

CASE REPORT

Nodal marginal zone lymphoma associated with extensive epithelioid histiocytes

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Abstract

Nodal marginal zone lymphoma (NMZL) is a rare type of non-Hodgkin lymphoma. In this report, we describe a similar condition affecting female 53-year-old presented with generalized lymphadenopathy and high LDH level. The patient underwent excision of cervical lymph node and bone marrow biopsy. Histopathological examination of the excised lymph node revealed florid infiltrate by epithelioid histiocytes, which greatly underscores the neoplastic process directing the diagnosis towards reactive lesions such as toxoplasmosis, marginal zone hyperplasia or monocytoid B-cell hyperplasia. Careful histopathological examination of interfollicular and parafollicular regions helped in recognition of the pale monomorphic neoplastic cells that showed immunoreactivity for CD20 and Bcl-2 and lacked expression for CD5, CD10 and CD23. The involvement of bone marrow by the same type of cells has excluded the possibility for reactive conditions. The recognition of NMZL is sometimes difficult when benign components predominate such as the presence follicular hyperplasia and epithelioid cell clusters. However, full clinical data including LDH level and asking for bone marrow biopsy were greatly helpful in identifying the correct lesion.

Keywords: nodal marginal zone lymphoma, epithelioid histiocytes.

Introduction

Marginal zone B-cells play an important role in the thymus independent type 2 immune response (Ti-2). They are the main group of splenic B-cells responsible for mounting a humoral immune response against bacteria present in the peripheral blood [1]. Normal marginal zone of lymphoid follicle is positive for CD20, CD79a, Bcl-2 and surface immunoglobulin, mostly IGM but negative for CD5, CD10 and CD23 [2]. Mucosa associated lymphoma (MALT), splenic MZL and nodal MZL arise from this zone with the same immunophenotyping [3].

Nodal marginal zone lymphoma (NMZL) accounts for less than 1% of all lymphoid neoplasms [3]. It is classified according to Kiel classification into monocytoid B-cell lymphoma [4] and according to Lukes–Collins [4] into parafollicular lymphoma, but it is not included in working classification [5] and listed under MZL in REAL classification [6]. In WHO, it is listed as a separate entity [7].

NMZL can be easily misdiagnosed as a reactive condition because of its association with benign components such as follicular hyperplasia and histiocytic collections. In this report, we describe a case of NMZL associated with extensive epithelioid histiocytes masking the neoplastic process. We describe the differential diagnosis and the criteria picked from clinical and histopathological features helping in the identification of this rare type of NHL.

Materials and Methods

Female patient, 53-year-old, presented with generalized lymphadenopathy (cervical, axillary and para-aortic lymph nodes) and high LDH level. Serological test for toxoplasmosis was done and revealed negative results. The patient underwent excision of cervical lymph node and bone marrow biopsy. The patient involved in this study signed a consent form approved by the Committee on Human Rights in Research of Menofiya University, Egypt. Bone marrow core biopsy and the excised cervical lymph node were submitted to routine tissue processing, where they were fixed in 10% neutral buffered formalin, dehydrated in ascending grades of ethanol followed by immersion in xylene then impregnated in paraffin. Fifteen 4-µm thick sections were cut from paraffin embedded blocks, one to be stained by Hematoxylin and Eosin for routine histopathological examination. The other sections were mounted on superfrost plus slides, to be stained immunohistochemically for CD20, CD3, Bcl-2, CD10, CD5, CD23 and CD68 using Streptavidin–Biotin amplified system.

Sections mounted on Superfrost Plus slides were submitted to subsequent steps of deparaffinization and rehydration in xylene and a graded series of alcohol, respectively. Antigen retrieval was performed by boiling in 10 mM citrate buffer (pH 6) for 20 minutes followed by cooling at room temperature. The slides were incubated overnight at room temperature with

