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Primary Cervical Non-Hodgkin Lymphoma; A Narrative Review

Leila Mousavi Seresht[1,*], Shamin Ghobadi[1]

[1] Obstetrics and Gynecology Department, Isfahan Medical Science School, Isfahan, Iran

**Corresponding author: Leila Mousavi Seresht, Assistant Professor, Fellowship of Gynecology Oncology, Obstetrics and Gynecology Department, Isfahan Medical Science School, Isfahan, Iran. Tel: +989039078376; Fax: +983132362191. E-mail: lmousavi.lm@gmail.com*

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Gynecological lymphoma is one of the rarest tumors of the female organs that need to be kept in mind in a suspected patient due to its different management protocol. Even though the reported cases of ovarian lymphoma are not limited; our knowledge about diagnosis and treatment of primary cervical lymphoma is restricted. There is a rising number of suggested imaging and pathological criteria that need precise analysis to confirm their benefits in achieving the appropriate outcome. Here, we aim to review the most relevant recent works about primary cervical non-Hodgkin lymphoma of the cervix as the most common type of this rare entity.

INTRODUCTION

Due to the high chemo-response of non-Hodgkin lymphoma (NHL), it should be considered in the case of cervical exophytic mass and vaginal bleeding the treatment and prognosis of which is different from squamous cell carcinoma (SCC). This malignancy of immune cells; as the commonest hematological cancer, is divided into Hodgkin (20-30%) and non-Hodgkin (70-80%) lymphoma. Non-Hodgkin Lymphoma (NHL) has itself aggressive subtypes including diffuse large B-cell lymphoma (DLBCL), peripheral T-cell lymphoma (PTCL), Burkitt's lymphoma, mantle cell lymphoma (MCL), AIDS-related lymphoma, and less aggressive ones such as follicular lymphoma [1]. Genital Non-Hodgkin lymphoma accounts for less than 1- 3% of these families and less than 0.5% of gynecologic cancer which mainly affects the ovaries [2, 3]. The rarest part for the primary presentation of NHL in the gynecologic organ is the vagina. To consider this lymphoproliferative disorder as a primary genital lymphoma and not a secondary extra nodal metastatic lesion, it needs to be limited to one location for months in the absence of peripheral blood or bone marrow involvement [4].

THE COURSE OF DISEASE

Age Distribution

According to its rarity, all of our knowledge is based on case reports; mainly describing the primary NHL of the cervix in the perimenopausal period with a median age of 40-59 years [4, 5].

Risk Factors

Chronic cervicitis is encountered to have a causative rule in progression to cervical NHL [3], and in this regard, there are some other etiological infectious agents including the Ebstein-bar virus, human immunodeficiency virus (HIV), exposure of immunosuppressive therapies, pesticides, and pollutant [3, 5].

Disease Presentation

Like squamous cell carcinoma, its most probable manifestations are vaginal bleeding and abnormal macroscopic appearance of the cervix [1, 4]. In addition, there are some other reported symptoms like vaginal discharge, pelvic pain, dyspareunia, abdominal distension, bloating, and postcoital bleeding. The surprising fact is the rarity of lymphoma-specific symptoms; including fever, night sweats, and weight loss. NHL could be presented as an obliterative, exophytic cervical mass in the shape of "champagne cork" with apparent involvement of parametrium or in the shape of polypoid cervical mass [4, 6]. Rarely, the cervical mass was identified in a regular examination of an incidental case of un-explained deep vein thrombosis or hydronephrosis [2, 7].

