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A Great Mimicker, Langerhans Cell Histiocytosis in a 28-Year-Old Man: A Case Report

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Abstract: Langerhans cell histiocytosis (LCH) is a rare myeloid neoplastic disorder typically seen in children and characterized by infiltrative bone lesions. The skin, the lungs, the liver, and the central nervous system may also be involved. Langerhans cell histiocytosis is even more unusual in adults and presents a diagnostic challenge, given that its imaging characteristics are similar to those of other, more prevalent neoplastic processes. We report a case of LCH in a 28-year-old man with neurologic symptoms due to a nonspecific suprasellar mass and a single lytic lesion in the right bony pelvis. The results of histologic evaluation of the lytic lesion confirmed the diagnosis of LCH.

Keywords: *suprasellar mass, Langerhans cell histiocytosis, lytic lesions*

Case Presentation

A 28-year-old man was presented to our institution with impaired orientation and attention as well as anisocoria. The patient's medical history was remarkable for repeated hospitalizations to different hospitals within the past few months. Initially, the patient was hospitalized with an onset of slurred speech. At that time, the patient's serum sodium concentration was elevated, and a computed tomography (CT) of the brain showed a hyperdense suprasellar mass. Subsequent laboratory results revealed panhypopituitarism and diabetes insipidus. The patient was prescribed hormone replacement therapy with desmopressin, hydrocortisone, and levothyroxine. Although luteinizing hormone was also suppressed, the patient declined testosterone replacement therapy.

Key Points

- Langerhans cell histiocytosis in adults is rare, but in the presence of a suprasellar mass with other relevant systemic findings, the disease should be included in the differential diagnosis.
- The imaging characteristics of Langerhans cell histiocytosis are nonspecific, and a histologic evaluation is required for definitive diagnosis.

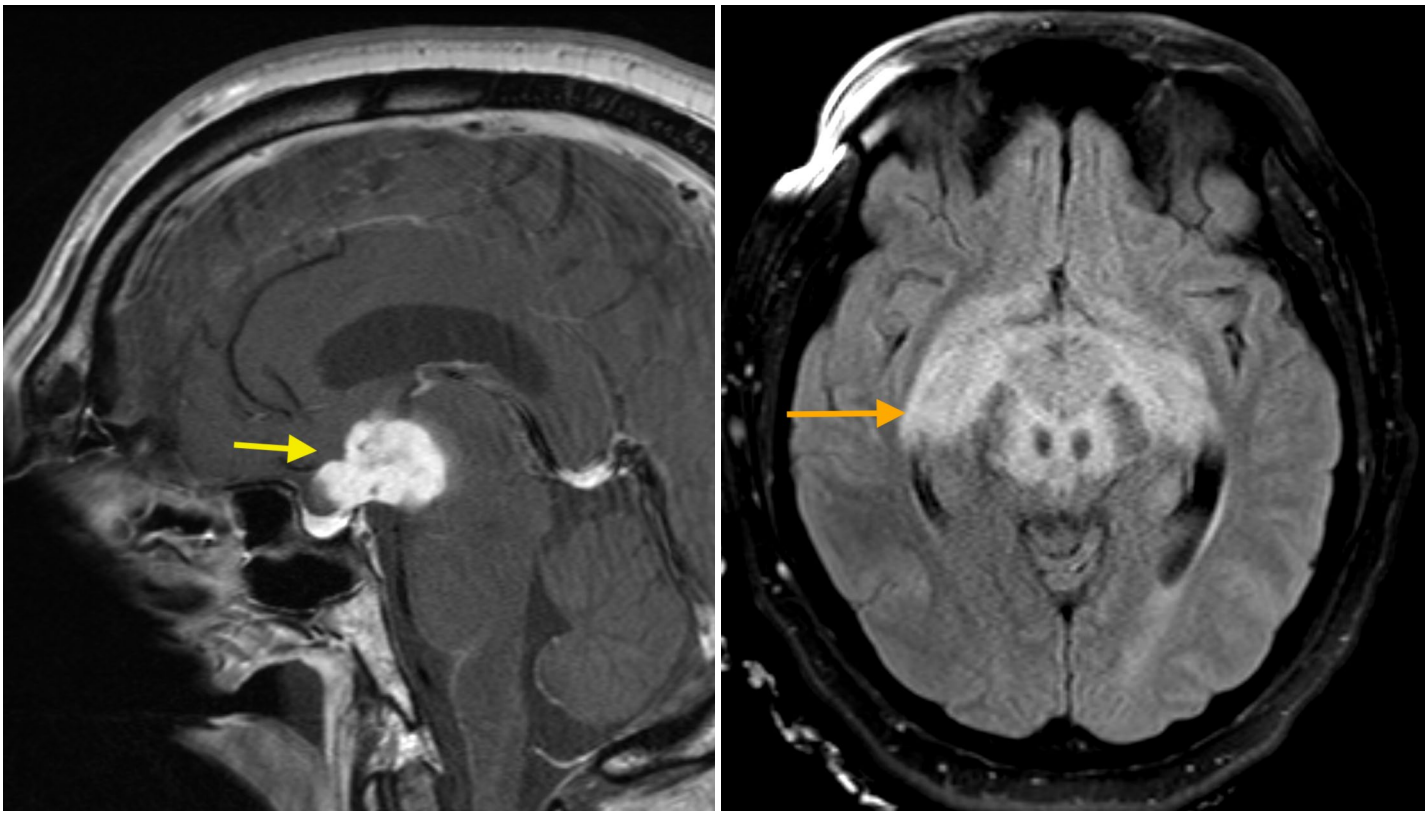
Approximately one month later, the patient underwent biopsy of the suprasellar mass. The findings of histologic examination were nondiagnostic. The results of a study of cerebrospinal fluid (CSF) were negative for the presence of malignant cells.

