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Langerhans cell histiocytosis. Five new cases and review of the literature

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Five cases of LCH diagnosed and treated in our department the last two years are described. The first case concerns an 8 year old boy with a history of back pain, collapse of the 5th lumbar vertebra and lytic lesions in the skull. The second concerns an 8 month old male with symptoms of chronic otitis media, persisting diaper rash, seborrhoeic dermatitis of the skull and organs' dysfunction. The third case concerns an 8 month old boy with diaper and vesicular rash with remissions and exacerbations of 3 month duration. The fourth case concerns a 3 year old girl with a history of claudication of the left leg and painless nodules over the head. The fifth case concerns a female infant born with necrotic dermatitis and skin nodules. Biopsy established the diagnosis with S-100 and CD1 positive histiocytes in all cases. Treatment ranged from simple observation to systemic therapy including steroids and Vinblastine or Etoposide. The atypical clinical presentation of LCH and the treatment policy in each case are discussed.

Key words: histiocytosis, Langerhans-cell

Introduction

Langerhans cell histiocytosis is a disease which frustrates both clinicians and scientists. Its aetiology is unknown, its pathogenesis is ill understood and the clinical course is unpredictable. LCH can appear at any period of life ranging from birth to old age with a peak between 1–3 years.[1] The incidence in the pediatric range has been estimated at 3–4 per million with males affected twice as commonly as females.[2] The disease has a wide clinical spectrum and prognosis varies accordingly. Five cases of LCH diagnosed and treated in our department the last two years are described.

Case 1

An eight year old boy, the second child of healthy parents was admitted with a history of back pain of a month duration. The X-rays and CT scan revealed collapsed body of 5th lumbar vertebra and lytic lesions in the skull. The physical examination and the laboratory tests did not show other organs to be affected. The diagnosis was established by biopsy of lytic lesion of the skull which revealed, infiltration comprising a mixed population of lymphocytes, occasional eosinophils and large pale cells with a central folded nucleus. Occasional multinucleate cells were present. Immunostaining showed these cells to be S-100, "peanut" agglutinin and CD1 antigen positive. Simple observation and analgesic drugs were the only treatment and at the present time, two years after diagnosis, the patient is in complete remission.

Case 2

An eight month old boy, who was born to healthy unrelated parents, was admitted with symptoms of chronic otitis media, persisting diaper rash and seborrhoeic dermatitis of the skull not responding to multiple local treatment.

The clinical examination revealed hepatosplenomegaly and the laboratory tests liver dysfunction

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and pancytopenia. X-rays showed diffuse mottling of both lungs fields and infiltration of mastoid. Diagnosis was confirmed by biopsy of skin lesion which showed infiltration of histiocytes S-100 protein and CD1 antigen positive. Despite aggressive chemotherapy with methylprednisolone, Vinblastine and Etoposide, the patient succumbed to the disease three months later.

Case 3

An 8 month old male was admitted with persisting diaper rash and reddish brown maculopapular, vesicular rash of the trunk, extremities and the skull, of six months' duration with exacerbations and remissions. The diagnosis was established by biopsy of the skin lesions (Figure 1) which showed infiltration of histiocytes S-100 protein and CD1 antigen positive. There was no anaemia, lymphadenopathy or hepatosplenomegaly and his nutrition was excellent. The bone marrow aspiration showed the presence of 8 % histiocytes. The X-rays did not reveal bone lesions, and the laboratory tests no organs' dysfunction. The patient was treated with methylprednisolone 30 mg/kg for 3 days, following by weekly Vinblastine 6 mg/kg for 24 weeks, according to the LCH I treatment protocol of Histiocyte Society, but also with local application of Nitrogen mustard on the skin lesions. The patient is in remission 15 months after completion of the treatment protocol.

Case 4

This case concerns a 3 year old girl with a history of claudication of the left leg, painless nodules over the head and acute torticollis. X-rays revealed lytic lesions of the skull (Figure 2) and collapse of 8th thoracic vertebra. The diagnosis was confirmed by biopsy of bone lesion which showed infiltration of Langerhans histiocytes on light microscopy and demonstration of CD1 positivity and S-100 protein immunohistochemically. The bone marrow aspiration did not reveal infiltration of the bone marrow. There was no anaemia, lymphadenopathy, hepatosplenomegaly or organs' dysfunction. This patient was also treated according to the LCH I protocol, Arm A, with methylprednisolone and Vinblastine for 24 weeks. During therapy, the number and the size of the skull lesions decreased, but two new soft tissue masses of the skull appeared and later dissappeared. Three months after the treatment protocol was completed, the clinical examination revealed a soft tissue mass of the left jaw and X-rays and MRI showed a lesion of the mandible.

