Colonic malakoplakia in a liver transplant recipient

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Malakoplakia is a rare inflammatory condition seen in transplant patients. There are two previously reported cases of malakoplakia involving the gastrointestinal tract in liver transplant patients. The present paper reports a case of colonic malakoplakia in a 58-year-old woman, a liver transplant recipient who was receiving immunosuppressive drugs. She presented with chronic diarrhea while on tacrolimus. There was no history of antecedent infection. Colonoscopy showed patchy mucosal edema, but no discrete yellow plaques or nodules. The diagnosis was made by colon biopsies, which showed chronic inflammation with many histiocytes containing Michaelis-Gutmann bodies. Although rare, malakoplakia is one of many potential causes of diarrhea in a transplant patient. The present case indicates that malakoplakia may be associated with chronic diarrhea, even if there are no macroscopic lesions seen during colonoscopy.

Key Words: *Liver transplant; Malakoplakia*

Malakoplakia, derived from the Greek words 'malakos', which means soft, and 'plax', which means plaque, is a rare inflammatory condition characterized by the presence of yellow-brown plaques comprised of aggregates of histiocytes. The histiocytes contain Michaelis-Gutmann bodies, which are pathognomonic inclusions containing accumulated bacterial products (1,2). The etiology of malakoplakia is still undetermined, but is thought to be caused by a dysfunction of bacterial clearance by neutrophils and macrophages (3). It has been associated with immunodeficiency states such as malignancy (1) and transplantation (3). Those patients often have coexisting Gram-negative infections (4). Malakoplakia is most commonly found in the genitourinary tract, but has been reported in the gastrointestinal tract (4,5), the lung (6) and the skin (7). Malakoplakia has rarely been reported in the setting of liver transplantation. The first case of malakoplakia in a liver transplant patient was reported (8) in 1995, and it involved the distal ileum and the mesentery. Two additional reports in liver transplant patients, involving the kidney (9) and the sigmoid colon (10), have been published. The present report describes a case of malakoplakia of the colon in a liver transplant recipient; this is the third reported case of post-liver transplant malakoplakia that involves the gastrointestinal tract and the second reported case that involves the colon.

Une malacoplasie colique chez une greffée du foie

La malacoplasie est une pathologie inflammatoire rare qu'on observe chez les greffés. On a déjà déclaré deux cas de malacoplasie dans le tube digestif de greffés hépatiques. Le présent article présente un cas de malacoplasie colique chez une femme de 58 ans greffée du foie qui recevait des immunosuppresseurs. Elle a consulté en raison d'une diarrhée chronique alors qu'elle prenait du tacrolimus. Elle n'avait pas d'antécédents d'infection. La coloscopie a révélé un œdème muqueux à foyers disséminés, sans plaques ou nodules jaunâtres discrets. Des biopsies du côlon ont permis de poser le diagnostic, car elles ont mis au jour une inflammation chronique accompagnée de nombreux histiocytes contenant des corps de Michaelis-Gutmann. Bien qu'elle soit rare, la malacoplasie est l'une des nombreuses causes potentielles de diarrhée chez un greffé. Le présent cas indique que la malacoplasie peut s'associer à une diarrhée chronique, même si aucune lésion malacoplasique n'est observée pendant la coloscopie.

CASE PRESENTATION

A 58-year-old Korean woman had undergone a cadaveric orthotopic liver transplant three years previously for hepatitis C-induced cirrhosis and portal hypertension. Her post-transplant recovery period was complicated by ischemia-reperfusion injury, documented during a liver biopsy, and further confirmed by multiple strictures of intrahepatic and extrahepatic biliary ducts upon endoscopic retrograde cholangiopancreatography. She developed jaundice, ascites and pruritus, and was relisted for a second liver transplant. She was maintained on 2 mg of tacrolimus twice daily, 200 mg of spironolactone daily, 120 mg of furosemide daily, 150 mg of rifampin twice daily and 500 mg of ursodiol twice daily. The tacrolimus dosage ranged from 3 ng/mL to 6 ng/mL. She was not maintained on any other immunosuppressive agents.

The patient had first reported diarrhea approximately one year previously. This progressed to the point that, for two months previously, she had reported up to 20 episodes per day of watery diarrhea. She had mild peripheral edema. The patient reported no antecedent travel history and no change in diet. Stool cultures, ova and parasite testing, and a *Clostridium difficile* toxin assay were negative. The patient was negative for the cytomegalovirus antigen. Her serum albumin level was 22 g/L. She did not have any significant weight loss. The

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Figure 1) Colonoscopic appearance of colonic malakoplakia in a liver transplant recipient, characterized by generalized edema, patchy erythema and multiple smooth nodules

patient complained of fatigue, but she was not in acute distress. An ultrasound of the abdomen did not reveal any ascites.

