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Case Report

Successful Resection of a Giant Mediastinal Non-Seminomatous Germ Cell Tumor Showing Fluorodeoxyglucose Accumulation after Neoadjuvant Chemotherapy: Report of a Case

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Abstract

A 32-year-old man presented with a mediastinal non-seminomatous germ cell tumor showing fluorodeoxyglucose (FDG) accumulation (maximum standardized uptake value = 22.21) and extremely elevated blood α-fetoprotein (AFP) level (9203.0 ng/ml). The patient underwent 4 cycles of neoadjuvant chemotherapy (cisplatin, bleomycin, and etoposide), which normalized the AFP level and reduced the tumor size, allowing complete resection without a support of extracorporeal circulation. Despite preoperative positron emission tomography revealing increased FDG uptake in the residual tumor (maximum standardized uptake value = 3.59), the pathologic evaluation revealed that no viable germ cell tumor cells remained. We believe FDG uptake should not be used as a criterion for surgical resection after neoadjuvant chemotherapy. It is appropriate to resect the residual tumor regardless of FDG uptake after induction chemotherapy if a tumor is resectable and the AFP level normalizes.

Key words : Mediastinum non-seminomatous germ cell tumor・Residual tumor・Positron emission tomography・Surgery

Introduction

Non-seminomatous germ cell tumor (NSGCT) originating from the mediastinum typically has a very poor prognosis. However, multimodality therapy with 4 cycles of bleomycin, etoposide, cisplatin (BEP) therapy, followed by surgery, proved to dramatically improve patient outcomes[1)]. Furthermore, to improve prognosis, it is recommended that any residual tumor after induction chemotherapy should be resected if the blood α-fetoprotein (AFP) level normalized and the tumor became resectable[1)]. However, the indications for surgery in post-chemotherapy NSGCT patients with both residual tumor and fluorodeoxyglucose (FDG) accumulation on positron emission tomography (PET) remain unclear. Here we report a case of a giant mediastinal non-seminomatous germ cell tumor that was successfully treated with BEP induction therapy, followed by surgical resection demonstrating FDG uptake without viable cells in the surgical pathology specimen.

Case Report

A 32-year-old man presented with stiff neck, chest tightness, and fever, with mediastinal enlargement on a chest X-ray. An enhanced computed tomography (CT) of the chest revealed a 12 × 8 cm mass located in the anterior mediastinum, which was widely adherent to the anterior chest wall, left lung, and great vessels (Fig. 1a).

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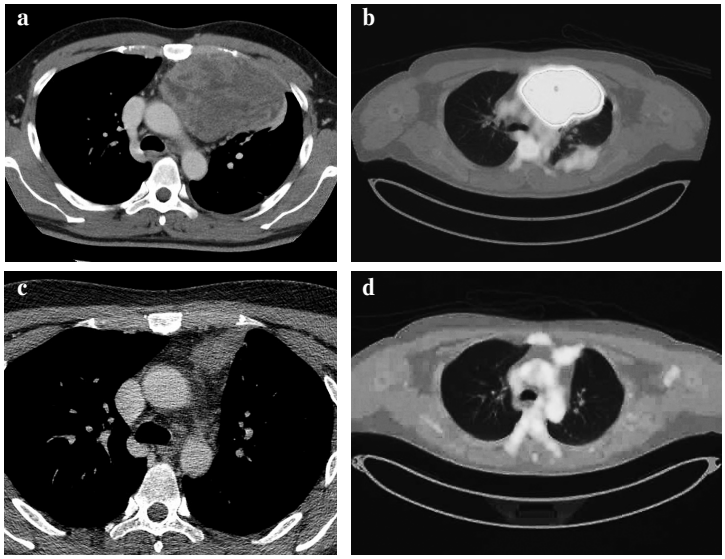

Fig. 1 Changes in computed tomography (CT) and fluorodeoxyglucose positron emission tomography (FDG-PET) before and after induction chemotherapy
Pre-treatment : CT (a) and FDG-PET (b). Post-treatment : CT (c) and FDG-PET (d).

