CASE REPORT

Antiglycine receptor antibody and encephalomyelitis with rigidity and myoclonus (PERM) related to small cell lung cancer

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SUMMARY

A 39-year-old man (a lifetime non-smoker) presented with a locked left jaw and leg myoclonus. Clinical and electromyographic findings were in keeping with progressive encephalomyelitis with rigidity and myoclonus (PERM) syndrome. A thoracic CT scan demonstrated a 19 mm right hilar nodule, which was proven to be small cell lung cancer on bronchoscopic biopsy. Serological evaluation of the patient's plasma revealed antibodies against glycine receptors (serology negative for anti-GAD, anti-Yo, anti-Hu, anti-Ri, anti-amphiphysin, anti-Ma2/Ta, anti-CRMP5 and anti-NMDA receptor). After his cancer was treated with chemotherapy and intravenous immunoglobulins (IVIg), neurological symptoms resolved but returned several months later without any evidence of cancer recurrence. Symptoms were refractory to corticosteroids and IVIg therapy. Rituximab was then initiated, which led to a dramatic and sustained resolution of symptoms. To our knowledge, this is the first case of PERM related to antiglycine receptor antibodies from paraneoplastic syndrome, which resolved with rituximab.

BACKGROUND

Small cell lung cancer is one of the leading malignant tumours associated with paraneoplastic syndromes. Although the exact pathophysiology remains largely unknown, they result from the remote effects of malignancy rather than from metastases or direct invasion of the nervous system. Most paraneoplastic neuromuscular disorders are caused by immune responses against onconeural antigens. These antigens, common to both neoplastic and normal neural tissue, are recognised as foreign and lead to the generation of autoantibodies that attack the nervous system. The most common neural paraneoplastic syndrome related to small cell carcinoma is Lambert-Eaton myasthenic syndrome, which is associated with antibodies against P/Q-type voltage-gated calcium channels. Progressive encephalomyelitis with rigidity and myoclonus (PERM), on the other hand, has been most closely associated with antibodies against glutamic acid decarboxylase (GAD) with titres usually greater than 1000 U/mL.¹⁻³ In our case patient, antiglycine receptor antibodies were most likely the culprit. PERM related to antiglycine receptor antibodies is rare but has been described previously with other types of tumours.

CASE PRESENTATION

A 39-year-old Filipino man, a lifetime non-smoker, presented to the emergency department at St Paul's

Hospital in Vancouver, British Columbia with a locked left jaw and spasm of his left masseter muscle. He was completely well until 5 days prior to presentation when he noticed difficulty swallowing food and could only open his mouth to about 3 cm. At the time of admission, he was unable to open his mouth beyond 1 cm and the patient was experiencing pain and spasm over both sides of the jaw. His last tetanus vaccine had been 3 years earlier. The remainder of his neurological examination was unremarkable. He received a course of metronidazole, baclofen, benzotropine and Botox injection directly to the masseter muscle, which slightly improved his symptoms.

He returned to the hospital 2 days later with symptoms of increased jaw pain with closure. Dysarthria and right-sided facial weakness were also noted. His medications were switched to trihexyphenidyl and levodopa which slightly improved his symptoms. However, his swallowing deteriorated and a feeding tube had to be inserted. He also began experiencing spasms of his right leg which limited his ability to ambulate on his own. Fasciculations and myoclonic jerks were present in the right leg. His symptoms improved transiently following treatment with dantrolene.

INVESTIGATIONS

Magnetic resonance imaging (MRI) of the head showed numerous small foci of high T2 fluid attenuation inversion recovery in the subcortical, deep and periventricular white matter of the cerebral hemispheres bilaterally (figure 1). MRI of spine did not demonstrate any significant abnormalities. Nerve conduction studies were normal. However, electromyography investigation demonstrated a typical pattern of continuous firing of normal appearing motor units in agonist and antagonist muscle groups in the right leg at rest. A thoracic computed tomography (CT) scan demonstrated a 19 mm right hilar lesion (figure 2). Bronchoscopy with endobronchial ultrasound revealed the lesion, which was proven to be small cell lung cancer on biopsy (figure 3). Serological evaluation of the patient's plasma revealed antibodies against glycine receptors. Antibodies against anti-Yo, anti-Hu, anti-Ri, anti-amphiphysin, anti-Ma2/Ta anti-CRMP5, anti-GAD and NMDA receptors were all negative.

