

## Favourable prognostic features in histiocytosis X: bone involvement and absence of skin disease

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**SUMMARY** The records of 70 patients presenting to this hospital since 1961 with histiocytosis X confirmed by biopsy examination have been reviewed. The patients were subdivided into three groups: group A, those under 2 years of age at diagnosis; group B, those between 2 and 5 years; and group C, those over 5 years. All eight patients who died (11% overall mortality) were under 2 years of age at diagnosis. Involvement of lung, liver, and bone marrow were confirmed as poor prognostic features. The presence of bone disease and absence of skin rash were identified as favourable features.

Langerhans' cells, Kupffer's cells, bone osteoclasts, microglial cells, and alveolar macrophages together with circulating monocytes are all histiocytes and are derived from a bone marrow stem cell.<sup>1</sup> Histiocytes are also found in pleura, peritoneum, lymph nodes, and spleen. The disease histiocytosis X can affect any of these organs and therefore has a wide clinical range. Although aetiology and treatment remain controversial,<sup>2</sup> there is uniform agreement with Komp<sup>3</sup> and Lahey<sup>4</sup> that young children under 2 years of age with vital organ (lung, liver, and bone marrow) dysfunction fare badly, with a 10–20% mortality. At the other end of the range, patients with single system bony disease have negligible mortality, although morbidity may be considerable.<sup>5,6</sup> These facts have led me to question whether the presence of bone disease in an otherwise poor prognostic group confers a more favourable outcome. Skin disease is the next most common presenting feature after bone disease but its importance as a prognostic factor has not been previously assessed.

### Patients and methods

The records of 70 patients with histiocytosis X confirmed histologically attending this hospital between 1961 and 1982 were reviewed to determine the incidence of specific disease manifestations at diagnosis and to establish their relative prognostic importance. For comparison with the prognostic groups described by Komp<sup>3</sup> and Lahey,<sup>4</sup> the patients were subdivided into three groups: group A, those

patients under 2 years at presentation; group B, those from 2 to 5 years, and group C, those over 5 years.

Tests for significant prognostic differences between groups of patients with different presenting features were carried out using either the  $\chi^2$  test, incorporating Yates's correction for continuity, or with small samples the Fisher exact probability test on 2x2 contingency tables.

### Results

The age range extended from <1 month, four children having been born with skin disease, to 14 years. Forty two patients were boys, which was in line with a reported 2:1 male:female preponderance.<sup>6</sup> Twenty patients had single system and 50 multisystem disease. The number of patients in each of the groups is given in Table 1.

**Mortality.** Eight patients (five boys and three girls) in the study died, an overall mortality of 11%. All of these patients were in group A and all had multisystem disease with involvement of vital organs (lung,

Table 1 *Details of the study groups*

Group	Age (years)	Total	Boys	Girls	Deaths
A	<2	40	22	18	8
B	2-5	15	7	8	0
C	>5	15	14	1	0
Deaths		8	5	3	

liver, and bone marrow). One child died at the age of 4 years but originally presented at 1 year with skin and scalp rash, widespread bony lesions, bone marrow infiltration, diabetes insipidus, and failure of growth hormone. At postmortem examination she was found to have widespread disease, including involvement of dura, pericardium, and gut. All the other children died before reaching 2 years of age.

**Bony disease.** Bone involvement was identified in 82% of patients studied. Flat bones, especially the skull, were involved more often than long bones. A soft tissue swelling invariably overlaid a typical radiotranslucent area on x ray film and produced symptoms depending on its location. These included proptosis from periorbital disease, suppurative mastoiditis from temporal bone involvement, and loss of teeth from gum disease. The axial skeleton was the next commonest site of bony lesions followed by the long bones. Lesions at these sites gave rise to regional pain and stiffness and resulted in voluntary immobilisation of the affected area.

Only five (16%) of the 32 patients with bony disease in group A had single system disease, whereas 10 (76%) out of 13 with bony disease in group C had single system disease. Of the 12 patients with multisystem disease who did not have bone involvement, four (33%) died, whereas of 38 patients who had multisystem disease that included bony disease only four (11%) died. This difference was significant ( $p < 0.02$ ) using the  $\chi^2$  test on a  $2 \times 2$  contingency table. For group A the difference was even more pronounced (50% (four of eight) of the patients with multisystem disease without bone involvement died, whereas only 15% (four of 27) of those with bone involvement died; Table 2). The smaller sample size, however, meant that this difference was not significant ( $p = 0.522$ ).

