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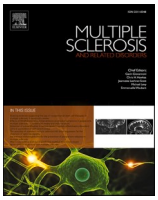

Correspondence

Simultaneous bilateral optic neuropathy and myelitis revealing paraneoplastic neurological syndrome associated with multiple onconeuronal antibodies

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ABSTRACT

Paraneoplastic neurological syndromes (PNS) are immune-mediated complications of cancer associated with a broad spectrum of clinical manifestations. Optic neuropathy (ON) and myelitis are frequent manifestations of multiple sclerosis and neuromyelitis optic spectrum disorders but are considered as non-classical in PNS. Here, we report a case of PNS revealed by simultaneous bilateral ON and myelitis related to a cluster of three neural autoantibodies, in the setting of small cell lung cancer.

1. Introduction

Paraneoplastic neurological syndromes (PNS) are immune mediated complications of cancer associated with a broad spectrum of clinical manifestations including limbic encephalitis, brainstem encephalitis, cerebellar degeneration, sensory neuropathy, or opsoclonus-myoclonus syndrome. Optic neuropathy (ON) and myelitis are frequent manifestations of multiple sclerosis (MS) and neuromyelitis optic spectrum disorders (NMOSD) but are considered as non-classical in PNS. Herein, we describe a 70-year-old patient who simultaneously developed bilateral ON and myelitis related to multiple co-existing paraneoplastic antibodies (Abs), in the setting of small cell lung cancer (SCLC).

2. Case presentation

A 70-year-old man with a 50-pack-year history of smoking was admitted to the neurology department 4 days after he developed subacute bilateral and painless vision loss. He did not complain of constitutional symptoms. The best corrected visual acuity was 7/10 in the right eye and 3/10 in the left eye. Fundoscopy showed bilateral disc swelling and peripapillary hemorrhages. Within a week of the initial visual symptoms, he developed left lower limb weakness (Medical Research Council grade 4), without pyramidal signs, sensory loss, or bladder dysfunction. Brain magnetic resonance imaging (MRI) did not reveal any optic nerve lesion or demyelinating lesion (Fig. 1A). Spinal cord MRI showed a T2-weighted hyperintensity at the C2 level, with gadolinium enhancement (Fig. 1B–D). The visual evoked potentials showed significant bilateral increase of P100 latencies. Cerebrospinal fluid (CSF) analysis showed a cell count of 149 cells/μl (91% lymphocytes), elevated protein concentration (99 mg/dl; $N < 45$), and positive CSF-restricted IgG oligoclonal bands. No malignant cells or infectious agents were detected in the CSF. Basic laboratory studies were not significant. Testing for aquaporin-4 and myelin oligodendrocyte glycoprotein Abs was negative. Whole body 18F-fluoro-2-deoxy-D-glucose positron emission tomography associated with computed tomography (^{18}FDG PET/CT) detected a nodule in the inferior lobe of the right lung associated with uptake of FDG in subcarinal lymph nodes as well as in the prostate gland (Fig. 1E and F). SCLC was finally confirmed by transbronchial needle aspiration. The temporal coincidence of neurological symptoms and detection of SCLC prompted us to search for paraneoplastic Abs. The paraneoplastic Ab panel showed a significant signal for anti-neuronal nuclear antibodies (ANNA)-1 (or "anti-Hu") in the serum (EUROLINE Neuronal Antigen Profile blots, EUROIMMUN). Anti-collapsin response mediator protein-5 (CRMP5) and -amphiphysin Abs were also detected, albeit at lower levels. Diagnosis of definite PNS was made. Treatment with intravenous methylprednisolone (1g daily for 8 consecutive days), followed by five rounds of plasma exchange, resulted in poor clinical improvement. No visual recovery was observed. It is to be noted that a second malignancy (prostate cancer) was highly suspected based on prostate-specific antigen level of 15.9 ng/mL (N 0.0–4.0 ng/mL), FDG PET/CT and prostate MRI results, but the patient and his family elected to withdraw from further investigation and treatment given the precarious medical condition. The patient received palliative care at home.

