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ORIGINAL ARTICLE

Malignancies of the colorectum and anus in solid organ recipients

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Summary

Patients undergoing solid organ transplantation (SOT) are at increased risk for developing malignancies due to the long term immunosuppression. Data on malignancies of the large intestine after various types of SOT are rare. A total of 3595 SOTs were performed between 1986 and 2005 at our center and retrospectively analyzed with regard to the incidence and course of malignancies of the colon, rectum, and anus. Standard immunosuppression consisted of calcineurin inhibitors in combination with azathioprine or mycophenolate mofetil and steroids with or without antithymocyte globulin or IL-2 receptor antagonist induction. A total of 206 patients (5.7%) developed malignancies. Colorectal adenocarcinoma was diagnosed in nine patients (0.25%; mean age at diagnosis 65 years) at a mean of 5.3 years after transplantation. Five patients (55%) died 7.2 years post-transplant due to cardiovascular disease ($n = 4$) and tumor progression ($n = 1$). Four patients developed anal neoplasia (0.11%) 7 years post-transplant with 100% 1-year survival. Five patients showed post-transplant lymphoproliferative disorders (PTLD) with intestinal involvement. The incidence of anal but not of colorectal cancers in our transplant recipients differed from that of immunocompetent individuals of corresponding age (0.11% vs. 0.002% and 0.25% vs. 0.3%). PTLD may involve the colon.

Introduction

Development of malignancies is a complication of solid organ transplantation (SOT) with an increasing incidence during the past decade. Post-transplant lymphoproliferative disorders (PTLD), and skin or lip cancers are the most common malignancies in transplant recipients when compared with immunocompetent individuals [1]. PTLD occurring during the early post-transplant course is associated with intensified immunosuppression such as antithymocyte globulin (ATG) or high maintenance levels of calcineurin inhibitors. Inhibition of T-cell immune responses may facilitate unlimited B-cell proliferation in response to latent Epstein–Barr virus (EBV)-infection [2]. Viruses play a crucial role in the development of the common malignancies in solid organ recipients. The most important pathogens are EBV, human herpes virus 8 (HHV8), hepatitis B and C virus (HBV, HCV) and human papillomavirus (HPV) and some may cause malignancies of the colon, rectum or anus. Early recognition of these pathogens by means of laboratory screening and routine histologic investigations is essential for prevention and successful treatment of post-transplant malignancies. In general, there are three possibilities for developing post-transplant malignancy in the recipient [3]:

- Recurrence of pretransplant existing recipient derived malignancy;

- *De novo* development of recipient derived malignancy;
- Transmission of malignancy from the donor.

The incidence of post-transplant colorectal adenocancer has been reported to be similar to that of the general population (0.01–3.9% vs. 3–5%) [4]. Since colorectal screening campaigns for early detection of colorectal cancer have arose in most national health systems, one might consider intensified colorectal screening in all transplant recipients for early detection of suspicious lesions. Parikshak *et al.* demonstrated that transplant patients are not more likely to develop metachronous polyps than the general population. This suggests that current routine screening criteria should also be used in patients following SOT [5].

There is currently no international consensus in terms of endoscopic surveillance of the colon, as different guidelines recommend different intervals between colonoscopies following detection of polyps [6]. The incidence of anal malignancy or malignant precursors (i.e. anal intraepithelial neoplasia, AIN) in the transplant population has been shown to be increased due to its association to HPV infection (e.g. HPV-16,-18) [7,8]. Still, there is controversy about the definition of AIN, with some authors including not only HPV-associated anogenital lesions [8,9]. However, all HPV infection associated proliferative anogenital lesions should be recognized as AIN, since the immunosuppressed patient is more likely to develop anogenital malignancy than the immunocompetent individual [10]. Additionally, no universally accepted consensus exists on the best approach for prevention and treatment of PTLD, which is often associated with EBV infection.

The aim of this retrospective study was to analyze the incidence and course of colorectal malignancies in a large series of patients who underwent SOT. We also analyzed the outcome in terms of patient survival, tumor recurrence, graft function, and secondary complications.

Patients and methods

Patients and transplants

Medical records of patients who underwent SOTs between 1986 and 2005 at the Department of General and Transplant Surgery of Innsbruck Medical University were retrospectively analyzed. This retrospective chart review was performed in accordance with the standards of the institutional ethics committee.

