Miliary Tuberculosis Coinfection with Human Immunodeficiency Virus

Erika Esteve, MD*
August Supervía, MD, PhD†
Oriol Pallàs, MD†
María T. Martínez, MD†
María M. Montero, MD*
Francisco del Baño, MD†

* Hospital del Mar, Department of Internal Medicine, Barcelona, Spain
† Hospital del Mar, Department of Emergency Medicine, Barcelona, Spain

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BACKGROUND

Tuberculosis was a major public health problem, given the estimated one billion people infected between 2000 and 2002.[1] A decrease in the incidence of tuberculosis was observed in the last decade, coinciding with improvements in social and healthcare conditions and availability of more effective antituberculous therapies. However, in the last two or three years, this decreasing trend has been interrupted by the presence of two emerging factors, the influx of immigrants and infection by the human immunodeficiency virus (HIV).[1] In the United States, this increase in the incidence of tuberculosis in recent years has been attributed, in part, to an increase in the diagnosis of this disease among immigrants from countries with a high prevalence of tuberculosis.[2] The case of an immigrant patient presenting with a septic respiratory clinical picture in which the final diagnosis was miliary tuberculosis and HIV coinfection is reported.

CASE REPORT

A 31-year-man from Guinea, who had moved to Barcelona three years before consultation, was admitted to the emergency department because of a wasting syndrome, characterized by asthenia, anorexia and weight loss. These symptoms had been insidiously developed over the past three months. The patient complained of cough, mucopurulent expectoration, nausea and vomiting and was unresponsive to antibiotic treatment during the last week. Family history and personal history were unrevealing. He was an active smoker. Physical examination showed fever (38ºC), a blood pressure of 75/35 mm Hg, a heart rate of 110 beats per minute and a respiratory rate of 32 breaths per minute with fatigue. Oxygen saturation breathing room air was 92%. Results of laboratory tests included serum creatinine level of 1.4 mg/dL, total bilirubin 2.1 mg/dL, aspartate aminotransferase 232 IU/L, C-reactive protein 20.8 mg/dL (normal range 0–0.8 mg/dL), white blood cell count 2060/μL (neutrophils 1860/μL, lymphocytes 160/μL), platelets 64000/μL and international normalized ratio 1.23. Baseline arterial blood gas analysis included PaO_2 61 mm Hg, $PaCO_2$ 26 mm Hg and pH 7.46. The chest radiograph revealed a micronodular interstitial pattern affecting both hemithoraces (Figure 1).

A tentative diagnosis of septic shock secondary to an infectious respiratory focus was established because of a lack of improvement after treatment with fluids. The patient received empirical antibiotic treatment with levofloxacin 500mg two times a day and trimethoprim sulfamethozaxole 160/800mg three times a day. A human immunodeficiency virus (HIV) test and Ziehl-Neelsen staining of the sputum smear were requested. The Ziehl-Neelsen test was positive

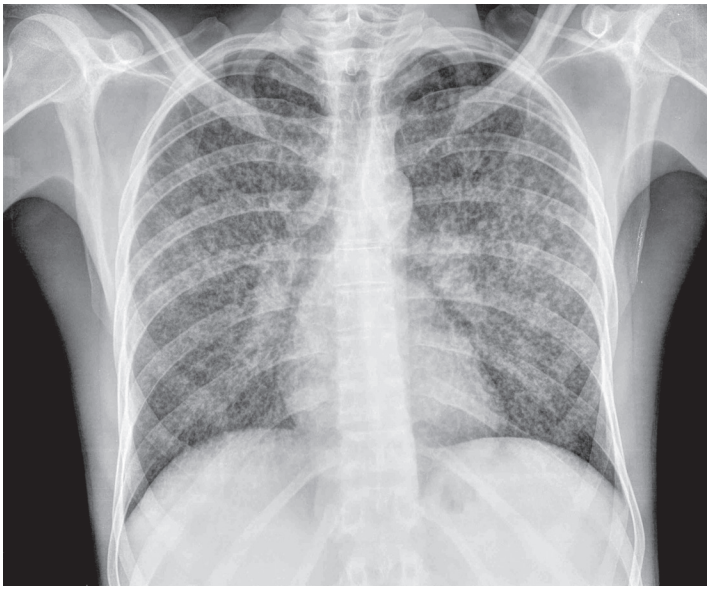

Figure 1. Bilateral micronodular interstitial pattern indicative of miliary tuberculosis.

(result was available at 12 hours of admission), and a diagnosis of miliary tuberculosis with pulmonary involvement was made. Quadruple antituberculous treatment (isoniazid, rifampin, pyrazinamide and ethambutol) was started. The clinical condition of the patient worsened, and he required admission to the intensive care unit (ICU). Continuous infusion of norepinephrine and invasive mechanical ventilation were required. One week after starting antituberculous treatment, the patient's clinical condition improved and he was discharged from the ICU.

HIV testing was positive (C3 category), the CD4 cell count was 44/mm^3 and the viral load 3,095,299 copies/mL. The sputum culture was positive for *Mycobacterium tuberculosis complex*, which was sensitive to all tuberculostatic agents. Treatment with antituberculous drugs was maintained, with good tolerance and favourable clinical course. Antiretroviral therapy was begun. The patient was discharged from the hospital 40 days after admission. The follow-up chest radiography obtained after one month of antituberculous therapy showed resolution of opacities (Figure 2).

