

## CASE REPORT

**TWO NEOPLASMS RICH IN SMALL LYMPHOCYTES, B1B2 THYMOMA AND SMALL LYMPHOCYTIC LYMPHOMA, INTERMINGLED IN ONE TUMOR MASS. A CASE REPORT**

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We present a case of a 52-year-old man with myasthenia gravis and a mediastinal tumor who was admitted to our hospital for surgical treatment. The pathologic examination of the resected tumor revealed a very rare case of a collision tumor: a B1B2 thymoma and a small lymphocytic lymphoma. Flow cytometry of the peripheral blood revealed the presence of a small number of leukemic cells. After postoperative irradiation of the mediastinum and chemotherapy a complete response in both diseases was achieved. The case confirms that a pathologist should always be aware that two different neoplasms can coexist in rare cases.

**Key words:** thymoma, small lymphocytic lymphoma, mediastinal tumors, immunohistochemistry, flow cytometry.

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## Introduction

Thymomas are rare mediastinal tumors composed of neoplastic epithelial cells of thymus intermingled with non-neoplastic immature T lymphocytes (thymocytes). The proportions of the cells vary depending on the histological type of a thymoma. B-cells are uncommon and usually dispersed around vessels. The only exception is micronodular thymoma, which contains prominent lymphocyte B-rich stroma and the very characteristic, nodular, architecture of epithelial cells.

An association between the thymomas and subsequent second malignancies including lymphomas has been observed by some authors [1, 2, 3]. However, cases of coincidence of thymoma and lymphoma are

very rarely discussed in the literature. Such cases can pose both diagnostic and therapeutic issues.

We would like to present a case of a collision tumor of two different clinically but histologically similar neoplasms: B1B2 thymoma and small lymphocytic lymphoma (SLL).

## Case presentation

### Clinical history

A 52-year-old man with a 6-month history of myasthenic symptoms and an anterior mediastinal tumor was admitted to our hospital for surgical treatment. The tumor was well-delineated on a computed tomography (CT) scan and no enlarged mediastinal

lymph nodes were described. On admission, the patient was in a good general condition and presented no symptoms except a slight left-sided ptosis. Peripheral lymph nodes were not enlarged on physical examination. Preoperative blood analysis revealed a slight elevation of the lymphocyte count ( $5.14 \times 10^9/l$ ), but the total white blood cell count, as well as other routine laboratory test results, were normal.

The patient underwent a longitudinal sternotomy and a thymectomy along with a resection of the mediastinal fat tissue and regional lymph nodes.

The resected surgical specimen comprised a thymus with a solid, lobulated tumor measuring  $7 \times 5 \times 3.5$  cm, as well as fat tissue and 14 mediastinal lymph nodes. Both the thymus and lymph nodes were evenly firm and white on cross section.

