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Langerhans Cell Histiocytosis Presenting as a Complicated Case of Otitis Media in a One-Year-Old Girl: A Case Report

ABSTRACT

Objective: To present a case of Langerhans cell histiocytosis mimicking bilateral otitis media and acute mastoiditis in a one-year-old girl, and to discuss the clinical presentation, diagnostic dilemma, management and prognosis of this disease.

Methods:

Design: Case Report
Setting: Tertiary Private Teaching Hospital
Patient: One

Results: A one-year-old girl with a three-month history of bilateral otorrhea, post-auricular lymphadenopathies and dermatitits unresponsive to multiple courses of antibiotics, developed osseous and soft tissue destruction around the temporal and occipital bones. Her multiple progressive symptoms eventually led to the diagnosis of Langerhans cell histiocytosis.

Conclusion: Langerhans cell histiocytosis is a multifocal disease that can present with ear symptoms and can cause management dilemmas. It may mimic acute or chronic infections of the ear and should be suspected when extensive bone erosion is present.

Keywords: *Langerhans cell histiocytosis; otitis; mastoiditis; temporal histiocytosis*

When otolaryngologists encounter a patient with a discharging ear, the management is usually quite straightforward. However, there are cases that fail to respond to the usual antibiotics and persist, leading to more complex decision-making dilemmas. We present one such case with multiple confounding conditions – an infant with unresponsive ear discharge, an ear canal mass, enlarging cervical lymphadenopathies and refractory dermatitis, who was initially misdiagnosed and treated for chronic otitis media. This was how we arrived at the unforeseen final diagnosis of Langerhans cell histiocytosis after three frustrating months.

CASE REPORT

A one-year-old girl with a two-month duration of diffuse erythematous scaly plaques on her scalp was referred to us due to persistent left-sided otorrhea. The patient was then being managed for seborrheic dermatitis (cradle cap) and *Ptyriasis amantacea*. She had concurrently enlarging firm, warm, and tender postauricular and occipital lymphadenopathies: 4.0 x 4.0 x 3.0 cm in the left postauricular area at level II, 3.0 x 3.0 x 1.0 cm in the right submandibular area at level 1B, and 2.0 x 2.0x 1.0 cm in the right postauricular area at level V. These seemed related to an infectious process on neck ultrasonography. Aural toilette revealed a stenotic left external auditory canal, with the tympanic membrane not visualized. There was also otorrhea of the contralateral ear. She was started on one week of Co-Amoxiclav, shifted to 10 days of

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Clindamycin, and then one week of Ampicillin-Sulbactam. Otic drops (Fluocinolone acetonide 250 mcg, Neomycin sulfate 3.5 mg, Polymyxin B sulfate 10,000 units) were started in both ears for two weeks, followed by Ofloxacin otic drops in both ears for two weeks. However, there was no resolution of the ear infection, lymphadenopathies or dermatitis.

Progressive increase in size of the adenopathies caused her left pinna to be displaced antero-inferiorly. Marked frontal bossing was also noted. Hematologic workups (because of a family history of leukemia presenting with lymphadenopathies in the maternal grandfather) were unremarkable.

Her symptoms worsened in the second month. The left postauricular lymphadenopathy continued to erode laterally and left-sided otorrhea became blood-tinged, with growth of a polypoid mass in the left ear canal. *(Figure 1)* Brain and neck computed tomography (CT) scans revealed an apparently aggressive 5.7 x 4.2 x 9.3 cm neoplasm causing significant osseous and soft tissue destruction around the temporal and occipital bones. *(Figure 2A, B)*

Histopathologic evaluation of incision biopsy specimens of the left postauricular lymphadenopathy and ear canal mass showed only suppurative and granulomatous inflammation and fibrosis. With seemingly inconsistent imaging and histopathology results, tuberculous (TB) adenitis was considered, being a common condition among Filipinos. However, a Mantoux tuberculin skin test was negative. Special stains for mycobacterial (AFB) and fungal organisms (PAS and GMS) were also negative. Re-examination of the deeper tissue sections revealed clusters of atypical mononuclear cells suggestive of an atypical lymphoid proliferation and immunohistochemical staining was requested. Meanwhile, her worsening scalp lesions remained uncontrolled, becoming more prominent in both postauricular regions. Similar skin lesions also ensued in the inguinal and gluteal areas.

