CASE REPORTS

Splenectomy for histiocytic medullary reticulosis

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SCOTT & Robb-Smith (1939) introduced the term histiocytic medullary reticulosis (HMR) in 1939 to describe a disorder of the reticulo-endothelial system characterized by fever, wasting and generalized lymphadenopathy, associated with splenic and hepatic enlargement and in the final stages jaundice, purpura and anaemia. Necropsy in their patients revealed an intense erythrophagocytosis by histiocytes within the medullary centres of bone and lymphoid tissues.

Although the diagnosis was established only after death in the earlier cases, there are now about sixty in the literature and in recent years the diagnosis has occasionally been made during life. The disease is in most cases progressive and rapidly fatal with a survival time ranging from 1 to 15 months (Zak & Rubin, 1961) and a median survival of 5½ months after diagnosis. The range of age of the patients is wide (17-78) (Zak & Rubin, 1961; Clark & Dawson, 1965) and a similar disease is seen in infants (De Villiers, 1969); there is no apparent sex predilection. Treatment has included antibiotics, cytotoxic agents, radiation therapy, splenectomy and corticosteroids; only the last two modalities have been thought to influence the course of the disease in any important way (Zak & Rubin, 1961; Natelson *et al.*, 1968; Asher, 1946).

We report the present case for a number of reasons: the patient was subjected to splenectomy relatively early in the course of her disease; her sur-

vival after the diagnosis of HMR was unusually long and we suspect that the splenectomy may have contributed to this; and the necropsy confirmed the diagnosis and suggested a possible pathogenesis for the episodes of sudden pain and subsequent fever.

Case report

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A 71-year-old woman was admitted to the Medical College of Virginia in April 1968 complaining of easy fatigability, some diminution in mental function and numbness and tingling in the fingers. She was found to be pale with some enlargement of liver and spleen. Hb 7.0 g/100 ml, WBC 3500/mm³, platelets 50,000/mm³. The bone marrow was extremely hyperplastic with intense erythroid activity and some megaloblastic cells. The serum vitamin B₁₂ level was 140 pg/ml. The liver scan showed moderate hepatic enlargement and a massively enlarged spleen.

The pancytopenia was ascribed to hypersplenism and on 6 May 1968 splenectomy was performed without incident. The spleen weighed 1286 g and microscopy showed 'intense diffuse proliferation of reticuloendothelial cells, some of which are atypical and show erythrophagocytosis'. Her postoperative course was complicated by several episodes of unexplained fever. At the time of her discharge the haemoglobin was 12.7 g/100 ml with normal WBC and platelets. Thereafter she did well until March 1969, when she again developed symptoms of anaemia; the haemoglobin ranged between 8.5 and 10.0 g/100 ml. Prednisone and folic acid were prescribed.

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In September she was admitted to the Massachusetts General Hospital with complaints of increased fatigue and weakness of the thigh muscles. Physical examination showed a chronically ill-looking woman with Cushingoid facies and scattered cutaneous ecchymoses. The heart and lungs were normal. A tender liver edge was palpable 8 cm below the right costal margin. No peripheral lymph nodes were felt. The initial Hb was 9.2 g/100 ml, PCV 29.3%, WBC 10,000/mm³ with bands 10%, polys 72%, lymphs 12%, monos 5% and nucleated RBCs 1%; platelets 11,000/mm³. Reticulocytes 16.6%, the peripheral film showed many spherocytes and frequent Howell-Jolly bodies. The serum bilirubin was 1.2 mg/100 ml, cholesterol 108 mg/100 ml, alkaline phosphatase 1.9 Bodansky units, SGOT 13 units, serum iron 140 µg/100 ml with 87% saturation. Serum electrolytes were normal. Serum vitamin B₁₂ was 55 pg/ml, folic acid 32 ng/ml, plasma haemoglobin 12.4 mg/100 ml. Serum proteins were albumin 2.6 g and globulin 1.7 g; immunoelectrophoresis showed a moderate decrease in IgG and IgA. The direct anti-globulin and sugar later tests were negative. A Wright's stained bone marrow aspirate showed a very cellular marrow with abundant megakaryocytes and marked erythroid hyperplasia with 24% megaloblastic cells; there were many giant histiocytes with intra-cytoplasmic red cells, white cells and platelets (Figs. 1 and 2). The Schilling test was normal. Radiographic studies of the chest, abdomen and lumbar spine were non-contributory; oral cholecystogram showed no evidence of stones.

