Four Cases of Invasive Anterior Mediastinal Tumors Definitively Diagnosed by the Chamberlain Procedure

Junzo Shimizu, MD,1 Tadashi Kamesui, MD,1 Makio Moriya, MD,1 Shuichi Murata, MD,2 Isao Nakanishi, MD,3 Motoko Sasaki, MD,4 and Hiroshi Minato, MD5

Percutaneous needle biopsy, commonly used for a definitive diagnosis of anterior mediastinal tumors, is sometimes inconclusive because of the small size of the biopsy specimens and the histologic heterogeneity of the tumors. We herein report 4 cases of invasive anterior mediastinal tumors, in which the definitive diagnosis was made using the Chamberlain procedure. [Case 1] A 33-year-old man was found to have an anterior mediastinal tumor on chest X-ray and computed tomography (CT). The tumor was histologically diagnosed as thymic carcinoma (squamous cell carcinoma) using the Chamberlain procedure. After 3 courses of preoperative chemotherapy, the patient underwent surgery and postoperative radiotherapy. He remains well, 35 months after the biopsy. [Case 2] A 17-year-old boy was found to have a tumor in the anterior mediastinum on chest CT. His serum alpha-fetoprotein level was elevated to 2,461 ng/mL. Histological diagnosis of yolk sac tumor was confirmed using the Chamberlain procedure. He was treated with one course of chemotherapy, followed by surgery; he remains well 57 months after the biopsy. [Case 3] A 72-year-old man was found, on chest X-ray and CT, to have a left upper anterior mediastinal tumor with invasion of the subclavian vessels. The tumor was confirmed histologically as thymic (sarcomatoid) carcinoma using the Chamberlain procedure. Despite 2 courses of chemotherapy, the tumor continued to enlarge and metastasized to the lung and bone. The patient died 7 months after the biopsy. [Case 4] A 62-year-old woman under treatment for rheumatoid arthritis (RA) was found, on a chest X-ray, to have a right anterior mediastinal tumor. Histological diagnosis using the Chamberlain procedure suggested lymphoproliferative disorder, and the RA medication was discontinued. This was followed by a decrease in the tumor size and avoidance of invasive surgery. The patient remains well, 15 months after the biopsy. [Conclusion] The Chamberlain procedure proved useful for definitive diagnosis in all 4 cases of invasive anterior mediastinal tumors. We recommend the Chamberlain procedure for biopsy since it enables safe, rapid, and successful collection of tissue samples.

Keywords: Chamberlain procedure, anterior mediastinal tumor, biopsy, thymus

1Department of Surgery, Hokuriku Central Hospital, Oyabe, Toyama, Japan
2Department of Chest Surgery, Toyama Rosai Hospital, Uozu, Toyama, Japan
3ALP Pathology Institute, Kanazawa, Ishikawa Japan
4Department of Pathology, Kanazawa University School of Medicine, Kanazawa, Ishikawa, Japan
5Department of Pathology and Laboratory Medicine, Kanazawa Medical University, Kahoku-gun, Ishikawa, Japan

Received: October 15, 2012; Accepted: February 5, 2013
Corresponding author: Junzo Shimizu, MD. Department of Surgery, Hokuriku Central Hospital, 123 Nodera, Oyabe, Ishikawa 932-8503, Japan
Email: junzo432@yahoo.co.jp
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Introduction

There are a number of techniques available for mediastinal biopsy. Percutaneous needle biopsy\textsuperscript{11} with radiological guidance has been useful in the evaluation of anterior mediastinal tumors. This procedure, although not requiring formal operation and general anesthesia, is not without complications and diagnostic errors. For instance, a pneumothorax after transthoracic needle biopsy develops in up to 34\% of patients.\textsuperscript{20} Furthermore, serious complications such as cardiac tamponade have been reported after needle aspiration of mediastinal masses.\textsuperscript{30} On the other hand, the diagnosis of anterior mediastinal masses like lymphoma or germ cell tumor often requires more tissue than can be obtained by fine-needle or core biopsy.\textsuperscript{4,5} Approximately 1 cm\textsuperscript{3} of tumor tissue currently is required for cytogenetics, immunophenotyping, and specialized molecular biological analysis, and this is not attainable with needle biopsy. Thoracoscopic procedures are used for mediastinal biopsy in both adults\textsuperscript{60} and children.\textsuperscript{7} Such procedures provide good access to the mediastinum but are more complex and may have a higher complication rate and longer hospital stay than percutaneous needle biopsy.

