Primary Epithelial Malignant Mesothelioma of the Pericardium With Deciduoid Features:

Cytohistologic and Immunohistochemical Study

Jorge S. Reis-Filho,[1] Leonora Z.B. Pope,[2] Fernanda Milanezi,[1] Cynthia M.S.R. Balderrama,[3] Maria José Serapião,[2] and Fernando C. Schmitt[1,4*]

Malignant mesothelioma with deciduoid features (MMWDF) is a recently characterized morphologic variant of epithelioid malignant mesothelioma, which frequently is misdiagnosed as peritoneal deciduosis or florid mesothelial hyperplasia. We report on the cytological, histological, immunohistochemical, and autopsy findings of a case of MMWDF arising in the pericardium of a 71-yr-old female patient. Cytology showed large, polygonal to round cells with pale to bright, eosinophilic cytoplasm, occasionally showing xantomatous pattern, containing a pleomorphic and vesicular nucleus with a single prominent nucleolus. Autopsy examination showed a neoplasm encasing the heart and great vessels. No other primary neoplasm was found. The histological analysis disclosed the typical features of MMWDF. Immunohistochemistry showed diffuse immunoreactivity for cytokeratin MNF116, HBME-1, and calretinin in the neoplastic cells, as well as focal positivity for epithelial membrane antigen positivity in a brush border-like pattern. All other markers were negative. We would like to stress that pathologists must be aware of the cytological and histological features of this rare variant of epithelioid malignant mesothelioma in order to avoid a misdiagnosis of a benign process or a metastatic malignancy. Diagn. Cytopathol. 2002; 26:117–122; DOI 10.1002/dc.10068

Key Words: mesothelioma; immunohistochemistry; cytology

Primary malignant cardiac mesotheliomas are defined as malignant neoplasms arising from the mesothelial cells of the pericardium,[1] without evidence of disease in other anatomic sites.[1] It usually exhibits highly malignant behavior, with 50% of the patients dying in the initial 6 months of follow-up.[1]

Classically, mesotheliomas have been classified according to the histological growth patterns in epithelioid, sarcomatoid, or biphasic.[1,2] However, in the last few years several subtypes were described, such as the lymphohistiocytoid[2] and the deciduoid variants.[3–13]

Deciduoid features in malignant mesotheliomas were first described by Talerman et al.[3] who reported a primary peritoneal malignant mesothelioma affecting a 13-yr-old girl, which was composed of sheets of large cells with a striking resemblance to decidual cells.[3] In 1994, Nascimento et al.[4] reported another two cases with the same morphological features and characterized a new entity, the so-called deciduoid malignant mesothelioma (DMM), which putatively were confined to the peritoneum of young females without any history of asbestos exposure.[4] In the last 2 yr, nine articles concerning the clinicopathological features of DMM[5–13] were published and it has been demonstrated that this entity may also afflict males, and it may arise in the pleural cavities. In only one report were the cytological features of DMM described.

To the best of our knowledge, there is no previous report on primary malignant cardiac epithelial mesothelioma with deciduoid features (PMCMDF). We describe the cytological, histological, and immunohistochemical features of a case of a PMCMDF and provide a brief review of the previously reported cases of DMM.

Case Report

A 71-yr-old female patient presented with a long history of progressive myasthenic syndrome associated with severe

[1]Institute of Molecular Pathology and Immunology, University of Porto (IPATIMUP), Portugal
[2]Department of Medical Pathology, Federal University of Paraná, Brazil
[3]Department of Surgery, Federal University of Paraná, Brazil
[4]Medical Faculty, University of Porto, Portugal
*Correspondence to: Fernando C. Schmitt, MD, PhD, Instituto de Patologia e Imunologia Molecular da Universidade do Porto (IPATIMUP), R. Roberto Frias, S/N, 4200, Porto, Portugal.
E-mail: fernando.schmitt@ipatimup.pt
Received 25 July 2001; Accepted 4 November 2001

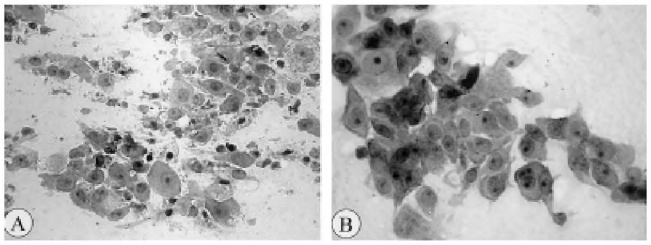

Fig. 1. Cytological features of epithelial malignant mesothelioma of the pericardium with deciduoid features. **A**: Population of isolated round to polygonal cells with pale to bright, deeply eosinophilic cytoplasm containing a large, pleomorphic, vesicular nucleus with a single prominent nucleolus. **B**: High-power magnification disclosing neoplastic cells with distinct cell borders, occasionally arranged in clusters.

