



## Case report

# Hemophagocytic lymphohistiocytosis as a paraneoplastic syndrome associated with ovarian dysgerminoma



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## ARTICLE INFO

## Article history:

Received 20 April 2016

Received in revised form 25 May 2016

Accepted 30 May 2016

Available online 4 June 2016

## Keywords:

Adnexal mass

Unexplained fever

Cytopenia

Splenomegaly

Hemophagocytic lymphohistiocytosis

## 1. Introduction

Hemophagocytic lymphohistiocytosis is a pathologic hyperinflammatory syndrome resulting from over-activation of CD8 + cytotoxic T-lymphocytes (CTL's) and benign macrophages with marked release of inflammatory cytokines, ultimately resulting in tissue invasion of the liver, spleen, and/or lymph nodes. Primary HLH is a genetic disorder arising from defects in the cytotoxic pathway whereas, secondary HLH may arise in the background of various disorders, including infection, malignancy, rheumatoid disease, or metabolic conditions. Secondary HLH has been reported as a paraneoplastic syndrome, predominantly in hematolymphoid malignancies, and is rarely associated with non-hematolymphoid neoplasms. In this report, we describe a case of HLH associated with an ovarian dysgerminoma, which to the best of our knowledge represents the first such case in the reported literature.

## 2. Case report

A 41-year-old women (gravida 1, para 1) presented with a progressively enlarging pelvic mass and menorrhagia. Imaging studies suggested the presence of uterine leiomyomata. Depot Lupron injections

were given in an attempt to reduce the size of the presumed leiomyomas. Following the injection, the patient developed diffuse redness and itching, improving with oral prednisone, but subsequently worsening with diffuse erythema, hyperpigmented macules, increased scaling, and desquamation. Skin biopsies showed findings consistent with drug reaction with eosinophilia and systemic symptoms (DRESS). The Registry of Severe Cutaneous Adverse Reactions (RegiSCAR) inclusion criteria for DRESS syndrome include acute rash, fever >38 °C, internal organ involvement like transaminitis, lymphopenia, thrombocytopenia with eosinophilia, and negative investigative results supporting alternative.

The patient underwent repeat imaging studies, showing further increase in the size of the pelvic mass. These findings prompted the decision to proceed with surgical removal of the mass. However, prior to the planned surgery, the patient developed fever and tachycardia, requiring admission to the hospital for systemic inflammatory response syndrome (SIRS). Laboratory testing revealed significant abnormalities, including neutropenia (WBC = 0.8 [4.0–11.0 K/ $\mu$ L]), low absolute neutrophil count (ANC = 0.05 [1.7–6.7 K/ $\mu$ L]), anemia (hemoglobin = 10.3 [11.7–15.7 g/dL]), elevated liver enzymes (AST = 173 [ $<$ 40 U/L]); ALT = 253 [ $<$ 80 U/L]); elevated alkaline phosphatase = 1889 [ $<$ 130 U/L]), hypoalbuminemia (albumin = 1.9 [3.5–5.0 g/dL]), hypertriglyceridemia (triglycerides = 310 mg/dL [ $<$ 150 mg/dL]), elevated D-dimer = 2971 [ $<$ 451 ng/mL], and elevated ferritin = 1459 [5–114 ng/mL] (Fig. 3).

Based on the clinical and initial laboratory findings, the diagnosis of HLH was considered since the patient met diagnostic criteria (fever >38.5 °C for >7 days, fibrinogen <150 mg/dL, and serum ferritin >500 ng/L). Elevated soluble IL-2 receptor levels of 8919 [45–1105  $\mu$ /mL] further supported the diagnosis of HLH. Additional workup included a liver biopsy, showing multifocal hepatocellular necrosis with increased sinusoidal and portal macrophages. Bone marrow biopsy and aspirate showed a cellular marrow with normal trilineage, maturing hematopoiesis. In addition, marked hemophagocytosis was noted with numerous enlarged histiocytes containing engulfed mature and nucleated red blood cells, platelets, and occasional polymorphonuclear (PMN) cells (Fig. 1). Serologies for Epstein-Barr virus, human herpes virus-6, antibody antinuclear antibody, anti-smooth muscle antibody, and viral hepatitis were negative.

