Clinico-Pathological Conference

Occult miliary tuberculosis in advanced HIV disease

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Case Report (Dr E L Corbett)

A 40 years old Caucasian homosexual retired civil servant was admitted to the HIV/AIDS Unit of UCL Hospitals in early November 1994. He had been admitted to another hospital in mid October 1994 complaining of rectal bleeding, diarrhoea and colicky abdominal pain. In the past ulcerative colitis had been diagnosed in April 1992 on the basis of barium enema and colonoscopy appearances and results from sigmoidoscopy and biopsy showing chronic active proctitis. His symptoms had been well controlled with oral mesalazine and colifoam enemas. Initially oral prednisolone had also been used but this had been tailed down and stopped in July 1992. In October 1994 stool culture had shown *Entamoeba histolytica* which was treated with metronidazole and at sigmoidoscopy an inflamed mucosa was seen. Oral prednisolone 10 mg once daily was added to the mesalazine and colifoam to control the abdominal symptoms. At this time the patient requested an HIV test. His partner had died of AIDS in 1990. The HIV test was positive and a CD4 lymphocyte count was $0.02 \times 10^9/l$ (normal range $0.35-2.2 \times 10^9/l$). In this setting the patient reported exertional dyspnoea, a non productive cough and fever. Further investigations included a chest radiograph, which showed bilateral lower zone reticulonodular shadowing, arterial blood gases (taking breathing room air), which showed a PaO_2 of 9.8 kPa, and an induced sputum sample, which was positive for *Pneumocystis carinii*. Treatment was begun with oral high dose co-trimoxazole. By day 6 of this therapy the patient had increasingly severe abdominal symptoms and so treatment was changed to intravenous pentamidine (4 mg/kg) given on alternative days. After three doses of this therapy nebulised pentamidine 300 mg once daily was commenced in order to complete the course of therapy. On day 12 of treatment the patient was transferred to this hospital.

On examination, on arrival, he was thin and clearly unwell. The respiratory rate was 28 per minute and there was marked oral candidiasis. The arterial oxygen saturation (on air) was 88%, measured using a transcutaneous oximeter. A chest radiograph showed diffuse interstitial shadowing: no lymphadenopathy, effusions or intrapulmonary cavities were present. Fibreoptic bronchoscopy was performed; in addition to confirming a diagnosis of *P*

carinii pneumonia there was evidence of a mixed bacterial infection; also CMV infection was detected by the presence of cytopathic inclusions, a positive DEAFF (Detection of Early Antigen by Florescent Foci) result and subsequent positive culture. Staining for acid and alcohol fast bacilli (AAFB) and culture for mycobacteria was negative. The full blood count showed an Hb of 15.1 g/dl, a WBC of $5.6 \times 10^9/l$ (86% neutrophils) and a platelet count of $241 \times 10^9/l$. Stool examination was negative for *Clostridium difficile* and other pathogens. The *P carinii* pneumonia was treated with methylprednisolone, initially 1 g intravenously for three days, and subsequently 0.5 gm intravenously for two days, thereafter prednisolone 40 g once daily was commenced. Instead of reducing to zero over a week the patient remained on 10 mg daily as treatment of inflammatory bowel disease. Initially intravenous pentamidine was given because of concerns about the potential effects of co-trimoxazole on the bowel symptoms. In addition cefuroxime was given in conventional doses to treat the mixed bacterial growth; because of continuing diarrhoea subcutaneous diamorphine was given using a syringe driver. After five days of treatment there was little impact on the patient's respiratory symptoms so intravenous co-trimoxazole was started and pentamidine discontinued. There was subsequently a steady recovery over 10 days in the respiratory symptoms. Recovery was complicated by a spontaneous left apical pneumothorax on day 14 of treatment; this was managed conservatively. The patient had persistent fever and diarrhoea. A rectal biopsy showed evidence of CMV proctitis and CMV was also detected in blood by a DEAFF test. Careful ophthalmological review showed no evidence of CMV retinitis. Intravenous ganciclovir 5 mg/kg twice daily for 14 days was given for treatment of the CMV pneumonitis and proctitis. With this therapy the patient became afebrile. Following this no maintenance CMV therapy was given. The patient was discharged to convalescence in mid December 1994. On discharge his chest radiograph showed residual reticulonodular shadowing of a non specific nature. The dose of prednisolone was subsequently reduced to 5 mg once daily and codeine phosphate was used as required to control diarrhoea.

