The clinicopathological features of metastatic tumors of the bladder: analysis of 25 cases

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Abstract: Objective: To introduce the histological features and immunohistochemical results of bladder metastatic tumors, with emphasis on the points of distinction from primary bladder tumors. Methods: A total of 25 cases were diagnosed as bladder metastatic tumors in the First Affiliated Hospital of Nanjing Medical University from January 1, 2009 to August 31, 2017. All of these were retrospectively analyzed, and immunohistochemical stainings were performed to confirm the diagnoses. Results: The most common primary sites in the 25 cases were the colon (24.0%), the prostate (24.0%), the stomach (16.0%), the cervix (12.0%), the kidneys (12.0%), the rectum (8.0%) and the breasts (4.0%). Most of the tumors in these areas reached the bladder by direct diffusion. The most common sites of tumor origin that metastasized to the bladder in the distance were the stomach (16.0% of all metastatic bladder tumors) and the breasts (4.0%). Histologically, 76% of the metastatic tumors were adenocarcinomas. Conclusion: Bladder metastases are uncommon, and distant metastases are rare. Metastatic tumors lack distinctive histological features, especially adenocarcinomas, which require a differential diagnosis in histology, hence knowledge of their medical history and clinical data are particularly important in their diagnosis.

Keywords: Bladder, metastatic tumor, immunohistochemistry, diagnosis, differential diagnosis

Introduction

Metastatic tumors of the urinary bladder are uncommon, accounting for only 2% of bladder tumors. Most metastatic tumors represent a direct extension of malignancies from surrounding organs (e.g., cervix, vagina, prostate, colon, and rectum), and a smaller proportion are metastases, most commonly gastric cancer, breast cancer, malignant melanoma, and lung cancer [1]. In a study of 282 cases of secondary neoplasms of the bladder, the primary sites most often were from the colon (21%), prostate (19%), rectum (12%) and cervix (11%); most tumors from these sites reached the bladder by directly spreading there [1]. However, among the origin sites of the tumors metastatic to the bladder, gastric cancer was the most common (4.3%), followed by melanoma (3.9%), lung cancer (2.8%) and breast cancer (2.5%) [1]. Metastatic tumors lack distinctive histological features, especially adenocarcinomas, which require a differential diagnosis in histology, hence the knowledge of their clinical data is of importance for diagnosis. In addition, from a therapeutic point of view, the treatment for metastatic and primary tumors of the bladder is different. In this study, we describe the prevalence of the metastatic tumors of the bladder and discuss the clinicopathological features, diagnosis, and differential diagnosis of these 25 cases. These will serve as a reference to pathologists, helping them avoid missing or misdiagnosing cases of metastatic tumors of the bladder.

Materials and methods

Clinical data

A total of 25 cases of bladder metastatic tumors were selected, including transurethral resection of bladder tumor (TURBT), bladder biopsy specimens, and outside consultations in the First Affiliated Hospital of Nanjing Medical University from January 1, 2009 to August 31, 2017. The clinical data includes age, gender, primary tumor and site, clinical symptoms and other metastatic sites. The tumors accepted for this study directly spread from advanced...
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Immunohistochemical staining

All specimens were fixed with 3.7% neutral buffered formalin and embedded in paraffin. The immunohistochemical antibodies included PSA, P504S, GATA3, CK, CKH, CKL, CK5/6, CK7, CK19, CK20, P63, EMA, Vim, SMA, CDX-2, villin, PAX-8, RCC, CD56, ER, PR, Syn, CgA and Ki-67. All of these were from Fuzhou Maixin Co., Ltd. (Fuzhou, P. R. China). All of the antibodies were ready-to-use and the immunostaining was performed according to the instructions.

Results

Clinical features

Among the 25 cases of bladder metastatic tumors, 8 were from females and 17 were from males, whose ages ranged from 38 to 85 years old. The most common sites of the primary tumors were the prostate (6/25, 24.0%), the colon (6/25, 24.0%), the stomach (4/25, 16.0%), the cervix (3/25, 12.0%), the rectum (2/25, 8.0%) and the breasts (1/25, 4.0%). The most common sites of tumors metastatic to the bladder from distant sites were the stomach (16.0%) and the breasts (4.0%). Adenocarcinomas accounted for 19 cases (76%), respectively, from the prostate, colon, stomach, rectum, and cervix. In addition, squamous cell carcinoma, clear cell carcinoma of the kidneys and breasts infiltrating lobular carcinoma, also metastasized to the bladder in this study (Table 1).