**Skin disease.** Thirty eight patients presented with skin involvement, an overall incidence of 54%. Four

babies were born with skin lesions. Skin disease was always an initial presenting feature. In no case did it first occur during subsequent course of the disease. There was a higher incidence of skin rash in group A (68%) than in groups B and C (Table 3). The rash varied from a few discrete pinhead lesions confined to the trunk to severe flexural eczematous lesions to florid haemorrhagic confluent weeping areas with crusting. The scalp rash was usually mistaken for chronic seborrhoeic dermatitis or 'cradle cap'.

Generalised skin disease at presentation was a poor prognostic factor. All patients who died had this feature, and the overall mortality for those with skin disease was 21%. None of the patients presenting without skin disease died. The significance of this difference using the  $\chi^2$  test was  $p < 0.025$ . Although skin disease was more common in the youngest, highest risk age group (group A), those presenting without skin disease within this group were significantly more likely to survive ( $p = 0.029$ , using the Fisher exact probability test; Table 3).

**Involvement of vital organs.** For the purpose of this study involvement of vital organs comprised bone marrow, liver, and lung as in most large series dysfunction of these organs is a poor prognostic feature. Involvement of vital organs was found most exclusively in group A, with lungs being the commonest organ involved at presentation. Only four children in group B presented with involvement of vital organs. Two children in group C presented with this feature and again the organ involved was the lung. Chest x ray films were used to assess involvement, with lung function testing being used in only a few patients. Liver function tests were usually only performed if there was clinical enlargement of the organ, and a bone marrow aspiration was performed if the peripheral blood count was abnormal in any way.

All the patients who died developed dysfunction of vital organs during the course of their disease, but

Table 2 *Incidence of disease involving bone in the three study groups. Numbers in parentheses are deaths*

	Total patients	Multisystem disease		Single system disease
		No bony disease	Bony disease	
Group A	40 (8)	8 (4)	27 (4)	5 (0)
Group B	15 (0)	2 (0)	8 (0)	5 (0)
Group C	15 (0)	2 (0)	3 (0)	10 (0)
Total	70 (8)	12 (4)	38 (4)	30 (0)
% Deaths	11	33	11	0

Difference between deaths with no bony disease compared with deaths with bony disease,  $p < 0.02$ .

Table 3 *Incidence of skin disease in the three study groups. Numbers in parentheses are deaths*

	Total patients	No with skin disease	No without skin disease	% With skin disease
Group A	40 (8)	27 (8)	13 (0)	68
Group B	15 (0)	8 (0)	7 (0)	53
Group C	15 (0)	3 (0)	12 (0)	20
Total	70 (8)	38 (8)	32 (0)	54
% Deaths	11	21	0	100

Difference between deaths with skin disease compared with deaths with no skin disease,  $p < 0.025$ .

Table 4 Involvement of vital organs in the three study groups

	Total patients	Organ involved		
		Lungs	Liver	Bone marrow
Group A	40	11	10	9
Group B	15	2	1	1
Group C	15	2	0	0
Deaths	8	8	8	8

bone marrow and liver dysfunction were rare presenting features (Table 4).

### Discussion

Identification of prognostic groups within the disease range of histiocytosis X has become more important with the changing concept of the disease from malignancy to an intercellular communication disorder.<sup>2</sup> It is no longer justifiable to treat this non-malignant disease with potential carcinogens, so that cytotoxic drugs are becoming reserved for very poor prognostic cases who do not respond to steroids. Prognostic groups have previously been described by Komp<sup>3</sup> and Lahey.<sup>4</sup> This study confirms that children under 2 years of age with involvement of vital organs form the poorest prognostic group. Within this group have been identified two other features of prognostic importance — presence of bony disease and skin rash at diagnosis.

Patients with disease totally confined to bone do well and require no treatment provided that the bone involved is not weight bearing or surrounding a vital structure, such as the optic nerve or spinal cord. Those patients in this series who had bone involvement as part of multisystem disease had a more favourable outcome than those who did not, and this was most pronounced in the youngest age group.

In this series skin involvement at diagnosis was most common in the youngest age group and carried

a considerably worse prognosis within this group. It was invariably part of multisystem disease.

In a disease characterised by spontaneous remissions and relapses assessment of therapeutic regimens is difficult. Both combination and single agent chemotherapy are associated with short and long term side effects,<sup>7</sup> which may not now be acceptable with the changing concept of the disease. Undoubtedly, children have been overtreated in the past. Very young children with multisystem disease, which includes bony disease, may not require potentially toxic treatment, but those without bone involvement who have vital organ disease, including skin disease, are the group with highest mortality and may benefit from new approaches to treatment.

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