Systemic Vasculitis Presenting with Central and Peripheral Involvement

Dear Editor,

Polyarteritis nodosa (PAN) is a systemic necrotizing vasculitis affecting medium-sized vessels. Patients usually exhibit systemic symptoms, such as fever and weight loss. The most frequent clinical presentations include mononeuritis multiplex and peripheral neuropathy, renal manifestations like hypertension, cutaneous manifestations like nodules and livedo reticularis, and gastrointestinal manifestations like abdominal pain.[1] This article discusses an atypical presentation of PAN, along with some errors of omission, leading to a delayed diagnosis and untoward outcome.

Our patient, a chronic smoker, presented with subacute onset, progressive weakness of all four limbs, which began symmetrically in the proximal lower limbs and then involved the proximal upper limbs. Subsequently, over one month, distal upper limbs got involved, and he developed a left foot drop. He also developed difficulty in speaking and swallowing to both liquids and solids. There was no history of chewing difficulty, diurnal variation, fatigability, respiratory symptoms or jaw claudication. He had generalized muscle wasting. Cranial nerve examination revealed poor gag reflex and nasal speech. Tone was decreased and power in the upper limbs was medical research council (MRC) grade 3/5 with weak hand grip bilaterally; power in the lower limbs was MRC grade 2/5 at the hip bilaterally, and 3/5 at the knee and right ankle; he had left foot drop (MRC-2/5). Deep tendon reflexes were symmetrically brisk except absent left ankle reflex; plantar reflexes were mute. Rest of the examination was normal. A possibility of polyradiculoneuropathy was kept first; the other differentials were anterior horn cells disorders and inflammatory myopathy. We also considered muscle-specific tyrosine kinase antibody (MuSK Ab) related myasthenia gravis, cranio-cervical junction abnormality, and other mimics of motor neuron disease.

Nerve conduction studies (NCS) done at the time of presentation are shown in Tables 1 and 2. At admission, he tested positive for COVID-19 and received intravenous immunoglobulin at a dosage of 2 g/kg. Following this, there

Table 1: Motor nerve conduction studies at admission, day-15, and day-45 of illness

Nerve and site	At admission			Day 15 of illness			Day 45 of illness		
	Latency ms	Amplitude mV	Conduction velocity m/s	Latency ms	Amplitude mV	Conduction velocity m/s	Latency ms	Amplitude mV	Conduction velocity m/s
Median.R									
Wrist	**4.11**	6.8		3.8	6.3		3.8	5.4	
Elbow	**8.23**	5.1	51	8.65	6.1	51	8.18	3	50
Ulnar.R									
Wrist	**3.85**	7		3.18	6		3.18	**3.2**	
Below elbow	**7.6**	5.6	61	8.18	5.8	52	7.08	**2.9**	64
Median.L									
Wrist	**4.58**	6.1		4.17	6.6		3.59	**3.2**	
Elbow	**9.69**	4.7	**41**	8.85	6.4	51	7.92	**1.9**	51
Ulnar.L									
Wrist	**4.38**	6.1		2.86	7		3.07	**3.7**	
Below elbow	**8.91**	5.8	51	8.23	6.7	47	7.4	**3**	56
Peroneal.L									
Ankle	**8.23**	**0.8**		**NR**	**NR**	**NR**	**NR**	**NR**	**NR**
Fibula (head)	**18.13**	**0.3**	**34**	**NR**	**NR**	**NR**	**NR**	**NR**	**NR**
Tibial.L									
Ankle	**NR**	**NR**	**NR**	**5.52**	**1.1**		**NR**	**NR**	**NR**
Popliteal fossa	**NR**	**NR**	**NR**	**15.1**	**0.7**	41	**NR**	**NR**	**NR**
Peroneal.R									
Ankle	**NR**	**NR**	**NR**	**5.68**	**0.5**		**NR**	**NR**	**NR**
Fibula (head)	**NR**	**NR**	**NR**	**14.64**	**0.3**	**35**	**NR**	**NR**	**NR**
Tibial.R									
Ankle	**9**	6.5		**6.41**	**2.7**		**NR**	**NR**	**NR**
Popliteal fossa	**19.95**	5.4	**33**	**15.16**	**0.9**	45	**NR**	**NR**	**NR**

ms: milli second, mV: milli Volt, m/s: meter per second, NR: Non recordable

Table 2: Sensory nerve conduction studies at admission, day-15, and day-45 of illness