antibodies raised against CD20 (mouse monoclonal, clone L26, Cell Marque, CA, USA) CD3 (rabbit polyclonal, Cell Marque, CA, USA), Bcl-2 (mouse monoclonal, clone 124, Cell Marque, CA, USA), CD10 (mouse monoclonal, clone 56c6, Cell Marque, CA, USA), CD5 (mouse monoclonal, clone 4c7, Cell Marque, CA, USA), CD23 (mouse monoclonal, clone 1b12, Cell Marque, CA, USA) and CD68 (mouse monoclonal, clone KP1, LabVision, CA, USA). The secondary antibody used was the UltraVision detection system anti-polyvalent HRP/DAB (ready to use) (Catalog #TP-015-HD, LabVision, CA, USA). The reaction was visualized by an appropriate substrate/chromogen (Diaminobenzidine, DAB) reagent with Mayer's Hematoxylin as a counter stain. For each tested slide, negative control was included using blocking buffer. Reactive follicular hyperplasia with sinus histiocytosis

was used as a positive control for CD20 (stained follicles), CD3 (stained paracortex), Bcl-2 (stained mantle zone), CD10 (stained germinal centers), CD5 (stained mantle zone), CD23 (stained follicular dendritic cells) and CD68 (stained histiocytes of sinus histiocytosis).

Results

Histopathological examination of the excised lymph node revealed prominent follicular hyperplasia (Figure 1A) with expansion of marginal zone by monomorphic cells that occupy the parafollicular region (Figure 1B). These cells are intermediate sized with abundant cytoplasm which is sometimes clear or faintly eosinophilic, their nuclei are slightly irregular (Figure 1, C and D).

