 IntroductIon
Malakoplakia is a rare chronic inflammatory reaction that usually affects the urinary tract in association with E. coli infection. The extravesical extension is usually rare and more aggressive. The term malakoplakia was coined by von Hansemann in 1903 and is derived from the Greek words malakos (soft) and plakos (plaque). A year before the publication of the paper of von Hansemann, Michaelis and Gutmann published similar results, and therefore, these two authors are associated with this disease, almost forgetting von Hansemann.

Malakoplakia, in the urinary bladder, is detected commonly as oval, yellowish plaques with central umbilication. Histologically, these plaques show numerous macrophages, called von Hansemann cells (MGB). The bodies have a concentric “birds-eye” or “owl-eye” (targetoid) appearance because of the development of a central hydroxy-apatite core. Almost 95% of the bodies are of organic material, the rest being iron, calcium, phosphorous, chloride, and sulphur. These structures, pathognomonic of malakoplakia, are positive for von Kossa stain (calcium), Perls’ stain (iron), and periodic acid-Schiff (PAS) stain. So far, Giemsa stain was not tested in these bodies.

Materials and Methods: Five suspected cases of malakoplakia that showed macrophages with inclusions called bodies of Michaelis-Gutmann (von Hansemann cells) in unstained urine sediment were processed with Papanicolaou, Giemsa, and periodic acid-Schiff (PAS) stains. The other patient had the characteristics cells in a routine urinalysis. Results: Papanicolaou stain revealed intracytoplasmic eosinophilic or basophilic bodies, single or multiple in macrophages. Such bodies were stained deep red with PAS technique. The bodies were stained with a faint basophilic coloration, sometimes with a central core. Bladder biopsies established the definitive diagnosis, showing bodies within and outside macrophages, with a concentric “birds-eye” or “owl-eye” (targetoid) appearance. Conclusions: Finding of von Hansemann cells in fresh urine sediment of patients with cystitis and a history of resistance to antibiotic scan leads to the diagnosis of malakoplakia. A correct diagnosis is important because the spread to ureters with bilateral stenosis and obstruction can lead to kidney failure.
The disease was also reported, to a lesser extent, in retroperitoneum, gastrointestinal tract, lung, lymphatic nodules, tongue, etc.[7,8] Malakoplakia is also associated with immunodeficiency states and hematopoietic malignancies.[9] The association of malakoplakia with immunosuppression comes from the finding of patients with a history of prolonged treatment with chemotherapeutic or immunosuppressive agents.

**Materials and Methods**

We present 5 cases of malakoplakia, detected in fresh urine sediments. The smears were stained with Papanicolaou, Giemsa, and PAS stains. In 3 patients, bladder biopsy samples were taken.

**Ethics statement**

The patients have given their informed consent for participation in the research study.

This study was approved by the Institutional Review Board at the Faculty of Biochemistry, Buenos Aires University. (Chairperson: Dr Luis Palaoro - N° 09032016-26 -Approval March 9th, 2016).

The researchers respect the Declaration of Helsinki in its latest version (World Medical Association Declaration of Helsinki 2013).

**Results**

The first patient, a woman 65-year-old, had a history of repeated cystitis with culture positive for *E. coli*, Klebsiella, and Proteus who developed resistance to the antibiotics used. Fresh urine sediment (undyed) showed abundant macrophages, epithelial squamous cells, and abundant bacilli. Macrophages had cytoplasmic inclusions of round, oval, and elongated bodies. Sometimes the bodies had irregular forms, similar to worms (“wormy” shapes) [Figure 1]. These inclusions are similar to those that Koss[10] published in urine samples stained with the Papanicolaou method in cases of Malakoplakia. Papanicolaou, Giemsa, and PAS stains were carried out in the urine samples. Papanicolaou stain revealed intracytoplasmic eosinophilic bodies, sometimes basophils, single or multiple in macrophages. Such bodies were stained deep red with PAS technique. Giemsa stain showed these bodies with a faint basophilic coloration, with net limits, and sometimes with a central core. Bladder biopsy confirmed the presumptive diagnosis [Figure 2]. The other 4 patients (60, 55, 52, and 32 years old) were studied in the same way as the first, confirming the disease in all cases. None of the cases presented had a history of immunosuppression. The youngest patient had no history of cystitis, but malakoplakia was suspected by observation of macrophages with inclusions in the urinary sediment.

**Discussion**

Malakoplakia of the bladder is a rare disease. Probably, the low number of reported cases are because there is no simple primary diagnosis but is detected in patients with histories of antibiotic resistance, in the biopsies taken from their typical lesions of the bladder.

