Unusual association of diseases/symptoms

Two malignant tumours in the anterior mediastinum positive for CD5

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Summary

To our knowledge, the simultaneous involvement of the anterior mediastinum by a thymic carcinoma and a B-cell chronic lymphocytic leukaemia has not been reported previously. The authors describe the case of a 62-year-old man, suffering from severe bronchitis. Chest x-ray and CT scan showed a mediastinal tumour, resected short-time after diagnosis. First, standard based histological examination revealed a thymic carcinoma admixed by a dense lymphatic infiltrate. Additional immunohistochemical staining for CD5-labelled epithelial thymic carcinoma cells as well as neoplastic B cells and led in combination with blood tests to confirm the diagnosis of the composite occurrence of a thymic carcinoma and a B-cell chronic lymphocytic leukaemia.

BACKGROUND

In general, thymic carcinomas are aggressive epithelial malignancies with rare incidence, occurring predominantly in middle-aged persons. The prognosis of these tumours depends mainly on tumour stage and resection margins.^{1,2} In addition, the histological classification according to the WHO^{3,4} has been shown to be of prognostic value. In comparison to other subtypes, especially type B3 thymomas and thymic carcinomas have a worse prognosis.^{2,5,6} Complete surgical resection remains the standard of care for both invasive, non-invasive thymomas and thymic carcinomas as it provides the best prognosis. Adjunctive chemotherapy and radiation treatment is used for the treatment of metastatic disease and locally invasive or inoperable tumours.

Additionally to thymomas and thymic carcinomas, which may contain a large number of lymphocytes, several subtypes of lymphomas can arise in the thymus including primarily mediastinal (thymic) large B-cell lymphomas, Hodgkin lymphomas,⁷ precursor T-cell acute lymphoblastic leukaemia/lymphoblastic lymphoma, MALT lymphomas^{8–10} as well as anaplastic large-cell lymphoma and mature T- and NK-cell lymphomas.⁴ Especially, the rare subtype of micronodular thymoma (MNT) is associated with monoclonal B-cell populations in one third of the cases.¹¹ Type AB, B1, B2 thymomas and thymic carcinomas (lymphoepithelioma-like thymic carcinomas) have a high number of non-neoplastic T lymphocytes intermixed with their epithelial component, making the detection of some types of lymphomas or leukaemias difficult. In type A, type B3 thymomas and some types of thymic carcinoma non-neoplastic lymphocytes are rare.³

We present the first description of a thymic carcinoma admixed by neoplastic B cells of a chronic lymphocytic leukaemia verified by CD5 immunoreactivity.^{12,13}

CASE PRESENTATION

In April 2000, a 62-year-old male patient with a past history of long-term smoking consulted his physician with severe bronchitis. First he underwent chest x-ray, which revealed a mediastinal tumour mass. Bronchoscopy showed an unspecific chronic bronchitis, and CT scan of the thorax revealed a well-defined soft-tissue mass located in the anterior mediastinum with a maximum diameter of 8 cm. Furthermore, hepatosplenomegaly and a slight enlargement of the mediastinal, mandibular and paraaortic lymph nodes were found. Three weeks after clinical examination the patient underwent tumour resection. The intraoperative frozen section was highly suspicious of a thymic carcinoma. At the following sternotomy and anterior thoracotomy a 12×9×5 cm measuring tumour was seen with extension from the left lung hilus to the right parasternal area. The tumour mass with grey cut surface, weighing 200 g, was resected together with mediastinal and retrosternal lymph nodes, parts of the innominate vein, the adjacent pericard, the left visceral pleura and the left phrenic nerve. The resected pericard (8×7 cm) was replaced with segments of gore-tex.

The histological examination of removed specimens confirmed the diagnosis of a thymic carcinoma with mediastinal and retrosternal lymph node metastases. The thymic tissue and lymph nodes showed a dense lymphocytic infiltrate. Histologically, complete surgical resection was obtained.

During the hospital stay differential blood count and flow cytometry revealed a normochrome anaemia, a discrete thrombocytosis, leucocytosis ($20.4 \times 10^9/l$) and absolute lymphocytosis ($10 \times 10^9/l$).

So from the clinical point of view, a B-cell chronic lymphocytic leukaemia was suspected. Additional immunohistochemical investigation showed a strong positivity of c-kit (thymic carcinoma) and CD5 on the surface of thymic

carcinoma cells and neoplastic B cells. Therefore, the diagnosis of the composite occurrence of a thymic carcinoma and a chronic lymphocytic leukaemia was affirmed.

