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Case Report

A Case of Invasive Cortical Thymoma Involving Unusual Multifocal B-Cell Hyperplasia with Germinal Centers

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Summary

An invasive cortical thymoma in the anterior left mediastinum of a 78 year-old Japanese female involved unusual multifocal B-cell hyperplasia forming germinal centers in its invasion. The invasive cortical thymoma showed a small number of keratin+epithelioid cells in lymphocytic stroma around some of blood-pooling microcysts and in the degenerative as well as invasive areas. In the invasive areas T-cell-rich stroma was associated with multifocal B-cell hyperplasia forming germinal centers. The Tcells included many proliferating cells. In the analysis of DNA extracted from paraffin sections by means of polymerase chain reaction for T-cell receptor β and γ and immunoglobulin genes, no clonal proliferation of T- and B-cells was detected. An invasive cortical thymoma was diagnosed because of no obviously detectable neoplastic natures in the lymphocytes, although the association of unusual multifocal B-cell hyperplasia forming germinal centers suggested a possibility of a secondary T-cell low grade malignant lymphoma corresponding to the nodal T-zone lymphoma.

Key Words: Thymoma, T-cell, B-cell, paraffin-immunohistochemistry, polymerase chain reaction, TCR β, TCR γ, immunoglobulin heavy chain gene

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Introduction

Primary thymic tumors in aged patients in Japan are thymomas, teratomas and lymphomas[1)]. There were some reports that a long-standing thymoma had non-Hodgkin malignant lymphoma[2,3)], indicating a possibility of the secondary occurrence of low-grade T-cell malignant lymphoma in cortical thymoma. But it was reported that the clonal proliferation of T-cells had not yet been recognized in lymphocytic thymomas. We experienced a case of invasive cortical thymoma involving multifocal B-cell hyperplasia forming germinal centers.

We report here the case of invasive cortical thymoma with analysis of T-cell receptor β and γ chain genes and immunoglobulin heavy chain gene by means of polymerase chain reaction and with discussion of its differential diagnosis from a composite case of cortical thymoma and non-Hodgkin malignant lymphoma.

Case

The patient was 78 year old Japanese woman. She complained sometimes of pain on her neck. Thymic mass was pointed out on her chest X-ray examination in medical check-up. Neither swelling of lymph nodes nor splenomegaly was noted. Number and nature of blood cells were not abnormal in her peripheral blood. The all laboratory data of her peripheral blood were within the normal range. Computed tomograph detected a thymic tumor revealing high and low density areas and clear outline and associating no regional swollen lymph nodes in her anterior left mediastinum. Under a clinical diagnosis of thymoma the tumor was removed. After the operation she was free from any complains and abnormal physiological and laboratory findings.

Pathology and paraffin-immunohistochemistry

The removed thymic mass was a 11×6×6 cm large, lobulated and solid, involving ligament of thyroid. On cut surface of the tumor, dark-red tumor had capsule-like tissue demarcating it from whitish invasion. There was a small amount of persistent thymic tissue around the tumor.

Microscopically the dark-red tumor parenchyma comprised blood-pooling microcysts surrounded by lymphocytic stroma and degenerated areas (Fig. 1a). In the degenerated areas spindle epithelioid cells were seen in epithelial arrangement (Fig. 1b). Paraffin-immunohistochemistry of anti-keratin antibody showed keratin + spindle cells along the degenerated cystic lesions (Fig. 1c). Some of the microcysts had keratin+ factor Ⅷ- epithelial lining. The cellular stroma (Fig. 1c) comprised many small CD3+ UCHL-1+ MT-1- T-cells, small clusters of L26+Mx-pan B+ MB-1- LN-1-LN-2-LN-3- cells and some histiocytes. Some histiocytes were positive for S100 protein. Epithelioid cells among the lymphocytes were negative for EMA, LN-2 and LN-3. Only a few epithelioid cells were positive for keratin.

