ACG CASE REPORTS JOURNAL

CASE REPORT | PANCREAS

Hemophagocytic Lymphohistiocytosis Syndrome: A Rare Manifestation of Acute Pancreatitis

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ABSTRACT

Hemophagocytic lymphohistiocytosis syndrome (HLH) is a rare hyperinflammatory disorder linked to acute pancreatitis. While there are only a few case reports available on this particular association, we would like to share the case of a 60-year-old man who experienced acute-onset abdominal pain typical of pancreatitis. Three days after admission, he developed fever, pancytopenia, hypertriglyceridemia, and hyperferritinemia. A bone marrow biopsy performed for evaluation of fever revealed hemophagocytosis. Initiation of treatment for HLH showed dramatic improvement. It is important to note that while HLH may be rarely associated with pancreatitis, early diagnosis and treatment is critical and can be life-saving.

KEYWORDS: acute pancreatitis; hemophagocytic lymphohistiocytosis syndrome; fever

INTRODUCTION

Hemophagocytic lymphohistiocytosis syndrome (HLH) is a clinicopathological condition characterized by hemophagocytosis throughout the reticuloendothelial system and activation and multiplication of benign macrophages.[1] HLH is commonly seen in association with viral infections, autoimmune diseases, genetic disorders, and malignant neoplasms. Fever, hepatosplenomegaly, liver failure, pancytopenia, and coagulation derangements are some of its hallmarks.[2] Rarely, acute pancreatitis (AP) has been linked to HLH.[3] We present a rare case of HLH seen in association with acute mild pancreatitis.

CASE REPORT

A 60-year-old man presented with acute-onset severe epigastric pain, radiating to the back for 6 days. Pain was associated with 2–3 episodes of vomiting at the onset. A detailed drug history was obtained, but none was found.

Three days later, he developed high-grade fever associated with body ache and headache. Gradually, over 3 days, he developed jaundice with pruritus. On examination, blood pressure, pulse rate, and temperature were 124/82 mm Hg, 102 per minute, and 101.2°F, respectively. Abdominal examination revealed epigastric tenderness and sluggish bowel sounds, but no organomegaly. The rest of the systemic examinations were normal. Initial investigations are shown in Table 1. In the clinical setting of upper abdominal pain with elevated serum amylase (3,445 IU/L; normal $<$100 IU/L), a diagnosis of AP was made. Abdominal ultrasound showed a bulky pancreas with a mildly dilated common bile duct (11 mm) and sludge in the gallbladder. Magnetic resonance cholangiopancreatography showed mildly dilated, clear common bile duct, and bulky pancreas. Etiological workup including lipid profile, serum calcium, and intact Parathyroid Hormone was normal. Antipyretics and intravenous fluids were given. Subsequently, on day 8, hematological parameters showed bi-cytopenia with hemoglobin 8.8 g/dL and platelet count of 95,000/cmm. Erythrocyte sedimentation rate, C-reactive protein, serum triglycerides, lactate dehydrogenase, serum ferritin, and serum albumin were 28, 118, 455 mg/dL, 1,124 U/L, $>$2,000 ng/mL, and 2.8 g/dL, respectively. Prothrombin time and fibrinogen were 13.2 seconds and 355 mg/dL, respectively. Peripheral blood smear revealed no schistocytes. Abdominal contrast-enhanced computed tomography demonstrated a bulky pancreas with peripancreatic fat stranding and no collection (Figure 1). As the fever continued despite treatment, a broad-spectrum antibiotic (piperacillin-tazobactam) was started after sending blood and urine culture samples. The serum galactomannan assay was normal. Subsequently, in view of

ACG Case Rep J 2024;11:e01457. doi:10.14309/crj.0000000000001457. Published online: August 17, 2024

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Table 1. Initial investigations at presentation

