Pediatric Pleural Mesothelioma

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27.1 Introduction

Malignant mesothelioma is an aggressive tumor that originates from the lining cells (mesothelium) that cover the serosal surfaces of the pleural and peritoneal cavities, or more rarely the tunica vaginalis testis and the pericardium (Moore et al. 2008). Based on the stage of the disease at the time of diagnosis, mesothelioma may present as discrete multifocal nodules or as a diffuse confluent mass encasing the adjacent organs and/or obliterating the serosal cavity from which the tumor has originated.

Although before the 1950s, the existence of adults mesothelioma was questioned by many pathologists (Moore et al. 2008), the increase in the incidence of mesothelioma, ensuing to the growing use of asbestos, definitely led to the acknowledgment of mesothelioma as a genuine clinicopathologic entity (Margery and Ruffié 2008). In children, because this is an even rarer tumor, its existence has long been debated and consequently its management neglected. Furthermore, because of the rarity of mesothelioma and the consequent difficulty in its diagnosis, a significant proportion of cases that have been diagnosed initially as pediatric mesothelioma were found to represent other entities upon a subsequent second pathological analysis (Fraire et al. 1988). Nevertheless, recent small series have been published using state-of-the-art adults diagnosis criteria (Moran et al. 2008). These recent studies have established the existence of pediatric mesothelioma and highlighted the lack of optimal strategy.

We will focus here on pleural mesothelioma and exclude peritoneal mesothelioma (see specific. Chap 43) as well as mesothelioma of the tunica vaginalis and

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Table 27.1 Key points to manage a child with pleural mesothelioma

Physical examination	Signs and symptoms (cough, dyspnea, fatigue, pallor, weight loss) Anamnesis: asbestosis exposure
Laboratory assessment	None specific
Radiological assessment	
- first assessment **- local staging**	Abdominal Computed Tomography (CT) scan
- diagnostic work-up	Chest and abdominal CT scan, Positron Emission Tomography (PET) MRI Cardiac echography
Pathological assessment	Surgical biopsy required Always need adult's pathologist experienced with mesothelioma To get confirmation of the diagnosis of malignant mesothelioma and subtype Application of an appropriate panel of immunochemical stains
Staging systems for risk-adapted treatment strategy	None validated
General treatment guidelines	Need for multidisciplinary approach Seek for national or European group for rare tumors advice Seek advice from centre with expert physician dedicated to the management of this cancer in adults
Surgery	Consider complete resection when it can be easily removable
Radiotherapy	Can be considered as part of multimodal therapy
Chemotherapy	First line : premetrexed-cisplatinum Second line or alternative : gemcitabine-pemetrexed Consider treatment with novel agents validated in adults

pericardial mesothelioma. The main challenge for pediatric oncologists remains to choose the optimal therapeutic strategy for a given patient. These options range from upfront palliative care to aggressive multimodal treatments. Meanwhile, we must increase our knowledge about this disease to codify its management (Table 27.1).

27.2 Epidemiology

In adults, it is estimated that mesothelioma represents less than 0.5% of all cancers. Among malignant mesothelioma, pleural mesothelioma is the most common localization (Fig. 27.1). In children, pleural mesothelioma is an extremely rare disease and no precise incidence of this disease is available. Our knowledge relies mostly on isolated case reports and rare small series. Of note, the first pediatric series was published in 1964 by Kauffman and Stout who reported five cases of both peritoneal and pleural mesothelioma (Kauffman and Stout 1964). Based on results of autopsies, pediatric mesothelioma would represent 2–5% of all mesothelioma cases, and according to epidemiologic studies would represent 0.5–1.0 case/10 millions/year (Kashanskiy and André 2010). We previously reviewed and reported epidemiologic data of 489 cases of pediatric mesothelioma; pleural mesothelioma represented approximately 60% of the cases, in line with other less extensive reviews of the literature (Fraire et al. 1988; Anderson et al. 1985).

As in adults, there is a higher frequency of pleural mesothelioma in boys (Kauffman and Stout 1964; Kashanskiy and André 2010; Brenner et al. 1981), with a sex ratio of 1.3: 1 (Kashanskiy and André 2010). The mean age at presentation was 13.0 ± 0.3 years, with no difference between sexes (Kashanskiy and André 2010).

