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Management of recipients of hepatic allografts harvested from donors with malignancy diagnosed shortly after transplantation

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Abstract: Transmission of undiagnosed malignancy with the graft is a dramatic complication of liver transplantation. Alternatives in the management of the recipients of livers, harvested from donors with malignancy diagnosed shortly after transplantation, are either early re-transplantation or close follow-up without re-operation. We reported 4 cases of liver recipients whose allografts were harvested from donors who were diagnosed with malignancy shortly after the liver transplantation. One recipient underwent re-transplantation, and the three other allografts were not removed. No recipient developed recurrence in the follow-up. While graft removal may be the only way to avoid tumor recurrence in recipients of liver graft harvested from donor with malignancy, close follow-up without re-operation may also be considered. The risk of tumor transferral may depend on the histopathological aggressiveness and metastatic potential of the donor tumor, and may be low for low-grade, local tumors. This risk should be evaluated by analyzing large series, using databases of Eurotransplant or United Network for Organ Sharing.

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Key words: hepatic allografts – malignancy diagnosis – transplantation

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Malignancy transmission from the donor to the recipient is a rare but dramatic complication of solid organ transplantation. In our institution, 1 kidney and 1 liver recipient both developed recurrence of an undiagnosed choriocarcinoma that led to donor's death (1). Since these two cases, we have received from Eurotransplant two liver allografts which were harvested from donors with undiagnosed malignancy and which were transplanted in our institution. We also diagnosed a renal-cell carcinoma in a renal graft, whose corresponding liver was split and transplanted into two recipients in two other centers.

Management of the recipients of liver allografts harvested from donors with malignancy diagnosed shortly after transplantation has not been established because only a few cases have been reported in the literature. The alternatives are either early re-transplantation or close follow-up without re-operation in order to detect any recurrence. Based on our first unfortunate experiences and on the literature (2), we initially recommended early re-transplantation (1). We successfully applied this policy in a recipient of a liver whose donor was later diagnosed with a disseminated epidermoid epithelioma. However, we recently chose not to re-transplant the recipient of a liver graft harvested from a donor with undiagnosed renal-cell carcinoma. The purpose of this paper was to report these cases and to explain the changes in our management policy.

Case series

Recipient 1

In June 1990, Eurotransplant sent a hepatic allograft harvested from a 35-yr-old female donor, who had died from spontaneous cerebral hemor-

rhage. We transplanted this graft into a 25-yr-old recipient. Donor autopsy was performed the day after the harvest. This autopsy and the histopathological examination of several lymph nodes demonstrated a disseminated, invasive, epidermoid epithelioma originating from the cervix uteri (1). The recipient was then screened for gross tumor involvement of the liver graft using ultrasonography and computed tomography. No evidence of tumor was shown. The patient was listed for emergent re-transplantation and underwent a second orthotopic liver transplantation (OLT) 7 d after the first transplantation. No evidence of any malignant process was detected during the re-operation and on histopathological examination of the explanted liver. The patient remained free of recurrence at the 7-yr follow-up.

Recipients 2 and 3

In August 1996, we received from Eurotransplant a kidney graft harvested from an 18-yr-old donor who had died from head trauma. The multi-organ procurement had been uneventful. We discovered a 2 mm renal-cell carcinoma in this kidney, and the transplantation was cancelled. However, at the time of histopathological diagnosis, the liver from this donor had already been split and transplanted into two recipients in two different institutions. Despite this diagnosis, the liver grafts were not removed. These two recipients remained free of recurrence at the 1-yr follow-up, as established by telephone contact with the institutions where the organs were transplanted.

Recipient 4

In October 1997, we received a liver allograft harvested from a 54-yr-old male donor who had died from spontaneous subdural hemorrhage. We transplanted this liver into a 49-yr-old male recipient. Shortly after graft reperfusion, the procurement team announced the discovery of an 8 mm renal-cell carcinoma in the right kidney. We carefully examined the liver graft, and performed an intra-operative ultrasonography. No evidence of metastasis was found and the OLT was completed. After discussion, we decided not to remove this graft. The recipient died from graft versus host disease 7 months after OLT. No evidence of tumor recurrence was found at autopsy and on histopathological examination of the liver.