The patient was seen for review in the out patients department in early February 1995.

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Figure 1 Chest radiograph on readmission showing more marked reticular shadowing and possible cavities in the right mid zone.

At this time he reported a two day exacerbation of his diarrhoea and in addition felt generally weak. Examination revealed asymptomatic CMV retinitis. The patient was admitted to begin induction treatment with intravenous ganciclovir 5 mg/kg twice daily. On admission it was noted that he was very forgetful and his mentation was slow. Investigation included an MRI scan of the head which showed marked atrophy and non specific white matter change. An EEG showed non specific abnormal slow wave activity. A chest radiograph (fig 1) showed marked reticular shadowing and possible cavitation in the right mid zone. At lumbar puncture analysis of CSF revealed no cells; staining and culture was negative for bacteria, mycobacteria, fungi and viruses. A test for cryptococcal antigen was negative; DNA amplification using cell free CSF was positive for CMV DNA.

On day 8 of the admission the patient developed a spontaneous right pneumothorax (fig 2), that required intercostal tube drainage. On reinflation the chest radiograph (fig 3) showed evidence of right apical consolidation and an increase in background infiltrates. On day 13 a

Figure 2 Chest radiograph showing a complete right pneumothorax. There are cavities within the collapsed lung.

Figure 3 Chest radiograph showing right apical consolidation and marked background infiltrates. A right intercostal drain is in place.

right sided Hickman line was inserted for continued administration of ganciclovir. At this time the patient continued to experience variable cough with no sputum expectoration. These symptoms persisted despite empirical treatment with cefuroxime in conventional doses and so a course of ceftazidime and teicoplanin was given. The chest radiograph (fig 4) showed further deterioration. There was now evidence of increased consolidation in the right upper lobe and also in the lingula together with bilateral pleural effusions. The patient had a variable low grade fever and intermittent diarrhoea. Culture of blood, urine and stool was negative for bacteria, fungi and mycobacteria (selective media were used for culture of mycobacteria). By day 26 of the admission the patient was very weak, clinically septic with hypotension, tachycardia and marked confusion. Investigations revealed evidence of disseminated intravascular coagulopathy. The patient was transferred to the

Figure 4 Chest radiograph taken just prior to death. There is marked right upper lobe and lingular consolidation with bilateral pleural effusions.

Intensive Care Unit where he suffered a cardio-respiratory arrest and died. An autopsy was performed.

Discussion (Dr R N Davidson)

This man clearly had advanced HIV disease when he first underwent HIV-antibody testing. I think the history of colitis is straight forward and notable only for the use of oral steroids, to control symptoms, for several months. Despite his advanced disease it is improbable that the cause was CMV colitis given the duration of the history. The *E histolytica* was probably a non-pathogenic zymodene, common in gay men, as he had not travelled to the tropics. This is now thought to be a separate species, *E dispar*, which although morphologically identical to *E histolytica*, is genetically distinct, and is non-invasive.¹ On transfer here in November you took the view that he had failed treatment of *P carinii* pneumonia and so it was completely appropriate to lavage him, to secure the diagnosis made by sputum induction and to identify any potential co-pathogens. By doing this CMV pneumonitis and a mixed bacterial infection were picked up.

