Fatal anaphylaxis in systemic mastocytosis

N. J. DODD AND M. G. BOND

From the Departments of Haematology and Nephrology, St Bartholomew's Hospital, London EC1, UK

SUMMARY A 42-year-old woman died after an episode of anaphylaxis associated with a raised serum histamine level. A diagnosis of systemic mastocytosis was established, with lymphadenopathy and hepatosplenomegaly, not associated with the usually pre-existing skin lesions of urticaria pigmentosa.

Mastocytosis is an uncommon disease characterised by abnormal proliferation of mast cells. It usually involves the skin alone, causing the typical pigmented macules of urticaria pigmentosa. In about 10% of such cases additional systemic involvement has been demonstrated (Sagher and Even-Paz, 1967) with infiltration predominantly of the reticuloendothelial system. This produces symptoms attributable both to direct tissue invasion and to release of histamine (Mutter *et al.*, 1963). Rarely, the systemic component occurs without urticaria pigmentosa.

We report a case of systemic mastocytosis with lymphadenopathy, hepatosplenomegaly, marrow infiltration, and widespread osteosclerosis, but without skin lesions, which terminated in anaphylactic shock associated with a raised serum histamine level.

Case report

A 42-year-old woman was admitted in a shocked state to East Ham Memorial Hospital in October 1976. Five years previously she had suffered epigastric pain, and a diagnosis of a probable duodenal ulcer was made after a barium meal examination. She had a four-year history of intermittent flushing and pruritus affecting the face and limbs, and a two-year history of recurrent bouts of profuse watery diarrhoea. Two days before admission she developed a 'flu-like' illness associated with vomiting and diarrhoea, as well as flushing and pruritus of the face, limbs, and trunk. On the day of admission her condition suddenly deteriorated, she became rapidly dyspnoeic and collapsed, and on arrival at East Ham Hospital was pulseless with an unrecordable blood pressure. Her condition improved after treatment with intravenous fluids, antibiotics, and hydrocortisone but she remained anuric and was transferred to St Bartholomew's Hospital for treatment of acute renal failure.

On examination at St Bartholomew's she was pale and had mild icterus, periorbital oedema, purpura, and ecchymoses; the pulse was 100/minute and blood pressure 120/90 mm Hg; bilateral expiratory rhonchi were present. There was moderate cervical and axillary lymphadenopathy; the liver was enlarged to 10 cm, and the spleen to 5 cm, below the costal margin.

The haemoglobin was 11.5 g/dl, reticulocytes 0.1%, white cell count $6.5 \times 10^9/l$, and platelets

Fig. 1 Abdominal x-ray October 1976: diffuse osteosclerosis affecting vertebral and pelvic bones.

Received for publication 15 June 1978

Fig. 2 Mast cells in the bone marrow exhibiting typical, finely granular cytoplasm and central, frequently indented nuclei (arrow). (Haematoxylin and eosin $\times 640$).

Fig. 3 Coarse, irregular bony trabeculae with mast cell infiltration of the marrow spaces. (H and E $\times 100$).

$37.0 \times 10^9/l$. The blood film showed moderate anisopoikilocytosis and a leucoerythroblastic picture (promyelocytes 3%, myelocytes 2%, metamyelocytes 1%, neutrophils 66%, lymphocytes 26%, monocytes 2% with 8% nucleated red cells). A buffy coat preparation revealed occasional circulating mast cells. Repeated attempts at marrow aspiration were unsuccessful. Neutrophil alkaline phosphatase score was 210 (normal range 15-100). Prothrombin time was 20 seconds (control 15 seconds), partial thromboplastin time normal, fibrinogen titre normal, and fibrinogen/fibrin degradation products greater than $10 \mu\text{g/ml}$ but less than $40 \mu\text{g/ml}$. Blood cultures were consistently negative. Urea was 23.1 mmol/l (140 mg/100 ml), Na^+ 124 mmol/l , K^+ 4.8 mmol/l , bilirubin $52 \mu\text{mol/l}$ (3.0 mg/100 ml), SGOT 1500 IU/l and HBD $> 5000 \text{ IU/l}$. Ca^{++} 2.09 mmol/l (8.36 mg/100 ml), PO_4 1.47 mmol/l (4.4 mg/100 ml), alkaline phosphatase 135 IU/l , uric acid 0.53 mmol/l (9.0 g/100 ml). Total protein was 63 g/l , albumin 34 g/l , with a normal electrophoretic pattern. Immunoglobulin electrophoresis was normal and IgE was 80 IU/l (normal $< 500 \text{ IU/ml}$). Urinary 5-hydroxyindoleacetic acid screen for carcinoid syndrome was negative.

X-rays demonstrated a diffuse osteosclerosis affecting the vertebral column, pelvis, and limb bones (Fig. 1).

Marrow trephine biopsy from the iliac crest, which was difficult due to extreme hardness of the bones, showed replacement of normal marrow elements by mast cells and fibrous tissue. The bone trabeculae were thickened and irregular (Figs 2 and 3).

