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Bone Metastasis of Urothelial Carcinoma

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Background: Bone metastasis of urothelial carcinoma is the third most common metastasis after the lungs and liver. Bone complications adversely affect the quality of life. They are also associated with increased mortality. The objective of this study is to describe the epidemiological, clinical and prognostic aspects of bone metastasis of urothelial carcinoma

Materials and Methods: This is a retrospective, monocentric study of 8 cases of bone metastases of urothelial carcinoma, collected from January 2018 to September 2020 at the Ibn Rochd University Hospital in Casablanca, Morocco. The analyzed data were collected on an exploitation sheet. Incomplete records were excluded from the study.

Results: The average age of our patients was 61.37 years. All the patients were male and smokers. Pain was the main calling sign and was marked in seven patients. Four patients had anemia and 50% of the patients had acute obstructive kidney disease.

CT scanning of the body was requested to all the patients and confirmed bone metastasis in seven patients with predominantly osteolytic lesions. The treatment was palliative and consisted of chemotherapy, radiotherapy or combined therapy. Among them,three patients died, two of them progressed to have new lesions and three others had stabilized lesions.

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Conclusion: The presence of bone metastasis of urothelial carcinoma constitutes an unfavorable moment in the evolution of this cancer. These metastases are responsible for many complications that require multidisciplinary management.

Keywords: Urothelial carcinoma; surgery; bone metastases; thoracoabdominopelvic scanner.

1. INTRODUCTION

Urothelial cancer is the second most common cancer in urology, consisting of bladder tumors and tumors of the upper excretory tract. These lesions are known for their seriousness with a high metastasizing power and a high mortality rate, directly related to the systemic spread of the disease. When urothelial cancer becomes metastatic, metastasis may be synchronous with the discovery of the disease or may occur during post-treatment surveillance of the primary lesion [1]. Numerous metastatic sites have been described in the literature, but the most common secondary sites of urothelial carcinomas are drainage nodes (90%) [2], lung (52%), liver (33%) and bone (26%) [3]. The prevalence of bone metastases in patients with advanced or metastatic urothelial cancer is 30-40% [4].

The objective of this study is to describe the epidemiological, clinical and prognostic aspects of bone metastasis of urothelial carcinoma.

2. MATERIALS AND METHODS

This is a retrospective, descriptive study conducted at the Ibn Rochd University Hospital of Casablanca over a period of 2 years and 8 months (32 months) from January 2018 to September 2020. In our study, we had selected patients with urothelial cancer with bone metastasis at the onset or during the course of the disease. Data were collected from medical records retrieved from the annual registries of the Urology and Oncology Department. Patient informations were collected from the operating sheets. These included epidemiological, clinical, biological, radiological (imaging), prognostic and therapeutic data.

3. RESULTS

Our series includes 8 cases, exclusively male and all of them smokers. The mean age of our patients is 61.37 years with extremes of 46 to 74 years. No risk of occupation (Table1).

All the eight cases were presented with hematuria and lower urinary tract symptoms of the irritative type (increased frequency and burning micturation). All the patients had undergone transurethral resection (TUR) of the bladder. The histopathological studies confirmed urothelial carcinoma (UC) infiltrating the smooth muscle in seven patients. One patient had urothelial carcinoma infiltrating the submuosa with vascular emboli. The Patients were subsequently evaluated for tumor extension by using thoraco-abdomino-pelvic tomography (TAP CT), which did not reveal any visceral or bone metastasis. Three patients had pelvic adenopathies.

A radical treatment (cystoprostatectomy) was proposed to all patients during our multidisciplinary consultation meeting . Four patients (50% of cases) accepted the procedure, two of whom had received neoadjuvant chemotherapy. For the remaining patients, they were lost the sight for follow-up after refusal of the proposed treatment. 50% of cases operated on (cystoprostatectomy), three patients were derived by an ileal conduit urinary diversion (Bricker) and one case was derived by enterocystoplasty (Table 2).

