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Case Report

Successful Treatment with High-Dose Chemotherapy Followed by Autologous Stem-Cell Transplantation in a Patient with Metastatic Germ Cell Tumor

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Keywords
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Abstract
Although testicular germ cell tumors (GCTs) are known to curable disease even in cases with metastatic disease, patients in intermediate or poor-risk group may experience disease progression or refractory to the initial chemotherapy and needed second-line therapy. Long-term disease-free survival was unsatisfactory in relapsed/refractory patients with poor-risk factors and clinical trials for those patients are still insufficient. High-dose chemotherapy (HDCT) with stem-cell rescue may be an effective alternative for conventional chemotherapy-resistant patients who are eligible for transplantation. Herein, we present successful treatment experience with HDCT followed by autologous stem-cell transplantation in a severely ill patient with heavily pretreated metastatic GCT.

Introduction

Testicular germ cell tumors (GCTs) are rare and accounts for <1% of all male tumors; however, they are the most common solid tumor in young males age <35 years old [1, 2]. GCTs are categorized into seminoma and nonseminoma. Nonseminoma is less common and more aggressive than seminoma [3]. Although GCTs are known to curable disease even with

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metastatic disease, patients in intermediate or poor-risk groups may experience disease progression or become refractory to initial chemotherapy and require second-line therapy [4]. Most patients will generally receive 4 cycles of Vinblastine/ifosfamide/cisplatin or paclitaxel/ifosfamide/cisplatin as a salvage regimen [5, 6]. However, long-term disease-free survival was unsatisfactory in relapsed/refractory patients with poor-risk factors. Likewise, clinical trials for these patients are often lacking [4, 7].

High-dose chemotherapy (HDCT) with stem-cell rescue may be an effective alternative for conventional chemotherapy-resistant patients in a transplant-eligible condition [1]. Since autologous bone marrow infusion therapy was introduced for malignant disease, HDCT followed by autologous stem-cell transplantation (ASCT) has become an important modality for patients with lymphomas, multiple myeloma, and some rare diseases [8]. Its therapeutic effects have been proven for several diseases. However, collecting enough stem cells from patients who have been heavily pretreated with cytotoxic chemotherapy and treatment-related mortality of HDCT is problematic. Herein, we present our successful treatment experience with HDCT followed by ASCT in a young, very sick male with chemoresistant metastatic GCT.

Case Presentation

In November 2018, a 35-year-old male visited our hospital with aggravating cough, hoarseness, and hemoptysis. From a chest computed tomography scan, a huge mediastinal mass with multiple lung nodules and enlarged lymph nodes were identified. At admission to the oncology department, the patient's general condition was good, with an Eastern Cooperative Oncology Group performance status of 1. Likewise, he did not have any specific disease history. Laboratory investigations showed meaningful data, with elevated lactate dehydrogenase, α-fetoprotein, and β-human chorionic gonadotropin (Table 1). The patient underwent a neck lymph node excisional biopsy, and histology revealed a metastatic embryonal carcinoma, a nonseminomatous type GCT (Fig. 1).

Multiple metastases, including the testes, were identified by a positron emission tomography-CT scan. As a first-line therapy, he received an etoposide, ifosfamide, and cisplatin combination regimen (VIP) to treat stage IIIC (cTxN3M1bS3) GCT. Right after the first VIP cycle, the patient developed respiratory failure due to a huge mediastinal mass compressing the bronchus. He was moved onto a ventilator until the end of the second VIP therapy. However, 2-VIP cycles were ineffective. After 4 cycles of TIP regimen as a second-line therapy, partial responses were identified and he underwent right radical orchiectomy with vasectomy in May 2019.

Table 1. Contemporaneous laboratory investigations

Marker (normal range)	Nov 2018 diagnosis	Jan 2019 after 2-VIP cycles	May 2019 after 4-TIP cycles	Sep 2019 after auto-SCT	Mar 2020 6 months	Sep 2020 12 months
LDH, U/L (≤250)	419	138	157	154	171	196
AFP, ng/mL (≤7)	2,345	10.6	5.54	6.08	3.12	3.76
β-hCG, mIU/mL (<1)	>200,000	45	6.4	1.8	<1	<1

AFP, α-fetoprotein; auto-SCT, autologous stem-cell transplantation; β-hCG, beta-human chorionic gonadotropin; LDH, lactate dehydrogenase; TIP, paclitaxel/ifosfamide/cisplatin; VIP, etoposide, ifosfamide, and cisplatin combination.

