T-cell/Histiocyte-rich B-cell Lymphoma

Turcu M.[1], Horvath Emoke[2], Chira Liliana[3], Cotoi O.S.[4]

[1] Department of Pathology, University of Medicine and Pharmacy, Department of Pathology, Emergency County Hospital, Targu-Mures
[2] Department of Pathology, University of Medicine and Pharmacy, Department of Pathology, Emergency County Hospital, Targu-Mures
[3] Department of Pathology, University of Medicine and Pharmacy, Department of Pathology, Emergency County Hospital, Targu-Mures
[4] Department of Cellular and Molecular Biology, University of Medicine and Pharmacy, Department of Pathology, Emergency County Hospital, Targu-Mures

Background: T-cell/histiocyterich B-cell lymphoma (T/HRBCL) is an uncommon morphologic variant of diffuse large B-cell lymphoma (DLBCL), representing less than 10% of all DLBCL cases. T/HRBCL has attracted considerable attention as a result of the difficult task of distinguishing it from similar entities, such as nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL), classic Hodgkin lymphoma and peripheral T/cell lymphoma, nonspecific.
Case report: We present the case of a 70-year-old female patient addressing her primary care physician for headaches, nausea and a large, painful tumor in her left axilla. The paraclinical examinations revealed minimal deviations of hematological tests, but showed elevated LDH values. Surgery was performed and a specimen, composed of 13 lymph nodes, (the largest one having the surface diameter of 130 mm) was removed and examined histologically. On microscopic evaluation, the HE stain showed portions of lymph node completely effaced and replaced by a vaguely nodular lymphoid proliferation composed of scattered, large cells, with abundant cytoplasm, multilobated vesicular nuclei and proeminent nucleoli, consistent with lymphocytes and histiocytes. The immunohistochemical study proved the proliferative mass to be constituted of a limited number of large, CD20 positive B-cells, with proeminent nucleolus, in a background of CD3 positive T-cells, together with a variable number of histiocytes, highlighted with CD68. The large B-cells were scattered and did not form any clusters or strips. A diagnosis of T/HRBCL was made.
Conclusion: T/HRBCL is a rare variant of DLBCL, with an aggressive clinical outcome. In such cases immunohistochemical analyses are mandatory to reach correct diagnosis.

Keywords: T-cell/histiocyte-rich B-cell lymphoma, diffuse large B-cell lymphoma

Introduction

T-cell/histiocyte-rich B-cell lymphoma (T/HRBCL) is an uncommon morphologic variant of diffuse large B-cell lymphoma (DLBCL), accounting for less then 10% of all cases of DLBCL.

Histologically, T/HRBCL is characterized by the presence of a limited number of disseminated, large, atypical B-cells, set in an abundant background composed of T-cells and histiocytes. This type of lymphoma affects mainly the lymph nodes, but bone marrow, liver and spleen involvement is not uncommon at the time of diagnosis [1].

T/HRBCL was first described as "T-cell-rich B-cell lymphoma" in 1988 by Ramsey et al. who reported five cases that had previously been misdiagnosed as peripheral T-cell lymphoma due to the predominance of T-cells surrounding large B cells [2]. Since then T/HRBCL has attracted considerable attention as a result of the difficult task of distinguishing it from morphologically similar entities, such as nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) and classic Hodgkin lymphoma. Nevertheless many studies suggest a tight linkage between these entities.

The aim of our study is to report a case of T/HRBCL and to discuss the major clinical, pathological and biological aspects that define this type of lymphoma, their understanding being essential in the adequate diagnosis and management of these patients.

Case report

We present the case of a 70 years old female patient addressing her primary care physician for headaches, nausea and a large, painful tumor in her left axilla, that became clinically apparent in a relatively short period of time (four months). The laboratory studies showed minimal deviations from the normal spectrum, count of white blood cells slightly lower 3,1x103, peripheral blood smear with unsignificant changes, no sign of anemia, normal hemoglobin and hematocrit levels, unmodified red blood cell count, without signs of thrombocytopenia. Laboratory test showed high values of LDH (781 U/l). Elevated values of seric transaminases were also found (GOT 92 U/l, GPT 58U/l).

