CASE REPORT

Langerhans Cell Histiocytosis in an Adult Female with Multisystem Involvement

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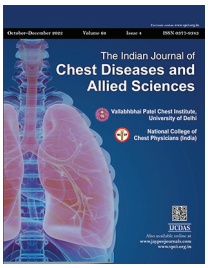

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Abstract

Langerhans cell histiocytosis (LCH) also known as histiocytosis X, is a rare systemic disorder arising from the clonal proliferation of myeloid dendritic cells (histiocytes) with a tendency to involve single or multiple organ systems with variable clinical course and prognosis. Clinical presentation usually depends on the site of involvement. The organs commonly affected in adults by order of decreasing frequency include lungs, bone, skin, pituitary glands, lymph nodes, and the liver. Vulval and perianal involvement is extremely rare in adults. We describe the case of a 31-year-old non-smoker adult female with multisystemic LCH involving the vulva, perianal region, and lung. Probable involvement of other sites with LCH included mandibular bone, pituitary gland, skin, lymph nodes, liver, thyroid, and colon. She is undergoing systemic chemotherapy and has completed two cycles of cytarabine and steroids without any complications. Treatment is not standardized due to the very less incidence of the disease and inadequate knowledge regarding its pathophysiology. Langerhans cell histiocytosis remains a major concern for treating physicians because of its rarity with many faces and requires careful consideration for management.

Keywords: Adult, Langerhans cell histiocytosis, Perianal, Vulva.

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Abbreviations used in this Article

DI = Diabetes Insipidus; FDG = Fluorodeoxyglucose; LCH = Langerhans cell histiocytosis; PET = Positron emission tomography (PET); CT = Computed tomography; MRI = Magnetic resonance imaging (MRI); HSV = Herpes simplex virus (HSV); H&E = Hematoxylin and eosin; GI = Gastrointestinal.

Introduction

Langerhans cell histiocytosis also known as histiocytosis X, is a rare disorder arising from the abnormal proliferation of myeloid dendritic cells (histiocytes) in various organs.[1,2] Langerhans cell histiocytosis predominantly affects the pediatric population with a peak incidence between 1 and 3 years but is rarely reported in adults with an annual incidence of one or two cases per 1 million adults.[3–5] LCH may affect any organ of the body, but those more frequently affected sites in adults are the lungs followed by bone, skin, pituitary glands, genital tract, endocrine system, central nervous system, lymphoreticular, and gastrointestinal (GI) systems (liver and spleen).[6] Here, we describe a case of disseminated or multisystem LCH in a 31-year-old female that presented with vulva and perianal lesions along with other sites of involvement including lung, mandibular bone, pituitary gland, skin, lymph nodes, liver, thyroid, and colon.

Case Description

A 31-year-old married non-smoker female with no comorbidities, and any significant medical history, presented with complaints of amenorrhea for the last two and a half years. She has been consulting various gynecological centers for these complaints. She also had complaints of polydipsia and polyuria for the last 6 months which were evaluated by the local physician but laboratory findings were unremarkable and treated conservatively with water restriction. However, all her issues remain unsolved as symptoms persisted with no response to treatment. Subsequently, she had itching and burning sensation over the perianal and vulvar regions accompanied by multiple non-healing ulcers and papillomatous lesions and also confluent skin lesions in the form of papules and plaques over submammary skin over the last 1 month (Figs 1A to C). These lesions increased gradually in size with no response to antibiotics and topical steroids. She was referred to a surgeon and an incisional biopsy of the lesions was planned for the establishment of diagnosis. A preanesthetic assessment was performed before the procedure. There were no prior respiratory complaints. Her vitals and oxygenation parameters were normal. Chest radiography revealed diffuse bilateral diffuse reticulonodular and cystic changes throughout the lungs. Findings of routine laboratory parameters, spirometry, and electrocardiogram

