Disseminated tuberculosis and idiopathic CD4+ T-lymphocytopenia

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The association between tuberculosis (TB) and $CD4^+$ T-lymphocytes depletion has been described [1,2], but is unclear whether the $CD4^+$ cell depletion was the cause or the consequence of TB. Previous reports suggest that TB may cause transient $CD4^+$ T-lymphocytopenia, which is reversible with effective treatment [3]. This report describes two cases of disseminated TB with severe and persisting $CD4^+$ T-lymphocytopenia consistent with the diagnosis of idiopathic $CD4^+$ T-lymphocytopenia (ICL) [4].

A 42-year-old white man was admitted to our hospital in April 1996 because of right wrist arthritis, fever and abdominal pain. He had a previous diagnosis of Crohn's disease supported by a substenotic ileocecal valve on coloscopy and non-caseating granulomas on histology of intestinal specimens; he received oral prednisone 60 mg/day and mesalamine 800 mg three times a day for 4 weeks without significant improvement. On admission the patient was feverish (38.5°C), had enlarged spleen and liver, right wrist arthritis and tenosynovitis of the extensor tendons with cold abscess. Laboratory findings were: increase of sedimentation rate (65 mm/h), of α_2-globulin (18.7%), and of C-reactive protein (11.9 mg/dL); slight anemia (hemoglobin 12 g/dL), and lymphopenia (total lymphocyte count 945/mm^3) with severe $CD4^+$ T-lymphocytopenia (94/mm^3; 9.9%). Immunoglobulin fractions were normal. Needle aspiration of wrist abscess showed purulent fluid, and Ziehl–Neelsen staining was positive for acid-fast bacilli (AFB). Microscopic examination of sputum and stool samples was also positive for AFB. Re-examination of ileocecal valve specimens stained with Ziehl–Neelsen showed numerous AFB. *Mycobacterium tuberculosis* was cultured from synovial fluid and sputum samples. Chest computed tomography (CT) scan revealed multiple small nodules evenly distributed throughout both lungs. Anergy to delayed skin test antigens was present (Multitest Merieux), and Mantoux test with 5 IU was negative. HIV laboratory tests were repeatedly negative (antibodies to HIV-1 and HIV-2, HIV RNA). Serologic tests for hepatitis B virus, hepatitis C virus and *Treponema pallidum* were all negative. Therapy with isoniazid, rifampin, ethambutol and pyrazinamide was started and continued for 2 years; *M. tuberculosis* was susceptible to all drugs. After 1 month of therapy, fever and abdominal pain resolved, chest CT improved, and sputum cultures were negative. Surgical debridement of the wrist was performed without total functional rescue. During a 2-year follow-up the $CD4^+$ T-lymphocytopenia persisted (Table 1, case 1) and the patient, in December 1996, developed monodermatomeric thoracic zoster. Serology to HIV-1/2 remained negative.

A 65 year-old white man with a history of weight loss, asthenia and dyspnea was admitted to the hospital in September 1995. He presented hepatosplenomegaly,

Table 1 Summary of lymphocyte studies

Date	Total WBC[a] /mm^3	Absolute lymphocyte count/mm^3	$CD4^+$ T-lymphocyte/mm^3 ($CD4^+$%)	$CD8^+$ T-lymphocyte/mm^3 ($CD8^+$%)	CD4/CD8
Case 1					
24 April 1996	4950	945	94 (9.9)	562 (59.4)	0.16
29 April 1996	4530	406	65 (15.9)	158 (39.9)	0.41
27 July 1996	4100	779	111 (14.2)	431 (55.3)	0.25
29 July 1996	3700	518	78 (15.1)	217 (41.8)	0.35
9 September 1996	5000	785	102 (13)	452 (57.6)	0.22
15 January 1997	6600	1372	139 (10.1)	719 (52.3)	0.19
27 October 1997	5700	1191	121 (10.2)	605 (50.8)	0.20
27 April 1998	6150	1230	196 (13)	566 (46)	0.34
Case 2					
2 March 1996	5800	754	105 (15)	400 (53)	0.26
10 April 1996	7300	1314	220 (16.7)	874 (66.5)	0.25
5 June 1996	5000	1590	153 (9.6)	1130 (71.1)	0.13
4 July 1996	4400	1360	92 (6.8)	1074 (79)	0.08
17 July 1996	4800	1589	146 (9.2)	1182 (74.4)	0.12
14 October 1996	4900	1715	135 (7.9)	1278 (74.6)	0.10
12 March 1997	4900	1568	121 (7.7)	1196 (76.2)	0.10
3 December 1997	4700	1119	102 (7.1)	1119 (79.9)	0.09
2 June 1998	4170	700	89 (12.6)	448 (63.9)	0.14