Nerve and site	At admission			Day 15 of illness			Day 45 of illness		
	Peak latency ms	Amplitude mV	Conduction velocity m/s	Peak latency ms	Amplitude mV	Conduction velocity m/s	Peak latency ms	Amplitude mV	Conduction velocity m/s
Median.R									
Digit II (index finger)	3.91	11.3	41	3.7	7.4	46	2.97	15.6	58
Ulnar.R									
Digit V (little finger)	3.39	11.8	50	3.59	16.5	43	2.81	12.1	56
Median.L									
Digit II (index finger)	4.11	15	42	3.54	13.5	51	2.81	7	63
Ulnar.L									
Digit V (little finger)	3.39	10	51	3.07	6.3	50	2.92	6.9	554
Sural.L									
Lower leg	**NR**	**NR**	**NR**	3.28	8.2	50	**NR**	**NR**	**NR**
Sural.R									
Lower leg	5.05	13.6	34	4.17	5.7	43	**NR**	**NR**	**NR**

ms: milli second, mV: milli Volt, m/s: meter per second, NR: Non recordable

was an improvement in the upper and lower limbs power to 4/5 and 3/5, respectively, but bulbar weakness and hyperreflexia persisted. Serum creatinine kinase was normal. Ice pack challenge, repetitive nerve stimulation test, anti-acetylcholine receptor (anti-AChR), and anti-MuSK antibody assay were negative. Electromyography showed no spontaneous activity and discrete recruitment of motor units.

Routine investigations showed transaminitis (three times upper limit of normal). Anti-nuclear antibody (ANA) was positive in a titer of 1:100 (homogenous); extractable nuclear antigen (ENA) profile, anti-neutrophil cytoplasmic antibodies (ANCA), anti-smooth muscle antibody (ASMA) and anti-liver-kidney microsomal antibody (anti LKM1), paraneoplastic profile and tumor markers were negative. Erythrocyte sedimentation rate was 40 mm in the first hour, and C-reactive protein was 273 mg/dl. Cerebrospinal fluid analysis showed 5 cells/mm^3 with normal glucose and protein levels of 20 mg/dl. Work up for infective etiology, which included bacterial, fungal, and tubercular stains, and cultures were negative, as was the malignant cytology. We started him on oral prednisolone in a dosage of 1 mg/kg and mycophenolate mofetil. Magnetic resonance imaging (MRI) of the spine was normal. MRI brain showed multiple infarcts and microhemorrhages [Figure 1]; MR angiography of head and neck vessels was normal. Positron emission tomography scan whole body did not show any evidence of metabolically active disease.

During hospital stay, he developed a new onset left wrist drop for which he received intravenous methylprednisolone. Repeat NCS on day-45 showed an axonal pattern [Tables 1 and 2] and we proceeded with a nerve-muscle biopsy [Figure 2]. He also developed a new onset hypertension during admission. Considering the possibility of systemic vasculitis, probably PAN, we planned cyclophosphamide induction therapy. However, in view of persistent transaminitis, it was withheld. Viral markers, anti-Hepatitis A and E antibodies, antibodies for autoimmune hepatitis, serum copper, ceruloplasmin, and IgG levels were normal. MRI Abdomen showed a pseudocyst in pancreas and old healed abscess in liver. The patient developed urosepsis during the hospital stay. Three days later, he developed sudden onset respiratory distress and shock, requiring mechanical ventilation. His electrocardiogram, chest roentgenogram, Troponin I were unrevealing; 2D-echo and venous Doppler of bilateral lower limbs were normal; but D-dimer was markedly elevated. We could not do a CT pulmonary angiography because of hemodynamic instability. The patient continued to deteriorate, went into refractory shock, and succumbed on the same day.

This gentleman presented with pure motor flaccid quadriparesis with bulbar weakness. Factors that made the clinical picture murkier were hyperreflexia and the NCS showing a demyelinating pattern. The penny finally dropped with the results of nerve and muscle biopsy. Brain imaging had showed multiple infarcts with microhemorrhages, both cortical and subcortical, which were initially attributed to small vessel disease. However, vascular imaging was normal. In hindsight, these findings coupled with transaminitis, new onset hypertension, neuropathy, and a high ANA titer should have been the first clue to suspect a systemic vasculitis.

PAN is a systemic necrotizing vasculitis, which affects medium-sized arteries.[1] Anti-neutrophil cytoplasmic antibodies are typically negative. Viral infections, particularly hepatitis B virus, may trigger PAN. Involvement of the central nervous system has been reported in 20%–40% of PAN cases, but mainly occurs at later stages. It is considered a poor prognostic indicator and manifests usually as cerebral infarction, hemorrhage, multifocal encephalopathy or transient

