Published Ahead of Print on December 12, 2022 as 10.1212/WNL.0000000000201697

Neurology®
The most widely read and highly cited peer-reviewed neurology journal
The Official Journal of the American Academy of Neurology

AMERICAN ACADEMY OF NEUROLOGY®

Neurology Publish Ahead of Print
DOI: 10.1212/WNL.0000000000201697

Clinical Reasoning: A 60-Year-Old Man With Asymmetric Weakness and Persistent Fever

Author(s):

Yang Zheng, MD, PhD[1]; Jing-Jing Xiang, MD[2]; Xiao-Fang Zhang, MD, PhD[3]; Shuo Zhang, MS[4]; Mei-Ping Ding, MD[5]; Jiao Huang, MD[3]

Corresponding Author:

Jiao Huang, huangjiao2001@163.com

Affiliation Information for All Authors: 1. Department of Neurology, The First Affiliated Hospital of Zhejiang Chinese Medical University, Hangzhou, China; 2. Department of Pathology, Affiliated Hangzhou First People's Hospital, Zhejiang University School of Medicine, Hangzhou, China; 3. Department of Rheumatology, Affiliated Hangzhou First People's Hospital, Zhejiang University School of Medicine, Hangzhou, China; 4. Department of Pharmacy, The First Affiliated Hospital of Zhejiang Chinese Medical University, Hangzhou, China; 5. Department of Neurology, Second Affiliated Hospital of Zhejiang University School of Medicine, Hangzhou, China

Equal Author Contribution:

Contributions:

Yang Zheng: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Analysis or interpretation of data

Jing-Jing Xiang: Major role in the acquisition of data; Analysis or interpretation of data

Xiao-Fang Zhang: Major role in the acquisition of data

Shuo Zhang: Analysis or interpretation of data

Mei-Ping Ding: Drafting/revision of the manuscript for content, including medical writing for content

Jiao Huang: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Study concept or design

Figure Count:

1

Table Count:

1

Search Terms:

[283] All clinical neurophysiology, [285] EMG, [131] All Immunology, [134] Vasculitis, Peripheral neuropathy

Acknowledgment:

We gratefully acknowledge the cooperation and patience of the patient, who made this work possible.

Study Funding:

This study was supported by the National Natural Science Foundation of China (Grant number

82201607; 82071443), and the Medical Science and Technology Project of Zhejiang Province (Grant number 2019KY482; 2020KY686)

Disclosures:

The authors report no relevant disclosures.

Preprint DOI:

Received Date:

2022-07-25

Accepted Date:

2022-11-01

Handling Editor Statement:

Submitted and externally peer reviewed. The handling editor was Ariel Lyons-Warren, MD, PhD.

Abstract

Peripheral neuropathies, especially those with atypical features, remain a diagnostic challenge. In this case, a 60-year-old patient presented with acute-onset weakness starting in the right hand then sequentially involving the left leg, left hand, and right leg over 5 days. The asymmetric weakness was accompanied by persistent fever and elevated inflammatory markers. Subsequent development of rashes combined with careful review of the history led us to the final diagnosis and targeted treatment. This case highlights clinical pattern recognition with the help of electrophysiological studies in peripheral neuropathies, which

provide shortcuts to narrow the differential diagnosis. We also illustrate important pitfalls from history taking to ancillary testing in diagnosing rare but treatable cause of peripheral neuropathy (eFigure 1).

SECTION 1

A 60-year-old right-handed man presented in a wheelchair with a 5-day history of progressive weakness. The weakness started in the right hand. Days later, he was unable to lift his right arm above the shoulder. He sequentially developed weakness in the left leg, the left hand, and lastly the right leg. Weakness progressed so rapidly that the patient was unable to walk independently on presentation. He also reported 2 days of distal numbness but denied any pain. The patient denied recent illness or travel, toxin exposure, insect bites, tobacco/alcohol addiction, or family history with similar presentations. No recent weight loss was noted. Medical history was remarkable for well-controlled diabetes mellitus. Surgical history included resection of pulmonary nodules found on routine examination 4 years ago.

