CASE REPORT

Malignant Ganglioneuroma Arising from Mediastinal Mixed Germ Cell Tumor

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Mixed germ cell tumors with non-germ cell malignant components rarely occur in the anterior mediastinum. We report a case of a 34-year-old man who presented with an anterior mediastinum mass. Mixed germ cell tumor was initially diagnosed based on the pathologic findings of germinoma on thoracoscopic biopsy and clinical findings of elevated serum α-fetoprotein and β-human chorionic gonadotropin. The patient received preoperative chemotherapy and subsequent complete resection of the residual tumor. Pathologic examination of the excised specimen showed predominantly malignant ganglioneuroma and small residual foci of teratoma. To our knowledge, this is the first reported case of a malignant ganglioneuroma arising from mediastinal mixed germ cell tumor. [J Chin Med Assoc 2007;70(2):76–79]

Key Words: malignant ganglioneuroma, mediastinal, mixed germ cell tumor

Introduction

The anterior mediastinum is the most frequent site of extragonadal germ cell tumors. Histologically, mature teratoma is the most common type and accounts for 75% of the total.1 Mixed germ cell tumors with somatic malignant transformation rarely develop in the anterior mediastinum. Non-germ cell malignancies have been reported to be squamous cell carcinoma, adenocarcinoma, poorly differentiated carcinoma and sarcomas such as embryonal rhabdomyosarcoma, angiosarcoma and myxoid liposarcoma.2–4 Herein, we report a case of malignant ganglioneuroma arising from mediastinal mixed germ cell tumor.

Case Report

A 34-year-old man was referred to our hospital due to dry cough for 2 months. He had a history of oligospermia and infertility for years but had otherwise been previously healthy. On physical examination, gynecomastia was noted. Chromosome study revealed normal male karyotype. Chest imaging studies, including X-ray, sonograph and computed tomography (CT), revealed a mass, measuring 18 × 16 × 12 cm (Figure 1A), in the left anterior mediastinum with pericardial and pleural effusions. Laboratory data showed elevation of serum α-fetoprotein (AFP) up to 151 ng/mL and β-human chorionic gonadotropin (β-hCG) up to 20.78 mIU/mL. Sonoguided biopsy showed germinoma. Clinically, the tumor was diagnosed as mixed germ cell tumor because of elevation of the above-mentioned serum markers.

The patient thus received 5 courses of chemotherapy (VP-16, cisplatin and bleomycin) in 5 months. The tumor shrank to 9 × 7 × 5.8 cm (Figure 1B), and serum AFP and β-hCG also dropped to 15.66 ng/mL and 0.25 mIU/mL, respectively. The patient underwent median sternotomy and tumor removal 2 months later after completion of chemotherapy. The tumor appeared poorly defined and severely adhered to the pericardium, superior vena cava and left upper lobe (LUL) of lung; after separation, it was completely excised, with partial resection of LUL of lung and pericardiectomy. Two months after the surgery, recurrent tumor in the anterior mediastinum and multiple nodules in both lungs and pleura consistent with metastases were found by chest CT. The patient received a further 3 additional courses of chemotherapy, including

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Mediastinal mixed germ cell tumor

VIP, ifosfamide and cisplatin, with partial response. Six months after tumor removal, he received radiotherapy 35 times (18 Gray for the whole lung field 12 times; 40 Gray for the recurrent tumor 23 times). The patient’s condition remained stable, although multiple nodular masses appeared in pleura 10 months after tumor removal. The patient has been regularly followed-up for 3 years since the surgical intervention; serum markers such as β-hCG and AFP were unremarkable.

Pathologic findings

Histologic examination of the initial thoracoscopic biopsy revealed features of germinoma, composed of large round to polygonal cells with prominent nucleoli, admixed with lymphocytes and separated by fibrous bands (Figure 2A). Tumor cells were positive for placental alkaline phosphatase immunohistochemically. No non-germinomatous component was seen in the limited specimen.

The excised tumor was yellow-brown in color and measured 9 × 7 × 5.8 cm in size. Its cut surface showed heterogeneous appearance with variegated areas of hemorrhage and necrosis (Figure 2B). Microscopically, the sarcomatous component was comprised mostly of spindle cells arranged in a twisted or fascicular pattern. High cellularity, marked pleomorphism, high mitotic figures (> 5/10 high-power field) and necrosis were apparent (Figure 2C). Neoplastic ganglion cells were seen dispersed among the spindle cells (Figure 2D). Immunohistochemically, the ganglion cells were clearly demonstrated by synaptophysin. The spindle cells and cartilage were diffusely positive for S-100 protein (Figure 2E), and focally positive for glial fibrillary acidic protein and epithelial membrane antigen. A diagnosis of malignant ganglioneuroma was rendered for this part of the tumor. Aside from the malignant ganglioneuroma, there were several foci of bland-looking cartilage, bone, glands, squamoid epithelium and adipose tissue, suggesting a pre-existing teratoma (Figure 2F). Confluent areas of shadows of round cells corresponding to the necrotic germinoma could be identified also.