I am not aware of any data from prospective studies showing benefit from maintenance ganciclovir, following induction treatment, for CMV colitis or pneumonitis so your decision not to give maintenance ganciclovir seems appropriate. Turning now to the second and final admission systemic steroid therapy had been continued during the 2½ months he was out of hospital. He was of course profoundly immunosuppressed and had lost weight since his discharge. I am concerned by the chest radiograph that showed (fig 3) possible small, thin-walled cavities within the collapsed right lung. Of the causes of pulmonary disease I would be most concerned about *Mycobacterium tuberculosis*, nocardia, *Staphylococcus aureus* and Gram negative infections. Fungal infections would be unlikely to cause cavitation in someone with such advanced HIV disease. Of the causes of cavitory pneumonia in AIDS, tuberculosis is the most important to diagnose, because it is eminently treatable, and because it poses a cross-infection hazard to other patients and to staff. HIV infected patients with tuberculosis are no more or no less infectious than HIV negative patients with tuberculosis.² Despite the fact that fewer HIV infected tuberculosis cases have cavitory disease, a similar proportion, around 60%, are smear-positive for *M tuberculosis*.³ Smear positivity means that over 5000 organisms of *M tuberculosis* are present per ml of expectorated sputum.⁴ Smear positivity generally implies that the patient is coughing large numbers of droplet nuclei containing *M tuberculosis*. These droplet nuclei are the source of infection, and in experimental models as few as 1-10 droplet nuclei can lead to infection.⁵ In one study, 96% of HIV infected patients with disseminated tuberculosis were smear-positive, indicative of the huge bacillary load in these patients.³ There are exceptions to the

principle that smear-negative cases of pulmonary tuberculosis have little or no infectivity to others.⁴ First, in some studies, smear-negative cases of pulmonary tuberculosis are highly infectious.² Second, children, and some adults such as this patient, are unable or reluctant to expectorate sputum for analysis, and gastric washings or bronchoalveolar lavage (BAL) is needed. Whilst DNA amplification using the polymerase chain reaction (PCR) for *M tuberculosis* is methodologically more difficult than for viruses, it may have a role in future in the early diagnosis of tuberculosis.⁶ The technique of PCR is oversensitive, and is thus suitable for screening; whilst a positive PCR signal for *M tuberculosis* does not signify that tuberculosis is currently "active", negative results from PCR should be useful in excluding *M tuberculosis*.

Clearly the tempo of the final admission was overshadowed by marked neurological deterioration and his advanced HIV disease. That together with a pneumothorax meant that you did not perform a repeat fiberoptic bronchoscopy. At this stage of HIV disease mycobacterial infection is frequently disseminated and culture of blood (using selective media) is frequently positive. In this case blood cultures were negative. An alternative strategy might have been to perform a bone marrow and trephine. This investigation has a high diagnostic yield for mycobacteria in this context.⁷ Of course it is important not to stain just the aspirate for AAFB but to culture it, in order to distinguish *M tuberculosis* from *M avium intracellulare* and other atypical mycobacteria, and to enable antibiotic sensitivity testing to be carried out. If your patient had superficial (or ultrasound scan evidence of) intra abdominal lymphadenopathy an aspiration of a lymph node might also have provided diagnostic information.⁷ I would be wary about carrying out a liver biopsy as, despite the potential diagnostic yield when performed in HIV infected individuals, this procedure is associated with a greater risk of haemorrhage and a higher mortality rate than in the general population.

The detection of CMV DNA in CSF strongly correlates with the presence of CMV disease, especially polyradiculopathy and encephalitis, in patients with AIDS,^{8,9} so I think his neurological deterioration may well have been due to CMV encephalitis and not to HIV encephalopathy.

Clinical diagnosis

- 1 Disseminated *Mycobacterium tuberculosis*
- 2 CMV encephalitis

Pathology (Dr S B Lucas)

The body was that of an emaciated Caucasian male, with old scars but no active skin ulceration. It was immediately obvious, on opening the chest and abdomen, that there was a disseminated military infection involving pleurae, liver and spleen. The likeliest aetiology, macroscopically, was then tuberculosis or possibly nocardiosis.¹⁰ The heart was normal

Figure 5 Lung macroscopic appearances of right upper lobe, showing widespread, nodular consolidation.

