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Mononeuritis Multiplex at the Crossroads of Etiology: Diagnostic Dilemma Between Vitamin B6 Deficiency and Eosinophilic Granulomatosis with Polyangiitis

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Abstract

Background: Eosinophilic granulomatosis with polyangiitis (EGPA), formerly known as Churg–Strauss syndrome, is a rare antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis characterized by asthma, peripheral eosinophilia, and multisystem necrotizing vasculitis. Neurological involvement, particularly mononeuritis multiplex, occurs in up to 60–70% of cases and represents an organ-threatening manifestation. However, peripheral neuropathy in young patients with prior tuberculosis exposure poses a significant diagnostic dilemma, especially when pyridoxine deficiency secondary to isoniazid therapy is also plausible. ***Case Presentation:*** We report the case of a 22-year-old male who presented with progressive burning pain in the palms and soles, distal weakness, and functional impairment over three months. He had a prior history of pulmonary tuberculosis treated without documented pyridoxine supplementation. Examination revealed stocking-glove sensory loss and diminished reflexes. Laboratory evaluation demonstrated marked leukocytosis with severe eosinophilia (24.6%; absolute eosinophil count 7,132/µL), thrombocytosis, elevated serum IgE, and positive perinuclear ANCA (MPO-ANCA). Bone marrow examination confirmed eosinophilic hyperplasia, and bronchoalveolar lavage showed 60% eosinophilia. High-resolution CT of the chest revealed fibrocavitatory changes with centrilobular nodules and ground-glass opacities. Nerve conduction studies were consistent with sensory-motor mononeuritis multiplex. Active tuberculosis was excluded by negative CBNAAT testing. The patient fulfilled ≥4 of the 2022 ACR/EULAR classification criteria for EGPA. Although isoniazid-induced pyridoxine deficiency neuropathy was considered, the presence of multisystem involvement, marked eosinophilia, and MPO-ANCA positivity supported EGPA as the primary diagnosis. He was treated with intravenous methylprednisolone followed by oral prednisolone; due to persistent neuropathy, rituximab was initiated with subsequent clinical remission. This case highlights the importance of comprehensive evaluation in patients with mononeuritis multiplex and underscores the need to distinguish systemic vasculitis from nutritional neuropathy to ensure timely immunosuppressive therapy and prevent irreversible organ damage.

Keywords: Eosinophilic granulomatosis with polyangiitis, Mononeuritis multiplex, MPO-ANCA, Pyridoxine deficiency, Isoniazid-induced neuropathy, Vasculitic neuropathy

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INTRODUCTION

Eosinophilic granulomatosis with polyangiitis (EGPA), previously known as Churg-Strauss syndrome, is a rare systemic vasculitis characterized by the triad of asthma, eosinophilia, and necrotizing vasculitis[1]. It represents a subset of ANCA-associated vasculitis (AAV) distinguished by its strong association with asthma, chronic rhinosinusitis with nasal polyps, and peripheral blood eosinophilia[1]. The 2022 ACR/EULAR classification criteria for EGPA include eosinophilia ≥1500 cells/µL, obstructive airway disease, extravascular eosinophil-predominant inflammation, involvement of 1-4 defined organs, mononeuritis multiplex or motor neuropathy, and/or ANCA positivity[1].

The disease typically manifests in three distinct phases: the prodromal phase characterized by atopic disease such as allergic rhinitis and asthma; the eosinophilic phase marked by tissue and blood eosinophilia affecting lungs and gastrointestinal tract; and the vasculitic phase involving necrotizing vasculitis of multiple organs including skin, peripheral nerves, kidneys, heart, and central nervous system[1][2]. Neurologic involvement occurs in approximately 60-70% of EGPA patients and manifests most commonly

as mononeuritis multiplex due to necrotizing vasculitis of the vasa nervorum[2]. This complication results from ischemic injury to peripheral nerves, commonly affecting the common peroneal, ulnar, radial, and internal popliteal nerves[1].

Vitamin B6 (pyridoxine) deficiency-induced neuropathy represents another important differential diagnosis in patients with sensory-motor neuropathy. Pyridoxine deficiency is particularly common in patients treated with isoniazid or hydralazine[3]. In tuberculosis patients, isoniazid inhibits pyridoxal phosphokinase, leading to depletion of bioactive pyridoxine and subsequently causing peripheral neuropathy in 2-17% of treated patients depending on dosage[3].

The resulting polyneuropathy is nonspecific, presenting as generalized axonal sensorimotor neuropathy[3].

This case report describes a diagnostic challenge in a young patient presenting with mononeuritis multiplex where both EGPA and isoniazid-induced pyridoxine deficiency were plausible etiologies, requiring comprehensive investigation to establish definitive diagnosis and appropriate management.

