Clinical case

Rhabdomyosarcoma arising in mediastinal teratoma in an adult man: a case report

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Received 12 February 2001; revised 18 April 2001; accepted 3 May 2001

We report a case of rhabdomyosarcoma which occurred in a mediastinal teratoma in a 44-year-old man. Presentation symptoms were chest pain, hoarseness and a cough. Diagnosis was fortuitous, performed by the histological and immunohistochemical study of a mediastinal tumour biopsy specimen that showed embryonal carcinoma and yolk sac tumour components associated with the rhabdomyosarcoma. After cisplatin-based chemotherapy (bleomycin–etoposide–cisplatin), surgical resection of the residual mediastinal tumour was performed. Histological and immunohistochemical study of this tumour confirmed the presence of mature teratoma and embryonal rhabdomyosarcoma. Evolution was marked by a local extension of the mediastinal tumour, occurrence of multiple metastases and bone marrow involvement. The patient died 8 months after diagnosis despite chemotherapy and radiotherapy. A review of the literature reveals that the development of rhabdomyosarcoma in primary mediastinal teratomas is unusual in adults. The diagnostic, therapeutic and prognostic implications of such an association are reviewed.

Key words: embryonal rhabdomyosarcoma, mediastinal germ-cell tumour, teratoma, yolk sac tumour

Germ-cell tumours are rare and generally occur in the testis and ovaries, as well as the mediastinum or retroperitoneum. Mediastinal germ-cell tumours in adult patients represent 2–5% of germ-cell tumours and only 1–10% of mediastinal tumours [1–3]. Germ-cell tumours are observed both in children below 7 years of age and in young adults from 15 to 35 years of age [4, 5]. They are more frequent in male patients. Primary mediastinal germ-cell tumours have the same histological pattern as their gonadal counterpart. One possible categorization of mediastinal germ-cell tumours is as follows.

1 Seminomas (less frequent than non-seminomatous tumours).
2 Non-seminomatous germ-cell tumours (NSCGT), which may have different pathological aspects—embryonal carcinoma or choriocarcinoma—which are frequently associated [2]. One of the most frequent and characteristic aspects is pure yolk sac tumour.
3 Mature teratoma.
4 Mixed NSCGT or mixed seminomas: the association of germ-cell tumours and non-germinal components, as has been described previously [6, 7].

Moreover, mediastinal germ-cell tumours are often associated with haematological malignancies that develop from yolk sac elements [8]. The prognosis of mediastinal germ-cell tumours is poor: only 30% of patients are cured [3].

We report on a case of mediastinal germ-cell tumour associated with embryonal rhabdomyosarcoma. Such an association is rare in adult patients.

Case report

Mr T.A. was a 44-year-old non-smoker who had no antecedent and, in particular, no prior cryptorchidy. He came to our department with intermittent chest pain, a cough and recent hoarseness. The clinical examination was not informative. Chest X-rays showed a mediastinum enlargement. Retrospective analysis of a chest X-ray performed 2 years earlier (because of chronic interscapular pain) showed the presence of a heterogeneous opacity of the superior and anterior compartment of the mediastinum, something that was missed at the time. The maximum transversal diameter was 5.4 cm and the mediastinum/thorax ratio was 25%. Flexible fibreoptic bronchoscopy did not show any abnormality. Serum α-fetoprotein (AFP) and human chorionic gonadotropin (hCG) levels were 491 IU/ml and <3 IU/l, respectively (normal values, less than 10 and 5, respectively). The computed tomography (CT) scans

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of the brain and abdomen were normal. Bone marrow aspiration did not show any abnormality. Tumour biopsy was performed by mediastinoscopy. The histological pattern was an association of embryonal carcinoma, yolk sac tumour and embryonal rhabdomyosarcoma. An immunohistochemical study showed a strong staining of anti-AFP antibodies in the yolk sac component and a positive reaction to anti-vimentine, anti-actine and anti-desmine antibodies in the rhabdomyosarcoma component. Clinical and ultrasonography examination of the testicles were normal. The diagnosis of NSCGT with embryonal rhabdomyosarcoma component was accepted at presentation.

The patient received three cycles of the standard BEP regimen of chemotherapy (30 mg bleomycin 1 day every week, 100 mg/m²/day etoposide and 20 mg/m²/day cisplatin from day 1 to day 5 every 3 weeks). He experienced a partial response on the CT scan with normalization of the serum AFP level after the first cycle of chemotherapy. The tolerance of chemotherapy was fair. After three cycles of chemotherapy, the patient had a surgical resection of the residual tumour that was adherent to the mediastinal vessels (right and left brachioencephalic vessels) and to the trachea. The resection was incomplete. The histological pattern was a mature teratoma with nervous and chondroid elements and presence of viable embryonal rhabdomyosarcoma.

