Small intestinal ulcers in hemophagocytic lymphohistiocytosis presenting as acute appendicitis

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1. Case report

A 3-year-old previously healthy female presented with an 8 day history of fever and malaise and 2 days of diarrhea, non-bilious/non-bloody emesis and abdominal pain. She was tachycardic, febrile at 39.6°C, and tachypneic. Her abdomen was tender to palpation in the right lower quadrant, the liver edge was palpable 2 cm below the right costal margin, and she had enlarged cervical and submandibular lymph nodes. Laboratory evaluation revealed a white blood cell count of 10.4 k/mm³, as well as elevated acute-phase reactants and transaminases (Table 1). An abdominal ultrasonogram showed an inflamed, thick-walled tubular structure in the right lower quadrant with surrounding fluid.

She was admitted to the pediatric surgery service for observation with concern for appendicitis. Due to her atypical presentation and ultrasound findings, an abdominal CT was performed. It revealed a distended, fluid-filled, hyperemic appendix, concerning for perforated appendicitis; ascites; and pleural effusions. She subsequently underwent exploratory laparoscopy for suspected perforated appendicitis. Examination revealed a mildly hyperemic appendix, and multiple 0.5–1 cm discrete, tan, hyperemic, plaque-like lesions were
identified on the serosa of the small intestine (Fig. 1A and B). An appendectomy was performed. The umbilical incision was then enlarged slightly, and an area of small bowel containing one of the lesions was externalized. A full-thickness biopsy was obtained, and the incision was closed transversely. The intraluminal surface of the biopsy site appeared yellow and ulcerated (Fig. 1C).

Histology of both the intestinal plaques and the appendix showed mucosal ulceration and necroinflammatory exudate. The submucosa contained a mixed inflammatory cell infiltrate composed of numerous histiocytes, neutrophils, eosinophils, and lymphocytes (Fig. 1D). Histiocytes contained phagocytosed cellular debris with foci suggestive of erythrophagocytosis. Immunohistochemical studies confirmed the presence of histiocytes and ruled out Langerhans cell histiocytosis and acute leukemia/lymphoma. An Epstein–Barr encoding region in situ hybridization study was negative for Epstein–Barr virus.

Postoperatively, she became increasingly ill with progressive tachycardia, tachypnea, abdominal distension, lethargy and transaminitis. She developed hypoxemia and required transfer to the intensive care unit. Based on review of the pathology, a serum ferritin was obtained, and the result was markedly abnormal with a value of 47,452 ng/ml. A comprehensive infectious, metabolic, and oncologic evaluation was performed and was otherwise unremarkable. She had high fevers for 12 days and over that time developed pancytopenia, hepatosplenomegaly, and hypertriglyceridemia, meeting 5 diagnostic criteria for HLH [4]. Multi-agent chemotherapy with etoposide, dexamethasone, and cyclosporine was initiated on postoperative day 4 [5]. With this treatment, she gradually improved and was discharged 11 days after beginning chemotherapy. An evaluation for HLH-causing mutations in PRF1, UNC13D, STXBP2, STX11, RAB27A was negative.

Her postoperative course was complicated by duodenal biopsy-proven cytomegalovirus infection and an abdominal wall wound dehiscence that required surgical repair. She is continuing chemotherapy and may ultimately undergo a matched, unrelated donor hematopoietic stem cell transplant.

2. Discussion

On initial presentation, HLH is frequently indistinguishable from manifestations of serious illness or sepsis, but it rarely mimics surgical disease [6]. This is the first report of hemophagocytosis in small intestinal ulcers prompting the diagnosis of HLH, and it is the first time such lesions have been identified intraoperatively.

HLH is a consequence of unregulated immune activation following an inflammatory stimulus. Mutations in the perforin/granzyme pathway are associated with primary or familial HLH. This pathway regulates lymphocyte cytotoxicity by natural killer cells, which is critical in eliminating activated antigen presenting cells. Without this negative feedback following an inflammatory

Table 1

<table>
<thead>
<tr>
<th>Study</th>
<th>Result*</th>
<th>Reference range</th>
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</thead>
<tbody>
<tr>
<td>Erythrocyte sedimentation rate</td>
<td>47 mm/h</td>
<td>0–20 mm/h</td>
</tr>
<tr>
<td>C-reactive protein</td>
<td>108.7 mg/l</td>
<td>&lt;10 mg/l</td>
</tr>
<tr>
<td>White blood cells</td>
<td>10.4 k/cumm</td>
<td>5–15.5 k/cumm</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>10.5 g/dl</td>
<td>11.5–13.5 g/dl</td>
</tr>
<tr>
<td>Platelets</td>
<td>164 k/cumm</td>
<td>140–440 k/cumm</td>
</tr>
<tr>
<td>Ferritin</td>
<td>47,452 ng/ml*</td>
<td>7–140 ng/ml</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>160 mg/dl*</td>
<td>177–401 mg/dl</td>
</tr>
<tr>
<td>ALT</td>
<td>209 units/l</td>
<td>10–40 units/l</td>
</tr>
<tr>
<td>AST</td>
<td>769 units/l</td>
<td>10–60 units/l</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>349 mg/dl*</td>
<td>0–150 mg/dl</td>
</tr>
<tr>
<td>Soluble IL-2 Receptor</td>
<td>11,616 units/ml*</td>
<td>&lt;2126 units/ml</td>
</tr>
</tbody>
</table>

* All results are from presentation, except for those followed by an *, which are from the time of diagnosis. At the time of diagnosis, the WBC increased to 14.6 k/cumm, Hg decreased to 7.5 g/dl and platelets decreased to 104 k/cumm.