By the third month, she persistently had left-sided bloody otorrhea and worsening dermatitis, as well as beginning abscess formations in her cervical lymphadenopathies. Incision and drainage of the abscesses was deferred because transfusion was prioritized due to anemia. A skin punch biopsy revealed histiocytosis while the immunohistochemical stain results were positive in Bcl2, Ki67, CD68, CD1a and Langerin, *(Figure 3A, B)* consistent with a diagnosis of Langerhans cell histiocytosis (LCH). Standard induction therapy which included Vinblastine and Prednisone was given for six weeks. This was followed by maintenance therapy consisting of Cytarabine and Vincristine. There was regression of signs and symptoms during the treatment course, while continuous monitoring and evaluation of risk organ involvement (such as the liver, spleen, lungs and central nervous system) remained unremarkable. Our patient completed 24 cycles of chemotherapy and is currently in remission. We continued serial aural toilette and hearing evaluation and noted regression of temporal lesions on skull radiographs. Close surveillance by otorhinolaryngology, pediatrics, dermatology and hematology-oncology continues to date.

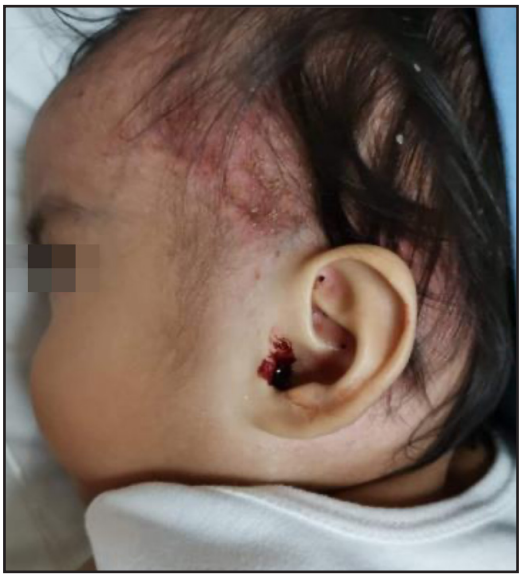

Figure 1. One year-old girl with bloody otorrhea, multiple lymphadenopathies, scalp dermatitis and frontal bossing. Photo published with permission.

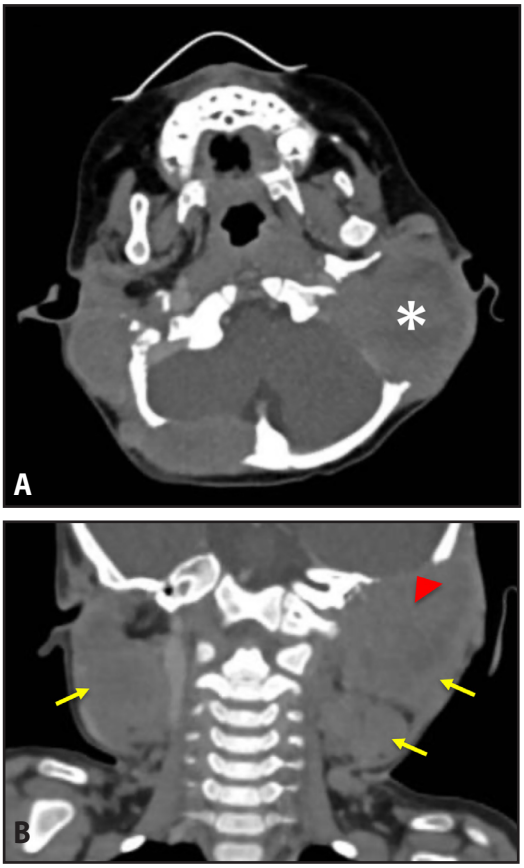

Figure 2. Computed tomography images: **A.** axial view showing the larger of the two lesions that measures 5.7 x 4.2 x 9.3 cm. (asterisk); and **B.** coronal view showing confluence of large, heterogeneously enhancing soft tissue lesions in bilateral temporal regions (arrows), with lytic destruction of the entire adjacent squamosal temporal bone and occipital bones and necrotic changes (arrowhead).

