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ONCOLOGY

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Multisystem Langerhans' cell histiocytosis (Hand-Schüller-Christian disease) in an adult: a case report and review of the literature

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Abstract Langerhans' cell histiocytosis (LCH) is a rare and enigmatic clonal disorder that affects mainly children. It is characterized by single or multiple granulomatous mass lesions composed of cells with the Langerhans' cell phenotype. Clinical presentation and behavior are heterogeneous and can range from a solitary lytic bone lesion (i.e., eosinophilic granuloma) with a favorable course to a fatal disseminated leukaemia-like form, with a wide spectrum of intermediate clinical presentations between these two extremes. Although LCH typically involves the bone, lesions can be found in almost all organs. We are reporting the case of a multisystem LCH in a 47-year-old patient who presented with a panhypopituitarism and diabetes insipidus, and who, 5 years later, developed mandibular, mastoid and femoral lesions. The final diagnosis of LCH was made on mandibular biopsy.

Keywords Langherhans' cell histiocytosis · Diabetes insipidus · Panhypopituitarism · Mastoiditis · Mandibular lytic lesions

Introduction

Langerhans' cell histiocytosis (LCH) encompasses a disparate group of diseases that has been referred to as Hand-Schüller-Christian disease, Letterer-Siwe disease, eosinophilic granuloma, histiocytosis X, Hashimoto Pritzker syndrome, self-healing histiocytosis, pure cutaneous histiocytosis, Langerhans' cell granulomatosis, type II histiocytosis and non-lipid reticuloendotheliosis [8]. Langerhans' cell histiocytosis is characterized by the proliferation of abnormal dendritic antigen-presenting histiocytes, known as Langherhans' cells, with an accompanying infiltrate of lymphocytes, eosinophils and neutrophils resulting in the destruction of a variety of tissues. Lesions may occur as localized lesions or as widespread systemic disease. Langherhans' cells have distinctive morphologic and immunohistochemical features (such as S-100 protein and CD1a antigen) and represent an immature stage in the development of interdigitating cells [7, 13]. Although some authors have recently demonstrated clonal proliferation in all forms of LCH, suggesting a neoplastic disorder, the exact etiopathogenesis of this enigmatic disease still remains obscure, and the clinical course is unpredictable [17, 19]. Langerhans' cell histiocytosis is usually considered to be a disease of childhood, with a peak incidence from 1 to 3 years. However, it should be included in the differential diagnosis of adult patients, particularly those with multisystem disease [18, 14, 4]. We are reporting a case of a 47-year-old patient with a multisystemic form of Langherhans' cell histiocytosis.

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Case report

A 42-year-old patient was referred to the endocrinological department in May 1997 for investigation of hypothyroidism. For 2 years, he had complained of chronic fatigue, memory impairment, diminished libido, impotence, a loss of hair, gynecomastia and polyuria/polydipsia, which had started a few months previously. Panhypopituitarism and central diabetes insipidus were diagnosed. Magnetic resonance imaging (MRI) showed evidence of an infiltrating hypothalamic lesion involving the mammillary bodies, a slightly thickened pituitary stalk (both homogeneously enhanced after intravenous gadolinium administration), a loss of the normal hyperintense signal of the posterior pituitary on T1-weighted images ("bright spot") and a partially empty sella (Fig. 1a). Microbiological cultures of blood and CSF and serological markers for *Treponema pallidum* (VDRL, TPHA), *Borrelia burgdorferi*, *Brucella*