weight loss and shortness of breath in the last 8 months. The patient smoked for more than 20 yr but there was no evidence of asbestos exposure. On admission, she was severely dehydrated and presented several episodes of diarrhea. The X-ray images showed a bulky tumor mass in the anterior mediastinum and in the cardiac area. A fine-needle aspiration biopsy was performed. During the first 48 hr at our institution she developed a hypovolemic shock and died of heart failure. An autopsy was performed.

Cytological Findings

Papanicolaou and Giemsa-stained smears were composed of sheets and clusters of large, round to polygonal cells with pale to bright, deeply eosinophilic cytoplasm containing a large, pleomorphic, vesicular nucleus with a single prominent nucleolus (Fig. 1A). Some binucleated cells could be found (Fig. 1B). A feathery outline in the cell borders was occasionally depicted, as well as scattered cells with intracellular lumens and xantomatous cytoplasm. Rare inflammatory cells, including lymphocytes, macrophages, and polymorphonuclear cells were admixed with the neoplastic population. A diagnosis of malignancy was made, suggesting a poorly differentiated carcinoma, consistent with a pulmonary or thymic origin.

Pathological Findings

At the autopsy examination the anterior mediastinum was filled by a lobulated, whitish mass, which encased the heart and great vessels (Fig. 2). The heart weighed 795 g and the pericardial cavity was filled by whitish, irregular nodules measuring 0.5–10 cm in maximum diameter, showing a heterogeneous, white to yellowish, granular cut surface. There was minimal superficial infiltration of the myocardium. The endocardial cavity and the cardiac valves were unremarkable. Scattered satellite nodules were depicted on the medial aspects of the left pleural cavity, as well as on the visceral pleura of the left lung. There was a generalized enlargement of pulmonary hilar lymph nodes, which presented a gross appearance that resembled the pericardial

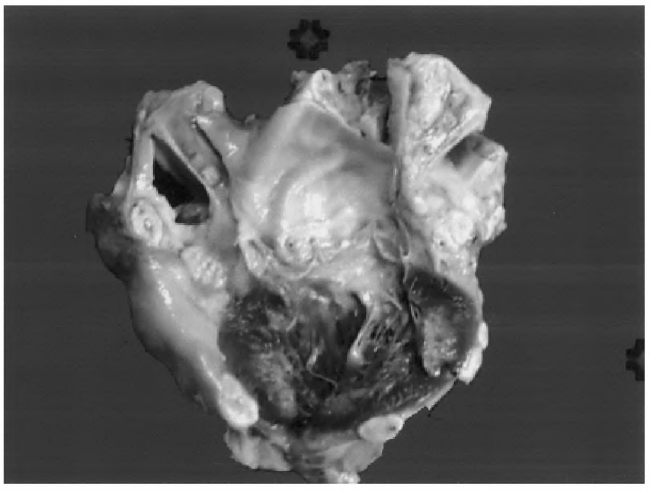

Fig. 2. Gross analysis of the heart showing the pericardial cavity filled by multiple nodules with a heterogeneous, white to yellowish, granular cut surface. The neoplasm encased the great vessels. Note the absence of neoplastic dissemination to the endocardial cavities.

mass. Both lungs showed anthracosis and the left lung was completely atelectatic. No other primary neoplasm was found. Representative tissue samples were collected from all of the nodules, as well as the pulmonary hilar lymph nodes, and from all other organs.

The 4-μm hematoxylin and eosin histological sections from the pericardial mass and from the pulmonary lymph nodes showed a neoplasm composed of solid sheets, nests, and cords of large, polygonal to oval cells with well-defined, abundant, bright eosinophilic to glassy cytoplasm, with a round to oval vesicular nucleus with occasional distinct nucleolus (Fig. 3A). At higher magnification the cell surface exhibited long microvilli with a thick brush border-like appearance (Fig. 3B and inset). Occasional xantomatous cells were seen, as well as scattered binucleated neoplastic cells. In some areas the neoplastic cells were arranged in papillary and glandular-like formations, which gradually merged with the solid areas of the neoplasm. The mitotic activity was low, with two mitoses per 10 high-power fields. Several necrotic foci and areas of geographic necrosis were observed.

