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Case Report

Parotid gland follicular lymphoma lacking both cytoplasmic and surface light chains: a rare case

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Abstract: Immunoglobulin light chain (LC) restriction is detected in the majority of B-cell non-Hodgkin lymphoma (B-NHL) by flow cytometric immunophenotyping (FCI) and serves as a surrogate marker of monoclonality. Even though it is known a small percentage of mature B-NHLs lacking surface LC, deficiency of *both* cytoplasmic and surface LCs has been reported in only three B-NHL cases. We report a primary parotid gland follicular lymphoma in a 63-year-old man and the lymphoma cells were deficient of cytoplasmic/surface LCs. Compared to previous reports, we used a more sensitive FCI method by combining both monoclonal and polyclonal anti-LC antibodies. Lacking LCs poses as a pitfall for the initial diagnosis of B-NHL, as well as for detecting minimal residual disease. It is important to be aware of this rare immunophenotypic aberrancy.

Keywords: Follicular lymphoma, immunoglobulin light chain, parotid gland, flow cytometry, light chain negativity

Introduction

In human being, Immunoglobulin (Ig) light chains (LCs) are encoded by Ig kappa locus (IGK@) on Chromosome 2 and Ig lambda locus (IGL@) on Chromosome 22. During B cell development, LC gene rearrangement happens at the stage of immature B cells, resulting in either a κ or λ LC expression in each mature B cell, known as allelic exclusion. LC expression persists through the subsequent B-cell developmental stages. Surface light chains are lost after B cells terminally differentiate into plasma cells.

B-cell non-Hodgkin lymphomas (B-NHLs) are clonal proliferation of neoplastic B cells. LC restriction is detected in the majority of B-NHLs by flow cytometric immunophenotyping (FCI). Earlier studies of LC expression using the less sensitive methods of immunohistochemistry are not within the scope of this report. Follicular lymphoma (FL) is the second most common mature B-NHL in western countries. The FL neoplastic cells derive from follicle center cells and usually show LC expression. FL primarily involves lymph nodes and other hematopoietic tissues. Non-hematopoietic tissues are uncommon primary sites for FL and primary salivary gland FL is rare [1-3]. We report a case of primary parotid gland FL, uniquely lacking both cytoplasmic LCs (cLC) and surface LCs (sLC).

Case presentation

The patient was a 63 year-old man with a past medical history of diabetes mellitus and hypertension. He initially presented with a left parotid gland mass, which was increasing in size for several months. A CT scan of the neck demonstrated a 2.3 × 1.4 cm, ill-defined enhancing lesion within the left parotid gland. No associated lymphadenopathy was seen. Fine needle aspiration demonstrated some atypical lymphocytes. Because FCI showed no light chain restriction of the B-cell population, a reactive condition was favored at that time. Eight months later, a new mass on the contralateral posterior neck was noticed, raising the suspicion of malignancy about the original parotid lesion. A left superficial parotidectomy was performed for histological examination.

