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BRIEF REPORT

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Malakoplakia of the caecum in a kidney-transplant recipient: presentation as acute tumoral perforation and fatal outcome

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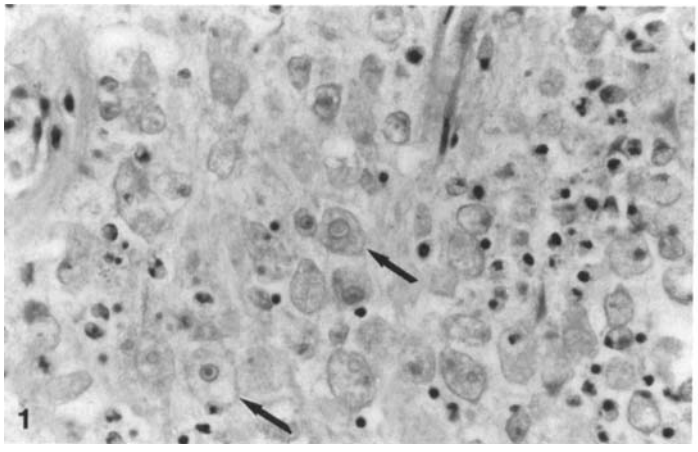
Abstract Malakoplakia is a rare pseudotumoral inflammatory disease known to affect immunocompromised subjects, mainly with a history of recurrent *Escherichia coli* infection. The urinary tract is the most frequent site of the disease, although all organs can be involved. In the present article, we report a case of malakoplakia of the caecum, that developed in a 52-year-old man, who had received a kidney transplant 9 years before and had a history of recurrent *E. coli* urinary tract infections. Malakoplakia presented as acute intestinal perforation, and, despite aggressive surgical and medical management, disease progressed toward a fatal outcome due to sepsis and multiple organ failure 9 months later. A defect in the macrophagic activity was demonstrated.

Key words Malakoplakia · Kidney transplantation · Immunosuppression · *Escherichia coli* infection · Macrophage dysfunction

Introduction

Malakoplakia is a rare chronic inflammatory disorder involving mostly the urinary tract and characterized histologically by an intracellular accumulation of bacterial products inside the macrophages, giving the pathognomonic appearance of Michaelis-Gutman bodies [19]. Its etiology is unclear, but a dysfunction of bacterial clearance by leukocytes is probably involved. The bactericidal function of macrophages or neutrophils has been found to be impaired, although not in a consistently similar manner [1, 2, 10, 16]. This dysfunction could occur as a result of decreased intracellular levels of cyclic guanosine monophosphate [1]. There is a well-recognized association between the disease and states of immunosuppression, as observed in lymphoma and other malignancies, HIV infection, therapy for autoimmune diseases, or among transplant patients [19]. A few cases have been reported in regard to renal transplant recipients [2, 6, 9, 10, 12, 14–16] and one case in connection with a liver transplant recipient [15]. Chronic *Escherichia coli* infections are involved in the pathogenesis in a majority



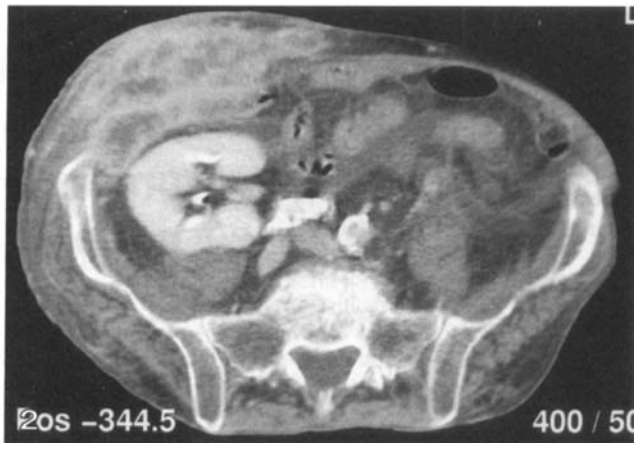


Fig. 1 Histological aspect of the intra-abdominal inflammatory pseudotumoral mass, demonstrating the presence of histiocytes containing typical target-like inclusions known as Michaelis-Gutman bodies (*arrows*) and pathognomonic for malakoplakia (HE × 100)

Fig. 2 Pelvic CT scan demonstrating a massive infiltration of the right lower quadrant abdominal wall by malakoplakia. The underlying kidney graft seems unaffected by the pseudotumoral inflammatory process

of patients [7, 19]. In the present article, we report a rare case of caecal malakoplakia in a renal transplant recipient who presented with acute local peritonitis, with clinical features highly evocative of perforated colon carcinoma.

Case report

In February 1987, a 52-year-old man received a cadaveric kidney transplant in another institution for end-stage renal failure due to autosomal dominant polycystic kidney disease with liver involvement. He suffered no rejection or other graft complication. His serum creatinine levels remained stable at 0.8–1.0 mg/dl. However, he had a long history of recurring *Escherichia coli* infection, with two episodes of urinary tract infection and three episodes of septicemia prior to transplantation, and five additional septicemic relapses since transplantation. By means of needle aspiration, infected liver cysts were found to be the source of *E. coli*. All infectious episodes were treated with long-term antibiotherapy.