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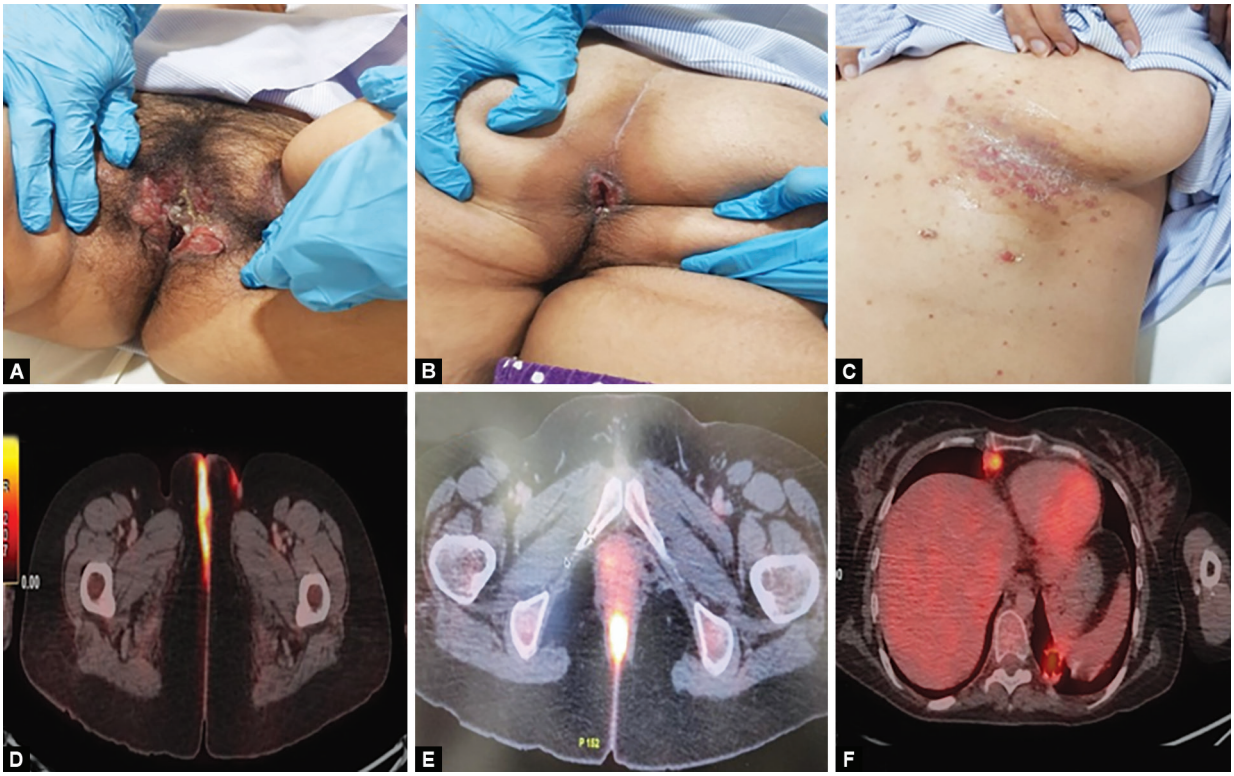