Initial investigation	Value	Reference range
Hemoglobin (g/dL)	10.3	13–16
WBC count (per cmm)	5,100	4–10 × 10^3
Neutrophil %	68	40–60
Lymphocytes %	30	20–40
Eosinophils %	2	1–4
Platelet count (per cmm)	2.3 L	(1.5–4) L
Reticulocyte count	1.69%	—
ALT/AST (IU/mL)	111/121	5–40
ALP (IU/dL)	180	35–150
Total bilirubin (mg/dL)	8	1–1.3
Total protein (g/dL)	5.98	6–8
Albumin (g/dL)	3.19	3.5–5.5
Blood urea (mg/dL)	21.2	12.8–42.8
Serum creatinine (mg/dL)	0.8	0.5–1.6
S. potassium (meq/L)	134	3.8–5.4
S. sodium (meq/L)	4	133–146
S. calcium (mg/dL)	7.2	8.5–10.2
Fasting blood glucose (mg/dL)	81	65–99
S. amylase (IU/dL)	3,444	22–80
S. lipase (IU/dL)	1,948	<38

ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; S., serum; WBC, white blood cell.

persistent fever with bicytopenia with no known possible etiology and nonresponse to antibiotics, the possibility of HLH was considered, and a bone marrow examination was performed. It showed cellular marrow with increased histiocytes and hemophagocytosis, suggesting the diagnosis of HLH (Figure 2). In combination with clinical and laboratory criteria, a diagnosis of HLH was established. In our patient, the H-Score was 206, with a probability of having HLH of 88%–93%. Secondary causes of HLH, such as cytomegalovirus, Epstein-Barr virus, and varicella zoster virus, were excluded by negative serological tests. Based on this diagnosis, he was started on tab dexamethasone (12 mg daily). On the third day of treatment initiation, he became afebrile. By day 14, his symptoms, cytopenia, liver function tests, lactate dehydrogenase, and ferritin elevations improved. He was discharged on day 16. The patient was asymptomatic and had normal laboratory parameters during the 2-week follow-up. The dose of dexamethasone was thereafter tapered gradually over the next 8 weeks.

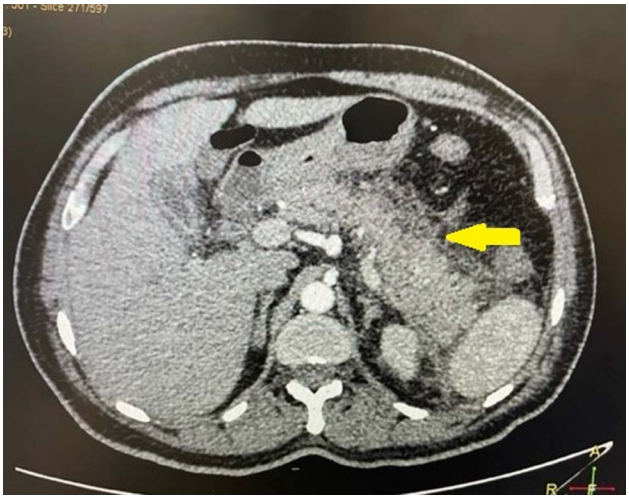

Figure 1. Abdominal contrast enhanced computed tomography showing a bulky pancreas with peripancreatic fat stranding (arrow).

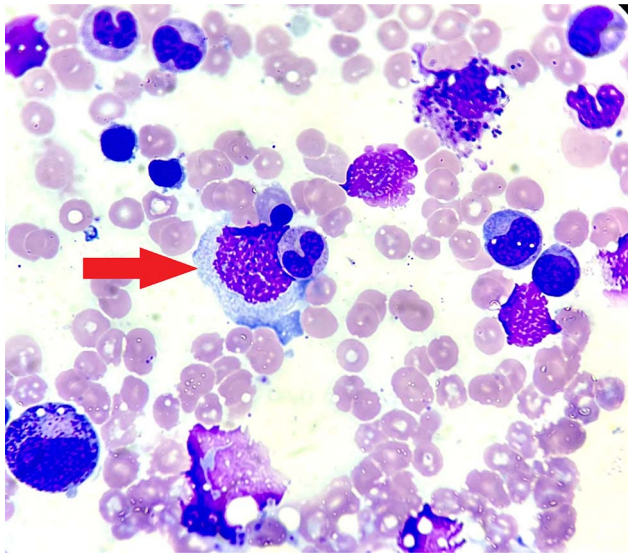

Figure 2. Bone marrow aspirate smear showing hemophagocytosis (neutrophil is engulfed by macrophage), red arrow (hematoxylin and eosin stain, 40×).