Tissue samples were examined using both standard dyes (hematoxylin and eosin) and immunohistochemical markers. The following immunohistochemical markers and their corresponding dilutions were used: CD20 (DAKO, 1/400), CD3 (LABVISION, 1/60), CD68 (DAKO, 1/75), CD30 (DAKO, 1/20) and CD10 (Novo Castra, 1/75).

Surgery was performed and a specimen, composed of 13 lymph nodes, was submitted for histologic examination to the Department of Pathology, Targu-Mures Emergency County Hospital. On gross examination the largest lymph node had a circumference of 130 mm, while the other 12 one had circumferences ranging from 40 to 15 mm. Microscopic evaluation, using HE, revealed portions of the lymph nodes completely effaced by a vaguely nodular lymphoid proliferation with scattered lymphocytes, appearing as mottled areas under low power magnification (Figure 1). High power magnification revealed that mottled areas were composed of scattered, large cells, with abundant cytoplasm, multilobated vesicular nuclei and prominent

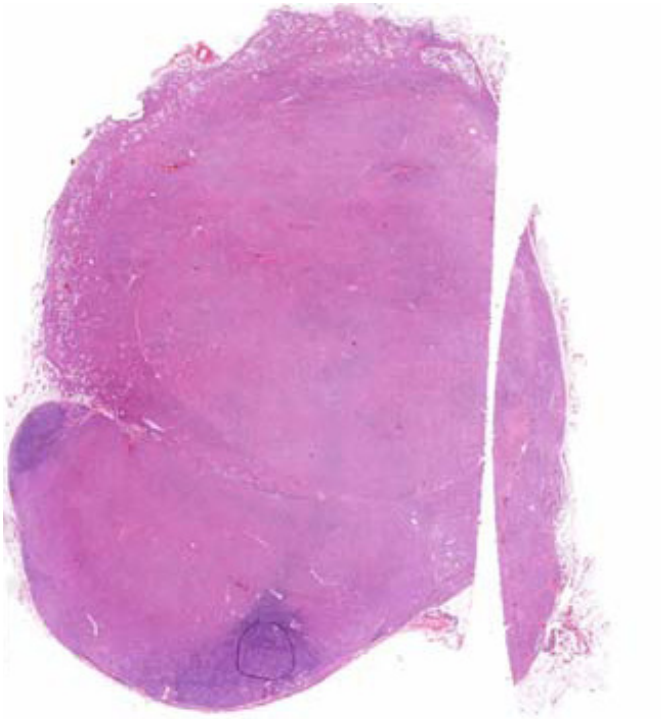

Fig. 1. T/HRBCL, HE stain, Ob. 2x.

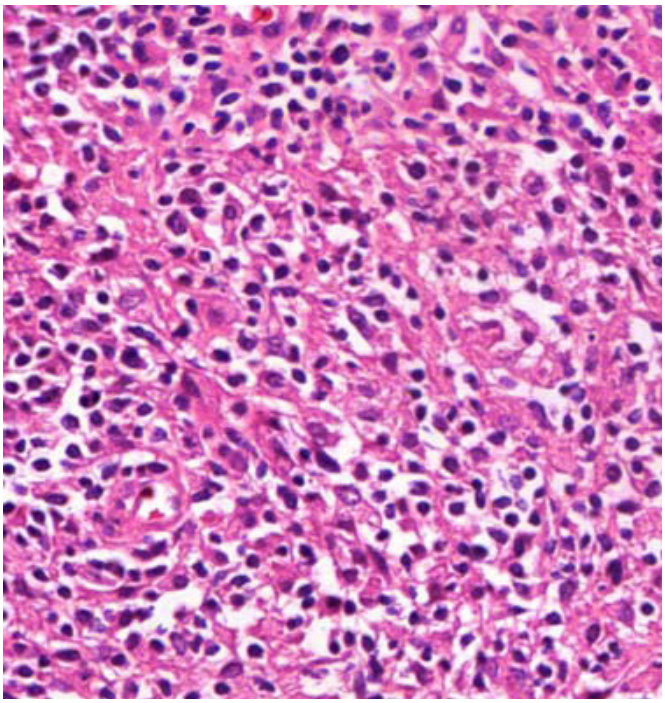

Fig. 2. T/HRBCL HE stain, Ob. 10x.

nucleoli, consistent with lymphocytes and histiocytes (Figure 2).

