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REVIEW ARTICLE

Langerhans cell histiocytosis

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Abstract Langerhans cell histiocytosis (LCH) is a complex disease entity comprised of three distinct clinical syndromes that demonstrate indistinguishable histology. These syndromes are: eosinophilic granuloma, which is predominantly osseous or pulmonary; Hand-Schûller-Christian's disease, which involves multiple organ systems and, most typically, the skull base; and Letterer-Siwe's disease, the most severe disease manifestation, which typically involves the abdominal viscera. This article reviews our current understanding of Langerhans cell histiocytosis by discussing the history, histology, etiology, and treatment of the disease. It focuses on the radiographic findings and imaging modalities that are the most useful in disease diagnosis and management.

Keywords Langerhans cell histiocytosis · Hand-Schûller-Christian's disease · Letterer-Siwe's disease · Eosinophilic granuloma · Radiography · MRI

Introduction

The clinical entity now known as Langerhans cell histiocytosis (LCH) has a long, confusing history, and the cause remains enigmatic [1, 2]. The first description was by Dr. Thomas Smith in 1865 [3]. He described a four-year-old child who died of whooping cough and was found at autopsy to have an erythematous skin disorder and several destructive lesions in his skull. In 1868, Paul Langerhans described a non-pigmentary dendritic cell in the epidermis, which he considered to be bone-marrow-derived and to represent the most peripheral output of the immune system [4]. There is now strong evidence that proliferation of these cells was not only the cause of Dr. Smith's patient's disorder, but was also one of a series of three entities subsequently known as Langerhans cell histiocytosis [1, 2].

In 1893, Alfred Hand, a physician in Philadelphia, described a three-year-old child with exophthalmos, polyuria, and great thirst [5]. Although Hand's initial impression was that the child had tuberculosis, he corrected that impression in 1921 [6] after Artur Schûller in 1915 described two children with similar findings who had no evidence of tuberculosis [7]. In 1920, Dr. Henry A. Christian described a five-year-old child with changes known as "Christian's triad," which consisted of calvarial lesions, diabetes insipidus, and exopthalmos [8]. This complex syndrome, which includes visceromegaly and skin lesions, is now known as Hand-Schûller-Christian's disease.

In 1924, Erich Letterer described an acute non-leukemic fatal disorder of the reticuloendothelial system in a six-month-old child [9]. Nine years later, Sture Siwe described

a similar case of a very young child with splenomegaly, hepatomegaly, lymphadenopathy, bone tumors, hemorrhaging, and generalized histocytic hyperplasia [10]. In 1936, Arthur Abt and Edward Denenholz reported another patient with similar findings, but, after reviewing the prior literature, decided that it was appropriate to name the disease Letterer-Siwe's disease [11].

Drs. Sadao Otani and Joseph Ehrlich from Mount Sinai and Lebanon Hospitals [12] and Louis Lichtenstein and Henry L. Jaffe from the Hospital for Joint Diseases [13] in New York City almost simultaneously reported solitary granulomatous histiocytic lesions of bone, which they named eosinophilic granuloma. The lesions, unlike those found in the other two forms of the disease, were confined to the bone and were benign in nature [14]. In 1942, William T. Green and Sidney Farber linked eosinophilic granuloma to Letterer-Siwe's disease and Hand-Schûller-Christian's disease on the basis of almost identical histologic patterns [15]. Jaffe and Lichtenstein [16] concluded the same. Lichtenstein [17] subsequently suggested that the three entities be named histiocytosis-X. It was, however, Friedman and Hanaoka in 1969 [18] and Nezelof et al. in 1973 who concluded that the cells which appeared in all three forms of the disease were Langerhans granuloma cells and proposed that the name be changed to Langerhans cell histiocytosis [19]. It is striking that the three diseases are so different in presentation, degree of disability, and survival, and, yet, the histology is indistinguishable.

The cause of the disease... remains a mystery

There have been multiple attempts by scientists to define the cause of the three disorders using extensive virologic analyses and genetic studies [20–34]. In favor of an infectious etiology is the disseminated nature of the disease and the almost spontaneous remission of the milder forms. In favor of a neoplastic etiology is the presence of generalized and fatal disease in some patients not unlike a lymphomatous or leukemic disorder.