It was decided to switch to a salvage chemotherapy regimen that aimed to treat the sarcomatous part of the tumour. The patient received alternating cycles of chemotherapy: carboplatin, epirubicin, vincristine (CEV), ifosfamide, vincristine, actinomycin (IVA) and ifosfamide, vincristine, etoposide (IVE). This treatment was poorly tolerated. The patient received three cycles but the tumour progressed in the mediastinum (occurrence of a vena cava syndrome) with pleural effusion and lung metastasis.

Radiotherapy to the mediastinum had a palliative effect on the local compression. The serum AFP level remained within normal limits. However, proof of progression of the embryonal rhabdomyosarcoma component was obtained by bone marrow aspiration, which was indicated by the occurrence of anaemia and thrombocytopenia. The patient died of disease progression and cranial haemorrhage 8 months after diagnosis.

**Discussion**

Mediastinal germ-cell tumours exhibit poor prognosis. Only 30% to 40% of patients are cured [2]. Moreover, long-term survivors may experience the occurrence of haematological malignancies with an incidence of 10% to 20% [8]. A more infrequent event was the development of a non-germinal malignant tumour within a germ-cell tumour [5]. This observation was first recognised in teratomatous elements after chemotherapy in testis cancer [6, 7]. This malignant transformation of teratomas was also described in mediastinal germ-cell tumours [9]. These malignant transformations are generally sarcomas and mostly rhabdomyosarcomas [10]. However, adenocarcinomas, neuroblastomas and other types of tumours have been observed [11]. The occurrence of both germ and non-germ-cell elements at diagnosis, before chemotherapy, has been described only in a few series or case reports [10, 11]. Our observation is a case of such an initial combination of two kinds of tumours.

Using cytogenetic arguments, the relationship between the germ-cell tumour and the embryonal rhabdomyosarcoma has been established. Germ-cell tumours have a common specific cytogenetic marker: the presence of the isochromosome [i(12p)] [12, 13]. This marker is also observed within the embryonal rhabdomyosarcoma component [14]. Moreover, the same chromosomal marker has been described in leukaemia associated with germ-cell tumours [14, 15]. It is derived from teratomatous elements of the germ-cell tumours. It also has been shown that haematopoetic stem cells may derive from yolk sac elements in mediastinal germ-cell tumours [16]. As malignant transformation of teratoma may occur both before and after chemotherapy, it seems very unlikely that chemotherapy might induce such a transformation. Conversely, it is probable that non-germ-cell elements derive from germlinal stem cells. The mechanism of action of this transformation is unknown.

Occurrence of the sarcomatous component in a mediastinal teratoma has no specific initial clinical feature. Teratomas that are likely to progress to such an outcome can not be differentiated from others on the basis of clinical or radiological criteria [6]. Diagnosis can be fortuitous at the time of histopathological examination of a tumour biopsy or after tumour resection or, more frequently, as a result of an unusual outcome with chemotherapy of a presumed non-teratomatous germ-cell tumour [3, 5].

Sarcomatous components of germ-cell tumours, especially rhabdomyosarcoma, have a proper metastatic potential and a poor prognosis, particularly in adults and if the primary site is mediastinal [11]. This prognosis can be influenced by many factors such as resectability of the tumour and histopathological subtype of the malignant component, its occurrence in a metastatic site and its sensitivity to chemotherapy [1, 6].

Embryonal rhabdomyosarcomas in adult patients are rare, mostly in the paratesticular area [10]. The prognosis is generally worse than that of their paediatric counterpart. Mediastinal rhabdomyosarcomas are most often resistant to chemotherapy. They have a poor prognosis, worse than their gonadal counterpart [10, 17], with a short survival of <2 years. Patients die mostly by regional involvement and multiple metastasis [5, 10]. At present, there is no standard schedule of chemotherapy in adult embryonal rhabdomyosarcoma and the paediatric protocols are often not effective in adults, and no chemotherapy is effective on both the germinal and non-germinal components. The most important prognostic factors in adult rhabdomyosarcomas are age, tumour size, extent of disease and complete resection [17]. The median survival in a population of 84 adult patients was 22 months, despite
aggressive multimodality management (associated chemotherapy and surgery).

It is noteworthy that in our case, as in others, the germ-cell component of the tumour was very chemosensitive. However, the embryonal rhabdomyosarcoma was refractory to a chemotherapy regimen which is generally considered as effective in this tumour type. A review of the literature [1, 5, 6, 10, 19–22] shown in Table 1 demonstrates that the prognosis of this disease is poor (only one out of 16 patients is cured). Of the 15 patients with mediastinal germ-cell tumours, reported by Gonzalez-Vela [19], four with sarcoma components died of disease, but six of 11 without sarcoma components lived. Experience proves that surgery is a very important part of treatment, and as is the case in active germ-cell residual tumours, complete surgical resection appears to be the most important prognostic factor of survival [23]. At present, little information concerning the disease’s behaviour and treatment modalities is available.