On examination, the patient was febrile (38°C) with age appropriate mental status. Asymmetric weakness was noted (right/left; Medical Research Council grades): abductor pollicis brevis (0/2), first dorsal interosseous (0/2), abductor digiti minimi (0/2), finger extensors (1/2), biceps (3/4), deltoids (3/4), knee flexors (3/3), knee extensors (3/2), tibialis anterior (4/3), gastrocnemius (5/5). The sensory examination revealed loss of pinprick in distal extremities. Deep tendon reflexes were absent in all four limbs. He had bilateral flexor plantar responses. Cranial nerves were intact.

Blood tests at admission were remarkable for leukocytosis of 23.7 x 10^9/L (neutrophils: 20.22 x 10^9/L, 85.5%; lymphocytes: 0.55 x 10^9/L, 2.3%; eosinophils: 1.92 x 10^9/L, 8.1%). He had

increased erythrocyte sedimentation rate (40 mm/h), and C-reactive protein (98.5mg/L). Other serum tests including liver/kidney functions, electrolytes, hemoglobin A1c level, thyroid function, and vitamin B12 were normal.

Questions for consideration:

1. How would you localize the patient's symptoms?

2. What is the differential diagnosis?

SECTION 2

The progressive weakness and sensory loss in all extremities, absent reflexes, and lack of pyramidal signs are consistent with peripheral nervous system (PNS) involvement. Notably, our patient had atypical neuropathy features, including asymmetric distribution, an acute onset, and systemic symptoms like fever and raised inflammatory markers that warranted extensive diagnostic testing. In particular, the asymmetric pattern of distribution raises concerns for the following localizations: mononeuritis multiplex, plexopathy or polyradiculopathy.[1] The sequential involvement of multiple noncontiguous nerves, rather than in a dermatomal/myotomal or plexus pattern, suggests mononeuritis multiplex in this patient.

Mononeuritis multiplex is a unique entity mainly attributed to immune-mediated causes, including vasculitis, Lewis-Sumner syndrome, multifocal motor neuropathy (MMN), sarcoidosis and paraneoplastic neuropathy. Other causes include infectious (hepatitis B/C, human immunodeficiency virus, leprosy etc.), neoplastic (leukemia, lymphoma etc.), or genetic diseases (hereditary neuropathy with liability to pressure palsies [HNPP], amyloidosis). In this patient, the acute onset, persistent fever and raised inflammatory markers were more suggestive of systemic immune-mediated or infectious causes, rather than neoplastic or genetic diseases.

To further examine the PNS pathology, nerve conduction studies (NCS) and needle electromyogram (EMG) were performed soon after admission (Table 1).

Questions for consideration:

1. What is the interpretation of the NCS/EMG results in Table 1?

2. What further investigations should be considered?

SECTION 3

On NCS, the most striking finding was a significant reduction in compound muscle action potential (CMAP) amplitude and an absent response in multiple nerves, suggesting a severe axonal loss. The prolonged latency and slowed conduction velocity were present but relatively mild, indicating a secondary demyelinating pathology. EMG revealed abnormal spontaneous activities and reduced recruitment of the first dorsal interosseous, further confirming the primary axonal damage. Taken together, the NCS/EMG studies were suggestive of axonal neuropathy in a multiple mononeuropathy distribution, which narrows the differential to certain immune-mediated causes including axonal GBS, sarcoidosis, vasculitis, or infectious neuropathies due to rare pathogens.

Ancillary studies including serum antinuclear antibodies and antineutrophil cytoplasmic antibodies (ANCA), rheumatoid factors and antiganglioside antibodies were unremarkable. Cerebral spinal fluid analysis was normal. To further exclude infectious causes, we performed metagenomic next-generation sequencing and blood cultures, which were negative. Chest computed tomography scan revealed only post-operative fibrosis of the right lung. Other tests including echocardiogram, renal and abdominal ultrasound were nonrevealing.

Given that immune-mediated neuropathies were the most likely diagnosis based on available data, empiric treatment with intravenous immunoglobulin (IVIG, 2g/kg) was administered over 5 days. However, the weakness progressed further and fever persisted, rendering the

patient practically bedbound. Repeated NCS showed a remarkable reduction of amplitudes in multiple nerves. Adding to the neurologic deterioration, the patient developed pruritic rashes as waxing and waning papules on the extremities, abdomen and back (Figure 1A). Based on these rashes, we investigated histopathology by performing muscle biopsy of the right biceps, which revealed transmural inflammation of the vessel wall with granulomatous inflammation (Figure 1B). The findings of palpable rash with leukocytoclastic vasculitis in the context of mononeuritis multiplex highly suggested systemic vasculitis as the underlying cause of the asymmetric neuropathy.

