Age and Ageing 2005; **34:** 190–193
doi:10.1093/ageing/afi017

Paraneoplastic limbic encephalitis—case report and review of literature

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Abstract

We report a 77-year old man who presented with a sub-acute dementia associated with aggressive behaviour, ataxia, rapid progression and death. No cause for his illness could be detected in his lifetime, but at post mortem he was found to have paraneoplastic limbic encephalitis and a bronchogenic tumour. A diagnosis of paraneoplastic limbic encephalitis should be considered in the differential diagnosis of unexplained dementias and appropriate investigations performed to diagnose the condition.

Keywords: *dementia, paraneoplastic syndrome, limbic encephalitis, elderly*

Introduction

Non-metastatic manifestations of internal malignancy (paraneoplastic syndromes) are not uncommon. Paraneoplastic neurological syndromes, however, are rare. We describe here an older person who presented with subacute dementia and a behavioural disorder. A bronchogenic tumour was found at post mortem and pathologic examination of the brain tissue established the diagnosis of limbic encephalitis. Despite extensive investigations the underlying malignancy could not be detected in his lifetime.

Case report

A 77-year-old man was admitted to the medical ward with a 2 month history of worsening mental state, unsteadiness and frequent dull headaches. His past medical history included hypertension, smoking and moderate alcohol consumption. Examination showed cognitive impairment with a Mini Mental Test score of 15/30 and a wide-based gait.

One week later he developed low-grade pyrexia, jaw twitching, and marked ataxia. He became progressively aggressive, confused and ataxic, and had an episode of tonic–clonic convulsion. His condition progressively worsened and he died after a total hospital stay of about 4 months.

Initial investigations showed normal full blood counts and routine biochemical tests. A CT scan of the brain showed generalised atrophy without any focal lesion.

Examination of the CSF revealed a minimally elevated protein at 0.49 g (normal 0.10–0.45). Antibodies to *Treponema pallidum* and polymerase chain reaction (PCR) tests for herpes simplex, varicella zoster, lymphocytic choriomeningitis and enterovirus were negative. Samples were sent to the CJD surveillance unit in Edinburgh and were negative for prion disease.

EEG recordings revealed excessive bilateral slow-wave activity without any localizing or epileptic features, suggestive of a diffuse pathological process. On MRI scanning a number of small high-signal foci were seen in the white matter on T2 weighted images, reported as ischaemic changes. The brainstem and cerebellar appearances were unremarkable. Tests for Whipple's disease

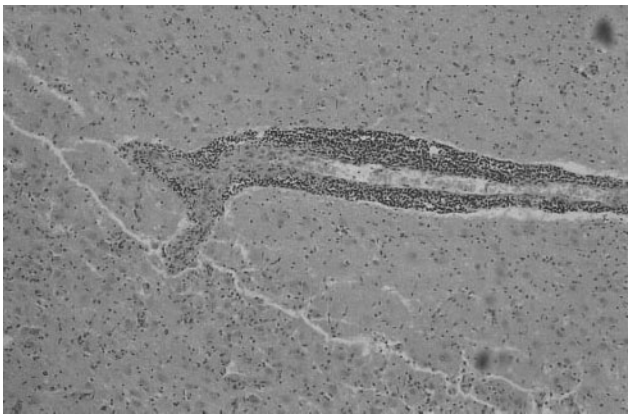

Figure 1. Photomicrograph showing perivascular lymphocytic infiltrate in the deep temporal lobe with neuronal loss and reactive gliosis seen on post mortem. A colour version of this figure is available as supplementary data on the journal website (http://www.ageing.oupjournals.org).

(duodenal biopsy) were negative. Tests for autoantibodies were negative. Serum angiotensin-converting enzyme level was normal.

A repeat CSF examination after 4 weeks did not show any abnormality. The bone marrow aspirate showed a large number of T cells (predominantly CD2+, CD3+, CD7+ and CD8+). The Ziehl–Neelson stain on the aspirate was negative for *Mycobacterium tuberculosis*. A CT scan of the thorax showed localized lymphadenopathy at the right hilum abutting the lower lobe pulmonary artery. A CT of the abdomen and a bronchoscopy were normal.

An autopsy showed a carcinoma arising from the right main bronchus spreading as a mass around the main bronchial wall and invading the adjacent lung. The kidneys showed multiple foci of recent infarction. Histology of the brain tissue showed changes consistent with limbic encephalitis (LE) (Figure 1).

Histology

Active encephalitis affecting the hippocampal region, putamen and upper midbrain was seen at autopsy. Neuronal inclusions were not seen and there was no evidence of metastatic disease. Figure 1 shows neuronal loss with perivascular infiltration by lymphocytes. The lung tumour was a small-cell anaplastic carcinoma.

