Diffuse Bony Metastasis from Transitional Cell Carcinoma of Urinary Bladder : A Case Report and Review of Literature

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Abstract

The incidence and mortality rate of bladder carcinoma remains high and is in fact increasing despite the application of new treatment strategies. Transitional cell carcinoma (TCC) is the most common carcinoma of the bladder (>90% of cases). We report a case of a 60 year-old man with multiple bony metastases of TCC affecting the humerus, femur, spine, iliac wing, and ribs. The metastases were discovered within a year after first presentation of hematuria with a subsequent biopsy diagnosis of TCC of bladder, Grade 3 of 3 with no definite muscle invasion. Metastasis of TCC of bladder to bone is an uncommon occurrence when compared with breast and prostate carcinoma. This may be due to intrinsic properties of tumor cells and/or mechanisms of metastases. Recent studies confirm that bone is the preferred site of metastasis (35%) of TCC outside of the pelvis, with the spine being the most common site (40% of bony metastases). Histologic grading, emphasizing the presence of invasion, is generally accepted as being very important prognostically. The importance of diagnostic screening tests including urothelial biomarkers profile in reducing the mortality rate from first onset of hematuria is discussed such as tumor - associated antigen M344 and DD23.

Key word : Transitional Cell Carcinoma of Urinary Bladder, Bone Metastases

Virtually all malignant neoplasms have been reported to give rise to bony metastases. By far, the most common skeletal metastases are from carcinomas of breast, lung, prostate, kidney, and thyroid. More than 80 per cent of these come from breast and prostate(1). Compared to the incidence of

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bony metastases from these aforementioned common carcinomas, bony metastases from transitional cell carcinoma (TCC) of the bladder is quite uncommon. This is interesting when it is realized that carcinoma of the bladder has a high yearly incidence, and a significant mortality rate. In 1997, bladder carcinoma was reportedly diagnosed in approximately 54,500 patients in the United States, and resulted in an overall mortality rate of about 22 per cent, or 11,700 deaths[2]. TCC accounts for more than 90 per cent of all bladder tumors[3]. Thus, TCC of the bladder and its metastatic behavioral characteristics is an important topic to recognize, review and explore. This tumor has a high incidence of either tumor recurrence (50-80%), or progression to invasive disease (Grade 1 approximately 2%, Grade 2 approximately 11%, Grade 3 approximately 45%)[4,5]. Importantly, the most serious complication is distant metastasis, which occurs in approximately 50 per cent of cases within 2 years of diagnosis[5], with a mortality rate of approximately 40 per cent[6] to 80 per cent[5], even with aggressive therapy.

As of approximately twenty years ago, there was only one report of metastasis of carcinoma of the bladder, reported from autopsy cases. This report showed a metastatic rate of about 66.7 per cent, with the most frequent site of metastasis being lymph nodes (37.9%). The next three most frequent sites were reported to be liver (29.9%), lung (29.9%), and bone (24.1%)[7]. The exact rate of metastasis of bladder carcinoma has not been well established. Recently, Sengelov L, et al[8] reported new clinical data that presented the rate and distribution of metastasis in groups of patients with disseminated urothelial cancer. The most common primary tumor of the bladder was TCC (85%). This study reported that bone is the most frequent site of metastasis outside of the pelvis (35%)[8]. Lymph node (extra-pelvic), lung, and liver metastases occurred at rates of approximately 26 per cent, 20 per cent, and 12 per cent, respectively. This suggests that the relatively low frequency of bone metastasis in autopsy studies might be due to insufficient examination of the skeletal system in autopsy cases. Other, more unusual metastatic sites include the omentum, psoas muscle, salivary gland, female reproductive organs, breast, eye, heart[9], and oral cavity[10].

Distant metastasis, the most serious complication of transitional carcinoma, remains a serious problem. We report a patient who developed diffuse bony metastases from TCC of the bladder. We will also discuss the distinctions of metastatic rate, problems and usefulness of histologic grading, treatment, and new directions aimed at decreasing this complication.

