Mandibular histiocytosis X and acute lymphoblastic leukemia

Herbert M. Kanter, D.D.S., Li-Min Lin, D.D.S., M.S.,** Robert A. Goepp, D.D.S., M.S., Ph.D.,*** and Roy E. Olson, D.D.S., M.S.,**** Chicago, Ill.*

ZOLLER DENTAL CLINIC, UNIVERSITY OF CHICAGO

The occurrence together of two major distinct diseases in the oral area is relatively rare. In this report, a case is presented in which histiocytosis X was found to develop in a child with acute lymphoblastic leukemia. The nature of the differentiated histiocytoses is explored, and the possibility of the relationship between a lymphoproliferative and a histiocytic disease entity is investigated.

A review of the literature reveals no previously reported cases of histiocytosis X occurring in a person with acute lymphocytic leukemia. However, one case of Letterer-Siwe disease terminating in acute monocytic leukemia has been reported by Cline and Golde.[1]

Letterer-Siwe disease, Hand-Schüller-Christian disease, and eosinophilic granuloma are a triad of diseases representing primarily disturbances of the reticuloendothelial system rather than disturbances of lipid metabolism. The microscopic appearances of these three entities, as well as their clinical manifestations, are so intimately related that most authorities consider them a single entity with varying clinical expressions. As such, the complex of disease states is often referred to as the nonlipid reticuloendothelioses.[2]

The cause of these lesions is generally considered to be enigmatic and related to an unknown etiologic agent, as reflected by the categorization of histiocytosis X. Early investigators of these lesions have postulated trauma[3] or infection of a viral origin as plausible causative agents.[4]

*Assistant Professor of Oral Surgery, also in the private practice of oral surgery in Chicago, Ill.

**Instructor of Oral Surgery.

***Associate Professor and Head, Section of Oral Pathology and Dental Radiology.

****Assistant Professor and Head, Section of Oral Surgery.

The basic histopathology of the lesions in all three disease states involves varying degrees of proliferation of nonreactive histiocytes. Cline and Golde,[1] in a review of the histiocytic disorders, have proposed a categorization of the nonreactive histiocytoses according to degree of cellular differentiation. On this basis, the Letterer-Siwe variant is considered a disease typified by moderate cellular differentiation, with the monocytic or immature macrophage the basic cell type. Hand-Schüller-Christian disease and eosinophilic granuloma are categorized by well-differentiated histiocytes, with immature and mature tissue macrophages representing the predominant cell structure.

Despite seemingly clear-cut differences in basic cell structure between the various histiocytosis X entities, overlapping of cellular types is common, and a clear-cut differentiation between the clinical disease states solely on the basis of histologic findings is often impossible.

Specifically, the lesions characteristic of the Hand-Schüller-Christian disease assume both an active and an inactive appearance, reflecting histopathologic as well as clinical differences in the disease state. In the active phase of the disease, there is a proliferation of histiocytes with scattered eosinophilic leukocytes. A vascular, granulomatous phase, characterized by lipid-laden macrophages leading to a diffuse xanthomatous phase characterized by so-called "foam cells," may be present until the final inactive phase is reached. This latter phase is characterized by a proliferation of densely fibrotic tissue and is seen when the disease becomes chronic.

The basic pathologic nature of the Letterer-Siwe disease appears similar to that of the Hand-Schüller-Christian complex, consisting primarily of a proliferation of somewhat less well-differentiated histiocytes or their precursors. Eosinophils may or may not be a feature. Generally, these histiocytes do not contain significant quantities of cholesterol, so that the so-called foam cells are not a feature of the disease; nor is fibrosis encountered as an end stage.

The histologic finding of the eosinophilic granuloma variant consists primarily of sheets of large, well-differentiated histiocytes. Interspersed among these may be mature granulocytes, chiefly eosinophils, in varying quantity. The histiocytes occasionally may coalesce to form multinucleated giant cells; however, no accumulation of intracellular lipids is generally detected. The finding of accumulations of eosinophils in the tissue specimen may be an important feature as a sign of the ultimate prognosis of the disease process. Oberman,[5] in a review of forty cases of histiocytosis X, was unable to document a single fatality among those cases in which the basic cell variants included a significant proliferation of eosinophilic leukocytes.