Peri- and post-transplant management

Surgical techniques and perioperative management were performed according standard techniques. Immunosuppressive therapy consisted of cyclosporin A (CsA) or tacrolimus (Tac) based triple drug therapy for the vast majority of patients with the addition of azathioprine or mycophenolate mofetil (MMF) and steroids. Antibody induction therapy with ATG or IL-2 receptor antagonists was used in most cardiac, lung, pancreas and intestinal recipients and in liver and kidney recipients in the case of high risk for rejection, part of renal sparing protocols or if they were included in multicenter trials which contained these agents. Maintenance trough levels for CsA were 100–200 ng/ml and for Tac 5–10 ng/ml in the first period after transplantation with reduction doses in the long-term follow-up.

Virological screening

Subsets of recipients were tested for anti-EBV antibodies by a serological assay (Enzygnost® anti-EBV-IgG and -IgM; Dade Behring, Marburg, Germany). Blood samples for serological testing were drawn at the time of registration and immediately prior to transplantation. For donors from our own center, EBV testing was carried out routinely during donor conditioning. A primary infection was defined as the appearance of IgM and IgG-antibodies against the virus capsid antigen (VCA, anti-EBV-IgM and IgG), against the early antigen (EA, anti-EBV recombinant early antigen ELISA; Biotest Diagnostics, Dreieich, Germany) and absence of antibodies to Epstein Barr nuclear antigen (EBNA, EBNA IgG ELISA; Biotest Diagnostics). A significant increase of the anti-VCA IgM and/or anti-EA in an IgG- and EBNA-positive patient was interpreted as reactivation of EBV-infection. Serology was complemented by viral DNA detection using polymerase chain reaction since 2001.

Diagnosis of malignancies and screening for colorectal and anal malignancies

In transplant recipients, colonoscopic screening is not performed at regularly defined intervals as long as the patients followed preventive screening guidelines (surveillance starting above the age of 50 years). Preoperative assessment of the colon and rectum is not mandatory before organ transplantation, apart from endoscopy of the upper gastrointestinal tract to exclude peptic ulcer disease, reflux disease, and malignancy.

The term ''anal intraepithelial neoplasia'' (AIN) has been introduced into pathology records in the last 5–10 years, as anal intraepithelial lesions associated with HPV infection have been summarized using the term Bowen disease.

Anorectal examinations in our center were performed by a specialized coloproctologist.

Results

A total of 3595 transplants (2074 kidney, 757 liver, 367 pancreas, 247 heart, 118 lung, 27 small bowel, and nine combined heart-lung transplants) were performed between 1986 and 2005. Four hand transplants were not included.

A total of 206 solid organ recipients (5.7%) developed malignancies during the post-transplant follow-up. Data were obtained from the medical records of the routine follow-up visits in our transplant unit. However, we cannot exclude that some of our recipients presented with colorectal or anal malignancies to other follow-up units. The cases reported here were all assessed during long-term follow-up.

Colorectal cancer

Nine patients (one female, eight male, mean age 65 years at diagnosis, range 56–73 years; two kidney, three heart, four liver recipients) had colorectal malignancies (0.25%) during a mean follow-up period of 7.3 years (Table 1). On average, the diagnosis of colorectal cancer (CRC) was made 5.3 years after transplantation. Five of the nine recipients (55%) with CRC cancer underwent colonoscopy prior to organ transplantation with only one male recipient being diagnosed with colonic adenoma (no. 1, Table 1). All tumor patients have been seen within our oncological surveillance program every 3 months during the first 2 years after diagnosis and at 6-month intervals until 5 years after diagnosis. Four cancers were located in the rectum or at the rectosigmoid junction and five were colonic cancers (five pT3, one pT2, and three pT1 stages, see Table 1). R0 resection was performed in all nine patients and all T3 rectal cancer patients ($n = 3$) received preoperative radiochemotherapy. Five patients were switched to rapamycin after completion of primary therapy (Table 1). Five patients (55%) died after a mean of 7.2 years following transplantation due to cardiovascular disease ($n = 4$) or tumor progression ($n = 1$). The 1-year-survival rate was 67% for T3 and 100% for T1 rectal cancers, 50% for T3 and T1 each and 100% for the only T2 colon cancer. In one cardiac recipient with rectal cancer, who was switched to rapamycin due to renal failure prior to radiochemotherapy and surgery, delayed wound healing of the sacral cavity (following rectal excision) was observed. Only after withdrawal of the mTOR inhibitor back to CsA the patient slowly recovered and healing of the sacral defect improved.