In an attempt to increase the ANC, the patient received the granulocyte colony-stimulating factor analog filgrastim. However, despite 14 days of continuous administration of filgrastim, the ANC failed to

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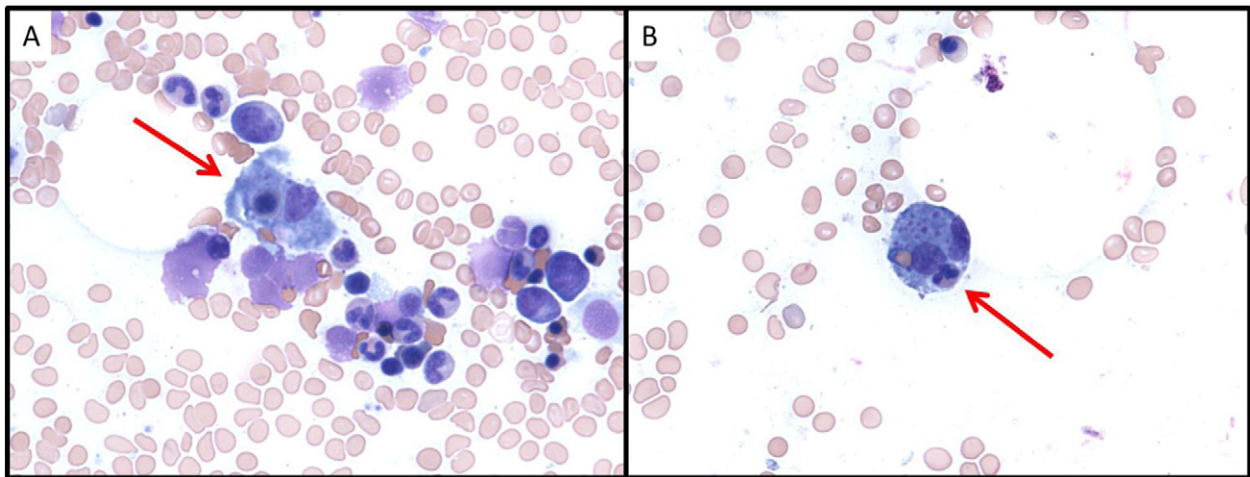


Fig. 1. Bone marrow aspirates demonstrating histiocytes with intracellular nucleated red blood cell (A, arrow) or intracellular neutrophil (B, arrow).

increase and the patient's severe neutropenia did not improve. Magnetic resonance imaging revealed a large solid abdominal–pelvic mass likely arising from the left ovary. Follow-up computerized tomography (CT) scan of the abdomen and pelvis demonstrated a well-circumscribed heterogeneous abdominal mass measuring  $19 \times 12$  cm with mass-effect on the surrounding structures, splenomegaly up to 16 cm, right parenchymal and aortopulmonary lymph nodes measuring 1.4 cm and 1.1 cm, respectively. A fine needle aspiration of the pelvic mass was performed. The pathology showed a malignant germ cell tumor. Serum markers including LDH = 1891 [ $<340$  U/L], CA-125 = 188 [ $<35$  U/mL], beta-hCG = 5 [ $<5$  mIU/mL], HE4 = 134 [ $<70$  pmol/L], and AFP = 4 [ $<10$  ng/mL] were supportive of the diagnosis of a germ cell tumor.

