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Hemophagocytic Lymphohistiocytosis and Pancreatic cancer: A Rare Association.

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CASE REPORT

Hemophagocytic Lymphohistiocytosis and Pancreatic Cancer: A Rare Association

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Abstract

Introduction: **Hemophagocytic lymphohistiocytosis (HLH) or hemophagocytic syndrome (HPS) is a life-threatening and relatively rare condition that usually presents as a multisystem febrile illness. It is associated with excessive activation of the immune system and hypercytokinemia, leading to an unregulated aggregation of macrophages and lymphocytes. Here, we present the first likely case of HLH with metastatic pancreatic carcinoma being the underlying etiology.**

Case: **A 44-year-old male with past medical history significant for heart transplant for which he was on tacrolimus, End-Stage Renal Disease (ESRD) on hemodialysis, recently treated CMV viremia, and necrotizing pancreatitis presented to the emergency with complaints of chills, decreased appetite, worsening non-bloody emesis, and dull left upper quadrant abdominal pain with radiation to the back for four days. No shortness of breath, fever, diarrhea, or blood in the stool was reported. Vitals on admission were blood pressure of 90/61 mmHg, a heart rate of 110 beats per minute, temperature of 98.1 °F, and respiratory rate of 18 per minute. Physical exam was significant for scleral icterus, decreased bibasilar breath sounds, moderate abdominal tenderness in the left flank and left upper abdominal quadrant without any palpable mass, and 1+ bilateral pedal edema. The remainder of the physical examination was benign. Electrocardiogram (EKG) showed sinus tachycardia without any ischemic changes, and chest x-ray showed mild pulmonary edema. Initial blood workup revealed WBC at 8.3 k/uL, hemoglobin of 10.2 g/dL, platelet count of 90 k/uL, and BUN/creatinine of 45/5.8 (baseline 40/5.0). Cardiac workup showed an elevated high sensitivity troponin level of 2479 pg/mL and brain natriuretic peptide (BNP) of 600 (0−100 pg/mL). The hepatobiliary profile showed an aspartate transaminase (AST) level of 2645 U/L, an alanine transaminase (ALT) of 2935 U/L, alkaline phosphatase (ALP) of 106 U/L, and lipase of 61 U/L, with total and conjugated bilirubin of 3.5 mg/dL and 2.1 mg/dL, respectively. Transthoracic echocardiogram (TTE) showed reduced left ventricular size with hyperdynamic systolic function. Computerized tomography (CT) scan of the abdomen (Fig. 1) revealed numerous new pulmonary nodules, ring-enhancing lesions within the liver, hyperenhancement of the pancreas with walled-off necrosis, and splenomegaly. Microbiological work-up was positive for cytomegalovirus (CMV) serologies (IgM and IgG) but absent viral load on Polymerase Chain Reaction (PCR). The initial diagnosis was systemic inflammatory respiratory syndrome (SIRS), likely septic versus distributive in the setting of pancreatitis, demand mediated non-ST segment elevation myocardial infarction (NSTEMI), and shock liver. Tacrolimus was held, and the patient was started on broad-spectrum antibiotics including vancomycin and cefepime for sepsis of unknown origin along with vasopressors for hypotension, requiring admission to the medical intensive care unit. Blood and urine cultures were collected on admission which remained negative throughout the course of hospital. CA19-9 levels were found elevated at 5587 U/mL. Liver biopsy was consistent with poorly differentiated adenocarcinoma of pancreatic origin. Both Infectious Disease and Hematology were consulted due to broad differential diagnoses. Due to the patient's continued hemodynamic instability and nonresponsiveness to the antibiotics, HLH was suspected with supporting labs as follows: ferritin 55,740 ng/mL (22−322 ng/mL), triglycerides 177 mg/dL (30−150 mg/dL), and fibrinogen 244 mg/dL (173−454 mg/dL), thus conferring 70−80% probability of HPS based on H-score. Soluble IL-2 R levels came out at 19,188 pg/mL (ref range 175−858 pg/mL). The patient couldn't be started on HLH treatment due to initial concerns of underlying infection and the delay in results of soluble IL-2 Receptor (IL-2 R) levels. The infection as a possible etiology was ruled out due to negative blood and urine cultures and HLH was attributed to pancreatic cancer.**

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A marrow biopsy couldn't be pursued as the patient died within a week of hospitalization. An autopsy was not performed as per family's request.

