Thymic epithelial neoplasms consist of thymomas, thymic carcinoids, and thymic carcinomas. Carcinomas are malignant tumors of the thymus characterized by obvious cytological anaplasia. They constitute only 4%–14% of thymic epithelial neoplasms. Thymic carcinoma rarely occurs in children. Research in the English literature carried out for the present study revealed only 14 cases younger than 18 years-of-age. Here we have reported a 16-year old girl who presented with respiratory distress due to huge anterior mediastinal mass. Histological and immunohistochemical studies confirmed lymphoepithelioma-like thymic carcinoma. She received systemic chemotherapy and radiotherapy. However, she died within 15 months due to progressive disease.

Key words: childhood; pediatric oncology; rare tumors; thymic carcinoma

INTRODUCTION

Mediastinal masses in children comprise a heterogeneous group of malignant and benign neoplasms. The majority of malignant tumors of mediastinum are Hodgkin’s and non-Hodgkin’s lymphomas, germ cell tumors, and neuroblastomas. Thymic tumors account for 1.5% of mediastinal masses in children [1]. Thymomas, thymic carcinoids, and thymic carcinomas constitute thymic epithelial neoplasms (TEN). Carcinomas are malignant tumors of the thymus characterized by obvious cytological anaplasia, extensive infiltration of surrounding tissues, and extrathoracic metastasis [2]. Carcinomas constitute only 4%–14% of thymic epithelial neoplasms [3,4]. Thymic epithelial neoplasms are usually seen in the fourth and fifth decades of life. Thymic carcinoma rarely occurs in children [3–5]. In addition to a review of previous cases in literature, here we report a case of thymic carcinoma in a child who presented with a mediastinal mass.

CASE REPORT

A 16-year-old girl was referred to our hospital for further evaluation of the mediastinal mass, which was found on a chest X-ray during an evaluation for chest pain and respiratory distress. She had been suffering from chest pain, weakness, anorexia, weight loss, intermittent fever, sweating, cough, and progressive respiratory distress for the previous 2 months. Physical examination revealed paleness, tachypnea (28/min), suprasternal and intercostal retractions, and decreased left chest breath sounds. Multiple lymphadenopathies were palpated in the left axillary region. Other physical examination findings were normal.

Laboratory findings revealed anemia (Hb: 10 g/dl), high sedimentation rate (94 mm/hr), elevated LDH (752 U/L), ferritin (261.3 ng/L), and CRP levels (15 mg/dl). All of her urine analysis, serum biochemical tests, blood gases, AFP, β-HCG, and urine VMA levels were normal. Bone marrow aspiration and peripheral blood smear were normal. Chest X-ray demonstrated a bulky mass in the anterior mediastinum. Computerized tomography of thorax showed an anterior mediastinal mass with a diameter of $12 \times 12 \times 10$ cm, surrounding blood vessels as well as invading the pericardium (Fig. 1). A nodular metastasis of 1 cm in diameter was obtained in the lower lobe of the left lung in addition to left pleural effusion and multiple lymphadenopathies in the upper mediastinum. The ultrasonography and computerized tomography of the abdomen and pelvis were normal.

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Whole body bone scan showed increased uptake in the sternum. Cytological examination of pleural fluid revealed mesothelial cells and abundant lymphocytic infiltration.

A biopsy from mediastinal mass was performed as it was considered inoperable. Histopathologic examination revealed a neoplasm composed of epithelial cells with a syncitial growth pattern, and a lymphocyte rich background (Fig. 2). Vesicular nuclei with a single eosinophilic nucleolus were noticed in neoplastic epithelial cells. Immunohistochemically, the neoplastic cells were keratin (AE1/AE3)-positive (Fig. 3); LCA-, vimentin-, CD30-, and S-100-negative. Histopathologic diagnosis was lymphoepithelioma-like thymic carcinoma (LELC) and she had Masaoka [6] stage IVb disease.

