Hodgkin's lymphoma presenting as a bladder tumour

Haematologica 2006; 91:(1)e6-e7

Sir: Lymphoma of the urinary bladder is a rare tumour, accounting for less than 1% of malignant bladder lesions. It may occur as a disease localized to the bladder (primary bladder lymphoma), as the site of first evidence of a disseminated disease (non-localized bladder lymphoma), or as a secondary involvement in patients with a previously diagnosed lymphoma (secondary bladder lymphoma).[1] Most lymphomas involving the bladder are B-cell non-Hodgkin's lymphomas.[2] Among primary bladder lymphomas low-grade marginal zone lymphoma of the MALT type is the most frequent type, and diffuse large B-cell lymphoma is the most common histotype in cases of secondary dissemination to the bladder.[1-3] Urinary bladder involvement by Hodgkin's lymphoma (HL) is extremely rare; the literature contains only two reports of primary HL of the bladder,[4,5] and occasional reports of secondary bladder infiltration in patients with a history of nodal HL.[3, 6, 7] We report herein the cytological and pathological findings in a patient with classical HL presenting as a bladder mass.

A 81-year-old woman with no significant past medical history presented with hematuria, asthenia, anorexia and worsening general condition. Physical examination revealed bilateral inguinal lymphadenopathy. Laboratory tests revealed a moderate anemia, a normal white blood cell count with slight hypereosinophilia and an elevated platelet count, increased inflammatory tests, and normal lactate dehydrogenase levels. A voided urine specimen submitted for cytologic examination showed marked cellularity composed mainly of inflammatory cells admixed with normal urothelial cells and scattered isolated large cells exhibiting large irregularly shaped hyperchromatic nuclei with prominent nucleoli (Figure 1), interpreted as highly suspicious for malignancy. An abdominal CT-scan demonstrated thickening of the bladder wall, dilatation of the right ureter and prominent bilateral iliac and inguinal lymphadenopathies ; the liver and spleen appeared normal. There was no mediastinal enlargement on chest X-ray. Scintigraphic bone scanning showed no evidence of tumor dissemination to bone. Cystoscopy disclosed a large ulcerated tumor. Pathological examination of the bladder biopsies showed mucosal ulceration by a diffuse and vaguely nodular tumor infiltrate extending downwards to the muscularis propria, consisting of large pleomorphic atypical cells suggestive of Hodgkin/Reed-Sternberg (HRS) cells admixed with an inflammatory background composed of lymphoid cells, histiocytes, neutrophils and eosinophils (Figure 2, A-B). The tumor contained areas of coagulative necrosis. By immunohistochemistry, the large atypical cells were strongly positive for CD30 and Pax-5 and variably positive for CD15 whilst being negative for CD20, CD3, CD5, CD45 and pALK (Figure 2 C-E). In situ hybridization for EBERs gave a strong positive signal in most HRS cells (Figure 2F). PCR for EBV typing showed an A-strain virus and no deletion within the LMP-1 gene. PCR for immunoglobulin heavy chain and TCR gamma chain rearrangements showed a polyclonal pattern. As a result of these findings, a diagnosis of classical Hodgkin's lymphoma was rendered. Given the poor general condition of the patient, no treatment was administered, and she died shortly after of a femoral neck fracture.

Extranodal presentation of HL is extremely rare, estimated to account for less than 1% of all HL cases in non-AIDS patients.[8] Thus, because of the rarity of true extranodal HL, it has been recommended that stringent morphologic and immunophenotypic criteria be used before establishing this diagnosis with certainty. In that respect, the diagnosis of HL in the two earlier case reports of primary bladder HL remains in our opinion quite uncertain. Indeed, the first case was categorized as *Hodgkin's paragranuloma* on morphology alone[4] and the second report of a mixed cellularity HL contains no detail of the pathological findings.[5] In the current case, the morphological, immunophenotypical and molecular findings are typical for classical HL and unequivocally establish the diagnosis of non-localized bladder HL.

Figure 1. Malignant Hodgkin/Reed-Sternberg cells in cytological preparation of urine specimen (Papanicolaou, x 1000).

