Langerhans cell histiocytosis presented as bilateral otitis media and mastoiditis

Charalampos E. Skoulakis[1], Emmanouil I. Drivas[2], Chariton E. Papadakis[2]
Argyro J. Bizaki[2], Pelagia Stavroulaki[1], Emmanuel S. Helidonis[2]
Departments of Otolaryngology, [1]General Hospital of Volos, Volos, and [2]University Hospital of Crete, Heraklion, Crete, Greece

SUMMARY: Skoulakis CE, Drivas EI, Papadakis CE, Bizaki AJ, Stavroulaki P, Helidonis ES. Langerhans cell histiocytosis presented as bilateral otitis media and mastoiditis. Turk J Pediatr 2008; 50: 70-73.

Langerhans cell histiocytosis (LCH) is a rare disease that may affect multiple organs. The etiology of LCH remains unclear to date. It is currently believed that clonal accumulation and proliferation of CD1a-positive Langerhans cells are causative. The term LCH or histiocytosis X refers to three separate illnesses (listed in order of increasing severity): eosinophilic granuloma, Hand-Schüller-Christian disease and Letterer-Siwe disease. A seven-month-old boy presented with history of recurrent bilateral otitis media and rash and seborrheic areas on his scalp. Two days prior, his mother noticed a small lump over the right mastoid. Lateral skull X-ray (Schüller) was evidence for lytic lesion on right temporal bone. The computerized tomography scan showed inflammatory changes with bone erosion. During surgical exploration, fragile slightly yellowish tissue with necrotic areas was found that was determined as LCH on histology. Chemotherapy was subsequently initiated. The initial presentation of LCH with bilateral ear and skull involvement is a very rare condition. The signs and symptoms of otologic histiocytosis can mimic those of acute and chronic infectious ear disease. Only a surgically obtained biopsy leads to definitive diagnosis and appropriate therapy.

Key words: eosinophilic granuloma, histiocytosis X, Langerhans cell histiocytosis, mastoiditis, mastoid granuloma, otitis media, otitis externa.

Langerhans cell histiocytosis (LCH) or histiocytosis X is a rare disease that may affect multiple organs. The term histiocytosis X was first proposed by Liechtenstein[1] in 1953 to describe a spectrum of disorders characterized by the idiopathic proliferation of histiocytes[2]. There are three well-established clinical subsets of LCH that should be defined: eosinophilic granuloma of bone, Hand-Schüller-Christian disease, and Letterer-Siwe disease[3]. Data accumulated during the last few years suggest that all forms of LCH result from a proliferate disorder of a subpopulation of the mononuclear phagocyte system called Langerhans cell. These cells are morphologically similar to histiocytosis on routine light microscopy, but differentiated by electron microscope and immunocytochemistry[4].

At the meeting of the Histiocytosis Society in 1985, the term "Langerhans cell histiocytosis" was recommended to replace all previous terms, including histiocytosis X[5]. It is now generally accepted that these entities are probably one disease with a spectrum of clinical manifestation[6]. The two extremes of this disease are really identified clinically. The most common form is solitary eosinophilic granuloma of bone, which has excellent prognosis[7]. At the other end of the spectrum, the disease affects multiple organs and tissues including bones, skin, pituitary, lung, liver, and the hematopoietic system[8]. This involvement may cause multiple organ dysfunctions and have a fatal outcome. A high index of suspicion is required to recognize the otologic manifestations of histiocytosis X for two reasons: the systemic manifestation of the disease is often so dramatic that the ear findings are overlooked, and the otologic findings of LCH can mimic more common diseases, including simple otitis externa, otitis media, aural polyps, acute mastoiditis, chronic

otitis media, and metastatic lesions. In the present study, a child with systemic LCH is presented, who was initially misdiagnosed and treated for non-specific otitis media. The diagnosis and the management of this relatively rare disease are discussed.

Case Report

A seven-month-old boy presented with a two-month history of recurrent bilateral otitis media and with rash and seborrheic areas on his scalp. The patient was given per os antibiotic therapy and corticosteroid ointment. Two days prior to his admission, his mother noticed a small lump over the right mastoid. On physical examination, right soft tender postauricular small swelling was noted. There was a whitish discharge from both ears and an apparent mass in the right ear canal. The patient did not have any paresis of facial nerve.