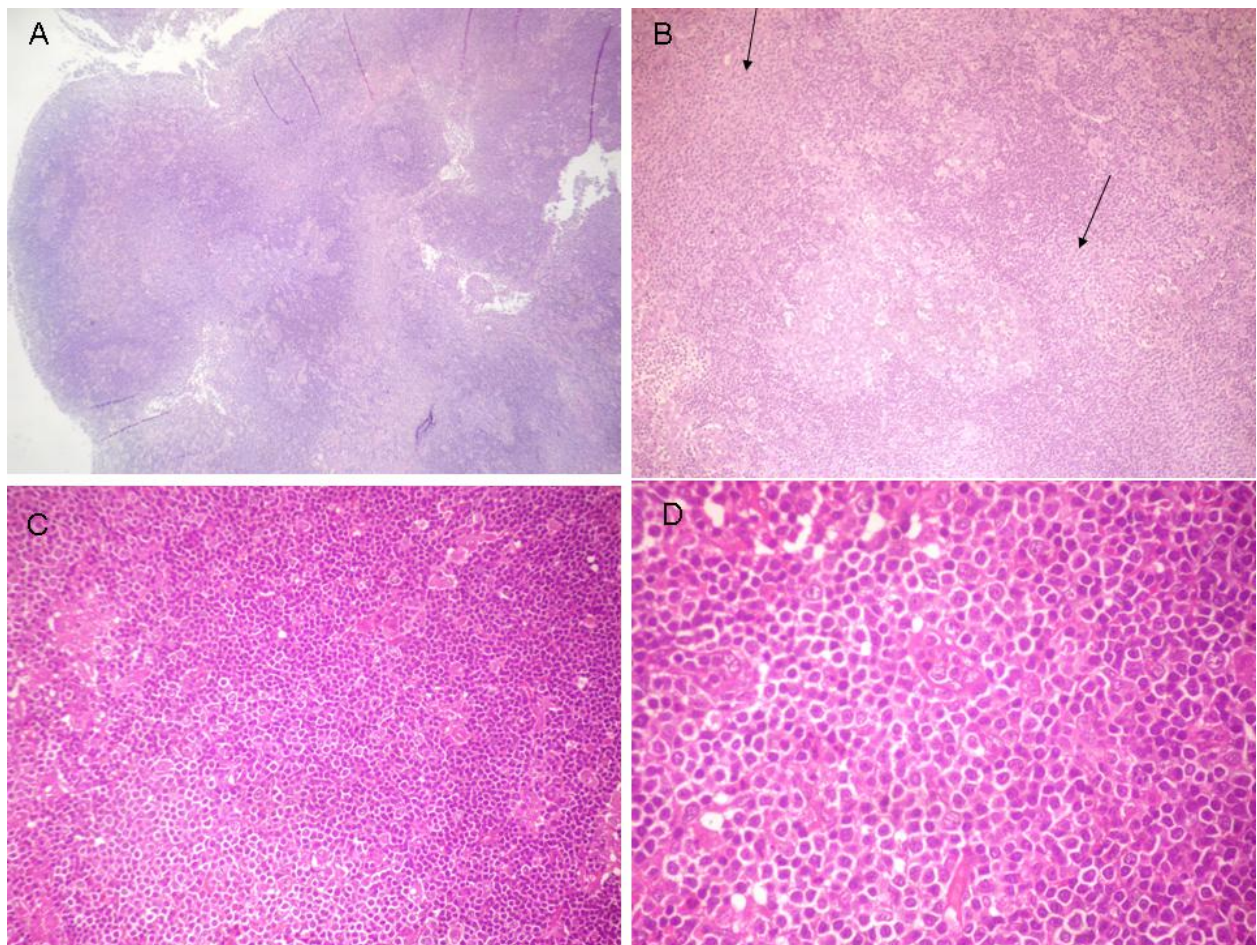


Figure 1 – (A) Prominent follicular hyperplasia with prominent germinal centers that are surrounded by irregular mantle zone (HE stain, 40×). (B) The parafollicular area showed expanded pale zone highlighted by arrows (HE stain, 100×). (C) and (D) High-power view showing population of intermediate sized cells with slight irregular nuclei, abundant faintly eosinophilic cytoplasm and clear cell border (HE stain, 200× for C and 400× for D).

Admixed large cells like centroblasts and immunoblasts not exceeding 20% of total neoplastic populations were also identified (Figure 2A). Sheets of mature plasma cells and extensive infiltration with epithelioid histiocytes were seen (Figure 2B) that masked the neoplastic process making the diagnosis of reactive conditions is more likely. However, bone marrow biopsy showed intertrabecular infiltration by the same

type of neoplastic cells (Figures 2, C and D). Immunophenotyping revealed positive membranous immunoreactivity for CD20 (Figure 3A) and Bcl-2 (Figure 3B) and negative reaction for CD5, CD10 and CD23 in the monomorphic cells that occupied the parafollicular region. The epithelioid histiocytic component showed cytoplasmic and granular immunoreactivity for CD68 (Figure 3C).