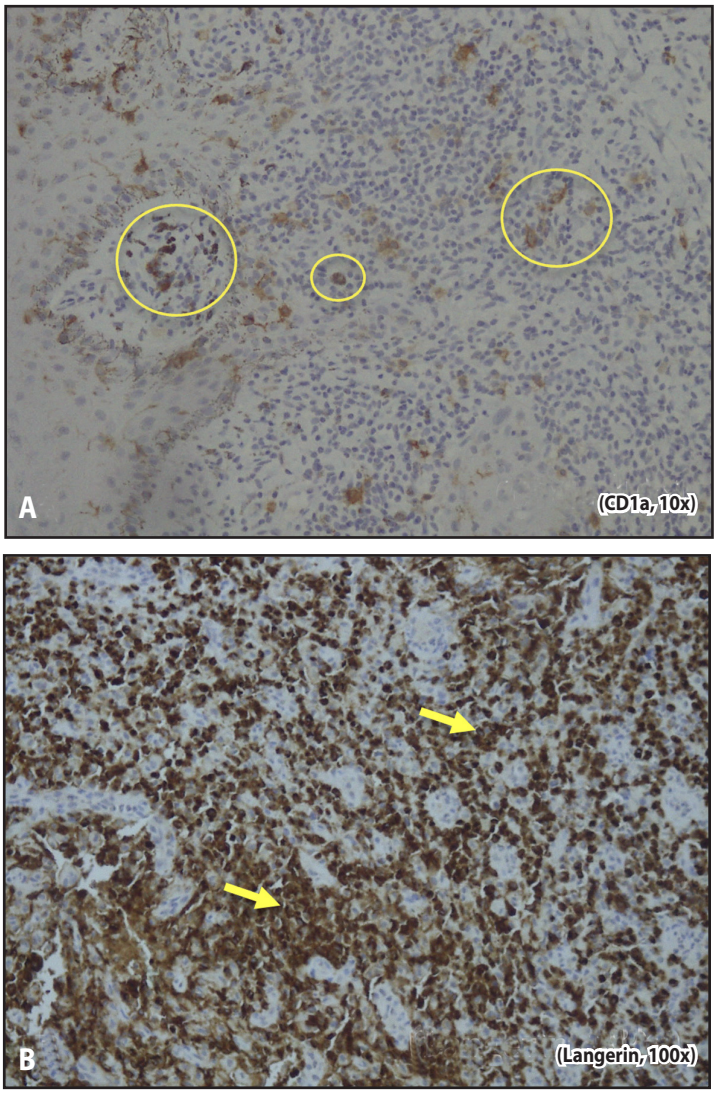

Figure 3. Histopathologic slides, immunohistochemical stains: **A.** clusters of histiocytes staining positive in CD1a (circles) 10x magnification; and **B.** Langerin (arrows), 100x magnification.

DISCUSSION

Our patient is a one-year-old girl presenting with 3-months history of bilateral otorrhea, post-auricular lymphadenopathies and dermatitis, unresponsive to multiple courses of topical and systemic antibiotics. Later, she developed significant osseous and soft tissue destruction around the temporal and occipital bones. The multiple array of progressive symptoms eventually led to the diagnosis of the complex disease, Langerhans cell histiocytosis (LCH). Previously known as Histiocytosis X, LCH is a systemic disease that may manifest as a primary otorhinolaryngology disease, causing diagnostic and management dilemma.[1] Its worldwide incidence ranges from 5 to 9 cases per million children per year and can be diagnosed in any age group but a clear predominance exists for the pediatric age group.[1] The clinical features of LCH depend on the site of lesions, number of involved sites, and the extent to which the function of the involved organs is compromised.[2] The current clinical classification differentiates between single system disease (SS-LCH) that can be unifocal or multifocal, and multisystem disease (MS-LCH), based on the extent of organ involvement at diagnosis.[2] Unifocal LCH is found most commonly in older children and adults, while multifocal LCH is most common in younger children, present in almost 50%–70% of cases.[3] The disease's occurrence in our patient aligns with the epidemiologic data.

The clinical spectrum of this disease includes an indolent, chronic, localized-to-bone eosinophilic granuloma on one end, to an acute, fulminant, disseminated disease called Abt–Letterer–Siwe disease on the other end.[3] The intermediate clinical form called Hand-Schuller-Christian disease is characterized by multifocal, chronic involvement and classically presents as the triad of diabetes insipidus, proptosis, and lytic bone lesion.[3] Among the three, Abt–Letterer–Siwe disease is considered in our patient due to its acute, multisystem, and aggressive disease presentation. It is characterized by cutaneous lesions, bone lesions, hepatomegaly, and splenomegaly, usually occurring in infants and newborns.[4] Ear and skull involvement as initial presentation may be observed in 14% to as high as 61% of cases.[4] They are more likely to occur as part of a multifocal or systemic LCH.[4] Ergo, an otologic condition, when presented alongside a cluster of signs and symptoms, raises suspicion of LCH. Although, up to 25% of patients are reported with ear involvement as their only symptom.[5] Consistent with our patient's symptomatology, LCH can be in the form of chronic otitis externa or otitis media, external ear canal mass or polyp, postauricular swelling, or conductive hearing loss.[6] Cutaneous lesions, on the other hand, can involve the head, trunk and skin folds.[7] When present in the scalp and retroauricular, the lesions resemble seborrheic dermatitis, characterized by erythematous lesions that may ulcerate and form crusts.[7]

Brown *et al.* in 2005 reported a misdiagnosis rate of ~72.7% (15/22) for LCH, primarily due to the clinical presentation resembling other more common conditions.[8] LCH is often missed. Therefore, a high index of suspicion is important for early recognition, in order to request for appropriate further testing and coordination with other specialists.

