Malakoplakia: An Update on Pathophysiology and A Review of the Last Ten Years

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ABSTRACT Purpose: Malakoplakia is an unusual chronic inflammatory condition affecting predominantly the genitourinary tract with special affinity for the bladder. A strong association with infectious processes and immunosuppression is well known. On several occasions, malakoplakia presents as a doubtful lesion misleading clinicians toward a suspicious of tumour. The aim of this review and analysis of the literature is to contribute to clarify the biological behaviour and prognosis of malakoplakia and to establish some key points in the clinical and surgical management.

Methods: A Medline (2008-present) database searches yielded 26 references.

Results: Most cases occurred in the fifth and sixth decades of life, with a mean age at diagnosis of 50 years old. Analyses of the literature revealed a strong female predominance just for bladder localization with a male/female ratio 1:4. Malakoplakia has been reported to occur at various sites, most commonly in the urinary tract in at least 70% of cases, with isolated reports in the gastrointestinal tract, central nervous tissue, skin, hepato-biliary tract, pancreas, liver, lymphnodes, respiratory tract, adrenal gland, vagina, brain, lung and bones.

Conclusions: Malakoplakia could be managed by a combined medical and surgical approach and is clinically prudent to exclude a cancer when diagnosed.

KEYWORDS malakoplakia, bladder, urinary tract, chronic inflammatory condition

Introduction
Malakoplakia is an uncommon type of chronic inflammatory disorder. Less than 1000 patients are diagnosed with malakoplakia every year in the US. Michaelis and Gutmann first described it in 1902, but it was von Hansemann who first identified the condition one year earlier and named the lesions as malakoplakia, meaning soft plaque. Although malakoplakia has been reported to occur at various sites, most commonly involves the urinary tract, with isolated reports related to the gastrointestinal tract, central nervous tissue, skin, hepato-biliary tract, pancreas, liver lymph nodes, respiratory tract, adrenal gland, vagina, brain, lung and bones [1-7]. On several occasions, malakoplakia presents as a doubtful lesion misleading clinicians toward a suspicious of the tumour. Common associations of malakoplakia include immune deficiency disorders and metabolic syndromes. There are two therapeutic approaches: antibiotics that can penetrate the cell membrane and concentrate on macrophages and bethanechol chloride, a cholinergic agonist, able to correct the lysosomal defect. Antibiotic therapy, in combination with surgery, provides the best chance of cure. The aim of this systematic review and analyses of the literature of the last ten years is to clarify the pathophysiology of malakoplakia and establish the key points for its clinical and surgical management.

Material and Methods
Systematic literature searches were conducted from 2008 through 2018, in a databases MEDLINE (via PubMed), for human-only reports written in English, and revised according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Eligibility criteria for inclusion in the systematic review were that it was a review and full-text
Figure 1: Histopathology feature of bladder malakoplakia. (a) CD68, 20X, (b) CK, 10X, (c) PAS, 20X, (d) PERLS, 10X.

manuscripts. Based on our search criteria, database searches yielded 26 references. An ethics committee approval for the study or informed written consent of the subjects included in the report is not requested as not applicable in this kind of study.

Results

Most patients were aged older than 50 years and male. In the urinary tract, females were more commonly affected than males with a 4:1 ratio. Malakoplakia is usually diagnosed between the fifth and seventh decades of life though it can occur at any age. Approximately 75% of cases of malakoplakia are located in the genitourinary system. Malakoplakia of the bladder may present as haematuria, acute or chronic renal failure, and signs of urinary tract infection such as hesitancy, dysuria and frequency. It is defined histologically by von Hansemann histiocytes and Michaelis Gutmann bodies. Von Hansemann cells are ovoid histiocytes which contain intracytoplasmic bodies: Michaelis Gutmann bodies. They have specific staining characteristics, being gram-negative and positive for von Kossa stain (calcium), Perl’s stain, Prussian blue (iron), and Periodic Acid-Schiff stain (Fig 1). Malakoplakia is usually associated with a variety of bacterial infections: coliform bacteria, particularly E. Coli, have been isolated from the involved sites of genitourinary malakoplakia in more than two-thirds of patients. Malakoplakia can form tumour-like nodules that clinically simulate malignancy in a variety of organs. The kidney is affected in only 15% of patients. The second most frequently involved site is the gastrointestinal tract, particularly the colon. The cutaneous form is less prevalent, and most commonly occurs in the perianal or genital regions. Involvement of various other sites continues to be reported in the literature (Table 1) [8-10]. Commonly, haematological parameters and urine indexes are within the normal range; urine culture does not reveal any growth. The definitive diagnosis is based on histological analysis of tissue involved: special stains such as periodic acid Schiff and von Kossa for calcium can be particularly helpful in highlighting the Michaelis-Gutmann bodies when these are obscured within dense lymphohistiocytic infiltrate. Furthermore, it is to keep in mind that malakoplakia sometimes coexists with malignant lesions, the differential diagnosis is of paramount importance and once more based on the histological findings.

