 days and methotrexate 15 mg/week Remission maintained until 6 months follow-up
8 [presented case]	82/F	Diffuse weakness, fatigability, dysphagia, weight loss, dyspnea, mononeuritis multiplex	EC: 8.8×10^9/L CK: 2627 ANCA: MPO positive (> 200)	Diffusely abnormal T2 signal intensity throughout LE. Minimal atrophy	NCS: subacute left sciatic neuropathy and mild left median neuropathy	Eosinophilic and histiocytic infiltrates in adipose tissue septi between muscle fascicles. Minimal endomysial infiltrate around blood vessels. Atrophic muscle fibers. No necrotic or regenerating fibers. No granulomas or inclusions	IV methylprednisolone 1 g/d×3 days followed by prednisone 1 mg/kg/day then taper. IV cyclophosphamide monthly for mononeuritis Clinical and biochemical remission achieved at 6 weeks. Continues to be in remission

ANCA antineutrophilic cytoplasmic antibodies, *CK* creatinine kinase, *EC* eosinophilic count, *EMG* electromyography, *LE* lower extremity, *MPO* myeloperoxidase antibodies, *NCS* nerve conduction studies, *STIR* short TI inversion recovery MRI, *UE* upper extremity

clinical history, physical examination as well as serological and histopathological assessment are key to securing the diagnosis. The diagnosis of EGPA has to be considered with eosinophilic myositis and is usually clear in the setting of late-onset asthma, peripheral eosinophilia, ANCA positivity and symptoms related to polyangiitis. However, as seen in this case, EGPA manifestations may mimic other diseases before the onset of vasculitis and it is important to have a high degree of suspicion for the diagnosis. There is growing recognition that the 1990 ACR criteria for vasculitis may not capture a significant proportion of cases, with declining sensitivity over time, due to a wider recognition of disease manifestations and novel diagnostic tests [32]. More recently, studies with EGPA patients such as the MIRRA trial (assessing efficacy and safety of mepolizumab in EGPA) have had very loose inclusion criteria, with only 10% of patients testing positive for ANCA and few vasculitic manifestations [33]. It is likely that future criteria will include a broader spectrum of disease to allow for more sensitivity in diagnosis.

In summary, it is important to consider EGPA in a patient presenting with myositis and peripheral eosinophilia. Although myositis is rarely the first presenting symptom in EGPA, patients can go on to develop other severe EGPA features such as mononeuritis multiplex. Identifying the condition early may therefore provide an opportunity for early diagnosis and treatment to reduce risk of disease progression and related morbidity.

Author contributions SK: writing of manuscript including editing and revisions, literature review at all stages of its production, and clinical management of patient. GA: writing of manuscript including editing and revisions, literature review at all stages of its production, and clinical management of patient. DJ: manuscript editing and revision at all stages of production, final approval of manuscript, and clinical management of patient. OV: manuscript editing and revision at all stages of production, final approval of manuscript, and clinical management of patient. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Compliance with ethical standards

Conflicts of interest The authors declare that they have no competing interests.

Ethical approval All the procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Written informed consent was obtained from this patient prior to submission of this article for consideration as a case-based review.

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