



Thymic tumors in children, very rare tumors requiring international cooperation: extended abstract

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Introduction

Malignant chest tumors in children and adolescents include various histologic subtypes originating either from the chest wall (mainly bone or soft tissue sarcomas) or from the mediastinum. Primary pulmonary malignancies are very rare at pediatric age, including pleuro-pulmonary blastoma, bronchial mucoepidermoid carcinoma or myofibroblastic inflammatory tumor. In children, mediastinal primaries are more frequent arising from the posterior mediastinum (paravertebral compartment, mainly neuroblastic tumors, or less frequently soft tissue sarcomas, including malignant peripheral nerve sheath tumor MPNST), from the middle mediastinum (visceral compartments, mainly lymphomas) or from the anterior mediastinum (prevascular compartment, mainly lymphomas, less frequently germ cell tumors, and rarely epithelial tumors) (1,2).

Thymic tumors, like other anterior mediastinal masses, are characterized by local symptoms, such as shortness of breath, persistent cough, chest pain, swallowing difficulties, appetite and weight loss or superior vena cava syndrome. However, slow-growing low-grade tumors may also be depicted incidentally. Initial diagnostic approach usually begins with CT-scan or Chest MRI as well as serum markers assay (AFP, b-HCG and total HCG) to rule out secreting malignant germ cell tumors (3). Unless typical radiological presentation (mature teratomas, thymolipoma)

or other more accessible anatomical location (lymphomas), primary imaging-guided transthoracic biopsy (core needle or surgical biopsies) is required to set up the correct diagnosis. As in adults, pediatric thymic epithelial tumors (TETs) encompass a variety of histologic subtypes associated with different clinical outcomes: thymoma—type A (with an indolent clinical course), AB, B1, B2, B3 or thymic carcinoma (highly malignant).

Pediatric thymic characteristics

Pediatric and adolescent TETs are considered as very rare tumor with an annual incidence rate $\leq 0.1/1,000,000$ in European cancer registries (4). In the literature, less than 300 pediatric cases have been described. An analyze from the European Cooperative Study Group for Pediatric Rare Tumors (EXPeRT), gathering all pediatric TETs cases from 5 large countries in Europe (France, Germany, Italy, Poland and United Kingdom) treated between 2002 and 2012, described only 36 patients: 16 patients with thymoma (median age 11 years; range, 4–17 years) and 20 patients with thymic carcinoma (median age 14 years; range, 4.5–19 years) (5). Similarly, only 23 pediatric “malignant thymomas” were registered in the American Surveillance, Epidemiology and End Results (SEER) database between 1973 and 2008 (2).

In the EXPeRT experience, 2 out of the 16 pediatric thymomas (A to B2) were associated with myasthenia gravis at diagnosis. Histological subtype was: A (1 case), AB (2 cases), B1 (10 cases) and B2 (3 cases). Masaoka staging was: I (8 cases), IIB (6 cases) and IVB (2 cases). Initial surgery was performed in 12 children and 3 additional patients had delayed surgery. Chemotherapy was used in 3 patients and one received radiotherapy. After a median follow-up of 5 years (range, 1–12 years), 14/16 patients survived. Among the 20 patients with thymic carcinomas, only 5 survived despite multimodal therapy including surgery (12 cases, 3 missing data), chemotherapy (11 cases), and radiotherapy (12 cases). Among them, 4 children presented at diagnosis with autoimmune and paraneoplastic symptoms: myasthenia gravis, polymyositis, nephrotic syndrome, and systemic lupus erythematosus associated with a hypertrophic pulmonary osteoarthropathy (5). Chemotherapy regimens were mainly based on cisplatin, anthracyclines, or alkylating agents like cyclophosphamide or ifosfamide. When assessable, the overall response rate (complete + partial responses) to chemotherapy (13 regimens) was 69%. Among thymic carcinoma patients, the 5-year overall survival (OS) was 21.0%±10%.

Discussion and conclusions

Pediatric TETs mainly occur during the adolescence. The clinical presentation of tumors occurring during childhood and adolescence seems to have a comparable behavior than in adults (6). In young patients with TETs, autoimmune and paraneoplastic symptoms are present at diagnosis in 16% of all cases (5,7,8). Low-grade thymomas have a favorable outcome after complete tumor resection. A complete resection including the whole thymus, performed through classical median sternotomy, video-assisted techniques, or robotic approach, is the mainstay of treatment in TET (9,10). The literature highlights the importance of complete resection in thymoma in early stages as well as the need for neoadjuvant chemotherapy when an aggressive histologic subtype is demonstrated, especially in case of mediastinal lymph node dissemination (11). Pediatric thymic carcinomas are relatively chemosensitive to conventional drugs but are associated with an overall poor outcome despite multimodal strategy.

Due to the rarity of such diseases, the European EXPeRT group for very rare pediatric tumors launched harmonized recommendations within the PARTNER project into the European Reference Network on pediatric Cancer (ERN

PaedCan) (12). The main aim of the PARTNER project was to develop a common European registry for very rare tumors (VRT) in children in order to collect data and improve knowledge for all tumors associated with an overall incidence less than 2/1,000,000 (13). As part of this project, an international advisory desk with a virtual consultation system has been established to provide international expert advice. In addition, EXPeRT/PARTNER members included actions to improve patient care through consensus-based guidelines for each specific VRT entities. The published recommendations for pediatric TETs are mainly based on medical oncologists' experiences (14). They stressed the importance of an initial multidisciplinary discussion at diagnosis with adults' experts including surgeons and systematic expert pathologists review of the initial biopsy, as ITMIG members (International Thymic Malignancy Interest Group). Due to the rarity of this disease at pediatric age, all efforts should be made to allow including these young patients in prospective trials and stimulate data collection in national or international databases.

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Footnote

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