

# Occurrence of Hematological Malignancy in Long-term Survivors With Advanced Thymic Cancer

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**Abstract.** *Background: Limited information is available on the occurrence of synchronous malignancy in patients with advanced thymic cancer (TC) who have achieved long-term survival due to sequential chemotherapy. Here, we present two cases of hematological malignancies in long-term survivors with advanced TC. Case Reports: A 56-year-old man underwent surgical resection following the diagnosis of TC with a histological indication of squamous cell carcinoma. He received sequential chemotherapy, including carboplatin plus paclitaxel, amrubicin, and S-1, due to multiple pulmonary metastases. After >4 years of first-line chemotherapy, he developed consistent myelosuppression and a definite diagnosis of acute promyelocytic leukemia was made following bone marrow analysis. A 49-year-old man with advanced TC received carboplatin plus paclitaxel with amrubicin as second-line therapy due to recurrence. Amrubicin was administered for 54 cycles but T-cell lymphoblastic lymphoma without recurrence of TC was confirmed following transbronchial nodal biopsy due to marked lymphadenopathy. Conclusion: Physicians should be alert to the occurrence of hematological malignancy in patients with thymic cancer.*

Thymic cancer (TC) is a rare neoplasm worldwide, and there is no standard treatment for significant survival prolongation. Platinum-based chemotherapies, such as carboplatin plus paclitaxel, are widely administered to patients with TC (1). Limited information is available on the therapeutic role of

second-line or further chemotherapy. In Japan, amrubicin or S-1 is considered the best candidate for patients with relapsed TC as some case reports have demonstrated the effectiveness of amrubicin or S-1 treatment (2-4). However, these limited reports do not guarantee extended survival following successful sequential chemotherapy in patients with advanced or recurrent TC. Therefore, the clinical course of patients who have experienced long-term survival after TC by subsequent treatment such as platinum-based regimen followed by amrubicin or S-1 is largely unknown. Here, we present two cases of hematological malignancies during long-lasting sequential chemotherapy in patients with advanced TC.

## Case Reports

Ethical approval was obtained and informed consent was given by the patients.

**Case 1.** A 56-year-old man underwent surgical resection following the diagnosis of TC with a histological indication of squamous cell carcinoma (stage III), which was followed by radiotherapy (60 Gy) in March 2013. Subsequently, the patient was treated with surgical resection for three pulmonary metastases in July 2015. However, there was obvious evidence of recurrence by multiple pulmonary metastases that were inoperable. Thus, systemic chemotherapy with carboplatin and paclitaxel was initiated from May 2016. Although his recurrent tumor yielded a partial remission after first-line chemotherapy, he experienced relapse and developed regrowth of pulmonary metastases in December 2016. As second-line chemotherapy, amrubicin monotherapy was initiated, following which marked shrinkage was noted at the sites of recurrence. He continued to receive 21 cycles of amrubicin without any recurrence until June 2018. Although chest computed tomography (CT) showed an obvious progression of pulmonary metastases, S-1 monotherapy as third-line chemotherapy was subsequently administered in December 2018. He experienced a partial response after oral intake of S-1, and S-1 treatment was continued until August 2019. However, the regrowth of some pulmonary metastases was

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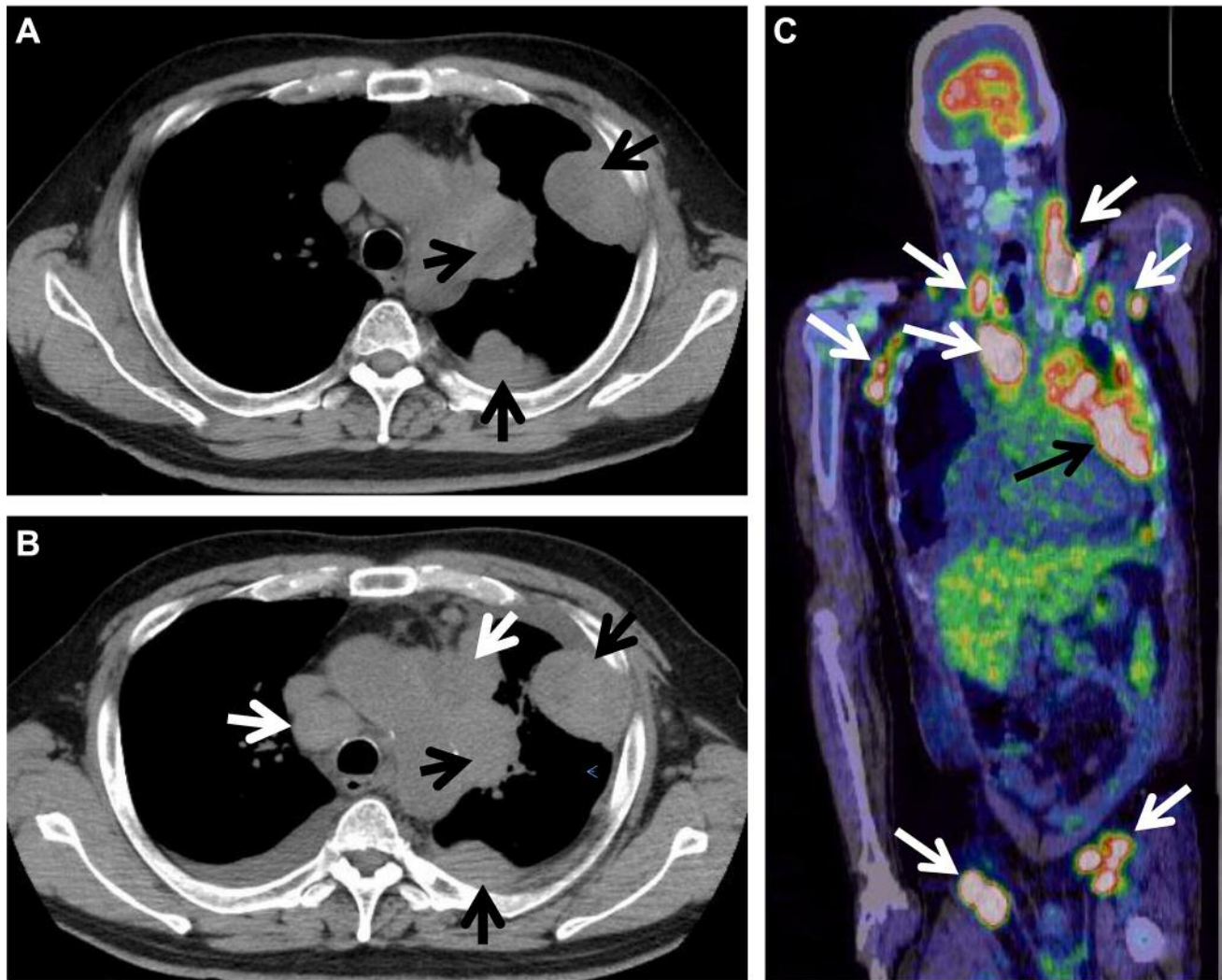