The next 8 weeks in hospital were punctuated by recurrent episodes of sudden severe back pain with fever and elevation of serum bilirubin and alkaline phosphatase. On no occasion could a definite cause for the pain and fever be established and they had usually resolved completely within a week. Her blood

FIG. 1. Posterior iliac spine bone marrow aspirate obtained during life. A number of large mononuclear cells with ingested red cells, white cells and platelets are visible. Wright stain, $\times 260$.

FIG. 2. Posterior iliac spine bone marrow aspirate. A single giant cell has engulfed at least twenty red and white blood cells, whose individual morphology is well preserved. Wright stain, $\times 348$.

counts ranged between: PCV 20 and 25%; WBC 7000 and 10,000/mm³, platelets 10,000 and 30,000/mm³. She received transfusions of packed cells and whole blood. She was treated at various times with pyridoxine, azathioprine and cyclophosphamide (100–150 mg/day); her clinical course seemed unaffected by these drugs and she was discharged on 20 November taking prednisone 30 mg/day.

Over the next 4 months she remained in a nursing home and was in reasonable health. The PCV ranged between 21 and 26%, WBC 7000 and 13,000/mm³, and platelets 52,000 to 250,000/mm³. On 30 March 1970, peripheral oedema was noted and the PCV was 22%, WBC 8000 and platelets 105,000/mm³. A film showed spherocytosis and macrocytes; there were numerous normoblasts. She died 3 days later, 23 months after her splenectomy.

Necropsy. The immediate cause of death was a recent myocardial infarction; the heart weighed 540 g and showed evidence of both old healed and recent myocardial infarct. There was extensive atheroma formation in the coronary arteries. There were bilateral pleural effusions; the lungs were congested and there was atelectasis of both lower lobes. The liver was enlarged and weighed 2700 g; the cut surface was mottled with pale tan foci against a dark red background. The spleen was absent. The gall bladder contained some small multi-faceted stones but the common bile duct was patent. The stomach, intestine and remainder of the abdominal contents were unremarkable. No enlarged lymph nodes were noted. The bone marrow was markedly hyperplastic and pale infarct-like areas were seen in multiple vertebral bodies.

Microscopy. The lungs showed congestion and numerous pigment-laden macrophages within the alveolar spaces. Apparently trapped in capillaries were scattered large bizarre-shaped cells with hyperchromatic nuclei and ingested red cells. The liver architecture was normal but the sinusoids contained many atypical mononuclear cells filled with phagocytosed red and white cells (Figs. 3 and 4). Iron pigment was prominent (Prussian blue reaction). Sections of thoracic lymph nodes showed general preservation of architecture but prominent anthracotic pigment; an occasional histiocyte with engulfed red cell was seen in the sinusoids. Sections of vertebral bone marrow showed packing with a variety of cells, the majority of which were erythroid precursors but numerous myeloid cells were also present. Comprising 10–20% of the cell population were mononuclear cells with indented vesicular nuclei, appearing both separately and in clumps (Fig. 5). Several large areas of infarcted bone marrow were also identified. Sections of femoral marrow showed a similar picture but with about 10% of the marrow consisting of fat cells. Megakaryocytes were also increased in number. The same bizarre phagocytosing macrophages were readily identified. Large accumulations of iron were seen in both marrow sites.

Discussion

The cause of HMR is unknown. Evidence in support of bacterial or other infectious agents is scant (Zawadski, Pena & Fisher, 1969), although Serck-Hanssen & Purchit (1968) have recently

FIG. 3. Section of liver obtained at necropsy showing preservation of hepatic architecture but sinusoids filled with large mononuclear cells of varying size. Haematoxylin and eosin, $\times 105$.

FIG. 4. Detailed view of liver showing mononuclear cells in the sinusoids, many containing ingested red and white cells. Liver cells contain abundant pigment. A few normal Kupffer cells are visible. Haematoxylin and eosin, $\times 210$.

reported fourteen cases seen in Uganda and suggested that some specific environmental (or genetic) factors might be involved. Others (Marshall, 1956; Rappaport, 1966) have regarded the disease as a neoplasm involving histiocytes, but tumour formation is not usually a feature and it is clear that Scott & Robb-Smith (1939) regarded it as a disease *sui generis*.

The clinical and pathological features encountered in this case justify the diagnosis of HMR. The patient had multiple episodes of unexplained fever; she had great enlargement of liver and spleen with persistent anaemia and thrombocytopenia, atypical histiocytes were present in spleen, liver, bone marrow and pulmonary capillaries and phagocytosis of red cells, white cells and platelets was prominent. She lacked lymphadenopathy but this is by no means essential for the diagnosis when the remainder of the picture is so distinct (Natelson *et al.*, 1968; Asher, 1946; Vaithianathan, Fishkin & Gruhn, 1967).

