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BRIEF COMMUNICATION

HIV and tuberculosis co-infection in south-western Sydney: experience from a case series

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Abstract

A case series of six patients with HIV and *Mycobacterium tuberculosis* co-infection is presented. All patients were overseas-born and in all but one there was profound immunodeficiency. We recommend HIV screening of all cases of *M. tuberculosis* and a high degree of suspicion of tuberculosis in immigrants with HIV infection from endemic areas. Management problems included delayed diagnosis, rapid progression, paradoxical reactions and requirement for surgical intervention in three patients. Therapeutic complications included possible drug malabsorption, adverse events and drug interactions. *M. tuberculosis* was fully drug sensitive in all cases. (Intern Med J 2004; 34: 203–206)

Key words: HIV, tuberculosis (TB)

Worldwide, tuberculosis (TB) is the leading cause of death resulting from a single infectious disease with an increasing incidence in both developing and industrialised nations, coinciding with the spread of the HIV epidemic. HIV infection has been identified as the most important predisposing factor for the development of TB, with infected persons at significantly increased risk of primary or re-activation TB.[1] Co-infection with HIV and TB represents an increasingly important diagnostic and management problem worldwide. In Australia, immigrants from high-prevalence TB regions represent a high-risk group. The salient features of six cases of HIV/TB co-infection occurring within a 2-year period in south-western Sydney are summarised in Table 1.

Case 1 had a history of poor adherence to antiretroviral regimens. TB was diagnosed upon presentation with fevers and clinical signs of upper lobe consolidation. Fevers persisted despite three weeks of 4-drug antituberculous therapy and repeat chest X-ray radiographs revealed new bilateral changes, with bronchoscopy specimens persistently positive for acid-fast bacilli. Further investigation revealed undetectable serum drug levels, and low levels of Vitamin A, D, albumin and iron, suggesting malabsorption as cause of treatment failure. Therapy was augmented with increase in dose of isoniazid and ethambutol, intravenous administration of rifabutin and addition of intramuscular capreomycin, intravenous ciprofloxacin and oral cycloserine. The patient made a gradual recovery and antiretroviral therapy was recommenced.

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Case 2 presented with a 2-month history of anorexia, fever, night sweats and 10 kg weight loss. Examination findings included splenomegaly, oral candidiasis and normal respiratory examination. Investigations revealed advanced HIV with CD4 count of 30, HIV viral load >750 000, and mediastinal and para-aortic lymphadenopathy on computed tomography (CT). Clarithromycin and rifabutin were commenced for presumed atypical Mycobacterial infection, with addition of amphotericin and fluconazole following isolation of cryptococcus from blood and cerebrospinal fluid. The patient remained febrile and deteriorated suddenly with development of abdominal distension, hypotension and renal failure. Repeat abdominal CT identified hepatic lucencies, ascites and intestinal oedema suggestive of tuberculous enteritis. Despite addition of antituberculous therapy, the patient continued to deteriorate and died. *Mycobacterium tuberculosis* was cultured from a lymph node aspirate after his death.

In Case 4 symptoms had been present for 3 months before diagnosis and disease progression was rapid despite changing to intravenous rifampacin.

In Case 5 presentation was again delayed and CT showed a $5 \times 4 \times 8$ cm abdominal mass causing right-sided hydronephrosis and hydroureter (Fig. 1). Aspiration of the mass revealed acid fast bacilli confirmed as *M. tuberculosis* by DNA probe. Despite 4-drug antituberculous therapy and combination antiretroviral therapy, fever continued and repeat CT showed an increase in size of the mass. Antituberculous therapy was administered intravenously and surgical debulking of tuberculous adenopathy with ureteric stent insertion performed with good result.