TREATMENT

The patient was treated for small cell lung cancer with chemotherapy, local chest radiation and prophylactic cranial irradiation. He was also treated

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Figure 1 A MRI of head findings. Numerous small foci of T2 weighted and fluid attenuation inversion recovery (FLAIR) hyperintensities are demonstrated in the subcortical, deep and periventricular white matter of the cerebral hemispheres bilaterally (shown as arrows).

with IVIg infusions and clonazepam. His symptoms completely resolved after treatment. A repeat CT scan and positron emission tomography (PET) scan of his body demonstrated no further abnormalities.

OUTCOME AND FOLLOW-UP

Two months after completing treatment he presented to the emergency department with bilateral ptosis (and binocular horizontal diplopia and decreased visual acuity), jaw spasm, torticollis and involuntary tongue biting. Repeat imaging showed no evidence of cancer recurrence. MRI scan of his head and whole body positive emission tomography (PET) scan did not reveal any signs of tumour recurrence. He was re-initiated on IVIg but without any clinical response. The patient was then treated with intravenous methylprednisolone 500 mg daily for 5 days (followed by oral prednisone 50 mg daily) and 5 days of plasma exchange with only minor and transient improvement in symptoms. He continued to experience blurred vision (owing to sixth cranial nerve palsy), dysarthria (from jaw spasms) and muscle cramps in his right calf. A trial of therapy with rituximab then led to a dramatic and sustained clinical response.

DISCUSSION

To our knowledge, this is the first case of PERM related to antiglycine receptor antibodies arising from small cell lung cancer in a lifetime non-smoker. Importantly, although the syndrome responded initially to a successful treatment of small cell lung

Figure 3 Biopsy specimen taken from the nodule demonstrating small cell lung cancer. The slide shows multiple round or oval (oat-like) cells with little cytoplasm and hyperchromatic nuclei. These malignant cells are clustered together in nests.

cancer, complemented by IVIg, the patient suffered a relapse following discontinuation of therapy despite no evidence of tumour recurrence. Re-initiation of systemic corticosteroids had no significant impact on patient symptoms. However, the use of rituximab, a chimeric monoclonal antibody against CD20 (a cell surface marker for B lymphocytes) resulted in near complete and durable resolution of the syndrome.

PERM related to antiglycine receptor antibodies is rare but has been described previously. When it does occur, it is characterised by progressive encephalomyelitis with rigidity and myoclonus and as in our case patient, the syndrome most often perturbs oculomotor function.^{3 4} Interestingly, our patient developed the oculomotor symptoms months after successful treatment of his underlying small cell lung cancer (and in the absence of any demonstrable evidence of tumour recurrence), which failed to respond to systemic corticosteroids, IVIGs and even plasma exchange, but responded successfully to rituximab, suggesting the importance of B lymphocytes in its pathogenesis. Rituximab is an anti-CD20 monoclonal antibody that is highly effective in treating certain lymphomas and several autoimmune conditions. It has been suggested as an alternative therapy in patients with anti-Hu or anti-Yo associated paraneoplastic neurological syndromes (PNS) as well as PNS affecting the neuromuscular junction.^{5 6} PERM can also occur as an autoimmune phenomenon and rituximab has also been used for treatment of PERM not associated with malignancy.⁷ Our patient's dramatic clinical improvement after therapy with rituximab highlights its potential efficacy for PNS.

Figure 2 A thoracic CT image demonstrating a 1.9 cm nodule in the right perihilar region.

Learning points

- ▶ Paraneoplastic disorders manifest a wide variety of symptoms and must be considered in the differential diagnoses for patients who present with unexplained neurological findings.
- ▶ Serological evaluation for antibody panels associated with paraneoplastic conditions may be helpful in confirming the diagnosis.
- ▶ Rituximab is an anti-CD20 monoclonal antibody which has thus far proven to be an effective therapy for encephalomyelitis with rigidity and myoclonus occurring as an autoimmune phenomenon and in the setting of malignancy.

Contributors All of the authors contributed to the management of the patient, drafting of the manuscript and finalisation of the manuscript.

Competing interests None.

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