

## CASE REPORT

## Pericardial Involvement by Thymomas

### *Entirely Intrapericardial Thymoma and a Pericardial Metastasis of Thymoma with Glomeruloid Vascular Proliferations*

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Thymomas are usually found in the anterior mediastinum, the normal location of the thymus. Involvement of the pericardium by thymic tumors is seen in invasive or metastasized thymoma. Very rarely, thymomas arise primarily in the pericardium. These tumors are believed to derive from thymic tissue which was misplaced in the pericardium during embryologic development. In contrast to patients with orthotopic thymoma who commonly suffer from paraneoplastic diseases, especially myasthenia gravis, patients with intrapericardial thymoma manifestations mainly have symptoms of congestive

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heart failure which are caused by local complications of tumor growth. In this study, we present two cases of thymoma involving the pericardium. Both tumors were polygonal-oval cell thymomas. In one of the cases diagnosis of an entirely intrapericardial thymoma was established by autopsy. In the other case, explorative thoracotomy revealed massive pericardial and pleural tumor manifestations. The latter tumor showed a peculiar histological pattern with multiple glomeruloid bodies, a finding reported only once for thymomas. (Pathology Oncology Research Vol 5, No 2, 160–163, 1999)

#### **Introduction**

The majority of thymomas is found in the normal location of the thymus, the anterior mediastinum. Thymomas involving the heart are usually extensions of orthotopic mediastinal tumors. Very rarely, they arise primarily intrapericardially. These primarily ectopic tumors are believed to originate from heterotopic islands of thymic tissue, which have been described in the parietal pericardium.<sup>8</sup> Only a few reports of the histological features of primary intrapericardial thymomas are available. A survey of literature reveals four cases in the AFIP series,<sup>8</sup> to which five cases have since been added.<sup>1,3,5,9</sup>

The most common clinical complication of orthotopic thymoma is a paraneoplastic syndrome, myasthenia gravis.

In contrast, patients with pericardial tumor manifestations often present with symptoms of impeded cardiac function. The pericardium has limited growing space. Symptoms caused by direct mechanical compression or pericardial effusion are therefore likely to occur early and represent the first clinical signs of the tumor. In this study we relate two new cases of thymoma involving the pericardium. One of these tumors was an entirely intrapericardial thymoma. In the other case, explorative thoracotomy revealed massive pericardial and pleural tumor infiltration. Histological examination of this tumor showed a peculiar vascular proliferation with a superficial resemblance to renal glomeruli. To the best of our knowledge this extraordinary finding has been reported only once before in a thymoma.<sup>12</sup>

#### **Clinical history**

##### *Case 1*

A 41 year old female patient was admitted to hospital with symptoms of right heart congestion. Two years before, a mediastinal high grade non-Hodgkin's lym-

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**Table 1. Antibodies used for the immunohistochemical examination of case 1**

<i>Antibody</i>	<i>Source</i>	<i>Dilution</i>	<i>Clone</i>	<i>Tumor cells</i>	<i>Glomeruloid bodies</i>
Pan CK	Dako	1:50	MNF 116	positive	negative
Cytokeratins 1,5,10,14	Dako	1:50	34BE12	positive	negative
Cytokeratin 8	Becton–Dickinson	1:6	CAM 5.2	positive	negative
Epithelial membrane antigen	Dako	1:100	E29	positive	negative
Ki-67 Antigen	Immunotech	1:50	MIB-1	10% pos.	negative
CD31	Dako	1:30	JC/70A	negative	positive
Vimentin	Dako	1:100	Vim3B4	negative	positive
Mesothelial cells	Dako	1:50	HBME-1	negative	negative
CEA	Dako	1:100	IL-7	negative	negative
Chromogranin A	Dako	1:100	polyclonal	negative	negative
LCA	Immunotech	1:1	ALB 12	negative	negative
Protein S-100	Dako	1:200	polyclonal	negative	negative