Postmortem percutaneous liver biopsy revealed a marked excess of mast cells, of varying degrees of maturity, within widened portal tracts, confirming the diagnosis of systemic mastocytosis (Fig. 4). The areas of mast-cell infiltration were associated with extensive fibrosis.

Despite effective peritoneal dialysis the patient died five days after admission. A full postmortem examination was refused.

Discussion

The histological diagnosis of systemic mastocytosis is frequently difficult, particularly if clinical suspicion of the disease is lacking. Examination of routine tissue sections stained with haematoxylin and eosin

Fig. 4 Portal tract containing numerous mast cells, the coarse metachromatic granules staining well with Giemsa stain ($\times 1000$).

has led to erroneous diagnoses in the past (Mutter *et al.*, 1963), the cells exhibiting non-specific, finely granular, eosinophilic cytoplasm and elongate nuclei. Specific staining with Giemsa or toluidine blue is essential to demonstrate the coarse metachromatic granules that readily identify the cells, Giemsa stain being used in this patient to confirm the diagnosis. Alcian blue is also of use, staining the mast cell granules bright blue, reflecting their high mucopolysaccharide content.

Tissue fibrosis is a frequent accompaniment of mast cell infiltration, as seen in this case in liver and bone marrow, presumably related to the chemotactic activity of mast cell products, for fibroblasts. The fibrotic process was associated with a widespread osteosclerosis, which was remarkably homogeneous in many bones, with no obvious lytic areas. This is unlike the more commonly reported appearance of mixed lytic and sclerotic lesions suggested as typical of the disease (Gagnon *et al.*, 1975).

The clinical course in this patient was typical, with a history of duodenal ulceration, intermittent diarrhoea, and skin flushing, but unusual in that no actual skin lesions were present. It was particularly interesting in its mode of termination. There have been few reported cases of systemic mastocytosis with fatal outcome (Sagher and Even-Paz, 1967). In the majority, death has followed extensive mast cell proliferation involving a variety of organs, leading to cachexia, marrow failure, or leukaemic transformation.

In our case, anaphylactic shock occurred with cardiovascular collapse and bronchospasm, suggesting a catastrophic release of histamine by mast cells. This interpretation was later supported by the finding of a grossly elevated serum histamine level of 31.0 ng/ml (normal serum < 0.5 ng/ml), as estimated by enzymatic isotopic assay (Beavan *et al.*, 1972). Previous workers have reported a variety of stimuli capable of causing histamine release in patients with this disease, including infection, radiation, and drugs (Mutter *et al.*, 1963), but we have not found any reported case where the effect on the patient has been so profound.

It may be that the tissue eosinophilia, so often seen in association with mastocytosis, is protective, perhaps by virtue of the eosinophils' capacity to phagocytose mast cell granules (Welsh and Geer, 1959). The eosinophil granule also contains several enzymes

which inactivate liberated vasoactive compounds, ie, aryl sulphatase, which inactivates slow reacting substance of anaphylaxis (Wasserman *et al.*, 1975), histaminase (Hubscher, 1975), and kininase (Melmon and Cline, 1967). In this case, no significant eosinophilia was found in blood or tissues, a situation which could have rendered the individual more susceptible to the effects of mast cell degranulation, thus resulting in the sudden death of a patient in whom the disease did not appear to have reached an advanced stage.

We should like to thank Dr L. R. I. Baker for permission to report this case, Dr A. Stansfeld for his interpretation of the histology, and Dr I. Smith of Smith, Kline, and French Laboratories for performing the histamine assay.

References

- Beavan, M. A., Jacobsen, S., and Horáková, Z. (1972). Modification of the enzymatic isotopic assay of histamine and its application to measurement of histamine in tissues, serum and urine. *Clinica Chimica Acta*, **37**, 91-103.
- Gagnon, J. H., Kalz, F., Kadri, A. M., and von Graefe, I. (1975). Mastocytosis: unusual manifestations; clinical and radiologic changes. *Canadian Medical Association Journal*, **112**, 1329-1332.
- Hubscher, T. (1975). Role of the eosinophil in the allergic reactions. I. EDI—an eosinophil-derived inhibitor of histamine release. *Journal of Immunology*, **114**, 1379-1388.
- Melmon, K. L., and Cline, M. J. (1967). Interaction of plasma kinins and granulocytes. *Nature*, **213**, 90-92.
- Mutter, R. D., Tannenbaum, M., and Ulmann, J. E. (1963). Systemic mast cell disease. *Annals of Internal Medicine*, **59**, 887-906.
- Sagher, F., and Even-Paz, Z. (1967). *Mastocytosis and the Mast Cell*. Year Book Medical Publishers, Chicago.
- Wasserman, S. I., Goetzl, E. J., and Austen, K. F. (1975). Inactivation of slow reacting substance of anaphylaxis by human eosinophil aryl sulfatase. *Journal of Immunology*, **114**, 645-649.
- Welsh, R. A., and Geer, J. C. (1959). Phagocytosis of mast cell granule by the eosinophilic leucocyte in the rat. *American Journal of Pathology*, **35**, 103-111.

Requests for reprints to: Dr N. J. Dodd, Department of Haematology, St Bartholomew's Hospital, West Smithfield, London EC1A 7BE, UK.