Case Report

Tropical mayhem: a chronic viral disease with superadded parasitic infection

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Coexistence of two illnesses in the same patient may result in atypical manifestations of either or both diseases. A case of hepatitis B virus-related cirrhosis in a patient who presented with a pharyngeal mucosal mass lesion as a manifestation of superadded *Leishmania* infection is presented here. The clue to the diagnosis was the origin of the patient from an area highly endemic for leishmaniasis and the presence of unexplained polyclonal hypergammaglobulinaemia. The patient responded very well to therapy with amphotericin B with complete disappearance of the mucosal lesion.

Introduction

The phenotypic presentation of leishmaniasis depends on the cell-mediated immunity status of the host. Coexistence with another disease (for example infection with human immunodeficiency virus) may alter the immune response to leishmanial infection and may result in atypical manifestations and atypical sites of involvement of *Leishmania*. We present a case and discussion of a patient who had coexistent chronic hepatitis B virus (HBV) infection and leishmaniasis.

Case report

In December 2005, a 33-year-old gentleman (resident of Bihar in eastern India, a region endemic for leishmaniasis) presented to the All India Institute of Medical Sciences, New Delhi, with difficulty in swallowing and low-to-moderate grade fever for 18 months. Twelve months prior to presentation to us, he had developed progressive hoarseness of voice. A physician had examined him, found a nodular lesion in the throat, made an empirical diagnosis of tuberculosis and started him on treatment with rifampicin, isoniazid, ethambutol and pyrazinamide. However, the patient discontinued the treatment after 4 months because of lack of relief in his symptoms. He was first seen by an otorhinolaryngologist at our centre and was diagnosed as having an inflammatory granuloma in the throat, based on a biopsy from the lesion. The aetiology of the granuloma could not be ascertained. He was referred to the department of gastroenterology for deranged liver function tests. He had a history of jaundice 15 years ago, which was diagnosed elsewhere as acute hepatitis B. He also

had a hernioplasty 20 years ago but did not receive any blood transfusions. He was not an alcoholic and denied any promiscuous sexual behaviour. He had pallor, mild icterus, bilateral cervical lymphadenopathy (2 × 2 cm in size, discrete, non-tender and mobile) and bilateral pitting pedal oedema. Oropharyngeal examination showed an ulcerated lesion covered with slough, involving the soft palate, posterior pharyngeal wall and bilateral tonsillar fossa, extending into the nasopharynx superiorly (Fig. 1). Abdominal examination showed a firm, non-tender, enlarged liver 6 cm below the costal margin with a smooth surface. The spleen was palpable 2 cm below the costal margin. A provisional diagnosis of a systemic infiltrative disease such as lymphoma or disseminated tuberculosis was made.

Investigations revealed microcytic hypochromic anaemia (Hb 9.8 g dl⁻¹), high erythrocyte sedimentation rate (99 mm 1st hour), elevated serum bilirubin (1.8 mg dl⁻¹), raised liver enzymes (aspartate transaminase 106 IU l⁻¹; alanine transaminase 50 IU l⁻¹; alkaline phosphatase 587 IU l⁻¹), low serum albumin (2.1 g dl⁻¹) and high serum globulin (6.2 g dl⁻¹). The Mantoux test (5TU) showed an induration which was 15 mm wide. Serum protein electrophoresis showed a polyclonal increase in gamma globulins. The patient was hepatitis B surface antigen-positive, hepatitis B envelope antigen-negative, IgM anti-hepatitis B core antigen-negative by ELISA and the HBV DNA load (by competitive inhibition PCR) was 6 log₁₀ copies ml⁻¹. Serology for hepatitis C virus, and HIV-1 and 2 was negative by ELISA. Oesophagogastroduodenoscopy showed an ulcerated, nodular mass lesion in the pharynx (Fig. 1) and grade II

Fig. 1. Endoscopic picture showing the pharyngeal nodular mass lesion (arrows). The arytenoids (small arrowhead) and epiglottis (large arrowhead) can be seen in the upper part of the image.

oesophageal varices. The rK 39 antigen test (>98 % sensitive and specific for leishmaniasis; Goswami *et al.*, 2003) was positive. The diagnosis of leishmaniasis was confirmed on endoscopic biopsies of the pharyngeal mass, which revealed *Leishmania donovani* bodies along with granulomas (Fig. 2). In addition, his bone marrow biopsy demonstrated *L. donovani* bodies as well as inflammatory granulomas. A liver biopsy was done to identify the predominant pathology in the liver and showed necroinflammation [histological activity index 7/18 and advance fibrosis (fibrosis stage 5/6) (Desmet *et al.*, 1994)] along with ill-defined granulomas in the portal tracts (Fig. 3). Hence a final diagnosis of mucosal and systemic leishmaniasis superadded over an underlying HBV-related cirrhosis was made and the patient was treated with amphotericin B

Fig. 2. Palatal biopsy reveals *Leishmania donovani* bodies (arrows) within the histiocytes.

