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## Malakoplakia of the urinary system

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**Abstract:** Malakoplakia is regarded as a chronic granulomatous inflammatory disease with a good prognosis. It usually affects the urinary system, especially the urinary bladder. Bacterial infections, including *E. coli* are thought to be the main factor in pathogenesis. It frequently coexists with chronic diseases and immunosuppression state. Histopathological examination of affected tissue samples is thought to be the best diagnostic method. The basic microscopic feature is mixed inflammatory infiltration containing foamy histiocytes known as von Hanseman cells, frequently with basophilic inclusions known as Michaelis-Gutmann bodies. Symptoms and the clinical course of malakoplakia depend on location and the extent of the lesions. The lesion is treated successfully with antibiotic therapy and surgical excision.

**Key words:** malakoplakia, von Hanseman cells, Michaelis-Gutmann bodies.

### Introduction

Malakoplakia (MPL) is a rare inflammatory disease. Its name is closely related with gross appearance of the lesion. Translated from Greek *malakos* means soft, *plakos* — plaques [1]. MPL is regarded as a chronic granulomatous disease and is commonly preceded or accompanied by an immunosuppressive state [1–3]. However, it is a benign, self-limiting condition with usually good prognosis [4].

The disease was first described by von Hansemann in 1901, and one year later Leonor Michaelis and Carl Gutmann published the morphological characteristics of the disease [5, 6].

MPL most commonly affects the urinary system, but has also been reported in the gastrointestinal tract, skin, genital tract, lung, brain, lymph node, adrenal gland, tonsil, conjunctiva, bone, abdominal wall, pancreas or retroperitoneum [1, 7]. Among urinary system locations, the urinary bladder is typically affected, especially in female patients [8]. However, the presence of lesions has also been noted in the kidney and urethra. In the second most common location, which is the gastrointestinal tract, signs of MPL are usually observed in rectum and colon [1, 7].

### Pathogenesis

The etiology and pathogenesis of MPL is still not fully understood, but many possible mechanisms have been suggested [7]. It is believed that impairment in bacteriocidal activity of macrophages is important in pathogenesis [1, 2]. Low cyclic guanosine monophosphate (cGMP) level and reduced  $\beta$ -glucuronidase activity have also been revealed [7]. They influence on the congregation of microtubules, which are essential for bacterial phagocytosis and lysosomal fusion. Therefore, incompletely digested microorganisms accumulate in lysosomes. Apart from the bacteria, there are also calcium and iron salts that sediment and form inclusions within cells [1, 7].

The condition is also associated with chronic diseases and immunosuppression [9]. In over 50% of cases, MPL occurs in patients with primary conditions associated with impairment of function of immune system, e.g. autoimmune disorders, myelodysplastic syndromes (MDS), various neoplasms, immunodeficiency states or treatment with immunomodulatory drugs, most commonly after transplantation [1, 5, 6]. There are case reports in which MPL is described in association with tuberculosis, sarcoidosis, allergy, cytotoxic chemotherapy, steroid use, alcohol abuse, poorly controlled diabetes, ulcerative colitis and malnutrition [1, 7]. Moreover, Michaelis-Gutmann bodies, typical local morphological feature of MPL, can be found in peripheral blood monocytes, which suggests a systemic problem underlying this condition [9]. Furthermore, many bacterial infections like *Escherichia coli* (80% of cases), *Klebsiella pneumoniae*, *Rhodococcus equi*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Aerobacter aerogenes*, *Mycobacterium bovis*, *Mycobacterium intracellulare*, *Corynebacterium sp.*, *Proteus sp.*, *Acinetobacter sp.*, *Streptococcus sp.* and *Enterococcus sp.* are involved in pathogenesis of malakoplakia [9, 10].

Coexistence of MPL with malignancies, including prostatic and colorectal adenocarcinoma, papillary urothelial carcinoma of the urinary bladder, chronic myeloid leukemia (CML) and extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT-lymphoma) of the urinary bladder had been also described in the literature [1, 11, 12]. Most cases of MPL in the kidney occur in graft recipients.

