

## Clinico-pathological Conference

# HIV encephalopathy presenting as hypomania

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### Case report (Dr I McGowan)

The patient was a 40 year old male Caucasian homosexual who had worked as a nurse. In 1987 he had right thoracic single dermatomal *Herpes zoster* infection. In February 1988 he was seen at another hospital with a history of chronic diarrhoea, weight loss and oral candidiasis, and was found to have *Entamoeba histolytica* in his stool. Following counselling, he had an HIV test which was positive. He then remained well until June 1988 when he represented with cough and dyspnoea. A chest radiograph was suggestive of *Pneumocystis carinii* pneumonia. He underwent bronchoscopy which confirmed the diagnosis. He was treated with twenty-one days of nebulised pentamidine and made a rapid recovery. He then began secondary prophylaxis with daily oral co-trimoxazole, and zidovudine was commenced. Following this, he was again well until June 1989 when he presented with a short history of retrosternal discomfort. At the time he had marked oral candidiasis, and a presumptive diagnosis of pharyngeal candidiasis was made. He was treated empirically with fluconazole, and his symptoms rapidly resolved.

In November 1989 he reported mild nocturia but had no other urinary symptoms. He had a recurrence of his retrosternal discomfort, and also complained of a mucoid rectal discharge and parasthesiae in his toes. An upper gastrointestinal endoscopy showed mild oesophagitis and also several small lesions of Kaposi's sarcoma in the pylorus. At sigmoidoscopy the rectum appeared normal but *Herpes simplex* was

cultured from a perineal swab. Treatment with acyclovir improved his rectal symptoms. Shortly after this, he became anaemic and leucopenic. His zidovudine was temporarily discontinued and then restarted at a lower dose.

In January 1990 he developed cytomegalovirus retinitis and began treatment with ganciclovir given via a Hickman line. In February he self-referred. On examination he had quite marked left-sided scrotal cellulitis. Culture from the skin revealed a heavy growth of *Staphylococcus aureus* and an ultrasound of the scrotum revealed co-existent epididymo-orchitis. He was treated with oral antibiotics, and his symptoms steadily resolved. In May that year he became non-specifically unwell with a low-grade fever and minimal dysuria. Examination at that time showed some tenderness around the Hickman insertion site. Pending the results of blood and urine cultures, broad spectrum antibiotics were begun. Subsequently a heavy growth of *Escherichia coli* was cultured from the urine. At this time the secondary prophylaxis against pneumocystis pneumonia was changed to monthly inhaled pentamidine. Later on in the summer the patient noted that the numbness and parasthesiae had now extended up to his calves. Carbamazepine was begun with good effect. In late July he re-presented acutely with a history of night sweats, fevers and rigors. *Escherichia coli* was cultured from blood and urine and also from a skin swab taken from the Hickman entry site. Other investigations, including a prostatic ultrasound, an abdominal ultrasound and a chest radiograph were all normal. Nerve conduction studies were also performed and were consistent with an HIV peripheral neuropathy. He was treated with parental antibiotics for his septicaemia, and made a rapid recovery.

In September 1990 it became apparent that the patient was behaving a little oddly. He was normally an outgoing and somewhat extrovert character. His behaviour had become a little inappropriate. He had taken to visiting his neighbours dressed in only his underwear. The patient was admitted for assessment, and was clearly hypomanic. He was euphoric, disinhibited, had marked flight of ideas, insomnia and verbalised several grandiose schemes. Investigations at this stage failed to reveal a metabolic cause for his