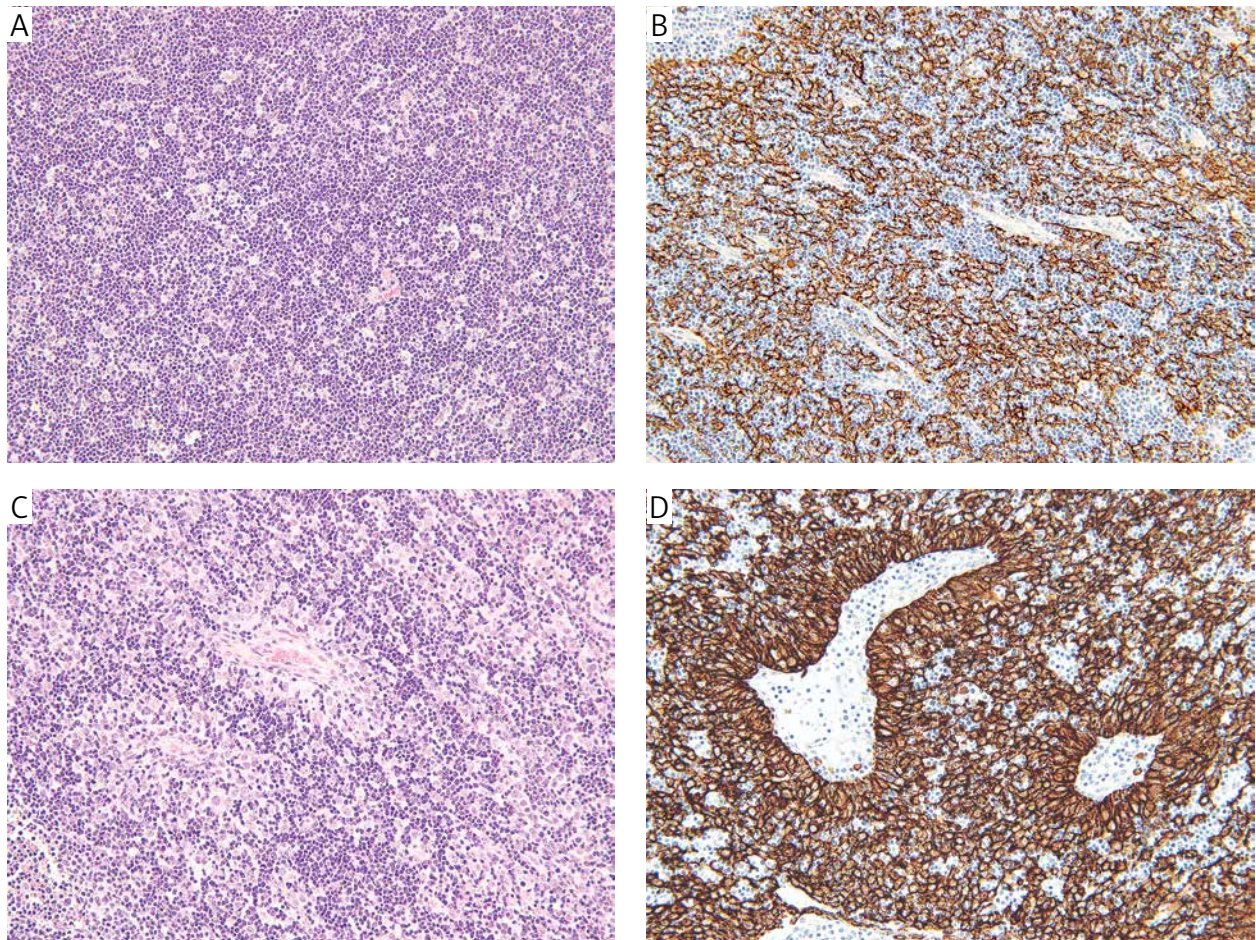
### Histological examination

Representative formalin-fixed cut specimens obtained from the surgical material were routinely embedded in paraffin and histological sections were stained with hematoxylin-eosin (HE). After micro-

scopic examination, a comprehensive panel of immunohistochemical reactions in BenchMark GX automated immunostainer (Ventana Medical System Inc., Tucson, Arizona) was performed and included the following antibodies: pancytokeratin (clone AE1/AE3, Ventana Medical Systems, VMS), CD3 (clone 2GV6, VMS), CD20 (clone L26, VMS), CD20 (clone L26, DAKO) and Ki-67 (clone 30-9, VMS).

Histological classifications of the World Health Organization (WHO) [4, 6] were used to establish the histological type of the neoplasms, and the stage of the thymic epithelial tumor was determined by employing the Masaoka-Koga staging system.

A microscopic examination revealed the coexistence of two neoplasms: thymoma and SLL. The thymic tumor visible macroscopically represented mostly the thymoma. The tumor was composed of lymphocyte-rich areas without discernible epithelial cells and perivascular spaces but with preserved cortico-medullary differentiation that resembled normal thymic architecture. However, there were also areas rich in polygonal epithelial cells that formed small