In the above case series, all patients were overseas-born and in all but one there was profound immunodeficiency with $CD4^+$ lymphocyte count of less than $200/mm^3$. Management problems included delayed

Table 1 Case history summary for six patients presenting with HIV and tuberculosis co-infection

Case	1	2	3	4	5	6
Age (years)	24	33	49	35	23	25
Gender	Female	Male	Male	Male	Male	Female
Country of birth	Ethiopia	Cambodia	Cambodia	East Timor	Cambodia	South Africa
Presentation	July 2000	October 1999	September 2000	October 2000	September 2000	November 2000
Sequence of diagnosis	HIV prior to TB (years)	HIV prior to TB (weeks)	TB prior to HIV (weeks)	HIV prior to TB (weeks)	HIV prior to TB (weeks)	HIV prior to TB (years)
CD4 count when TB diagnosed	150	30	50	120	80	690
Site of TB	Pulmonary	GIT Lymph node (para-aortic)	Pulmonary (miliary) Ankle joint	Lymph node (cervical) Bone marrow Occult pulmonary	Lymph node (abdominal)	Lymph node (cervical)
Treatment	isoniazid rifabutin ethambutol pyrazinamide capreomycin cycloserine	isoniazid rifabutin ethambutol pyrazinamide clarithromycin amikacin amphotericin	isoniazid rifampicin ethambutol pyrazinamide	isoniazid rifampicin ethambutol pyrazinamide	isoniazid rifampicin ethambutol pyrazinamide	isoniazid rifampicin ethambutol pyrazinamide
HAART	AZT/3TC/NEV	d4T/3TC/NFV	AZT/3TC/EFV	AZT/3TC/EFV	d4T/3TC/ddI	d4T/ddI/EFV
Complications	Treatment failure Drug malabsorption Non-compliance Drug interaction	Delayed diagnosis Rapid progression Dissemination Death	Drug rash – pyrazinamide Drug malabsorption Ankle joint collection	Treatment failure Rapid progression Death	Paradoxical reaction Hydronephrosis	Nil
Management of complications	Drug levels Dose increase – ethambutol 2nd line agents iv rifabutin	iv therapy Attempted resuscitation	Cessation of pyrazinamide Ankle joint drainage	iv therapy Dose increase Attempted resuscitation	iv therapy Surgical debulking Ureteric stent	Surgical excision
Concurrent opportunistic infections	Nil	MAC cryptococcosis CMV	Systemic candidiasis	Nil	Nil	Nil
Mycobacterium tuberculosis isolation	Sputum Stool	Lymph node	BAL Ankle joint	Lymph node Sputum (delayed)	Lymph node	Lymph node
Sensitivity	Sensitive	Sensitive	Sensitive	Sensitive	Sensitive	Sensitive
Outcome	Slow recovery	Death from tuberculous enteritis	Slow recovery	Death from pulmonary haemorrhage	Slow recovery	Recovered

AZT, azidothymidine; BAL, bronchoalveolar lavage; CMV, cytomegalovirus; ddI, didanosine; d4T, stavudine; EFV, efavirenz; GIT, gastrointestinal tract; HAART, highly active antiretroviral therapy; MAC, *Mycobacterium avium* complex; NEV, nevirapine; NFV, nelfinavir; TB, tuberculosis.

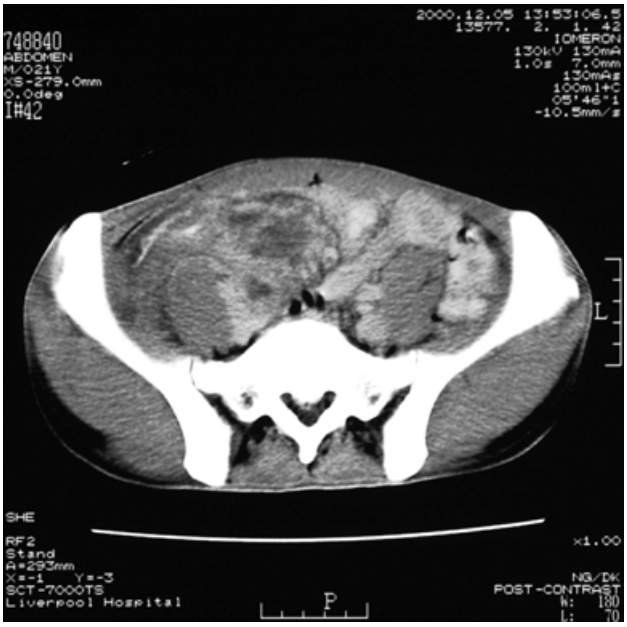

Figure 1 Abdominal computed tomography scan of patient five, revealing a right-sided abdominal mass.

diagnosis, rapid progression, paradoxical reaction and requirement for surgical intervention in three patients. Therapeutic complications included drug malabsorption, side-effects and interactions. *M. tuberculosis* was fully sensitive in all cases.

