

## Acute myeloid leukemia following a primary mediastinal germ cell tumor

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### ABSTRACT

**Introduction:** There is a known association between primary mediastinal germ cell tumor (PMGCT) and hematologic malignancy that is not linked to treatment. They are exceptionally rare entities with a low morbidity and a poor prognosis.

**Case presentation:** An 11-year-old boy presented with an anterior mediastinal mass diagnosed as a malignant germ cell tumor on the basis of an excisional biopsy. He was found to have acute myeloid leukemia (AML) two years after the chemotherapy for his germ cell tumor. The clinical course was very aggressive with a survival time of only 1 week after diagnosis of AML associated with PMGCT.

**Conclusion:** AML associated with PMGCT needs to be diagnosed correctly. Relevant examinations should be carried out in patients with PMGCTs during and after chemotherapy, and long-term follow-up is still necessary to reduce the risk of morbidity and mortality.

### KEYWORDS

Primary mediastinal germ cell tumor, Acute myeloid leukemia, Chemotherapy

## INTRODUCTION

Primary mediastinal germ cell tumors (PMGCTs), which account for 1%–4% of mediastinal tumors, are infrequent and rarely associated with leukemias. Hematologic disorders have been found to be associated with mediastinal germ cell tumors, including acute megakaryocytic leukemia (M7), acute monocytic leukemia (M5), malignant tissue cell disease, and acute

myelomonocytic leukemia (M4). Multicenter data showed that the incidence of leukemia in patients with germ cell tumors was 5.9%<sup>1</sup>; the most common type was M7.<sup>2,3</sup> Hartmann et al<sup>2</sup> found that the risk of developing a germ cell tumor-related leukemia was highest during the 1st year after the diagnosis of a PMGCT, and the risk decreased from 4.8% in the first 12 months to 1.5% and 0.6% during the 2nd and 3rd years, respectively. Because of its rarity, the unknown

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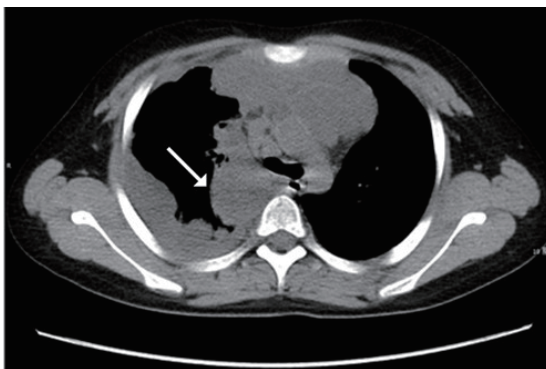
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and debated etiology, the absence of specific genetic, clinical, or other confirmatory tests, and the poor prognosis, leukemia associated with PMGCT poses significant clinical challenges to practitioners. Here we describe a case of an 11-year-old boy diagnosed with a PMGCT and subsequently found to have acute myeloid leukemia (AML) two years after ending chemotherapy treatment. We review the cardinal features of the disease and distinguish it from therapy-related leukemia in all aspects. We also explore the pathogenesis and improve the understanding of these two rare entities.

## CASE REPORT

An 11-year-old boy was referred to a local hospital with a three-month history of chest pain. Computed tomography (CT) scan of the chest showed a giant mediastinal mass. The complete surgical resection of the mediastinal tumor was done on December 30, 2014. The pathological result supported the diagnosis of a mediastinal yolk sac tumor. Immunohistochemistry (IHC) showed that the tumor was cytokeratin (+), placental alkaline phosphatase (+), alpha-fetoprotein (AFP) (+), CD3 (some cells +), Ki-67 (30% +),  $\beta$ -hCG (-), CD30 (-), EMA (-),  $\alpha$ -inhibin (-), vimentin (-), CEA (-), and CD31 (-). Serum AFP after the operation was 7847  $\mu$ g/L, and his human chorionic gonadotropin (HCG) level was normal. No further treatment was given at the local hospital.

The patient was referred to the Hematology Oncology Center, Beijing Children's Hospital for further chemotherapy on February 2, 2015. The chest CT scan revealed a right atelectasis and pleural effusion as well as multiple mediastinal masses 13.8 cm  $\times$  13.4 cm  $\times$  19.3 cm, which were considered to be recurrent residual masses in the anterior superior mediastinum (Figure 1). AFP increased to 22 391  $\mu$ g/L. The bone marrow aspirate and biopsy were normal. Pathologic consultation at our hospital supported the diagnosis of a primary mediastinal yolk sac tumor.