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To prolong long-term survival without disease progression, the patient received HDCT with 700 mg/m^2 carboplatin plus 750 mg/m^2 etoposide for 3 days, followed by autologous stem-cell rescue (CD34+ stem-cell dose: 1.77 × 10^6/kg) in September 2019. After ASCT, he has been in good general condition without relapse and is maintaining normalized lactate dehydrogenase, α-fetoprotein, and β-human chorionic gonadotropin levels (Table 1; Fig. 2). Informed consent for publication was obtained from the patient.

Discussion

The International Germ Cell Cancer Collaborative Group established a prognostic factor-based staging system for metastatic germ cell cancers, and >40% of patients in poor prognostic group would have disease relapse or be refractory to the platinum-based chemotherapy [4]. Furthermore, the International Prognostic Factors Study Group for metastatic GCTs classified patients who experienced treatment failures with first-line chemotherapy into 5 prognostic groups; the 2-year progression-free survival and 3-year overall survival of the very high-risk group were 5.6 and 6.1%, respectively [7]. Our patient corresponded to the very high-risk group and was refractory to conventional-dose chemotherapy (CDCT), thereby needing a more effective salvage therapy.

Since ASCT for GCT was introduced with high-dose carboplatin in 1986 [9], carboplatin plus etoposide-based HDCT with stem-cell rescue has improved the outcomes of relapsed/refractory GCT patients [1, 10, 11]. Einhorn et al. [1] demonstrated that metastatic GCT was curable by HDCT followed by ASCT, even when this regimen was used as a third-line or later therapy, or in patients with platinum-refractory disease. In a retrospective analysis of CDCT versus HDCT as first salvage treatments in metastatic GCT, patients treated with HDCT showed superior survival outcomes when compared with patients with CDCT [11]. According to data from 2,395 GCT patients at the Center for International Blood and Marrow Transplant Research, 49% of patients had intermediate/poor-risk disease based on the International Germ Cell Cancer Collaborative Group classification, and 29% had platinum-resistant/refractory disease. From multivariate analyses, residual disease at the time of transplantation, >1 line of chemotherapy before HDCT, and nonseminoma were associated with inferior long-term outcomes. In contrast, HDCT as the first salvage therapy and tandem transplantation may be beneficial for patients with unfavorable factors [12].

Although HDCT with ASCT showed benefits for high-risk metastatic GCT patients, CDCT remains the preferred approach for first-line salvage in many centers due to issues with adequate stem-cell collection (the optimal stem-cell dose for transplantation is ≥8 × 10^6 CD34+ cells/kg) and transplantation-related mortality [12, 13]. Hamid et al. [14] recently reported that plerixafor played a role in stem-cell mobilization for relapsed GCT. Moreover, improvements in supportive care after HDCT may reduce nonrelapse mortality after transplantation [12].

Fig. 1. Neck lymph node histology at the time of diagnosis showing representative features and immunohistochemical findings. **a** Embryonal carcinoma shows necrosis (black arrowheads), hemorrhage (white arrow), and fibrosis (black arrows, surrounding tumor cells in a linear pattern) (**a** ×12.5 HE). **b** Embryonal carcinoma characterized by various histological patterns: tubular patterns (**b** ×100 HE). **c** papillary patterns (**c** ×100 HE), and **d** solid patterns (**d** ×100 HE). **e** Bizarre tumor cells, marked pleomorphism, vesicular nuclei, and prominent nucleoli are observed (**e** ×200 HE). **f** Immunohistological findings of positive staining for cytokeratin (**f** ×200), **g** CD30 (**g** ×200), and **h** PLAP (**h** ×200).

(For figure see next page.)

