Hemophagocytic lymphohistiocytosis, or HLH, is a rare, but life-threatening condition caused by over-activation of the immune system. Immunotherapy is a relatively new method of cancer treatment. We present a case of Pembrolizumab-induced HLH. We report a case of an elderly man, with metastatic disease of unknown primary, who progressed through 2 lines of chemotherapy. He was started on third-line immunotherapy using Pembrolizumab. He remained persistently pancytopenic and febrile despite treatment for sepsis. Bone marrow biopsy showed results consistent with HLH. He was treated with Dexamethasone, then Etoposide without improvement. He eventually suffered from intracranial hemorrhage due to thrombocytopenia and was transitioned to hospice. He passed away soon after. HLH should be suspected when patients on immunotherapy present with pancytopenia and fever. Although rare, it is a life-threatening condition and early interventions may be able to halt the progression of disease. The diagnosis can have a large impact on patients both in the field of Oncology as well as in the field of Surgery.

**Keywords:** Immunotherapy, Pembrolizumab, Hemophagocytic lymphohistiocytosis, PD-L1, Immune checkpoint inhibitors

Hemophagocytic lymphohistiocytosis is a rare, but life-threatening condition caused by over-activation of the immune system. Triggers such as infection, autoimmune disorders, and malignancy often bring about HLH[1]. The diagnosis is difficult to make due to a variable clinical presentation and rarity of the diagnosis.

The diagnostic criteria used to determine if a patient has HLH was published by the Histiocyte Society in 2004, as documented by Sadaat and Jang[2]. Five of the following 8 criteria must be fulfilled:

1. Fever of 38.5°C or more.
2. Splenomegaly.
3. Cytopenias (affecting at least 2 of 3 cell lineages in the peripheral blood) defined as hemoglobin <90 g/L (in infants <4 weeks old; hemoglobin <100 g/L), platelets <100×10^9/L or neutrophils <1.0×10^9/L.
4. Hypertriglyceridemia and/or hypofibrinogenemia.
   - Fasting triglycerides ≥ 3.0 mmol/L (ie, ≥ 26.5 mg/dL).
   - Fibrinogen ≤ 1.5 g/L.
5. Hemophagocytosis in bone marrow or spleen or lymph nodes or liver.
6. Low or absent natural killer cell activity.
7. Ferritin ≥ 500 mg/L.
8. Soluble CD25 (ie, soluble IL-2 receptor) ≥ 2400 U/mL.

Supportive criteria to help make the diagnosis of HLH include: neurological symptoms, conjugated hyperbilirubinemia and transaminitis, hypoalbuminemia, hyponatremia, elevated D-dimers, and lactate dehydrogenase. Of note, the absence of hemophagocytosis (in the bone marrow) does not exclude a diagnosis of HLH[2].

If the above is not enough to make the diagnosis, one other criteria can be fulfilled to make the diagnosis[2];

1. A molecular diagnosis consistent with HLH: pathologic mutations of PRF1, UNC13D, STXBP1, RAB27A, STX11, SH2D1A, or XIAP.

The over-activation of the immune system in HLH is thought to be due to defunct normal downregulation of the immune system[1]. Natural killer cells and cytotoxic lymphocytes (CD8) are responsible for destroying foreign antigens presented by macrophages. In HLH, the natural killer cells and cytotoxic lymphocytes (CD8) fail to eliminate foreign antigens presented by active macrophages[1]. This causes the activated macrophages to release excessive amounts of inflammatory mediators, which ultimately leads to severe tissue damage and organ failure[1].

HLH should be suspected when patients on immunotherapy or postoperatively present with pancytopenia and fever[1,3]. Although rare, it is a life-threatening condition and early interventions may halt the progression of disease.

**Methods**

A 61-year-old man presented to emergency department with a pathologic compression fracture. He had a past medical history...
of hypothyroidism, recurrent deep venous thrombosis with Factor V Leiden heterozygosity, hemochromatosis, and porphyria cutanea tarda. He was complaining of subjective fevers and chills. He was initially at his functional baseline. He was alert and oriented 3×3, with no abnormalities on physical examination other than exhibiting mild abdominal tenderness to the right and left upper quadrants.