The gold standard for diagnosing LCH is by electron microscopy.[9] To aid in diagnosis, Computed tomography is sensitive in demonstrating the extent and progress of the disease, being able to delineate radiolucent areas and can identify bony destruction of the petrous apex better than MRI.[5] LCH typically appears as a lytic or "punched out" lesion, as in our case, demonstrating a 5.7 x 4.2 x 9.3 cm neoplasm with significant osseous and soft tissue destruction around the temporal and occipital bones. The masses infiltrated the external auditory canals, mastoids, and partly the middle ear on both sides; also eroding the bilateral round windows and left middle ear ossicles. Radiologically, the diagnosis of LCH was already considered. However, since the hematologic work-up and incision biopsy of the ear canal mass were

unremarkable, the team decided to explore on Tuberculosis (TB) as probable diagnosis.

There may be confusion with LCH and other diseases in the head and neck, particularly granulomatous inflammations, such as tuberculosis (TB). Many of the clinical features of LCH mimic this highly endemic disease in the Philippines.[10] In our case, even the histopathology result of the postauricular lesion and ear canal mass was initially read as granulomatous inflammation. Microscopically, both diseases show aggregates of histiocytes. Histiocytes of tuberculosis are epithelioid and spindle-shaped, while histiocytes seen in LCH are large, ovoid, mononuclear cells.[11] A local study by Fellizar and Chiong in 2008 documented a similar dilemma of TB mimicking LCH.[11] In both cases, disease involved the middle ear and temporal bones and presented with granuloma-like pattern of cells and aggregates of histiocytes on histopathology.[11] In these situations, immunohistochemistry becomes fundamental to establish diagnosis, being able to distinguish Langerhans cells as they express CD1a and Langerin, both of which turned out positive in our patient.[11]

The burden of therapy may be extremely heavy, and must be individualized.[13] The treatment for LCH necessitates chemotherapy. Our patient was able to complete 24 cycles of chemotherapy, and is currently on remission. The most relevant prognostic factors are age at the time of diagnosis, multisystem involvement, and vital organ dysfunction. Age younger than two years at the time of diagnosis, such as this patient, is correlated with increased mortality rate.[13] Our patient, who is one-year old at time of diagnosis, underwent multi-organ assessment, concluding involvement of the ears, skull, lymphatics as well as the skin. The prognosis of LCH localized to the ear and temporal bone alone may be favorable. However, multisystemic involvement has greater risk of permanent disabilities and poor outcome. Nearly half of patients with multisystemic disease exhibit reactivation, which occurs in an unpredictable manner. Some patients experience reactivation several times. Most of the first reactivations occur within two years after diagnosis, most frequently in the bone and are rare in risk organs.[14] This necessitates increased monitoring via thorough multiorgan evaluation and close follow-up.[15]

Haupt *et al.* suggested that monitoring of these patients should continue at least up to adolescence and possibly into adult life.[2] They suggest that involvement of the middle or inner ear and the temporal bone requires audiometry at diagnosis to assess hearing acuity, and that this should be done again at end of treatment and reassessed at start of school or if any new symptoms develop.[2] Early diagnosis and interventional strategies such as hearing aids, as well as collaboration with other specialists are vital to achieve better treatment outcomes.

In conclusion, Langerhans cell histiocytosis is a multifocal disease, which can present with a cluster of seemingly coincidental symptomatology. It should be included in the differential diagnosis in a patient presenting with persistent ear discharge, especially in the pediatric population. This infiltration may mimic common primary otorhinolaryngology disorders; hence suspicion should be made when extensive bone erosion is seen. These seemingly unresponsive ear conditions, when presented with a cluster of signs and symptoms, should warrant further testing and coordination with other specialists. They are frequently difficult to distinguish on a purely clinical basis and requires corroboration by histopathologic and immunohistochemical results for definite diagnosis. This case report hopes that otolaryngologists will be able recognize and manage cases of LCH early enough, to ensure a better rate of recovery and quality of life in future patients with a similar set of clinical clues.

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