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P-ANCA vasculitic neuropathy with 12-year latency between onset of neuropathy and systemic symptoms

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Abstract

Background: The differential diagnosis of chronic progressive multifocal asymmetric neuropathies is challenging. Vasculitic neuropathies, multifocal forms of chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathies, and asymmetric lower motor neuron disorders are important considerations.

Case presentation: We report a patient with an unusually long 12-year course of nonsystemic vasculitic neuropathy prior to the development of systemic manifestations.

Conclusion: We discuss some of the difficulties involved in the diagnosis of chronic progressive multifocal asymmetric neuropathies.

Background

Vasculitic neuropathies may occur in the setting of systemic vasculitides or in the absence of systemic features (nonsystemic vasculitic neuropathy, NSVN).[1,2] The antineutrophil cytoplasmic antibody (ANCA) associated systemic vasculitides include Wegener's granulomatosis, microscopic polyangiitis, Churg-Strauss syndrome, and necrotizing crescentic glomerulonephritis.[3] Two distinct ANCAs have been noted. C-ANCAs bind to the antigen proteinase 3 and result in a diffuse cytoplasmic staining pattern on immunofluorescence and are highly associated with Wegener's granulomatosis, while p-ANCAs bind to myeloperoxidase, have a perinuclear staining pattern, and are associated with microscopic polyangiitis and Churg-Strauss syndrome. ELISA studies available for both antibodies are useful to confirm the antigenic specificity and quantitate the ANCA when immunofluorescence shows either this diffuse or perinuclear staining pattern.

We report a patient with an unusually long 12-year course of vasculitic neuropathy prior to the development of systemic manifestations and an eventual diagnosis of p-ANCA microscopic polyangiitis. We discuss some of the difficulties involved in the diagnosis of progressive multifocal asymmetric neuropathies.

Case Presentation

In 1989, this 47-year-old man developed mild painless weakness of ulnar and median innervated hand and median innervated forearm muscles along with ulnar sensory loss. Weakness gradually progressed over the following several years. In 1992, he developed a painless sensory deficit in the left pectoral region that never subsequently resolved and a year later a similar deficit in the left inguinal region, which did resolve over months. Initial electrodiagnostic studies in February 1994 (Table 1) showed a normal right median-APB compound muscle action po-

Table 1: Initial Electrodiagnostic studies in February 1994

Sensory

Nerve	Amplitude (μV)		Velocity (m/sec)	
	R	L	R	L
Median-D2	22	12	59	47
Ulnar-D5	16	13	55	55
Dorsal ulnar	9	13	60	57
Radial	23	31	63	71
Sural	17	18	55	46

Motor

Nerve	Amplitudes (mV)¶	Distal motor latency, velocities (msec, m/sec)§	F-wave minimum latency (msec)¥
R Median-APB	7.9/7.3/7.6	3.6/50/65	Absent
L Median-APB	11.0/10.6	4.0/53	27.1
R Ulnar-ADM	2.5/2.5/2.1/2.1	3.3/51/56/50	Absent
L Ulnar-ADM	7.3/6.7/5.4	3.3/61/42	29.4
R Peroneal-EDB	5.4/5.8/5.7	4.9/44/60	52.2
L Peroneal-EDB	3.5/3.1/2.9	5.2/46/45	Absent
R Tibial-AH	14.4/11.2	3.7/42	55
L Tibial-AH	11.7/9.9	4.8/51	55

¶ Amplitudes from sites as follows: median – wrist at 7 cm, elbow, axilla; ulnar – wrist at 7 cm, below elbow, above elbow, axilla; peroneal – ankle at 9 cm, below fibular head, above fibular head; tibial – ankle at 9 cm, popliteal fossa. § The first value is the distal motor latency and subsequent values segmental velocities. ¥ F-wave persistence and chronodispersion not recorded in the medical records

tential (CMAP) amplitude of 7.9 mV. F-wave responses were absent on the right and normal on the left. The left ulnar sensory nerve action potential (SNAP) had normal amplitude (13 μV) despite a clinical sensory disturbance in the medial hand splitting the 4th finger. Cerebrospinal fluid (CSF) protein was 87 mg/dl (normal < 50 mg/dl) and there were no cells present. Serum anti-GM1 antibodies were absent. Erythrocyte sedimentation rate (ESR) was 6 sec (normal < 15 sec). Chest x-ray was normal.

In March 1994, he developed acute left buttock and thigh pain severe enough to interfere with sleep, weakness of left hip flexion and knee extension, and parasthesias in the anterior thigh. Needle EMG studies done acutely showed reduced recruitment of motor unit action potentials (MUAPs) without fibrillation potentials or positive sharp waves in the left vastus medialis (VM) and L4 paraspinal muscles. Other leg muscles, including iliopsoas and adductor magnus, had normal needle EMG findings. He was treated with prednisone 60 mg every other day and his left leg weakness and pain resolved, and the prednisone was tapered over 2 months. In May 1994, he developed an acute painless right peroneal neuropathy. Needle EMG studies showed reduced recruitment of MUAPs with normal spontaneous activity in right tibialis anterior (TA), peroneus longus (PL), and extensor hallucis longus (EHL). He was treated with intravenous immunoglobulin (IVIg) and his right foot weakness improved rapidly over 1 week. IVIg treatment was continued for 8 months until January 1995 and by October 1995 his left proximal and right distal leg strength was normal. In February 1996, he developed painless left hand weakness. Needle EMG studies showed reduced recruitment of MUAPs again without abnormal spontaneous activity in left first dorsal interosseous (FDI), abductor pollicis brevis (APB), and extensor digitorum communis (EDC). He was treated with prednisone for several weeks, and his strength rapidly improved.

