



Letter to the Editor

High PR3-ANCA positivity in a patient with chronic inflammatory demyelinating polyneuropathy



Keywords:

PR3-anti-neutrophil cytoplasmic antibody (PR3-ANCA)
Chronic inflammatory demyelinating polyneuropathy (CIDP)
Vasculitic neuropathy

1. Introduction

Anti-neutrophil cytoplasmic antibody (ANCA) has utility as a marker of systemic vasculitis. Proteinase 3 (PR3)-ANCA reportedly has greater specificity for granulomatosis with polyangiitis (GPA; formerly termed as Wegener's granulomatosis) than myeloperoxidase (MPO)-ANCA. To our knowledge, the present report represents the first description of a case of chronic inflammatory demyelinating polyneuropathy (CIDP) with high PR3-ANCA positivity.

2. Case reports

A 19-year-old woman with normal development presented with a two-month history of upper limb weakness and paresthesia of the fifth fingers without any preceding infection. She had no family history of neurological disease. Physical examination showed no abnormality of the ears, nose, eyes, chest, abdomen, or skin. Neurological examination demonstrated muscle weakness of the upper extremities (manual muscle testing score of 4 in both proximal and distal muscles), predominantly left-sided dysesthesia in the fourth and fifth fingers and hyporeflexia in all extremities, which are suggestive of mononeuritis multiplex.

Laboratory examinations demonstrated high positivity for PR3-ANCA (97.1 U/mL; normal < 3.5 U/mL) using a chemiluminescent enzyme immunoassay (SRL Inc., Tokyo, Japan) but otherwise normal findings of inflammatory markers, including C-reactive protein and erythrocyte sedimentation rate. She was afebrile and had no symptoms indicating vasculitis. Lumbar puncture demonstrated an elevated protein level (138 mg/dL) with normal cell count (1/mm³). Gadolinium-enhanced cervical MRI demonstrated no abnormality of the nerve roots or brachial plexus. Anti-ganglioside IgG antibodies to GM1, GD1a, GD1b, GD3, and GQ1b, were all negative.

Nerve conduction studies revealed prolonged distal latency affecting the upper extremities (left median nerve, 5.0 ms; ulnar nerve, 4.2 ms), reduced nerve conduction velocities in the motor nerves of the upper extremities (left median, 44 ms; ulnar, 49 ms), and prolonged F-wave latency in both upper and lower extremities (left median, 37.7 ms; ulnar, 44.6 ms; tibial, 51.6 ms). Conduction block was detected in the right radial nerve, in addition to conduction delay in the left cubital

tunnel. Somatosensory evoked potentials in the left median and posterior tibial nerves revealed delayed conduction most prominent at the proximal sensory nerve root.

Although serum PR3-ANCA levels were highly positive, there were no signs of systemic vasculitis. Electrophysiological studies revealed demyelination fulfilling the European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS) criteria (prolongation of F-wave latency $\geq 20\%$ above the upper limit of normal values in two nerves). A diagnosis of CIDP was made according to these findings.

Her symptoms partially improved in response to 400 mg/kg per day of intravenous immunoglobulin (IVIg), which was discontinued after 3 days due to the development of aseptic meningitis. Two months later, upper limb weakness, dysesthesia of all fingers recurred and was successfully treated with oral prednisolone 30 mg per day plus a 5-day course of IVIg. No adverse events were observed during prednisolone treatment. Five months later after prednisolone doses had been tapered to 8 mg per day, upper limb weakness recurred again. This recurrence was recovered with oral prednisolone 20 mg per day plus IVIg for 5 days. During the subsequent 10 months of follow-up, no signs of systemic vasculitis were observed. Although levels had slightly decreased at 11 days after immunotherapy, PR3-ANCA remained highly positive (64.4–97.1 U/mL).