Diagnosis

The suggestive radiological clues in favor of cervical lymphoma are lobulated, expansive, and well-vascularized solid masses in cervical view of ultrasonography or homogenous and hyperintense masses on MRI, T2 sequence [2]. On the contrary to the cervical stroma, the cervical lymphoma is manifested as hypointense masses with a strong uniform enhancement pattern with intact epithelium on postcontrast imaging in the T1-weighted sequence of MRI [2]. Nevertheless, PET/CT has no distinct feature, and similar to SCC a high uptake of fluorodeoxyglucose is observed. It is essential to be aware of this diagnosis and the high likelihood of false-negative pap smears and even superficial biopsies. The fact that it is originating from the stroma but not the superficial epithelium may lead to the missing of this differential diagnosis. In most cases, there is also a need for several deep sampling with the aim of cervical conization to reach the exact diagnosis [2, 4]. Although there are some controversies, using immunohistochemistry sounds beneficial in terms of overexpression of CD20, CD30, CD5, CD3, CD45, BCL6, BCL2, ki67, RF4/MUM1, MYC, and CD23; while CD10, cytokeratin, HMB45, CD 99, chromogranin, desmin, synaptophysin, myogenin, and Cyclin are negatively stained [3, 5, 8-10]. Polymerase chain reaction analysis of immunoglobulin (IgH gene) could also be helpful [8]. To classify this tumor based on Ann Arbor staging, there is a need to examine the whole-body lymph nodes, hepatosplenomegaly, or involvement of the Waldeyer ring. It is necessary to analyze the blood count, renal and liver function test, a sample of bone marrow aspirate, and perform at least a thoracoabdominal computed tomography (CT scan) [4]. The use of positron emission tomography (PET) scan has shown some benefits in staging and evaluation of bone marrow involvement [1].

Differential Diagnosis

Firstly this malignancy should be distinguished from the similar benign neoplasm named lymphoma-like lesions. In NHL, monomorphous lymphoid infiltration is present in the form of sclerotic and perivascular masses with preservation of epithelium [4]. Other malignancies with similar presentation are SCC, uterine stromal sarcoma, poorly differentiated carcinoma, neuroendocrine tumors, malignant melanoma, pseudolymphoma, rhabdomyosarcoma, Ewing's tumor, primitive neuroectodermal tumor (PNET), and metastasis from malignant round cell tumors [3].

Treatment

Combined chemotherapy regimens like CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone) are applied with Rituximab (anti-CD20) with the superiority of preserving fertility. However, Rituximab could be replaced with a chimeric monoclonal antibody against the CD20 B-cell antigen [4]. The total number of chemotherapy cycles depends on the tumor size [10]. Some expert-recommended combination of methotrexate with another chemotherapy agent has been advised to decrease the risk of central nervous relapse [2]. Although there are some case reports on surgical approaches with or without adjuvant therapy, it seems that surgery is beneficial only in limited cases, and radiotherapy does not add any benefit except in more bulky tumors with

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a partial initial response to chemotherapy (11). On the other hand, it is recommended to consider a fertility specialist consultant for potential GNRH-A administration and egg/embryo freezing in the case of reproductive-aged patients with fertility desire. Near half of NHL patients need the addition of RICE (Rituximab fractionated iFOSFamide cARBOplatin etoposide) to their chemotherapy regimen to achieve complete response [5]. There are also some suggestions on autologous stem cell transplantation as a clinical trial approach in recurrences or refractory patients [1]. Traditional chemotherapy regimens with lower tolerability include R-ACVBP (rituximab plus doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisone) or R-EPOCH (rituximab plus etoposide, prednisolone, oncovin, cyclophosphamide, and hydroxydaunorubicin) [10].

Prognosis

There is no confirmed data on the actual overall survival of cervical lymphoma due to its rarity and lack of standard treatment guidelines. Although preliminary reports were in support of early-stage detection of the most proportion of cases, later it was illuminated that two-thirds of the detected cases were categorized in advance stage [2]. Moreover, contrary to prior belief, cervical NHL had not revealed proper response; particularly in advanced stages, and is estimated to have an overall 5-year survival of 73-86% in early stages [4, 6].

CONCLUSION

In conclusion, cervical uterine lymphomas have favorable outcomes with on-time management and must be considered as a differential diagnosis in cases with a cervical mass. It must be even possible despite a regular Pap smear and even a non-criticize superficial sampling. Fertility-sparing management should be offered to patients of reproductive ages.

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Hereby we want to thanks all health care providers who sacrifice their lives to save patients' life.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

ETHICS APPROVAL

This is a mini-review article and did not include any human or animal participate. So it does not need additional ethical approval.

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