CASE REPORT

A 60-year-old man presented with an approximate one-year history of hematuria. Cystoscopy and biopsy of the bladder was performed at an outside hospital. The biopsy material revealed papillary transitional cell carcinoma, Grade 3 out of 3. No definitive muscularis propria invasion was present. No definitive treatment was initiated at that time. Four months later, multiple thoracic spinal metastases were discovered. Surgery was performed to stabilize the T6, T7, and T8 vertebrae. The patient then received 4 courses of adjuvant chemotherapy, and 2 courses of radiation therapy. Nine months later, the patient presented with a pathologic fracture of the right humerus. Skeletal survey revealed multiple sites of bone metastases including the humerus, femur, spine, iliac wing and ribs. Suspected liver metastases were also present on imaging studies. Open reduction and internal fixation of the humeral pathologic fracture was performed. The patient was subsequently lost to follow-up until he presented with bowel obstruction involving the ascending colon. The patient became septic and died 2 months later. The patient died 1 year and 2 months after the initial diagnosis. An autopsy was not performed.

MATERIAL AND METHOD

Tissue from the biopsy specimens was fixed in 10 per cent buffered formalin and processed according to standard technique.

Immunohistochemistry

Immunohistochemical studies were performed on formalin-fixed, paraffin-embedded tissue section using the horseradish peroxidase-labeled streptavidin-biotin method. Primary antibodies employed included keratin (AE1/AE3, 1:1000, Boechringer-Mannheim) and Vimentin (1;1000, DAKO).

RESULTS

Histologically, solid sheets of neoplastic cells infiltrated diffusely between bony trabeculae.

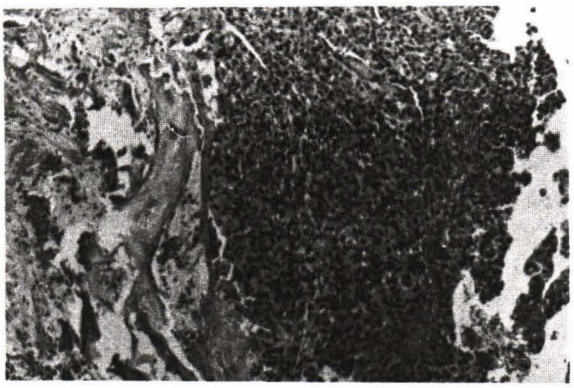

Fig. 1. Sheet of polygonal neoplastic cells infiltrating between bony trabeculae. The nuclei are round, centrally located hyperchromatic and contain distinct nucleoli and cytoplasmic is ample. (Hematoxyline-eosin stain; original magnification x 200)

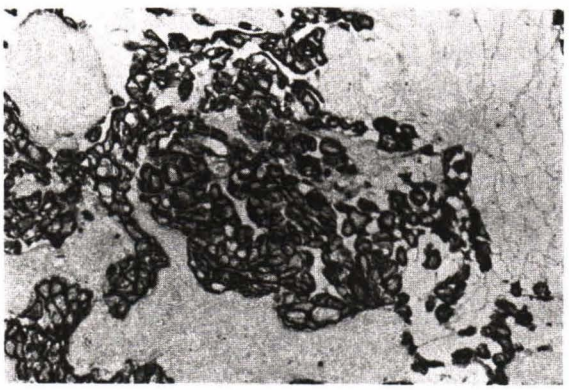

Fig. 2. Strongly diffuse membranous staining with keratin in the metastasis of TCC of bladder (Immunoperoxidase stain; original magnification x 400)

Some papillary formations were evident. Mitotic figures were numerous. Diffuser areas of hemorrhage and necrosis were present as well (Fig. 1).

Immunohistochemical staining of neoplastic cells revealed strong reactivity for keratin (Fig. 2), but no reactivity for vimentin.