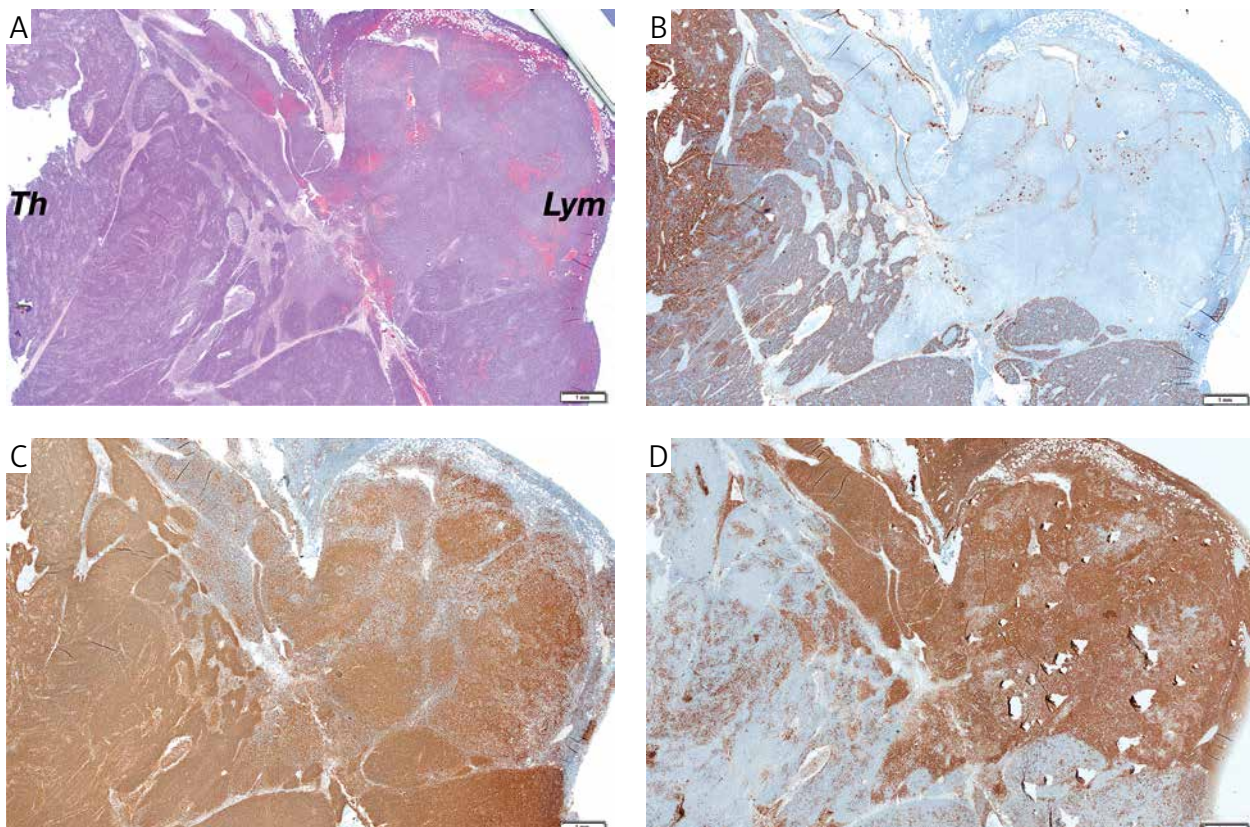
**Fig. 1.** A) Component B1 of the thymoma with dispersed epithelial cells (HE staining, magnification  $200\times$ ). B) dilacerated net of the epithelial cells seen in reaction with cytokeratin (AE1/AE3, magnification  $200\times$ ). C) Component of B2 thymoma (HE staining, magnification  $200\times$ ). D) The density of the epithelial cells in B2 thymoma is higher and the reaction with cytokeratin is more pronounced. Note distinct perivascular palisading of neoplastic cells (AE1/AE3, magnification  $200\times$ )

clusters and palisades around the perivascular spaces. The epithelial nature of the tumor was confirmed by the reaction with anti-cytokeratin antibody (AE1/AE3). The lymphatic component of the tumor expressed CD3 that corresponds with T lymphocytes. The morphology of the tumor combined features of B1 and B2 thymoma (Fig. 1). The thymoma invaded the perithymic fat tissue (stage IIA) and involved the surgical margin (pR1). No lymph node metastases were observed.