The proliferative mass replacing normal lymph node architecture was constituted by a limited number of large, CD20 positive B-cells, (Figure 3), embedded in a background of CD3 positive T-cells, (Figure 4), together with a variable number of CD68 positive cells (histiocytes) (Figure 5).

The large B-cells were dispersed and did not form clusters nor strips. Based on the above findings, a diagnosis of T/HRBCL was established.

Discussion

An accurate diagnosis of T/HRBCL requires experience on the pathologist side in order to differentiate this entity from other lymphoproliferative disorders that may show histological similarities. In this regard, both neoplastic and normal cellular background are extremely important for the diagnosis.

T/HRBCL has a diffuse or, rarely, a vaguely nodular growth pattern, replacing most of the lymph node's parenchyma. It is composed of scattered large B-cells (comprising less than 10% of the cellular component of the lymphoid tissue), set in a background of small lymphocytes, which are mostly T-cells and, eventually, a variable number of histiocytes. The tumor cells are always dispersed without cluster formation, an important diagnostic clue in this type of lymphoma.

Neoplastic cells can mimic classical centroblasts or immunoblasts found in DLBCL or they may show similarities to Reed-Sternberg cells of classical Hodgkin lymphoma or "popcorn" cells of nodular lymphocyte-predominant Hodgkin lymphoma [2–6].

Tumor cells are typically found within clusters of non-epithelial histiocytes with a blurred aspect that may not be readily seen on conventional examination. These histiocytes represent a distinct component of T/HRBCL and recognizing them is useful for the diagnosis [1], however there are cases when they may be absent. The cellular background is mostly composed of T lymphocytes. Eosinophils and plasma cells are absent.

Histologically, T/HRBCL is similar to nodular lymphocyte predominant Hodgkin lymphoma where the lymphocytes infiltrate the extrafollicular compartment. In case of nodular lymphoma, T/HRBCL-like areas do not represent progression towards T/HRBCL and does not have prognostic significance [7]. Still, there are some cases of progression of the lymphocyte-predominant nodular lymphoma towards T/HRBCL, in which the process is entirely diffuse and the histological appearance is practically indistinguishable from de novo T/HRBCL. The relationship between secondary and primary T/HRBCL remains controversial. They may represent distinct entities, nevertheless have many morphological and immunophenotypical similarities.

In the spleen, multifocal or micronodular involvement of the white pulp can be found and in the liver lymphomatous areas are localized within portal spaces. In these extra-nodular locations, as well as in the bone marrow, the lesion has the same aspect as in lymph nodes [5; 6]. On recurrence, the number of atypical cells may increase, resembling DLBCL. This forecasts an unfavourable evolution in a short time. Several studies recognized morphologically similar cases but without histiocytes. Whether these represent the same entity as T/HRBCL is still unclear [3; 7; 8;]. Studies including cases rich in T-cells with or without his-