(265 g) without pericarditis. The right lung (1205 g) was adherent to the pleura at the apex, the left (915 g) had a clear pleural effusion of one litre, and both pleural surfaces had numerous white spots. On cutting, the right upper lobe (fig 5) had widespread nodular consolidation with a 1 cm focus of cavitation; the right and left lower lobes were similary consolidated without cavitation. The trachea and bronchi wre reddened. The liver (2130 g) was studded throughout by 1-5 mm pale nodules, as was the spleen (505 g; fig 6); the pan-

Figure 6 Spleen macroscopic appearances; showing multiple pale nodules 1-5 mm in diameter.

Figure 7 Spleen, showing non-reactive tuberculosis. There is a central zone of necrosis surrounded by non-activated macrophages. Haematoxylin and eosin, magnification $\times 100$.

creas capsule also had white flecks. The adrenals had scanty 1 mm white spots. Paratracheal and mediastinal hilar nodes were yellow and necrotic, whilst the other node groups were atrophic. No old calcified tuberculous lesions

Figure 8 Bronchial ulcer. The normal bronchial epithelium is disrupted and there is associated inflammation. Haematoxylin and eosin, magnification $\times 20$.

Figure 9 High power view of edge of bronchial ulcer showing enormous numbers of AAFB (staining pink) Zeihl-Neelsen, magnification $\times 100$.

were identified. The kidneys were large (combined weight 435 g) and pale indicating shock, with numerous white spots on cut surfaces. The intestinal mucosae and serosae seemed normal. The brain was of normal size (1505 g) although on cutting there was ventricular dilation.

Histopathology showed that the disseminated infection was tuberculosis with the typical histology found in immunosuppressed patients: non-reactive and multibacillary.¹¹ Liver, lungs, spleen, bone marrow, nodes, adrenals, epididymes and large bowel serosa had small to large zones of necrosis containing karyorrhetic nuclear debris, surrounded by hydropic non-activated macrophages, and containing vast numbers of acid-fast bacilli (fig 7); epithelioid cells and Langhans' giant cells were not seen. Tuberculous ulcerations of trachea and bronchi could be identified histologically, (fig 8) shedding acid-fast bacilli (fig 9); the lungs and kidneys showed evidence of shock (hyaline membranes and acute tubular necrosis respectively). Cytomegalovirus (CMV)—associated necroses were seen in adrenals and there was CMV endymitis and micronodular encephalitis, although HIV giant cell encephalitis was not seen. There was no tuberculous meningitis. Samples of spleen and lung were cultured and grew *M tuberculosis*, fully sensitive to standard anti-mycobacterial drugs.

Morbid anatomy alone cannot discriminate a reactivated from a new tuberculous infection, but in this patient there was no positive evidence of earlier healed disease.

Discussion (Dr R N Davidson)

Because his BAL was smear and culture-negative for *M tuberculosis* in November 1994, he was non-infectious then. However, on his sec-

ond admission to hospital, despite the failure to find AAFB in his sputum—we are told that he did not expectorate sputum—I suspect, from the slides we have seen showing ulceration and inflamed large conducting airways, containing huge numbers of *M tuberculosis*, that he was nonetheless producing large numbers of infectious droplet nuclei. He may have only recently "reactivated" a latent tuberculous infection or have been recently infected. *M tuberculosis* takes around three weeks to form colonies, being intrinsically slow-growing, so infection may have occurred at one of the health care facilities where he spent his last few months. Most cases of tuberculosis in the community occur from unknown sources. In hospital outbreaks, the source case is usually a smear-positive case who has been "missed", though contact with such source cases may only be transient, and not face-to-face.^{12 13} As an HIV infected individual, he would have been at far greater risk of acquiring tuberculosis than HIV negative individuals.² It seems very likely that this man became infected during or soon after leaving hospital, following his first admission. The infectivity of tuberculosis in HIV positive patients is greater than in the general population and there are several reports of nosocomial transmission occurring in HIV units with only transient exposure to other patients with tuberculosis. Do the microbiologists think that he was highly infectious?