CASE PRESENTATION

Demographics and Clinical History

A 22-year-old male patient presented to our hospital with a chief complaint of severe, progressive burning pain bilaterally in the soles and palms over 2-3 months. The pain was accompanied by progressive weakness in both hands with difficulty in performing fine motor tasks including writing, and difficulty in rising from a sitting position. While sensorimotor in nature, the sensory component was more prominent than motor symptoms.

The patient reported a prolonged history of constitutional symptoms including repeated episodes of breathlessness and fever for 8 months, chronic cough for 6 months, and intermittent hemoptysis for the past 6 months. He had a significant past medical history of pulmonary tuberculosis diagnosed 2 years prior, for which he had completed anti- tuberculous therapy. Notably, the patient denied receiving pyridoxine supplementation during his previous tuberculosis treatment. There was no family history of vasculitic or autoimmune diseases.

Differential Diagnosis

Based on the clinical presentation of progressive sensorimotor peripheral neuropathy in a patient with pulmonary symptoms and prior tuberculosis exposure, the initial differential diagnoses considered were:

1. Isoniazid-induced pyridoxine deficiency neuropathy (given inadequate B6 supplementation during prior TB therapy)
2. Eosinophilic granulomatosis with polyangiitis (EGPA) with neurological and pulmonary involvement

Physical Examination Findings

Detailed neurological examination revealed diminished deep tendon reflexes bilaterally with negative Babinski reflex. There was no evidence of cranial nerve involvement or bladder/bowel dysfunction. The patient demonstrated sensory deficits in a stocking-glove distribution consistent with peripheral neuropathy. Motor examination showed mild weakness in hand grip and hip flexors. General examination revealed mild pallor but no rash or other dermatological manifestations of vasculitis.

Diagnostic Evaluation

Hematological and Serological Investigations

Complete blood count revealed:

- Hemoglobin: 9.7 gm/dL (indicating mild anemia)
- Total Leucocyte Count: 29,140/µL (markedly elevated)
- Differential count: Neutrophils 64.9%, Lymphocytes 6.8%, Monocytes 3.4%, **Eosinophils 24.6%** (abnormally elevated)
- Basophils: 0.3%
- Platelet Count: 852,000/µL (marked thrombocytosis)
-

The presence of severe eosinophilia (>20%) was a key finding suggestive of EGPA. Additional serological investigations revealed:

- Serum total IgE antibody: 827 IU/mL (elevated, normal <100 IU/mL)
- ANA Blot: Negative for 18 antigens
- Cytoplasmic ANCA-PR3 (c-ANCA): Negative (<2.00 RU/mL)

Perinuclear ANCA-Myeloperoxidase (p-ANCA-MPO): Positive, 78.5 RU/mL

Erythrocyte Sedimentation Rate (ESR): 33 mm/hr (elevated)

The positive p-ANCA-MPO was crucial in establishing EGPA diagnosis. ANCA positivity in EGPA is present in approximately 35-40% of patients, with MPO-ANCA being more common than PR3-ANCA[2].

Microbiological Investigations

Sputum samples were collected on three consecutive mornings and processed for Cartridge-Based Nucleic Acid Amplification Test (CBNAAT), which came back negative, effectively ruling out active tuberculosis infection.

Bone Marrow Examination

Bone marrow biopsy was performed given the marked eosinophilia and thrombocytosis. The findings were consistent with hypercellular marrow with eosinophilia of 40%, confirming the tissue-level eosinophilic infiltration characteristic of EGPA's eosinophilic phase.

Bronchoscopic Evaluation

Fiber-optic bronchoscopy was performed, revealing extensive ulceration of the tracheo- bronchial tree, indicative of vasculitic involvement of the respiratory tract.Bronchoalveolar lavage (BAL) fluid analysis showed 60% eosinophilia, providing direct evidence of pulmonary eosinophilic infiltration and supporting diagnosis of EGPA.

Figure 1

Figure 2

Radiological Imaging

High-resolution computed tomography (HRCT) of the chest revealed:

- Fibrocavitatory lesions in the right upper lobe with multiple tiny calcific foci Partial collapse of apical and posterior segments of the right upper lobe Multiple calcified nodules and granulomas in bilateral upper lobes
- Multiple centrilobular nodules with ground-glass opacities arranged in linear branching pattern in bilateral lung parenchyma, consistent with bronchiolitis pattern

These findings were consistent with vasculitic lung involvement in EGPA, though some features also overlapped with sequelae of prior tuberculosis.