DISCUSSION

Bone metastases are a frequent clinical problem in patients with carcinoma. Metastasis of carcinoma to bone involves multiple steps and variable factors. Bone provides an extremely hospitable microenvironment for the formation of metastatic colonies that has proven especially suitable for breast, prostate, and lung carcinomas. This partially explains why some carcinomas have a higher metastatic rate to bone. Urothelial carcinomas, as well as carcinomas of the endometrium, and head and neck result in bone metastases far less frequently than breast and prostate carcinoma. Each step in the evolution of metastasis depends on specific intrinsic properties of cancer cells. One of the first steps includes detachment from the primary site utilizing proteolytic enzymes, and expression or loss of the cell adhesion molecule (CAM). CAM is also essential for accumulation of tumor cells at the metastatic site. A second step involves the invasion of malignant cells into the surrounding soft tissues, intravasation, extravasation, and bone matrix degradation. A third step involves migratory activity facilitating vascular circulation. The fourth step involves insuring survival from host immune surveillance[11]. The final step involves bone destruction as a result of stimulation of osteoclasts by chemical mediators including parathyroid hormone-related peptide (PTH-rP), interleukin-1, tumor necrosis factor, prostaglandin E_2, and others[12]. However, prostatic carcinoma also stimulates osteoblastic activity. Currently, therapeutic strategies to reduce bone turnover and skeletal complication from metastatic cancer by a new-generation of biphosphonate drugs that inhibit osteoclast generation or promote increased apoptosis of mature osteoclasts are being explored. Understanding the mechanisms of metastasis is essential to improve efficacy of treatment, therapeutic intervention and prevention of the metastatic process[11]. Tumor metastases to bone occur primarily *via* the hematogenous pathway, with tumor cells finding purchase in the more vascular areas of the bone, especially the bone marrow. Bone metastases most commonly affect the axial skeleton and the proximal ends of the long bones, the ribs, and the vertebral column[1,13]. The vertebral plexus of veins (Batson's plexus) doesn't have a system of valves to control blood flow. When increased pressure in the chest or abdomen occurs, blood from this area conveniently reaches the vertebral plexus. One theory holds that this is one reason why metastases from bladder tumors commonly affect the axial skeleton, particularly the spine[13]. Sengelov et al[8] reported on the skeletal distribution rate from transitional cell carcinoma. He found metastatic tumors

affecting the spine (40%), pelvis (26%), femur (10%), ribs (10%), humerus (5%), tibia (3%), skull (2%), clavicle (2%), mandible (1%) and sternum (1%). Additionally, 71 per cent of patients had 2 or more metastatic sites. In patients who developed multiple bony metastatic sites, the initial site was most commonly the spine, resulting in pathologic fracture, which is the most common pattern for late complication in the end stage of the disease. This pattern should be recognized when evaluating the patient for treatment. Other factors important in management of these patients include early detection, role of pathologic diagnosis, and case appropriate treatment strategies, as will be discussed further.

The histological grade and clinicopathologic stage are the most significant parameters in predicting prognosis. The histological grading of transurethral resection of bladder tumor (TURBT) is certainly important when considering the appropriate treatment modality. The distinction between superficial and muscle (deep) invasion remains a very important one as the natural history and treatment of these are markedly different[14]. Recent advances in molecular and genetic studies show that these tumors with different invasive components truly have a distinctly dichotomous nature and genetic pathway[15]. Depth of invasion remains a most significant parameter. Fragmentation of the biopsy material, along with orientation in the paraffin block, introduces a variable that may make determination of the exact depth of invasion with regard to muscle difficult to establish. This may result in under-evaluation or the assignment of an erroneously low stage, resulting in unreliable information when making decisions as to whether therapy will consist of cystectomy with or without adjuvant or neoadjuvant chemotherapy. Additionally, if the initial biopsy shows muscle invasion, prompt evaluation for distant metastases should be undertaken. Delay of treatment or less than adequate treatment based on under-staging, will alter treatment strategy, and result in a poor prognosis. Accuracy of diagnosis with regard to level of muscle invasion has important prognostic implications as well.