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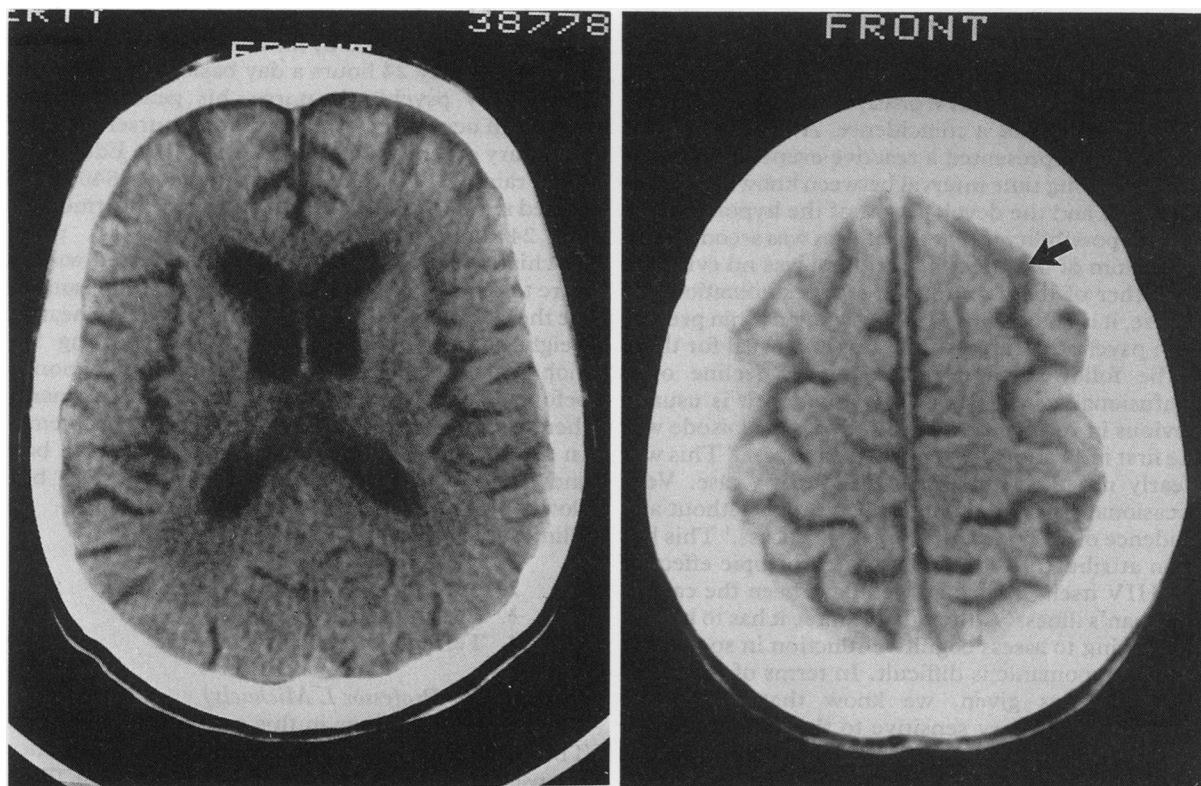


Figure 1 CT head scan taken at level of (a) the lateral ventricles (b) the hemispheres showing cortical atrophy; the sulci are widened (arrow).

problems, and a septic screen was negative. A formal psychiatric opinion was sought and the diagnosis of hypomania was confirmed. Haloperidol was commenced; this therapy was complicated by extrapyramidal side-effects which were successfully treated with procyclidine. Over the next week or so his hypomania settled. It was then planned to send him home with community psychiatric nurse support, and input from the Community Care Team. Once at home the patient discontinued his haloperidol abruptly, and rapidly became hypomanic once more. He began to spend money recklessly. He was readmitted and treated with chlorpromazine in place of haloperidol. Again there was rapid lysis of his problems. Investigations at this stage revealed that he was anaemic and he was transfused with four units of blood. CT of his head (fig 1) showed evidence of cortical atrophy with widened sulci; no focal abnormalities were evident. The patient's condition, whilst on the ward, gave continued cause for concern. He began to refuse his other medication, as he felt that to discontinue it would help him gain weight. It was felt that he was causing himself harm by his inappropriate behaviour, and after careful discussion it was decided to section him. The patient was informed of this decision, but before the section

could be activated, he left the ward and returned home. He was subsequently admitted as a voluntary patient to a psychiatric unit in another hospital, and then was discharged home once more. He was then managed in the community by the Bloomsbury Community Care Team and a community psychiatric nurse, together with a group of supportive friends and neighbours. Over this eight-week period prior to death, the patient continued to live at home. There was a steady deterioration with further weight loss and increasing weakness. Terminally he developed a bronchopneumonia and died.

#### Discussion (Dr M Potter)

This man was clearly hypomanic. He was restless, overactive, he had a labile mood and was disinhibited. In addition he exhibited bizarre behaviour, for example, on one occasion drawing around all his joints with a felt tip pen. We also heard that he was spending recklessly, and also had grandiose plans. He had no personal or family history of previous psychiatric problems, but he had a somewhat extrovert, premorbid personality. The patient did not drink alcohol excessively, nor did he use opiates or cocaine.

