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A RARE CASE OF TRANSPLANT HEPATECTOMY FOR METACHRONOUS COLORECTAL CANCER METASTASIS (*DE NOVO*)

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In the presented case, a patient who underwent liver transplant procedure for cirrhosis resulting from chronic hepatitis C was diagnosed with colorectal cancer 12 years after the operation. A combined treatment plan consisting of right hemicolectomy followed by nine cycles of adjuvant polychemotherapy using the FOLFOX6 regimen was performed. Seven months following the conclusion of treatment, 22×35 mm foci in segment 8 was detected as a sign of metastatic liver disease. The patient had a transplant hepatectomy. At present, the relapse-free survival is 22 months.

Keywords: liver transplantation, transplant hepatectomy, cirrhosis, colorectal cancer, liver metastasis.

INTRODUCTION

The number of organ transplant recipients continues to grow, reflecting significant advancements in transplant care within our country. According to the 15th Report from the Registry of the Russian Transplant Society, approximately 21,969 organ recipients were under medical follow-up in Russia by the end of 2022 – equivalent to 151.0 per 1 million population [1]. As clinical experience in managing these patients increases, so does the length of their post-transplant follow-up. However, the use of immunosuppressive therapy, an essential component of post-transplant care, remains a known risk factor for the development of malignancies at various time points after surgery [2].

Immunosuppressive therapy following organ transplantation compromises the recipient's ability to control viral infections, thereby increasing the risk of infection-associated malignancies such as non-Hodgkin's lymphoma, Kaposi's sarcoma, liver cancer, and cervical cancer. Certain immunosuppressive agents, particularly calcineurin inhibitors and azathioprine, have been shown to promote *de novo* carcinogenesis through mechanisms that extend beyond their immunosuppressive effects. The rising average age of transplant recipients further contributes to the overall increased risk of malignancy. In liver transplantation (LT) for hepatocellular carcinoma (HCC), tumor recurrence remains a significant concern. It is essential to differentiate between post-transplant recurrence of the primary tumor and the emergence of *de novo* malignancies. Less frequently, cancer may arise from latent malignancies in the donor that went undetected prior to organ procurement. However, current evidence suggests that the risk of donor-derived cancer transmission is extremely low – estimated at no more than 0.05% [3].

In Russian literature, studies addressing the risk of malignant neoplasms in transplant recipients are extremely limited [4]. In contrast, the international literature contains a substantially greater number of studies exploring the risk factors, incidence, and types of malignancies that occur following organ transplantation. Malignant tumors diagnosed in transplant recipients are more aggressive. Median survival rates for cancers such as colorectal, lung, breast, prostate, and bladder cancer are significantly lower in transplant patients compared to the general population [5–8].

A 2021 Mayo Clinic study examined the risk and timing of the most common gastrointestinal (GI) malignancies – particularly colorectal cancer (CRC) and pancreatic cancer – in liver transplant recipients, with the aim of optimizing screening strategies for this population. The study analyzed data from the United Network for Organ Sharing (UNOS) on the incidence of malignancies over a 20-year period (1997–2017) in post-transplant patients compared to the general population. A total of 866 *de novo* GI malignancies were identified, including 405 cases of CRC. The highest incidence of CRC was observed among recipients with primary sclerosing cholangitis, as well as in recipients over the age of 50 with cirrhosis due to nonalcoholic steatohepatitis, HCC, or cholangiocarcinoma. These findings help define a high-risk group of liver transplant recipients who may benefit

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from more intensive and individualized CRC screening protocols [9].

A 2021 study from South Korea analyzed 8,734 liver and kidney recipients, 66 of whom were diagnosed with *de novo* CRC. The incidence of *de novo* CRC in liver recipients was 3.1-fold higher in males and 2.25-fold higher in females. *De novo* CRC was diagnosed in 13.6% of patients within the first year after surgery, in 31.8% between 1 and 5 years, and in 54.6% more than 5 years after surgery [10].