Case 5

The fifth case concerns a female infant born to healthy unrelated parents with necrotic lesions and nodules in the skin. The diagnosis of LCH was made by skin biopsy which showed diffuse infiltration of histiocytes with large pale cytoplasm and central folded nucleus. The demonstration of both CD1 antigen and S-100 protein was positive. There

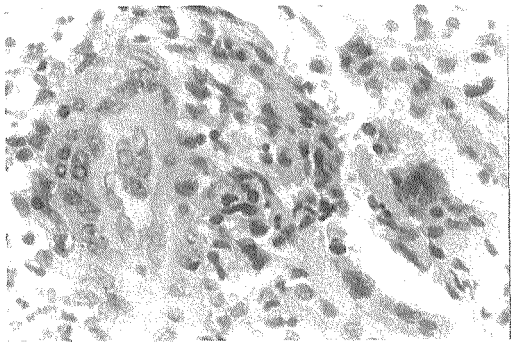

Figure 1. Diffuse proliferation of Langerhans cells in a skin biopsy (Hematoxylin-Eosin x 400).

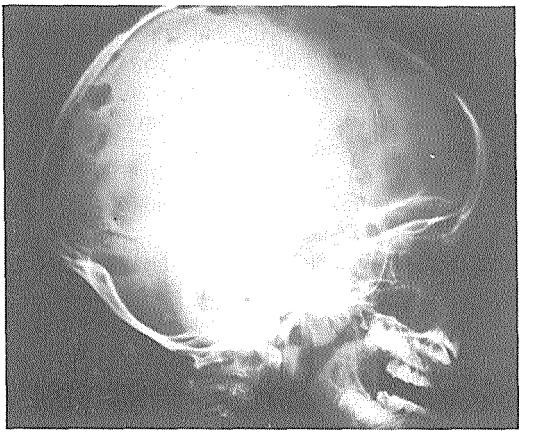

Figure 2. Bone lesions of the skull.

was no anaemia, lymphadenopathy or splenomegaly but the liver was palpable 2 cm. Liver function was normal but the LDH = 350U/l. Skeletal survey showed no lytic lesions but chest X-rays and MRI revealed diffuse mottling (Figure 3) of both lung

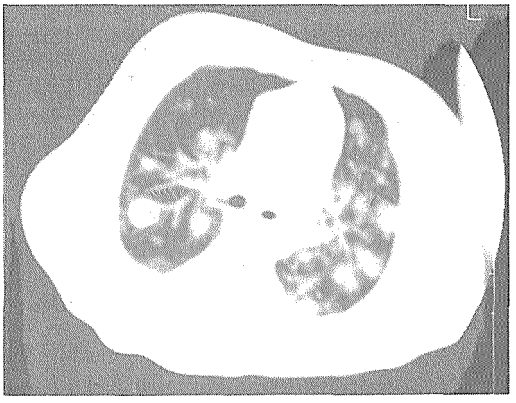

Figure 3. Multiple pulmonary nodules of both lungs fields on chest MRI.

fields. Bone marrow aspiration showed the presence of histiocytes ≥ 6 %. The baby was decided to be treated with prednisolone 1 mg/kg and she responded well with increase of her body weight.