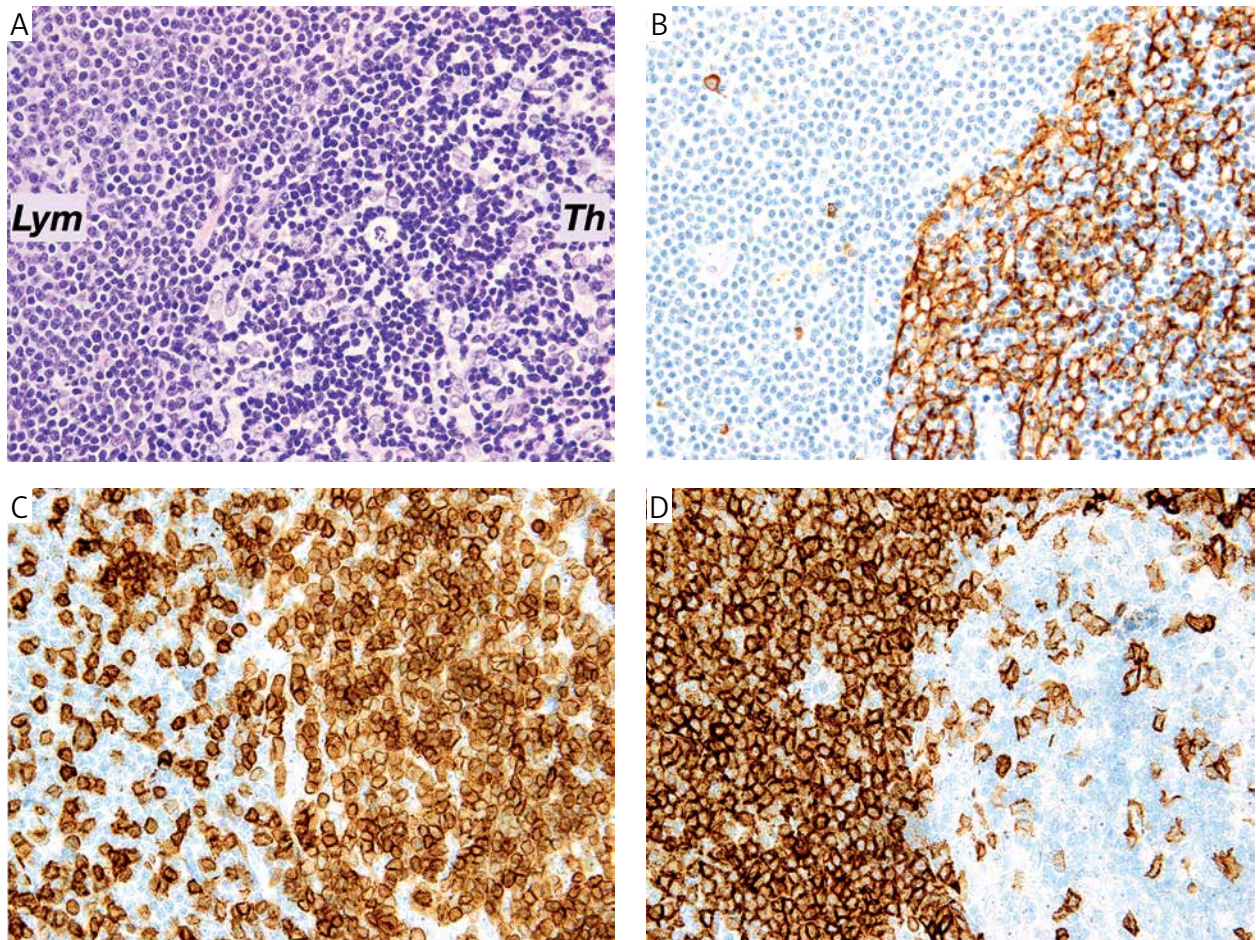
However, additional monotonous infiltrations of small lymphocytes were found among the lobules of the thymoma and the morphology, and the immunophenotype of the infiltrations clearly differed from the main tumor mass. Lymphocytic infiltrates revealed a pseudofollicular pattern of regularly distributed pale areas corresponding to proliferation centers containing larger cells in a dark background of small cells. The predominant cells were small lymphocytes with clumped chromatin, round nuclei and small nucleoli. Proliferation centers contained prolymphocytes (medium-sized cells with relatively clumped chromatin and small nucleoli) and some paraimmunoblasts (larger cells with round nuclei, dispersed chromatin,

