Neuronal antibodies and paraneoplastic sensory neuropathy in thymoma

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Abstract
Thymoma, a common anterior mediastinal tumour, may present with paraneoplastic neurological symptoms. The presence of neuronal anti-Hu paraneoplastic antibodies in thymoma patients is very rare. Here, we describe a patient who presented with symptoms of a sensory peripheral neuropathy in the presence of onconeural antibodies cross-reactive with Hu antigen, in whom an underlying thymoma was diagnosed. Subsequent minimally invasive thymomectomy improved her neurological symptoms significantly.

Keywords: Paraneoplastic syndrome • Thymoma • Anti-Hu antibodies

INTRODUCTION
Thymoma is a neoplasm of the thymic epithelium and accounts for ~50% of all anterior mediastinal tumours. A number of autoimmune disorders are associated with thymoma, most commonly myasthenia gravis, found in over 30% of thymoma patients. Thymoma has also been linked to the presence of a range of neuronal autoantibodies (to ganglionic acetylcholine receptors, voltage-gated potassium channels (VGKC) and related proteins, glutamic acid decarboxylase (GAD), antineuronal nuclear, or Hu antigen and Collapsin response mediator protein 5, or CRMP-5), accompanying a number of autoimmune neurological paraneoplastic disorders, such as encephalopathy, hearing loss, autoimmune neuropathy and peripheral nerve hyperexcitability [1].

The presence of Anti-Hu paraneoplastic antibodies in patients with thymoma, with or without associated neurological illness, is rare [2, 3]. In an institutional review of all thymoma cases from one centre (n = 172), anti-Hu antibodies were detected only in five (3%) [2]. Two of these cases had an associated neuropathy with vertigo, and a third had encephalopathy with myasthenia gravis, with one case of myasthenia as the sole presentation. Here, we report on a patient with thymoma and sensory peripheral neuropathy whose serum cross-reacted with the recombinant anti-Hu protein.

CASE REPORT
An 87-year old woman presented in March 2010 with a 3-month history of a symmetrical, painful tingling and numbness in both feet, spreading to the level of the knees. She had no other neurological or constitutional symptoms, or other medical illnesses, and had never smoked. Examination revealed bilateral absent ankle reflexes and altered light touch sensation distally in both legs, with no other abnormal findings. There were neurogenic changes in the lower limb muscles, with slightly reduced sensory nerve action potentials on neurophysiological testing. Extensive peripheral neuropathy screening blood tests were all normal, other than neuronal nuclear staining in a Hu antibody pattern on monkey cerebellum commercial sections using the standard protocol (Binding site, Birmingham, UK). Subsequent CT thorax imaging revealed an anterior mediastinal mass with lymphadenopathy, thought to represent a thymoma. A right video-assisted thoracoscopic thymectomy was performed by three ports and a complete thymectomy was performed. We did not perform a maximal thymectomy as it is our protocol in the presence of thymomas not to extend the surgery to all the peri-cardial fat. We would have done so in cases of myasthenia without the presence of a thymoma. Histology revealed the complete excision of an encapsulated thymoma, B3 subtype, with only reactive changes in lymph-node tissue. The thymoma was measured at 2.5 × 2 cm. Due to the reasonably small size and the advanced age of the patient and local expertise, we elected to perform the surgery by video-assisted thoracic surgery (VATS), which is our routine approach for mediastinal masses smaller than 4 cm. By 6 weeks postoperative follow-up, her peripheral neuropathy symptoms were significantly improved from a recorded power scale of 3–4/5 in different muscle groups to 5/5 on clinical examination.