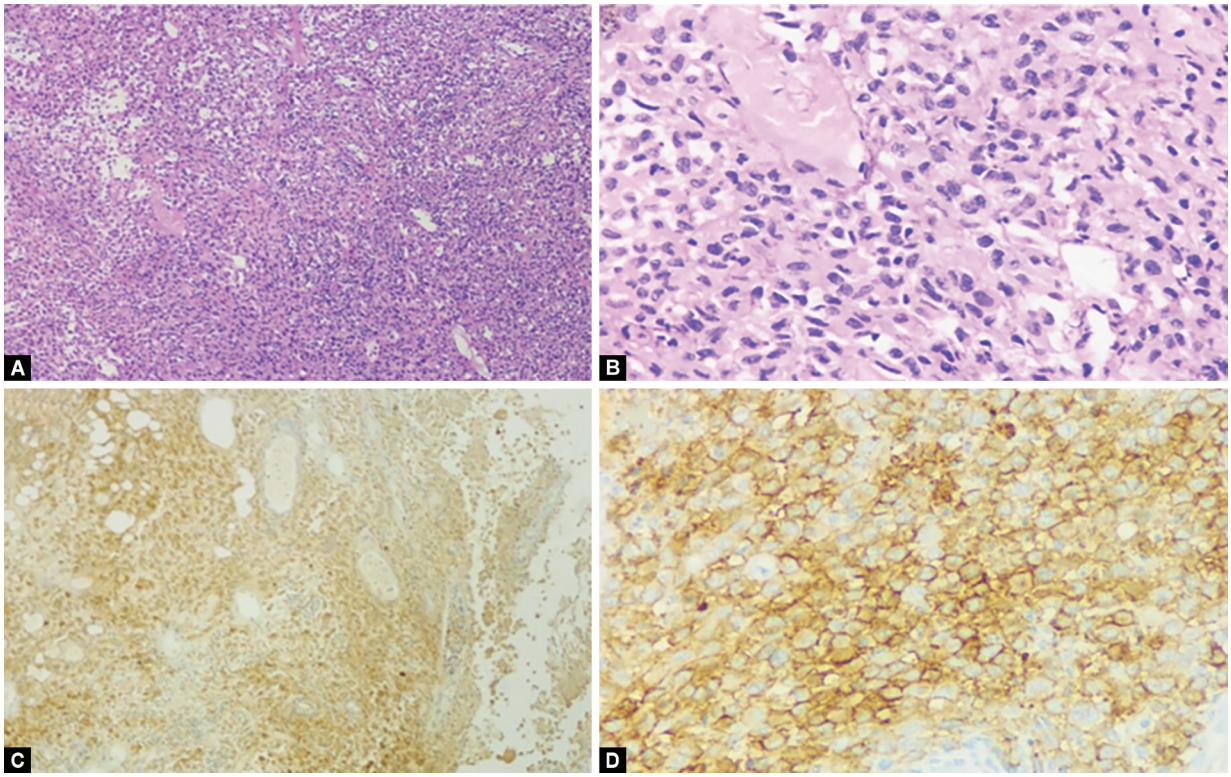
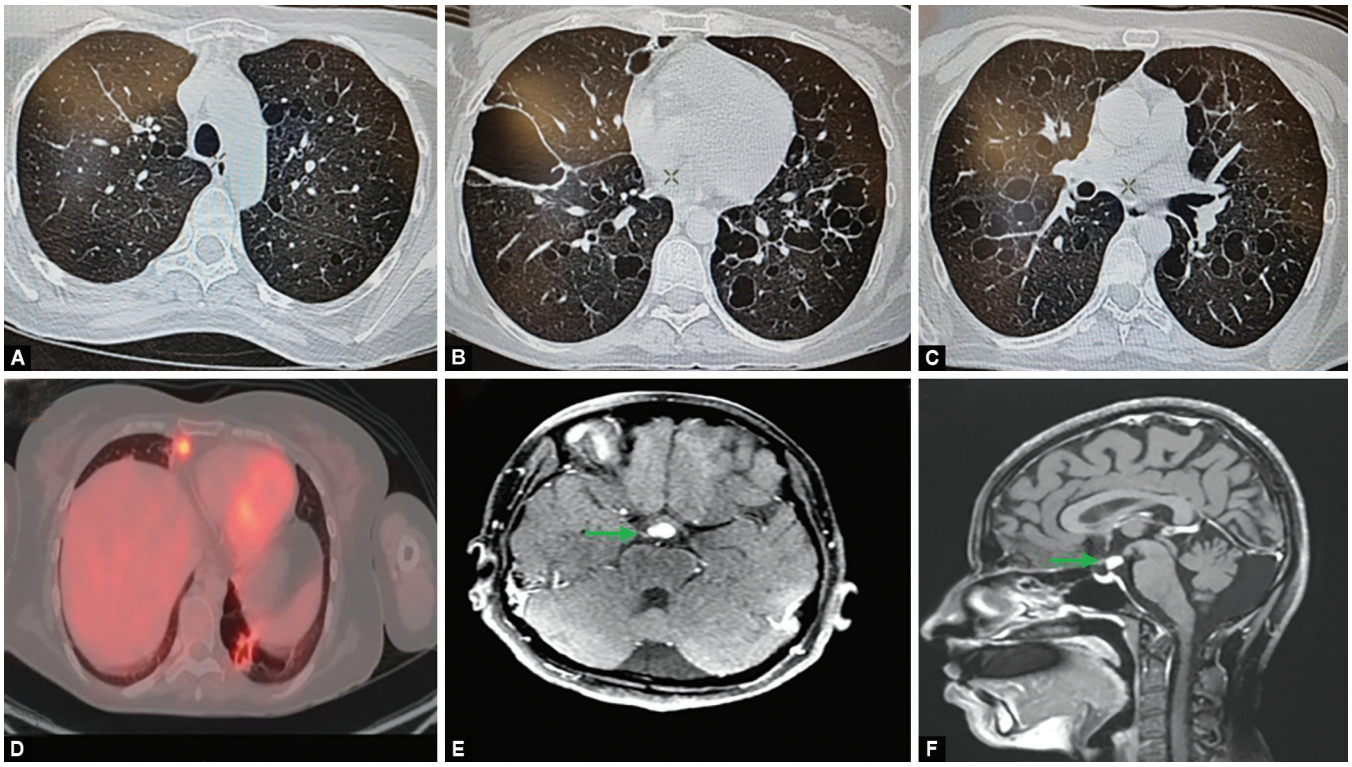