It was suggested in 1991 that the Epstein-Barr virus was the cause [35]. In 1993, it was proposed that the diseases were caused by Human Herpes virus 6 (HHV6) or Herpes virus 9 (HHV8) [27, 29]. McClain et al., on a very thorough analysis, were unable to find evidence for the presence of the HHV, adenovirus, CMV, Epstein-Barr virus, herpes simplex, HIV, T-cell leukemia 1 or 2, or parvovirus [30]. Attempts at identifying a genetic error have failed to find a consistent abnormality in the gene structure for the three diseases. Currently, the genetic constitution of the Langerhans cell has not been found to differ significantly from other interdigitating dendritic cells [21, 22, 24, 26, 28, 36]. Although an occasional positive family history has been reported, the finding is rare [20, 37]. Exposure to noxious agents has not been identified as a potential cause.

The disease has some similarity to Erdheim-Chester disease, another histiocytosis that involves the bone marrow, but there are significant differences in the appearance of the cells and clinical course [24].

Unusual histology of Langerhans cell histiocytosis

As implied in the above description of the contribution of Paul Langerhans, the principal cell present in all three of the lesions that comprise the entity is a monocyte that has some unusual characteristics. As described by Langerhans, the cell is a non-pigmentary dendritic cell, which he considered to be bone-marrow-derived and to represent the most peripheral output of the immune system, residing in the epidermis [1, 24, 25]. The cell resembles other monocytic elements, but has a vesicular nucleus with a groove parallel to the long axis and vacuolated cytoplasm (Fig. 1) [24]. Occasionally, binucleate cells are evident, but cell replication is unusual [22, 24, 38]. Tiny linear-rod-shaped inclusions in the cytoplasm called Birbeck's granules are best seen on electron microscopy [22, 24, 39]. Most of the Langerhans cells are positive for S-100 protein and CD1a, CD40, CD52, and CD154 [22, 24, 26, 28, 36]. The levels of the tumor suppressor P-53 may be

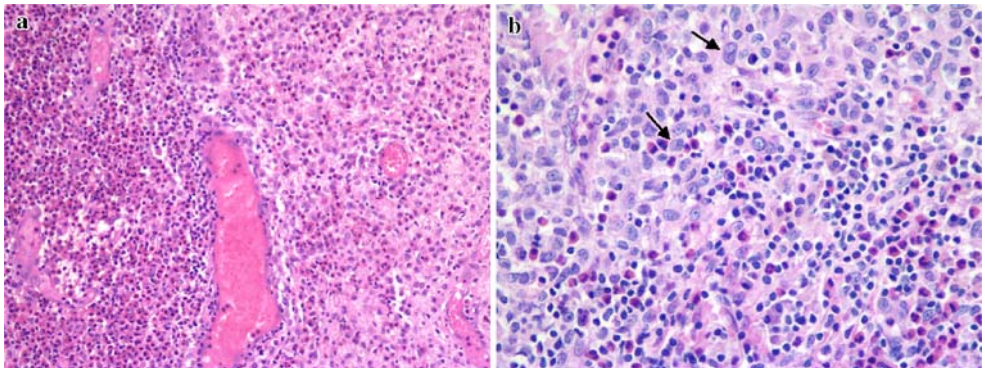

Fig. 1 **a** Low-power micrograph, demonstrating histiocytes with some atypical cells and a large population of eosinophils (stained pink). **b** High-power micrograph of the same specimen with nuclei demonstrating prominent longitudinal grooves (*arrows*) typical of Langerhans cells and multiple eosinophils

decreased in some of the cells, but its expression level has not been correlated with outcome [40], suggesting that the gene is not involved in regulating the proliferation of these cells.

Perhaps the most striking feature of the histology is the presence of eosinophils, which are sometimes so frequent so as to dominate the histologic presentation [22, 24, 38]. The combination of histiocytes and eosinophils is unusual in pathologic specimens. The principal differential for histiocytosis is from Hodgkin's lymphoma, in which eosinophils are often present. However, Hodgkin's lymphoma has a distinguishing feature, the multinucleated Reed-Sternberg cell, which is not present in Langerhans histiocytosis [22, 24].

Presentation of the three syndromes

Eosinophilic granuloma

Eosinophilic granuloma is a benign disease limited to bone or lung and most often found in children under 15 years of age [21, 23, 41–43]. While bone lesions are most often asymptomatic, they may be the site of fracture and be a source of pain, swelling, deformity, and, sometimes, a soft tissue component [44]. Pulmonary eosinophilic granuloma in children is part of multisystem disease, unlike in adults [45]. It is often symptomatic with tachypnea, dyspnea, cough, and complications of spontaneous pneumothorax and pleural effusions; however, radiographic findings may precede symptoms [45, 46]. In children, pulmonary disease is not associated with a worse prognosis and isolated pulmonary involvement is rare [47]. In children younger than 10 years of age, it can regress spontaneously.

