Multifocal, Multisystem Presentation of Adult-Onset Langerhans Cell Histiocytosis on 18F-Fluorodeoxyglucose Positron-Emission Tomography–Computed Tomography: A Rare Case Report

Abstract

Langerhans cell histiocytosis (LCH), also known as histiocytosis X, is a rare systemic disorder arising from clonal proliferation of immature CD207-positive (langerin) myeloid dendritic cells (histiocytes) in the skin and visceral organs with a tendency to involve single or multiple organ systems with variable clinical course and prognosis. The incidence of LCH is very less in adult and occurs almost exclusively in children. Genital, perianal, and lung lesions are considered to be rare manifestations of adult LCH. We describe a case of 31-year-old, nonsmoker female who presented in February 2020 with itching and burning sensation in perianal and vulvar regions accompanied with multiple nonhealing ulcers and papillomatous lesions. These lesions gradually increased in size with no response to antibiotics and topical steroids. She was advised positron-emission tomography–computed tomography (PET-CT) scan for further evaluation. After PET-CT scan, her provisional diagnosis of multisystem, multifocal Langerhans cell histiocytosis with high-risk organ involvement was made. Both vulvar and perianal lesions were biopsied which was suggestive of Letterer–Siwe variant of LCH. The prognosis of this variant is very poor even with aggressive chemotherapy and 5-year survival rate of only 50%. Hence, it requires careful consideration during diagnosis and management.

Keywords: *Fluorine-18-fluorodeoxyglucose positron-emission tomography–computed tomography, Histiocytosis X, Langerhans cell histiocytosis*

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Introduction

Langerhans cell histiocytosis (LCH) also known as Hand–Schüller–Christian disease or histiocytosis X is a rare systemic disease with an incidence of 0.5–5.4 cases/million/year. It is a rapidly progressing disease which involves clonal proliferation of immature CD207-positive (langerin) myeloid dendritic cells (histiocytes) in the skin and visceral organs and may involve single or multiple organ systems.[1,2] The LCH commonly affects pediatric population at a rate of 1 in 200,000, usually occurring between 1 and 3 years of age.[3] In adults, the incidence is roughly 1–2 cases/million, predominantly affecting those between the ages of 20 and 35 years.[4] The disease shows variable clinical course and prognosis depending on the site of involvement. The organs commonly affected in adults in decreasing frequency include lungs, bone, skin, pituitary glands, lymph nodes, and liver. Genital and perianal involvement is extremely rare in adults. The Letterer–Siwe variant of LCH has the worst prognosis with 5 year survival rate only 50% even with aggressive chemotherapy.

Case Report

A 31-year-old nonsmoker female with no significant past medical history presented with a chief complaint of itching and burning sensation over perianal and vulvar regions. The patient also reported amenorrhea for the last 2.5 years. She complained of polydipsia and polyuria for the past 6 months which was evaluated by a local physician, but laboratory findings were unremarkable and treated conservatively with water restriction; however, all her symptoms persisted with no response to treatment. On examination, multiple ulcers and papillomatous lesions were seen in the perianal and vulvar regions. Papules and plaques were manifested over submammary skin over the past 1 month. These lesions gradually increased in size with no response

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to antibiotics and topical steroids. Hence, she was advised positron-emission tomography–computed tomography (PET-CT) scan for further evaluation.

Her initial PET CT scan done in March [Figures 1 and 2], Column 1) showed intensely fluorodeoxyglucose (FDG) avid (SULpeak 9.7) thickening in bilateral external auditory canal, FDG avid osteolytic lesion in mandible, FDG avid hypodense nodule in left lobe of thyroid (SULpeak 5.6, 1.1 × 0.6 cm), non FDG avid and mildly FDG avid thick walled cystic lesions in bilateral lungs, FDG avid (SULpeak 3.7) fibro consolidative lesions in bilateral lower lobes, FDG avid (SULpeak 3.2) right pleural soft tissue deposit in anterior mediastinal pleura, multiple FDG avid (SULpeak 3.1) hypodense lesions in liver, and mildly FDG avid hypodense lesion in segment III of liver. FDG avid (SULpeak 8.7) thickening noted in perianal and vulvar regions and left infra mammary fold. FDG avid thickening was noted in hepatic flexure of the colon. Non FDG avid hypodense lesion was noted in the pituitary fossa. Multiple FDG avid (SULpeak 4.6) mediastinal, bilateral hilar, abdominal, bilateral inguinofemoral and left popliteal lymph nodes were noted. After PET-CT scan, her provisional diagnosis of multisystem, multifocal Langerhans cell histiocytosis with high-risk organ involvement was made.

