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CASE REPORT

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Hemophagocytic Lymphohistiocytosis syndrome (HLH) associated with acute pancreatitis: A case report

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Abstract

Hemophagocytic Lymphohistiocytosis syndrome is fatal hyper-inflammatory condition due to over-activation of the immune system, being of primary and secondary types. This case report emphasizes the difficulty and challenge in and of the HLH diagnosis, and therapy should be employed promptly given the high mortality associated with HLH.

KEYWORDS

Hemophagocytic Lymphohistiocytosis syndrome, hemophagocytosis, histiocyte and acute pancreatitis

1 | INTRODUCTION

We present a case of HLH associated with acute pancreatitis. Hemophagocytic lymphohistiocytosis (HLH) is a rare syndrome that is often fatal despite treatment. It is caused by a dysregulation in the natural killer T-cell function, resulting in activation and proliferation of histiocytes with uncontrolled hemophagocytosis and cytokines overproduction. The syndrome is characterized by fever, hepatosplenomegaly, cytopenias, liver dysfunction, and hyperferritinemia. HLH can be either primary, with a genetic etiology, or secondary, associated with malignancies, autoimmune diseases, or infections.

2 | CASE PRESENTATION

A 28-year-old female presented with low grade fever associated with sweating, chills, nausea, anorexia, easy fatigability, and frequent presyncopal attacks. During that time she developed recurrent episodes of pneumonia that had been treated multiple times as an outpatient but with minimal improvement.

She has non-significant past medical history, she denied any chronic or recent drug intake, with negative family history, she is married with one child.

On presentation in the emergency department, the patient had been conscious, oriented, GCS 15/15. The patient was febrile with temperature 38 C, BP 110/60 mmHg, Heart rate 105/ minute with regular sinus rhythm, respiratory rate of 22/minute, SPO2 of 95% on ambient air.

On Examination, she had scleral icterus with pallor, bilateral pitting oedema of the legs up to the knee joints, there was no cyanosis nor clubbing. There was tender hepatosplenomegaly with abdominal distension that is suggestive of ascites, and non-tender lymphadenopathy in the right axilla. The rest of physical examination was unremarkable.

Initial investigation at the time of admission is shown in the Table 1. Abdominal Ultrasound reveals moderate hepatosplenomegaly with moderate to severe ascites, bilateral pleural effusion. Chest CT scan revealed bilateral

TABLE 1 The initial investigations done at the time of presentation of the patient.

Initial Investigation	Value	Reference range
RBC count	1.82 10^{12}/L	3.8–5.2 10^{12}/L
Hemoglobin	5.2 gm/dL	11.5–15.5 gm/dL
MCV	83.5 fL	78–96 fL
MCH	28.6 pg	27–34 pg
MCHC	34.2 g/dL	32–36 g/dL
RDW-SD	55.9 fL	37–54 fL
RDW-CV	18.3%	11.5–14.5%
WBC count	2.81 10^{9}/L	4–11.00 10^{9}/L
Neut %	81.1	39.3–73.7
Lymph%	10.3	18–45.3
Eos %	0.0	0.7–6
PLT count	73 10^{3}/L	155–450 10^{3}/L
Retic Count	1.2%	1%–2%
ALT	332 U/L	3–40 U/L
AST	706 U/L	5–40 U/L
ALP	1471 U/L	35–105 U/L
Total Bilirubin	3.3 mg/dL	0.2–1.2 mg/dL
Total Protein	4.5 gm/dL	6.4–8.3 gm/dL
Albumin	2.8 gm/dL	3.5–5 gm/dL
Blood Urea	42 mg/dL	15–45 mg/dL
Serum Creatinine	0.4 mg/dL	0.3–0.9 mg/dL
S.Potassium	3.9 mmol/L	3–5.2 mmol/L
S.Sodium	140 mmol/L	136–155 mmol/L
S.Chloride	95 mmol/L	90–110 mmol/L
S.Calcium	7.7 mg/dL	8.5–10 mg/dL
Glucose	110 mg/dL	

TABLE 2 Additional investigations helped for the final diagnosis and further evaluation of the patient.