Histochemical and Immunohistochemical Findings

Conventional Schiff's periodic acid (Merck, Darmstadt, Germany) with (D-PAS) and without (PAS) diastase (a-amylase A-3176; Sigma, Steinheim, Germany) digestion and colloidal iron at pH 2.5 stains were performed. The neoplastic cells were uniformly negative for PAS and D-PAS; conversely, colloidal iron-positive glycosaminoglycans were seen in the cytoplasm of the neoplastic cells, as well as in the stroma of the neoplasm.

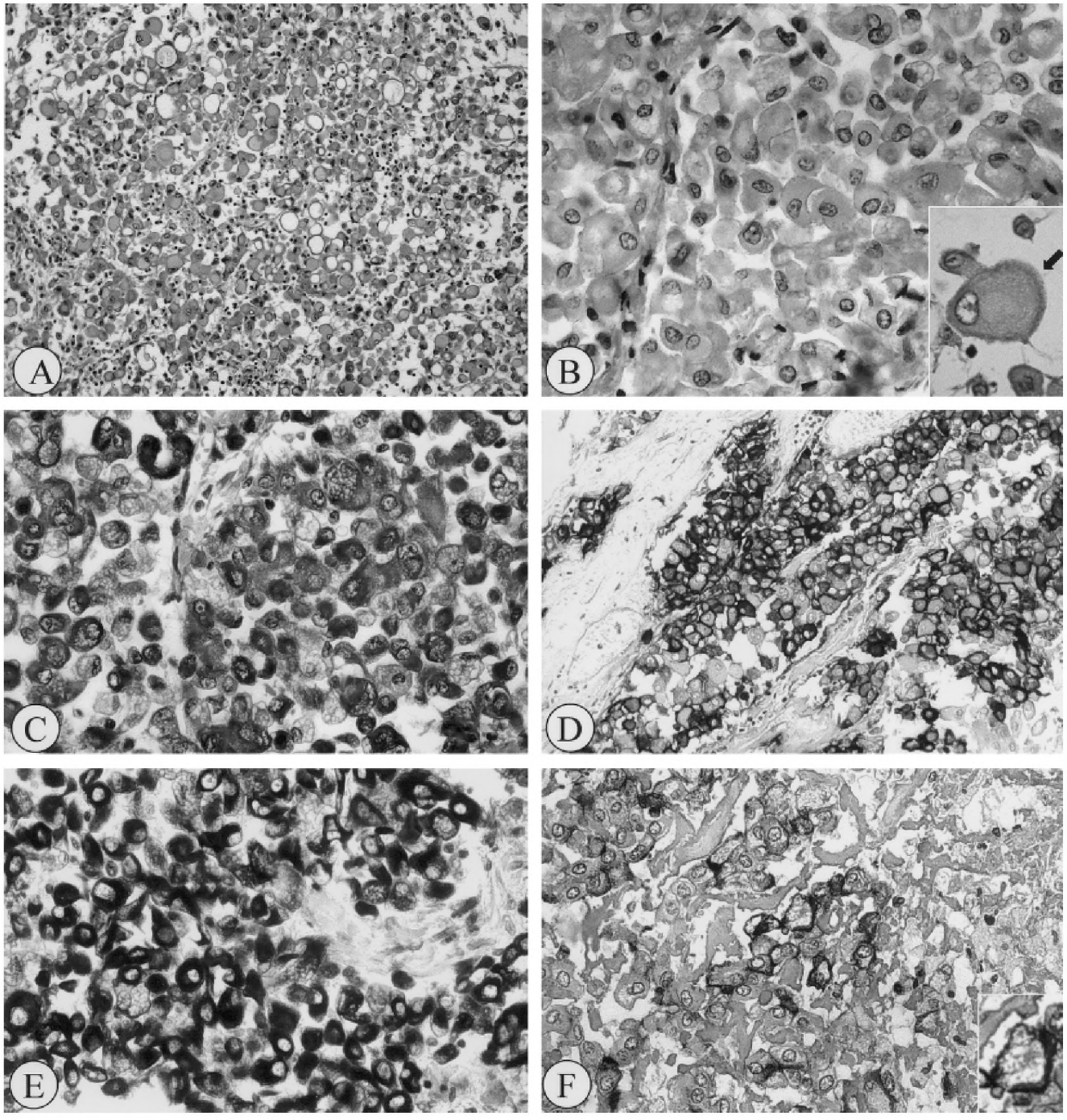

Fig. 3. **A**: Sheets of large, polygonal to oval cells with well-defined, abundant cytoplasm, intermingled with lymphocytes. **B**: High-power magnification showing neoplastic cells with abundant, bright eosinophilic to glassy cytoplasm, sometimes with fine vacuolation, distinct cell borders and round to oval, vesicular nucleus, with occasional distinct nucleolus. Inset: neoplastic cell with brush border-like cell membrane(arrow). **C**: Immunohistochemistry for calretinin showing nuclear and cytoplasmic staining in the neoplastic cells. **D**: HBME1 antibody showed immunoreactivity in a distinct cytoplasmic and membranous pattern in the neoplastic cells. **E**: Diffuse and strong immunoreactivity for MNF116. **F**: Focal membranous EMA immunoreactivity in a circumferential fashion around neoplastic cells. Inset: detail of a neoplastic mesothelial cell with EMA immunoreactivity in a "thick" membrane / brush border-like pattern.

Immunohistochemical analysis according to the streptavidin-biotin-peroxidase technique using antibodies against cytokeratin MNF116, epithelial membrane antigen (EMA), vimentin, calretinin, HBME1, carcinoembryonic antigen (CEA), and S100 protein was performed. Table I summarizes the antigen retrieval technique, the source, and the

Table I. Immunocytochemical and Immunhistochemical Features of PMCMDF

Antibody	*Source*	*Dilution*	*Antigen retrieval*	*Immunoreactivity in the neoplastic cells*
Vimentin	Dako	1:50	No	Negative
Cytokeratin MNF116	Dako	1:40	Pepsin	Diffuse and intense positivity
Calretinin	Zymed	1:30	Retrieval solution	Diffuse and intense nuclear and cytoplasmic positivity
HBME1	Dako	1:20	No	Diffuse and intense cytoplasmic positivity
CEA (polyclonal)	Dako	1:1500	No	Negative
EMA	Dako	1:10	No	Focal reactivity in brush borderlike pattern
S100 protein (polyclonal)	Dako	1:700	No	Negative
CD15 (Leu-M1)	Dako	1:10	No	Negative

CEA: carcinoembryonic antigen; EMA: epithelial membrane antigen.

