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REVIEW

Malakoplakia of the urinary bladder: A review of the literature

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Summary *Objective: The aim of the study is to make a review of the literature about bladder malakoplakia.*
Material and Methods: We searched articles on the PUBMED web-literature database with the following keywords: "vesical malakoplakia" and "bladder malakoplakia". In the literature we found 254 articles. At final we have excluded 219 articles, including in our study only 35 articles.
Results: The overall average age found was 50.85 years. The average age of men was 43.22 years, while that of women was 53.37 years. 75% of the patient cases were women and 25% were men. Regarding comorbidities, in 5.55% of the cases were missing whereas 47.22% of the patients suffered from recurrent urinary tract infection (UTI) and 19.44% from immune system disorders. Urine culture was positive in 69.44% with E.coli being isolated in 92% of cases. Hydroureteronephrosis was present in 44.44% of the cases: left in 6.25% of cases, right in 18.75% and bilateral in 75%. The mean serum creatinine of patients with hydroureteronephrosis was 5.11 (1-21) mg/dl. The most frequent site of the lesion was the vesicoureteral junction (VUJ) (42.31%), followed by the trigone (38.46%). 30.56% of patients were treated with antibiotic and surgery (transurethral resection of bladder, partial or radical cystectomy), less frequent options were antibiotics alone and surgery alone. The recurrence rate was 15%.
Conclusions: Malakoplakia is a disorder usually related to other affections, like UTI and immunodepression, and it seem to be caused by an abnormal macrophage function.
In almost half of the described cases of isolated bladder malakoplakia, hydroureteronephrosis and renal failure were present.Treatment is not standardized, but both medical and surgical therapies are effective to avoid recurrence.

KEY WORDS: *Malakoplakia; Rare disorder; Urinary tract infection.*

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INTRODUCTION

Malakoplakia is a rare disorder which was described for the first time in 1902 by *Michaelis* and *Gutmann*. It affects both sexes, mostly people over 40 years old, patients with immunosuppression, diabetes mellitus, renal transplantation, long-term therapy with systemic corticosteroids and patients with a prior infection of *E. coli* (1).
It usually occurs in the genitourinary tract [commonly the bladder (40%), renal parenchyma (16%), prostate and rarely the ureter (11%)], but it can affect all body organs (2, 3).
Bladder malakoplakia can manifest as nodules, plaques, or ulcers with voiding symptoms and it can mimic cystitis or bladder tumor (4). At cystoscopy it appears as a yellow soft tiny plaque or ulcer (1).
The exact etiology is unknown, but it seems to be caused by a defect of phagocytic or degradative functions of histiocytes in response to *E. coli* or *Proteus* infection resulting in a chronic inflammatory process (5). The lesions are characterized by presence of large macrophages; foamy histiocytes (known as *von Hansemann* cells) containing *Michaelis-Gutmann* bodies (6).
The gold standard for diagnosis and treatment has not yet been decided. Only case reports about vesical malakoplakia can be found in the literature, hence there is a lack of a review of this disease. For this reason the aim of our study was to review all the case reports about bladder malacoplakia in order to compare them.

MATERIALS AND METHODS

We searched articles on the PUBMED web-literature database with the following keywords: "*vesical malakoplakia*" and "*bladder malakoplakia*". The including criteria for our study were: case report and primary bladder malakoplakia as central topic. In the literature we found 254 articles. Of this, we excluded 172 articles because they did not respected the including criteria. So we selected 82 case reports. Furthermore 47 articles have been discharged because articles were unavailable or subject of the paper was off topic. At final we have included in our study 35 articles.

RESULTS

From the 35 articles analyzed, we obtained 36 case reports. The major problem was to find all the information considering that many case reports were incomplete or unclear in their writing, in particular regarding follow-up. The main characteristics of the patients and the pathology are shown in Table 1.

No conflict of interest declared.

Table 1.
Characteristics of the patients and the pathology.

