A new anti-neuronal antibody in a case of paraneoplastic limbic encephalitis associated with breast cancer
R Scheid, J Honnorat, E Delmont, H Urbach, R Biniek

Paraneoplastic neurological syndromes are rare remote effects of different types of cancer. Paraneoplastic limbic encephalitis is a specific syndrome, most often associated with small cell lung carcinoma. This report describes the case of a pure limbic encephalitis in association with breast cancer. An anti-neuronal antibody was found in the serum and CSF of the patient which has not been reported so far.

Paraneoplastic neurological syndromes are disorders of the nervous system, which are associated with cancer but are not caused by the growth of a tumour itself or by metastasis to the nervous system; nor are they a result of non-metastatic complications such as metabolic, secondary infectious, ischaemic, or nutritional disorders or from side effects of antitumour therapy.

Among these strictly defined paraneoplastic neurological syndromes, clinically the most important are Lambert-Eaton myasthenic syndrome (LEMS), paraneoplastic cerebellar degeneration, and paraneoplastic encephalomyelitis, which mostly presents as paraneoplastic sensory neuropathy. Paraneoplastic limbic encephalitis, first described by Brierley et al in 1960, may be a part of the paraneoplastic encephalomyelitis syndrome. Associated tumours are most often small cell lung carcinomas and testicular carcinomas, but there are reports of an association with thymoma, Hodgkin's disease, and non-small-cell lung carcinomas.

We report the case of a patient with pure limbic encephalitis associated with breast cancer.

CASE REPORT
In February 1998 a 46 year old woman with a medical history of arterial hypertension and hysterectomy because of a myoma started to complain of forgetfulness. A depressive syndrome was diagnosed and antidepressant drugs were prescribed. During a flight to Turkey at the end of March 1998, the patient developed an acute confusional state. She was referred to a hospital in Manavgat, Turkey, the same day, where the diagnosis “cerebrovascular accident” was made.

Admission to the medical department of a German hospital followed. The diagnostic procedure included cerebral computed tomography, routine blood laboratory tests, ECG, chest x ray, and ultrasound of the abdomen, heart, and extracranial arteries. These investigations were all normal.

In April 1998, the patient was referred to a neurological department. On admission she was disoriented. She did not remember her trip to Turkey and had only shadowy remembrance of her stay in hospital in her home town. Her most prominent symptom was a severe anterograde amnesia. Neurological examination was unremarkable.

Laboratory findings were as follows: routine blood and chemistry tests including C reactive protein, vitamin B-12, and folic acid were normal. TSH and thyroid hormone levels were in the normal range. Screening for autoantibodies (ANA, ENA, AMA, ds-DNA) and immune electrophoresis was also normal. Tumour markers (CEA, CA 15-3, MCA) were within the normal range. CSF showed mild lymphocytic and monocytic pleocytosis (9/mm³) without abnormal cells; total protein was 49 mg/dl, IgG 3.4 mg/dl, and glucose 58 mg/dl; oligoclonal bands were positive. Antibody screening in blood and CSF for Treponema pallidum, Borrelia burgdorferi, Bartonella henselae, HIV1/HIV2, HSV1/HSV2, varicella-zoster virus, and bornavirus was negative. Tests for classical paraneoplastic antibodies in serum and CSF were negative and included anti-Hu, anti-Yo, anti-Ri, anti-amphiphysin, anti-CV2 (Dr Honnorat, Lyon, France), and anti-Ma antibodies (Dr Dalmay, Little Rock, Arkansas, USA). However, serum and CSF contained a high titre of IgG anti-neuronal antibodies (serum end point dilution by immunofluorescence, >1/30 000; CSF, >1/5000). By immunohistochemistry on adult rat brain (see Antoine et al, 1995 for methods), the cytoplasm and processes of neurones situated in the granular layer of the dentate gyrus were highly labelled by IgG (fig 1A), as were the CA1 area of the limbic system and the brain stem catecholaminergic neurones. Weaker staining of a few neurones was also observed in the cortex, the striatum, and the thalamus. Cerebellar sections did not express the antigen. By western blot analysis of rat brain protein extracts, the patient’s IgG recognised a band of 40 kDa that was different from Hu and Ma protein (fig 2). This antigen was brain specific, as lung, kidney, liver, testicle, spleen, and muscle were negative by western blot. Antibiot expression in tumour samples was studied on paraffin sections of a lymph node metastasis after biotinylation of the patient’s IgG using a previously described technique (fig 1B/C). This newly described antibody seems to be very rare, as we found only one case among more than 200 sera of patients with different kinds of paraneoplastic neurological syndromes.

