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Carcinoma of donor origin after liver-intestine transplantation in a child

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Abstract: Tumor-related complications after intestinal transplantation in children have been principally EBV driven post-transplant disorders. We describe the clinical course of a child, with a diagnosis of microvillus inclusion disease who received a liver and intestine allograft at the age of 9 months. His postoperative course was significant for multiple episodes of acute intestinal allograft rejection and eventually the development of post-transplant lymphoproliferative disorder (PTLD), which resolved. At 8 yr post-transplant he presented with masses in the intestine allograft mesentery and in the right lobe of the allograft liver, biopsy of which revealed a relatively undifferentiated tumor, suggestive of a carcinoma. *In situ* hybridization for X and Y chromosomes, revealed his tumor to be of donor origin. Treatment included debulking of the mesenteric mass with segmental enterectomy of the intestinal allograft, and stopping his immunosuppression for a period of 4 months; this resulted in complete resolution of his malignancy. Immunosuppression with tacrolimus and steroids was restarted because of intestinal allograft rejection; he died suddenly of unknown causes at 17 months post-diagnosis of carcinoma.The severely immunosuppressed state produced in this patient allowed for the development of an unusual donor derived carcinoma, which resolved spontaneously with withdrawal of immunosuppression. The mechanism of such regression of tumor may be related to restitution of immunologic competence, but is yet to be determined.

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Post-transplant lymphomas account for the majority (53%) of malignancies seen after solid organ transplantation. In decreasing frequency, skin and lip carcinomas (19%), sarcomas (4%), carcinomas of the vulva and anus (4%), hepatic neoplasm (3%), carcinomas of the thyroid (3%), and Kaposi's sarcoma (2%) account for the remainder (1). After intestinal transplantation in children, post-transplant malignancies have been generally associated with EBV-driven PTLD, which has occurred at a significantly increased frequency, exceeding 25% (2, 3). This patient population has also seen the occurrence of the unusual EBV-driven PTSD (4). With either disease the implication of the donor or recipient cell nature of the malignancy has yet to be ascertained. With bone marrow transplantation, although tumor post-transplantation are less frequent, they are usually donor derived (5).

Primary tumors of donor origin (the allograft) are rarely encountered in children. This report describes a donor-derived carcinoma arising from a small bowel allograft in a 9-yr-old boy after combined liver–intestine transplant.

Case report

This boy received a liver-intestine allograft from a 1.5-yr-old female donor at the age of 9 months as treatment for intestinal failure secondary to microvillus inclusion disease and total parenteral nutrition (TPN)-induced cirrhosis. Over the course of the eight post-transplant years, this child experienced seven episodes of acute cellular rejection. These episodes ranged in severity from mild (n = 6) to moderate (n = 1) (6). Each episode resolved with bolus steroid therapy as

Abbreviations: CMV, cytomegalovirus; EBV, Epstein–Barr virus; PTLD, post-transplant lymphoproliferative disease; PTSD, post-transplant spindle cell disease.

previously described (7), adjustments in tacrolimus levels target to levels of 15 ng/mL.

He developed EBV-positive cells in his allograft documented at surveillance allograft endoscopy and biopsy 8 yr after transplant and 1 yr after the most recent episode of acute cellular rejection. His EBV-PCR at that time was 2000 viral genome copies per 10^5 peripheral blood mononuclear cells (8). No masses or lymphadenopathy were observed on physical examination or CT scan of the abdomen, chest, and neck. His tacrolimus dose was reduced and he received antiviral therapy with CMV immunoglobulin (Cytogam®; Massachusetts Public Health Biologic Laboratories, Boston, MA, USA) and ganciclovir (9). After 1 month, his EBV-PCR rose to 5000 viral genome copies per 10^5 peripheral blood mononuclear cells and a new endoscopy with biopsy of the allograft ileum showed a polymorphous PTLD. *In situ* hybridization for EBV (EBER-1 stain) revealed numerous positive lymphocyte nuclei, up to 20 per high power field; only rare lymphoid cells in the infiltrate expressed CD20 immunostaining. Immunosupression was stopped and anti-CMV immunoglobulin and ganciclovir were administered as previously described (7). Further endoscopies showed improving PTLD lesions in the allograft ileum, but a biopsy showed evidence of acute cellular rejection which was treated with steroids. At the end of the treatment, his EBV-PCR was undetectable and EBER-1 stain of the last biopsy showed rare positive cells (3 cells/hpf). The patient was restarted on tacrolimus, rapamycin and prednisone.