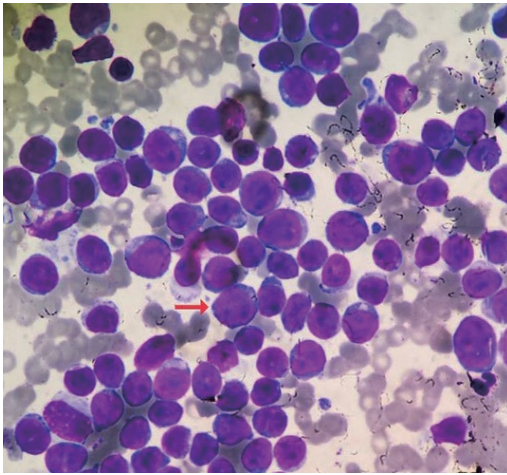
**FIGURE 1** Computed tomography scan of the chest showed that the right atelectasis, pleural effusion and multiple mediastinal masses in the boy with primary mediastinal yolk sac tumor.

Chemotherapy was initiated on February 5, 2015. After

four cycles of chemotherapy with the C-PEB protocol (C-cyclophosphamide, P-cisplatin, E-etoposide, and B-bleomycin), his AFP level decreased to 11.8 ng/mL. The CT scan showed that the tumor was reduced in size to 5.0 cm  $\times$  3.0 cm  $\times$  1.5 cm. Surgery was then performed on May 7, 2015 at the Department of Thoracic Surgery at our Hospital. Following surgery, his AFP level decreased into the normal range (normal < 9.0 ng/mL). Then another five cycles of chemotherapy were given to the patient from May 21, 2015 to August 18, 2015, which included C-BEP, C-BEP, CE, CE, and C-BEP, successively. His AFP level remained in the normal range. He finished chemotherapy in August 2015. He was followed up on a regular basis for two years, during which time his AFP and bone marrow aspirate were examined, and chest CT scans were performed. These tests were all normal.

On September 1, 2017, the patient presented with fever, headache, and pain in the left groin and right lower limb. Complete blood count was done at the local hospital and his white blood cell (WBC) count was  $43.2 \times 10^9/L$ , hemoglobin was 131.0 g/L, and platelets were  $27.0 \times 10^9/L$ . On September 5, 2017, the patient was admitted to our hospital. A few scattered petechiae were found on both upper extremities, and several mung-like lymph nodes could be touched on the bilateral neck and armpit and were accompanied with a swollen right lower limb. The complete blood count showed that his WBC was  $257.5 \times 10^9/L$ , monocytes were  $222.5 \times 10^9/L$ , platelets were  $20.0 \times 10^9/L$ , and hemoglobin was 97.0 g/L. A bone marrow aspirate showed that original monocytes accounted for 93.5% (Figure 2). Leukocyte immunophenotyping showed expression of CD33, CD34, CD13, CD117, CD56, and CD17. Immunohistochemical staining showed the following: a peroxidase (POX) chromosome positive rate of 24%, a glycogen staining positive rate of 7%, naphthol AS-D esterase staining (+), and naphthol AS-D esterase inhibition reaction (+). Fluorescence in situ hybridization (FISH) of his bone marrow showed that the fusion gene was MLL/AF9. Chromosome analysis was 46, XY, t (9; 11). AFP was normal. A chest CT scan did not show a recurrence of his PMGCT. An enhanced CT examination of the pulmonary vessels revealed the possibility of a small thrombus. A cranial CT scan showed multiple hemorrhages in the bilateral cerebral hemispheres. The right lower extremity ultrasound showed phlebitis.

Therefore, the child was diagnosed with AML-M5a, hyperleukocytosis, an intracranial hemorrhage, a pulmonary embolism, and a vascular embolism of the right lower limb. On September 7, 2017, his WBC count increased exponentially to  $325.0 \times 10^9/L$ . A low dose of cytarabine (60 mg) was given to the patient. His WBC reached  $400.6 \times 10^9/L$  on September 8, 2017. Despite treatment, the patient died on September 10, 2017.