The osseous lesions of eosinophilic granuloma present more than 50% of the time as a lytic, modestly destructive lesion of a flat bone, such as the skull, mandible, ribs, and pelvis (Fig. 2) [43]. In the skull, the lesions are characteristically areas of osteolysis with sharp borders, giving a characteristic "punched out" appearance [45] and measure 1–4 cm in diameter [44]. The lytic lesions of the skull may retain a small, residual bone fragment or sequestrum, resembling that seen in other diseases, such as osteomyelitis [43, 44]. Lesions of the pelvis may present as poorly defined areas of osteolysis that become progressively circumscribed as they mature [43]. Lesions of the scapula may demonstrate an ovoid pattern of lysis that may or may not have a sclerotic margin (Fig. 3) [43].

Lesions within a long bone are often in the diaphysis of the femur, tibia, or humerus. They may be present in the metaphysis or extend to the physis and epiphysis; however, isolated epiphyseal involvement is rare [44]. Solitary long-

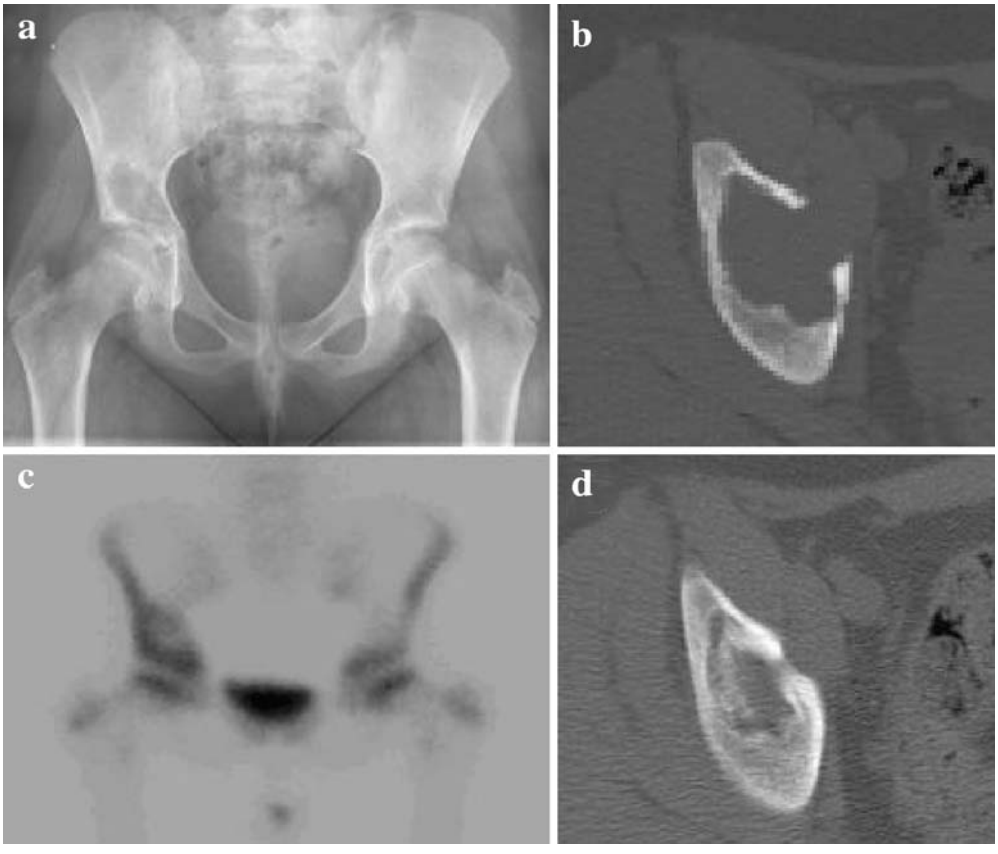

Fig. 2 **a** Lytic, well circumscribed lesion of the right iliac bone. **b** Axial computed tomography (CT) image demonstrates a lytic lesion with a fracture of the medial cortex with a soft tissue, noncalcified matrix. **c** Tc-99 MDP bone scan demonstrates mild, increased uptake in the margins of the lesion. **d** Lesion 3 months after steroid injection

