Langerhans' cell histiocytosis: case reports and literature review

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Langerhans' cell histiocytosis (LCH), formerly known as histiocytosis X, is one of a group of poorly understood diseases of histiocytes. The clinical spectrum of disease ranges from the chronic, localized form to an acute leukemia-like disease with a fatal outcome. Alfred Hand was the first to report a case of histiocytosis in 1893.[1] Later, in 1941, Farber described this condition when reporting the overlap among diseases that would later be termed histiocytosis X.[2,3] Since that time, numerous case reports have appeared in the dental literature, each having a diverse focus and using inconsistent terminology. The purpose of this review article is to enhance the understanding of LCH and to report two cases of very young children demonstrating skull and jaw lesions.

LCH previously has been considered a reactive polyclonal disease of immune regulation and not a true neoplasm. More recent evidence, however, has demonstrated clonal proliferation, a key neoplastic feature.[4-6] LCH afflicts young children primarily, some adolescents, and a few young adults. The classic presentation involves lytic lesions of bone, particularly of the skull.[7] The pathophysiology of LCH involves histiocytes — cells derived from monocytes of the granulocyte/macrophage series after extravascular diapedesis. Histiocytes function either as antigen-processing cells, phagocytic cells, or as antigen-presenting cells.[8] Langerhans' cells are specialized histiocytes with immune functions similar to other dendritic cells and macrophages. Langerhans' cells function immunologically by presenting antigen to T lymphocytes.[9,10] In LCH, these cells undergo pathologic change and appear histologically within an inflammatory background with a varied microscopic appearance that necessitates additional analysis in order to establish a diagnosis.[11,12] The number of Langerhans' cells may be scarce and mixed with macrophages, lymphocytes, eosinophils, giant cells, neutrophils and plasma cells when viewed under light microscopy.[13] Pathologic Langerhans' cells are characterized by the presence of antigenic surface markers that react with a specific monoclonal antibody and by the histologic presence of Langerhans' granules (also called Birbeck's granules).[14] Birbeck's granules are rod-shaped ultrastructural organelles that may have a vesicular portion giving it a so called "tennis racquet" appearance under electron microscopy.[14-16] The presence of Birbeck's granules is pathognomonic of LCH.[8,17]

Although the etiology of LCH has not been established, several theories exist regarding this disease. Pathologic Langerhans' cells are thought to be derived from precursor cells or through alteration of normal histiocytes.[16,18] The mechanism by which this proliferation and accumulation takes place remains unknown. Viruses have been implicated as inciting agents in LCH but their involvement remains theoretical.[8,16] Considerable effort has been made to assess the role of the immune system in the etiology of LCH. The bulk of evidence for this theory relates to abnormal thymic biopsies of patients with LCH, particularly those with multisystem involvement. Findings such as thymus involvement and macrophage activation in the childhood histiocytoses seem to support an immune system etiology.[16,19,20] However, the fact that there seems to be no histologic difference between patients with localized disease and those with multisystem involvement has prompted some to suggest that the above findings may be secondary occurrences in the disease process.[11] Newer x-linked polymorphic DNA probes have demonstrated that LCH is a highly variable monoclonal neoplastic disorder whose specific etiology remains unestablished.[6]

Classification

The term histiocytosis X was a generic term developed as a result of similarities in the pathophysiology among the diseases of histiocytes as well as the shared clinical and histologic features.[3,22] Letterer-Siwe syndrome was an earlier term used to describe an acute disseminated multisystem disease process of the reticuloendothelial system that typically affected children younger than 3 years of age. Hand-Schüller-Christian syndrome was used to describe an intermediate,

chronic, disseminated form of the disease that generally affected children older than 3. The classic triad associated with Hand-Schüller-Christian disease, which often did not occur together, included exophthalmos, diabetes insipidus, and multiple bone lesions of the skull, the second two largely due to sella turcica involvement. The mildest form of diseases of histiocytes was termed eosinophilic granuloma and presented as solitary bony lesions of the ribs, pelvis, or mandible and usually afflicted older children and young adults. Hashimoto-Pritzker syndrome is yet another term that was used to describe a congenital form of the disease that presented with deep subcutaneous skin lesions.[11, 16] Numerous other terms also were utilized to describe diseases of histiocytes, which often confused the diagnosis. By 1987, it was widely established that the Langerhans' cell was pathognomonic of diseases of histiocytes and that classification should now be determined on the cellular basis of the disease.[21] The International Histiocyte Society in 1987 established a classification of histiocytoses into three groups as follows:

I. Langerhans' cell histiocytosis

II. Histiocytoses of mononuclear phagocytes other than Langerhans' cells

III. Malignant histiocytic disorders.[11, 17, 21]

Even though this classification does not reflect recent neoplastic evidence, it is universally accepted. The vast majority (99%) of patients are diagnosed with the type I or II variety.[23] The diagnostic criteria for a definitive diagnosis for type I (LCH) is the presence of Birbeck's granules and is utilized by the International Histiocyte Society for establishing a positive diagnosis of LCH.[17] A more recent method for LCH diagnosis is the positive immunostaining for S100 protein and the CD1a antigen.[8, 13, 20] This review will focus on the type I variety, LCH.

Clinical presentation

Approximately 200 new cases of LCH are diagnosed each year in the US.[11] Children from 1 to 15 years of age are the most commonly afflicted. The peak incidence is from 2 to 4 years of age, and a predilection for black patients has been reported.[11, 24] Pathologic Langerhans' cells infiltrate various organs such as bone, skin, liver, spleen, lung, and brain and may result in a variety of clinical signs and symptoms depending on the degree of individual organ infiltration and functional compromise. The clinical course of LCH varies considerably depending on the extent and number of organs involved as well as the age of the patient at the time of diagnosis. Bones of the skull, particularly orbital and temporal bones, the sella turcica, and mandible, as well as the ribs and pelvis are commonly involved.[7, 22] The relative frequency of organ system involvement is as follows: bone, 80%; skin, 60%; liver, spleen, lymph nodes, 33%; lungs, 25%; orbit, 25%; and maxillofacial, 20%.[8] Initial physical findings often include skin rash, otitis media, fever, organomegaly, anemia, and diabetes insipidus.[11, 22, 25] Pituitary and pulmonary involvement also is common, particularly in males.[20] The differential diagnosis relates to the particular organ system involved and includes some of the following conditions: juvenile xanthogranuloma, chronic osteomyelitis, interstitial pneumonia, sclerosing cholangitis, dermatopathic lymphadenopathy, odontogenic cysts, and periodontal disease.[11, 22]

Oral involvement is a frequent finding. Ten to twenty percent of initial symptoms are nonspecific oral findings that include: gingival enlargement, oral ulceration, mobility of teeth with alveolar expansion, jaw pain, facial swelling, as well as the classic intraosseous lesions and scooped out radiolucencies of the alveolar process.[8, 22, 26, 28] Children with multiple organ and bone lesions commonly have mandibular involvement with destructive radiolucencies, alveolar bone loss, and teeth that appear to be "floating in air".[22] Mandibular lesions are commonly associated with maxillary involvement, but rarely is maxillary disease seen without mandibular radioluciencies.[28]

Dental considerations

LCH is included in the differential diagnosis for children presenting with advanced periodontal disease and/or bone loss in the primary dentition. As mentioned, oral involvement is common in LCH and may be the initial chief complaint. Other entities with similar presentations may include: prepubertal periodontitis, leukemia, neutropenia, hypophosphatasia, fibrous dysplasia, and Papillon-Lefèvre syndrome. Prepubertal periodontitis is associated with the microorganism *Actinobacillus actinomycetemcomitans* (Aa) and may result in mobility and tooth loss by age 3. Differentiation from LCH is based on the limited gingival inflammation with marginal bone loss and demonstration of Aa from subgingival culture.[29] Acute myelogenous leukemia (AML) may present with gingival hypertrophy and appear as LCH. AML accounts for 15% of childhood leukemia and is distinguished from LCH by systemic symptoms that generally lead to confirmation of leukemia through bone marrow aspiration.[30] Various neutropenic disorders also may result in significant gingival inflammation and alveolar bone loss. Reduced neutrophil counts may be the result of bone marrow production defects or neutrophil destruction and generally are associated with systemic findings such as splenomegaly and infection. Distinction from LCH is based on laboratory data.[31] Hypophosphatasia is characterized by low serum alkaline phosphatase levels and excessive excretion of phosphoethanolamine in the urine. The classic oral findings differ from LCH in that premature tooth loss generally involves the mandibular primary incisors, which often have abnormally large pulp spaces.[32] Fibrous dysplasia is a progressive expansile non-neoplastic bone lesion that may result in primary tooth loss. Cheek swelling produces the so-called "eyes-raised-to-heaven" or cherub look that distinguishes this condition from

LCH.[33] Papillon-Lefèvre syndrome is associated with marked destruction of alveolar bone with premature primary tooth loss. This condition is differentiated from LCH by the associated hyperkeratosis of the palms and soles.[34] This brief list includes conditions commonly included in the differential diagnosis for patients with destructive periodontal disease and tooth loss in the primary dentition.

