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LETTER TO EDITOR

Malakoplakia: A rare pathology?

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To the Editor

More than a century has passed since 1903, when *Professor David von Hansemann* described the presence of macrophages deposited in the form of a soft plaque and coined the term of Greek origin, *malakoplakia* (MLP). A year later, the morphology of this cell with its own name was completed by the contribution of *Michaelis* and *Gutmann*, who pointed out the inclusions in its cytoplasm (1).
Since then, these aggregates of soft plaques have been found in various tissues such as the thyroid gland, brain, adrenal gland, lung, gastrointestinal tract (2), and especially the bladder. In all these cases, the definitive diagnosis is the presence of macrophage deposits in the corresponding biopsies, known as Von Hansemann cells, with inclusions in the form of a bird's eye (*Michaelis-Gutmann bodies*) (3).
The origin of this pathology is still unclear. In 90% of patients it is an *E. coli* infection, but it could also be caused by other bacteria (4). An intrinsic failure of macrophages caused by several factors has also been proposed: a deficiency of cyclic GMC, which is necessary for the formation of clathrin-coated vesicles; another possibility is a low synthesis of *tumor necrosis factor* (TNF) and a third theory is that beta-glucuronidase is not fully effective (5). Perhaps there is a combination of these three deficiencies that results in the cell having poor bactericidal function and that the noxious agent remains in the *Michaelis-Gutmann bodies*. This could explain why there are patients who have recurring urinary tract infections. The bacteria are not killed and return after some time and are even resistant to the same antibacterial treatment (6, 7).
There are many reports of single or a few cases of MLP in different organs, with the bladder being perhaps the most common. Years after our first publication, we trained many biochemistry students and interns and repeatedly received smears in which we observed von Hansemann cells in fresh urine sediments (8). Therefore, we decided to investigate the actual prevalence of this disease in our hospital and whether it is as rare as reported or whether it is a misinterpretation of the cells in the sediment.

MATERIALS AND METHODS

Samples

From January to October 2023, we detected 45 fresh urine sediments suspected of containing Von Hansemann cells in our cytology service at the *Clinical Hospital "José de San Martín"*, Buenos Aires, Argentina. They all came from hospitalized and outpatients. These were selected to be stained with *Giemsa* and *Papanicolau*, as previously reported.

Staining techniques

Giemsa

The smear was air-dried on a microscope slide. It was then soaked in methanol for 5 minutes and then in 1/10 diluted Giemsa for 15 minutes and washed off with distilled water.

Papanicolaou

The study was carried out according to *Carson* and *Hladik*, 2009 (9).

Microscopic visualization

The diagnosis was made by two cytologists examining the same sample. First, the fresh urine sediment was centrifuged at 2000 rpm and the pellet was isolated and viewed on 6 slides, two for direct observation and the others for appropriate staining.

Results

Over a period of 10 months, we observed 45 samples in fresh urine sediments suspected of containing *von Hansemann* cells. These patients had symptoms of urinary tract infection or were hospitalised for follow-up.
The patients were 19 men and 26 women, with an average age of 49 years and a range of 5 to 85 years (Figure 1).
The smears stained with *Giemsa* or *Papanicolaou* were examined by two cytologists. 27 of 45 had von Hansemann cells in one or both staining techniques (Figure 2).

Figure 1.
Distribution of patients by gender.

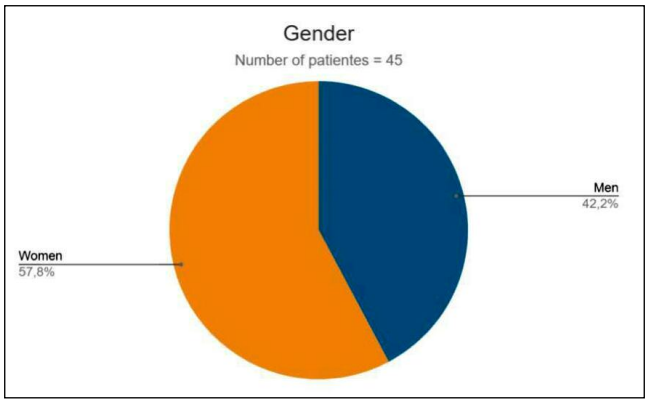


Figure 2.
After suspicious von Hansemann cells were detected in the fresh smear, 45 urine samples were selected for staining, and in 27 of them (60%) these particular cells were confirmed by Giemsa or/and Papanicolaou.