HIV/TB co-infection is not uncommon in Australia because of the diverse ethnic background of the population and must be considered in at-risk patients. Australian national surveillance data from 1992 to 1998 reveal 25% of adults diagnosed with AIDS were born outside Australia. The diagnosis of several infectious complications varied by region of birth, most markedly for TB. TB prevalence was 1%, 10% and 25% for patients born in industrialised regions, Asia-Pacific and sub-Saharan Africa, respectively.[2] The demographics of our case series are consistent with this finding and we recommend Mantoux testing of all immigrants with HIV.

Tuberculosis may develop during any stage of HIV infection. Clinical and radiological features vary with the degree of HIV-related immunodeficiency, with an increase in extrapulmonary disease, dissemination and atypical pathology seen with declining immunocompetence. The most common extrapulmonary sites are lymph nodes, pericardium, pleura, bone and skin.[1]

Synergy between the two infections is well documented, with evidence that active *M. tuberculosis* infection can increase plasma HIV viral loads by as much as 160-fold[3] possibly as a result of cytokines induced by the TB process. In addition, TB per se reduces the CD4 count additive to that as a result of HIV infection, thus accelerating the decline in immunocompetence.[1] This synergy is associated with aggressive disease progression as seen in two of our patients.

Current Centre for Disease Control guidelines recommend standard quadruple-drug therapy for a minimum of 6 months; HIV patients should demonstrate little difference in response rates, but may require extension of therapy if clinical or bacteriological response is delayed. Strategies of directly observed therapy are strongly advised.[4]

A number of our patients required dosage modification on the basis of known drug interactions between antiretrovirals and antituberculous medications. Complex bi–directional interactions occur as a result of cytochrome P450 3A induction by rifamycins, with both protease inhibitors (PI) and non-nucleoside reverse transcriptase inhibitors (NNRTI) to a variable degree being substrates and inhibitors of this isoform. The use of rifampicin, the most potent enzyme inducer, is contraindicated with protease inhibitors as a result of profound reductions in protease inhibitor concentrations. Rifabutin, a much less potent enzyme inducer, can be used with nelfinavir or indinavir, with dose reduction of rifabutin to avoid toxicity secondary to inhibition of its metabolism.[5] We would recommend either a delay in initiation of antiretroviral therapy during acute phases of TB infection or avoidance of PI and NNRTI in the therapeutic regimen.

Drug malabsorption is a common cause of treatment failure and drug resistance and is associated with a low CD4 count, malnutrition, HIV enteropathy, opportunistic gastrointestinal infections and achlorhydria.[5] Although routine monitoring of drug levels is not recommended, evaluation of drug absorption should be strongly considered in adherent patients who do not respond to antituberculous therapy.[6] We found the use of intravenous therapy beneficial in at least two patients with suspected malabsorption.

The initial worsening of symptoms and radiology with treatment seen in Case 5 is consistent with a paradoxical reaction. These consist of worsening clinical signs and radiology following commencement of treatment, and are greatly increased by concomitant antiretroviral therapy. Paradoxical reactions are usually self-limited and are considered to represent inflammation secondary to a boosted immune response.[7]

The mortality of HIV-related TB is more than double that of non-HIV TB, with half of deaths occurring within the first month.[1]

In conclusion, the above six cases of HIV/TB co-infection presented to Liverpool hospital within a 2-year period. Experience from the above case series has led to a lower threshold for clinical suspicion of HIV/TB co-infection and a more aggressive approach to diagnosis and management. Our management protocol now includes the use of intravenous therapy at diagnosis in patients with profound immunodeficiency, measurement of markers of malabsorption with drug levels if response is delayed with oral therapy, awareness of drug interactions and paradoxical reactions, investigations for extrapulmonary disease and early surgical intervention if required.

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