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# 종격종 자세포종양 항암 치료 2개월 후 발생한 골수형성이상증후군

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# Myelodysplastic Syndrome (RAEB-II) Development 2 Months after Chemotherapy for a Primary Non-seminomatous Mediastinal Germ Cell Tumor

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Here, we report on a 20-year-old patient with a primary nonseminomatous mediastinal germ cell tumor (MGCT) who developed myelodysplastic syndrome (MDS) 2 months following chemotherapy with cisplatin, etoposide, ifosfamide, and paclitaxel. Bone marrow examinations revealed that the MDS was a refractory anemia with excess type II blasts and complex chromosomal abnormalities. With the onset of MDS occurring rapidly following chemotherapy, it is unlikely to have been caused by the therapy. We discuss the association between primary nonseminomatous MGCTs and hematological malignancies, including the possibility of a common clonal origin. (Korean J Med 2016;90:460-463)

**Keywords:** Mediastinal germ cell tumor; Myelodysplastic syndromes; Therapy-Related

## INTRODUCTION

Chemotherapy for hematologic malignancies and solid tumors is associated with an increased risk for developing secondary myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML) [1]. More than 10% of MDS and AML cases are induced by chemotherapy or radiation therapy for malignant diseases [2]. Two main differences between therapy-related myeloid neoplasms (t-AML or t-MDS), and MDS or AML that develop from the same progenitor cells are the time interval from the onset of chemotherapy to the development of myeloid neoplasms, and the type of chromosomal abnormalities present.

The median interval from chemotherapy to the development of t-AML and t-MDS is 94 months (2 to 8 years) [3]. t-MDS is characterized by one of two types of chromosomal abnormality. The first type occurs 3-5 years following the use of alkylating

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agents and frequently presents with -7/del 7q and/or -5/del 5q. The second type is associated with DNA topoisomerase II inhibitor therapy and shows balanced chromosomal aberrations, including translocations at 11q23 and 21q22 [2].

Here, we report on a 20-year-old male who was diagnosed with a mediastinal germ cell tumor and developed MDS 2 months following the onset of chemotherapy. Karyotyping combined with the short time interval from the onset of chemotherapy to the diagnosis of MDS suggested that the two diseases evolved from common progenitor cells rather than being due to therapy.

## CASE REPORT

A 20-year-old male with an unremarkable medical history presented with pleuritic chest pain and was admitted to Kyungpook National University Hospital, Daegu, Korea. Chest X-rays and enhanced computed tomography revealed an anterior mediastinal mass (Fig. 1). Based on a percutaneous needle biopsy in August 2014, the patient was diagnosed with a primary nonseminomatous mediastinal germ cell tumor (MGCT) (Fig. 2). Laboratory analyses showed the patient had a hemoglobin level of 14.5 g/dL, a leukocyte count of 10,770/mm$^3$ (neutrophils 70%, lymphocytes 21%, no blasts), and a platelet count of 257,000/mm$^3$. The patient also had a serum alpha-fetoprotein (AFP) level of 4,086 ng/mL, a human chorionic gonadotropin level of 0.323 mIU/mL, and a lactate dehydrogenase (LDH) level of 487 IU/L, suggesting a primary nonseminomatous germ cell tumor. The patient received two cycles of chemotherapy with ifosfamide, etoposide, and cisplatin between September and October 2014, and was transferred to a second hospital for treatment with ifosfamide, paclitaxel, and cisplatin in November 2014. Following recovery, the patient underwent tumor resection at the Samsung Medical Center (Seoul, Korea) in November 2014 where he suffered a sudden cardiac arrest from rupture of the right ventricle. After 10 minutes of cardiopulmonary resuscitation, the patient recovered and was supported by extracorporeal membrane oxygenation that was halted following surgical repair of the right ventricle in December 2014.

In December 2014, a peripheral blood examination revealed the patient had a hemoglobin count of 7.1 g/dL, a leukocyte count of 42,710/mm$^3$ (46% neutrophils, 29% lymphocytes, 2% atypical lymphocytes, 18% monocytes, 2% myelocytes, 6% metamyelocytes, 0% blasts), a platelet count of 21,000/mm$^3$, a serum count of AFP 2.1 ng/mL, and an LDH count of 2,666 IU/L.

A bone marrow aspiration test showed the patient had complex cytogenetic abnormalities with trilineage dysplasia, suggesting MDS. Additionally, the presence of increased immature granulocytes and absolute monocytosis indicated myelodysplastic-myeloproliferative neoplasms. Bone marrow biopsies also showed about 80% cellularity and cytogenetic analyses revealed the patient had a 48, XY, +8, +21 karyotype. MDS/AML profiling using fluorescence in situ hybridization (FISH) were normal, and FISH analyses for CEP8 generated three signals, consistent with

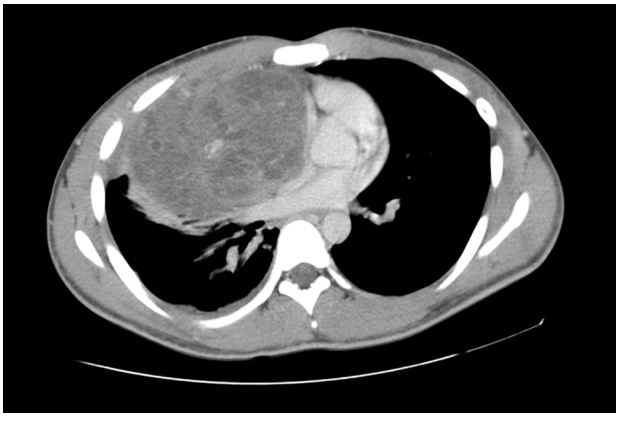

**Figure 1.** Mediastinal mass. The chest computed tomography scan revealed a large anterior mediastinal mass surrounding the pericardium.

