Clinico-Pathological Conference

Disseminated *Toxoplasma gondii* infection presenting with a fulminant pneumonia

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**Case presentation (Dr R F Miller)**

A 34 year old heterosexual Caucasian health worker first presented to the Outpatients department in January 1988; at this time she was fit and well. She reported that her husband, a haemophiliac, had become HIV-1 antibody positive in 1985. She had undergone HIV testing in January 1986 at another hospital. At this time she was HIV-1 antibody negative. She recalled a mild seroconversion illness, with 'flu like symptoms and a diffuse macular rash, in the autumn of 1986; a repeat HIV test was positive in November 1986. The patient remained fit and well until the autumn of 1993. Her husband had died following an episode of *Pneumocystis carinii* pneumonia in July 1991. In November 1993 she represented complaining of intermittent fever of four weeks duration. At that time examination was normal. Investigations included a normal full blood count and differential, and a CD4 lymphocyte count of 0.32 x 10^9/l (normal range = 0.35-2.2 x 10^9/l). Other investigations included a toxoplasma latex agglutination titre of 1:512. Serological tests for Hepatitis B and syphilis were negative. Her symptoms were self limiting.

In March 1994 she had recurrent intermittent fevers. Examination then revealed seborrhoeic dermatitis on the face and oral hairy leucoplaika. Urea and electrolytes, liver function tests and the full blood count were all normal as was a chest radiograph, mid stream specimen of urine, an ultrasound examination of the abdomen and plain radiology of the paranasal sinuses. The CD4 count was 0.18 x 10^9/l. The patient declined zidovudine therapy but started co-trimoxazole as primary prophylaxis against *Pneumocystis carinii* pneumonia. Within a few days she had a severe generalised rash and fever and so discontinued treatment. Instead dapsone 100 mg once daily was tried, this also produced fever and rash within a few days and so nebulised pentamidine, 300 mg given once monthly, was commenced in June 1994. A CD4 count in July 1994 was 0.09 x 10^9/l; at this time the patient had a variable low grade fever.

By September 1994 the patient was feeling more unwell with increased fatigueability and a non productive cough associated with nasal discharge and stuffiness. In addition she reported low grade fungal infection of her nails and also noted that her hair was thinning and falling out more easily. Examination at that time was unremarkable. Investigations included a normal chest radiograph. Staining and culture of an induced sputum sample, blood and urine was negative for bacteria, mycobacteria and fungi: a CD4 count was 0.06 x 10^9/l. Doxycycline treatment improved the patients symptoms of sinusitis. The patient commenced zidovudine 100 mg four times a day in mid October 1994.

She was admitted in mid November 1994 with a six day history of right upper quadrant abdominal pain, colicky in nature, associated with nausea and vomiting, anorexia and malaise but without fever or sweats. She denied diarrhoea, urinary frequency and dysuria. On examination she was pyrexial, temperature 38-2°C, and had a diffuse macular rash over the trunk and limbs. In the abdomen there was tenderness in the right upper quadrant and renal angle. The liver edge was just palpable. Investigations included urinalysis, which showed 1 plus of protein, a full blood count which showed Hb = 9.5 g/dl (MCV = 89-5), WBC = 2.5 (neutrophils = 1.0) x 10^9/l and platelets = 186 x 10^9/l. A clotting screen was normal. Liver function tests showed AST = 672 (normal < 40) IU/L, alkaline phosphatase = 362, (normal < 280) IU/L, bilirubin = normal. Serological tests for hepatitis A, B, C, cytomegalovirus and Epstein Barr virus were all negative. An ultrasound scan of the abdomen was normal. Culture of blood, urine and stool was negative for bacteria, mycobacteria and fungi. Zidovudine was stopped and there was a rapid improvement in the AST level (it fell to 358 IU/L over 72 hours) but the alkaline phosphatase remained elevated at 643 IU/L. It was felt therefore that this episode possibly represented zidovudine induced hepatitis and a planned liver biopsy was cancelled. The patient was discharged.

A month later the patient reported a return of her symptoms of sinusitis and fever with a non productive cough. Examination revealed a tender liver edge. Liver function tests were repeated and the AST had risen to 199 IU/L but the alkaline phosphatase had fallen to 362 IU/L; bilirubin was normal. The sinusitis was treated with co-amoxiclav, with good clinical response.

The patient was admitted as an emergency one evening in late December 1994, reporting a 10 day history of anorexia, malaise, fever, nasal discomfort and discharge and non productive cough. On examination she was alert,
Figure 1 Chest radiograph, taken 12 hours after admission showing bilateral lower zone infiltrates with a "ground glass" appearance. There is a small right pleural effusion.