Anal cancer

Four anal neoplasia (one AIN III°, three anal cancers, pT1 and pT2; mean age 46 years at diagnosis, range

Table 1. Transplant recipients with colorectal cancer in long-term follow-up.

Patient no.	Gender	Age at diagnosis (years)	Organ	Colorectal tumor	Time to diagnosis (years)	Staging	Treatment	Status	Other malignancies	IS	Graft rejection
1	M	73	Kidney	Rectum	2.5	pT3N1M0	TME alone	Deceased	Skin, prostate, renal cell	CsA, Aza, steroids	None
2	M	70	Liver	Asc. colon	10	pT3N1M0	Resection + Cx	Alive	None	CsA, Aza, steroids	None
3	M	59	Liver	Trans. colon	10	pT1N0M0	Resection	Deceased	None	CsA, Aza, steroids	2x
4	M	66	Liver	Asc. colon	10	pT2N0M0	Resection + Cx	Deceased	None	CsA, Aza, steroids	1x
5	M	59	Liver	Desc. colon	3	pT1N0M0	Resection	Alive	None	CsA, Aza, steroids	1x
6	M	71	Heart	Rectum	5	pT3N0M0	APE + RCx	Deceased	None	ATG, CsA, Aza, steroids	None
7	M	68	Heart	Rectum	1.5	pT3N0M0	APE + RCx	Alive	None	ATG, CsA, Aza, steroids	1x
8	M	63	Heart	Rectum	4.5	pT1N0M0	Resection	Alive	None	ATG, CsA, Aza, steroids	1x
9	F	56	Kidney	Asc. colon	1.5	pT3N0M0	Resection	Deceased	None	CsA, Aza, steroids	1x

TME, total mesorectal excision; Cx, chemotherapy; APE, abdomino-perineal excision; RCx, radio-chemotherapy; CsA, cyclosporin A; Aza, azathioprine; ATG, antithymocyte globuline; IS, immunosuppression.
Recipients no. 1, 2, 4, 7, and 8 were switched to mTOR inhibitors after diagnosis of malignancy.

35–61 years, Table 2) were observed 7 years after transplantation (0.11% vs. 0.001% in the general population) [10] with a 100% 1-year-survival rate. All patients were switched to rapamycin after completion of primary treatment.

Treatment of anal malignancy was performed following standardized protocols with radical excision of anal marginal cancers (<2 cm in size) and combined radiochemotherapy with mitomycin 10 mg/sm day 1 and day 30 and 5-floururacil 1000 mg/sm/24 h in week 1 and week 5 and simultaneously application of long-term irradiation (1.8–2.0 Gy through 5 weeks) in anal canal cancers [11].

A 37-year-old woman who underwent kidney transplantation for nephrotic syndrome showed a positive PAP smear on routine genital examination and a noninvasive cervical cancer 1 year after transplantation. Conisation and later on resection of the uterus were performed due to recurrence. After a 10-month tumor free interval she developed lesions within the vagina, vulva, and anal canal and biopsies revealed vaginal intraepithelial neoplasia (VIN II°), cervical intraepithelial neoplasia (CIN III°) as well as AIN III°. After laser ablation, the lesions rapidly relapsed and the patient was switched to rapamycin and received intralesional injection of cidofovir. The lesions completely disappeared and she remained free of recurrence after 2 years.

PTLD

Table 3 shows the data of patients with intestinal involvement of PTLD following SOT in our cohort. A total of 50 recipients developed PTLD (1.4%), 15 of them with intraabdominal PTLD (mean age at diagnosis 38 years) and five of them ($n = 5$) presenting with intestinal involvement 3.8 years (mean) following transplantation. Three of them died of tumor progression or sepsis. In three patients, (no. 1, 4, 5, Table 3), intestinal or colonic PTLD led to perforation ($n = 3$). The small bowel recipient (no. 5, Table 3) developed PTLD infiltration of the graft and the colonic remnant with subsequent perforation. Finally the graft was removed, but this patient ultimately died from sepsis and multiorgan failure. In a heart recipient, a spontaneous coecal perforation was observed. This case was previously reported in detail [12]. A combined pancreas-kidney recipient presented with fever and diarrhea 1 year after transplantation and multiple colonic ulcers at colonoscopy suspecting ulcerative colitis. CMV colitis could not be confirmed. Within few days, the patient also developed pulmonary nodules and invasive aspergillosis was suspected. Treatment with voriconazole was initiated, which resulted in a dramatic increase of Tac trough levels. Biopsies from the colonic lesions and CT-guided percutaneous lung biopsies revealed PTLD

Table 2. Transplant recipients with anal neoplasia in long-term follow-up.

