CASE REPORT

Paraneoplastic neurological syndrome as an initial indicator of small cell carcinoma of the lung

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SUMMARY

Paraneoplastic syndromes are indirect manifestations of cancer due to functional peptides/hormones produced by a tumour, or due to cross reactivity between tumour and host antigens. Here the case of a 58-year-old woman presenting with ataxia, paraesthesia and subacute and progressive loss of vision is reported. The patient exhibited strong serum positivity for anti-Hu and anti-CV2 antibodies, and a chest CT scan showed a hypodense nodule in proximity of the right upper lobe bronchus and an enlarged ipsilateral paratracheal lymph node that was not visible on a lung x-ray. Histopathological examination of a biopsy specimen from this lymph node showed that small cell carcinoma of the lung was present. The patient's deficits were subsequently diagnosed as three coexisting paraneoplastic neurological syndromes (PNSs): subacute cerebellar ataxia, sensory neuropathy and retinopathy, respectively. Although rare, PNSs can be the first manifestations of cancer, and their rapid recognition facilitates an early treatment.

BACKGROUND

Manifestations of cancer are often classified as direct or indirect. The former includes local tumour growth and metastatic disease,[1] while the latter includes paraneoplastic syndromes (PSs). PSs are not related to tumour mass, but rather related to the production of functional peptides/hormones and cross reactivity that can occur between tumour and host antigens.[1 2] PSs can affect most of the organs and tissues and it has been reported that 7–15% of all cancers are associated with PSs.[3 4] Paraneoplastic neurological syndromes (PNSs) can affect any part of the nervous system. For example, some of them affect only a single area or a specific cell type, others operate at multiple levels.[5 6] The global incidence of PNSs is less than 0.01%.[5] Currently, it is hypothesised that PNSs are primarily, if not entirely, immune-mediated diseases. The mechanism relates to the ectopic expression by a tumour of antigens that are also presented by the nervous system. For reasons not yet understood, these antigens are seen as foreign. Currently, detection of antineuronal antibodies is the most effective diagnostic test for PNSs. Accordingly, there are several antineuronal antibodies, and tumours that have been associated with particular PNSs (table 1). However, in 50% of PNS cases, known antibodies are not detected.[5–7]

A PNS usually evolves gradually and progressively, and unfortunately, can eventually lead to severe disabilities or even death. The severity of the condition is due to early and irreversible destruction of neuronal structures secondary to an inflammatory response.[7] Of all the tumour types that have been associated with PSs and PNSs, lung tumours are the most common. PSs are described in 10% of lung tumours.[8] In contrast, PNSs are associated with only 1% of small cell carcinoma of the lung (SCCL) cases.[7] Furthermore, in most of the patients, manifestations of PNS are the first sign of disease. However, in 60% of SCCL cases, the disease has already metastasised at the time of diagnosis.[4 5] There have been multiple PNSs associated with cases of SCCL, and in some cases, more than one PNS coexists in the same patient.[7] The most common PNSs include Lambert-Eaton myasthenic syndrome, sensory neuropathy, subacute cerebellar ataxia and subacute encephalopathy. PNSs that are less often described are *opsoclonus-myoclonus* and retinopathy.

CASE PRESENTATION

A 58-year-old woman was referred to the internal medicine-stroke in young adults outpatient department for a consultation based on suspicion of ischaemic stroke. The patient reported the onset of ataxia over the previous 6 months with a progressive inability to perform routine tasks, numbness in both the hands and reduced sensitivity in the left foot and leg. The patient also experienced pain in both the thighs, yet had an absence of lower back pain. The patient complained of visual deficit in the left eye that had a sudden onset and then remained for 8 months. A weak visual deficit in the right eye was also reported by the patient. On examination, the patient presented with a right gaze-evoked nystagmus, with both horizontal and rotational components, a predominantly axial gait ataxia with a broadened base and movement asynergia with difficult turning, a positive Romberg test with very slight swaying, left dysmetria on the finger-to-nose test and a diminished aquilian tendon reflex. An ophthalmological examination also detected anterior uveitis in the right eye.

The patient had a personal history of smoking (40 cigarettes a day for 44 years) and a family history of schizophrenia, consanguinity, and 'movement disorders'. The patient reported being healthy prior to the current condition and was not taking any chronic medication. The patient further denied any alcohol or drug abuse.

INVESTIGATIONS

The patient underwent CT and MRI of the brain, and arterial microvasculopathy was suggested.

