Systemic mastocytosis, myelofibrosis and portal hypertension

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SUMMARY A case of systemic mastocytosis is described in which the finding on initial presentation was hepatosplenomegaly. No dermatological abnormality was present, and the bone marrow histology originally caused some confusion with primary myelofibrosis. The clinical course and the importance of distinguishing between these two diseases is discussed. The dermatological manifestation of systemic mastocytosis, in the form of urticaria pigmentosa, is well recognised, and alerts the physician to the underlying disease. In the absence of cutaneous signs, however, the diagnosis is less obvious. The case reported had predominantly marrow and splenic involvement by the disease process, giving rise to portal hypertension, and illustrates the problems of diagnosis which can arise.

Case report

A 51-year-old man reported to his general practitioner in October 1969 for a routine medical examination. Although totally asymptomatic, he was found to have a firm, smooth, non-tender liver edge palpable 6 cm below the right costal margin and firm enlargement of the spleen 6 cm below the left costal margin. Clinical examination was otherwise unremarkable. There was no history to suggest previous hepatitis or exposure to hepatotoxins, including alcohol, and none of residence abroad.

Further investigation revealed a haemoglobin of 11.1 g/dl, leucocytes $9.2 \times 10^9/l$ (normal differential count) and platelets $181 \times 10^9/l$. The red cells were normochromic and showed moderate anisopoikilocytosis. Urea and electrolyte concentrations were normal. Serum bilirubin was 4 $\mu\text{mol/l}$, alkaline phosphatase 180 IU/l (normal 25-100 IU/l), albumin 33 g/l, aspartate aminotransferase 9 IU/l (normal 6-40 IU/l) and alanine aminotransferase 25 IU/l (normal 5-35 IU/l). A liver biopsy showed some portal fibrosis but no convincing evidence of cirrhosis, and there was a moderate amount of apparent myeloid metaplasia. Several attempts at bone marrow aspiration yielded no marrow particles and an iliac crest trephine biopsy was performed. The latter showed two areas of focal increase in reticulin with accumulation of fibroblasts. It was

noted that the fibroblasts showed "a somewhat concentric arrangement reminiscent of granulomata." No definite pathological diagnosis was offered, but the possibility of early myelofibrosis was suggested. Radiology showed sclerotic ribs, scapulae, clavicles, vertebrae and pelvis, and this seemed to support a diagnosis of osteomyelosclerosis. It was decided that the only management required was close observation.

The patient remained well for three years and then began to develop ascites. His haematological and biochemical parameters remained unaltered from the time of initial presentation. The ascites resolved with treatment with spironolactone, and remained well controlled for a further six years. During this period the only change of note in the results of the laboratory investigations was the occasional presence of an eosinophilia during the last year (up to $1.15 \times 10^9/l$).

In 1979, however, the ascites became troublesome once again and the patient was admitted to hospital for reassessment. In view of there having been no significant change in the peripheral blood haematological values over the preceding 10 yr, it seemed likely that the diagnosis of primary osteomyelosclerosis required revision. The serum albumin had fallen to 30 g/l but the remainder of the previously measured liver function tests had remained unaltered. Hepatitis B surface antigen, antinuclear factor, anti-smooth muscle and antimitochondrial antibodies were not detected. Alpha-1-antitrypsin, alpha-

fetoprotein and copper oxidase activities were normal.

Barium swallow and endoscopy were suggestive of early oesophageal varices. The wedged hepatic venous pressure was raised at 18 mm Hg (normal 5-12 mm Hg). Percutaneous splenoportal venography revealed patent vessels. Liver biopsy was repeated and this showed the previously noted portal fibrosis, though without evidence of cirrhosis. The portal tracts contained an inflammatory cell infiltrate, including many mast cells. A marrow trephine biopsy was performed. This showed a marrow of normal cellularity with normal haemopoiesis. There were however several rounded foci of cells as noted in the initial marrow trephine ten years previously. These again bore a superficial

resemblance to granulomata (Fig. 1), but metachromatic staining showed that they consisted almost entirely of mast cells with variable quantities of collagen.

