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RESEARCH ARTICLE

CENTRAL DIABETES INSIPIDUS REVEALING A MULTISYSTEM LANGERHANS CELL HISTIOCYTOSIS : A CASE REPORT

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Abstract

Introduction: Langerhans Cell Histiocytosis (LCH) is a rare myeloid precursor disorder primarily affecting young individuals, in which hypothalamic-pituitary involvement is uncommon but often diagnostically challenging due to non-specific clinical and radiological features.

Case report: We present the case of a 22-year-old woman referred for evaluation of sudden-onset polyuro-polydipsic syndrome and secondary amenorrhea. MRI revealed a thickened pituitary stalk, and biochemical investigations confirmed central diabetes insipidus and anterior pituitary hormone deficiencies. Skin lesions observed on examination were biopsied and underwent histopathological and immunohistochemical analysis, revealing findings consistent with LCH (CD1a+, CD68+, S100+, and CD34-). Subsequent work-up revealed multisystemic involvement including hematologic, hepatic, pulmonary, osseous,and lymphatic manifestations.

Despite initiation of corticosteroid therapy and consideration for systemic chemotherapy, the patient developed fatal septic shock.

Conclusion : This case highlights the diagnostic value of skin biopsy in inaccessible lesions and the importance of early diagnosis and multidisciplinary intervention in aggressive multisystemic LCH.

Introduction:-

Langerhans Cell Histiocytosis (LCH), also known as Histiocytosis X or Hand-Schüller-Christian Syndrome, is a rare disorder of the reticuloendothelial system characterized by the clonal proliferation of Langerhans cells; myeloid progenitor cells that share phenotypic features with epidermal dendritic cells [1]. LCH primarily affects children and young adults and presents with a highly variable course, with mortality rates reaching up to 80% in case of advanced multisystem involvement [2]. Neurological manifestations are relatively rare with a predilection for the hypothalamic-pituitary axis [3]. The involvement of the sellar region is difficult to diagnose due to non-specific

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findings and limited access to pituitary tissue, making histological analysis of accessible lesions crucial for diagnosis and treatment planning. We report the case of a young woman whose initial presentation of LCH involved the pituitary gland and was subsequently confirmed by immunohistochemical and histopathological analysis of a skin lesion. The disease evolved rapidly to multisystem involvement and culminated in fatal multiorgan failure. This case underscores the critical importance of early diagnosis and comprehensive systemic evaluation in patients with suspected LCH.

Case Report:

A 22-year-old female patient was referred to the Endocrinology Department at Hassan II University Hospital in Fez for etiological investigation of a sudden-onset polyuria-polydipsia syndrome associated with secondary amenorrhea evolving over a period of six months. History-taking revealed additional symptoms including chronic headaches and changes in vision suggestive of a pituitary tumor syndrome, alongside asthenia and an unintentional weight loss of 7 kilograms over six months. On clinical examination, the patient had a low body mass index (BMI) of 16 kg/m². She exhibited a severe polyuria-polydipsia syndrome (PPS) with 24-hour fluid intake of 12 liters and urine output of 13 liters. Dermatological examination revealed multiple small erythematous papules and seropapules on the trunk, which were non-painful and non-pruritic, along with subcentimetric vesicles and occasional pustular lesions. Breast examination showed no spontaneous or provoked galactorrhea, with Tanner stage V.

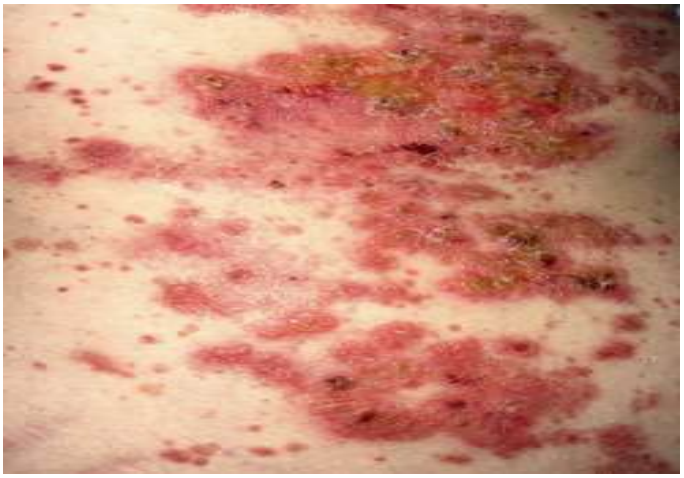

Figure 1 : clinical images of the patient showing multiple small erythematous papules and seropapules