The parasternal mediastinotomy (the Chamberlain procedure)\textsuperscript{8–10} provides excellent access to the anterosecond or third costal cartilage. The pectoralis major muscle was divided in the line of incision over the cartilage, which was then removed. The internal mammary vessels were preserved whenever possible. The pleura was separated from the sternum and mediastinum, and opened if there was inadequate exposure or severe adhesions. The target tissue was excised using a scalpel and forceps to ensure that a specimen with a diameter of more than 10 mm was obtained. When the pleura was opened, a chest tube was temporarily placed. Finally, a chest radiograph was taken to check for any evidence of a pneumothorax after the biopsy.

Case Reports

Case 1 was a 33-year-old man who was found to have an abnormal opacity on the chest X-ray during a routine medical examination in November 2009. He was referred to our hospital for further evaluation and treatment. Serum levels of tumor markers were 3.0 ng/mL for alpha-fetoprotein (AFP), <0.4 ng/mL for beta subunit of human chorionic gonadotropin (hCG), 4.4 ng/mL for cytokeratin 19 fragment (CYFRA), and 11 ng/mL for neuron-specific enolase (NSE); the serum levels of CYFRA and NSE were slightly elevated. Chest X-ray on admission showed a solid mass with a slightly irregular margin in the left anterior mediastinum, 65 \times 55 mm in size, associated with elevation of the left diaphragm. CT of the chest revealed a heterogeneous mass, with suspected invasion of the left main pulmonary artery (Fig. 1a). Based on the above findings, the patient was suspected to have thymic carcinoma, and the Chamberlain procedure was performed to obtain a definitive diagnosis. Histological examination showed solid nests of large epithelioid cells with oval nuclei, large nucleoli, and several mitotic figures (Fig. 2a1). A mild lymphocytic infiltration was seen in the tumor nests. Immunohistochemically, the tumor cells were positive for cytokeratin AE1/AE3, cytokeratin 5/6, p63, and CD5 (Fig. 2a2). A few CD1a positive mononuclear cells were present in the tumor. Based on these findings, the diagnosis of poorly-differentiated...
Squamous cell carcinoma of the thymus was made. The patient was discharged from the hospital 7 days after the biopsy. At another hospital, the patient received 3 courses of preoperative chemotherapy with cisplatin, vincristine, doxorubicin and etoposide (CODE), followed by surgery (resection of the tumor with removal of the left upper lobe of the lung, left brachiocephalic vein, left vagal nerve, left phrenic nerve, and a part of the pericardium) and postoperative radiotherapy at total radiation dose of 50 Gy. He remains well until now, 35 months after the biopsy.

Case 2 was a 17-year-old adolescent boy who presented to our hospital with the chief complaint of anterior chest oppression since January 2008. Chest X-ray and CT (Fig. 1b) revealed a well-circumscribed mass measuring 87 × 62 mm in size protruding from the right anterior mediastinum into the right lung field, with suspected invasion of the superior vena cava, pericardium, and right upper and middle lobes of the lung. Marked elevation of the serum AFP level to 2,416 ng/mL and slight elevation of the serum CYFRA and NSE levels to 5.1 ng/mL and 20 ng/mL, respectively, was noted, while the serum levels of carcinoembryonic antigen (CEA), β-hCG, and pro-gastrin-releasing peptide (pro-GRP) were within the normal range, respectively. On the basis of these imaging findings and serum tumor marker levels, a primary yolk sac tumor in the mediastinum was suspected. A biopsy using the Chamberlain procedure was performed for a definitive diagnosis. Histologically, a diffuse, reticular, and papillary growth of pleomorphic tumor cells were seen with necrosis (Fig. 2b1). Eosinophilic hyaline droplets were evident both within and outside the tumor cells. Immunohistochemistry showed positive staining for AFP (Fig. 2b2), but not for placental alkaline phosphatase.
Diagnosis of Anterior Mediastinal Tumor by Chamberlain Procedure