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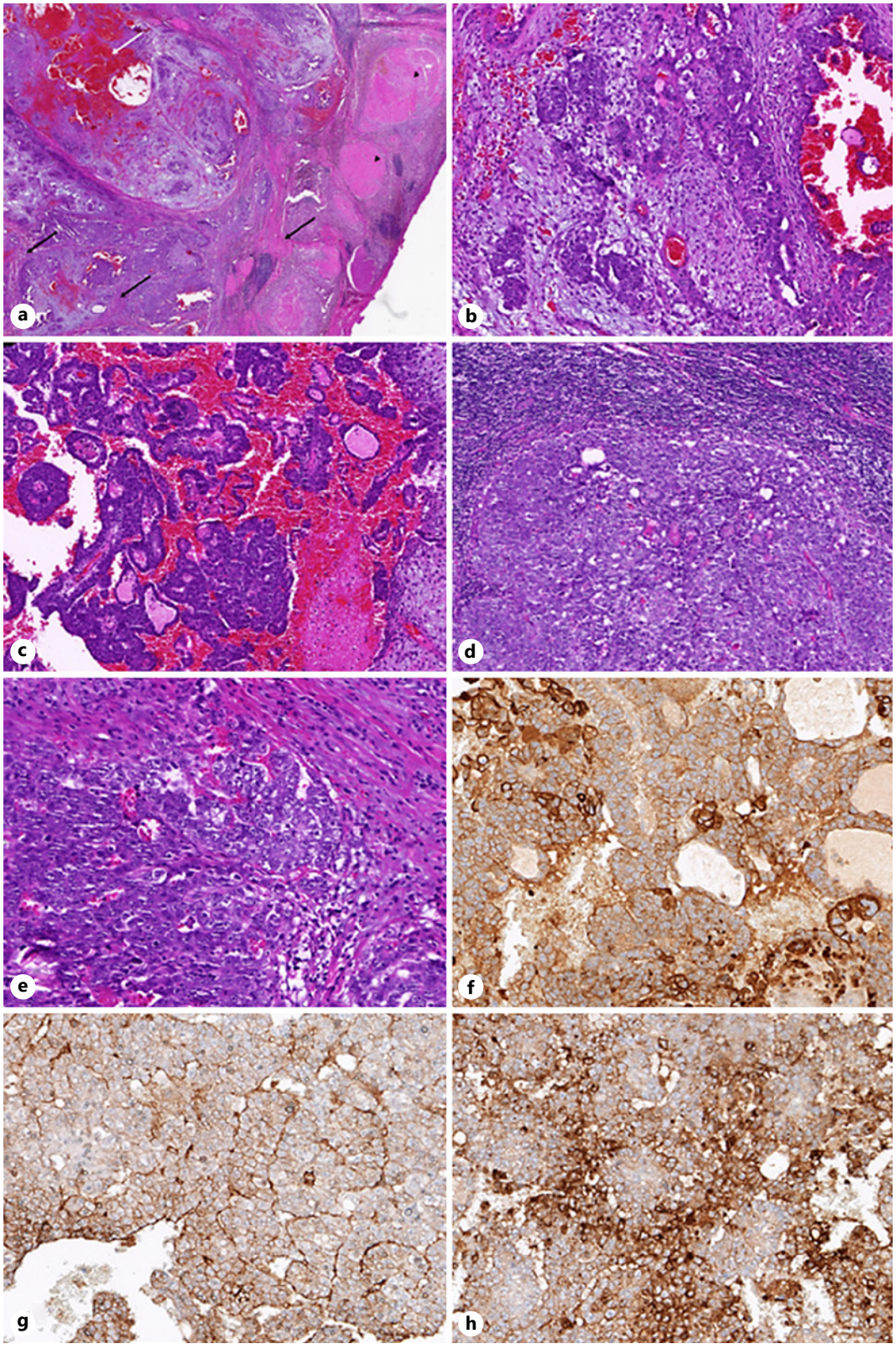