Patient no.	Gender	Age at diagnosis (years)	Organ	Anal neoplasm	Time to diagnosis (years)	Staging	Treatment	Status	Co-morbidities	IS	Graft rejection
1	M	61	Kidney	Anal cancer (margin)	12.5	pT2N0M0R0GII	Excision	Alive	Tubulovillous rectal adenoma	CsA, Aza, Steroids	none
2	M	39	Kidney	Anal cancer (margin)	2	pT1N0M0R1GII	Excision + RCx	Alive	Anal condyloma	CsA, Aza, Steroids	none
3	F	49	SPK	Anal canal cancer	10	pT2N1M0R0GII	RCx	Alive	None	CsA, Aza, Steroids	1x
4	F	35	Kidney	AIN III°	3.3	AIN III°	Laser + excision, imiquimod + cidofovir	Alive	CIN III°, VIN II°	CsA, Aza, Steroids	1x

SPK, simultaneous pancreas and kidney transplantation; RCx, radio-chemotherapy; CsA, cyclosporin A; Aza, azathioprine; CIN/VIN/AIN, cervical/vulva/anal intraepithelial neoplasia; IS, immunosuppression.

Table 3. Intestinal involvement of post-transplant lymphoproliferative disease.

Recipient no.	Age at diagnosis (years)	Gender	Organ	Year of Tx	Lymphoma	Localization	Years post-Tx	Treatment	State
1	27	M	Heart	2002	B-NHL	Intestinal	1	Surgery, anti-CD20, RCx	Alive
2	28	M	Kidney	1989	B-PTLD	Intestinal	5	Surgery, RCx	Alive
3	61	F	Kidney	2003	T-NHL	Intestinal	0	Surgery	Deceased
4	50	M	SPK	2002	B-NHL	Intestinal	1	Anti-CD20	Deceased
5	24	F	Small bowel	2005	B-PTLD	Intestinal	0	Surgery, anti-CD20	Deceased

Tx, transplantation; RCx, radio-chemotherapy; SPK, simultaneous pancreas and kidney transplantation.

(EBV associated CD-20 positive diffuse large B-cell lymphoma, Fig. 1a and b). Immunosuppression was switched to sirolimus and the patient was treated with an anti-CD20 antibody (rituximab) resulting in a massive tumor lysis and perforation of the transverse colon (Fig. 1c). The perforated segment was resected and a transverse colostomy performed. However, the patient died from massive tumor lysis, pulmonary hemorrhage, sepsis, and multiorgan failure.

Discussion

Post-transplant malignancies are a challenging problem with an increasing incidence. PTLD and skin cancer (including melanomas) are the most common malignancies. In our cohort, the incidence of colorectal cancer following SOT was equivalent to the general population in the SEER database (0.25% vs. 0.3%) [13]. Anal neoplasia, however, showed a higher incidence as compared with the general population due to an increased occurrence of squamous cell cancers of the skin in the transplant population (0.11% vs. 0.002%).

Although post-transplant colonoscopy is not proposed to be performed more frequently than outlined in current recommendations for the general population [5], screening for anal neoplasia appears to be indicated according to our data of increased incidence for post-transplant anal neoplastic lesions (0.11%). Recipients developing colorectal and anal neoplasia were switched to mTOR inhibitors (everolimus or sirolimus), although in one patient delayed wound healing of the sacral cavity (following rectal excision) was observed after administration of rapamycin. Those not receiving mTOR inhibitors showed a higher death rate when compared with the recipients being switched to rapamycin or everolimus (Table 1), however, with tumor progression observed in only one case. In addition to the antitumor effect [14] mTOR inhibitors have been proposed to possess antiproliferative properties that mainly affect hematopoietic and smooth muscle cells, thus preventing vascular hyperplasia and subsequent vasculopathy – the morphological sign of chronic allograft failure. Several protocols include mTOR inhibitors as an alternative to calcineurin inhibitors for the treatment of early impairment or delay in renal function or the long-term complication of post-transplant malignancy.

Malignant transformation of the perianal skin or anal canal is most likely associated with infection of high-grade human papilloma viruses (e.g. HPV 16, 18, 31, and 45), similar to that seen in CIN. It is well known that HPV infection is widespread in the general population even in the immunocompetent individual (50%) [15]. In our series only one case of high-grade AIN was documented, although assumed to be more often in immunosuppressed individuals [16]. It must be noted that proctologic examination is not yet routinely included in our follow-up visits of transplant recipients, indicating that anogenital HPV-associated lesions might have been missed.