DISCUSSION

Miliary tuberculosis is an extrapulmonary form of tuberculosis due to hematogenous dissemination of *Mycobacterium tuberculosis*, and occurs more frequently in infants, young children, elderly subjects and immunocompromised patients. Miliary shadowing was present in 29% of patients with disseminated tuberculosis.[3] Extrapulmonary tuberculosis has become more common since the advent of HIV infection. HIV is a recognised risk factor for extrapulmonary tuberculosis.[4] In adults, miliary tuberculosis may be secondary to a recent infection or due to reactivation of an old focus. Miliary dissemination occurs in 10% of HIV-infected patients and up to 38% in patients with HIV and extrapulmonary tuberculosis.[5] Clinical manifestations are non-specific and varied in relation to the predominant localization, including severe presenting forms with septic shock and respiratory insufficiency. Symptoms include fever, nocturnal sweating, anorexia and weight loss.[6] In patients with respiratory involvement, cough and other respiratory symptoms are present. In about 85% of patients, the chest radiograph shows a reticulonodular pattern with nodules of 2–3 mm in diameter.[5,6] The diagnosis may require sputum smear studies, fiberoptic bronchoscopy with bronchoalveolar lavage, blood cultures for *Mycobacterium spp.* or culture and histological detection of granulomas (caseous necrosis) in liver, lung or bone marrow biopsies.[5,6] Moreover, in case of HIV-infected patients with advanced immunosuppression, a differential diagnosis with other opportunistic infections, like *Pneumocystis jiroveci* pneumonia, should be established. In these patients, the diagnosis of miliary tuberculosis when the acid-fast stain is negative requires a high index of clinical suspicion.

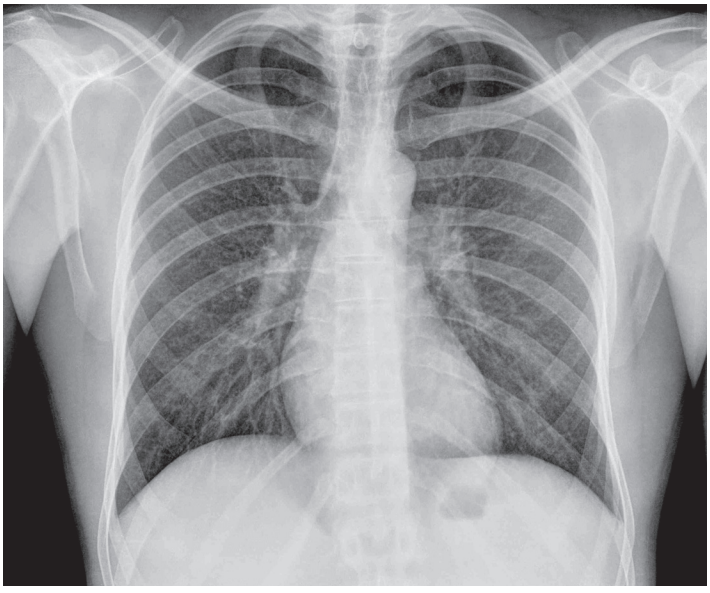

Figure 2. Resolution of bilateral micronodular interstitial pattern after one month of treatment..

In the case here reported, two aspects should be highlighted: firstly, the fact that positive bacilloscopy is exceptionally recorded in a patients with a miliary radiological pattern without pulmonary infiltrates, and secondly, the severity of the tuberculosis infectious process in a patient with HIV coinfection. Septic shock associated with miliary tuberculosis in HIV infection has a high mortality, but in this case, treatment was successful and allowed complete resolution of radiological findings.

In the last decades, a better clinical and immunological control of HIV-infected patients following the use of highly-active antiretroviral treatment has been associated with a decrease in the incidence of opportunistic infections, including infections caused by *Mycobacterium* spp.[7,8] However, in recent years, resurgence of these infections in the Western world (United States[9], United Kingdom, Sweden[10], Spain,[2,11]) have occurred probably in relation to the high immigration fluxes of people from countries with a high prevalence of tuberculosis. It is reported that many immigrants may be carriers of latent tuberculosis infection; a positive tuberculin test is found in 34.3–48.2% of the immigrant population, which is higher than rates found in the Spanish population.[12,13] In addition, the prevalence of latent tuberculosis in immigrants is related to the country of origin and its socioeconomic level, with higher rates among people from Asia, Central Africa, South Africa and Eastern Europe than in those from Latin America, North African countries and Commonwealth countries.[12] Extrapulmonary tuberculosis is more frequent in immigrant populations in some Western countries. Therefore, the relative increase in extrapulmonary forms of tuberculosis in these countries may be related to high rates of tuberculosis in immigrants.[12,13] Pleura and lymph nodes are the most frequent extrapulmonary sites in immunocompetent subjects, whereas miliary and lymph node involvement are most frequent in

immunocompromised patients.[15]

In summary, extrapulmonary and disseminated forms of tuberculosis infection may occur in our environment in relation to an increase in the immigrant population, occasionally associated with low socioeconomic status. These forms may have atypical presenting manifestations that together with cultural and idiomatic barriers may be difficult to diagnose and delay a correct diagnosis of tuberculosis.

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Address for Correspondence: August Supervía, MD, PhD, Department of Emergency Medicine. Hospital del Mar, Ps Marítim 25-29, 08003, Barcelona, Spain. Email: Asupervia@imas.imim.es

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