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Primary Adenocarcinoma Of Urinary Bladder Initially Diagnosed As Metastatic Adenocarcinoma: A Case Report

Ayşegül Sarı*, Aylin Çallı*, Zuhal Kuş*, Murat Ermete*, Cengiz Girgin**

* Department of Pathology, Izmir Ataturk Training and Research Hospital, Izmir, Turkey
** Department of Urology, Izmir Ataturk Training and Research Hospital, Izmir, Turkey

Primary adenocarcinoma of the urinary bladder is a rare neoplasm sometimes causing diagnostic challenge because it can be indistinguishable morphologically from adenocarcinoma secondarily involving the bladder by metastasis or direct extension. Identifying the primary origin of the tumor is important in staging, determining appropriate therapy and assessing prognosis. We report herein a case of primary adenocarcinoma of the bladder misdiagnosed as metastatic adenocarcinoma and reviewed the histopathologic features and diagnostic characteristics of primary adenocarcinoma of bladder in view of literature.

Key Words: Adenocarcinoma, Bladder , Bladder neoplasms

Metastatik Adenokarsinom Tanısı Almış Primer Mesane Adenokarsinomu: Olgu Sunumu

Mesanenin primer adenokarsinomları mesaneyi metastaz veya direkt yayılım yolu ile sekonder olarak tutan adenokarsinomlar ile morfolojik olarak benzerlik gösteren ve bazen tanısal güçlüğe yol açan nadir neoplazmlardır. Tümörün primer orijinini belirlemek, tümörü evreleyebilmek, uygun tedaviye başlamak ve prognozu tahmin edebilmek açısından önemlidir. Bu makalede başka bir merkezde metastatik adenokarsinom tanısı almış olan mesanenin primer adenokarsinom olgusunu sunduk ve mesanenin primer adenokarsinomunun tanısal ve histopatolojik özelliklerini literatürler eşliğinde gözden geçirdik.

Anahtar Kelimeler: Adenokarsinom, Mesane, Mesane neoplazmları

Primary adenocarcinoma of urinary bladder is a rare neoplasm comprising only 0,5 to 2% of all bladder tumors. The normal bladder mucosa is lined by transitional cell epithelium with absence of glandular epithelium. There must be an explanation for the formation of adenocarcinoma in an organ which normally does not contain glandular tissue. Widest acceptance has been gained by 2 major theories 1) the metaplastic change of the normal urothelium to a mucinous or glandular epithelium and 2) the embryologic persistence of endodermal intestinal tissue.[1] In the former one, chronic irritation (infection, calculi, indwelling catheters) and exposure to carcinogens may induce epithelial proliferation forming epithelial nests (Brunner nests), then some of them may become cystically dilated (cystitis cystica) or differentiates into columnar mucin-secreting glands (cystitis glandularis). Malignant transformation of mainly metaplastic intestinal-type epithelium associated with cystitis glandularis results in an adenocarcinoma of the urinary bladder.[2-5] Such tumors are located most commonly in the trigone. The latter mechanism is proposed for neoplastic transformation of the glandular epithelium lining the intravesical portion of the urachal remnants. Consequently, neoplasms arising from the urachal origin are usually found in the dome and anterior wall of the bladder.[3]

When a histological examination of the bladder tumor discloses adenocarcinoma, there are several possible diagnoses. It may represent a metastatic carcinoma, an urachal carcinoma, or a primary adenocarcinoma.[2] In the diagnosis of the latter one other primary sites must be ruled out.[5] Intestinal type of adenocarcinoma is the one especially posing diagnostic challenge for pathologists. The reported case testifies to this problem and contributes to a better understanding of urinary bladder adenocarcinoma.

CASE REPORT

A 66 year-old man without any significant history had been admitted to an outside institution with flank left inguinal pain in January 2004. After clinical examination he underwent a transurethral resection of the bladder. The diagnosis was metastatic adenocarcinoma of probable colonic origin. Then he was referred to our hospital for further treatment and the tumoral blocks from the outside instution were received in consultation.