In interpreting the clinical spectrum of disease, it should be noted that a precise diagnosis on the basis of clinical and histopathologic findings is sometimes impossible. Prevailing opinions maintain that the Letterer-Siwe syndrome and Hand-Schüller-Christian disease may actually represent the acute and chronic variants of the same basic disease process. These observers also hold that, although the eosinophilic granuloma variant may remain localized to bone in adults, in children and young adults it may well represent only an early clinical manifestation of a progressive, systemic illness.[6]

The clinical appearance of Letterer-Siwe disease, or the so-called acute disseminated histiocytosis X, involves a rapidly progressive, often fatal disease, with involvement of the skin and viscera, generally occurring in infancy, prior to the age of 3. The clinical signs include a generalized skin rash suggestive of seborrheic dermatitis or eczema and prominent hepatosplenomegaly and lymphadenopathy. In addition, a hemorrhagic diathesis may be found.[1] Death, when it ensues, may be the result to recurrent infection and hemorrhage, the consequence of pancytopenia and thrombocytopenia, in turn secondary to extensive marrow replacement by the histiocytic proliferations.

The chronic disseminated form of histiocytosis X, or the Hand-Schüller-Christian variant, is generally demonstrated in children under the age of 10, although cases have been reported in adolescents and young adults. This disease is frequently characterized by a triad of symptom complexes—calvarial defects, diabetes insipidus, and exophthalmia—the latter two representing histiocytic infiltration of the posterior pituitary stalk or hypothalamus and retro-orbital tissue. However, the complete triad is perhaps seen in fewer than 10 per cent of the cases. Cline and Golde[1] found chronic otitis media with radiographic changes in the mastoid bone or petrous portion of the temporal bone to be the most common presenting finding in one series of cases subsequently documented as Hand-Schüller-Christian disease. Diabetes insipidus was seen in less than one half of these cases, and exophthalmia in less than one third. As with the acute disseminated form of the disease, an erythematous and scaling skin involvement is frequently encountered.

Lichstein[4] established the infiltration of histiocytes into the periportal areas of the liver, with fibrosis and intrahepatic biliary obstruction resulting in cirrhosis, in eight of seventeen cases of chronic disseminated histiocytosis X. In addition, pulmonary involvement, exclusive of the hilar lymph nodes, with resulting dyspnea and nonproductive cough, is also documented in this same study. Bony involvement may include infiltration of the femur, ribs, vertebrae, pelvis, humerus, and scapulae as well as the mandible.

Oral manifestations are variable, with nonspecific ulcerations, gingivitis, and periodontal suppuration encountered in 5 to 75 per cent of all cases.[2] Loss of supporting alveolar bone appearing like advanced periodontal disease and resulting in premature exfoliation of teeth is perhaps the most significant oral feature of the disease process.

The so-called eosinophilic granuloma of bone, of the monostotic or polyostotic variety, is most frequently encountered in older children and young adults. Bony tumescence and bone pain were the two most frequent presenting findings in a review of forty cases of histiocytosis X by Oberman.[5] The skull, ribs, femur, and pelvis were the most frequently encountered sites of bone involvement. Roentgenographically, the lesions appear as irregular radiolucencies which may produce cortical bone expansion. When present in the jaws, the lesions may result in loss of alveolar bone support for the dentition, creating the clinical description of "floating teeth."

Two patients in Oberman's group with eosinophilic granuloma demonstrated significant eosinophilia in a peripheral blood smear. Similarly, only six of forty

patients with histiocytosis X of any variant type demonstrated peripheral eosinophilia. Thus, the value of peripheral eosinophilia in a differential blood count is of questionable value in the diagnosis of eosinophilic granuloma.[5]

Systemic manifestations in the unifocal monostotic form of eosinophilic granuloma are rare. In the multifocal variant of eosinophilic granuloma there is often a clear overlap with the symptoms of Hand-Schüller-Christian disease. This leads to difficulty in separating these entites according to both histologic and clinical criteria.

