Findings that shed new light on the possible pathogenesis of a disease or an adverse effect

An interesting collection of paraneoplastic syndromes in a patient with a malignant thymoma

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Summary

Paraneoplastic neurological syndromes are conditions that manifest as the remote effects of cancer. These are very rare, occurring in 1/10000 patients with a malignancy, and include Lambert–Eaton myasthenic syndrome, limbic encephalitis, subacute cerebellar ataxia, opsoclonus-myoclonus, Stiff–Person Syndrome, retinopathies, chronic gastrointestinal pseudo-obstruction and sensory neuropathy. This report describes a case of 41-year-old man who presented with elements of multiple paraneoplastic syndromes, including chronic gastrointestinal pseudo-obstruction, myasthenia gravis–Lambert–Eaton overlap syndrome and polymyositis, and who was subsequently found to have a malignant thymoma. There are only three reported cases in the literature describing cases of Lambert–Eaton myasthenic syndrome in association with a thymoma, and only one case of a myasthenia gravis–Lambert–Eaton overlap syndrome in a patient with thymoma. However, there are no documented cases in the literature of this constellation of syndromes in a patient with a malignant thymoma.

BACKGROUND

Paraneoplastic neurological syndrome (PNS) is the remote neurological manifestation of a malignancy that is not caused by the tumour mass or by its metastasis. These are very rare, occurring in less than 0.01% of patients with cancer.¹ Most PNS appear months or years before the underlying cancer becomes clinically evident and consist of isolated and often well-recognised neurological syndromes, which can co-exist and sometimes overlap.

Our case shows an unusual combination of PNS including chronic gastrointestinal pseudo-obstruction (CGP) (or paraneoplastic autonomic neuropathy with prominent gastrointestinal dysfunction), myasthenia gravis–Lambert–Eaton overlap syndrome, radiological features of limbic encephalitis (LE) and polymyositis.

To our knowledge this is the first case of such constellation of syndromes in a patient with a malignant thymoma.

CASE PRESENTATION

A 41-year-old, non-smoker male presented initially with episodic constipation and diarrhoea. He had lost 19 kg in weight over 2 years. He also had history of abdominal distension, nausea and occasional vomiting. His gastrointestinal symptoms were investigated with blood tests, upper gastrointestinal tract endoscopy, duodenal biopsy, colonoscopy, CT pneumocolon, CT enteroclysis and MRI. All of these investigations were normal with the exception for a mild lymphocytosis which was attributed to normal reactive T lymphocytes.

Two years after his initial presentation, the patient began to have generalised weakness associated with muscle wasting and lethargy. He found crossing his legs difficult and had difficulty in walking. The patient also reported

autonomic symptoms of dry mouth, postural dizziness and vertigo, which was worse on movement.

Clinical examination revealed bilateral, symmetrical wasting, normal tone and proximal weakness more marked than distal weakness in the upper and lower limbs. Sensation and reflexes were normal except for equivocal plantar reflexes were noticed. There were no cerebellar signs, and Hallpikes manoeuvre was negative.

Blood tests showed a total creatine kinase of 89 U/l, lymphocytosis and raised antiacetylcholine receptor (anti-AchR) antibodies of 252×10^{-10} mol. Voltage-gated calcium channels (VGCC) and voltage-gated potassium channel antibodies were negative. Western block for anti-Hu, anti-Ri, anti-Ma, anti-yo, anti-CV2/CRMP5 and antiampiphysin antibodies were all negative. Electromyography was consistent with myopathic weakness, with no incremental or decremental responses.

CT-scan of his chest, abdomen and pelvis showed a large mass measuring 11×8×7.4 cm in his anterior and superior mediastinum (figure 1). A positron emission tomography scan showed low-grade uptake in the thymus and in the left lung base. Gadolinium enhanced MRI brain scan showed a T2 parenchymal signal abnormality affecting the mesial temporal lobes and cingulate gyri bilaterally, these features are in keeping with LE.

CT-guided biopsy from the mediastinal mass confirmed this as a thymoma with cortical differentiation. Muscle biopsy revealed myopathic features and focal inflammatory changes of a perimysial and perivascular lymphocytic infiltrate composed of B and T cells.

Thymectomy was planned and the patient was given intravenous immunoglobulins (vigam) and was started on oral steroids (prednisolone) before surgery.

Figure 1 Mediastinal CT slide shows the big size thymoma in the anterior mediastinum.

At operation, a myasthenia protocol was used for anaesthesia in view of the patient's unconfirmed neurological diagnosis. Following median sternotomy, the tumour was found in the anterior and superior mediastinum. It was invading the left brachiocephalic vein and was adherent to the left lung and also attached to the pericardium at the right ventricle outflow tract/pulmonary artery region.

Complete resection of the tumour required resection and reconstruction of the brachiocephalic vein and the attached pericardium. The left phrenic nerve could not be spared. Postoperatively, he was extubated early with the avoidance of neuromuscular blocking agents.

OUTCOME AND FOLLOW-UP

Histological examination of the surgical resection specimen revealed a wildly invasive type B3 atypical thymoma (T3, Nx, Mx Masaoka stage 3).