central eosinophilic nucleoli and slightly basophilic cytoplasm). The lymphocytes were positive for CD20 with the Ki-67 index up to 30% and were not accompanied by epithelial cells. The morphological and immunohistochemical character of the infiltration was typical for B-cell lymphoma (Figs. 2, 3). The architecture of the whole residual thymic tissue and all found lymph nodes were also destroyed by a diffuse infiltration of B-lymphocytes. A suggestion of concurrent small lymphocytic lymphoma was made. This diagnosis was subsequently confirmed by hematopathologists, who broadened the immunohistochemical panel: the lymphoma cells showed surface anti-CD5 (clone 4c7, DAKO) and CD23 (DAK-CD23, DAKO) expression. On the other hand, cyclin D1 (clone, EP12, DAKO), CD10 (clone, 56C6, DAKO) and BCL6 (clone PG-B6P, DAKO) were negative. The differential diagnosis included mantle cell lymphoma small cell and classical variant, marginal zone lymphoma and follicular lymphoma, but the morphology and immunophenotype were characteristic of SLL.

The diagnosis was also confirmed by flow cytometry (FCM) analysis of cellular suspension obtained by the fine needle aspiration biopsy from the involved



**Fig. 2.** A) A low-power image of the collision tumor composed of the thymoma (*Th*) and small lymphocytic lymphoma (*Lym*). Note the fat tissue infiltration by the lymphoma cells (upper right) (HE staining, magnification 7 $\times$ ). B) The reaction with cytokeratin is evident in the thymoma. In the area involved by the lymphoma only thymic tissue remnants are immunopositive (AE1/AE3, magnification 7 $\times$ ). C) CD3-positive non-neoplastic lymphocytes are dispersed within both the thymoma and lymphoma tissue (CD3, magnification 7 $\times$ ). D) A great number of CD20-positive lymphocytes are seen in the cytokeratin-negative area (CD20, magnification 7 $\times$ )



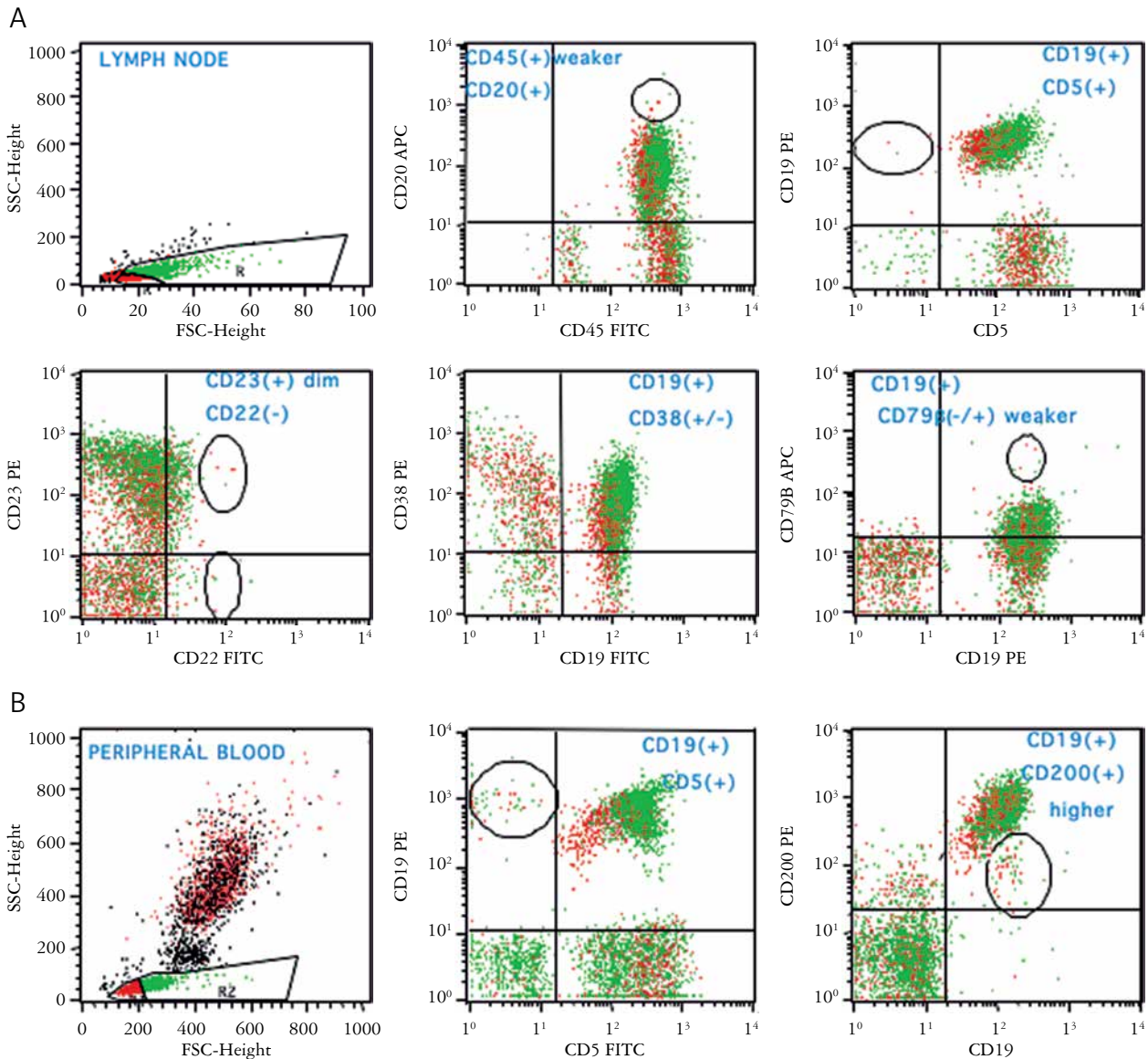
**Fig. 3.** A) A high-power image of the collision tumor composed of the thymoma (*Th*) and small lymphocytic lymphoma (*Lym*) (HE staining, magnification 400×). B) Neoplastic epithelial thymoma cells reveal positive reaction with cytokeratin (AE1/AE3, magnification 400×). C) CD3-positive non-neoplastic lymphocytes are densely packed in the area of thymoma and loosely dispersed within lymphoma tissue (CD3, magnification 400×). D) CD20-positive lymphocytes fill the cytokeratin-negative area (CD20, magnification 400×)

