URTICARIA PIGMENTOSA AND POLYCYTHAEMIA VERA

A CASE REPORT

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Urticaria pigmentosa has proved to be a condition of exceptional interest since it was first described by Nettleship (1869). The accumulations of mast cells which compose the macular or nodular cutaneous lesions are now considered to be a constant feature of the histological picture, and the alleged occurrence of cases without such cells is explained by the rapid disintegration of the characteristic granules if careful precautions are not taken in the collection of material (Beare, 1958). Interest has been stimulated by the demonstration of the production and storage by mast cells of heparin, histamine, and perhaps other substances (West, 1958), and the clinical significance of the condition has been extended by the recognition of extracutaneous lesions, which have been reviewed by Berlin (1955) and Beare (1958).

For many years urticaria pigmentosa was considered exclusively a dermatosis, and its predominantly benign nature was reflected in the paucity of necropsy reports in the literature. With the description by Ellis (1949) of the case of a 1-year-old child, showing associated mast-cell lesions of the liver, spleen, lymph nodes, bone-marrow, and other organs, the systemic manifestations began to emerge. These include splenomegaly and hepatosplenomegaly (Touraine, 1939; Bluefarb and Salk, 1954; Reilly *et al.*, 1955; Brodeur and Gardner, 1956), lymphadenopathy (Little, 1905; Gray, 1938; Degos *et al.*, 1952), and osseous lesions (Sagher *et al.*, 1952; Clyman and Rein, 1952; Sagher *et al.*, 1956). Cases are also described in which systemic mast-cell infiltrations are found in association with skin lesions other than urticaria pigmentosa, and there appears to be a series of distinct but related mast-cell disorders differing mainly in the pattern of organ involvement (Sagher, 1956).

The relationships of these disorders are still being defined. The following case has features of both urticaria pigmentosa and polycythaemia vera.

Case History

A chartered accountant aged 48 complained of episodic epigastric pain unrelated to meals in November, 1957, at which time his florid facies was first observed. The pain continued at intervals, and a year later it was found frequently to be associated with palpitations, which at other times occurred independently. In December, 1958, he developed nocturnal "red-hot" pains in the feet, in attacks lasting 5 to 10 minutes, and episodes of paraesthesiae and numbness about the neck and the ulnar borders of his hands, together with a sensation of "being touched by a cold hand" from time to time on the limbs. Two weeks later he complained of impaired vision with dazzling, which

did not improve on changing his spectacles, and experienced a few transient episodes of motor uselessness of his left hand and foot, which occurred chiefly on rising in the morning.

At this time he began a course of psychotherapy, but at a further ophthalmic examination he was found to have dilated retinal veins and was referred for a neurological opinion, being admitted under Dr. E. A. Blake Pritchard.

Physical examination in January, 1959, showed him to be an anxious man of florid aspect with a universal violaceous macular skin rash especially dense about the lower limbs and trunk. This had been present for eight years and was not pruritic. Mild papulation occurred with friction, the skin marked easily on pressure, and there was moderate dermographism. The clinical appearance of the rash was typical of urticaria pigmentosa.

The fundi showed well-coloured optic disks but no papilloedema, and the retinal veins were engorged. The deep tendon reflexes were brisker on the left than on the right, but the plantar responses were flexor. There was no other abnormality in the nervous system. The spleen was palpable one finger-breadth below the left costal margin, and was firm and not tender. The liver edge was just palpable. No other abnormalities were discovered apart from a blood-pressure of 150/95.

Investigations

Haemoglobin, 137% (20.1 g./100 ml.); haematocrit, 58.5%; red-cell count, 6,440,000/c.mm.; white-cell count, 7,000/c.mm. (polymorphonuclears 87%, lymphocytes 10.5%, monocytes 1%, eosinophils 1.5%); E.S.R., less than 1 mm. in the first hour; platelet count, 620,000/c.mm. The differential marrow count showed increased myelocytes (32.5%), while the neutrophil (24%) and normoblast (30%) counts were at the upper limits of normal. Megakaryocytes were in normal numbers. By special staining with methyl green and pyronine (Unna-Pappenheim) Dr. P. J. Hare was able to demonstrate scattered accumulations of mast cells in the bone-marrow.

The prothrombin concentration by the one-stage method was 61% of normal, and the prothrombin deficiency was confirmed by the two-stage method. The thromboplastin generation test and bleeding- and clotting-times were normal. Arterial oxygen saturation was 95.5%, and the blood urea was 57 mg./100 ml.; a clean specimen of urine contained occasional granular and hyaline casts, and the concentration-dilution test revealed a specific gravity range of 1004 to 1024. Empirical liver-function tests showed no abnormality.

A barium-meal examination showed no abnormality in the oesophagus, stomach, or duodenum, and extensive skeletal radiography disclosed only an anomaly of one foramen ovale and a small opacity of doubtful significance in the lower end of the left tibia. The E.C.G. revealed evidence of recent myocardial infarction, and electroencephalography suggested a lesion of the right cerebral hemisphere. Lumbar puncture showed a pressure of 100 mm. of C.S.F. with normal manometrics, and the fluid contained one lymphocyte per c.mm. and 25 mg. of protein per 100 ml.

