Sensory neuronopathy as a possible paraneoplastic neurological syndrome linked with pancreatic cancer

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Introduction

Neurological syndromes associated with underlying cancer may reflect a chance concurrence of two separate disease processes, but may sometimes be aetiologically associated as paraneoplastic neurological syndromes. In some, but not all, of these cases, tumour-specific (onconeural) antibodies which cross react with both tumour and nervous tissue may be relevant to disease pathophysiology. In the absence of defined onconeural antibodies, diagnosis of a paraneoplastic neurological syndrome may be challenging, since tumours may be small and occult. Sophisticated imaging modalities may sometimes help in these circumstances, as shown in this case.

Discussion

This patient fulfilled suggested diagnostic criteria for 'possible sensory neuronopathy', specifically the following items: ataxia in the upper limbs at onset or full development, sensory loss not restricted to the lower limbs at full development, at least one sensory action

CASE REPORT

A 63-year-old woman was referred for neurological opinion with an approximately 6-month history of numbness in her arms and legs, extending to the buttocks. She had difficulty in holding and manipulating objects in her hands. When walking, her legs had a tendency to give way with occasional falls, and she mobilized by holding on to others or furniture for support. She could not distinguish hot from cold.

These problems developed while she was undergoing investigation and treatment for obstructive jaundice resulting from a bile duct stricture for which no specific cause had been found. Although a pancreatic tumour was suspected, no evidence to support this was forthcoming from either abdominal computed tomography or fine needle aspiration undertaken during endoscopic retrograde cholangio-pancreatography for bile duct stenting. The patient also had a prior history of cervical spondylotic myelopathy requiring cervical laminectomy, from which she had made good recovery.

On general medical examination she was cachectic. Examination of the nervous system showed the cranial nerves to be intact. Limb tone was reduced. There was apparent limb weakness greater distally (Medical Research Council grade 2/5) than proximally (4/5), with bilateral wrist drop and foot drop; pseudoathetosis (sensory ataxia) was evident when the arms were extended. Reflexes were reduced in the arms and absent in the legs. On sensory examination, sensation to pinprick was absent to the hip and shoulder, likewise joint position (proprioception) and vibration sensation.

The subacute evolving neurological syndrome with largely symmetrical sensorimotor dysfunction was thought most likely to reflect a peripheral neuropathy. By the time of referral she had already had magnetic resonance imaging of the complete neuraxis which showed neither intraparenchymal inflammation nor spinal cord or root compression. Electromyography and nerve conduction studies showed global absence of sensory responses in upper and lower limbs, but with normal motor studies and F wave latencies bilaterally. Electromyography showed normal units and recruitment. The findings, consistent over two studies, were indicative of a sensory neuronopathy or ganglionopathy.

Further investigations were undertaken in light of recognized causes of sensory neuronopathy. There were no stigmata of Sjögren's disease and antibodies for anti-Ro and anti-La were negative, as was an extensive autoantibody screen including antibodies for coeliac disease and gangliosides. CSF was normal (protein, cell count, cytology, no oligoclonal bands), including polymerase chain reaction for herpes simplex, varicella zoster, enterovirus and parechovirus.

A paraneoplastic cause was thought the most likely aetiological explanation for sensory neuronopathy in this patient. A panel of onconeural antibodies (Hu, Yo, CV2/CRMP5, Ri, Ma1, Ma2, amphiphysin, Tr, SOX1, GAD65) was negative. Of tumour markers, α-fetoprotein and CA-125 were normal, but there was persistent elevation of carcinoembryonic antigen (6.5–9.5 ng/ml; normal range 0–3.5 ng/ml) and CA19-9 (285–737 U/ml; normal range 0–37 U/ml). The elevated tumour markers in this clinical context were presumptive evidence of an underlying pancreatic tumour and hence prompted further investigation. As computed tomography scanning of the abdomen remained negative, and endoscopic retrograde cholangiopancreatography with fine needle aspiration had provided no definitive evidence, 18F-fluoro-2-deoxyglucose-positron emission tomography was performed. This showed an avid ('high-grade') fluoro-2-deoxyglucose focus of uptake in the posterior aspect of the body of the pancreas. The clinical and investigative findings were thought to be consistent with a diagnosis of pancreatic cancer.