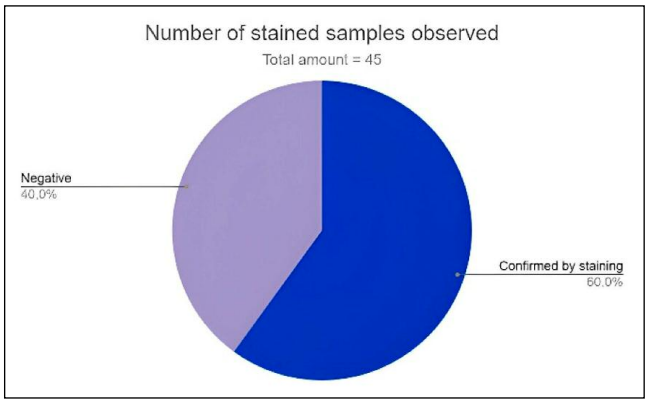
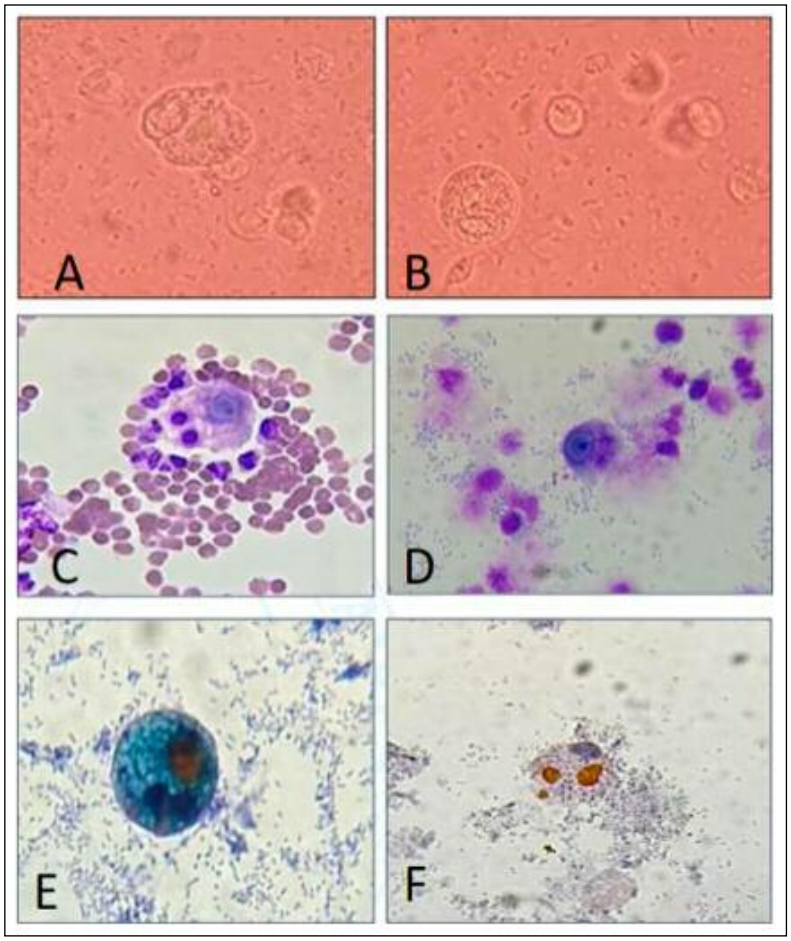


Figure 3.
A and B show the suspect cells, macrophages with birefringent inclusions (direct observation, 400x, zoom); Four different samples confirming the presence of von Hansemann cells in C and D (Giemsa, 400x, zoom) and E and F (Papanicolaou, 400x, zoom).