Nine months after the resolution of PTLD the patient was admitted with fever and a palpable abdominal mass. An abdominal CT scan demonstrated a large lobular mesenteric mass (95.3 cm^3), extending from the level of the lower pole of the right kidney into the right pelvis (Fig. 1). There were six low-density liver lesions, the largest being 1 cm, spread through the right and left hepatic lobes. The bone scan did not show skeletal metastases and the bone marrow aspirate was negative for malignant cells.

Percutaneous biopsy of the liver lesion revealed a relatively undifferentiated tumor, suggestive of a carcinoma. The patient eventually underwent an exploratory laparotomy and open biopsy of the mesenteric mass which showed a poorly differentiated carcinoma of the small bowel that was initially thought to be unresectable. Postoperatively, the patient experienced two episodes of small bowel perforation treated first with operative closure and subsequently with diversion ileostomy. The fistulas recurred and at the next exploration the tumor was resected

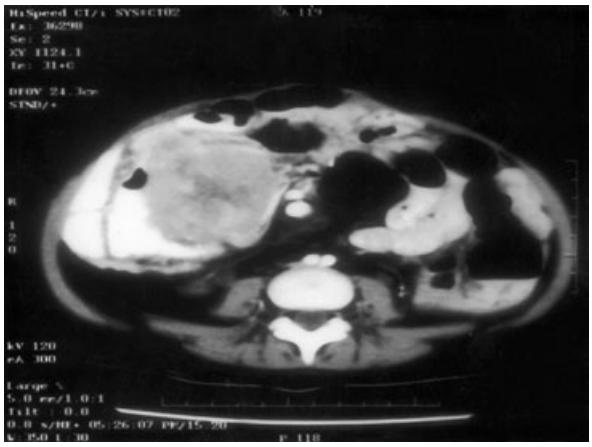

Fig. 1. Abdominal CT-scan showing the intestinal allograft tumor.

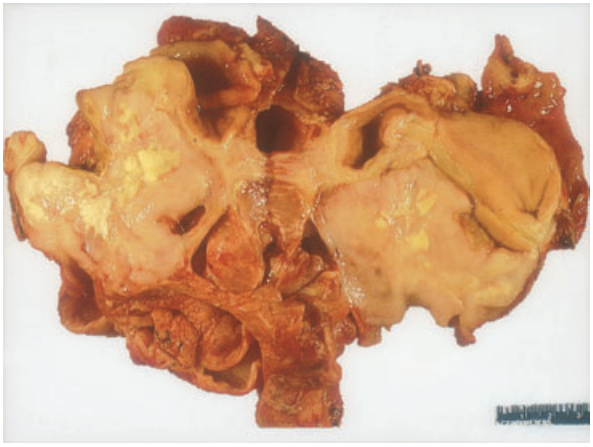

Fig. 2. Gross tumor in small bowel mesentery encasing segment of allograft intestine.

along with a segment of small bowel allograft (100 cm) (Fig. 2). Gut continuity was reestablished with an ileocolic anastomosis; approximately 80 cm of small bowel allograft were left. The final pathology revealed a primary allograft small intestinal carcinoma of pleomorphic histology, with neuroendocrine and undifferentiated components (Fig. 3), multiple lymph node metastases, an adenomatous polyp in the resected allograft ileum with no evidence of acute cellular rejection, and *in situ* hybridization for EBV (EBER-1 stain) negative. *In situ* hybridization for X and Y chromosomes was performed on the tumor tissue, utilizing a dual color probe. Targeted hybridization of 203 cells showed 202 of 203 cells containing two chromosome X centromeres (99.5%) and one of 203 cells (0.5%) containing one X centromere and one Y satellite III region suggesting that the tumor tissue was of a female donor genotype.