phoma (T-lymphoblastic lymphoma, R.E.A.L. classification) was diagnosed and treated with various cytostatic regimens for one year. On radiologic examination after therapy, however, a residual tumorous mass was seen. Irradiation of the mediastinum, and chemotherapy for another year were administered. At present, magnetic resonance imaging of the chest revealed a lesion involving the pericardium, expanding around large vessels and involving both pleural cavities. Massive pericardial and bilateral pleural effusions were present. The differential diagnosis included recurrence of the non-Hodgkin's lymphoma. An explorative left antero-lateral thoracotomy showed a massively thickened pericardium. The pericardium was fenestrated and two biopsies were taken and processed for histological examination. The thoracoscopic examination of the right side revealed the presence of tumor nodules in the parietal pleura and the diaphragm. One year later, a biopsy taken from a liver tumor with a diameter of approximately 10 cm revealed the presence of carcinoma tissue morphologically and immunohistochemically consistent with a metastasis of the thymoma.

#### Case 2

The previous history of a 53 year-old female mentioned a ductal invasive breast carcinoma (pT2, N1, Mx) diagnosed five years before which had been treated by a segment resection, and combined radio-chemotherapy. She was admitted to the hospital with dyspnoe and retrosternal pain. Chest X-ray revealed a tumorous mass in the left anterior mediastinum suspicious of metastatic breast carcinoma. Surgery was performed and a predominantly encapsulated, intrapericardial tumor was removed (*Figure 3*). The patient died two days after surgery from pul-

monary thromboembolism. An autopsy was performed. No residual thoracic tumor, and especially no tumor of the thymus were detectable.

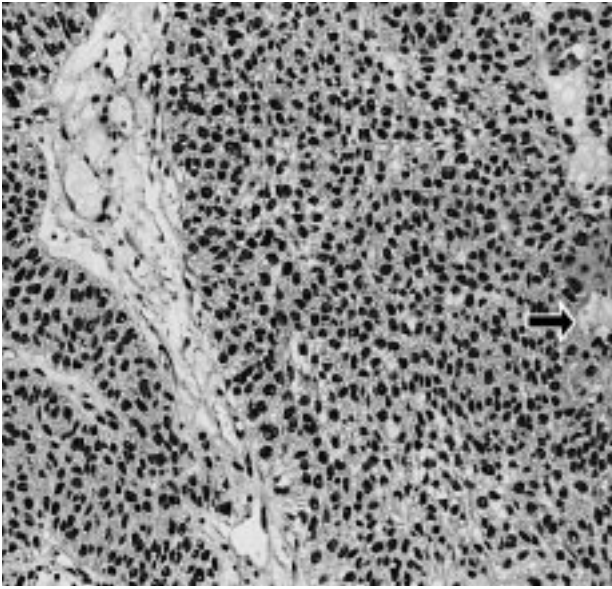
#### Materials and methods

In both cases, formalin fixed, paraffin-embedded tissue was histologically examined using conventional stains. For immunohistochemical investigation in case 1, 3 µm thick sections of paraplast-embedded tissue were dewaxed, rehydrated, and pretreated by boiling in 10 mM citrate buffer, pH 6, either in a pressure cooker for 5 min or in a microwave for 3x5 min. The sections were incubated at room temperature with the primary antibody. Antibodies used are listed in *Table 1*. After washing in Tris-buffered saline the sections were incubated in a 1:200 solution of biotinylated rabbit-anti-mouse antiserum or biotinylated swine-anti-rabbit immunoglobulin antiserum (Dako), thereafter with avidin-biotin-complex/alkaline phosphatase (Dako). Finally, the sections were developed in new fuchsin-naphtol AS-BI (Sigma) and counterstained with hematoxylin.

