



Malakoplakia of testis and epididymis: A Review of the Literature

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Abstract

Malakoplakia of the testis / epididymis is uncommon therefore most clinicians globally would be unfamiliar with the disease. Malakoplakia is an extremely rare chronic inflammatory disease which usually affects the genitourinary tract and it is often associated with Escherichia coli infection. Malakoplakia characterized by the observation of Von Hansemann cells and intracytoplasmic inclusion bodies called “Michaelis-Gutmann Bodies (M-G bodies).” The testes are affected in 12% of cases of malakoplakia and isolated malakoplakia of the epididymis is even rarer. To the knowledge of the author, less than 50 cases of malakoplakia of the testis and less than 15 cases of malakoplakia of the epididymis have been reported so far world-wide. Malakoplakia of the testis / epididymis may present with pain in the testicular area, fever, chills and or a hemi-scrotal mass. Malakoplakia of testis / epididymis is usually seen in middle aged men and they tend to appear clinically as epididymo-orchitis or testicular enlargement with fibrous consistency and some soft areas. Ultrasound scan findings of the testis are non-specific revealing hypo-echogenic or hyper-echogenicity with increased vascularity on Doppler scanning. A number of cases of malakoplakia of the testis and epididymis are associated with immunosuppression, renal transplantation and diabetes. Treatment of malakoplakia includes medical and surgical treatment. The quinolones and trimethoprim-sulfamethoxazole have been most commonly used. Orchidectomy has been the only way to differentiate malakoplakia from other malignant and infective processes. If a patient with malakoplakia of testis is immunosuppressed then a period of withdrawal may perhaps be beneficial to speed up the recovery process. With the knowledge that malakoplakia of the testis is more common in middle aged men and the fact that testicular tumours are uncommon in the middle aged group perhaps ultrasound guided biopsy of a hypo-echoic or hyper-echogenic testicular lesion with increased vascularity could be undertaken to establish the diagnosis if there is evidence of coliform urinary tract infection and a clinical diagnosis of epididymo-orchitis has been made but the lesion has not resolved. In that case perhaps prolonged antibiotic treatment with quinolones may help the lesion to resolve and thus avoiding orchidectomy. Malakoplakia involving the testis and or epididymis is an uncommon chronic inflammatory condition which clinicians should consider in the differential diagnosis of testicular swellings. The disease tends to be associated with gram negative infections especially coliform infections.

Key Words: Malakoplakia of testis; Malakoplakia of epididymis; Michaelis-Gutmann Bodies; coliforms; epididymo-orchitis; quinolones; orchidectomy; ultrasound-guided biopsy.

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Introduction

Malakoplakia of the testis and Malakoplakia of the epididymis are so rare that most clinicians throughout the world would not have encountered the disease. The ensuing paper contains a review of the literature on malakoplakia of the testis and malakoplakia of the epididymis. The paper is divided into two parts (A) which contains an overview and (B) miscellaneous narrations and discussion from some reported cases.

Methods

Various internet data bases were used to search for case reports, case series, review papers and other documentations on malakoplakia of testis and malakoplakia of the epididymis in order to obtain information on the presentation, epidemiology, pathophysiology, investigation and management of the disease. The key words that were used were: Malakoplakia of testis and Malakoplakia of epididymis. In all 13 references were identified to be suitable to document literature on the disease.

Results / Literature Review

(A) General Comment

Malakoplakia of testis (MOT) may affect the testis alone or it may affect both the testis and epididymis [1].

Quite often in malakoplakia of testis culture grows presence of coliforms [1].

Definition and back ground: Kiel and James [2] defined malakoplakia as an inflammatory condition which presents as a plaque or a nodule which usually affects the genitourinary tract system but malakoplakia may rarely affect the skin. Kiel et al. [2] also stated that malakoplakia was first described in the early 1900s as yellow soft plaques which were seen on the mucosa of the urinary bladder. The microscopic feature of malakoplakia is characterized by the presence of foamy histiocytes with distinctive basophilic inclusions, which are called Michaelis-Gutmann bodies.