Dr N Shetty

A previous case report, in 1992, described an HIV infected patient admitted to hospital in the United States with fever and cough, who was diagnosed as having concurrent infections with both *P carinii* and *Mycobacterium avium-intracellulare*.¹⁴ Having secured two diagnoses for the pneumonia, tuberculosis was not suspected. Sputum smears for AAFB were consistently negative and *M tuberculosis* in culture was initially overgrown by *M avium intracellulare*. After tuberculosis was diagnosed, contact tracing revealed that 19 (20%) of 93 hospital workers and 6 (45%) of 11 visitors had converted to a positive tuberculin skin test. This episode underscores the fact that HIV infected patients may have several concurrent diagnoses that obscure the presence of tuberculosis. This and other reports also demonstrate that smear negative patients can be infectious and undiagnosed tuberculosis is a risk for health care workers including laboratory workers and mortuary staff.¹⁵ Rare patients are hyperinfectious¹⁶ and non-pulmonary tuberculosis, for example abscess fluid, can be infectious.¹⁷ The risk of transmission to health care workers seems to increase if bronchoscopy is carried out, or if the patient is intubated.¹⁸ This patient, despite being unable to expectorate sputum was clearly infectious. Once the results of the necropsy were known the case was reported to the local Consultant in Communicable Disease Control—as tuberculosis is a notifiable disease, regardless of whether the patient is HIV infected or not. In addition contact tracing of the patients' house-

hold contacts and close associates was undertaken. Another HIV infected patient, who was on the ward at the same time as this patient, was found to have extra pulmonary tuberculosis. Typing of the two isolates of *M tuberculosis* by the technique of Restriction Fragment Length Polymorphism show that they were indistinguishable. This strongly suggests that the other patient who was on the ward was infected by the patient who died of disseminated tuberculosis.

Dr R F Miller

Should we have done anything differently and what should we be doing if we meet a similarly immunosuppressed patient with a chest radiograph atypical for tuberculosis and respiratory symptoms? We already have a very high index of suspicion for tuberculosis in all our patients but we don't for example have the facilities to isolate every patient nor do we have negative pressure ventilation in our cubicles.

Dr R N Davidson

In the UK guidelines drawn up by the Joint Tuberculosis Committee of the British Thoracic Society^{19,20} HIV infected patients with tuberculosis are treated as potential sources for nosocomial transmission of *M tuberculosis* in exactly the same way as HIV negative patients with tuberculosis. The main aim is to prevent the droplet nuclei, which leave the patient, from being breathed in by people in other areas. The organism in this case was fully sensitive—but multi-drug resistant *M tuberculosis* is being increasingly reported in HIV infected patients. Single cubicles are only useful if they are well ventilated to the exterior, and if the door is kept shut. Alternatively, UV light may be used in future to sterilise airborne *M tuberculosis*. In the USA sub-micron face masks are worn by medical/nursing staff who have contact with tuberculosis patients—this is logical, and UK centres could adopt these. Personal high efficiency particle extraction (HEPA) filters have been recommended but their use remains controversial.²¹ In patients with advanced HIV disease and pulmonary tuberculosis chest radiographs are often atypical and I think the key thing is to have a high index of suspicion for tuberculosis and to consider the possibility of this diagnosis in all HIV positive patients with respiratory symptoms¹⁹.

Dr S B Lucas

Clearly constant awareness and eternal vigilance is required for infections like tuberculosis; they catch one unawares when one's guard is down—and this will always be the case.