Q：1. What is your diagnosis given the new-onset rash and ancillary testing results?

2. How would you treat the patient?

SECTION 4

The most common type of systemic vasculitis associated with peripheral neuropathy includes ANCA-associated vasculitis (AAV), polyarteritis nodosa, cryoglobulinemia or vasculitis secondary to rheumatoid arthritis and other connective tissue diseases.[2] For further classification, we recalled the history of the pulmonary nodule 4 years ago (Figure 1C). Review of medical records unveiled prominent eosinophilia (white blood cells: $18.2x10^9$/L, eosinophils: $2.57x10^9$/L, 14.1%) in the middle of that hospitalization. Pathology of the pulmonary nodule showed noncaseous granulomatous inflammation (Figure 1D). According to the 2022 AAV classification criteria (eTable 1), the presence of mononeuritis multiplex and episodes of peripheral eosinophilia qualified the patient for the diagnosis of eosinophilic granulomatosis with polyangiitis (EGPA).[3]

Corticosteroid was initiated (80mg/d, i.v.), resulting in a remarkable improvement in weakness and fever, as well as a reduction of peripheral eosinophils (0.2×10^9/L, 1.4%). However, the weakness relapsed upon oral tapering to 15mg/d. We initiated rituximab (RTX) with two initial infusions of 500 mg given a fortnight apart for remission induction and subsequent infusions of 500 mg every 6 months for maintenance. At the latest follow-up one year after RTX treatment, the patient remained relapse-free. He was even able to ride a bicycle without assistance despite residual claw-hand and claw-toe deformities due to irreversible nerve damage.

DISCUSSION

EGPA, which manifests as nonspecific symptoms in the early phase, presents a diagnostic challenge. Previously known as Churg-Strauss syndrome, it is an ANCA-associated vasculitis (AAV) subtype histologically defined by eosinophil-rich, necrotizing granulomatous inflammation mainly affecting the small-sized arteries.[3] According to recently updated criteria,[3, 4] three core features, i.e. peripheral eosinophilia, obstructive airway disease and nasal polyps, constitute the hallmarks of EGPA diagnosis. Mononeuritis multiplex and eosinophilic inflammation on biopsy serve as important discriminant classifiers.[3] By contrast, cANCA/anti-PR3 positivity and hematuria are red flags indicative of an alternative diagnosis.[3] Neurological complications of EGPA are common, including PNS involvement in 53-78% of patients.[5] Our patient presented with an acute onset mononeuritis multiplex with concomitant systemic findings. Despite an extensive workup, the diagnosis was only unveiled after he developed diffuse rashes all over the body, leading to the biopsy that revealed small-vessel vasculitis. The diagnosis of EGPA was further confirmed with the history of pulmonary granuloma and repeated episodes of peripheral eosinophilia.

The three atypical characteristics of neuropathy, i.e., the onset, distribution and associated systemic features (ODS), have guided our investigation. Fulfillment of any of the ODS criteria, i.e. an acute or subacute onset, a non-length-dependent pattern of distribution, or systemic features, allows rapid diagnosis for immune-mediated neuropathies with a sensitivity of 96% and specificity of 85%.[6] NCS/EMG is especially valuable to establish the

diagnosis, which helps confirm the pattern of nerve/muscle involvement and determine the axonal/demyelinating nature of the neuropathy. Electrodiagnostic studies are also important in excluding vasculitis mimics which may also fulfill the ODS criteria, including hereditary neuropathy with liability to pressure palsies (slowing across sites of entrapment), multifocal motor neuropathy (motor nerve conduction block), and the Lewis-Sumner syndrome (motor and sensory nerve conduction block).[1]