NEURONAL ANTIBODY INVESTIGATIONS
Indirect immunofluorescence on commercial sections of the primate cerebellum (binding site FS221.A) showed a Hu pattern neuronal nuclei staining. Immunoblots for recombinant HuD (Euroimmun, Lübeck, Germany) showed a positive HuD band on...
repeated testing, both before, and 3 months and 5 months post-
thymectomy. However, a subsequent HuD ELISA performed in
our laboratory on a preoperative stored serum sample was nega-
tive. Indirect immunofluorescence on Hep-2 cells was negative
for antinuclear antibodies at concentrations from 1:100 to
1:6400, and immunoblots were negative for a number of anti-
odies to antinuclear antigens [Anti-mitochondrial (PDH),
dsDNA, Anti-La (SS-B), Anti-Sm, Ro 60 (SS-A), Anti-RNP,
Anti-Jo-1, Ro52, Scl-70, Pm Scl, Anti-centromere, PCNA (prolif-
erating cell nuclear antigen), nucleosome, histone, ribosomal P) (Euroimmun, Germany). Antibodies to acetylcholine receptors
and muscle-specific kinase, and other onconeural antibodies
including voltage-gated calcium channels, VGKC, contactin-
associated protein 2 (CASPR2), GAD, Yo, Ri, Ma2, CRMP5,
Amphiphysin, NMDAr and glycine were all negative.

**DISCUSSION**

Although autoimmune disorders occur frequently in patients
with thymoma, only rarely do such patients harbour neuronal nuclear antibodies with associated neurological paraneoplastic
symptoms. Our patient developed sensory peripheral neur-
opathy prior to the discovery of her thymoma, with the reso-
lution of symptoms on tumour removal. Unusually, although
primate brain section immunofluorescence pattern and immu-
noblot studies suggested the presence of Hu antibodies, the sub-
sequent ELISA was negative, indicating that perhaps the Hu
antibody titre was rather low, or that the patient had antibodies
to a novel neuronal nuclear antigen that cross-reacted with the
HuD antigen. In our experience, western blot or immunoblot is
a more sensitive assay than ELISA when the Hu titre is low, due
to the ELISA value falling below the cut-off for positivity com-
pared with normal controls. In a separate study, we failed to
detect anti-Hu antibodies in a further 29 patients with thymoma
and myasthenia gravis, indicating that the presence of these
neuronal antibodies is unusual (Maddison, unpublished data).
Uniquely, our patient had no other detectable neuronal anti-
bodies nor did she develop myasthenia gravis.

Thymoma is a typical tumour associated with numerous
neurological paraneoplastic presentations such as myasthenia
gravis with acetylcholine receptor antibodies, Morvan’s syndrome
or neuromyotonia, often with CASPR2 antibodies, and enceph-
alomylitis with CRMP5 antibodies. Its association with anti-Hu
antibodies is extremely rare, described in only 6 cases to date [2,
3]. In general, the most common paraneoplastic presentation
seen in over half of patients with anti-Hu antibodies is sensory
neuropathy [4]. Approximately three quarters of anti-Hu antibody
positive patients have an underlying lung tumour, usually small-
cell lung cancer. These tumours, of neuroectodermal origin, are
known to express the Hu antigen, although other cancers have
also been shown to exhibit Hu immunoreactivity (prostate,
breast, oesophageal, colon, ovarian, bladder) [4]. To date, there
have been no Hu expression studies in thymoma patients with
Hu-antibody-associated paraneoplastic conditions [4]. The
thymoma tissue from our patient, like others previously reported,
did not express markers of neuroendocrine differentiation
(negative S100, CD56 and chromogranin immunohistochemistry).
Nevertheless, it is possible that neuronal antigen expression in
her tumour could have triggered the development of the sensory
neuropathy. Typically, as in our patient, Hu antibodies do not
become negative after tumour treatment, probably reflecting the
fact that the Hu antibodies are not directly pathogenic [5].

We have proposed that the clinical presentation with
sensory neuropathy and neuronal antibodies was paraneoplas-
ic in nature because the symptoms occurred much before
the discovery of an asymptomatic thymoma; the Hu-like anti-
bodies would be expected to most commonly cause symp-
toms of neuropathy [4], and her symptoms improved on
complete removal of the tumour. Given that our patient was
a lifelong non-smoker, with no evidence of a second malign-
nancy that may have alternatively triggered the autoimmune
anti-Hu response 2 years after the neurological symptom
onset, we suspect that the thymoma was the initial stimulus
for her paraneoplastic sensory neuropathy.

**CONCLUSION**

We conclude that paraneoplastic sensory neuropathy in the
presence of a mediastinal mass should be referred for definitive
management. In patients with anti-Hu antibodies, thymus gland
pathologies should be considered. Early and complete treatment
of thymus disease may improve the associated neurological
paraneoplastic symptoms.

**Conflict of interest:** none declared.

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