Postoperatively, prednisolone was stopped 6 months after surgery, and 4 months postoperatively the patient developed diabetes mellitus required insulin therapy (IDDM). An MRI brain performed seven months after thymectomy showed complete disappearance of the MRI features of LE. Follow-up at 16 months postoperatively showed complete recovery from the neuromuscular symptoms, but positive (anti-AchR) antibodies.

DISCUSSION

PNS is the remote neurological manifestations of cancer that is not caused by the tumour mass or by its metastasis. Our patient has a definite diagnosis of PNS according to the diagnostic criteria recommended by an international panel of neurologists in 2004.² This patient presented initially with the classical picture of CGP.¹ This is a neurological PNS that is rare and is usually associated with raised anti-Hu antibody and CV2 antibody (CV2-AB) and mostly occurs in association with small cell lung carcinoma (SCLC).¹ However, the presence of autonomic dysfunction

symptoms and the absence of the classical antibodies make the diagnosis of paraneoplastic autonomic neuropathy with prominent gastrointestinal dysfunction also possible. Such a presentation is usually associated with a thymoma and SCLC.¹

Disorders of the neuromuscular junction can be classified into presynaptic and postsynaptic disorders such as LEMS and myasthenia gravis (MG), respectively. These two groups are relatively common and distinct but a mixed and atypical pattern of these disorders (overlap myasthenic syndrome) also occurs.^{3–8} Paraneoplastic overlap myasthenic syndrome is rare and is usually associated with lung cancer. Our literature search found only one case report of such overlap in a patient with a malignant thymoma.⁹

LEMS is an autoimmune disease in which anti-VGCC-Ab play a major role in decreasing the amount of acetylcholine (ACh) released. This results in skeletal muscle weakness and autonomic symptoms. LEMS is associated with malignancy, mainly SCLC, which is found in 50%–60% of patients with LEMS. LEMS is a rare condition, affecting 1 in 100 000 people, 50% of whom have a malignancy.¹⁰

This case does not present a clear-cut paraneoplastic syndrome. The muscles weakness and the autonomic dysfunction suggest the diagnosis of LEMS more than MG. However, the (anti-AchR) antibodies were grossly elevated, raising the possibility of a diagnosis of MG. In addition, the anti-VGCC-Ab was negative, making the diagnosis of LEMS uncertain, although LEMS with negative VGCC has been reported previously.⁸ There have been only three documented cases of LEMS in a patient with a confirmed thymoma.^{11–13}

Another unusual feature was the presence of radiological picture of LE. Our patient did not have cognitive or memory disorders but the MRI brain scan was highly suggestive of LE.¹⁴ Complete resolution of the radiological feature of LE postoperatively suggests a positive relationship

between successful thymectomy and LE treatment. Also the late development of IDDM is mostly due to an autoimmune mechanism secondary to his thymoma, which is a very rare condition.¹⁵

Lastly, the result of the muscle biopsy was also unusual, as it did not show a picture typical of dermatomyositis. The myopathic features and the focal inflammatory changes are compatible with those reported as thymoma-associated dermatomyositis¹⁶ (also can be seen in myasthenia gravis). However, the histopathology shows no membrane attack complex deposits in endomysial capillaries, and MHC class I expression limited to some fibres, which are unusual feature for idiopathic and cancer-related dermatomyositis. Also the patient never presented with the typical rash of paraneoplastic dermatomyositis, which supports the diagnosis of polymyositis, rather than dermatomyositis. Such a casual relationship between thymic malignancy and polymyositis has been recently reported and discussed.¹⁷ Therefore and for all the above reasons this case clinically was very challenging, as the PNS including overlap myasthenic syndrome, CGP, autonomic paraneoplastic syndrome, LE and polymyositis were all present, though incomplete or overlapped.

Our patient underwent both medical and surgical treatment of thymoma. His symptoms did not improve dramatically on the medical treatment. Thymectomy was indicated for both; surgical excision of the thymoma and treatment of the paraneoplastic syndrome. Postoperatively, his muscle strength and autonomic dysfunction recovered completely. The mechanism of action remains unclear as to how performing a thymectomy improves the symptoms of myasthenia, or other such paraneoplastic syndromes, however some suggested mechanisms include removal of the antigenic stimulus by removing the thymus, or by alterations in immune regulation.¹⁸

Learning points

- ▶ Our search revealed this is the first case to be reported as invasive thymoma associated with such multiple paraneoplastic syndromes. Paraneoplastic syndromes involve a wide range of clinical pictures that are associated with malignancies. Most of them are distinctly recognised, but some are still difficult to be categorised as a result of their overlap.
- ▶ This case is a good example to learn about the diversity, complexity and the wide spectrum of features in PNS. New pictures of PNS will probably continue to be discovered which could be due to the autoimmune aspect of the disease process, which can affect different organs and tissue, and in different severity.
- ▶ Continuation in reporting new pictures of PNS may be the best way to help in build up more experience and knowledge about this complex medical disorder.

Competing interests None.

Patient consent Obtained.

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