The tumor parenchyma was demarcated by thick fibrosclerotic capsular tissue from the extracapsular whitish areas (Fig. 2a). The extracapsular areas were the invasion, comprising T-cell rich areas (Fig. 2b) with a few keratin+ epithelioid cells, fibrosclerotic stroma and multifocal proliferation of L26+LN-1+LN-2+ LN-3+pale B-cells associating a small number of CD3 + UCHL-1+ T-cells. In some of the foci of the pale B-cells germinal center with mantle zone was formed (Fig. 2c). The lymphocytes in the T-cell rich areas and in the B-cell hyperplastic areas showed a few regular mitoses and included many proliferating cells labeled in antigen-retrieval paraffin-immunohistochenistry of PCNA and MIB1 (Ki-67).

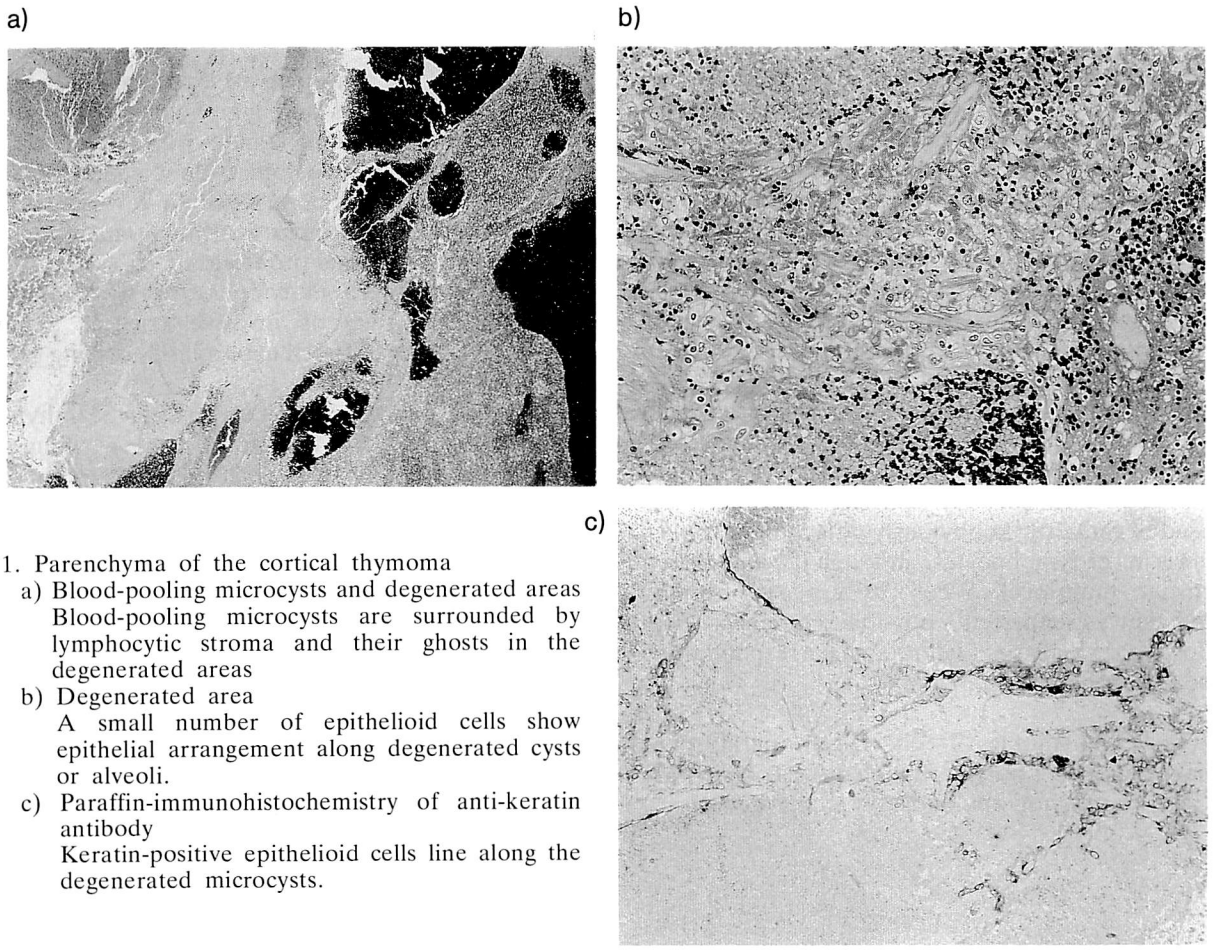

Fig. 1. Parenchyma of the cortical thymoma
a) Blood-pooling microcysts and degenerated areas
Blood-pooling microcysts are surrounded by lymphocytic stroma and their ghosts in the degenerated areas
b) Degenerated area
A small number of epithelioid cells show epithelial arrangement along degenerated cysts or alveoli.
c) Paraffin-immunohistochemistry of anti-keratin antibody
Keratin-positive epithelioid cells line along the degenerated microcysts.