dilution of each antibody. The neoplastic cells showed diffuse and intense nuclear and cytoplasmic reactivity calretinin (Fig. 3C), as well as being positive for cytokeratin and HBME1 in a cytoplasmic fashion (Fig. 3D,E). Scattered cells exhibited EMA immunoreactivity in a thick brush border-like membranous pattern (Fig. 3F). CEA, CD15 (Leu-M1), vimentin, and S100 protein were all negative in the neoplastic cells. A final diagnosis of primary epithelial cardiac mesothelioma with deciduoid features was made.

Discussion

Malignant mesothelioma (MM) has received great attention in the medical literature in the last 25 yr,[2,7,14] due to the alarming increase in its incidence.[2] The special attention devoted to MMs and their wide range of morphological appearances[7] lead pathologists to expand the classification of MMs in epithelioid, sarcomatoid, or biphasic types.[1,2,14] In the last few years several histological variants of the epithelioid and sarcomatoid types have been reported,[2–12] including wholly clear cell,[2,7] oncocytoid or granular-cell,[2] tubulopapillary,[2] microcystic,[7] large polygonal cell,[2] polyhedral stromal mucin-producing,[2] "medullary" epithelioid,[2] small-cell,[2,7] signet-ring,[7] lymphohistiocytoid,[2] and deciduoid variants.[3–13]

Epithelial mesotheliomas composed of sheets of large cells that present a histological resemblance to an exuberant decidual reaction are rare, and to the best of our knowledge only 20 cases were reported in Western countries, including our case. Table II summarizes the clinicopathological features of the previously published cases. Ten cases affect females and 10 males; age range 13–78 yr, mean 48 yr. Ten cases arose in the peritoneal cavity and nine in the pleural cavities. Our report describes the first case of DMM that arose primarily in the pericardium.

In 1994 Nascimento et al.[4] suggested that DMM could be a distinct histological entity, which putatively would affect young female patients without any history of asbestos exposure.[4] However, Shanks et al.[6] reported six cases of DMMs, in which one arose in the pleura and three had a confirmed history of asbestos exposure.[6] Since then five other articles[7–10,13] reported DMM arising outside the peritoneum and four patients had a previous history of asbestos exposure.[7,12,13] In three cases a history of previous radiotherapy to another malignancy were reported.[7,9,10] However, up to now there is no proven etiological factor for DMM. In our case there were neither antecedents of asbestos exposure nor a previous history of radiotherapy.