Figs 1A to F: (A) Vulvar and (B) perianal lesion of LCH; (C) Skin lesions over submammary skin; PET showing FDG avid uptake in (D) Vulvar; (E) Perianal, and (F) ill-defined hypodense lesions of liver



Figs 2A to D: Histopathological examination showing infiltrating histiocytes within vulvar lesion on hematoxylin and eosin (H&E) stain – magnification 10× (A) and 40× (B); Immunohistochemical staining of LCH cells S-100 (C) and CD1a (D) – magnification 40×

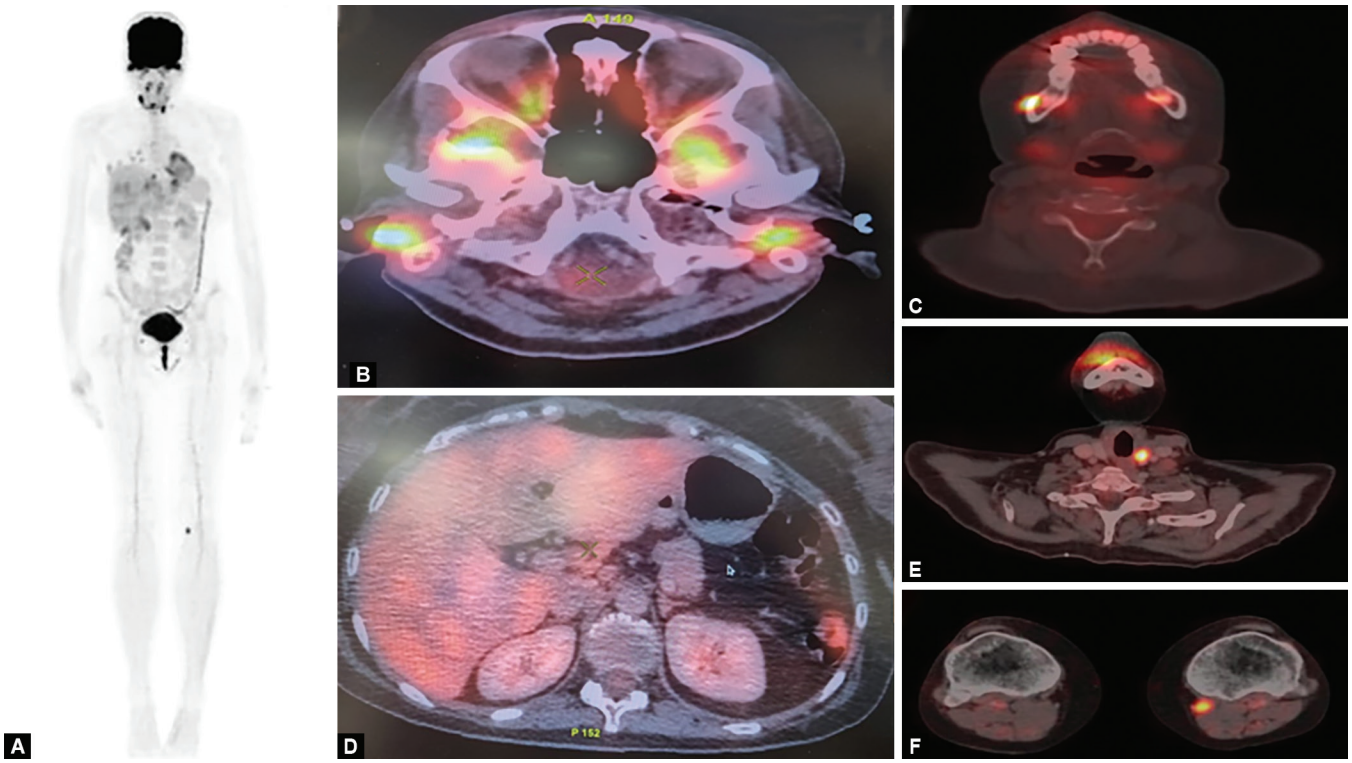


Figs 3A to F: (A to C) HRCT thorax showing multiple bizarre-shaped cysts and nodules in both lungs; (D) The PET imaging showing mild FDG avid uptake in lung cyst in left lower lobe; (E) Axial and (F) Sagittal contrast-enhanced MRI T1W1 shows an enhancing exophytic nodular lesion arising from the hypothalamus projecting into the suprasellar cistern (green arrows)

were unremarkable. Both vulvar and perianal lesions were biopsied without any complication after getting clearance from a pulmonologist. Microscopic findings of lesions from both sites 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 (Figs 2A and B). There was no evidence of granuloma or malignancy. Immunohistochemistry further confirmed the diagnosis as histiocytic cells stained positive for S-100 and CD1a (Figs 2C and D). Other staining such as HMB-45, Melan-A, CD-20, and CD-3 were negative. After histopathological confirmation, evaluation was continued further to rule out any systemic involvement. Computed tomography (CT) thorax showed pleural-based fibro-consolidative lesions in both lower lobes of the lungs with bilateral extensive thick-walled cystic lesions (Figs 3A to C) positron emission tomography (PET) scan findings revealed multiple sites of involvement (Fig. 4A) with fluorodeoxyglucose (FDG) avid thickening in perianal and vulvar regions (Figs 1D and E), ill-defined multiple hypodense lesions in both lobes of the liver (Fig. 1F), predominantly non-FDG avid and mildly FDG avid thick-walled cystic lesions in bilateral lungs (Figs 3A to D), FDG avid bilateral external auditory canal thickening (Fig. 4B), osteolytic lesion in the mandible (Fig. 4C), thickening in hepatic flexure of the colon (Fig. 4D), a hypodense nodule in the left lobe of the thyroid (Fig. 4E), mildly FDG avid thickening in the left inframammary fold and mildly FDG avid subcarinal, bilateral hilar, abdominal, inguinofemoral and left popliteal lymph nodes (Fig 4F). Contrast-enhanced magnetic resonance imaging (MRI) brain T1W1 revealed an enhancing exophytic nodular lesion arising from the hypothalamus projecting into the suprasellar cistern with contiguous thickening of pituitary infundibulum (Figs 3E and F) and altered signal in bilateral petromastoid bones involving the air cells with the presence of associated abnormal soft tissue within the external auditory canals. All these sites were presumed to be due to the involvement of LCH. Routine laboratory parameters were unremarkable. Relevant investigations such as serum electrolytes, hemoglobin electrophoresis, tumor markers, and hormonal profile were within normal limits. Serum osmolality at admission was 291 mOsm/kg and urine osmolality was 72 mOsm/kg. A water deprivation test was performed and after 10 hours, serum osmolality reached 310 mOsm/kg and urine osmolality was stable with a variation of less than 40 mOsm/kg, ranging from 90 to 110 mOsm/kg. We applied 0.1 cc of desmopressin intranasally and urine osmolality was followed serially. After application, urine osmolality markedly increased to 590 mOsm/kg after 2 hours, and diagnosis of central diabetes Insipidus (DI) was confirmed. Herpes simplex viral serology was negative. The patient has received two cycles of chemotherapy with intravenous cytarabine (150 mg for 5 days every month) and prednisolone along with inhaled desmopressin (0.1 cc twice daily). She is doing well with minimal regression of vulvar, perianal, and submammary skin lesions and currently under regular surveillance.