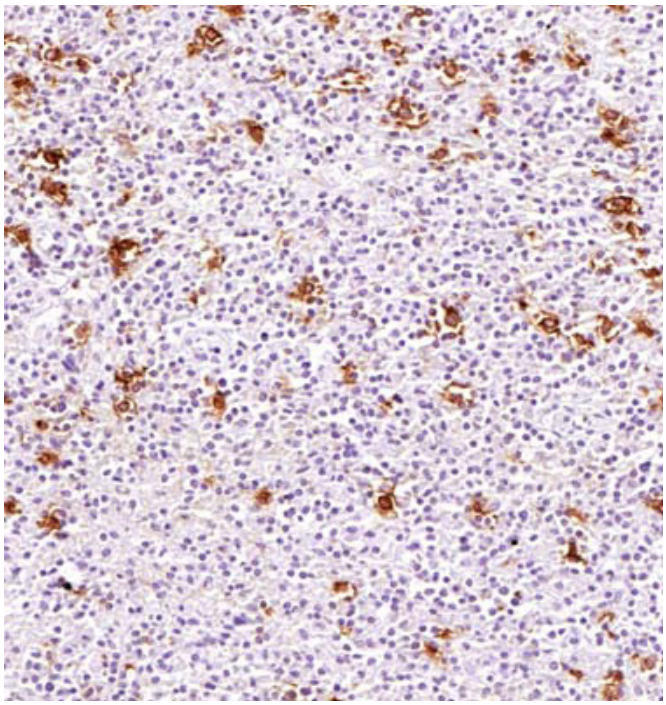

Fig. 3. T/HRBCL. Immunohistochemistry – large B-cells, CD 20 positive

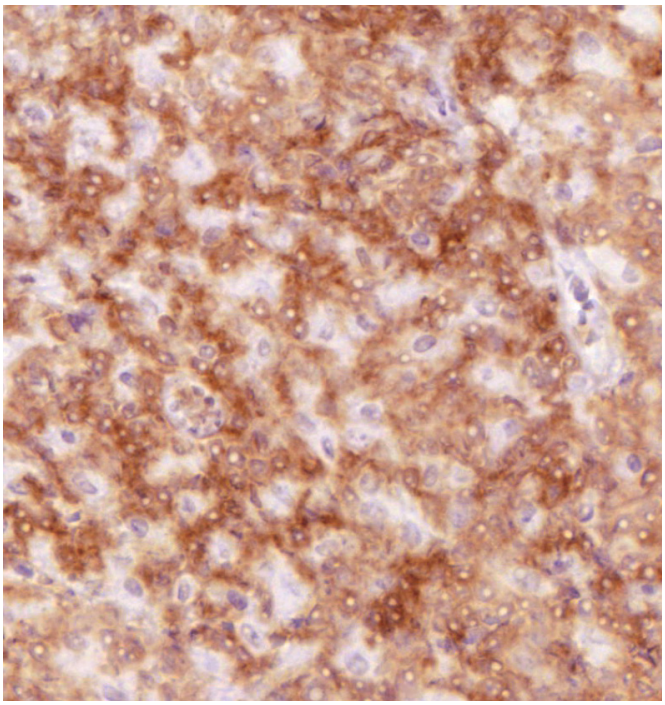

Fig. 4. T/HRBCL. Immunohistochemistry – small T lymphocytes, CD 3 positive

tiocytes defined a more heterogeneous group of large B-cell lymphomas which, probably, include more than one entity. Future studies should clarify the relationship between them. At present, while cases with few histiocytes can be included in T/HRBCL, the absence of histiocytes should be recorded. B-cell lymphomas with similar morphology (clusters or strips of medium to large B-cells) should not be included in the T/HRBCL category, but rather considered a subtype of DLBCL [9,10].