The long-term dentofacial development of patients treated for LCH has not been reported. Sequelae for patients with childhood leukemia are known and correlate to LCH patients undergoing similar treatment protocols. Chemoradiation's influences on craniofacial growth and dental development are age related and most significant for children younger than 5 years of age.[35] The incidence of salivary gland dysfunction, enamel dysplasias, tooth/root agenesis, and alteration of mandibular growth is greater in patients receiving combined radiation and chemotherapy.[36, 37] The long-term dental management of LCH patients begins with a review of the specific disease, location, and the therapeutic protocol the child received. Displaced teeth and/or developing follicles with altered eruption patterns are common for children with a history of oral involvement.[28] Parents should be aware of the possibility of localized enamel defects, agenesis of roots and/or crowns, altered dentoalveolar growth, as well as orthopedic sequelae for those having undergone craniofacial radiation therapy.

Medical management and prognosis of LCH

Prognostic indicators for LCH include: 1) age — children less than 2 years generally have disseminated disease and a poorer prognosis; 2) number of sites involved — multisystem disease carries a poorer prognosis; and 3) organ dysfunction, which, if present, also results in a diminished outlook.[11, 38] Liver dysfunction at the time of diagnosis (indicated by hypoproteinemia or hyperbilirubinemia) as well as hemopoietic system involvement (indicated by thrombocytopenia, neutropenia, and anemia) both are associated with a poorer outlook.[24, 39] The prognosis is particularly grave for children younger than 2 years old who present with multiple organ involvement and associated dysfunction.[40] Mortality rates for this group exceed 60%.[6, 41] Second tumors such as leukemia or thyroid carcinoma are potential complications for long-term suvivors.[42] Older children with multisystem disease at presentation also demonstrate considerable morbidity. Many develop chronic problems such as liver dysfunction, diabetes insipidus, chronic otitis, and learning disabilities that stem from the various treatment modalities.[11, 24]

The heterogeneity of disease in patients with LCH has made development of specific treatment protocols difficult. Often the particular therapeutic approach has little influence on the prognosis for infants presenting with disseminated disease, who have a relatively poor prognosis, or those presenting with the mild form of LCH, who have an excellent prognosis.[8] Treatment of single system disease is generally benign and may include observation for spontaneous regression, radiation, surgical curettage, or intralesional infiltration with steroids.[41]

Protocols for young children with disseminated disease are similar to those for childhood leukemia and employ chemotherapeutic agents such as vinblastine sulfate, vincristine sulfate, prednisone, methotrexate, cyclophosphamide, and 6-mercaptopurine.[8, 24, 41, 43] The use of cyclosporine is also thought to be effective in combination therapy for children with milder forms of LCH.[8] Although no chemotherapeutic regimen has been demonstrated as superior, evidence suggests that etoposide, which is known to be effective for malignancies of monocyte/macrophage origin, maybe useful in patients with vital organ involvement or those not responding to more conservative treatment.[8, 41, 43, 44]

These newer combination therapies are being recommended for front-line therapy only for the severe multisystem form of LCH. Significant morbidity, such as second tumor development, may be associated with aggressive therapy and should be reserved for patients with a poor prognosis and those with disease progression while undergoing conservative therapy.[41, 43]

Young patients with disseminated LCH are at increased risk for disease progression because of the concern over radiation effects and reluctance to employ this treatment modality in the younger age groups.[41] Radiation therapy in children younger than 6 years of age has been associated with altered growth, adverse intellectual effects, and arrested dental development as well as second tumor development.[22] Radiation treatment of 600–1500 cG in 200-cG daily fractions is highly effective in children beyond the age of such concerns or in solitary lesions in very critical areas, such as sella turcica.[22, 45]