Treatment of anogenital warts with use of imiquimod (Aldara^{TM}; Laboratories 3M Santé, Cergy-Pontoise, France) ointment or anal tampons has been suggested to stimulate hematopoietic cells (T-cells) and, therefore, is not to be used as first line therapy in transplant recipients. Our group investigated a new treatment option with use of cidofovir injections (Vistide^{TM}; Pfizer Enterprises, Luxembourg) intralesionally (H.B., unpublished observations). Here, we report of a 37-year-old female renal allograft recipient (no. 4, Table 2) who developed anogenital warts soon after renal transplantation with recurrent disease after primary fulguration and laser vaporization according to concurrent cervical infection. Ultimately, switch to rapamycin and intralesional cidofovir injections led to disappearance of the intraepithelial lesions and the patient is still free of recurrence.

However, guidelines for anal screening are still lacking [17]. Especially in patients at risk, such as HIV-positive and immunosuppressed individuals, screening should be conducted concurrently with cervical cancer screening due to their common etiology.

According to the data by Scholefield *et al.* [18], only high-grade AIN (AIN III°) in immunosuppressed patients underwent malignant transformation to invasive squamous cell carcinoma in 50% of cases during a 5-year follow-up.

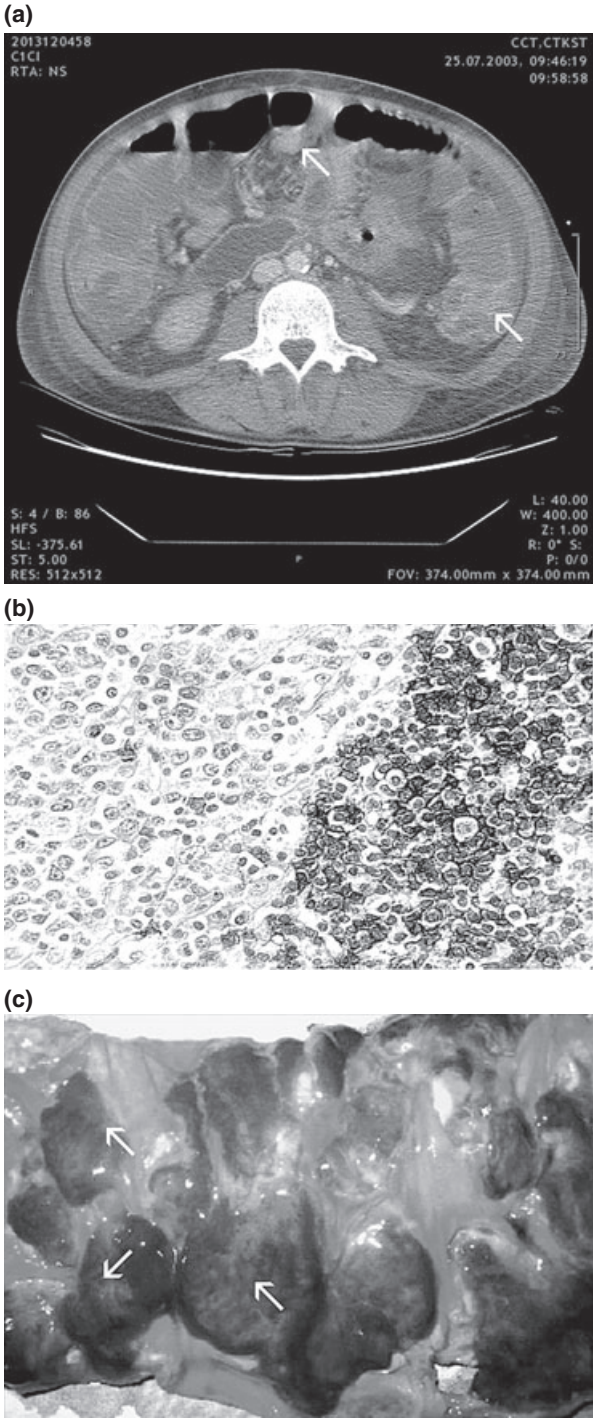

Figure 1 (a) Abdominal CT scan of a 50-year-old male recipient (no. 4, Table 3) following simultaneous pancreas and kidney transplantation with post-transplant lymphoproliferative disorders (PTLD) affecting the colon which resulted in perforation of the transverse colon. *White arrows* indicate colonic lymphoma. (b) Immunohistochemical staining of CD20 positive B-cells; monomorphic B-cell lymphoma obtained from colonic biopsies of the same patient. (c) Massive lymphoma infiltration of the colonic wall found on autopsy *(white arrows)*.