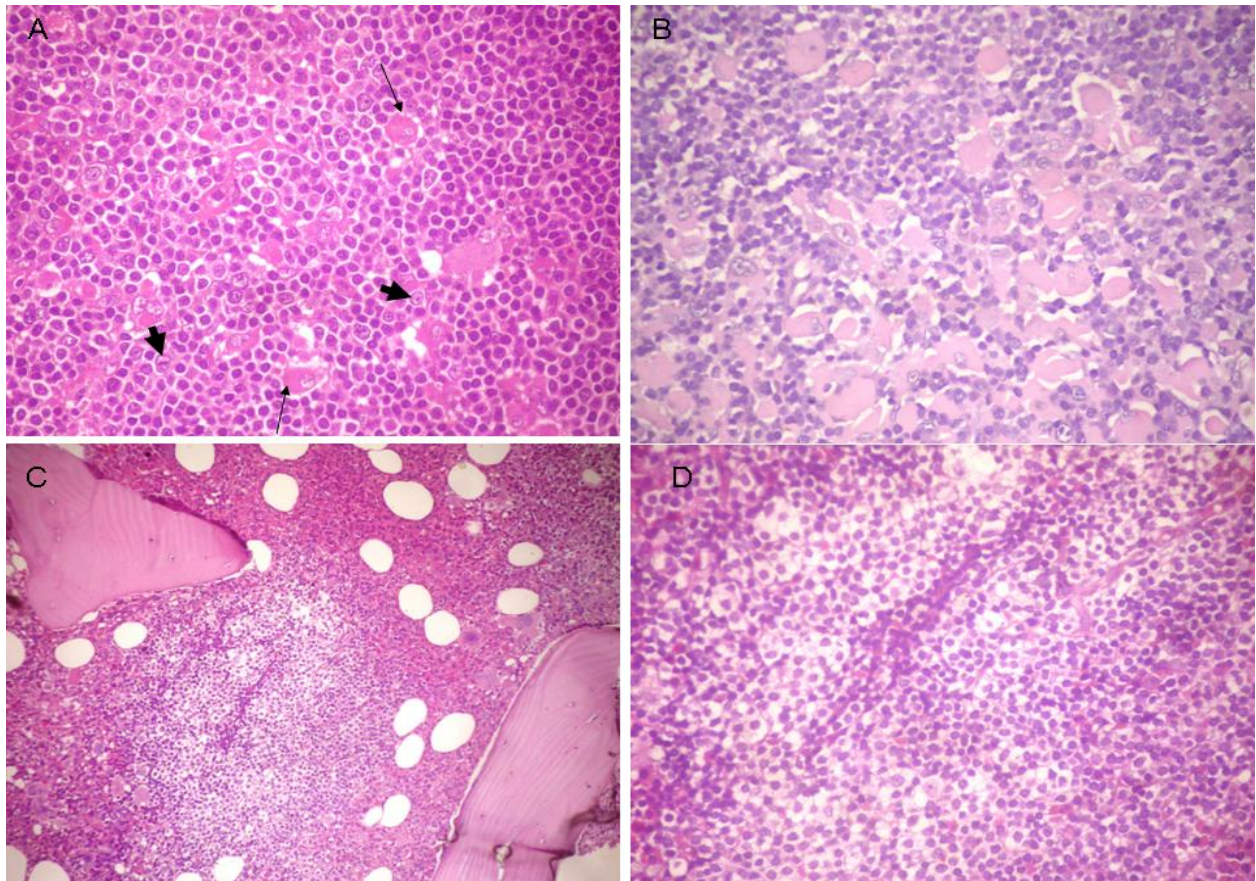


Figure 2 – (A) The neoplastic infiltrate is admixed with few large cells (thick arrows) and epithelioid histiocytic cells with abundant eosinophilic cytoplasm (thin arrows) (HE stain, 400 \times). **(B)** Florid epithelioid histiocytic collections and mature plasma cells (HE stain, 400 \times). **(C)** and **(D)** Involvement of bone marrow by the same neoplastic cells with prominent clear cytoplasm (HE stain, 100 \times for C and 400 \times for D).