Various modalities have been recommended for the treatment of these diseases. The likelihood of spontaneous remission of the bony lesions makes the assessment of these treatment modalities difficult. Early treatment forms have included radiation therapy and curettage of bony lesions. More recently, antifolic agents and vinca alkaloids have been advocated for the therapy of the acute and chronic disseminated forms.[7] Surgical curettage and low-dose radiation (850 to 1,000 rads) for inaccessible lesions have been advocated for the treatment of the monostotic and polyostotic lesions of eosinophilic granuloma.[8]

CASE REPORT

In March, 1974, F. W., a 3½-year-old Negro boy, was diagnosed by the Pediatric Hematology Service of the University of Chicago, as having acute lymphoblastic leukemia. The patient's past medical history to that date was unremarkable, and the current diagnosis was established on the basis of peripheral smear and bone marrow biopsy. Chemotherapy was instituted with a course of oral prednisone and vincristine sulfate over a 4-week period.

In April, 1974, CNS radiation, with a total dose of 2,400 rads, was undertaken in the usual fashion. Subsequent treatment consisted of intermittent doses of methotrexate, prednisone, and vincristine.

The patient remained stable until approximately July 27, 1974. At that time, the onset of pain and swelling of the left mandible, with elevated temperature (38 to 39° C.) of 3 days' duration, resulted in readmission to the Pediatric Hematology Service. Physical examination at that time revealed a temperature of 39° C., and a respiratory rate of 28 per minute. The cardiovascular and respiratory systems were assessed as being unremarkable. In addition, the abdominal examination was benign, with no hepatosplenomegaly observable.

Head and neck examination demonstrated a diffuse swelling of the left mandible, tender and firm in consistency, with palpable submandibular lymph nodes. An expansile mass was described as being present in the left mandibular buccal vestibule. No gingival hemorrhage, hyperplasia, or mucous membrane petechiae were detected. Laboratory data secured at this time revealed the following:

White blood count—5,060
Hemoglobin—12.1 per cent
Hematocrit—37 per cent
Reticulocytes—6.1 per cent
Differential:
Metamyelocytes, 1 per cent
Monocytes, 1 per cent
Lymphocytes, 18 per cent
Semented neutrophils, 53 per cent

A sternal bone marrow biopsy was interpreted as being consistent with partial remission of the leukemic process.

A skull radiograph demonstrated a "lytic lesion of the left mandible with periosteal

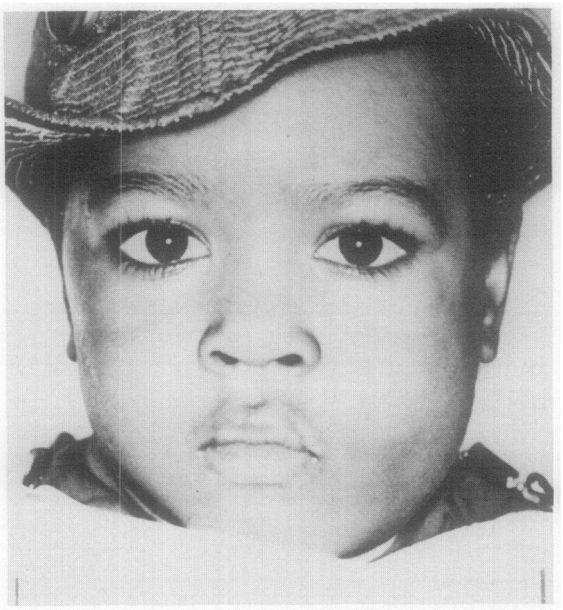


Fig. 1. Appearance of patient's face demonstrating marked facial asymmetry.