Table 1. Epidemiology data

	Age (years)	Sex	Profession	Smoking
1st case	54	Male	Employee	Positive
2nd case	54	Male	Hitchhiker	Positive
3rd case	60	Male	Tourism Agent	Positive
4th case	68	Male	Peasant	Positive
5th case	74	Male	No occupation	Positive
6th case	66	Male	No occupation	Positive
7th case	69	Male	No occupation	Positive
8th case	46	Male	No occupation	Positive

Table 2. Endoscopic aspect, operative procedure and anatomopathological study

	Endoscopic aspect	Endoscopic gesture	hist-pathological study
Case 1	Left postero-lateral wall tumor with an intra-diverticular	incomplete TUR	Transitional cell carcinoma of high grade infiltrating the lamina propria (pT1 high grade), vascular emboli, detrusor muscle was seen and uninfiltrated
Case 2	Diffuse bladder papillomatosis	Incomplete TUR	Transitional cell carcinoma infiltrating bladder muscle (pT2)
Case 3	Left trigonal and posterolateral tumor	Complete TUR	Transitional cell carcinoma infiltrating the muscularis (pT2)
Case 4	Large tumor of the left side wall	Complete TUR	Transitional cell carcinoma infiltrating the muscularis (pT2)
Case 5	Tumour occupying almost the entire bladder	Incomplete TUR	pTa high grade, muscle not seen
		TUR2 (Second look)	Transitional cell carcinoma pT2
Case 6	Large tumor occupying almost all the bladder lumen	Incomplete TUR	Transitional cell carcinoma pT2
Case7	Right postero-lateral wall tumor, right ureteral meatus not seen	Complete TUR	Transitional cell carcinoma pT2
Case 8	Retro-trigonal and right lateral wall tumor	Complete TUR	Transitional cell carcinoma pT2

Clinically, the time to diagnosis of bone metastasis ranged from 6 months to 3 years after the initial diagnosis of urothelial cell carcinoma.

The circumstances of discovery were dominated by pain, which was present in seven of our patients (87.5% of cases). The pain was dominently pelvic in 6 patients, one patient had pelvic and spinal back pain. One patient had no pain. Signs associated with pain were: altered general condition and functional impotence of one or two lower limbs. These signs were present in a variable manner (Table 3).

Biologically, 4 patients (i.e. 50% of cases) had a poorly tolerated anemia. In 3 cases it was a microcytic hypochromic anemia and only one patient had a normochromic microcytic anemia. The cytobacteriological examination of urines was positive in 3 patients and the isolated germ was multi-sensitive E.Coli.

Renal function was normal in 50% of the cases (4 patients) and acute obstructive renal failure was noted in 4 of our patients (50% of the cases), one of whom had died. The hydro-electrolyte balance showed variable results.

Table 3. Clinical presentation

	Pain		Alteration of the general condition	Functional impotence of one or 2 lower limbs
	Basin	Lumbar and Pelvis		
1st Case	+		+	+
2nd Case	+		+	+
3rd Case		+	+	+
4th Case			+	
5th Case	+			
6th Case	+			+
7th Case	+		+	
8th Case	+		+	+

Thoraco-abdomino-pelvic CT scan (TAP CT) was requested to all of them (100% of the cases). Bone metastases were found in 7 patients (87.5% of cases). The pelvic bones were the most affected with 87.5% of cases, lumbar and dorsal vertebrae in 37.5% of cases, costal lesions in 25% of cases and cranial lesions in one case (Table 4).

One patient (12.5% of cases) had not shown bone metastases on CT scan and the diagnosis was confirmed by bone scan. On CT scan, lesions were osteolytic in 6 patients (75% of cases), osteocondensate in one patient (12.5% of cases) and mixed in one patient (12.5%) of cases(Table 5).