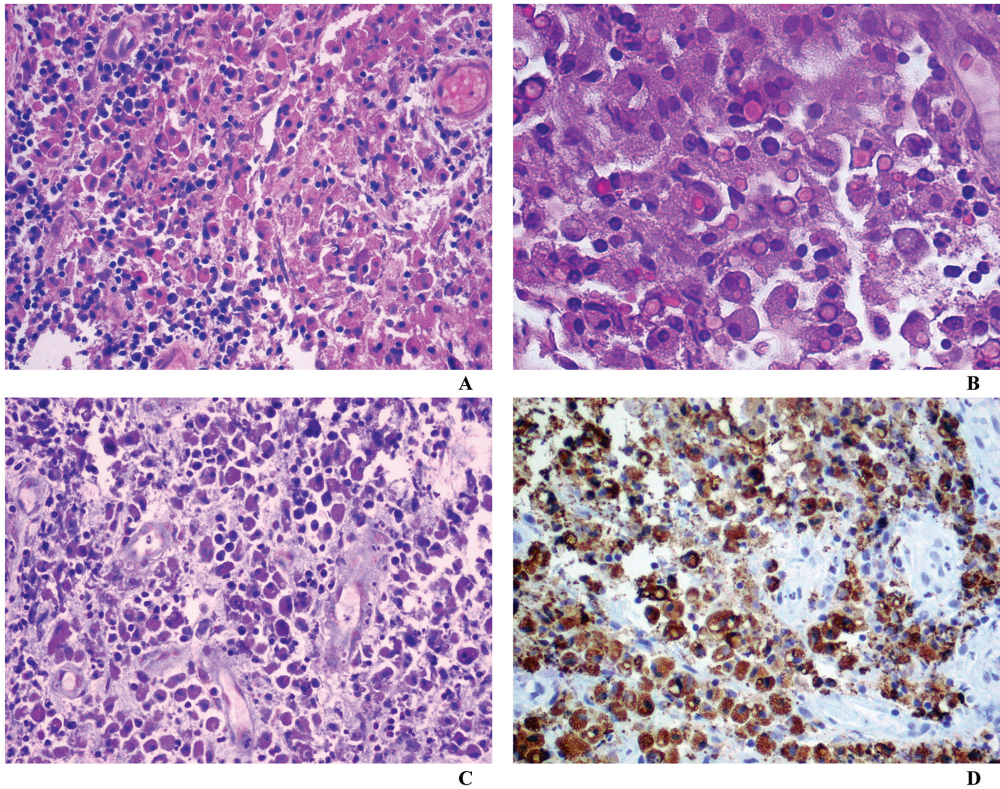
Only one case of MPL in a healthy young patient, without any other coexisting conditions has been reported [7].

### **Morphology**

Initially MPL usually presents as a soft, yellow to tan mucosal plaque and at the late stage as raised, grey to tan lesion of various sizes, with central depression and peripheral redness [1, 7]. It may also form a yellow, shaggy masses simulate malignancy or cystic lesions filled with blood clots and necrotic debris [13]. Its border may be poorly demarcated [14]. Gross appearance depends on location and in some organs may present slightly different features [1, 7].

Microscopically, the lesions are characterized by presence of histiocytes known as von Hanseman cells (histiocytes) (Fig. 1A–C) with granular, acidophilic, periodic acid-Schiff (PAS)-positive cytoplasm (Fig. 1C) and basophilic, periodic acid-Schiff, diastase-resistant, 1–10 µm inclusions, so-called Michaelis-Gutmann bodies (Fig. 1B). Inclusion bodies may be laminated or exhibit targetoid appearance and may be located also extracellularly within the stroma. Targetoid appearance is a consequence of the initial mineralization of the matrix cores and peripheral accumulation of phospholipids and microvesicles, that represent incompletely digested debris [1, 15]. Von Hanseman cells may occur in many forms or shapes — from fusiform to plump or polygonal with eccentric nuclei [14, 16]. They are usually placed without a pattern but may sometimes form fascicles [14]. Von Hanseman cells admixed with mononuclear cells, plasma cells, and neutrophils.

Immunofluorescence shows a positive reaction for IgA, IgG, IgM, polyvalent globulins and light chains within the von Hanseman cells [14]. Immunohistochemically, the cells are CD68 (Fig. 1D), CD163 and alpha-chymotrypsin positive [17]. Those findings indicated that von Hanseman cells are macrophages that underwent specific pathological changes. This can be also confirmed by the fact that von Hanseman cells may contain intact or partially digested bacteria, in form of rod-shape structures [14].



**Fig. 1A–D.** Rare, incidentally diagnosed urethral malakoplakia in a 63-year-old woman with stress urinary incontinence: A) Dense inflammatory infiltration composed mostly of von Hanseman cells, with B) many scattered Michaelis-Gutmann bodies. C) Periodic acid-Schiff- and D) CD68-positive reaction in von Hanseman cells (A and B: HE, objective magnification A — 20×; B — 40×; C: PAS, objective magnification 20×; D: immunohistochemical reaction with CD68, objective magnification 20×).

As mentioned before, apart from von Hanseman cells, variety of inflammatory cells as well as abundant fibrous background can be found in the microscopic picture of the disease [1, 10, 16]. The histological appearance of MPL differs in time. In the first phase many plasma cells infiltrate the stroma and the number of macrophages is limited. Congregates of glycolipids believed to be precursors of Michaelis-Gutmann bodies can also be distinguished at this period. After that, an increasing number of von Hanseman cells appears in the area. This is the most characteristic phase, when Michaelis-Gutmann bodies are most abundant and most easily distinguished. Finally, fibrous stroma begins dominating and there are less von Hanseman cells [18].

