Malakoplakia as a cause of severe hypercalcemia through ectopic 25-hydroxyvitamin D3 1-alpha-hydroxylase expression

A case report

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1. Introduction

Malakoplakia is a rare disease characterized by the presence of nongranulomatous macrophage infiltration located in the urinary tract in most cases,\textsuperscript{[1,2]} although localizations outside the urinary tract, especially in the gastrointestinal system, have been described.\textsuperscript{[21]} It primarily affects women over 40 years old.\textsuperscript{[3]} Malakoplakia is characterized by an infiltration of macrophages with a granular eosinophilic cytoplasm (von Hansemann cells) containing Michaelis–Gutmann bodies.\textsuperscript{[1]} The clinical manifestations are usually direct consequences of anatomical and functional alterations of the affected organ and may be associated with signs of general inflammation, such as fever or weight loss. For instance, patients with renal parenchymal malakoplakia commonly present with fever, loin pain and enlarged kidneys with inconstant renal dysfunction.\textsuperscript{[4–6]} We report here\textsuperscript{[7]} a new systemic manifestation of malakoplakia. In this patient, malakoplakia was indeed responsible for severe hypercalcemia through ectopic expression of 25-hydroxyvitamin D3 1-alpha-hydroxylase in the von Hansemann cells.

2. Case report

A 65-year-old woman under tramadol was admitted in our institution because of fever and confusion after a 10 days course of ceftriaxone for an Escherichia coli-induced pyelonephritis. She was diagnosed with an acute renal injury, which had favored tramadol adverse effects since confusion receded after tramadol withdrawal. Regarding the acute renal injury, serum creatinine (Scr) was 182 μmol/L (eGFR\textsubscript{CKD-EPI} 25 mL/min/1.73 m\textsuperscript{2}), the urinary protein-to-creatinine ratio was 0.43 g/mmol (with a profile suggesting nonglomerular proteinuria), and urine microscopy revealed leukocyturia with Enterococcus faecalis. Imaging
studies revealed medullary sponge kidneys without an obstructive cause for renal failure and bilateral nephromegaly (right kidney 165 mm and left kidney 155 mm). A renal biopsy was performed, revealing interstitial nephritis composed of macrophages with an abundant eosinophilic cytoplasm (von Hansemann cells) and Michaelis–Gutmann bodies in keeping with renal malakoplakia (Fig. 1A). The patient was given prolonged antibiotic therapy with cotrimoxazole. In addition, this patient with chronic kidney disease had 25-OH vitamin D insufficiency (56 nmol/L), for which she was prescribed oral cholecalciferol (100,000 IU per month) in spite of normal serum calcium (2.21 mmol/L) and parathyroid hormone (PTH) levels (38 ng/L). At the one-month follow-up after renal biopsy, her renal function had improved (Scr 137 μmol/L), as well as her 25-OH vitamin D serum levels and calcemia (67 nmol/L and 2.49 mmol/L respectively).

Two months later, she was admitted to our unit for dehydration and hypercalcemia (3.64 mmol/L) with normal 25-OH vitamin D (113.1 nmol/L) and PTH (15 ng/L) levels and high 1,25-dihydroxyvitamin D levels (336 pmol/L), suggesting ectopic 25-hydroxyvitamin D₃ 1-alpha-hydroxylase activity. Extensive investigations, comprising ¹⁸ fluorodeoxyglucose positron emission tomography, bone marrow biopsy, thoracic computed tomography scanning, sputum examination for tuberculosis and a second renal biopsy, did not reveal a superimposed granulomatous disease. We suspected the malakoplakia cells to be responsible for the abnormal 25-hydroxyvitamin D₃ 1-alpha-hydroxylase activity, and we performed immunohistochemistry for 25-hydroxyvitamin D₃ 1-alpha-hydroxylase in slides from the renal biopsies (Fig. 1B). The test revealed ectopic expression of this enzyme by the infiltrating macrophages, whereas the infiltrating cells of a nonhypercalcemic sarcoidosis patient did not, although the tubular cells of this same patient did (data not shown). Cholecalciferol was stopped, the patient was rehydrated with intravenous physiological saline, and prednisone was initiated to decrease the enzyme activity. She was discharged with normal serum calcium (2.25 mmol/L). Six months later, serum calcium was 2.37 mmol/L, 25-hydroxyvitamin D was 99 nmol/L, 1,25-dihydroxyvitamin D was 100 pmol/L, and PTH was 147 ng/L (Fig. 2). Her renal function had stabilized at 202 μmol/L (eGFR₉₀₋₁₉₉, eGFR₁₉₉₋₂₂₀).
Enterococcus faecalis co-infection. malakoplakia is a urinary bladder manifestation of sarcoidosis[8], which was con- sidered to be secondary to chronic local infections, favoring the decreased bactericidal activity displayed by the patients’ macrophages[11,12] and accounting for the higher frequency of this disease in immunocompromised patients[13–15].

Management of malakoplakia consists of the administration of intracellular penetrating antibiotics, such as quinolones and sulfamethoxazole-trimethoprim, associated with surgical resection or drainage[16], as well as withdrawal/reduction of immunosuppressive drugs when possible[17]. In the present case, cotrimoxazole was chosen over ciprofloxacin because of the Enterococcus faecalis co-infection.