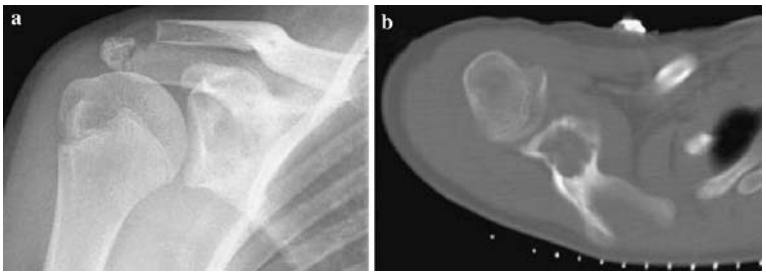

Fig. 3 **a** Expansile, lobulated lytic lesion of the right glenoid of the scapula without identifiable fracture. **b** Pre-biopsy axial CT demonstrating the mildly expansile lesion with internal septae and a soft tissue matrix

bone lesions average in size from 4 cm to 6 cm [43]. They typically produce a "scallop from within" appearance (endosteal scalloping) without a break in the cortex or soft tissue mass. Cortical thinning, intracortical tunneling, and medullary widening are often demonstrated on radiography [44]. While less common, periosteal reaction or a permeative pattern of cortical involvement may be present at an early phase of disease, giving the lesion a more aggressive and pseudomalignant appearance (Fig. 4) [43–45].

Lesions may occur in the spine and, on occasion, in multiple sites [22, 24, 38]. A vertebral segment lesion is characteristically osteolytic initially, but results in a "vertebra plana"—a symmetrical flattening of the vertebra, often in a growing child, with intervertebral disc space preservation and sparing of the posterior elements (Fig. 5) [16, 21–24, 27, 42].

Once a primary osseous lesion is identified, evaluation of the skeleton for additional lesions is usually undertaken. Clinically, alkaline phosphatase may be slightly elevated [22, 24]. A skeletal survey using conventional radiography is sensitive for lesion detection. However, some lesions are detected by radionuclide bone scan that are not detected by skeletal survey and vice versa [48–51]. For this reason, the authors have recommended the use of both imaging modalities for the initial evaluation of eosinophilic granuloma, with follow up using either skeletal survey [48] or bone scan [49, 51]. However, the radiation dose is higher for skeletal survey compared to bone scintigraphy. The bone scan is often positive at the site of actively growing bone lesions (Fig. 2c), while it may be negative when lesions are stable in size and are being treated [52].

Evaluation of eosinophilic granuloma and the osseous lesions of Langerhans cell histiocytosis with CT is helpful to confirm the presence of a lesion, and to determine the extent of cortical destruction and the amount of soft tissue involvement [45, 52]. Small lesions may not be detected on routine radiography and may first be identified on CT. In addition, CT is useful in guiding biopsy to diagnose eosinophilic granuloma as a cause of vertebral osteolysis or vertebra plana (Fig. 6d).

Magnetic resonance imaging (MRI) is a highly sensitive, but nonspecific, modality to detect bone marrow involvement and soft tissue mass in eosinophilic granuloma [52]. The lytic lesions seen on radiography and CT are low signal, or isointense to muscle, on T1-weighted images and high signal on T2-weighted images (Figs. 6 and 7) [22, 24, 52]. Acute lesions may also demonstrate edema of marrow, periosteum, and soft tissues (Fig. 8) [45, 52]. Healing is

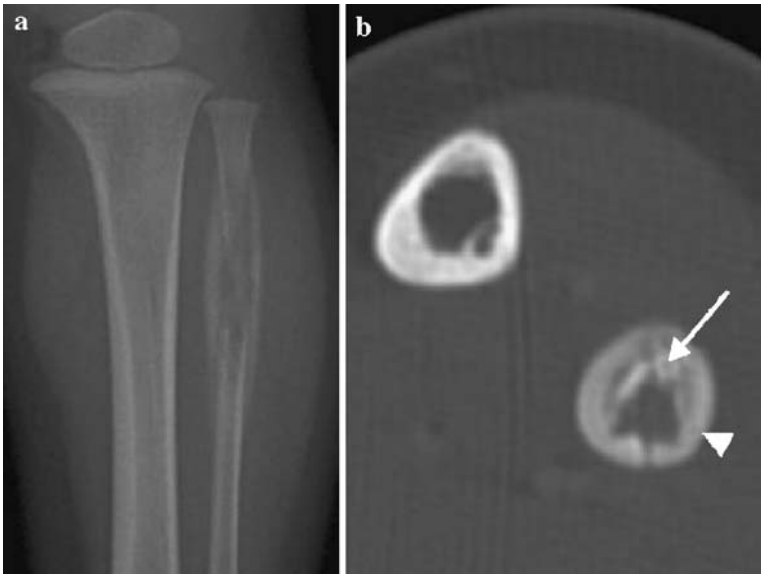

Fig. 4 **a** Anteroposterior (AP) radiograph of the proximal left tibia and fibula, demonstrating an aggressive appearing lesion with periosteal elevation, a moth eaten appearance, and cortical destruction of the fibula. **b** Axial CT demonstrating cortical destruction of the fibula (cortical bone, shown by *arrow*) and periosteal new bone formation (*arrowhead*)