Case reports

Case 1

A 15-month-old Hispanic female presented to Medical Center Hospital emergency room in May of 1993 with chief complaints of diarrhea, diminished appetite, and refusal to walk because of ankle swelling. Clinical examination revealed significant hepatosplenomegaly. The recent medical history consisted of anemia and recurrent otitis media. After medical evaluation, a provisional diagnosis of malignant histiocytosis was made. This diagnosis was based largely on results of liver biopsy and bone marrow aspiration. Lab values were as follows: WBC 8,000/mm^3, Hb 8.2 g/dL, MCV 89.4 μg/dL, and platelets 145,000/mm^3. The fact that Birbeck's granules had not been identified from the initial liver biopsy, although not unusual, led to the provisional malignant histiocytosis diagnosis. The child was placed on a regimen consisting of methylprednisolone (10 kg/day) and vinblastine (0.1 mg/kg at weekly intervals). She was transferred to Santa Rosa Children's Hospital.

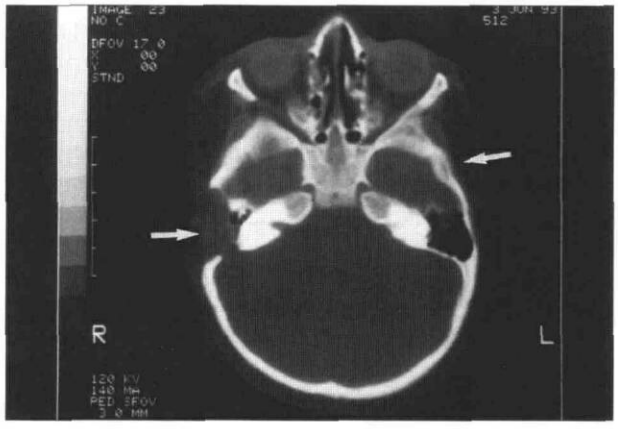


Fig 1. CT scan of 16-month-old female that demonstrates right temporal bone involvement as well as expansion of the left alveolus surrounding the maxillary left primary first molar.

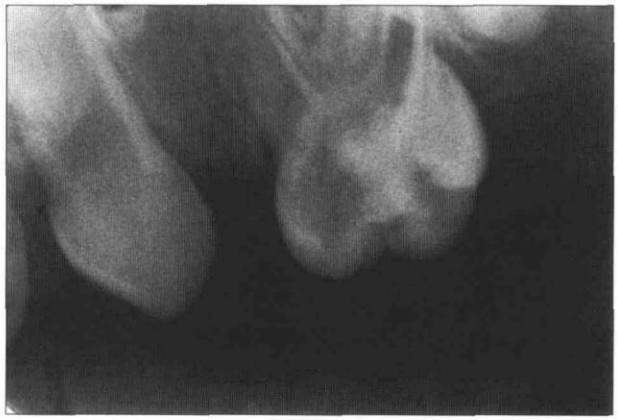
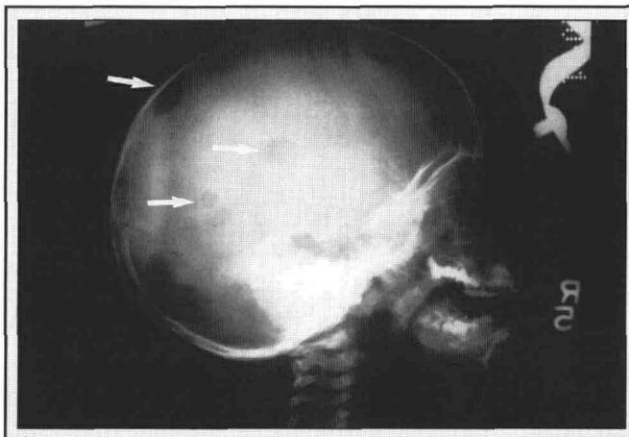


Fig 2. Periapical radiograph of this 27-month-old's maxillary left primary second molar indicates abnormal pulpal architecture and root anatomy.