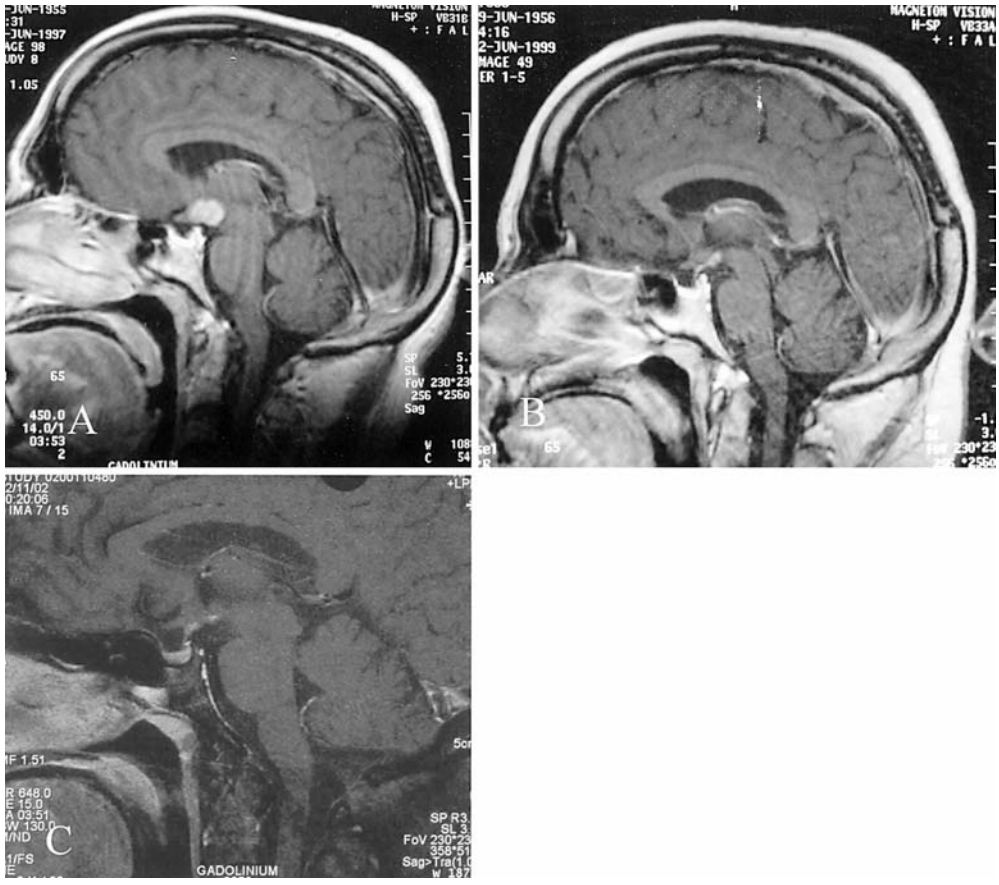

Fig. 1 **A** Sagittal T1-weighted MRI images showing an infiltrating hypothalamic lesion involving the mammillary bodies and a slightly thickened pituitary stalk both homogeneously enhanced after intravenous gadolinium administration. **B** Sagittal T1-weighted MRI images after 3 months of prednisone therapy showing a slight regression of the hypothalamic lesion following gadolinium administration. **C** Sagittal T1-weighted MRI images after 5 years showing an important regression of the hypothalamic lesion

melitensis, *Bartonella henselae* and HIV were negative. The results of cerebrospinal fluid immunoelectrophoresis were normal. The level of angiotensin-converting enzyme, tested in blood and CSF, was normal. Further work up with chest X-ray for sarcoïdosis was normal. Neuropsychological tests showed a fronto-subcortical syndrome characterized by severe short- and long-term memory impairment (verbal and spatial) and marked executive dysfunction. Replacement therapy was begun with oral levothyroxine 0.15 mg daily, oral hydrocortisone acetate 20 mg daily, intramuscularly testosterone enantate 250 mg weekly and intranasal DDAVP 10 µg twice daily. In July 1998, the patient presented with hyperosmolar diabetic decompensation, and treatment with insulin and metformine 850 mg twice daily was begun. A stereotaxic biopsy was performed in January 1999 because the neuropsychological status of the patient had become worse. Histopathologic examination revealed gliosis together with non-specific perivascular chronic inflammatory infiltration. Oral prednisone 60 mg daily for 3 months was begun in March 1999, which stabilized the situation temporarily. The follow-up MRI in June 1999 demonstrated a slight regression of the hypothalamic lesion and the intensity of the contrast enhancement following I.V. gadolinium administration (Fig. 1b). In July 2001, the patient complained of intermittent mandibular pain located in the right molar and symphyseal areas. Periapical X-ray showed a discrete periapical radiolucent lesion associated with a non-vital mandibular right second molar (Fig. 2a) and a large periapical radiolucent lesion associated with the non-vital mandibular incisors (Fig. 2b). The right second mandibular molar was extracted and a devitalisation of the left central and lateral incisors and right central incisor was performed. The panoramic radiograph in December 2001 demonstrated a 3.5×3-cm well-defined non-corticated radiolucency with a scalloped superior border of the right