After ruling out common causes of PPS, laboratory investigations revealed a biochemical profile consistent with diabetes insipidus: low urinary osmolality at 190 mOsm/kg, borderline high plasma osmolality at 296 mOsm/kg, and a serum sodium concentration of 143 mmol/L. For her secondary amenorrhea, a gonadotropic hormonal workup was also performed, revealing hypogonadotropic hypogonadism. Complete pituitary hormonal assessment showed associated corticotropic and somatotropic insufficiency, along with moderate hyperprolactinemia likely due to pituitary stalk disconnection. Given the biological profile suggestive of diabetes insipidus and gonadotropic insufficiency, a hypothalamic-pituitary MRI was performed. It revealed a spontaneously hyperintense nodular thickening of the pituitary stalk, with homogeneous enhancement after contrast injection. The lesion measured 15 × 15 × 18 mm (anteroposterior × transverse × height), suggesting a tumoral origin such as a dysgerminoma or a granulomatous process. All these findings supported the diagnosis of central diabetes insipidus.

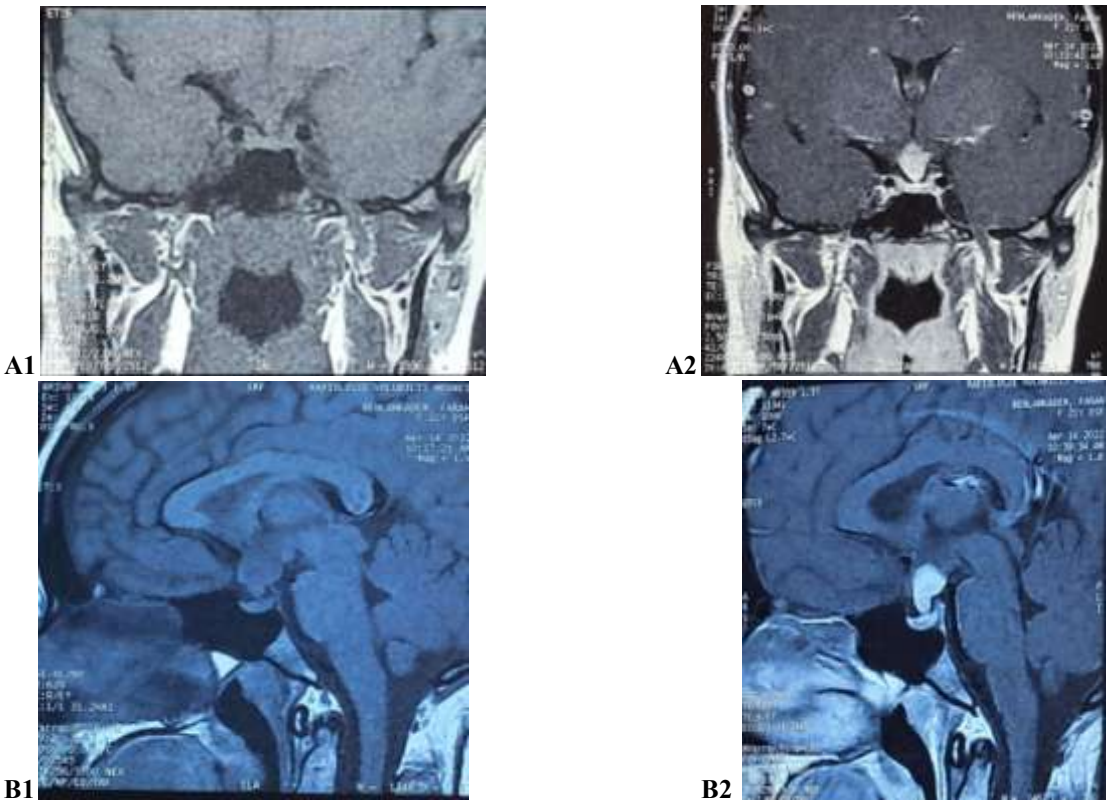

Figure 2: Coronal (A) and sagittal (B) section of T1-weighted (1) and post-gadolinium T1-weighted (2) MRI images of the patient showing a nodular thickening of the pituitary stalk, spontaneously hyperdense, with homogeneous enhancement following contrast administration (performed at Hassan II University Hospital, Fez, Morocco)