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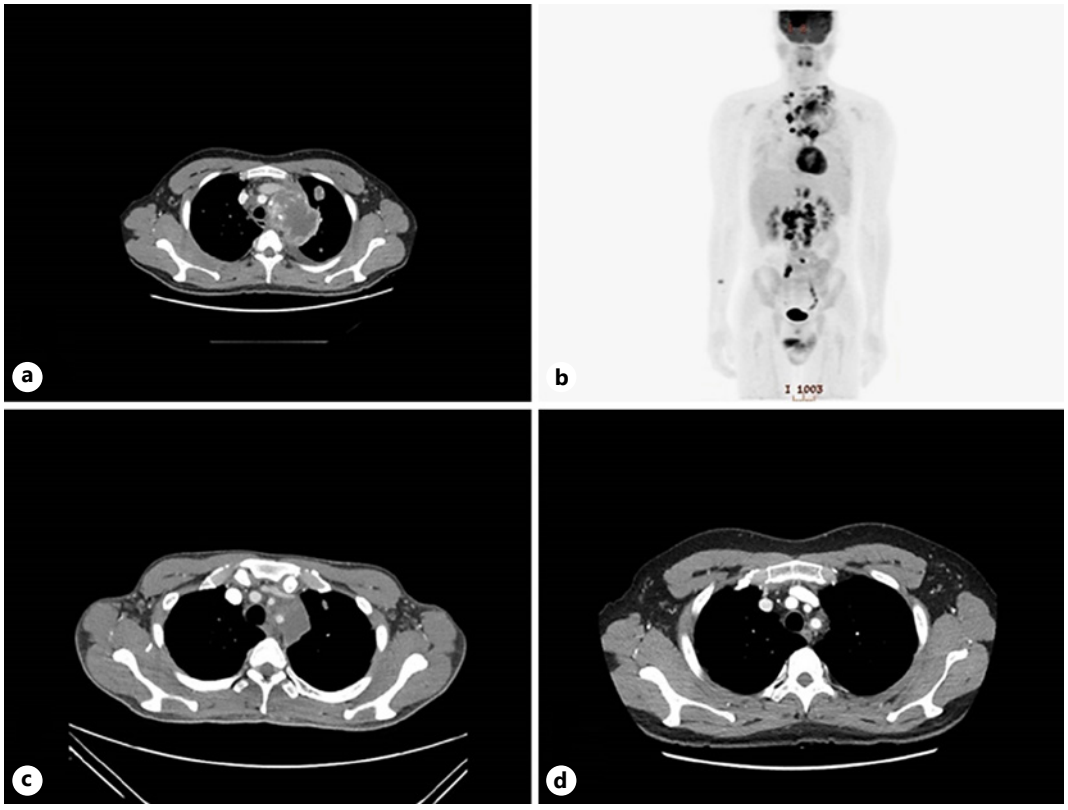

Fig. 2. a Chest CT scan at the time of diagnosis in November 2018 showing a huge mediastinal mass and multiple lung nodules. **b** Positron emission tomography scan at the time of diagnosis in November 2018. Increased fluorodeoxyglucose uptake was identified in the right testis, mediastinum, and multiple lymph nodes. **c** A chest CT scan after 4 cycles of paclitaxel/ifosfamide/cisplatin showing a partial response. **d** A recent chest CT scan in December 2020. The mediastinal mass was dramatically reduced after ASCT, and an impressive response was maintained without progression. TIP, paclitaxel/ifosfamide/cisplatin; ASCT, autologous stem-cell transplantation; CT, computed tomography; PET, positron emission tomography; FDG, fluorodeoxyglucose.

At present, a carboplatin plus etoposide-based regimen is considered an optimal conditioning regimen [10, 12]. Therefore, HDCT followed by ASCT should be actively recommended to relapsed/refractory high-risk GCT patients.

Statement of Ethics

Written informed consent for publication of this case report was obtained from the patient. This study was approved by the Institutional Review Board of Kyungpook National University Hospital (IRB No. KNUH 2021-03-011).

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Byung Woog Kang and Dong Won Baek conceived of the presented idea. Byung Woog Kang, Dong Won Baek, and Jung Min Lee were involved in management of the patient. Man-Hoon Han carried out the diagnosis of the tumor. All the authors read and approved the final manuscript.

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