Although the typical Schiller-Duval bodies were not found, the diagnosis of pure yolk sac tumor was made. Despite one course of chemotherapy with bleomycin, etoposide and cisplatin (BEP), a chest X-ray showed a slight increase of the tumor diameter. Accordingly, the tumor response was classified as NC (no change) and the chemotherapy was discontinued. The patient underwent surgery (resection of the tumor with removal of the right upper and middle lobes of the lung, right phrenic nerve, and a part of the pericardium) and received an additional 2 courses of BEP therapy. He remains well 57 months after the biopsy, with his serum AFP levels maintained within the normal range. Histologically, a large part of the tumor exhibited coagulative necrosis, and the histopathological response to chemotherapy was nearly complete response.

Case 3 was a 72-year-old man who presented with the chief complaint of hoarseness since August 2011 to a local hospital, where a chest X-ray revealed a tumor in the upper anterior mediastinum and elevation of the left diaphragm. He was referred and admitted to our hospital for further evaluation and treatment. The serum levels of tumor markers were in the normal range: CEA, 2.3 ng/mL; AFP, 1.8 ng/mL; β-hCG <0.44 ng/mL; CYFRA, 2.0 ng/mL; NSE, 5.8 ng/mL. A chest CT showed a tumor measuring 35 mm in diameter located in the upper anterior mediastinum, with suspected invasion of the subclavian vessels (Fig. 1c). The differential diagnosis included thymic carcinoma, malignant lymphoma, and lung cancer, and to obtain a definitive diagnosis, a biopsy using the Chamberlain procedure was performed. Histological examination revealed that the tumor showed malignant spindle and polygonal cell proliferation with abundant mitoses and pleomorphism, and invaded the adjacent veins and nerve bundles (Fig. 2c1), but not into the lung parenchyma. Immunostaining revealed strongly positive staining for CD5 (Fig. 2c2) and negative staining for calretinin, desmin, S-100, CD34, and synaptophysin. There were a few α-smooth muscle actin (α-SMA)-positive cells, which led to the diagnosis of thymic sarcomatoid carcinoma. Despite 2 courses of combined paclitaxel plus carboplatin (TC) therapy, the tumor continued to enlarge and invaded the thoracic wall and subclavian vessels. Subsequently, chemotherapy was discontinued, and surgery was abandoned. The tumor metastasized to the lung and bone, and the patient died 7 months after the biopsy.