Conclusion: **HLH can occur secondary to solid cell malignancies including those from the pancreas and should be kept high in the differential in critically ill cancer patients who are nonresponsive to antibiotics. H-score has been reported to be a more sensitive tool compared to the HLH protocol, especially if used earlier during the presentation. Further research is needed to compare diagnostic efficacy for HLH protocol verses H-score especially in critically ill patients as they might benefit from steroid trial.**

Keywords: HLH, Pancreatic cancer, Internal medicine, Immunology, Hematology

1. Introduction

Hemophagocytic lymphohistiocytosis (HLH) or hemophagocytic syndrome (HPS) is a life-threatening and relatively rare condition that usually presents as a multisystem febrile illness. It is associated with excessive activation of the immune system and hypercytokinemia, leading to an unregulated aggregation of macrophages and lymphocytes.[1,2] The common presentation of HLH is fever with low cell count and the enlargement of spleen and liver, but many atypical and unfamiliar presentations have been documented in the literature.[3] HLH has two subtypes that can be challenging to distinguish: a primary form and a secondary one, both of which result from dysregulated immune response.[2,4] Secondary HLH can be due to a variety of infectious and noninfectious causes, of which malignancy is a well-known one.[5] Here, we present the first likely case of HLH with metastatic pancreatic carcinoma being the underlying etiology.

2. Case presentation

A 44-year-old male with past medical history significant for heart transplant for which he was on tacrolimus, End-Stage Renal Disease (ESRD) on hemodialysis, recently treated CMV viremia, and necrotizing pancreatitis presented to the emergency with complaints of chills, decreased appetite, worsening non-bloody emesis, and dull left upper quadrant abdominal pain with radiation to the back for four days. No shortness of breath, fever, diarrhea, or blood in the stool was reported. Vitals on admission were blood pressure of 90/61 mmHg, a heart rate of 110 beats per minute, temperature of 98.1 °F, and respiratory rate of 18 per minute. Physical exam was significant for scleral icterus, decreased bibasilar breath sounds, moderate abdominal tenderness in the left flank and left upper abdominal quadrant without any palpable mass, and 1+ bilateral pedal edema. The remainder of the physical examination was benign. Electrocardiogram (EKG) showed sinus tachycardia without any ischemic changes, and chest x-ray showed mild pulmonary edema. Initial blood workup revealed WBC at 8.3 k/uL, hemoglobin of 10.2 g/dL, platelet count of 90 k/uL, and BUN/creatinine of 45/5.8 (baseline 40/5.0). Cardiac workup showed an elevated high sensitivity troponin level of 2479 pg/mL and brain natriuretic peptide (BNP) of 600 (0−100 pg/mL). The hepatobiliary profile showed an aspartate transaminase (AST) level of 2645 U/L, an alanine transaminase (ALT) of 2935 U/L, alkaline phosphatase (ALP) of 106 U/L, and lipase of 61 U/L, with total and conjugated bilirubin of 3.5 mg/dL and 2.1 mg/dL, respectively. Transthoracic echocardiogram (TTE) showed reduced left ventricular size with hyperdynamic systolic function. Computerized tomography (CT) scan of the abdomen (Fig. 1) revealed numerous new pulmonary nodules, ring-enhancing lesions within the liver, hyper-enhancement of the pancreas with walled-off necrosis, and splenomegaly. Microbiological work-up was positive for cytomegalovirus (CMV) serologies (IgM and IgG) but absent viral load on Polymerase Chain Reaction (PCR).

The initial diagnosis was systemic inflammatory respiratory syndrome (SIRS), likely septic versus distributive in the setting of pancreatitis, demand mediated non-ST segment elevation myocardial infarction (NSTEMI), and shock liver. Tacrolimus was held, and the patient was started on broad-spectrum antibiotics including vancomycin and cefepime for sepsis of unknown origin. Patient was also started on vasopressors due to persistent hypotension, requiring admission to the medical intensive care unit. CA19-9 levels were found elevated at 5587 U/mL. Liver biopsy was consistent with poorly differentiated adenocarcinoma of pancreatic origin (Fig. 2).

