Two patients with a neuroendocrine tumour of the small intestine and paraneoplastic myasthenia gravis

M A W Hermans, B M L Stelten¹, H R Haak, W W de Herder² and M W Dercksen

Department of Internal Medicine, Maxima Medical Centre, Ds Theodor Fliednerstr 1, 5631BM, Eindhoven, The Netherlands

¹Department of Neurology, Canisius Wilhelmina Hospital, Weg door Jonkerbos 100, 6532SZ, Nijmegen, The Netherlands

²Department of Internal Medicine, Erasmus University Medical Centre, Gravendijkwal 230, 3015CE, Rotterdam, The Netherlands

Correspondence should be addressed to M A W Hermans
Email maud.hermans@mmc.nl

Summary

This paper reports on two patients with a long-standing diagnosis of an ENETS stage IV neuroendocrine tumour (NET) of the small intestine who developed neurological symptoms. The first patient only had bulbar symptoms and tested positive for acetylcholine receptor antibodies. The second patient had more classical symptoms of fatigable diplopia and muscle weakness of the legs, but no detectable antibodies. The diagnosis of paraneoplastic myasthenia gravis (MG) was postulated. Both patients were treated with pyridostigmine for MG and octreotide for the NETs. Interestingly, treatment of the NETs resulted in improvement of myasthenic symptoms. Paraneoplastic MG has been described to occur with certain malignancies, mainly thymoma. Herein, we prove that the association with gastrointestinal NETs, however, rare, is also one to be considered by clinicians dealing with either of these diseases. The pathogenesis has yet to be elucidated.

Learning points:

- NETs are rare malignancies with a wide variety of symptoms.
- Paraneoplastic MG can occur with various types of malignancies.
- Herein, we provide evidence of paraneoplastic MG in association with a grade IV NET of the small intestine.
- Treatment of the NETs resulted in remission of myasthenic symptoms in one patient.

Background

Neuroendocrine tumours (NETs) are rare malignancies with a wide variety of symptoms. In this paper, we report on two patients with an ENETS stage IV NET of the small intestine, who develop paraneoplastic myasthenia gravis (MG) in concurrence with progression of their NETs. This is a rare autoimmune phenomenon related to gastrointestinal NETs. To our knowledge, this association was described only once before in the current literature. There are few other case reports of associated MG with NETs of the lung and pancreas (1) (2). Therefore, it is important for clinicians, dealing with either of these diseases, to be aware that MG can occur as a paraneoplastic phenomenon with NETs.

Case presentation

Patient A

The first patient is a 72-year-old Caucasian male who was diagnosed with a WHO grade I NET of the ileum for which partial resection of the ileum was performed in 1995.
that time, hepatic and mesenterial metastases were already present. Owing to the indolent behaviour, including stable 5-HIAA production, he was only treated symptomatically with colestyramine for diarrhoea. He did not suffer from other features of the carcinoid syndrome. The patient did not have any other relevant medical conditions. The follow-up was unremarkable with very slowly growing intra-abdominal metastases until March 2012, when the patient presented with progressive complaints of dysarthria and dysphagia that had developed over a period of 3 weeks. He denied having any visual difficulties. The dysarthria worsened when involved in a long conversation. Physical examination only revealed dysarthria and an ineffective swallowing reflex. Magnetic resonance imaging of the brain examination did not show any abnormalities. The diagnosis of (bulbar) swallowing reflex. Magnetic resonance imaging of the brain examination only revealed dysarthria and an ineffective swallowing reflex. Magnetic resonance imaging of the brain did not show any abnormalities. The diagnosis of (bulbar) MG was postulated on the basis of positive (>2.0 mmol/l) anti-acetylcholine receptor (AChR) antibodies and a declining response following repetitive nerve stimulation during electromyography (EMG). Accordingly, he was treated with pyridostigmine and a partial clinical response was achieved. CT scan of the chest did not show a thymic mass.

Patient B

Our second patient is a 61-year-old Caucasian male with a WHO grade II, ENETS stage IV NET of unknown primary tumour site (most likely ileum) with mesenterial and lymph node metastases since 2008. He was steadily treated with octreotide that has caused a significant reduction in tumour markers to near-normal values as well as reduction of symptoms and radiologically stable disease. Of interest, in parallel with decreasing tumour markers, the myasthenic symptoms have disappeared and pyridostigmine could be stopped. To this date, no myasthenic symptoms have reappeared.

Patient B developed side effects of diarrhoea, for which the pyridostigmine dose had to be lowered to 60 mg two times daily with persistent relief of myasthenia. Currently, peptide receptor radiotherapy with lutetium-177 octreotide is being considered for the treatment of the NET metastases.

Discussion

We present two patients with an ENETS stage IV NET of the small intestine with paraneoplastic MG occurring simultaneously with progression of the tumour. To our knowledge, this association was only described once in the current medical literature (3).

Of course, MG as a paraneoplastic phenomenon of thymoma is a widely recognised association. Next to thymic neoplasms, NETs of the lung (1) as well as pancreatic NETs (2) and haematological malignancies (4) have been described to coincide with MG.

Neuroendocrine tumours

NETs are rare, with an estimated incidence in the Western world of ~2/100 000 (5). The main primary sites are the
lungs, gastrointestinal tract and pancreas (5) (6). These tumours are capable of secreting various bioactive substances that can cause symptoms depending on the amount and type of substance secreted, and on the presence of hepatic metastases. The most well-known clinical presentation is the carcinoid syndrome (7). As they are often asymptomatic for a long period of time, NETs have often already metastasised at the moment of diagnosis (5) (6). This implicates that the best treatment option, being complete surgical resection, is generally not feasible for most patients. In the presence of extensive metastases, there are several palliative pharmacotherapeutic options.

Most commonly used are somatostatin (sst) analogues that mainly give relief of symptoms. They also may have minor cytostatic effects, thereby improving progression-free survival (8).

Secondly, molecular targeted therapies with everolimus or sunitinib are very promising but these drugs are not yet approved for the treatment of gastrointestinal NETs (9).

**Myasthenia gravis**

Although being a rare disease, MG is the most common disorder of the neuromuscular junction. The prevalence is estimated to be 10–15 per 100 000 (10). It is an autoimmune disease affecting the neuromuscular junction, in which antibodies against AChRs play an important role, but other antibodies can also be found (11). EMG is another tool to support the diagnosis of MG. Myasthenia can be exacerbated by various stressors among which are many drugs. The natural course of MG is very variable and unpredictable (10). The keystone of treatment is acetylcholinesterase inhibition by pyridostigmine. When patients with NETs. Finding the right ‘cocktail’ of octreotide and pyridostigmine can be challenging, as seen in the second patient.

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The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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**Author contribution statement**
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