Ophthalmologic evaluation performed to assess for intracranial involvement revealed bilateral stage 1 papilledema, with no abnormalities on Goldman-type visual field testing. The etiological workup conducted in the context of pituitary stalk thickening revealed bicytopenia, consisting of normochromic, normocytic, non-regenerative anemia and leukopenia with agranulocytosis and lymphopenia, without circulating blasts. This was associated with a significant biological inflammatory syndrome, but no other paraclinical abnormalities suggestive of a tumoral or granulomatous cause (Table 2).

Table 1 : Etiological Workup in the Presence of Pituitary Stalk Thickening

Investigations for Germinoma:
Tumor markers: • **Serum alpha-fetoprotein (AFP)** and **free beta-human chorionic gonadotropin (β-hCG)**: Negative • **Cerebrospinal fluid (CSF) AFP and free β-hCG**: Negative
Investigations for Sarcoidosis :
Complete blood count (CBC): • Hemoglobin: 8.7 g/dL • Mean corpuscular volume (MCV): 82 fL • Mean corpuscular hemoglobin concentration (MCHC): 32 g/dL • Hematocrit: 17% • White Blood Cell Count (WBC): 1.15 × 10^9/L • Neutrophils: 0.23 × 10^9/L • Lymphocytes: 0.74 × 10^9/L • Platelets: 245 × 10^9/L

Iron studies:
- Serum iron: 0.35 mg/L (reference range: 0.6–1.8 mg/L)
- Ferritin: 136 µg/L (reference range: 10–120 µg/L)

Peripheral blood smear:
- No blasts
- Anisochromia
- Leukocyte differential confirmed on smear

Inflammatory markers:
- Erythrocyte sedimentation rate (ESR), 1st hour: >120 mm/h
- C-reactive protein (CRP): 17 mg/L
- Procalcitonin: 0.04 ng/mL

Serum protein electrophoresis (SPEP):
- Hypoalbuminemia
- Increased alpha-1 globulins
- Polyclonal hypergammaglobulinemia, suggesting an inflammatory or autoimmune process

Angiotensin-converting enzyme (ACE) level: 14.04 IU/L (reference range: 8–52 IU/L)

Thoracic CT scan:
- No radiological findings suggestive of sarcoidosis

Tuberculosis Workup:

Three sputum samples for acid-fast bacilli (AFB): **Negative**

Chest X-ray: **No abnormalities detected**

From a therapeutic standpoint, the patient was started on hormone replacement therapy. Desmopressin was administered at a dose of 120 µg/day for the treatment of central diabetes insipidus, leading to the resolution of polyuria–polydipsia syndrome. Hydrocortisone was also prescribed at 20 mg/day to address corticotropic insufficiency. Growth hormone and gonadotropic deficiencies were not substituted at this stage, pending the exclusion of an underlying neoplastic process.

The patient was subsequently referred to the Department of Internal Medicine for further evaluation of hematologic abnormalities. Initial bone marrow aspiration revealed a hypercellular marrow infiltrated by 28% blasts, raising suspicion for acute myeloid leukemia. However, a repeat bone marrow aspiration followed by a core biopsy demonstrated a hypercellular marrow with granulocytic hypoplasia, erythroblastic hyperplasia, and features of dysplasia. The blast population comprised of 18% undifferentiated cells and immunophenotyping revealed 7% myeloid blasts expressing markers of immaturity (CD34+, CD38+, HLA-DR+, CD45+), which were suggestive of a myelodysplastic syndrome (MDS).

Given the suspicion of a multisystem inflammatory disease and the inaccessibility of the pituitary region for biopsy, a skin biopsy was performed. Histological examination revealed skin tissue lined by an acanthotic epidermis with overlying ortho- and parakeratotic hyperkeratosis. The papillary dermis showed a moderate lymphocytic inflammatory infiltrate along with a sheet of large oval cells exhibiting eccentrically placed, occasionally kidney-shaped nuclei and abundant eosinophilic cytoplasm. Immunohistochemistry demonstrated positivity for CD1a, CD68, and S100, and negativity for CD34. These histopathological and immunohistochemical findings were consistent with a diagnosis of Langerhans cell histiocytosis.