Due to the patient's continued hemodynamic instability and nonresponsiveness to the antibiotics, HLH was suspected with supporting labs as follows: ferritin 55,740 ng/mL (22−322 ng/mL), triglycerides 177 mg/dL (30−150 mg/dL), and fibrinogen 244 mg/dL (173−454 mg/dL), thus conferring 70−80% probability of HPS based on H-score. Soluble IL-2 R levels came out at 19,188 pg/mL (ref range 175−858 pg/mL). The patient couldn't be started on HLH treatment due to initial concerns of underlying infection and the delay in results of soluble IL-2

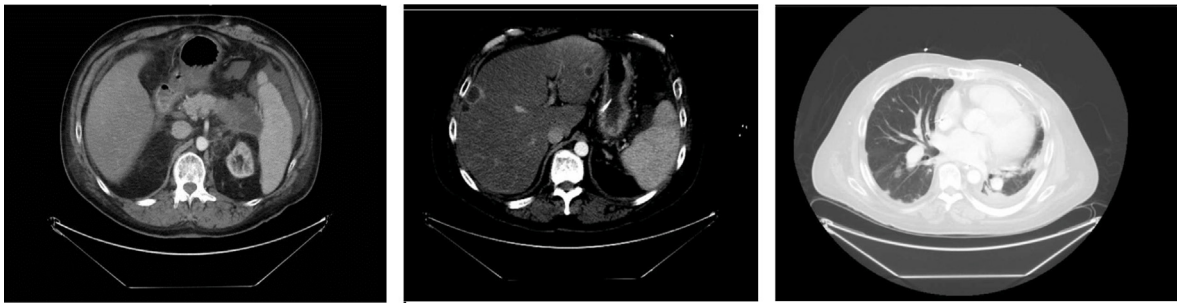

Fig. 1. CT abdomen showing hyper-enhancement of pancreas with walled off necrosis, multiple ring-enhancing hepatic lesions, splenomegaly and numerous pulmonary nodules.

Receptor (IL-2 R) levels. The infection as a possible etiology was ruled out due to negative blood and urine cultures and HLH was attributed to pancreatic cancer. A marrow biopsy couldn't be pursued as the patient died within a week of hospitalization. An autopsy was not performed as per family's request.

3. Discussion

Hemophagocytic lymphohistiocytosis (HLH) is a hyperinflammatory syndrome that was first reported by Rob-Smith and Scott. It predominantly affects the pediatric population but is known to affect all age groups.[5,6] Primary HLH manifests in childhood and is often associated with genetic mutations and inborn disorders of cytotoxic leukocytes with an incidence of 1.2/1,000,000 children per year.[7] Secondary HLH, also known as acquired HLH, has a mortality rate of 40% and can result from several infectious and non-infectious etiologies, including but not limited to hematologic malignancies, auto-immune disorders, some medications, and certain infections with viral etiologies being the most common ones.[8-10] Though HLH is significantly related to hematologic malignancies, a high level of suspicion should be made in patients with findings concerning for HLH and the presence of triggers like solid malignancies. Malignancy-associated HLH (M-HLH) is a rare and aggressive form of secondary HLH that occurs in the context of malignancy. M-HLH can occur in various malignancies, including lymphomas, leukemias, solid tumors, and some viral-associated tumors. The reported incidence of M-HLH varies among studies, but it is estimated to be around 1−2% of patients with malignancies.[11] Since the pathophysiology of HLH is linked with excessive immune activation leading to hyperinflammation, steroids are usually the 1st line treatment to tackle the ongoing inflammation.[12] The expedient diagnosis, however, remains the main trial as most patients are critically ill, requiring emergent therapeutic intervention.[13] HLH shares certain clinical features with sepsis/systemic inflammatory response syndrome (SIRS) and requires a precise approach in the diagnosis as the treatment of the two conditions is different.[14] The diagnosis of M-HLH is challenging and requires a high index of suspicion. The diagnosis is made based on clinical, laboratory, and histological criteria