An emerging area of particular clinical interest is the occurrence of CRC metastases in transplanted livers. The management and treatment strategies for such cases continue to be a subject of active research.

The world's first documented case of CRC metastasis in a transplanted liver was reported by Spanish authors in 2017. The patient was diagnosed with a well-differentiated colon adenocarcinoma 12 years after undergoing LT. Following colon resection, the patient's immunosuppressive regimen was modified to include an mTOR proliferative signaling inhibitor (everolimus). Six months later, follow-up imaging revealed metastatic lesions in segments IV and VII of the liver graft. The patient subsequently underwent a left hemihepatectomy combined with radiofrequency ablation of the lesion in segment VII [11].

In light of such occurrences, a 15-year follow-up case of a liver transplant recipient from our own clinical practice presents particular interest and is worthy of detailed discussion.

CASE DESCRIPTION

A 67-year-old male patient (52 years old at the time of LT) underwent orthotopic LT from a deceased donor on August 8, 2009, due to hepatitis C virus (HCV)-induced liver cirrhosis, classified as Child-Pugh class C. The indication for transplantation included decompensated cirrhosis with portal hypertension, grade 1–2 esophageal varices, splenomegaly with hypersplenism, and ascites. The postoperative period was uneventful.

The patient was initiated on standard immunosuppressive therapy with cyclosporine at a dose of 75 mg twice daily. In October 2009, routine biochemical testing revealed elevated liver enzyme levels. A liver biopsy was performed, confirming acute graft rejection. Glucocorticoid pulse therapy was administered, with a total dose of 2000 mg.

A month later, under the influence of glucocorticoid therapy, an increase in the patient's HCV viral load was observed. As a result, antiviral therapy with pegylated interferons combined with ribavirin was initiated in December 2009. A delayed virologic response was achieved by June 2010.

In August 2010, a protocol biopsy of the liver graft revealed moderate fibrosis, corresponding to F2 on the Knodell, METAVIR, and Ishak scoring systems. However, six months after completing antiviral therapy, in December 2010, HCV reappeared in the bloodstream.

From May 27 to July 21, 2016, the patient was hospitalized due to graft dysfunction caused by severe acute rejection, confirmed by histological examination. Two courses of intravenous methylprednisolone pulse therapy were administered. In response to ongoing graft dysfunction, immunosuppressive therapy was modified – cyclosporine was discontinued and replaced with tacrolimus at a dose of 2.5 mg twice daily. Following clinical improvement, the patient was discharged for continued outpatient follow-up.

In the autumn of 2016, the patient underwent antiviral therapy for hepatitis C using a regimen of direct-acting antivirals (DAAs), specifically sofosbuvir and ledipasvir, administered over a 6-month course. Since the initiation of DAA therapy, hepatitis C RNA has remained undetectable in the blood by polymerase chain reaction (PCR).

In September 2017, the patient presented with severe generalized weakness, jaundice, and itching. Diagnostic evaluation revealed an anastomotic biliary stricture causing obstructive jaundice. Management was staged: initially, percutaneous transhepatic cholecystostomy was performed under ultrasound guidance for external biliary drainage, aiming to decompress the biliary system and reduce bilirubin levels. Following stabilization, a Roux-en-Y hepaticojejunostomy was performed on September 17, 2017.

The postoperative period was complicated by intra-abdominal bleeding and the formation of an abdominal hematoma, necessitating multiple relaparotomies and abdominal cavity sanitation procedures. The patient developed sepsis, which was managed successfully with intensive antibacterial therapy. After stabilization, the patient was discharged and has since been monitored on an outpatient basis.

In January 2021, following a COVID-19 infection, a routine follow-up examination revealed a decrease in the patient's hemoglobin level to 89 g/L for the first time. In accordance with the diagnostic protocol for anemia of unclear etiology, standard tests were initiated. Video-guided esophagogastroduodenoscopy showed no abnormalities. However, video-guided colonoscopy identified a tumor in the hepatic flexure of the colon (Fig. 1). A biopsy was performed, and histological analysis confirmed a moderately differentiated adenocarcinoma of the colon.

