Two cases of colon LST in transplanted liver patients

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Abstract

Long-life immunosuppressive therapy increases the risk of de novo tumors in liver transplant recipients by decreasing the immune surveillance against malignant cells and oncogenic viruses. However, no cases of colon precancerous lesions have been reported in these subjects.

Patient n. 1, a 73 yrs old male treated with calcineurin and purine synthesis inhibitors, showed at a per-protocol colonoscopy a 3 cm laterally spreading tumor (LST). Patient n. 2, a 73 yrs old male treated with calcineurin inhibitors, showed at a screening colonoscopy an LST occupying one third of the lumen circumference. Both subjects were asymptomatic, had been transplanted 14 years before, and in both cases, lesions showed severe dysplasia.

LSTs represent 17.2% of advanced colorectal neoplasia (CRC) and risk factors are multifactorial. Immunosuppression may play a role which is however not completely understood. Based on this report, surveillance colonoscopy in liver transplanted patients should be considered. (Acta gastroenterol. belg., **2017**, 80, **313-315**).

Key words : Colorectal Cancer, liver transplantation, immunosuppression laterally spreading tumors.

Introduction

Colorectal cancer (CRC) is the third leading cause of cancer death in women, and the second in men. Liver transplant recipients have a high risk to develop de novo neoplasia through a variety of mechanisms. Basically, long-life immunosuppressive therapy decreases immune surveillance against malignant cells and against a variety of viruses with oncogenic properties (1).

Epidemiological investigations estimate that about 6% of orthopaedic liver transplantation (OLT) recipients develop cancer after a median time of 5 years of immunosuppression, with an overall cancer risk 1.4-fold higher than in the corresponding general population (2).

The current guidelines for CRC screening in general population recommend high-sensitivity fecal occult blood testing and colonoscopy beginning at age of 50 years and continuing until age of 75 years. People at higher risk of developing colorectal cancer should begin screening at a younger age (3).

Case report

In a series of 64 transplanted patients followed up for a median time of eight years, colonoscopy was performed in 32 between January 2012 and April 2015. Adenomatous polyps were found in four patients (12.5%). Laterally spreading tumor (LST) was found in two patients (6.25%). Here we describe the clinical and endoscopical characteristics of the latter cases. Patient n. 1, a 73 years old white male subject, had been transplanted in 2001 for HCV-related cirrhosis complicated by hepatocellular carcinoma (HCC) and subsequently treated with a calcineurin inhibitor (cyclosporine) and purine synthesis inhibitors (mycophenolate mofetil). He also had type 2 diabetes and Hashimoto's thyroiditis and assumed insulin and hormonal substitutive therapy. After transplantation he never complained of abdominal pain, bowel habits changes or rectal bleeding. In 2006 he underwent a per-protocol colonoscopy which did not show any lesions, while a second screening colonoscopy in 2014 showed a 3 cm lesion in the coecum. This lesion was classified as an LST of homogeneous granular type, with a 3L pit pattern, according to Kudo classification. The patient was referred to endoscopy for mucosectomy. Saline-assisted en block mucosectomy was performed without complication using an asymmetric mucosectomy snare. The histology showed high-grade dysplasia of the glandular epithelium. A surveillance colonscopy six months later showed scarring at the site of the previous mucosectomy with no residual adenoma (figure 1).

Patient number 2 received OLT in 2007 for HCV/HBV-related cirrhosis complicated by HCC. Immunosuppressive therapy with calcineurin inhibitor (tacrolimus) was started soon after. A colonoscopy performed a few months before OLT did not show any lesion. In 2014, a screening colonoscopy showed the presence of a LST granular type located opposite to the ileocoecal valve and occupying more than one third of the lumen circumference. The patient underwent colonic surgery and, at histology, high-grade dysplasia limited to the glandular epithelium was found. Clinical and laboratory characteristics of the two patients are showed in table I.

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

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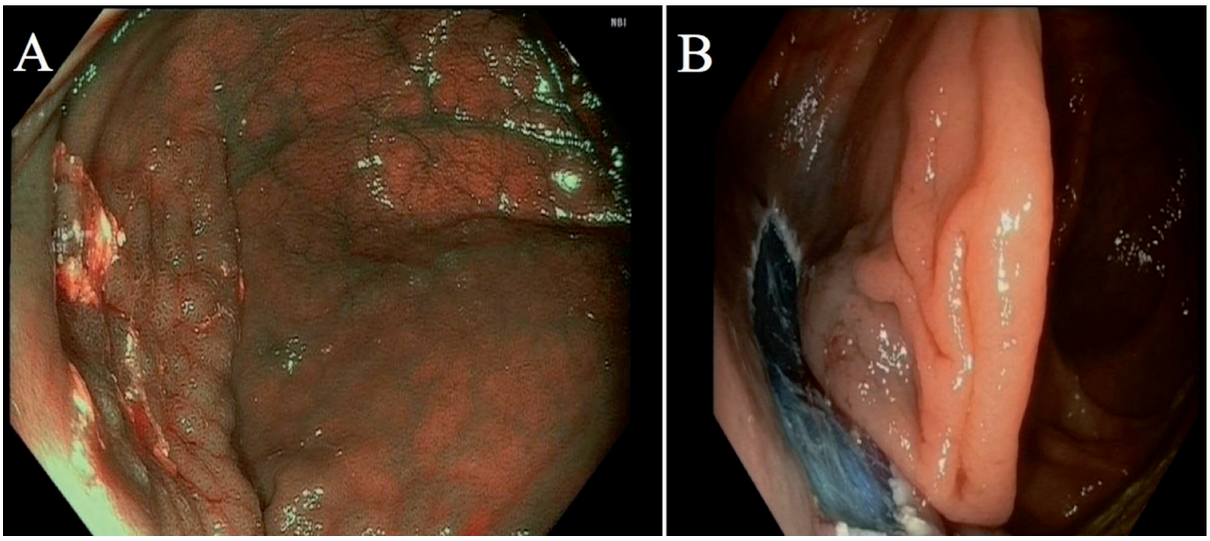