Fig. 1. Diagnostic laparoscopy revealed multiple, discrete, tan, hyperemic lesions throughout the small bowel (A, B). Open biopsy showed a focal, yellow, ulcerated mucosal surface (C). Pathology demonstrated mucosal ulceration with necroinflammatory exudate and histiocytes containing phagocytosed cellular debris (D).
stimulus, unabated immune activation leads to the clinical presentation of HLH [4].

Rapid identification and initiation of treatment for HLH is critical to patients’ survival [3]. In this case, biopsy of these lesions helped direct and confirm diagnosis. Untreated, the disease is universally fatal, but 5-year survival increases to 54% with chemotherapy and hematopoietic stem cell transplant [3]. Our case stresses the need for a high index of suspicion for HLH, as well as the importance of an early diagnosis both with respect to treating the disease and reducing morbidity.

Diagnosis requires 5 of the 8 following criteria: fever; splenomegaly; cytopenia affecting at least 2 cell lineages; hypertriglyceridemia or hypofibrinogenemia; hemophagocytosis in bone marrow, spleen or lymph nodes; low or absent NK activity; ferritin ≥500 ug/l; and soluble CD25 ≥2400 U/ml [4]. Notably, the presence of hemophagocytosis is neither necessary nor sufficient for the diagnosis of HLH, and in this case, a bone marrow biopsy performed after the initial biopsy but before initiation of chemotheraphy revealed no definitive evidence of hemophagocytosis.

Our patient’s ferritin level above 10,000 ng/ml was also suggestive of HLH. Ferritin can be elevated with a variety of conditions, including shock, bone marrow transplant, heart disease and liver disease; however, elevation above 10,000 ng/l is 90% sensitive and 96% specific for HLH [7]. While not included amongst the diagnostic criteria, pleural effusion, liver dysfunction, elevated transaminases, lymphadenopathy, edema, neurologic symptoms and disseminated intravascular coagulation are additional common presenting features of HLH [6,8].

HLH may rarely present with signs and symptoms suggestive of a surgical abdomen, and it may also unexpectedly complicate postoperative recovery. A recent case series reported four children diagnosed with HLH after different clinical presentations: 1) neonatal abdominal distention and bilious emesis concerning for necrotizing enterocolitis, 2) ileostomy closure and Hirschsprung’s disease, 3) iatrogenic sigmoid perforation and Crohn’s disease; however, elevation above 10,000 ng/l is 90% sensitive and 96% specific for HLH [7]. While not included amongst the diagnostic criteria, pleural effusion, liver dysfunction, elevated transaminases, lymphadenopathy, edema, neurologic symptoms and disseminated intravascular coagulation are additional common presenting features of HLH [6,8].

In rare adult cases, HLH has mimicked acute cholecystitis and toxic megacolon [9–11]. However, this case is the first report of HLH mimicking acute appendicitis. Gastrointestinal signs and symptoms such as abdominal distention, vomiting and diarrhea are rare in HLH [1], and since this child’s presentation suggested appendicitis, her underlying HLH was not suspected preoperatively.

Our patient is unique in that intestinal histology demonstrated a lymphohistiocytic infiltrate with foci suggestive of hemophagocytosis at the time of diagnosis. An autopsy series of 27 children with HLH identified the most common sites of hemophagocytosis in postmortem examinations: central nervous system (89%), lymph nodes (74%), spleen (71%), bone marrow (39%), thymus (18%) and liver (11%) [8]. However, in some cases, the heart, lungs, intestines, kidneys and pancreas also demonstrated evidence of hemophagocytosis [8]. One of these patients suffered an intestinal perforation during treatment for her disease, and postmortem examination revealed lymphohistiocytic infiltration of the intestine and hemophagocytosis [8]. It is unclear whether or not the small intestinal ulcerations observed in our patient would be at risk for perforation if left untreated.

3. Conclusion

In conclusion, HLH can mimic acute appendicitis or other surgical conditions at presentation. A high index of suspicion and rapid diagnostic evaluation are necessary for early recognition and treatment of HLH. While surgery may be useful to treat certain sequelae of HLH or instigating pathologies for secondary HLH, chemotherapy remains the mainstay of treatment.

Disclosures

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References