[a]WBC, leukocyte count.

abdominal and mediastinal lymphadenopathy, and pleural and peritoneal effusion. Biopsy of retroperitoneal lymph nodes showed non-caseating granulomas compatible with sarcoidosis, and oral prednisone was administered at 40 mg/day for about 6 months. In March 1996, due to progressive worsening of the patient's general condition, he was again admitted to the hospital. Investigations revealed persistent hepatosplenomegaly, mediastinal and abdominal lymphadenopathy with retroperitoneal mass, slight anemia (Hb=10.6 g%), microscopic hematuria, and $CD4^+$ T-lymphocytopenia ($CD4^+ = 105/mm^3$). Immunoglobulin fractions were normal. Mantoux test was negative. Bone marrow biopsy showed granulomas not consistent with hematologic malignancy. The patient developed abdominal obstruction requiring surgery. Ziehl–Neelsen staining of intestinal biopsy showed numerous AFB. Chest X-ray revealed a miliary infiltrate, and intravenous pyelogram demonstrated papillary necrosis. *M. tuberculosis* was cultured from intestinal biopsy and urine. Diagnosis of disseminated TB with involvement of chest, intestinal tract and kidney was made, and anti-TB therapy was started with isoniazid, rifampin, ethambutol and pyrazinamide. The isolate was susceptible to all anti-TB drugs. The patient obtained progressive clinical improvement. After 2 years of anti-TB therapy and follow-up, the patient is doing well. However, $CD4^+$ T-lymphocyte count was persistently low (Table 1, case 2). HIV laboratory tests were repeatedly negative (serology for antibodies to HIV-1 and HIV-2, and p24 antigen) as well as serologic tests for hepatitis B virus, hepatitis C virus, and *Treponema pallidum*.

These two cases of disseminated TB infections may be considered as a manifestation of ICL. The diagnosis of ICL is supported by the severe and persistent lymphocytopenia not fully explained by other causes.

Our patients were neither HIV-infected nor affected by B-cell immunodeficiency or lymphoproliferative disorders. It might be argued that TB may be the cause and not the consequence, of $CD4^+$ T-lymphocytopenia, but TB infection may cause transient, non-selective $CD4^+$ T-lymphocytopenia, which is reversible with successful treatment [3]. Our patients presented selective and persistent depletion of $CD4^+$ T-lymphocytes, despite effective anti-TB treatment. It might also be argued that steroid therapy could have contributed to the $CD4^+$ T-lymphocyte depletion, at least in the patient receiving 6 months of treatment. However, steroid-induced $CD4^+$ T-lymphocyte depletion is transient, reversible and accompanied by $CD8^+$ T-lymphocyte depletion, without any alteration of the CD4/CD8 ratio [5]. Our patients have neither known exposure to TB, nor a history of previous TB illness. Corticosteroids were administrated erroneously only after illness manifestations, and may be considered an aggravating factor for TB manifestations, but not the cause of TB reactivation.

Disseminated tuberculosis is a very rare manifestation of ICL: only one case has been described in a patient with previous Kaposi's sarcoma [1]. In dealing with TB infection, underlying ICL should be considered. TB may be included in the manifestations of ICL.

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Do the quinolones still constitute valid empirical therapy for community-acquired urinary tract infections in Spain?

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Urinary tract infections (UTIs) are among the most frequent bacterial infections in humans. *Escherichia coli* is, by far, the bacterium most commonly isolated in community-acquired UTI, varying according to series from 70% to 90%. Because of the high percentage of resistance to ampicillin and co-trimoxazole—approximately 60% and 30% respectively [1]—found in the strains of *E. coli* isolated in our area, the fluoroquinolones have become one of the first-choice therapies in the empirical treatment of UTI in Spain. Resistance to the quinolones in *E. coli* strains isolated in urine samples from out-patients has increased in