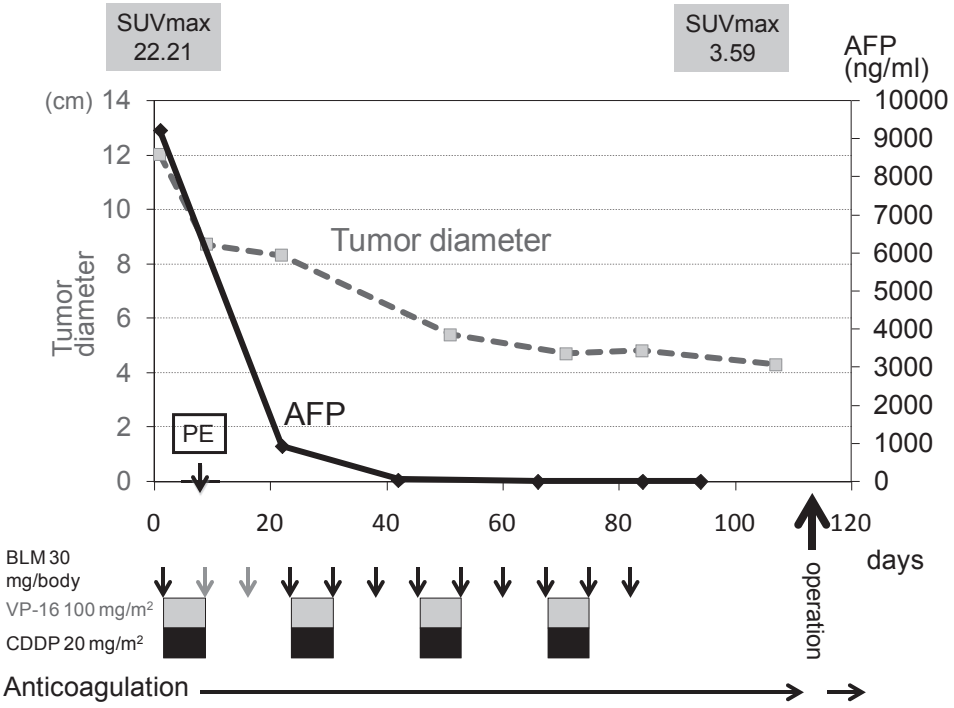

Fig. 2 Clinical course of the tumor diameter and blood AFP level
In the first cycle, bleomycin was skipped on days 8 and 15 because of pulmonary embolism (PE).
CDDP : cisplatin, BLM : bleomycin, VP-16 : etoposide, PE : pulmonary embolism, AFP : α-fetoprotein, SUVmax : maximum standard uptake value

FDG-PET revealed increased FDG uptake in the mass; the maximum standard uptake value (SUVmax) was 22.21 (Fig. 1b). In addition, the blood AFP level was extremely elevated at 9203.0 ng/ml (Fig. 2). The blood lactate dehydrogenase (LDH) level was 235 U/L and beta-human chorionic gonadotropin (β-hCG) level was within normal limits. A CT-guided core needle

biopsy was conducted and immunohistochemistry of the tumor revealed a yolk sac tumor (Fig. 3a).

Neoadjuvant chemotherapy was conducted according to the International Germ Cell Consensus Classification (IGCCC) standard regimen, with 4 cycles of BEP chemotherapy. This comprised : bleomycin 30 mg/body weight on days 1, 8, and 15 ; etoposide 100 mg/m^2 on days 1–5 ; and CDDP 20 mg/m^2 on days 1–5. This therapy was complicated by the occurrence of pulmonary embolism (PE) on day 6 of the first cycle, but was effectively managed with a combination of anticoagulation therapy with warfarin and chemotherapy; no other adverse events were observed during the chemotherapy. After the 4 cycles of BEP chemotherapy, blood AFP had completely normalized (6.0 ng/ml) (Fig. 2) and the tumor size had dramatically reduced to 5.5 × 4.5 cm in diameter (Fig. 1c). The clinical course is graphically illustrated in Figure 2. However, abnormal FDG uptake was observed in the residual tumor (SUVmax 3.59 ; Fig. 1d).

