INTRODUCTION
Hemophagocytic lymphohistiocytosis (HLH) is a rare syndrome characterized by pathologic systemic hyper inflammation which in adults is easily overlooked due to non-specific clinical features. Most of the data available are on paedriatic population, making the diagnosis of HLH in adults challenging for the clinician. Here we report a case of HLH in a 48-year male who presented with pyrexia of unknown origin for 2 months but remained undiagnosed despite extensive workup. Due to a high index of suspicion, re-evaluation of bone marrow biopsy was done which showed hemophagocytosis, earlier reported as normal. It led to specific investigations, needed for establishing the diagnostic criteria of HLH. Even though chemotherapy was initiated, the patient did not survive. The aggressive nature of this disease makes it crucial for the physician to be aware of its signs and symptoms for the early diagnosis and immediate introduction of adequate treatment.

CASE REPORT
A 48-year businessman with no known comorbid conditions, resident of Quetta, was admitted to the Medical Unit through Emergency, in May 2014. His major complaints were fluctuating fever and epigastric pain for 2 months with significant weight loss (> 10 kg) in last 6 months. He had received multiple broad spectrum antibiotics and was put on anti-tuberculous treatment (ATT) for 20 days which he discontinued when no response was seen. His medical records showed an extensive work up for pyrexia of unknown origin (PUO). His blood and bone marrow cultures, MP-ICT, Brucella antibodies level, antinuclear factor, rheumatoid factor, anti-DS-DNA, hepatitis and HIV serology were all negative. Ultrasound abdomen was normal. However, ESR and serum ferritin were elevated at 110 mm after first hour and 1299 ng/ml, respectively.

On admission, patient had mild to moderate epigastric pain, was vitally stable with BP of 140/80 mm Hg, pulse rate of 86/minute, respiratory rate of 18/minute and fever of 100°F. An initial assessment of disseminated tuberculosis, occult malignancy, sero-negative rheumatoid arthritis and chronic cholecystitis was made. His baseline labs showed deranged LFTs (serum total bilirubin=1.9 mg/dl, alkaline phosphatase=677 U/L, gamma GT=250 U/L). Urine DR showed 10 - 12 pus cells with mild proteinuria (24 mg/dl). ESR was 140 mm after first hour. Serum ferritin was elevated at 1394 ng/ml. Anti-CCP, ANA profile, anti-ds-DNA, stool for H. pylori antigen, MP-ICT, serum amylase, serum lipase, dengue and viral serology were repeated and found negative. Three sets of blood cultures and urine cultures were requested and broad spectrum antibiotics started. Ultrasound abdomen done in ER was unremarkable.

On the fourth day of admission, patient had mild to moderate epigastric pain, was vitally stable with BP of 140/80 mm Hg, pulse rate of 86/minute, respiratory rate of 18/minute and fever of 100°F. An initial assessment of disseminated tuberculosis, occult malignancy, sero-negative rheumatoid arthritis and chronic cholecystitis was made. His baseline labs showed deranged LFTs (serum total bilirubin=1.9 mg/dl, alkaline phosphatase=677 U/L, gamma GT=250 U/L). Urine DR showed 10 - 12 pus cells with mild proteinuria (24 mg/dl). ESR was 140 mm after first hour. Serum ferritin was elevated at 1394 ng/ml. Anti-CCP, ANA profile, anti-ds-DNA, stool for H. pylori antigen, MP-ICT, serum amylase, serum lipase, dengue and viral serology were repeated and found negative. Three sets of blood cultures and urine cultures were requested and broad spectrum antibiotics started. Ultrasound abdomen done in ER was unremarkable.

On the fourth day of admission, patient developed severe epigastric pain with vomiting. CT abdomen was suggestive of acute acalculus cholecystitis. Surgical team advised percutaneous cholecystostomy. Patient improved after the procedure and pigtail insertion.

Few days later, he started complaining of shortness of breath; pain shifted to left hypochondrium and low grade fever persisted. On auscultation, absent/reduced air movement in the left hypochondrion region was noted. On auscultation, absent/reduced air movement in the left hypochondrion region was noted. A repeat ultrasound showed gallbladder wall thickening. CT abdomen repeated which showed diffuse gallbladder wall thickening with pericholecystic fluid. A diagnosis of acute on chronic cholecystitis was made. Four sets of blood cultures were also requested and antibiotics were changed to broad spectrum agents. He also developed a recurrence of fever which was controlled with a single dose of intravenous ceftriaxone. He was discharged with a prescription for oral moxifloxacin and ceftriaxone, and was advised to visit the out-patient department on a regular basis.

