Editorial

Paraneoplastic encephalomyelitis: an update of the effects of the anti-Hu immune response on the nervous system and tumour

The finding that patients with lung cancer and paraneoplastic sensory neuropathy harboured antineuronal antibodies led Wilkinson and Zeromski to hypothesise in 1965 that patients with the "encephalomyelitic form of carcinomatous neuropathy" should be investigated "for the presence of circulating anti-brain antibodies, particularly as lymphocytic infiltration is a prominent feature in these patients". About 30 years later, the characterisation of the anti-Hu antibody (HuAb)^{2,3} and Hu antigens has shown that patients with cancer whose serum contains the HuAb have developed an immune response to a family of neuronal RNA binding proteins, that are highly homologous to a drosophila protein (Elav), a protein critical for nervous system development of the fly.⁴⁻⁸ The exact function of the Hu proteins is unknown, but their homology to Elav and their early expression during embryogenesis of the mammalian nervous system^{9,10} suggest that they are likewise crucial for development and maintenance of the neuronal phenotype.

This review updates the effects of the HuAb immune response on the nervous system and the tumour of these patients.

HuAb: markers of small cell lung cancer and paraneoplasia

About 4% of patients with small cell lung cancer develop a paraneoplastic neurological syndrome (table 1).¹¹ By far the most common disorder is Lambert-Eaton myasthenic syndrome.¹² Much less frequent but usually more disabling is an encephalomyelitis and/or a sensory neuronopathy (PEM/SN) associated with HuAb (the anti-Hu syndrome, table 2).¹³ HuAb is detected in serum and CSF by immunohistochemistry, immunoblot of cortical neurons, or recombinant Hu proteins (HuD, HuC, and Hel-N1), or enzyme linked immunosorbent assay (ELISA) of these proteins.^{4-6,13,14} The most sensitive and specific technique is the immunoblot of recombinant proteins,^{14,15} whereas immunohistochemistry may detect antibody reactivities other than the anti-Hu antibody. We consider that a serum contains high titre of HuAb when the HuD immunoblot reactivity is detectable at serum dilutions above 1:10 000; this threshold, however, varies with the type of antigen used.^{15,16} More than 85% of patients with HuAb, at high or

low titres, harbour a small cell lung cancer; some patients may have other tumours, including neuroblastoma, prostate cancer, and sarcoma; rarely no tumour is found.^{13,17}

The exact role of the HuAb in the pathogenesis of paraneoplastic symptoms is unknown. It is known, however, that HuAb at high titre is a marker of PEM/SN, because (1) most patients with small cell lung cancer with this disorder harbour HuAb, and (2) these antibodies are not detected in normal subjects, or in other neurological disorders.^{14,18}

In 17% of patients with small cell lung cancer, but without PEM/SN, the HuAb is detected at low titre (usually orders of magnitude less than in patients with paraneoplastic symptoms).^{15,19} The titre may fluctuate during chemotherapy, but usually remains detectable.²⁰ Whether these patients have mild neurological symptoms is not known, but a prospective study of 150 patients with small cell lung cancer showed that about 50% had neurological symptoms; the HuAb status was not examined.¹² By contrast, a low HuAb titre has significant prognostic implications with respect to the tumour (see later).

Table 1 Paraneoplastic neurological syndromes in small cell lung cancer

Unifocal syndromes:
Lambert-Eaton myasthenic syndrome (LEMS)
Paraneoplastic cerebellar degeneration (PCD) *
Paraneoplastic sensory neuronopathy (PSN) *
Limbic encephalopathy *
Opsoclonus-myoclonus *
Paraneoplastic visual symptoms
Cancer associated retinopathy
Optic neuritis
Motor neuron syndrome*, lower motor neuron or both upper and lower motor neuron
Neuromyotonia
Myotonia
Vasculitis of the nerve and muscle
Multifocal syndromes:
Paraneoplastic encephalomyelitis (PEM) and PSN
PEM and optic neuritis
PEM and vasculitis of the nerve and muscle
Overlapping syndromes:†
LEMS and PCD
LEMS and PEM

* They may evolve to PEM or remain isolated.

† Independent pathogenic mechanisms.