Clinical manifestations of malakoplakia are usually related to local infiltration, which induces pseudotumoral lesions, alters the architecture and function of the affected organ and may cause general symptoms such as asthenia and fever. In the present case, malakoplakia was also responsible for severe hypercalcemia through a 25-hydroxyvitamin D$_3$ 1-alpha-hydroxylase enzymatic activity unmasked by vitamin D supplementation. We decided to give her oral vitamin D supplementation although she had insufficient and not deficiency because of the expected benefit in patients with chronic kidney disease[18] and the usual safety of this treatment. However, she unexpectedly developed severe hypercalcemia with low parathyroid hormone and requires careful monitoring of serum calcium. Conversely, it can be assumed that hypercalcemia with low parathyroid hormone and high 1,25-dihydroxyvitamin D may reveal malakoplakia.

3. Discussion
Malakoplakia is rare condition mostly affecting women over 40 years old. In most cases, it is localized in the urinary tract. It is identified by a pathological examination revealing macrophages with Michaelis–Gutmann bodies and Schiff-positive inclusions, which also stain for calcium and iron,[11] corresponding to phagolysosomes containing residual bacteria remnants and, more especially, E. coli.[14–16] Indeed, malakoplakia is thought to be secondary to chronic local infections, favoring the decreased bactericidal activity displayed by the patients’ macrophages[11,12] and accounting for the higher frequency of this disease in immunocompromised patients.[13–15]

In conclusion, this case demonstrates that malakoplakia cells may exhibit ectopic 25-hydroxyvitamin D$_3$ 1-alpha-hydroxylase activity and cause severe hypercalcemia upon vitamin D supplementation. Therefore, such supplementation should not be given in malakoplakia patients without an actual deficiency and requires careful monitoring of serum calcium. Conversely, it can be assumed that hypercalcemia with low parathyroid hormone and high 1,25-dihydroxyvitamin D may reveal malakoplakia.

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References
[1] Lasco MA, Fogo AB, Najafian B, et al. AJKD atlas of renal pathology: malakoplakia. Am J Kidney Dis 2016;68:27–8.
[2] Yousef GM, Naghibi B, Hamodat MM. Malakoplakia outside the urinary tract. Arch Pathol Lab Med 2007;131:297–300.
[3] McClure J, Malakoplakia. J Pathol 1983;140:275–330.
[4] Tam VKK, Kung WH, Li R, et al. Renal parenchymal malakoplakia: a rare cause of ARF with a review of recent literature. Am J Kidney Dis 2003;41:E13–17.
[5] Diwakar R, Else J, Wong V, et al. Enlarged kidneys and acute renal failure—why is a renal biopsy necessary for diagnosis and treatment? Nephrol Dial Transplant 2008;23:401–3.
[6] Alibitar S, Genin R, Fen-Chong M, et al. The febrile patient presenting with acute renal failure and enlarged kidneys—another mode of presentation of malakoplakia. Nephrol Dial Transplant 1997;12:1724–6.
[7] Gagner JJ, Kienele G, Altman DG, et al. The CARE guidelines: consensus-based clinical case reporting guideline development. Glob Adv Health Med 2013;2:38–43.
[8] Joh K, Azawaa S, Furusato M, et al. Antigenicities of enteropathogenic Escherichia coli, lysozyme, and alpha-1-antichymotryptsin on macrophages of genitourinary malakoplakia. Pathol Int 1995;45:215–26.
[9] McClurg FY, D’Agostino AN, Marin JH, et al. Ultrastructural demonstration of intracellular bacteria in three cases of malakoplakia of the bladder. Am J Clin Pathol 1973;60:780–8.
[10] Lewin KJ, Fair WR, Steigbigel RT, et al. Clinical and laboratory studies into the pathogenesis of malacoplakia. J Clin Pathol 1976;29:354–63.
[11] Abdou NI, NaPombejara C, Sagawa A, et al. Malakoplakia: evidence for monocyte lysosomal abnormality correctable by cholinergic agonist in vitro and in vivo. N Engl J Med 1977;297:1413–9.
[12] van Crevel R, Caris J, van der Ven AJ, et al. Functional and morphological monocyte abnormalities in a patient with malakoplakia. Am J Med 1998;105:74–7.
[13] Altwegg M, Hinrikson HP. Shigella boydii as cause of malacoplakia in a human immunodeficiency virus-infected patient. Clin Infect Dis 1999;29:1602.
[14] Archer SR, Abramowsky CR, Kobrynski L, et al. Malakoplakia and primary immunodeficiency. J Pediatr 2014;165:1053–6.
[15] Hill GS, Droz D, Nochy D. The woman who loved well but not too wisely, or the vicissitudes of immunosuppression. Am J Kidney Dis 2001;37:1324–9.
[16] van der Voort HJ, ten Velden JA, Wassenaar RP, et al. Malacoplakia. Two case reports and a comparison of treatment modalities based on a literature review. Arch Intern Med 1996;156:577–83.
[17] Biggar WD, Crawford L, Cardella C, et al. Malakoplakia and immunosuppressive therapy. Reversal of clinical and leukocyte abnormalities after withdrawal of prednisone and azathioprine. Am J Pathol 1985;119:5–11.
[18] Westerberg P-A, Sterner G, Ljunggren O, et al. High doses of cholecalciferol alleviate the progression of hyperparathyroidism in patients with CKD stages 3–4: results of a 12-week double-blind, randomized, controlled study. Nephrol Dial Transplant 2017;33:466–71.
[19] Baughman RP, Lower EE. Goldi5ocks, vitamin D and sarcoidosis. Arthritis Res Ther 2014;16:111.
[20] Redewill FH. Malakoplakia of the urinary bladder and generalized sarcoidosis, striking similarity of their pathology, etiology, gross appearance and methods of treatment. J Urol 1943;49:401–7.