Primary Non-Hodgkin's Lymphoma of the Uterine Cervix: Report of Three Cases with Immunohistochemical Study

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Abstract: Primary Non-Hodgkin's lymphoma (NHL) involving the uterine cervix and other parts of female reproductive tract are extremely rare and the treatment modalities of this disease are also not well defined. We describe three cases of primary non-Hodgkin's lymphoma of the cervix, confirmed to be diffuse large B cell lymphoma on histopathological examination and immunohistochemical study. All other possible primary sites were excluded clinically and radiologically in all the three cases. The clinical history, histopathological features, immunohistochemical features, differential diagnoses and review of literature regarding these cases are described.

Keywords: Non-Hodgkin's lymphoma, cervix, histopathology, immunohistochemistry.

INTRODUCTION

Non-Hodgkin's lymphoma (NHL) involving the female genital tract as the primary site is extremely rare. NHL of the uterine cervix is still rarer. Reported incidence of NHL of the cervix is about 1 in 730 cases of non-Hodgkin's lymphomas or 1 in 175 cases of extra nodal lymphomas [1]. The majority of NHLs arising from the uterine cervix is represented by high-grade lymphomas with diffuse large B-cell histotype [2].

Non-Hodgkin's lymphoma (NHL) is sometimes part of the differential diagnosis of poorly differentiated malignancies. Immunohistochemistry on tissue sections reveals the tumor cell to be positive (diffuse, strong, membrane) staining for CD 45 (LCA) and negative staining with CK, S-100, HMB45, Chromogranin. CD20 (a pan lineage marker for Blymphocytes) positivity helps categorizing the diagnosis of diffuse large B-cell lymphoma (DLBCL).

The management of this disease is not well defined in the literatures. It is due to the lack of agreement regarding the effectiveness of various modalities as a consequence of its low incidence. Treatment of lymphoma of cervix may involve irradiation therapy alone, irradiation combined with hysterectomy, or chemotherapy in conjunction with radiotherapy/surgery or chemotherapy alone if reproductive potential conservation is desired.

CASE REPORTS

Case 1

A 25 year-old lady presented with foul smelling discharge per-vaginal (P/V) for 2 years and irregular bleeding per-vagina (P/V) for 2 months. She is para(P2+0). General examination revealed pallor. No palpable cervical, axillary or inguinal node found. Perspeculum (P/S) - examination showed a large smooth surfaced mass, Per-vaginal (P/V) examination - Growth is smooth, arising from the anterior lip of cervix with no pedicle. Per-rectal (P/R) examination - mass felt anteriorly, rectal mucosa was free. Adnexae was free. Bilateral parametrium free. The case was clinically staged as carcinoma cervix stage IB (FIGO). Vulva and vagina - no abnormality detected. USG abdomen- 8 weeks intrauterine pregnancy and a large cervical mass possibly neoplasia. CT scan abdomen does not reveal any parametrial infiltration and pathologic lymphadenopathy. Pre operative cervical punch biopsy revealed poorly differentiated carcinoma. The case was taken up for total radical abdominal hysterectomy and pelvic lymphadenectomy as family was completed. Specimen was sent for histopathological examination. Section from cervical mass revealed diffuse infiltration by atypical large round cells with minimal intervening stroma. Diagnosed as round cell tumor of cervix (D/D-NHL). Lymph nodes were reactive.

ISSN: 1929-2260 / E-ISSN: 1929-2279/12

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We report three cases of a rare disease, diffuse large B-cell lymphoma (DLBCL) of the uterine cervix from our institution. All other possible primary sites were also excluded clinically and radiologically in all the three cases.

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Case 2

A 60-years-old woman, presented to the gynecology clinic at our institution with a history of post menopausal bleeding bleeding and white discharge for 6 months. Blood investigations were within normal limit. No pathologic lymphadenopathy by CT scan abdomen. Clinically and radiologically diagnosed as carcinoma cervix stage III-B(FIGO). Punch biopsy from the cervical growth was taken and sent for histopathological examination. Histopathological examination revealed diffuse sheets of neoplastic cells with round to ovoid, vesicular nuclei surrounded by vascular septa and lined by hyperplastic squamous epithelium. Diagnosed as poorly differentiated malignant neoplasm of cervix Immunohistochemistry was advised to rule out NHL.