The patient's laboratory values at that time were significant for WBC 0.4 K/ $\mu$ L, ANC  $< 0.02$  K/ $\mu$ L, hemoglobin 8.3 g/dL, platelets 115 K/ $\mu$ L, AST 382 U/L, ALT 304 U/L, alkaline phosphatase 1813 U/L, albumin 1.6 g/dL, and D-dimer 9954 ng/ml (Fig. 3). Given the presence of an ovarian malignancy, the decision was made to proceed with surgical resection of the adnexal mass despite the presence of severe immunosuppression and anticipated high perioperative infectious risk. The patient underwent an exploratory laparotomy, which revealed a large mass from the left ovary, without evidence of disease outside of the ovary. No enlarged lymph nodes were appreciated throughout the abdomen and pelvis. A left salpingo-oophorectomy was performed, but staging was omitted in an attempt to limit the length of surgery and surgical complications. The final pathology showed a dysgerminoma, measuring 19.5 cm in greatest dimension (Fig. 2). Immunohistochemical stains demonstrated positive staining for SALL4, OCT3/4, and CD117, supporting the morphologic diagnosis of dysgerminoma. Pelvic washings contained suspicious cells and the left fallopian tube showed endometriosis. The patient recovered well from surgery without postsurgical complications. Following surgery, the patient's laboratory tests normalized: (WBC = 5.4 K/ $\mu$ L post-operative day #14 (POD #14), ANC = 4.24 K/ $\mu$ L (POD #28), and platelets = 173 K/ $\mu$ L (POD #1) (Fig. 3). She received four cycles of bleomycin, etoposide, and cisplatin (BEP) for adjuvant therapy of stage IC dysgerminoma. The patient was without any evidence of disease or symptoms of HLH at the last follow-up visit 24 months after diagnosis.

### 3. Discussion

To the best of our knowledge, this case represents the first reported secondary HLH in association with a malignant ovarian germ cell tumor. Hematolymphoid malignancies, particularly T-cell and natural killer (NK) cell lymphomas, are much more commonly associated with HLH, compared to any solid tumors. The exact incidence of secondary HLH

is largely unknown. However, a single-institution retrospective analysis of malignancy-associated acquired HLH estimated the rate to be 0.36/100,000/year (Machaczka et al., 2011). Only 3% of all HLH-associated neoplasms are solid tumors, including hepatocellular carcinoma, small cell lung cancer, prostate cancer, and mediastinal germ cell tumors (Rosado and Kim, 2013). Early recognition of HLH is critical, since patients can develop severe pancytopenia and life-threatening infections due to immunosuppression. HLH has a high mortality rate ranging

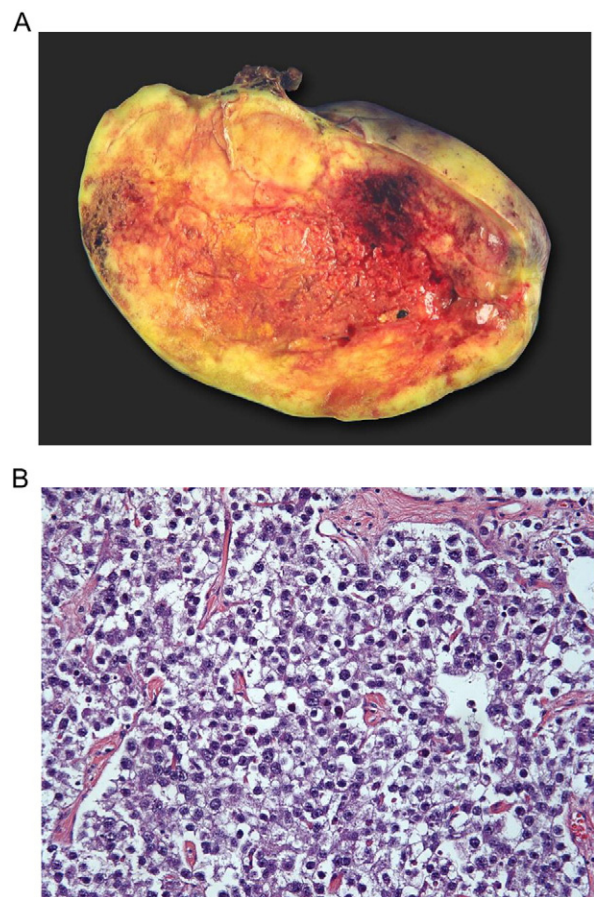


Fig. 2. Ovarian dysgerminoma on gross examination with a tan-yellow cut surface with central necrosis and hemorrhage (A) and on microscopic examination showing nests of large, uniform cells with prominent nucleoli and abundant pale to clear cytoplasm, separated by fibrous septa (B).