Table 1 Major paraneoplastic neurological syndromes and their associated tumours and antibodies

Paraneoplastic neurological syndromes	Most commonly associated tumours	Antineuronal antibodies
LEMS	SCCL	VGCC-Ab
Subacute cerebellar ataxia	SCCL Ovary, Breast Hodgkin's disease	Hu-Ab Yo-Ab CV2-Ab
Limbic encephalitis	SCCL Testicular	Hu-Ab, Ma2-Ab CV2-Ab
Opsoclonus-myoclonus	Neuroblastoma Breast, lung	Hu-Ab Ri-Ab
Retinopathy	SCCL Melanoma	Recoverin-Ab CV2-Ab, Rod-bipolar-cell-Ab
CGP	SCCL	Hu-Ab, CV2-Ab
Sensory neuropathy	SCCL	Hu-Ab, CV2-Ab
Stiff-Person syndrome	Breast	Amphiphysin-Ab
Encephalomyelitis	SCCL	Hu-Ab, CV2-Ab Amphiphysin-Ab, Ma2-Ab

Ab, antibody; CGP, chronic gastrointestinal pseudo-obstruction; LEMS, Lambert-Eaton myasthenic syndrome; SCCL, small cell carcinoma of the lung.

There were no lesions compatible with stroke, or cerebellar or trunk abnormalities. To study the visual deficit of the left eye, a visual evoked potential was performed. A moderate decrease in amplitude of the evoked response suggested that damage to the optic nerve axonal had occurred. An electromyogram also detected sensory axonal, symmetrical, predominantly distal polyneuropathy of moderate severity.

Laboratory assays revealed normal blood counts, normal renal, liver and thyroid function and an absence of vitamin and folic acid deficiencies. Ceruloplasmin and urinary copper measurements were also normal. Syphilis, HIV, hepatitis, Lyme disease, cytomegalovirus, human T-lymphotropic virus type I, as well as *Tropheryma whipplei* infection, were all excluded.

Autoimmune studies were positive for antinuclear antibodies (1/320), a granular pattern and the presence of normal complement factors. Extractable core antigens, antineutrophil cytoplasmic antibodies, antiphospholipid syndrome antibodies and antitissue transglutaminase antibodies were all negative. No significant elevation in the levels of C reactive protein, erythrocyte sedimentation rate or ferritin was found. Blood electrophoresis and urinary analysis were normal.

Figure 1 Chest CT scan showing a 9×8 mm^2 hypodense nodule near the right upper lobe bronchus and a right-tracheal enlarged lymph node.

An elevated white cell count (32 leucocytes/mm^3, mononuclear), protein level (135 mg/dl) and an IgG monoclonal pattern (isoelectric focusing) were detected in the cerebrospinal fluid (CSF). Cultures were germfree and cytology was negative for malignant cells. Furthermore, CSF serum tests were negative. Contrast-enhanced spinal cord and brain MRI showed numerous small hyperintense lesions present on T2-weighted images, without relevant diffusion restriction in the subcortical and periventricular white matter, suggesting vasculitis. However, the absence of other manifestations made this diagnosis unlikely. Owing to a family history of consanguinity and 'movement disorders', the patient was also tested for Huntington's disease, and those results were negative.

A diagnosis of PNS was then considered. An analysis of antineuronal antibodies present in the serum showed a strong positivity for anti-Hu antibodies and anti-CV2 antibodies. A contrast chest CT scan showed a 9 × 8 mm^2 hypodense nodule near the right upper lobe bronchus. Slight signs of lymphatic spread distally to its location and a right-tracheal enlarged lymph node was observed. The latter was found to be necrotic and infiltrative, with a diameter of 32 mm (figure 1). Results of a histopathological examination of the lymph node were compatible with SCCL.

TREATMENT

The patient was put on corticosteroids (prednisolone orally 1 mg/kg/day) and was referred to the oncology department to initiate first-line chemotherapy.

OUTCOME AND FOLLOW-UP

After completing the first cycle of first-line chemotherapy, and since the patient maintained her clinical status, intravenous immunoglobulin (0.4 mg/kg) was administered on a monthly basis. Although there was no improvement in gait ataxia, the paraesthesias diminished with administration of pregabalin (150 mg three times a day).

DISCUSSION

In most of the cases, PNS manifestations occur before the diagnosis of pulmonary carcinoma is made.[5] However, this case was particularly challenging since the patient only exhibited neurological symptoms, and these symptoms are not specific to PNS. Furthermore, cases of PNSs are rare and thus are not readily considered as a diagnosis. It is the identification of antineuronal antibodies that is crucial. Different PNSs can coexist in the same patient,[7] and this was illustrated in the present case. Subacute and progressive ataxia associated with nystagmus and dysmetria indicate cerebellar dysfunction. Paraneoplastic subacute cerebellar ataxia is usually secondary to a relatively selective loss of neuronal Purkinge cells.[9] Moreover several antineuronal antibodies have been associated with this syndrome. For example, 23% of patients have anti-Hu antibodies when subacute cerebellar ataxia is subsequent to a lung tumour,[7] and anti-CV2 antibodies are associated with subacute cerebellar ataxia and SCCL.[7] Dysaesthesia, pain and electromyogram findings helped to establish a diagnosis of axonal symmetrical sensory polyneuropathy. Sensory neuropathy is a consequence of axonal damage, the myelin sheath remains relatively preserved. SCCL is responsible for 77% of all the paraneoplastic sensory neuropathy cases, and most of these patients have anti-Hu, anti-CV2 or antiamphiphysin antibodies.[4 7] Ophthalmological tests established the presence of uveitis, and