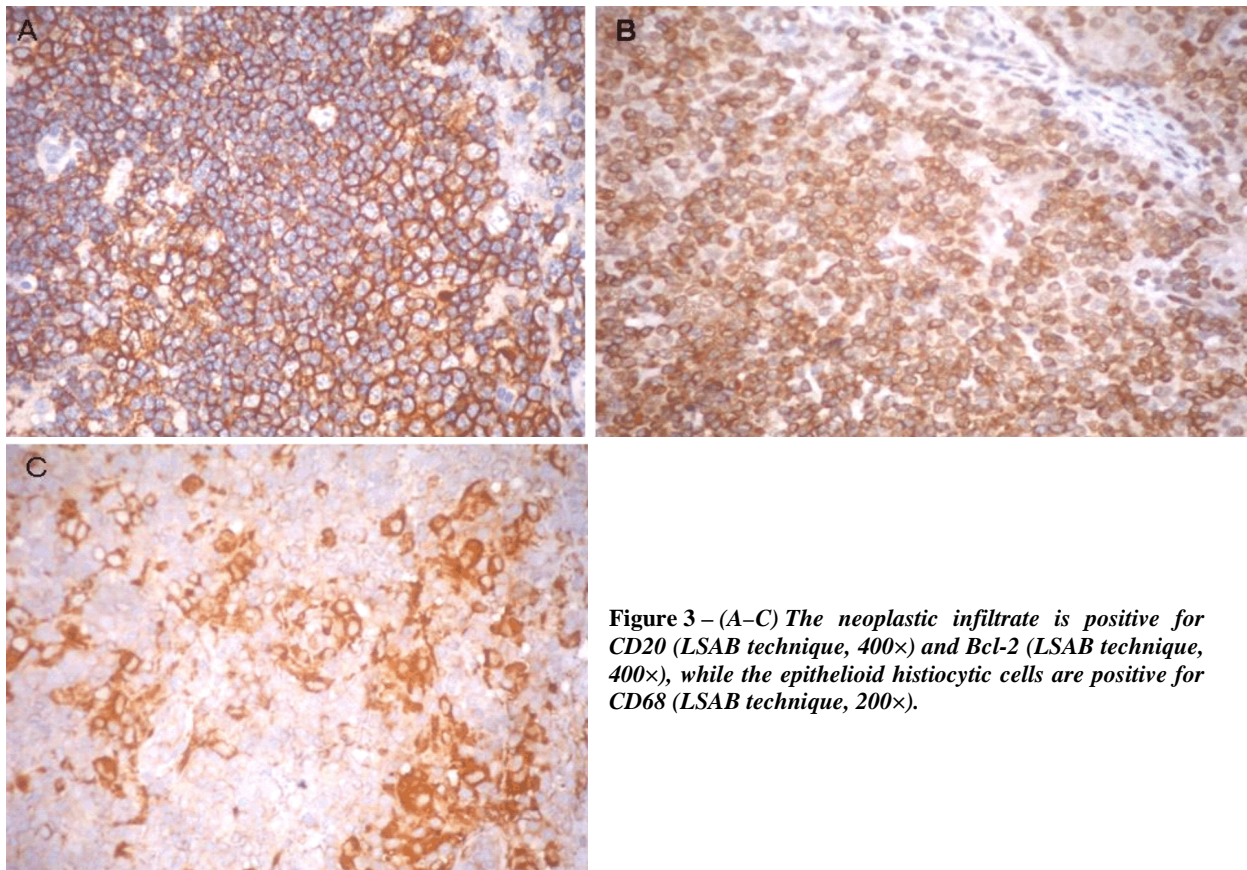


Figure 3 – (A–C) The neoplastic infiltrate is positive for CD20 (LSAB technique, 400 \times) and Bcl-2 (LSAB technique, 400 \times), while the epithelioid histiocytic cells are positive for CD68 (LSAB technique, 200 \times).

Discussion

Nodal marginal zone lymphoma (NMZL) affects usually old people but it may affect a wide range of age from 20 to 85 years. Females are more affected than males with a reported 1.8:1 as a female to male ratio. The case under discussion was a 53-year-old female.

Histopathologically, it is characterized by collections of monocytoid, centrocytoid B-cells, mature plasma cells, plasmacytoid, few large transformed cells and occasional clusters of epithelioid cells. Reactive germinal centers as in our case or regressive centers with a Castleman-like pattern are also reported [8]. It may be associated with epithelioid granuloma, which commonly seen with Hodgkin disease, and sometimes with non-Hodgkin lymphoma [9]. The impact of the presence of these cells on patient's prognosis is manifested by a delay in diagnosis because of simulation with reactive lesions and also subsequently delay in treatment. The presence of this florid granulomatous reaction was reported in splenic marginal zone lymphoma (SMZL) [10] and in marginal zone B-cell lymphoma involving the parotid gland [11].

Our case showed bone marrow involvement with intertrabecular pattern, which was helpful in reaching the right diagnosis. In SMZL, the reported frequency of bone marrow involvement is between 86% and 100% [12] while for NMZL, it is between 28% and 43% [13]. The pattern of involvement may be intravascular, interstitial, intertrabecular or juxtatrabecular [8].

The differential diagnosis of NMZL includes reactive conditions as well as other types of lymphomas. Marginal zone hyperplasia seen in reactive conditions may simulate NMZL but it does not form sheets in the interfollicular region. Reactive monocytoid B-cell hyperplasia such that seen in toxoplasmosis may also be confused with NMZL, but they are negative for Bcl-2 and lacked surface immunoglobulins expression [12]. It should also be differentiated from other lymphomas like mantle cell lymphoma by cyclin D1 and CD5, follicular lymphoma by CD10, lymphoplasmacytic lymphoma by Bcl-2, CD20 and CD97a, plasmacytoma/myeloma by CD20 and SLL/CLL by CD23 and CD5.

Conclusions

The presence of florid histiocytic collections and prominent follicular hyperplasia greatly masked the adjacent lymphoma process in the presented case. Fortunately, getting full clinical data including LDH level, asking for bone marrow biopsy, careful examination of interfollicular and parafollicular regions,

and the characteristic immunophenotypic picture helped in recognizing NMZL and excluded other similar non-neoplastic processes.

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