In terms of management of AIN or HPV-related dysplastic lesions, it remains unclear if radiation and/or chemotherapy in cancer patients may not have a negative effect as they increase the level of immunosuppression. Lowering the immunosuppression certainly may be of benefit but set recipients at higher risk of rejecting their organs. Also it is unclear whether immunostimulatory agents, such as imiquimod should be given to solid organ recipients as they may trigger acute graft rejection. The use of antivirals is a tempting approach; however, thus far no clinical trials have been reported.

Additionally, other viral infections, such as EBV, play an important role in the development of post-transplant malignancy due to immunosuppression. EBV-associated PTLD may also involve the gastrointestinal tract with serious complications including perforation of the intestinal wall, as observed in three recipients of our cohort (no. 1, 4, 5, Table 3). Consequently, two of them died despite immediate surgical intervention. After biopsy-proven diagnosis of PTLD as well as detection of primary or reactivation of EBV infection, the immunosuppressive medication was significantly reduced in one and discontinued in the other recipient. The incidence of PTLD in our cohort (1.4%) is similar to that described by others (0.8–20%) with an overall reported survival rate of only 25–60% [19,20]. The gut is likely to be affected in PTLD multicentrically or solitarily since it represents the largest lymphoid organ [21,22]. PTLD can continuously spread from surrounding tissue in particular from the mesenteric root. A significant increase in the overall incidence of PTLD has recently been observed and high risk groups such as children or recipients of intestinal grafts have been identified [23]. A remarkable difference in age at diagnosis between CRC, anal malignancies and PTLD could be demonstrated in our patients (65, 46, and 38 years respectively). Also the time point of diagnosis after transplantation differed between the tumor entities (5.3, 7, and 3.8 years respectively) with PTLD occurring in the youngest recipients earlier after transplantation.

However, clinical features in immunosuppressed recipients with gastrointestinal PTLD, such as anemia, gastrointestinal bleeding, weight loss, fever, hypoalbuminemia and protein-losing enteropathy, are similar to those of gastrointestinal lymphomas in patients without immunosuppression [21]. This justifies lower and upper gastrointestinal tract endoscopy at shorter intervals in order to establish the diagnosis of gastrointestinal PTLD and other malignancies [22].

In fact, there is a major difference in terms of risk for development of PTLD between the different types of transplanted organs. The EBV match between donor and recipient is a crucial factor, with EBV seronegative recipients receiving an EBV positive graft being at highest risk

[23,24]. It is also well established that the type and level of immunosuppression are important cofactors. Since 2003, a monoclonal anti-CD20 antibody (rituximab) is used in our center in recipients with intraabdominal PTLD.

In summary, post-transplant screening for viral infections, in particular HPV and EBV, and concomitant anogenital lesions such as CIN and AIN should be integrated into routine examinations of allograft recipients. One should also bear in mind, that PTLD can initially present with diarrhea or abdominal pain and lymphoma must be ruled out in these cases. Currently no evidence has been provided that routine colonoscopy for detection of colorectal cancer should be performed more frequently in the transplant population than currently recommended for the general population [4]. However, any nonspecific gastrointestinal symptom such as bleeding, protein-losing enteropathy, and weight loss in immunosuppressed patients should alert the clinician of the possibility of gastrointestinal PTLD, which demands colonoscopic evaluation. For this reason, endoscopically diagnosed pathologies such as polyps or ulcers, should be further investigated by biopsy and special immunohistologic techniques. In addition, serology and viral detection in blood or tissue specimens may help establishing an accurate diagnosis. Once malignancies have developed post-transplant, switch of the immunosuppressive regimen from calcineurin inhibitors to mTOR inhibitors, which seem to possess an antitumor effect, may be a promising strategy. Given the recent increase in long-term survivors of organ transplantation and the intensified immunosuppression that is applied today, one must be prepared for an increase in the incidence of post-transplant malignancies and also a change in the presentation, clinical course and outcome of their complications. Modern immunosuppressive drugs directed at potential antineoplastic effects (e.g. mammalian target of rapamycin, mTOR inhibitors) and overall less immunosuppression long-term may improve the prognosis of colorectal and anal malignancies following SOT.

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