The spleen in this patient was removed during life; it weighed 1286 g and microscopy showed greatly thickened cords and erythrophagocytosis. The majority of reported cases of HMR were diagnosed only after death, but five patients who underwent splenectomy are described in the literature. One patient (Asher, 1946) was moribund at the time of surgery but he improved to such an extent that he was able to leave the hospital after 3 weeks and spent the next 4 months without any symptoms. The eighth case in Marshall's series (Marshall, 1956) was described at necropsy as having undergone

FIG. 5. Section of vertebral bone marrow obtained at necropsy. The marrow is hyperplastic and some giant mononuclear cells are seen. A circumscribed clump of smaller mononuclear cells is shown (right centre). Haematoxylin and eosin, $\times 190$.

splenectomy, but further details and date of surgery are not supplied; it is noteworthy that the patient's disease lasted 1 year, longer than that of any other patient in that series. The patient described by Greenberg *et al.* (1962), underwent splenectomy but survived only 4 months after surgery. The patient reported by Hirsh *et al.* (1964), had considerable improvement in clinical and haematological features after splenectomy and experienced a remission lasting ten weeks. A fifth patient is reported (Willcox, 1952) who underwent splenectomy in 1950 and died 3 days later with rapidly increasing anaemia; the death may reasonably be regarded as a complication of surgery. For the other four patients, however, it appears that splenectomy offered moderate or considerable if temporary benefit.

The spleen reaches considerable size in HMR. The median weight at necropsy in forty reported cases is 1080 g and a number of them exceed 2 kg (Marshall, 1956; Greenberg *et al.*, 1962; Boake, Card & Kimmey, 1965). Microscopy usually shows enormous hypertrophy of the cords with histiocytic proliferation and erythrophagocytosis; there is no suggestion that the spleen is functionally useful in HMR and its removal early in the course of this patient's disease may have contributed to her long survival. It seems that splenectomy should at least be considered in any case diagnosed during life where the spleen appears to be large.

This patient had haemolytic anaemia and severe thrombocytopenia during her final hospital admission. Her reticulocytes varied between 8 and 20% and she had a persistent mild leucocytosis; both features are not typical but have been seen before in HMR (Marshall, 1956), and might in this case have been due to the absence of the spleen. Ferrokinetic studies (Lynch & Alfrey, 1965) have suggested that erythrophagocytosis by histiocytes is the cause of the anaemia and the presence of large amounts of iron within phagocytic histiocytes in the marrow offers support for this hypothesis (Natelson *et al.*, 1963; Lynch & Alfrey, 1965). This patient had a serum cholesterol of 108 mg/100 mg. Marked reduction in total serum cholesterol has been noted before (Greenberg *et al.*, 1962; Medford, 1965; Lutman & Senhauser, 1966) and it may be that histiocytes sequester membrane lipid fractions and cholesterol from the ingested red cells as well as iron.

At necropsy phagocytosing histiocytes were identified in the liver sinusoids, bone marrow and the occasional lymph node. In the lungs their presence exclusively in the alveolar capillaries suggests that they may lodge there after filtration from the circulation; in other cases they have been identified in the peripheral blood (Clark & Dawson, 1969; Chih-Pei *et al.*, 1960). A number of areas of infarcted vertebral bone marrow were identified; if they had occurred acutely they were very likely to have been painful;

it may be speculated that they accounted for the repeated episodes of sudden pain and subsequent fever and hyperbilirubinaemia for which no other cause could be found. The pathogenesis of the infarcts is quite unknown.

Our patient died a relatively sudden cardiopulmonary death almost 2 years after HMR was diagnosed. She had proven coronary artery disease but undoubtedly the chronic anaemia contributed to her death and the normoblasts in her peripheral blood had risen shortly before death to 25% of nucleated cells. We know of no previous patient who survived so long and this case suggests that the prognosis in HMR need not be as uniformly gloomy as previous reports would imply.

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Idiopathic retroperitoneal fibrosis

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IDIOPATHIC retroperitoneal fibrosis is now a recognized clinical entity, about 200 cases having been reported since Ormond first described it in 1948. While reviewing the literature we discovered that Albaran, a French urologist, first reported a case of ureteral envelopment and obstruction by a fibrous mass in the pelvis in 1905, and he performed ureterolysis for it. Many names have been given to

it: periureteral fibrosis, Gerota's fasciitis, perirenal fasciitis, sclerosing retroperitonitis, sclerosing lipogranuloma and non-specific retroperitoneal inflammation, but usually idiopathic retroperitoneal fibrosis or Ormond's syndrome.

This disease is an aggressive, non-malignant, mid-line fibro-proliferative process which envelops the major retroperitoneal vessels and secondarily