These cells can be identified as macrophages with birefringent inclusions in their cytoplasm (Figures 3A, B), which in most cases may be round. On staining, these inclusions are recognised as pale vesicles in *Giemsa*, similar to biopsies, in the form of a "*bird's eye*" or "*targettoid*" (Figures 3C, D) and as a red spot in *Papanicolaou* (Figures 3E, F). It could be a single or multiple inclusions.

Discussion

The term malakoplakia is not well known among physicians, not even among biochemists. Pathologic urine can be very challenging for those who are not cytologists, as many different cells can indicate numerous and complex diseases, such as viral and bacterial infections, lithiasis, renal abnormalities, and of course bladder cancer. This is the main reason why it is important to stain each sample and perform a cytological analysis, althoughstaining these smears is not always possible in many emergency laboratories.
In 2019, our group published a report of 6 cases confirming the correlation between the biopsy and the presence of Hansemann cells in fresh urine stained with *Giemsa* and *Papanicolaou*. Since then, we have received many consultations because these cells were observed in several hospitals by our students, and that was the reason why we thought that it was not a rare pathology.
This study shows that in 10 months we found several patients with pathologic urine

that had suspicious cells, which we could confirm after staining that they were *von Hansemann* cells. The presence of 27 randomly selected patients may indicate that this disease is more common than reported. The other 18 patients who were negative did not show the cells in the *Giemsa* or *Papanicolaou* test or the smear was insufficient. It is thought this finding is more common in women, causing recurrent urinary tract infections, possibly due to the *Michaelis-Gutmann* corpuscles carrying the resistant bacteria remaining in the pathognomonic cells, but we had almost 40% males and even three infants (two of 5 and one of 7 years), although the staining was negative.

Vesical malacoplakia is the most commonly publicised form of the disease, but it has been found in many different organs. This could indicate a phagocytosis deficit in all macrophages, but this is not yet entirely clear, and two main mechanisms have been proposed: a deficiency of cGMP, which contributes to the formation of clathrin-coated vesicles or an insufficient amount or inefficient activity of beta-glucuronidase, an intracellular enzyme that is crucial for the clearance of microorganisms.

Either or both malfunctions lead to poor bactericidal activity, and this is why vitamin C and betanechol are important as treatment (both increase cGMP levels) and cell-penetrating antibiotics are necessary (10-12). The soft plates diagnosed in the colon (13), brain (14), lung (15, 16), thyroid (17), kidney (18), skin (19, 20) and cervix (21), although most of them are found at necropsy, may indicate that the disease is silent until a symptom such as urine infection occurs. During our research on this topic, we came across a genetic disorder that is associated with a defect in the same enzyme, beta-glucuronidase. This is mucopolysaccharidosis type VII or Sly syndrome, and among the symptoms reported we find recurrent ear and respiratory infections (22). This hereditary alteration is also described as rare (ultra-rare), but more than 30 mutations have been identified in the gene, affecting a variety of phenotypes: indeterminate, attenuated and severe (23). We propose the theory that malacoplakia may be an unknown phenotype of Sly syndrome or mucopolysaccharidosis VII.

Conclusions

We found 27 cases of malakoplakia in a 10-month period, which could mean that this disease is more common than reported. Confirmation was possible by staining the fresh urine sediments with *Giemsa* and *Papanicolaou*, which allowed us to observe the *von Hansemann* cells with the *Michaelis-Gutmann* bodies. The etiology of this pathology is not entirely clear, but it shares the deficiency of the enzyme beta-glucuronidase with Sly syndrome or mucopolysaccharidosis VII, and we propose that malakoplakia may be an undetermined phenotype of this genetic disorder.

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Declarations

Ethical approval and consent for participate: *Not applicable.*

Consent for publication: *Not applicable.*

Availability of data and material: *The datasets used and analyzed during the current study are available upon reasonable request from the corresponding author.*

Competing interests: *The authors declare that they have no competing interests.*

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