To further evaluate, her brain magnetic resonance imaging (MRI) [Figures 3a-c] was done which showed an isodense exophytic nodular lesion with homogeneous enhancement arising from the hypothalamus projecting into the suprasellar cistern with contiguous thickening of the pituitary infundibulum and abnormal soft tissue within the external auditory canals. The bright spot of the pituitary gland was not visualized.

Biopsy taken from vulva, cervix and perianal lesions which was suggestive of LCH [Figure 4].

She was referred to oncologist and received four cycles of induction chemotherapy with injection cytarabine and steroids till June 27, 2020. Her second PET-CT scan was done in July 2020 which showed partial treatment response; therefore, her treatment was changed, and she received five cycles of second-line chemotherapy with injection cladribine from July 20, 2020. She developed an allergic rash with injection cladribine; hence, her chemotherapy regimen was changed to injection cytarabine from August 19, 2020, and she completed five cycles till November 21, 2020. Her third PET-CT scan was done in December 2020 which again showed partial treatment response Figure 5.

She presented with sudden-onset shortness of breath with left side chest pain on March 27, 2021. Her chest X-ray was done which was suggestive of left-sided pneumothorax. Intercostal drainage tube was placed on April 1, 2021. Left pleurodesis and intercostal drainage tube (ICD) removal was done on April 9, 2021. At present, she is stable with

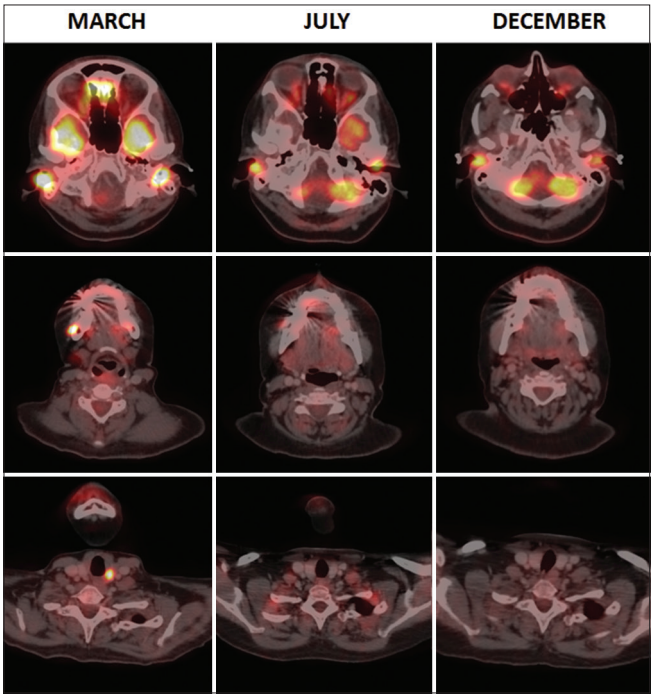

Figure 1: Initial transaxial images of positron emission tomography–computed tomography scan images of March (Column 1) show intensely fluorodeoxyglucose avid lesions in bilateral external auditory canal, fluorodeoxyglucose avid osteolytic lesion in mandible, fluorodeoxyglucose avid hypodense nodule in left lobe of thyroid. Latter positron emission tomography–computed tomography images of July and December (Column 2 & 3) show complete response in mandible and thyroid lesion and moderate response was seen in bilateral external auditory canal lesions

