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Colonic Malakoplakia and Therapy-related Myelodysplastic Syndrome in Liver Transplant Recipient

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***Abstract*: Reported herein are two rare complications occurring in a liver transplant recipient: Colonic malakoplakia and therapy (azathioprine)-related myelodysplastic syndrome (Rx-MDS) with complex cytogenetic abnormalities. The patient, a 65-year-old male, received a liver transplant in April 2012, followed by 16 months of maintenance azathioprine/prednisone. In December 2014, he presented with severe chronic diarrhea and unexplained refractory pancytopenia. Two months earlier, his marrow was normocellular and devoid of dysplasia, although chromosomal analysis at this juncture disclosed complex cryptogenic defects, with abnormal chromosome 7. Colonic malakoplakia was evident by colonoscopy. Both CBC and diarrhea resolved upon azathioprine withdrawal, steroid dose adjustment, antibiotic administration (ciprofloxacin, 20 days), and other supportive measures. Chronic diarrhea is common in liver transplant recipients who develop Colonic malakoplakia. Immunotherapeutic intervention (plus antibiotic and cholinergic treatment) is effective and is potentially curative. Azathioprine heightens the risk of developing Rx-MDS, which likewise may remit upon withdrawal.**

***Keywords*: Colonic malakoplakia, liver transplant, azathioprine-related myelodysplastic syndrome, cytogenetic abnormalities.**

I. INTRODUCTION

Malakoplakia is a rare and chronic multisystem granulomatous inflammatory disease resulting from a defective phagocytic activity of macrophages. The name derived from the Greek words malakos and plakos, meaning soft plaque. This disorder more common in patients with histories of diabetes, solid organ transplantation, lymphoma, steroid therapy, or alcoholism who are immunodeficient[2]. Those affected show impaired digestion of engulfed bacteria due to low levels of cyclic-GMP, thus promoting organic and inorganic deposits. Histologically, sheets of foamy macrophages (Von Hansemann cells) with granular eosinophilic cytoplasm and basophilic Michaelis-Gutmann bodies are present[1].

Medical treatment entailing a cholinergic agonist [3], an antibiotic [4], and withdrawal of immunosuppressive medications [5], generally satisfactory. Bethanechol chloride is a cholinergic agonist that increases intracellular levels of cyclic-GMP, improving the phagocytic capacity of macrophages. Antibiotics of choice are those capable of achieving high concentrations within macrophages, such as quinolones or combination trimethoprim/sulphamethoxazole.

The prevalence of malakoplakia unknown, but the number of reported cases is increasing. Genitourinary involvement is most common, accounting for two-thirds of reported cases, followed by gastrointestinal sites. Recently, respiratory tract, adrenal gland, pancreas, mesenteric lymph nodes, testis, epididymis, vagina, bone, and brain have also been implicated. Only a single case report has recorded the coexistence of malakoplakia (renal) and myelodysplastic syndrome (MDS). This occurred in a 62-year-old female with a 2-year history of diarrhea and a 20q deletion. Despite evidence of systemic involvement, Colonic malakoplakia could not be proven in this instance, given a lack of biopsy support. [6]

To date, there are three published reports of Colonic malakoplakia in liver transplant patients [7-9], making this is the fourth. Moreover, it is the second reported instance in which azathioprine withdrawal led to spontaneous remission of therapy-related MDS (Rx-MDS) with chromosome 7 abnormalities. Also, this is the first report to detail the coexistence of two conditions in a liver transplant patient, Colonic malakoplakia and Rx-MDS with complex cryptogenic abnormalities (chromosome 7 inclusive), in the course of long-standing immunosuppressive therapy (prednisone, tacrolimus, and azathioprine).

II. CASE PRESENTATION

The patient, a 56-year-old Saudi male, had undergone living-donor liver transplantation (April 2012) subsequent to autoimmune hepatitis. Mycophenolate and tacrolimus were initiated postoperatively. Two months later, he presented with severe gastritis, diarrhea, tacrolimus (FK) level elevation, and acute kidney injury. The medications were suspended, and he recovered a few days later. Mycophenolate was discontinued to relieve the severe gastrointestinal symptoms. Azathioprine was then introduced, and tacrolimus and prednisone were resumed (at lower doses).