A computed tomography (CT) scan of the abdomen and pelvis revealed thickening of the colonic wall in the region of the hepatic flexure, with no evidence of additional focal pathology in the abdomen. A chest CT scan showed no signs of pulmonary lesions. Tumor marker levels were as follows: carbohydrate antigen (CA) 19-9 at 15.4 U/mL and carcinoembryonic antigen (CEA) at 2.28 ng/mL. Based on clinical and histological findings, the patient was diagnosed with colon cancer of the hepatic flexure: cT4aN0M0 G2 (moderately differentiated

adenocarcinoma), corresponding to stage IIB, clinical group 2. Immunosuppressive therapy was modified by reducing the dose of tacrolimus and introducing everolimus.

On December 02, 2021, the patient underwent radical surgical treatment – extended right hemicolectomy, D3 lymphadenectomy. Histological examination of the tumor: moderately differentiated adenocarcinoma pT4aN1c.

After surgical treatment, the patient underwent 9 cycles of adjuvant polychemotherapy (PCT) using the FOLFOX6 regimen. This included oxaliplatin (85 mg/m^2 administered intravenously over 2 hours on day 1), calcium folinate (400 mg/m^2 intravenously over 2 hours), followed by an intravenous bolus of fluorouracil (400 mg/m^2), and a continuous 46-hour infusion of fluorouracil (total dose 2400 mg/m^2, 1200 mg/m^2 per day). All PCT cycles were completed without dose reduction by August 2021.

During a routine follow-up examination on March 22, 2022 – seven months after completing chemotherapy – an abdominal CT scan revealed a mass in the right lobe of the liver graft, measuring 22×35 mm (Fig. 2).

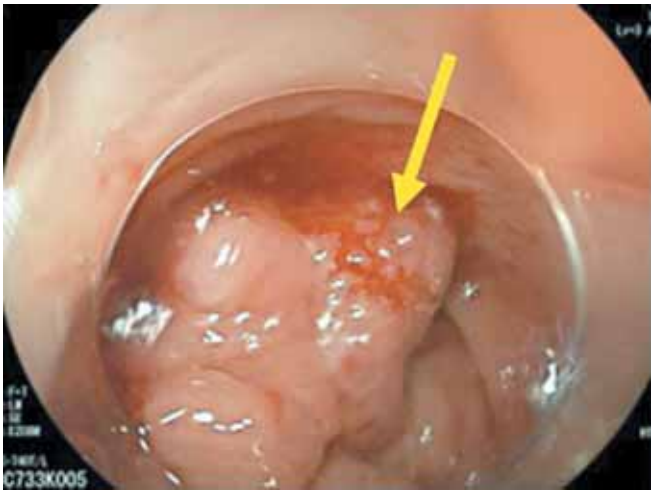

Fig. 1. Video colonoscopy. Hepatic flexure colon cancer in a patient (arrow)

A PET-CT scan performed on April 7, 2022 (Fig. 3) revealed a secondary lesion in the liver graft, demonstrating increased metabolic activity with a maximum standardized uptake value (SUVmax) of 5.61. No other hypermetabolic foci were detected.

As part of the diagnostic protocol, the patient underwent video colonoscopy on April 11, 2022. The findings were consistent with status post right hemicolectomy, and no focal pathology was observed. Blood tumor marker levels were as follows: CA 19-9 at 20.1 U/mL and CEA at 4.55 ng/mL. The Fong Clinical Risk Score for colorectal cancer recurrence was 2, indicating an estimated one-year survival of 89% and a 5-year survival of 40% following metastasectomy.

On May 16, 2022, the patient underwent atypical resection of liver segment 8. Intraoperatively, the liver appeared steatotic. A focal lesion measuring 25×35 mm was identified on the diaphragmatic surface of segment 8. Intraoperative ultrasound of the liver graft confirmed the absence of additional focal lesions (Fig. 4).