Discussion

Langerhans cell hystiocytosis, previously known as histiocytosis X, is a reactive proliferative disease, characterized by the accumulation of abnormal histiocytes that form infiltrates typical for the disease. The etiology of LCH is unknown and the pathogenesis is not exactly understood.[3-4] For decades the disease has been widely accepted to be a reactive immunologic process rather than a malignancy.[5-7] Recent laboratory studies have demonstrated that the cells in all forms of LCH are clonal exprasions of Langerhans cells or their precursors in the bone marrow and other organs.[8, 9] However clonality does not necessarily indicate a malignant process.[10] LCH includes a wide range of clinical presentations which reflect different facets of the disease. The course of the disease is unpredictable. Patients with localized disease, in general have a good prognosis.[11] Bone is the most common organ affected. Three of the five reported cases here, had bone lesions from skeletal survey while two of them (1st, 4th) had no other organ or affected systems. The first case, a 8 year old boy with collapse of the 5th lumbar vertebra and lytic lesions in the skull, did not receive any treatment except analgesic drugs and simple observationl. The patient is in complete remission two years following inital diagnosis. In older children "single system" disease, usually affecting bones, is a common presentation and may spontaneously regress or require minimal treatment.[12]

Two of the patients described in this report were affected with multisystem disease, and one of them had also organs' dysfunction. This patient, despite aggressive chemotherapy, succumbed to the disease. The other infant has been treated with prednisolone for two months now and is responding well. In very young babies, the most common presentation is that of multisystem disease[13-15] with sometimes organ failure also. Skin rash is particularly common in infants and it is difficult to dinstinguish it from seborrhoeic eczema.[16, 17] The 8 month old male was presented with diaper and vesicular rash with remissions and exacerbations of 3 month duration without other affected organs, except for the presence of 8 % histiocytes in the bone marrow. This patient is in complete remission 15 months following the completion of treatment protocol.[15, 18] His inital presentation points out that persisting diaper rash should be investigated for LCH. The difficulty in diagnosing LCH is more often the result of a failure to consider the diagnosis, rather than a failure to distinguish it from other diseases.

The fourth patient who had multiple bone lesions and soft tissue masses in the skull relapsed three months after the completion of the treatment protocol. Since the patient is in an excellent condition, she remains under observation before any other treatment is decided upon.

In all cases the diagnosis was based upon histological features from the biopsy of the lesion and was confirmed by the typical characteristics of LCH on light microscopy, as well as the additional demonstration of CD1 antigen positivity and S-100 protein immunohistochemically. LCH cells and normal Langerhans cells (LCs) constituvely express a number of phenotypic markers. Most important are class II MCH molecules and CD1a complex. A number of markers are used to identify LCs in tissue specimens but detection of CD1a glycoprotein and identification of Birbeck granules are the two most specific tests. The Birbeck granule can only be identified directly at the ultrastructural level. Surface ATPase is useful in frozen tissue and S-100 in paraffin embedded tissue but neither is specific for LC. Expression of CD1a has been identified by the

Writing Group of the Histiocyte Society (1987) as a feature which establishes a definitive diagnosis in LCH. Three markers, placental alkaline phosphatase (PLAP), peanut agglutinin (PNA) and the interferon gamma receptor, are especially valuable in differentiating normal Langerhans Cells from LCH cells. The Histiocyte Society have also established "confidence levels" for the diagnosis of LCH.[1] Presumptive diagnosis is permitted when examination of conventionally-processed tissue reveals lesions consistent with those defined in the literature. A higher level of diagnostic confidence, referred to as "diagnosis", is justified when these findings are supplemented by the presence of at least two of the following positive stains: S-100 protein, ATPase, a-D-mannosidase or peanut lectin binding. "Definitive diagnosis" requires the demonstration either of Birbeck granules in lesional cells by electron microscopy, or of CD1 a antigenic determinants on the surface of lesional cells.

The outlook for patients with single system disease is excellent with minimal long term sequelae so long as treatment is conservative.[8] For very young infants with bone marrow failure and/or liver dysfunction, mortality of 30–50 % regardless of treatment is reported[11, 12, 14] and this bad prognosis occurred in the 2nd patient, who had organ dysfunction. Most patients have multisystem disease without organ dysfunction and 50 % suffer long term sequelae including small stature, growth hormone deficiency, diabetes insipidus, partial deafness, cerebellar ataxia, loss of dentition, orthopaedic problems, pulmonary fibrosis and biliary cirrhosis.[11, 16, 17, 19]

Although complications of some types of therapies are now well known, the safest and most effective treatment for LCH has not yet been established. The risk: benefit ratio of using chemotherapy and/or radiotherapy, and the manner of their use, need to be weighed carefully.

The continuously changing aspects of the etiology of the disease, the heterogenicity of clinical presentation and the phasma of treatment modalities make LCH a continuous challenge not only to the clinician but also to the scientists.

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