case report

Mediastinal endodermal sinus tumor associated with fatal hemophagocytic syndrome

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The association of endodermal sinus tumor, known also as yolk sac tumor, of the mediastinum with hemophagocytic syndrome is exceedingly rare with only a few cases on record. We report a 24-year-old male who had a large mediastinal germ cell tumor, proven to be an endodermal sinus tumor on biopsy. The patient developed pancytopenia and coagulopathy related to associated hemophagocytic syndrome, with a fatal outcome. A brief review of the relevant literature is presented as well.

Germ cell tumors constitute up to 20% of all mediastinal masses.1 2 Their symptoms are commonly caused by compression or invasion of surrounding structures, and patients usually present with weight loss, fatigue, respiratory distress, and pyrexia. The association of mediastinal germ cell tumors with hematological disorders including leukaemias, myelodysplastic syndrome, malignant histiocytosis and hemophagocytic syndrome had been documented.3 4 We present a patient who had a mediastinal endodermal sinus tumor (EST) (known also as yolk sac tumor) who developed pancytopenia due to marked hemophagocytic syndrome.

CASE
A 24-year-old male patient presented with a 3-month history of fever, dry cough and weight loss. On examination the right side of the chest was dull on percussion and breath sounds were absent. His chest x-ray and computerized tomography (CT) scan showed a large mediastinal tumor with right-sided pleural effusion (Figure 1). Laboratory investigations revealed pronounced hematological abnormalities, including low hemoglobin (5 g/dL, normal range: 12-17 g/dL), leukopenia (WBC count of 2.7×10^9/L, normal range: 4.5-11×10^9), anemia (RBC count of 2.09×10^{12}/L, normal range: 4.3-5.7×10^{12}/L) and thrombocytopenia (platelet count of 6×10^9/L, normal range: 150-400×10^9/L). D-dimers were significantly increased (1335 mg/L, normal: 0.5 mg/L). Alpha-fetoprotein levels were markedly elevated (12 000 ng/mL, normal: 44 ng/L). A CT-guided needle biopsy of the mediastinal mass was done after blood and platelet transfusion. The histopathology result showed an endodermal sinus tumor (Figure 2). Bone marrow biopsy revealed many macrophages with engulfed red blood cells present within their cytoplasm (Figure 3). One liter of hemorrhagic pleural fluid was drained from the right pleural cavity. A cytological examination was negative for malignant cells. The patient was placed on steroids and a chemotherapy regimen of cisplatin, etoposide and bleomycin. Following the first cycle of chemotherapy his condition deteriorated. It was decided to stop further chemotherapy as he was not in condition to withstand a second cycle of chemotherapy. The patient was referred to palliative care, and he expired one week later.

DISCUSSION
Mediastinal germ cell tumors are rare. However, they are the most common location for primary extragonadal germ cell lesions, representing 10% to 20% of all neoplasms in this location 1 and up to 15% of anterior me-
diastinal tumors. In a review of 322 cases of primary
germ cell tumors of the mediastinum, the distribution of
tumor types were 44% teratomas, 37% seminomas, 16% 
non-seminomatous germ cell tumors including endoder-
mal sinus tumors (EST), and 3% combined tumors.

There are several reported cases of EST of the medi-
astinum, including a short series of ten cases and seven 
cases as well as a large series of 38 cases from the Armed 
Forces Institute of Pathology (AFIP). These studies em-
phasized the predilection of this tumor to affect young 
adult males as in the present case, with a mean age of 26
to 30 years, and the lethal outcome of the tumor, par-
ticularly when it is unresectable. The aggressive nature of 
primary non-seminomatous tumors of the mediastinum 
is clear, with 72% of the patients dead of their tumor 6 
to 36 months after diagnosis despite aggressive therapy. 
The association of mediastinal EST and other non-sem-
inomatous germ cells with hematological disorders and 
malignancies had been documented in several reports. In 
one large study of 635 patients with extragonadal germ 
cell tumors, including 341 mediastinal tumors, treated 
at major hospitals in the USA and Europe, 17 patients 
were found to have hematological disorders. All of these 
patients had a mediastinal non-seminomatous germ cell 
tumor. The hematological conditions include myelodys-
plastic syndrome (5 cases), acute megakaryocytic leukem-
ia (5 cases), acute myeloblastic leukemia (1 case), acute 
myelomonocytic leukemia (1 case), acute undifferen-
tiated leukemia (2 cases), mast cell leukemia (2 cases) and 
histiocytosis (1 case). All these patients died within two 
years after diagnosis of their hematological malignancy 
with a median survival time of 5 months (range 0-16 
months). In another review of patients with mediastinal 
germ cell tumor who received chemotherapy prior to the 
development of hematological malignancies, a total of 19 
patients with non-seminomatous germ cell tumors, in-
cluding 3 patients who had EST component, developed 
various types of acute myelogenous leukemia.