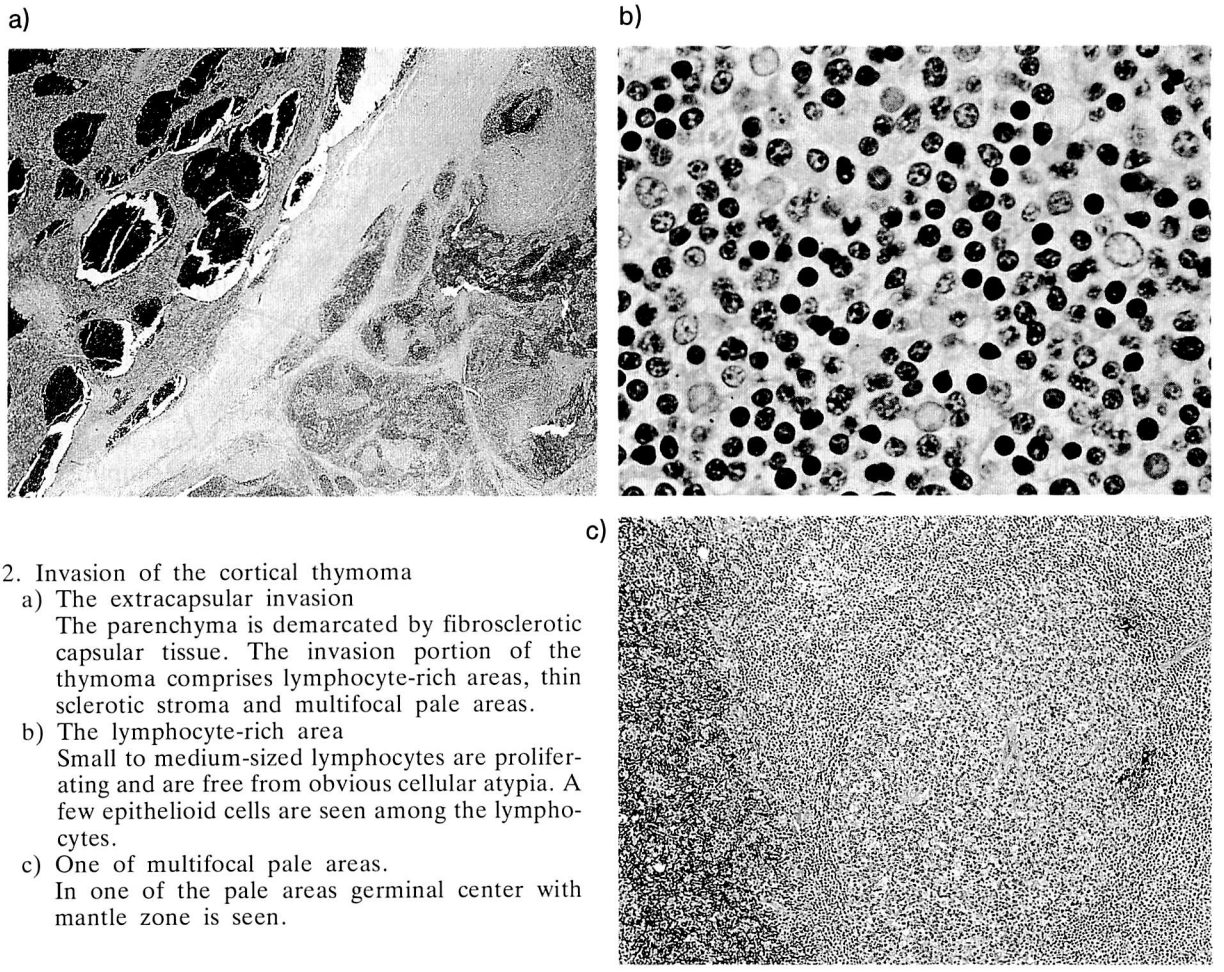

Fig. 2. Invasion of the cortical thymoma
a) The extracapsular invasion
The parenchyma is demarcated by fibrosclerotic capsular tissue. The invasion portion of the thymoma comprises lymphocyte-rich areas, thin sclerotic stroma and multifocal pale areas.
b) The lymphocyte-rich area
Small to medium-sized lymphocytes are proliferating and are free from obvious cellular atypia. A few epithelioid cells are seen among the lymphocytes.
c) One of multifocal pale areas.
In one of the pale areas germinal center with mantle zone is seen.

Polymerase chain reaction (PCR) of T-cell receptor (TCR) β and γ chain genes and immunoglobulin heavy chain gene

DNA extracted from one 10 micrometer thick paraffin section of this thymic tumor was examined by PCR to see whether any of TCR β and γ-chain and immunoglobulin heavy chain genes of the lymphocytes is rearranged or not. When an enough amount of the extracted DNA was the template DNA of the PCR, amplified DNA bands could not detected in the agar-gel electrophoresis of the PCR products of 6 pairs of primers TCR β V, D1, D2, J1 and J2[4], 4 pairs of TCR γ V11, V101, Jγ and Jp[5] and a pair of IgJHI and IgJH2[6].

Discussion

Histopathological differentiation of lymphocytic thymoma from the primary thymic lymphoma is sometimes difficult but the existence of cyst is considered to be pathognomic for lymphocytic thymoma[7]. But there were some thymoma patients reported to suffer from secondary non-Hodgkin malignant lymphoma such as T-cell lymphoblastic lymphoma and chronic lymphocytic leukemia[2,3], while a composite case of thymoma and non-Hodgkin malignant lymphoma have not yet been reported. Molecular analysis of lymphocytes in lymphocytic thymomas could not show their monoclonal proliferation[8], although it is unknown whether unusual lymphocytic thymomas like this case were included in those cases studied. There seems to be a possibility of outcome of low grade malignant lymphoma in lymphocytic thymoma.