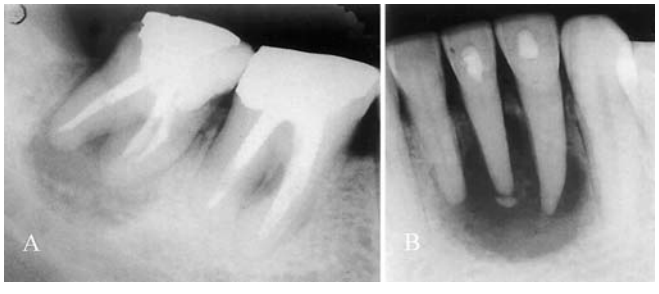

Fig. 2 Periapical radiographs showing well-defined radiolucency associated with the apex of the right mandibular second molar (**A**) and mandibular incisors (**B**)

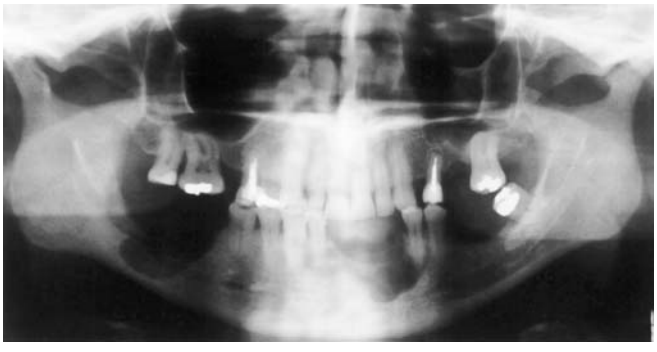

Fig. 3 Panoramic radiograph showing two unilocular radiolucencies with well-defined margins in the right mandibular angle and symphyseal region

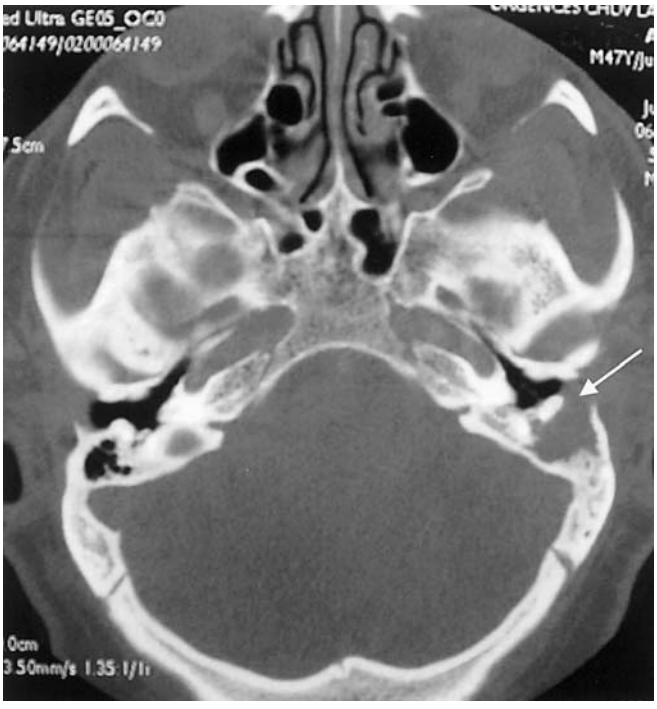

Fig. 4 CT scan showing left mastoid infiltrated by soft tissue with the destruction of the bony cortex (*arrow*)

mandibular area and the persistence of a punched-out radiolucency in the symphyseal region (Fig. 3). Chronic osteomyelitis of the mandible was diagnosed, and antibiotic and antiphlogistic therapy was prescribed without any modification of the symptomatology. In February 2002, the patient underwent a surgical curettage and enucleation of both mandibular lesions, and the histologic diagnosis was that of chronic osteomyelitis. Follow-up panoramic radiographs in April and August 2002 demonstrated no changes in the size or radiographic characteristics of the mandibular lesions, but the patient was asymptomatic. The patient presented in June 2002 with a 1-month history of transient otalgia, pain in the left retro-auricular area, disturbances of gait, dizziness and left hypoacusia, which had started 1 week previously. Otitis externa was diagnosed and antibiotic and antiphlogistic therapy was given with a slight modification of the symptomatology. One week later, he presented at the hospital for the persistence of the symptomatology, appearance of fever and significant red pulsatile swelling in the mastoid region. Audiological evaluation revealed mixed hearing loss. The CT-scan of the temporal bone revealed a massive destruction of the bone of the mastoid area, and the patient underwent a left mastoidectomy (Fig. 4). The mastoid was destroyed by adherent granulations to the peri-temporal tissues, which prevented complete surgical exeresis. Histopathological diagnosis was that of a chronic non-specific inflammatory infiltrate.