Cutaneous malakoplasia is rarely seen but it presents in patients who have been immunocompromised and they have defects in macrophage function. Malakoplakia lesions, are yellow-to-pink papules, nevertheless, they can present as nodules or ulcerations. Malakoplakias quite often are diagnosed following histological examination of biopsy specimens. Culture of malakoplakia lesions can yield bacteria of which *Escherichia coli* is the most common organism cultured. Malakoplakia may also rarely affect the testis and the epididymis.

Pathophysiology

Kiel and James [2] stated that:

- It has been understood that malakoplakia emanates from inadequate killing of bacteria by macrophages or monocytes which exhibit defective phagolysosomal activity.

- Partially digested bacteria accumulate in monocytes or macrophages and this lead to the deposition of calcium and iron on residual bacterial glycolipid.
- The presence of the resulting basophilic inclusion structure, the Michaelis-Gutmann body, is regarded pathognomonic for malakoplakia.
- Studies had indicated that a decreased intracellular cyclic guanosine monophosphate (cGMP) level may interfere with adequate microtubular function and lysosomal activity which lead to an incomplete elimination of bacteria from macrophages and monocytes.

Epidemiology

Kiel and James [2] stated that:

- The total number of patients with malakoplakia is less than 500 in the United States of America.
- Majority of patients who have malakoplakia have genitourinary tract disease, even though malakoplakia involving the gastrointestinal tract and other visceral organs has been described.
- International frequency of malakoplakia is the same as in the United States of America.
- Malakoplakia most frequently occurs in patients who have been immunocompromised.
- Quite often malakoplakia is resistant to treatment.
- Mortality in patients afflicted by malakoplakia is most commonly a result of an underlying disease.
- Significant morbidity in malakoplakia is related to the chronicity of the condition, which can resist local and systemic therapy. Drainage of sinuses, persistence of disfiguring cutaneous lesions, and the involvement of visceral organs would constitute significant morbidity in patients who have malakoplakia.

Presentation

- Patients with malakoplakia of testis and epididymis may present with fever, chills, and testicular pain.
- The patients may also present with a testicular mass.
- Patients with malakoplakia of testis / epididymis have a history of renal transplantation, diabetes, multiple urinary tract infections and immunosuppression.

Malakoplakia of testis tends to occur in middle aged men and in most cases it involves one testis.

Clinical examination findings: Some of the clinical examination findings in malakoplakia of testis / epididymis include: a scrotal mass: tenderness over the epididymis and or testis which may make the clinician to establish a provisional diagnosis of epididymo-orchitis.

Laboratory findings: There may be coliform urinary tract infection associated with malakoplakia of testis.

Radiology / Ultra-sound scan: The ultrasound scan appearances of malakoplakia of the testis / epididymis are non-specific. Ultra-sound scan of testis that had been afflicted by malakoplakia may reveal a hypo-echoic mass which is not diagnostic. At times ultrasound scan may reveal a hyper-echogenic mass in the testis. Diagnosis of malakoplakia of the testis can only be confirmed by histological examination of testicular biopsy specimen or orchidectomy specimen. Ultra-sound scan of testes and scrotal contents in malakoplakia of epididymis may reveal a mass in the inferior scrotum which may not be clearly separated from the testis. The mass may be iso-echoic to hypo-echoic with increased vascularity on Doppler scan evaluation in comparison with normal testicular parenchyma.

Macroscopic appearance: In malakoplakia of testis gross examination tends to reveal a tan-yellow-brown enlarged testis [1]. Malakoplakia of testis tends to be associated with abscesses and thrombosed vessels. [1]

Microscopic features: (see figures 1, 2 and 3) Microscopic examination of the testis with malakoplakia shows testicular atrophy, sheets of histiocytes with Michaelis-Gutmann bodies which is the name given to intracellular and extracellular round structures containing iron and calcium. There is usually evidence of destroyed tubular architecture in the testis.

Electron microscopy features: Electron microscopic examination of the testis, affected by malakoplakia reveals bacteria within phagolysosomes of histiocytes [1]

Diagnosis: Diagnosis of malakoplakia of testis or epididymis can be established by histological examination of biopsy specimens from the mass or excised specimens. It is characterized by the presence of Von Hansemann and intracytoplasmic inclusion bodies called Michaelis-Gutmann bodies [3].