Because we considered the possibility that some viable cells may remain in the residual tumor, we acquired informed consent from the patient for complete resection of the tumor. The tumor was successfully resected with the ready to keep the patient on percutaneous cardiopulmon-

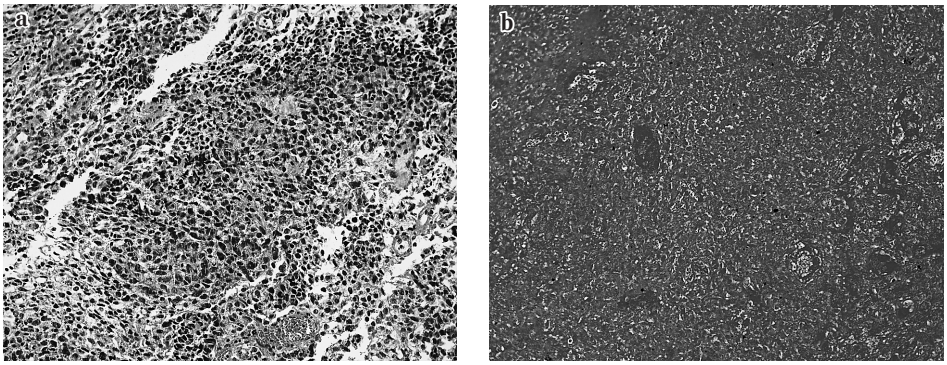

Fig. 3 Representative micrographs of the mediastinal tumor stained with hematoxylin–eosin, magnification × 200
a : the core needle biopsy findings prior to induction chemotherapy and b : the resected tumor indicating no residual tumor

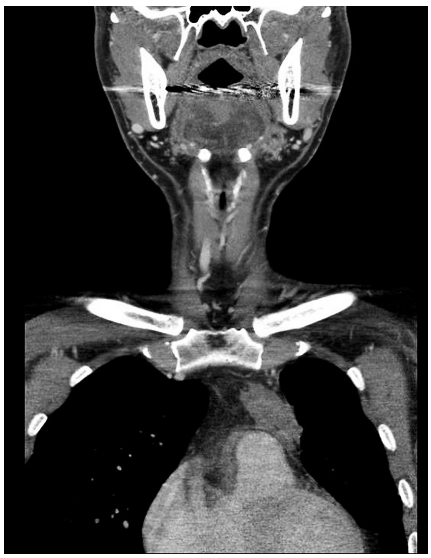

Fig. 4 Chest computed tomography image of the mediastinal tumor after 4 cycles of chemotherapy. The tumor was adherent to ascending aorta.

ary support (PCPS) at any time because the residual tumor was adherent to great vessels (Fig. 4). The patient's postoperative course was uneventful and he was discharged 15 days after the operation. The pathological examination revealed that no viable tumor cells remained, which showed fibroadipose tissue with aggregation of foamy macrophages, some multinucleated giant cells, chronic inflammatory cell infiltrate and massive necrosis (Fig. 3b). No recurrence was observed for 10 months after the operation.

Discussion

We herein describe a giant mediastinal NSGCT that was successfully resected after 4 cycles of BEP neoadjuvant chemotherapy. The key observations in this case were as follows. First, a giant yolk sac tumor adjacent to vital organs could be resected after induction chemotherapy. Second, although the post-chemotherapy PET-CT showed slight FDG uptake in the tumor, the resected tumor showed complete pathological response to induction chemotherapy. Third, when conducting induction chemotherapy in such a tumor, the risk of thrombosis should be taken into consideration.

Yolk sac tumors, which are a subclass of NSGCTs, have a reported 5-year survival of 32%-45%[2)3)]. They are considered to be highly malignant neoplasms that are usually unresectable at the initial diagnosis because of their invasiveness and propensity to metastasize[4)]. As observed in our case, patients typically present with symptoms of chest pain or pressure, cough, dyspnea, hoarseness, or superior vena cava syndrome[5)]. In addition, accompanying constitutional symptoms, such as weight loss, weakness, and fever, are common observations in patients with NSGCT. The pathognomonic hallmarks of NSGCT are young men, elevated AFP or LDH, and high FDG accumulation; AFP elevations are never observed in pure mediastinal seminomas[6)].