A systemic workup was subsequently performed to assess for multisystem involvement. In addition to the previously identified pituitary, hematologic, and cutaneous manifestations, the assessment revealed hepatic involvement with hepatomegaly, interstitial lung disease mainly in the apices, and bilateral lymphadenopathy in cervical, axillary, and inguinal regions.

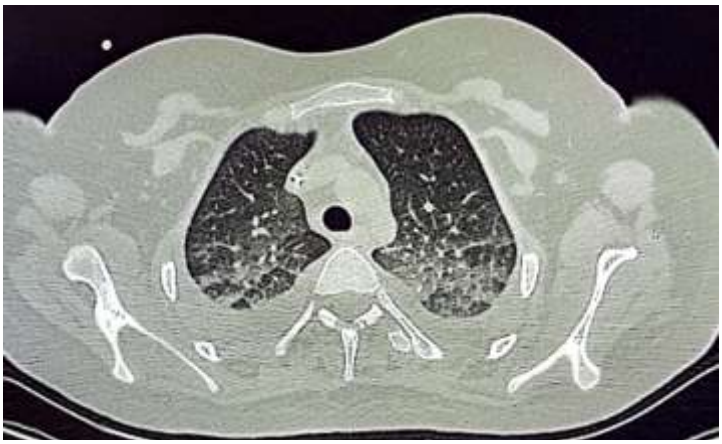

Figure 3: Axial section of a parenchymal window of contrast enhanced CT scan image showing interstitial lung pattern, predominantly affecting the apical regions (performed at Hassan II University Hospital, Fez, Morocco)

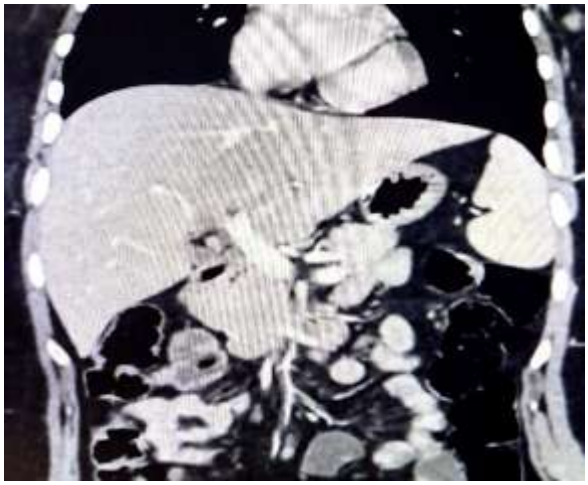

Figure 4 : Coronal reconstruction of a contrast enhanced abdominal CT scan revealing hepatomegaly (hepatic arrow at 18 cm) (performed at Hassan II University Hospital, Fez, Morocco)

Following completion of the diagnostic workup, a diagnosis of multisystem Langerhans cell histiocytosis was established, with involvement of risk organs, including the bone marrow and liver. The patient was started on prednisone at a dose of 1 mg/kg/day and was considered a candidate for vinblastine-based chemotherapy. However, the disease progressed rapidly, and her clinical condition deteriorated. She developed a refractory sepsic shock originating from a cutaneous infection, secondary to a Klebsiella pneumonia, which ultimately resulted in death. The exact cause of death could not be confirmed, as no autopsy was performed.

Discussion:-

Langerhans Cell Histiocytosis (LCH) is a rare disease characterized by the abnormal clonal proliferation of myeloid precursors that differentiate into Langerhans cells (CD1a+/CD207+), which are related to antigen-presenting dendritic cells normally found in the epidermis [1]. The exact pathophysiological mechanisms of LCH remain unclear; however, environmental, infectious (e.g., HHV-6), immunological, and genetic factors have been suggested [1]. Initially considered an inflammatory disorder secondary to immune dysregulation, LCH is increasingly recognized as a malignant hematologic disease [4], particularly following the identification of somatic oncogenic mutations. The most well-known of these involves the BRAF V600E mutation, which encodes an activated protein kinase. Other mutations have been identified in genes of the MAPK–ERK signaling pathway, including MAP3K1, KRAS, MAP2K1, MAPK/ERK, ARAF, HRAS, NRAS, and ERBB3 [5]. Understanding these mutations is essential, as they carry significant therapeutic implications, particularly regarding the use of targeted therapies [6].