Fig. 3. Liver biopsy slides showing cirrhosis with nodule formation (a; low-power view), extensive fibrosis on reticulin staining (b; low-power view) and ill-defined granuloma formation (c; high-power view).

(total dose 1.5 g) and lamivudine (100 mg per day). Within 2 weeks of starting treatment, the pharyngeal mass disappeared, his voice became normal and the liver function tests improved. He was given a total of 1.5 g amphotericin B and was continuing lamivudine until last follow-up. One year after discharge from the hospital, he had remained afebrile, was free of any mucosal disease and did not show any clinical signs of liver decompensation.

Discussion

Leishmaniasis may have varied clinical manifestations, such as self-limited infection, cutaneous ulcerating disease, mucosal disease and visceral leishmaniasis. Both parasite and host factors influence the expression of the disease phenotype. However, the major determinant of the disease

phenotype in leishmaniasis is the host immune system (Carvalho *et al.*, 1992). At one end of the spectrum, a high parasite burden and compromised cell-mediated immunity are seen in patients with visceral leishmaniasis and post kala-azar dermal leishmaniasis. At the other end of the spectrum, a low parasite burden and maintained cell-mediated immunity results in asymptomatic infection or self-healing cutaneous disease. Then there are patients with destructive mucosal disease, who have an exuberant and deranged cell-mediated immune response (Bacellar *et al.*, 2002). In patients with immunocompromised states, leishmaniasis can present with lesions at atypical sites and with atypical manifestations (Singh, 2004). In fact, one-third of patients with mucocutaneous leishmaniasis have an underlying immunocompromised state (HIV-positive or post organ transplant) (Aliaga *et al.*, 2003).

Cirrhosis of the liver is an immunocompromised state with suboptimal cell-mediated immunity and poor opsonophagocytic function (Cheong *et al.*, 2006; Fiuza *et al.*, 2000). As a result, cirrhotics are predisposed to develop bacterial, fungal and mycobacterial infections. In our case, the altered cell-mediated immunity (in a patient with cirrhosis) possibly altered the presentation of leishmaniasis, which manifested in the form of a mucosal laryngopharyngeal lesion. Leishmanial infection may also have affected the natural history of underlying HBV-related cirrhosis in the present case by causing rapid progression and decompensation of liver disease, which had remained silent for almost 15 years. Decompensation of cirrhosis due to visceral leishmaniasis has previously been described in the literature (Pagliano *et al.*, 2007). It has also been shown that patients with visceral leishmaniasis may develop advanced liver fibrosis, with 28% demonstrating bridging fibrosis (el Hag *et al.*, 1994). Liver biopsy in the present case had demonstrated cirrhosis along with granulomas. HBV-related hepatic necroinflammation is not associated with a granulomatous response, which, in the present case, most likely represents an immunoinflammatory response to leishmanial antigens, even though no *L. donovani* bodies were demonstrable. Further, patients with visceral leishmaniasis may well have hepatic fibrosis, but cirrhosis has never been documented in these patients as a direct consequence of leishmaniasis alone. In a systematic study among 60 kala-azar patients (18 of whom underwent a liver biopsy), none had any evidence of cirrhosis or portal hypertension (Aggarwal *et al.*, 1990). This case shows the possible effects of interaction between two diseases. Leishmaniasis could have accelerated the hepatic fibrosis, causing ascites and the appearance of oesophageal varices. On the other hand, HBV-induced chronic liver disease could have predisposed the patient to develop atypical leishmanial lesions.

The parasitic superinfection with systemic manifestations in a patient with underlying chronic liver disease also posed a diagnostic challenge in the present case. The fact that leishmaniasis itself produces certain histological changes in the liver created a further diagnostic dilemma. Appropriate

diagnosis and therapy of both diseases was needed to prevent progressive liver failure and the consequences of disseminated leishmaniasis. The leishmaniasis in our patient was treated with intravenous amphotericin B. Other drugs such as sodium stibogluconate, pentamidine and meglumine have also been found to be equally effective in treating mucosal leishmaniasis (Amato *et al.*, 2007). The present case highlights the importance of considering a diagnosis of leishmaniasis in patients originating from a highly endemic area and having hypergammaglobulinaemia even if the presentations are atypical (Baba *et al.*, 2006). The state of Bihar harbours about 45% of the world's cases of visceral leishmaniasis (Desjeux, 2004). In the present case, the most probable initial differential diagnoses were tuberculosis, lymphoma, Langerhan's cell histiocytosis or sarcoidosis, but it turned out to be mucosal leishmaniasis and the vital clue was the hyperglobulinaemia in a patient who was a resident of an area hyperendemic for leishmaniasis.

In conclusion, the coexistence of two commonly occurring infections in a geographical region may modify each other's clinical expression and make diagnoses difficult. Detecting both illnesses is essential in order to treat and prevent further morbidity and mortality.

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