The most common extralymphatic sites for HL are the lung and the bone.[9] Primary gastrointestinal involvement by HL is quite rare, but seems to occur in a specific clinical setting. Indeed, most intestinal cases have been reported in patients with inflammatory bowel diseases (IBD), in particular Crohn's disease. Interestingly, EBV positivity has been documented in all intestinal cases tested for EBER reactivity.[10,11] Thus it has been suggested that HL in that clinical setting occurs as the result of an EBV-driven lymphoproliferation, similar to lymphomas arising in immunodeficient states, and that immunologic defects inherent to IBD, immunosuppressive therapy and ongoing chronic inflammation may contribute to its development. In the case of bladder lymphomas, chronic antigenic stimulation has also been postulated as a pre-

Figure 2. Vaguely nodular lymphomatous infiltrate in the bladder mucosa containing numerous pleomorphic HRS cells admixed with an inflammatory background (A and B). Lack of CD45 expression by HRS cells (C). Positivity of HRS cells for CD30 (D), CD15 (E) and EBERs (F).

disposing factor to the development of primary MALT lymhpomas, as a history of chronic cystitis is typically encountered in those patients.[1,2] There is no indication that such mechanism may be incriminated in the present case ; the association with EBV infection raises the possibility of an EBV-driven proliferation perhaps favored by a relative age-related immune depression in an elderly patient.[12] This is the first detailed report of a classical HL presenting in the bladder. Collection of other cases may be necessary to delineate the clinicopathological features of this extremely rare disease.

Laurence de Leval, MD PhD, Claire Jardon-Jeghers, MD, Christine Gennigens°, MD, Jacques Boniver, MD PhD

From the Department of Pathology, CHU Sart-Tilman, Liège, Belgium, and the Department of Internal Medicine°, CH Pelzer, Verviers, Belgium

Correspondence: Laurence de Leval, MD PhD
Department of Pathology CHU Sart-Tilman Tour de Pathologie, B23 B – 4000 Liège
Phone: + 32 4 3662405. Fax: + 32 4 3662919.
E-mail: L.deLeval@ulg.ac.be

References

1. Kempton CL, Kurtin PJ, Inwards DJ, Wollan P, Bostwick DG. Malignant lymphoma of the bladder: evidence from 36 cases that low-grade lymphoma of the MALT-type is the most common primary bladder lymphoma. Am J Surg Pathol 1997;21:1324-33.
2. Marx A. Lymphomas. In: Eble J, Sauter G, Epstein J, Sesterhenn I, editors. Pathology and Genetics - Tumours of the urinary system and male genital organs. Lyon: IARC Press; 2004. p. 147.
3. Bates AW, Norton AJ, Baithun SI. Malignant lymphoma of the urinary bladder: a clinicopathological study of 11 cases. J Clin Pathol 2000;53(6):458-61.
4. Marconis J. Primary Hodgkin's (paragranulomatous type) disease of the bladder. The Journal of Urology 1959;81(2):275-281.
5. Jones M. Primary Hodgkin's disease of the urinary bladder. Br J Urol 1989;63:438.
6. Bocian JJ, Flam MS, Mendoza CA. Hodgkin's disease involving the urinary bladder diagnosed by urinary cytology: a case report. Cancer 1982;50(11):2482-5.
7. Sosna J, Lossos IS, Libson E. Hodgkin's lymphoma of the urinary bladder. Clin Radiol 2000;55:405-6.
8. Burke J. Hodgkin's disease: histopathology and differential diagnosis. In: Knowles D, editor. Neoplasic hematopathology. Philadelphia: Lippincott Williams & Wilkins; 2001. p. 623-665.
9. Diehl V, Re D, Josting A. Hodgkin's disease: clinical manifestations, staging, and therapy. In: Hoffman R, Benz E, Shattil S, Furie B, Cohen H, Silberstein L, et al., editors. Hematology, basic principles and practice: Elsevier Churchill Livingstone; 2005. p. 1347-1377.
10. Li S, Borowitz MJ. Primary Epstein-Barr virus-associated Hodgkin disease of the ileum complicating Crohn disease. Arch Pathol Lab Med 2001;125:424-7.
11. Kumar S, Fend F, Quintanilla-Martinez L, Kingma DW, Sorbara L, Raffeld M, et al. Epstein-Barr virus-positive primary gastrointestinal Hodgkin's disease: association with inflammatory bowel disease and immunosuppression. Am J Surg Pathol 2000;24:66-73.
12. Herling M, Rassidakis GZ, Medeiros LJ, Vassilakopoulos TP, Kliche KO, Nadali G, et al. Expression of Epstein-Barr virus latent membrane protein-1 in Hodgkin and Reed-Sternberg cells of classical Hodgkin's lymphoma: associations with presenting features, serum interleukin 10 levels, and clinical outcome. Clin Cancer Res 2003;9:2114-20.