Discussion

Adult LCH is rare and many cases remain undiagnosed. An increasing number of cases have been reported in adults over the last decade, particularly with disseminated involvement or multisystem disease.[4,5] Most clinical studies are confined to small case series.[7] Although our case presented to us with vulval



Figs 4A to F: The PET imaging showing FDG avid uptake with probable involvement with LCH in (A) All involved sites; (B) Bilateral external auditory canal; (C) Osteolytic lesion in mandible, (D) Hepatic flexure of colon; (E) Hypodense nodule in left lobe of thyroid; (F) Left popliteal lymph node

and perianal involvement that was pathologically confirmed but also considered to have multisystem involvement based on imaging findings of LCH as observed in the lung, mandibular bone, pituitary gland, skin, lymph nodes, liver, thyroid, and colon. Langerhans cell histiocytosis was first classified historically in 1953 based on the pediatric cohort. It included a wide range of clinical manifestations of three forms of eosinophilic granuloma, Hand–Schüller–Christian disease, and Letterer–Siwe disease carrying different prognoses.[8] The first classification of histiocytosis was developed by the Histiocyte Society which included the following three categories: Langerhans cell histiocytosis, non-LCH, and malignant histiocytosis.[9] The same society has recently developed a five-group classification in 2016 where LCH was placed in group L.[10] Langerhans cell histiocytosis can be classified as a single-system or multisystem disease. Single-system involves only a single organ but may be further categorized as unifocal or multifocal (multiple bones involvement). Multisystem disease involves two or more organs that may include risk organs. Involvement of risk organs such as the liver, spleen, hematopoietic system, and bones of the skull especially basal ones causing central nervous system involvement, may lead to poor prognosis.[11,12] The diagnosis of LCH is based on clinical and radiological findings in combination with histopathological analyses of the involved site, identifying tissue infiltration by histiocytes with ultrastructural (Birbeck granules) or immunophenotypic characteristics (CD1a, S100, and CD207) of LCs.[13] The course of LCH is unpredictable, ranging from spontaneous regression of lesions to life-threatening disseminated disease and multiorgan dysfunction with poor outcomes.[10]

We performed a systematic search of PubMed, Google Scholar, IndiaMed, and ResearchGate (from the year 2000 to 2021) to identify the studies reporting cases of adult LCH involving vulval and perianal involvement (single or multisystemic) as shown in Tables 1 and 2, respectively. Pediatric cases with age below 12 years were excluded from the study. Clinical presentation usually depends on the site of involvement. Genital, as well as perianal involvement, is rarely reported. Genital involvement with LCH has been previously reported in literature with various patterns such as pure genital LCH, genital tract LCH with subsequent multiorgan involvement, oral or cutaneous LCH with subsequent genital and multiorgan involvement, and diabetes insipidus with organ involvement.[48–50] Vulva is the most commonly involved site followed by the vagina, cervix, endometrium, and ovary. Genital involvement can occur at any age but is most commonly seen in young adults. Lesions of LCH may mimic either neoplasia, venereal diseases such as herpes simplex virus (HSV), lichen sclerosus, or other inflammatory diseases.

Anal involvement by LCH in the adult population is uncommon. Most reported cases were perianal lesions, around the anal orifice, and mainly confined to the perianal skin[56,58,60] Perianal involvement has been reported previously with or without systemic involvement in three cases. Systemic involvement with organs including bone, liver, and lung was also reported along with the perianal involvement.[56] Other sites in the GI tract like colon, rectum, stomach and small intestine, may be affected.[58,60] Most cases have been diagnosed by GI endoscopy, and up to 50% of patients were asymptomatic.[61] A solitary polyp is a common finding, and usually occurs without multisystem involvement.[58,61] Multiple polyposis due to LCH has also been reported in adults.[62] Other findings include the nodular, marginated, infiltrative, necrotic, or ulcerative appearance of lesions. Lesions of the perianal region may mimic condyloma accuminata and malignancy such as lymphoma, signet ring carcinoma, and melanoma.

Table 1: Cases of adult Langerhans cell histiocytosis with involvement of vulva reported from India