He was admitted and worked up. Pathology indicated metastatic poorly differentiated carcinoma, positive for CK AE1/AE3, CK7, and CK20. Immuno stains for CDX2, GATA-3, Inhibin, Melan-A, desmin, CD 34, and ERG were negative. CD-45 was equivocal. MIB-1 index was high. The staining pattern suggested an upper gastrointestinal or pancreatobiliary primary origin.

He underwent 2 upper endoscopy procedures which did not reveal any esophageal or gastric lesions. A positive emission computed tomography (CT) scan showed metastasis in the cervical spine, liver, and right adrenal gland, along with portacaval lymphadenopathy.

The patient progressed through 2 lines of therapy with 7 cycles of Folinic acid, Fluorouracil, and Oxaliplatin (otherwise known as FOLFIRI), and 4 cycles of Gemcitabine and Abraxane. Since his PD-L1 expression was 20% and he was not responding to chemotherapy, the decision was made to treat him with immunotherapy using Pembrolizumab. He received a total of 7 cycles of Pembrolizumab.

The patient presented in clinic for his cycle 8 of Pembrolizumab and was found to have a have a white blood cell count of 0.81 (normal range of 4.5–11.0 × 10^9/L), and a platelet count of 21 (normal range 150–400 × 10^9/L). These lab values prompted his Oncologist to send him to the Emergency Department.

His home Enoxaparin medication was held due to his low platelet count. A bone marrow biopsy was planned for 4 days later. At that time, his counts had dropped further to a white blood cell count of 0.85 and a platelet count of 7. He was also febrile to 101.3°F.

He was initially started on broad spectrum antibiotics with Vancomycin and Cefepime with concerns for febrile neutropenia. Antibiotics were deescalated to Cefepime alone once culture data was negative for gram positive organisms. The patient remained pancytopenic and counts were refractory to multiple transfusions. Hence, we started a work up for refractory pancytopenia.

### Outcomes/follow-up

The patient then started to deteriorate clinically. He became encephalopathic and developed multiple physical examination abnormalities including increasing abdominal tenderness to the right and left upper quadrants, crakles in the bilateral lung bases, and petechiae. Work up revealed a haptoglobin <10 (normal range 50–220 mg/dL) and a lactate dehydrogenase level elevated to 1277 from 628 on admission (normal range 140–280 U/L). Disseminated intravascular coagulation (DIC) panel showed fibrinogen of 85 (normal range 200–400 mg/dL), fibrin degradation product 20–40 (normal range <10 mg/dL), international normalized ratio 2.1 (normal range <1.1). The patient was started on high-dose Methylprednisolone, 1.5 mg/kg daily. The steroid served a 2 in 1 effect as the patient also had worsening liver function tests which were thought to be due to autoimmune hepatitis.

A CT of the abdomen pelvis demonstrated splenomegaly measuring 23 cm, increased from 18 cm 2 months prior.

Hematology was consulted. A peripheral smear was reviewed which showed rare schistocytes. This made DIC and thrombotic microangiopathy unlikely. Hematology recommended checking a ferritin level to look for HLH. Ferritin was elevated to 58,243 (normal range 20–250 ng/mL).

At this point, the patient met 5 of the 8 criteria for HLH. A soluble IL2 activity level and natural killer cell activity level were ordered.

We performed the H score for reactive HLH which was 233 giving the diagnosis of HLH 98%–99% probability. After the bone marrow biopsy results revealed increased histiocytes with numerous intracytoplasmic nucleated and non-nucleated red cells, the score increased to 268, making the probability >99%. An example of a bone marrow biopsy showing the diagnosis of HLH is listed below.

The driver for the HLH diagnosis in this patient was thought to be his immunotherapy regimen. On the basis of previous case reports that had reported efficacy of treatment for immunotherapy-related HLH, we continued high-dose steroids, but switched to Dexamethasone 10 mg/m² based on the HLH 94 protocol[21].

After 6 days of high-dose Dexamethasone, the patient’s counts continued to be low, refractory to transfusions, as outlined in Table 1 below. The patient was therefore started on twice weekly Etoposide 75 mg/m², which was a 50% dose reduction from the HLH 94 protocol due to his impaired renal function and cytopenias. The patient’s laboratory values did not improve over the next 3 days. When the second dose of Etoposide was due, the patient had a seizure lasting ~30 seconds. A STAT CT scan of the head was done showed a subarachnoid and a subdural hemorrhage. The images can be found below. Because of his rapidly declining condition, his family withdrew care, and the patient was transitioned to hospice. He passed away 3 days later due to intracranial hemorrhage.