Psychosis in HIV +ve patients, unassociated with delirium or dementia, is fairly uncommon.<sup>12</sup> In this case the possibilities are that his hypomanic episode was unrelated to his HIV disease—the two occurring together merely as a coincidence. Alternatively this could have represented a reactive event, but against this is the long time interval between knowing he was HIV +ve and the development of the hypomania. A further possibility is that this illness was secondary to a delirium or a dementia, but there was no evidence for either of these on mental state examination. Of course, it is known that HIV +ve patients can present with psychotic features first, but it is usual for these to be followed by rapid cognitive decline or a confusional state.<sup>13</sup> In such a situation it is usually obvious in retrospect that the psychotic episode was the first indication of a dementing process.<sup>4</sup> This was clearly not the situation in this man's case. Very occasionally psychotic illness can occur without any evidence of an underlying organic process.<sup>1</sup> This has been attributed to some direct neurotropic effect of the HIV itself. This may well have been the case in this man's illness. Although of course it has to be said that trying to assess cognitive function in somebody who is hypomanic is difficult. In terms of the treatment he was given, we know that HIV +ve individuals are very sensitive to the anticholinergic and extrapyramidal side-effects of neuroleptic drugs.<sup>1</sup> This patient clearly showed extrapyramidal problems with haloperidol. In retrospect perhaps, thioridazine, which has fewer extrapyramidal side-effects than haloperidol, might have been a better choice of drug.<sup>1</sup>

Grounds for detention under the Mental Health Act are quite clear. The patient must be showing evidence of causing harm to himself or to others. The patient was behaving in a reckless way and refusing his medication. However, it was still a difficult decision to make. You were faced with the options of placing this patient on a section for assessment for a month, or for treatment over 6 months knowing that the patient's overall prognosis was severely limited anyway. Another practical problem, having sectioned somebody, is attempting to contain them and this may pose significant problems particularly on an acute medical ward. It was probably a tactical error to inform the patient that he was going to be sectioned some time before the assessment was due to be carried out, since he then absconded from the ward. It might have been better for him to have been managed on a psychiatric ward, but one is faced with the ethical dilemma of restraining somebody in hospital towards the end of his life a considerable distance from his friends and neighbours and away from his own environment.

*Dr R J D George*

We looked after this man in his own home in another

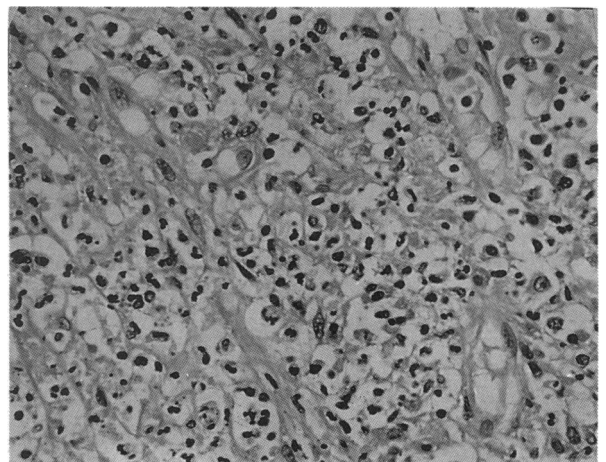
suburb of London for several weeks before he died. The care was provided by his friends and neighbours on a day-to-day 24 hours a day basis, guided by the community psychiatric nurse, his general practitioner, an occupational therapist and ourselves. The voluntary organisation ACET (Aids Care Education and Training—National Information: 081-840 7879) visited regularly and co-ordinated and supplemented the 24 hour care network. Despite his prior psychiatric problems the patient's expressed wishes were to remain at home for as long as possible and to die there. He was fully aware of his worsening health; weight loss, progressive neuropathy affecting his mobility and deteriorating visual acuity. A month before death he decided to stop all his treatment; there was no recurrence of his psychiatric problems. In the last weeks of his life he was immobile in bed and had a urinary catheter; there was a clear but slowly progressive decline in mental function.