Histological features and immunohistochemical staining results

Male genitourinary system

Prostate adenocarcinoma (6 cases): The age range was 72-83 years old. Cystoscopy examinations of the bladders revealed that 3 cases had multiple nodules within the bladder, and 3 cases were located in the left side of the tri-

Table 1. Clinicopathologies of metastatic tumors to the urinary bladder

<table>
<thead>
<tr>
<th>Age/Gender</th>
<th>Primary Site</th>
<th>Diagnosis</th>
<th>Location in Bladder</th>
<th>Other Metastasis</th>
<th>Times (Months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>74/Male</td>
<td>Prostate</td>
<td>Adenocarcinoma</td>
<td>Multiple nodular</td>
<td>No</td>
<td>Synchronous</td>
</tr>
<tr>
<td>72/Male</td>
<td>Prostate</td>
<td>Adenocarcinoma</td>
<td>Left side of trigone</td>
<td>Bone</td>
<td>Heterochronous, 4 years</td>
</tr>
<tr>
<td>73/Male</td>
<td>Prostate</td>
<td>Adenocarcinoma</td>
<td>Multiple nodular</td>
<td>Bone</td>
<td>Heterochronous, 1 years</td>
</tr>
<tr>
<td>79/Male</td>
<td>Prostate</td>
<td>Adenocarcinoma</td>
<td>Left side of trigone</td>
<td>Bone</td>
<td>Synchronous</td>
</tr>
<tr>
<td>83/Male</td>
<td>Prostate</td>
<td>Adenocarcinoma</td>
<td>Multiple nodular</td>
<td>Bone</td>
<td>Heterochronous, 3 years</td>
</tr>
<tr>
<td>79/Male</td>
<td>Prostate</td>
<td>Adenocarcinoma</td>
<td>Left side of trigone</td>
<td>No</td>
<td>Heterochronous, 3 years</td>
</tr>
<tr>
<td>38/Male</td>
<td>Rectum</td>
<td>Adenocarcinoma</td>
<td>Not Known</td>
<td>No</td>
<td>Heterochronous</td>
</tr>
<tr>
<td>85/Female</td>
<td>Rectum</td>
<td>Adenocarcinoma</td>
<td>Not Known</td>
<td>No</td>
<td>Heterochronous</td>
</tr>
<tr>
<td>50/Male</td>
<td>Colon</td>
<td>Adenocarcinoma</td>
<td>Left wall</td>
<td>Small intestine</td>
<td>Heterochronous, 8 years</td>
</tr>
<tr>
<td>77/Male</td>
<td>Colon</td>
<td>Adenocarcinoma</td>
<td>Right wall</td>
<td>Liver</td>
<td>Heterochronous, 3 months</td>
</tr>
<tr>
<td>48/Male</td>
<td>Colon</td>
<td>Adenocarcinoma</td>
<td>Left wall</td>
<td>Abdominal wall</td>
<td>Heterochronous, 5 years</td>
</tr>
<tr>
<td>46/Female</td>
<td>Colon</td>
<td>Adenocarcinoma</td>
<td>Multiple nodular</td>
<td>Abdominal multiple metastasis</td>
<td>Heterochronous, 1 years</td>
</tr>
<tr>
<td>69/Female</td>
<td>Colon</td>
<td>Adenocarcinoma</td>
<td>Multiple nodular</td>
<td>No</td>
<td>Heterochronous, 5 years</td>
</tr>
<tr>
<td>46/Male</td>
<td>Colon</td>
<td>Adenocarcinoma</td>
<td>Right wall</td>
<td>No</td>
<td>Heterochronous</td>
</tr>
<tr>
<td>48/Male</td>
<td>Kidney</td>
<td>Clear cell carcinoma</td>
<td>Right wall</td>
<td>Lung, bone and adrenal</td>
<td>Heterochronous, 4 years</td>
</tr>
<tr>
<td>83/Male</td>
<td>Kidney</td>
<td>Clear cell carcinoma</td>
<td>Right wall</td>
<td>Lung</td>
<td>Heterochronous, 19 years</td>
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<tr>
<td>61/Male</td>
<td>Kidney</td>
<td>Clear cell carcinoma</td>
<td>Posterior wall</td>
<td>No</td>
<td>Synchronous</td>
</tr>
<tr>
<td>55/Female</td>
<td>Cervix</td>
<td>Adenocarcinoma</td>
<td>Not Known</td>
<td>Not Known</td>
<td>Heterochronous</td>
</tr>
<tr>
<td>43/Female</td>
<td>Cervix</td>
<td>Squamous cell carcinoma</td>
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<td>Not Known</td>
<td>Heterochronous</td>
</tr>
<tr>
<td>70/Female</td>
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<td>Squamous cell carcinoma</td>
<td>Not Known</td>
<td>Not Known</td>
<td>Heterochronous</td>
</tr>
<tr>
<td>58/Female</td>
<td>Breast</td>
<td>Infiltrating lobular carcinoma</td>
<td>Not Known</td>
<td>Not Known</td>
<td>Heterochronous</td>
</tr>
<tr>
<td>62/Male</td>
<td>Stomach</td>
<td>Adenocarcinoma</td>
<td>Posterior wall and the trigone</td>
<td>No</td>
<td>Heterochronous, 2 years</td>
</tr>
<tr>
<td>85/Male</td>
<td>Stomach</td>
<td>Adenocarcinoma</td>
<td>Posterior wall and the trigone</td>
<td>No</td>
<td>Heterochronous, 2 years</td>
</tr>
<tr>
<td>63/Female</td>
<td>Stomach</td>
<td>Adenocarcinoma</td>
<td>Top and left wall</td>
<td>No</td>
<td>Heterochronous, 4 years</td>
</tr>
<tr>
<td>54/Male</td>
<td>Stomach</td>
<td>Adenocarcinoma</td>
<td>Top and left wall</td>
<td>No</td>
<td>Heterochronous, 4 months</td>
</tr>
</tbody>
</table>
Clinicopathological features of bladder metastatic tumors