Soon after, the patient was hospitalized with agitation and confusion, thought to be secondary to hypernatremia, and then was hospitalized again with worsening lethargy and headaches.

Figure 1. Contrast-enhanced Magnetic Resonance Imaging (MRI) of the Brain of a 28-Year-Old Man with Langerhans Cell Histiocytosis.

A Gadolinium-enhanced T1-weighted MRI, sagittal view

B Fluid-attenuated inversion recovery (FLAIR) MRI, axial view



(A) Gadolinium-enhanced T1-weighted image of the brain, sagittal view, shows a suprasellar mass with vivid contrast enhancement (A, yellow arrow). The mass measures 29 x 32 x 18 mm in three orthogonal planes (anteroposterior, transverse, and craniocaudal). (B) Fluid-attenuated inversion recovery image of the brain, axial view at the level of the midbrain, shows vasogenic edema (B, orange arrow) surrounding the suprasellar mass that extends into the optic chiasm, the midbrain, the medial temporal lobes, and the inferior frontal lobes.

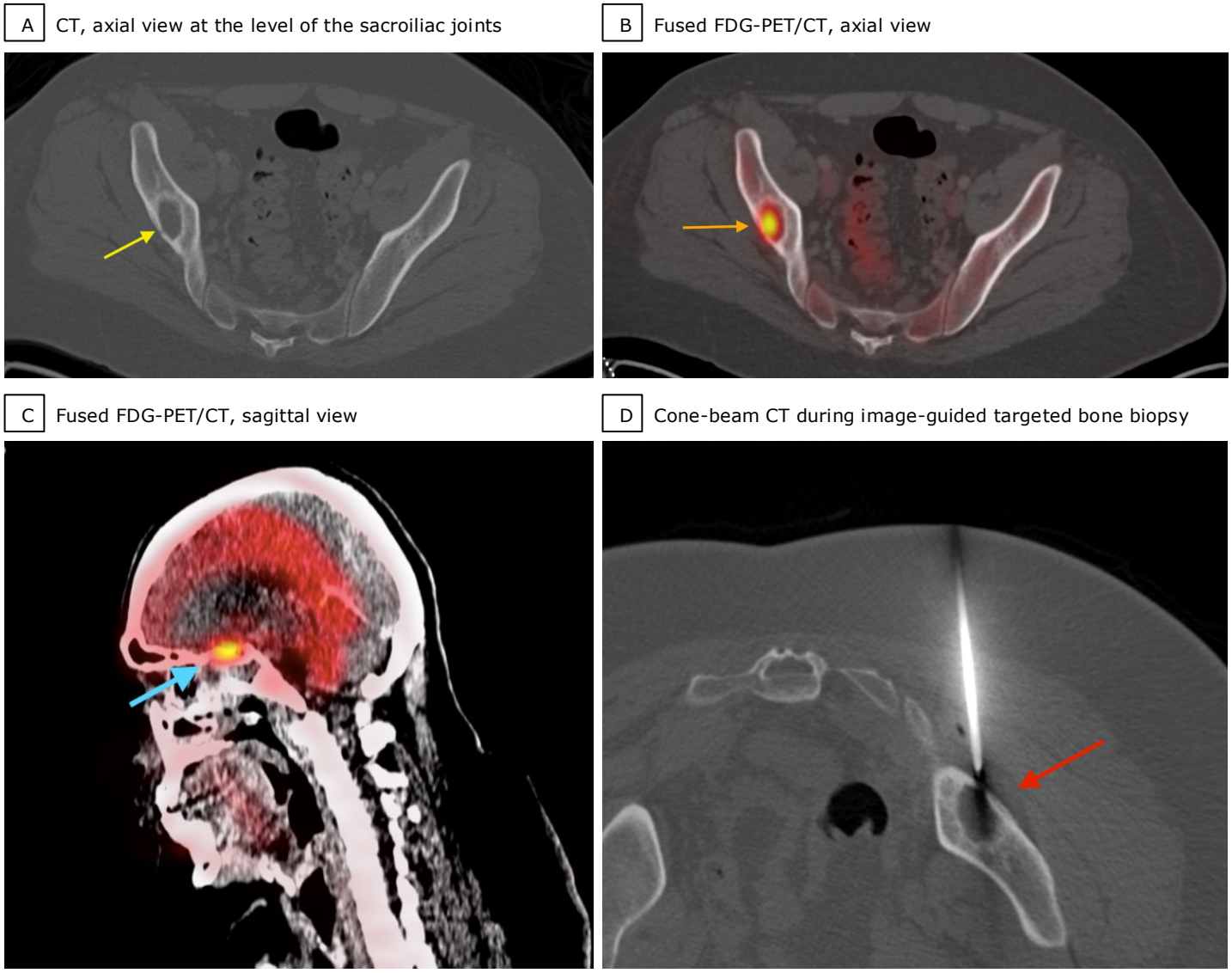
The patient underwent imaging of the brain with CT and magnetic resonance (MR), which showed a stable, enhancing suprasellar mass with increasing intracranial mass effect and vasogenic edema (Figure 1). Hypertonic saline and corticosteroids were administered to the patient, and an extraventricular drain was placed to relieve elevated intracranial pressure.

Upon presentation to our institution, the results of the patient's physical examination were unreliable because of limited patient cooperation. Although left temporal hemianopsia had been previously documented, it was not reproduced at our institution. The results of repeated CSF studies for the presence of fungal and bacterial cultures/stains were negative.

Repeated MR imaging of the pituitary gland showed a slight decrease in both the size of the mass and in the intensity of the vasogenic edema. Differential diagnosis at this time included optic chiasm glioma and steroid-responsive germinoma. Prior to a second biopsy of the suprasellar mass, a CT of the chest, the abdomen, and the pelvis was performed in search for additional lesions more suitable for tissue sampling. The examination revealed scattered nodules and nodular consolidations in the lungs, hepatosplenomegaly, and a 2-cm osteolytic lesion with well-defined margins in the right iliac bone (Figure 2A).