entry on right lower and mid zones was noted. Repeat ultrasound abdomen showed moderate to severe right sided pleural effusion. Suspecting tuberculosis, pleural fluid was tapped for analysis. Bone marrow biopsy was ordered with routine and AFB cultures. Working diagnoses now included subclinical abdominal TB, pulmonary TB and occult malignancy. ATT using standard four-drug regimen was started. However, after two days, he developed vomiting and hyper-bilirubinemia. Pleural fluid analysis report was exudative as per Light's Criteria. Ultrasound guided lymph node biopsy of abdominal lymph nodes was not possible due to difficult approach. Symptoms of nausea and vomiting persisted with increase in fever spikes to 101°F. Bone marrow biopsy report came which was suggestive of HLH (Figure 1 and 2). The criteria of HLH were met as serum ferritin, and fasting triglyceride levels were also elevated. Induction chemotherapy using HLH-94 Study Protocol was started with injection Etoposide 150 mg/m² per dose I/V on alternate days and Inj. Dexamethasone 10 mg/m² daily, along with supportive treatment.

Two weeks post-admission, patient again became short of breath with exacerbation of epigastric pain and vomiting. CT chest showed moderate to massive bilateral pleural effusion and 1500 ml of pleural fluid was drained. Repeat cytology was negative for malignant cells. ATT was discontinued as total bilirubin increased markedly along with development of neutropenia. His condition worsened as he became drowsy and irritable with persistent vomiting and high grade fever. Suspecting CNS involvement, MRI brain was ordered which was normal. Serum sodium was found to be elevated and was corrected, but his neutropenia persisted. Amphotericin B, anti-virals and granulocyte growth factors were added in the treatment regimen.

On day 23rd of admission, the patient’s condition deteriorated further. He developed hypotension, dropped saturation, and was put on ventilator and inotropic support. His blood counts did not improve, and he expired on day 10 of chemotherapy.

**DISCUSSION**

Incidence of HLH in adults is very low world over. However, large series of cases have been reported from Asia, especially Hongkong and Taiwan. From Pakistan, sporadic case reports have been published showing association of dengue and malarial infection with HLH in adults. Diagnosis of HLH is based on a collection of clinical and laboratory abnormalities. Out of the 8 clinical signs or blood tests, it requires five or more clinical criteria.6 This case fulfilled 6 criteria: fever, splenomegaly, cytopenias, hemophagocytosis in the bone marrow, hyper-triglyceridemia, and a high ferritin level. Special tests, i.e. NK cell function and soluble CD25 levels are more specific but not easily available. Hence, the reference standard for the diagnosis remains the presence of hemophagocytic macrophages in histological specimens which may be absent in the early stages of the disease, a feature seen in our patient. The more specific CD 163, a hemoglobin-haptoglobin scavenger immuno-histochemical marker, was not applied due to non-availability. In this patient, diagnosis was delayed due to confounding presence of acute cholecystitis. Although the precipitating factor for HLH remained elusive; presence of protracted illness, weight loss, lymphadenopathy in chest and abdomen, elevated ESR, exudative nature and recurrence of pleural effusion make disseminated tuberculosis and lymphoma the more likely diagnoses. In a systematic review from India, Rajgopala et al. have reported tropical diseases like tuberculosis as a triggering factor seen in 51% cases of HLH among adults. Unfortunately, lymph node biopsy or isolation of acid fast bacilli from blood, bone marrow, and fluid

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**Figure 1:** Photomicrograph of bone marrow aspirate showing large aggregates of hemophagocytosis (Leishmann stain x20). Inset shows an arrow pointing at a single macrophage with engulfed neutrophil, myelocytes, normoblasts and RBCs.(Leishmann stain x100).

**Figure 2:** Photomicrograph of bone marrow trephine at high magnification showing increase number of macrophages. (H&E x 60) Inset shows these macrophages with strong positivity to immuno-histochemical marker CD-68 (x40).
cultures were not achieved. Empirical treatment with ATT had to be withdrawn after 10 days due to hyperbilirubinemia.

Therapy of HLH is based on suppression of the hyper-inflammatory status and treatment of any existing HLH triggers. The Histiocytic Society-94 Protocol has reported a 54% survival with a median follow-up of 6 years. Etoposide and dexamethasone are given as induction therapy followed by cyclosporine and intra-thecal methotrexate for CNS disease. Anti-thymocyte globulin or alemtuzumab, interferon-γ monoclonal antibodies, and hematopoietic stem cell transplantation are additional available modalities for HLH treatment.

However, survival after a diagnosis of HLH is dismal, especially among those with malignancy-associated HLH. This patient was placed on HLH-94 Protocol along with antibiotics, anti-virals, and blood component support but did not respond. The cause of death was most likely fulminant sepsis due to the combined effects of underlying pathophysiology of HLH and immunosuppression secondary to chemotherapy administered.

HLH due to complexity of clinical situation, difficulty in differentiation from sepsis, and multi-organ dysfunction can lead to delayed diagnosis. Hence, a multi-disciplinary approach, early suspicion and re-evaluation of patient, if needed, must be sought for optimum management.

REFERENCES