Treatment: Treatment of malakoplakia may be medical or a combination of medical and surgical treatments. Antibiotics that are intracellular bactericidal agents are usually used.

Differential diagnosis: The differential diagnosis of malakoplakia of testis include: Granulomatous orchitis and Leydig cell tumour. [1]

(B) Miscellaneous narrations and discussions from some reported cases.

Siders et al. [4] reported a 74-year-old man who presented with an acute onset of fever, chills and testicular pain. He was noted to be a diabetic who had undergone renal transplantation 11 years earlier. He had had multiple urinary tract infections associated with immunosuppression. On examination a 3-cm scrotal mass was palpable and a provisional diagnosis of epididymo-orchitis was made, even though the nature of the mass was not clear. He had ultra-sound scan of scrotum which revealed a 2.2 cm x 2.4 cm x 2.5 cm mass on the left side in the inferior scrotum (see figure 1). The mass was not clearly separated from the testis and was iso-echoic to hypo-echoic with increased vascularity on Doppler ultrasound evaluation in comparison with normal testicular parenchyma (see figure 2). The initial ultrasound scan findings were non-specific; nevertheless, based upon the acute onset of symptoms an inflammatory process with bilateral reactive secondary hydrocele was suggested. He had a follow-up ultrasound scan after he had had antibiotic treatment and clinical improvement which revealed a 2.5 cm mass in the left scrotum with echogenicity and hyper-vascularity similar to the previous scan (see figure 3). He was observed and examined regularly for six weeks but the mass remained unchanged. In view of his history of immunosuppression and the fact that the mass had remained the same it was felt malignancy had to be excluded. He underwent a radical orchidectomy with high ligation of the cord structures. Macroscopic examination of the specimen revealed a nodular mass at the junction of the spermatic cord and epididymis with obliteration of the tail of the epididymis. The mass was adherent to the tunica albuginea with indentation of the underlying testis. Histological examination of the specimen revealed typical findings consistent with a diagnosis of malakoplakia without involvement of testis or tunica.

Figure 1: This figure shows a haematoxylin and eosin stained section of malakoplakia of testis.

Comments: Testicular involvement is seen in 10% - 12% of cases of malakoplakia of genitourinary tract. Tubular architecture is completely destroyed and germ cells are replaced by histiocytes with abundant eosinophilic cytoplasm. Several such tubules are seen here. The interstitium contains a lympho-plasmacytic

infiltrate. The figure was reproduced with permission from Web Pathology.com

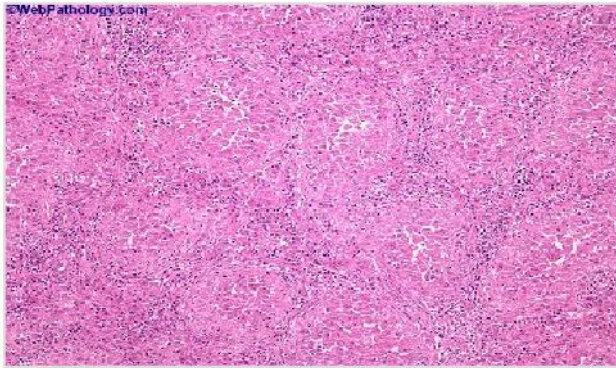
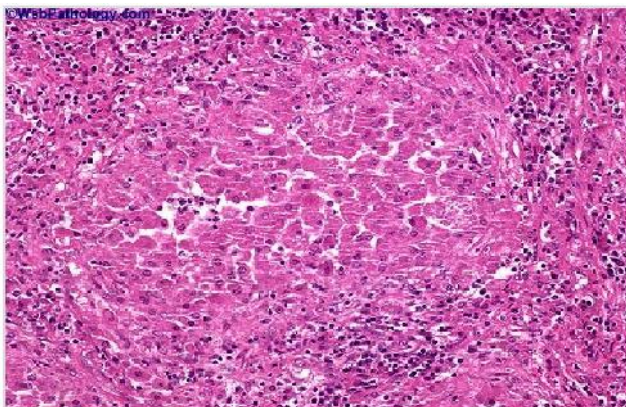