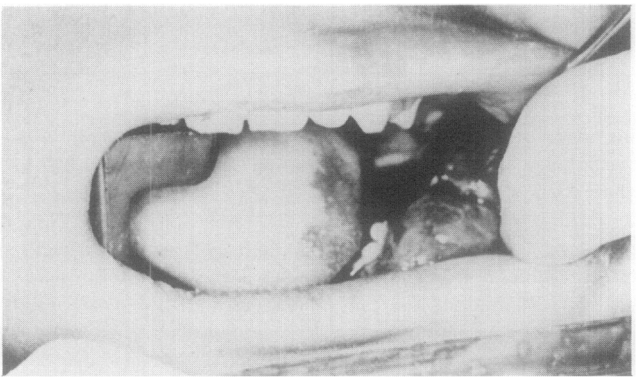


Fig. 2. Intraoral appearance of mass found arising from buccal surface of mandible.

reactivity." A bone scan on Aug. 9, 1974, to follow up the abnormal skull radiograph, demonstrated "abnormal uptake in the mandible with no other abnormal accumulation."

With this information, the patient was referred to the Oral Surgery Service on Aug. 14, 1974, for examination and evaluation. Examination of the head and neck confirmed the presence of a firm, diffuse, nonfluctuant, noncaloric mass occupying the left buccal, submasseteric, and submandibular spaces. This resulted in marked facial asymmetry (Fig. 1). There was no apparent submental or cervical extension of the lesion, and the patient was without respiratory compromise. Obvious cushingoid facies were noted to be present.

Oral inspection revealed a fungating mass of erythematous, friable, easily bleeding tissue, appearing somewhat gray and necrotic in the most central aspect, obliterating the left mandibular buccal sulcus. The lesion extended from approximately the retromolar trigone to the deciduous canine area (Fig. 2). The deciduous second molar tooth was present in

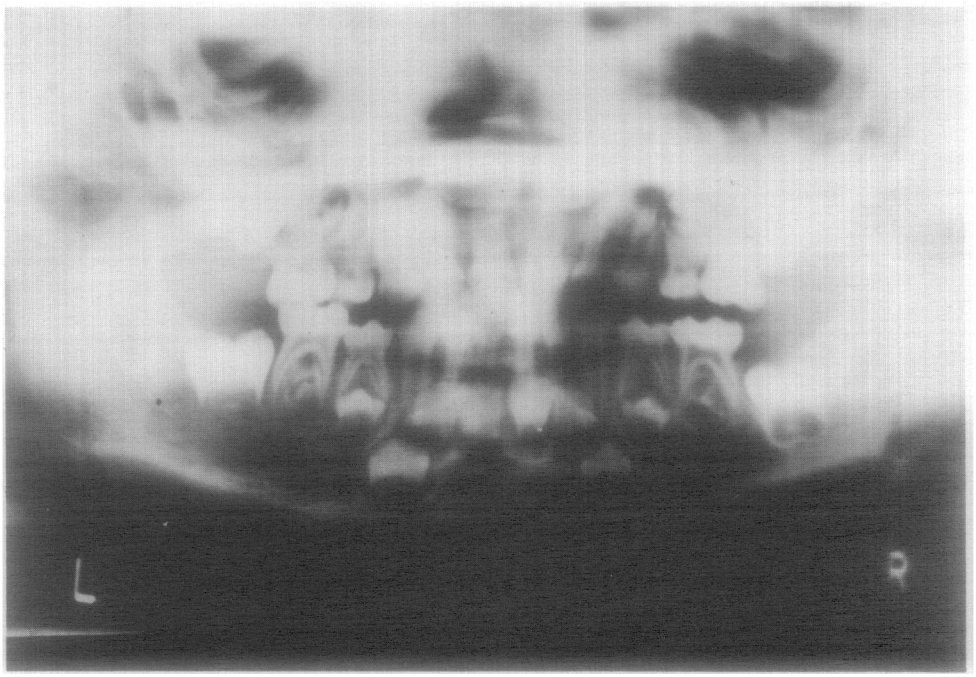


Fig. 3. Panoramic film revealing poorly circumscribed radiolucent lesion occupying the left mandible with displacement of the left second deciduous molar and first permanent molar tooth bud.

the center of this mass of tissue, and extreme mobility of the tooth was noted on digital palpation. The remainder of the oral examination was unremarkable and was otherwise consistent with the patient's age.

