Pleuropulmonary blastoma: a differential diagnosis of chronic cough. Long-term survival after multimodal aggressive therapy

Blastoma pleuro-polmonare: rara diagnosi differenziale da tosse cronica. Remissione a lungo termine dopo aggressiva terapia multimodale

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Summary

Pleuropulmonary blastoma (PPB) in childhood is a rare clinicopathologic entity distinct from adult pneumoblastoma. This tumour may originate from the lung, the pleura, or the mediastinum; it can metastasize and is usually associated with a poor outcome. We report the case of a 5-year-old boy who developed PPB manifesting with respiratory distress. At the standard x-ray and magnetic resonance imaging of the chest there was opacity covering the entire right lung. The histological and immunohistological tests led to the diagnosis of blastematous, malignant mesenchymatous PPB with pluridirectional differentiation. Treatment consisted of preoperative chemotherapy to reduce tumour volume, complete surgical resection of the residual tumour mass, and post-surgical chemotherapy. Following this approach, the child is alive in continuous complete remission 9 years after diagnosis.

Riassunto

Il Blastoma Pleuro-Polmonare (BPP) infantile è un’entità clinico patologica ben distinta dal Pneumoblastoma dell’adulto. Questo tumore può prendere origine dal polmone, dalla pleura o dal mediastino; può metastatizzare e ha spesso una prognosi infausta. Ripor­tiamo il caso di un bambino di 5 anni, in cui il BPP si manifestò con un distress respiratorio; la radiografia del torace e la Risonanza Magnetica hanno evidenziato una grossa massa che occupava l'emitorace destro. L’esame istopatologico ha permesso di porre la diagnosi di BPP. Il paziente è stato trattato con chemioterapia, che ha ridotto il volume della massa, con asportazione del tumore e chemioterapia post-operatoria; tale tratta­mento ha consentito l’eradicazione della malattia; il paziente è in remissione completa continua a 9 anni dalla diagnosi.

Introduction

Pleuropulmonary blastoma (PPB) is an extremely rare and aggressive malignancy of childhood. It was originally described as a distinct entity by Manivel et al. Prior to its identification it was reported in the early literature by Spencer as pulmonary blastoma or embryonic sarcoma. It is characterized by primitive mesenchymal tissue and epithelial tubular structures resembling the foetal lung. The eponymous PPB defines the paediatric variety of pulmonary blastoma. In PPB, the dysembryonic neoplasm shows blastematous and sarcomatous components and a lack of carcinomatous components (which are instead present in adult pulmonary blastoma), sometimes on previous dysplastic pulmonary conditions. PPB is classified in 3 subtypes: type I (cystic), type II (mixed solid and cystic) and type III (solid).
The predominant clinical features are cough, tachypnea, fever, respiratory distress; secondary pneumothorax and chest pain have also been reported. Since these features are not specific, an infectious disease is often erroneously diagnosed; hence, when eventually detected, the neoplasm is often very large, may even involve an entire hemithorax, and present metastases. Despite the different therapeutic procedures—surgery, chemotherapy and radiotherapy—prognosis is often poor: Indolfi et al. report 42% and Priest et al. 45% of event free survival (EFS) at 2 years. Poor prognostic factors are histological subtype II or III, a maximum diameter greater than 5 cm, failure to completely remove the mass, extrapulmonary effusion such as pleura or pericardium, metastases.

We report the case of a five-year-old child who, despite the large tumour size at diagnosis and histological subtype II, after a treatment with chemotherapy before and after surgery, is in continuous complete remission (CCR) nine years after the diagnosis.

Case report

A 5-year-old boy was admitted to our ward for hypoxia, cough, shortness of breath, progressive thinning and pallor in the previous 2 months. The physical examination showed poor clinical conditions, tachypnea (R.F. 45/min.), hypophonesis and reduction of the physiologic vesicular murmur of the middle and lower regions of the right lung, meteoric abdomen with the liver margin 5 cm below the right costal margin.

The results of the laboratory investigations were Hb 8.5 g/dl, white blood cells 18.800/µl (N 68%, L 22%, M 6%, E 4%), platelets 611.000/µl, VES (K.I.) 65, CRP 292 ng/dl, LDH 1261 u/l, ferritin 2.4 mg/dl; serum levels of copper 168 µg/dl, ferritin 6%, E 4%), platelets 611.000/µl, VES (K.I.) 65, CRP 292 ng/dl, LDH 1261 u/l, α-FP 6.3 u/l.

Chest radiographs showed a bulky mass in the right hemithorax displacing the mediastinum leftward and the liver downward (Fig. 1).

The thoracic-abdominal ultrasound scan showed a poorly confined voluminous mass, having diameters of 120 x 86 mm, with echogenic-hyperechogenic structure and some hypo-anechogenic areas, arising in right hemithorax and displacing the liver and right kidney downwards.

A magnetic resonance imaging (MRI) of the thorax showed a mass involving entirely the right hemithorax, with a central hemorrhagic component that displaced the mediastinum and the heart to the left.

