Late onset myasthenia gravis and carcinoid tumour: paraneoplastic syndrome?

Introduction

Neurological syndromes associated with underlying cancer may reflect the chance concurrence of two separate disease processes, or may be aetiologically related as paraneoplastic neurological syndromes. Tumour-specific, or onconeural, antibodies which cross react with both tumour and nervous tissue may be relevant to disease pathophysiology. In the absence of defined onconeural antibodies, the definition of a paraneoplastic neurological syndrome may be challenging, as shown in this case.

Discussion

This case raised a number of interesting issues. First, the patient's age at disease onset (early 80s). The incidence of myasthenia gravis is markedly age-dependent, with peaks at both 10–30 years and over the age of about 60 years, and about half of patients presenting after the age of 40 years. Myasthenia gravis has previously been markedly underdiagnosed in people over the age of 75 years (Vincent et al, 2003) and the apparent increase in myasthenia gravis frequency revealed by epidemiological studies appears to be the result of an increased incidence of late-onset disease (e.g. Somnier, 2005; Alkhawajah and Oger, 2013). These epidemiological data should prompt a greater awareness of the possibility of myasthenia gravis in older persons.

Older patients with myasthenia gravis typically present with focal weakness, often ocular or bulbar. However, a high index of clinical suspicion may be required to make the diagnosis since the typical clinical features may be more difficult to spot in older individuals: age-related decrease in total eyelid area with sagging of the lower eyelids may make ptosis less easy to diagnose, and diplopia may not be detected as a result of impaired vision secondary to macular degeneration or cataract formation (Sathasivam and Larner, 2012).

A second issue relates to the finding of a tumour in this patient. Myasthenia gravis may be classified as one of the 'non-classical' paraneoplastic neurological syndromes (see Table 1 in Graus et al, 2004) because of its association in some cases, around 10–15%, with an underlying thymus gland tumour (thymoma). Myasthenia gravis with thymoma has a peak onset in the fifth and sixth decades. Paraneoplastic myasthenia gravis related to thymoma causes a distinctive non-limb symptom profile at onset, characterized by bulbar, ocular, neck and respiratory symptoms. It shares not only this clinical but also an immunological profile with late onset myasthenia gravis (Skeie and Romi, 2008). Certainly all late onset cases of myasthenia gravis should be evaluated for possible paraneoplasia, at minimum with computed tomography of the thorax; dependent on the precise syndrome, specific onconeural antibodies may be sought. Thyroid tumours (papillary carcinoma) have also been reported on occasion in association with paraneoplastic myasthenia gravis (Illa et al, 1995).

A third issue was the unexpected finding of a thymic carcinoid tumour in this patient with late onset myasthenia gravis. Association of myasthenia gravis with carcinoid (neuroendocrine) tumours has rarely been reported. One patient, separately reported on two occasions (Wroe et al, 1985; Keens et al, 1986), developed myasthenia gravis around 14 months after diagnosis of a malignant carcinoid presenting with obstruction of the small bowel with only weakly positive acetylcholine receptor antibody. Wu et al (2004) reported the onset of myasthenia gravis 3–4 weeks after the biopsy of a thoracic mass, found incidentally, which proved to be a thymic carcinoid. Hermans et al (2014) reported two patients with long-standing small intestinal neuroendocrine tumours who presented with myasthenic symptoms, one with and one without acetylcholine receptor antibodies.

CASE REPORT

An 83-year-old woman presented with a 6-month history of double vision, drooping of her right eyelid, and dysphagia. Similar symptoms had occurred 2 years previously but remitted spontaneously after a few weeks. Neurological examination disclosed a variable ptosis and ophthalmoplegia with subjective diplopia, but was otherwise normal – in particular there was no limb weakness. There was no history of xerophthalmia or xerostomia.

A diagnosis of myasthenia gravis was suspected clinically. There were no clinical features to suggest Lambert–Eaton myasthenic syndrome (e.g. no proximal limb weakness, xerophthalmia or xerostomia, or reflex loss with post-tetanic potentiation), a 'classical' paraneoplastic neurological syndrome (Graus et al, 2004) with which myasthenia gravis is sometimes confused. Acetylcholine receptor antibody assay proved strongly positive (143×10^{-10} mol, normal range 0–2.5×10^{-10} mol), confirming the clinical diagnosis. The patient was initially given symptomatic treatment with pyridostigmine and then disease-modifying therapy with intravenous immunoglobulin, with clinical benefit.

Further investigation included computed tomography of the thorax which showed a lobulated soft tissue mass (2.8x4.0 cm) lying in the anterior mediastinum adjacent to the right heart border. Transthoracic biopsy of this lesion showed features of a thymic carcinoid tumour. Thymic tumour tissue was composed of small monomorphic epithelioid cells without any mitosis on haematoxylin and eosin staining. These cells were positive for neuroendocrine markers (CD56, synaptophysin) and keratin. The proliferative index, assessed using Ki-67, was less than 2%. The patient was deemed not fit to undergo surgical tumour resection.

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A fourth issue is the relevance of the carcinoid tumour to the myasthenia gravis. Considering the limited literature, this might represent a chance concurrence of two rare disorders. However, paraneoplasia is another possibility, as suggested by Hermans et al (2014), which the authors favour. A few case reports and case series (e.g. Tschernatsch et al, 2008) have reported carcinoid tumours in association with other paraneoplastic neurological syndromes such as sensory neuropathy, limbic encephalitis, myelopathy and brainstem encephalitis – both classical and non-classical paraneoplastic neurological syndromes. Neuroendocrine tumours of lung (Burns et al, 1999) and pancreas (Bertani et al, 2011) have also been reported in association with myasthenia gravis. Clinicians should be alert for new associations between paraneoplastic neurological syndromes and unusual tumour types (Taib et al, 2015). **BJHM**

LEARNING POINTS

- The incidence of late-onset myasthenia gravis appears to be increasing, mandating a heightened clinical awareness of this disorder in older people.
- Myasthenia gravis is one of the 'non-classical' paraneoplastic neurological syndromes, since in some cases it is associated with thymoma and more rarely with other tumours.
- The diagnosis of late-onset myasthenia gravis should prompt a search for an underlying tumour, at minimum with computed tomography of the thorax.
- Paraneoplastic neurological syndromes associated with carcinoid (neuroendocrine) tumours have rarely been described, but this case suggests that the possible association between myasthenia gravis and carcinoid should be further pursued.

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