Primary uterine diffuse large B-cell lymphoma involving the urinary bladder with urinary cytology mimicking carcinomas: A case report

ABSTRACT

We report a rare case of a 69-year-old woman in whom diffuse large B-cell lymphoma (DLBCL) originated from the uterus and involved the urinary bladder. The cervical smears of the case mostly consisted of discohesive atypical round cells, which were highly suggestive of lymphoma; however, in voided urine smears, a majority of the cells formed large aggregates of degenerated cells, mimicking those of urothelial carcinoma (UC). The smears also represented some small loose clusters, in which tumor cells formed short chains with nuclear molding, mimicking those of small cell carcinoma. The cytodiagnosis got definitive when we identified the atypical cells that showed CD20+/CD3-/cytokeratin-/NSE- immunophenotype. These are of particular concern as they may have misleading similarities to other epithelial neoplasms when examining lymphoma involving the urinary bladder. Accordingly, this case highlights the importance of immunocytochemistry to rule out malignant lymphoma when encountering large and/or small loose clusters of atypical round cells on urinary cytology.

Key words: Immunocytochemistry; lymphoma; urinary bladder; urine; uterine cervix

Introduction

Extranodal non-Hodgkin’s lymphomas (NHLs) make up approximately 25% of all cases of lymphomas, with the most common sites being gastrointestinal tract and skin.[1] Despite the increasing incidence of NHLs during the last few decades, only 1-1.5% arises from female genital organs.[1] Among them, the ovaries, uterus, and fallopian tubes are the most common sites, and only 0.12% of all NHLs originate from the uterine cervix.[2] The most common subtype of cervical NHLs is diffuse large B-cell lymphoma (DLBCL); therefore, the lymphoma cells in smears typically appear as discohesive cells with scant cytoplasm, indistinct cellular membranes, irregular nuclear contours, one or more large prominent nucleoli, and irregular clearing of the nuclear chromatin.[3] We report a rare case of DLBCL in the uterine cervix directly invading the urinary bladder, in which tumor cells were identified in the urine smears. Interestingly, the voided urine smears consisted predominantly of cohesive clusters mimicking those of epithelial neoplasms arising in the urinary bladder.

Case Report

A 69-year-old menopausal woman presented to the urology department of our institution with a 1-month history of lower abdominal discomfort, back pain, and sudden hematuria. The
patient underwent a cystoscopy procedure which revealed a smooth, large protruded lesion of the posterior bladder wall. Cytological smears of voided urine were interpreted as a lymphoma with a confirmation by immucytochemistry. Subsequent computed tomography (CT) scan and magnetic resonance imaging (MRI) of the pelvis revealed a solid tumor (5.0 × 5.0 cm in dimension) occupying the uterine cervix and lower part of the body [Figure 1a], thickening of the posterior bladder wall, and bilateral hydronephrosis. A few pelvic lymph nodes were slightly enlarged. Speculum examination showed a large, irregular surfaced mass with no pedicle arising from the anterior lip of the cervix. Specimen from the cervix and endometrium were taken and sent to cytopathology; cytologic interpretation was of malignant lymphoma [Figures 1b and 2a] and pathological diagnosis was that of DLBCL, nongerminial center subtype.

The patient was hospitalized and systemic CT scan revealed slightly enlarged systemic lymph nodes. A staging bone marrow aspirate showed microscopic neoplastic infiltrate. These findings were compatible with stage IV of DLBCL arising from the uterus where the cervix appears to be the primary site of disease. The patient was successfully treated with one course of cyclophosphamide, hydroxydaunorubicin, oncovin, and prednisone or prednisolone (CHOP) and five courses of CHOP with the drug rituximab (R-CHOP) chemotherapy. She has maintained complete remission for 3 years since the final course of the chemotherapy.