Article	Age (years)	Sex	Comorbility	Serum creatinine levels (mg/dl)	Urine culture/ bacteria	Presence of ohydro-Nephrosis at imaging	Site of lesion
Hina S et al. JCPSP 2019 (5)	55	Female	Recurrent UTI, diabetes	1.1	*E. coli*	Right	Right VUJ
Rabani S et al. Urol J 2019 (6)	1.7	Female	Recurrent UTI	Normal	*E. coli*	None	Right lateral wall
Sirithanaphol W et al. JECR 2018 (2)	66	Female	Panniculitis, sistemic sclerosis, pulmonar fibrosis	Normal	Negative	None	\
Parkin CJ et al. BJ 2020 (15)	82	Female	Recurrent UTI, diabetes, LNH	2.66	*E. coli*	Bilateral	Right and left VUJ and the trigone
Gao P et al. JIMR 2021 (4)	48	Male	Diabetes	1.4	*E. coli*	Right	Right lateral wall involving right VUJ
Shah A et al. PSI 2005 (8)	11	Male	Recurrent UTI, megalo-urethra and PUJ	Normal	*E. coli*	None	Postero and left lateral walls
Ristic-Petrovic A et al. VP 2013 (3)	53	Female	Recurrent UTI	\	*E. coli*	\	Trigone, left VUJ, posterior wall
Nabeshima A et al. J UOEH 2012 (16)	65	Female	No significantpasthistory	Normal	*E. coli*	\	Trigone
Bruce R et al. UR 1990 (17)	86	Female	Recurrent UTI, small cell carcinoma	\	*E. coli*	none	Bladder dome
Stamatiou K et al. NUM 2014 (1)	72	Male	Recurrent UTI, diabetes, CVD	21	Positive	Bilateral	Trigone, left VUJ, posterior wall
Mukha RP et al. IUN 2010 (18)	40	Male	Recurrent UTI	2.8	\	Bilateral	\
Jordaan HF et al. Clin Exp Dermatol 1990 (19)	68	Female	Recurrent UTI, pemfigo and immunodeficiency	\	*E. coli*	Normal	\
Minor L et al. J Urol 2013 (9)	16	Female	\	3	*E. coli*	Bilateral	\
Patniak R et al. Cases J 2009 (11)	18	Male	No significantpasthistory	1.6	Negative	Bilateral	Trigone, left VUJ, bladder neck
Berney DM et al. Histopathology 1996 (12) first case	72	Female	No significantpasthistory	\	Negative	\	\
Berney DM et al. Histopathology 1996 (12) second case	57	Male	Acute renal failure	\	\	\	\
PozoMengual B et al. Actas Urol Esp 2003 (14)	76	Female	No urological history	Normal	Negative	None	Postero wall and bladder dome
Sulman A et al. Urology 2002 (20)	40	Female	Recurrent UTI	\	*E. coli*	None	Bladder neck and left lateral wall
Billis A. Nephron 1994 (21)	27	Female	CRI/ESDR	\	Negative	\	Trigone
Nukui M et al. Hinyokika Kiyo, 1997 (22)	63	Female	No significant past history	2.9	\	Bilateral	Trigone and bilateral VUJ
Batchelor JS. Br J Urol 1991 (23)	63	Female	Recurrent UTI	\	\	\	Posteriorwall
Bylund J et al. Nat Clin Pract Urol 2008 (24)	51	Female	Recurrent UTI, blood hypertension	3.4	*E. coli*	Bilateral	\
Feldman S et al. J Urol 1980 (25)	50	Female	Recurrent UTI	3.8	*E. coli*	Bilateral	Ureteral orifices were not visualized
Stanton MJ. J Urol 1983 (13)	48	Female	Recurrent UTI	\	*E. coli*	None	Right hemitrigone, right lateral wall and bladder neck
Fariña Perez LA. Actas Urol Esp 1999 (26)	69	Male	CVD, TBC	\	Corynebacteriumurealyticum	None	Postero and bilateralwall
Kohda N Hinyokika K et al. 1984 (27)	44	Female	Recurrent UTI	0.7	Negative	None	Posterior, left and right wall
Zornox DH et al. J Urol. 1979 (28)	69	Female	No significantpasthistory	Normal	*E. coli*	None	Right lateralwall
Kato T et al. Hinyokika K 2001(29)	70	Female	Recent pyelonephritis, HCV	Normal	*E. coli*	Right	Trigone, bilteral VUJ and neck
Stripling JR et al. South Med J 1979 (30)	38	Male	No significantpasthistory	15	*E. coli*	Bilateral	Trigoneoblitering the ureteral orifices
Cavallone B, et al. Urologia 2018 (31)	65	Female	Recurrent UTI, diabetes, obesity	9.3	*E. coli*	Bilateral	Anterior and left lateral wall
Tsai R et al. AJR Am J Roentgenol 2016 (32)	31	Female	\	\	Negative	None	Left wall
Steele B et al. Pediatr Radiol 2003 (33)	16	Female	CRI, VUR	2.8	*E. coli*	Bilateral	\
Tsung SH. Urology 1982 (34)	50	Female	No significantpasthistory	Normal	*E. coli*	\	\
Cowie AG et al. Br J Surg 1970 (35)	50	Female	Recurrent UTI	Normal	*E. coli*	None	Internal meatus
Andress MR et al. Br J Radiol 1968 (36)	36	Male	Dystrophia myotonica	\	*E. coli*	Bilateral	Widely distributed, with bilateral involvment of VUJ
Melicow MM. J Urol 1957 (37)	64	Female	Cholecystectomy	\	*E. coli*	Left	\