Figure 2 Chest radiograph, taken 36 hours after admission showing more confluent bilateral reticulomodular shadowing: the right pleural effusion has increased in size.

Figure 3 Chest radiograph taken on the ICU (48 hours after admission to hospital). The patient has been intubated and a trans-oesophageal doppler probe is in place. Extensive bilateral consolidation is evident, with air bronchogram formation.

Pyrexial, T = 38.5°C and pale. There was non tender 2 cm hepatomegaly without splenomegaly. Examination of the skin, mouth and fundi showed no abnormality. No focal neurological deficit was evident. There was multiple cervical axillary and left inguinal lymphadenopathy—1/2 cm diameter slightly tender firm lymph nodes were palpable. The chest was clear. The arterial oxygen saturation (measured with an oximeter) was 95% (breathing room air). Other investigations showed Hb 8.0 g/dl, WBC = 6·4 × 10⁹/l, platelets = 90 × 10⁹/l. The serum sodium = 130 mmol/l (but the other electrolytes were normal), alkaline phosphatase = 654 IU/L, AST = 1412 IU/L, bilirubin = normal. Serological tests for legionella and mycoplasma were negative. Blood and urine cultures were negative for bacteria, mycobacteria and fungi. A serum cryptococcal antigen (CRAG) test was negative, and a chest radiograph was normal. The patient was admitted and over night her temperature rose to 40°C and she became tachypnoeic. Re-examination showed that the chest was clear. Arterial blood gases (with the patient breathing room air) showed PaO₂ = 6·4 kPa and PaCO₂ = 3·5 kPa. A chest radiograph (fig 1) showed diffuse interstitial shadowing and small bilateral pleural effusions. At this time point the patient was slightly obtunded, but this was attributed to the profound hypoxaemia. She was treated with 60% oxygen by tight fitting face mask and with this the PaO₂ rose to 18·2 kPa. Treatment for presumed severe pneumocystis pneumonia was begun with IV methylprednisolone 1 gm (with the intention of giving two further doses on consecutive days) and IV pentamidine 4 mg/kg/day in view of the previous history of septrin hypersensitivity. Repeat blood cultures and serum CRAG were both negative. An ultrasound examination of the abdomen showed that in the liver there was generalised increased echogenicity but the biliary tree, pancreas, kidneys and spleen were normal, no ascites were detected and there was no intra abdominal lymphadenopathy.

The patient's condition remained stable over the next 24 hours and then she became more unwell with increasing tachypnoeas and fine bi-basal crackles were noted in the chest. The jugular venous pressure was not raised. Blood gases showed PaO₂ = 7·1 kPa and PaCO₂ = 3·5 kPa (taken with the patient breathing 60% oxygen). A further chest radiograph (fig 2) showed more extensive radiographic abnormalities. The patient was transferred to the Intensive Care Unit for continuous positive airways pressure (CPAP) ventilation (FiO₂ = 1·0 and PEEP = + 10 cm H₂O). With this manoeuvre the PaO₂ rose to 14·4 kPa. Cefuroxime and erythromycin, in conventional doses, were added empirically to treat a possible severe community-acquired pneumonia and the patient received a 2 unit blood transfusion. Transoesophageal doppler studies showed good cardiac function with a cardiac output of 7·2 litres per minute. Examination revealed widespread fine end-
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inspiratory crackles throughout both lung fields. Repeat investigations were unchanged save for evidence of abnormal clotting with a thrombin time of 20 seconds (control = 12 seconds) and an INR of 2.0. The patient became increasingly tired and was intubated and mechanically ventilated. A further chest radiograph showed extensive abnormalities (fig 3). Her condition worsened steadily with refractory hypoxemia and hypotension. Terminally she could not be resuscitated from a cardiac arrest. A post mortem examination was performed.

Discussion (Dr N T Bateman)

This heterosexual woman was presumably infected by her husband, a haemophiliac. From her baseline investigations it is clear that she has been infected with Toxoplasma gondii at some stage of her life. Although the illness in autumn 1986 was ascribed to HIV seroconversion, in retrospect, it has many features of acute Toxoplasma gondii infection.1 Over the year from November 1993 onwards her HIV disease was clearly progressing and she had a rapidly falling CD4 lymphocyte count. You attempted primary prophylaxis with cotrimoxazole and then dapsone both of which are thought to have activity against toxoplasmosis as well as P carinii, but she was intolerant of both drugs and so began inhaled pentamidine which has no affect against toxoplasmosis. Through this period the patient was troubled by sinusitis. This is a frequent clinical problem in HIV infected individuals with low CD4 counts,2 occurring in approximately 4% of individuals. Radiographically the prevalence of abnormalities on MRI may be even higher.3 The aetiology is unknown, although some cases are associated with microsporidiosis.

