CASE REPORT

Occult testicular cancer presenting as paraneoplastic limbic encephalitis

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Introduction

Paraneoplastic neurological syndromes associated with carcinoma are rare. Paraneoplastic limbic encephalitis (PLE) is a well recognized but poorly understood non-metastatic neurological condition. We report an interesting case of PLE with anti-Ma2 antibody in a young man with only apparently benign microcalcification of the testes on imaging. Post-mortem, however, demonstrated an intratubular germ cell tumour.

This case confirms the conclusion of a recent study that the combination of PLE and anti Ma2 antibody is invariably associated with testicular cancer even in the subclinical stage. This report also highlights a clinical and ethical dilemma as to the role of orchidectomy as a potentially lifesaving procedure in the absence of overt disease together with the problem of obtaining informed consent from a semi-comatose patient.

Case report

A 23-year-old man, previously fit and well, presented with 1 week’s history of increasing drowsiness, confusion and profound short-term memory loss. There was no history of drug abuse, recent foreign travel or HIV infection risk. On examination, he was aphyreal with no features of meningism. He was haemodynamically stable but had a Glasgow Coma Score fluctuating between 12 and 15. No focal neurology was elicited.

Initial routine investigations including full blood count, clotting profile, urea, electrolytes, creatinine, glucose, liver function tests, C reactive protein, erythrocyte sedimentation rate and chest radiograph were normal. Cerebrospinal fluid (CSF) study revealed a normal serum glucose, an elevated protein (3.6 g/l) and a lymphocytosis of 13 cells/mm³.

An urgent magnetic resonance imaging (MRI) was performed and revealed an area of extensive signal alteration (low signal on T1-W and high signal on T2-W) centred on the hypothalamus, extending symmetrically into either side of the midline and with further extension superiorly to involve the floor of the third ventricle and inferiorly to the level of interpeduncular cistern. The lesion enhanced avidly following administration of contrast medium. A further signal change was noted within the medial aspect of the left temporal lobe but no associated mass effect or hydrocephalus. There was no evidence of pathological leptomeningeal enhancement (Figs. 1-3).

A subsequent infection screening and serology for bacterial, viral or fungal infection were normal and HIV status was negative. CSF cytology revealed a reactive lymphocytosis and no malignant cells, and an autoimmune screen and plasma electrophoresis were normal. An EEG was non-diagnostic.

As the MRI appearances were more in keeping with a neoplastic process such as a lymphoma or germi-noma, whole-body computed tomography (CT) and whole-spine MRI were performed. The results of these investigations turned out to be normal.

With this acute presentation of a deteriorating patient, empirical treatment with intravenous acyclovir for suspected herpes simplex encephalitis was commenced. Nonetheless the man’s clinical condition continued to decline. Repeated CSF studies were non-contributory. As the diagnosis was still unclear, a stereotactic brain biopsy was...
performed, but only non-specific inflammatory changes were observed.

A putative diagnosis of an autoimmune encephalitis was made, and an immunosuppressive regimen was commenced including steroids, plasma exchange and intravenous immunoglobulin. A dramatic clinical improvement was seen and was mirrored in repeat MRI.

More detailed immunological investigation, including a paraneoplastic antibody screen, revealed the presence of anti-Ma 2 antibodies. As anti-Ma 2 antibody has an association with testicular cancer, a search for this tumour was undertaken. Clinical examination of the testes was normal and ultrasound showed only bilateral testicular microlithiasis and no associated mass lesion. Serum tumour markers, \( \alpha \) fetoprotein and \( \beta \) HCG, were normal and whole-body positron emission tomography (PET) was also negative. In the absence of any direct evidence for a testicular tumour, the urologist did not feel orchidectomy was appropriate.

Unfortunately, the man’s condition deteriorated further, with the development of seizures. Repeat MRI showed a recrudescence of earlier changes which now involved the cerebral peduncles and upper pons. A repeat course of immunoglobulin and steroids produced no clinical response. The patient became comatose and developed bronchopneumonia leading to death.