We studied, for several years, the correlation between cells of the urinary sediments in fresh, colored with Papanicolaou/Giemsa and their corresponding bladder biopsies and were able to demonstrate the usefulness of the observation in fresh as primary diagnosis of various diseases.[11]

Taking advantage of this knowledge, we could detect von Hansemann cells (pathognomonic of malakoplakia) in fresh urine sediments, which were confirmed by various methods. Fresh urinary cytology in Malakoplakia suggests

**Figure 1:** von Hansemann cells in fresh urine sediment. (a): Abundant von Hansemann cells in fresh urine sediment (*Fresh urine sediment* × 400). (b): von Hansemann cell with a big M-G body in fresh urine sediment (*Fresh urine sediment* × 400 × x)

**Figure 2:** Stained von Hansemann cells in urine sediment and in biopsy. (a): Big MGD into a macrophage. (b): Macrophage with MGD showing strongly stained edge and central core. (c): PAS stain in a von Hansemann cell. (d): Biopsy of malakoplakia of the bladder. A round Michaelis-Gutmann body (arrow) is observed in foam cells. (a: Papanicolaou stain 400 ×; b: Giemsa stain 400 ×; c: PAS stain 400 ×; d: Hematoxylin and eosin 400 ×)
this pathology, but confirmation should be made with the described colorations, especially that of Giemsa, which shows the central core.

Malakoplakia is probably the result of an acquired defect in macrophage function causing impairment of bactericidal activity. It is now believed that the disease may be related to abnormal microtubular assembly. Microtubules are responsible for normal invagination and degranulation of lysosomes, which are important in the destruction of bacteria in phagocytosis. cGMP stimulates while cAMP inhibits the assembly of microtubules. However, lysosomal function also depends on the enzyme β-glucuronidase and the redox state of the cell.[12] Alteration in the redox state, with the reduction in the ratio of cGMP/cAMP could be the triggers in malakoplakia.

Supporting this theory, monocytes with intracytoplasmic lysosomal inclusions, abnormal release of the enzyme β-glucuronidase, low intracellular levels of cyclic GMP, and depressed bactericidal activity have been reported in retroperitoneal malakoplakia.[13]

Therefore, treatments with bethanechol, agonist cholinergic drug, aim to increase the concentration of intracellular cGMPc. Some antimicrobials, capable of intracellular penetration such as trimethoprim-sulfamethoxazole were used with some success. In addition, there were cases of malakoplakia successfully treated by ciprofloxacin.[14]

So far, as we know, it is the first report of the detection of MGB in fresh urine samples. The biopsies showed MGB often exhibiting a targetoid appearance with a central core. The targetoid appearance may not be apparent if the plane of section does not pass through the dense central core. The central core could be observed in some cells of fresh urine sediment. Moreover, Giemsa stain, performed for the first time in the urine cells from malakoplakia, showed in some cases the characteristic central core of MGB. These bodies must be differentiated from other inclusion bodies: Melamed-Wolinska bodies (MWB)[15] and eosinophilic inclusions of urothelial necrotic cells (EIUC). MWB were reported in urothelial cells of patients with urothelial carcinoma, mainly. Although they have a certain morphological similarity with MGB, their origin is different because the latter are observed in macrophages of patients with a history of resistance to antibiotics. The Giemsa stain allows to differentiate between MWB and MGB because the latter show the typical central core. EIUC are observed especially in viral infections, as small eosinophilic bodies of varying size, inside necrotic urothelial cells.[16] [Table 1].

By electron microscopy, the inclusions have crystalline structure with a central dense body, an intermediate halo, and a peripheral laminated ring. Moreover, there is material that reminds bacterial debris in the center of the inclusion.[17] In four of our patients, their urines contained numerous bacilli, according to their histories of resistance to antibiotics. Malakoplakia is difficult to diagnose from the symptoms alone, although in retrospect most patients are found to have a urinary tract infection. The bladder involvement is associated with irritative urinary symptoms and hematuria; a correct diagnosis is important because the spread to ureters with bilateral stenosis and obstruction can trigger kidney failure.[18]

**Table 1: Differential diagnosis between inclusion bodies in urine cells**

| Inclusion body | Cell        | Background              | Giemsa stain         |
|----------------|-------------|-------------------------|----------------------|
| MGB            | Macrophage  | Antibiotic resistance   | Central core in the  |
|                | Urothelial  | Urothelial carcinoma    | inclusion body       |
| MWB            | Urothelial  | Virus infection         | Negative             |
| EIUC           | Urothelial  |                         | Negative             |

MGB=Michaelis-Gutmann bodies, MWB=Melamed-Wolinska bodies, EIUC=Eosinophilic inclusions in urothelial cells

**Conclusion**

Finding of von Hansemann cells in fresh urine sediment of patients with cystitis and a history of resistance to antibiotics can lead to the diagnosis of malakoplakia. Giemsa stain can show in some cases the characteristic central core of Michaelis-Gutmann bodies. So far, as we know, this paper is the first report of the presence of these cells in urine undyed and the value in diagnosing malakoplakia.

The dissemination of these results could help to detect more cases in patients with cystitis and history of antibiotic resistance, which could then be treated with other drugs, avoiding future complications such as kidney failure.

**Declaration of patient consent**

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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**Conflicts of interest**

There are no conflicts of interest.

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