Histopathological examination of the resected liver specimen confirmed the diagnosis of metastatic colorectal adenocarcinoma. The demarcated edge located in non-tumorous liver tissue (R0) (Fig. 5).

Molecular genetic analysis of the extracted DNA revealed an activating G13D mutation in exon 2 (codon 12) of the KRAS gene (NM_033360.3), which is known to confer resistance to anti-epidermal growth factor receptor (EGFR) therapy.

In light of these findings, immunosuppressive therapy was adjusted to monotherapy with everolimus, a proliferation signal inhibitor in the mammalian target of rapamycin (mTOR) drug class.

The patient was discharged from the hospital on postoperative day 7 in satisfactory condition. However, on day 14, his condition deteriorated with the onset of tachyarrhythmia. He was urgently admitted to a city cardiology on-call hospital with an episode of paroxysmal atrial fibrillation, which was managed conservatively.

During further evaluation, right-sided hydrothorax was identified. Repeated pleural punctures were perfor-

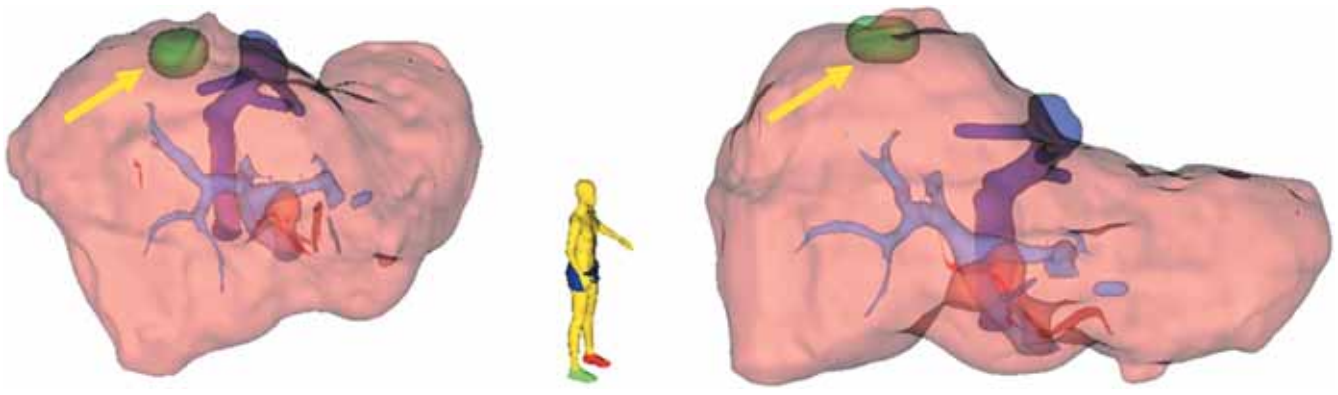

Fig. 2. CT modeling of a focal liver graft mass in a patient. Metastasis is indicated by an arrow

med, and serous fluid was evacuated. Subsequently, the patient developed pleural empyema accompanied by signs of sepsis. In this connection, he was transferred to an oncologic dispensary for inpatient management.

From June 23 to August 1, 2022, he underwent treatment for pleural empyema and hemothorax, which included drainage and sanitation of the right pleural cavity, along with antibacterial therapy. He experienced