DISCUSSION

HLH syndrome is characterized by an overwhelming, inappropriate, cytotoxic activation of natural killer cells and/or T lymphocytes, leading to increased serum cytokine levels with an accumulation of activated T cells and macrophages in target organs such as the spleen, liver, lymph nodes, and bone marrow in addition to hemophagocytosis.[1]

Persistent fever, usually nonresponsive to antibiotics; splenomegaly and/or hepatomegaly; and lymphadenopathy are the clinical characteristics of HLH.[2] Cytopenia, elevated hemolysis parameters, hypofibrinogenemia, hypertriglyceridemia, and high ferritin levels are the common laboratory findings seen.[4] Bone marrow aspiration and biopsy generally show normal maturation of all cell lines, normal or increased cellularity, and infiltration with macrophages or histiocytes associated with hemophagocytosis.[5] Diagnosis is difficult and needs to be based on a combination of clinical and laboratory criteria.[2] It is a very severe condition and, if left untreated, can lead to rapid clinical deterioration and death.[6]

Table 2. Clinical profiles and outcome of HLH and acute pancreatitis cases

Reference	Country	No. of cases	Age	Sex	Etiology of pancreatitis	CTSI	Severity	Type	Organ failure	Survival
Mechi et al 2023[11]	Iraq	1	28	Female	NA	NA	Moderately severe	Interstitial	No	No
Bérar et al 2021[10]	France	1	57	Female	NA	5	Moderately severe	Necrotic	No	Yes
Han et al 2020[3]	China	1	46	Male	Alcohol	NA	Moderately severe	Interstitial	No	Yes
Abdallah et al 2005[9]	France	1	31	Female	NA	NA	Moderately severe	Interstitial	No	Yes
Kanaji et al 1998[8]	Japan	1	25	Male	NA	NA	Mild	Interstitial	No	Yes
Our case	India	1	60	Male	Idiopathic	5	Mild	Interstitial	No	Yes

CTSI, CT Severity Index; HLH, hemophagocytic lymphohistiocytosis syndrome; NA, not available.

A novel diagnostic scoring method for HLH, the H-Score, was introduced recently. When compared with the HLH 2004 diagnostic criteria, the H-Score was more accurate, with a sensitivity and specificity of 90% and 79% for adults, respectively.[7]

The rare association between AP and HLH was first published by Kanaji et al in 1998, where he described HLH in AP in a patient with fulminant ulcerative colitis.[8] We conducted a literature survey for HLH and AP and could retrieve only 5 cases of AP-associated HLH with full clinical details. The clinical spectrum and outcomes of these 5 patients are reported in Table 2. Two cases were reported from France, while our case is possibly the first reported case from India.[9,10] Of these 6 cases, 3 were male (50%), and the average age of the patients was 41.16 years. Regarding the etiology of AP, alcohol was the causative agent in 1 patient, while other cases were idiopathic, including our case.[3] Four patients (66.6%) had moderately severe disease, and 2 (33.3%) had mild pancreatitis like our case. Two patients with moderately severe pancreatitis needed interventions in the form of drainage of peripancreatic fluid collection.[3,9]

Fever in the first week of pancreatitis is generally associated with inflammation, while in the second week onward, sepsis is the usual incriminating cause.[3] After ruling out sepsis, HLH should be considered in the differential diagnosis of unexplained fever. It is more likely if the patient has persistent myelosuppression. Owing to a lack of awareness, HLH is not kept in the differential diagnosis. HLH may be seen even in mild pancreatitis, as in our case. Kanaji et al also described a similar case in mild pancreatitis.[8]

In conclusion, since the data is scant regarding the unusual association between HLH and AP, it is important to consider this differential and investigate accordingly. As in our case, early suspicion of HLH, appropriate investigation, and timely treatment initiation can be life-saving. This case highlights that HLH should be considered as one of the extrapancreatic manifestations of AP.

DISCLOSURES

Author contributions: GJ Borah: data collection, manuscript writing and is the article guarantor. K. Balankhe and NK Wodeyar: literature search and input on the discussion. P. Das: data collection. S. Mohindra and SR Kumar: manuscript editing.

Financial disclosure: None to report.

Informed consent was obtained for this case report.

Received April 8, 2024; Accepted July 1, 2024

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