Langerhans cell histiocytosis (LCH) predominantly affects children, with adult cases accounting for approximately 30% of the total [1]. The estimated incidence is 0.54 to 0.9 per 100,000 children per year and 1 to 2 cases per million adults annually [7]. The disease shows a male predominance, with a peak incidence occurring between the ages of 33 and 40 years in adults, and between 1 and 3 years in children [7]. Clinically, LCH is highly heterogeneous, ranging from isolated bone lesions—such as eosinophilic granuloma, to severe multisystem involvement with organ dysfunction, as seen in Letterer–Siwe disease. The current classification system for adult LCH is based on the number of lesions, the number of organs or systems involved, and whether high-risk organs are affected (e.g., liver, spleen, or bone marrow) [3].

Table 2 : Classification of Langerhans Cell Histiocytosis in Adults [3]

Subtype	Definition
Unifocal	Single lesion involving one organ
Multifocal single-system disease	Multiple lesions within a single organ
Multisystem disease - Withoutrisk-organinvolvement - Withrisk-organinvolvement	Involvement of two or more organs/systems (liver, spleen, or bone marrow)

In adults, Langerhans cell histiocytosis (LCH) is rare and often presents with non-specific symptoms, leading to delayed diagnosis. In adults, the most commonly affected sites include the bones (57%), lungs (58%), skin (36%), and pituitary gland (29%), whereas hepatic, splenic, lymph node, and extensive skeletal involvement are more frequently observed in pediatric cases [8]. Pulmonary involvement typically appears as reticulonodular infiltrates with cystic changes, while skin lesions are highly variable in form. Hematopoietic and lymphoreticular involvement, though less common, can include lymphadenopathy, hepatosplenomegaly with functional impairment, and bone marrow infiltration causing cytopenias [1].

Involvement of the hypothalamic–pituitary axis (HPA) is among the most frequent manifestations of Langerhans cell histiocytosis (LCH), with an incidence ranging from 40% to 70% depending on the series [9]. It represents the most common endocrine and neurologic complication of the disease, occurring more frequently in multisystem forms [8], as was the case with our patient. HPA involvement typically presents as central diabetes insipidus (CDI), reported in approximately 25% of cases [10]. CDI may be the initial manifestation of LCH, as observed in our patient, or may precede or follow the diagnosis by several years [3]. It can remain isolated or occur alongside other anterior pituitary hormone deficiencies (APHDs), either concomitantly, as in our case, or subsequently [3]. These deficiencies are often irreversible and have been reported in up to 94% of cases in some series [10].

Among the APHDs, growth hormone deficiency is the most common (40%–67%), followed by gonadotropin deficiency (33%–58%). Adrenocorticotropic and thyrotropic deficiencies are less common (11%–30%), typically presenting as part of a panhypopituitarism picture [10, 11]. Disconnection hyperprolactinemia is also observed in approximately 20% of cases [10, 11]. The underlying mechanisms of these deficiencies may include direct infiltration of the hypothalamic–pituitary region, autoimmune destruction mediated by anti-pituitary antibodies, vascular injury with microlesions leading to hypoperfusion and fibrosis, or cytokine-mediated effects from adjacent osseous lesions [12]. Our patient exhibited an endocrine pattern consistent with published data, except for the absence of thyrotropic deficiency. She also presented with a pituitary mass syndrome, a manifestation that is frequently reported in the literature.