lymph node and from the peripheral blood. The data were collected by a BD FACSCalibur cytometer and processed using the BD CellQuest software. The FCM results are shown in Fig. 4. Analysis showed small, normal T and B lymphocytes and slightly larger, neoplastic cells reaching up to 80% and 24% of all cells of the lymph node and peripheral blood, respectively. SLL diagnosis requires lymphadenopathy, no cytopenias due to bone marrow infiltration by SLL/CLL cells and a number of peripheral blood B-cells in FCM  $< 5 \times 10^9$  cells/l. This case met all these conditions. SLL cells expressed CD45 (weaker), CD19, CD20 (dim), CD23 (dim), HLA-DR (dim), CD5, CD43, CD200 (higher), ZAP70, BCL-2, CD25, CD52, CD62L and kappa/IgD/IgM. The mean fluorescence intensity (MFI) of CD19 expression was higher in comparison to MFI of CD20. The subpopulation of SLL cells also revealed the expression of CD79 $\beta$ , CD38, CD11c and CD71. The neoplastic cells were negative for CD22, CD10, FMC7, lambda, IgG and IgA.

Two months after surgery, adjuvant irradiation of the mediastinum was performed (total dose 5400 cGy, 200 cGy per fraction) due to the advanced stage of thymoma and positive surgical margin. Radiotherapy was complicated by slight postradiation esophagitis. One year later progression of lymphoma with peripheral lymph node enlargement was observed. The patient received six courses of chemotherapy: rituximab, fludarabine and cyclophosphamide (R-FC) with a complete response in criteria of the RECIST 1.1 (Response Evaluation Criteria In Solid Tumors) scale. Two years after surgery and one year before this report no signs of recurrence of either neoplasm were observed.

## Discussion

Lymphocyte-rich tumor of the anterior mediastinum always requires differentiation between thymoma and lymphoma. Essentially, the differentiation should not be difficult – the thymomas are epithelial