Dental examination revealed a soft tissue lesion in the maxillary left primary first molar area that seemed to surround the erupting first molar crown. A gingival biopsy was obtained and the involved tooth was extracted. Electron microscopy revealed Birbeck's granules from histiocytic cells of the oral lesion. Based on this information it was later determined that Birbeck's granules also were present on a few sections of the original liver biopsy. CT scan of the skull confirmed the maxillary left posterior alveolar defect as well as involvement of the petrous portion of the right temporal bone (Fig 1). From these results, the diagnosis was changed to the LCH form of histiocytosis, which was important because it has a significantly different prognosis than that of malignant histiocytosis. The child was continued on oral prednisone and vinblastine and rapid improvement of the organomegaly was observed. Radiation was given to the petrous bone using a linear accelerator.

At age 2.3 years — 12 months after the initial diagnosis — further intraoral pathology was noted. The maxillary disease resulted in alveolar bone destruction with malformation of the maxillary left primary second molar as demonstrated on the periapical radiograph



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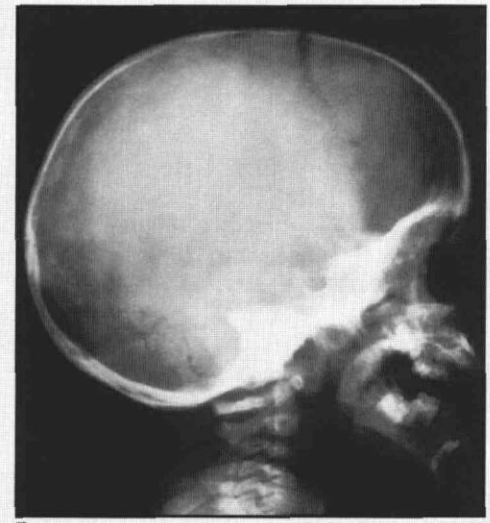

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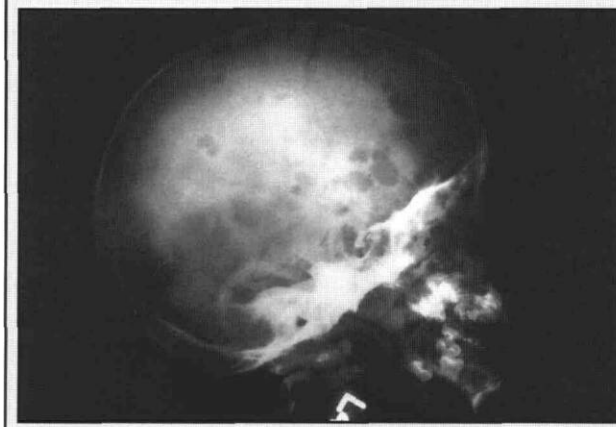

C

Fig 3. This lateral radiograph (A) demonstrates relapse of LCH in a 17-month-old male. Classic multiple radiolucent lesions of the skull are noted. Chemotherapy was resumed and the patient followed with radiographic resolution noted at age 3.1 years (B). The patient again relapsed with significant radiographic changes (C) diagnosed just 4 months after the previous film, age 3.5 years.

(Fig 2). The maxillary left primary second molar extraction was accomplished during conscious sedation using midazolam and local anesthesia. Three months later, it became apparent radiographically and by physical examination that the lesion in the petrous portion of the temporal bone had not resolved and indeed seemed active. An excisional biopsy and mastoidectomy revealed significant necrosis and residual disease. After healing, radiation with an additional 1000 cG was administered to the petrous bone. The patient has been asymptomatic since that time (15 months). Maintenance therapy with dexamethasone and vinblastine is anticipated to continue until radiographic resolution of the cranial lesions has occurred.

Case 2

A 2-month-old male was referred to Santa Rosa Children's Hospital in September 1990 by his pediatrician because of fever, anemia, and splenomegaly. The family history revealed a maternal cousin had died of "histiocytosis X" in childhood. Physical examination identified multiple small, flaky skin and scalp lesions. The abdomen was enlarged with no lymphadenopathy noted. Lab values were as follows: WBC 10,600/mm^3, Hb 9.1 g/dL, MCV 77 µg/dL, and platelets 137,000/mm^3. A diagnosis of Langerhans' cell histiocytosis was made based on skin biopsy of the abdomen and needle biopsy of the liver, both suggestive of LCH. No osteolytic lesions were seen on a skeletal survey. Therapy was begun with six courses of intravenous etoposide and methylprednisolone and continued for 12 months. In December 1991, 3 months after discontinuation of therapy, the child presented with fever, otitis and skin rash. A skeletal survey demonstrated multiple lytic lesion of the frontal and parietal bones (Fig 3A). Weekly chemotherapy was resumed using intravenous vinblastine and was continued until September of 1993. The patient was followed with resolution noted radiographically (Fig 3B).