Figure 1. Prostate adenocarcinoma metastatic to the bladder. A. The urothelial epithelium was intact with no atypia, and nested neoplastic cells with infiltrative growth in the lamina propria were observed (HE, ×200). B. The urothelial epithelium was positive for GATA3, but the tumor cells were negative (HE, ×200). C. The tumor cells were positive for PSA (HE, ×200). D. The tumor cells were positive for CK7 (HE, ×200).

Figure 2. Clear cell renal carcinoma metastatic to the bladder. A. Tumor cells formed large, solid cell nests with interstitial compartments and abundant blood vessels were in the interstitium (HE, ×200). B. The tumor cells were positive for CK (HE, ×200). C. The tumor cells were negative for CK7 (HE, ×200). D. The tumor cells were positive for PAX8 (HE, ×200).

gone. Five cases were admitted for gross hematuria and/or dysuria, and only 1 case had no obvious symptoms. A cystoscopic biopsy or TURBT exhibited that the surface urothelial epithelium was intact with no atypia. In the lamina propria, nested neoplastic cells with infiltrative growth were observed. Some of the glands were arranged in a cribriform pattern, with large cellular nuclei, a high ratio of nuclei to cytoplasm and obvious nucleolus. The immunohistochemical results showed that the tumor cells were positive for PSA, and negative for GATA3, CK7, CK20 and P63 (Figure 1). Two of them were found to have lesions in both the prostate and bladder at the same time and others had a history of prostate cancer for a few years. Two patients were Gleason grade 5+4, and 2 patients were Gleason grade 4+4. Serum PSA was higher than normal. Bone metastasis was found in four patients, and others had no other metastasis.