Accordingly the sensory neuronopathy was thought to be a paraneoplastic syndrome. The most appropriate treatment in paraneoplastic syndromes with an identified tumour is surgical excision of the lesion, but this was contraindicated given the patient's comorbidities. She was therefore given a course of intravenous immunoglobulin and tapering oral steroids for her neurological symptoms, which temporarily improved dexterity and mobility for a few weeks before she deteriorated once again.

potential absent, less than two nerves with abnormal motor nerve conduction studies in the lower limbs (Camdessanché et al, 2009). Unlike distal peripheral neuropathies, symptoms and signs in sensory neuronopathy are not 'length-dependent', e.g. glove and stocking sensory loss. Moreover, there may be associated apparent weakness, despite normal motor neurophysiology studies, which may be explained by the profound proprioceptive loss, perhaps exacerbated in this patient by neural damage as a result of her prior spondylotic myelopathy.

Considering the differential diagnosis of sensory neuronopathy, a paraneoplastic aetiology was considered most likely in this patient. Sensory neuronopathy is recognized as one of the 'classical' paraneoplastic neurological syndromes, along with encephalomyelitis, limbic encephalitis, opsoclonus or myoclonus, subacute cerebellar degeneration and Lambert–Eaton myasthenic syndrome. Other neurological syndromes may occur in association with underlying neoplasia on occasion, and are termed 'non-classical' paraneoplastic neurological syndromes (Graus et al, 2004). On conservative application of the suggested diagnostic criteria, this patient may be characterized as fulfilling criteria for 'possible paraneoplastic neurological syndromes', specifically a classical syndrome (sensory neuronopathy), no onconeural antibodies, and no (definitive) cancer but at high risk of having an underlying tumour (Graus et al, 2004).

Paraneoplastic neurological syndromes associated with pancreatic cancer have rarely been reported. Of the classical paraneoplastic neurological syndromes, single cases of opsoclonus (Aggarwal and Williams, 1997) and encephalomyelitis with anti-GAD antibodies (Hernandez-Echebarria et al, 2006) have appeared; of the 'non-classical' paraneoplastic neurological syndromes, Guillain–Barré syndrome has been reported occasionally (Klingon, 1965; Lim et al, 2008).

Conclusions

To the authors' knowledge this is the first report of sensory neuronopathy associated with pancreatic cancer. Admittedly the latter diagnosis was provisional in the absence of tissue confirmation, based on consistently elevated tumour markers (CEA, CA19-9) and the findings from 18F-fluoro-2-deoxyglucose-positron emission tomography (FDG-PET) imaging. The latter modality has become established as a valuable investigation in cases of suspected paraneoplasia when other structural imaging modalities have failed to detect an underlying malignancy, including cases of sensory neuronopathy (Rees et al, 2001). Its use has been recommended in patients with clinically suspicious paraneoplastic neurological syndromes even in the absence of onconeural antibodies (Matsuhisa et al, 2012) because of its incremental role, although the overall pick-up rate may be quite low (Bannas et al, 2010) and serial studies may be required. **BJHM**

LEARNING POINTS

- Sensory neuronopathy, or ganglionopathy, is recognized as one of the 'classical' paraneoplastic neurological syndromes.
- The diagnosis of sensory neuronopathy, based on clinical and neurophysiological findings, should prompt a search for recognized causes, especially Sjögren's disease and paraneoplasia.
- If structural imaging fails to disclose a tumour in suspected paraneoplastic sensory neuronopathy, functional imaging with 18F-fluoro-2-deoxyglucose-positron emission tomography (FDG-PET) should be obtained, sometimes serially, as this may disclose avid uptake in a tumour mass.
- Paraneoplastic syndromes associated with pancreatic cancer have rarely been described.

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