3. Discussion

Here, the best evidence for the autoimmune etiology of the multifocal neurological manifestations relies on the demonstration of multiple onconeuronal Abs in the serum, together with evidence of inflammatory changes in the CSF (pleocytosis, presence of CSF-exclusive oligoclonal bands), and in MRI studies (radiological features suggestive of myelitis). We will focus here on three main aspects about this clinical case. First, simultaneous occurrence of ON and myelitis is a neuromyelitis optica-like phenotype, which can also be observed, to a lesser extent, in MS, but it represents an extremely rare paraneoplastic manifestation. So far, only a few cases with combination (concomitant or sequential) of ON and myelitis have been reported in association with CRMP5-IgG (Cross et al., 2003; Ducray et al., 2007; Keegan et al., 2008; Jarius et al., 2012). The malignancies involved were SCLC, thymoma, thyroid, kidney and prostate cancer (Cross et al., 2003; Ducray et al., 2007; Keegan et al., 2008; Jarius et al., 2012). Amphiphysin-IgG have

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been detected in patients with isolated paraneoplastic myelitis and ON, and up to a quarter of ANNA-1 positive patients can have spinal cord dysfunction (Graber and Nolan, 2010; Flanagan et al., 2011; Liu et al., 2019; Xu et al., 2019). To the best of our knowledge, no case of concomitant bilateral ON and myelitis has been reported so far as manifestation of ANNA-1 or amphiphysin autoimmunity. We therefore assumed that our patient's symptoms were likely to be driven by anti-CRMP5 autoimmunity. However, we cannot exclude that our patient had overlapping autoantibody neurological syndromes, with ON attributable to CRMP5 or amphiphysin autoimmunity and myelitis to anti-ANNA-1 or amphiphysin autoimmunity (Pittock et al., 2004). Second, our case highlights that paraneoplastic autoimmunity may be driven by multiple tumour-derived onconeural antigens, and that multiple concurrent auto-Abs may be generated by a sole tumour (Pittock et al., 2004). This observation is clinically relevant because clustering of paraneoplastic Abs increases the likelihood of cancer detection and may highly influence on tumour-type prediction (Pittock et al., 2004; Horta et al., 2014). For example, breast cancer is more likely than SCLC in amphiphysin-IgG–positive women, but the addition of CRMP5-IgG or ANNA-1-IgG makes SCLC more likely (Pittock et al., 2004; Horta et al., 2014). This observation has important implications, as diagnostically important auto-Abs may be missed by a single or limited serological evaluation. Screening for a panel of neuronal Abs should be systematically performed when paraneoplastic neurological manifestations are suspected because duo or trio clusters may help clinicians in the cancer search. Finally, our patient probably had a second neoplasm (prostate cancer). Prostate cancer is one of the most common types of cancer in men, and PNS is rarely reported among prostate cancer patients (Strostein et al., 2016). Here, prostate cancer is likely to be coincidental, but we cannot exclude a contribution of this unproven malignancy since neurological manifestations of ANNA-1 and CRMP5 autoimmunity have been reported in association with this type of cancer (Jarius et al., 2012; Strostein et al., 2016). Therefore, we may postulate that each tumour of our patient expressed ≥ 1 neuronal antigens, resulting in a mixed immune response. In conclusion, simultaneous involvement of optic nerves and spinal cord is a rare manifestation of PNS. This presentation should prompt screening for a panel of onconeuronal Abs and for an underlying malignancy, particularly in older adult smokers who are rather unlikely to have MS or NMOSD.