Discussion

Paraneoplastic neurological syndromes (PNNS) are remote neurological effects of cancer caused by immune or other mechanisms, and are not due to direct tumour invasion, opportunistic infections, complications of drugs or radiotherapy, or malnutrition. PNNS may precede or follow the diagnosis of a tumour by weeks to months [1]. The PNNS can involve brain, spinal cord, peripheral nerves, neuromuscular junction or muscles, separately or in various combinations. For further details of various types of PNNS, please see Appendix 1 available as supplementary data on the journal website.

LE is characterized by profound memory impairment, dementia, seizures (usually complex-partial type) and psychiatric disturbances including depression, personality changes, and loss of social inhibition [**2**, **3**]. Three-quarters of cases are associated with small-cell carcinoma of the lung. Other tumours known to be associated are transitional cell carcinoma of the bladder [**3**], mediastinal teratoma [**4**], malignant thymoma [**5**], and testicular carcinoma [**6**].

Pathogenesis

Paraneoplastic LE is believed to be caused by autoimmune mechanisms involving reactions against antigens co-expressed by tumour cells and neurons [13, 14]. In support of this hypothesis, specific antineuronal antibodies have been detected [**6–10**] in LE. The histological features of tumours in PNNS are no different from other tumours, except that these tumours may be markedly infiltrated with inflammatory cells [14]. The antineuronal antibody type 1, also called the anti-Hu antibody, in the CSF and serum is highly associated with small-cell lung carcinoma [**3**, 11, 12]. Anti-Hu is a polyclonal complement-fixing IgG directed against a 35–40 kD protein concentrated in the nuclei of neurons throughout the central and peripheral neuraxes [14]. The presence of these antibodies has a specificity of 99% and a sensitivity of 82% in detecting PNNS [15]. Patients with LE and testicular or bronchial tumours may have serum antibodies against Ma2, a protein expressed both in the brain tissue and the testicular tumour [16]. It has been postulated that the autoantibodies cross-react with antigens on the normal cells, such as the neurons, resulting in tissue-specific cytotoxicity, or they can form complexes with a circulating antigen to induce end-organ damage through immune complex deposition [17]. The antineuronal antibodies may serve as a useful diagnostic tool, but their actual role in causing neuronal injury and clinical disease still remains unclear [18–20]. The ability to establish a causal link between specific antibody production and a clinical syndrome has been confounded by the findings that many cancer patients without neurological symptoms express neuronal autoantibodies and that some affected patients lack the expression of the putative antibody [17]. Unfortunately, these antibodies were not measured in our case, as there was no strong pointer for an underlying carcinoma. In a recent study, the median delay between the onset of symptoms and Hu-antibody diagnosis was 4 months [21]. A potentially reversible, non-paraneoplastic, voltage-gated potassium channel antibody-associated LE has recently been described with good response to immunotherapy [22].

Neuroanatomical considerations

It is useful to translate the clinical manifestations of a patient into neuroanatomical terms. Certain structural abnormalities of the nervous system can cause persistent agitated states associated with the inability to concentrate and form new memories. These manifestations are most

commonly seen with the lesions that affect a heavily linked group of structures that ring the inferior cerebrum. This ring or 'limbus' embraces the amygdala, hippocampus, hippocampal gyrus, septal nuclei, cingulate cortex, orbital frontal and polar temporal cortices, and hypothalamus [23, 24]. Such limbic structures are connected to the brainstem nuclei, the thalamus and basal ganglia [25]. All the functions of the limbic system are duplicated bilaterally, and a destructive lesion on one side does not cause disordered function. Hippocampal damage contributes to dementia, as seen in Alzheimer's disease [24].

Our patient had developed increasing verbal aggression, with physical threats to the staff. Amygdala stimulation has been reported to generate intense emotional reactions, with reports of patients feeling 'like an animal' [26, 27]. Abnormalities in sexual behaviour can also occur in hypothalamic lesions. Confusion, agitated behaviour and fear are common manifestations of seizure activity in the hippocampal gyrus and amygdala [23].

For further details of investigations and diagnosis of LE, please see Appendix 2 available as supplementary data on the journal website.

Treatment

The treatment of PNNS is generally unsatisfactory. There are two aspects of the treatment: the first is to remove the antigen source by treating the underlying malignancy, and the second is to suppress the immune reaction with the use of immunosuppressive strategies, e.g. corticosteroids, cyclophosphamide, azathioprine, tacrolimus, plasma exchange, intravenous immunoglobulin and immunoadsorption [15]. The treatment of an underlying tumour has been reported to achieve a remission in psychiatric and neurological manifestations with improvement of memory function in some cases [**9**, 31, 35–37, 39]. Patients with limbic encephalitis and small-cell lung carcinoma who are negative for anti-Hu antibodies are less likely to develop paraneoplastic encephalomyelitis and seem to improve more often after treatment of the cancer than those who have anti-Hu antibodies [**9**].