Author/Year	*Age*	*Involved sites*	*Disseminated disease at diagnosis*	*Treatment advised*	*Outcome*
Solano et al.[14]	40 years	Vulva and vagina	No	Vincristine, local, and partial excision	No response after chemotherapy Complete response with no recurrence till 18 months after surgery
Pather et al.[15]	45 years	Vulva	No	Excision biopsy and radiotherapy	Recurrence after excision biopsy Complete response with no recurrence till 24 months after radiotherapy
Rizvi et al.[16]	41 years	Vulva	No	Local excision	Complete response with no recurrence after 6 months of surgery
Santillan et al.[17]	33 years	Left vulva Right labium majus Mons pubis and superior aspect of both labia Buttocks and perineum	No	Radiotherapy, wide local excision on recurrence Second recurrence: High dose radiotherapy Third recurrence: Wide radical vulvar excision Fourth recurrence: Thalidomide	Complete response to treatment after starting thalidomide with no recurrence till 1 year
Singh et al.[18]	32 years	Vulva	No	Radiotherapy First recurrence: Surgical excision Second recurrence: Radiotherapy Third recurrence: Radical excision Fourth recurrence: Thalidomide	Final outcome not specified
Padula et al.[19]	31 years	Vulva	No	Radiotherapy, vulvectomy, thalidomide	Recurrence despite radiotherapy and vulvectomy for 3 years, remission after thalidomide, complete response till 19 months
	52 years	Vulva Bone Mouth	No Subsequent dissemination	Radiotherapy	Dissemination to other sites despite radiotherapy
Ishigaki et al.[20]	65 years	Vulva	No	Surgical excision	Complete response till 12 months
Dietrich et al.[21]	41 years	Vulva Brain Skull	Yes	Radiotherapy, Chemotherapy Wide local excision and adjuvant methotrexate chemotherapy	Radiation therapy: No response Chemotherapy: Complete response Final outcome not specified
	29 years	Vulva	No	Radiation therapy and oral steroids First recurrence: Clobetasol cream and local excision Second recurrence: Radiation therapy and excision	Partial response to treatment, final outcome not specified
Venizelos et al.[22]	64 years	Vulva	No	Surgical excision and radiation therapy	Complete response, no disease till 22 months
Mlyncek et al.[23]	63 years	Vulva	No	Vulvectomy with lymphadenectomy, topical steroids	Complete response, no disease till 12 months
Mottl et al.[24]	16.5 years	Vulva	No	Topical steroids and excision biopsy First-line chemotherapy: Vinblastine and oral steroids Second-line chemotherapy: 2-Chlorodeoxyadenosine	Partial response to first-line chemotherapy Complete response to second-line chemotherapy No evidence of disease till 18 months of second-line chemotherapy
Liu et al.[25]	32 years	Brain, vulva, gingiva, and jaw	Yes	Chemotherapy: Cyclophosphamide, etoposide, and steroids	Complete response of vulvar lesion No response for gingival lesion

(Contd...)

Table 1: *(Contd...)*

Author/Year	*Age*	*Involved sites*	*Disseminated disease at diagnosis*	*Treatment advised*	*Outcome*
Ehsani et al.[26]	22 years	Brain, lung, salivary glands, and vulva	Yes	Oral steroids and vinblastine	Complete response after 3 months
Elas et al.[27]	76 years	Vulva	No	Topical steroids; Chemotherapy: Vincristine and vinblastine	Complete response and no disease till 9 months
Beneder et al.[28]	49 years	Vulva	No	Surgical excision: Five consecutive sessions for recurrences followed by adjuvant radiotherapy and again surgical excision for sixth recurrence	Complete response till 51 months after surgical excision for sixth recurrence
Pan et al.[29]	49 years	Vulva	No	Local radiotherapy	Complete response
Triantafyllidou et al.[30]	52 years	Vulva	No	Surgical excision	Complete response with no evidence of disease after 10 months
Brazeal et al.[31]	65 years	Vulva, scalp, inframammary folds, axilla, groin, and lungs	Yes	Not specified	Not specified
Simons et al.[32]	33 years	Vulva	No	Topical steroids, tacrolimus, radiotherapy, and CO_2 laser therapy	Not specified
Foley et al.[33]	62 years	Vulva	No	Topical steroids	Complete response with no evidence of disease after 13 months
Madnani et al.[34]	38 years	Vulva Perianal area Bones Liver Brain	Yes	Etoposide 50 mg daily in a cyclical regime of 3 weeks on and 1 week off, followed by 6-mercaptopurine 100 mg daily Prednisolone 40 mg on alternate days Desmopressin puffs.	Complete response
Aruna et al.[35]	26 years	Gingiva Bilateral submandibular lymph nodes Vagina	Yes	Conservative palliative treatment: Scaling, root planning and curettage Excision of clitoral growth Cynomycin for 45 days	Complete response
Fernandes et al.[36]	57 years	Vulva, scalp, face, ear, trunk, and axilla	Yes	Topical steroids and thalidomide	Complete response till 4 months Recurrence on stopping thalidomide Treated with maintenance dose
Jiang et al.[37]	46 years	Vulva	No	Topical steroids; partial vulvectomy; Chemotherapy: Vinblastine and steroids	No response with topical steroids Complete response after vulvectomy and chemotherapy with no evidence of disease after 40 months
	40 years	Vulva	No	Partial vulvectomy; Chemotherapy: Vinblastine and steroids Thalidomide; Chemotherapy: Vinblastine and steroids First recurrence: Hysterectomy	Complete response with no evidence of disease after 36 months Complete response after first recurrence with no evidence of disease after 12 months
	23 years	Cervix	No		
El-Safadi et al.[38]	59 years	Vulva	No	Radical vulvectomy; Chemotherapy: Methotrexate First recurrence: Lenalidomide	Complete response after treating first recurrence with no evidence of disease after 31 months