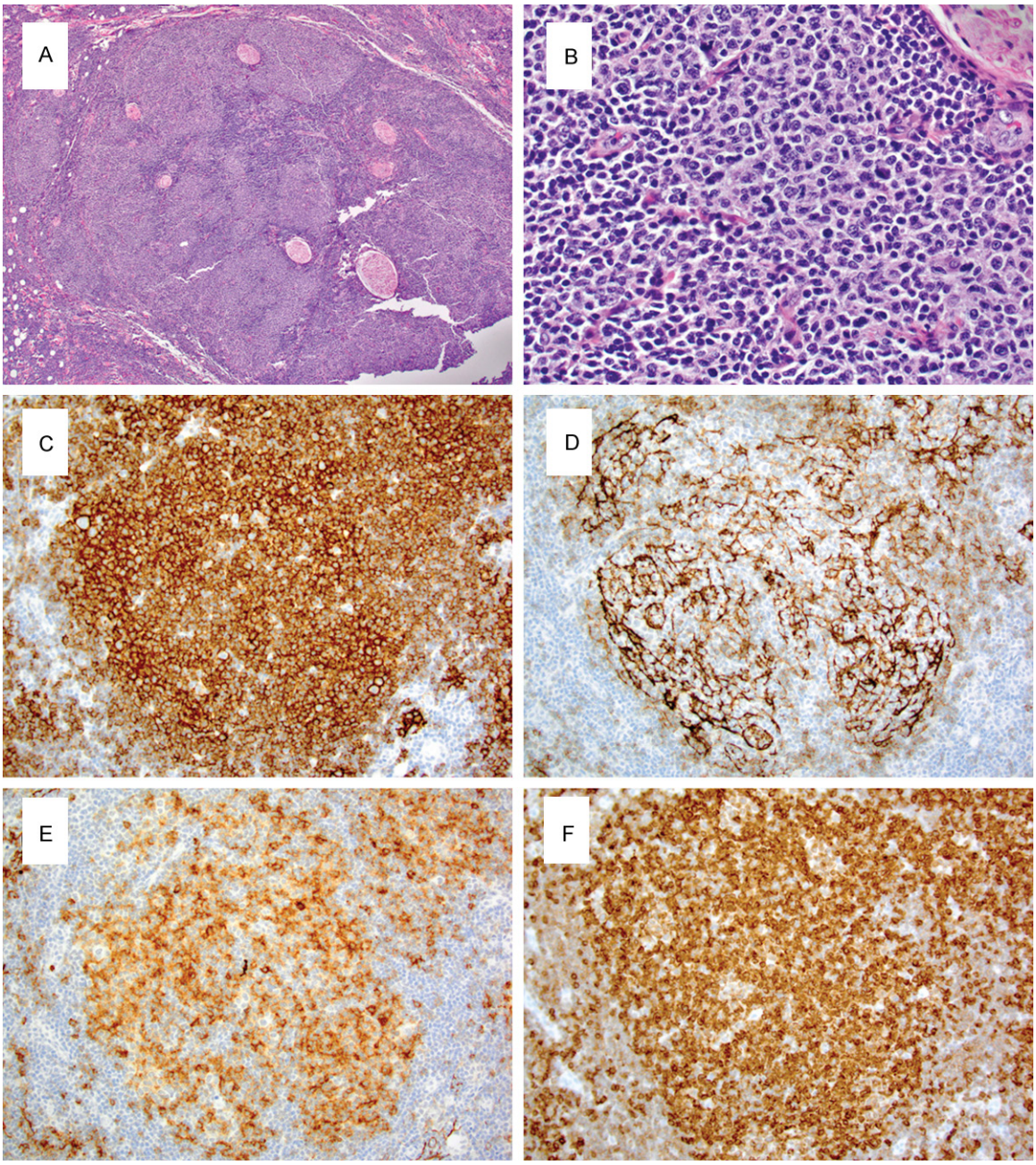

Figure 1. Morphology of the parotid gland follicular lymphoma. (A) Low magnification reveals a lymphoid infiltrate with many irregularly shaped neoplastic follicles. (B) The neoplastic cells are predominantly small in size with irregular nuclear contours and inconspicuous nucleoli (centrocytes). Large-sized centroblasts are rare. The neoplastic cells within the follicles are CD20+ B cells (C). CD21 highlights the expanded of follicular dendritic meshworks (D). The lymphoma cells co-express CD10 (E) and BCL-2 (F).

Microscopically, the salivary gland parenchyma was infiltrated and replaced by a lymphocytic proliferation composed of many irregularly shaped follicles. No fibrous capsule was seen around the lymphoid infiltrate. The neoplastic follicles had attenuated to absent mantle zones with no polarization or tangible-body macrophages identified (**Figure 1A**). The lymphocytes within the follicles were predominantly small to intermediate sized, with irregular nuclear contours and inconspicuous nucleoli (centrocytes). Large-sized neoplastic cells (centroblasts) were less than 10 cells per high power field (**Figure 1B**).

