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Full clinical cases submission template

TITLE OF CASE ***Do not include "a case report"***

A sensory neuronopathy associated with cholangiocarcinoma diagnosed six years after symptom onset.

SUMMARY ***Up to 150 words summarising the case presentation and outcome (this will be freely available online)***

A pure sensory neuronopathy (also referred to as a sensory ganglionopathy) is one of a handful of classical neurological paraneoplastic syndromes. Current guidelines recommend that in cases of sensory neuronopathy, a search for an underlying malignancy be pursued for up to four years. We report the case of a 52-year old lady with a sensory neuronopathy who was eventually diagnosed with a cholangiocarcinoma six years after the onset of her disease. A CT FDG-PET scan performed 18 and 24 months after disease onset failed to identify an underlying neoplasm. Immunomodulatory treatment with corticosteroids, intravenous immunogolobulins and plasma exchange were ineffective. Investigations for Sjogrens disease were negative. A third FDG-PET performed six years after symptoms onset identified a cholangiocarcinoma which was confirmed histologically following open resection. Since the tumour was removed our patient's condition has not progressed but there has been no improvement and she remains severely disabled.

BACKGROUND ***Why you think this case is important – why did you write it up?***

A pure sensory neuronopathy (also referred to as a sensory ganglionopathy) is one of a handful of recognised neurological paraneoplastic syndromes. Current guidelines recommend that in cases of sensory neuronopathy, a search for an underlying malignancy be pursued for up to four years. [1] In this case, a cholangiocarcinoma was detected six years after disease onset and in the absence of an onconeuronal antibody, one cannot be certain that this is causal of her neuropathy. Evidence of causality will be strengthened by the identification of additional patients with cholangiocarcnoma and a sensory neuronopathy.

CASE PRESENTATION ***Presenting features, medical/social/family history***

A 52-year old right handed female first developed symptoms in 2009 starting with the inability to feel the pedals of her sewing machine. The numbness in her feet persisted and after two years she developed pain and paraesthesia in the hands and progressive difficulty with her balance that prompted her to attend her general practitioner. Over the following year (2012) her balance deteriorated rapidly such that she required the use of a wheelchair. Examination in 2012 revealed a tonic left pupil and severe sensory ataxia that mimicked a choreiform movement disorder and rendered her unable to walk. This is demonstrated in the video clip in which the patient is shown attempting to bring her index fingers together with her eyes closed. Limb power was normal and she was areflexic. There was severe impairment of all modalities of sensation. Neurophysiology revealed normal compound muscle action potentials and electromyography but absent sensory action potential in the upper and lower limbs consistent with a sensory neuronopathy.

INVESTIGATIONS ***If relevant***

Initial investigations in 2012 revealed a vitamin B12 level of 168 pg/ml (108-914), however, despite parenteral supplementation her symptoms progressed. The patient was referred to our service in 2013, four years after the onset of her symptoms. A full blood screen including ANA, ENA, ANCA, dsDNA, vitamins B1 and B6, copper and caeruloplasmin, HIV, Hepatitis B and C

and serum protein electrophoresis were normal. The anti-neuronal antibody, anti CRMP5 was weakly positive when first tested but was subsequently negative on repeated testing. Anti-Hu antibodies were negative. CSF examination revealed a white cell count of 6 (normal <5), protein 0.52 g/l, glucose 3.0 mmol/l and matched oligoclonal bands. MRI revealed flattening and signal change of the dorsal columns of the cervical and thoracic cords due to a loss of sensory afferent fibres (See figure 1). A CT of the chest, abdomen and pelvis and FDG-CT PET at the time of referral and after 6 months were both normal (see figure 1). A sural nerve biopsy revealed a severe chronic axonal neuropathy with minimal epineurial inflammation. Schirmer's test was positive but a labial minor salivary gland biopsy, to investigate the possibility of Sjogrens disease, revealed non-specific mild chronic sialadenitis.

DIFFERENTIAL DIAGNOSIS ***If relevant***

Peripheral neuropathies that solely affect the sensory nerves are termed pure sensory neuropathies, sensory neuronopathies or dorsal root ganglionopathies. Paraneoplasia accounts for approximately 20% of cases of sensory neuronopathy with the remainder being either idiopathic, toxic (cisplatin or excess pyridoxine) or mitochondrial (Sensory Ataxic Neuropathy Dysarthria and Ophthalmoplegia Syndrome). [2]

TREATMENT ***If relevant***

A diagnosis of an acquired sensory neuronopathy was made and the patient was treated for a possible inflammatory aetiology based on our previous experience with three courses of intravenous immunoglobulin with no response. [3] Corticosteroids were briefly tried but were not tolerated. Two courses of plasma exchange were ineffective.

OUTCOME AND FOLLOW-UP

Six years after the onset of symptoms the patient underwent a 3rd FDG-PET and CT scan which revealed both FDG avid uptake and thickening of the gallbladder fundus (see figure 1). A laparoscopic examination revealed cancer of the gallbladder and the patient underwent an open cholecystectomy, gallbladder fossa resection, lymphadenectomy and port excision. Histology revealed a poorly differentiated cholangiocarcinoma. Since the tumour was removed our patient's condition has not progressed but there has been no improvement and our patient remains severely disabled. On the basis of published guidelines on paraneoplastic neurological syndromes [4], as the cholangiocarcinoma was not detected within 5 years of symptom onset and in the absence of an onco-neuronal antibody, one cannot be certain that the cholangiocarcinoma was causal of the sensory neuronopathy.