Chang et al.[39]	68 years	Vulva	No	Biopsy of lesion; topical steroids	Association with lichen sclerosus Complete response to treatment with no recurrence till 6 months
Kurt et al.[40]	60 years	Vulva	No	Vulvectomy or local excision combined with radiotherapy	Not specified
Ibrahim et al.[41]	43 years	Vulva	No	Radiation therapy First recurrence: Surgical excision Second recurrence: Repeat radiation therapy and surgical excision Third and fourth recurrence: Thalidomide switched to lenalidomide in case of adverse drug reaction with thalidomide	Satisfactory response after lenalidomide
Khoummane et al.[42]	47 years	Vulva Previous involvement with perineum	No	Excision	Not specified
Sun et al.[43]	28 years	Vulva	No	Interferon, prednisone, and methotrexate	Complete response Disease-free for 18 months
Singh et al.[44]	50 years	Brain, lung, and vulva	Yes	Not specified	Not specified
Wieland et al.[45]	26 years 67 years 31 years	Vulva Labia majora Cervix Other sites of involvement such as brain and skin	No	Excision of involved lesion for biopsy Topical steroid; excision of lesion for biopsy Simple hysterectomy	Complete response Disease-free for 23 months Disease-free for 10 years 10 months Disease-free for 54 months
Zudaire et al.[46]	59 years	Vulva: Bilateral labia minora Skin: Left inframammary fold Bone: Pelvis, seventh and eight right ribs, and dorsal vertebrae levels 10 and 11	No Dissemination after 2 years	Biopsy of vulvar and skin lesions Cytarabine chemotherapy	Not specified
Vellucci et al.[47]	49 years	Vagina, Cervix Lung Liver	Yes	Therapy with cortisone 25 mg Hyaluronic acid Topical vaginal gel	Partial response of genital symptoms
Martinez-Cordero et al.[48]	63 years	Genital Jaw Brain	No Dissemination after 11 years	Cyclophosphamide and steroids First recurrence: Etoposide and vinblastine	Complete response after second recurrence
	54 years	Cervix Vagina Skull and spine Auditory nerve	No Dissemination after 10 years	Second recurrence: Cladribine Hysterectomy with pelvic lymphadenectomy and radiotherapy First recurrence: Radiotherapy, steroid, and vinblastine Second recurrence: Cladribine	Complete response after second recurrence
Sirka et al.[49]	54 years	Vulva Perineum	No	Prednisolone and methotrexate	Complete response to treatment over 4 months with no recurrence

Table 2: Cases of adult Langerhans cell histiocytosis with perianal involvement

Author/Year	*Age*	*Sex*	*Involved sites*	*Treatment advised*	*Outcome*
Foster et al.[50]	19 years	Male	Skull and orbit Perianal Brain	Craniotomy and titanium cranioplasty Chemotherapy: Prednisolone, vincristine, and mercaptopurine Surgical excision Intranasal desmopressin	Complete response with no recurrence till 5 years
Field et al.[51]	70 years	Male	Perianal and left tibia	Corticosteroid and potassium permanganate	Not specified
Mango et al.[52]	34 years	Male	Perianal Other sites not mentioned	Triamcinolone and thalidomide	Complete response
Mittal et al.[53]	45 years	Male	Bone Lungs (quiescent at presentation) Perianal	Nitrogen mustard, Topical and systemic corticosteroids, topical pentostatin; Surgery: Proctectomy, diversion procedure with abdominoperineal resection of rectum and end colostomy	Complete response with no recurrence till 3 years
Shahidi-Dadras et al.[54]	20 years	Male	Perianal	Thalidomide	Partial response after 6 months
Dere et al.[55]	45 years	Female	Perianal Distal femur and proximal tibia	Topical steroids and methotrexate	Complete response
Abdou and MaherTaie[56]	33 years	Male	Brain Perianal	Methotrexate	Not specified
Gul et al.[57]	36 years	Male	Perianal Left lateral lobe of thyroid	Rectal surgery and postoperative radiotherapy Fine needle aspiration biopsy of thyroid nodule, total thyroidectomy, and postoperative levothyroxine replacement Chemotherapy: Prednisone and vinblastine	Not specified
Mansour et al.[58]	32 years	Male	Brain Perianal Lung	First-line chemotherapy: Vinblastine and prednisone Second-line chemotherapy in view of disease progression: Cytarabine and vinblastine along with steroids Third-line chemotherapy in view of polyp (hemorrhoidal fibroma): Gemcitabine and cisplatin	Complete response for GI lesions Partial response for pulmonary lesions

Our case had lung involvement with multiple nodules and cysts affecting the upper and middle lung zones with sparing of lung bases which is a characteristic finding for pulmonary LCH on CT thorax. However, it was an incidental finding as our case did not complain of any respiratory symptoms with preserved lung volumes, and also there was no prior history of smoking. Previous cases have reported the incidental finding of pulmonary LCH on radiography in 25–30%.[63–65] Pulmonary LCH Symptoms are usually non-productive cough and dyspnea with or without constitutional symptoms such as fever and weight loss. Chest pain can occur if there is spontaneous pneumothorax.[63] Lung involvement in LCH is usually seen in adults and is associated with smoking.[63,66] Few have reported even in non-smokers.[67,68] Nodular pattern is predominant in the initial phase of pulmonary LCH, whereas the cystic pattern is typically predominant in the later phase.[63,69] Pulmonary LCH transforms from a cellular nodule to a cavitary nodule and finally into a cyst as the course of the disease progresses. Furthermore, LAM, LIP, and other causes of cystic lung disorders need to be considered as differential diagnoses.

The incidence of liver involvement in adult LCH is reported between 10–30%, although 90% occurred in multisystemic LCH.[70,71] Natural history of liver LCH exists into two stages: early stage with periportal infiltration of histiocytes and inflammation that corresponds to multiple hypodense liver nodules on CT scan and late stage with sclerosis and dilatation of the biliary tree (sclerosing cholangitis) and cirrhosis.[71,72] Periportal fatty infiltration of histiocytes can also be seen, corresponding to fat attenuation hypodense nodules, indicating xanthomatous type lesions. Hepatomegaly, deranged liver function tests, and imaging findings can provide clues to establish the diagnosis. Liver biopsy with specific IHC studies remains the cornerstone of the diagnosis and staging. An alternate diagnosis of hepatic malignancy needs to be ruled out.