A panoramic radiograph was obtained at this time (Fig. 3). This demonstrated the presence of a 2 by 4 cm. poorly circumscribed, radiolucent lesion, without peripheral osteitis, occupying the left mandible and extending from the left angle of the mandible to the canine area. The permanent tooth bud of the mandibular left second molar tooth was seen to be displaced superiorly into the ascending ramus. The second deciduous molar tooth was extruded above its normal occlusogingival position.

On Aug. 15, 1974, following induction of nitrous oxide analgesia and injection of 2 c.c. 2 per cent lidocaine with epinephrine 1:100,000, several specimens of tissue were obtained from the bony and soft-tissue lesions of the left mandible. In addition, the mandibular left second deciduous molar, apparently free-floating in bone, was also removed. Following the biopsy procedure, hemostasis was achieved with 3-0 chromic sutures and gauze packs for pressure tamponade.

The histologic specimens demonstrated sheets of plump histiocytes, some with lipid-laden cytoplasm. No abnormal mitoses or lymphoblastic cells were identified. A few eosinophilic leukocytes were seen to be present as well (Fig. 4). A tentative diagnosis of histiocytosis X, consistent with the monostotic eosinophilic granuloma type, was established.

A bone marrow core taken on Aug. 13, 1974, revealed a relapse of the lymphoblastic leukemia. Reinduction therapy with vincristine sulfate and oral prednisone was again instituted. Three weeks following the initiation of therapy, the patient began to demonstrate signs of remission, as determined by the complete blood count, differential count, and bone marrow specimens. In addition, some clinical improvement of the mandibular mass was noted. The diffuse soft-tissue enlargement was diminished in size, and the intraoral

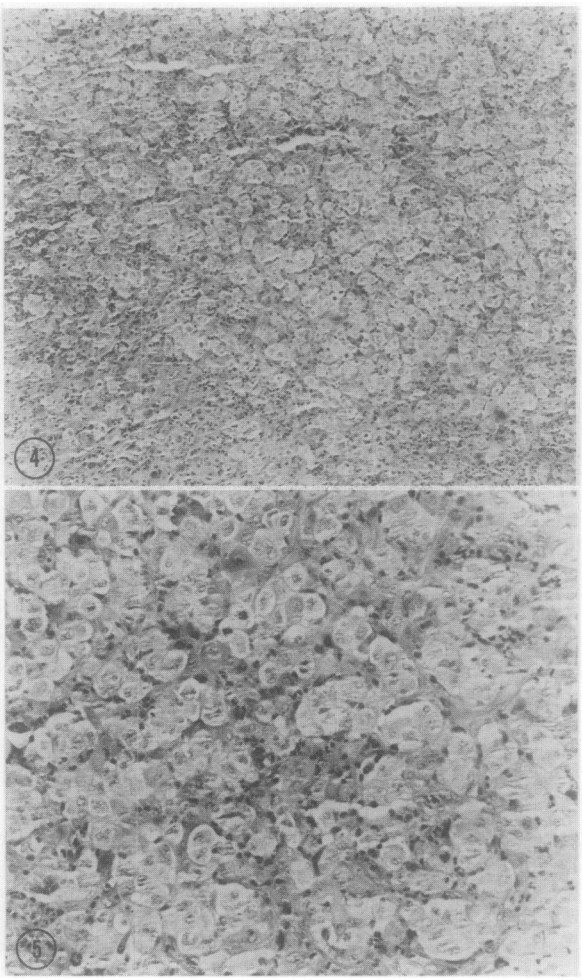


Fig. 4. Microscopic section demonstrating sheets of closely spaced histiocytes with foamy cytoplasm. Eosinophils are also seen in the specimen. (Magnification, ×100.)