Clear cell renal carcinoma (3 cases): The age range was from 48 to 83 years old. A cystoscope examination of the bladder revealed that 2 cases were located in the right wall of bladder, and 1 case was in the posterior wall. All of the 3 patients had gross hematuria, and 2 of them had a history of renal cancer, and then a cystoscopy biopsy was performed. One patient was found with lesions in both kidneys and the bladder at the same time, then a nephrectomy and bladder resection were performed. Microscopically, the tumor cells formed large, solid cell nests with interstitial compartments and abundant blood vessels in the interstitium. Large tumor cells were cubic with transparent cytoplasm and round or oval nuclei. The tumor cells were positive for CK, EMA, Vim and PAX-8, but nega-
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**Female reproductive system**

Cervical adenocarcinoma (1 case): The patient was 55 years old. Microscopically, irregular linear or glandular structures of the tumor cells could be observed, with diffuse stroma infiltration, irregular luminal size, and irregular structure. The tumor cells had large nuclei with mild nuclear atypia, obvious nucleoli and eosinophilic cytoplasms. Immunohistochemistry showed that the tumor cells were positive for CKH, CKL, CK7, and negative for CD56 and Syn (Figure 3). This case was a consultation case. The patient had a history of cervical adenocarcinoma, with no more immunohistochemical staining. However, this morphology was consistent with primary cervical adenocarcinoma.

Cervical squamous cell carcinoma (2 cases): The patients were 43 and 70 years old, respectively. The biopsy showed nested squamous cells with large and deeply stained nuclei, moderate nuclear atypia and abundant cytoplasms. Squamous cells infiltrated the stroma in a cord-like or nested pattern, without coverage of the urinary epithelium. The tumor cells were positive for p16, CKH, CK, CK7, CK5/6, and P63, but negative for SMA (Figure 4). These two cases also came to our hospital from another hospital for consultations, without additional clinical data.

**Gastrointestinal system**

Gastric adenocarcinoma (4 cases): The age range was from 54 to 85 years old. A cystoscope examination of the bladder revealed that 2 cases were located in the posterior wall and...
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3 patients presented with gross hematuria, and the other patient had a presentation of abdominal distension and abdominal adhesions. Microscopically, a small amount of atypical cells was observed in the fibrous connective tissue cells, with the existence of the surface of the urinary epithelium. The tumor cells were positive for CDX-2 (HE, ×200). The tumor cells were positive for CEA (HE, ×200). The tumor cells were positive for CK7 (HE, ×200). The tumor cells were negative for CK20 (HE, ×200). The tumor cells were positive for villin (HE, ×200).

Breast cancer (1 case): The patient was 58 years old with a history of invasive lobular carcinoma. Microscopically, the biopsy tissue showed that the tumor cells were scattered in the interstitium with large nuclei, and rich and eosinophilic cytoplasms. Ocular nucleoli were observed occasionally, and the nuclei were deviated. Dual or multiple nuclei were visible. Immunohistochemistry showed that the tumor cells were positive for CK, CK7, ER, and mammaglobin, Ki-67 (10% +), but negative for PR, Syn, CgA, and CD68 (Figure 6). All of them had a history of lumpectomy. 4 patients also metastasized to other sites, namely, the small intestine, the liver, the abdominal wall, and to an abdominal multiple metastasis.

Intestinal adenocarcinoma (8 cases including 2 rectum and 6 colon): The age range was 38-85 years old. A cystoscopy examination revealed that multiple bladder nodules were noted in 2 patients, 2 cases were located in the left bladder wall, and the other 2 cases were in the right wall. 5 patients presented with gross hematuria, but the others had no obvious symptoms. The surface of the urinary epithelium was intact. Tumor cells were in a glandular pattern, with an irregular glandular cavity, large and deeply stained nuclei, abundant cytoplasms, moderate nuclear atypia, and were visibly mitotic. The tumor cells were positive for CK20, CDX-2 and villin, but negative for PSA, GATA3 and CK7 (Figure 5). All of them had a history of lumpectomy. 4 patients also metastasized to other sites, namely, the small intestine, the liver, the abdominal wall, and to an abdominal multiple metastasis.

Discussion

According to the 2016 WHO classification, bladder metastases make up less than 2% of all bladder tumors. The most common metastatic tumors involving the bladder are of genitourinary origin (including the prostate, vagina, cervix, and uterus), followed by colorectal cancers. True metastatic tumors of the bladder are very rare [1, 2]. Effective surgical treatment of
Clinicopathological features of bladder metastatic tumors

In this study, the most common sites of the primary tumors were from the prostate (24.0%), the colon (24.0%), the stomach (16.0%), the cervix (12.0%) the kidney (12.0%), the rectum (8.0%) and the breast (4.0%). The most common sites of tumors metastatic to the bladder from distant sites were the stomach (16.0%) and the breast (4.0%). It has been reported in the literature that the most common sites of origin of tumors metastatic to the bladder were the skin (melanoma), the breasts, the stomach, and the lungs [1].