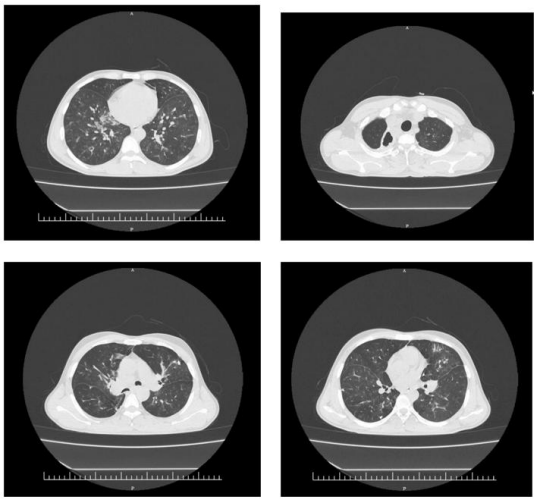

Figure 3

Electrophysiological Studies

Nerve conduction velocity (NCV) testing revealed findings diagnostic of sensory-motor mononeuritis multiplex with asymmetric involvement of multiple peripheral nerves. The pattern of nerve involvement was consistent with vasculitic neuropathy secondary to necrotizing vasculitis of the vasa nervorum, the hallmark of EGPA-related neuropathy.

Diagnostic Synthesis

The combination of clinical, laboratory, and investigative findings established the diagnosis of EGPA:

Table 1: ACR/EULAR 2022 Criteria for EGPA—Patient Fulfills ≥4 Criteria

Diagnostic Feature	Finding in this Patient	EGPA Criterion
Eosinophilia (≥1500/μL)	24.6% (7,132 cells/μL)	✓
Asthma/Obstructive disease	Chronic cough, breathlessness	✓
Extravascular eosinophilic involvement	Bone marrow and BAL eosinophilia	✓
Mononeuritis multiplex	NCV confirmed mononeuritis multiplex	✓
ANCA positivity (MPO or PR3)	p-ANCA-MPO positive	✓

While isoniazid-induced pyridoxine deficiency neuropathy remained a plausible differential diagnosis, it was considered less likely as the primary diagnosis because: (1) the patient had no documented history of isoniazid therapy in excess of 6 mg/kg/day, (2) the multi-organ involvement with severe eosinophilia and vasculitic features were not typical of uncomplicated B6 deficiency neuropathy, and (3) positive p-ANCA-MPO and elevated IgE more strongly supported EGPA pathophysiology.

TREATMENT AND CLINICAL COURSE

Induction Therapy

Following diagnosis, the patient was initiated on induction therapy for EGPA:

Corticosteroid pulse therapy: Intravenous methylprednisolone 500 mg once daily for 5 consecutive days was administered, followed by oral prednisolone in a tapering schedule beginning at 50-75 mg/day with gradual reduction over 4-5 months targeting maintenance dose of 5 mg/day.

Adjunctive therapy: Given the dual consideration of potential pyridoxine deficiency contribution to neuropathy, oral pyridoxine supplementation was initiated concurrently with corticosteroid therapy.

Clinical Response and Relapse

Following the initial intravenous methylprednisolone pulse therapy, the patient's respiratory symptoms including breathlessness, fever, and hemoptysis showed marked improvement. Peripheral eosinophilia normalized. However, the neuropathic pain persisted despite maximal glucocorticoid therapy, indicating steroid-refractory neurological involvement.

Biologic Therapy

Given the inadequate response of mononeuritis multiplex to corticosteroid monotherapy, intravenous rituximab 500 mg was administered once every 4 weeks. Rituximab, an anti- CD20 monoclonal antibody targeting B lymphocytes, is recommended as a first-line agent for ANCA-associated vasculitis and EGPA[4]. Following initiation of rituximab therapy, the patient entered a remission phase with gradual improvement in neuropathic symptoms and stabilization of neurological status.

DISCUSSION

This case illustrates the complex diagnostic challenge of mononeuritis multiplex presenting in the context of multiple potential etiologies. EGPA represents a rare but important cause of mononeuritis multiplex with significant morbidity and mortality if delayed or missed in diagnosis[2].

Neurological Manifestations in EGPA

Neurologic involvement in EGPA is highly prevalent, affecting 60-80% of patients[1][2]. Mononeuritis multiplex, occurring as a consequence of necrotizing vasculitis of the vasa nervorum, is the most common neurological manifestation[2]. Ischemic injury to peripheral nerves results in asymmetric sensorimotor deficits. The most frequently affected nerves are the common peroneal (leading to foot drop) and ulnar nerves, though radial and internal popliteal nerves may also be involved[1]. Some patients experience cranial nerve involvement, and 10-39% of neurological manifestations may involve central nervous system vasculitis with risk of cerebral infarction or hemorrhage,

which represents an organ-threatening complication[2][5].
The presence of ANCA positivity in EGPA correlates with a higher incidence of vasculitic manifestations including mononeuritis multiplex, myocarditis, and glomerulonephritis[2].

This patient's MPO-ANCA positivity predicted the severe vasculitic phenotype with prominent neurological and pulmonary involvement.