Fig. 5. High-power view of specimen shown in Fig. 4. (Magnification, ×250.)

tissue gradually assumed a less necrotic appearance, although the obliteration of the vestibule persisted.

With the leukemic condition in partial remission, the patient was admitted to the Oral Surgery Service on Sept. 12, 1974, for definitive oral therapy. The blood was typed and cross matched, and the child was taken to the general operating room on Sept. 14, 1974. Curettage of the mandibular lesion with removal of the involved teeth was performed, leaving only a pencil-thin inferior border of the left mandible remaining. The buccal and lingual cortices of bone had been eroded in the area extending from the angle of the mandible to the left deciduous canine. A pathologic fracture in the area of the second deciduous molar tooth was observed, but no attempt at stabilization or immobilization of the fracture was undertaken. The surgical defect was packed with iodoform gauze impregnated with Neosporin ointment. No blood transfusions were given. The patient tolerated the procedure well and without complication. Discharge was arranged on the third postoperative day.

Microscopic examination of the tissue samples obtained again demonstrated proliferations

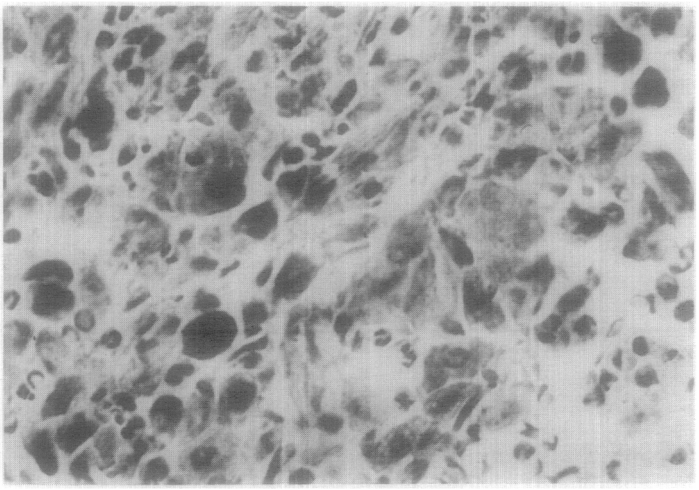


Fig. 6. A portion of the specimen containing an infiltrate of atypical cells with a mononuclear configuration. (Magnification, ×400.)

of histiocytes and associated leukocytic infiltrates. However, areas of tissue also demonstrated the presence of bizarre, atypical monocytes, with abnormal cytologic and nuclear configurations suggestive of a monocytic leukemic process (Fig. 6).

One month postoperatively, the patient functioned well, the mandible was stable, and the left facial appearance had gradually returned to normal. However, submandibular lymphadenopathy was persistent during this time, and a 2 cm. nodular mass persisted in the left buccal vestibule.

A skull radiograph obtained on Nov. 7, 1974, revealed a solitary lytic lesion, measuring 12 by 16 mm., in the right parietal area, with associated soft-tissue swelling. It was thought that this lesion most likely represented an area of histiocytosis X or a leukemic infiltrate.

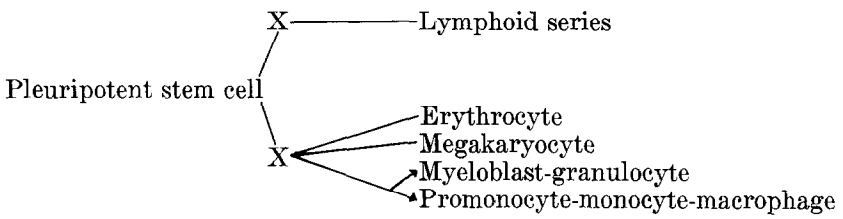
On Nov. 11, 1974, the patient was readmitted to the Pediatric Hematology Service because of the onset of nausea with vomiting for 24 hours and a persistent headache of 1 week's duration. The patient appeared pale and weak, with moderate eyelid edema, pretibial edema, and marked hepatomegaly. The impression at the time of admission was that of acute lymphocytic leukemia, in relapse, with possible involvement of the central nervous system. The plan of therapy was to reinduce remission of the leukemia with vincristine sulfate, prednisone, and intrathecal methotrexate. The hemoglobin value at this time was 4.5 grams, and therapy was to be directed at achieving a hemoglobin level of 10 grams with transfusions of packed cells.