In addition to bone lesions, for patients who were not undergone cystectomy, CT scan had shown bladder lesions in all cases, but had not shown any upper excretory tract lesions (UET) . The TAP CT scan had also shown ureterohydronephrosis in 4 patients (50% of cases) (bilateral in 3 patients and right-sided unilateral in 1 patient), lung lesions in 4 patients (50% of cases), liver lesions in 2 patients (25% of cases), splenic lesions in 1 case (12.5% of cases) and retroperitoneal adenopathies in 50% of cases (4 patients).

Three of our patients (37.5% of the cases) had performed bone scans that showed bone metastasis. One patient (12.5% of the cases) had benefited from magnetic resonance imaging (MRI) which showed bone lesions and pedicular(vertebral) damage. One patient underwent a CT-guided bone biopsy and pathological examination confirmed metastasis whose histological appearance was compatible with a urothelial carcinoma with squamous inflection sector.

Treatment of these bone metastases was palliative. Two patients (25% of cases) had received chemotherapy alone, another patient (12.5% of cases) had received radiotherapy alone. Four patients (50% of cases) had received palliative chemotherapy, analgesic and haemostatic radiotherapy (Table 6).

One patient had received zoledronic acid for threatening bone metastases, two patients were derived by percutaneous nephrostomy, and one patient was derived by urinary catheterization to improve renal function for ureterohydronephrosis with renal failure. Four patients had received a red blood cell transfusion for poorly tolerated anemia, and three patients were treated for multi-sensitive E.Coli urinary tract infection. All patients had received analgesics (Table 7).

Three patients (37.5% of cases) had stabilized lesions after chemotherapy and radiotherapy. They still continue palliative care, two patients (25% of cases) had progressed to worsening with the appearance of pulmonary, liver and splenic metastases, in addition to the bone adenopathies and metastases that existed before the treatment. They received immunotherapy, three patients (37.5% of cases) had died, two of them before starting treatment and one after treatment.

Table 4. Bones Affected by CT Scans

Type of bone affected	Number of cases (%)
Pelvic bone	7 cases (87.5%)
Lumbar and dorsal vertebrae	3 cases (37.5%)
Ribs	2 cases (25%)
Skulls	1 case (12.5%)

Table 5. Radiological appearance (CT scan) of bone metastases

Type of bone metastases	**Number of cases (%)**
Osteolytic	6 Cases (75%)
Osteocondensing	1Case (12.5%)
Mixed (osteolytic and osteocondensing)	1Case (12.5%)

Table 6. Treatment

Type of treatment	**Number of cases**
Chemotherapy	2 cases
Radiotherapy	1 case
Chemotherapy and radiotherapy	4 cases

Table 7. Associated treatment

Associated treatment	Number of cases
Zoledronic acid	1 case
Nephrostomy	2 cases
ureteral probe ascent	1 case
blood transfusion	4 cases
Treatment of urinary tract infection	3 cases
Antalgic	8 cases

Bladder ultrasound: heterogeneous mass of the left postero-lateral and intradiverticular bladder wall (Fig. 1). CT scan: Large intravesical tumor (Fig. 2).

The most common metastatic sites (CT scans): Node involvement (Fig. 3), lung metastases (Fig. 4), liver metastasis (Fig. 5), bone metastasis (Figure 6).

Osteolytic bone metastasis and osteocondensing bone metastasis (Fig. 7) in the pelvis.

Osteolytic bone metastasis in the pelvis (Fig. 8).

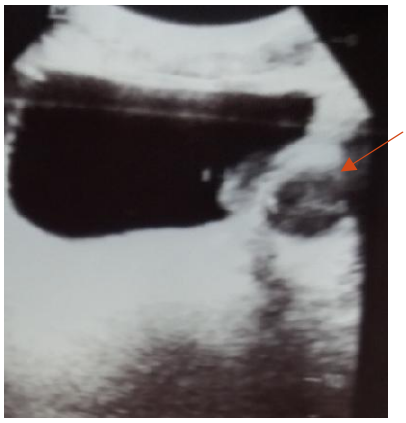

Fig. 1. Bladder ultrasound: tissue processes of the left posterolateral and intradiverticular bladder wall

