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Florid reactive lymphoid hyperplasia (lymphoma-like lesion) of the uterine cervix

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Abstract Lymphoma-like lesion (LLL) of the female genital tract is an older term in the literature that describes a florid reactive lymphoid proliferation that can be misinterpreted as lymphoma. Multiple causes of LLL have been suggested but most cases remain unexplained. We describe the clinicopathologic features of 6 patients with LLL involving the uterine cervix. Five patients presented with abnormal Papanicolaou test (Pap smear), and 3 patients had a biopsy procedure performed prior to detection of LLL in a loop electrosurgical excision procedure (LEEP). In each specimen, surface epithelial erosion was associated with a superficial, polymorphous lymphoid infiltrate with numerous scattered large cells, without cellular necrosis or sclerosis. Squamous dysplasia was present in 4 patients. Immunohistochemical studies revealed a mixed population of B- and T-lymphoid cells. T-cells were more numerous but B-cells and formed aggregates or sheets in areas. The large cells were predominantly B-cells positive for CD20 and negative for CD3 in all cases. CD30 was positive 3 cases, and Epstein-Barr virus-encoded RNA was positive in 3 cases. Assessment for clonality in 1 patient using polymerase chain reaction (PCR) methods revealed monoclonal immunoglobulin heavy chain (IgH) gene rearrangements. At last clinical follow-up there was no evidence of progressive or systemic disease. We conclude that LLL of the cervix has a number of etiologies and that a prior surgical procedure, present in 3 patients in this study, is another possible etiology. As has been reported by others, monoclonal IgH gene rearrangements can be detected in this entity which has a benign clinical course.

Keywords: Lymphoma-like lesion; Cervix; IgH; Polymerase Chain Reaction (PCR); Papanicolaou test (Pap smear)

1. Introduction

Chronic inflammation involving the cervix is frequent. Although unexplained in many patients, infectious etiologies are common and include Human papillomavirus (HPV) infection and bacterial infections such as *Chlamydia trachomatis*, *Neisseria gonorrhea*, and Epstein-Barr virus (EBV) in a subset of patients [1-3]. Infrequently, inflammatory lesions of the cervix can be exuberant with numerous small lymphocytes that form sheets. In some cases, large lymphoid cells can be numerous that mimic diffuse large cell lymphoma [4-10]. However, lymphomas involving the female genital tract are uncommon, and lymphomas arising within the cervix are rare [11].

The term *lymphoma-like lesion* (LLL) of the lower female gynecologic tract was initially coined by Young et al [10] in 1985. They reported the clinicopathologic features of 16 cases of inflammatory lesions, most commonly involving the cervix but less often the endometrium or vulva, that were florid, leading the submitting pathologists to consider or even misdiagnose the lesions as lymphoma [10]. Histologically, LLLs are typically superficial lesions without deep extension into the cervical wall and are polymorphous: key features that distinguish LLL from lymphoma. Despite being

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considered a reactive and benign process based on long-term clinical follow-up, monoclonal immunoglobulin heavy chain (IgH) gene rearrangements have been identified in a subset of cases [5,6].

In the present study, we report our experience with 6 patients who had florid, reactive lymphoid proliferations that meet the criteria for LLL, half of which were initially misinterpreted as lymphoma. Three patients in this group had a cervical biopsy before the diagnosis of LLL was established in a loop electrosurgical excision procedure (LEEP).

2. Materials and methods

The 6 cases in this study were retrieved from the pathology files of 3 institutions. Hematoxylin-eosin–stained slides from all 6 cases were reviewed. The patients' medical records were examined with particular attention to pertinent clinical findings, staging studies, and follow-up.

2.1. Immunohistochemistry, molecular studies, and in situ hybridization

Immunohistochemical stains were performed using formalin-fixed, paraffin-embedded tissue sections. The antibody panel used was variable but included CD3, CD10, CD20, CD30, PAX-5, ALK-1, cyclin D1, BCL-6, κ, λ, and herpes simplex virus.