More rarely, LCH may present as a hypothalamic syndrome, with symptoms such as hyperphagia and secondary obesity, thermoregulatory disturbances, sleep and behavioral disorders, as well as cognitive, memory, and thirst regulation deficits (adipsia), all of which significantly complicate therapeutic management [11]. Radiologically, Langerhans cell histiocytosis (LCH) involving the hypothalamic–pituitary axis most commonly presents as thickening of the pituitary stalk (seen in approximately 70% of cases), often associated with loss of the posterior pituitary bright spot on T1-weighted MRI [13]. Less frequently (8–18% of cases), it may manifest as pseudo-tumoral lesions of the pituitary, hypothalamic involvement, or even an empty sella syndrome [13]. It is important to note that none of these findings are specific, and nearly 50% of patients with LCH-related hypopituitarism show no detectable abnormalities on hypothalamic–pituitary MRI, suggesting other underlying mechanisms [14]. Pineal gland thickening or cyst formation has also been reported more frequently in patients with LCH, although it typically occurs without significant functional impairment in melatonin secretion [15].

Due to the non-specific nature of clinical, biochemical, and radiological findings, definitive diagnosis of LCH involving the hypothalamic–pituitary axis relies on histological confirmation. This entails identification of Langerhans cell infiltration, characterized by histiocytes with pale eosinophilic cytoplasm, irregular "coffee bean–shaped" nuclei with nuclear grooves, fine chromatin [3,9]. On electron microscopy, Birbeck granules may be observed. Immunohistochemically, these cells express CD1a, S100, and CD207 (langerin) [1, 3, 9]. However, due to the inaccessibility of the pituitary region, the small size of lesions, and the potential morbidity of biopsy, pituitary biopsy is rarely performed and should be considered on a case-by-case basis [3]. It is typically indicated in the presence of an expansive pseudo-tumoral mass or a pituitary stalk thickening >7 mm with no evidence of extrapituitary involvement. In multisystemic disease, the diagnosis is usually established based on histopathological features observed in other affected tissues [1,3], as was the case in our patient, where the diagnosis was confirmed through skin biopsy.

The search for the BRAF V600E mutation is now systematically performed in all patients with LCH, either on biopsy specimens or through blood and/or urine testing [3]. This mutation is present in over 50% of cases and is associated with higher relapse rates and multisystem disease [3]. It carries major therapeutic implications, particularly with the recent development of targeted therapies such as BRAF inhibitors [3]. Once the diagnosis of Langerhans cell histiocytosis (LCH) is confirmed histologically, a thorough assessment of disease extent is essential, as it determines both therapeutic strategy and prognosis. The diagnostic workup is guided by initial clinical findings and first-line laboratory or imaging results [3].

It is recommended that all patients with confirmed or suspected LCH undergo a whole-body 18F-FDG PET/CT scan, not only to assess disease dissemination and identify potential biopsy sites, but also to evaluate therapeutic response. In HLCH, PET/CT appears to be more sensitive and detects lesions earlier than MRI in many cases [1,3]. Staging also allows for the detection of coexisting malignancies, which have been reported at increased frequency in LCH patients. Several studies have demonstrated a higher incidence of hematologic malignancies, particularly acute myeloid leukemia (AML), but also chronic myeloid leukemia, other myeloproliferative neoplasms, and lymphomas. Solid tumors—such as lung and thyroid cancer—have also been reported [16, 17]. This was the case in our patient, who initially presented with a myeloid proliferative state on bone marrow aspiration, raising suspicion for AML. Although AML was ultimately ruled out, a myelodysplastic syndrome was diagnosed, an association that remains very rare [16, 17].

Following the staging evaluation in our case, a diagnosis of multisystem LCH was established, with involvement of the pituitary gland, skin, lungs, and lymph nodes, along with risk organ involvement (liver and bone marrow), which is associated with a poorer prognosis [13].The management of Langerhans cell histiocytosis (LCH) depends primarily on the patient's age, the extent and distribution of lesions (focal vs. multisystem), and the presence of risk organ involvement. Active surveillance or local therapy, including surgical excision, topical corticosteroids, or radiotherapy, is generally recommended as first-line treatment when feasible [3]. In cases of isolated, asymptomatic, non-expansive LCH without mass effect, a wait-and-see approach with close monitoring is appropriate [3]. Systemic corticosteroids (e.g., 0.5 to 1 mg/kg/day for 6–12 months) may be considered in recently diagnosed, symptomatic nodular forms [9,12].