There is a strong relationship between exposure to asbestos and the subsequent development of pleural mesothelioma in adults (Moore et al. 2008). Nevertheless, in our experience, there was no such association in children. Indeed, we found only five cases with a known previous exposure to asbestos among the 110 pediatric pleural mesothelioma cases for which the exposure to asbestos was well documented (Kashanskiy and André 2010). In line with this observation, the reported pediatric cases with a prior exposure to asbestos are anecdotal. Moreover, in many countries in which the exposure to asbestos is high because of the presence of mines like in

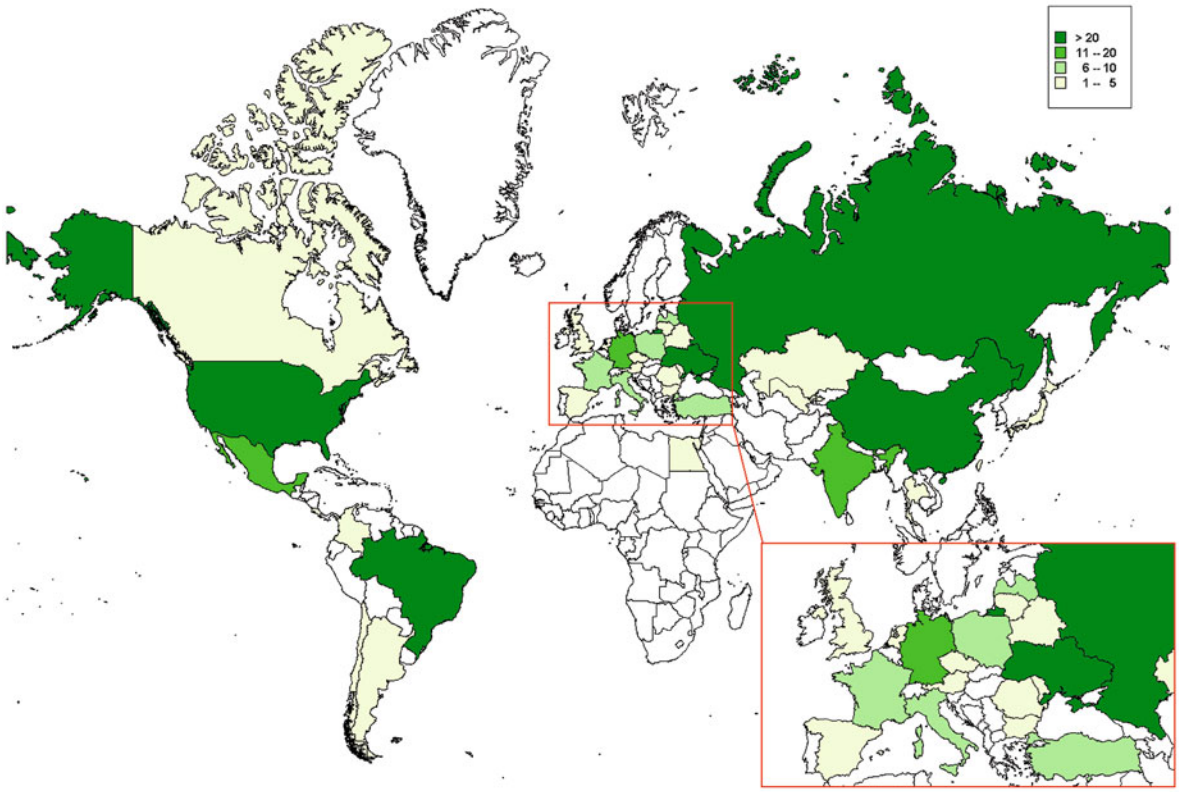

Fig. 27.1 Geographical distribution of published cases of pediatric pleural mesothelioma

Australia, Finland, or the South African Republic, no cases have been reported. Lastly, it is generally accepted that it takes approximately 20–30 years after asbestos exposure to develop a mesothelioma so that it seems very unlikely that asbestosis is implicated in the genesis of mesothelioma in children. Thus, most pediatric mesotheliomas might belong to the so-called idiopathic forms of mesothelioma, which can also occur in adults with an estimated incidence of 1/million (Moore et al. 2008).