Cytopathological findings
A voided urine specimen was collected and processed by the centrifuge method. The sample was centrifuged at 700 g for 3 min, fixed in 95% alcohol, and stained with May-Grünwald-Giemsa and Papanicolaou methods. The smears consisted predominantly of large aggregates with marked cellular crowding, nuclear overlapping, and short chains composed of degenerated medium-sized round cells [Figure 2b]. These cells contained relatively abundant cytoplasm and reduced round nuclei, resulting in a relatively low nuclear to cytoplasmic ratio. Some of the cells were arranged as short chains with nuclear molding but chromatin smearing was rare [Figure 2c]. However, discohesive fairly uniform cells were scattered around the clusters [Figure 2d]. Differentiating between epithelial neoplasms and malignant lymphoma was difficult from these findings; therefore, we performed immucytochemistry. We employed the polymer-peroxidase method without antigen retrieval, using Histofine Simple Stain MAX-PO (Nichirei Biosciences, Tokyo, Japan) and monoclonal antibodies against CD20 [L26, diluted 1/500; DAKO Cytomation (DC, Glostrup, Denmark)], CD3 (2GV6, prediluted; Roche, Basel, Switzerland), cytokeratin (AE1/AE3, 1/100; DC), and neuron-specific enulase (NSE) (BBS/NC/VI-H14, 1/100; DC). The immunophenotype of CD20+/CD3-/cytokeratin/-NSE- was consistent with a B-cell lymphoma [Figures 3a-d].

Meanwhile, the cervical smears, collected and processed by the centrifuge method, demonstrated a dispersive cellular population with single cells of intermediate to large size in a clear background. Majority of these cells were discohesive and contained a moderate amount of cytoplasm and round nuclei with finely granular chromatin and a few small nucleoli. Cell borders were conspicuous and nuclear contours were relatively smooth. Histology of the cervical biopsy revealed a highly cellular tumor of fairly monotonous lymphoid proliferation with a diffuse infiltrating pattern. Immunohistochemistry on formalin-fixed paraffin-embedded sections showed that the tumor cells were positive for CD45, CD20, CD79a, and multiple myeloma oncogene 1 (MUM1) and negative for CD3, CD5, CD10, cyclin D1, Bcl-2, Bcl-6,
and TdT that were consistent with DLBCL, nongerminal-center type.

Discussion

Cytologic evaluation of voided urine specimen is the most common method for the detection and diagnosis of neoplasms in the urinary bladder. Typical cytologic features of bladder lymphoma are discohesive population of atypical large lymphocytes, whereas those of urothelial carcinoma (UC) are cohesive clusters with marked cellular crowding and nuclear overlapping. Thus, neoplastic cells with lack of cohesion are generally considered as a useful finding for distinguishing lymphoma cells from epithelial cells. However, we described here an unusual cytomorphological pattern of DLBCL presenting predominantly as cohesive clusters of cells on urine smear, mimicking epithelial neoplasms.

It is known that some specific types of lymphoma are prone to form aggregates in cytological specimens. For example, anaplastic large cell lymphoma and adult T-cell leukemia/lymphoma may show clusters of highly atypical cells. Apart from these specific types, other types of lymphoma may form cohesive groups of degenerated neoplastic cells in the urine. Indeed, some previous reports represented cases of high-grade DLBCL and low-grade lymphoma of the mucosa-associated lymphoid tissue (MALT) type where neoplastic cells appeared as clusters with cellular crowding and cohesion, mimicking those of UC. In addition, short chains with nuclear molding of lymphoma cells may have misleading similarities to small cell carcinoma. In the urine specimen, neoplastic cells of small cell carcinoma often show loose clusters and isolated single cells with scant cytoplasm, mimicking those of lymphoma cells. These are of particular concern and may have misleading similarities to epithelial neoplasms when examining lymphoma involving the urinary bladder.

In addition, the type of preparation may affect interpretation. Compared with the centrifuge method, thin layer preparations are more cellular with better cell preservation and cleaner backgrounds. Such characteristics facilitate the identification of isolated malignant cells. However, cells in centrifuge method preparations are prone to form relatively tight clusters. Therefore, cytodiagnosis of lymphoma involving the urinary bladder should be based on the awareness that these patterns contain potential pitfalls and misleading mimics, and should be supported by adequate immunocytochemical analysis.

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Conflicts of interest

There are no conflicts of interest.

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