With the diagnosis otitis media, external otitis and mastoiditis, the patient underwent bilateral myringotomies under general anesthesia. There was a whitish discharge from both ear canals, while no purulent discharge was found in the middle ears. Needle aspiration from the postauricular lump was negative for the presence of purulent pus. The patient continued the therapy with intravenous antibiotics and eardrops.

Eight days later the general condition of patient showed no improvement and the lump over the right mastoid was enlarged. Lytic lesion of the temporal bone was evident on lateral skull X-ray (Schüller) (Fig. 1). The patient was re-operated immediately. After the postauricular incision was performed, a reddish and friable mass was found, which had expanded and already destroyed the mastoid bone. No purulent pus was found. Biopsy was taken from this area and the findings were characteristic for LCH. Biopsies from seborrheic areas on his scull were also positive for LCH. The computerized tomography (CT) scan of the head was typical for LCH lytic lesion over the right mastoid (2-3 cm) (Fig. 2). The rest of the workup for histiocytosis revealed hepatosplenomegaly (spleen 6-7 cm, liver 3-4 cm), anemia (Hb 6 g/dl, while upon admission 8.8 g/dl), slightly elevated SGOT (106) and SGPT (210), and albumin 33 g/L. The skeletal survey was normal. There was no diabetes insipidus. The biopsy revealed infiltration by histiocytic cell positive for CD1a and S-100 and negative for CD 45 and CD 15.

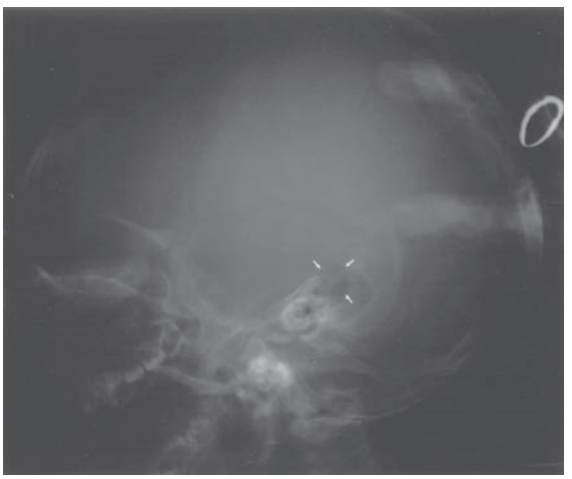

Fig. 1. Lateral skull X-ray (Schüller) demonstrating histiocytosis X in right temporal bone (with arrows).

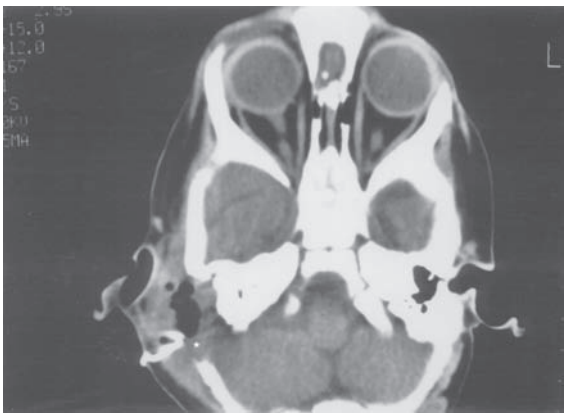

Fig. 2. Computerized tomography scan showing a lytic lesion with destruction of the temporal bone on the right (asterisk).

The patient was referred to the pediatric hematological oncology department for therapy and died from his disease four months later.

Discussion

Although LCH lacks the histologic appearance of a malignancy and fails to exhibit metastasis as in classic malignant disease, this benign process has the propensity to be locally aggressive, osteolytic, and recalcitrant, and to produce multiple synchronous lesions that involve multiple systems and organs[4].