Data considered and collected were: age, sex, comorbidity, serum creatinine, presence of bacteria in urine, hydroureteronephrosis, site of injury, treatment and follow-up.

The presence or absence of hydronephrosis was derived from imaging examinations: ultrasound, *computerized tomography* (CT), *intravenous pyelography* (IVP), etc.

As shown in the Table 2, the antibiotics used for the treatment were quinolones, Trimethoprim-sulfamethoxazole and β-lactams. As not all the articles reported the antibiotic used, we decided to analyze the data by generally referring to the use of antibiotics or not and the same applies to the type of intervention performed.

The overall average age found was 50.85 years. The average age of men was 43.22 years, while that of women was 53.37. 75% of the patient cases were women and 25% were men.

Regarding comorbidities, in 5.55% of the cases they were missing whereas 47.22% of the patients suffered from recurrent *urinary tract infections* (UTI) and 19.44% from immune system disorders (such as diabetes).

Urine culture was positive in 69.44%. The infection was sustained in 92% of cases by *E. coli*. Missing or negative culture are reported in 30%. On the other hand *Corynebacterium* was occasionally reported.

Corynebacterium urealyticum is the cause of encrusting cystitis. It is usually missed in routine urine cultures since it does not grow after an overnight incubation. It grows in special media on longer incubation period in special medias. Inaccurate search for it could explain the high rate of negative cultures.

Of the patients with negative urine culture, 85.71% had no history of recurrent UTI. Of the patients with positive urine culture, 60% had a history of recurrent UTI.

Table 2.
Treatment and follow up.

Article	Treatment	Follow up
Hina S et al. JCPSP 2019 (5)	Antibiotics, ascrorbic acid, TURB	\
Rabani S et al. Urol J 2019 (6)	Partial cystectomy, trimethoprim-sulfamethoxazole	No recurrence after 9 years
Sirithanaphol W et al. JECR 2018 (2)	Ciprofloxacin, TURB	No recurrence
Parkin CJ et al. BJ 2020 (15)	Amoxicillin-clavulanic acid, TURB	No recurrence after 2 months
Gao P et al. JIMR 2021 (4)	TURB, tazobactam	Bladder recurrence at 6 months with right idroureteronephrosis
Shah A et al. PSI 2005 (8)	Antibiotics	Bladder recurrence 2 and 3 years later
Ristic-Petrovic A et al. VP 2013 (3)	TURB	\
Nabeshima A et al. J UOEH 2012 (16)	TURB	\
Bruce R et al. UR, 1990 (17)	Antibiotics	\
Stamatiou K et al. NUM 2014 (1)	Quinolones, TURB	He died 8 months later after a further worsening of renal failure and complications of the cardiovascular system
Mukha RP et al. IUN, 2010 (18)	Radical cystectomy	\
Jordaan HF et al. Clin Exp Dermatol 1990 (19)	Trimethoprim-sulfamethoxazole, bethanechol, ascorbic acid	No recurrence
Minor L et al. J Urol 2013 (9)	Quinolones, bethanechol	No recurrence
Patniak R et al. Cases J 2009 (11)	Antibiotics	No recurrence after 10 years
Berney DM et al. Histopathology 1996 (12) first case	Antibiotics, radical cystectomy	The patient initially improved, but developed renal failure and died 3 months after cystectomy
Berney DM et al. Histopathology 1996 (12) second case	Radical cystectomy	He died a month after radical cystectomy
PozoMengual B et al. Actas Urol Esp 2003 (14)	Ciprofloxacin, TURB	At 15 day the patient developed a sepsis and she died after 48 hours
Sulman A et al. Urology 2002 (20)	Antibiotics, TURB	\
Billis A. Nephron 1994 (21)	\	\
Nukui M et al. Hinyokika Kiyo 1997 (22)	TURB, trimethoprim sulfamethoxazole, bethanecol, ascorbic acid	No recurrence after 20 months.
Batchelor JS. Br J Urol 1991 (23)	Follow up	No recurrence after18 months but the patient developed LHN
Bylund J et al. Nat Clin Pract Urol 2008 (24)	Ciprofloxacin, ascorbic acid, bethanechol, TURB	No recurrence after 6-9 months
Feldman S et al. J Urol 1980 (25)	Follow up	Bladder recurrence after 2 months. The patient underwent total cystectomy
Stanton MJ. J Urol 1983 (13)	Trimethoprim-sulfamethoxazole, ascorbic acid, bethanechol	No recurrence after 18 months
Fariña Perez LA. Actas Urol Esp 1999 (26)	TURB	After 30 days, he died for heart failure
Kohda N Hinyokika K et al. 1984 (27)	TURB	\
Zornox DH et al. J Urol 1979 (28)	trimethoprim-sulfamethoxazole, ascorbic acid, TURB	No recurrence after 12 month
Kato T et al. Hinyokika K 2001(29)	TURB	No recurrence after 7 months
Stripling JR et al. South Med J 1979 (30)	Cephalosporin, TURB	No recurrence
Cavallone B et al. Urologia 2018 (31)	Ciprofloxacin, ascorbic acid, TURB	\
Tsai R et al. AJR Am J Roentgenol. 2016 (32)	Bethanechol, rifampicin and trimethoprim-sulfamethoxazole	No recurrence after 2 months
Steele B et al. Pediatr Radiol 2003 (33)	Ciprofloxacin	No recurrence, decrease in the number and size of lesions
Tsung SH. Urology 1982 (34)	Antibiotics	\
Cowie AG et al. Br J Surg 1970 (35)	Antibiotics, cystotomy	No recurrence, small residual nodule that was fulgurated. No further cystoscopic abnormality has developed
Andress MR et al. Br J Radiol 1968 (36)	TURB, antibiotics	\
Melicow MM. J Urol 1957 (37)	Cystectomy	\

