Paraneoplastic cerebellar degeneration and limbic encephalitis in a patient with adenocarcinoma of the colon

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Abstract
The rare association of two neurological paraneoplastic syndromes, paraneoplastic cerebellar degeneration and limbic encephalitis occurred in a 55 year old woman with a microscopic adenocarcinoma in a colonic polyp. Complete removal of the tumour by polypectomy brought about a favourable recovery from limbic encephalitis but the cerebellar ataxia remained. High titres of antineuronal nuclear antibody resembling anti-Hu were demonstrated in serum by immunohistochemistry using rat brain as a substrate. The antibody identified a protein band of 41 kDa on a Western immunoblot.

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Paraneoplastic cerebellar degeneration and limbic encephalitis are two neurological paraneoplastic syndromes which rarely occur in association with various malignant tumours without direct neoplastic invasion into the nervous system. We report both these paraneoplastic syndromes in a patient with a minute adenocarcinoma in the submucosal tissue of a colonic polyp.

Case report
A 55 year old housewife became aware of dizziness in November 1987 and her gait became gradually unsteady. In July 1988 her difficulty in walking progressed rapidly, and she was no longer able to walk without support. CT brain scans showed no abnormality. On 22 August an ill-defined low density area was noted in the medial part of the right temporal lobe. It became larger and by 31 August extended to the base of the right frontal lobe. There were enhanced areas in the low density area. T2 weighted MRIs on 2 September also showed an area of homogeneous high intensity signals with a relatively distinct margin in the medial half of the right temporal lobe and the base of the frontal lobe. The medial part of the left temporal lobe showed slightly increased signals (fig 1). An EEG showed a low voltage delta wave focus in the right temporal lobe. A brain biopsy disclosed mild gliosis with perivascular lymphocytic infiltration and oedema. In November she was emaciated, having lost 17 kg of weight in one year. She was alert, but exhibited scanning speech and severe disequilibrium. Mild impairment of memory function and attention were noted. Tendon reflexes were slightly hyperactive throughout, but without a Babinski sign. The sensory system was intact.

An immunohistochemical test for antineuronal antibodies in her serum was positive (fig 2A). Tumour markers were all negative. A gynaecological work up, radiographs of the chest, a bronchoscopical study and cytological studies of bronchial brushings and sputa disclosed no malignant lesion or cells. Gallium scintigrams showed no abnormal increase in the brain.
Uptake. Examination of the upper gastrointestinal tract showed no significant abnormality, but finally a polyp was found in the sigmoid colon by barium enema and colonoscopy. A polypectomy was performed on 13 December. In spite of the polyp’s benign macroscopic appearance, histological analysis revealed a completely removed tubular adenocarcinoma localised in the submucosa and surrounded by normal tissue.

The CSF on 2 December showed a lymphocyte count of 18/mm³, protein 25 mg/dl and glucose 57 mg/dl, and two oligoclonal IgG bands. There was no significant increase of the antiviral antibodies against herpes simplex, varicella, cytomegalovirus, Epstein-Barr virus, measles, mumps, and rubella in either the serum or the CSF.

Electrophysiological studies showed no denervation and normal motor and sensory nerve conductions.

She experienced epileptic seizures on 27, 29 November and 1 December. An EEG on 29 November showed a delta wave focus (1-2c/s) in the right anterior temporal lobe and bilateral irregular rhythmic delta activity in the frontal lobe. Seizure activity appeared in the temporo-occipital area, and occasion-
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80°C for 10 minutes. An aliquot of the treated sample (10 μl, 10 μg as protein) was subjected to SDS-PAGE analysis on 10% gel. After transfer to a nitrocellulose membrane, the protein blots were immunostained with serum samples diluted 1:1000. For molecular weight estimation, we used a set of SDS molecular weight markers (MW-SDS-70L, Sigma).

We confirmed that the positive control serum identified a 52 kDa protein. In contrast, serum from the patient reacted with a distinct single protein band of 41 kDa (fig 3, lane 1). Two serum samples from the patients with spinocerebellar degeneration and three from the normal subjects did not recognise any specific band.

Discussion

The association of paraneoplastic cerebellar degeneration and limbic encephalitis is rare, although other combinations such as paraneoplastic cerebellar degeneration and Lambert-Eaton myasthenic syndrome or subacute sensory neuropathy and other forms of encephalomyelitis have been reported. One malignant tumour can cause two or more different paraneoplastic disorders in a patient, but the pathological process or mechanism leading to the neurological deficits may not be the same.

In our patient the symptoms began with slowly progressive ataxia, but during this period brain CT scans disclosed no abnormality. Later CT and MRI scans showed abnormalities consistent with limbic encephalitis which became smaller without any specific treatment. Clinically, however, epileptic seizures and EEG abnormalities became worse even after the radiological improvement. Since the temporal lobe symptoms lessened around the time of the excision of the tumour, it seems likely that the clinical improvement resulted from the removal of the tumour.

Abnormal intensity areas were not observed in the cerebellum or brainstem on CT scans or MRIs, but about 15 months after the onset of paraneoplastic cerebellar degeneration, atrophy of the cerebellum became evident.

Early diagnosis and early extirpation of the tumour are essential to curtailing the progression of neurological deficits as well as to a favourable prognosis for life. When a neurological paraneoplastic syndrome is suspected, a test for antibodies against brain tissue is an excellent diagnostic aid for confirmation of the existence of a malignant tumour.

Immunohistochemical analysis showed that the patient’s serum had high titres of anti-neuronal nuclear antibody against rat brain. The reaction of neurons was positive or negative and depended upon their anatomical localisations in the brain. The immunohistochemical staining pattern of this antineuronal nuclear antibody resembled that of anti-Hu antibody which often rises in sera from patients with subacute sensory neuropathy associated with small cell lung cancer. However, Western immunoblotting gave different results. Our antibody reacted with a single protein band of 41 kDa, while anti-Hu antibody recognises several bands of 35 to 40 kDa; a cDNA clone that encodes a neuronal antigen (HuD) recognised by anti-Hu antibody has recently been isolated.

Our patient did not show any evidence of polyneuropathy. Furthermore the causative tumour was not small cell lung cancer, but adenocarcinoma of the colon. We thus consider our antibody to be different from anti-Hu antibody. We are now trying to clone a cDNA encoding the antigen recognised by our antibody.

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