The histologic hallmark of this disease is a proliferation of the Langerhans dendritic cell in a background of inflammatory cells with

sheets of eosinophils, as well as presence of Birbeck granule on electron microscopy. Immunohistochemical staining demonstrates positivity for CD1a and S100. The exact nature of LCH is under investigation as it has become apparent that LCH is not a true malignancy and does not behave as other malignant disorders of histiocytes[4]. Distinct lesions are usually seen in soft tissue and bone. Bony disease was the most common finding and occurred in 79% of patients[5]. LCH can affect almost every organ in the body. Organs involved were the lungs, spleen, liver, brain, heart, pancreas, stomach and muscle[7]. The lesions are soft and yellow to brown with frequent areas of necrosis and hemorrhage. Microscopically, a histiocytic and eosinophilic infiltrate is seen. Giant cells may be seen, which are believed to represent fused histiocytes[8-13].

The majority of patients suffering from this disorder first present (63%) or later develop head and neck manifestations[9-10]. The skull is frequently involved (42%); the temporal bone can be affected either as a solitary lesion or as part of a multisystem involvement in up to 61% of patients. When the temporal bone is involved, 30% of affected patients demonstrate bilateral disease[11-12]. Manifestations of LCH may be confused with more common disorders such as chronic suppurative otitis media and acute mastoiditis, which are not responsive to medical therapy[10], thereby delaying the diagnosis, as observed in our case.

The cases presented demonstrate the classic postauricular swelling, which is seen in 10-30% of all patients with LCH. The ear often protrudes anteriorly, since the mass is subgaleal and lifts the entire auricle away from the temporal bone. There is frequently erosion of the bony posterior external auditory canal with sagging of the canal wall skin in such a way that the visualization of the tympanic membrane is difficult. Because the lesion infrequently involves the middle ear, the tympanic membrane is usually normal. This characteristic offers important differentiation between the lesion of LCH and acute mastoiditis, since acute mastoiditis is almost always associated with middle ear disease. Interestingly, although the facial nerve is exposed in the middle ear in 50% of all individuals, there have been only 14 reported cases of facial nerve paralysis in patients with LCH in the English literature. Other areas of erosion include the tegmen tympani, the bony plate covering the sigmoid sinus, the squama of the temporal bone and rarely the vestibular labyrinth. The mastoid air cell system is usually destroyed when this disease involves the temporal bone. Palpation of the mass reveals soft pseudofluctuation with associated cutaneous erythema but no tenderness. Because of the propensity of this condition to erode the posterior canal wall, a secondary external otitis and stenosis may develop. Perforation of the tympanic membrane is uncommon and vestibular abnormalities are rare[10-11].

Exophthalmos results from lesions involving the orbital walls and the surrounding soft tissue reaction. The skin is a common site of involvement in more advanced LCH and the scalp is particularly apparent in this condition. A seborrheic rash with almost dandruff-like condition can result, although much more profound greasy, weeping dermatitis is also seen at times[11].

The flat bones of the skull, ribs, pelvis and scapula are most commonly involved. In the cranium, the frontal areas are most commonly involved and lesions may be single or multiple. The most commonly involved sites are the mandibles, especially posteriorly and along the alveolar ridges. The oral cavity can also be the site of mucosal ulcerations and stomatitis, which histologically reveal the typical histiocytic and eosinophilic infiltration. The dermatic lesions due to seborrheic dermatitis and the recurrent ear infections will raise the suspicion of LCH, while anemia, splenomegaly, hepatomegaly, and the transaminase increase indicate systemic manifestation of the disease.

The incidence of LCH is estimated to be three cases per 1,000,000 children per year - more than 50% of all cases are seen in patients under age 10 - even though recent studies have shown that approximately 30% of LCH cases occur in adults, with an incidence rate of 1.8/1,000,000[14-15]. The average age of onset is 1 to 3 years, and the disease occurs more commonly in males[16-17]. The natural history of this disorder is interesting because it has the potential for spontaneous resolution when the child enters adulthood.

Treatment is not specific and depends on the extent of disease at the time of diagnosis[18]. The localized form of LCH as an isolated

bone lesion usually 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. This is particularly true in children younger than two years of age who are at the highest risk of severe morbidity and mortality. Even so, benefits of treatment with cytotoxic agents should be weighed against long-term side effects of chemotherapy. Most common drugs used for treatment are corticosteroids, vinca alkaloids, mercaptopurine, methotrexate, and etoposide (VP16). Recent reports of successful treatment of recurrent or refractory disease with 2-chlorodeoxyadenosine (2CdA), a purine analogue, and cyclosporine, an immune modulator, offer a welcome addition to management of LCH[19].