It is important to conduct a multimodality therapy and to monitor blood AFP level when treating NSGCTs. The standard treatment strategy for germ cell tumor is induction chemotherapy, followed by surgical resection of persistent tumors[1)]. Germ cell tumors are known to be sensitive to cisplatin-based combination chemotherapies, and currently, the favored regimen for primary mediastinal nonseminomatous germ cell tumors requires 4 cycles of BEP chemotherapy. Surgical intervention is often necessary in patients whose AFP levels normalize but who have residual mediastinal tumors. To improve the prognosis, almost all patients with mediastinal NSGCT require residual tumors to be resected after chemotherapy[1)]. Postoperative chemotherapy is recommended for those patients in whom the tumor markers do not normalize, complete resection is not achieved, or rapid post-operative relapse is experienced[7)].

The implication of the change in SUVmax between the pre-chemotherapy and post-chemotherapy PET-CTs is unclear in treating germ cell tumor. It has been reported that, in a seminoma, FDG accumulation post-chemotherapy could be a potential sign of residual viable cells[8)]. On the other hand, Karin et al. reported that FDG-PET could not give a clear additional clinical benefit to poredict the tumor viability in residual masses after chemotherapy[9)]. In our case, the histology was not a seminoma, the resected tumor showed a complete response on pathological examination, despite persistent (if reduced) FDG accumulation after induction chemotherapy, which might reflect an inflammatory response (Fig. 3b). Santis et al[10)]. reported that FDG-PET does not help to determine the need for surgery, indicating that NSGCT should be resected regardless of either the FDG uptake when the tumor is resectable. We have conducted the residual tumor resection because the possibility that some viable cells might remain in our case. To the best of our knowledge, this is the only approach that can ensure a high probability of complete cure in such patients.

In addition, we should consider the possibility of

a thromboembolism because of the hypercoagulable state associated with giant tumors[11]. Blood coagulation status should be strictly monitored because the dissolution of tumor tissue may lead to the release of prothrombotic cytokines and other factors. Prophylactic low-molecular weight heparin during therapy may offer a potential solution this problem[12].

In this era of molecular biology, future chemotherapeutic regimens should include the option of using molecular-targeted drugs. From the beginning of the 1970s, vincristine, actinomycin D, and cyclophosphamide (VAC) therapy have proved to be effective for the treatment of germ cell tumors. Thereafter, the alternative cisplatin, vinblastine, bleomycin (PVB) regimen became a major trend; BEP therapy has now been the standard regimen for these tumors for approximately 20 years[13]. Molecular-targeted agents, such as tivantinib (ARQ197), which is a small MET receptor tyrosine kinase inhibitor, are now being developed. However, this has not shown any clinical benefit in phase 2 studies with germ cell tumors (The majority of the patients was non-seminoma and the primary tumor site was testis)[14]. Further investigation of potential molecular targets against germ cell tumors is necessary.

In conclusion, we have reported a case of giant mediastinal NSGCT that was successfully resected following BEP induction chemotherapy. Complete surgical resection should be pursued regardless of FDG accumulation, to maximize the benefits of induction chemotherapy and to minimize the risks of recurrence.

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（和文抄録）

術前化学療法後に FDG 異常集積を認めた縦隔原発非セミノーマ性巨大胚細胞性腫瘍の一切除例

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症例は 32 歳男性．縦隔原発の非セミノーマ性胚細胞性腫瘍の診断で，PET-CT で FDG 異常集積（SUVmax 22.21），血液検査で AFP の異常高値（9203 ng/ml）を認めた．術前化学療法（シスプラチン，ブレオマイシン，エトポシド）4 サイクル施行後に AFP の正常化と腫瘍の縮小を認め，体外循環を使用することなく完全切除可能であった．術前の PET-CT で残存腫瘍に FDG 異常集積（SUVmax 3.59）を依然認めていたにも関わらず，術後の病理診断では生存している悪性細胞を認めなかった．術前化学療法後に外科的切除を行うかどうかの判断基準の一つに，FDG 異常集積を用いるべきではない．導入化学療法後に，腫瘍が切除可能で AFP の値が正常化していれば，FDG の集積とは関係なく，残存病変を切除することが望ましいと考えられる．