#### Results

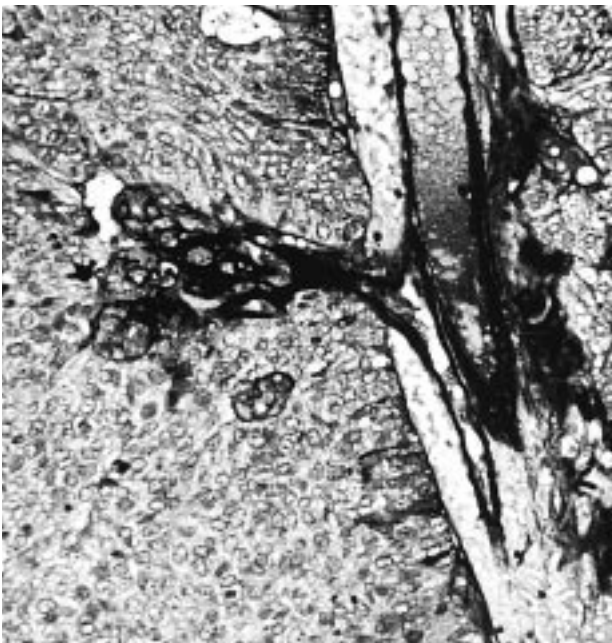
##### Case 1

The biopsy consisted of two greyish specimens of irregular shape with a maximum diameter of 2,8 cm. Histologically, the tumor revealed a predominantly epithelial trabecular pattern with only a few lymphocytes. The tumor cells displayed round to oval nuclei, an eosinophilic cytoplasm and no distinct cell borders. Perivascular spaces formed by palisading epithelial cells contained lymphoid cells (*Figure 1*). Additionally, areas with multiple glomeruloid bodies in perivascular, microcystic spaces were



**Figure 1.** Low magnification of the intrapericardial thymoma, showing the polygonal-oval cell pattern with perivascular spaces filled with lymphatic cells, and a glomeruloid body in a microcystic space (arrow).

found (Figures 1,2,3). Evaluation of consecutive sections proved the spherical nature of the bodies. The microcystic spaces were filled with serous fluid. Immunohistochemistry showed intensive reactivity for epithelial antigens in the tumor cells. The fraction of proliferating MIB-1 positive cells was estimated to be 10% of all epithelial cells.



**Figure 2.** In contrast to the tumor cells the glomeruloid bodies were positive for vimentin.

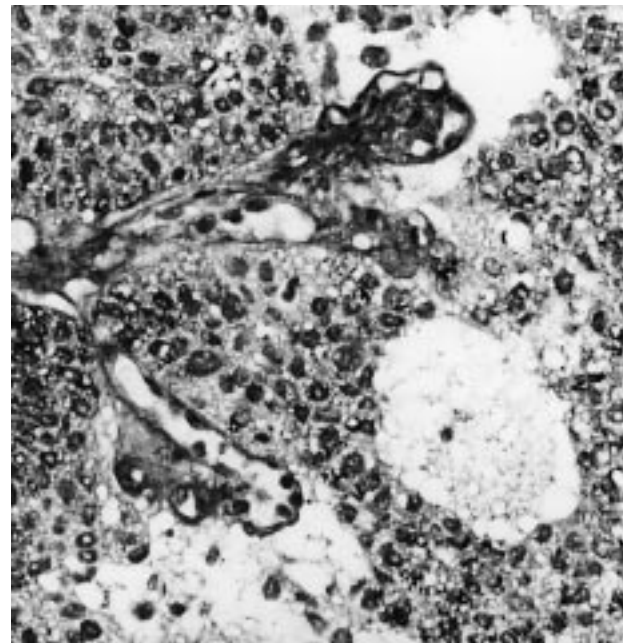
Originating from the small vessels the glomeruloid bodies showed a positive immunoreactivity for Vimentin and CD31 (Figure 2). The results of immunohistochemical analysis are listed in Table 1. No T-lymphoblastic lymphoma tissue was seen. The tumor nodules located in the right parietal pleura and in the diaphragm were not examined histologically. – *Final diagnosis:* Epithelial cell predominant, polygonal-oval cell thymoma with metastasis (present AFIP classification<sup>12</sup>), Cortical thymoma (classification according to Marino and Müller-Hermelink<sup>7</sup>).