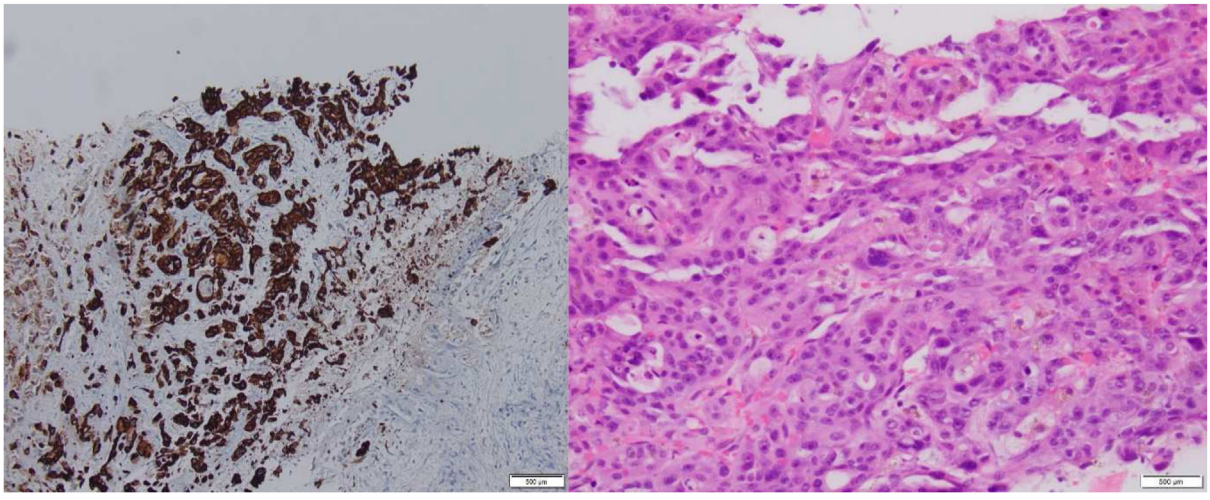

Fig. 2. Liver biopsy revealing poorly differentiated adenocarcinoma of pancreatobiliary origin.

established by the HLH-2004 diagnostic criteria. Treatment of M-HLH involves aggressive management of the underlying malignancy and suppression of the hyperinflammatory response. According to the refined HLH treatment protocol (HLH-2004), HLH diagnosis is based on eight criteria: fever, splenomegaly, cytopenia, elevated triglycerides, decreased fibrinogen levels, decreased/absent NK cell activity, elevated ferritin levels, high soluble IL-2 R levels, and hemophagocytosis. According to this protocol, five of these eight criteria must be met to qualify for HLH diagnosis unless family history or molecular diagnosis is consistent with HLH.[15] The H-score, a recent diagnostic tool, is often used to evaluate the probability of HLH.[16] In adults with suspected HLH, the H-score has better diagnostic efficacy with 90% sensitivity and 79% specificity compared to the HLH-2004 protocol, especially if used earlier during the presentation.[17] Our patient fulfilled only 3 out of the 5 required criteria based on HLH-protocol. However, his H score at presentation was 184, indicating a 70−80% probability of having HLH. Also, worth mentioning is that the bone marrow biopsy in case of suspected HLH should only be used as a supportive test and the whole clinical picture should be taken into consideration as biopsy alone neither proves or disproves HLH.[18,19] In critically ill patients with concerns for sepsis but worsening clinical status despite antibiotics, HLH should be suspected, and a trial of steroids might prove beneficial, as delay in treatment leads to poor outcomes, as in our patient.

4. Conclusions

HLH can occur secondary to solid cell malignancies including those from the pancreas and should be kept high in the differential in critically ill cancer patients who are nonresponsive to antibiotics. H-score has been reported to be a more sensitive tool compared to the HLH protocol, especially if used earlier during the presentation. Further research is needed to compare diagnostic efficacy for HLH protocol verses H-score especially in critically ill patients as they might benefit from steroid trial.

Conflict of interests

The authors have no conflict of interests.

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