Besides asbestos exposure, other predisposing factors have been implicated in the pathogenesis of mesothelioma in children; for instance, irradiation or genetic syndromes. These suggestions rely on reported cases of pleural mesothelioma occurring after irradiation (Anderson et al. 1985; André et al. 2009; Falchero et al. 1996), as secondary malignancies especially after a Wilms' tumor or Hodgkin's disease (Anderson et al. 1985; André et al. 2009; Falchero et al. 1996; Antman et al. 1984), or in children with Proteus syndrome (Gordon et al. 1995; Malamitsi-Puchner et al. 1990). These cases suggest that in some patients, a non-identified underlying genetic background may contribute to the occurrence of a mesothelioma. Mutation of WT1 has been reported in sporadic cases of mesothelioma (Park et al. 1993) and is also frequent in patients with Wilms' tumor (Haber and Buckler 1992). However, the role of this gene in the genesis and progression of the tumor is not clear (Park et al. 1993). Some familial cases of mesothelioma have been reported with a deletion of the short arm of chromosome 9 that carries the CDKN2A gene. This gene encodes for $p16^{INK4a}$ and $p14^{ARF}$. The inactivation of $p16^{INK4a}$ has been frequently reported in mesothelioma (You et al. 2007; Ugolini et al. 2008). Nevertheless, no children have been reported to be affected in these familial series.

27.3 Clinical Presentation

Typical presenting features of children with pleural mesothelioma are chest pain, dyspnoea, or both in most of the cases (Fraire et al. 1988; Kauffman and Stout 1964; Brenner et al. 1981; André et al. 2009).

These symptoms develop usually quickly in a previously nonsymptomatic child. Fever is sometimes an associated symptom. Additionally, patients may very rarely present with breathlessness secondary to a pleural effusion without chest pain. A chest wall mass, weight loss, and abdominal pain and ascites due to peritoneal involvement are also common presentations. Indeed in the SFCE series, involvement of multiple serosal cavities was seen in one third of the patients (André et al. 2009)

27.4 Radiological Presentation

Radiological imaging is critical for both the diagnosis and staging and in turn the management of mesothelioma.

27.4.1 CT

Intravenous contrast-enhanced CT is the primary imaging modality for suspected pleural malignant disease, where it can help distinguishing malignant from benign pleural disease. The most helpful CT findings suggesting a malignant pleural disease in adults are: (1) a circumferential pleural rind, (2) nodular pleural thickening, (3) diffuse pleural thickening, and (4) mediastinal pleural involvement. While these features have a high positive predictive value, absence of these signs does not reliably exclude the diagnosis of pleural malignancy (Moore et al. 2008; Wang et al. 2004)

27.4.2 MRI

In adults, MRI is not used routinely to assess malignant mesothelioma. However, it can be a valuable tool to confirm the potential surgical resectability. More specifically, using gadolinium enhancement, MRI can improve the identification of tumor extension into the diaphragm or chest wall, allowing better assessment of the individual for surgical treatment (Moore et al. 2008; Wang et al. 2004).

27.4.3 PET Scan

PET scan has been reported to have a 97% sensitivity and a 88% specificity to distinguish benign from malignant pleural disease in adults (Moore et al. 2008). Additionally, PET scanning has also increased the accuracy to diagnose mediastinal nodal metastases so that overall PET scan is useful in the staging and preoperative evaluation of mesothelioma (Moore et al. 2008; Wang et al. 2004). PET scan may also help to identify the optimal site for CT-guided pleural biopsy. Lastly, changes in the fluorodeoxyglucose (FDG) uptake within the tumor might indicate response to treatment, suggesting its role to assess the response to chemotherapy. Nevertheless, the value of PET scan to adequately stage the disease remains controversial and its use in routine is not yet recommended in adults (Pilling and Dartnell 2010; Scherpereel et al. 2010). In children, very little is known regarding the use of PET scanning, but in one case, decrease in size and uptake of FDG by a mesothelioma was documented during a treatment with pemetrexed and cisplatinum (Milano et al. 2006).