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**Table 1**

<table>
<thead>
<tr>
<th>Lab Value</th>
<th>Day 1</th>
<th>Day 4 (Steroids started)</th>
<th>Day 5</th>
<th>Day 9 (Etoposide started)</th>
<th>Day 12 (Patient made CMO)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet count (×10^9/L)</td>
<td>5</td>
<td>5</td>
<td>6</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>8.2</td>
<td>6.8</td>
<td>7.8</td>
<td>7.6</td>
<td>7.1</td>
</tr>
<tr>
<td>WBC (×10^9/L)</td>
<td>0.76</td>
<td>0.61</td>
<td>0.77</td>
<td>0.56</td>
<td>0.51</td>
</tr>
<tr>
<td>ANC (×10^9/L)</td>
<td>0.49</td>
<td>0.48</td>
<td>0.68</td>
<td>0.45</td>
<td>0.49</td>
</tr>
<tr>
<td>Ferritin (ng/ml)</td>
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<td>Not checked</td>
<td>58,243</td>
<td>52,429</td>
<td>46,123</td>
</tr>
<tr>
<td>Fibrinogen (mg/ml)</td>
<td>Not checked</td>
<td>85</td>
<td>97</td>
<td>99</td>
<td>82</td>
</tr>
<tr>
<td>LDH (U/L)</td>
<td>628</td>
<td>1277</td>
<td>1797</td>
<td>1093</td>
<td>868</td>
</tr>
</tbody>
</table>

Our patient’s HLH lab values.

HLH indicates hemophagocytic lymphohistiocytosis; LDH, lactate dehydrogenase; WBC, white blood cell.
Discussion

Recently there have been an increasing number of case reports describing immunotherapy-related HLH. Pembrolizumab belongs to a class of drugs more formally known as “Immune Checkpoint Inhibitors” or ICI[4]. Immunotherapy is vastly different from more traditional chemotherapy agents and carries a host of different side effects. Pembrolizumab is a monoclonal antibody helps the body’s immune response to malignancies by binding to the PD-1 ligand of host T cells[4]. Tumor cells have a PD-L1 ligand attached which is used to bind the PD-1 ligand of host T cells, inactivating host T-cell immune response against tumor cells[4]. Pembrolizumab prevents the tumor cells from inactivating host T cells through the inhibition of the PD-L1 and PD-1 binding mechanism, thus allowing the body’s T cells to attack tumor cells[4]. Through their mechanism of action, ICIs are associated with mostly autoimmune-related side effects and toxicities. Some common examples of these toxicities include hypothyroidism, colitis, pneumonitis, skin rashes, and other organ toxicities[4]. These toxicities can vary in severity and are highly dependent on the combination of ICI agents given, the patient, as well as co-morbidities. Hematological toxicities are rarely seen with ICIs compared with traditional chemotherapy agents[4]. Since ICIs enhance the body’s immune response against tumor cells, hyper-activation of their immune-modulating actions could result in HLH.

ICI-related HLH is being reported more frequently. In a recent study conducted by Noseda et al[4], 49,883 cases of ICI adverse effects were monitored. HLH developed in 38 cases, within which 34 cases were attributed to a single ICI agent as the main culprit[4]. Pembrolizumab specifically was implicated as the cause of HLH in 8 of 38 ICI-related HLH cases, 7 of these with Pembrolizumab as the sole offender and 1 of these with Pembrolizumab and Yervoy (Ipilimumab) given sequentially[4].

HLH is an extremely relevant diagnosis to be aware in the field of surgery as well. Because of the extreme presentation of HLH, it can often falsely present as a surgical disease. This is best illustrated by a case series published in the Journal of Pediatric Surgery by Siminas and colleagues. Four children with an acute surgical presentation were examined. The 4 surgical presentations were as follows: neonatal abdominal distension, ileostomy closure, and Hirschsprung disease, iatrogenic sigmoid perforation and Crohn’s disease, and streptococcal toxic shock syndrome complicated by primary peritonitis[5]. Each of these patients underwent surgical treatment, but developed prolonged, postoperative sepsis of unclear etiology[5]. In an effort to uncover the etiology of each of the children’s postoperative sepsis complication, a total of 6 exploratory laparotomies were performed, all of which were unremarkable[5]. Eventually, each of the 4 children were found to have worsening pancytopenia, persistent fevers, and hepatosplenomegaly[5]. A diagnosis of HLH was made in each of them. Their clinical course was improved with initiation of high-dose steroid treatment followed by Etoposide and Cyclosporine administration[5].