The patient's ascites responded to medical management and he underwent splenectomy several months thereafter. The spleen weighed 1010 g and demonstrated a remarkable degree of capsular fibrosis (Fig. 2). Histology showed thick collagen bands in the parenchyma with numerous mast cells and eosinophils in the sinuses of the red pulp, characteristic of splenic mastocytosis. There was no evidence of myeloid metaplasia.

Discussion

Systemic mastocytosis is an uncommon condition which is often misdiagnosed and the true diagnosis made only in retrospect. Characterised by an abnormal proliferation of tissue mast cells, it was first described by Nettleship in 1869 in the form of urticaria pigmentosa.¹ This is the commonest form of the disease, accounting for some 90% of cases, where the tissue infiltration is limited to the skin only, giving rise to maculopapular lesions distributed mainly over the trunk which urticate on stroking the skin. Some 64 years after the initial description of urticaria pigmentosa cases were reported with mast cell infiltration of other organs in addition to the skin,² those most commonly involved being bone, liver, spleen and lymph nodes. A small proportion of patients have systemic organ involvement without dermatological manifestations, as demonstrated by this case report, and it is mostly in these cases that the diagnostic difficulty arises.

Fig. 1 One of the well defined foci in the bone marrow

Fig. 2 Splenectomy specimen. The "sugar-icing" capsular fibrosis is well shown

Confusion with myelofibrosis or osteomyelosclerosis has occurred in previously reported cases.^{3,4} In our patient this diagnosis was tentatively made in order to explain the anaemia, hepatosplenomegaly, mild marrow fibrosis and osteosclerosis demonstrated radiologically. In retrospect, the granuloma-like lesions in the marrow should have prompted the true diagnosis. These have been reported in several cases,^{3,5} with or without diffuse infiltration of the marrow by mast cells with varying quantities of collagen. It is of note that fibrosis which occurs is not necessarily confined to the marrow, and our patient demonstrated portal fibrosis in the liver and a considerable degree of splenic fibrosis. The association between the mast cell and fibrosis has been noted by many workers^{6,7} and it has been suggested that it may be the result of secretion of pharmacologically active agents by the mast cells. It has been observed that mast cells in fibrotic areas contain granules of very low density, which are thought to represent those that have released their contents.⁸ The active agents in these granules include histamine and heparin. The former can induce an acute inflammatory response, and the latter when added to a solution of collagen results in the formation of collagen fibrils.⁹ The mast cell has been suggested as a contributory agent to the fibrosis in primary myelofibrosis.¹⁰

Radiological similarity to the bone changes in osteomyelosclerosis can also occur in systemic mastocytosis, as in our patient. Not only is diffuse osteosclerosis seen, but generalised osteoporosis, isolated lytic lesions and isolated sclerotic lesions are recognised. The association of heparin with osteoporosis is known¹¹ and its elaboration by the mast cells could explain this aspect of the bony changes seen. The aetiology of the sclerotic changes remains uncertain.

Portal hypertension as a complication of systemic mastocytosis was not described until 1978¹² and the mechanisms involved are not necessarily the same in all cases. In one patient it was considered that the raised portal pressure was due to both pre- and post-sinusoidal block due to infiltration of the hepatic parenchyma and portal areas by mast cells and/or fibrosis.¹² The portal tract fibrosis and infiltration noted in the liver biopsies in our patient was not particularly marked, neither was there any

convincing evidence of cirrhosis, and it may well be that increased splenic blood flow is a major contributory factor to the raised portal pressure. As supportive evidence for this "forward" theory of portal hypertension, one case of systemic mastocytosis has been described where a raised pressure fell rapidly to normal limits following splenectomy.⁴ It is tempting to ascribe such an increase in splenic blood flow to local release of vasoactive amines by mast cells leading to the formation of many small arterio-venous fistulae within the splenic substance.

The diagnosis of systemic mastocytosis in this type of case will often rest largely on the physician and pathologist being aware of the possibility and, thereafter, the application of the necessary cytochemical techniques to demonstrate the tissue infiltration.

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