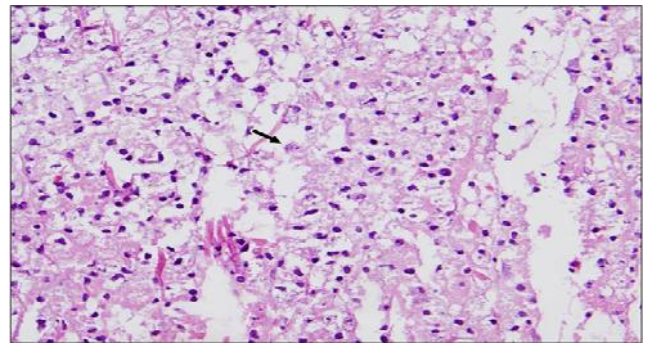
Figure 2: This figure shows a haematoxylin and eosin stained section of malakoplakia of testis. **Comments:** The differential diagnosis of malakoplakia involving testis includes Leydig cell tumour and idiopathic granulomatous orchitis. This figure was reproduced from webpathology.com website with permission from Web Pathology.com



Dubhashi et al. [3] reported a 24-year-old man who presented with pain in his left hemiscrotum of three weeks duration. He did not have any urinary tract symptoms. His clinical examination revealed a swelling in his left hemiscrotum with an erythematous overlying skin. The swelling on palpation, felt firm associated with local rise in temperature. He did not have any lymph node enlargement. An initial diagnosis of pyocele was made. His urinalysis revealed a few pus cells. He had ultrasound scan of the scrotum which showed an enlarged testis with hypo-echoic echo-texture with highly increased vascularity on Doppler scanning. The ultrasound scan also showed a 9 mm size hypo to iso-echoic wedge shaped lesion at its anterior aspect with no vascularity which was suggestive of haematoma. A diagnosis of left orchitis with small intra-testicular haematoma was made. He was given

analgesia and anti-inflammatory treatment. His clinical condition did not improve after 5 days. His urine culture grew *Escherichia coli*. He underwent scrotal exploration which revealed that the tunica albuginea was thickened and showed haemorrhagic areas. Thick, purulent fluid within the left testis with yellowish plaques was found (see figure 4). A left orchidectomy was undertaken and histological examination of the excised testis showed eosinophilic cytoplasm. The histocytes exhibited intracytoplasmic Michaelis-Gutmann bodies and PAS stain also confirmed Michaelis-Gutmann bodies. A diagnosis of malakoplakia of testis was confirmed by the histological examination. The purulent fluid on culturing grew *Klebsiella pneumonia* which was sensitive to Quinolones. He was treated with ciprofloxacin for 3 months and he remained asymptomatic with a follow-up of one year at the time of publication of the paper.

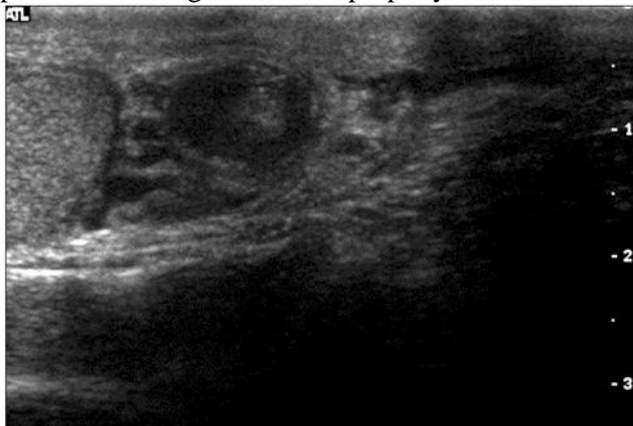
Figure 3: Epididymal mass shows numerous histiocytes and Michaelis-Gutmann bodies (arrow) (Haematoxylin and Eosin x 400). This figure was reproduced from Kang Y J, Kim S W, Lee Y S, Kim K H. Malakoplakia of epididymis. *Korean Journal of Urology* 2013 Apr; 54(4): 274 – 278 with permission from the journal, given under the open access article distributed under the terms of the creative commons attribution Non-Commercial Licence (<http://creativecommons.org/licenses/by-nc/3.01>), which permits unrestricted and non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.