27.5 Pathology

The pathological diagnosis of mesothelioma is acknowledged as difficult. As for adults, pathologic analysis should be performed on representative biopsy specimen obtained by surgery. Given the histological heterogeneity of mesothelioma and the fact that it may mimic a variety of epithelial and mesenchymal neoplasms, needle biopsies are commonly of limited value as diagnostic tool. It is generally recommended that all cases be confirmed by a panel of pathologists including one with experience in adults mesothelioma. According to the WHO classification, malignant mesothelioma can be classified into epithelioid, sarcomatoid, or mixed (biphasic) subtypes based on tissue obtained by biopsy. The majority (almost 60%) of pediatric pleural mesotheliomas are of the epithelial subtype (Kashanskiy and André 2010).

On scanning magnification, the tumor classically displays sheets of medium-sized or large epithelioid cells with distinct cell borders arranged into well-developed tubulo-papillary structures, commonly with intermixed solid areas and occasional adenomatoid pattern. At higher magnification, tumor cells have a bland cytological appearance, being polygonal in shape, with moderate amount of pale eosinophilic cytoplasm, round nuclei, and inconspicuous nucleoli (Fig. 27.2). Usually, only rare mitotic figures can be

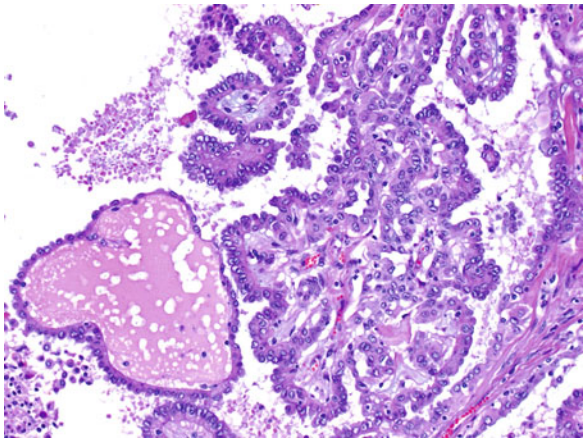

Fig. 27.2 Typical tubulopapillary pattern of mesothelioma with relatively bland-looking cuboidal cells (H&E stain, original magnification ×200)

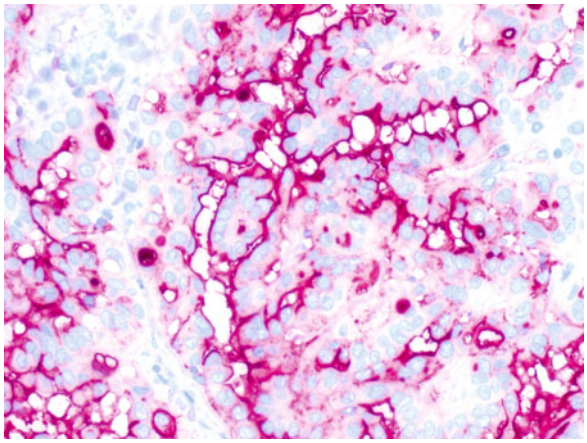

Fig. 27.3 HBME-1 showed characteristic apical (luminal) membranous staining in msothelioma cells

identified (<1/mm^2). In some areas, the epithelioid cells form gland-like structures and communicating cords set within abundant mucinous or myxoid stroma (Moran et al. 2008; Brenner et al. 1981; Anderson et al. 1985). The tubules occasionally contain a wispy bluish secretion that stains positive with alcian blue and disappears after predigestion with hyaluronidase. In contrast to adenocarcinoma, true PAS-positive mucin is usually absent in mesothelioma.