Hydroureteronephrosis was present in 44.44% of the cases, was absent in 36.11%, and was missing in 19.44%. In the patients with hydroureteronephrosis, 6.25% had left, 18.75% right and 75% bilateral hydroureteronephrosis.. The mean serum creatinine of patients with hydroureteronephrosis was 5.11 (1-21) mg/dl.

Regarding the site of the lesion, this information was missing in 10 cases (27.78%). In most of the remaining 26 cases the disease occurred in more than one area of the bladder. Location, in order of frequency, was *vesicoureteral junction* (VUJ) in 42.31%, trigone in 38.46%, left lateral wall in 30.77%, right lateral wall in 26.92%, posterior wall in 26.92%, bladder neck in 15.38%, bladder floor in 7.69% and anterior wall in 3.85%.

With regard to treatment, we excluded from the analysis nephrostomies, urinary shunts without cystectomy and ureteral stent placement aimed at treating hydroureteronephrosis and not bladder pathology. Treatment in 2.78% of cases was not reported. 30.56% of patients were treated with antibiotic and surgery (transurethral resection of bladder, partial or radical cystectomy). The remaining were treated as follows: 13.89% with antibiotics alone, 22.22% with surgery alone, 5.56% with antibiotic and bethanechol, 5.56% with antibiotic, bethanechol and ascorbic acid, 5.56% with antibiotic, bethanechol, ascorbic acid and surgery, 8.33% with antibiotic, ascorbic acid and surgery and 5.56% with follow-up only.

In total, therefore, the two most frequently used treatments were antibiotic therapy (69.44%) and surgery (66.67%). Regarding surgery, 75% of operations were *transurethral resection of the bladder* (TURB), the remaining being partial or radical cystectomy.

Regarding recurrences, they were missing in 12 case reports (33.33%). Out of the remaining 24 case reports, we excluded 2 cases because the patient had had a cystectomy and could not perform bladder follow-up and 2 other articles due to sudden death from other causes within about one month after diagnosis. In the remaining 20 reports, the recurrence rate was 15%. Cases treated with medical therapy alone (without surgical removal) that demonstrated a reduction of the bladder mass on fol-

low-up imaging were not considered as recurrences. The shortest follow-up was 2 weeks and the longest was 10 years.
The recurrence rate of patients treated with antibiotics alone was 1/3 (33.33%).
The recurrence rate of patients treated with antibiotic and surgery was 1/7 (14.29%).
The recurrence rate of patients treated with follow up was 1/2 (50%).
On the other hand, according to the single treatment, the recurrence rate of antibiotic use was 11.76%, of surgery 9.09% and follow-up only 50%.