The patient underwent surgical thoracotomy, which revealed an unencapsulated mass with smooth surface and tense-elastic consistency, entirely covered by pleura, not adherent to the thoracic wall; since the conspicuous extension of the mass did not allow resection, only a biopsy was performed.

Microscopically, the biopsy specimen showed a predominantly solid neoplasm with focal cysts. The tumour contained mesenchymal elongated cells arranged in sheets, and more primitive blastematous foci. There was no evidence of typical rhabdomyoblasts or cartilage. Cysts exhibited an epithelial lining, with flattened to columnar cells and an underlying layer of primitive mesenchymal cells. The morphologic appearance was consistent with a diagnosis of PPB type II. Immunostains emphasized the double component with a positive staining for cytokeratin (MNF116, pancytokeratin) in the epithelial component and a positive vimentin staining in mesenchymal component. Occasional spindle cells were positive for desmin; α-fetoprotein, S-100 protein, CD99, NB84A were negative in both the epithelial and the stromal component.

In order to stage the disease the patient underwent total body bone scan with 99mTc-MDP, brain and abdominal CT scan, and bone marrow aspirate; no metastatic spread was detected, and a stage III was defined.

The child underwent chemotherapy with carboplatinum (CBP) 400 mg/m² + etoposide (VP16) 150 mg/m² days 1, 2; vincristine (VCR) 1.5 mg/m² + actinomycin-D (ACT-D) 1.5 mg/m² day 21 + ifosfamide (IFO) 1500 mg/m² days 21-23, for overall 3 cycles; thereafter, 2 cycles were scheduled, including VCR 1.5 mg/m² + ACT-D 1.5 mg/m² day 1, doxorubicin 40 mg/m² days 1-2 and IFO 1500 mg/m² days 1-3. The number of cycles were established according to the features of imaging studies.

A chest x-ray survey showed a very good response (Fig. 2) to chemotherapy. Six months after the diagnosis complete resection of the tumour was performed through a right posterior-lateral thoracotomy by the fifth intercostal space. The tumour was capsulated and located between the upper and middle lobe of the right lung, displacing caudally the middle and lower pulmonary lobes. The central zone of the mass was composed of hyalinized fibrous stroma nodules and very small fragments of blastomatous tumoral tissue, at about 2 cm from the resection borders. The neoplasm was almost entirely necrotic.

Fig. 1. Posterior-anterior chest radiograph at presentation, showing a bulky mass, displacing the mediastinum.
After surgery the patient underwent 2 more cycles of chemotherapy with CBP 400 mg/m² + VP16 150 mg/m²/day x 2 days.

There was clinical and imaging evidence of a progressive normalisation of lung morphology and function. The patient was monitored with clinical and radiological investigations according to the following schedule: chest radiograms every 3 months the first year, every 6 months the second and third year, every 12 months for the 4th, 5th and 6th year; MRI at 1 and 3 years after withdrawal of therapy.

Nine years after the diagnosis, the child is in continuous complete remission.

Discussion

PPB in childhood is very rare. Our patient, as most of those reported in the literature, presented unspecific respiratory symptoms; the x-ray revealed a large intrathoracic mass, suggesting the need for further imaging studies. It is important to emphasize the role of an early imaging examination (x-ray, ultrasound scan, CT or MRI) to detect as soon as possible the mass, in order to proceed to more specific investigations to elucidate the nature and staging of this malignant tumour. Radiographic findings of pleuropulmonary blastoma are not specific, especially when most of the neoplasm is cystic, resembling the radiographic features of teratoma. In this respect we note that PPB may initially manifest with clinical and radiologic signs and symptoms of pneumothorax and may arise from other dysplastic conditions; as a matter of fact, cystic pulmonary adenomatoid malformation (CPAM) can be associated with PPB, which is also described in association with some congenital dysplasms as cystic nephroma. The clinical and radiological presentation in our patient showed mediastinal involvement; the mass was not excisable at the first surgical look because the neoplasm involved the pleura and was very large. The histopathologic diagnosis was consistent with type II PPB.

The features described usually correlate with a poor prognosis. The patient was submitted to intensive multiagent neoadjuvant chemotherapy, which reduced the tumour mass, making complete surgical resection feasible, and allowing eradication of the malignancy.

Such intensive multiagent chemotherapy is in most cases necessary for the reduction and complete excision of the tumor, which represents the most favourable factor for long term survival.

In a recent report describing 11 patients, two underwent total excision of the tumour at diagnosis, and were both alive without disease at 23 and 132 months respectively, with no adjuvant chemotherapy administered in the latter; another 3 patients remained disease free, two after macroscopic total resection and polychemotherapy and one after polychemotherapy and delayed complete surgery.

The effectiveness of chemotherapy has also been reported by other Authors. The choice of the antistatic agents used in our patients was due to their known effectiveness on mesenchymal and epithelial tumors. Our patient was not treated with radiotherapy, which has proven to be effective in few patients.

In conclusion, this case suggests that PPB may be taken in consideration for the differential diagnosis in respiratory distress. According to our experience and to other literature reports, total remission of this condition may be achieved with complete surgical excision (primary or delayed) and intensive chemotherapy.

References

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