Microscopic examination of the transurethral resection showed almost total intestinal metaplasia of the urothelium which exhibited dysplastic changes merging with the invaginating glandular elements. In surface epithelium a small foci of transition of the urothelium to intestinal metaplastic change (figure 1) and another small field of cystitis glandularis was present. Haphazardly distributed numerous glands lined by intestinal type of epithelium containing goblet cells were embedded in a loose stroma Almost all of the glands showed mild to severe dysplasia up to adenocarcinoma insitu with cell stratification, nuclear hyperchromasia and increased mitoses (figure 2 and 3). In occasional glands cauterization artifact was too great that presence or absence of atypia was hard to discriminate. Deep in the lamina propria intestinal type of cribriform and complex atypical glands infiltrating the muscularis propria revealed the diagnosis of adenocarcinoma of intestinal type (figure 3). Coexistence of cystitis glandularis and the demonstration of nonneoplastic bladder epithelium to adenocarcinoma in the present case confirmed the tumor was of urinary bladder in origin. After this diagnosis, radical cystectomy with pelvic lymphadenectomy was performed. Macroscopic examination of the cystectomy specimen showed a 2-cm tumor in anterior wall of bladder which was sessile and ulcerated without any luminal projections. In microscopic examination, in surface epithelium cystitis glandularis was present associated with areas of ulceration secondary to previous transurethral resection. Deep in the muscularis propria nests of complex atypical intestinal type glands floating in pools of mucin was present (figure 4). Mucinous type of adenocarcinoma was the diagnosis. The pelvic lymph nodes were free of metastases. Clinically there was no evidence of any other organ involvement. He didn't have radiotherapy or chemotherapy. 22 months postoperatively, clinical examinations, chest x-rays and CT scans were normal without distal spread and any recurrence.

Figure 1- Transition of urothelial epithelium to intestinal metaplasia showing dysplastic changes. (HEX100)

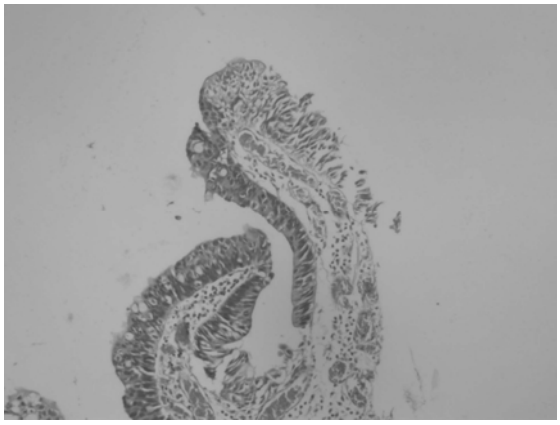


Figure 2- Numerous intestinal-type glands many of which showing mild to severe atypia (left) and adenocarcinoma with infiltrative atypical cribriform glands (right), There were other foci of intestinal type adenocarcinoma elsewhere. (HEX20)

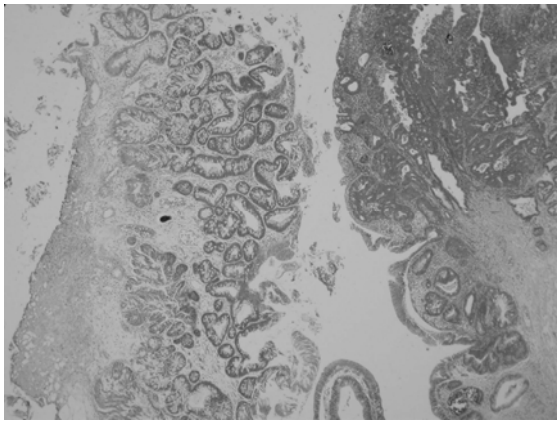


Figure 3- Cystitis glandularis, intestinal type; showing in situ carcinomatous changes. (HEX200)