Lymphocytic thymoma is recently classified as cortical type thymoma[9]. Cortical type thymoma often associates Myasthenia gravis and its stromal lymphocytes are regarded as stimulated peripheral T cells[10]. L26+non-lymphoid cells are reported to be found in thymomas and normal thymus[11] and clusters of the L26+ Mx-pan B+MB- 1- LN-1- LN-2- LN-3- cells in this case may be the L26+ non-lymphoid cells. The stimulated T-cells may induce proliferation of B-cells. Multifocal B-cell hyperplasia in the invasion areas of this cortical thymoma might be explained by the function of the activated peripheral T-cells in a cortical thymoma. But multifocal B-cell hyperplasia forming

germinal centers can not be often found in a cortical thymoma. And such hyperplastic lymph follicles are seen in nodal T-zone lymphoma[12].

It is the problem in the differential diagnosis of this invasive cortical thymoma from the secondary outcome of T-zone lymphoma in the long-standing thymoma what method can detect neoplastic features of peripheral T-cells in a cortical thymoma. The lymphocytes in this thymoma proliferated, showing many labeled cells by PCNA and MIB1 (Ki-67) and regular mitosis. No obvious presence of atypical mitoses in them suggests their reactive nature rather than neoplastic one. Recently, PCR analysis is introduced in hematopathology to detect rearrangement of TCR β and γ-chains and immunoglobulin heavy chain genes in malignant lymphomas and lymphocytic leukemias[4,5,6]. Rearrangement in one or the both genes of TCR β and γ-chain, a proof of clonal proliferation of T-cells, is reported to be detected in more than 80% cases of T-cell malignant lymphomas[5]. The PCR analysis of this cortical thymoma could not show rearrangement in any of the genes, suggesting no obvious neoplastic nature in the T- and B-cells in this cortical thymoma.

Consequently, this case should be diagnosed as invasive cortical thymoma involving unusual multifocal B-cell hyperplasia forming germinal centers, although a possibility of a secondary T-cell lymphoma corresponding to the nodal T-zone lymphoma in this invasive cortical thymoma could not be denied completely.

Acknowledgement

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