Discussion

Malacoplakia is a rare inflammatory and granulomatous disease. It was first identified by *Michaelis* and *Gutmann* in 1902 and its histological features were described by *Von Hansemann* in 1903.
The term '*malacoplakia*' originates from the Greek '*malakos*' and '*plakos*' and means '*soft plaque*' (7).
According to recent literature, the age of onset is over 50 years with a prevalence four times higher in women.
Malacoplakia mainly affects the urinary tract, particularly the bladder, followed by the kidney, the prostate and rarely the ureter (4, 5, 38). However, it may also affect other parts of the body including the conjunctiva, tonsils, adrenal glands, spleen, pancreas, retroperitoneum, mesenteric lymph node, brain, lung, and skin and potentially any organ. In addition, urinary involvement is more frequent in women and extra urinary involvement in men (8).
The exact etiology is still unclear. However, a close association has been seen with recurrent urinary infections (especially from *E. coli*) and immunodepression (diabetes, kidney transplant) (7).
In fact, *Malakoplakia* is believed to result from defective phagocytosis [due to reduced intracellular levels of *cyclic guanosine monophosphate* (cGMP)], resulting in inadequate killing of bacteria. It results in granulomatous reaction caused by an accumulation of bacterial degradation products. Partially digested bacteria become calcified and accumulate in macrophages, forming the pathognomonic *Michaelis-Gutmann* bodies (9).
In addition, the macrophages involved in malacoplakia contain high immunoreactive α1-antitrypsin levels unlike other inflammatory processes (except for tuberculosis and xanthogranulomatous pyelonephritis). Thus, immunohistochemical search for α1-antitrypsin can be useful for a differential diagnosis (10).
Clinically, it presents with irritative *lower urinary tract symptoms* (LUTS) such as dysuria, pollakiuria, urinary urgency and haematuria. These symptoms may mimic cystitis and bladder cancer.
Diagnosis is histological by biopsy of the visible mass on cystoscopy which as mentioned above, it appears as a yellow soft tiny plaque or ulcer (11).
It is characterized histologically by *Von Hansemann* oval histiocytes which contain basophilic lysosomal inclusion bodies called *Michaelis Gutmann* bodies (12).
Imaging examinations (ultrasonography, CT and IVP) may be useful to identify concomitant hydroureteronephrosis and to identify minus defects of the upper urinary tract, indicating its involvement. Currently there are no validated guidelines regarding its treatment (5). Antibiotics are generally administered to treat the underlying infection, such as quinolones, trimethoprim and rifampicin, in combination or not with ascorbic acid and/or bethanechol (4).
Ascorbic acid and bethanechol (cholinergic agent) both seems to increase intracellular cyclic guanine monophosphate levels increasing bactericidal phagocytosis function of macrophages (13).
Surgical intervention is recommended when medical intervention fails (14).
The results listed below are in agreement with the data described in the literature:
- the average age was found to be around 50 years,
- the disease is more frequent in women than in men,
- malacoplakia seems to be associated with recurrent UTI and immune system disorders.
- about 90% of positive urine cultures are sustained by *E. coli*.

In our study of the epidemiology, we found a lower mean age of incidence in men than in women by about 10 years, with a women:men frequency ratio of 3:1, instead of 4:1 as reported in the literature.
In our review, we decided to look at the site of the disease and found that the most frequently affected sites were the trigone and ureteral meatuses.
For the first time in our analysis, we found that about one third of patients had hydronephrosis (mono or bilateral) and that this correlated with involvement of the trigone and/or VUJ. In the cases examined, hydronephrosis almost always led to renal failure with mean serum creatinine values of 5.1 mg/dL (the highest value found in a case of acute renal failure was 21 mg/dL).

Conclusions

Nowadays, malakoplakia is a disorder not well know, that seems related to other affections, like UTI and immunodepression, and is thought to be the result of abnormal macrophage function.
In accordance with the literature, it can present with a very-variable spectrum of symptoms although we have shown that in isolated bladder malakoplakia without ureteral involvement, hydroureteronephrosis and renal failure are very common (in almost half of the cases).
Treatment is not standardized, but both medical and surgical therapies seem to be effective in curing the condition and avoiding recurrence, although we did not collect sufficient data to perform a statistical analysis.

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