Skin biopsy performed by Dr. P. J. Hare confirmed the diagnosis of urticaria pigmentosa. Splenic aspiration produced no evidence of myeloid or mast-cell infiltration. It was concluded that the patient had urticaria pigmentosa, polycythaemia vera, and secondary thrombotic lesions of the heart and cerebrum. He was treated with bed rest and a course of busulphan, the haemoglobin falling from 20.1 to 14.8 g./100 ml. in eight weeks.

Discussion

Haematological abnormalities have often been described in association with urticaria pigmentosa, but even recently their relationship has been regarded as

controversial (Wiener, 1955). However, enough cases have now been described to confirm that the mast-cell disorders can affect the blood-picture profoundly. Touraine (1939) described a case showing anaemia, leucopenia, and eosinophilia; and Reilly *et al.* (1955) recorded slight anaemia and granulopenia. In Berlin's (1955) case there was a severe progressive macrocytic anaemia, leucopenia, and thrombocytopenia, and many tissue mast cells were demonstrated in the bone-marrow. Eosinophilia was present in the cases of Asboe-Hansen and Kaalund-Jørgensen (1956), Brodeur and Gardner (1956), and Efrati *et al.* (1957). Monocytosis was described in one case by Hissard *et al.* (1951) and a terminal monocytic leukaemia by Sagher (1956) in a patient with extensive mast-cell infiltrations and fibrosis of bone. Balbi's (1950) patient died from "acute haemocytoblastic leukaemia," and termination in mast-cell leukaemia was found by Efrati *et al.* (1957) and Waters and Lacson (1957).

Until more is known of the aetiology of both urticaria pigmentosa and polycythaemia vera it will not be possible to state definitely whether the association of the two conditions is coincidental, especially as we have not been able to trace any similar recorded cases. There are, however, many points in which the mast-cell syndromes approach the myeloproliferative disorders. Concerning urticaria pigmentosa, Reilly *et al.* (1955) have stated that "the disorder is best defined as a systemic hyperplasia of one of the cells of the reticulo-endothelial system," and there is a similar tendency to involve the spleen, liver, bone-marrow, and lymph nodes.

There is a trend to fibrosis of the bone-marrow and osteosclerosis, occasionally hepatic cirrhosis, and the possibility of termination in a leukaemic condition. The comparison fails principally on the mast cell not being a member of the myeloid series, and its distinction from the blood basophil on morphological grounds has been strongly maintained (Waters and Lacson, 1957). On the other hand, the fibroblast may play a prominent part in the myeloproliferative process, and the eosinophil leucocyte in the mast-cell syndromes, showing that an absolute difference between myeloid and non-myeloid cells does not exist in this respect. Asboe-Hansen and Kaalund-Jørgensen (1956) described the bone-marrow of a patient with urticaria pigmentosa, systemic mast-cell involvement, and xanthomata, finding it to be maximally hyperplastic and "suggestive of incipient myeloid leukaemia" with myeloid hyperplasia and eosinophilia and with slightly reduced erythropoiesis. Reilly *et al.* (1955) also observe that "other elements of the reticulo-endothelial system" than the mast cell show proliferation in the bone-marrow.

Vaughan and Harrison (1939) suggested, as the result of their studies of myelosclerosis following polycythaemia, that there might be an unidentified stimulus to excessive activity of fibroblasts, osteoblasts, haemocyto-blasts, and megakaryocytes, all of which are derived from primitive reticulum cells. This concept was also supported by Beattie and Withey (1953), and is implicit in the unitarian view of the myeloproliferative disorders (Dameshek, 1951). It would not require a radical extension of this view for it to include the mast cell, which has been held to have a close relationship to the fibroblast (Drennan, 1957). The nature of the stimulus is at present speculative, but there is evidence of a circulating erythropoietic factor in polycythaemia vera (Contopoulos *et al.*, 1957), one possible source of which

might be the erythropoietic stimulating factor of pituitary origin associated with corticotrophin (Van Dyke *et al.*, 1957). There is also some evidence that the mast cell may be under hormonal control in that its proliferation is stimulated by thyrotrophin and inhibited by cortisone (Asboe-Hansen and Iversen, 1950; Asboe-Hansen, 1952; Bloom, 1952). The relevance of these observations remains to be elucidated in detail, but the evidence is suggestive that there may be mast-cell stimulating factors in common with, or related to, those believed to be responsible for myeloid proliferation, and that when these are acting simultaneously a mixed syndrome such as that described here may result.

Summary

The case is described of a patient with urticaria pigmentosa and polycythaemia vera.

The relationship of the mast-cell disorders to the myeloproliferative syndromes is discussed, and it is suggested that both represent hyperplastic conditions of mesenchymal cells.

The possibility is considered that the occurrence of the two conditions in one patient may be due to a stimulus or related stimuli of the kind postulated for the myeloproliferative disorders, acting both on the tissue mast cells and on the bone-marrow simultaneously.

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