In November 2002, the patient presented with a worsening of mandibular pain associated with a discharge of whitish material in the mouth. The intraoral exam revealed the persistence of a sinus tract in the retromolar and symphyseal regions from which whitish secretions were exuding. The panoramic radiograph demonstrated no changes in the size or radiographic characteristics of the mandibular lesions. The patient underwent a new surgical curettage and enucleation of both mandibular lesions. Microscopic examination showed a diffuse infiltration of large pale-staining mononuclear cells with indistinct cytoplasmic borders and indented vesicular nuclei with a histiocytic appearance (Fig. 5a). The infiltrate was also composed of a large amount of eosinophils, plasma cells and lymphocytes. Immunohistochemical studies using CD1a and S-100 protein antibodies showed that the histiocytic cells were consistent with Langerhans' cells (Fig. 5b). The final diagnosis was that of a

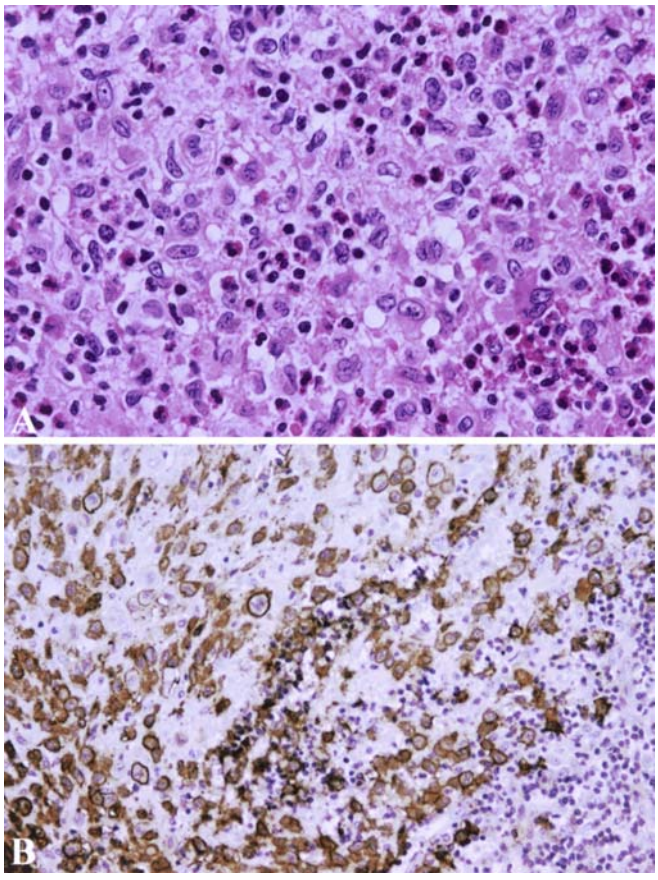

Fig. 5 **A** Photomicrographs of the mandibular biopsy specimen showing the cells of the infiltrate exhibiting the characteristic morphologic features of Langerhans' cells with a convoluted shape, elongated nuclei exhibiting longitudinal grooves, and pale cytoplasm. Numerous eosinophils are also visible (haematoxylin-eosin, original magnification ×25) **B** Immunostaining revealing numerous strongly positive Langerhans' cells for the CD1a antibody (immunoperoxidase, original magnification ×25)

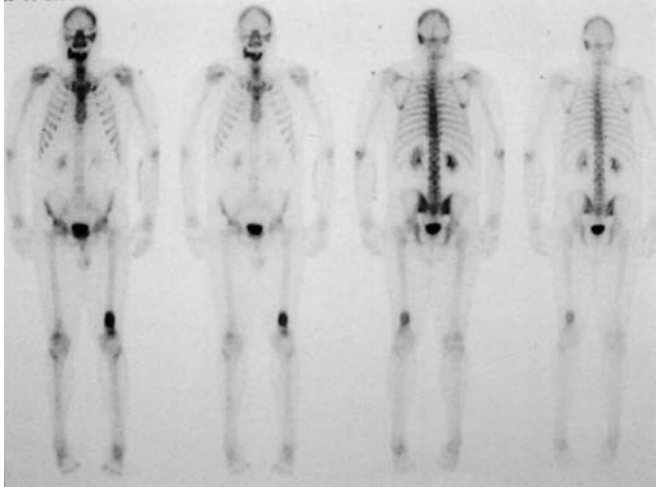

Fig. 6 Technetium-99-m bone scan showing a lesion of the distal epiphysis of the left femur, the persistence of a left temporal and mandibular lesions and a frontal bone lesion