Notably, several diagnostic pitfalls should be considered. Firstly, EGPA is the AAV subtype characterized by a low prevalence of ANCA positivity (only 40-60%).[3] A negative ANCA testing should not exclude the diagnosis of AAV. Secondly, by the time of evaluation, the confluence of sequential neuropathies may falsely lead to a clinical impression of generalized axonal polyneuropathies. The focal nature of disease onset, often affecting the territory of a single nerve, and an asymmetric pattern of disease progression may be evident only by history. Thirdly, EGPA typically develops in sequential phases, with the upper/lower airway involvement and peripheral eosinophilia preceding the ultimate systemic vasculitic phase.[7] Comprehensive review of the history is important to identify previous eosinophilia or respiratory involvement. Lastly, a tissue biopsy is helpful to confirm the diagnosis but not always necessary. A nerve biopsy can miss the vasculitis because of the patchy nature of the disease (sensitivity for definite vasculitis around 30-50%).[8]

Early and aggressive treatments are essential to prevent irreversible nerve damage for AAV including EGPA. Multidisciplinary management of systemic vasculitis is essential, especially when choosing between the various treatment options. First-line therapy includes high-dose systemic glucocorticoid, along with rituximab or cyclophosphamide.[9] A steroid-sparing agent, such as methotrexate, azathioprine, mycophenolate mofetil or rituximab, is often required for remission maintenance in AAV with PNS involvement.[9]

WNL-2022-201515_efig1 --http://links.lww.com/WNL/C541

WNL-2022-201515_etab1 -- http://links.lww.com/WNL/C542

REFERENCES

1. Callaghan BC, Price RS, Chen KS, Feldman EL. The Importance of Rare Subtypes in Diagnosis and Treatment of Peripheral Neuropathy: A Review. JAMA Neurol 2015;72:1510-1518.

2. Gwathmey KG, Burns TM, Collins MP, Dyck PJ. Vasculitic neuropathies. Lancet Neurol 2014;13:67-82.

3. Grayson PC, Ponte C, Suppiah R, et al. 2022 American College of Rheumatology/European Alliance of Associations for Rheumatology Classification Criteria for Eosinophilic Granulomatosis with Polyangiitis. Ann Rheum Dis 2022;81:309-314.

4. Koster MJ, Warrington KJ. ACR and EULAR bring AAV classification into the twenty-first century. Nat Rev Rheumatol 2022;18:309-310.

5. Wolf J, Bergner R, Mutallib S, Buggle F, Grau AJ. Neurologic complications of Churg-Strauss syndrome--a prospective monocentric study. Eur J Neurol 2010;17:582-588.

6. Karam C, Tramontozzi LA, 3rd. Rapid screening for inflammatory neuropathies by standardized clinical criteria. Neurol Clin Pract 2016;6:384-388.

7. Pagnoux C, Guillevin L. Churg-Strauss syndrome: evidence for disease subtypes? Curr Opin Rheumatol 2010;22:21-28.

8. Bennett DL, Groves M, Blake J, et al. The use of nerve and muscle biopsy in the diagnosis of vasculitis: a 5 year retrospective study. J Neurol Neurosurg Psychiatry 2008;79:1376-1381.

9. Chung SA, Langford CA, Maz M, et al. 2021 American College of Rheumatology/Vasculitis Foundation Guideline for the Management of Antineutrophil Cytoplasmic Antibody-Associated Vasculitis. Arthritis Care Res (Hoboken) 2021;73:1088-1105.

Table 1. Results of nerve conduction studies and needle electromyogram studies

CMAP	**Recording site**	**Distal latency, ms**	**Amplitude, mV**	**Conduction velocity, m/s**
R median	APB	**NR**	**NR**	
	wrist	**NR**	**NR**	**NR**
L median	APB	**NR**	**NR**	
	wrist	**NR**	**NR**	**NR**
R ulnar	ADM	3.40	**0.31**	
	wrist	8.24	**0.35**	**39.3**
L ulnar	ADM	2.95	**0.28**	
	wrist	6.99	**0.25**	**52.0**
R peroneal	EDB	4.66	**0.42**	
	ankle	10.9	**0.16**	44.9
L peroneal	EDB	3.59	**0.65**	
	ankle	9.85	**0.65**	43.1
R tibial	AHB	3.53	11.2	
	medial malleolus	11.9	7.9	37.0
L tibial	AHB	3.15	**2.5**	
	medial malleolus	11.3	3.9	39.3
SNAP	**Recording site**	**Peak latency, ms**	**Amplitude, mV**	**Conduction velocity, m/s**
R median	Digit II	**NR**	**NR**	**NR**