In the currently discussed case, the patient presented with hematuria. The initial biopsy (TURBT) examination showed no definitive muscularis propria invasion. The patient underwent no further treatment at that time. Following the discovery of multiple bony metastases, additional treatment consisting of radiation and chemotherapy was instituted.

Bane[14] proposed a new standard investigational protocol for patients presenting with hematuria. This protocol consists of urinalysis, Papanicolaou stained cytologic examination, and an urothelial biomarker profile, followed by an IVP and cystoscopy. The emphasis of this study was on the importance the utilization of biomarkers and imaging techniques in association with other standard methods of examination, to try to more accurately determine the behavior of a tumor in a particular patient. Actually a large number of biomarkers for diagnostic, prognostic and therapeutic monitoring have been identified[14]. The use of tumor-associated antigens M344 and DD23 represent a new development for screening and diagnosis when combined with DNA ploidy. This combination results in increased sensitivity for detection, as well as more specificity for both low and high grade TCC[14]. Data from recent research indicates that the evaluation of biomarkers will add a new and useful dimension to the conventional clinical and pathological evaluation of bladder carcinoma, and will lead to improved treatment strategies.

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การแพร่กระจายของมะเร็งกระเพาะปัสสาวะชนิดทรานสิชันนัล เซลล์ คาร์ซิโนมา สู่กระดูก : รายงานผู้ป่วยและทบทวนวารสาร

วรนุช ปัญญาวรวุฒิ, พ.บ. , Scott D. Nelson, พ.บ.***

อุบัติการและอัตราการตายของมะเร็งกระเพาะปัสสาวะในปัจจุบันยังคงสูงถึงแม้ว่าจะมีการนำวิธีการที่ทันสมัยมาใช้รักษาโดยพบว่า Transitional cell carcinoma (TCC) พบเกิดขึ้นมากที่สุด (> 90%) รายงานนี้ได้นำเสนอผู้ป่วยอายุ 60 ปีและได้รับการวินิจฉัยจากชิ้นเนื้อเล็กที่เป็น TCC, grade 3 of 3 และไม่พบการลุกลามเข้าสู่ชั้นกล้ามเนื้อที่ชัดเจน พบมีการแพร่กระจายไปสู่กระดูกหลายๆตำแหน่ง โดยทั่วไปแล้วมะเร็งที่มีการแพร่กระจายไปสู่กระดูกมากที่สุดมักมาจากมะเร็งเต้านม, มะเร็งต่อมลูกหมาก และมะเร็งปอด ซึ่งเมื่อเปรียบเทียบอัตราการแพร่กระจายสู่กระดูกแล้วจะพบว่ามะเร็งจากกระเพาะปัสสาวะพบเกิดขึ้นน้อยมาก เนื่องมาจากคุณสมบัติเฉพาะภายในของเซลมะเร็งที่แตกต่างกัน และ/หรือ กระบวนการในการแพร่กระจายที่เกิดขึ้นแตกต่างกันซึ่งได้กล่าวถึงในรายละเอียด

จากรายงานล่าสุดพบว่าการแพร่กระจายออกนอกอุ้งเชิงกรานเกิดขึ้น 35% และไปสู่กระดูกสันหลัง 40% นอกจากนี้ยังได้กล่าวถึงปัจจัยต่างๆซึ่งส่งผลต่อการพยากรณ์โรคได้แก่ ลักษณะทาง Histology ที่แบ่งออกเป็นระดับ, การชี้ชัดของการรายงานผลซึ่งเน้นเรื่องการดูการลุกลามเข้าสู่ชั้นของกล้ามเนื้อ และได้นำเสนอการใช้วิธีการใหม่ในการวินิจฉัยผู้ป่วยที่มีอาการแสดงเริ่มต้นด้วยปัสสาวะเป็นเลือดและการตรวจคัดกรองโดยใช้ Urothelial biomarker profile เช่น Tumor-associated antigen M344 และ DD23 เป็นต้น

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