Ultimately, the patient underwent a second biopsy of the suprasellar mass. The results of histopathologic examination were again nondiagnostic, showing neuroglial tissue with reactive changes and prominent macrophage infiltrate. Differential diagnosis at this time included inflammatory processes, such as

Figure 2. Positron Emission Tomography/Computed Tomography (PET/CT) and Percutaneous CT-guided Biopsy of a 28-Year-Old Man with Langerhans Cell Histiocytosis.



(A) CT of the pelvis, axial view shows a single well-marginated lytic lesion measuring 2.2 x 1.2 cm (A, yellow arrow) at the right iliac bone. No other osseous lesions were identified. (B) Fused FDG-PET/CT image of the pelvis, axial view, shows FDG-avid lytic lesion at the right iliac bone (B, orange arrow) revealing a standardized uptake value (SUVmax) of 17.0 (Reference SUVmax for liver – 3.7; for blood pool – 3.1). (C) Fused FDG-PET/CT image of the brain, sagittal reconstruction, shows focal intense FDG-uptake in the suprasellar region (C, blue arrow) above background parenchyma corresponding with the suprasellar mass on anatomical images presented in Figure 1. (D) Intraprocedural, cone-beam CT image of the right iliac bone with the patient in the prone position. A coaxial biopsy system is seen accessing the osteolytic lesion (D, red arrow) for core biopsy.

neurosarcoidosis, granulomatosis with polyangiitis, Langerhans and non-Langerhans cell histiocytoses, or immunoglobulin G4-related disease, but histopathologic examination lacked characteristic findings. Although immunohistochemical analysis revealed rare *CD1A*-positive cells, their morphologic features were not sufficient for diagnosis of Langerhans cell histiocytosis (LCH). However, the brain parenchyma was positive for langerin staining.

Next, a whole-body positron emission tomography/computed tomography (PET/CT) was performed in search for additional biopsy targets. The previously described right iliac lesion showed intense fluorodeoxyglucose (FDG) uptake (Figure 2B). The suprasellar mass appeared similar to the

one seen on the prior CT and showed intense FDG uptake (Figure 2C). The right iliac lesion was subsequently biopsied with CT guidance (Figure 2D). The findings of histologic evaluation were consistent with LCH (Figure 3). Given the *CD1A* and langerin positivity of cells in the biopsied specimen of the brain, the suprasellar mass was retrospectively diagnosed as another manifestation of LCH.