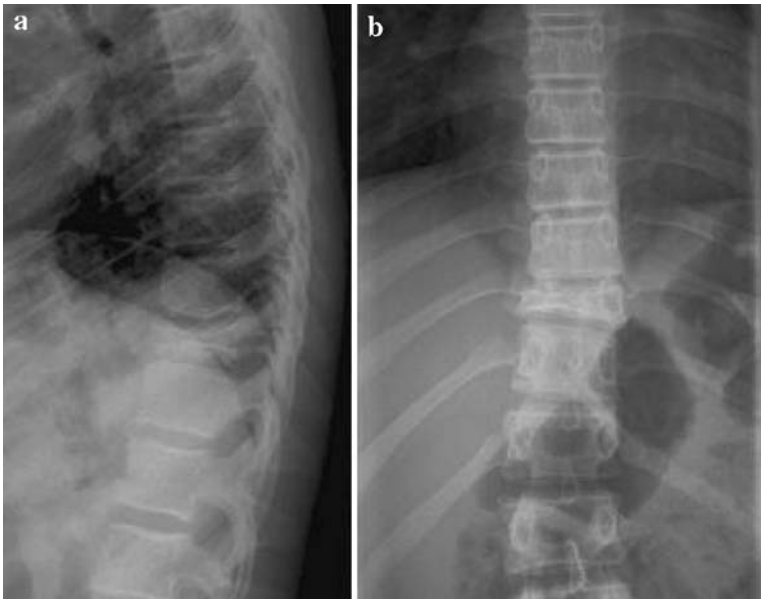

Fig. 5 **a** Lateral radiograph demonstrating near complete loss of vertebral body height at T10 with sparing of the posterior elements (vertebra plana). **b** AP radiograph of the same patient demonstrating an asymmetric flattening with a compensatory dextroconvex scoliosis inferiorly

associated with a decrease in T2 signal intensity. Given its specificity for the detection of metastatic disease [53], whole-body inversion recovery MRI may be effective in imaging the entire body for the extent of bone involvement of Langerhans cell histiocytosis in children with the significant benefit of no radiation exposure [54].

Experience with FDG-PET in evaluating osseous eosinophilic granuloma is limited and its use is still investigational. Early studies suggest that it is highly sensitive for lesion detection and specific for the phase of activity [55, 56]. In one small study of three patients [55], both bone scan and FDG-PET were able to detect active eosinophilic granuloma and the FDG-PET activity returned to base line in healed lesions, unlike bone scintigraphy. A second small study demonstrated that FDG-PET could detect lesion response to chemotherapy, which could not be distinguished with bone scanning [56].

Hand-Schûller-Christian's disease

Hand-Schûller-Christian's disease generally occurs in children under the age of 10 years old. It may occasionally appear in patients in their 20s and 30s, and more frequently in males [20, 22–24, 41, 42, 57, 58]. Retarded growth and development may be present and one third of the patients present with diabetes insipidus [21–23, 42, 57, 59, 60]. Anemia is present in a high percentage of patients and many have hepatosplenomegaly [21–24]. Patients also often present with exophthalmos, which may lead to blindness, and hearing loss is frequently present [20, 22, 23, 42, 61]. Many of the patients develop a progressive cerebellar ataxia after several years [62, 63].

One of the most distressing findings is a scaly seborrheic skin rash, often present at hair lines and hands and feet, and which may be the cause of bleeding [2, 7, 9, 12, 17, 20–24,