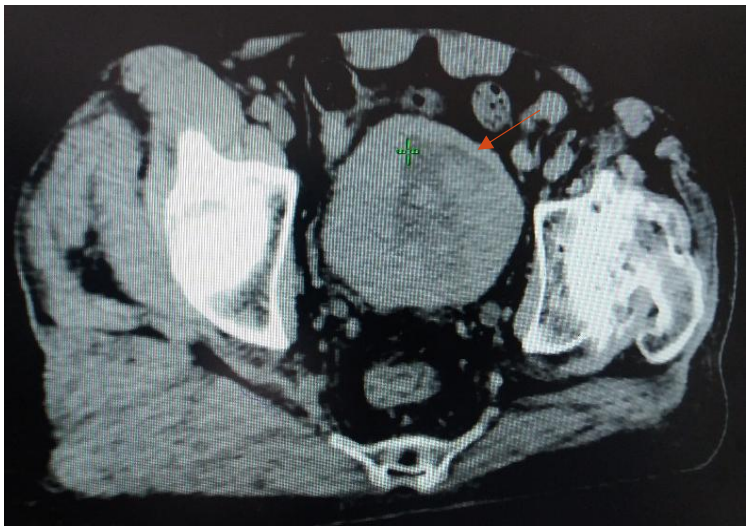

Fig. 2. (CT scan): Large intravesical tumor

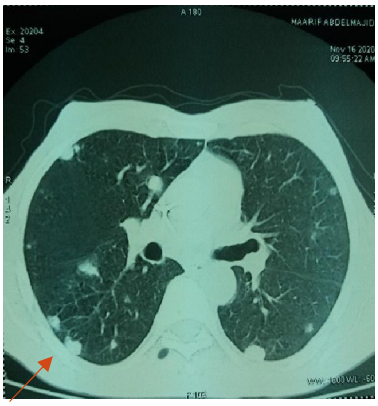

Fig. 3. Left lateroaortic adenopathy

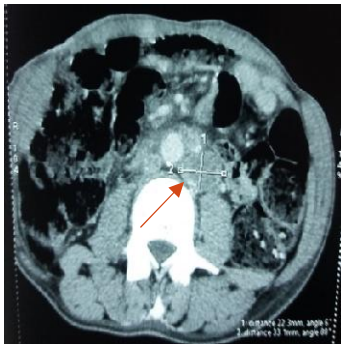

Fig. 4. Lung metastases

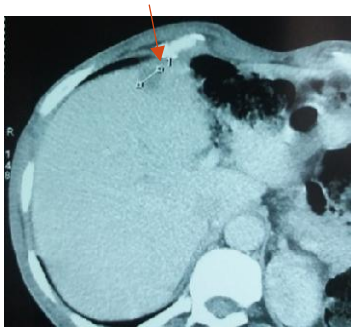

Fig. 5. Liver metastase

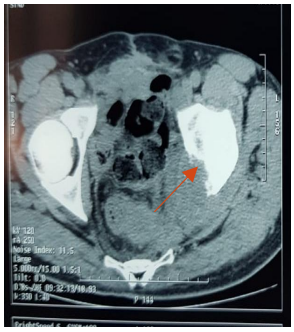

Fig. 6. Bone metastase

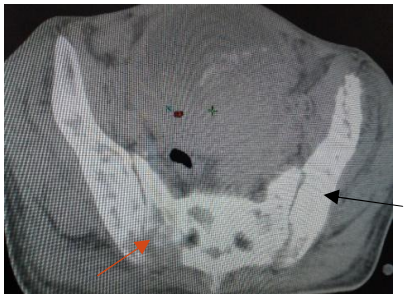

Fig. 7. Osteolytic bone metastasis (orange arrow) and osteocondensation bone metastasis (Black arrow) in the pelvis