Traditionally, a panel of positive and negative immunohistochemical markers is recommended to reliably diagnose mesothelioma. The tumor cells commonly express mesothelin, HBME-1 (Fig. 27.3) cytokeratin (CK) 5/6, calretinin, D2–40 (podoplanin), and vimentin. The low-molecular-weight CK (CAM5.2) is helpful in identifying less well-differentiated tumors that have lost other differentiation markers. More recently, Wilms' tumor-1 antigen (WT1) proved of value as a further marker. However, given the fair expression of this marker by serous carcinomas of the female genital tract, careful interpretation in the appropriate context is necessary. Markers that are usually absent in mesothelioma but are variable expression in carcinomas include Ber-EP4, carcinoembryonic antigen (CEA), and thyroid transcription factor 1 (TTF-1).

27.6 Treatment

In adults, no standard optimal treatment strategy is currently available owing to the rarity of this tumor and the limited efficacy of treatments. Recent data and guidelines in adults suggest that multimodal (extrapleural pneumectomy–neoadjuvant/adjuvant chemotherapy and radical hemithorax irradiation) should be proposed to patients when possible (Scherpereel et al. 2010) and within prospective randomized trials. Nothing is known about this global strategy in children; the aggressive surgery and its related mortality and morbidity, as well as radiotherapy associated side effects should make one highly cautious about using this strategy in children.

27.6.1 Surgery

Surgery aiming at removal of all malignant tissue is only very rarely associated with persistent durable complete remission as the disease usually has spread, at least microscopically, within the pleural cavity. Some examples can be found in pediatric literature (Flores et al. 2006). Therefore, we advocate for complete surgery only in cases of easily removable tumor. Besides, pleurectomy/decortication can be proposed but without curative intent and considered in patients to help obtaining symptom control.

27.6.2 Chemotherapy

While the combination of pemetrexed–cisplatinum is a standard first-line chemotherapy in adults with pleural mesothelioma (Vogelzang et al. 2003), there is currently no such standard chemotherapy regimen for pleural

mesothelioma in children. Anyhow, these new molecules (pemetrexed, gemcitabine) indeed seem to bring clinical benefit for children with mesothelioma (Antman et al. 1984; Ugolini et al. 2008; Milano et al. 2006). Recent studies have shown molecular alterations (mutations) involving the EGFR signalling pathway in about one third of adults mesothelioma. These findings might bring a new hope by targeting these molecular pathways in analogy to the current treatment regimens for EGFR-mutated non-small-cell lung cancer, but this remains an issue of future studies.

27.6.3 Radiotherapy

Radiotherapy has not been demonstrated to be an effective treatment in mesothelioma in adults (Scherpereel et al. 2010), and its use is mostly restricted to try to control disease for patients receiving palliative care. As mentioned above, in adults radical hemithorax radiotherapy has been proposed within a multimodal strategy (Scherpereel et al. 2010).

27.6.4 Outcome

Historically, the prognosis of pleural mesothelioma in children had been reported to be extremely poor. Thus, Grundy and Miller reported that death occurred within 6 months in 8 out of 12 patients with pleural mesothelioma, with the longest survival being 24 months (Grundy and Miller 1972). A more recent review only partially confirmed these findings. Indeed, the authors also reported long-term survival in two children (66 and 84 months), among whom one was treated with standard MTD chemotherapy (Brenner et al. 1981). Interestingly, Mutafoglu-Uysal et al. reported a case of relapsing malignant pleural mesothelioma that responded to the combination of VAC–ICE chemotherapy and who was alive without evidence of disease 36 months after discontinuation of the treatment (Mutafoğlu-Uysal K et al. 2002). Additional cases responding to MTD chemotherapy have been reported (Kung et al. 1995). Thus, although, we should be ready to face rapid progression and refractory disease, in some cases pediatric pleural mesothelioma can respond to chemotherapy and be long-term survivors. Biologic and/or genetic differences underlying this difference of behavior must be unveiled.

27.7 Conclusion

Mesothelioma is a very rare tumor in pediatric oncology. Pediatric mesothelioma seems to be different from its adults counterpart, with less frequent primary pleural localization. Although the outcome of children with peritoneal mesothelioma is good despite frequent relapses, the outcome of pediatric pleural mesothelioma is dismal. This is in line with data obtained from adults. New therapeutic strategies need to be properly evaluated in children within international studies, and an international registry is mandatory to increase our knowledge of this disease.

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