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Annotations

Histiocytosis X—current controversies

Circulating monocytes, cutaneous Langerhans cells, Kupffer cells, bone osteoclasts, microglial cells, and alveolar macrophages are all histiocytes and are derived from a bone marrow stem cell.[1] Histiocytes are also found in the lymph nodes, spleen, pleura, and peritoneum. Diseases affecting these cells may therefore have a broad clinical spectrum.

In 1953, Lichtenstein[2] suggested that eosinophilic granuloma, Hand-Schuller-Christian and Letterer-Siwe disease were variants of a single clinicopathological entity affecting tissue histiocytes. He suggested the use of the term 'histiocytosis X' to encompass the entire spectrum of disease, 'X' representing the unknown causal factor. Over 30 years later this fascinating and varied disorder remains an enigma and is still surrounded by controversy.

Immunological disease, malignancy—or something else?

Traditionally, histiocytosis X has been regarded as a malignant disease. Although some features of the disease suggest cancer, the high incidence of spontaneous remission and certain histologic features argue against this view. There is no positive evidence of an in situ, uncontrolled proliferation of a uniform population of cells, as seen in most malignancies, nor is there a reliable correlation between the degree of 'differentiation' of histiocytes and the clinical course of disease.[3] Circumstantial evidence, including the identification of histiocytes outside their normal tissue site (breaching of the dermal/epidermal junction by Langerhans cells, for example)[4] and the occasionally observed rapid regression of bony lesions points to an abnormality of migration of histiocytes rather than their in situ proliferation.

Recent studies[5 6] have suggested that the disease has an immunological basis. Most patients with histiocytosis X have a deficiency of circulating suppressor (T8) lymphocytes and an increased peripheral blood helper (T4) : suppressor (T8) ratio. In some of these patients there is histological evidence of an abnormal thymus.[5] A crude extract of calf thymus (thymosin) has been shown in vitro to restore the T4:T8 ratio to normal, but in vivo results of treatment with intramuscular thymic extract have been variable.[5 6] Spontaneous remission of disease has also been associated with a return of the T4:T8 ratio to normal.[7] Whether the deficiency of suppressor cells is a cause of histiocytosis X, an effect, or merely a 'paraphenomenon' remains speculative. It is known that suppressor T cells probably terminate excessive immune responses after antigenic stimulus by 'switching off' the macrophage/helper cell interaction.[8] Failure of this cellular homeostatic mechanism could result in abnormal macrophage behaviour and to a breakdown in normal intercellular 'conversation'. Histiocytosis X could be the result.

Staging and prognosis

There is uniform agreement that children under 2 years of age with vital organ dysfunction fare badly with 10 to 20% mortality in some series.[9 10] Morbidity is high with residual disabilities in 50% of survivors,[11–13] most of them in children with 'smouldering' disease of more than five years' duration. Diabetes insipidus, short stature, deafness, and orthopaedic and pulmonary complications account for most disabilities. Lahey has proposed a 'scoring' system with a score of 1 for each organ affected by disease. Lukaya[14] has related this score to outcome so that patients with a score of 1 to 2 have a mortality of 5% and a 20% chance of sequelae; a score of 7 to 9 results in 100% mortality. These staging and scoring systems are based on clinical assessment together with simple investigations such as chest radiograph for evaluation of lung disease, full blood count for evaluation of bone marrow disease, and liver function tests. Of 16 recently diagnosed children, judged at presentation to our unit as having 'single system' disease, half proved to have occult multisystem disease after full evaluation including respiratory function tests and trephine bone marrow biopsies. This 'occult' involvement did not adversely affect short term prognosis, confirming Lahey's suggestion that it is organ failure rather than organ involvement per se that confers a poor prognosis.

'Aggressive' *v* 'non-aggressive' treatment

Ignorance of the pathogenetic mechanism inhibits development of a rational treatment policy. Some general principles, however, have emerged from clinical observation. It is uniformly agreed that patients with single system disease (usually bone or lymph node) have a good prognosis with a high rate of spontaneous remission and negligible mortality. Bony lesions in weight-bearing bones with the risk of spontaneous fracture or those causing pain or disfigurement were traditionally treated with low dose (700–1000 cGy) radiation. The 5% risk of inducing secondary malignancy as in Greenberger's large series[15] was acceptable during an era when histiocytosis X was thought to be a malignancy. In view of changing concepts of the disease, is this form of treatment still justifiable? Local injection of methyl prednisolone, under circumstances in which radiotherapy would previously have been used, has led to exellent response in five of six children treated by us, though the tendency to spontaneous remission must always be borne in mind in interpretation of results, especially when numbers are small. We now reserve radiotherapy for treatment of those lesions, inaccessible to local injection, which threaten vital structures such as spinal cord or optic nerve.

The management of the child with multisystem disease is much more controversial. As there are no detectable histological,[3] immunohistochemical,[4] or immunological[6] differences between single system and multisystem disease, it seems reasonable to anticipate that spontaneous remission may also occur in multisystem disease. Recently we have reported two such cases in infants.[7] During the period when histiocytosis X was regarded as a malignancy, treatment was with a variety of cytotoxic drugs either as single agents or in combination. Whatever regimen is used, the total response rate is between 50 to 70%[16] and the mortality in multisystem disease has declined only marginally since the introduction of chemotherapy. The harmful side effects of multiagent regimens, including sometimes fatal immuno- and myelosuppression, possibly outweigh their benefits.[16–18] High dose prednisolone (2 mg/kg)[19] is as effective as combinations of cytotoxic drugs and has less severe side effects, especially if used in relatively short courses of two to three months. This last observation provides some evidence that 'maintenance' treatment has little advantage for the individual patient and leads to extra morbidity. It is hoped that these issues will eventually be resolved by well designed randomised studies.

In view of the recent changes in our understanding of the disease, emphasis has been put on 'immune replacement' rather than 'immune suppression'. Osband's[5] initial clinical success in patients with in vitro evidence of response to crude bovine thymic hormone (thymosin) has not been repeated by others using synthetic preparations.[6] Further trials of this form of treatment are in progress, using more refined thymic hormone preparations.

Conclusions

Several important questions concerning the aetiology, management, and prognosis of this rare disease (30 to 40 cases annually in the United Kingdom) remain unanswered. Central referral of patients for assessment of extent of disease and treatment planning should improve standardisation and encourage critical comparison of treatment methods. Laboratory investigation of the biology of the histiocyte and its interactions with lymphoid cells will only be possible when reliable methods are developed for growing this remarkable cell in culture. Until then the 'X' remains.

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V BROADBENT AND J PRITCHARD
Department of Haematology and Oncology,
Hospital for Sick Children,
Great Ormond Street,
London WC1N 3JH