PostScript

LETTERS

Anti-Ta-associated paraneoplastic encephalitis with occult testicular intratubular germ-cell neoplasia

Anti-Ta-associated encephalitis is a paraneoplastic inflammatory brain disorder with immune-mediated neurological symptoms. The well-characterised onconeural antibody, anti-Ta, reacts with the paraneoplastic protein PNMA2 (former antibody name: anti-Ma2).¹ Neurological symptoms often include abnormalities in eye movement, short-term memory loss, seizures, irritability, personality change or confusion.^{2,3} The symptoms tend to precede tumour diagnosis and are often more debilitating than the malignancy itself.² The first study of anti-Ta-related paraneoplastic encephalitis reported 10 young men with testicular cancer.³ Other tumours occur in females⁴ and approximately 30 cases have been reported.^{2,5} Several tumours express the protein that, in healthy adults, is restricted to brain and testicular germ cells.³ In contrast to other paraneoplastic syndromes, a remarkable number of patients show neurological improvement if the underlying tumour allows complete surgical resection.² We report a patient's history of anti-Ta-associated neurological syndrome with atypical parkinsonism and massive rigidity due to occult testicular cancer.

Case report

In 2001, a 66-year-old man suddenly developed disorientation, restlessness, psychomotor agitation and fever. A bradykinetic syndrome with rigidity was noted. Verbal output was reduced and the patient responded only in short sentences. Head CT and lumbar puncture examinations were normal, and EEG demonstrated a right temporal epileptic focus.

After 2 weeks, the patient was admitted to the Department of Neurology, Charité, University Medicine Berlin, Berlin, Germany, with further neurological deterioration. He was drowsy, with markedly reduced verbal output, and only occasionally followed simple instructions like closing the eyes. He had mask-like facies, rigidity of the trunk and limbs, and leg reflexes were absent. Pupillary responses were normal, but eye fixation was impaired and he could not perform smooth-pursuit eye movements. However, vestibulo-ocular reflexes were intact and there was no gaze palsy. Babinski's sign was negative, but primitive reflexes like palmomental reflex, grasp and root reflex, pursing reflex and non-habituating glabellar sign were present.

Laboratory examinations of blood and urine showed no abnormalities, cerebrospinal fluid showed elevated protein, normal glucose, no pleocytosis or immunoglobulin synthesis. Cerebral MRI (fig 1A) showed generalised atrophy with periventricular leucoencephalopathy without contrast enhancement. Body CT and abdominal ultrasound examinations showed no suspicious masses.

After 3 months, he deteriorated neurologically and opened his eyes only to painful stimuli. He had low-grade fever and tachycardia, and profuse sweating without any signs

of infection. The neurological examination revealed an akinetic-rigid syndrome, bilateral ptosis, slow pupillary response, and he was unable to fixate. Eye movements were conjugate with absent oculocephalic reflex. He had generalised muscular atrophy and absent reflexes. A new MRI displayed marked progression of the general cerebral atrophy (fig 1B).

Anti-Ta antibodies were detected, while other onconeural antibodies such as anti-Hu, anti-Yo, anti-Ri, anti-GAD, anti-amphiphysin, anti-CV2 and anti-PNMA1 antibodies were negative. The anti-Ta antibody together with the compatible neurological symptoms proved a paraneoplastic origin and expedited the search for a malignancy. Endoscopy, body 2 (fluorine 18)fluoro-2-deoxy-D-glucose positron emission

tomography, repeated body CT examination and bone marrow biopsy revealed no neoplastic changes. Genitourinary examination was normal as well as tumour markers PLAP, α -fetoprotein and β human chorionic gonadotrophin. Testicular ultrasound examination revealed homogeneous echo pattern, no atrophy and no masses suspicious for malignancy.

Because of life-threatening neurological deterioration, the patient's wife consented to bilateral orchiectomy. The original pathological evaluation was negative for testicular malignancies, but detailed review using PLAP-stained slides verified multiple bilateral microscopic intratubular germ-cell neoplasia (fig 1C-E).

At 10 days after surgery, the patient was awake, displayed spontaneous eye opening,

Figure 1 T2-weighted, axial MRI slices (A) at the time of admission and (B) after 3 months. (A) The initial MR study already showed cortical and subcortical atrophy, indicated by enlarged sylvian fissures and ventricles. (B) A further increase in size with respect to the anterior horns of the lateral ventricles is noted (arrows), indicating progressive atrophy. Microangiopathic lacunar lesions are depicted in both studies (small arrows) without significant progression. (C) High-magnification photograph ($\times 400$) of testes showing seminiferous tubules with disturbed spermatogenesis (H&E-stained slice). (D,E) Immunohistochemistry for placental-like alkaline phosphatase (PLAP) highlighted multiple bilateral microscopic tumour cells with remarkably enlarged nuclei and clear cytoplasm (arrows).

responded when his name was called, followed simple instructions, and focused objects. The rigidity was markedly reduced enabling the patient to extend his limbs. Grasp and root reflex, pursing reflex and non-habituating glabellar sign disappeared. After 4 months he used up to six words and recognised his relatives.

The patient was admitted to a nursing home and had long-term stabilisation. He died from pneumonia 18 months later, and no autopsy was obtained.