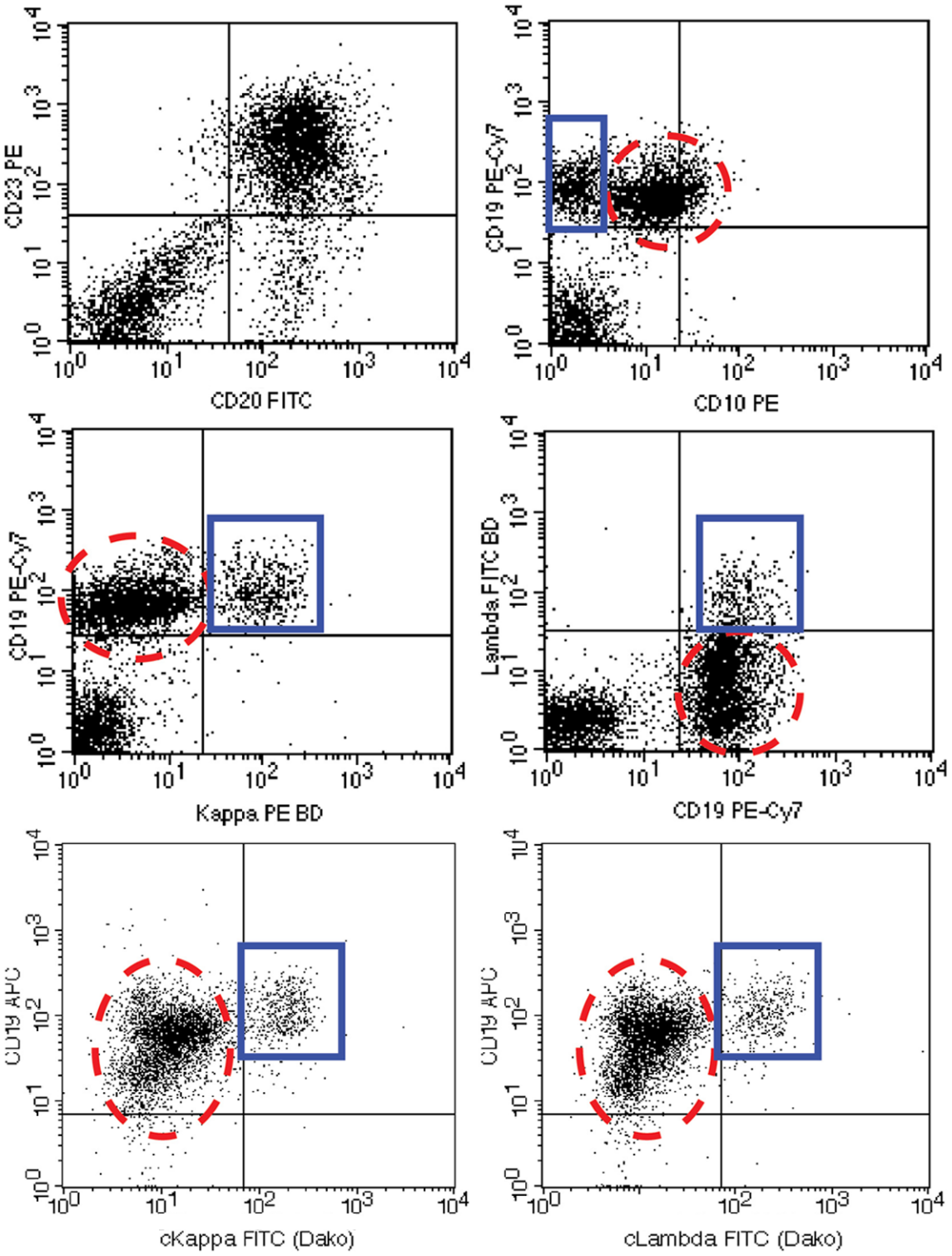

Figure 2. Flow cytometric immunophenotyping of the parotid gland lesion. There are two distinct B cell populations: the abnormal population (dashed red circle) is dimly CD10-positive and lacks both surface and cytoplasmic light chains; the polytypic B-cell population (solid blue rectangle) is CD10-negative and shows mixed kappa and lambda expression. (cKappa: cytoplasmic Kappa; cLambda: cytoplasmic Lambda).

Immunohistochemistry showed the neoplastic follicles were composed predominantly of CD20+ B cells (**Figure 1C**). CD21 highlighted the disrupted follicular dendritic meshworks

underlying the neoplastic follicles (**Figure 1D**). The neoplastic cells also expressed BCL6 (not shown) and CD10 (**Figure 1E**). The neoplastic follicles were positive for BCL-2 (**Figure 1F**). Ki67 revealed a proliferative index of approximately 30% within the follicles (not shown).