While the most important differential diagnosis of DMM arising in the peritoneum is an exuberant or pseudo-tumoral decidual reaction,[3–7] metastatic adenocarcinoma and atypical mesothelial hyperplasia are the major mimickers of DMM in pleural cavities and pericardium.[6–10] In accordance with our findings, in the case reported by Henley et al.[10] an initial misdiagnosis of large-cell carcinoma was performed. In both cases a thymic primary was one of the primary sites considered at the initial diagnosis due to the neoplastic extension to the anterior mediastinum.[10] In our case, the cytology showed cells that resembled the features of a large-cell carcinoma, with noncohesive large cells with pleomorphic nuclei, and deeply eosinophilic cytoplasm. However, the lack of other primary neoplasia outside the pericardium during the autopsy examination, the typical histological and histochemical features, and the immunohistochemical findings, with immunoreactivity for cytokeratin, calretinin, HBME1, and EMA in a "thick" cell membrane (brush border-like) pattern, associated with lack of reactivity for CEA, CD15, and S100, were consistent with a diagnosis of primary cardiac epithelioid malignant mesothelioma with deciduoid features. Interestingly, despite the lack of specificity of EMA immunostaining in the differential diagnosis of mesothelioma and adenocarcinoma, this marker might give support to a diagnosis of malignant mesothelioma, because it shows a distinctive immunoreactivity in mesothelial cells in a "thick membrane" / brush border-like pattern[15–17] that is not observed in adenocarcinomas. According to previous studies,[15–17] this "thick" membranous staining pattern is observed in the periphery of cell clusters and circumferentially around individual cells in almost all cases of mesothelioma, either in cytological preparations and histological sections.[15–17] Another eye-catching feature in histological sections of malignant mesothelioma is that microvilli, better observed in EMA immunostaining and ultrastructural studies, are circumferentially arranged around the neoplastic mesothelial cells infiltrating stromal

Table II. Summary of Clinicopathological Findings of the Deciduoid Malignant Mesothelioma Previously Published Cases

Reference	*Sex/age*	*Asbesto exposure*	*Anatomical site*	*Primary diagnosis*	*Final diagnosis*	*Follow-up*
3	F/13	No	Peritoneum	Diffuse pseudotumoral deciduosis	DMM	DOD, 7 months
4	F/23	No	Peritoneum	Deciduosis	DMM	DOD, 4 months
	F/24	No	Peritoneum	Deciduosis	DMM	Not available
5	F/15	No	Peritoneum	MM	DMM	DOD, 11 months
6	M/59	Yes	Peritoneum	Epithelial MM	DMM	DOD, 4 months
	F/53	Putative	Peritoneum	DMM	DMM	DOD, 9 months
	M/65	Yes	Peritoneum	DMM	DMM	DOD, 4 months
	M/55	Yes	Peritoneum	Rhabdomyosarcoma	DMM	NED, 5 years
	F/55	No	Peritoneum	DMM	DMM	DOD, 4 months
	M/52	Yes	Pleura	DMM	DMM	AWD, 4 months
7	F/46	No	Pleura	DMM	DMM	DOD, 6 months
	M/64	Yes	Pleura	Epithelial MM	DMM	DOD, 8 months
	M/60	No	Pleura	Epithelial MM	DMM	DOD, 5 months
	M/78	Yes	Pleura	Not available	DMM	Not available
8	F/40	No	Pleura	Metastatic adenocarcinoma	DMM	Not available
9	M/41	No	Pleura	Epithelial MM	DMM with rhabdoid change	DOD, 21 months
10	M/30	No	Pleura	Undifferentiated, large cell carcinoma, consistent with a thymic primary	DMM	AWD, 5 months
12	F/50	Yes	Peritoneum	Reactive mesothelial hyperplasia	DMM	AWD, 1 year
13	M/66	Yes	Pleura	DMM	DMM	Not available
Our case	F/71	No	Pericardium	Poorly differentiated carcinoma, suggestive of a pulmonary or thymic primary	DMM	Diagnosed at autopsy

AWD: alive with disease; DMM: deciduoid malignant mesothelioma; DOD: dead of disease; MM: malignant mesothelioma; NED: no evidence of disease.

connective tissue and these microvilli might show interdigitation with stromal collagen fibers, another feature that is not observed in metastatic carcinomas.[16]