Langerhans' cell histiocytosis. Previous temporal and mandibular biopsies were reviewed and showed similar histological aspects.

Further work up for multifocal LCH with Technetium-99-m bone scan (Fig. 6) and with chest and abdominal CT scans showed evidence of a lesion of the distal epiphysis of the left femur, the persistence of left temporal and mandibular lesions and a frontal bone lesion. The brain MRI showed a significant regression of the hypothalamic-pituitary axis lesion (Fig. 1c).

Given that the patient presented no symptoms at the 3-month follow-up and given the lack of an international consensus concerning treatment for adult LCH, the oncologists decided to propose no further treatment.

Discussion

In 1893, Hand reported a case of "polyuria and tuberculosis" in a 3-year-old boy who presented with diabetes insipidus (DI), skull lesions and exophthalmos [6]. In retrospect, he gave the first detailed clinical description of a new group of polymorphic disorders involving the reticuloendothelial system (RES) and characterized by a histiocytic infiltrate. In 1953, Lichtenstein proposed the general term "histiocytosis X" to describe a group of disorders including Hand-Schuller-Christian syndrome, Letterer-Siwe disease and eosinophilic granuloma [12]. Twenty years later, Nezelof identified the Langerhans' cells as the original cells of histiocytisis X [15]. The Langerhans' cell (LC), first described by the Berlin medical student Paul Langerhans in 1868, is a bone-marrow-derived dendritic, antigen-presenting cell network, related to the mononuclear phagocyte system [10]. These cells are found in the skin, lymph nodes, bone marrow, spleen and probably also the brain, and have characteristic surface proteins, which identify them as immature or mature. Within the LC is a five-layered structure, the Birbeck granule, first seen by electron microscopy in 1961 [13]. The gene coding for the endocytic receptor that induces the formation of Birbeck granules has been identified and the protein called "langerin" [13, 17, 19]. Pathological LC is positive for HLA-DR, CD1a, S100 and Fc receptor, as with their normal counterparts [8, 13, 17, 19, 18]. In 1987, the Histiocyte Society established a new classification of these disorders based on the lineage of lesional cells and biological behavior related to the ontogeny of histiocytes, and distinguished three classes: class I or Langerhans' cell histiocytosis (LCH); class II or non-Langerhans' cell histiocytosis; class III or malignant histiocytosis [18].

Two main forms of LCH have been described: localized LCH (eosinophilic granuloma) and multisystem LCH (formerly Hand-Schuller-Christian syndrome or chronic disseminated disease and Letterer-Siwe disease or acute disseminated disease).

Langerhans' cell histiocytosis often presents as a puzzling syndrome, which renders the diagnosis problematic. Four important considerations explain the reasons for a delayed diagnosis of LCH in our patient. First is the age of the patient (42 years) at the time of the first symptoms. In fact, these disorders are typically found in children – more than 50% of all cases are seen in patients under age 10 – even though recent studies have shown that approximately 30% of LCH occur in adults, with an incidence rate of 0.18/100,000 [18, 14, 4].

The second consideration concerns the presenting feature, namely the hypothalamic-pituitary lesion. In a series of 47 adults with LCH, posterior pituitary involvement was found to be the site of presentation in only 11 patients [14]. By contrast, CNS involvement is not uncommon and is strongly associated with the systemic disease, but it is rarely found alone. The hypothalamic-pituitary axis remains the unexplained site of predilection of CNS LCH; however, hypothalamic mass lesions, as found in our patient, are not frequently encountered [5, 9]. Grois et al. reviewed 38 patients with CNS LCH and found only 4 patients (10%) with such lesions, whereas 22 patients (63%) presented with structural changes in the pituitary region (infundibular thickening in 8 patients and empty sella in 14 patients) [5]. Diabetes insipidus (DI) is the most common endocrine abnormality, reported in 5–50% of patients with LCH, and it occurs when more than 80% of the paraventricular-supraoptic neurons are destroyed [9]. Diabetes insipidus occurs in only 5% of patients at the time of original diagnosis, whereas it develops in one quarter to one third of patients within 5 years of the diagnosis. Although panhypopituitarism is reported in only 5–20% of patients, it is almost always associated with DI [9].

