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RESEARCH ARTICLE

UROTHELIAL BLADDER CANCER IN YOUNG PATIENTS UNDER 40 YEARS OLD

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Abstract

Bladder cancer is the 2nd urological cancer, most known in people over 50 years old. We are witnessing increased number ofcases in subjects under 40 years of age, mostly due to several factors. The purpose of our study is to study the pathologic and clinical features of urothelial tumors of the urinary bladder in young patients and to understand the particularity of this entity.Retrospective, descriptive study, on 17 patients, treated at two centers, the urology department of the University Hospital of Souss-Massa (Center A) and Urology department ofUniversity Hospital Ibn Sina in Rabat (Center B).From March 1, 2019 to March 1, 2022.This study concerns 17 patients hospitalized in center A and B with an average age of 35 years, sharing the same risk factors. the pathology was revealed by hematuria. our patients benefited from an initial TUR-V resection, the follow-up was then based on the results of anatomopathology.These tumors were preferentiallylocalized on the lateral face of the bladder, and retrotrigone with an average size of 3 cm in both centers. The most common histologic type wasurothelial carcinomapTa Low Grade in both centers.

Bladder tumors in young people are unusual, favored by the presence of risk factors. However, these factorscannot be incriminated due to the short exposure time. Superficial bladder tumors seem to have a good prognosis with little recurrenceunlike infiltrating tumors.

Introduction:-

Bladder cancer is a widely spread disease, it is the 2nd urological cancer and the 5th cancer in the world and it mainly concerns subjects over 50 years. However, we are witnessing an increase in the frequency of young subjects with bladder cancer, whereas it is considered rare in patients under 40 years of age and represents only 0.4 to 1% of urothelial tumors. [1][2][3][4].

The development of these bladder tumors is related to environmental influences and changes in our lifestyle. Smoking is an important factor in the genesis of these tumors and other factors may be involved, such as industrial carcinogens or genetics.

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Methods:-

Retrospective, descriptive study of 17 patients in the Urology Department A of the University Hospital of Sous-Massa (Centre A) and the Urology department ofUniversity Hospital Ibn Sina in Rabat (Centre B).

From March 1/2019 to March 1/2022.

Over a 3-year period, 17 patients were hospitalized on both departments for bladder tumor with an age less than 40 years, 12 patients in Center A and 5 patients in Center B.

An operative form was established specifying identity, risk factors, circumstances of discovery, tumor characteristics, treatment and follow-up.

This study includes all patients with bladder tumor and aged less than or equal to 40 years. All patients with an age greater than 40 years or with incomplete records were excluded.

Results:-

Over a period of 3 years, 17 patients were followed in our departments for bladder tumor whose age was less than 40 years, 12 in Center A and 5 in Center B.

Patients in Center A had a mean age of 34 years (26 - 39) and 35.6 years (31 - 40) in Center B, there was a predominance of male with only two females, one from each center.

All patients in both centers shared the same smoking risk factor, with an average of 10 packs/year. Two patients in center A had professional exposure, one working as a painter, the second in a textile factory. No professional exposure was detected in Center B.

The most common presenting symptom was hematuria in all 17 patients, 8 of them had an irritative lower urinary tract syndrome in addition.

In Center A, the average size of bladder tumors was 3.2 cm, with extremes ranging from 1 to 5 cm, located on the lateral face of the bladder in 5 patients, and in decreasing order, retro trigonal then anterior face. For Center B, the average size was 2.3 cm (from 1 to 4 cm) and the lateral face was the most represented localization.

Table 1

In addition, the anatomopathological study had revealed in patients of Center A, one case of carcinoma in situ and an extensive squamous inflection in another case. For Center B, we found one case of associated undifferentiated carcinoma.

All patients underwent an initial transurethral bladder resection (monopolar for Center A and bipolar or monopolar for Center B) for diagnostic and therapeutic purposes.

