Case Report

Hodgkin’s lymphoma with marked granulomatous reaction: a diagnostic pitfall

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Received April 17, 2019; Accepted May 22, 2019; Epub July 1, 2019; Published July 15, 2019

Abstract: Hodgkin’s lymphoma (HL) is a lymphoid malignant tumor characterized by the presence of Hodgkin and Reed-Sternberg (HRS) cells, the variants of which are reported to be involved in the inflammatory reaction. Epithelioid histiocytes, representing granuloma formation, often occur in the environment as single cells or clustered in nodules. This study was performed to report a case of HL in a cervical lymph node, accompanied by a notable granulomatous reaction. A granulomatous reaction might mask the presence of lymphomas, which is easily misdiagnosed as lymph node tuberculosis and other granulomatous lesions. This present case report may provide new insight for avoiding misdiagnosis of such lesions.

Keywords: Hodgkin’s lymphoma, granulomatous reaction, tuberculosis

Introduction

Hodgkin’s lymphoma (HL) is commonly characterized by various specific mixed inflammatory cells, including non-neoplastic small lymphocytes, eosinophils, neutrophils, histiocytes, plasma cells, as well as fibroblasts and collagen fibers [1]. Histiocytes may resemble epithelial cells, presenting a capacity to form granulomatous clusters. It has been well-established that epithelioid granuloma is commonly observed in HL. Accumulating studies have provided evidence demonstrating that about 9% of HL cases are accompanied by non-caseous necrotizing epithelioid granuloma [2]. However, HL with pronounced granuloma formation has rarely been reported. The masking, overlying granulomatous reaction may lead to a misdiagnosis as tuberculosis or sarcoidosis. The current paper reports a case of a 24-year-old male who was diagnosed with HL with significant granuloma formation.

Case presentation

A 24-year-old male was observed with painless cervical lymph node enlargement, which lasted for more than 2 months without any obvious inducement. Accompanying fever, night sweat, rash or other autoimmune diseases were absent. No enlargement of lymph nodes was found in the rest of the body, and no significant weight loss was observed since the onset of the disease. Due to an unfavorable response to anti-inflammatory treatment, a lymph node biopsy was performed. Normal lymph node structure and multiple epithelioid granulomatous nodules were observed following H&E staining. In addition, the nodules were separated from the lymphocyte-rich stroma (Figure 1A). The majority of epithelial nodule cells were oval or spindle-shaped, displaying small heterogeneous nuclei, consistent morphology, homogeneous chromatin, and abundant cytoplasm. Eosinophilic cytoplasm was observed with very rare mitotic figures. In the epithelioid granulomatous nodules, scattered Hodgkin and Reed-Sternberg (HRS) cells were visible (Figure 1B). The HRS cells had large size and abundant microbasophilic cytoplasm, accompanied by one or two large round nuclei, clear nuclear membrane, light chromatin, eosinophilic nucleoli, and perinuclear halos. Immunohistochemical analysis was performed to identify the positive expression of pertinent markers. Epithelioid cells in nodules expressed CD68
Hodgkin’s lymphoma with granulomatous reaction

Figure 1. A. Hematoxylin and eosin staining (× 50). Multiple epithelioid granulomatous nodules of varying sizes are forming in the lymph nodes. B. Within the granuloma, a scattered distribution of HRS cells is seen (× 200). C. CD68 positive expression in epithelial cells (× 100). D. Immunohistochemical staining for CD30 expression shows high expression in the Golgi region of the cell membrane and cytoplasm (× 100). E. Strong Mum1 positive nuclear expression in HRS cells. F. HRS cells weakly express PAX5. G. A few tumor cells with weakly CD15 positive expression. H. CD3 positive expression shows T cells surrounding the HRS cells. I. negative EBER in situ hybridization in large cells.