Surgical excision is reserved for patients with expansive or symptomatic lesions, although recurrence may occur despite treatment [15]. Low-dose stereotactic radiotherapy (≤22 Gy) is generally indicated in isolated localized LCH with sporadic recurrence or in cases where surgery poses a high risk [10, 18]. Patients with pituitary involvement and confirmed hypopituitarism require systematic hormone replacement therapy, along with regular endocrine evaluations to detect emerging deficiencies [3,13]. In unifocal LCH where local treatment is not feasible due to anatomical inaccessibility or procedural risks, as in hypothalamic-pituitary involvement, patients should be managed similarly to those with multifocal disease, with systemic chemotherapy indicated [3].

In cases of multisystem LCH or extensive/refractory multifocal single-system LCH, systemic chemotherapy with cladribine or cytarabine is recommended due to their durable remission rates and favorable safety profile [3]. Vinblastine in combination with prednisone may serve as an alternative regimen; however, it carries a higher relapse rate and a notable risk of vinblastine-induced neuropathy [3]. Targeted therapies, including BRAF-inhibitors (e.g. vemurafenib) for BRAF V600E mutations and MEK-inhibitors (e.g. trametinib) for MAP2K1 mutations, are indicated in refractory LCH or in the setting of risk organ dysfunction unresponsive to first-line therapy [3].

Langerhans cell histiocytosis (LCH) typically exhibits an unpredictable course, often progressing in relapsing episodes. The disease may spontaneously regress or evolve into a disseminated form, compromising vital organ function and leading to life-threatening complications [1,3]. Localized forms of LCH usually follow a slow and indolent course, with a favorable response to treatment and a 5-year survival rate of approximately 90% [23]. In contrast, systemic forms involving the liver, spleen, bones, or lungs, young adult patients, and lack of clinical response within six weeks of therapy are associated with a poor prognosis [13]. This was the case in our patient, who unfortunately succumbed to septic shock originating from a cutaneous infectious focus. The fatal outcome was largely precipitated by profound immunosuppression, primarily due to hematologic involvement manifesting as severe neutropenia. This highlights the critical role of immune surveillance in patients with multisystem LCH and underscores the importance of early recognition and aggressive management of infectious complications in the context of cytopenias.

Conclusion:-

Langerhans cell histiocytosis (LCH) is a rare disease with a wide and heterogeneous clinical presentation [1]. Involvement of the pituitary gland is often non-specific, both clinically and radiologically, which may lead to delayed diagnosis and severe, sometimes fatal, outcomes—as seen in our case [1, 3]. LCH should be considered in any patient presenting with abnormalities of the hypothalamic–pituitary axis, particularly when central diabetes insipidus and anterior pituitary insufficiency are present [9]. A histological confirmation remains essential for diagnosis, preferably through biopsy of an accessible lesion such as the skin. When no other tissue is available, pituitary biopsy may be considered on an individual basis [3].Early recognition of LCH in atypical endocrine presentations may improve outcomes through timely diagnosis and appropriate treatment. A thorough systemic evaluation is crucial to identify silent organ involvement, especially in high-risk locations, and to guide multidisciplinary management. The prognosis largely depends on the number of organs involved and the patient's initial response to therapy [3]. Long-term follow-up is vital, as relapses and persistent dysfunction are common and can lead to progressive organ damage over time.

Summary Points:

- Langerhans cell histiocytosis (LCH) must be systematically considered in any patient presenting with hypothalamic-pituitary axis (HPA) abnormalities, particularly Central Diabetes Insipidus (CDI), alone or associated with one or more Anterior Pituitary Hormone Deficiencies (APHDs).
- Given the non-specific nature of radiological findings (pituitary stalk thickening) and the potential morbidity of pituitary biopsy, definitive diagnosis relies on histological confirmation via biopsy of an accessible peripheral lesion, such as the skin.
- A complete and early systemic workup (including 18F-FDG PET/CT) is crucial to identify silent organ involvement and guide the therapeutic management.
- Multisystem LCH with involvement of high-risk organs (bone marrow and liver, as demonstrated in this case) is associated with a poor prognosis and necessitates the rapid initiation of aggressive systemic chemotherapy.
- Infectious complications (sepsis/septic shock) are a frequent cause of mortality in multisystem LCH. Close immunological monitoring and aggressive management of cytopenias (especially neutropenia) are vital in these patients.
- It is essential to actively search for associated hematologic malignancies (such as myelodysplastic syndrome, as seen in this patient) as they complicate management and can significantly influence prognosis.

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