In January 1994 the patient again relapsed and impressive lytic lesions were evident radiographically (Fig 3C). These as well as rib lesions were not present 4 months earlier. The panoramic radiograph of this now 3.6-year-old child demonstrates the multiple mandibular lesions associated with LCH (Fig 4). Intravenous chemotherapy with vinblastine was reinstituted along with cranial radiation 800cG to the base of the skull. The tumor board's decision was to avoid mandibular radiation. The concern related to diminished intellectual development and the adverse growth effects to the maxilla and mandible associated with cranial radiation in children of this age.

Radiographic surveys in December 1994 revealed a marked improvement of the lytic lesions of the skull and mandible compared with those taken at the time of relapse in early 1994. Despite the major mandibular involvement, no periodontal involvement, mobility of teeth, alveolar expansion, jaw pain or facial swelling were found during the periodic dental evaluations from January 1994 to the time of this report. The patient continues on maintenance chemotherapy with vinblastine awaiting radiographic resolution of the cranial lesions. He is currently in remission, 5.4 years after the initial diagnosis, but with a guarded long-term prognosis.

The presence of destructive periodontal disease and/or tooth loss during the primary dentition should alert the practitioner to the possibility of serious systemic disease. LCH is included in the differential diagnosis of such a condition, which may be the patients' initial chief complaint. The diagnosis for LCH may be confirmed through immunofluorscence for the S100 protein (Fig 5). Sufficient gingival biopsy material, with or without tooth extraction, should be obtained for that purpose. The two cases presented both had oral involvement but a quite different presentation at the time of diagnosis. The first case involved maxillary involvement without mandibular association, which is rare. In the second case, the impressive mandibular radiolucencies were evident, yet the intraoral soft tissues were unremarkable with no apparent dental involvement.

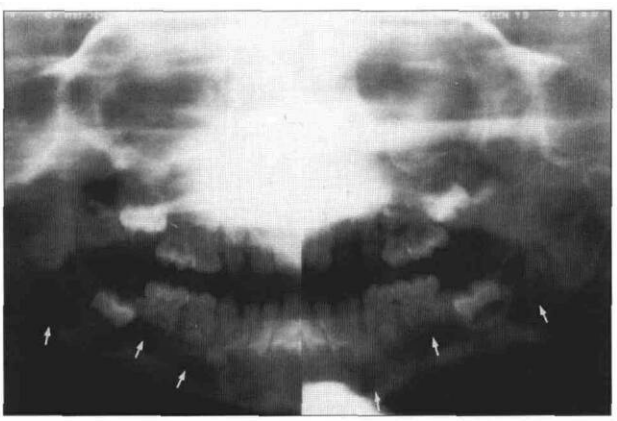

Fig 4. Panoramic radiograph of the patient at 3.6 years of age depicts mandibular involvement often associated with LCH. The numerous lytic lesions are apparent.

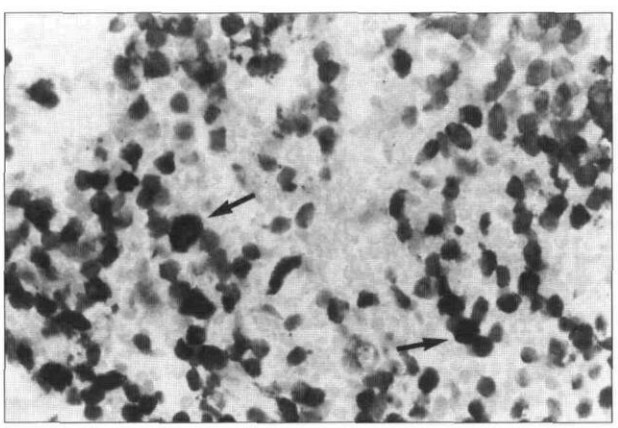

Fig 5. This gingival biopsy exemplifies the immunohistochemical staining of LCH cells for S-100 protein (original magnification 25x). The reaction product is diagnostic of LCH since the cytoplasm of normal histiocytes does not stain in this manner.

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