(\textbf{Figure 1C}). High expression of CD30 (\textbf{Figure 1D}), and Mum1 (\textbf{Figure 1E}), as well as weak expression of PAX5 (\textbf{Figure 1F}) were identified in the Golgi region of the membrane and cytoplasm of HRS large cells. Several tumor tissues were CD15 positive (\textbf{Figure 1G}). In addition, CD3+ and CD5+ mature T lymphocytes (\textbf{Figure 1H}) were observed with rosette-like formation around large cells. The HRS cells did not express EMA, CD20, ALKp80 and CD68, corresponding to a negative EBER in situ hybridization (\textbf{Figure 1I}). Moreover, the results of acid-fast staining, PAS staining and tuberculosis PCR were also negative. Based on the combination of histologic examination and immunohistochemical results, classic HL was diagnosed.

\textbf{Discussion}

Granulomas have been well-recognized histologically as discrete nodules composed of epithelioid histiocytes or multinucleated giant cells, that are commonly accompanied by small lymphocytes. The underlying mechanism of granulomatous changes in HL remains largely unknown. Recent studies have provided possible mechanisms, which include: T cell-mediated nonspecific inflammatory response and Th1 cell-mediated immune response to tumor antigens [3], delayed hypersensitivity associated with cytokines or decomposition products generated by the tumor cells [4], and continuous stimulation of tumor antigen, which usually results in fibrosis and subsequent granuloma formation. Accordingly, granuloma represents a local tissue response to tumor, which may predict a more favorable prognosis [5]. However, a prior study has also documented that HL with formation of necrotizing granulomas may indicate a poor prognosis [6]. Additionally, no mediastinal tumor was found in the patient of this case report. Notably, the patient was followed up for 10 months after treatment with standard doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) chemotherapy regimen. No recurrence occurred. Due to the limitation of sample size of such cases, further reports are required to supplement and understand the biologic behavior.
Hodgkin’s lymphoma with granulomatous reaction

The differential diagnosis of this disease should be emphasized carefully. First, lymph node granulomatous inflammation should be examined to identify the presence of tuberculosis or other special infection. Tuberculosis infection nodules are usually characterized by irregular shapes, with more Langhans giant cells and typical caseous necrosis. In addition, the tuberculosis can be excluded with the use of acid-fast staining and negative detection of tuberculosis bacteria by means of PCR. Sarcoidosis represents epithelioid granulomas forming nodules that are widely distributed in lymph nodes, accompanied by fibrotic nodule formation. Generally, no central necrosis is observed, similar to this granuloma. However, sarcoidosis often presents a similar size and shape, multiple systemic involvement, and it is more commonly found in bilateral hilar lymph nodes. Second, histiocytic proliferative lesions should also be distinguished. Third, large B-cell lymphomas, rich in T cells and histiocytes, predominantly present in the elderly. Due to the young age of the patient and the absence of CD20 expression in large cells, large B-cell lymphoma could be excluded. Fourthly, anaplastic large cell lymphoma (ALCL) cannot be neglected, and can be distinguished by the combined expression of CD30 and PAX5 from ALK-negative ALCL. Fifth, Epstein-Barr virus (EBV) infectious lesions mainly manifest themselves with significant expansion of the interfollicular area and hyperplasia of lymphocytes with high pleomorphism, and often occur in children and adolescents. The cells exhibit plasmacytoid or immunoblast-like differentiation, and RS cell-like cells are also observed. In this case, HRS cells robustly expressed CD30 and weakly expressed PAX5, accompanied by negative EBV hybridization. Last but not least, Lennert lymphoma should be taken into consideration, in which, immunohistochemical analysis would identify histological cells that are non-T cells to be epithelioid cells.

In summary, malignant lymphoma is one of the potential underlying causes of granuloma. Notably, some prominent granulomatous lesions may mask the morphologic changes in lymphomas. With the help of special staining, infection can be excluded during the process of clinicopathologic diagnosis. For young patients with lymph node granulomatous lesions, HL should be excluded first. Moreover, the tumor cells masked by the granuloma should be carefully identified to avoid misdiagnosis.

Acknowledgements

This study was supported by Program of Science and Technology Department of Liaoning Province (No. 201602877).

Disclosure of conflict of interest

None.

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References