Additional investigation	The result	Reference range
LDH	1124 U/L	240–480 U/L
Fe (Iron)	160 µg/dL	25–156 µg/dL
Total cholesterol	162 mg/dL	50–199 mg/dL
HDL cholesterol	14 mg/dL	40–60 mg/dL
Triglycerides	455 mg/dL	0–149 mg/dL
Uric acid	3.8 mg/dL	3–7 mg/dL
TSH	3.90 U/mL	0.40–5.0 U/mL
Total T4	66.06 nmol/L	66–181 nmol/L
Total T3	1.0 nmol/L	1.2–3.1 nmol/L
Free T4	13.12 pmol/L	
Free T3	1.54 pmol/L	
INR	2.0	
PT	22.0 s	11–17 s
aPTT	33.4 s	25–40 s
Serum ferritin	3000 ng/mL	20–250 ng/mL
CRP	100 mg/dL	Less than mg/dL

moderate to severe pleural effusion, bilateral axillary Lymphadenopathy and mild pericardial effusion.

Based on the clinical presentation and the initial investigations, the patient had been on empirical broad spectrum antibiotic (meropenem) and other supportive treatment after blood and urine cultures were drown for culture and sensitivity and further infectious screen. Despite broad spectrum antibiotic, the patient is still febrile.

Further investigation as shown in the Table 2, reveals the following results: that Triglycerides 455 mg/dL, LDH 1124 U/L, serum ferritin 3000 ng/mL, serum albumin 2.8 gm/dL, elevated PT and aPTT, INR 2.0, and negative direct coombs test. Viral serology of hepatitis B, hepatitis C and HIV was excluded by negative laboratory results and also negative testing of COVID-19. SLE and Autoimmune hepatitis had been excluded by negative ANA and anti-dsDNA Ab, anti-smooth muscle Ab and anti-LK microsomal antibody, respectively. Blood culture result was negative and also the urine culture. CD25 had not been tested in the patient as it was not available.

Peritoneal aspiration was down with clear serous fluid of transudate characters. On 7th day of admission, the patient developed severe abdominal pain mainly epigastric radiated to the back, unrelated to the meal associated with repeated vomiting, physical examination shows soft abdomen but severely tender epigastric region. The Lab results showed elevated serum lipase and serum amylase. Abdominal CT scan was performed to the patient, it revealed in addition to pre-existing findings of hepatosplenomegaly and ascites, there is diffusely enlarged, thickened and swollen pancreas, so the diagnosis of acute pancreatitis is done. The patient maintained on intravenous fluid, prophylactic antibiotics and analgesia, after 3 days the abdominal pain improved and her general condition got better but she was still febrile, jaundiced.

Bone Marrow Biopsy showed prominence of histiocytes with hemophagocytic activity, as shown in the Figure 1–5, suggesting the diagnosis of HLH syndrome, together with the other clinical and laboratory criteria, the diagnosis of HLH has been established. However, after 3 days the general condition of the patient rapidly deteriorated and then the patient died despite the treatment.

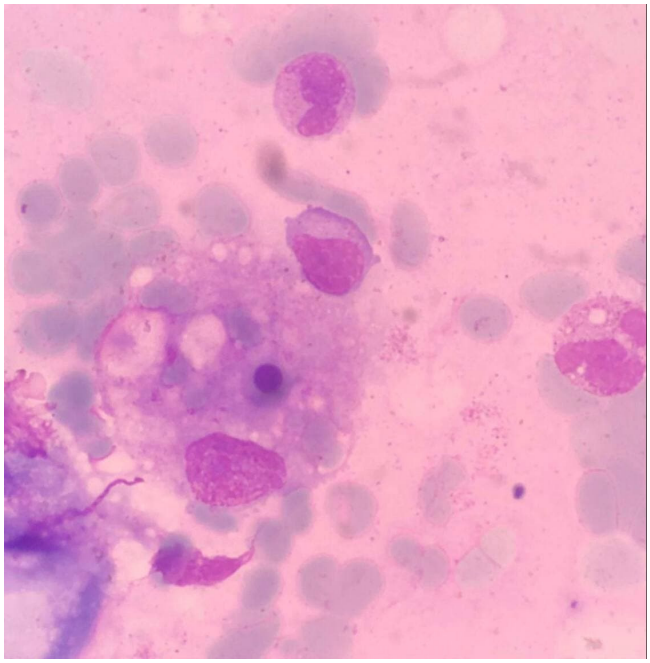

FIGURE 1 Bone marrow aspirate showed histiocyte engulfing late erythroid precursor, mature red blood cells, and platelets (hemophagocytosis).

