Desperation surgery for a chemorefractory lung lesion in a patient with an extragonadal germ cell tumor

Yu Ishizuya¹ · Takuya Okusa¹ · Koji Hatano¹ · Yasutomo Nakai¹ ·
Masashi Nakayama¹ · Ken-ichi Kakimoto¹ · Kazuo Nishimura¹

Received: 20 January 2016 / Accepted: 24 March 2016 / Published online: 6 April 2016
© The Japan Society of Clinical Oncology 2016

Abstract We report a case of recurrent and chemorefractory extragonadal germ cell tumor successfully treated with desperation surgery. A 25-year-old man presented with a mediastinal tumor with multiple lung metastases. Serum human chorionic gonadotropin (hCG) level was elevated. He was diagnosed with a mediastinal germ cell tumor (GCT) with multiple lung metastases. After second-line chemotherapy, serum hCG levels normalized. After a total of 10 cycles of chemotherapy, the mediastinal tumor was resected, with no viable tumor detected in the resected tissue. One month after the resection, serum hCG increased, accompanied by the appearance of a new lesion in the lung. After various regimens of salvage chemotherapies, serum hCG failed to normalize. Then, salvage surgery for the lung metastasis was performed. The resected tissue contained a viable choriocarcinoma. The patient remained free of disease without adjuvant therapy at 38 months after pneumonectomy.

Keywords Extragonadal germ cell tumor · Choriocarcinoma · Lung metastases · Desperation surgery · Human chorionic gonadotropin

Introduction

Desperation surgery (salvage surgery in patients with increased serum tumor marker expression after chemotherapy) for recurrent/refractory germ cell tumors is

indicated in cases with certain characteristics, such as a confined and resectable tumor (particularly tumors confined to the retroperitoneal lymph nodes), and a persistent elevated alpha fetoprotein (AFP) level. We recently encountered a case of a recurrent extragonadal germ cell tumor where human chorionic gonadotropin (hCG) failed to normalize after various regimens of salvage chemotherapy but resection of the residual lung lesion resulted in long-term remission. Herein, we report this case along with a literature review.

Case report

A 25-year-old man developed back pain in August 2010. He had no remarkable medical history. Chest radiography revealed multiple lung nodules. He was referred to the Department of Internal Medicine of our hospital. Chest computed tomography (CT) revealed a mediastinal tumor. Nothing noteworthy was identified upon physical examination.

Blood test results revealed high C-reactive protein (CRP) levels (7.47 mg/dl). Tumor marker levels were also high (hCG, 64,000 mIU/ml; β -hCG, 770 ng/ml; lactate dehydrogenase, 326 IU/l). AFP was within the normal range. The other hematological and biochemical parameters were within the normal ranges. Chest CT revealed an irregular mass, 6 × 5 cm, in the anterior mediastinum (Fig. 1a). Numerous nodules of varying sizes were noted in both lungs (Fig. 1b). CT-guided needle biopsy of the mass in the anterior mediastinum supported the diagnosis of a germ cell tumor that was probably a choriocarcinoma or embryonal carcinoma. The patient was diagnosed with a mediastinal germ cell tumor accompanied by multiple lung metastases, and his International Germ Cell Consensus Classification was “poor prognosis”.

✉ Kazuo Nishimura
nisimura-ka2@mc.pref.osaka.jp

¹ Department of Urology, Osaka Medical Center for Cancer and Cardiovascular Diseases, 1-3-3, Nakamichi, Higashinari-ku, Osaka 537-8511, Japan

Fig. 1 CT images of mediastinal tumor and lung metastases; **a** mediastinal tumor before chemotherapy. **b** Lung metastases before chemotherapy. **c** Mediastinal tumor after four courses of VIP and six courses of TIP. **d** Lung metastases after four courses of VIP and six courses of TIP. VIP etoposide, ifosfamide and cisplatin, TIP paclitaxel, ifosfamide and cisplatin

Fig. 2 The clinical course with serum hCG levels of the patient. After four courses of VIP and three courses of TIP, serum hCG levels fell into within normal limit. VIP etoposide, ifosfamide and cisplatin. TIP paclitaxel, ifosfamide and cisplatin