Fig. 2 (a1) Epithelial tumor cells with large oval nuclei, large nucleoli, and some mitotic figures. Mild lymphocytic infiltration in tumor nests. (HE, × 100) (a2) Immunohistochemically, tumor cells were diffusely positive for CD5. (Case 1) (b1) A diffuse, reticular, and papillary growth of pleomorphic tumor cells. Eosinophilic hyaline droplets were evident both within and outside the tumor cells. (HE, × 100) (b2) Immunohistochemistry showing positive staining for α-fetoprotein (AFP). (Case 2) (c1) Malignant cells, spindle-shaped or polygonal, exhibiting abundant mitoses and nuclear atypia and invading adjacent veins and nerve bundles. (HE, × 40) (c2) Immunostaining revealing strongly positive staining for CD5. (Case 3). (d1) The tumor consisting of aggregations of lymphoid cells. Neither the normal structure of the lymph node nor epithelial cell components are present. (HE, × 4) (d2) A large magnification shows abundant mature small lymphocytes and plasma cells, with a small number of large lymphoid cells. (HE, × 40), (Case 4)
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Prograf since 1994. She was on regular annual medical follow-up, and was found to have an abnormal opacity on a routine chest X-ray for the first time in 2011. Chest CT revealed a well-circumscribed heterogeneous mass measuring 90 mm in diameter protruding from the anterior mediastinum into the right lung field (Fig. 1d). Tumor marker measurements revealed slight increases in the serum CEA and interleukin-2 (IL-2) receptor levels: CEA, 5.8 ng/mL; AFP, 9.7 ng/mL; β-hCG <1.0 mIU/mL; CYFRA, 1.7 ng/mL; NSE, 10.4 ng/mL; pro-GRP, 46.7 pg/mL; IL-2 receptor, 690 U/mL. The differential diagnosis included thymic carcinoma and malignant lymphoma, and for a definitive diagnosis, a biopsy using the Chamberlain procedure was performed. As shown in Fig. 2d1 and 2d2, histological examination revealed that the tumor consisted of an aggregation of small lymphocytes and plasma cells, with a small number of large lymphoid cells. Neither the normal structure of the lymph node nor epithelial cell components were present. Immunohistochemistry revealed many CD3-positive mature T-cells admixed with relatively small number of CD 20-positive B-cells and plasma cells. The small number of large lymphoid cells were positive for CD30, but negative for CD15. No typical Hodgkin-Reed-Sternberg cell was found. The plasma cells were negative for IgG4. Light chain restriction was not obvious by kappa and lambda stain. Based on these findings, lymphoproliferative disorder was suggested, though EBER-ISH was positive. The RA medications were discontinued, and the patient was followed up closely. Subsequently, the tumor size decreased, and invasive surgery was avoided. The patient remains well 15 months after the biopsy and continues to be followed up without any treatment for RA.

No patient in our series developed major bleeding requiring blood transfusion or wound infection. The Chamberlain procedure was useful for obtaining a definitive diagnosis in all 4 cases (Table 1). All of the patients who had undergone the Chamberlain procedure began appropriate therapy according to the histologic diagnosis without delay. Three of the patients received preoperative chemotherapy and 1 was followed up with the discontinuance of the medication. One of the patients died of disease progression 7 months after the Chamberlain procedure while the other 3 remain well 57, 35, and 15 months after the procedure.

Discussion

Thymomas (including thymic carcinoma) and germ

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Gender</th>
<th>Age (years)</th>
<th>Histologic diagnosis made from the Chamberlain procedure</th>
<th>Surgery</th>
<th>Chemotherapy</th>
<th>Desired Answer Achieved?</th>
<th>Prognosis (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Male</td>
<td>33</td>
<td>Thymic cancer (squamous cell carcinoma)</td>
<td>CODE</td>
<td>Total thymectomy (combined resection of LUL, lt-brachiocephalic vein, lt-vagal nerve)</td>
<td>Yes</td>
<td>Alive (35)</td>
</tr>
<tr>
<td>2</td>
<td>Male</td>
<td>17</td>
<td>Thymic cancer (squamous cell carcinoma)</td>
<td>CODE</td>
<td>Total thymectomy (combined resection of RUL, RML, pericardium, rt-phrenic nerve)</td>
<td>Yes</td>
<td>Alive (57)</td>
</tr>
<tr>
<td>3</td>
<td>Male</td>
<td>72</td>
<td>Thymic cancer (sarcomatoid carcinoma)</td>
<td>TC</td>
<td>none</td>
<td>Yes</td>
<td>Died from metastases to lung and bone (7)</td>
</tr>
<tr>
<td>4</td>
<td>Female</td>
<td>66</td>
<td>Lymphoproliferative disorders</td>
<td>none</td>
<td>none</td>
<td>Yes</td>
<td>Alive (15)</td>
</tr>
</tbody>
</table>