Case 3

A 54 year-old lady presented with history of irregular menstrual bleeding and pain abdomen for last 2 months. Her past medical history was completely uneventful. Physical examination revealed pallor. No abnormal findings was found on systemic examination. Investigations- Hb-9.3gm%, ESR- 70mm 1st hr, others within normal limits. No palpapable cervical, axillary or inguinal node found. CT scan abdomen does not reveal any pathologic lymphadenopathy. Per-vaginal (P/V) examination- smooth growth seen on cervix with indurated lateral fornices. Per-rectally parametrium was indurated medial half, rectal mucosa free. Clinically and radiologically diagnosed carcinoma cervix stage II-B(FIGO). A biopsy from the cervical growth was taken and sent histopathological examination. Histopathological examination revealed poorly differentiated malignancy of cervix and Immunohistochemistry was advised to rule out NHL.

Immunohistochemical Study

Histopathological examination in all the cases revealed almost similar pictures (Figures 1, 2) and Immunohistochemistry were performed to rule out NHL. The immunohistochemistry on formalin-fixed tissue sections revealed the tumor cells to be diffuse strong positive for CD45 and CD20 and negative for pan cytokeratin and CD3 (Figures 3, 4). CD45 and CD20 using polymer HRP system and DAB chromogen stained membrane and part of cytoplasm of tumor cells. Final diagnosis of diffuse large B-cell lymphoma of the cervix was established.

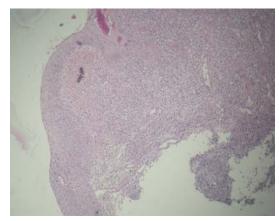


Figure 1: Photomicrograph showing Diffuse large B-cell lymphoma of cervix with sparing of the squamous epithelium (H&E, 100x).

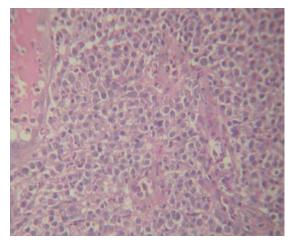


Figure 2: Diffuse sheets of tumor cells with round nuclei, scanty cytoplasm and prominent nucleoli (H&E, 400x).

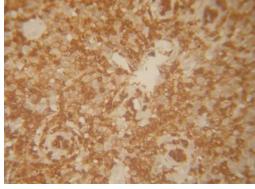


Figure 3: Immunohistochemical staining showing tumor cells are positive for CD20 (H&E, 400x).

CD45 (LCA) is a transmembrane protein-tyrosine-phosphatase present on all mature B and T lymphocytes, thymocytes and macrophages. This is useful in differentiating lymphomas from nonlymphoid tumors as neoplastic B and T cells in non-Hodgkin's lymphoma stain positive for CD45 and hence can be distinguished from sarcomas and carcinomas. Expression of CD20 antigen is generally restricted to

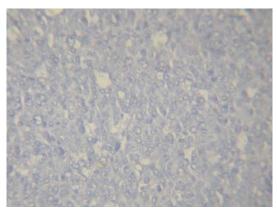


Figure 4: Immunohistochemical staining showing tumor cells are negative for CD3 (H&E, 400x).

the B-cell lineage and CD3 stains only cells of T-cell origin. Thus CD20 and CD3 help in differentiating B and T cell Lymphomas. Cytokeratins on the other hand are a family of water-insoluble proteins forming a major part of the cytoskeleton of epithelial cells and thus forms an important aid in the classification of epithelial neoplasm.

Treatment

1 was subsequently taken up Case chemotherapy, 6 cycles according to CHOP protocol (cyclophosphamide, adriamycin, vincristine prednisone) and she responded well and under follow up for 5 years. Case 2 received external radiation 5000 cGy over 25 fractions in 5 weeks followed by chemotherapy (CHOP protocol). She responded very well and she is under follow up for 3 years. Case 3 was planned for radiotherapy & chemotherapy. She received external radiotherapy 5000 cGy over 25 fractions in 5 weeks but subsequently she was lost to follow up.