INVESTIGATIONS

For histological examination, parts of the resected tumour were fixed in 4% phosphate buffered formaldehyde, then dehydrated in graded alcohols and paraffin embedded. For histological examination, the 4- μ m thick sections were stained with haematoxylin and eosin. For immunohistochemical analysis, the slides were first deparaffinised, followed by blocking endogenous peroxidase activity for 10 min with 3% hydrogen peroxide (diluted in methanol) at room temperature. After rinsing with PBS, primary antibodies directed against CK5/6 (Clone D5/16 B4, monoclonal, 1/50), c-kit (polyclonal, 1/100), CD20 (Clone L26, monoclonal, 1/700), Ki-67 (Clone MIB-1, monoclonal, 1/100 – all antibodies mentioned so far were purchased from Dakocytomation, Glostrup, Denmark), CD5 (NCL-CD5-4C7, monoclonal, 1/150; Novocastra Laboratories Ltd., Newcastle upon Tyne, UK), CD43 (monoclonal, 1/200; BD Biosciences Pharmingen, CA, USA), cytokeratin KL1 (monoclonal, 1/25; Immunotech, Marseille, France) and cyclin D1 (polyclonal, 1/100; Neomarkers, CA, USA) were applied. For breaking protein cross-linkages formed by formalin fixation, the slides received either heat-mediated autoclave antigen retrieval (CK5/6, CD5, cyclin D1, Ki-67), microwave antigen retrieval (c-kit, CD20) using 0.01 M citrate buffer (pH 6.0) or pre-treatment with proteinase K for 4 min (CD43, KL1). The staining was visualized by using the EnVision System (Dakocytomation, Glostrup, Denmark), in accordance with the manufacturer's instructions.

The resected specimen showed a thymic carcinoma, consisting of large and polygonal atypical epithelia with round-oval nuclei and prominent nucleoli growing in a lobular pattern, particularly limited by a capsule and delineated by fibrohyalin bands (figures 1 and 2).

The epithelial cells were positive for CK5/6, CD5 (figure 3), c-kit (CD117, figure 4) and the cytokeratin marker KL1, and finally the diagnosis of a thymic carcinoma (squamous type) was established. Between epithelial cells dense lymphoid aggregates were found, invading through the capsule and extending into surrounding adipose tissue (figure 2). These cells consisted of small to medium sized cells with a scant, pale cytoplasm and prominent nucleoli, resembling paraimmunoblasts. Initial immunohistochemistry revealed a homogenous expression of CD20. On the basis of this finding, additional immunohistochemical investigations were performed, displaying an expression of CD43, a weak expression for CD5 (figure 3), negativity for cyclin D1 and a low proliferative activity (<10% Ki67-positive nuclei). The resected lymph nodes were nearly completely occupied by the atypical lymphoid infiltrate.

DIFFERENTIAL DIAGNOSIS

Differential diagnosis of a lymphocytic infiltration in the thymus includes:

- normal thymus tissue without involvement by any other disease
- lymphomas (Hodgkin and non-Hodgkin lymphomas)
- metastasis of a carcinoma
- thymic carcinomas
- thymomas (especially B1 thymomas and MNTs).

Figure 1 The mediastinal tumour mass with composite occurrence of thymic carcinoma and B-CLL infiltrate. The epithelial cells are circumscribed by a discrete fibrous capsule (haematoxylin-eosin, original magnification $\times 10$).

Figure 2 The carcinoma component with typical perivascular spaces and the lymphocytic infiltration, invading the capsule and infiltrating the pericapsular adipose tissue (haematoxylin-eosin, original magnification $\times 40$).

Figure 3 Both the carcinoma cells (marked by a long black arrow) and the lymphoid infiltrate of the B-cell chronic lymphocytic leukaemia (short black arrow) are positive for CD5 with an obvious stronger expression in the lymphoid cell population (immunoperoxidase with haematoxylin counterstain, original magnification $\times 40$).

Figure 4 Positive cytoplasmatic c-kit-staining of the carcinoma cells (immunoperoxidase with haematoxylin counterstain, original magnification $\times 40$).

TREATMENT

After release from hospital 2 weeks later, adjunctive irradiation of the mediastinum (60 Gy total dose) was performed. Postoperatively, the patient suffered under episodes of tachyarrhythmia absoluta and achieved therefore an antiarrhythmic therapy. Concerning the chronic lymphocytic leukaemia, the patient did not obtain any other therapy because the leucocytes did not rise again.

OUTCOME AND FOLLOW-UP

In May 2002, a coin lesion in the liver, measuring 2.4 $\times$ 2.3 cm, was detected by CT. CT scan-guided fine-needle aspiration showed a diffuse lymphocytic leukaemic infiltrate in the periportal fields. Three months later an enlarged and metastatic left supraclavicular lymph node with infiltration of both the thymic carcinoma and the B-CLL was removed. After surgical resection, the patient received an irradiation of the right and left supraclavicular region (50–60 Gy total dose). Two years after initial diagnosis multiple metastases of the thymic carcinoma recurred. During the following cisplatin-based radiochemotherapy the patient collapsed and denied further treatment. The patient died in 2006 due to tumour progress.