Table 2 Paraneoplastic encephalomyelitis and sensory neuropathy associated with HuAb (the anti-Hu syndrome)

Symptom	Presenting symptoms* (%)	Site of pathology
Sensory deficits (usually asymmetric) with or without pain†	69	Dorsal root and trigeminal ganglia
Motor incoordination, tremor, ataxia	23	Cerebellum
Limbic encephalopathy: memory loss, depression, seizures	16	Hippocampus, insular cortex
Motor weakness, fasciculations, hyporeflexia, or hyperreflexia	14	Spinal cord
Dysphagia, dysarthria, ocular paresis, opsoclonus	11	Brainstem
Orthostatic hypotension, intestinal pseudo-obstruction, sexual impotence, urinary retention, abnormal pupillary reflex	10	Autonomic nervous system

* In 173 patients with anti-Hu syndrome and pathologically confirmed small cell lung cancer, 31% had more than one presenting symptom.

† Sensory deficits and pain are the most frequent symptoms, either in isolation or associated with any of the other symptoms.

HuAb associated immune response: effects on the nervous system

Symptoms of PEM/SN usually precede the diagnosis of cancer.¹³ An asymmetric sensory neuropathy, sometimes resembling a mononeuritis multiplex, is the most common presentation (table 2). Regardless of the presenting symptom, the disorder usually evolves in a few weeks or months, to a widespread encephalomyelopathy with sensory and autonomic deficits. An acute respiratory or cardiac dysautonomia can cause sudden death.^{13 21} Occasionally, the sensory symptoms may remain mild and localised^{22 23} or even resolve.²⁴ The development of a cerebellar or brainstem encephalopathy, or a motor neuron syndrome, usually have a dismal prognosis.^{13 16 25 26} Plasma exchange, intravenous immunoglobulin, immunosuppressants, and steroids are usually ineffective (although limbic encephalitis may improve in some patients).^{13 25 27–29} In rare instances, paraneoplastic encephalomyelitis improves spontaneously²⁴; this possibility should be considered whenever the response to any treatment is evaluated.

Paraneoplastic syndromes without HuAb: overlapping syndromes and overlapping antibodies

In patients with small cell lung cancer, not all paraneoplastic syndromes are associated with HuAb (table 1). Patients with unifocal symptoms (pure cerebellar syndrome or limbic encephalopathy), may be either HuAb positive or negative. The relevance of the presence or absence of HuAb has been explored.^{16 25} When patients with HuAb and limbic encephalopathy²⁵ or cerebellar degeneration¹⁶ were compared with similar cohorts of patients without HuAb, the seropositive patients were more likely to be female, to develop multifocal neurological deficits, and to have a neurological death. HuAb negative patients with limbic encephalopathy were also more likely to improve (spontaneously or with treatment) than the HuAb positive patients.²⁵

Some patients may have overlapping paraneoplastic syndromes (table 1). Of 57 patients with small cell lung cancer and paraneoplastic cerebellar degeneration, nine (16%) also had Lambert-Eaton myasthenic syndrome, independent of the HuAb status.¹⁶ Nine per cent of HuAb positive patients and 36% of HuAb negative patients had P/Q type voltage gated calcium channel antibodies (a specific marker of Lambert-Eaton myasthenic syndrome) suggesting that in the HuAb negative group Lambert-Eaton myasthenic syndrome was overlooked, or that voltage gated calcium channel antibodies may cause cerebellar dysfunction, or both.¹⁶ The importance of identifying these overlapping syndromes is that patients with Lambert-Eaton myasthenic syndrome improve appreciably with treatment (3,4-diaminopyridine, intravenous immunoglobulin, or plasma exchange), whereas paraneoplastic cerebellar degeneration or paraneoplastic encephalomyelitis do not usually improve.^{16 29–31}

Additionally, a few patients with paraneoplastic encephalomyelitis may harbour other antineuronal antibodies

in addition to HuAb; they include anti-Ri, anti-CV2, anti-amphiphysin, and other unknown antineuronal antibodies.^{15 16 32 33}

The HuAb immune response: effects on the tumour

For many years, neurologists and oncologists have thought that patients who develop paraneoplastic syndromes have a more indolent tumour behaviour than patients without these syndromes. In patients with HuAb associated PEM/SN, the small cell lung cancer is usually confined to the thorax.¹³ Often, the tumour is difficult to demonstrate, or is only detected at necropsy. Sometimes the necropsy is negative³⁴ suggesting that (1) the tumour was present but not detected, (2) the tumour had spontaneous regression—some of these patients are heavy smokers who develop anorexia, weight loss, and chest CT abnormalities which resolve without treatment; in one patient even the neurological symptoms improved spontaneously^{16 24 35}—or (3) that a similar syndrome can develop without a tumour: two of our patients were young adults (ages 22 and 32), without history of smoking; one of them underwent necropsy and no tumour was found (unpublished data).