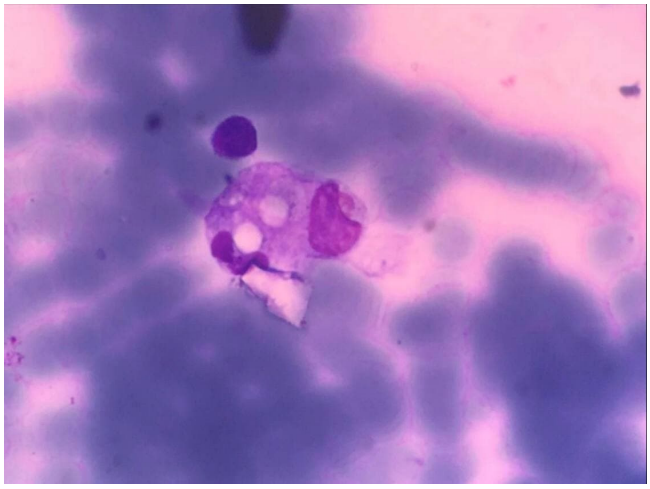

FIGURE 2 Bone marrow aspirate showed histiocyte engulfing mature red blood cell, segmented neutrophil, and myelocyte (hemophagocytosis).

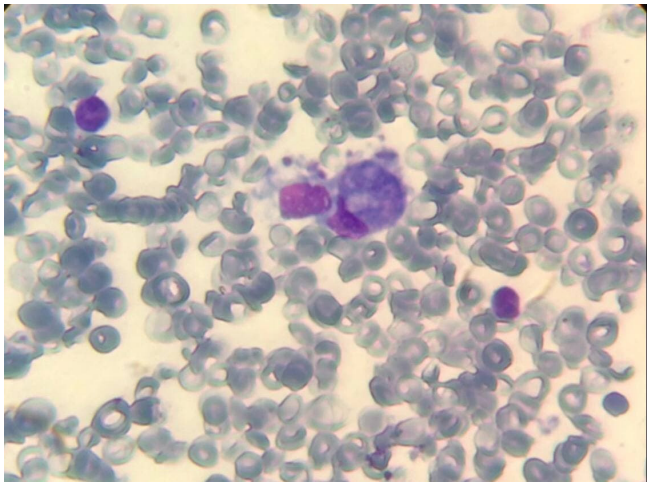

FIGURE 3 Bone marrow aspirate showed histiocyte engulfing mature red blood cell and platelets (hemophagocytosis).

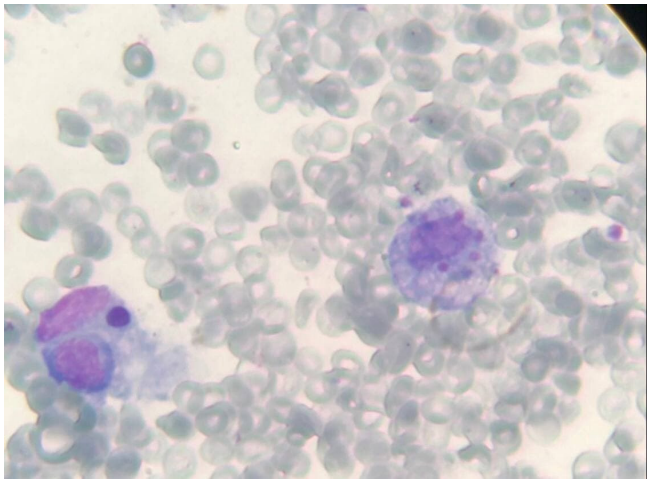

FIGURE 4 Bone marrow aspirate showed two histiocytes engulfing platelets and nucleated red blood cells (hemophagocytosis).

3 | DISCUSSION

Hemophagocytic lymphohistiocytosis (HLH) is a critical hyperinflammatory condition characterized by a sustained over-activation of the mononuclear phagocytic immune system that may result in an extreme but ineffective immune response. It can be classified as primary and secondary types of HLH. The Primary HLH is also known as familial HLH, usually presenting in childhood and can be associated with specific gene mutations of the cytolytic secretary pathway. While the Secondary HLH is also known as acquired HLH and usually presents in adulthood, it has been considered as an inflammatory endpoint for a variety of conditions including infections, malignancies, autoimmune and metabolic diseases.[1]