DISCUSSION

To date, no other case of a simultaneous involvement of the thymus by a thymic carcinoma and a B-CLL has been described in the English medical literature.

Only one case of a patient suffering from a B-cell chronic lymphocytic leukaemia/small lymphocytic lymphoma but associated with a thymoma has been reported by Khoury et al¹⁴ in 2003. They supposed that thymoma seem to be a

predisposing factor for the development of secondary neoplasms.¹⁴

In general, metastases of intra- and extrathoracic tumours, lymphomas (Hodgkin and non-Hodgkin), thymic neoplasms and germ cell tumours are the most common malignancies occurring in the anterior mediastinum. Certain subtypes of thymomas and thymic carcinomas usually contain more or less lymphocytes, and so at first glance, lymphocytes are a normal feature of thymomas and certain subtypes of thymic carcinomas (eg, lymphoepithelial subtype).

However, in the case presented here, there were dense and circumscribed aggregates of lymphocytes even unusual for a thymic carcinoma of the lymphoepithelial subtype. These aggregates were also found in the adjunct fatty tissue of the mediastinum and in resected lymph nodes.

In some cases, for example, the so-called MNT, the detection of a lymphoma or leukaemic manifestation in the thymus is very difficult. In 1999, Suster and Moran¹⁵ published 18 cases of sometimes cystic thymomas, showing a micronodular growth pattern associated with lymphoid hyperplasia and named them MNT with B-cell hyperplasia.

They interpreted these cases as an unusual morphological variant of spindle cell thymomas with possible transition to lymphoepithelioma-like carcinomas because one histologic section showed areas of poorly differentiated squamous cell carcinoma.

Since that time, many reports of this special subtype have been documented. In 2004, Ströbel et al¹¹ published a study with 18 patients suffering from MNT, demonstrating monoclonality of B-cell population in six cases by Ig heavy chain-directed PCR. In three of these six patients a MALT lymphoma could be detected. This example illustrates the difficulties of dealing with lymphomas within thymomas.

In addition to the rare occurrence of low grade B-cell lymphomas, other lymphomas have to be considered when dealing with malignant diseases of the thymus, especially Hodgkin lymphomas.^{11,16} In the mediastinum Hodgkin lymphomas are the most frequent malignant lymphomas (50–60%), sometimes with derivation from thymus tissue. Differential diagnosis between lymphocyte-rich thymomas, particularly type B1 thymomas and Hodgkin lymphomas (especially the lymphocyte predominant subtype), can be difficult.^{7,16}

Besides, primary mediastinal (thymic) large B-cell lymphoma as well as precursor T-cell acute lymphoblastic leukaemia/lymphoblastic lymphoma may mimic an epithelial neoplasm of the thymus. Furthermore, the hyalinised blood vessels are sometimes very similar to Hassall's corpuscles, and the dense lymphocytic infiltrates, observed in Castleman's disease (angiofollicular lymph node hyperplasia) have to be distinguished from normal or hyperplastic thymic tissue.

Dependent on the subtype, thymic carcinomas often show a positive immunohistochemical staining for different epithelial markers such as AE 1+3, KL-1 or CK5/6 and sometimes for CD5 and c-kit.

CD5, a 67-kDa surface glycoprotein receptor, typically expressed on T lymphocytes, on the surface of peripheral blood cells and endothelial cells, is the only antigen which is also expressed by neoplastic cells in the B-cell lymphoproliferative disorders small lymphocytic lymphoma/chronic lymphocytic leukaemia and mantle cell lymphoma.¹⁷ These diseases are thought to arise from CD5-positive pre-follicular centre lymphocytes. The reason for CD5 expression on malignant thymic cells is not fully understood.

In our present case CD5 was a helpful marker leading to the final diagnosis of a thymic carcinoma^{12,13} admixed by a lymphoid infiltrate of a chronic lymphocytic leukaemia.

In conclusion, our case report shows that lymphocytic infiltrates observed in many thymomas or thymic carcinomas may themselves be neoplastic. Lymphomas involve the thymus in relative high frequency, and therefore both the epithelial and the lymphocytic component of thymic tumours need to be thoroughly investigated and analysed.

Learning points

- ▶ Tissue of the thymus regularly consist of lymphocytes, but we must always be aware, that a lymphocytic infiltration can also be a part of a leukaemia, lymphoma or metastasis of another carcinoma.
- ▶ In general, thymic carcinomas are aggressive malignancies with poor survival. Conventional chemotherapy for thymic carcinomas often results in minimal or no response.
- ▶ CD5, expressed by neoplastic cells in small lymphocytic lymphoma/chronic lymphocytic leukaemia, mantle cell lymphoma and most of thymic carcinomas led to the confirmed diagnosis of a thymic carcinoma associated with a B-CLL.

Competing interests None.

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