Clinical diagnoses:

1. Hypomania
2. Encephalopathy—HIV?, or CMV?
3. Cytomegalovirus retinitis
4. Terminal bronchopneumonia.

#### **Pathology** (*Professor L Michaels*)

The necropsy findings in this man were surprising. There was generalised lymphadenopathy. The nodes themselves were very pale. The spleen was three times its normal size, and within it there were large yellow areas. With all these changes in the reticulo-endothelial system, I thought this was going to turn out to be a lymphoma. Histologically, the lymph nodes and spleen showed massive necrosis with inflammatory cell changes (fig 2). Under high power inflammatory cells were seen to be plasma cells and some histiocytes among them. Staining of the lymph



**Figure 2** Para-aortic lymph node showing plasma cell and macrophage infiltration with necrosis. ( $\times 400$ . Haematoxylin and Eosin.)

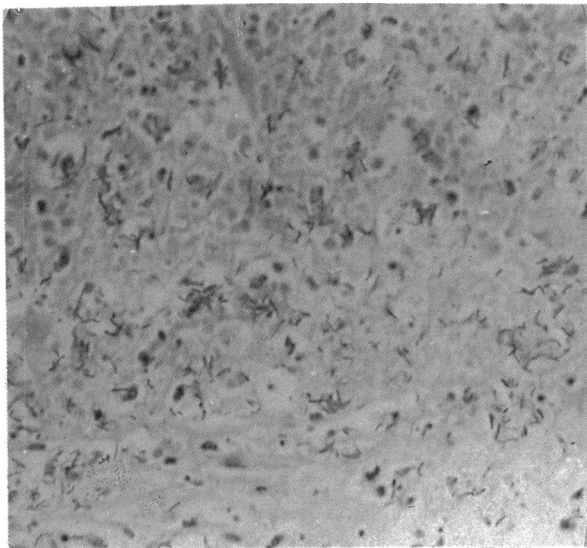


Figure 3 Para-aortic lymph node showing infiltration with vast numbers of acid fast rod shaped organisms—atypical mycobacteria. ( $\times 1000$ , Zeihl-Neelsen.)

nodes and spleen with Zeihl-Neelsen revealed vast numbers of acid-fast bacilli (fig 3). This is quite different from *Mycobacterium tuberculosis* in the pattern of inflammatory reaction. With the absence of granuloma formation this is likely to be an atypical mycobacterium, such as *Mycobacterium-avium intracellulare*.

In the lungs the lower lobes were consolidated. Microscopically there was evidence of bronchopneumonia. There were numerous Gram-positive cocci. *Pneumocystis carinii* were not seen, and there was no evidence of mycobacteria. In the apices, in a subpleural distribution, there was marked emphysematous change. Elsewhere in the upper

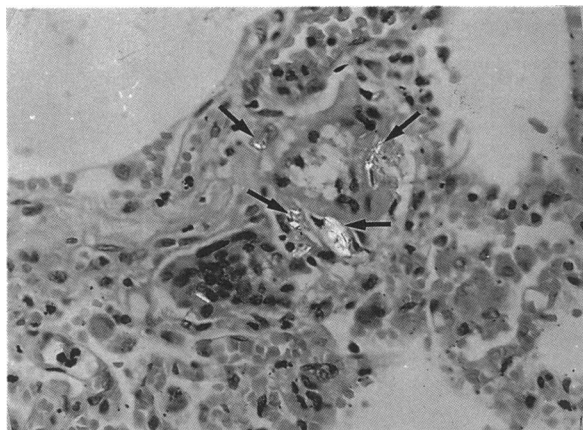


Figure 4 Left upper lobe of lung showing giant cell and macrophage reaction to numerous birefringent crystals (of pentamidine) (arrows). ( $\times 400$ , Haematoxylin and Eosin) photographed through partially crossed polaroids.