In a third study from the University of Indiana, 16 
patients had mediastinal germ cell tumors and hemat-
ological neoplasms. All patients had non-seminomatous 
germ cell tumors, with EST or embryonal carcinoma 
in combination with teratoma was quite common. The 
two most common hematological neoplasms in this 
series were acute megakaryocytic leukemia and mali-
gnant histiocytosis. This association between medi-
astinal non-seminomatous germ cell tumors, particularly 
EST, prompted Orazi and his colleagues to look into a 
hypothesis postulating that these leukemic conditions 
originated from progenitor cells within these tumors 
that were capable of undergoing hematopoietic differ-
entiation. They examined histological tumor material 
from six patients using immunohistochemical mark-
ers for different bone marrow cell lineages. They found 
identifiable hematological cells within the yolk sac tu-
mor component of four patients.

A case of unusual association of mediastinal terato-
ma with EST and myelomonocytic leukemia associated 
with Klinefelter syndrome was reported in a 14-year-
old male who underwent thoracotomy and biopsy of 
the mediastinal tumor, but died a week later.

In another case, an unusual association of a medi-
astinal mixed germ cell tumor containing elements of 
seminoma, immature teratoma, EST, embryonal carci-
noma and angiosarcoma with a histiocytic sarcoma of 
the spleen occurred in a 15-year-old boy who presented 
with chest pain.

The association of mediastinal EST or other non-
seminomatous germ cell tumors with the hemophago-
cytic syndrome has been documented in sporadic case 
reports. This syndrome is synonymous with hemo-
phagocytic lymphohistiocytosis, can be of primary 
or familial with autosomal recessive inheritance, or 
secondarily associated with infections, malignan-
cies and rheumatologic disorders. The pathophys-
iology of this syndrome appears to involve the marked 
activation of lymphocytes and macrophages, with an 
abnormal expression of perforin, hMunc13-4 (UNC 
13D) and syntaxin 11, all cytotoxic granule associated 
proteins, resulting in a release of cytokines produced 
by these cells including IFN-gamma, IL-6, IL-10, IL-
12, IL-16, IL-18, and TNF-alpha. This can result in organ dysfunction due to organ infiltration and excessive phagocytosis of blood cells and their precursors in bone marrow, liver, spleen and other organs.

When hemophagocytic syndrome is associated with non-malignant pathology such as viral, bacterial, protozoal, and collagen disorders, it usually resolves once the basic disease is treated. However, when it is associated with malignancy, the prognosis is very poor and the median survival is 3 to 4 months from the onset of disease.

Hemophagocytic syndrome associated with mediastinal germ cell tumor is very rare. To the best of our knowledge thirteen cases have been reported in the literature to date, including four cases associated with reactive hemophagocytic syndrome while the rest were associated with malignant histiocytosis or histiocytic sarcoma.

Our case is the fifth case of reactive hemophagocytic syndrome associated with mediastinal non-seminomatous germ cell tumor that is composed mainly of endodermal sinus (yolk sac) tumor. The outcome of these tumors in association with hemophagocytic syndrome is very poor irrespective of metastatic status, and patients survive only for a few months from the onset of disease despite the various treatment modalities including steroids immunotherapy and chemotherapy. When mediastinal germ cell tumors are not associated with hemophagocytic syndrome, the 5-year survival is 50% with conventional chemotherapy. There are two chemotherapy regimens: conventional alone and high dose chemotherapy (HDCT) with autologous stem cell transplantation, which have been given in many trials. Randomized trials in the United States and Europe using HDCT in patients at poor risk with metastasis, did not show any survival benefit. When non-seminomatous germ cell tumors are not associated with hemophagocytic syndrome the 5-year survival is 50% with conventional chemotherapy.

Author contributions
Ikram Ul Haq Chaudhry: Wrote case report and part of discussion. Shoukat Ahmad Bojal: Wrote case report. Adel Attia: Obtained X-rays and commented on radiological studies. Battal Al-Dossary: Prepared part of the references for the discussion Afra Q Al Dayel: Examined bone marrow, made diagnosis of hemophagocytosis and took microscopic picture of bone marrow and commented on it. Samir S Amr: Wrote the discussion and most of references. Made the diagnosis of yolk sac tumor and took micrographs with comments.
ENDODERMAL SINUS TUMOR

REFERENCES