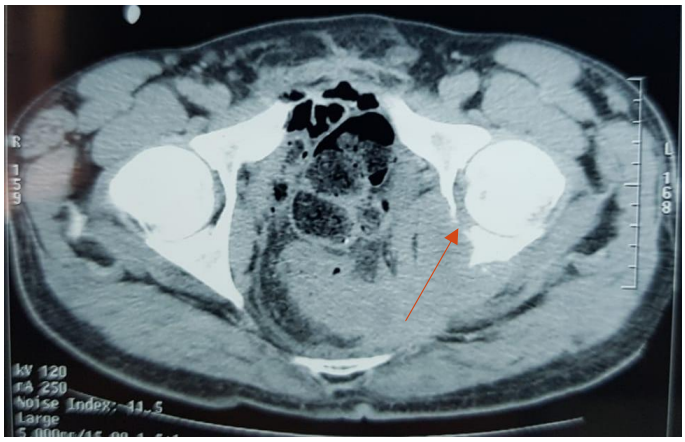

Fig. 8. Osteolytic bone metastasis in the pelvis

4. DISCUSSION

Urothelial carcinoma is a major public health problem [5]. Secondary bone tumors, or bone metastases, are the localization and development of tumor lesions in bone tissue from cells that have migrated by blood or lymphatic route from a primary tumor. These are the most common bone tumors (60%) [6].

Tumors of the bladder appear after the age of 60 in the majority of cases [7,8]. In France, with an estimated 12,305 new cases in 2015, 80% of which will be in men, bladder cancer ranks fourth in incidence and seventh in deaths from all cancers and is the second most common urological cancer after prostate cancer [7].

Transitional cell carcinoma is the most predominant histological type, found in more than 90% of cases [9,10].

Tumors of the upper excretory tract (TUET) account for 5% of urothelial carcinomas [3,11]. The peak incidence is between 70 and 90 years of age with a male/female ratio close to 2:1 [3].

For our study focused on bone metastases of urothelial carcinoma, our data are consistent with the literature where most tumors appear after the age of 60 years and where urothelial carcinomas of the bladder are more common than tumors of the upper excretory tract (TUET).

These cancers occur more frequently in men than in women, but women have a poorer prognosis [5].

Our series of eight patients consisted exclusively of males with no female cases. This is consistent with most of the data in the literature where the male sex is predominant.

At the initial diagnosis of urothelial tumors, 5% of tumors are metastatic from the outset [12,13]. The majority of metastases occur in the course of progression after treatment of urothelial carcinoma [1,4]. The most frequent secondary sites of urothelial carcinoma are the lung (52%), liver (33%), and bone (26%) [3].

Bone metastases are the main cause of pain at the time of cancer. They are responsible for many serious complications in addition to pain: pathological fracture, spinal cord compression, ponytail compression, paralysis of cranial nerves, hypercalcemia, bone marrow infiltration with deficit of one or more blood lines. These complications lead to a significant reduction in quality of life [14]. Bone metastases (BM) can be asymptomatic [6].

Our data are consistent with those of most authors where pain is the main and revealing manifestation of bone metastases. It was present in seven of our patients and absent in only one.

The renal insufficiency in half of our patients was due to tumor obstruction or compression of the excretory pathways by adenopathies. The recommended extension workup for urothelial carcinoma is uroscanning coupled with chest CT [3,7]. The CT scan is necessary to confirm the malignancy of a bone lesion. MRI is complementary to CT, especially for the examination of the spinal cord and tumor extensions [15]. Bone scans are not routinely

indicated in muscle-invasive bladder tumors (MITT), but remain the first-line examination when there is a clinical point of care [7,16]. A guided puncture biopsy under CT scan should be considered as a last resort if there is still doubt [16].

Our results are consistent with those in the literature because bone scans were not systematically requested, and were performed in only 3 patients in our series. Also for the bone biopsy, which was performed only in one patient. It was the TAP CT scan that had already objectified bone metastases.