Figure 1. A: Chest computed tomography showing nodules in contact with the left pleura (arrows), indicating disseminated lesions due to thymic cancer. B: Chest computed tomography revealing nodules arising from thymic cancer (black arrows) and marked mediastinal lymphadenopathy (white arrows). C: 2'-Deoxy-2'-[ $^{18}\text{F}$ ] fluoro-D-glucose positron-emission tomography revealing increased accumulation in the cervical, axillary, mediastinal and inguinal regions (white arrows) and nodules secondary to thymic cancer (black arrow).

observed and carboplatin with nab-paclitaxel was administered in September 2019. The patient had consistent severe myelosuppression from October 2019 to December 2019 despite cessation of chemotherapy, indicating grade 4 neutropenia and grade 3 thrombocytopenia. Therefore, the patient was referred to a hematological physician and a definite diagnosis of acute promyelocytic leukemia was made using bone marrow analysis. All-*trans* retinoic acid was initially administered to the patient. His condition improved and he continues to receive chemotherapy.

**Case 2.** A 49-year-old man was referred to our Institution because of dyspnea. Pleural biopsy revealed the definite diagnosis of advanced TC with pleural effusion in December

2015. As first-line chemotherapy, carboplatin with paclitaxel was initiated for 6 cycles. As there was confirmed evidence of pleural dissemination, he was treated with amrubicin monotherapy as second-line chemotherapy in August 2016. The amrubicin treatment was effective in reducing tumor progression, and he received 54 cycles of amrubicin until November 2019 (Figure 1A). However, chest CT for response evaluation revealed marked lymphadenopathy in the mediastinum (Figure 1B). Positron-emission tomography revealed increased uptake of 2'-deoxy-2'-[ $^{18}\text{F}$ ] fluoro-D-glucose, indicating new lesions on CT (Figure 1C). Transbronchial nodal biopsy confirmed T-cell lymphoblastic lymphoma without recurrence of TC. Steroid therapy was initiated, and his condition was improved.

## Discussion

To the best of our knowledge, these are the first case reports to present the occurrence of hematological malignancies during long-lasting sequential chemotherapy in patients with advanced TC. Both cases received sequential therapeutic regimens of carboplatin with paclitaxel, followed by amrubicin for an extended period. Since there are no established strategies for systemic chemotherapy in patients with advanced TC, limited information is available on long-term survivors who received subsequent chemotherapy. Cancer patients with long-term survival due to effective chemotherapy do experience recurrent cancer. However, it is unclear whether hematological malignancies can occur in long-term survivors with advanced TC who have received systemic chemotherapy, such as a taxane-based regimen and amrubicin.

In both our cases, amrubicin was clinically effective in controlling tumor progression for an extended period. Amrubicin hydrochloride, a completely synthetic 9-aminoanthracycline, is converted to the active metabolite, amrubinol, *via* reduction of its C-13 ketone group to a hydroxyl group by carbonyl reductase (5). Although it is unknown whether hematological malignancy can be triggered by continuous long-term exposure to amrubicin, our cases suggest the potential of simultaneous cancer in patients who received extended amrubicin monotherapy for TC.

There have been reports regarding cases of synchronous thymoma and T-cell lymphoblastic lymphoma (6). In cases with lymphoma and thymoma, the lymphomatous component can be misinterpreted as an activated non-neoplastic lymphoid component in a lymphocyte-rich thymoma (6). However, little is known regarding synchronous and asynchronous thymic epithelial tumors and leukemia.

In conclusion, we report two cases of hematological malignancies arising in patients with advanced TC that were effectively treated with cytotoxic chemotherapy. Physicians should be aware of the potential for hematological malignancies occurring during extended sequential chemotherapy in patients with advanced TC.

## Conflicts of Interest

All Authors have declared no conflicts of interest.

## Authors' Contributions

KK and IN: conception and preparation of the article. KK, IN, SS and HK: management of the patient. KK: statistical analysis and patient data collection. KK and HK: revising the article. All Authors contributed and agreed with the content of the article.

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