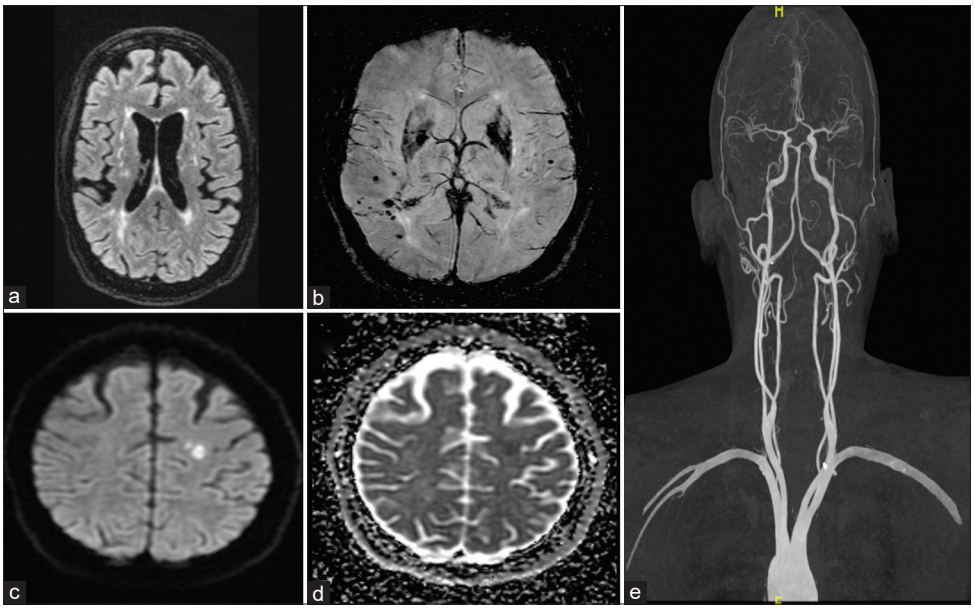

Figure 1: MRI brain axial FLAIR image (a) shows multiple focal and confluent white matter FLAIR hyperintensities in bilateral centrum semiovale, bilateral corona radiata, frontal and parietal white matter. Axial SWI image (b) shows multiple foci of blooming in both cortical and subcortical locations. DWI and corresponding ADC map (c, d) show focal area of diffusion restriction is seen in left centrum semiovale s/o acute lacunar infarct. (e) Contrast enhanced MR angiography showing normal head and neck and intracranial vasculature. FLAIR: Fluid attenuated inversion recovery, SWI: Susceptibility weighted imaging, DWI: Diffusion weighted imaging, ADC: Apparent Diffusion Coefficient

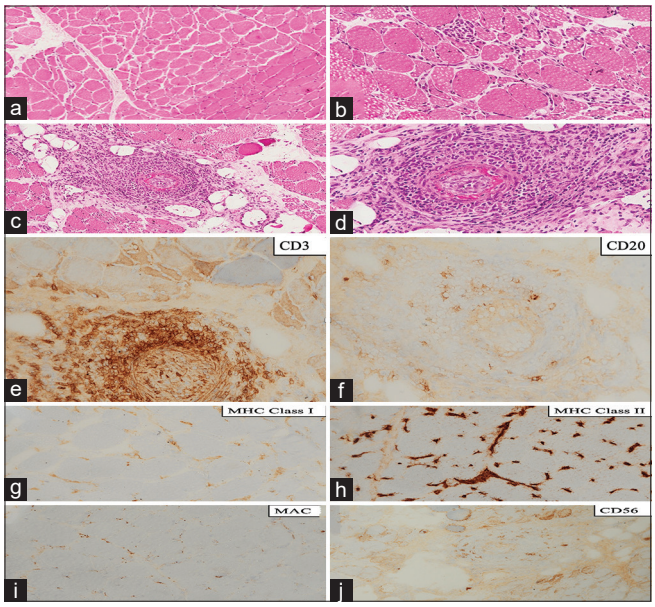

Figure 2: Microphotograph from snap frozen section stained with haematoxylin and eosin (a) shows maintained fascicular architecture with variation in fiber size, (b) shows degenerating myofibers with mild endomysial inflammatory infiltrate, (c) shows perivascular dense inflammatory infiltrate, (d) shows fibrinoid necrosis of vessel wall with nuclear debris. (e) Immunohistochemical examination showed predominantly CD3 positive T cells around blood vessel with (f) few CD20 positive B cells. Immunohistochemical examination (g) showed no upregulation of MHC class I and (h) MHC class II, (i) granular MAC deposits on endomysial blood vessel wall, (j) CD56 immunostain highlights regenerating myofibers

neurological deficits. Peripheral nervous system involvement is seen in 60%–70% cases, the common patterns being mononeuropathy, polyneuropathy, and mononeuritis multiplex. Our patient fulfilled four criteria of the 1990 American college of rheumatology for PAN, i.e., weight loss, neuropathy, diastolic hypertension, myalgias, and weakness. As per the 2021 American college of rheumatology/vasculitis foundation guideline for the management of polyarteritis nodosa, nerve muscle biopsy is recommended to aid in the diagnosis of PAN in patients with neuropathy.[2] A demyelinating pattern at inception on electrophysiology has been reported in vasculitic neuropathy.[3]

Involvement of the liver is not common, and manifestations can range from asymptomatic transaminitis to hepatic aneurysms.[4] Pancreatic pseudocyst formation and infarcts in the spleen and liver can be seen rarely.[5] The American college of rheumatology/vasculitis foundation guidelines (2021) recommend using high-dose glucocorticoids with cyclophosphamide for newly diagnosed active, severe disease. Mycophenolate mofetil has not been studied well in PAN.[6] The clinical picture of our patient was well explained by the central and peripheral involvement secondary to PAN. In summary, systemic vasculitic neuropathy can present an intriguing picture; a holistic approach and a high index of suspicion are quintessential.

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Conflicts of interest

There are no conflicts of interest.

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