For secondary HLH, 8 diagnostic criteria are proposed (fever, hemophagocytosis in biopsy, splenomegaly, high ferritin, elevated soluble CD25, cytopenia, low natural killer cell activity, and hypertryglyceridemia or hypofibrinogenemia) and the presence of 5/8 of these criteria confirms the diagnosis in the correct scenario.[2]

Prompt recognition of the HLH and start of therapy is critical and lifesaving. However, initiation of therapy is often delayed due to challenges in establishing

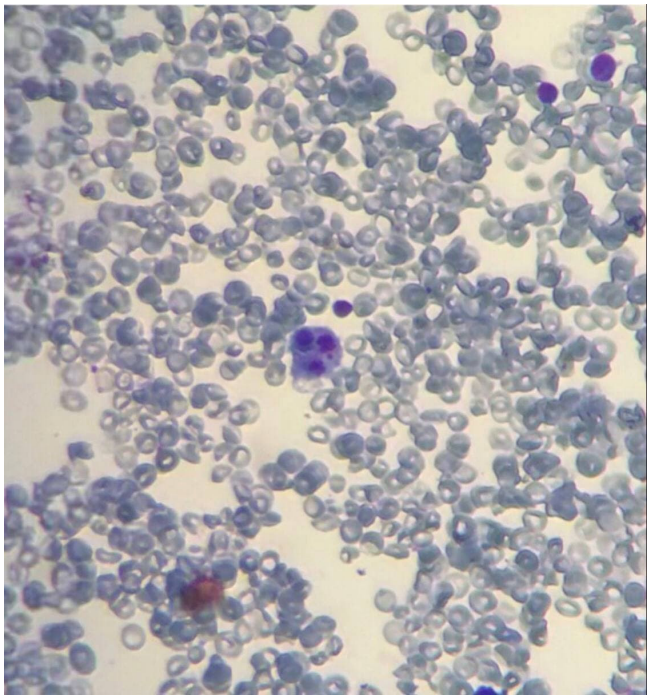

FIGURE 5 Bone marrow aspirate showed one histiocyte engulfing platelets and nucleated red blood cells (hemophagocytosis).

the diagnosis, so high degree of suspicion and awareness is essential to diagnose it especially in patients presenting with splenomegaly, elevated liver enzymes, increased inflammatory markers and cytopenias.[3] Hemophagocytosis alone is neither pathognomonic for, nor required for an HLH diagnosis, it can be a marker of excessive macrophage activation and supports the diagnosis of HLH.[1,4]

HLH is a rare manifestation of acute pancreatitis. However, the relation between acute pancreatitis and HLH was first considered in 1998 by Kanaji et al, who found that HLH can be associated with fulminant ulcerative colitis and acute pancreatitis.[5,6] Acute pancreatitis and HLH are sporadically observed in the course of systemic lupus erythematosus.[5,7,8] However, 3 case reports of HLH to be associated with acute pancreatitis have been reported.

In our patient, the diagnosis has been delayed because of the vague presentation and the restricted investigations facilities because of COVID-19 outbreak. We initially considered that the patient had pancytopenia and hepatic dysfunction as a result of multiorgan failure secondary to infectious or autoimmune disease in addition to the complication of acute pancreatitis that occurred during her admission, till bone marrow biopsy is done to exclude acute leukemia or other bone marrow disease and ultimately showed evidence of HLH syndrome and the treatment protocol for the patient was with steroids, etoposide and other supportive therapy.

4 | CONCLUSION

Hemophagocytic Lymphohistiocytosis syndrome has wide variety of patient presentations making the diagnostic approach confusing, difficult and challenging, so high degree of suspicion required for the possibility of its diagnosis and the prompt confirmation should be done through the diagnostic criteria in addition to looking for the predisposing associated factors.

AUTHOR CONTRIBUTIONS

Ahmed Mohamad Mechi: Conceptualization; data curation; investigation; project administration; resources; supervision; visualization; writing – original draft; writing – review and editing. **Alhan Abbas Al-Khalidi:** Conceptualization; data curation; investigation; resources; visualization; writing – original draft. **Thulfiqar Azeez Hasan:** Data curation; investigation; resources; visualization; writing – original draft.

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None.

CONFLICT OF INTEREST STATEMENT

No Conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

INFORMED CONSENT

Written informed consent was obtained from the patient and her next of kin to publish this report in accordance with the journal's patient consent policy.

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