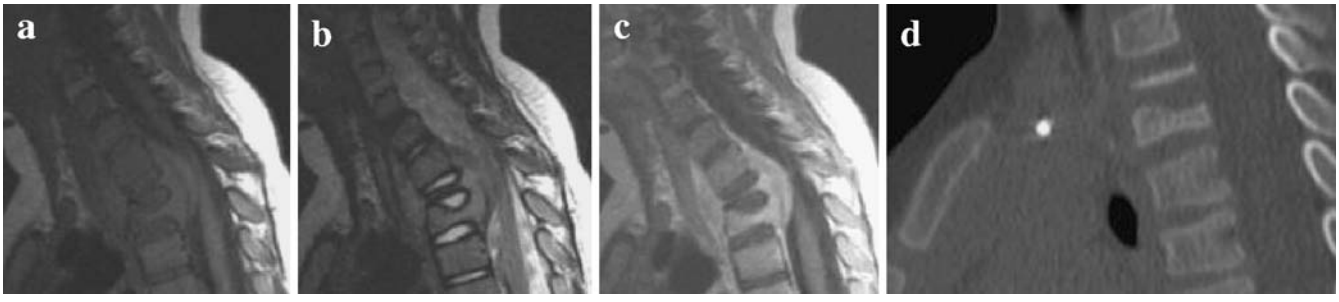

Fig. 6 **a** T1-weighted image demonstrating complete flattening of the T2 and approximately 50% loss of height of the T3 vertebra with posterior bowing of the vertebral bodies. There is a posterior soft tissue component demonstrating similar signal to the vertebra, which is isointense to muscle. **b** T2-weighted image demonstrating increased signal of the vertebral bodies and the posterior soft tissue component with narrowing of the spinal canal and mass effect on the cervical cord, which demonstrates increased T2 signal. **c** Contrast-enhanced T1-weighted image demonstrating diffuse enhancement of the involved vertebra and the soft tissue mass. **d** Sagittal reformatted CT of the same patient, which does not clearly demonstrate the soft tissue component

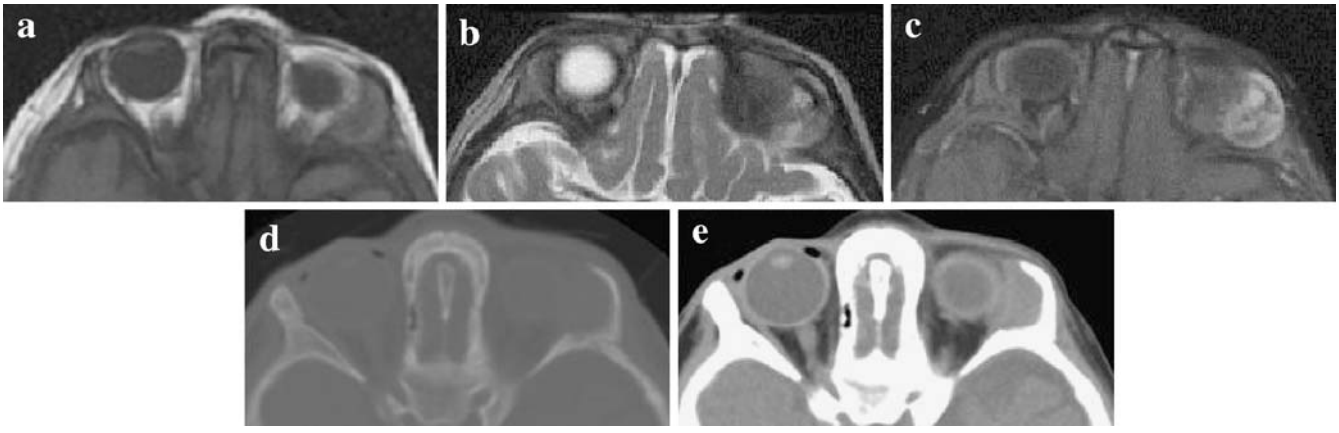

Fig. 7 **a** T1-weighted image demonstrating a soft tissue mass isointense to the brain of the lateral, left orbit with thinning of the bone. **b** T2-weighted image demonstrating heterogeneous high T2 signal replacing part of the lateral wall of the orbit. **c** Post-gadolinium imaging demonstrating heterogeneous enhancement. **d**, **e** CT scan has superior depiction of the bone destruction and also demonstrates the soft tissue mass

28, 58]. Pulmonary fibrosis may be present in the lungs and may cause serious, restrictive pulmonary disease, and even death [22, 62].

The condition has a propensity to form lesions at the base of the skull, and to involve the pituitary, which presumably accounts for the diabetes insipidus and exophthalmos. Pituitary involvement can sometimes be clearly identified by PET scanning [64]. Calvarial lesions are present in over 60% of the patients (Fig. 9) [21, 22, 24]. These are frequently multiple and may be sufficiently destructive to cause injury to the underlying neural tissue [62]. Teeth and gum problems are present in approximately 20% of the patients and mandibular deformity is a common finding [6]. Osseous lesions in other sites may be present in almost 50% of the patients and are often much more destructive than the lesions seen in eosinophilic granuloma [22, 24, 38, 41, 62].