Fig. 1. — Colonoscopy showing an LST in the cecum prior to (A) and after (B) mucosectomy.

Table I. — **Clinical and laboratory characteristics (categorical data) of the patients**

	Patient n. 1	Patient n. 2
Age (years)	73	73
Gender	Male	Male
Hemoglobin(g/dL)	11.2	15.1
Platelets (x $10^3/\mu$L)	242	109
HCV viremia (UI/mL)	2800000	2200000
HBVtherapy	-	Lamivudine/Ig anti-s
LiverDisease	Hepatitis	Cirrhosis
Istology colon	High grade dysplasia	
Immunosuppression	Tacrolimus/mycophenolate	Tacrolimus
Follow up of the LST (years)	13	7

Discussion

Surgical technique improvements, postoperative management and immunosuppressant regimens have improved the long term survival of patients undergoing OLT. The overall survival at 5 years is currently at 70%, with variations depending on the underlying liver disease (4).

"De novo" malignancy is the most common cause of death, after cardiovascular diseases, in recipient patients. Its impact is three-folds higher than in the general population. In 534 American patients who underwent OLT after an average check up of 5.7 ± 3.2 years, 80 cancers developed in 73 subjects (13.4%), and 50% of them were solid tumors. The most common tumor site was aero-digestive (SIR 3.1 CI 95%). Other studies also showed that, comparing the tumor risk in the general population of the same age and gender, the cumulative risk of de novo cancer increases from 3-5% at 1 year to 11-20% at ten years after transplant (5, 6).

Whether the increased risk of de novo tumors in transplanted patients is accounted for by long-lasting immunosuppressive therapy is still an object of debate. A number of studies have shown an association between cancer development and use of tacrolimus or cyclosporine (7).

A study conducted on 257 transplanted patients, revealed that colorectal neoplasm prevalence was not greater as compared to the general population, except for subjects under 40 years. However, this study also showed that advanced forms at diagnosis were more frequent particularly in younger patients who had received organ

transplantation (8). The incidence of colorectal cancer seems to be higher in the OLT recipients population vs the general population while are not conclusive for incidence of adenomatous polyps and LST in OLT recipients (9). In a multicenter nationwide study conducted in Italy on 27,400 colonoscopies, the prevalence of LST was 0.93 (i.e. 254/27,400). With the limitations due to the large difference in population size, based on this report, the OR for LST in liver transplanted patients compared to general population is 7.12 (95% CI 1.69-28.97 p<0.007).

In both cases, LSTs were localized in the right colon which is the prevalent site for this lesion in people over 70 years of age. LST is a colorectal flat pre-cancerous lesion, greater than 10 mm in diameter, which typically extends laterally rather than vertically along the colonic wall (10). LST is a non polypoid colorectal neoplasia and can be further distinguished based on its granular or non granular, homogenous or non-homogenous appareance (11).

Recent studies have indicated that LSTs represent 17.2% of advanced colorectal neoplasia (12) and that these lesions may progress into a high-grade dysplasia with an incidence rate ranging from 20.9% to 33.8%.

LSTs generally have a low incidence of submucosal invasion, and, therefore, most of them can be removed endoscopically. However, surgery must be considered based on a careful morphologic analysis, taking into account the size and surface with nodules or depression or when submucosal invasive carcinoma is diagnosed (13).

One of the lesions in our report was susceptible to endoscopic treatment with mucosectomy. The procedure was performed without complications and a follow-up colonoscopy performed 6 month later, showed no residual or recurrent adenoma. The second patient, conversely, needed surgical excision of the lesion because of its extension. In both cases, histology showed high-grade dysplasia.

Risk factors for developing de novo malignancy in recipients are multifactorial. The exact role of immunosuppression is not completely understood. Probably it is dose- related and minimization of dose to the lowest tolerable level is needed. Surveillance protocols are the key for cancer prevention. Based on this report, a surveillance colonoscopy protocol is suggested in liver transplanted patients.

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