DISCUSSION ***Include a very brief review of similar published cases***

The non-length dependent nature of the sensory loss (involvement of the face, lips and trunk), areflexia, and predominantly large fibre sensory loss suggest the presence of a sensory neuronopathy as opposed to a sensory neuropathy. As is typical for patients with a sensory neuronopathy, despite severe disability, power is preserved. Paraneoplastic sensory neuronopathies are most frequently associated with small cell lung and breast cancer. [1] Cholangiocarcinoma is a recognised cause of paraneoplastic hypercalcaemia, necrotic migratory

erythema and alopecia but is rarely associated with paraneoplastic neurological disease. [5-7] Due to the significant time interval between symptom onset and detection of the cholangiocarcinoma and the absence of an onconeuronal antibody, one cannot be certain that our patient has a paraneoplastic as opposed to an idiopathic sensory neuronopathy. This case raises the important question of how long such patients should be investigated for an underlying tumour after disease onset. This case also illustrates the difficulty in proving causality of a tumour detected after several years. As sensory neurons are unable to regenerate following presumed apoptotic cell death, removal of a causal tumour is unlikely to lead to a clinical improvement but may halt progression.

LEARNING POINTS/TAKE HOME MESSAGES ***3 to 5 bullet points – this is a required field***

1. A thorough search for an underlying tumour should be performed in patients presenting with a sensory neuronopathy
2. A search for an underlying tumour in potentially paraneoplastic disease should continue for several years unless an alternative cause for the neuropathy is identified
3. In the absence of onconeural antibodies the discovery of a tumour after five years of follow-up may not definitely demonstrate that the neurological syndrome is paraneoplastic

REFERENCES ***Vancouver style (Was the patient involved in a clinical trial? Please reference related articles)***

1. Vedeler CA, Antoine JC, Giometto B, Graus F, Grisold W, Honnorat J, et al. Paraneoplastic Neurological Syndromes. European Handbook of Neurological Management. Oxford, UK: Wiley-Blackwell; 2010. p. 447–57.
2. Sheikh SI, Amato AA. The dorsal root ganglion under attack: the acquired sensory ganglionopathies. Pract Neurol. 2010 Nov 20;10(6):326–34.
3. Marquez-Infante C, Murphy SM, Mathew L, Alsanousi A, Lunn MP, Brandner S, et al. Asymmetric sensory ganglionopathy: a case series. Muscle Nerve. 2013 Jul;48(1):145–50.
4. Graus F, Delattre JY, Antoine JC, Dalmau J, Giometto B, Grisold W, et al. Recommended diagnostic criteria for paraneoplastic neurological syndromes. J Neurol Neurosurg Psychiatry. 2004 Aug 1;75(8):1135–40.
5. Yen Y, Chu PG, Feng W. Paraneoplastic syndromes in cancer: Case 3. Parathyroid hormone-related hypercalcemia in cholangiocarcinoma. J Clin Oncol. 2004 Jun 1;22(11):2244–5.
6. Chiyomaru K, Takai T, Ohashi A, Nishigori C. Necrolytic migratory erythema with cholangiocarcinoma: Pseudoglucagonoma syndrome. Eur J Dermatol. Jan;20(2):238–9.
7. Antoniou E, Paraskeva P, Smyrnis A, Konstantopoulos K. Alopecia: a common paraneoplastic manifestation of cholangiocarcinoma in humans and animals. BMJ Case Rep. 2012 Jan;2012.

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FIGURE/VIDEO CAPTIONS ***figures should NOT be embedded in this document***

Figure 1. This figure shows a T2 weighted MRI of the cervical (A) and thoracic (B) cords demonstrating flattening and signal change of the dorsal columns due to a loss of sensory afferent fibres (highlighted by the red arrows). C shows a normal FDG-CT PET at the time of referral. D and E show images from a 3rd FDG-PET and CT scan performed six years after symptom onset demonstrating FDG avid uptake and thickening of the gallbladder fundus (highlighted by the red arrows).

Video. This video shows the patient attempting to bring the index fingers of her outstretched arms together, initially with her eyes open and subsequently with her eyes closed. As a result of loss of proprioception the patient is unaware of the position of her limbs with the eyes closed and is unable to bring her index fingers together. Abnormal movements in sensory neuronopathies are typically athetoid. The striking asymmetry in the movements correlates with more severe sensory loss on the left side on examination. Pseudoathetoid movements were present in the feet.

PATIENT'S PERSPECTIVE ***Optional but strongly encouraged – this has to be written by the patient or next of kin***

Date: 02/08/2016

PLEASE SAVE YOUR TEMPLATE WITH THE FOLLOWING FORMAT:

Corresponding author's last name and date of submission, eg,

Smith_September_2014.doc