Although radiation therapy has been a traditionally viable and even popular option, it is not recommended in the head and neck secondary to significant potential side effects and does not offer control in a primary or adjuvant fashion that is acceptable. In addition, there are reports of secondary malignancy resulting from radiation treatment[20].

The role of ear, nose and throat surgery in LCH is limited to diagnostic biopsy and to the treatment of localized disease (curettage, aural polypectomy). In the case of multifocal LCH, as in our patient, an invasive surgical approach is not suitable and chemotherapy should be administered. A multidisciplinary approach to LCH patients and in particular of the otolaryngologist is required to recognize LCH early, and to plan the best management of such a delicate site of disease.

REFERENCES

1. Appling D, Jenkins HA, Patton GA. Eosinophilic granuloma in the temporal bone and skull. Otolaryngol Head Neck Surg 1983; 91: 358-365.
2. Kimmelman CP, Nielsen E, Snow JB Jr. Histiocytosis X of the temporal bone. Otolaryngol Head Neck Surg 1984; 92: 588-590.
3. Devaney KO, Putzi MJ, Ferlito A, Rinaldo A. Head and neck Langerhans cell histiocytosis. Ann Otol Rhinol Laryngol 1997; 106: 526-532.
4. Buchmann L, Emami A, Wei JL. Primary head and neck Langerhans cell histiocytosis in children. Otolaryngol Head Neck Surg 2006; 135: 312-317.
5. Dimentberg RA, Brown KL. Diagnostic evaluation of patients with histiocytosis X. J Pediatr Orthop 1990; 10: 733-741.
6. Osband ME. Histiocytosis X Langerhans cell histiocytosis. Hematol Oncol Clin North Am 1987; 1: 737-751.
7. Smith RJ, Evans JN. Head and neck manifestations of histiocytosis X. Laryngoscope 1984; 94: 395-399.
8. Jones RO, Pillsbury HC. Histiocytosis X of the head and neck. Laryngoscope 1984; 94: 1031-1035.
9. Sellari-Franceschini S, Forli F, Pierini S, et al. Langerhans' cells histiocytosis: a case report. Int J Pediatr Otorhinolaryngol 1999; 48: 83–87.
10. DiNardo LJ, Wetmore RF. Head and neck manifestations of histiocytosis-X in children. Laryngoscope 1989; 99: 721-724.
11. Kleinjung T, Woenckhaus M, Bachthaler M, et al. Langerhans' cell histiocytosis with bilateral temporal bone involvement. Am J Otolaryngol 2003; 24: 265-270.
12. Postovsky S, Daitzchman M, Dale A, et al. Unusual presentation of mastoid eosinophilic granuloma in a young patient. Pediatr Hematol Oncol 2001; 18: 283-289.
13. Chu T, D'Angio GJ, Favara BE, et al. Histiocytosis syndromes in children. Lancet 1987; 2: 41-42.
14. Cochrane LA, Prince M, Clarke K. Langerhans' cell histiocytosis in the pediatric population: presentation and treatment of head and neck manifestations. J Otolaryngol 2003; 32: 33-37.
15. Haupt R, Nanduri V, Calevo MG, et al. Permanent consequences in Langerhans cell histiocytosis patients: a pilot study from the Histiocyte Society-Late Effects Study Group. Pediatr Blood Cancer 2004; 42: 438-444.
16. Surico G, Muggeo P, Muggeo V, et al. Ear involvement in childhood Langerhans' cell histiocytosis. Head Neck 2000; 22: 42-47.
17. Nicholson HS, Egeler RM, Nesbit ME. The epidemiology of Langerhans cell histiocytosis. Hematol Oncol Clin North Am 1998; 12: 379-384.
18. Yetiser S, Karahatay S, Deveci S. Eosinophilic granuloma of the bilateral temporal bone. Int J Pediatr Otorhinolaryngol 2002; 62: 169-173.
19. Stine KC, Saylors RL, Saccente S, et al. Efficacy of continuous infusion 2-CDA (cladribine) in pediatric patients with Langerhans cell histiocytosis. Pediatr Blood Cancer 2004; 43: 81-84.
20. Gold DG, Neglia JP, Dusenbery KE. Second neoplasms after megavoltage radiation for pediatric tumors. Cancer 2003; 97: 2588-2596.