Pulmonary Blastomas of Childhood: Histologic, Immunohistochemical, Ultrastructural Aspects and Therapeutic Considerations

ABSTRACT Pulmonary blastomas are rare neoplasms typically occurring in patients of pediatric age, clinically characterized by fever, respiratory distress, and radiologic findings of a pulmonary cystic and/or solid mass with partial or complete obliteration of emithorax. Their behavior is aggressive and outcome is poor due to frequent relapses and metastases. The histological, immunohistochemical, and ultrastructural aspects of a personal series of 6 cases of pulmonary blastoma are described and the differences between childhood and adult types are stressed. Due to the aggressiveness of these rare tumors, therapeutic management is quite difficult. The expression of the transmembrane tyrosin kinase receptor c-kit in all the solid cases of this series leads the authors to hypothesize new possible therapeutic implications for these tumors.

KEYWORDS pleuropulmonary blastoma, therapeutic management, transmembrane tyrosin kinase receptor c-kit, ultrastructural pattern

Pulmonary blastomas are rare neoplasms whose histologic patterns are suggestive of recapitulation of early embryonic development of the lung. Childhood pulmonary blastomas were classified by Dehner as type I (purely cystic), type II (cystic and solid), and type III (purely solid) on the basis of their cystic versus solid composition [1]. On histological ground are purely mesenchymal lesions. The classic pulmonary blastoma of adulthood is quite different [2], and occurs generally as a peripheral lung nodule with a peculiar biphasic histologic pattern composed of epithelial glands and tubules embedded into an undifferentiated mesenchyma. Classic pulmonary blastoma is only rarely observed in pediatric age.

MATERIALS AND METHODS

Six cases of pulmonary blastoma were retrieved from the files of our department: 1 cystic Dehner type I, 1 solid and cystic type II, 3 purely solid
Dehner type III, and 1 classic biphasic type occurred in pediatric age. In all cases conventional histology, immunohistochemistry, and ultrastructure were reviewed. Immunohistochemical stainings, performed using the peroxidase–anti-peroxidase method, encompassed vimentin, muscle-specific actin, desmin, alpha-fetoprotein, alpha-1-antichymotrypsin, S-100 protein, MNF116 cytokeratin, EMA, NSE (Dako), and surfactant protein B Ab1(Neomarkers). Additional immunohistochemistry was performed on formalin-fixed, paraffin-embedded tissue using peroxidase antiperoxidase method with primary antibody for c-kit: CD117(Dako).

RESULTS

A summary of the clinical data is shown in Table 1. The resected tumors ranged from cystic to completely solid masses measuring from 3 to 10 cm in greatest diameter. On cut section the cystic type was characterized by a bland multicystic appearance strictly similar to congenital cystic adenomatoid malformation of the lung. The solid types (Dehner type III) and the solid component of Dehner type II tumors appeared as large masses surrounded by an incomplete capsule, in continuity with visceral pleura in 2 cases, parietal pleura and thoracic wall in 2 cases. On cut section, they appeared as white-gray solid proliferative masses with glistening areas and extensive haemorrhage and necrosis. The biphasic type was a solid, grayish white, homogeneous, well-demarcated nodule in the peripheral area of the excised lobe.

Histology and Immunohistochemistry

On light microscopy, the cysts of cystic blastoma Dehner type I were lined by benign-looking epithelial cell (Figure 1) and showed a distinct subepithelial “cambium layer” of rhabdomyoblastic appearing cells (Figure 2). The intense positivity for desmin of these cells confirmed their rhabdomyoblastic nature.

On light microscopy, solid blastomas showed a complex pattern, with blastematous, mesenchymal spindle cell, rhabdomyoblastic and cartilaginous features (Figure 3). The blastematous cells were closely packed small cells with hyperchromatic nuclei and scant cytoplasm. The mesenchymal cells were spindle shaped and arranged in interlacing bundles. In all the tumors scattered cells with rhabdomyoblastic features and islands of cartilage were observed. On immunohistochemistry, mesenchymal cells were immunoreactive for vimentin, while blastemal cells were vimentin negative and showed variable actin and desmin positivity; rhabdomyoblastic cells reacted intensively for desmin and cartilaginous cells for S-100 protein. Furthermore, the antibody for CD117 revealed diffuse positivity on mesenchymal cells (Figure 4).

On light microscopy of biphasic pulmonary blastoma of adult type, glands and branching tubules lined by epithelial cells in a primitive, quite uniform, mesenchymal stroma of spindle cells were observed (Figure 5). The epithelial cells lining the glands were columnar or cuboidal in shape, with clear cytoplasm and uniformly rounded nuclei. The mesenchymal cells were spindle shaped, with elongated nuclei and slightly eosinophilic cytoplasm.