## Symptoms and complications

The reports of MPL in urinary system regard the lesions found in urinary bladder or kidneys. In urinary bladder, MPL may give clinical and laboratory symptoms of inflammation [12], like hesitancy, dysuria and increased frequency of urine output [19]. In some cases, it might mimic a neoplasm [12, 20]. Urinary bladder malakoplakia may even cause blockage in the flow of urine and contribute to renal failure [4]. There is a report of MPL after a renal transplant that affected both the bladder and the graft. It was treated with antibiotics and lowering doses of immunomodulatory drugs and this solution appeared to be successful [2]. It has been also reported that MPL of the urinary bladder can coexist with bronchial asthma. It is unclear if it is a coincidence, or if the same mechanisms can trigger both diseases [20]. In one pediatric case of a 9-year-old girl MPL of the urinary bladder was associated with xantogranulomatous cystitis and bladder perforation as the main complication [19]. Apart from mimicking a neoplasm, one must bear in mind that MPL may coexist with carcinoma [11].

In renal localization, patients present clinical signs of acute pyelonephritis and laboratory tests show strong signs of acute inflammation [3, 5, 13, 21]. MPL itself may form a tumor-like mass and therefore may mimic a neoplasm [3, 5, 13, 18, 21], however, it may also occur in a diffuse non-tumor like form [16]. Rarely MPL can present with abdominal pain [18] or lumbar tenderness with no general or laboratory symptoms and signs of inflammation [22]. In the former case MPL coexisted with both, urinary tract obstruction and MDS. There is a report of CML following malakoplakia [19], although there is no evidence that one condition led to the other, however literature suggests that similar conditions may coexist due to some unknown changes in function of the immune system.

Urethral MPL has a clinical course like bladder disease. While benign, it may sometimes have tendency to recur [8].

## Diagnosis

Histopathological examination under the light microscope is the basic diagnostic tool in case of MPL, used for confirmation of the clinical suspicion. The material may come from a biopsy, or surgical excision [20, 22]. Diagnosis depends on typical cellular pattern containing von Hansemann cells with demonstration of Michaelis-Gutmann bodies, which are pathognomonic, however are not necessary for the diagnosis [3]. In questionable cases, apart from hematoxylin and eosin staining, some additional histochemical methods may be useful, such as PAS as well as alizarin red, von Kossa stain, and Prussian blue stain, that visualize calcium or iron, being a component of bodies. Von Hansemann cells give positive reactions with immunohistochemical



markers, such as CD163 and CD68. Gram stain may show Gram-negative bacteria [3]. Fig. 1A–D.

In MPL affecting the urinary bladder and urethra, cystoscopy may be a helpful diagnostic tool [12]. Unfortunately, imaging techniques such as computed tomography, ultrasound and magnetic resonance imaging are not precise enough to distinguish MPL from neoplastic diseases or other inflammatory lesions. However, there is a single reported on contribution of an 18-fluoro-deoxyglucose positron emission tomography (FDG-PET) in diagnosis and follow-up of MPL [18].

Conditions that should be considered in differential clinical diagnosis of MPL of the urinary system are malignant and benign neoplasms and chronic inflammatory diseases. Depending on the location of MPL, they include among others: xantogranulomatous cystitis/ nephritis, chemotherapy-related cystitis, inflammatory pseudotumor, urothelial, squamous cell or renal cell carcinomas, lymphomas and Langerhans cell histiocytosis [1, 12, 13]. Histopathological examination of tissue samples taken from suspicious areas is pivotal to set the final diagnosis, because clinical presentation and gross appearance are not specific enough.

## Treatment

Treatment of MPL depends on the extent of disease and the co-morbidities of the patient [22]. There are no standardized treatment guidelines, although it is known that administration of quinolones has improved patient's survival [6]. Sulphonamides are similarly active against MPL [2]. Antibiotics that concentrate in macrophages (e.g. ciprofloxacin and trimethoprim-sulfamethoxazole) as well as penicillins and clofazimine are associated with a high cure rate [1, 22]. Those can be used long-term at low doses to prevent recurrence [20]. The optimal duration of antibiotic treatment is not clear [2].

Antibiotic therapy directed against Gram-negative bacteria in combination with surgery provides a better chance of cure [1, 22]. Surgical treatment may be necessary depending on the organ affected and is required in bladder MPL when obstruction of urine output threatens, or in extensive pelvic lesions involving the bowel [20].

A part of treatment strategy in patients being treated with immunosuppressive drugs is also minimization of the dose of those medications [2]. Data in the literature suggests that azathioprine plays a specific role in pathogenesis of malakoplakia. The contribution of azathioprine to the macrophage dysfunction seen in malakoplakia has been documented [9].

## Conclusions

Malakoplakia of the urinary system is a rare condition that usually coexists with other local or systemic diseases. The main factor that induces the development of typical lesions is thought to be a bacterial infection caused by Gram-negative pathogens, especially *Escherichia coli*. Since symptoms of the disease are not specific and depend on the location and extent of the disease, it is difficult to suspect MPL only based on clinical data. The histopathological examination of detected and surgically removed lesions is the most reliable diagnostic method. Surgery in combination with antibiotic treatment seems to be the best solution and is used to prevent the recurrence of the disease.

## Conflict of interest

None declared.

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