A stormy hospital course ensued, characterized by multiple transfusions of washed packed cells and platelets, as the patient appeared to be hemolyzing in response to minor blood group incompatabilities. A bone marrow biopsy performed on Dec. 10, 1974, demonstrated the leukemic process to be in remission. However, large clumps and sheets of fat histiocytes were seen. These were thought to represent the onset of a process of disseminated histiocytosis X. In view of the apparent dissemination of this process, despite the use of prednisone, vincristine, and methotrexate, a course of Cytoxan therapy was instituted. This was begun because of its known antileukemic effects and in an effort to halt the spread of the histiocytosis.

Despite the institution of this rather aggressive therapy, the child died on Dec. 17, 1974, of cardiorespiratory failure. A problem list established just prior to death included diffuse histiocytosis X, acute lymphoblastic leukemia, hepatosplenomegaly, and pancytopenia with septicemia. At the request of the patient's mother, no autopsy was performed.

DISCUSSION

The question of a relationship between a lesion implying histiocytic proliferation and one representing a lymphoproliferative disorder may best be regarded by taking into account the pleuripotent stem cell theory. Stated simply, this theory maintains that a single pleuripotent cell divides into two main cell series, one of which gives rise to the lymphoid cell types, and the other of which produces the erythroid, megakaryocyte, myeloblastic, and monocytic series. This may be represented diagramatically as follows:



Further, one must recognize that the mature tissue histiocyte represents the terminus of a progression of cell types which begin as monoblasts or promonocytes in the bone marrow and has the peripheral, blood-borne monocyte as an intermediate cell type. Taken in this context, then, it might be plausible to explain the relationship of a reported case of Letterer-Siwe disease which terminated in acute monocytic leukemia, since the basic cell types involved would be merely variants of a single cell precursor. Perhaps a state of dedifferentiation or anaplasia is reflected by this cell transformation. However, the occurrence of acute lymphoblastic leukemia and histiocytosis X in a single patient, representing a lymphoproliferative disorder and a histiocytic disease, cannot be explained by this theory. In fact, the stem cell theory would seem to preclude any causal relationship between these entities on a cellular level.

An interesting feature of the histiocytosis X lesion presented here is the finding of atypical monocytes, suggestive of a monocytic leukemic infiltrate in the later biopsy sample. Perhaps this feature represents a stage of cellular dedifferentiation similar to that reported by Cline and Golde.[1]

In addition, the case described appeared to progress from a monostotic histiocytosis X to a disseminated histiocytosis, despite treatment with prednisone and vincristine sulfate, as has been advocated for the treatment of the histiocytosis X complex. This apparent dissemination also tends to support the contention by Rappaport and others that a monostotic histiocytosis X lesion in a child may be the only clinically and radiographically obvious manifestation of a potentially systemic, progressive disease process.[6]

SUMMARY

The first known case of histiocytosis X in a child with acute lymphoblastic leukemia is presented. The clinical significance of the relationship of these disease entities is equivocal. From a histologic standpoint, taking into consideration the pleuripotent stem cell theory, the relationship of these disease processes appears tenuous, at best.

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Reprint requests to:
Dr. Herbert M. Kanter
Assistant Professor of Oral Surgery
Zoller Dental Clinic
University of Chicago
950 East 59th St.
Chicago, Ill. 60637