In late November 1996, he started to develop a swelling in the right iliac fossa. The swelling was associated with dull pain and rapidly increased in size, which led to a suspicion of colonic tumor. A colonoscopy was proposed, to which the patient refused to submit himself. At that time, he was under immunosuppressive therapy consisting of cyclosporin A (200 mg/day), azathioprine (100 mg/day), and prednisone (7.5 mg/day).

He was admitted to the emergency ward in the same institution on December 31 for sudden exacerbation of pain, fever, alteration of physical condition, and 3 kg weight loss. Abdominal examination revealed the presence of a large, hot, tender mass in the right hemiabdomen. An abdominal CT scan showed a large tumor of the caecum, with local invasion and signs of perforation. The kidney graft in the right iliac fossa was uninvolved in the tumoral mass. A diagnosis of perforated cancer of the caecum was suggested, and operation was decided upon. Laparotomy confirmed the presence of a caecal tumoral mass with localized fibrinous peritonitis, and a right hemicolectomy with immediate ileocolostomy was performed.

Macroscopically, there was a large ulcerated tumor infiltrating all layers of the colonic wall. Histologically, however, there was no carcinoma, but a proliferation of numerous inflammatory cells within the ulcerated zones. Cellular composition of the infiltrate included plasmocytes, eosinophilic polynuclear cells, a few lymphocytes, but mostly histiocytes (CD 68-positive), frequently containing intracytoplasmic inclusions with a "target" aspect (Fig. 1). Special stainings were done to better characterize these inclusions, which were PAS-positive and von Kossa-positive. These inclusions were recognized as Michaelis-Gutman bodies, and a diagnosis of malakoplakia was established. However, no treatment specific to malakoplakia was introduced.

After discharge on postoperative day 10, a persisting inflammatory syndrome with low-grade fever, slow alteration of physical condition, and continuing weight loss marked the evolution.

This eventually led to readmission at a second hospital on April 6, 1997 for a relapse of the abdominal mass, exulcerative in the abdominal wall. Surgical drainage of the abcess was performed, and *E. coli* was isolated from the wound. A CT scan showed a recurrence of the intra-abdominal mass, and the patient underwent a second laparotomy 2 days later. Massive recurrence of the inflammatory disease involving the ileum, peritoneal cavity, and abdominal wall was confirmed. Extensive ileal resection was performed with immediate ileocolonic anastomosis and local resection of the abdominal wall. Histologic examination confirmed the diagnosis of malakoplakia involving the ileum and abdominal wall. The patient was referred to our hospital for follow-up a few days later.

The postoperative course after the second laparotomy was slowly favorable. Azathioprine therapy was discontinued, prednisone was tapered, cyclosporin A doses were reduced, and a treatment of ciprofloxacin (2 × 500 mg/day) and betanechol chloride (2 × 10 mg/day initial dose, with gradual increase) was started. A CT scan performed 3 weeks after surgery showed persistent infiltration of the abdominal wall but no intra-abdominal recurrence, and the patient was discharged 6 weeks later.

He was followed on a regular basis at our outpatient clinic and showed persistence of a hard, 10 × 3 cm subcutaneous infiltration in the surgical wound area. A second relapse occured 1 month later, and he was readmitted on June 19 with extensive cutaneous infiltration and a fistula with *E. coli*-infected discharge. A CT scan

Table 1 Antibacterial activity of circulating polymorphonuclear neutrophils (*NBT* nitroblue tetrazolium)

Analysis	Patient		Controls ($n = 15$)
	June 26	July 10	
NBT dye reduction[a,b]			
Spontaneous	12%	13%	6–20%
Stimulated	61%	56%	> 80%
Phagocytosis[b]	96%	97%	> 80%

[a] Whole heparinized blood was incubated with NBT dye solution at 37 °C with (stimulated reduction) or without (spontaneous reduction) *Staphylococcus aureus*. After 30 minutes of incubation, smears were made and stained with aceto-orcein

[b] Counts were performed by light microscopy

showed a recurrence of the mass in the abdominal wall, extending into the abdominal cavity (Fig. 2), with ascites. The antibacterial activity of circulating blood polymorphonuclear neutrophils was assessed in vitro by the standard nitroblue tetrazolium (NBT) dye reduction test [11, 13]. The results indicated a significant decrease of *Staphylococcus aureus*-stimulated NBT reduction. In contrast, phagocytic activity was normal (Table 1).

Intravenous antibiotics were started (ciprofloxacin, ceftriaxone) and cyclosporin A was stopped altogether. This therapy procured a partial clinical response, with markedly decreased – but persisting – local inflammatory signs, and on CT scan, a disappearance of the ascites and shrinkage of the abdominal wall infiltration. The patient was discharged again 1 month later and declined ambulatory care at our outpatient clinic.