Figure 2 shows the course of treatment. Because the patient had multiple lung metastases, we selected etoposide + ifosfamide + cisplatin (VIP) therapy instead of bleomycin + etoposide + cisplatin therapy, after considering the risk of bleomycin-induced lung disorders. After 4 cycles of VIP every 3 weeks without dose reduction, the mediastinal tumor and lung metastases had diminished in size. hCG decreased to 4.7 mIU/ml but failed to reach the normal range. Therefore, 3 cycles of second-line therapy with paclitaxel + ifosfamide + cisplatin (TIP) were administered. hCG levels normalized, and CT revealed a continuing trend of mediastinal tumor shrinkage. After a total of 6 cycles of TIP, the mediastinal tumor shrank to 3 × 2 cm, accompanied by shrinkage of the multiple lung metastases to a similar extent (Fig. 1c, d). Positron emission tomography (PET)-CT revealed slight fluorodeoxyglucose (FDG) accumulation in the mediastinal

tumor but no significant accumulation in the lung metastases. In July 2011, the mediastinal tumor was resected, with no viable tumor detected in the resected tissue. The patient was followed closely thereafter without any additional treatment.

One month after the mediastinal tumor resection, serum hCG increased to 12.7 mIU/ml, accompanied by the appearance of a new lesion in the left lung (Fig. 3a). The previously existing metastatic lesions in the lungs showed no growth. The course of treatment after recurrence is shown in Fig. 4. Salvage chemotherapy (gemcitabine + oxaliplatin therapy and irinotecan + nedaplatin therapy) was administered, but serum hCG continued to rise, accompanied by growth of the new lesion in the left lung (Fig. 3b). Thus, TIP, which had been an effective second-line therapy, was started again. After 3 cycles of TIP, the lesion in the left lung shrank (Fig. 3c), and hCG levels decreased to 5.3 mIU/ml but did not reach the normal range. Intense myelosuppression was noted, forcing the start of the next cycle of treatment to be delayed. By the time, the next cycle of treatment was started, serum hCG had risen again and the left lung lesion also showed growth. After 6 cycles of TIP therapy, PET-CT revealed slight FDG accumulation in the left lung lesion. But other metastatic lesions in the lungs showed no growth during salvage chemotherapy and were free of FDG accumulation on PET-CT images. In July 2012, 31 days after the start of the last TIP cycle, the left lung lesion (Fig. 3d) was resected. The resected tissue was histopathologically found to contain a viable tumor, stained positively for hCG, and allowed a final diagnosis of choriocarcinoma (Fig. 5). Postoperatively, hCG normalized and no additional treatment was administered. As of 38 months after pneumonectomy, the patient was free from recurrence.

Fig. 3 CT images of a new lesion in the left lung (arrow). **a** At diagnosis of relapse. **b** After one course of GO and another course of IrN. **c** After three courses of TIP. **d** After six courses of TIP. GO gemcitabine and oxaliplatin, IrN irinotecan and nedaplatin, TIP paclitaxel, ifosfamide and cisplatin

Fig. 4 The clinical course with serum hCG levels of the patient after resection of mediastinal tumor. GO gemcitabine, oxaliplatin, IrN irinotecan, nedaplatin, TIP paclitaxel, ifosfamide and cisplatin

Discussion

If tumor markers fail to normalize after salvage chemotherapy for a recurrent/refractory germ cell tumor, the patient is usually not indicated for resection of residual lesions [1]. However, even among these chemotherapy-

resistant cases, long-term survival may sometimes be achieved by resection of residual lesions. The long-term survival rate after desperation surgery is 33–73 % [1–8]. When desperation surgery is selected, it must be kept in mind that it is often quite invasive and has a risk for treatment-related death. Because systemic chemotherapy needs to be suspended during the perioperative period, it also has a risk of sudden increase of disease activity. Reported preoperative factors associated with the prognosis after desperation surgery include location of residual lesions, either AFP or β -hCG being the tumor marker not yet normalized.

Eastham et al. reported that long-term survival was achieved by 5 (50 %) of the 10 patients in whom the retroperitoneal lymph nodes were the location of residual lesions, while it was achieved by only 1 (14 %) of the 7 patients who had organ metastasis [2]. Similarly, Habuchi et al. reported that long-term survival was achieved by 9 (53 %) of the 17 and 1 (14 %) of the 7 patients with residual lesions confined to the retroperitoneal or mediastinal lymph nodes and with organ metastasis,

Fig. 5 Resection of the lung lesion. **a** Macroscopic features of the specimen. **b** hCG immunostaining

respectively [4]. Thus, desperation surgery is indicated in cases where residual lesions are located in the lymph nodes (particularly the retroperitoneal lymph nodes).