Most of the bladder metastases (68%) in this study occurred in males, and the most common presentation was gross hematuria. Most bladders were located in the triangle, the posterior wall, or the left and right walls. 8 patients were found with other sites with metastasis, such as: the lungs, bones, liver, and the adrenal and abdominal walls.

In this study, we found that among a total of 25 metastatic tumors, adenocarcinomas were the most common (19/25, 76%), respectively from the prostate, colon, stomach, rectum, and cervix. However, primary adenocarcinomas of the bladder only accounted for 1%. When the histological diagnosis of bladder cancer is adenocarcinoma, it first needs a differential diagnosis with metastatic adenocarcinoma of the adjacent organs (such as the prostate, colorectum, cervix, etc.) and the distant organs (such as the stomach). Morphologically, primary adenocarcinoma of the urinary bladder has different histological subtypes, including intestinal, mucus, signet-ring cell type, etc. Therefore, it is difficult to distinguish morphologically between primary and metastatic adenocarcinoma of the bladder because, without a history of primary tumors, distinguishing between the two is more difficult and often requires immunohistochemical staining to support the diagnosis.

Identification of metastatic gastrointestinal adenocarcinoma

The typical urothelial markers include GATA3, p63, 34βE12, uroplakin II/III, thrombomodulin and CK5/6, with two or more positive markers supporting the urothelial origin. 34βE12 was reported to be positive in 66% of primary adenocarcinomas and 11% of colon adenocarcino-

Figure 6. Intestinal adenocarcinoma metastatic to the bladder. A. The surface of the urinary epithelium was intact. The tumor cells were in a glandular pattern, in an irregular glandular cavity, had large and deeply stained nuclei, had abundant cytoplasm, moderate nuclear atypia, and were visibly mitotic (HE, ×200). B. The urothelial epithelium was positive for GATA3, but the tumor cells were negative (HE, ×200). C. β-catenin was found through nuclear and cytoplasmic stainings in the tumor cells, with staining of the membrane in the urothelial epithelium (HE, ×200). D. The urothelial epithelium was positive for CK7, but the tumor cells were negative. E. The tumor cells were focal positive for CK20. F. The tumor cells were positive for CDX-2 (HE, ×200).
Clinicopathological features of bladder metastatic tumors

The combination with the immunolabeling CK7, CK20, CDX-2, and villin, together with the above markers, often aids in the identification of both, but due to the limitations of sensitivity and specificity, the usefulness of these markers will be limited. Of these markers, CK7 and CK20 are neither sensitive nor specific for diagnosis. An immunohistochemical study of bladder biopsies in the diagnosis of adenocarcinomas [5] showed that the CK7+, CK20+ or the CK7+ and CK20- phenotypes indicate a high probability of lung adenocarcinoma or bladder urothelial carcinoma, while the CK7- and CK20+ phenotypes are more likely indicating adenocarcinoma from the intestine and bladder. Being negative for CK7, but positive for CK20 and CDX-2 is a common expression pattern in gastrointestinal tumors, especially colorectal carcinomas. It was reported that the CK7 positive rate was 82%, and the CK20 positive rate was 73%, while the rate of the CK7 negative and CK20 positive rates was 29% in primary adenocarcinomas of the bladder [6]. In gastric adenocarcinomas, CK7 is usually positive and CK20 negative. The positive expression rates of CK7 and CK20 in enteric primary gastric adenocarcinomas were 63% and 32%, while they were 75% and 42% in signet ring cell carcinomas, respectively [7]. CDX2 nuclear and cytoplasmic stainings were found in 81%-95% of colorectal adenocarcinomas, and staining of the membranes and cytoplasms was found in 88%-92% of primary adenocarcinomas of the bladder and 100% of urothelial carcinomas with glandular differentiation [10]. In a study comparing primary bladder adenocarcinoma and metastatic intestinal adenocarcinoma [11], strong nuclear with cytoplasmic-membranous staining of β-catenin was seen in 75% of metastatic intestinal adenocarcinomas but only 16.7% of primary bladder carcinomas (< 10% of staining cells).