The first case of malakoplakia of testis was reported in 1958 by Haukohl and Chincinian. [5] A number of postulates exist regarding the aetiology of malakoplakia. McClure [6] suggested that malakoplakia may be an expression of microtubular / microfilamental dysfunction. Alvares Bandres et al. [7] stated that:

- Various postulates exist with regard to the aetiology of malakoplakia, with three factors playing a major role including: altered phagocytic function of macrophages, gram-negative infection, and an abnormal immune response.
- Ineffective phagocytosis occurs as a result of defect in the lysosome response of macrophages to bacterial infections which are usually caused by *Escherichia coli*. There appears to be an imbalance between cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP), which causes inadequate lysosomal degradation in monocytes.
- Other disease conditions may co-exist with malakoplakia and some of these include cancer, diabetes, tuberculosis and alcoholic-liver disease.
- Malakoplakia is an uncommon chronic granulomatous condition of a benign nature which preferentially tends to occur in the genitourinary tract.
- Testes are affected in 12% of cases of malakoplakia and the first case of malakoplakia of the testis was reported in 1958 and since then by the time of the report of their case of malakoplakia of testis in 2009 40 cases of malakoplakia of the testis had been reported worldwide prior to their publication.

Figure 4: Ultrasonography showed a mass lesion of mixed echotexture in epididymal tail. This figure was reproduced from Kang Y J, Kim S W, Lee Y S, Kim K H. Malakoplakia of epididymis. *Korean Journal of Urology* 2013 Apr; 54(4): 274 – 278 with permission from the journal given under the open access article distributed under the terms of the creative commons attribution Non-Commercial Licence (<http://creativecommons.org/licenses/by-nc/3.0/>), which permits unrestricted and non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.



Alvarez Badres et al. [7] reported a case of testicular and epididymal malakoplakia in a 68-year-old man diagnosed with complicated epididymo-orchitis who underwent orchidectomy to rule out a malignant tumour. Histopathological examination of the specimen showed a chronic inflammatory infiltrate with histiocytes with eosinophilic cytoplasm containing Michaelis-Gutmann bodies diagnostic of malakoplakia.

In 1980, McClure made the ensuing statements [8]:

- The association between coliform urinary tract infection and malakoplakia of the testis could be explained by the fact that infection of the testis may be acquired via retro-grade spread from the urinary tract and malakoplakia of the testis is intra-tubular initially.
- Macroscopically, malakoplakia lesions are yellowish soft plaques or nodules; and upon microscopic examination of the lesions tend to reveal Von Hansemann cells which are intensely PAS-positive structures; Michaelis-Gutmann bodies are pathognomonic of malakoplakia.
- *Escherichia coli* was cultured in four out of six cases in whom testicular tissue was cultured for micro-organisms, *Klebsiella pneumoniae* and *Proteus* were cultured in the other cases.

Minor and Lindgren [9] reported an increased frequency of malakoplakia in immunocompromised patients in up to 40% of cases. Christensen et al. [10] stated that treatment of malakoplakia with antibiotics that concentrate in macrophages (e.g. quinolone, trimethoprim-sulfamethoxazole) is associated with a high cure rate. Kiel and James [2] stated that:

- Antibiotic treatment which is directed against *Escherichia coli* in combination with surgery provides the best chance of cure.
- Bethanecol, a choline agonist, had been used in combination with antibiotics and surgery to treat malakoplakia. Bethanecol may correct the decreased cGMP levels which are understood to interfere with complete bacterial killing.
- Ascorbic acid had been used to increase the cGMP and cyclic adenosine monophosphate (cAMP) levels in monocytes, which may represent an effective strategy for treatment. An insufficient number of patients had been treated with ascorbic acid to determine its overall effect.
- Discontinuation of immunosuppressive drug therapy is usually needed to effectively treat malakoplakia.