**Conclusion**

Rhabdomyosarcomas arising in primary mediastinal germ-cell tumours are rare in adults. Such tumours have special diagnostic and therapeutic features: they are resistant to chemotherapy and generally have poor prognosis. Because of the risk of occurrence of sarcomatous contingent in mediastinal germ-cell tumour and the lack of availability of an effective chemotherapy treatment, surgical resection of residual masses

**Table 1. Treatment and outcome of patients with mediastinal embryonal rhabdomyosarcoma reported in the literature**

<table>
<thead>
<tr>
<th>Authors</th>
<th>Initial pathological aspect of mediastinal GCT</th>
<th>Treatment</th>
<th>Pathological aspect after treatment</th>
<th>Complementary treatment</th>
<th>Course</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ulbright et al. [10]</td>
<td>S, ERMS, ML</td>
<td>Initial surgical excision then PVBA</td>
<td>ERMS</td>
<td>PVBA</td>
<td>Local progression, DOD at 8 months</td>
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<tr>
<td></td>
<td>IT, EC</td>
<td>Initial surgical excision then PVBA</td>
<td>IT, ERMS, CS, GBM</td>
<td>Multiple surgical resections and ACVc</td>
<td>Local progression survival &gt;33 months</td>
</tr>
<tr>
<td></td>
<td>IT, YST, ML</td>
<td>Initial surgical excision then PVBA</td>
<td>ERMS, ML, CP, AG</td>
<td>ACVc</td>
<td>Progression, DOD at 15 months</td>
</tr>
<tr>
<td>Ahmed et al. [6]</td>
<td>IT</td>
<td>PEB then surgical excision</td>
<td>ERMS, EC, CC</td>
<td>VAB-6</td>
<td>Progression, DOD at 12 months</td>
</tr>
<tr>
<td>Dulmet et al. [1]</td>
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<td>Surgical excision</td>
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<td>Motzer et al. [5]</td>
<td>IT, sarcoma</td>
<td>PEB then surgical excision</td>
<td>IT, ERMS, NHL</td>
<td>CAV</td>
<td>Progression with bone marrow involvement, DOD 8 months</td>
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<td>Gonzalez-Vela et al. [19]</td>
<td>IT, EC, ERMS</td>
<td>Cisplatin CT, then surgical excision</td>
<td>ERMS</td>
<td>Anthracyclin</td>
<td>DOD at 6 months</td>
</tr>
<tr>
<td></td>
<td>IT, ERMS, angiosarcoma</td>
<td>Cisplatin CT, then surgical excision</td>
<td>ERMS?</td>
<td>Cisplatin CT</td>
<td>DOD at 32 months</td>
</tr>
<tr>
<td></td>
<td>IT, S, EC, ERMS, angiosarcoma</td>
<td>Surgery then cisplatin CT</td>
<td>?</td>
<td>CT?</td>
<td>DOD at 9 months</td>
</tr>
<tr>
<td>Caballero et al. [20]</td>
<td>YST, T</td>
<td>Surgery then A, C, Vc, M, Ac</td>
<td>0</td>
<td>0</td>
<td>Alive after 7 years</td>
</tr>
<tr>
<td></td>
<td>YST</td>
<td>CAV, PE then surgical excision</td>
<td>ERMS</td>
<td>TRT</td>
<td>DOD 7 months</td>
</tr>
<tr>
<td>Rebishung et al. [21]</td>
<td>Four cases</td>
<td>Cisplatin CT then surgical excision</td>
<td>ERMS</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Fizazi et al. [22]</td>
<td>IT, ERMS</td>
<td>Cisplatin CT then surgical excision</td>
<td>ERMS</td>
<td>TRT, anthracyclin</td>
<td>Progression DOD 20 months</td>
</tr>
<tr>
<td>Present observation</td>
<td>EC, YST, ERMS</td>
<td>PEB than surgical resection</td>
<td>MT, ERMS</td>
<td>CEV, IVA, IVE, TRT</td>
<td>Progression DOD at 8 months</td>
</tr>
</tbody>
</table>

Abbreviations: GCT, germ-cell tumour; S, seminoma; ERMS, embryonal rhabdomyosarcoma; ML, myxoid liposarcoma; IT, immature teratoma; EC, embryonal carcinoma; CS, chondrosarcoma; GBM, glioblastoma multiform; YST, yolk sac tumour; CP, cystosarcoma polypoides; AG, atypical ganglioblastoma; CC, choriocarcinoma; NHL, non-Hodgkin’s lymphoma; PVBA, cisplatin–vinblastine–bleomycin; VAB-6, vinblastine–doxorubicin–bleomycin–cisplatin; PEB, cisplatin–etoposide–bleomycin; CAV, cyclophosphamide–doxorubicin– vincristine; CEV, carboplatin–epirubicin–vincristine; IVA, ifosfamide–vincristine–actinomycin; IVE, ifosfamide–vincristine–etoposide; PE, cisplatin–etoposide; A, doxorubicin; Ac, actinomycin; C, cyclophosphamide; M, methotrexate; Vc, vincristine; TRT, radiotherapy; DOD, death of disease.
should always be considered after first-line cisplatin-based chemotherapy in order to eradicate the chemotherapy-resistant germ-cell components.

References