The third consideration concerns the difficulty in obtaining a correct diagnosis of LCH from cerebral biopsy. According to the literature, whether or not a biopsy should be taken from such lesions still remains controversial. Nevertheless, neurosurgeons are not inclined to approach lesions in certain delicate regions, such as the hypothalamus, pons, basal ganglia and cerebellar peduncles, for only the purpose of biopsy [5]. Normann et al. described four stages of CNS LCH: hyperplastic-proliferative, granulomatous, xanthomatous and gliosis. The histological and immunohistochemical LCH diagnostic features are more likely to be found in the hyperplastic-proliferative stage, whereas in the gliosis stage, as in our patient's case, these are more likely to be absent [5].

Finally, the fourth consideration concerns the clinical presentation of the LCH, especially in a diabetic patient, which can mimic an acute or chronic infection. Temporal bone involvement may mimic otitis media and/or acute mastoiditis [11, 1, 16], and the mandibular involvement may mimic a periapical infection and/or an osteomyelitis [3].

The skull is the most common site involved in both adults and children, with calvarial bones as the most common site for solitary lesions [8, 14, 4]. Ear disease has been reported in 18–61% of cases, and when the temporal bone is involved, 30% of patients present with bilateral disease [11, 1]. A helpful feature that can distinguish LCH from infectious otomastoiditis is the lack of middle ear or posterior canal wall suppuration, because the LCH rarely involves the middle ear cavity [16]. Our patient, on the contrary, presented with supporative otitis externa as well as a significant involvement of the middle ear cavity, with granulations adherent to the tympanic ossicles.

Jaw involvement (particularly the mandible) is usually found in LCH patients. Howarth et al. [8] reviewed 314

patients of the Mayo Clinic and found osseous lesions in 60%, 7% of whom had mandibular lesions. Of 47 patients in the study by Baumgartner [4], the primary sites were jaw (30%), skull (21%), extremities (17%), vertebrae (13%), pelvis (13%), and ribs (6%). This is in contrast to children, where the skull is the major bone area involved (40%), and the jaw is involved in only 8% of those patients.

Radiographically, LCH lacks pathognomonic characteristics and may mimic a wide spectrum of lesions such as radicular cysts, periodontal disease, osteomyelitis and malignancies. Most often, lesions appear as sharply punched-out radiolucencies, and when extensive alveolar involvement occurs, the teeth appear as if they are "floating in air." Ardekian et al. reviewed 25 patients with 41 eosinophilic granulomas and found pain to be the most common presenting symptom (92% of patients), often accompanied by swelling [3].

Treatment for LCH remains empirical even though significant progress has been made in the understanding of the pathophysiological basis of this disorder [8, 2]. Usually, the localized form of LCH as an isolated bone lesion requires minimal treatment involving only biopsy or curettage. If the patient is asymptomatic, then a "wait and see" attitude is also possible, given the sometimes spontaneous resolution and healing of these lesions. Treatment for multifocal/multisystem LCH normally benefits from systemic therapy, which usually reduces morbidity and mortality. As suggested by different international trials, three important observations result: (1) the importance of identifying the risk group that could benefit from treatment with systemic cytotoxic agents; (2) that patients with minimal involvement require minimal or no treatment; (3) that in patients with extensive involvement, the initial response to therapy predicts outcome [2].

Our patient benefited from enucleation and curettage for temporal and mandibular lesions, as recommended by the international literature [8, 14, 4, 2]. Although systemic prednisone therapy considerably reduced the size of the diencephalic lesion, substitutive hormonal treatment was required. In fact, standard treatment for preventing or delaying hormonal deficit is yet to be determined; therefore, the damage to the pituitary/hypothalamus axis results in life-long hormonal replacement.

In conclusion, it should be kept in mind that multisystem LCH can occur in adults and that particular attention must be paid to osteolytic jaw lesions associated with endocrine or neurological symptoms.

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