In addition to the above markers, CDH17 and SATB2 are also commonly used in the identification of gastrointestinal adenocarcinomas. Cadherin-17 (CDH17), also known as hepcidin or human peptide transporter-1, has recently been identified as a sensitive and specific marker of gastrointestinal adenocarcinomas, especially colorectal adenocarcinomas [12]. It was reported that CDH17 was expressed in 96% of colorectal adenocarcinomas and about 50% of gastric and pancreatic adenocarcinomas, but it was rarely expressed in tumors other than those in the gastrointestinal tract [13]. Park [14] also found a high degree of consistency in the staining of primary and metastatic colorectal cancers. However, some stud-
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ies [10] found that CDH17 was also expressed in primary adenocarcinomas of the bladder (92%) but was negative in urothelial carcinomas with glandular differentiation. SATB2 is a marker of nuclear matrix-related transcription factors and epigenetic regulators. Magnusson [15] reported that SATB2 combined with CK20 could recognize more than 95% of colorectal cancers, but gastric and pancreatic ductal adenocarcinomas were usually negative for SATB2. Some studies [16] reported SATB2 was expressed in 49% of the adenocarcinomas of the bladder, while SATB2 and CDX-2 were expressed in 46% of the primary bladder adenocarcinomas and 77% of the metastatic intestinal adenocarcinomas. The above discoveries indicate that a variety of markers are useful for the distinction between primary and metastatic adenocarcinoma of the bladder, but sometimes the usefulness of antibodies is limited, so the clinical examination and any other data from patient histories are particularly important.

Identification of metastatic female genital tumors

The female genital organs (especially the vagina, cervix, and uterus) adjoin the bladder. The majority of these tumors involve the bladder by direct extension. In addition to cervical adenocarcinomas, cervical squamous cell carcinomas of the bladder also commonly metastasize to the bladder. Many markers, such as P40, CK5/6, P63, and SOX2, are indicative of squamous differentiation. CK5/6 and P40 are the most reliable indicators of squamous differentiation, whereas urothelial carcinomas with squamous differentiation also express both P40 and CK5/6.

GATA3 was reported to be a valid marker of urothelial carcinomas, with a positive rate of 86% in urothelial carcinomas [17, 18]. A study of the expression of GATA3 in high-grade urothelial carcinomas and cervical squamous cell carcinomas [19] showed that positive staining for GATA3 in urothelial carcinomas was characterized as non-punctate and moderately intense or strongly stained, while GATA3 had focal weakly positive expression in only 19% of cervical squamous cell carcinomas. Miettinen [20] showed that GATA3 was positive in 33% of cervical squamous cell carcinomas. Chang [19] found that, of 31 cervical carcinomas, 6 showed weak GATA3 staining and 2 demonstrated focal moderate staining. GATA3 was lower expressed in urothelial carcinomas with squamous differentiation (20%) compared with the conventional urothelial carcinomas (80%), but GATA3 staining was lost in areas with squamous cell carcinomas [21]. Therefore, GATA3 is a sensitive and specific marker for the diagnosis of the urinary epithelium. If it is presents strongly diffuse positive, a bladder origin is suggested. If only a few cells are weakly expressed and strongly positive for P40, CK5/6 and P63, cervical squamous cell carcinoma is more likely.

Another controversial antibody is P16. P16 has now been used as an alternative marker of HPV infection to assess cervical lesions. However, P16 overexpression and P16 positive staining have been found in primary bladder tumors, including urothelial carcinomas with squamous differentiation, primary bladder squamous cell carcinomas, and primary bladder adenocarcinomas, which indicates that being P16 positive cannot rule out the primary bladder cancers [22]. Alexander et al. [23] found that P16 staining was positive in 31% of squamous cell carcinomas of the bladder and 33% of urothelial carcinomas with squamous differentiation. Therefore, the use of P16 is limited, and its combination with HPV in situ hybridization is more conducive to the identification of the two.

Differentiation with other sites of the origin of cancers

Such as prostate cancer, breast cancer, renal cell carcinoma, lung cancer, etc.