In December 2014 he again presented, complaining of chronic diarrhea for months and lower abdominal pain. He had also suffered symptomatic anemia and anorexia, with significant weight loss (74 kg → 46 kg over six months). There were no signs of bleeding or hemolysis. He spiked a fever on Day 1 of hospitalization, prompting empirical intravenous piperacillin-tazobactam treatment. Repeated full septic screens, including stool samples, were unremarkable; liver enzymes and renal function were normal, and CMV antigenemia testing was negative. Complete blood counts and the peripheral blood film revealed profound pancytopenia. Two months ago prior to this admission, he was investigated by a hematologist for long-standing macrocytic anemia. The peripheral blood film showed mild macrocytic anemia, with few red cell fragments (<5%). No atypical/dysplastic cells were evident. An adequate bone marrow aspirate was obtained, showing 40% overall cellularity. The marrow was normocellular, with no dysplasia or infiltrative process. However, chromosomal analysis revealed complex cytogenetic abnormalities, including aberrancy of chromosome 7 (karyotype: 43-45,XY,del(12)(q21)[cp2]/45,XY,i(7)(p10),-9[1]/46,XY[9]). FISH testing confirmed a 7q31 (D7S522) defect. Colonoscopy showed diffuse endoscopic colitis, more severe in the ascending segment up to cecum, with multiple patches of clean-based ulcers. All biopsies displayed diffuse histiocytic infiltrates harboring intracellular inclusions. The latter stained positively for calcium and periodic acid-Schiff. Overall features were characteristic of malakoplakia. A whole-body positron emission tomography-computed tomography (PET-CT) scan showed avid wall thickening in large bowel loops, more prominent at hepatic flexure and transverse colon, but not elsewhere (Fig. 1).

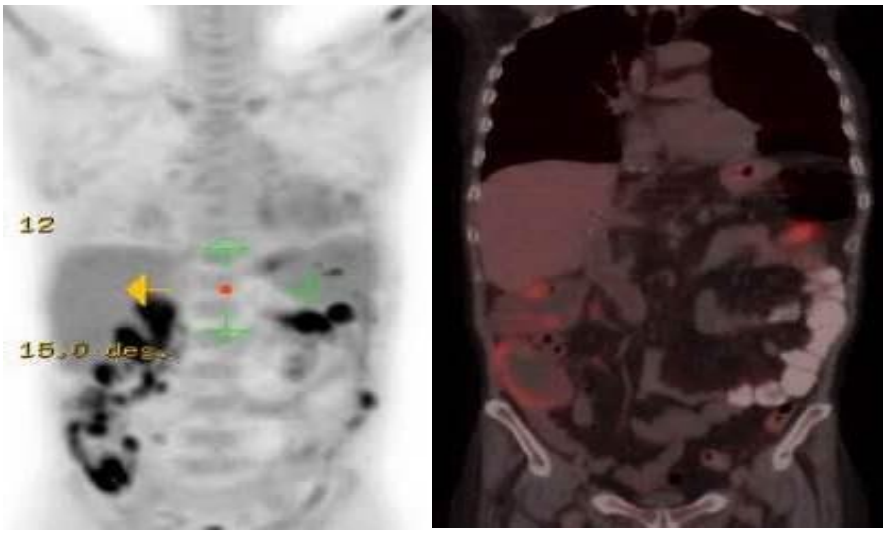

Fig. 1: PET-CT images showing high FDG uptake signals in large bowel loops, corresponding to colonoscopy lesions in ascending and transverse colon.

The patient's immunosuppressive regimen was modified, discontinuing azathioprine, tapering prednisone to 5 mg, and reducing tacrolimus to 0.5 mg. ; ciprofloxacin given for 20 days and supportive measures were also instituted (granulocyte colony-stimulating factor [G-CSF]; packed red blood cells, four units). At the end of Week 3, his clinical condition had improved. The CBC recovered slowly over the course of 6 months. He has remained asymptomatic during the 24 months since discharge, maintaining a current body weight of 68 kg and stable CBC.