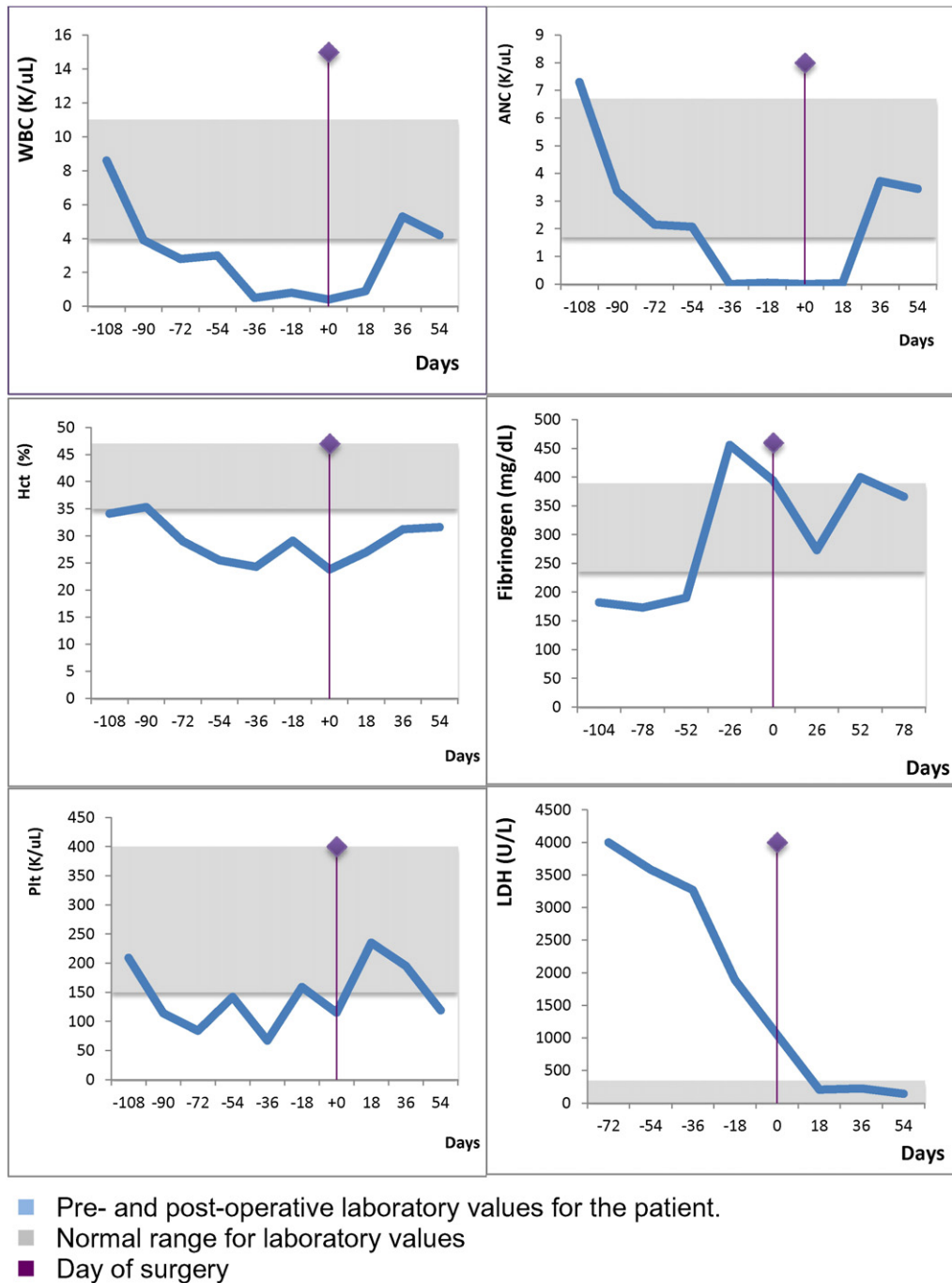


Fig. 3. Laboratory values.

from 50–100% (Price et al., 2014). The diagnosis is often delayed since patients typically present with symptoms that are more commonly associated with SIRS (including pyrexia of undetermined origin, tachycardia, and leukopenia), disseminated intravascular coagulation (DIC), and organomegaly (splenomegaly, hepatomegaly) (Lehmborg and Ehl, 2012). HLH patients may also present with hepatic dysfunction or neurological deficits. Furthermore, the broad symptoms of HLH can present with mild manifestations and interval exacerbations.