He was readmitted for the last time on September 19, in an alarming physical condition, severely cachexic, with extended inflammatory infiltration of the abdominal wall, and multiple abscessed foci. His serum creatinine was unchanged (0.8 mg/dl), representing a calculated clearance of 31 ml/min. Surgical drainage of the abscesses was performed repeatedly and *E. coli* was recovered from this material. Intravenous antibiotherapy and parenteral nutrition were started. In spite of this intensive treatment, he died of sepsis and multiple organ failure on October 6, 1997. An autopsy was performed and revealed an extended intra-abdominal inflammatory process, involving the abdominal wall, small and large bowel, liver, kidney transplant and spleen. Michaelis-Gutman bodies were found in all these organs (Fig. 1). Perianal condylomas discovered at autopsy also contained Michaelis-Gutman bodies.

Discussion

Malakoplakia was first described by von Hansemann in 1903 [5], and only about 400 cases have been reported since [19]. Macroscopically, it consists of soft tumor-like nodules arising from the mucosa and submucosa and mimicking a malignant neoplasm. Presence of Michaelis-Gutman bodies within the macrophages is the pathognomonic histological feature of the disease. These intracellular inclusions are thought to be partially degraded bacterial products. *Escherichia coli* is the most frequent bacterial pathogen and is consistently retrieved from these patients in over 90% of the cases [5, 17]. This case is a conspicuous example of a chronic *E. coli* infection since the patient had sustained a great number of *E. coli* septic episodes, interestingly both before and after transplantation. *E. coli* was retrieved repeatedly from the inflammatory mass and from blood cultures.

Malakoplakia among kidney transplant recipients has been reported to involve most frequently the genitourinary tract, including the grafted kidney [12], although all organs can be affected [17]. Despite the gastrointestinal tract being the second most frequent location, this is to our knowledge, the first reported case of malakoplakia in connection with a renal transplant recipient to be located in the right colon. One account involving the rectum has already been published [14].

A noteworthy aspect of the disease in regard to our patient was its tumor-like behaviour with locally invasive features, a phenomenon that has occasionally been reported, although not with the same severity [17, 18]. It is accepted that surgical resection is the treatment of choice for colonic locations of malakoplakia [3], but in our case, the perforation and ensuing local spread of the inflammatory process prevented it from being effective. If this patient had been more compliant, an early colonoscopy could have revealed the tumoral mass and prompted surgical resection, which would possibly have altered the course of the disease. Unfortunately, long-term medical treatment was required, with alternate episodes of response and recurrence.

Each of the pathogenic aspects of malakoplakia is addressed by medical therapy:

1. Immunosuppression is dramatically reduced. For our patient, it was stopped altogether, with the exception of low doses of prednisone, without any ensuing rejection episode. Acute rejection as a result of low immunosuppression has only been reported once with respect to such patients [17].
2. Ciprofloxacin (2 × 500 mg) penetrates macrophages well, which helps these cells kill and digest the ingested bacteria and makes it an antibiotic drug of choice [4]. In connection with our patient, who was kept continuously on ciprofloxacin from his referral to our institution until his death, this monotherapy proved to be insufficient. Repeated courses of parenteral antibiotics were necessary to obtain control of the disease, which recurred systematically after cessation.
3. Cholinergic agonists (i.e., betanechol chloride, 2 × 10 mg initial dose, to be increased gradually to 3 × 40 mg if necessary) raise the intracellular levels of cyclic guanosine monophosphate in the leukocytes, thus enhancing their microbicidal function. The efficacy of cholinergic agonists is controversial [2, 19].

The duration of this therapy depends on the extent of the disease and clinical response, but can be expected

to last for over 2 years. Despite these measures, our patient failed to respond, probably because of the initial colonic perforation and ensuing wide abdominal spread of the disease. Theoretically, some benefit for macrophage function could be expected from the administration of granulocyte-macrophage colony-stimulating factor [8], but data are not available for patients with malakoplakia. The discovery of a quickly growing abdominal mass in a patient under immunosuppression with ever-recurring *E. coli* septic episodes should have alerted the physician and suggested the diagnosis of malakoplakia. An earlier diagnosis could have led to the surgical removal of the pseudotumoral mass before perforation and prevented a dramatic outcome. Obviously, the scarcity of this pathology, which is usually a once-in-a-lifetime encounter (one case in this institution for 2650 kidney transplantations), is to blame for this shortcoming.

Malakoplakia can be life-threatening. Although not a malignancy, it displays features of local invasiveness and progression under therapy, with a capacity to recur. This was clearly illustrated in the case of our patient, in which the disease progressed inexorably, in spite of maximal medical and surgical treatment, until the eventual fatal outcome. Therefore, rapid identification of the disease is mandatory to provide adequate therapy without delay. It has to be emphasized that, for this patient, appropriate medication was unable to control the disease.

Malakoplakia is a heterogeneous disease, with different patterns of aggressiveness. The differences in behaviour observed could be related to the location of the disease, degree of local invasion at the time of diagnosis and treatment, and possibly to the different patterns of leukocyte dysfunction which have been reported [1, 2, 10, 16]. Altough malakoplakia is a rare complication in organ transplantation, it is a classic one and should therefore be familiar to the transplantation physician.

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