Letterer-Siwe's disease

Letterer-Siwe's disease is the rarest of the Langerhans histiocytic lesions and also the most aggressive. The age for patients with Letterer-Siwe's disease is usually less than 2 years, and males are more often affected than females. After a short period of normal growth and development, the affected children develop visceromegaly and lymphadenopathy [21, 22, 24, 42]. Hepatomegaly is especially common and some patients have damage to large- and medium-sized bile ducts. Those patients with bile duct involvement may present with findings of primary sclerosing cholangitis [65, 66]. They become severely stunted in growth and lose weight. Their intellectual development becomes severely impaired. Laboratory studies show marked anemia and thrombocytopenia.

Most of the children show destructive lesions in the skull, associated with brain damage, and lesions in the peripheral bones, associated with frequent fractures [21,

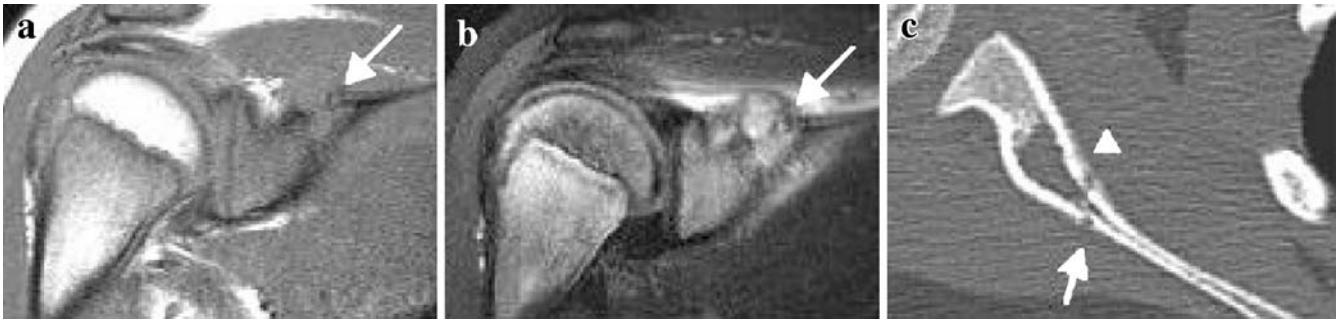

Fig. 8 **a** Coronal T1-weighted image of the right shoulder, demonstrating a soft tissue mass with cortical destruction and extra-osseous extension, as well as decreased T1 signal within the scapula, representing edema. **b** Coronal T2-weighted image demonstrating the mass is T2 high signal (*arrow*) with surrounding fluid signal in the periosteum and the traversing supraspinatus muscle. **c** Axial CT scan demonstrating loss of internal trabeculae in the scapula, with areas of cortical disruption anteriorly and posteriorly, and periosteal elevation