visual evoked potentials were compatible with optical neuropathy. These are particular forms of paraneoplastic retinopathy that are also associated with anti-CV2 antibodies.[7] The patient reported here had indications of an inflammatory response in CSF, with a monoclonal IgG pattern identified that was not present in the serum. These findings indicate IgG intrathecal synthesis, and in some cases this has been found to occur with PNSs.[10–13] A CT scan of the brain and MRI may also show atrophy in subacute cerebellar ataxia. However, in the early stages of the disease, these examinations tend to include normal findings.

Currently, the best way to stabilise patients with a PNS is to treat the tumour present. Immunomodulatory therapy is not an effective option, as neurological symptoms result from irreversible neuronal damage. For some cases of subacute cerebellar ataxia, improvement with corticosteroids, intravenous immunoglobulin and plasmapheresis has been reported.[14 15] However, the outcome for patients generally remains poor.

Recognition of PNS remains difficult, yet is essential since early recognition can facilitate a more successful treatment outcome. Treatment of the tumour is the most effective method for control of PNSs. It is also important for clinicians to recognise that the progression of severe and disabling neurological manifestations is highly suggestive of PNS particularly in cases that involve a history of heavy smoking and lung cancer it should be a key concern.

Learning points

- Paraneoplastic neurological syndromes (PNSs) are an indirect manifestation of cancer, and are mostly, if not entirely, a consequence of cross reactivity between tumour and host antigens.
- Different PNSs can coexist in the same patient.
- Recognition of PNS is difficult, yet essential, particularly when it is the first sign of disease.
- Progressive evolution of severe and disabling neurological manifestations is highly suggestive of PNS.
- Small cell lung carcinoma is the most frequent cancer associated with PNSs.

Competing interests None.

Patient consent Obtained.

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REFERENCES

1 Abeloff MD. Paraneoplastic syndromes: a window on the biology of cancer. *N Engl J Med* 1987;317:1598–600.
2 Pelosof LC, Gerber DE. Paraneoplastic syndromes: an approach to diagnosis and treatment. *Mayo Clin Proc* 2010;85:838–54.
3 Heinemann S, Zabel P, Hauber HP. Paraneoplastic syndromes in lung cancer. *Cancer Ther* 2008;6:687–98.
4 Gámez BJ, De Lucas MDG, Rodríguez MG. Cancer de pulmón y syndromes paraneoplásicos. *An Med Interna* 2001;18:440–6.
5 Darnell RB, Posner J. Paraneoplastic syndromes involving the nervous system. *N Engl J Med* 2003;349:1543–54.
6 Graus F, Delattre JY, Antoine JC, *et al*. Recommended diagnostic criteria for paraneoplastic neurological syndromes. *J Neurol Neurosurg Psychiatry* 2004;75:1135–40.
7 Honnorat J, Antoine JC. Paraneoplastic neurological syndromes. *Orphanet J Rare Dis* 2007;2:22.
8 Elrington GM, Murray NM, Spiro SG, *et al*. Neurological paraneoplastic syndromes in patients with small cell lung cancer. A prospective survey of 150 patients. J Neurol Neurosurg Psychiatry 1991;54:764–7.
9 Mason WP, Graus F, Lang B, *et al*. Small-cell lung cancer, paraneoplastic cerebellar degeneration and the Lambert-Eaton myasthenic syndrome. *Brain* 1997;120(Pt 8):1279–300.
10 Storstein A, Monstad SE, Honnorat J, *et al*. Paraneoplastic antibodies detected by isoelectric focusing of cerebrospinal fluid and serum. *J Neuroimmunol* 2004;155:150–4.
11 Psimaras D, Carpentier AF, Rossi C. PNS Euronetwork. Cerebrospinal fluid study in paraneoplastic syndromes. *J Neurol Neurosurg Psychiatry* 2010;81:42–5.
12 Greenlee JE, Boyden JW, Pingree M, *et al*. Antibody types and IgG subclasses in paraneoplastic neurological syndromes. *J Neurol Sci* 2001 1;184:131–7.
13 McCombe PA, Brown NN, Barr AE, *et al*. Monoclonal immunoglobulin bands in the cerebrospinal fluid. *Aust N Z J Med* 1991;21:227–9.
14 Pelosof LC, Gerber DE. Paraneoplastic syndromes: an approach to diagnosis and treatment. *Mayo Clin Proc* 2010;85:838–54.
15 Vedeler CA, Antoine JC, Giometto B, *et al*. Paraneoplastic Neurological Syndrome Euronetwork. Management of paraneoplastic neurological syndromes: report of an EFNS Task Force. *Eur J Neurol* 2006;13:682–90.

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