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Single Case

Hepatitis and Vasodilatory Shock due to an Unsuspected Culprit: A Rare Presentation of Multisystem Langerhans Cell Histiocytosis

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Keywords
Multisystem Langerhans cell histiocytosis · Secondary sclerosing cholangitis · Shock

Abstract
Introduction: Langerhans cell histiocytosis (LCH) is a rare hematologic condition which can affect multiple organ systems and has variable presentation. LCH is more commonly seen as a malignancy of childhood. LCH in adulthood can have poor outcomes depending on the involvement of critical organs. ***Case Presentation:*** We report a case of a 71-year-old female who presented with progressive weakness, weight loss, diarrhea, and jaundice, and had been undergoing outpatient workup for elevated liver enzymes for the last 2 years. She required admission to the intensive care unit for vasodilatory shock, requiring vasopressor and chronotropic support. Imaging showed an underlying multiorgan process involving the gastrointestinal tract, liver, spleen, and central nervous system. A repeat liver biopsy after a prior inconclusive one revealed the diagnosis of multisystem LCH presenting as secondary sclerosing cholangitis. ***Conclusion:*** The uniqueness of this multisystem LCH case lies not only in its rarity but also in the diagnostic journey that necessitated a repeat biopsy for a conclusive diagnosis. Early identification and targeted intervention can help in ensuring better patient outcomes, especially when the presentation can overlap with various other possible conditions.

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Introduction

Langerhans cell histiocytosis (LCH) is a rare blood-borne malignancy that originates from clonal proliferation of histiocytes [1]. It is a disease more common in pediatric patients with an incidence of 5 cases per million per year [2]. While the exact incidence in adults is unknown, it is predicted to be between 1 and 1.5 cases per million per year [1].

LCH involves the accumulation of clonal histiocytes in either a focal site within one organ or diffuse multiorgan involvement that results in disseminated organ dysfunction [3]. Variable organ involvement leads to a variety of clinical manifestations among patients, making its diagnosis challenging. We review a case of multisystem LCH in an elderly female who presented with subacute hepatic dysfunction. The initial inconclusive liver biopsy and the multisystem involvement with infrequent gastrointestinal manifestation highlights the diagnostic challenges inherent in LCH.

Case Presentation

A 71-year-old female with a history of acid reflux presented to the emergency department following a syncopal episode, along with progressive diarrhea, weight loss, worsening jaundice, and fatigue. She had been undergoing outpatient evaluation for elevated liver enzymes over the past 2 years prior to admission. She was trialed on ursodiol and low-dose prednisone without much benefit prior to arrival.

In the emergency department, her vitals were remarkable for hypotension with a blood pressure of 72/53 mm Hg and a nadir HR of 62. Physical exam was significant for jaundice and cachexia. Blood work demonstrated leukocytosis 27.7 × 10^9/L (normal 3.4–9.6 × 10^9/L) with neutrophilic predominance. Hepatic function panel showed an aspartate transaminase level of 85 U/L (normal 8–43 U/L), alanine aminotransferase 85 U/L (normal 7–45 U/L), bilirubin 9.3 mg/dL (normal <1.2 mg/dL), and alkaline phosphatase of 2262 U/L (normal 35–104 U/L). Gamma-glutamyl transferase was elevated to 494 U/L (normal 5–36 U/L). C-reactive protein was 52 mg/L (normal <8 mg/L). TSH was elevated to 22.8 mL U/L (normal 0.3–4.2 mlU/L) with undetectable T3 and T4 levels. Review of a 6-month prior outside liver biopsy was consistent with periportal fibrosis with lymphocytic and scattered neutrophilic infiltrates in the portal tracts. No infiltrating histiocytes were noted in the biopsy.

The patient was admitted to the intensive care unit for vasodilatory shock, requiring vasopressors and chronotropic agents along with antibiotics. Computed tomography (CT) of the abdomen and pelvis with contrast illustrated diffusely heterogenous liver parenchymal enhancement without ductal dilatation, duodenitis, and diffuse colonic thickening concerning pancolitis (shown in Fig. 1a). CT chest was performed which showed centrilobular ground glass opacities bilaterally with mild pulmonary edema. Echocardiogram did not reveal any cardiac abnormality. Brain magnetic resonance imaging (MRI) with contrast revealed abnormal enhancement and thickening of the pituitary infundibulum and stalk most consistent with lymphocytic hypophysitis (shown in Fig. 1b).