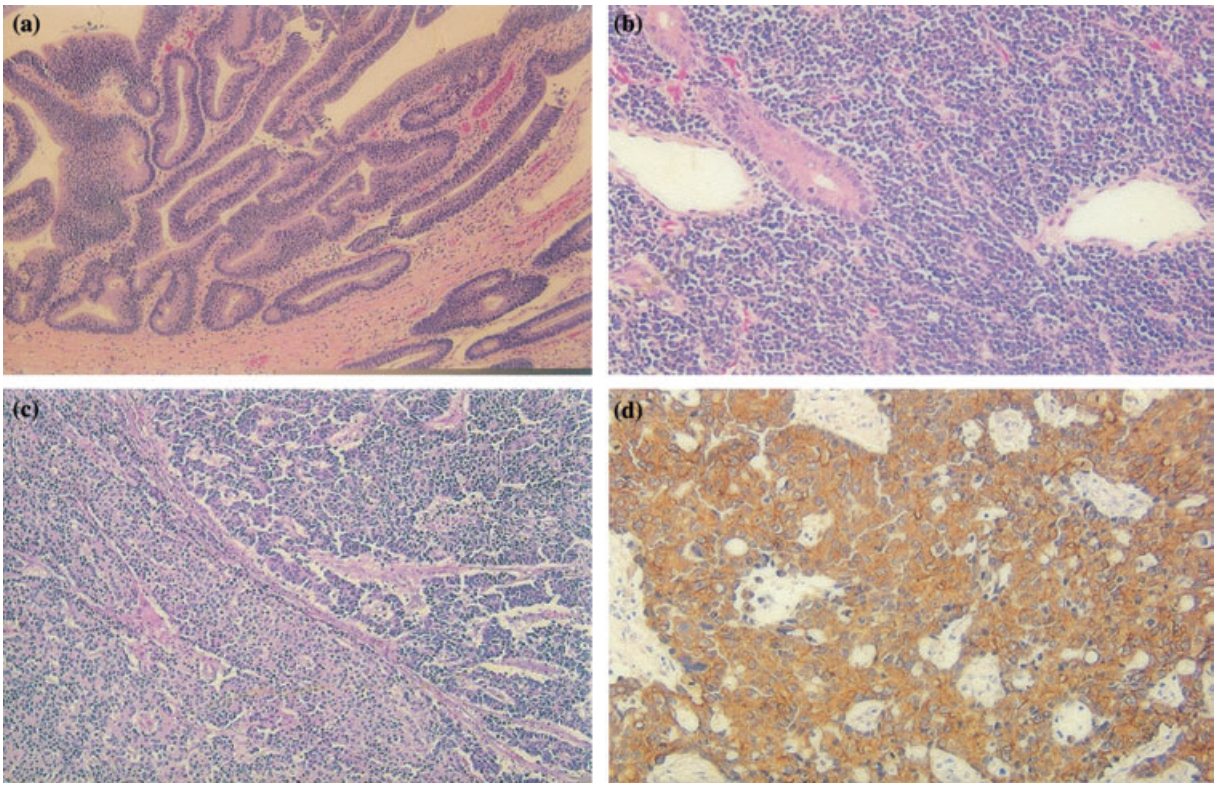

Fig. 3. (a) Intestinal epithelium at the edge of the ulcer is hyperplastic and proliferative. (b) Tumor in many areas was undifferentiated and mimics lymphoma. The cells in this area also express cytokeratins. (c) Tumor appearance varies. In most areas the tumor formed sheets and nests, reminiscent of carcinoid as seen in the lower left field. The other half of the field has features more suggestive of a carcinoma. (d) Cytokeratin staining shows intense and diffuse positivity in a cohesive carcinomatous pattern.

Postoperatively, immunosupression was completely withdrawn. It was elected to treat the patient with a chemotherapeutic regimen consisting of Carboplatin and VP-16. Intense neutropenia after the first cycle of chemotherapy responded to infusion of granulocyte colony stimulating factor (Neupogen®; Amgen Inc., Thousand Oaks, CA, USA), however, the parents refused additional chemotherapy. Immunossupression was restarted after 4 months as a result of mild rejection of the small bowel allograft. At this time he received 50% of his caloric intake orally, and 50% of his caloric intake via total parenteral nutrition given at night. A follow-up abdominal CT scan at 10 months showed no metastatic liver lesions and no recurrent abdominal masses. Although it appeared that the child had attained significant recovery, he died suddenly at home from unknown causes 12 months after diagnosis of carcinoma, and no autopsy was performed.