Since the mass surrounding the aorta also invaded the pericardium, radical surgery could not be performed. Neoadjuvant chemotherapy was begun to improve respectability of the mass. A chemotherapy protocol containing cisplatin (100 mg/m²/day, for 1 day), etopside (120 mg/m²/day, for 3 days), and doxorubicin (20 mg/m²/day, for 2 days) was administered and repeated every 3 weeks. Before starting the third cycle, 9 weeks after the diagnosis, a computed tomography of thorax was repeated and the size of the mass measured to be 7 × 7 × 6 cm. About 30% reduction in tumor size was obtained and surgical excision was planned. However, the patient complained of pain in the left pubic area. Pelvic MRI showed a mass located on left acetabular region, extending through the soft tissues. Repeated whole body bone scan showed increased uptake in the left clavicle, left coxae, and L3 vertebra. Surgery was postponed due to metastatic progression of the disease. Patient was treated with 4,300 cGy radiotherapy to the tumor area in the mediastinum as well as palliative treatment with 5-FU and cisplatin.
irradiation to areas of bone metastasis. A second-line of chemotherapy protocol containing cisplatin (100 mg/m²/day, for 1 day), vincristine (1.4 mg/m²/day, for 1 day), ifosfamid (2 g/m²/day, for 2 days), and doxorubicin (40 mg/m²/day, for 2 days) was began and repeated every 4 weeks. However she died 15 months after diagnosis due to progressive disease.

**DISCUSSION**

Thymic epithelial neoplasms represent a diverse group of tumors ranging from well-differentiated thymomas to obviously malignant tumors [2,7]. Neoplasms arising from thymic epithelium were all considered as thymomas by the previous studies [8,9]. However, in more recent sub-typing proposed by Marino and Müller-Hermelink [7] and WHO [2] thymic carcinomas have been described as a separate group. These contemporary classification system satisfactorily managed concerns related to terminology, histopathologic typing, and prognostication [10,11].

Thymoma and thymic carcinomas have similar histogenesis, and both arise from the medullary epithelium. However, they are morphologically and biologically different neoplasms [2,4,7]. Malignant thymomas histologically represent the thymomas that have invasive and rarely metastatic potential but lack the cytological evidence of malignancy. In thymic carcinomas, thymic epithelial cells lose their phenotypical and functional features and appear to have obvious anaplasia indicated by the presence of nuclear prominence, vesicular chromatin, abundant mitotic activity, increase in nucleo-cytoplasmic ratio, and frequent areas of necrosis [2,7]. They have considerably greater potential for invasion and metastasis. In contrast to thymomas, carcinomas are rarely associated with paraneoplastic syndrome [4,8]. Several subtypes of thymic carcinoma have been recognized, including squamous cell carcinoma, lymphoepithelioma-like carcinoma, clear-cell carcinoma, and undifferentiated carcinoma [2,8,12,13].

The histopathologic subtype in our case was LELC. LELC is reported to constitute 12%–32% of all thymic carcinomas [8,13]. It is characterized by large cells with a moderate amount of eosinophilic cytoplasm consisting of large vesicular nuclei and prominent nucleoli [12,14]. Neoplastic cells are surrounded by dense lymphoid infiltrate abundant mitoses. A causal association has been inferred between the LELC and Epstein–Barr virus as has been the case for other lymphoepithelial tumors in other sites such as the nasopharynx. Epstein–Barr virus DNA and nuclear RNA have been demonstrated in the biopsy tissue of LELC but were not detectable in other types of thymic carcinomas [15,16]. LELC behaves more aggressively, and has significantly higher invasive and metastatic potential than other types [8,13,14]. Pleura, diaphragm, and pericardium are involved in nearly 20%–25% of patients. Approximately 67% of cases with LELC show extrathorasic metastasis. Lymphatic metastases is seen in 46% of cases. Hematogenous spread to lungs, liver, bones, kidneys, and brain were reported in 43%, 46%, 29%, 18%, and 11% of cases, respectively [8]. Lymphoepitheliomallike patterns have the poorest prognosis among the subtypes of carcinomas [8,13,14]. The average survival time is 20 ± 18 months [8]. In a series reported by Wick et al. [12], 12 of 13 patients with LELC died within maximum 36 months. Among the 305 cases reviewed by Chung et al. [13], 16 were LCLC cases and 12 of them developed metastasis. Of all LELC the patients, only two survived for 2 years and none survived for 5 years.

Thymic carcinomas are rarely seen in childhood. Only two pediatric cases were described in 19 clinicopathological studies including 305 cases analyzed by Chung [13].