Given the cholestatic nature of liver injury, magnetic resonance cholangiopancreatography was performed which showed multifocal nodular hepatic steatosis and hepatomegaly without any focal liver abnormality; in addition, multiple indeterminate bony lesions were read as non-specific focal sclerosis and cystic lesions. Autoantibody screening including antinuclear antibody, SS-A and SS-B antibodies, and anti-smooth muscle antibody were negative. IgG4 subclass levels were normal. A bone marrow biopsy showed 40% cellularity and reactive marrow changes without any blasts or infiltrate. Subcutaneous fat aspirate was negative for amyloid deposition on Congo red staining.

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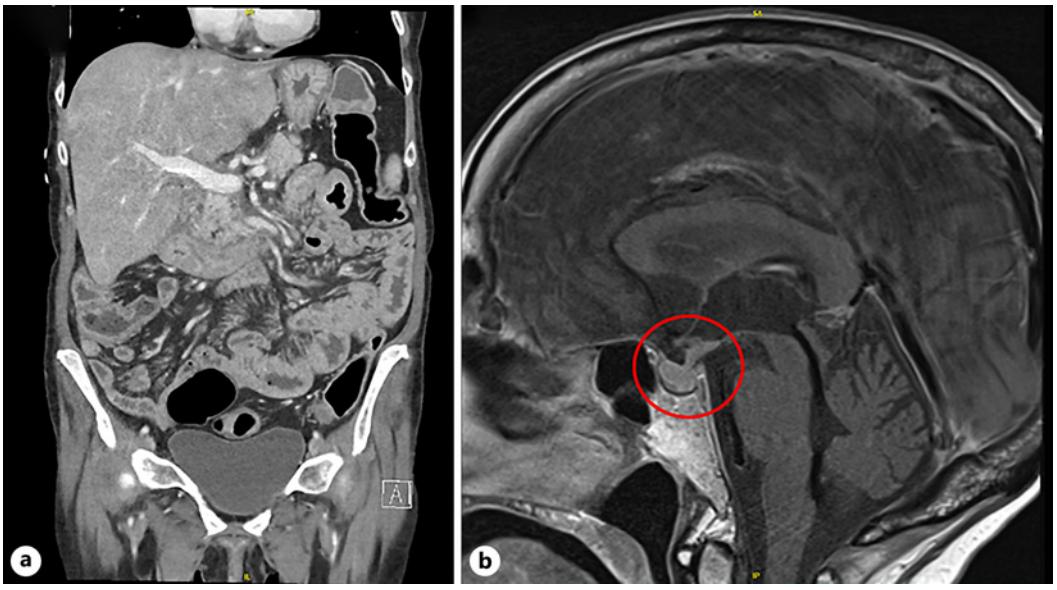

Fig. 1. a A coronal section of the computerized tomography of abdomen and pelvis showing heterogenous liver parenchymal enhancement, duodenitis, and diffuse pancolitis with colonic wall edema. **b** A sagittal section of the MRI of the brain demonstrating enhancement of the pituitary (circle) suggesting pituitary hypophysitis.

The patient was being optimized for a possible esophagogastroduodenoscopy and colonoscopy once more stable. A repeat liver biopsy revealed histiocytes infiltrating the biliary tree with chronic biliary tract injury. Tissue stained positive for CD1a and S100, markers of Langerhans cells, and *BRAF*V600E-mutated protein, commonly found in various malignancies (shown in Fig. 2). No evidence of IgG4 sclerosing cholangitis was observed. A diagnosis of secondary sclerosing cholangitis and cirrhosis secondary to multisystem LCH was confirmed.

Treatment was initiated with hydrocortisone and levothyroxine for panhypopituitarism. The patient was eventually started on dose reduced b-rapidly accelerator fibrosarcoma (BRAF) inhibitor, vemurafenib, after multidisciplinary discussion. The patient's hospital course was also complicated by acute necrotizing pancreatitis, poorly controlled blood sugars, and new onset central diabetes insipidus that required treatment with desmopressin. Repeated hospitalizations in the following 3 months prompted her to opt for comfort care with palliative measures.

Discussion

Multisystem LCH is a rare neoplastic condition. The prevalence of this condition in adults is debated given the paucity of data due to likely underdiagnosis [3]. In patients below the age of 19, age-standardized incidence rate is 0.70 per million population in the USA with higher rates noted among Hispanics [4]. Gold standard for diagnosis is a tissue biopsy which stains histiocytes positive for CD1a or CD207 (Langerin) [1, 3]. We, therefore, present a unique case of biopsy proven multisystem LCH involving the central nervous system, liver, spleen, and gastrointestinal tract in a Hispanic woman of advanced age.