Secondary bone lesions may be: most often diffuse (predominantly in the axial skeleton: mainly lumbar spine, pelvis, upper extremities of femurs, scapular belt, skull), sometimes isolated or associated with other visceral metastases. Lytic or condensing, depending on whether osteoclasia or osteoblastic reconstruction processes predominate [6].

Radiologically, there are three types of bone reactions: lytic, condensing or mixed [15]. Osteolytic metastases are the most common [14].

The results of our series were consistent with those in the literature because osteolytic lesions were predominant. In addition to the CT scan, one patient received an MRI scan that confirmed pedicular damage, but the patient died before starting treatment. The reference treatment for metastatic urothelial cancers is based on Cisplatin-based chemotherapy.

The combination of M-VAC (methotrexate, vinblastine, adriamycin, cis-platin) is the reference treatment for patients eligible for this chemotherapy with a median survival of 14 to 15 months [1,7]. The initial standard first-line treatment protocol is MVAC, MVAC HD (intensified) or gemcitabine-carboplatin (GC). Pembrolizumab (anti-PDL-1) is recommended for second-line therapy [7]. Prior to the development of effective chemotherapy, patients with metastatic cancer rarely had a median survival of more than 3-6 months [17].

In the literature, Karnofsky's performance status (PS) less than or equal to 80% and the presence of visceral metastases were independent prognostic factors of low survival after MVAC treatment [18]. In the case of visceral metastases, mean survival is 4 months. Creatinine clearance of less than 60 ml/min is also a prognostic factor as it would contraindicate the use of cisplatin, which has been shown to be the most effective protocol. Thus, patients are classified into two groups according to their performance status and creatinine clearance: patients eligible for platinum-based combination chemotherapy (FIT) and those not eligible (UNFIT).

Whether at the time of diagnosis or in the follow-up of tumors already known and treated, the management of urothelial metastases is essentially based on chemotherapy [1]. Local irradiation (radiotherapy) of the metastasis, in addition to its direct antitumor effect, reduces pain by reducing edema and peritumoral inflammation.

It is the most effective and quickest treatment, especially in terms of analgesia. Surgery is useful for treating pathologic fractures, although simple immobilization does not allow for any bone consolidation, and additional radiotherapy must be administered in all cases [14]. Bone complications have a negative effect on pain and therefore on quality of life. They are also associated with increased mortality [19].

Biphosphonates reduce the risk of vertebral or non-vertebral pathologic fractures, spinal cord compression, malignant hypercalcemia, and reduce the need for surgery or radiation [14].

Bisphosphonates limit and delay these events by inhibiting bone resorption. Denosumab is a monoclonal antibody that binds to and neutralizes RANKL (nuclear factor-KB ligand receptor activator), thereby inhibiting osteoclast function and thus generalized bone resorption and local bone destruction. Thus, RANKL is as good as zoledronic acid at preventing or delaying bone complications [20]. Denosumab has fewer kidney complications than bisphoshonates.

Our series joins the data in the literature because our patients (FIT) had received Cisplatin-based chemotherapy, those who were UNFIT had received carboplatin with gemcitabine. They had also received analgesic and haemostatic radiotherapy. One patient had received zoledronic acid (biphosphonate) to prevent bone events. No patients had received Denosumab or had undergone bone surgery.

The prognosis is generally unfavorable with limited life expectancy and significant morbidity

and mortality, as evidenced by our series. While the small number of cases is the limitation of our study, we have nevertheless achieved our goal of describing the epidemiological, clinical and prognostic aspects of bone metastases of urothelial carcinoma.

5. CONCLUSION

Bone involvement in urothelial carcinoma is common and represents a turning point in the evolution of this cancer. With a very poor prognosis, they are responsible for many serious complications that significantly affect the quality of life. The therapeutic management of these problems requires a multidisciplinary approach (often decided in a multidisciplinary consultation meeting) in order to stabilize these lesions, improve quality of life and prolong the survival of these patients

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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