Discussion

Mediastinal germ cell tumors occur predominately within the anterior mediastinum and account for 10–20% of mediastinal tumors.5,6 Due to their close relationship with the thymus, they are believed to be derived from extragonadal germ cells in the thymus or thymic cells with germ cell potential,1,7,8 although the existence of intrathymic germ cell tumor is still controversial. Clinically, the tumor predominately affects young men, and is more common in those with Klinefelter’s syndrome. The patient described here had infertility with oligospermia and gynecomastia. However, cytogenetic study did not show the karyotype of Klinefelter’s syndrome. Whether there is direct relationship between mediastinal germ cell tumors and infertility in this patient is still uncertain.

The initial biopsy revealed a pure population of germinoma. Nevertheless, we consider the specimen to be a part of mixed germ cell tumor, given the obvious elevated serum level of AFP and β-hCG. The existence of nonseminomatous component was further confirmed by the teratomatous foci found in the subsequent excisional biopsy. On the other hand, the seminomatous or other treatment-sensitive components were mostly regressed due to preoperative chemotherapy and radiotherapy. The predominant component we encountered at last operation was a malignant ganglioneuroma. Although the tumor was totally removed, as it was so adhesive with great vessel and lung tissue, recurrence may be predicted. Due to the rarity of

Figure 1. (A) Chest computed tomography: note the huge solid mass, which occupies almost the entire left anterior mediastinum. (B) Marked shrinkage of the tumor after chemotherapy.
pathologic findings, few reports discuss the options for operation; that is the reason why the patient had not had further operation when pleural metastasis was found. While the malignant part may have been existent in the first presentation, we believe that it developed from the teratomatous foci after chemotherapy. Ulbright et al reviewed 11 cases of testicular germ cell tumors. Eight of the 9 cases with malignant transformation

Figure 2. (A) Sonoguided biopsy: the tumor is composed of germinoma only (hematoxylin & eosin, 200×). (B) Cut surface of the tumor: the tumor is firm and heterogeneous, with areas of hemorrhage and necrosis. (C) Sarcomatous component: spindle cells with pleomorphism, high mitotic rate and necrosis highlights the malignancy (hematoxylin & eosin, 200×). (D) Ganglion cells are admixed with twisted or fasciculated spindle cells (hematoxylin & eosin, 200×). (E) The cartilage and spindle cells are immunoreactive for S100 stain (S100, 200×). (F) Various components, such as bone, cartilage, squamoid epithelium and gland, are seen in the tumor (hematoxylin & eosin, 40× and 400×).
had teratoma in the primary tumor, and teratoma was found in subsequently resected tissue in 1 case that was similar to ours. They proposed that cisplatin-based chemotherapy frequently “unmasked” the non-germ cell malignant elements by destroying the more chemosensitive germ cell tumors. Oosterhuis et al claimed that the occurrence of sarcomatous elements following chemotherapy for germ cell tumors could result from induction of differentiation among the totipotential germ cells or by malignant transformation of pre-existing teratoma.9 Malignant transformation from germ cell tumor may be carcinomatous or sarcomatous.10,11 The occurrences of sarcomatous components have been documented in many locations, especially in the mediastinum.4 Among the sarcomas, rhabdomyosarcomas are the most frequently found in the mediastinum.3,4,11,12 Other types such as angiosarcoma,4 chondrosarcoma, myxoid liposarcoma, epithelioid leiomyosarcoma,5 and extraskeletal osteosarcoma13 have also been reported.

The major differential diagnosis for the present case is primary mediastinal ganglioneuroma containing metaplastic heterologous elements. However, the presence of germinoma and teratoma argues against such a possibility. Mediastinal malignant tumors of neural origin are rare,14–17 and no case has been reported to occur in a mediastinal germ cell tumor. In summary, we report a case of malignant ganglioneuroma arising from mediastinal mixed germ cell tumor. To the best of our knowledge, it is the first report of such a combination in the medical literature.

References