LCH can present with myriad manifestations depending on the organ systems involved. The skeletal system is the most common organ system for infiltration by Langerhans cells, ranging from 30 to 50% [1] of cases. Our patient had cystic bone lesions which were not lytic

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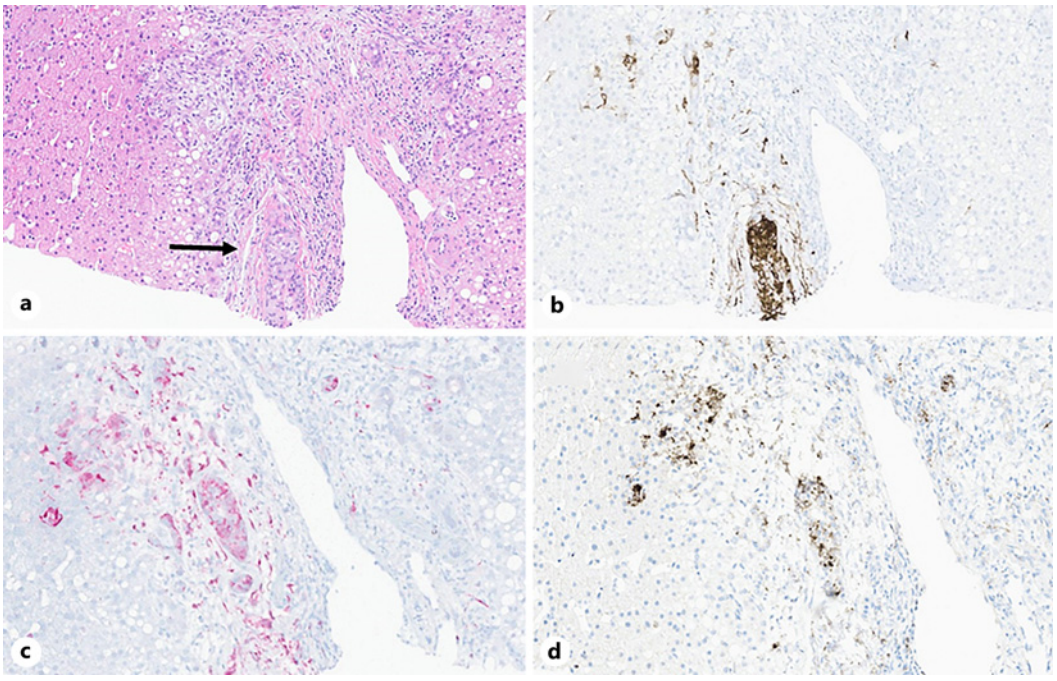

Fig. 2. Pathology results from the liver biopsy. **a** Bile duct infiltrated by atypical histiocytic cells (arrow) as shown on H&E stain. These cells are positive for CD1a (**b**), S100 (**c**), and BRAFV600E (**d**) confirming the diagnosis of LCH.

in character as classically seen in LCH, thus complicating diagnosis [1]. In about 25% of cases, central diabetes insipidus is LCH's manifestation of endocrine involvement, and about 15–20% cases have nervous system involvement [1]. Our patient's brain MRI also showed enhancement of the pituitary infundibulum and stalk; parts of the posterior pituitary where vasopressin is produced.

Our patient initially presented with gastrointestinal symptoms of diarrhea, jaundice, and elevated liver enzymes. The differential diagnoses were broad which included autoimmune cholangitis such as IgG4 sclerosing cholangitis, autoimmune pancreatitis, hepatic and other non-gastrointestinal malignancies. Only 10–20% [5] of patients with LCH manifest hepatic involvement. Our patient was found to have secondary sclerosing cholangitis and cirrhosis secondary to LCH as confirmed by tissue biopsy. Gastrointestinal infiltration of Langerhans cells is rare, but if present it manifests as diarrhea and abdominal discomfort. In our patient, the extensive liver involvement of LCH made it challenging to parse out that the resultant shock, hypoglycemia, and hyponatremia were not just the result of liver disease, but rather extensive multiorgan involvement of LCH.

The organ systems involved also impact the way LCH is classified and the overall prognosis. In April 2022, an international expert consensus proposed a revised classification system for LCH in adults based on the number of affected organ systems and sites involved [1]. For example, unifocal LCH involves solitary lesion involving any organ, whereas multisystem LCH involves more than or equal to two organ systems [1]. Both unifocal and multifocal LCH have 5-year overall survival rates of ≥90 in children and about 70% in adults [1, 3]. However, the liver, spleen, and bone marrow are considered "risk organs" which bear unfavorable disease prognosis [6]. Our patient had liver involvement in the form of sclerosing cholangitis and splenic lesions, conferring a poorer prognosis.