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Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent

For this type of study no informed consent is required

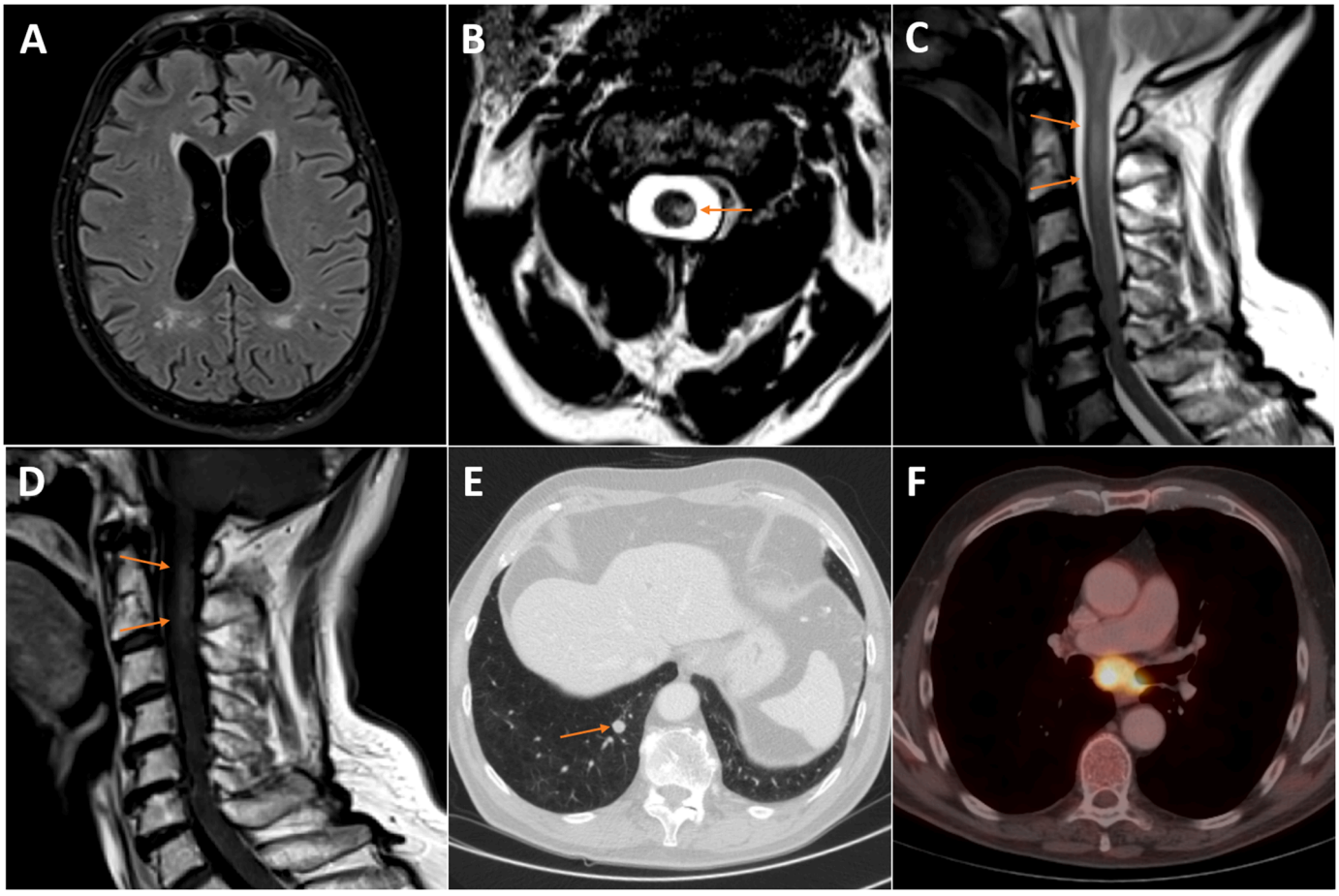

Fig. 1. Radiological studies
(A) Axial fluid attenuated inversion recovery (FLAIR) images showing several supratentorial white matter hyperintensities of presumed vascular origin but did not reveal any demyelinating lesion. (B and C) T2-weithed images showing hyperintense lesion at the level C2 (arrow) with contrast enhancement (D, contrast-enhanced T1-weighted images). (E) Computed tomography image showing a nodule in the inferior lobe of the right lung associated with (F, FDG PET/CT) uptake of fluorodeoxyglucose in subcarinal lymph nodes.

Declaration of Competing Interest

The authors declare no conflict of interest regarding this case report.

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