Comment

We report a patient's history of anti-Ta-associated paraneoplastic neurological syndrome (PNS) with an occult testicular malignancy despite unsuspicious tumour diagnostics. Our patient developed atypical parkinsonism with a severe hypokinetic syndrome, striking reduction of verbal output, and massive rigidity, thereby supporting the findings in five patients of a previous report that parkinsonian-hypokinetic features seem to happen more frequently with anti-Ta encephalitis than with other PNS.² Regarding the revised criteria for PNS, the presence of the well-characterised anti-Ta antibody together with the appropriate clinical and imaging findings in our patient fulfils the requirements for definite PNS.³

The decision for orchiectomy without tumour detection was based on (1) life-threatening deterioration, (2) the remarkable number of patients with neurological improvement after tumour resection in cases of anti-Ta-associated encephalitis, (3) the absence of suspicious masses using magnetic resonance, CT, positron emission tomography and endoscopic imaging and (4) the high frequency of testicular cancer in patients with anti-Ta-associated PNS. At the time of presentation, all previously reported cases with anti-Ta encephalitis had testicular neoplasms.³ Up to now, other tumours were found in females to cause Ta-associated paraneoplastic encephalitis.⁴ The underlying mechanisms are thought to consist of tumour proteins triggering an auto-immunological response against the nervous system.³ The first neurological symptoms of our patient preceded tumour diagnosis by about 6 months, which is the median time in the original report on anti-Ta antibodies.³

A special feature of anti-Ta-related paraneoplastic encephalitis is the response to therapy. This could be partly explained by testicular malignancies that respond better to treatment than breast or lung tumours.² After orchiectomy, our patient had improvement in the neurological symptoms including alertness, spontaneous eye opening, following simple instructions, focusing objects and using a few words. Moreover, the rigidity of all extremities was markedly reduced and most primitive reflexes disappeared.

Given that the immunohistochemical staining in this case revealed microscopic tumour despite unsuspicious findings in repeated testicular ultrasonographic examination, the presence of anti-Ta antibodies together with appropriate clinical findings should prompt every effort to find an underlying malignancy. This case underscores the high specificity of anti-Ta antibodies. According to the new diagnostic criteria, six PNS defining reactivities were identified so far,⁵ among which anti-Ta is the most recently identified. One has to keep in mind that failure to make premortem tumour detection is common, also due to possible anti-cancer

effects of the immune response, reducing tumour enlargement and metastasis. This case demonstrates that even resection of healthy-appearing tissue might, in exceptional cases, be necessary and justified, if extensive investigation failed to demonstrate tumour masses.

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Consent was obtained for publication of the patient's details described in this report.

doi: 10.1136/jnnp.2006.101964

Competing interests: None declared.

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Intracranial fluid filled collection and superficial siderosis

Superficial siderosis (SS) of the CNS is caused by repeated haemorrhage into the subarachnoid space with resultant haemosiderin deposition in the subpial layers of the brain and spinal cord.^{1–4} The commonest neurological manifestation is that of slowly progressive gait ataxia and impaired hearing. A remote history of injury is common. A fluid-filled intraspinal cavity of variable dimension is a frequently noted finding on neuroimaging.^{3–6} A high prevalence of CSF containing cysts in SS supports the hypothesis of bleeding from a dural defect as the origin of SS.⁷ Removal of the likely bleeding source is a logical therapeutic strategy.

Case report

A 58-year-old man was evaluated for a 10 year history of progressive decline in hearing and imbalance. Additional symptoms included a 5 year history of slurred speech and a 1 year history of increasing falls. His past history was remarkable for a motor vehicle accident at 7 years of age. This was followed by a prolonged hospitalisation but no evident neurological sequelae. His examination was remarkable for decreased hearing, an ataxic dysarthria, a wide based ataxic gait with increased lower limb tone and hyperreflexia. Rapid alternating movements with the hands and feet were irregular and the heel–shin and finger–nose tests were positive. T2 weighted head MRI showed typical MRI changes of superficial siderosis with the characteristic hypointensity involving the cerebellum (fig 1A), brainstem (fig 1A) and the frontotemporal regions. Also present was post-traumatic encephalomalacia involving the anterior frontal lobes. A CSF study was remarkable for increase in red blood cells to 380 cells/mm³ and a protein concentration of 94 mg/dl. No abnormality was noted on head and neck magnetic resonance angiography. A small cystic lesion was noted behind the cerebellum on T2 weighted axial (fig 1A) and sagittal head MRI (fig 1B), and on axial head CT (fig 1C). This was felt to be of no consequence until a review of the head CT (fig 1C) with careful attention to the bone sequence (fig 1D) revealed discontinuity of the inner skull table underlying the cyst (fig 1D). A CT myelogram of the spine, performed to look for a bleeding source, showed extravasation of the dye from the fourth ventricle into the cystic structure (fig 1E1 and E2).

Discussion

Recent reports have noted that intraspinal fluid filled collections are frequently seen in SS.^{3,7} In some cases the associated dural defect has been repaired surgically, and decrease or resolution of the cavity and CSF red blood cells has been documented.^{3,5,6} This experience prompted us to surgically explore the identified intracranial cystic structure. A burr hole was opened in the superolateral portion of the right suboccipital region. A CSF filled cavity was encountered within the bone. The outer table was removed, a defect in the inner table was identified and was noted to overlie a large dural defect (fig 1F1). CSF from the fourth ventricle was flowing directly out of the defect into the cavity. Nervous tissue discoloured by haemosiderin deposition was noted. A fascia lata graft was harvested from the right thigh and was used to patch the dural defect (fig 1F2). Macerated muscle was placed over the repaired dura which was then buttressed with Gelfoam.

A fluid filled collection in the posterior fossa is often interpreted as an incidental cyst or prominent cisterna magna. The overlying fracture of the inner table and the perioperative finding of a large dural defect communicating with the cyst suggests that the cause was likely post-traumatic. Intraspinal fluid filled cavities associated with SS are a recently recognised finding. This report suggests that an intracranial dural defect may also be the underlying cause of SS. Bleeding from friable vessels in the cyst wall of intraspinal fluid filled cavities has been considered to be a likely bleeding source.³ Our patient had no demonstrable cyst wall. Friable vessels in the diploic space were the