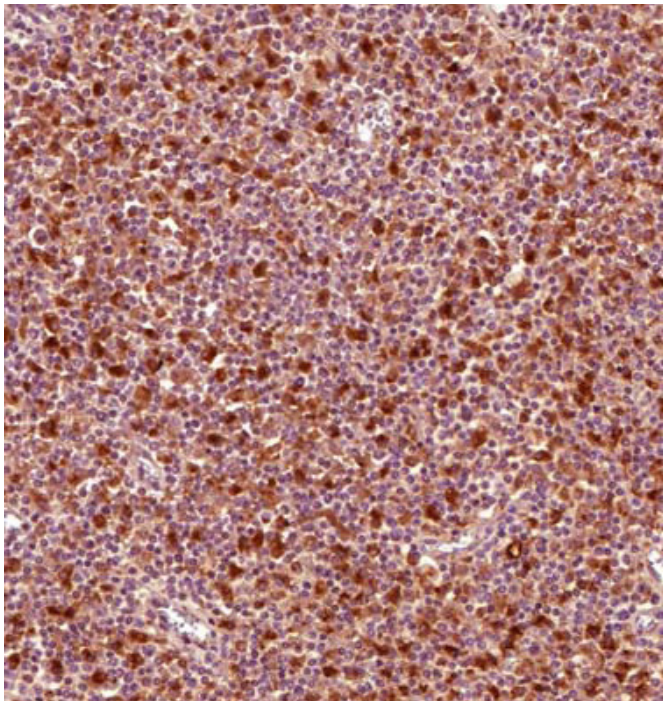

Fig. 5. T/HRBCL. Immunohistochemistry – Histiocytes (macrophages), CD68 positive cells

Malignant B-cells of T/HRBCL express CD 20, CD 45 and the B-cell transcription factors PAX5/BSAP [6,7,11; 12]. These cells are uniformly negative for CD15 and only rarely show weak positivity for CD30 [13–15], CD5 and CD138 are not expressed. Bcl6 and CD79a are expressed in most tumors [16,17].

The background is composed of a variable number of CD68 positive histiocytes and CD3, CD 5 positive T-cells. Lack of residual IgD positive mantle cells and follicular dendritic cell network helps to differentiate T/HRBCL from DLBCL.

Association with Ebstein-Barr virus has only rarely been observed in T/HRBCL and has been associated with a classical Hodgkin lymphoma phenotype, suggesting a biological overlap between the two types of lymphoma [13,14].

Genes belonging to both heavy and light chains of the immunoglobulins are detected. They are clonally rearranged and have a large number of structural mutations in the variable regions. These mutations can also be bound in the PIMI, MYC, RhoH/TTF (ARHH) and PAX5genes. Approximately 30% of the DLBCL cases have anomalies concerning region 3q27 and involve the gene BCL6, the most frequent chromosomal translocation encountered in DLBCL. Gene expression studies identified a subgroup of DLBCL characterized by weak immune response of the host and an unfavorable prognosis bore by the majority of cases diagnosed with T/HRBCL.

T/HRBCL is considered an aggressive lymphoma, although clinical heterogeneity does exist. Moreover, the presence of histiocytes characterize a more homogeneous group of patients with a very aggressive lymphoma, a frequent inefficiency of current cures and a high IPI (Inter-

national Prognostic Index) score, the IPI score being the only parameter with a prognostic significance. However, case series studies regarding T/HRBCL might have underestimated the response and survival rates, as most have included cases that were originally misdiagnosed and subsequently treated for other diseases [18,19].

T/HRBCL should be treated aggressively with chemotherapy containing Anthracyclin and using a common formula as for DLBCL. The introduction of the monoclonal anti CD20 antibody (Rituximab), improved survival when it was added to chemotherapy regimens of both young and old DLBCL patients [20–22]

Conclusions

T/HRBCL is a rare morphologic variant of DLBCL, remarkable for its unique clinical and biological features. The defining characteristic of this disease is an aggressive host inflammatory response which is inefficient in assuring the organism's defense, this being even a possible factor in promoting tumor growth. Morphologically, T/HRBCL is composed of large B-cells, scattered in a background of small lymphocytes (T-cells) and a variable number of histiocytes; the latter may be absent. The differential diagnosis include the nodular lymphocyte predominant Hodgking lymphoma and the classical lymphocyte-rich Hodgkin lymphoma. Differentiating these entities is important because of the different therapeutical approaches. In this regard immunohistochemistry is mandatory.

Similar to other types of DLBCL, T/HRBCL follows an aggressive clinical course and patients should be treated according to their stage-matched DLBCL with combinations containing Anthracyclin and the anti CD20 antibody Rituximab. Unfortunately, the response to chemotherapy is weak.

Further studies are necessary for a better understanding of these diseases, of their pathogenesis along with the development of efficient therapies.

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