Discussion

Solid organ allograft acceptance requires continuous long-term immunosupression. Cancer development has been linked to this immunossupressed state (10). The most common tumors in pediatric organ allograft recipients are lymphomas (53%) with a preponderance of recipients of non-renal organs (61%) (11). This patient population is also increased risk for developing an assortment of viral infections, including EBV. This common viral pathogen can cause B cell growth transformation by expressing certain viral factors such as EBNA-2 and LMP-17. In the immunossupressed state, these viral growth factors cause a sustained proliferation of B lymphocytes, which frequently result in malignant transformation (12). Because EBV transmission approaches 60–80% in EBV seronegative children in the early post-transplant period, these patients are at a particularly higher risk for developing EBV-related lymphomas (1, 11, 12).

Immunosupression after solid organ transplantation may also increase the risk for development of smooth muscle tumors and a few such cases have been described (4, 13, 14) Leiomyosarcomas after solid organ transplantation are also related to EBV infection; recently,

monoclonal or biclonal latent EBV infection have been documented in some cases of smooth muscle tumors associated with AIDS (15).

In this case, the carcinoma was not EBV driven; however, there was a need for high levels of immunosuppression to maintain intestinal allograft function. *In situ* hybridization showed a donor-derived adenocarcinoma with 202 of 203 tumor cells presenting two X-chromosomes centromeres; this showed the female genotype of the tumor cells. This is the first report of a donor derived epithelial tumor of allograft intestine. Upon identification of the donor origin in our patient we notified the regional organ procurement agency and none of the recipients of the same donor's kidney or heart, all transplanted at other centers, have evidence of donor-derived carcinoma.

The diagnosis of small bowel tumors is based on a high index of clinical suspicion. Palpable masses develop in 10–20% of patients with small bowel tumors and even in the presence of symptoms (obstruction, anemia, weight loss) the diagnoses has proven to be difficult (16). The treatment of small intestine adenocarcinomas is based on surgical resection. Total removal of the malignancy with contiguous excision of surrounding zones of anticipated spread is the most rational approach (16). Because of the low incidence of adenocarcinoma of the small bowel, experience with the use of chemotherapy is sparse (17). For the most part, chemotherapy has been reserved for metastatic disease.

De novo and recurrent malignancies are the second leading causes of late death in liver transplant recipients, following age-related cardiovascular complications (18); few cases of non-lymphoid solid organ tumors from donor origin have been reported. Florman et al. (19) had described their experience with a patient with squamous cell carcinoma of donor origin treated with withdrawal of immunosuppression and liver retransplantation, Chan et al. (20) described *de novo* sarcoma of donor origin in a liver allograft, and Stephens et al. (21) published their experience with fatal transfer of malignant melanoma from multiorgan donor to four allograft recipients. The nature of *de novo* malignancies in the transplant setting has certainly established its relationship with immunosuppressive drug therapy and in some cases infection with EBV (principally lymphoid tumors) (18). However, the donor derived nature and significance is yet to be determined, other than that it may carry a worse prognosis (22).

In this case it was elected to withdraw immunossupression as it played a major role as a cause for the development of the tumor, although this was not an EBV-driven process. More so, the donor derived nature of this tumor suggested the restitution of the patient's immunity could have facilitated resolution. With resection of the primary tumor and withdrawal of the immunossupression the patient resolved the liver metastases and had a tumor-free survival of 19 months. The need for reinstitution of immunosuppression for maintenance of intestinal allograft is very common with this type of organ transplant, unlike recipients of liver allograft where immunosuppression may sometimes be withheld indefinitely (23). The eventual sudden and unexpected death of this child was in essence predictable, given the complex post-transplant course (including the need to resume TPN), but leaves many unanswered questions for which we cannot speculate.

In summary, the incidence of post-transplant donor origin non-lymphoid tumors is low and no standard treatment has been established (19– 22). Withdrawal of immunosuppresssion has been shown to be effective in the treatment of this condition; however, close monitoring of these patients is required because of the increased risk of rejection. Retransplantation may be curative if the malignancy is limited to the transplanted organ. The benefit of the use of chemotherapy or radiation therapy for these tumors is speculative and should be individualized, as such conventional therapy may harmful in this case.