Our case had an osteolytic lesion in the mandible based on PET–CT findings probably due to LCH. Bone involvement in LCH may manifest with a wide spectrum of lesions, ranging from a single system with unifocal or multifocal lesions to multisystem involvement. It is relatively more common in children than adults. Any bone can be involved but LCH involves the skull, jaw, long tubular bones, vertebrae, pelvis, and ribs in decreasing order of frequency.[72] In the skull, frontal and parietal bones are commonly involved followed by the jaws.[73] Mandible is more commonly

involved when compared to the maxilla.[73,74] CT or PET–CT, MRI, or bone scan can delineate the extent of bone and soft tissue involvement. The typical radiographic appearance is a lytic bony lesion with clear demarcation and remodeling at later stages.[72] Bone biopsy is required for the diagnosis of LCH but also to rule out other types of lesions such as metastatic carcinoma, myeloma, aneurysmal bone cyst, and Ewing's sarcoma.

Our case probably had involvement of the pituitary gland based on MRI findings with central DI, although CNS is an uncommon site of involvement with LCH in adults.[72,75] The hypothalamic-pituitary axis is the most common site of intracranial involvement and is usually associated with clinical findings of central DI and neurodegeneration.[76] Anterior pituitary disease may also be involved. The MRI findings involving the hypothalamic-pituitary region included infundibular thickening above 3 mm with an enhancement of the pituitary stalk, accompanied by lack of the normal T1WI shortening in the posterior pituitary (50%), infundibular atrophy or thread-like narrowing with width below 1 mm (29%), absence of hyper-intensity in posterior pituitary and infundibular or hypothalamic mass lesions (10%).[76] However, other diagnoses such as metastasis, sarcoidosis, and lymphocytic hypophysitis also need to be excluded although difficult to differentiate and require biopsy for confirmation.[76,77] Although isolated CNS LCH is reported, CNS LCH is mainly diagnosed as multisystemic disease, and the majority of CNS LCH patients are men.[72,78–80]

The treatment of adult LCH is not well defined and standardized due to very less incidence of disease and inadequate knowledge regarding its pathophysiology. It has been still debated whether LCH might have a neoplastic nature rather than an inflammatory or reactive nature.[81,82] Clonal proliferative disorder *via* different genetic mutations such as BRAF V600E, MAP2K1, or activation of MAPK/ERK pathway has been considered as possible pathogenetic mechanisms for LCH.[83] Treatment modality depends on the clinical features, extent of involvement, single system or multisystem, involvement of high-risk organs and clinical course or prognosis.[84,85] Multidisciplinary approach is desired as treatment modality remains highly variable ranging from observation, systemic chemotherapy, radiotherapy, and surgery of resectable site. The treatment modalities including the outcome of reported adult LCH cases have been described in Tables 1 and 2. The recommended chemotherapy regimen for pediatric cases with multisystem LCH is 12 months of therapy with prednisone and vinblastine.[84] Mercaptopurine is added if there is a risk of organ involvement. This regimen also can be used in adult multisystem LCH. However, vinblastine is less favored in adult LCH cases due to the risk of neurotoxicity. Adult cases with mild severity or single system without risk organ involvement are treated with methotrexate or azathioprine.[85] Thalidomide is usually indicated in single-system multifocal or skin and soft tissue involvement. Adult multisystem LCH with or without risk organ involvement is treated with cladribine, cytarabine, and etoposide for at least 6 months. Etoposide can be used if there is a relapse with risk organ involvement. Our case has been treated with cytarabine and has completed two cycles of chemotherapy without any complications. Treatment of vulvar LCH includes local excision or vulvectomy, topical corticosteroids, systemic chemotherapy, or radiotherapy in a few cases.[16] Treatment options in case reports concerning perianal involvement in LCH varied between surgical excision, successful use of thalidomide, systemic chemotherapy with cladribine, and radiotherapy.[17,19] Furthermore, PET CT can be used for staging, assessment of therapy response, and detection of recurrence. Targeted therapy may have a promising role but is still experimental and should only be considered judiciously as an adjuvant therapy rather than as a primary therapy. Vemurafenib, a BRAF V6000 inhibitor, may be considered for the subset of high-risk patients with BRAF V6000 mutations showing poor response to steroids and vinblastine.[84] Trametinib and Cobimetinib, MEK inhibitors, may be considered for high-risk patients with mutations in the MAPK pathway.[84] Organs involved with LCH as detected on imaging, may not show any clinical manifestations. Ideally, all sites suspected on imaging should be biopsied for staging and also to rule out alternative diagnoses including malignancy. Adult patients with LCH are at risk of secondary malignancies such as basal cell carcinoma, papillary thyroid carcinoma, gastric cancer Hodgkin lymphoma, lymphoblastic leukemia, and solid tumors.[14,84–86] The limitation of our study is that there is a lack of comprehensive diagnostic evaluation of involved sites including genetic mutation studies. Langerhans cell histiocytosis remains a major concern for treating physicians because of its rarity with many faces and requires careful consideration for evaluation and treatment.

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