Magnetic resonance imaging (MRI) of the brain in April 1998 was unremarkable (T1, T2, gadolinium enhanced). A follow up study in June 1998 showed non-enhancing hyperintense signal alterations (T2, FLAIR) in the hippocampi, corpora amygdalae, posterior parts of the thalami, and the cingulate cortex, more on the left than on the right. Multiple EEG recordings between April and May 1998 inconsistently revealed bitemporal sharp-slow wave activity. Anticonvulsant treatment (valproate 1000 mg/day) was without clinical effect. The patient did not receive immunomodulatory treatment.

Mammography in May 1998 showed multiple microcalciﬁcations in the superior outer quadrant and lateral perimammary area of the right breast, suspicious of carcinoma. In June 1998 the patient underwent surgery (right mastectomy and axillary dissection), followed by chemotherapy (epirubicin, cyclophosphamide). The tumour was staged as pT1c, N1, M0, G3; the histopathological diagnosis was multicentric.
carcinoma with parts of invasive lobular carcinoma and poorly differentiated ductal carcinoma.

Up to the last follow up in July 2002 there were no signs of tumour progression or metastasis. The patient was still suffering from a severe amnesic syndrome without improvement over time. She was living at her home but was not able to lead an independent life.

**DISCUSSION**

The prominent clinical feature of the patient was a memory disorder consisting of severe anterograde amnesia. There was subacute onset with rapid progression, which was possibly initiated by a complex partial epileptic seizure. Signs and symptoms of the disease, as well as CSF and neuroradiological findings, are compatible with the diagnosis of limbic encephalitis. The search for an underlying tumour resulted in the diagnosis of a multicentric breast carcinoma. Hence there is strong evidence for a paraneoplastic neurological syndrome. The diagnostic criteria of paraneoplastic limbic encephalitis, recently published by Gultekin et al, are fulfilled.

The case history shows the difficulty of making a clinical diagnosis of paraneoplastic limbic encephalitis. Reliable clinical signs are lacking and there are no specific laboratory tests. At an early stage of the disease, MRI can be negative and might not be helpful. In about two thirds of cases, paraneoplastic limbic encephalitis is associated with small cell lung carcinomas and the anti-Hu antibody is most often found. The second most common finding is the association with testicular neoplasms and the presence of anti-Ma2 antibodies. However, the absence of classical paraneoplastic anti-neuronal antibodies does not remove the need to search for a tumour.

The association of breast neoplasm and paraneoplastic limbic encephalitis is rare. Among the 137 published cases of paraneoplastic limbic encephalitis in the English literature, there are four reports of the association with breast cancer. However, a closer look at these previously published cases reveals doubt over whether there was really a causal relation between the clinical and tumour findings in all the reports. In a case report by Lacomis et al, the patient had a history of mastectomy for localised infiltrating ductal carcinoma four years before the neurological symptoms appeared. There was no evidence of recurrence, and antineuronal antibodies were not detected. The two cases published by Kodama et al are even more uncertain. One woman suffered from a thymoma and not from breast carcinoma, while the other had a history of breast cancer 15 years ago, without recurrence or metastases. The first report of paraneoplastic limbic encephalitis and breast cancer in an anti-Ma2 positive patient was published recently.

It appears that we have detected a new anti-neuronal antibody. This antibody shows a unique—and with respect to the memory impairment—more specific staining pattern than the typical and atypical antibodies so far reported. It reacts with a 40 kDa protein expressed by neurones in the CA1 area and the dentate gyrus of the limbic system. The anatomical site of the immune reaction fits into the clinical syndrome of limbic encephalitis observed in our patient. A specific role of the 40 kDa protein for the pathogenesis of...
limbic encephalitis in this case could be possible. Our findings might therefore support the hypothesis that para-neoplastic limbic encephalitis is caused by immunologically mediated damage to neuronal tissue.

ACKNOWLEDGEMENTS
We thank Dr K Tschubel, Department of Pathology, University of Bonn, Germany for having placed samples of the lymph node metastasis at our disposal.

Authors’ affiliations
R Scheid, Day Clinic of Cognitive Neurology, University of Leipzig, Max-Planck-Institute of Cognitive Neuroscience, Leipzig, Germany
J Honnorat, E Delmont, Neurologie B, Inserm U 433, Hopital Neurologique, Lyon, France
H Urbach, Department of Neuroradiology, University of Bonn, Bonn, Germany
R Biniek, Department of Neurology, Rheinische Kliniken, Bonn

Correspondence to: Dr Rainer Scheid, Day Clinic of Cognitive Neurology, University of Leipzig, Liebigstr 22a, 04103 Leipzig, Germany; scheid@cns.mpg.de

Received 28 March 2003
In revised form 23 May 2003
Accepted 13 June 2003

REFERENCES
A new anti-neuronal antibody in a case of paraneoplastic limbic encephalitis associated with breast cancer

R Scheid, J Honnorat, E Delmont, H Urbach and R Biniek

J Neurol Neurosurg Psychiatry 2004 75: 338-340
doi: 10.1136/jnnp.2003.015388