CODE: CDDP + Vincristine + Doxorubin + Etoposide; BEP: Bleomycin + Etoposide + CDDP; TC: Paclitaxel + Carboplatin LUL + Sepparine lobe; RUL: rt-upper lobe; RML: rt-middle lobe.
cell tumors are two major types of tumors occurring in the thymus. As surgical resection of the tumors is considered the final treatment of the lesions, accurate histological diagnosis of the tumors is a prerequisite for appropriate surgical treatment. For germ cell tumors in particular, it is essential to establish a histological diagnosis because initial treatment strategies depend on the subtypes of the tumors. Since delay in diagnosis and treatment of germ cell tumors could result in poor outcomes or even death, prompt diagnosis should be made, and appropriate treatment initiated as soon as possible if these tumors are suspected based on increased serum tumor marker levels, including AFP and hCG.14)

Thymomas and germ cell tumors are known to exhibit enormous histologic heterogeneity. To obtain accurate histological diagnosis of the tumors, it is necessary to obtain as large biopsy specimens as possible by means other than percutaneous needle biopsy.15,16) The limited amount of the specimens using percutaneous needle biopsy sometimes fails to provide a definitive and accurate diagnosis because of histologic heterogeneity of the tumors. In addition, for tumors filled with necrosis substances, a definitive diagnosis with percutaneous needle biopsy is difficult. Hence, we attempted to collect relatively large biopsy specimens by using the Chamberlain procedure to obtain a definitive diagnosis.

Recent improvement of video-assisted thoracoscopic surgery (VATS) has enabled collection of relatively large specimens from anterior mediastinal tumors, as in the presented cases. Moreover, VATS can be performed for not only anterior mediastinal tumors, but also for tumors of the middle and posterior mediastinum. VATS is, however, contraindicated in patients with extensive pulmonary adhesions or those who cannot tolerate single-lung ventilation. It is also associated with the risk of intraoperative dissemination of tumors in the thoracic cavity.17) Furthermore, Dmitriev18) reported a case of intraoperative complication during thoracoscopic excision of the tumor. It was bleeding due to electrosurgical damage of the aorta during coagulation of small vessels that required urgent thoracotomy and suture of aorta. We decided that thoracoscopic excision would be dangerous in the technical aspect.

This study involved 4 cases of invasive tumors of the anterior mediastinum that were large and in extensive contact with the anterior thoracic wall. The Chamberlain procedure was considered to be best suited for biopsy in all of these cases, in terms of successful collection of relatively large biopsy specimens, reliability of the histological diagnosis, and safety and feasibility of the procedure.18–20) No major complications delaying the commencement of appropriate tumor therapy occurred. In our practice, we use the Chamberlain procedures for those lesions more lateral and anterior in the mediastinum. For more centrally located lesions lying superiorly in the mediastinum, close to the trachea, we would use a mediastinoscopy. If we could present the demerit of the Chamberlain procedure, it is requiring formal operation and general anesthesia.

It has been well known that thymic follicular hyperplasia has been associated with autoimmune diseases such as RA and the RA medications.21) Among the cases presented here, cases like our case 4 are relatively rare. Because of the large diameter and rapid growth rate of the tumor in this case, a malignant tumor was initially suspected. However, an accurate diagnosis of lymphoproliferative disorder was made by biopsy using the Chamberlain procedure, and invasive surgery was avoided. This case underscores the importance of accurate histological diagnosis obtained before making decisions on invasive surgery.

In conclusion, the Chamberlain procedure was employed for the biopsy in all the 4 cases of invasive tumors of the anterior mediastinum and provided definitive diagnoses in all cases. The results of this study show that the procedure is recommended for biopsy in case of invasive tumor of the anterior mediastinum since it enables safe, rapid, and successful collection of the tissue samples.

**Disclosure Statement**

The authors have no conflicts of interest to declare.

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