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Table 1. Patient's cytokine panel as reported in picograms per milliliters (pg/mL) with normal values included in parentheses

Tumor necrosis factor (<10.0)	61.7
Interleukin-6 (<5.0)	16.8
Interferon-beta (<20.0)	<20.0
Interleukin-10 (<7.0)	<7.0
Monocyte chemoattractant protein-1 (≤198.0)	416.0
Interleukin-1 beta (<20.0)	54.0
Interferon-gamma (<60.0)	68.2
Macrophage inflammatory protein-1 alpha (<220.0)	<220.0
Granulocyte macrophage colony-stimulating factor (<15.0)	<15.0
Interleukin-2 receptor alpha soluble (≤959.0)	1,458.0
Interferon-alpha (<20.0)	<20.0
Interleukin-18 (≤468)	1,593

For a long time, the underlying pathophysiology for LCH was unclear. Initially, LCH was thought to be the result of immune dysregulation [3]. This theory was supported by the role of the Langerhans cells as antigen presenting cells to the body's lymphocytes, and the associated inflammatory cytokines that assist in the formation of LCH lesions [6]. Cytokines such as interleukin (IL)-1 beta and IL-6 [2], as reported in our patient's cytokine release panel, contribute to the formation of LCH lesions (Table 1). In particular, multisystem LCH with risk organ involvement had significantly high levels of IL-18 [7], as was also seen in our patient, which is considered to be associated with worse treatment outcomes (Table 1).

With the advancement of next generation gene sequencing, underlying neoplastic pathophysiology of LCH has become clearer. A study performed by Badalian-Very et al. [8] in 2010, identified that 57% of LCH lesions carried the gain of function *BRAF*V600E mutation, as also seen in our patient. Subsequent studies found the same mutation in bone marrow aspirates of high-risk patients [9]. The second most common mutation in LCH is mitogen-activated protein kinase (MAPK) 2K1 [3, 10]. Since both BRAF and MAPK2K1 proteins are part of the MAPK signaling pathway, they are strongly implicated in hyperproliferation of histiocytes through upregulation of cellular machinery [3, 11].

In recent years, our understanding of LCH has grown significantly which has positively contributed to investigation of treatment options. Conventionally, cytotoxic agents have been the cornerstone of treatment [6]. While there is no standard therapy regimen, vinca alkaloid (for example, vincristine and vinblastine) combined with prednisone is often the first line [1, 11, 12]. This combination generally has a high response rate, but it is also associated with high relapse rates [1]. For patients with central nervous system manifestation, anti-metabolites such as cytarabine and cladribine that can penetrate the blood-brain-barrier are preferred [1]. Liver transplant has been recommended for patients with sclerosing cholangitis [5]. Our patient was evaluated by the in-house transplant team and was deemed ineligible due to high disease burden.

After the landmark 2010 study by Badalian-Very et al. [8], *BRAF*V600E mutation became an important clinical biomarker for LCH. This led to investigation of drugs such as vemurafenib as a targeted treatment option. Vemurafenib inhibits BRAF protein in the MAPK signaling pathway [6, 11] and thereby inhibits proliferation and differentiation of precursor cells [6, 11]. As per the international expert consensus guidelines for the treatment of

multisystem LCH, our patient was treated with vemurafenib. However, only about 3 weeks of therapy could be administered before the patient opted for palliative care.

In conclusion, we present a rare case of multisystem LCH in late adulthood with advanced cirrhosis. Non-specific symptoms that can also be attributed to the underlying liver disease can complicate clinical presentation and can make the condition challenging to diagnose. Additional screening must be performed to identify any concomitant hematologic or neoplastic condition. Continued development of novel therapies that target specific mutations has the potential to offer individualized care to LCH patients. Vemurafenib has shown promise in patients with multisystem LCH; however, more prospective studies are needed to further investigate their efficacy and associated side effects. Lastly, the CARE Checklist has been completed by the authors for this case report, attached as supplementary material.

Statement of Ethics

Ethical approval is not required for this study given that it is a case report and does not meet the criteria to be considered "research" based on national guidelines. Written informed consent was obtained from the patient's next of kin for publication of the details of their medical case and any accompanying images.

Conflict of Interest Statement

All authors have nothing to disclose as there are no competing/financial interests.

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Author Contributions

Shubhang Bhatt: conceptualization, methodology, investigation, writing – original draft, review, and editing. Nikita Ashcherkin: investigation and writing – review and editing. John Fanous: writing – review and editing. Rish Pai: investigation, writing – review and editing, and supervision, Janhavi Athale: conceptualization, resources, writing-review and editing, and supervision.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary materials (for all online suppl. material, see https://doi.org/10.1159/000538794). Further inquiries can be directed to the corresponding author.

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