Malakoplakia of the epididymis without involvement of the testis was first reported by Green in 1968. [11] Siders et al. [4] stated that:

- Malakoplakia of the epididymis most often appears as an extension from an adjacent involved testis.
- By the time of publication of their paper in 2005, malakoplakia confined to the epididymis had been reported 10 times previously.
- The pathologic and imaging features of malakoplakia are the result of macrophage failure with incomplete digestion of bacteria and granulomatous inflammation.
- Microscopic examination of malakoplakia shows giant histiocytes with basophilic inclusions known as Michaelis-Gutmann bodies, which are formed from incomplete phagocytosis of bacteria and these inclusions act as foreign bodies and contribute to chronic inflammation and calcifications.
- Grove et al. [12] suggested that endarteritis and vascular thrombosis are involved in the disease process and manifestations.
- Imaging findings in malakoplakia are non-specific and they can range from hypo-echogenicity to hyper-echogenicity often with increased vascularity. Hyper-echoic foci which represent calcifications from chronic infections may also be seen.

Guccion et al. [13] in 1978 reported a case of malakoplakia localized to the epididymis. They stated that ultra-structural study had revealed the presence of bacterial bodies in phagolysosomes of malakoplakic macrophages.

Kang et al. [14] reported a 61-year-old man who presented with a painful mass in his left epididymis of several months duration. He did not have any fever or a history of trauma. His haematological blood parameters were normal and his urinalysis was normal. His urine culture did not grow any organism. He had ultra-sound scan of the left epididymis which showed a mass lesion of mixed echo-texture in the left epididymal tail (see figure 4). He underwent epididymectomy. Histological examination of the specimen showed an epididymal mass which comprised of sheets of histiocytes with histiocytes with granular eosinophilic cytoplasm (see figure 3) admixed with neutrophils, lymphocytes, and plasma cells. Many of the histiocytes contained small round to oval targetoid structures which were morphologically consistent with Michaelis-Gutmann bodies. The histological findings were characteristic

of malakoplakia. His post-operative recovery was unremarkable and he had remained well for up to 8 months when his case was published.

Summary

Malakoplakia is a rare benign chronic inflammatory process which manifests with granulomatous changes and quite often it involves the urogenital system.

Malakoplakia of the testis and or epididymis is very rare and may present with testicular pain / lump, fever and chills and these symptoms mimic the presentation of other testicular diseases like epididymo-orchitis and testicular tumour.

A number of cases of malakoplakia of testis / epididymis may be associated with renal transplantation, immunosuppression, diabetes, or tuberculosis.

Quite often malakoplakia of testis is diagnosed based upon histological examination of the testis following orchidectomy which has been performed as a result of persistent symptoms and persistent testicular mass following a period of antibiotic treatment to exclude malignancy.

Ultrasound scan findings in malakoplakia of testis and epididymis are non-specific and they range from hypo-echoic lesions with increased vascularity to hyper-echoic lesions with increased vascularity.

A number of cases of malakoplakia of the testis / epididymis are associated with positive urine culture evidence of urinary tract infection of which coliforms are the most common.

If there is evidence of urinary tract infection and ultrasound scan evidence of hypo-echogenicity/hyper-echogenicity with increased vascularity and the symptoms and testicular mass have not resolved following a period of antibiotic therapy ultrasound guided biopsy of the testicular / epididymal lesion would yield specimens for histological confirmation of malakoplakia. Presence of Michaelis-Gutmann bodies in the histological specimen of the testis and or epididymis is diagnostic of malakoplakia.

Malakoplakia of testis / epididymis may be treated by a combination of medical / antibiotic treatment (Quinolones, trimethoprim-sulfamethiazole) and surgery.

Malakoplakia of testis / epididymis may be initially misdiagnosed as epididymo-orchitis or testicular tumour.

If a patient diagnosed with malakoplakia is on immunosuppression then a period of cessation of the immunosuppressant may be beneficial to the recovery of the patient.

Conclusions

Malakoplakia involving the testis and or epididymis is an uncommon chronic inflammatory condition which clinicians should consider in the differential diagnosis of testicular swellings. Malakoplakia of the testis and or epididymis tend to be associated with gram negative infections especially coliform infections.

Conflict of Interest: None

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