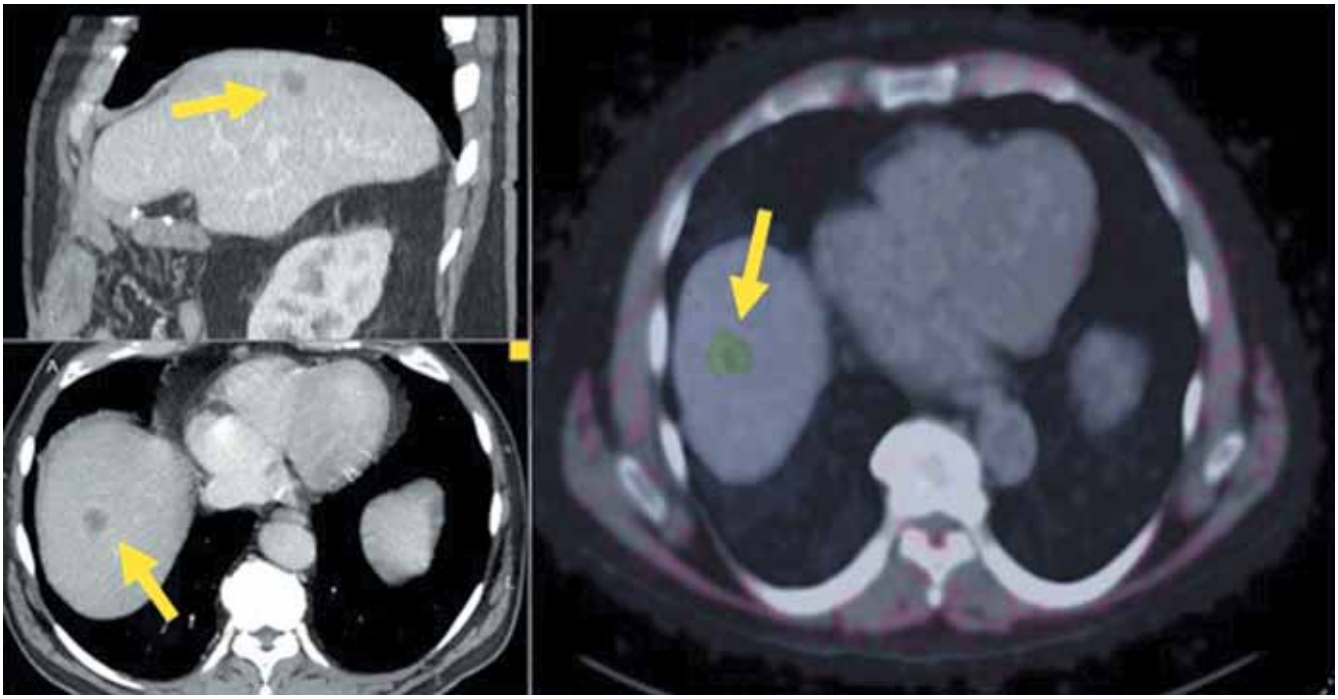

Fig. 3. Computed tomography and positron emission tomography images in a patient. Metastasis is indicated by an arrow