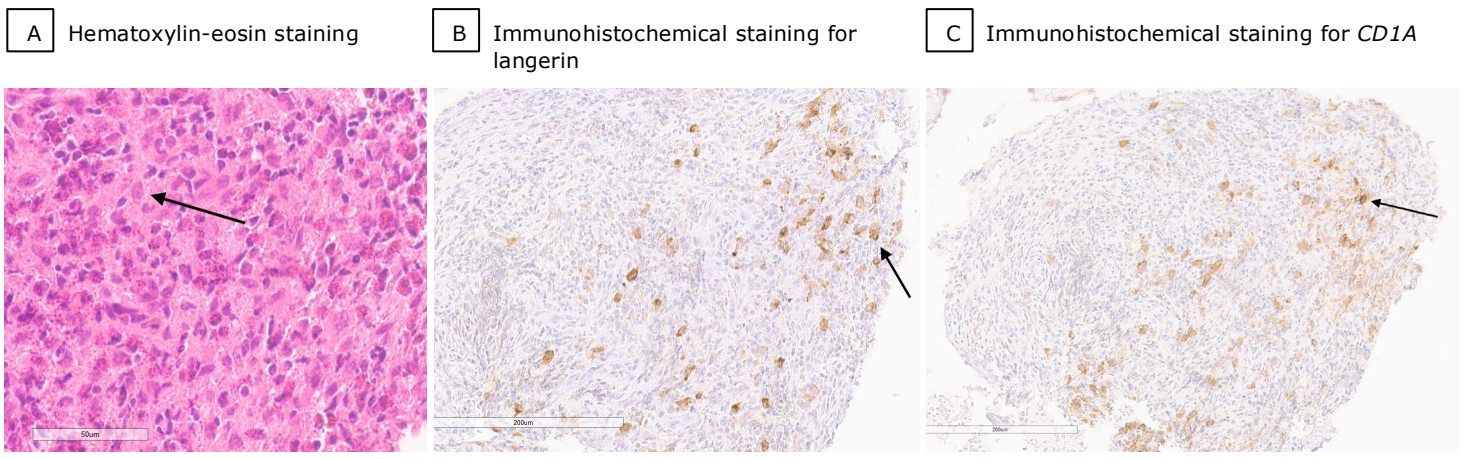
Discussion

Langerhans cell histiocytosis (LCH) is the most common of the histiocytoses, a group of proliferative disorders involving cells of the mononuclear phagocyte system.[1,4] The name of the disease is associated with understanding of its pathogenesis as a proliferation of abnormal or pathologically active Langerhans cells – dendritic cells or histiocytes predominantly found in the epidermis.[1] However, current evidence shows that LCH is an inflammatory myeloid neoplastic disorder that is caused by mutations in mitogen-activated protein kinase signaling pathway at critical stages of myeloid differentiation.[1]

Langerhans cell histiocytosis is seen mostly in children, with an estimated incidence rate of 5 per million children versus 1-2 per million adults affected by the disease, although there is a paucity of epidemiologic data, given the disease's rarity in adults.[1,5] One of the largest registries of LCH in adults 18 years and older included 274 patients with histologically proven disease.[2] According to the registry, the mean age of diagnosis of LCH in males was 33 years (SD; 15 years) and in females was 35 years (SD; 14 years), with a few patients older than 80 years.[2]

Four categories of LCH have been described: unifocal, multifocal unisystem, multifocal multisystem (disseminated), and adult pulmonary.[3,5] Unifocal disease involves a single or few bones and is the most common, affecting approximately 70% of patients with LCH.[4] Multifocal unisystem disease involves multiple sites of one of the organ systems and/or the reticuloendothelial system.[4] Multifocal multisystem disease is described as fulminant and often fatal; it comprises 10% of cases and usually manifests itself with anemia and thrombocytopenia in the first two years of life.[4] The pulmonary form of the disease arises primarily in adult smokers.[4,5] Multisystem disease is the most common type of LCH in adults, with 69% of patients having multisystem involvement.[2] Our patient experienced a multisystem type of LCH.

Figure 3. Histopathologic Examination of a Biopsy Specimen from the Right Iliac Lesion in a 28-Year-Old Man with Langerhans Cell Histiocytosis.



(A) Photomicrograph of the specimen reveals an admixture of eosinophils and histiocyte-like cells with oval nuclei (A, arrow) (hematoxylin-eosin, original magnification x40). (B and C) Photomicrographs of immunohistochemical stains for langerin (B) and *CD1A* (C) show histiocyte-like cells with positive immunoreactivity (B and C, arrows) to both markers, supporting the diagnosis of LCH (original magnification x20).