The epithelial cells showed positivity for cytokeratin and surfactant apoprotein B (Figure 6). A bland expression of NSE was also present, consistent with formation of neurosecretory granules, as observed at pseudoglandular stage of fetal lung development. The mesenchymal cells were slightly actin positive.

### TABLE 1 Profile of Patients

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<td>Met.</td>
<td>DFS (4 mo)</td>
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FIGURE 1  Cystic (Dehner type I) blastoma. The lining of the cysts is composed of mono- or bilayered cuboidal epithelium, with scattered mucin-containing cells. H-E, ×5.

FIGURE 2  Cystic (Dehner type I) blastoma. Under the cyst’s epithelial lining there is a distinct cambium layer composed by large cells with eosinophilic cytoplasm, resembling rhabdomyoblasts. H-E, ×40.
FIGURE 3  Solid (type III) blastoma. Interlacing fascicles of spindle cells associated with nests of closely packed blastematous cells, islands of cartilage and scattered rhabdomyoblasts. H-E, ×25.

FIGURE 4  Solid (Dehner type III) blastoma. Strong positive staining for CD117 of mesenchymal spindle cell component. Immunostaining for CD117, ×50.

FIGURE 6  Biphasic pulmonary blastoma. The epithelial cell lining the glands and tubules are marked by surfactant protein B. Immunohistochemical stain for surfactant protein B, ×25.
Electron Microscopy

On electron microscopy, the cystic type I tumor, under the benign-appearing single layer of columnar epithelial cells, showed “cambium layer” cells characterized by parallel thick and thin filaments and Z band-like material that confirmed their rhabdomyoblastic nature (Figure 7). In the solid type, small round cells showing poorly developed cytoplasm with free-lying ribosomes, rough endoplasmic reticulum and few mitochondria were observed. Nuclei had smooth profiles with some indentations and prominent nucleoli. Primitive cell junctions were evident (Figure 8). Rhabdomyoblasts and randomly scattered cells with myofibroblastic features were also present. In biphasic pulmonary blastoma epithelial cells lining the glands were surrounded by a basal lamina, connected by apical junctional complexes, with microvilli on their luminal surface (Figure 9). The cytoplasm contained sparse organelles, glycogen, and lamellar inclusion bodies typical of type II pneumocytes (Figure 10). The mesenchymal cells were covered by flocculent material and contained microfilaments with focal densities, suggestive of myofibroblastic differentiation (Figure 11).

DISCUSSION

Pulmonary blastomas are rare tumors of pediatric age that are characterized by aggressive behavior. Barnard first described these neoplasms in 1952 and called them “pulmonary embryomas” due to their resemblance to fetal lung tissue [3]. In 1961

FIGURE 7  Cystic (Dehner type I) blastoma. Ultrastructural aspect of cells in the cambium layer: thick and thin cytoplasmic filaments and Z-band like material typical of rhabdomyoblasts. Uranyl acetate and lead citrate stain, ×8000.
Spencer coined the term “pulmonary blastoma,” suggesting an origin from mesodermal blastema, in analogy to nephroblastoma [4]. The unusual and polymorphic features of these tumors often led to confusion with benign entities such as congenital adenomatoid cystic malformation of lung or other neoplastic entities such as rhabdomyosarcoma [5]. However, there are quite strict similarities between pleuropulmonary blastoma and rhabdomyosarcoma, so a common origin from the same undifferentiated mesenchymal cell can easily be supposed. Pleuropulmonary blastomas, classified by Dehner in 3 types, most frequently occur in pediatric age [6–9], while the classic biphasic pulmonary blastoma typically occurs in adulthood and only occasionally is described in childhood [10].

The main treatment of these tumors is surgical resection, often in association with chemotherapy.
and radiotherapy, but recurrences and metastases are frequently reported, especially in the solid Dehner type III lesions, which are associated with the worst prognosis. Furthermore, the rarity of pleuropulmonary blastoma represents undoubtly a serious obstacle to the identification of a most active therapeutic scheme [11].

The transmembrane tyrosinkinase receptor c-kit (CD117) is expressed in various normal tissues and in some tumors such as gastrointestinal stromal tumor, acute myeloid leukemia, small cell lung carcinoma, renal tumors [12], and also in pediatric tumors as neuroblastoma, synovial sarcoma, and Ewing sarcoma [13]. Several clinical trials have demonstrated the efficacy of a potent inhibitor of tyrosin kinases (Gleevec) for treatment of these tumors [14].

We evaluated c-kit expression by means of immunohistochemistry in our cases of pulmonary blastoma. Three of 6 cases (the solid Dehner type III cases) revealed strong cytoplasmic staining of mesenchymal component. Although these findings need further confirmation on a more numerous series, we hypothize a possible therapeutic role of tyrosinkinase inhibitors for such aggressive tumors.
REFERENCES