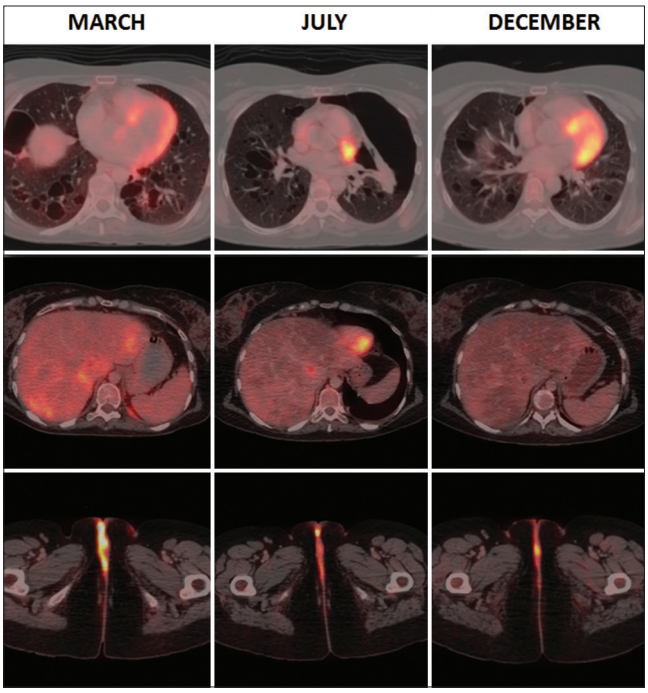

Figure 2: Positron emission tomography–computed tomography scan images of March (Column 1) show mildly fluorodeoxyglucose avid nonfluorodeoxyglucose avid thick walled cystic lesions in bilateral lungs, multiple fluorodeoxyglucose avid hypodense lesions in liver and fluorodeoxyglucose avid thickening in perianal and vulvar regions. Positron emission tomography–computed tomography images of July and December (Column 2 & 3) show complete response in lung lesions, moderate response in liver lesions, and mild response in perianal and vulvar lesions

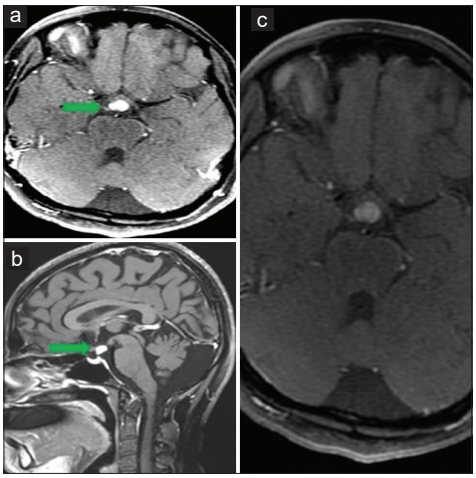

Figure 3: Brain magnetic resonance imaging [a (axial) & b (sagittal)- green arrow] and c (axial zoomed image) showed an isodense exophytic nodular lesion with homogeneous enhancement arising from the hypothalamus projecting into the suprasellar cistern with contiguous thickening of the pituitary infundibulum

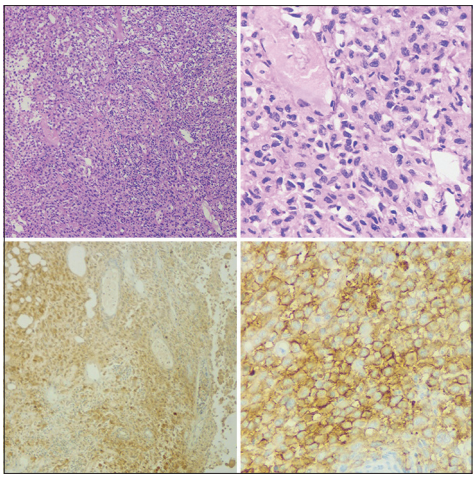

Figure 4: Histopathology images (10 X and 100 X) from cervical, vulvar and perianal lesions revealed keratinized stratified squamous epithelium with ulceration and patchy inflammation comprising abundant histiocytes, lymphoplasmacytic and polymorphs, and few eosinophils in underlying tissues, suggestive of Langerhans cell histiocytosis

minimal regression of vulvar, perianal, and submammary skin lesions and under regular follow-up.

Discussion

LCH is a rare systemic disorder. The Histiocyte Society classifies LCH based on the number of organ systems involved and whether or not disease activity is unifocal or multifocal in each organ system [Table 1].[5] They also classify disease based on the involvement of high-risk organs.

It is rare to encounter a case of adult LCH. Clinical presentation usually depends on the site of involvement. Lesions may mimic either neoplasia, venereal diseases such as herpes simplex virus, lichen sclerosus, or other inflammatory diseases. Genital as well as perianal involvement is rarely reported though cases with systemic involvement of organs such as bone, liver, and lung along with the perianal lesions have also been reported.[6] The case presented to us had both genital involvement and perianal involvement which was pathologically confirmed but also considered to have multisystem involvement based on PET-CT findings.

Pulmonary LCH symptoms are usually nonproductive cough and dyspnea with/without fever and weight loss. Chest pain can occur if there is spontaneous pneumothorax.[7] Our case initially had asymptomatic lung involvement which was picked up on PET-CT. She started to develop breathlessness and chest pain post chemotherapy and diagnosed with spontaneous pneumothorax on chest X-ray.

The incidence of liver involvement in adult LCH is reported between 10% and 30%, although 90% occurred in multisystemic LCH. Bone involvement in LCH is relatively more common in children than adults.[8,9] Both liver involvement and bone involvement were seen in our case.