In this study, 6 patients had a history of prostate cancer that metastasized to the bladder. Some markers, such as PSA, P504S and NKX3.1 can support the diagnoses. First, we can choose PSA/PSAP to identify prostate cancers and GATA3 to identify urothelial carcinomas, and then p63/p40 and HMWK. If the tumor shows strong PSA or PSAP positivity and is negative for p63/p40 and HMWK, the findings are diagnostic for prostate cancers. If the tumor is negative for PSA/PSAP but diffusely positive for HMWK and p63/p40, the findings are diagnostic for urothelial carcinomas. If the tumor is equivocal or weak or negative for PSA/PSAP, and negative or focal positive for p63 and HMWK, we need to do p501S, NKX3.1 and GATA3.
There was one case of breast invasive lobular carcinoma that metastasized to the bladder in this study. Markers, such as mammaglobin, GCDFP-15, ER, PR, and Her-2 are useful in breast cancers. Common metastatic sites for breast cancers include the lymph nodes, lung, liver, and bone. So far, more than 40 cases of breast cancer metastatic to the bladder have been reported. Although breast ductal carcinoma is more common than lobular carcinoma, invasive lobular carcinomas accounts for one third of all bladder metastatic breast cancers [24]. Lobular carcinomas can mimic some morphological variations of urothelial carcinomas, such as signet ring-like or plasmacytoid urothelial carcinomas. Immunohistochemistry can be helpful in the identification of breast cancer, and a combination of mammaglobin, ER, and uroplakin II/III are also useful in distinguishing it from plasmacytoid urothelial carcinomas [25].

Three cases of renal clear cell carcinoma developed bladder metastases in this study. Bladder metastasis of renal cell carcinomas is uncommon, and in a total of 1451 renal cell carcinoma biopsies, only 23 (2%) showed bladder metastases, and only one was an isolated bladder metastasis [26]. Histological subtypes of renal cell carcinomas that metastasized to the bladder have been reported as clear cell renal cell carcinoma and papillary renal cell carcinoma [27], most of which were clear cell types [28]. Therefore, it needs to be distinguished from other clear cell tumors in the bladder, such as urothelial carcinomas with clear cell features and clear cell adenocarcinomas. Immunohistochemistry can help differentiate between metastatic renal cell carcinomas (PAX8) and primary bladder urothelial carcinomas (GATA3) [29]. Urothelial carcinomas are usually GATA3 positive and negative in bladder metastatic renal cell carcinomas. Other markers such as high molecular weight cytokeratin (HMWCK) and P63 are also useful in distinguishing upper urothelial carcinoma (usually HMWCK and P63 positive) and bladder metastatic renal clear cell carcinoma (HMWCK and P63 negative) [29].

Published studies have also found that the lungs and the skin are also a common site of bladder metastasis [1]. However, lung cancers that metastasize to the bladder are very rare, with adenocarcinomas being the most common type of metastasis. Lung adenocarcinomas can be diagnosed with the combination with CK7, CK20, TTF-1, and Napsin-A, etc. 89% of the cases reported individually in the last 10 years were lung adenocarcinomas, and only 1 case was squamous cell carcinoma [30]. As for bladder metastatic skin melanoma, it has not been reported in China. Positive staining for S-100, Melan-A and HMB-45 contribute to the diagnosis. The differential diagnosis includes primary melanoma of the bladder. In this situation, a skin examination of the whole body and a clinical history are crucial. In addition, there are reports of bladder metastatic gastrointestinal stromal tumors, gastrinomas, and renal collecting duct carcinoma [31].

In summary, the bladder is an uncommon site for metastases, and they usually occur in the later stages of disease. Patients may present with urinary symptoms. In order to diagnose metastatic bladder cancers, clinical examination, any history of the tumor elsewhere, as well as the combination of immunohistochemical staining, will help clear the diagnosis of bladder cancer. If the bladder is the first site, the histological type makes it difficult to confirm the origin, so whole body examinations, especially of the gastrointestinal tract and the female genital tract, are essential. The immunohistochemical antibodies GATA3, p63, CK7, CK20, CDX-2, villin, mammaglobin, ER, TTF-1, and others can provide some help.

Disclosure of conflict of interest

None.

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