3. Discussion

The measurement of ANCA antibodies has a utility in diagnosing systemic vasculitis. Although false-positive p-ANCA and MPO-ANCA results are frequently observed in various inflammatory disorders, such as SLE, sarcoidosis, ulcerative colitis, and bacterial infections, c-ANCA and PR3-ANCA are relatively specific for GPA (sensitivity, 66–92%; specificity, 98–99%) [1,2]. In a retrospective study of the patients positive for c-ANCA/PR3-ANCA without vasculitis, no patient developed vasculitis over a follow-up duration of 3–12 years (mean, 6.8 years), indicating that c-ANCA/PR3-ANCA positivity reflects neutrophil-activating properties that are not specific to systemic vasculitis [1]. PR3-ANCA titers in patients without vasculitis were lower (predominantly below 30 U/mL) than in patients with vasculitis, with high PR3-ANCA titers in the absence of vasculitis typically accompanied by acute systemic inflammation (fever, arthritis, etc.) [1]. PR3-ANCA levels were persistently high in the present case in the absence of systemic inflammation.

In patients with GPA, the prevalence of neuropathy is reportedly 11–44%, and more than half of the patients develop neuropathy before the diagnosis of vasculitis [3]. The typical clinical finding in GPA is mononeuritis multiplex or distal symmetric neuropathy, predominantly characterized by axonal neuropathy [3]. Our patient showed no signs of systemic vasculitis after one year of observation; however, segmental demyelination was observed, which is instead a characteristic of CIDP and is clearly distinguishable from vasculitic neuropathy.

Although CIDP patients may present with MPO-ANCA positivity [4], the prevalence of PR3-ANCA positivity remains unknown [4,5]. The findings of the present case demonstrate that CIDP patients may have

high PR3-ANCA positivity in the absence of vasculitis. The differentiation of CIDP from vasculitis is clinically important as the treatments differ markedly for CIDP and vasculitis.

The significance of PR3-ANCA positivity in the present case is unknown. This finding may represent an incidental complication or be related to the pathophysiology of a certain subtype of CIDP, although the role of neutrophils in the pathogenesis of CIDP patients is currently unknown. Further studies are required to fully elucidate the pathogenesis of CIDP and clinical significance of PR3-ANCA positivity.

Conflicts of interest

The authors declare no conflict of interest.

Acknowledgements

We thank Professor Atsuro Chiba and Dr. Ayumi Uchibori of the Kyorin University School of Medicine, Tokyo, for the measurement of anti-ganglioside antibodies.

References

- [1] A. Knight, A. Ekbom, L. Brandt, et al., What is the significance in routine care of c-ANCA/PR3-ANCA in the absence of systemic vasculitis? A case series, *Clin. Exp. Rheumatol.* 26 (3 Suppl. 49) (2008) S53–56.
- [2] U. Schönermarck, P. Lamprecht, E. Csernok, et al., Prevalence and spectrum of rheumatic diseases associated with proteinase 3-antineutrophil cytoplasmic antibodies (ANCA) and myeloperoxidase-ANCA, *Rheumatology* 40 (2001) 178–184.
- [3] K. de Groot, D.K. Schmidt, A.C. Arlt, et al., Standardized neurologic evaluations of 128 patients with Wegener granulomatosis, *Arch. Neurol.* 58 (2001) 1215–1221.
- [4] C.H. Chalk, H.A. Homburger, P.J. Dyck, Anti-neutrophil cytoplasmic antibodies in vasculitis peripheral neuropathy, *Neurology* 43 (1993) 1826–1827.
- [5] A. Abraham, H. Albulaihe, M. Alabdali, et al., Frequent laboratory abnormalities in CIDP patients, *Muscle Nerve* (Nov. 17, 2015) <http://dx.doi.org/10.1002/mus.24978> (Epub ahead of print).

Masanori Kurihara

Department of Neurology, Mitsui Memorial Hospital, Tokyo, Japan

Department of Neurology, Graduate School of Medicine, University of

Tokyo, Tokyo, Japan

Corresponding author at: Department of Neurology, Graduate School of Medicine, University of Tokyo, 7-3-1, Hongo, Bunkyo-ku, Tokyo 113-8655, Japan.

E-mail address: mkurihara-tyky@umin.ac.jp

Yu Kurata

Department of Nephrology, Mitsui Memorial Hospital, Tokyo, Japan

Izumi Sugimoto

Department of Neurology, Mitsui Memorial Hospital, Tokyo, Japan

Yuki Hatanaka

Department of Neurology, Mitsui Memorial Hospital, Tokyo, Japan

Department of Neurology, Teikyo University School of Medicine, Tokyo, Japan

Yasuhisa Sakurai

Department of Neurology, Mitsui Memorial Hospital, Tokyo, Japan

29 September 2016