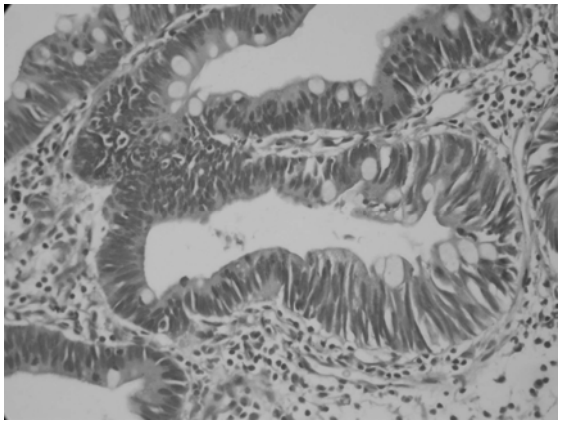
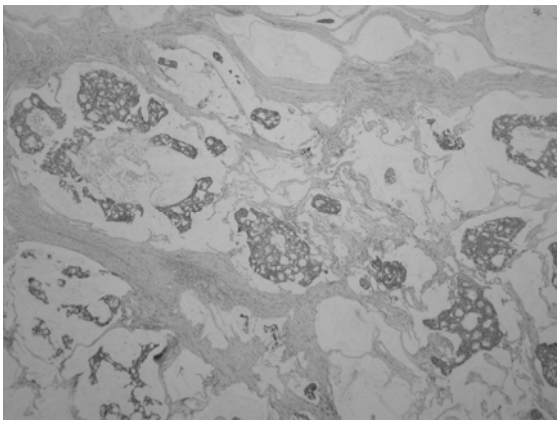


Figure 4- Pools of mucin with or without tumor cells dissecting through muscularis propria. Mucinous carcinoma, cystectomy specimen. (HEX40)



DISCUSSION

Cystitis glandularis, although rare, is one of the most seen benign epithelial abnormality of the urinary bladder. In its commonest form (nonintestinal) it is characterized by glands lined by cuboidal to columnar often surrounded by transitional cells. In intestinal type of cystitis glandularis (cystitis intestinalis), glands in the lamina propria resemble colonic epithelium often containing goblet cells. These types of cystitis glandularis may coexist although intestinal variant is much less common than the typical variant.[6] Relationship between cystitis glandularis and adenocarcinoma has long been emphasized, based mainly on the high incidence of the coexistence of these lesion.[7] The great majority of cases associated with malignancy have been of the intestinal type.[6] Only rare striking solitary case reports have described that cystitis glandularis, almost always of intestinal type can progress over years to adenocarcinoma.[8] Cystitis glandularis is present in invasive adenocarcinoma ranging from 14-67% of cases, but its role in pathogenesis of invasive adenocarcinoma remains controversial. [9]

Based on the original site of the tumor, adenocarcinoma of the bladder may be classified into 3 categories: primary, urachal and metastatic. Among them metastatic adenocarcinoma is the commonest form and usually represents a direct extension from a primary lesion in the colon, prostate or the female tract.[2] Identifying the primary origin of the tumor is important in staging, determining appropriate therapy and assessing prognosis. The histological similarity of urinary bladder adenocarcinoma to colorectal neoplasms, prostatic and female genital tract carcinomas is well known and the distinction between these may be impossible.[10] Finding areas of glandular metaplasia or transition between the tumor and the adjacent urothelium should suggest a vesical primary. [11] But it should be kept in mind that absence of these features does not rule out a primary bladder tumor. In that condition immunohistochemical studies might help [12, 13] but still, the diagnosis is largely a clinical one requiring a thorough search for a primary tumor elsewhere.[10] Therefore to avoid unnecessary diagnostic procedures (such as colonoscopy, etc) meticulous histopathologic evaluation is essential for finding clues leading to diagnosis of primary adenocarcinoma.