DISCUSSION

Primary Non-Hodgkin's lymphoma (NHL) of the cervix is an extremely rare tumor of the female genital tract. Chorlton et al. reported that only 0.12% of all non-Hodgkin's lymphoma originates from the uterine cervix [1]. A review of the literature corroborates the rarity of the disease as not many cases are reported and are mostly in the form of case reports and small case series [3]. The age at presentation ranges from 20 to 80 years, with the median age varying from 40 to 59 years [4]. 70% of these tumors are of diffuse large cell type and 20% are low grade follicular lymphomas.

Malignant lymphoma of cervix presents with vaginal bleeding, and a subepithelilal mass without obvious

ulceration, most are diffuse large B cell lymphomas and many are accompanied by extensive fibrosis [5]. Cervical cytology is typically negative or non-specific. Diagnosis invariably requires a biopsy. Our cases presented in the correct decade and had corroborative symptoms and were subjected to biopsy and then immunohistochemistry to obtain the diagnosis.

Non-Hodgkin's lvmphoma (NHL). especially extranodal NHL are increasing in incidence, but the etiology of much of this increasing is still unclear [6].

An important differential diagnosis is with lymphoma like lesions resulting from focally florid lymphoid proliferations associated with chronic cervicitis or as an expression of infectious mononucleosis [7]. These are identified by polymorphic nature of infiltrate including mature plasma cell, small lymphocytes and neutrophils, surface ulceration, minimal or no sclerosis and evidence of polyclonality by immunoperoxidase staining.

Diffuse large B cell lymphoma (DLBCL) of centroblastic type, may contain other type of cells including plasma cells. DLBCL of centroblastic type may have antecedent low grade lymphoma of various types including lymphoplasmacytoid lymphoma; it can explain presence of plasmacytoid cells in otherwise classical DLBCL of centroblastic type. Non-Hodgkin's lymphoma (NHL) is sometimes part of the differential diagnosis of poorly differentiated large malignancies. Most forms of lymphoma can be ruled out by the use of antibodies to CD 45 (LCA), cytokeratin, S- 100, HMB45, and chromogranin.

A hematologic malignancy that must be included in the differential diagnosis is extramedullary myeloid cell tumor (EMCT), also known as granulocytic sarcoma and chloroma. Well to moderately differentiated neoplasms have granulocytic or eosinophilic myelocytes and can be recognized histologically. However, poorly differentiated EMCT can closely mimic lvmphoma and must immunohistochemically. EMCT are usually positive for myeloperoxidase, CD43, CD68 and lack lymphoid markers [8].

Thus NHL must be kept in mind in the work-up of histologically difficult uterine neoplasms to avoid misdiagnosis [9].

Cervical lymphoma generally has a good prognosis as compared to nodal lymphomas with an overall median survival of 4 years. Extent of disease, size of primary tumor and the type of lymphoma are significant prognostic features [10]. The adequate treatment of this malignancy has never been standardized [11]. According to case reports and short series, the cornerstone of therapy is radiation alone or irradiation combined with either chemotherapy or surgery. Others used only combination chemotherapy [12].

Rarity of patients of primary lymphoma of cervix makes standard treatment difficult to define. Main therapy consists primarily of chemotherapy alone or a combination of chemotherapy with surgery and chemotherapy and radiation. Elisabetta *et al.* [13] suggests that young patients even with bulky lesions may benefit from chemotherapy alone as initial treatment. Andras *et al.* [14] describes a case successfully treated by neoadjuvant chemotherapy according to CHOP protocol (cyclophosphamide, adriamycin, vincristine, and prednisone), followed by radical hysterectomy. Stroth *et al.* [12] found the combination of chemotherapy and irradiation to be the most effective treatment regime for all uterine and cervical lymphomas.

One of our cases was treated with surgery and chemotherapy. One case was treated with external radiation followed by Chemotherapy and one case received radiotherapy. Two out of three of our patients responded well and one patient was lost to follow up, but still we have included her in our study because of the rarity of the case and also she had completed her radiation and after the completion of radiation her symptoms disappeared and on examination there was satisfactory local response.

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