The patient agreed to start zidovudine in October 1994 but presented one month later with a hepatic illness which you thought at the time was zidovudine related. On stopping zidovudine the liver function tests improved rapidly and plans to perform a liver biopsy were abandoned. Although there was a close temporal relationship with hepatitis and commencing therapy reports of zidovudine hepatitis are infrequent and I would have been concerned about opportunistic infections as a cause even though you had excluded most viral infectious causes of hepatitis. I am aware that anecdotally there is an increased risk of complication from liver biopsy in HIV + patients (including haemorrhage and death); however, tissue would have enabled a diagnosis of mycobacteria, fungal or protozoal disease. I think you effectively excluded other causes of abnormal liver functions tests and abdominal pain including cholangitis, by negative findings on abdominal ultrasound and negative cultures of blood, stool and urine. Even though the transaminase enzyme fell rapidly on stopping zidovudine the patient was still not better. She clearly had persistent fever, sinusitis and her liver enlarged and became tender. Again at this stage I would have done a liver biopsy, or if you had been worried about complications, a bone marrow aspirate and trephine would have provided useful information and helped to identify or exclude disseminated non-bacterial zoonosis.

By the time she presented with her agonal illness she was too sick and the disease course so fulminant that full investigation was not possible. I think this woman had toxoplasmosis throughout and this infection accounted for most of her symptoms. The lack of fundal abnormalities, focal brain lesions, and muscle necrosis don’t exclude this diagnosis.

She was clearly far too ill to perform fibreoptic bronchoscopy and even if you had performed bronchoalveolar lavage it is possible that you would not have made the diagnosis as T gondii resides in the lung interstitium rather than the alveolar space. Even if your Unit policy was to perform transbronchial biopsies you would not have performed them in this woman because of her profound hypoxemia and the significant risks of pneumothorax and haemorrhage.4 So, in this situation you were left with treating her empirically for presumed severe pneumocystis pneumonia. This was an appropriate decision.

If the final admission was caused by pulmonary toxoplasmosis, which I think it was, then the chest radiograph is typical. Other radiographic abnormalities described with pulmonary toxoplasmosis include poorly defined nodular opacities 3–5 mm in diameter. Predominantly in the mid and lower zones or rather more course nodular opacities or medium to coarse reticular shadowing.5 6 Of course if this patient had not been hypersensitive to sulphonamides then theoretically high dose co-trimoxazole might have been effective against toxoplasmosis but I suspect by the time of the final admission infection had disseminated and was overwhelming and that any alternative treatment for example clindamycin and pyrimethamine, would have been ineffective. Her final deterioration clinically and radiographically was typical of adult respiratory distress syndrome which has been described in association with many infections including pneumocystis pneumonia6 and toxoplasmosis.7

Clinical diagnosis

1 Disseminated toxoplasmosis
2 Adult respiratory distress syndrome
3 Toxoplasma gondii pneumonia
4 Sinusitis

Autopsy (Dr S Lucas)

Externally the body was that of a non wasted Caucasian woman. There were no lesions on the skin and no peripheral lymphadenopathy was detected. In the lungs there were bilateral clear pleural effusions (500 ml volume), the right lung weighed 935 g and the left 825 g. On section they were uniformly dark and oedematous suggesting shock lung. The liver weighed 1895 g and was pale with scanty 3–4 mm diameter red foci, the biliary tree was normal. The spleen weighed 165 g and had atrophic white pulp. Within the abdomen there was paraortic and mesenteric lymphadenopathy. She was a heavy drinker and history of haemorrhage was obtained.

Bone marrow aspiration was performed and this confirmed a diagnosis of toxoplasmosis. This was confirmed by direct parasitological examination of the bone marrow. The diagnosis was confirmed by serology and by PCR on liver tissue.

I am concerned about the management of the patient. The patient died before any treatment was begun. If the patient had been treated promptly I do not think that this patient would have died. I would have begun treatment without delay. The patient would have made some improvement and the patient would have lived for some time. This patient should have been treated promptly, but not as an emergency. The patient would have benefited from this treatment. The patient would have died within days if the patient was treated promptly. I do not think that the patient would have died if the patient was treated promptly. The patient would have died within days if the patient was treated promptly.
phadenopathy with nodes up to 2 cm in diameter. Bone marrow, kidneys, pancreas, thyroid, adrenal, pituitary and parathyroids all appeared normal. The brain weighed 1260 g; the meninges were normal as were the cut sections. The spinal cord was also normal macroscopically.