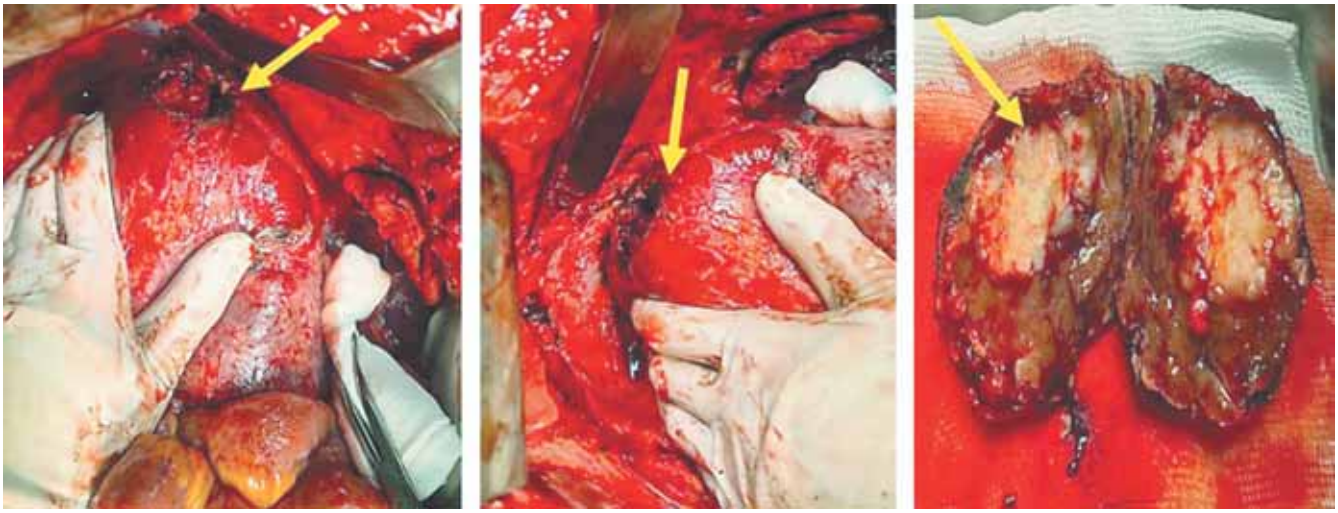

Fig. 4. Intraoperative photo (arrows indicate liver graft metastasis)

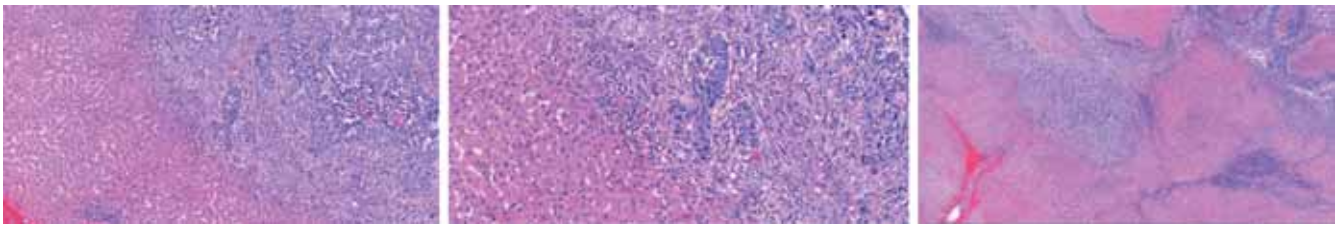

Fig. 5. Morphological examination of the removed liver graft metastasis

a prolonged febrile period with body temperatures reaching 38–39 °C. Once his condition stabilized, he was discharged for outpatient follow-up.

At the end of August 2022, the patient again developed a fever reaching 38.9 °C. From September 5 to October 11, 2022, he underwent inpatient treatment in the surgical organ transplant department, Privolzhsky District Medical Center, presenting with right-sided hydropneumothorax and pneumonia of the upper lobe of the left lung. Despite antibacterial therapy with Thienam (2 g/day), the fever persisted. Microbiological culture of the right pleural cavity revealed Acinetobacter baumannii at a concentration of 10^5 CFU/mL. Following a change in antibiotic therapy to Baccefort (4 g/day), the patient's fever subsided, and he was discharged in satisfactory condition.

At present, the patient remains under regular outpatient follow-up. Colonoscopy, as well as abdominal and chest CT scans, are conducted according to established surveillance protocols. As of the time of writing this paper, there is no evidence of recurrence of the oncologic process, and liver graft function remains satisfactory. The duration of follow-up since the transplant hepatectomy is 22 months.

DISCUSSION

Liver transplant recipients face an elevated risk of developing *de novo* malignancies due to prolonged immunosuppressive therapy required to prevent acute and chronic graft rejection. The overall incidence of CRC in this population is higher compared to the general population. Although current strategies aimed at reducing immunosuppressive load have helped mitigate the risk of *de novo* cancers, they do not fully eliminate the potential for graft fibrosis and rejection.