Differential Diagnosis: Pyridoxine Deficiency Neuropathy
Isoniazid-induced peripheral neuropathy due to pyridoxine deficiency remains an important differential diagnosis in tuberculosis patients, particularly those inadequately supplemented with vitamin B6[3]. Isoniazid inhibits the enzyme pyridoxal phosphokinase, preventing conversion of pyridoxine to its biologically active form (pyridoxal phosphate), which is essential for neurotransmitter synthesis and maintenance of myelin integrity[3].

The incidence of neuropathy increases substantially with higher isoniazid doses: standard doses (3-5 mg/kg/day) cause neuropathy in approximately 2% of patients, while doses exceeding 6 mg/kg/day are associated with neuropathy in at least 17% of patients[3]. Risk factors for development of neuropathy include elderly age, malnutrition, and "slow acetylator" phenotype of N-Acetyltransferase-2 enzyme[3]. The resultant polyneuropathy is typically nonspecific, presenting as generalized axonal sensorimotor neuropathy or, rarely, severe sensory neuropathy with dysesthesias and sensory ataxia[3].
While this patient had prior tuberculosis exposure and lacked documented pyridoxine supplementation during treatment, several factors made uncomplicated pyridoxine deficiency an unlikely sole etiology: (1) the presentation 2 years after tuberculosis treatment completion suggested acute process rather than chronic nutritional deficiency, (2) multi-organ involvement with constitutional symptoms, profound eosinophilia, and hemoptysis were not typical of B6 neuropathy alone, and (3) positive p-ANCA-MPO and elevated IgE provided serological evidence of vasculitic pathophysiology. However, pyridoxine supplementation was appropriately initiated to address potential contribution to neuropathy.

Diagnostic Challenge and Importance of Comprehensive Investigation
As noted in this case, the diagnostic approach to mononeuritis multiplex requires consideration of multiple potential etiologies. Both EGPA and isoniazid-induced neuropathy can present with sensorimotor peripheral neuropathy and would produce abnormalities on nerve conduction studies. The critical distinguishing features in this case were:

1. Hematological abnormalities: The marked eosinophilia (24.6%) with elevated IgE and thrombocytosis were highly suggestive of EGPA rather than nutritional neuropathy
2. ANCA serology: Positive p-ANCA-MPO strongly supported EGPA diagnosis
3. Multi-organ involvement: Simultaneous pulmonary, hematologic, and neurologic manifestations indicated systemic vasculitis
4. Bronchoscopic findings: Direct visualization of tracheo-bronchial ulceration and elevated BAL eosinophilia provided tissue-level confirmation
5. Bone marrow examination: Eosinophilic infiltration confirmed systemic eosinophilic disorder

Without comprehensive investigation including serology and tissue examination, EGPA might have been missed, resulting in inadequate immunosuppressive therapy and progressive organ damage.

Treatment Considerations and Evolving Recommendations
The 2024 EULAR guidelines recommend specific treatment approaches for EGPA based on disease severity[4]. For non-severe, new-onset EGPA without organ involvement, corticosteroids alone may suffice. For patients with organ-threatening manifestations (including neurological involvement as in this case), combination therapy with glucocorticoids and a biologic agent is indicated[4].

Rituximab has emerged as a preferred agent for ANCA-associated vasculitis induction therapy, showing superiority over cyclophosphamide in relapsing disease[4]. Additionally, anti-IL-5 targeted therapies (mepolizumab, reslizumab, benralizumab) have been recently approved and recommended for EGPA, particularly for reducing relapse rates[1][4]. These agents represent significant advances in EGPA management, offering targeted immunosuppression with potentially better long-term tolerability compared to conventional agents.

In this patient, the use of rituximab for steroid-refractory neurological disease was appropriate and yielded clinical remission. Consideration of anti-IL-5 therapy may be warranted during maintenance phase to reduce relapse risk.

CONCLUSION

This case illustrates a diagnostic and therapeutic challenge in a young patient presenting with mononeuritis multiplex in the setting of multiple concurrent risk factors for peripheral neuropathy. While both EGPA and isoniazid-induced pyridoxine deficiency neuropathy can present similarly with sensorimotor nerve dysfunction, comprehensive diagnostic evaluation including serology, tissue examination, and multi-organ assessment was essential to establish definitive diagnosis.

The clinical presentation of mononeuritis multiplex should prompt consideration of EGPA, particularly when accompanied by constitutional symptoms, eosinophilia, respiratory involvement, or ANCA positivity. Early recognition and prompt institution of appropriate immunosuppressive therapy are crucial to prevent irreversible neurological damage and organ involvement. This case also underscores the importance of adequate pyridoxine prophylaxis in all patients receiving isoniazid for tuberculosis treatment, as this simple preventive measure may avert significant neurotoxicity.

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