**TABLE I. Thymic Carcinoma Cases Reported in Literature**

<table>
<thead>
<tr>
<th>Total cases</th>
<th>Age/sex</th>
<th>Histopathology</th>
<th>Metastasis</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wick, 1982 [12]</td>
<td>20 TC</td>
<td>4/M</td>
<td>Lymphoepithelioma-like</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Marino, 1985 [7]</td>
<td>71 TEN</td>
<td>14/M</td>
<td>Lymphoepithelioma-like</td>
<td>Intrathoracal</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>10/F</td>
<td>Small cell</td>
<td>Lung–liver–bone</td>
<td>PE + RT + CT</td>
<td>Died (7 mo)</td>
</tr>
<tr>
<td></td>
<td>14/M</td>
<td>Undifferentiated</td>
<td>Liver–bone–LN</td>
<td>PE + CT</td>
<td>Died (15 mo)</td>
</tr>
<tr>
<td>Suster, 1991 [14]</td>
<td>60 TC</td>
<td>10/F</td>
<td>NA</td>
<td>Bone</td>
<td>CT</td>
</tr>
<tr>
<td>Lee, 1993 [18]</td>
<td>Case report</td>
<td>9/M</td>
<td>Squamous cell</td>
<td>Bone</td>
<td>CT</td>
</tr>
<tr>
<td>Ilhan, 1994 [19]</td>
<td>Case report</td>
<td>13/F</td>
<td>Lymphoepithelioma-like</td>
<td>No</td>
<td>CT + RT</td>
</tr>
<tr>
<td>Lucchi, 2001 [17]</td>
<td>13 TC</td>
<td>11/M</td>
<td>Undifferentiated</td>
<td>NA</td>
<td>PE + CT + RT</td>
</tr>
<tr>
<td>Emir, 2001 [21]</td>
<td>Case report</td>
<td>13/F</td>
<td>NA</td>
<td>Bone</td>
<td>CT</td>
</tr>
<tr>
<td>Toretsky, 2003 [22]</td>
<td>Case report</td>
<td>15/M</td>
<td>Squamous cell</td>
<td>Bone</td>
<td>CT</td>
</tr>
<tr>
<td>Present case</td>
<td>Case report</td>
<td>16/F</td>
<td>Lymphoepithelioma-like</td>
<td>Lung–bone–LN</td>
<td>CT + RT</td>
</tr>
</tbody>
</table>

TEN, thymic epithelial neoplasms; TC, thymic carcinomas; F, female; M, male; LN, lymph node; CT, chemotherapy; RT, radiotherapy; E, excision; PE, partial excision; mo, month; yr, year; wd, with disease; wod, without disease; NA, not available.
In the English literature, we could find only 14 cases [5,7,12,14–22] younger than 18 years of age that were either single case reports or existed in case series (Table I). In some series of TEN, no age was mentioned for the reported cases [11], while in some other series containing adult and pediatric cases, no diagnostic differentiation was made between thymoma and carcinoma [9,10]. Therefore, the cases reported in those series could not be included in this review. Malignant thymoma cases were also excluded. Histopathologic definition was available in 12 of 14 cases. Only five of them were lymphoepithelioma-like carcinoma, like ours. The median age of cases was 13 years and there was a male predominance (M/F:9/5). As was the case in our patient, most of the cases in literature presented with an anterior mediastinal mass, and suffered from chest pain, cough, fever, weight loss, and respiratory distress. Radiologically, masses may be associated with pleural effusions and involvement of neighboring structures such as pleura and pericardium are frequently observed. Myasthenia gravis and other paraneoplastic syndromes are rarely associated with thymic carcinomas. Of the 14 cases reviewed, 1 had systemic lupus erythematosus [20], 1 had scleroderma [21], and 3 had hypertrophic osteoarthropathy [15,19,20].

Since thymic carcinomas occur rarely in children, experiences on treatment come from adult series. A multimodality approach that includes surgery, chemotherapy, and radiation therapy is suggested for treatment. Surgery is the mainstay of the treatment. However, complete resection is generally impossible or not feasible at diagnosis because of local invasion of important structures and metastasis. Radiotherapy improves the local control of the disease. Cisplatin based regimens have also proved to be effective in the treatment [3,9,13,14]. In cases similar to ours, neoadjuvant chemotherapy was proposed to improve the respectability of the mass [17,23]. The average survival time of thymic carcinomas in adult series was about 2.5 years [3,9,13,14]. Most of the pediatric cases reviewed, including ours, died due to progressive disease.

REFERENCES