On histopathological analysis there was evidence of disseminated toxoplasmosis in lungs (figs 4 and 5), liver, heart (fig 6), stomach, adrenals, pancreas, pituitary, bone marrow (fig 7), nodes, brain (fig 8) and spinal cord. In the lung there was evidence of hyaline membrane disease (shock lung) with focal small necroses; no P carinii or cytomegalovirus was found. In the heart there were multifocal small necroses. The liver had irregular 1 mm zones of necrosis with Toxoplasma gondii tachyzotes, but no viral inclusions were present. In the brain and spinal cord the pattern of infection was nodular diffuse and non-necrotic with numerous cysts. An incidental finding was calcification of the blood vessels of the basal ganglia. The kidneys showed evidence of acute tubular necrosis but no evidence of toxoplasmosis. The nodes were necrotic and fibrotic with occasional toxoplasma cysts.

Pathological diagnosis
1 Disseminated toxoplasmosis
   (a) diffuse nodular encephalitis
   (b) multi organ necroses including shock lung

Discussion (Dr R F Miller)

With the benefit of hindsight we should have carried out the liver biopsy. Although liver function tests showed an improvement clearly the patient's clinical condition did not mirror this. We were certainly influenced by reports of increased complications from liver biopsy in this patient group, and also by the patient's own wishes. I agree with Dr Bateman's comment and faced with this clinical situation again I would think very carefully about either a liver biopsy or alternatively perform a bone marrow biopsy. There are reports of isolation of Toxoplasma gondii from the peripheral blood leucocytes (contained in the buffy coat) of a patient with AIDS who had serological reactivation of toxoplasmosis, and also from cul-

Figure 4 Lung: Medium power view showing shock lung with hyaline membrane (left) and an area of necrosis. (Haematoxylin and eosin); (× 40).

Figure 5 Lung: High power view. Amidst the necroses are small clusters of toxoplasma zyotes. (Haematoxylin and eosin); (× 200).

Figure 6 Heart: Medium power view. There is myocarditis with some necrotic myocytes and chronic inflammation. The toxoplasma are not visible at this magnification. (Haematoxylin and eosin); (× 40).

Figure 7 Bone marrow: High power view. In the necrosis is a cluster of tachyzotes (centre). (Haematoxylin and eosin); (× 200).

Figure 8 Cerebrum: High power view. A cluster of toxoplasma bradyzys, each containing hundreds of parasites. (Haematoxylin and eosin); (× 200).
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... of peripheral blood. This latter technique requires only 10 ml of venous blood, white blood cells are separated by leucapheresis with dextran and inoculated on a monocyctic cell culture. After four days parasites in the culture are revealed by immunofluorescence with an anti-P30. In one study T gondii was isolated from the blood of 12 of 31 patients with toxoplasmosis, including 10 with cerebral toxoplasmosis, one with pulmonary infection and one with ocular infection. In two patients parasites were detected in blood before onset of clinical symptoms, in another P carinii pneumonia the method permitted treatment of unsuspected toxoplasmosis. Conventional blood cultures, performed in 19 of the 31 patients were negative for T gondii.

On a separate note I think that in future I would attempt desensitisation if faced with a patient who was allergic to co-trimoxazole and who had T gondii antibodies—knowing that co-trimoxazole is effective prophylaxis against toxoplasmosis as well as P carinii infection.

Dr S B Lucas

In over 100 AIDS autopsies that I have performed at University College London Hospitals this is the only example of diffuse nodular toxoplasmic encephalitis I have encountered. Toxoplasmosis causing multiorgan necroses is uncommon, but has been documented as a cause of the adult respiratory distress syndrome.6

We thank Jane Rutherford for typing the manuscript. Figures 1, 2 and 3 are taken from "Fulminant Toxoplasmosis gondii pneumonia in a patient with AIDS" by Rottenberg G T et al published in Clinical Radiology (in press) and are reproduced with permission of the authors and the editor of Clinical Radiology.

Key points box

- Disseminated Toxoplasma infection may rarely occur in HIV infected individuals.
- Toxoplasma gondii may be isolated from peripheral blood cultures.
- Co-trimoxazole is effective prophylaxis against toxoplasmosis as well as P carinii infection.
- If co-trimoxazole allergy occurs, consider desensitisation.

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