BCL2-Negative Follicular Lymphoma of the Uterine Cervix: A Case Report and Literature Review

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ABSTRACT
Lymphoma involving the female genital tract is rare and the uterine cervix is an uncommon site for lymphoma. Follicular lymphoma is the second most common Non-Hodgkin’s lymphoma involving the uterine cervix. The t(14;18)(q32;q21) chromosome abnormality is the genetic hallmark of Follicular lymphoma and can be detected in about 80% of Follicular lymphoma involving the gynecologic tract. The t(14;18)(q32;q21) negative follicular lymphoma is unusual and may cause confusion for the pathologist not familiar with its clinical, histologic and immunohistochemical features. This case report intends to create awareness of this rare clinical entity. Lymphoma should be included in the differential diagnosis of gynecologic malignancies.

Keywords
Follicular lymphoma, Pediatric-type, Uterus, Cervix, BCL2.

Introduction
Lymphomas are a heterogeneous group of distinct diseases that can be divided into Hodgkin lymphoma and non-Hodgkin lymphoma (NHL). The gynecologic tract is an uncommon site for NHL and the incidence of NHL in the female genital system is 0.5 - 1% of all the NHL [1,2]. NHL involving the gynecologic tract can be the primary manifestation of this disease or it may occur as genital recurrences of lymphomas initially diagnosed elsewhere. Cervix is the second most common site for primary lymphoma of the female genital tract [3]. The most frequently encountered primary cervical lymphomas are diffuse large B-cell lymphoma, followed by follicular lymphoma (FL), mantle cell lymphoma, and Burkitt lymphoma [4].

The 2008 World Health Organization (WHO) Classification defines FL as a neoplasm of germinal center cells which usually has at least a partially follicular pattern [5]. The t(14;18)(q32;q21) chromosome abnormality is the genetic hallmark of FL and can be detected in about 80% of cases with varying frequencies depending on the methods used for the detection of translocations and ethnic background. The 2016 WHO Classification recognizes pediatric-type FL (PFL) as a definite entity. PFL is an indolent clonal proliferation which is predominantly seen in children, but may occur in adults. BCL2 rearrangements must not be present. PFL is nearly all localized [6]. Despite frequently showing more aggressive cytologic features (grade 2 or 3 and high proliferation index), patients with PFL show excellent response rates to local surgical resection or minimal chemotherapy and have very low recurrence rate [7]. PFL is reported to have distinctive morphologic features, including large expansile follicles with numerous centroblasts [8]. Here we described a case of t(14;18)-negative FL involved the uterine cervix, which caused diagnostic difficulty.

Case Presentation
A 57 year old female presented to the gynecology outpatient clinic for a routine screening. The vaginal examination was within normal limits. The patient denied vaginal bleeding, discharge, or other symptoms (including fever, night sweats, weight loss or fatigue). Cytologic diagnosis was atypical squamous cells of undetermined

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significance (ASCUS) with high risk HPV 18 positivity. A cervical biopsy showed a minute strip of detached dysplastic squamous epithelium. A loop electrosurgical excision procedure was performed. Grossly, the specimen showed no obvious lesions. Histology showed multiple lymphoid follicles within the cervical stroma. The expanded germinal centers were irregular in shape with diffuse proliferation of large atypical lymphoid cells which had open chromatins and a high nuclear-cytoplasmic (N/C) ratio. The centrocytes were absent. Rare small reactive lymphocytes with dense chromatin were present in germinal centers (Figure 1A-B). The squamous epithelium and endocervical glands were not involved. Immunohistochemically, the neoplastic lymphoid cells were positive for CD20, CD10, BCL-6, negative for BCL2, C-MYC, MUM1 and CD3 (Figure 2A-G). The proliferation index as assessed by Ki67 with manual immunohistochemical stain (IHC) was approximately 90% (Figure 2H). Epstein-Barr Virus Small RNA (EBER) in situ hybridization for Epstein-Barr virus was negative. Fluorescence in situ hybridization (FISH) for IgH/BCL2 showed no definitive evidence of rearrangement. The molecular test for IgH gene rearrangement was positive for a clonal population of B-lymphocytes. The histological, immunohistochemical, and molecular studies were consistent with a BCL2-negative follicular lymphoma, Grade 3A.