L median	Digit II	**NR**	**NR**	**NR**
R ulnar	Digit V	**NR**	**NR**	**NR**
L ulnar	Digit V	**NR**	**NR**	**NR**
R sural	lateral malleolus	1.93	6.1	41.5
L sural	lateral malleolus	1.78	5.5	56.2
R superficial peroneal	dorsum of foot	2.26	7.1	**39.8**
L superficial peroneal	dorsum of foot	1.70	11.0	55.9
EMG	**Insertional**	**Spontaneous activity**	**Motor unit morphology**	**Recruitment pattern**
L tibialis anterior	Normal	None	Normal	Normal
L first dorsal interosseous	Increased	**Fibs+/PSWs +**	**No units**	**No units**
F wave	**Recording site**	**Persistence, %**	**Minimal latency, ms**	**Chronodispersion, ms**
L posterior tibial	AHB	**NR**	**NR**	**NR**
R posterior tibial	AHB	**NR**	**NR**	**NR**

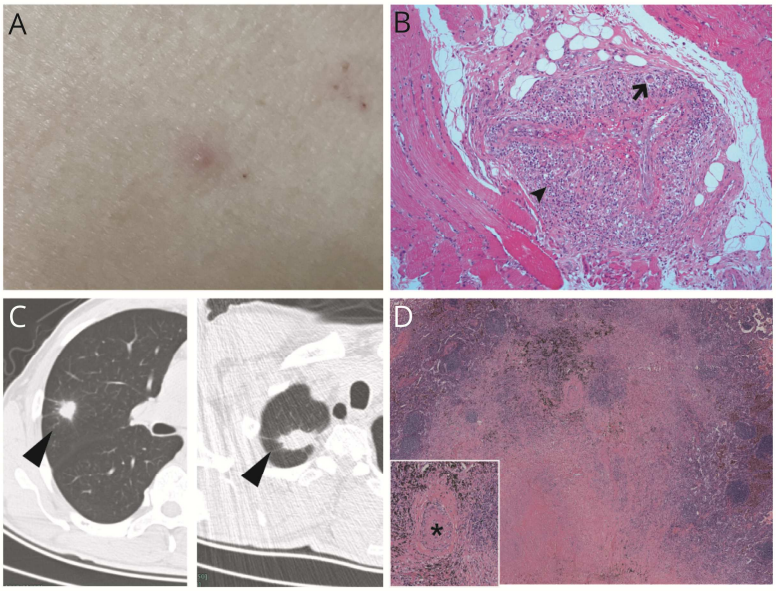
Nerve conduction studies revealed absent response in multiple motor and sensory nerves. A low amplitude CMAP was observed in bilateral ulnar, left tibial and peroneal motor nerves, along with mildly slowed conduction velocities of the right ulnar and bilateral tibial motor nerves. F-waves were absent in bilateral posterior tibial nerves. Needle electromyogram showed active denervation in the lower extremity from first dorsal interosseous muscle.

The abnormal results are labeled in bold.

Abbreviations: AHB, abductor hallucis brevis; APB, abductor pollicis brevis; ADM, abductor digiti minimi; CMAP, compound muscle action potential; SNAP, sensory nerve action potential; NR, no response

Figure Legends

Figure 1. The skin rash and pulmonary granulomas of the patient with eosinophilic granulomatosis with polyangiitis. (A) Papules on the trunk and bilateral extremities of the patient, which appear as pruritic, tiny and raised bumps (B) Leukocytoclastic vasculitis in the dermis showing multinucleated giant cells (arrow) with eosinophilic infiltration (arrowhead) (Hematoxylin & Eosin [H&E] stain, x100) (C) Chest computed tomography scan 4 years ago showed two pulmonary nodules (triangle) in the right upper and lower lobe respectively, both with spiculated and unclear margins. (D) Surgical biopsy of the right upper nodule demonstrated necrotizing noncaseous granulomatous inflammation (H&E stain, ×20) with small-vessel vasculitis (asterisk, H&E stain, ×100).



Clinical Reasoning: A 60-Year-Old Man With Asymmetric Weakness and Persistent Fever

Yang Zheng, Jing-Jing Xiang, Xiao-Fang Zhang, et al.

Neurology published online December 12, 2022
DOI 10.1212/WNL.0000000000201697