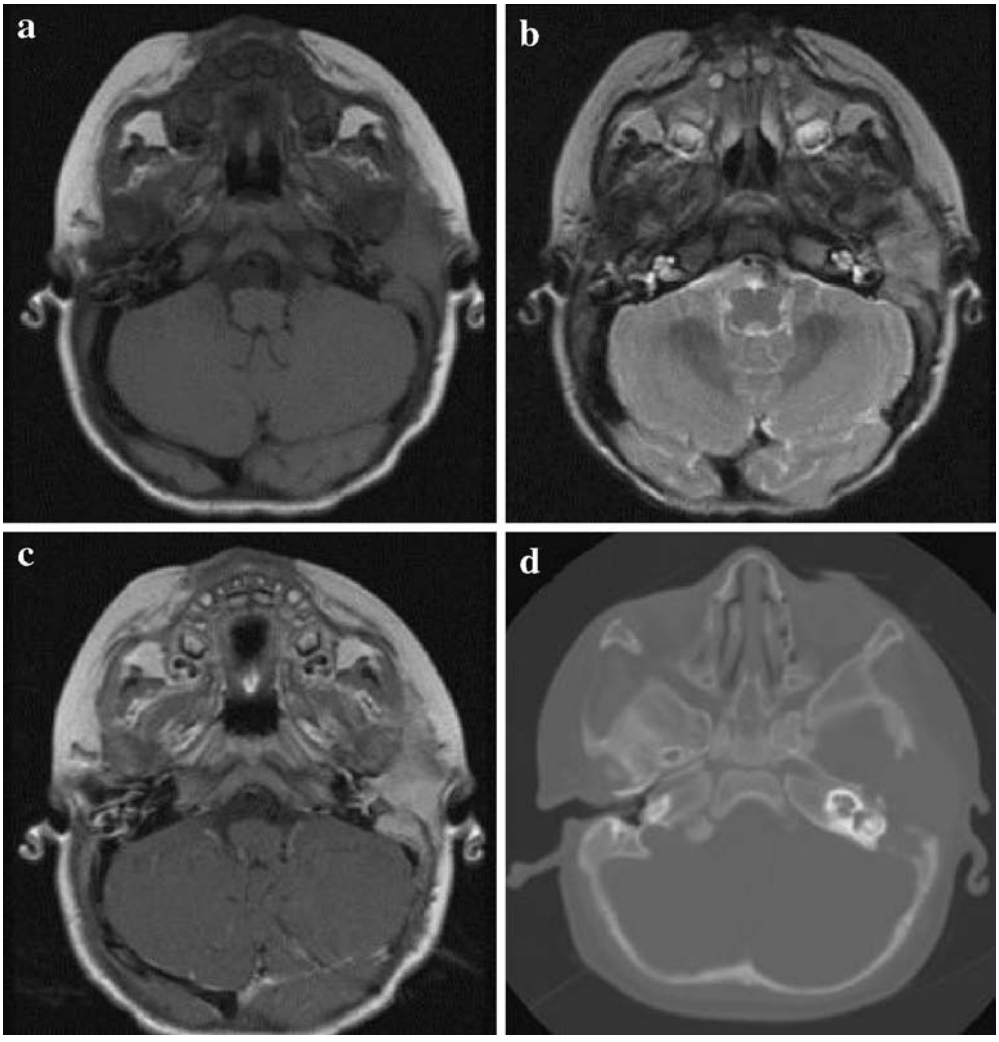

Fig. 9 **a**–**c** T1, T2, and post-gadolinium images of the skull base, demonstrating a destructive mass which is isointense to the brain on T1- and T2-weighted imaging. **d** Axial CT better demonstrates the bone destruction by the lesion

22, 24, 42]. The most evident clinical sign is a widespread papular, crusting hemorrhagic rash, which is associated with a severe neutropenia and thrombocytopenia. Treatment has, until recently, had little effect, and early demise was the rule for these very ill children [22, 25, 62].

Treatment of patients with Langerhans cell histiocytosis

It should be evident that the three syndromes are so markedly different that the treatment is very variable. For eosinophilic granuloma, treatment of a solitary lytic lesion affecting a long bone is best accomplished by curettage of the affected site and implantation of allograft bone chips or polymethylmethacrylate [22, 24] or injections of corticoids into the site [67, 68] (Fig. 2d). The lesions rarely recur and most of the patients remain free of disease for the remainder of their lifetimes. Vertebra plana lesions are sometimes best treated by observation [69, 70]. It is a curious fact that partial, or even complete, reconstitution of vertebral body height may occur with healing of the lesion.

Treatment of Hand-Schûller-Christian's and Letterer-Siwe's diseases is much more complex and, for the most part, not very effective. Corticosteroids have been utilized and seem effective initially, but, generally, they do not reverse the course of the diseases. Methotrexate and vinblastine can help the patients with Hand-Schûller-Christian's disease, but are of little value for patients with Letterer-Siwe's disease [71]. The use of growth hormones has been useful for patients with Hand-Schûller-Christian's disease in terms of increasing their development to a modest extent [59]. More recently, interferon alpha with etoposide has shown some modest success [72, 73]. A recent report suggests that 2-chlorodeoxy-adenosine may allow for a complete remission of symptoms for patients with Hand-Schûller-Christian's disease, and may be useful in maintaining survival for patients with Letterer-Siwe's disease [74–78]. Marrow transplant has been utilized and seemed successful in several cases for a relatively short

period of time [79]. Extensive bone lesions have been treated with bisphophonates with some improvement [80], and thalidomide appears to help severe skin problems [81].

It is somewhat distressing to realize that the three disorders with the name of Langerhans cell histiocytosis, which were originally described in the 19th century and are vastly different in presentation, have, thus, strongly resisted attempts to identify a neoplastic, infectious, or genetic cause. The distinctive feature for the three entities, which are very different in presentation and outcome, is the unique histologic characteristics which are characterized by the appearance of the Langerhans cells, the Birbeck's granules, and the eosinophils. The treatment protocols, although better than they were 25 years ago, are still problematical for the two more severe disorders, and patients with both of these still disorders are, at times, severely affected and eventually die of disease.

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