The patient underwent a colonoscopy with biopsies. The mucosa throughout the colon appeared edematous, with a patchy loss of the vascular pattern and mild, patchy erythema, as illustrated in Figure 1. There was a slight yellowish tinge to some of the erythematous patches, and several had pale, target-like centres. Biopsies revealed active inflammation, cryptitis, occasional crypt abscesses and sheets of histiocytes with Michaelis-Gutmann bodies (Figure 2). Erythematous, edematous areas, as well as intervening mucosa that appeared normal, were both involved. The cytomegalovirus immunostain was negative, and no infectious agents were identified on hematoxylin and eosin stain.

DISCUSSION

The gastrointestinal tract is the second most common site of involvement by malakoplakia, and most of those cases involve the colon and the rectum (11). Malakoplakia of the colon has a distinctive gross and microscopic appearance. Colonic involvement can be either segmental or diffuse. In the early stages, the lesions appear soft, flat and tan-coloured. Later, they can develop into raised, tan-grey and hyperemic lesions (10). Histologically, malakoplakia is characterized by aggregates of large histiocytes (known as von Hansemann cells) with intracellular and extracellular inclusions (known as Michaelis-Gutmann bodies), which are phagolysosomes that have become encrusted with calcium and iron salts. These findings are pathognomonic and establish the diagnosis of malakoplakia.

The etiology of malakoplakia is still not fully understood, but there is an association with Gram-negative bacterial infections, particularly with *Escherichia coli*. The likely mechanism of malakoplakia is defective lysosomal processing of microorganisms by macrophages in the accumulation of debris in lysosomes and subsequent mineralization.

Another potential contributing factor to the development of malakoplakia is an impaired immune response (eg, immunosuppression used to prevent rejection in organ transplant patients). In a review by Long and Althausen (12), approximately 40% of

Figure 2) Microscopic appearance of colonic malakoplakia in a liver transplant recipient, as illustrated by the periodic acid-Schiff stain with diastase digestion, demonstrating the Michaelis-Gutmann bodies (arrows)

malakoplakia cases that did not involve the urinary tract were associated with immunosuppression. In a review of the literature, there have been three cases (8-10) of malakoplakia in liver transplant recipients. Two of those case reports (9,10) involved the gastrointestinal tract (the small bowel and mesentery, and the sigmoid colon). The indications for transplantation included hepatitis C infection and hepatocellular carcinoma. The clinical presentation of malakoplakia included small bowel obstruction and chronic diarrhea. No coexisting infection was reported, although the patient described by Rull et al (8) died four weeks after a laparotomy for bowel obstruction secondary to pneumonia that was caused by *Pseudomonas* species. In the patient described in the present paper, the degree of immunosuppression was relatively mild, consisting of tacrolimus monotherapy with low trough drug levels. Perhaps her decompensated liver disease contributed to her susceptibility to malakoplakia. There have been no reports of tacrolimus directly inducing lysosomal dysfunction or malakoplakia.

Attempts at treatment of malakoplakia have included two main approaches: the administration of a cholinergic agonist to improve macrophage function, and antibiotic therapy. Abdou et al (13) reported a patient with rectal and retroperitoneal malakoplakia. They documented that the patient had monocytes that had decreased bactericidal activity against *E coli*, abnormally large lysosomal granules, low levels of cyclic GMP in mononuclear cells and poor release of beta-glucuronidase in a bactericidal assay (13). Low levels of cyclic

GMP in cultured malakoplakia cells were corrected by treatment with carbachol, a cholinergic agonist. The patient's clinical course improved after oral treatment with bethanechol chloride. The rationale for antibiotic therapy is to administer antibiotics that concentrate in macrophages. van Furth et al (14) reported two patients with malakoplakia who were treated with ciprofloxacin and experienced regression of their lesions with long-term therapy. Yousif et al (15) also reported a case of rectal malakoplakia that was successfully treated with a six-month course of ciprofloxacin, along with a reduction of immunosuppression (15).

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CONCLUSIONS

The present paper presents the third reported case of malakoplakia of the gastrointestinal tract in a liver transplant recipient. The presentation of malakoplakia depends on the location and the degree of involvement. Two of the three reported patients presented with diarrhea. Although rare, malakoplakia is one of the many potential causes of diarrhea in a liver transplant patient and can be readily diagnosed from mucosal biopsies of the colon. It is typically a benign, self-limited condition that responds to antibiotic therapy and to a reduction of immunosuppression.