FCI identified a B-cell population with co-expression of CD20, CD10 (dim), and CD23 (**Figure 2**, dashed red circle). Surprisingly, this population was deficient of both sLC (detected by mouse monoclonal antibodies, Becton-Dickinson) and cLC (detected by rabbit polyclonal antibodies, DakoCytomation). Noticeably, a smaller population of polyclonal B cells was also present (**Figure 2**, solid blue square), which served as internal control of antibody integrity. Neither of CD34 nor terminal deoxynucleotidyl transferase (TdT) was expressed in this CD10-positive, LC-negative B-cell population (not shown), excluding the possibility of B lymphoblastic lymphoma.

Fluorescent In Situ Hybridization with IgH-BCL2 dual fusion probes detected t(14;18)(q32;q21) translocation in approximately 60% of cells. Molecular studies with Polymerase Chain Reaction confirmed the presence of the IGH-BCL2 fusion transcript, in addition to clonal rearrangements of IgH@ and IgK@. The overall findings were consistent with a primary follicular lymphoma of the parotid gland, with an aberrant LC-negative immunophenotype.

Discussion

A small percentage of B-NHLs (2% to 12%) are negative for sLCs by FCI [4-7]. LC negativity is believed to, at least partially, result from epitope change or loss due to LC gene mutations, and/or defective posttranslational processing. However, the majority of prior studies did not analyze *cytoplasmic* LC. Epitope modification and preservation might be different between cLC and sLC, potentially resulting in discrepancy in LC detection. There is only one FCI-based study that analyzed both sLC and cLC expression of 30 cases of chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) [8]. Interestingly, the majority of sLC-negative CLL/SLL cases (6 out of 7 cases) have detectable cytoplasmic LC antigen. Of note, this study used only one type of anti-LC antibodies for both sLC and cLC analysis. The findings suggest that, in terms of epitope preservation/modification, cLC is different from sLC in CLL/SLL. Therefore, detecting both sLC and cLC antigens would significantly increase the chance of detecting LC restriction, at least in CLL/SLL. It is unclear whether this conclusion is applicable to other types of B-NHLs.

Another important factor affecting LC detection is the type and number of anti-LC antibodies used. It is controversial whether polyclonal antibodies are superb to monoclonal antibodies. Not exclusively, some studies showed that using two types of anti-LC antibodies increases the FCI sensitivity, most likely due to the expanded epitope coverage. For example, Horna *et al.* compared monoclonal and polyclonal anti-LC antibodies in detecting sLC expression in B-NHL cases. When using only one anti-LC antibodies (either monoclonal or polyclonal), approximately 12% of the 564 B-NHL cases are considered as sLC-negative (67 by polyclonal antibodies only; 69 cases by monoclonal antibodies only). Combining both monoclonal and polyclonal antibodies increases the rate of sLC detection and only 7.4% (42 cases) are still sLC-negative [9]. Our case is the first sLC/cLC dual negative FL, and the aberrancy is confirmed by two types of anti-LC antibodies.

Lacking both sLC and cLC in B-NHLs is extremely rare. Only one CLL/SLL and two Burkitt Lymphomas with similar findings are found in the literature [8, 10]. Both studies used only a single type of anti-LC antibodies, which is less sensitive than our method.

Lacking LC expression in B cells warrants additional analysis to exclude certain differential diagnoses, including B lymphoblastic leukemia, plasma cell neoplasm, hematogones in bone marrow and florid follicular hyperplasia. On the other hand, a B-cell population deficient of LCs may give a false impression of "normal" κ-to-λ ratio if some benign B cells are also present. Therefore, while evaluating B-cell populations, it is important to not only evaluate the κ-to-λ ratio, but also compare the count of LC-expressing B cells with that of total B cells. Any significant discrepancy should alert the pathologist to rule out aberrant LC expression.

LC negativity makes it difficult to detect abnormal B-cell populations under certain situations. The examples include: 1) presence of a signifi-

cant proportion of polytypic B cells; 2) limited FCI analysis due to low quantity; 3) FCI evaluation without morphologic correlation, etc. Since detection of LC restriction carries the paramount importance in diagnosing B-NHL, it is recommended to use two different types of anti-LC antibodies and analyze both surface and cytoplasmic LCs in equivocal cases.

Disclosure of conflict of interest

None.

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