- Petri WA, Clark CG, Diamond LS. Host-parasite relationships in amebiasis: conference report. *J Infect Dis* 1994;169:483-4.
- Nunn P, Mungai M, Nyawaya J, et al. The effect of human immunodeficiency virus type-1 on the infectiousness of tuberculosis. *Tuber Lung Dis* 1994;75:25-32.
- Smith RL, Yew K, Berkowitz KA, Aranda CP. Factors affecting the yield of acid-fast sputum smears in patients with HIV and tuberculosis. *Chest* 1994;106:684-6.
- Dutt AK, Stead WW. Smear-negative pulmonary tuberculosis. *Semin Respir Infect* 1994;9:113-9.
- Bloom BR, Murray CJ. Tuberculosis: commentary on a reemerging killer. *Science* 1992;257:1055-64.
- Walker DA, Taylor IK, Mitchell DM, Shaw RJ. Comparison of polymerase chain reaction amplification of two mycobacterial DNA sequences, IS6110 and 65kDa antigen gene, in the diagnosis of tuberculosis. *Thorax* 1992;47:690-4.
- Small PM, Schecter GF, Goodman PC, Sande MA, Chaisson RE, Hopewell PC. Treatment of tuberculosis in patients with advanced human immunodeficiency virus infection. *N Engl J Med* 1991;324:289-94.
- Gozlan J, El Amrani M, Baudrimont M, et al. A prospective evaluation of clinical criteria and polymerase chain reaction assay of cerebrospinal fluid for the diagnosis of CMV-related neurological disease during AIDS. *AIDS* 1995;9:253-60.
- Fox JD, Brink NS, Zuckerman MA et al. Detection of herpesvirus DNA by nested polymerase chain reaction in cerebrospinal fluid of human immunodeficiency virus infected individuals with neurological disease: a prospective study. *J Infect Dis* 1995;172:1087-90.
- Lucas SB, Hounnou A, Peacock CS, et al. Nocardiosis in HIV positive patients—an autopsy study in West Africa. *Tuber Lung Dis* 1994;73:301-7.
- Nambuya A, Sewankambo N, Mugerwa R, Goodgame RW, Lucas SB. Tuberculous lymphadenitis associated with HIV in Uganda. *J Clin Pathol* 1988;41:93-6.
- Wenger PN, Otten J, Breeden A, Orfas D, Beck Sague CM, Jarvis WR. Control of nosocomial transmission of multidrug-resistant *Mycobacterium tuberculosis* among healthcare workers and HIV-infected patients. *Lancet* 1995;345:235-40.
- Kent RJ, Uttley AHC, Stoker NG, Miller RF, Pozniak AL. Transmission of tuberculosis in a British centre for patients infected with HIV. *BMJ* 1994;309:639-40.
- Pierce JR, Sims SL, Holman GH. Transmission of tuberculosis to hospital workers by a patient with AIDS. *Chest* 1992;101:581-2.
- Kantor H, Poblete R, Pusateri S. Nosocomial transmission of tuberculosis from unsuspected disease. *Am J Med* 1988;84:833-8.
- Haley C, McDonald R, Rossi L, Jones W, Haley R, Luby J. Tuberculosis epidemic among hospital personnel. *Control Hosp Epidemiol* 1989;10:204-10.
- Hutton M, Stead WW, Cauthen G, Bloch A, Ewing WW. Nosocomial transmission of tuberculosis associated with a draining abscess. *J Infect Dis* 1990;161:286-95.
- Malasky C, Jordan T, Potulski F, Reichman L. Occupational tuberculosis infections among pulmonary physicians in training. *Am Rev Respir Dis* 1990;142:505-7.
- Guidelines on the management of tuberculosis and HIV infection in the United Kingdom: Subcommittee of the Joint Tuberculosis Committee of the British Thoracic Society. *BMJ* 1992;304:1231-3.
- Control and prevention of tuberculosis in the United Kingdom: Code of Practice 1994. Joint Tuberculosis Committee of the British Thorax Society. *Thorax* 1994;49:1193-1200.
- Jarvis WR, Bolyard EA, Bozzi CJ. Respirators, recommendations, and regulations: the controversy surrounding protection of health care workers from tuberculosis. *Ann Intern Med* 1995;122:142-6.