Previously, the patient first presented with an eight month enlarged left cervical adenopathy and was diagnosed as follicular lymphoma, Grade 3A stage 1A in 2016. Immunohistochemically, the centroblasts were positive for CD20, CD10, PAX5, BCL2, BCL6, C-MYC, but negative for CD5 and BCL1. The proliferation as assessed by Ki67 with manual IHC was approximately 90% in lymphoid cells. Flow cytometry demonstrated a lambda-light chain restricted population of B-cells. Molecular study for IgH/BCL2 translocation was positive. IgH (V-D-J) clonality assay by fragment size analysis demonstrated a clonal population of B-cells. She was on radiation therapy for a total of 30 Gy in 15 fractions. She felt well with no other palpable adenopathy, no fevers, no night sweats, no weight loss, and no evidence of recurrence by the time of the uterine cervical biopsy.

Meanwhile, the clonal peaks of the current case (Figure 3B) were different from the previous two results on peripheral blood and neck biopsy (Figure 3A) as shown in Figure 3. Both IgH/BCL2 gene rearrangement and IgH clonality studies demonstrate a different lymphoproliferative disorder in the current specimen.

**Discussion**

Lymphoma involving the female genital tract is rare and the uterine cervix is an uncommon site for lymphoma. The clinical diagnosis of uterine lymphoma can be challenging, partly because affected patients are often asymptomatic or only have nonspecific symptoms. The most common symptoms of lymphoma in the cervix are abnormal vaginal bleeding, cervicouterine enlargement, and fixed uterine cervix on pelvic examination [9,10].

The clinical workup leading to an accurate diagnosis is extremely challenging given the varied clinical presentations as well as laboratory findings of uterine cervical lymphomas. The differential diagnosis includes chronic cervicitis, carcinoma,
carcinosarcoma, endometrial stromal sarcoma, melanoma and primitive neuroectodermal tumor and other hematopoietic lesions [4]. Grossly, cervical lymphomas usually present as a diffuse enlargement, a poly or a solitary mass. Mucosal lesions are uncommon, thus causing diagnostic difficulties by Pap test or superficial cervical biopsy. The high incidence of benign lymphoid aggregates in this area further complicates diagnosis of cervical lymphomas [11]. Histologically, the specimen of our case showed enlarged lymphoid follicles closely resembling reactive follicular hyperplasia. Immunohistochemistry and molecular gene rearrangements are helpful in making the correct diagnosis [12].

Follicular lymphoma is the second most common subtype of non-Hodgkin lymphoma and the most frequent indolent lymphoma, accounting for 22-32% of all new non-Hodgkin lymphoma diagnoses in Western countries [13] FL is also the second most common lymphoma involving the uterine cervix [4]. The t(14;18) (q32;q21) chromosome abnormality is the genetic hallmark of FL and can be detected in about 80% of cases. Studies in other hematological diseases have shown that clinical relapse is often caused by the rise of a more aggressive subclone, which was mostly present, but not predominant, at initial diagnosis [14-17]. In our reported case, the primary cervical nodal FL was positive, while the uterine cervical FL was negative for IgH/BCL2 gene rearrangement. IgH clonality assay showed different peaks between these two FLs. Based on the different IgH gene amplification and clonal peak patterns between these two different biopsies, though it cannot be entirely rule out an evolved FL from previous disease, the FL in the current cervical biopsy is most likely a de novo FL and best classified as pediatric type FL based on the immunophenotype and morphology. Although PFL are predominantly seen in children, previous studies showed PFL can manifest in the adult population as well [8,18]. However, the criteria for PFL must be strictly applied to avoid underdiagnosing conventional grade 3 FL, with particular caution required before making this diagnosis in an adult [6].

Although it is rare, lymphoma should be in the differential diagnosis of gynecological malignancies, and its clinical, radiological and laboratory signs must be actively sought. When morphologically abnormal lymphoid aggregates present, even with the initial work-up appears as negative, the t(14:18)(q32;q21) negative follicular lymphoma has to be considered. Additional immunohistochemistry and molecular assays work up is justified to reach the correct diagnosis.

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References