Discussion

The most common site involved by malakoplakia is the urinary tract. In the bladder, it often appears as white plaques noted on cystoscopic examination. The main differential diagnoses include primary or metastatic malignancies, especially when the lesion is ulcerated or involves lymph nodes. It is necessary to distinguish renal malakoplakia from renal tumours or other inflammatory and infective diseases, including renal cell carcinoma, xanthogranulomatous pyelonephritis, renal tuberculosis, and renal fungus infection. The differential diagnosis of malakoplakia of the gastrointestinal tract includes Crohn disease, tuberculosis, Whipple disease, sarcoidosis, other infectious or noninfectious granulomas, histiocytic storage diseases as well as malignancy. In the skin, malakoplakia must be differentiated from other skin diseases, including fungal infections and other granulomatous lesions. Three possible mechanisms have been suggested to explain its aetiology. The first hypothesized that microorganisms might play a role in the pathogenesis: several organisms have been implicated, particularly E. Coli, Mycobacterium tuberculosis, Proteus, and Staphylococcus aureus. Malakoplakia is associated with certain bacteria such as gram-positive coccobiococcus Rhodococcus equi, but also Pseudomonas aeruginosa, Staphylococcus aureus, Mycobacterium bovis and gram-negative E. Coli and Klebsiella pneumonia. Genitourinary malakoplakia is usually associated with long-standing urinary tract infections with gram-negative enteric bacilli mainly E. Coli.  

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<th>Site</th>
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<tr>
<td>Thyroid gland</td>
<td>Vitkovski et al. 2015</td>
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<td>Ovary and tube</td>
<td>Boubess et al. 2015</td>
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<td>Testis</td>
<td>Alvarez et al. 2009, Roy et al. 2011</td>
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<td>Head and neck region</td>
<td>Coates et al. 2016, Garg et al. 2010</td>
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<td>Skin</td>
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<td>Trachea and larynx</td>
<td>Akilesh et al. 2011</td>
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R. Equi has been implicated in the majority of cases with pulmonary malakoplakia. Lung lesion is mostly associated with AIDS [11-15]. Various bacteria are found in certain categories of patients, for example, coliform bacteria in patients with chemotherapy and Rhodococcus equi in patients with acquired immunodeficiency syndrome. Such association support another hypothesis: an altered immune and as chronic prolonged illness as possible key points in the pathophysiology of malakoplakia. The third hypothesis is an abnormal macrophage response. The macrophages show normal phagocytic activity but manifest abnormal intracellular killing or digestion of bacteria, probably secondary to defective lysosomal degranulation and impaired acidification of phagolysosomes, which is thought to be related to low levels of intracellular cyclic guanosine monophosphate (cGMP) and diminished release of b-glucuronidase, which may interfere with adequate microtubular function and lysosomal activity, leading to incomplete elimination of bacteria from macrophages and monocytes. Partially digested bacteria accumulate in monocytes or macrophages and lead to the deposition of calcium and iron on residual bacteria glycolipid, resulting in the Michaelis-Gutmann bodies.

This would explain the suggested treatment option with cholinergic agonist bethanechol chloride, which acts by increasing the levels of cGMP. Why the great majority of immune deficient patients do not present with the lesions of malakoplakia remains unclear; specific errors in mechanisms involving the cyclic guanosine monophosphate pathway that regulates lysosomal function appear to play a determining role. The diagnosis is made by demonstrating some histological features such as Von Hansemann histiocytes and Michaelis-Gutmann bodies [16-20].

The treatment options for malakoplakia include two main approaches: the administration of antibiotics and surgical excision, depending on the site and extent of involvement. The most effective available treatment is the combination of long antibiotics therapy with quinolones, rifampicin, macrolides, tetracyclines, trimethoprim-sulfamethoxazole using drugs with good penetration into macrophages and surgical resection of the infected tissue. Fluoroquinolones, have been utilized in the management of malakoplakia, due to their ability to achieve therapeutic concentrations within histiocytes. Trimethoprim-sulfamethoxazole may be helpful because of the ability of trimethoprim to enhance the killing of viable indigested microorganisms inside macrophages. Duration of treatment is not well defined, it depends on the site, extent of tissue, type of isolated organism and the immune status of the patient. Sometimes several months are necessary for cure. Discontinuation of immunosuppressive therapy can also facilitate cure. Bethanechol chloride has been tried. However, there is not any convincing evidence of its clinical efficacy. Surgical treatment may be required depending on the organs affected. In case of large lesion of the bladder, a transurethral resection may be necessary. Patients with extensive pelvic malakoplakia will often need large, complex abdominal surgery, especially if the bowel is involved. Misinterpreting the large, rapidly growing nodules of malakoplakia as tumours might lead to unnecessary radical surgical intervention. Malignant transformation has not been reported. Close follow up of these patients is needed because multiple locations can be affected.

Conclusion
Malakoplakia is a self-limiting benign condition associated with a good prognosis; it could be managed by a combined medical and surgical approach and is clinically prudent to exclude cancer when diagnosed.

Competing Interests
None

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None

References