Central nervous system (CNS) is an uncommon site of involvement with LCH in adults.[10] Although isolated CNS-LCH is reported, CNS-LCH is mainly diagnosed as multisystemic disease with male predominance.[8,11,12] Our case also had involvement of the pituitary gland based on MRI findings with central diabetes insipidus.

The treatment of adult LCH is not standardized due to its rare incidence and inadequate knowledge regarding its pathophysiology. It is still debated whether LCH has a neoplastic or reactive nature.[13,14] Clonal proliferative disorder through different genetic mutations such as BRAF V600E and MAP2K1 or activation of mitogen-activated protein kinase/extracellular signal-regulated kinase pathway has been considered as possible pathogenetic mechanisms for LCH.[15] Treatment depends on the clinical features, the extent of organ involvement, and clinical course.[16,17] Multidisciplinary approach is desired as treatment modality remains highly variable, ranging from observation, systemic chemotherapy, radiotherapy to surgery of resectable site.

PET-CT can be used for staging, assessment of therapy response, and detection of recurrence. Organs involved with LCH as detected on imaging may not show any clinical manifestations to begin with; however, they can change the further management. Ideally, all sites suspected on imaging should be biopsied for staging and to rule out alternative diagnoses, including malignancy. Adult patients with LCH are at risk of developing secondary malignancies such as basal-cell carcinoma, papillary thyroid carcinoma, gastric cancer, Hodgkin's lymphoma, lymphoblastic leukemia, and solid tumors.[16-18]

LCH remains a major concern because of its rarity with many faces and requires careful consideration for staging evaluation and treatment. PET-CT plays an important role as the entire body can be assessed by a single imaging

Table 1: Clinical classification of Langerhans cell histiocytosis

Type	Involvement
Single-system LCH (one organ/ system involved, uni- or multifocal)	Bone: unifocal (single bone) or multifocal (>1 bone)
	Skin
	Lymph node (not the draining lymph node of another LCH lesion)
	Lungs
	Hypothalamic-pituitary/central nervous system
	Other (e.g., thyroid, thymus)
Multisystem LCH (two or more organs/systems involved)	With or without the involvement of "risk organs" (hematopoietic, liver, spleen, and lung)

LCH: Langerhans cell histiocytosis

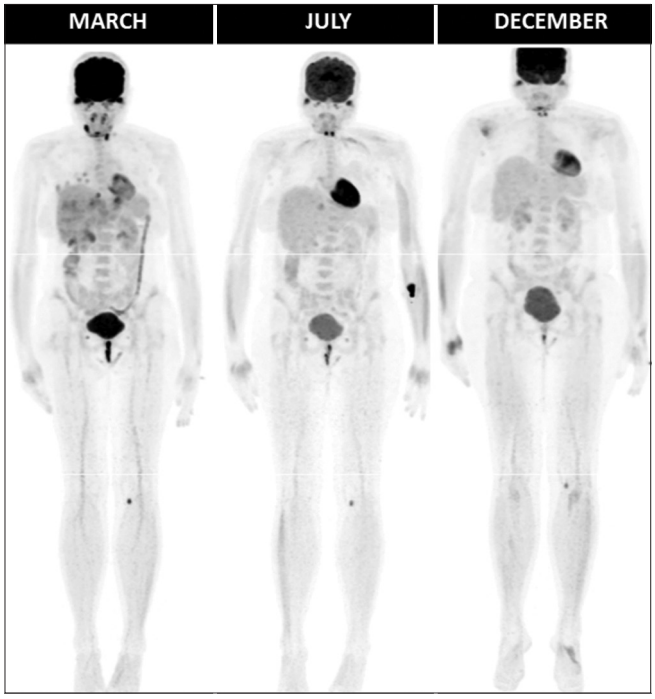

Figure 5: Maximum intensity projection image of positron emission tomography–computed tomography scan done on March 2, 2020 at baseline, July 2020 after she received four cycles of induction chemotherapy with injection cytarabine and steroids; and in December 2020 after she received five cycles of second line chemotherapy with injection cladribine and five cycles of chemotherapy with injection cytarabine showing complete response in lung lesions, moderate response in liver lesions, and mild response in perianal and vulvar lesions

modality. Multidisciplinary approach is desired as multiple organs are involved and treatment modality remains highly variable. The limitation of our case is that there is a lack of comprehensive diagnostic evaluation of all involved sites, including genetic mutation studies.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient (s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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