Missed Diagnosis

Hypersplenism due to fungal infection of spleen in a successfully treated patient with Hodgkin’s disease

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Summary: A 58 year old woman, with dermatitis herpetiformis was found to have Hodgkin’s disease following the discovery of an abdominal mass and splenomegaly. Combination chemotherapy was given. Although the abdominal mass and systemic symptoms resolved, the splenomegaly did not and the patient developed severe prolonged anaemia and pancytopenia. Splenectomy resulted in a complete reversal of the haematological abnormalities. Histopathological examination of the spleen revealed fungal granulomas of Candida albicans. No residual Hodgkin’s disease was found.

The patient thus had hypersplenism due to fungal granulomas in the spleen. This form of presentation of fungal granuloma is very rare and resulted in delay in diagnosis and considerable morbidity to the patient.

Introduction

Fungal infections of spleen occur with increasing frequency in patients with haematological malignancies as a result of a more intensive chemotherapeutic approach.¹ These patients commonly present with persistent pyrexia, unresponsive to broad spectrum antibiotics. Diagnosis requires a high index of suspicion as blood cultures and serology are helpful in only a small number of cases and can sometimes be misleading.²³ Hypersplenism, although well known with various bacterial infections, is extremely rare due to fungal infections. We present such a case.

Case report

A 58 year old woman was diagnosed as having dermatitis herpetiformis in 1981. Dapsone was prescribed with partial control of symptoms but she then developed mild haemolytic anaemia. In August 1986, the patient complained of weakness, night sweats and weight loss. A pelvic mass was found. Laparotomy carried out by a gynaecologist revealed a large unresectable mass in the left side of the pelvis and splenomegaly. Unexpectedly, biopsy of the pelvic mass revealed Hodgkin’s lymphoma, of lymphocyte-depleted type. Whole body computed tomographic (CT) scanning revealed mediastinal lymphadenopathy. Marrow aspirate and trephine biopsy were clear and the patient was staged III B. A second laparotomy with splenectomy at this time was considered unnecessary since appropriate management with chemotherapy was planned. Six courses of combination chemotherapy (MOPP/EVAP hybrid schedule) were given as follows: intravenous mustine hydrochloride, 6 mg/m², vincristine, 1.4 mg/m² – Day 1; adriamycin, 25 mg/m², vinblastine, 6 mg/m² – Day 8; VP16, 150 mg/m² – Days 8 and 9; oral prednisolone, 25 mg/m² – Days 1–14; procarbazine, 100 mg/m² – Days 1–8. The cycles were repeated four-weekly. The patient’s symptoms resolved after the first course. After 4 months’ therapy, CT scan confirmed complete disappearance of the mediastinal lymphadenopathy and abdominal mass but splenomegaly persisted. However, disturbing features noted around this time were significant worsening of anaemia and appearance of pancytopenia, the patient requiring frequent blood transfusions. The resolution of her systemic symptoms and lymphadenopathy seemed at variance with the persistent splenomegaly and worsening anaemia. Investigations at this time revealed haemoglobin in the range of 5–6 g/dl, total leucocyte count of 1–2 × 10⁹/l, granulocyte count of 0.5–1.2 × 10⁹/l, and platelet count 70–80 × 10⁹/l. Two further courses of chemotherapy did not result in any resolution of splenomegaly. Pancytopenia and severe anaemia continued long after stopping chemotherapy. There was, surprisingly, no reticulocytosis at this time and other investigations for haemolysis, e.g. Coomb’s test, plasma haemoglobin, haptoglobin Ham’s test and red cell enzyme studies, were all normal. A bone marrow aspirate showed hypercellularity and increased iron stores. Withdrawal of dapsone for a month did not result in any improvement. The patient was transfused a total of 74 units of blood over a 6 month period.

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During the courses of chemotherapy, the patient had developed four brief episodes of pyrexia. In two of these, *Staphylococcus aureus* were grown from the blood. All episodes of pyrexia were treated successfully. A vaginal swab at one stage revealed *Candida albicans.*

In view of the clinical picture, residual Hodgkin's disease in the spleen was suspected. A post-chemotherapy laparotomy with splenectomy was performed in May 1987. The spleen weighed 650 g and contained multiple 2–3 mm necrotic granulomas (Figure 1), in which fungal hyphae were found on special stains (Figure 2). There was no evidence of Hodgkin's disease in the spleen or any other tissue. No systemic antifungal treatment was given. There was a remarkable improvement in her condition thereafter, the patient not requiring any more blood transfusions. Haemoglobin has stabilized around 11 g/dl and all blood counts have returned to normal. Retrospective analysis of serum, taken before splenectomy, revealed high titres of precipitins against *C. albicans*. These have disappeared from a post-splenectomy serum sample.

**Discussion**

We suspect that the patient acquired candidal infection during chemotherapy. This localized to the spleen and later resulted in hypersplenism. Blood cultures were negative for fungi during all four episodes of pyrexia. Furthermore, all pyrexial episodes resolved with antibiotics. Fungal infection was, therefore, not considered a serious possibility. Hypersplenism due to fungal infection of spleen is extremely rare and we are aware of only one previous case. That patient had developed hypersplenism during a remission from acute myelogenous leukaemia and haematological features were reversed by splenectomy. Fungal infections of the spleen without causing hypersplenism, on the other hand, are known to occur with variable frequency. Page reported three proven cases of fungal infection of spleen in patients with leukaemia. Johnson reported 19 patients with fungal splenic abscesses. Maksyunick reported 235 fungal infections in cancer patients over a 4-year period. Reactive splenomegaly was found in 9% of their patients with systemic candidiasis but actual splenic involvement by fungi was found in only one patient at autopsy. In another series by Radaelli of 54 cases of fungal infection in patients with haematological malignancies, the spleen was not involved in any way. Brereton *et al.* found fungal splenic involvement to be very rare and only noted at post-mortem in his series of 168 consecutive patients. No hypersplenism was reported in any of these series.

The diagnosis of fungal splenic infection is difficult without a high index of clinical suspicion. By far, the commonest presentation is pyrexia. Urine and blood cultures for fungus are frequently negative and, when positive, may be dismissed as being of uncertain clinical significance. Our patient, however, did not present with these classical features and hence the diagnosis was only made following splenectomy.

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**Figure 1** The centre of the granuloma in the left of the picture is necrotic. The dark pigment in the splenic red pulp is haemosiderin. Haematoxylin and eosin × 23.0.

**Figure 2** Short fungal hyphae can be seen in the necrotic centre of this granuloma. Methenamine silver × 177.0.
References


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