Post-mortem investigation revealed the presence of abnormal tissue around the hypothalamus, left amygdala, hippocampus and medial aspect of the left temporal lobe, the midbrain and pons. Microscopic examination showed features consistent with encephalitis, with a severe destructive inflammatory reaction with depletion of neurons and reactive astrocytosis accompanied by perivascular and parenchymal mononuclear inflammatory cells. There were no inclusion bodies nor any neoplastic change. Both testes appeared macroscopically normal but, on histological examination, abnormal rounded cells with large nuclei and scanty cytoplasm were seen within the seminiferous tubules of one testis. The tubules expressed placental alkaline phosphatase, a marker for germ cell tumours. These findings were consistent with an intratubular germ cell tumour. The other testis was normal.
Discussion

We report a case of paraneoplastic limbic encephalitis (PLE) with anti-Ma2 antibody in a young man with only testicular microlithiasis on investigation, but found on post-mortem to have an intratubular germ cell tumour.

Paraneoplastic neurological syndromes associated with carcinoma are rare (<1%) and usually occur several months or years before discovery of the underlying tumour. The spectrum of syndromes includes PLE, paraneoplastic encephalomyelitis, paraneoplastic cerebellar degeneration, paraneoplastic opsoclonus, paraneoplastic sensory neuropathy and Lambert–Eaton myasthenic syndrome. These conditions are believed to be caused by an autoimmune reaction against antigen co-expressed by tumour cells and neurons. Several well characterized autoantibodies have been identified in some persons with paraneoplastic neurological disease. For example, voltage-gated calcium channel antibody is often associated with Lambert–Eaton myasthenic syndrome, and anti-Hu antibody is detected in patients with PLE, paraneoplastic sensory neuropathy and cerebellar degeneration. Both these antibodies are strongly associated with small-cell lung cancer.

PLE is a well recognized but poorly understood non-metastatic neurological process characterized by an inflammatory infiltration of the hippocampus and medial temporal lobe of the brain. These features were seen in the present case. The clinical manifestations of PLE are characterized by personality changes, irritability, depression, partial seizures, memory loss and dementia. PLE is probably under-diagnosed because of the diversity of symptoms and lack of specific diagnostic markers. Abnormalities involving the limbic system apparent on MRI, and the presence of pleocytosis, elevated proteins and oligoclonal bands in the CSF, are suggestive of PLE but are not pathognomonic. It appears that Ma2 is a major autoantigen seen in paraneoplastic disorders that target the temporal-mesolimbic, diencephalic and brainstem regions. Anti Ma2 antibody is strongly associated with testicular cancer, but has also been reported in cases of breast cancer and lung cancer.

In this case, initial MRI showed avidly enhancing lesions of the hypothalamus and left medial temporal lobe, which were thought to be atypical of PLE, and a neoplastic process was considered more likely. The typical findings on MRI for PLE are increased signal intensity on T2-W and no enhancement, although enhancement has been previously described in some cases. The enhancement of this young man’s lesions may have been secondary to a marked degree of perivascular lymphatic infiltration or a breach of the hypothalamic blood–brain barrier. His clinical condition improved after immunosuppressive therapy, which was mirrored by a reduction in the enhancement pattern on subsequent MRI, presumably a reflection of reduction in the inflammatory response elicited by the inciting neuronal antigen.

The role of elective orchidectomy was controversial in this case as there would have been a dilemma as to which testis to remove. All previous studies were able to identify an abnormality in one of the testes, thus guiding treatment. In the present case bilateral testicular microlithiasis was seen but no other significant pathology identified, so there was no indication as to which testis was involved. The clinical significance of testicular microlithiasis is an association with germ cell (or intratubular germ cell) tumours and infertility. It is accepted practice that the management of testicular microlithiasis is follow-up with annual ultrasound examination. A less aggressive view is that testicular microlithiasis is a completely benign condition and follow-up is unnecessary. Therefore, in current opinion, the presence of testicular microlithiasis does not warrant elective orchidectomy.

No definitive treatment has been agreed for PLE: treatment of the primary malignancy has been

Figure 3 Post-contrast axial T1-W MRI shows avid enhancement of the hypothalamic and left medial temporal lobe lesions.
known to stabilize or reverse the course of PLE in some cases.\textsuperscript{6,12–14} Failure to make a premortem diagnosis is not uncommon.\textsuperscript{15} This has been attributed to a possible anti-tumour effect of the paraneoplastic response, limiting tumour growth and metastases and hindering early tumour detection by conventional methods.

This case highlights both ethical and clinical issues, as to whether to perform an urgent orchidectomy and, if so, should it be bilateral in an attempt to salvage a person in a rapidly deteriorating condition. It also confirms the usefulness of anti-Ma2 as a serological marker for testicular cancer in the presence of PLE, and its potentiality to identify occult tumour in the testes.

**Acknowledgements**

We are most grateful to Dr D. Briley for his permission to report the case.

**References**