In Center A, transurethral resection was curative in 8 patients, two of them had received intravesical βCG therapy (the 6-cure protocol).

Three patients of this Center underwent radical cystoprostatectomy with a Studer enterocystoplasty or urinary diversion type Bricker, indicated for a pT2 or an endoscopically uncontrollable tumor.

The last one had a palliative surgery with cutaneous ureterostomy because of the intraoperative discovery of an inextricable tumor with peritoneal carcinosis.

Four patients from center B, had curative transurethral bladder resection and one of them had intravesical BCG therapy. The last patient of this center had a radical cystoprostatectomy with a urinary diversion type Bricker for a pT2 tumor.

In Center A, the surveillance consisted in performing control cystoscopy every 3-6 months in patients with superficial tumor, while patients with high risk tumor, they had systematically a second look after the 1st resection. 2 patients recurred after an interval of 4 months.

For patients benefiting from radical procedures, a quarterly check-up of renal function and a control CT scan were also performed at 6 months after the operation, as well as an assessment of the tolerance of the type of diversion. 10 of the 12 patients could be contacted, and 9 of them are still alive undergoing regular follow-up as mentioned above. As for the last one, he died due to the evolution of his disease.

For Center B, the follow-up protocol consisted of regular cystoscopies every 3-6-12 months depending on the risk. In this group of 5 patients, 3 of them still alive ensuring regular follow-up. Of the 3 patients with low-grade pTa tumors, one had his first follow up cystoscopy very recently and no recurrence was detected, the other had a recurrence detected 10 months after the initial resection and will be reoperated soon. The last one died 18 months after the initial resection due to severe comorbidities. No recurrence has been detected in the meantime.

The patient with the pT1 tumor has a continuous follow up of 5 years, with the second examination showing no residual tumor and no recurrence detected on subsequent cystoscopies. The patient with the pT2 tumor died 1 month after the cystectomy due to a meningeal carcinomatosis despite a neoadjuvant chemotherapy.

Discussion:-

Urothelial carcinoma of the bladder is the most common neoplasm of the urinary tract, usually occurring in the sixth decade[1,2], however it becomes very rare before the age of 40. Several studies show that bladder tumors account for only 0.4% to 2.0% of bladder tumors in young patients under 40 years of age [3,4] and this since the 1st case was reported by Smythe in 1872.[5]

In the literature, there is a clear male predominance, variously assessed by the authors, with a sex ratio of 3.6 to 9 men for one woman [6][7][8][9]as in our study, we had 15 men for only 2 women.

It should be kept in mind that bladder tumors may express themselves in an atypical clinical form with signs of bladder irritation. Nevertheless, hematuria is the most common clinical expression in patients with bladder cancer[10].

Smoking is defined as a recognized risk factor for urothelial tumors responsible for about 50% of cases in the literature [3] and 100% in our two centers. Moreover, it appears that bladder cancer is more aggressive among smokers [11], and this risk increases with the number of packets/year and the degree of smoke inhalation [11]. However, it is difficult to confirm the harmful role of smoking in young subjects because of the short duration of exposure in our series. Although the 2007 WHO report shows that 15.5% of smokers are between 13 and 15 years of age and that 24% of young smokers started before the age of 10 years [12].

In our series, we found that two patients were exposed to chemicals, the first patient worked as a painter and the second in a textile factory. These occupational risk factors were highlighted in a study by Benton and Henderson [13] with a duration of exposure varying between 3 and 11 years. Besides smoking, exposure to aromatic amines is the main environmental risk factor established for bladder cancer.

The risk of bladder cancer may be increased by 50-100% in patients with a history of first-degree bladder cancer, especially when diagnosed at an early age[14].

In addition to these risk factors, genetic predisposition to bladder neoplasia has been reported in several retrospective studies and for the first time by Fraumeni in 1967[15]. The tumor protein p53 (TP53) is now identified as a known mutated gene related to bladder cancer [16]. In his study Guang Wu found TP53 mutation in 50% of bladder cancer patients, and concluded that TP53 mutation was associated with a lower TP53 mRNA expression level, more advanced tumor stage and higher histologic grade[17].