**Fig. 4.** Flow cytometric immunophenotyping in fine-needle aspiration biopsy of axillary lymph node (A) and peripheral blood (B) of small lymphocytic lymphoma case. Forward scatter/side scatter pictures (dot plots A and G) show the coexistence of small normal T/B lymphocytes (red dots) with slightly larger lymphoma cells (green dots). CLL/SLL cells express: CD45(+weaker)/CD20(+dim)/CD19(+)/CD23(+dim)/CD5(+)/CD200(+higher) as well as weak intensity of CD38(+/-) and CD79(-/+) on a small subpopulation of CLL/SLL cells (dot plots E-F). Mean fluorescence intensity: CD19 > CD20. The cells are negative for CD22(-). Compare the antigen expression of normal B lymphocytes shown in circles "R" (dot plots B-D, F, H-I)

tumors, so immunostaining with a panel of anti-cytokeratin antibodies usually resolves the problem. However, both neoplasms can appear very similarly in routine HE staining. A pathologist should suspect a neoplasm of lymphatic origin rather than a thymoma if the microscopic appearance is very monotonous and thymic corticomedullary architecture identified as pale-staining medullary islands surrounded by dark-staining cortical areas is effaced. A lymphoma often infiltrates into vessel walls or between individual cells of mediastinal fat tissue and usually lacks a fibrous capsule or interlobular septa. The main types of primary mediastinal lymphomas are classi-

cal Hodgkin lymphoma (cHL), primary mediastinal large B-cell lymphoma, T lymphoblastic leukemia/lymphoma (T-LBL/ALL) and anaplastic large cell lymphoma. Other types such as extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) or CLL/SLL are less common [4].

Lymphocyte-rich types of thymomas comprise B1, B2 and often AB type. The morphology of B1 type can be especially misleading and can suggest a lymphoma due to the extremely high number of lymphocytes and inconspicuous epithelial cells. However, immunohistochemical anti-cytokeratin staining reveals a loose network of epithelial cells dispersed more or

less evenly within the whole tumor [4]. Another histological type of thymoma rich in lymphocytes which should be mentioned is micronodular thymoma with lymphoid stroma. The epithelial cells of this thymoma are elongated, densely packed and form small, confluent nodules embedded in abundant lymphoid stroma with follicular hyperplasia. The stroma is devoid of epithelial cells and lymphocytes reveal the immunophenotype of B-cells, which is an unusual phenomenon for thymomas. Ströbel et al. showed that micronodular thymoma increases the risk of developing intrathymomatous low-grade B-cell lymphomas of MALT type; however, the authors did not find any correlation between the thymoma and systemic lymphomas [5].

Thymomas are regarded as a risk factor for the development of an additional primary malignancy. The debilitation of the protective function of the thymus, the main immune organ, by a growing tumor, is a potential explanation of this phenomenon [1]. Second malignancies are more often metachronous than synchronous and can develop years after or before the thymic tumor. The risk of a second neoplasia reported in different publications was between two and 18 times higher in patients with thymomas in comparison to the normal population [1, 2, 3]. Primary sites of second malignancies indicated by the authors varied significantly. They reported cHL and non-Hodgkin lymphomas, as well as cancers of solid organs: digestive system, lung, breast, thyroid, kidney, cervical and prostate carcinomas [1, 2, 3].

Cases of collision tumors composed of thymoma and lymphoma are very rarely discussed in the literature. Most of them involve T-cell lymphomas (T-LBL/ALL, peripheral T-cell lymphoma not otherwise specified) [7, 8, 9, 10, 11]. There are two cases of simultaneous thymoma and cHL [12, 13] and two thymic epithelial tumors accompanied by SLL/CLL [14, 15]. One of the latter cases was a thymoma composed of bland spindle cells forming nests (the exact type was not specified) [14] and the second was squamous cell thymic carcinoma [15]. In both cases the patients did not demonstrate symptoms characteristic for thymic malignancy and mediastinal tumors were found during a chest examination performed for other reasons. CLL/SLL was detected fortuitously on microscopic examination. In our case, the patient suffered from myasthenic symptoms, so the thymoma was suspected clinically. However, careful microscopic examination revealed not only a thymoma but also SLL. To our knowledge such a combination of lymphocyte-rich thymoma and small lymphocytic lymphoma is unique in the literature.

From the therapeutic point of view, the coexistence of these types of neoplasms did not create any complications because the therapeutic approaches did not interfere with each other. The thymoma treatment re-

quired surgical resection with subsequent radiotherapy, while the lymphoma progression observed one year later was treated with chemotherapy. The progression of lymphoma does not seem to be induced by previous irradiation. It involved mainly peripheral rather than mediastinal lymph nodes, and irradiation by itself is not regarded as a risk factor of SLL/CLL [16].