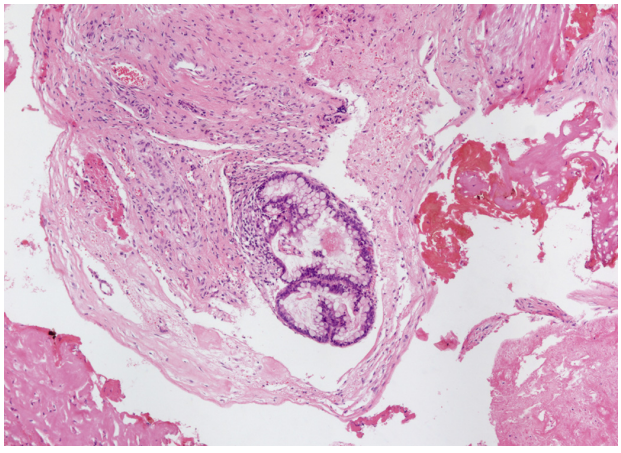

**Figure 2.** Enteric-type glands in the fibrotic-stroma containing spindle cells and fibrosis (H&E, 100× magnification).

the karyotyping data.

From the collective data, it was hypothesized that the patient had MDS, and more specifically, refractory cytopenia with multilineage dysplasia. Due to the short time frame between the diagnoses of the two tumors, it was proposed that the myeloid neoplasm and the mediastinal germ cell tumor developed concurrently from a common origin. The patient's poor performance prevented intervention; therefore, he was provided transfusions and discharged.

In February 2015, the patient attended the emergency room with fever and abdominal pain. A complete blood cell count showed a hemoglobin level of 7.9 g/dL and a leukocyte count of 7,990/$mm^3$ (54% neutrophils, 20% lymphocytes, 13% blasts; platelet count 13,000/$mm^3$). Based on these findings, MDS transformation to acute leukemia was hypothesized. A bone marrow examination revealed an increase in blast percentage from 3.25% to 6.5% without Auer rods and cellularity of 80-90%. Cytogenetic examinations revealed clonal evolution of 48, XY, +8, +21 [14]/47, sl, -8, del (20) (q11.2) [3]/47, sdl1, -del (20), +mar [3] cells. Based on a diagnosis of refractory anemia with excess type II blasts, as well as international and World Health Organization prognostic scoring system assessments revealing scores indicative of high risk, hypomethylating therapy was initiated with decitabine.

## DISCUSSION

Hematological malignancies that occur concurrently with germ cell tumors must be distinguished from therapy-related secondary diseases. The two types of therapy-related myeloid neoplasms depend on the type of treatment received, and are characterized according to specific chromosomal changes, the time from the onset of chemotherapy to diagnosis, and the specific chemotherapeutic agents used [2,4,5].

In the case presented here, hematological transformation developed 2 months after the onset of chemotherapy targeting a malignant germ cell tumor. The short timeframe suggested that the germ cell tumor and the hematological malignancy originated from a common progenitor cell, and were unrelated to the chemotherapy. However, isochromosome 12p—a chromosomal abnormality that frequently occurs in patients with germ cell tumors and myeloid neoplasms—as well as other common chromosomal abnormalities associated with therapy-related myeloid neoplasm were not found in this patient [6,7].

While some patients have isochromosome 12p in the primary tumor cells and leukemic clones, which suggests the leukemia is derived from the primary germ cell tumor, other patients do not [8]. For example, a 39-year-old male with a large mass extending from the anterior mediastinum did not receive a tumor biopsy because of severe thrombocytopenia; however, a bone marrow aspiration test revealed a complex karyotype without isochromosome 12p. Following 3 months of induction therapy, the tumor was resected and found to be a mediastinal germ cell tumor.

Why some patients with nonseminomatous MGCTs develop hematologic disorders is unclear. Cytogenetic findings, including isochromosome 12p, suggest that hematologic disorders and germ cell tumors develop concurrently from a common clone. While some patients do not exhibit isochromosome 12p, this does not preclude MDS cells from originating from the same cells as the germ cell tumor. The risk of developing leukemia from the same clonal cell line as a germ cell tumor is highest in the first year following the diagnosis of a germ cell tumor and occurs exclusively with primary mediastinal nonseminomatous germ cells [3,9]. Although the patient in this study was treated with an alkylating agent, the interval between the onset of chemotherapy and the development of MDS was 2 months, which is too rapid to suggest a therapy-related myeloid neoplasm [10].

In conclusion, AML or MDS that occurs following the development of a malignant germ cell tumor may be either therapy-related or transformed from a common progenitor cell. Latency between the first tumor treatment and the onset of the hematologic malignancy may distinguish between therapy-related leukemia and hematological transformation of the malignant germ cell tumor. Comparative genomic hybridization analyses or molecular profiling allow for more complete differentiation when two tumors evolve from a common clone.

**중심 단어:** 종격종 자세포종양; 골수형성이상증후군; 치료 연관성

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