Iori[18] and Linn [19] found a high mutation rate on 2 chromosomes in their population of young subjects.

Thus, in presence of any patient under 40 years of age with a bladder tumor, a genetic predisposition must be evoked by looking for the family history, in order to detect the risk requiring close urological surveillance.

From a histologic point of view, in all previously published articles, there is a clear predominance of low-risk disease at presentation, as demonstrated by Claire M. de la Calle in her serie of more than 300,000 patients [20], which found the presence of invasive disease (cT2-4) in 18.7% of the cases in the group > 40 years old group versus 9.8% in older patient group.

This was confirmed by Eva Compérat concluding that papillary urothelial neoplasia with low malignant potential dominates the younger age group of patients under 30 years[21].

Bladder tumors in young subjects seem to have a variable and heterogeneous prognosis, it seems to be more favorable for superficial tumors developed before 30 years of age, which are most often papillary, with low p53 overexpression, unifocal and poorly progressive[22], as demonstrated by many studies as Yu-Ching Wen with 87.2% low grade bladder cancer [2] and Volkan Sen with 82.5% of a low grade[3] .

In fact, higher grade and stage tumors progressively increase in proportion with age. For those under 30 years of age, cancer behavior is favorable, attributed to low grade and stage at presentation[22].

In young people, previous studies suggest that the genetic alterations frequently seen in elderly bladder cancer patients were extremely rare[22]. In her study, Sun-WhaIm identified numerous genomic alterations: HRAS mutation and FGFR3 gene fusion, which were associated with a good prognosis without progression to muscle invasive tumors.[16]

A genomic study identified mutations in the P53 (TP53)/RB1 tumor suppressor pathway in 93% of tumors, activation of the PTEN/PI3KCA oncogene pathway in 72%, with frequent loss of function of histone-modifying enzymes (ML2, MLL3, UTX, and ARID1a) in 89% described by the Cancer Genome Atlas (TCGA) project[23]. Tumors of different stages have different mutation rates (genomic profiling analysis showed a similar frequency of mutations in TERT, TP53, RB1, PTEN, PIK3CA, KMT2D, and ARID1A at presentation amoungprogressors and non-progressors), which is associated with relatively high neoantigen load and response to checkpoint inhibitors, as demonstrated in melanoma and lung cancers, where response to the immunotherapeutic agents Nivolumab and Pembrolizumab directly correlated with total mutational load (TMB)[24,25].

Currently, both cytology and cystoscopy are used as first-line diagnostic, prognostic, and monitoring tools. Despite the low sensitivity of cytology and the variation in interpretation of cystoscopy.

Nowadays, some non-invasive methods are emerging, such as liquid biopsies capable of identifying and quantifying proteins such as circulating tumor cells and DNA, RNA, proteins and peptides, metabolites and extracellular vesicles in urine[26], which can detect and classify bladder cancer and even show a significant difference between the urine proteome in patients with different stages of bladder cancer, as shown by Falcão G. and All.[27].

Surveillance of these bladder tumors requires regular cystoscopies, which makes this operation expensive in terms of cost per patient and uncomfortable.

Conclusion:-

Bladder tumors in young people are rare, favored by the presence of the described risk factors. However, our study could not objectify the whole action of these factors, because of the short duration of exposure, and the lack of family investigation when family historyis important.

Analyzing its evolution, superficial bladder tumors seem to have a good prognosis with low recurrence, whereas infiltrating tumors have a poor prognosis with a particular aggressive potential.

Table 1:- The histological type was urothelial carcinoma.

Histological type		Center A	Center B
pTa	Low grade	3	3

	High grade	2	0
pT1	Low grade	1	1
	High grade	4	0
pT2		2	1

Conflicts of interests:
All authors declare that they have no conflicts of interest.

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