In situ hybridization analysis for EBV-encoded RNA 1 (EBER-1) using formalin-fixed paraffin-embedded sections, a fluorescein-labeled peptide nucleic acid probe specific for EBER-1, and the DAKO hybridization kit according to the manufacturer's instructions was performed in 4 cases (cases 1, 3, 4, and 5). As part of this study, IgH gene rearrangement studies were performed by polymerase chain reaction (PCR) in 2 cases as previously described [12].

3. Results

3.1. Clinical findings

The clinical findings are summarized in Table 1. The age range of the 6 patients was 19 to 57 years; 5 patients were younger than 30 years. Five patients had an abnormal Papanicolaou test result. The abnormalities detected by Papanicolaou test were low-grade squamous intraepithelial lesion (cases 1 and 5), "atypical squamous cells" (case 2), abnormal but not specified (case 3), and atypical squamous cells of uncertain significance (case 6). Case 4 had a normal Papanicolaou test result, but high-risk HPV was detected by DNA testing. The diagnosis of LLL was established in a LEEP specimen in 5 patients, of which 3 patients had a cervical biopsy and 1 patient had a cone biopsy before the LEEP. In 1 patient (case 4), lymphoma was suspected on the initial biopsy, but none of the other cases had any reported inflammation in the initial cervical biopsies. In addition to the presence of LLL, cervical intraepithelial neoplasia (CIN) was diagnosed in 4 patients (cases 1, 2, 5, and 6). No patient had generalized B-symptoms. Clinical and radiologic staging studies were known and were negative in 4 patients (cases 1, 3, 4, and 5). Bone marrow was examined and was negative for lymphoma in 1 patient (case 3). Clinical follow-up was available and uneventful in 3 patients (cases 1, 3, and 5).

3.2. Histologic findings

3.2.1. Case 1

The initial cervical cone biopsy showed low-grade CIN (CIN-1) and HPV change. Subsequent anterior cervical LEEP excision, performed 7 months later, showed extensive surface ulceration associated with a dense lymphoid infiltrate in the superficial cervical stroma. The infiltrate was polymorphic and composed of small lymphocytes, plasma cells, and variable numbers of neutrophils. Admixed were numerous large cells with vesicular chromatin, 1 to 3 nucleoli, and moderate amount of eosinophilic cytoplasm (centroblasts and immunoblasts). In

Table 1
Summary of clinical findings in 6 patients with florid reactive lymphoid hyperplasia (LLL) of the cervix

Case	Age (y)	Initial workup	Previous biopsy	Diagnostic procedure	Associated pathologic diagnosis	Other clinical findings	Clinical follow-up
1	25	Abnormal Papanicolaou test result showed LGSIL	Cone biopsy	LEEP	CIN 1-2	No symptoms, negative staging studies	NED, 7 mo
2	19	Abnormal Papanicolaou test result showed "atypical squamous cells"	None	LEEP	CIN 1-2	Not available	Lost to follow-up
3	24	Abnormal Papanicolaou test result	None	LEEP	Koilocytosis	No symptoms, negative staging studies	NED, 21 mo
4	57	Normal Papanicolaou test result but positive for high-risk HPV	Cervical biopsy	LEEP	None	No symptoms, negative staging studies	NED
5	25	Routine screening Papanicolaou test result showed LGSIL	Cervical biopsy	LEEP	CIN 1-2	No symptoms, negative staging studies	NED, 6 mo
6	19	Routine screening Papanicolaou test showed ASCUS	Cervical biopsy	LEEP	CIN-2	Not available	Lost to follow-up

ASCUS indicates atypical squamous cells uncertain significance; LGSIL, low-grade squamous intraepithelial lesion; LEEP, Loop electrosurgical excision procedure; CIN, cervical intraepithelial neoplasia; NED, no evidence of disease.