Gynecologic Oncology Reports 17 (2016) 38–41

Contents lists available at ScienceDirect

Gynecologic Oncology Reports

journal homepage: www.elsevier.com/locate/gynor

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, rheumatory 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/μL]), low absolute neutrophil count (ANC = 0.05 [1.7–6.7 K/μL]), 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 μ/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, maturating 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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http://dx.doi.org/10.1016/j.gore.2016.05.013

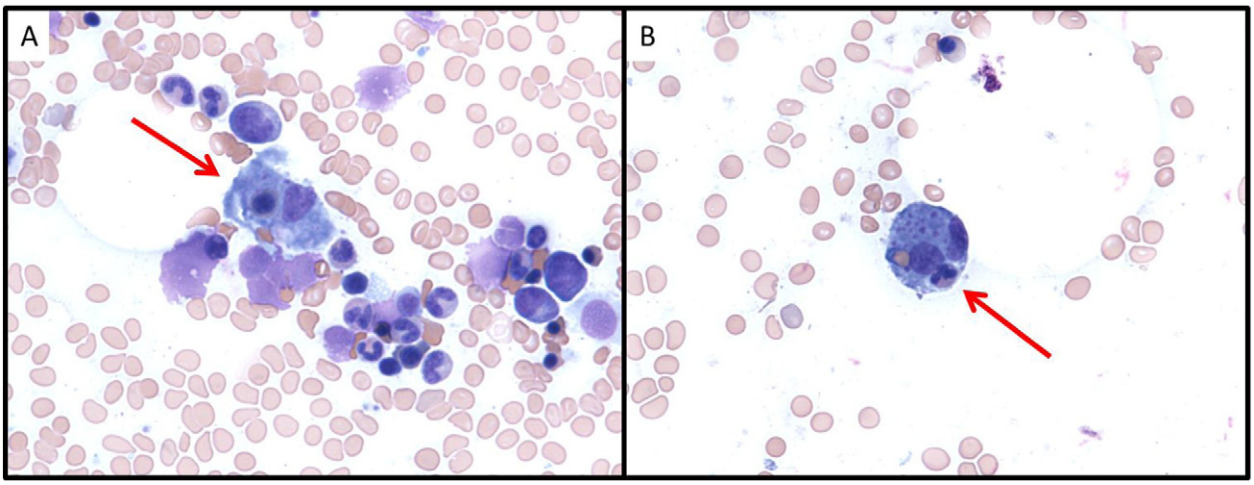

Fig. 1. Bone marrow aspirates demonstrating histiocytes with intracellular nucleated red blood cell (A, arrow) or intracellular neutrophil (B, arrow).

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 × 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/μL, ANC < 0.02 K/μL, hemoglobin 8.3 g/dL, platelets 115 K/μl, 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/μL post-operative day #14 (POD #14), ANC = 4.24 K/μL (POD #28), and platelets = 173 K/μL (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

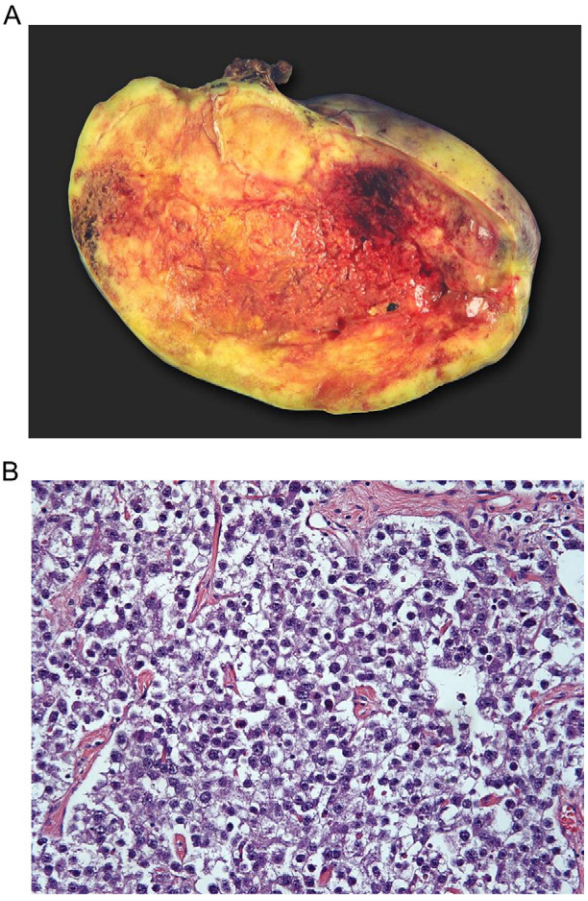

Fig. 2. Ovarian dysgerminoma on gross examination with a tan-yellow cut surface with central necrosis and hemorrhage (A) and on microscopic examination showing nests of large, uniform cells with prominent nucleoli and abundant pale to clear cytoplasm, separated by fibrous septa (B).