In addition, Habuchi et al. reported long-term survival after desperation surgery in 5 (29 %) of the 17 and 7 (58 %) of the 12 patients with elevated hCG and AFP levels, respectively. The prognosis was significantly poorer in patients with high hCG levels than in patients with normal hCG levels [4]. Wood et al. reported that postoperative recurrence was seen in all the 5 and in 6 (60 %) of the 10 patients with elevated hCG and AFP levels, respectively [5]. However, Beck et al. analyzed 114 patients with high tumor markers who underwent excision of retroperitoneal lymph nodes, reporting no significant difference in prognosis between the high preoperative hCG group and the high preoperative AFP group [6]. In their study, 50 of the 114 patients underwent resection of residual lesions after primary chemotherapy, and an elevated hCG level was identified as an independent poor prognosis factor for the 64 patients who underwent surgery after second-line and salvage chemotherapy. Accordingly, desperation surgery should be considered in cases where AFP is the tumor marker not yet normalized.

The tumor marker trends before surgery may also affect the survival outcome. Ong et al. analyzed 48 patients with elevated tumor markers who underwent retroperitoneal lymph node dissection (RPLND) [8]. In their study, the overall 5-year survival was 58 % in 26 patients with ‘upward marker’ and 82 % in 22 patients with ‘downward or stable marker’. Although this difference between the groups was not statistically significant, these results showed a trend to higher survival in patients with ‘downward or stable marker’.

In the present case, lung metastases were the residual lesions, and multiple lesions remained in the lungs after resection. It was difficult to resect these residual lesions completely. Furthermore, the tumor marker not yet normalized in this case was hCG. These features suggested that this case was unlikely to have a favorable prognosis after desperation surgery and was therefore not positively indicated for such surgery. However, normalization of tumor markers by chemotherapy seemed to be difficult in this case for the following reasons: (1) tumor marker normalization had not been achieved by fourth-line chemotherapy; (2) no other established treatment regimen was available; and (3) myelosuppression was severe. Of the multiple residual lesions, only one lesion responded to chemotherapy, and the change in its size was consistent with the change in serum hCG levels. Therefore, desperation surgery was performed at the time of downward trend of serum hCG, resulting in long-term survival of the

patient. This experience suggests the importance of carefully observing the time course of tumor markers and the tumor size.

The following features of our case seemed unfavorable: (1) high serum hCG, (2) residual lesions located in the lungs, and (3) multiple residual lesions present. Despite these unfavorable features, this patient achieved long-term remission after surgery. Although this is a very rare case, only one lesion changed in its size, correlating with the change in serum hCG during chemotherapy. For such a case, desperation surgery for active residual lesions after chemotherapy may be a treatment option that deserves consideration.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Research involving human participants and/or animals This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent Informed consent was obtained from the patient.

References

1. Bajorin DF, Herr H, Motzer RJ, Bosl GJ (1992) Current perspectives on the role of adjunctive surgery in combined modality treatment for patients with germ cell tumors. *Semin Oncol* 19:148–158
2. Eastham JA, Wilson TG, Russel C et al (1994) Surgical resection in patients with nonseminomatous germ cell tumor who fail to normalize serum tumor markers after chemotherapy. *Urology* 43:74–80
3. Ravi R, Ong J, Oliver RT et al (1998) Surgery as salvage therapy in chemotherapy-resistant nonseminomatous germ cell tumours. *Br J Urol* 81:884–888
4. Habuchi T, Kamoto T, Hara I et al (2003) Factors that influence the results of salvage surgery in patients with chemorefractory germ cell carcinomas with elevated tumor markers. *Cancer* 98:1635–1642
5. Wood DP Jr, Herr HW, Motzer RJ et al (1992) Surgical resection of solitary metastases after chemotherapy in patients with nonseminomatous germ cell tumors and elevated serum tumor markers. *Cancer* 70:2354–2357
6. Beck SD, Foster RS, Bihle R et al (2005) Outcome analysis for patients with elevated serum tumor markers at postchemotherapy retroperitoneal lymph node dissection. *J Clin Oncol* 1(23):6149–6156
7. Cary C, Pedrosa JA, Jacob J et al (2015) Outcomes of postchemotherapy retroperitoneal lymph node dissection following high-dose chemotherapy with stem cell transplantation. *Cancer* 121:4369–4375
8. Ong TA, Winkler MH, Savage PM et al (2008) Retroperitoneal lymph node dissection after chemotherapy in patients with elevated tumour markers: indications, histopathology and outcome. *BJU Int* 102:198–202