#### Case 2

A 5x4x3 cm predominantly encapsulated tumor (Figure 3) of white-greyish colour was examined. The tumor displayed a lymphocyte predominant pattern with polygonal to oval epithelial tumor cells and ill-defined cell borders. *Final diagnosis:* Lymphocyte predominant, polygonal-oval cell thymoma (present AFIP classification<sup>12</sup>); Cortical thymoma (classification according to Marino and Müller-Hermelink<sup>7</sup>).

#### Discussion

Pericardial involvement by thymic tumors is usually a late stage observation in primary mediastinal thymomas. The development of massive pericardial effusion associated with pericardial metastasis of thymoma is described by various authors. In some cases it was the first clinical sign of an orthotopic thymic tumor.<sup>2,6,10,13</sup> Thymomas originat-



**Figure 3.** Two glomeruloid bodies, showing vascular lumina and flattened endothelial cells (PAS).

ing primarily in the pericardium, however, are rarely reported neoplasms. A review of literature reveals a total of nine cases of primary intrapericardial thymoma: four in the AFIP series,<sup>8</sup> two reports addressing diagnostic procedures and follow-up issues,<sup>3,5</sup> and three incidental autopsy cases.<sup>1,9</sup> Patients were mostly elderly women and presented clinically with symptoms of right heart congestion. The predominantly described histological subtype of primary intrapericardial thymoma is the spindle cell or medullary variant, classified either as proposed by Shimosato and Mukai<sup>12</sup> or by Marino and Müller-Hermelink.<sup>7</sup>

We present the clinical and histological data of two cases of intrapericardial manifestation of thymoma. In one case, the presence of orthotopic mediastinal thymoma was excluded by autopsy establishing the diagnosis of a primarily intrapericardial thymoma. In the other case, the mediastinum had been irradiated, and prolonged chemotherapy had been administered because of a malignant T lymphoblastic lymphoma. In this case the primary location of the thymoma could not be clearly established but it is of note that the pericardial tumor manifestations predominated in extent and determined the clinical course.

Both patients presented with symptoms of right heart congestion similar to those reported in the previous cases. It is likely that symptoms of intrapericardial tumor growth due to cardiac compression occur earlier than other thymoma-related complications, especially myasthenia gravis. The previous history of both patients mentioned a malignant neoplasm different from a thymoma. The present mediastinal processes were suggestive of recurring manifestations of the initial tumors. Especially in the case of the patient with preceding non-Hodgkin's lymphoma, the histological examination was carried out thoroughly to confirm the epithelial nature of the neoplasm and to rule out recurring lymphoma. One of the tumors revealed peculiar histological features with areas containing multiple glomeruloid bodies in microcystic perivascular spaces. To the best of our knowledge this pattern has only been described once in a thymoma of the AFIP series.<sup>12</sup> Our immunohistochemical and histological data indicates that these glomeruloid bodies derive from small vessels. We are inclined to interpret this vascular abnormality as a reactive process induced by the thymoma. Tumor-associated vascular proliferation with a superficial resemblance to renal glomeruli is a common phenomenon in high grade glial tumors<sup>11</sup> but has also been described many extracranial tumors of neural or neuroendocrine nature.<sup>4</sup> The

pathogenesis of this particular vascular proliferation is poorly understood. As for other phenotypes of reactive vascular proliferation, up-regulation of angiogenic factors as well as down-regulation of antiangiogenic factors by the tumor cells seems to be the most plausible theory.

In summary, the cases reported confirm that the pericardium is a possible yet rare location of thymic tumor manifestations and that pericardial involvement by thymomas should be considered in cases of right heart congestion combined with pericardial thickening. We further describe a peculiar morphological pattern with glomeruloid bodies in one of the tumors which we consider an uncommon thymoma phenotype rather than an alteration specific to intrapericardial manifestation of thymoma.

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