Bone lesions are the most common radiographic feature of LCH in both adults and children, occurring in approximately 80% of patients and predominantly involving the flat bones, with the most involved bones including the skull, the mandible, the ribs, the pelvis, and the spine.[4,6,7] Beveled lytic lesions are a characteristic finding of LCH that affects calvaria.[4,6] Aggressive, poorly defined expansile LCH lesions of the long bones can be seen in children.[4] Well-circumscribed lytic lesions of isolated flat bones, as described in our patient, are more common in adults.[7] The imaging features of these lytic lesions are nonspecific as they are similar in appearance to metastatic tumors and myeloma/plasmacytoma that are much more common in adults.[7] LCH lesions can also mimic common benign osseous lesions such as fibrous dysplasia.[7]

Diabetes insipidus is overall the most common central nervous system (CNS) manifestation of LCH, particularly with concomitant anterior hypopituitarism,[8] as seen in our patient, and is encountered in 29% of adults and in 17%-25% of pediatric patients.[2] In cases of LCH, both diabetes insipidus and anterior hypopituitarism are secondary to LCH infiltrates in the hypothalamus region or the posterior pituitary.[4,8] On MRI, this can be seen as an enhancing T2-hyperintense mass, loss of the posterior pituitary bright spot on T1-weighted imaging, and/or thickening of the pituitary stalk to greater than 3 mm.[4,8,9] In the absence of characteristic imaging findings and extra-CNS involvement, it may be difficult to differentiate LCH of the hypothalamic-pituitary axis from other suprasellar lesions, such as glioma, germinoma, or neurosarcoidosis and will necessitate tissue sampling for a definitive diagnosis.[4] On immunohistochemical examination, there is dense infiltration of the CNS parenchyma by *CD1A*-positive histiocytes, *CD68*-positive macrophages, as well as T cells and B cells, resulting in almost complete neuronal atrophy.[8] Zones of infiltration are surrounded by T-cell-dominated inflammation co-occurring with profound gliosis.[8] Other aspects of CNS involvement in LCH include extra-axial lesions in the meninges, the pineal gland, or the choroid plexus (all without blood-brain barrier protection), and more rarely, intra-axial, symmetrical neurodegenerative changes in the cerebellum, the basal ganglia, or the pons.[8,9]

Common sites of extraosseous LCH in adults include the lungs and the skin, in 58% and 37% of cases, respectively.[2] Isolated pulmonary LCH has a well-known strong association with smoking[2,4,5,10] and is seen on CT as centrilobular micronodules in a bilateral, symmetric upper-to-middle lung distribution.[4,10] These nodules undergo central necrosis that may lead to predominantly cystic disease with confluence of the cysts into a bullous formation.[4,10] Radiologically, pulmonary nodular LCH can appear similar to silicosis, sarcoidosis, metastases, and hematogenous infections, while cystic LCH can resemble lymphangioleiomyomatosis, emphysema, or bronchiectasis.[10] It is unclear whether the scattered lung nodules found on chest CT of our patient were the manifestations of pulmonary LCH, given the absence of the characteristic symptoms of the disease, the patient treatment with steroids, and near resolution of the nodules on PET/CT 19 days after the patient hospitalization.

The hepatosplenomegaly seen on CT of our patient may also reflect LCH. Hepatic and splenic involvement indicates less favorable prognosis in cases of LCH and is seen in 16% of adult patients.[2,4] Manifestations of hepatic disease on imaging include diffusely decreased attenuation on CT, decreased echogenicity on ultrasound, and discrete solid or cystic mass-lesions with peribiliary and periportal T1 and T2 hypointensity on MRI, indicative of periportal fibrosis.[4] This may lead to sclerosing cholangitis, a devastating complication of hepatic LCH.[4]

Conclusion

We report a case of histologically proven LCH in a 28-year-old man who presented with a suprasellar mass and then was found to have a single lytic lesion in the right pelvis. Although rare, LCH should remain in the differential diagnosis of a suprasellar mass in adults, especially in the presence of osseous lesions or other findings suggestive of LCH.

Author Contributions

Conceptualization, L.L.S. and S.M.D.; Acquisition, analysis, and interpretation of data, J.T.Y., P.F.W., and S.M.D; Writing – original draft preparation, J.T.Y.; Review and editing, L.L.S. and J.T.Y.; Supervision, L.L.S. and S.M.D. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Disclosures

None to report.

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