The treatment of an underlying malignancy appears to have more effect on the neurological outcome than the use of immune modulation [**3**]. Nevertheless, a varied proportion of patients show neurological improvement with immunosuppressive treatments [13, 38, 39].

Immunotherapy and/or resection of the primary tumour are only rarely associated with improvement. Remarkable spontaneous remissions have been seen but the syndrome is usually irreversible. There are no established protocols for the treatment of LE or other PNNS, but combinations of either plasma exchange or intravenous immunoglobulin and immunosuppressive agents such as corticosteroids, cyclophosphamide, or tacrolimus have been recommended. Since the pathological features in these disorders suggest a destructive immune process, treatment with immune suppression should begin as expeditiously as possible [**2**, 39]. However, it is likely that many patients have already suffered irreversible neuronal injury at the time of diagnosis [13]. No evidence for stimulation of the growth of tumours by immunosuppression has been reported, although theoretically this is possible [39].

The prognosis of the paraneoplastic LE is variable and there are occasional reports of remission following tumour treatment [39, 40]. Unfortunately, for the more common paraneoplastic syndromes such as paraneoplastic cerebellar degeneration or limbic encephalitis, treatment is still unsatisfactory, and further research into the exact pathophysiology is clearly needed.

Key points

- A diagnosis of PNNS should be considered in patients with acute or subacute dementia even in the absence of an overt malignancy.
- If the clinical state of the patient suggests PNNS, thorough search should be made to detect the underlying malignancy.
- Various antineuronal antibodies in serum or CSF have been found in PNNS and should be measured to aid diagnosis.
- There is no proven therapy for PNNS, but treatment of the underlying malignancy and immunomodulation may bring remission.

Please note

The very long list of references supporting this review has meant that only the most important are listed here and are represented by **bold type** throughout the text. The full list of references is available on the journal website (http://www.ageing.oupjournals/org) as Appendix 3.

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Received 3 July 2004; accepted in revised form 3 November 2004

Age and Ageing 2005; **34:** 193–194
doi:10.1093/ageing/afi032

Low-molecular-weight heparin-associated fat necrosis of the breast

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Abstract

Fat necrosis of the breast is a well-recognised complication of unfractionated heparin. The following is a case of fat necrosis due to low-molecular-weight heparin in a 91-year-old woman admitted to hospital with unstable angina.

Keywords: *heparin, fat necrosis, breast*

Introduction

Fat necrosis of the breast has been reported previously in cases with unfractionated heparin (UH), but not (to our knowledge) with low-molecular-weight heparin (LMWH).

Case report

A 91-year-old woman with diabetes and hypertension was admitted with angina-like pain. Clinical examination was normal. Her ECG revealed sinus tachycardia with ST depression in lateral leads. A diagnosis of unstable angina was made and she was treated with subcutaneous enoxaparin. A troponin level taken at 12 hours was normal and chest pain settled over the next few days.

Five days after admission she complained of breathlessness. A repeat chest X-ray was unremarkable. A CT pulmonary angiogram was performed. This showed minor bibasal collapse with small pleural effusion but no pulmonary embolus. However, there was extensive induration of the skin and subcutaneous fat of the upper part of the left breast and the reporting radiologist raised the suspicion of breast carcinoma.

Subsequent clinical examination revealed a hard indurated area fixed to the skin over the upper and inner quadrant of the left breast (Figure 1). There was bruising of the overlying skin. A few patches of ecchymosis were also noted over other parts of her body, but none was noticed at the injection site on the abdomen. A repeat coagulation screen and platelet count were normal.

A mammogram revealed asymmetrical nodular densities over the upper and inner quadrant of the left breast. Targeted ultrasound of this area was consistent with fat necrosis. She was subsequently discharged with advice to avoid heparin in future. Four months later, clinical examination of the left breast was normal and a mammogram revealed considerable reduction of asymmetry of the previously affected area.

Discussion

Tissue necrosis is a rare, but well-recognised complication of subcutaneous injection of UH or LMWH. Fat necrosis is uncommon with LMWH therapy [1]. Very rarely it can be due to incorrect (intradermal) administration [2]. In the majority of cases, pathogenesis remains uncertain. An immune-mediated reaction can explain necrosis at sites distant from the injection, and type I, III, and IV hypersensitivity