Table 2: Temporal Profile of Right Median and Ulnar CMAP and SNAP Amplitudes

Nerve	Feb 1994	March 1996	March 2000	May 2001
CMAP Amplitudes (mV)				
Right Median-APB	7.9	6.0	2.1	0.1
Right Ulnar-ADM	2.5	–	2.0	Absent
SNAP Amplitudes (μV)				
Right Median-D2	22	19	15	28
Right Ulnar-D5	16	–	20	25

For the nearly 4 year period from March 1996 – January 2000, he remained stable with moderate right median and ulnar weakness and right ulnar sensory loss, with no further episodes of weakness and was not treated with any medication. He felt well and had no systemic symptoms. In January 2000, his right hand weakness and atrophy started to progress again, and over the next year, he became unable to use the hand for many activities he was previously capable of. He was treated for the following 2 years as follows: IVIg for 9 months, then intravenous cyclophosphamide 1.6 gm monthly for 6 months, and then IVIg 1 gm/kg every 2 weeks for 9 months. During this time, there was very gradual but definite progressive selective motor axon loss in the right hand without other clinical nerve involvement. For example, the right median-APB CMAP amplitude was 6.0 mV in March 1996, 2.1 mV in March 2000, and 0.1 mV in May 2001, while the SNAP amplitudes remained stable. Urinalysis in August 2001 was normal.

Treatment was stopped in December 2001 to reassess its need. One month later he developed polyarthralgias, fever, chills, drenching night sweats, cough, nasal stuffiness, and hemorrhagic nasal discharge. There was no current or history of asthma. Laboratory evaluation was remarkable for erythrocyte sedimentation rate (ESR) of 62 sec (normal < 15 sec), rheumatoid factor of 26 units (normal < 15 units), and a p-ANCA immunofluorescence pattern, with ELISA confirmed p-ANCA antibody titer of 130 units (normal < 2.8). There was no eosinophilia. Urinalysis showed 2+ protein, 2+ blood, and RBC casts. Chest x-ray showed streaky lung opacities and chest CT scan showed multiple hazy ground glass opacities and subpleural linear opacities. Corrected diffusion lung capacity (DLCO) was 80% predicted.

Discussion

This patient had a chronic progressive multiple mononeuropathy characterized by both acute nerve lesions, on one occasion with significant pain, as well as a chronic progressive nerve lesion. The CSF protein was elevated. Systemic symptoms were absent for 12 years before their appearance led to a diagnosis of a p-ANCA systemic vasculitis, which is usually associated with microscopic polyangiitis but maybe associated with Wegener's granulomatosis. In a large series of patients with Wegener's granulomatosis, the mean interval between onset of the neuropathy and systemic features was 8.4 months.[4] Although treatment with immunosuppressive agents could have accounted for the absence of systemic symptoms for the last 2 years, the patient went at least 10 years without substantial treatment likely to have masked systemic symptoms, the last 4 of these without any immunosuppressive treatment.

Prior to the development of systemic manifestations, our patient might best have been classified as having nonsystemic vasculitic neuropathy. Nonsystemic vasculitic neuropathy was noted by Kissel et al. in 6 patients, painless in 1 patient, followed for up to 24 months and by Dyck et al. in 20 patients with up to 35 years of symptoms.[1,2] In the latter series, the median duration of peripheral nerve disease without appearance of systemic symptoms was 11.5 years, providing evidence for the existence of an isolated vasculitic neuropathy without systemic features. However, the extent to which these patients' treatment with immunosuppressive agents might have masked the appearance of systemic features was not discussed. Our patient developed systemic features for the first time 1 month after discontinuing IVIg after 2 straight years of treatment with IVIG and cyclophosphamide. The very long 12-year time course of our patient limited to the peripheral nerves suggested nonsystemic vasculitic neuropathy, though it eventually became clear that he had a systemic vasculitis. Nonsystemic vasculitic neuropathy must be considered only an interim diagnosis and a high suspicion of underlying systemic vasculitis maintained. This view is supported by a study of 32 patients initially diagnosed with isolated clinical vasculitic neuropathy, though follow-up for a mean of 5 years resulted in diagnoses of systemic vasculitis in 34%.[5]

The differential diagnosis of chronic progressive asymmetric multifocal neuropathies remains a very challenging situation for neuromuscular specialists. Distinguishing multifocal asymmetric forms of chronic inflammatory demyelinating neuropathy (CIDP) from vasculitic neuropathy can be difficult. Dyck et al. discussed the difficulties they had in excluding multifocal inflammatory demyelinating neuropathies in their 20 patients, particularly given that only 4 had diagnostic nerve biopsies.[2] They questioned whether NSVN was the same disorder as multifocal demyelinating neuropathy with conduction block previously reported by Lewis et al.,[6] and noted that 2 of their NSVN patients had conduction block. Indeed, since the last few years of our patient's presentation were dominated by progressive painless atrophy and weakness of his right hand, the patient was at one point incorrectly diagnosed as having an axonal form of multifocal motor neuropathy.[7]

We also note the value of the ANCA test in our case. A previous report noted the limited diagnostic usefulness of ANCA testing as a screening test in patients referred for evaluation of peripheral neuropathies due to false-positives.[8] However, in the context of a neuropathy with characteristic features of a vasculitic neuropathy, its value is likely higher, and a recent report and accompanying editorial recommended that ANCA testing be considered in the evaluation of idiopathic neuropathies.[9]

Competing interests
None declared.

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