A French national study found that 13.45% (1,480) of 11,004 adult patients who received a liver transplant between 2000 and 2013 developed a *de novo* malignancy. The most common types of *de novo* malignancy were: hematological malignancy (22.36%), non-melanoma skin cancer (19.53%), and lung cancer (12.36%); CRC (4.9%) ranked 6th [12]. According to a systematic review and meta-analysis including 29 studies, the risk of developing CRC in patients who have had a liver transplant is 2.6 times (95% CI 1.7–4.1) higher than in the general population, and the risk of *de novo* cancer gradually increases starting from the first year after transplantation and peaks after 6–10 years of follow-up [13, 14]. In this regard, the International Liver Transplantation Society (ILTS) at the ILTS-SETH conference (2022) adopted a consensus on prevention and early detection of *de novo* malignancies after liver transplantation with recommendations to perform colonoscopy 1 year after transplantation and then 3–5 years later. Earlier and more frequent screening is indicated for high-risk patients (liver transplantation for hepatocellular carcinoma, primary sclerosing cholangitis, over 50 years of age, with a history of colon polyps) [15].

CRC is still the third most commonly diagnosed malignancy in the general population, accounting for 7.2% [16].

Long-term survival of liver recipients and the increasing trend for patients to receive a donor organ at an older age have added additional risks of developing CRC. CRC after LT is more often a right-sided lesion, is aggressive, and is associated with a higher rate of metastasis and poor survival [17].

Specialized treatment for relapsed or *de novo* cancer in transplant recipients should adhere to general oncologic principles as outlined in current clinical guidelines [18].

In the presented clinical case, the patient underwent definitive surgical intervention as the initial step, which remains the optimal treatment approach for a primary localized colorectal malignancy. Based on histopathological analysis of the resected specimen, the disease was restaged as pT4aN1c, warranting the initiation of adjuvant chemotherapy using the FOLFOX regimen to reduce the risk of disease progression [19].

Large-scale studies have demonstrated that adjuvant chemotherapy significantly improves both overall survival and progression-free survival in patients with stage $N \geq 1$ or stage T3N0M0 colorectal cancer [20, 21]. Notably, adjuvant chemotherapy can be administered effectively alongside standard immunosuppressive therapy without the need for dose reduction [22].

In the general population, 30–50% of CRC patients develop liver metastases [23]. In the present clinical case, dynamic follow-up revealed metastatic lesions within the liver graft. Transplant hepatectomy, at this stage of surgical advancement, remains a relatively rare procedure. A significant contribution to the understanding of liver resections in transplant recipients was provided by the Charité Clinic in 2020. Between 2004 and 2017, the clinic performed 4,100 liver resections, of which 14 were in patients who had previously undergone LT (0.34%). The primary indications for liver resection after transplantation included recurrent combined hepatocellular-cholangiocarcinoma and post-LT biliary and vascular complications leading to liver abscesses. However, metastatic lesions developing in a transplanted liver in the context of a *de novo* cancer are extremely rare.

According to European, American, and Asian guidelines, surgical resection is the recommended first-line treatment for resectable colorectal liver metastases, given its high efficacy compared to other methods [24–27]. Following these clinical guidelines, the patient underwent surgical treatment, specifically an R0 liver resection. Early diagnosis and radical treatment in accordance with established standards have resulted in a favorable long-term outcome, with the patient remaining recurrence-free for 22 months.

CONCLUSION

As the number of organ recipients increases, along with the age of recipients and the duration since transplantation, the risks of malignancies also rise. These trends are becoming more prominent in contemporary medical practice.

To detect *de novo* cancers early in solid organ recipients, regular follow-ups with both transplant surgeons and oncologists are essential. Upon the detection of cancer, immunosuppressive therapy should be switched to mTOR proliferation signal inhibitors. The treatment of malignancies in organ transplant recipients should adhere to general oncological principles as outlined in clinical guidelines. While a history of solid organ transplantation in cancer patients necessitates adjustments to immunosuppression, it does not limit the use of systemic polychemotherapy.

This clinical case highlights the need for a multidisciplinary approach in managing patients after organ transplantation, emphasizing the collaborative efforts of transplant specialists, hepatologists, infectious disease experts, oncologists, chemotherapy specialists, and other healthcare professionals.

The authors declare no conflict of interest.

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