HLH is described as a multisystem inflammatory process from excessive and persistent activation of antigen presenting cells, macrophages, histiocytes, CD8+ T cells, and overt proliferation and abnormal migration of T cells (Filipovich, 2009). In HLH, NK cell function is impaired, but the absolute quantity can be unaffected, as seen in this patient with HLH and normal laboratory levels of NK

cells (George, 2014). The most common finding in patients with HLH includes prolonged fevers, likely due to cytotoxic T lymphocytes and NK-mediated hypercytokinemia, rather than a direct result of an infectious agent (Price et al., 2014). Such fevers typically do not resolve despite the use of empiric antibiotics. Despite overlapping clinical features, the treatment of HLH differs from systemic inflammatory response syndrome (SIRS). HLH-specific therapy is based on the HLH-94 protocol, consisting of eight weeks of induction therapy with etoposide, dexamethasone, and intrathecal methotrexate for those patients with CNS involvement. The primary goal of this regimen serves to suppress the fatal inflammatory process underlying HLH. The management of SIRS differs as it primarily consists of treatment of underlying infection if present and supportive care (Trottestam et al., 2011).

While the diagnosis of HLH can be difficult, the Histiocyte Society set forth HLH-2004 diagnostic guidelines, including: 1. Fever; 2. Splenomegaly; 3. Cytopenia involving at least 2 of 3 cell lineages (Hgb < 9 g/dL, ANC < 1.0 K/ $\mu$ L, platelets < 100 K/ $\mu$ L); 4. Hypertriglyceridemia (fasting triglycerides  $\geq$ 3.0 mmol/L) and/or hypofibrinogenemia (fibrinogen  $\leq$ 1.5 g/L); 5. Hemophagocytosis (in biopsy samples of bone marrow, spleen, or lymph nodes); 6. Low or absent natural killer cell activity; 7. Serum ferritin  $\geq$ 500  $\mu$ g/L; and 8. Elevated soluble IL-2 (CD25) levels ( $\geq$ 2400 U/mL or very high for age) (Henter et al., 2007). In general, the diagnosis of HLH is supported if five of the preceding eight criteria are satisfied.

Hemophagocytosis is defined as the engulfment of nucleated hematopoietic cells by activated macrophages and histiocytes as an abnormality in the immune regulatory system (Henter et al., 2007). Although this is the hallmark histologic finding of HLH, it is not required for diagnosis. Both ferritin and soluble IL2R $\alpha$  serve as markers of generalized inflammation. Elevated IL2R $\alpha$  is a more specific indicator for HLH, as it does not seem to be elevated in other processes. Ferritin is stimulated during the anti-inflammatory activity of macrophages in scavenging of heme via the CD163 receptor (George, 2014). Up-regulation of CD163 on monocytes and macrophages allows for hemophagocytosis (George, 2014). In our case, both IL2R $\alpha$  and ferritin levels were consistently elevated preoperatively.

In malignancy-associated HLH, the HLH symptoms may precede the diagnosis of the malignant neoplasm, occur after the diagnosis, or become apparent during chemotherapy (Canna and Behrens, 2012). It has been proposed that HLH might be initiated by the release of IFN- $\gamma$  and CD25 (alpha chain of the IL-2 receptor) from neoplastic cells, leading to significant macrophage activation (Canna and Behrens, 2012). IFN- $\gamma$  induces the classically activated M1 pro-inflammatory subtype of macrophages, in contrast to the “alternatively” activated immunosuppressive M2 phenotype (Vogel et al., 2014). Interestingly, IFN- $\gamma$  and macrophage colony-stimulating factor (M-CSF) have both been shown to be expressed in ovarian dysgerminomas (Suzuki et al., 1998).

In summary, we report the first case of HLH associated with an ovarian dysgerminoma. The incidence of HLH associated with non-hematolymphoid malignancies is very low, but may be underestimated given the generalized and non-specific nature of symptoms. While there remains a great need to gain a better understanding of the disease mechanisms of HLH, it is paramount to recognize the clinical manifestations of the disorder in order to achieve a prompt diagnosis, followed by appropriate management. Moreover, it is important to recognize HLH as

a possible secondary manifestation or paraneoplastic syndrome of ovarian pathology.

## Disclosure

None of the authors have a conflict of interest.

## Financial Support

None.

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