**FIGURE 2** Bone marrow aspirate (Wright stain  $\times 1000$ ) showed original cells accounted for 93.5%.

## DISCUSSION

In 1985, Nichols et al<sup>4</sup> and DeMent et al<sup>5</sup> first focused on the association between hematological malignancies and PMGCTs. First, the leukemia associated with a PMGCT must be identified with a therapy-related leukemia. Chemotherapy and radiotherapy can increase the incidence rate of secondary tumors, especially myelodysplastic syndrome or AML, which are also known as therapy-related leukemia.<sup>6</sup> Alkylating agent-induced leukemias are characterized by complete or partial deletion of chromosome 5 or 7, a mean latency period of 5–7 years, and most commonly exhibited a French-American-British classification (FAB) subtype M1 or M2.<sup>7,8</sup> Topoisomerase II inhibitor-related secondary leukemias are frequently associated with translocations of the long arm of chromosome 11 (11q23), generally diagnosed 2–3 years after chemotherapy, and most commonly exhibited a FAB M4 or M5 phenotype.<sup>9,10</sup> The most common karyotypic abnormality in a PMGCT and in associated leukemic blasts is isochromosome (12p), which suggests that i(12p) might be a potential predictive marker for the development of AML.<sup>8</sup> The clinical, morphologic, and cytogenetic characteristics of the leukemia in this case were definitely different from an alkylating agent-induced leukemia but seemed to be similar to topoisomerase II inhibitor-related secondary leukemias. A topoisomerase II inhibitor and an alkylating agent were included in the chemotherapy of the PMGCT in this case. Smith et al<sup>11</sup> found that for cumulative etoposide doses of 5.0 g/m<sup>2</sup> or less, the risk of a secondary leukemia was lower than that contributed by the other agents used in chemotherapy regimens. In our case, after nine courses of chemotherapy with the C-PEB protocol, the dose of etoposide had accumulated to 3.96 g/m<sup>2</sup> (i.e., less than 5.0 g/m<sup>2</sup>). According to the research of Smith et al<sup>11</sup> the risk of developing a secondary leukemia after epipodophyllotoxin treatment in our case was lower than that using an alkylating agent, which also indicated that AML-M5a occurring in the patient may

have been a primary leukemia and not related to etoposide treatment. However, the leukemia in this case did not have i(12p) but only an *MLL* gene rearrangement. Whether an *MLL* gene rearrangement is related to the leukemia associated with PMGCT still needs to be clarified with further study.

The causal relationship between PMGCT and leukemia remains unclear. It was considered that cells of PMGCT after spreading to the marrow cavity become capable of transforming into leukemia in that microenvironment. Another theory suggested that the mesenchyme-like component of yolk sac tumors acts as a pluripotential source for the transformation of primordial germ cells into malignancies typical of nongermlinal tissue.<sup>12,13</sup> Wick et al<sup>13</sup> found that the hematologic precursors were presented within the PMGCT stroma and vessels within the yolk sac tumor component of these tumors. It was also found that immunohistochemical and cytogenetic evidence had previously suggested the clonal relationship between PMGCT and hematologic malignancy.<sup>14</sup> In our case, bone marrow immunophenotyping was positive for CD34. Immunohistochemical staining of tumor cells was also partially positive for CD34, which showed that these two kinds of tumor cells could be homologous.

The clinical course of the hematologic neoplasia associated with PMGCT is very aggressive with a median survival time of 5 months after diagnosis.<sup>9,14</sup> Prognosis for PMGCT with a hematologic malignancy is always poor, and a substantial proportion of these patients die before treatment.<sup>15</sup> This is what happened to the patient in our case, in which the survival time of this child was only 1 week after diagnosis. Treatment of AML has traditionally been performed with an anthracycline- or cytarabine-based induction chemotherapy. Here, a low dose of cytarabine was given, but the patient did not respond to the antileukemic treatment. Allogenic stem cell transplantation may be curative for a subset of patients<sup>1,10</sup>; however, this requires further study.

In summary, a patient with a history of PMGCT is at higher risk of developing a hematologic malignancy. Despite advances in chemotherapeutic options, the overall outcome in patients with PMGCTs who have hematologic malignancies remains poor. This phenomenon needs to be addressed. Therefore, relevant examinations should be carried out in patients with PMGCTs during and after chemotherapy, and long-term follow-up is still necessary for such patients.

## CONSENT FOR PUBLICATION

Consent was obtained from the patient's guardians.

## CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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