The distinction between urinary bladder adenocarcinoma and urachal adenocarcinoma also cannot be made on the basis of histology alone, and additional criteria must be considered.[10] Wheeler and Hill, Begg and as well as Mostofi proposed that it was justifiable to consider all adenocarcinomas of the dome as urachal unless a transition from nonneoplastic bladder epithelium to adenocarcinoma was demonstrated.[4, 5] Urachal carcinomas may be associated with cystitis glandularis but dysplastic changes should not be present because dysplastic changes of the mucosa or the presence of dysplastic intestinal metaplasia would tend to exclude an urachal origin.[9] The importance of urachal and non-urachal adenocarcinoma differentiation lies in the significant treatment differences between them : radical cystectomy for primary bladder carcinoma versus partial cystectomy en-bloc resection of all tissue in the line of the urachus from the bladder to the umbilicus, including the latter, for urachal carcinoma.[4, 10]

Several histologic subtypes of primary adenocarcinoma have been described: glandular not otherwise specified (NOS), mucinous (colloid), colonic (enteric) type, signet ring cell, and clear cell (mesonephric) type. The tumors may show a single histologic pattern or any combination of them.[2, 10] Colonic and glandular NOS are the most frequent varieties.[10] In a series of 72 adenocarcinoma cases Grignon JD et al found that NOS category was the most frequent one, mixed type was the least seen one.[4] In our case in TUR specimen the colonic type and in cystoprostatectomy specimen colloid type were the existing histologic patterns. The central issue in here is whether these different varieties have any effect on survival or indicate prognosis. Several authors have emphasized the poor prognosis of patients with signet-ring morphology,[4] but Mekresh

et al failed to detect any influence of tumor cell type or site of mucin deposition on survival. [14]

Adenocarcinoma, although represents less than %2 of all bladder carcinomas , is the most commonly reported tumor of extrophic bladders.[2] This is explained by the presence of long standing intestinal metaplasia which is secondary to chronic irritation of the bladder mucosa.[5] This supported the belief of some investigators that intestinal metaplasia is a premalignant lesion in the development of adenocarcinoma but this belief has recently been questioned by a study where none of the 53 patients with extrophy and intestinal metaplasia followed for more than 10 years developed adenocarcinoma, suggesting that intestinal metaplasia is not a risk factor for the development of malignancy.[15]

Intestinal metaplasia which is also referred to as cystitis glandularis of intestinal type is present in significant proportion of adenocarcinomas of bladder.[15] It is certain that adenocarcinoma does not develop in all cases with intestinal metaplasia. Long-standing irritative phenomena may act as a promoter in the presence of an initiator (chemical, radiation, virus) which might result in carcinogenesis. [10]

Histologically, coexistence of cystitis glandularis with demonstration of the transition of adjacent urothelium to metaplastic intestinal epithelium and varying degrees of precancerous atypia up to adenocarcinoma in situ confirmed that the reported case was primary adenocarcinoma of the urinary bladder which has originated from cystitis glandularis and intestinal metaplasia .The prognosis of primary adenocarcinoma is poor, survival at 5 years being 31-35%. [9] The poor prognosis of adenocarcinoma of bladder is attributed to the commonly encountered non-papillary, sessile and infiltrative growth pattern of the tumor which might be the reason for the late symptoms regardless of the tumor localization. [2, 7] Stage is the most important prognostic factor for the disease.[4, 5, 9, 10] Radical cystectomy offers the best therapeutic results in terms of survival. The potential benefit of chemotherapy has not been clearly established.[2, 14] Our patient's clinical stage was T2bN0M0 at presentation. Radical cystectomy with pelvic lymphadenectomy was the only therapy performed and he has been disease free for 22 months.

In the represented case we dealt with an example of a problem where misdiagnosis of a metastatic adenocarcinoma of urinary bladder could be prevented with careful evaluation of histopathologic features and we think that with these histopathologic features, our case encourages the belief that cystitis glandularis of intestinal type is a premalignant lesion.

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Corresponding Author:
Ayşegül Sarı MD.
1391 sokak, Akder Eczanesi,
No: 4/B 35220 Alsancak- İzmir
E-mail: aysegulakder@gmail.com
Mobil phone : +90 532 526 5215
Work phone : +90 232 244 4444- 2686