III. DISCUSSION

Colonic lesions account for 10% of malakoplakia in published reports[10], whether confined to colon or part of multisystem involvement. A recent article has documented coexistent pancreatic and colonic malakoplakia, confirmed by fine-needle aspiration [11]. This condition may mimic colonic cancer in presentation [12]. In a review by McClure, nearly half of the 38 reported cases of Colonic malakoplakia were associated with rectal or colon cancer. Aside from adenocarcinoma of the colon, such lesions have also developed in conjunction with adenomas [13] and with the absence of other pathology [14]. In another report, malakoplakia was identified in the left kidney of a liver transplant recipient three years post-transplantation, [15]. The patient presented with a history of recurrent urinary tract infections, flank pain, and elevated serum creatinine level. A left renal mass detected by ultrasound and then histologically confirmed as malakoplakia. However, the immunosuppressive regimen wasn't disclosed.

The FDG-PET CT scan, findings may contribute to the diagnosis of malakoplakia [16]. Here the whole-body FDG-uptakes corresponding to colonoscopy lesions in ascending and transverse colon, but not elsewhere (Fig.1).

Chronic diarrhea for months was the presenting complaint in three of four case reports of Colonic malakoplakia in liver transplant recipients (including this patient). None of the four patients had evidence of concurrent infections. Although one patient died four weeks post-laparotomy [7], the other three recovered. The indication for liver transplantation in this instance was autoimmune hepatitis, as opposed to hepatitis C infection and hepatocellular carcinoma in the others.

A presumptive diagnosis of the MDS can be made in the presence of certain genetic abnormalities [17] if unexplained refractory pancytopenia exists with no discernible morphologic dysplasia. Azathioprine is a well-known cause of bone marrow suppression and severe hematologic complications [18][19]. Rx-MDS has been documented with long-term azathioprine therapy [20],[21],[23]. Results of 26 successful karyotypes performed in 33 of 56 reported cases have shown that a defect of chromosome 7 is the most common abnormality, and findings were similar for chromosomal analysis of azathioprine-related MDS (N=14) in the Düsseldorf MDS Registry. Aberrations were present in nine of 10 patients karyotyped, with eight of 10 showing defects of chromosome 7. Another report of azathioprine-related MDS has cited four instances of complex karyotypic anomalies in seven patients, including chromosome 7 defects. Spontaneous remission of therapy-related MDS, with monosomy 7, has been reported in a renal transplant recipient following discontinuation of azathioprine, confirmed four months later by karyotyping and fluorescence in situ hybridization analysis [22]. Unfortunately, cytogenetic remission was not confirmed. This patient did not consent to bone marrow examination, but blood counts (all three lineages) in the past 18 months were in normal range, and regular follow-up is ongoing. It is a well-known fact among hematologists that Rx-MDS carries a poor prognosis, with a median survival rate of less than one year [23]. In the present case, however, pancytopenia began to recover spontaneously three weeks after withdrawal of Azathioprine and remained within the normal range for two years after diagnosis.

Modification of immunotherapy may thus reverse Colonic malakoplakia. Low-dose immunosuppression is well tolerated, helping to reduce high-dose complication risks beyond the early post-transplantation phase.

IV. CONCLUSION

Malakoplakia of the colon is a serious complication in liver transplant recipients, the most common presenting complaint being chronic diarrhea (three of four published case reports). Immunosuppressive therapy is the primary contributing factor. Key histopathologic features are essential for diagnosis. Low-doses of immunosuppression are well tolerated and possibly serve better long-term, beyond early post-transplantation phase. Low-dose prednisone and tacrolimus may reverse the inflammatory process and maintain remission of colonic malakoplakia in the liver transplant patient.

Azathioprine increases the risk of developing Rx-MDS through large cumulative doses. However, withdrawal may lead to remission. Spontaneous remission of azathioprine-related MDS, with chromosome 7 defects, has been documented in at least two patients after azathioprine withdrawal.

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