The belief that paraneoplastic tumours are more indolent may represent an artifact of anticipation in that the development of neurological symptoms prompts a tumour search many months before it would otherwise be discovered. Furthermore, the frequent neurological death of patients with PEM/SN, limits the evaluation of the natural history of the tumour. To circumvent these limitations, two studies were designed to determine whether the immune response of patients with low HuAb titre (without PEM/SN) had any effect on the tumour. The first study was a retrospective analysis of 44 patients, and showed that those with low HuAb titres (16%) were more likely to be female and have limited stage disease at the time of diagnosis.¹⁹ The second study was a prospective evaluation of 170 patients with small cell lung cancer¹⁵: 16% of them had low HuAb titres. A significant correlation was found between positive serology, limited tumour stage, response to chemotherapy, and longer survival. When serum samples from these patients were examined for p53 antibodies, 16% were found to be positive (these patients did not overlap with the HuAb positive), but there was no correlation between p53 antibodies and tumour prognosis or survival.³⁶ These studies indicate that tumours associated with paraneoplastic immune responses are indeed more indolent than those without this association.

Immunopathological findings

The CSF of patients with PEM/SN usually contains a few (10–40) white blood cells, increased protein, oligoclonal bands, and intrathecal synthesis of HuAb.^{13 16 25 37} Prominent mononuclear inflammatory infiltrates found in the nervous system and the tumour³⁴ indicate that cytotoxic T cell or cytokine related mechanisms may have a pathogenic role in the disease (table 3).^{38–40}

Table 3 Immunopathological findings

	Nervous system	Tumour (small cell lung cancer)
Hu expression	Constitutive in neurons	Expression in all small cell lung cancer, no mutations found
Anti-Hu deposits	+	+
B cells	+ pv	+
CD4 + T cells	+ pv; + is	+
CD8 + T cells	+ is	+
Macrophages	+ is	
MHC expression		Higher in small cell lung cancer associated with anti-Hu syndrome

pv = Perivascular; is = interstitial.

The nervous system and tumour also contain deposits of HuAb which may have pathogenic relevance.⁴¹⁻⁴² Some studies support these findings: (1) In vitro internalisation of HuAb has been shown in neuronal and tumour cell lines,⁴³⁻⁴⁴ (2) Hu antigen-like molecules are expressed in the surface of neuroblastoma cell lines, suggesting a mechanism of cell surface antibody binding and internalisation,⁴⁵ and (3) internalisation of antinuclear antibodies are pathogenic in other diseases (systemic lupus erythematosus and anti-dsDNA).⁴⁶⁻⁴⁷ In animal studies, the role of the HuAb has been explored in several ways, including the passive transfer of HuAb and immunisation with recombinant Hu proteins. In the later experiments, animals developed high HuAb titres but no disease.⁴⁸ None of these studies, however, modelled the intrathecal synthesis of HuAb that occurs in patients with PEM/SN.

Whereas major histocompatibility proteins class I and II (required for antigen presentation) expression is usually turned off by small cell lung cancer, these proteins often remain expressed by paraneoplastic small cell lung cancer.⁴⁰ A similar finding has been made in neuroblastomas of patients with HuAb.⁴⁰ The importance of this finding is unknown, but it may mean that these neoplasms are more immunogenic than the non-paraneoplastic neoplasms, and provides an explanation of why only some tumours trigger the HuAb response. The HLA haplotype of the patients is not relevant.⁴⁹

Although no animal model of PEM/SN is available, there is compelling evidence that in most patients with small cell lung cancer, PEM/SN is mediated by an immune response (antibody mediated, T cell mediated, or both) against antigens expressed by the tumour and nervous system. A mild immune response (indicated by low HuAb titres) is a good tumour prognostic factor, but an intense immune response (high HuAb titres) is associated with severe neurological disease, which often causes death.

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