Furthermore, HLH can complicate treatment in patients where surgical treatment may be indicated. This is best illustrated by a case series and literature review conducted by Popeskou and colleagues, published in the Case Reports in Surgery Journal. The first patient detailed in the case series was a 26-year-old man with Crohn’s disease[5]. He presented with febrile pharyngitis secondary to an active Epstein-Barr virus infection[5]. On hospital day 7, the patient developed a massive lower gastrointestinal (GI) bleed[3]. Initial colonoscopy showed pancolitis with ulcerations in multiple sites which was attributed an acute flare of his Crohn’s disease[5]. He became hemodynamically unstable thereafter, requiring a total colectomy with ileostomy[3]. Despite the surgery, the patient continued to decline clinically postoperatively with worsening pancytopenia, fevers, and recurrent upper GI bleeds refractory to multiple transfusions[3]. Upper endoscopy revealed multiple bleeding ulcers[3]. Eventually, blood work revealed an elevated lactate dehydrogenase and ferritin levels[3]. The patient had a bone marrow biopsy done showing a diagnosis of HLH[3]. He was treated with high doses of steroids which showed transient improvement in his lab work[3]. However, he passed away from multiple organ failure 12 days later[3].

The second patient detailed in the case series was a 61-year-old man who presented with a massive lower GI bleed[3]. A similar episode had occurred 4 months prior, accompanied by persistent episodes of fever[3]. An upper endoscopy revealed a small Mallory-Weiss tear, not thought to be the source of bleeding[3]. A CT angiogram did not reveal a source of the bleeding[3]. Initially, the patient was managed conservatively. However, he became hemodynamically unstable 3 days later with anemia, thrombocytopenia, elevated lactate dehydrogenase, and elevated ferritin levels[3]. Emergent laparotomy with intraoperative colonoscopy was performed, followed by resection of 60 cm of the ileum[3]. Postoperative sepsis occurred 2 days later[3]. A repeat CT scan of the chest, abdomen, and pelvis did not reveal a source[3]. Neither did a “second look” laparotomy procedure[3]. The patient developed DIC and a new episode of lower GI bleeding[3]. HLH was suspected, and the patient was treated empirically for the diagnosis with cyclophosphamide, doxorubicin, oncovin, and prednisone (CHOP regimen) plus etoposide[3]. The patient did not improve, and eventually passed away. Postmortem marrow biopsy confirmed the diagnosis of HLH.

With regards to our patient, it was very difficult to suspect HLH, as he was immunocompromised at baseline from the metastatic carcinoma of unknown origin. There were other, seemingly, more likely explanations for what seemed to be an infectious presentation. Therein lies the challenge of making this diagnosis. As detailed in the review of the literature above, HLH is appearing more frequently as a byproduct of immunotherapy.
treatment. The statistics from Noseda and colleagues fall in line with the outcome of our patient. The surgical cases detailed by Popeskou and colleagues illustrate how HLH can mimic septic presentations, which occurred in our patient as well given how we initially approached the treatment of his pancytopenia and fevers with broad spectrum antibiotics. With more case reports like ours, we believe HLH will be able to be suspected and diagnosed earlier in treatment courses (Figs. 1 and 2).

**Conclusion**

As ICIs became more prevalent as a treatment option across the oncology landscape, it is important to be aware of the various side effects they can cause. HLH is one of these side effects, albeit a rare one. HLH can have a large impact on the surgical landscape as well, often contributing to unnecessary surgical evaluation and/or complicated postoperative courses. By continuing to study the outcomes associated with ICI therapy and by detailing cases of HLH, we can enhance our ability to treat our patients effectively.

**Assistance with the study**

None.

**Ethical approval**

Complied with HIPPA and IRB regulations.

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**Author contribution**

All authors were involved in data collection and interpretation.

**Conflict of interest disclosure**

The authors declare that they have no financial conflict of interest with regard to the content of this report.

**Research registration unique identifying number (UIN)**

None.

**Guarantor**

None.

**References**