References

1. Penn I. De novo tumors in pediatric organ transplant recipients. Transplant Proc 1994: 26: 1–2.
2. Reyes J, Tzakis A, Green M, et al. Posttransplant lymphoproliferative disorders occurring under primary FK 506 immunosuppression. Transplant Proc 1991: 23: 3044–3046.
3. Reyes J, Mazariegos GV, Bond GMD, et al. Pediatric intestinal transplantation: historical notes, principles and controversies. Pediatr Transplant 2002: 6: 193–207.
4. Lee ES, Locker J, Nalesnik M, et al. The association of Epstein-Barr virus with smooth-muscle tumors occurring after organ transplantation. N Engl J Med 1995: 332: 19–25.
5. Baker KS, DeFor TE, Burns LJ, Ramsay NK, Neglia JP, Robison LL. New malignancies after blood or marrow stem-cell transplantation in children and adults: incidence and risk factors. J Clin Oncol 2003: 21: 1352–1358.
6. White FV, Reyes J, Jaffe R, Yunis EJ. Pathology of intestinal transplantation in children. Am J Surg Pathol 1995: 19: 687–698.
7. Reyes J, Bueno J, Kocoshis S, et al. Current status of intestinal transplantation in children. J Pediatr Surg 1998: 33: 243–254.
8. Rowe DT, Webber S, Schauer EM, Reyes J, Green M. Epstein-Barr virus load monitoring: its role in the prevention and management of post-transplant lymphoproliferative disease. Transpl Infect Dis 2001: 3: 79–87.

9. Green M, Reyes J, Webber S, Rowe D. The role of antiviral and immunoglobulin therapy in the prevention of Epstein-Barr virus infection and post-transplant lymphoproliferative disease following solid organ transplantation. Transpl Infect Dis 2001: 3: 97–103.
10. Penn I. Post-transplant malignancy: the role of immunosuppression. Drug Safety 2000: 23: 101–113.
11. Penn I. De novo malignancy in pediatric organ transplant recipients. J Pediatr Surg 1994: 29: 221–226.
12. Younes BS, McDiarmid SV, Martin MG, et al. The effect of immunosuppression on posttransplant lymphoproliferative disease in pediatric liver transplant patients. Transplantation 2000: 70: 94–99.
13. Danhaive O, Ninane J, Sokal E, et al. Hepatic localization of a fibrosarcoma in a child with a liver transplant. J Pediatr 1992: 120: 434–437.
14. Timmons CF, Dawson DB, Richards CS, Andrews WS, Katz JA. Epstein-Barr virus-associated leiomyosarcomas in liver transplantation recipients. Origin from either donor or recipient tissue. Cancer 1995: 76: 1481–1489.
15. McClain KL, Leach CT, Jenson HB, et al. Association of Epstein-Barr virus with leiomyosarcomas in children with AIDS. N Engl J Med 1995: 332: 12–18.
16. Ashley SW, Wells SA. Jr. Tumors of the small intestine. Semin Oncol 1988: 15: 116–128.
17. Neugut AI, Marvin MR, Rella VA, Chabot JA. An overview of adenocarcinoma of the small intestine. Oncology (Huntingt) 1997: 11: 529–536.
18. Fung JJ, Jain A, Kwak EJ, Kusne S, Dvorchik I, Eghtesad B. De nove malignancies after liver transplantation: a major cause of late death. Liver transpl 2001: 7: S109–S118.
19. Florman S, Bowne W, Kim-Schluger L, et al. Unresectable Squamous cell carcinoma of donor origin treated with immunosuppression withdrawal and liver retransplantation. Am J Tranplant 2003: 4: 278–282.
20. Chan SC, Cheung ST, Leung SY, Liu CL, Fan ST, Lo CM. De novo sarcoma of donor origin in a liver allograft determined by microsatellite analysis: a short report. Liver Tranpl 2004: 10: 320–323.
21. Stephens JK, Everson GT, Elliott CL, et al. Fatal transfer of malignant melanoma from multiorgan donor to four allograft recipients. Transplantation 2000: 70: 232–236.
22. Ng IO, Shek TW, Thung SN, et al. Microsatellite analysis in post-transplantation lymphoproliferative disorder to determine donor/recipient origin. Mod Pathol 2000: 13: 1180–1185.
23. Cacciarelli TV, Reyes J, Jaffe R, et al. Primary tacrolimus (FK 506) therapy and the long-term risk of post-transplant lymphoproliferative disease in pediatric liver transplant recipients. Pediatr Transplant 2001: 5: 359–364.