To achieve a correct diagnosis, cytopathologists and surgical pathologists must have a high index of suspicion to not overlook the large, round to polygonal cells, with eosinophilic to xantomatous cytoplasm, vesicular nuclei with distinct nucleoli as an atypical mesothelial hyperplasia, as emphasized by Gillespie et al.,[12] who described the cytological features of the ascitic fluid and intraoperative sections of their case of DMM, which looked like a reactive mesothelial proliferation. In addition, those authors stressed that despite the low nuclear:cytoplasm ratio, cells were larger than reactive mesothelial cells and also presented a coarse granular chromatin, and the nucleoli were more conspicuous when compared to benign reactive mesothelium.[12] Moreover, we concur with the statement that feathery cell borders, windows, and mitotic figures are not useful features to distinguish between malignant epithelial mesothelioma and florid mesothelial hyperplasia.[12,14]

In conclusion, the authors described the first case of epithelial malignant mesothelioma with deciduoid features arising in the pericardial cavity. We would like to emphasize that pathologists and cytopathologists should be aware of this rare histological variant of epithelial mesothelioma and to not misdiagnose it either as a metastatic adenocarcinoma or as mesothelial reactive hyperplasia, mainly because DMM usually presents a very aggressive clinical course, with 68% of the patients dying during the first year of follow-up despite therapy.

References

1. Burke A, Virmani R. Malignant mesothelioma of the pericardium. In: Burke A, Virmani R, editors. Tumors of the heart and great vessels. Atlas of tumor pathology, 3rd series. Washington, DC: AFIP, 1996. p 181–194.
2. Wick MR, Mills SE. Mesothelial proliferations. An increasing morphologic spectrum. Am J Clin Pathol 2000;113:619–622.
3. Talerman A, Montero JR, Chilcote RR, Okagaki T. Diffuse malignant peritoneal mesothelioma in a 13-year-old girl. Report of a case and review of the literature. Am J Surg Pathol 1985;9:73–80.
4. Nascimento AG, Keeney GL, Fletcher CD. Deciduoid peritoneal mesothelioma. An unusual phenotype affecting young females. Am J Surg Pathol 1994;18:439–445.
5. Orosz Z, Nagy P, Szentirmay Z, Zalatnai A, Hauser P. Epithelial mesothelioma with deciduoid features. Virchows Arch 1999;434:263–266.
6. Shanks JH, Harris M, Banerjee SS, et al. Mesotheliomas with deciduoid morphology: a morphologic spectrum and a variant not confined to young females. Am J Surg Pathol 2000;24:285–294.
7. Ordonez NG. Epithelial mesothelioma with deciduoid features: report of four cases. Am J Surg Pathol 2000;24:816–823.
8. Gloeckner-Hofmann K, Zhu XZ, Bartels H, Feller AC, Merz H. Deciduoid pleural mesothelioma affecting a young female without prior asbestos exposure. Respiration 2000;67:456–458.
9. Puttagunta L, Vriend RA, Nguyen GK. Deciduoid epithelial mesothelioma of the pleura with focal rhabdoid change. Am J Surg Pathol 2000;24:1440–1443.

10. Henley JD, Loehrer PJ Sr, Ulbright TM. Deciduoid mesothelioma of the pleura after radiation therapy for Hodgkin's disease presenting as a mediastinal mass. Am J Surg Pathol 2001;25:547–548.
11. Desai S, Kane S, Bharde S, Kulkarni JN, Soman CS. Malignant peritoneal mesothelioma deciduoid or anaplastic variant? A point to ponder. Indian J Pathol Microbiol 2000;43:479–483.
12. Gillespie FR, van der Walt JD, Derias N, Kenney A. Deciduoid peritoneal mesothelioma. A report of the cytological appearances. Cytopathology 2001;12:57–61.
13. Monaghan H, Al-Nafussi A. Deciduoid pleural mesothelioma. Histopathology 2001;39:104–106.
14. Bedrossian CW. Diagnostic problems in serous effusions. Diagn Cytopathol 1998;19:131–137.
15. Leong AS, Parkinson R, Milios J. "Thick" cell membranes revealed by immunocytochemical staining: a clue to the diagnosis of mesothelioma. Diagn Cytopathol 1990;6:9–13.
16. Leong AS, Stevens MW, Mukherjee TM. Malignant mesothelioma: cytologic diagnosis with histologic, immunohistochemical, and ultrastructural correlation. Semin Diagn Pathol 1992;9:141–150.
17. Leong AS, Vernon-Roberts E. The immunohistochemistry of malignant mesothelioma. Pathol Annu 1994;29:157–179.