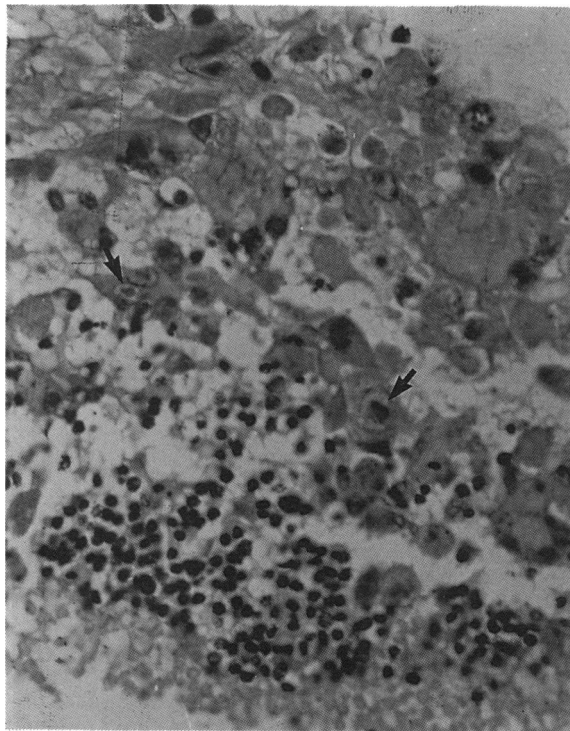


Figure 5 Ganglion cell layer of retina showing swelling and necrosis of cells, many of which show large basophilic intranuclear inclusions (arrows). The granular cell layer is not affected.

lobes, there was a granulomatous chronic inflammatory change. Within this were giant cells which had formed in reaction to foreign body material. At high power this was seen to be crystalline material (fig 4). This man had received nebulised pentamidine, and I wonder if it was pentamidine crystals that were seen deposited in the upper lobes. When nebulised pentamidine therapy is given it is at the limit of its saturation in water. It would not be surprising if some of the pentamidine were to crystallise out during inhalation and may then deposit within the lungs. A granulomatous response to pneumocystis infection has previously been reported in patients who have received inhaled pentamidine therapy.<sup>5</sup> There was no evidence of Kaposi's sarcoma in the tracheobronchial tree, within the lung parenchyma or on the pleura.

In the kidneys, lying within the tubules, there were large numbers of Gram-negative rods. Although the kidneys were not cultured this was probably an *E coli* infection. In the liver there was some inflammatory change, particularly around the sinusoids, and within these were mycobacteria.

Histological examination of the left eye showed widespread retinal necrosis, foci of cells showing the inclusions of cytomegalovirus in the ganglion cell layer (fig 5).

*Dr F Scaravilli*

Macroscopically in the brain there was some patchy areas of discolouration but otherwise there were no gross abnormalities. At this point several possible diagnoses can be ruled out, including progressive multifocal leucoencephalopathy. Very rarely does toxoplasma encephalitis occur without macroscopic abnormalities. But macroscopically this still could be cytomegalovirus encephalitis or HIV encephalitis. On histological examination the myelin stain showed diffuse myelin pallor particularly in the hemispheres. There were no other identifying abnormalities, so this is a rather non-specific finding. The white matter did not show any abnormality other than diffuse oedema and a little perivascular cuffing with lymphocytes. In conclusion, on the basis of the histology, we were not able to make a specific diagnosis and we had to use histochemical methods.

*Miss E Sinclair*

Sections of the brain were stained with an anti-HIV antibody (p24, Dupont), and we detected HIV antigen, both in macrophages and microglial cells. Positive cells were detected scattered throughout the white matter, but no such cells were seen in the cortical grey matter. Using the polymerase chain reaction (PCR), proviral HIV DNA was sought. When using this technique to detect HIV, it is necessary to amplify DNA from more than one region of the genome to preclude false negative results which may occur due to sequence alterations. We routinely amplify sequences from three genes, the *gag* (which codes for HIV core protein), *pol* (which codes for reverse transcriptase) and *env* (which codes for virus cell membrane). PCR was applied separately to both cortical grey and white matter from the brain. In this case HIV sequences were detected in both grey and white matter.

*Dr F Scaravilli*

The presence of non-specific white matter abnormalities and the scattered inflammatory changes,

together with the evidence of HIV infection, means that this man had HIV encephalopathy. By glial fibrillary acidic protein (GFAP) staining we were able to show the extent of glial cell involvement in this process. Throughout the brain there was evidence of increased numbers of glial cells expressing GFAP, indicating that there was indeed diffuse cerebral pathology which was not detected by standard histological methods. Undoubtedly this would have accounted for the changes in higher cerebral function in this patient.

In the spinal cord at the thoracic level there was evidence of marked demyelination and vacuole formation. The patient had a vacuolar myelopathy which might explain his peripheral neurological problems.

## Pathological diagnosis:

1. Disseminated mycobacterial infection
2. Terminal bronchopneumonia
3. Apical foreign body granulomatous response in the lungs
4. HIV encephalopathy
5. Vacuolar myelopathy

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