## Conclusions

We have presented a very rare case of simultaneous B1B2 thymoma and SLL forming a collision tumor in a patient with myasthenic symptoms. The case indicates the necessity of careful microscopic examination supported by immunohistochemical analysis in each case of mediastinal tumor. A lymphocyte-rich mediastinal tumor can represent both a neoplasm of actually epithelial origin such as a thymoma and a true lymphoma. Pathologists should be aware of the possibility of coexistence of both malignancies.

*The authors declare no conflict of interest.*

## References

1. Granato F, Ambrosio MR, Spina D, et al. Patients with thymomas have an increased risk of developing additional malignancies: lack of immunological surveillance? *Histopathology* 2012; 60: 437-442.
2. Filosso PL, Galassi C,
3. Ruffini E, et al. Thymoma and the increased risk of developing extrathymic malignancies: a multicentre study. *Eur J Cardiothorac Surg* 2013; 44: 219-224.
4. Weksler B, Nason KS, Mackey D, et al. Thymomas and extrathymic cancers. *Ann Thorac Surg* 2012; 93: 884-888.
5. Müller-Hermelink HK, Engel P, Kuo TT, et al. Tumours of the Thymus. In: Travis WD, Brambilla E, Muller-Hermelink HK, et al. (eds.). *WHO Classification of Tumours. Pathology and Genetics. Tumours of the Lung, Pleura, Thymus and Heart*. IARC Press, Lyon 2004; 145-248.
6. Ströbel P, Marino M, Feuchtenberger M, et al. Micronodular thymoma: an epithelial tumour with abnormal chemokine expression setting the stage for lymphoma development. *J Pathol* 2005, 207: 72-82.
7. Swerdlow SH, Campo E, Harris NL, et al. (eds.) *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues*. 4rd ed. IARC, Lyon 2008.
8. Friedman HD, Inman DA, Hutchison RE, Poiesz BJ. Concurrent invasive thymoma and T-cell lymphoblastic leukemia and lymphoma. A case report with necropsy findings and literature review of thymoma and associated hematologic neoplasm. *Am J Clin Pathol* 1994; 101: 432-437.
9. Ito J, Yoshida A, Maeshima AM, et al. Concurrent thymoma, thymic carcinoma, and T lymphoblastic leukemia/lymphoma in an anterior mediastinal mass. *Pathol Res Pract* 2015; 211: 693-696.
10. Macon WR, Rynalski TH, Swerdlow SH, Cousar JB: T-cell lymphoblastic leukemia/lymphoma presenting in a recurrent thymoma. *Mod Pathol* 1991; 4: 524-528.
11. Rovera F, Billo P, Capella C, Dominiononi L. Concurrent epithelial thymoma and T-cell lymphoblastic lymphoma. *Interact Cardiovasc Thorac Surg* 2003; 2: 537-540.

12. Fraser CR, Rios C, Kaya B. Composite lymphocyte-rich thymoma and peripheral T-cell lymphoma not otherwise specified. *Lab Med* 2012; 43: 4-8.
13. Nemoto K, Ishikawa H, Ohnishi Y, et al. Hodgkin's disease accompanied with thymoma. *Acta Pathol Jpn* 1987; 37: 1505-1512.
14. Ridell B, Larsson S. Coexistence of a thymoma and Hodgkin's disease of the thymus. A case report. *Acta Pathol Microbiol Scand A* 1980; 88: 1-4.
15. Khoury JD, Amin HM, Jorgensen JL, et al. Composite thymoma and chronic lymphocytic leukemia/small lymphocytic lymphoma involving the anterior mediastinum. *Arch Pathol Lab Med* 2003; 127: E76-E79.
16. Steger CM, Morresi-Hauf A, Krugmann J, et al. Two malignant tumours in the anterior mediastinum positive for CD5. *BMJ Case Rep* 2010; 2010: pii: bcr0920092289.
17. Slager SL, Benavente Y, Blair A, et al. Medical history, lifestyle, family history, and occupational risk factors for chronic lymphocytic leukemia/small lymphocytic lymphoma: the InterLymph Non-Hodgkin Lymphoma Subtypes Project. *J Natl Cancer Inst Monogr* 2014; 2014: 41-51.

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