Discussion

The first reports of malignancy transferral with solid organ transplantation were published in the 1960s, when the risks of cancer transmission into immunosuppressed patients were not known (2). Today, it has become obvious that the immunosuppressive treatment enhances the risk of tumor recurrence in recipients of organs harvested from donors with malignancy (3). Therefore, with the relative exception of the primary central nervous system tumors (2, 4, 5), patients with a recent known history of malignancy are actually rejected for organ donation. Moreover, donors should be carefully screened for undiagnosed or infraclinic malignancy (1, 6). Based on our unfortunate experience of tumor transferral in two recipients, we recommended a severe policy of tumor detection in the donor (1), based on (a) the careful examination of the donor during procurement; (b) the immediate frozen section of any suspicious lesion; (c) intra-operative ultrasonography of liver and kidney grafts; (d) donor autopsy; and (e) beta-human chorionic gonadotrophin (βHCG) screening in all female donors of child-bearing age, in order to diagnose choriocarcinoma. Using this policy, we recently discovered an undiagnosed renal-cell carcinoma in a donor who had died from spontaneous cerebral hemorrhage, and we cancelled the procurement (6). However, this policy cannot completely avoid transplantation of grafts harvested from donors with undiagnosed malignancy because: (a) some tumors can be too small to be diagnosed by examination or intra-operative ultrasonography (7); (b) immediate frozen sections are not available in every procurement hospital, and/or their results may be communicated too late (1, 7); (c) intra-operative ultrasonography is not available in many community hospitals (7); (d) permission for donor autopsy is seldom given (7); (e) βHCG testing is not available in every hospital (7); (f) the organ donor shortage has lead to the use of 'suboptimal' and/or older donors, whose risk of undiagnosed malignancy is increased (6); (g) the thoracic organs are usually harvested and transplanted prior to any extensive donor dissection (8). Consequently, there will always be sporadic cases of transplantation of grafts harvested from donors with undiagnosed malignancy.

Management of the recipients of liver grafts, harvested from donors with malignancy diagnosed shortly after the OLT, can be a matter of debate. The alternatives are either early removal of the liver graft and recipient re-transplantation (2), or close follow-up without re-operation. Based on our experience, we initially recommended early re-

transplantation (1). We successfully applied this policy in Recipient 1, who was still alive without recurrence at the 7-yr follow-up. However, we did not find evidence of malignancy in the explanted graft, and it is likely that this recipient could have remained tumor-free without re-operation. In Recipients 2 and 3, the surgeons who transplanted the two parts of the corresponding liver did not re-transplant the recipients despite our diagnosis of renal-cell carcinoma in a kidney graft. Recently, we chose not to re-transplant Recipient 4, despite the evidence of an 8 mm renal-cell carcinoma in the donor. This policy change may seem controversial, because early re-transplantation could be the only way to avoid malignancy recurrence in the recipients. However, re-transplantation should be recommended only if the benefits of the decrease in the risk of tumor recurrence are greater than the risks and the costs of the re-transplantation.

It is difficult to estimate the risk of malignancy transmission after transplantation of a liver graft harvested from a donor with malignancy. This risk depends certainly on several factors, as the type, the size and the grading of the tumor, as well as the type of post-transplantation immunosuppressive regimen. It is well known that the liver is a usual metastasis site and the risk of recurrence after liver transplantation is therefore irrefutable. For instance, it is estimated that more that 25% of patients with renal-cell carcinoma have metastases at the time of diagnosis, and that the liver is a site of metastasis in 30–40% of cases (9). Since the 1960s, the Cincinnati Transplant Tumor Registry (CTTR) has collected reports of tumors occurring in transplanted patients. The CTTR has also recorded the discoveries of malignancy in organ donors, including primary brain tumors. According to this registry, 248 recipients received organs from such donors up to 1995, and 103 of these recipients (42%) developed tumor recurrence (7). However, we believe that the overall risk of recurrence after OLT is still unknown. Most of the CTTR cases involve kidney grafts. As a matter of fact, up to 1995, only 10 liver recipients whose organ donors were diagnosed with malignancy were listed in the CTTR (7). Furthermore, the high recurrence rate reported by the CTTR may be biased, as it is easier to report a complication, such as tumor transferral, than to report the absence of complication, such as the absence of tumor transferral. In the absence of a study on the outcome of recipients of liver harvested from donors with undiagnosed malignancy, we consider that the risk of tumor transferral with liver graft is still unknown. This risk may be lower than previously published and may depend on the histopathologic aggressiveness and metastatic potential of the donor tumor. This risk may be moderate for local, low-grade tumors, or if the intra-operative ultrasonography of the liver graft shows no evidence of metastasis.

The immediate removal of the liver graft after diagnosis of donor's tumor will not avoid the risk of tumor recurrence from malignant cell seeding and dissemination at the time of graft reperfusion. The risks and the costs of early re-transplantation must also be considered. The morbidity and the mortality of re-operation are not negligible. Re-transplantation also consumes an additional liver allograft, during a time when many patients awaiting OLT are dying because of organ shortages. For all these reasons, early re-transplantation may appear to be a costly and high-risk procedure, whose effectiveness for avoidance of tumor recurrence has yet to be established.

In conclusion, removal of a liver graft harvested from a donor with malignancy diagnosed shortly after OLT may be the only way to avoid tumor recurrence in the recipient. However, in the absence of a study demonstrating the efficacy of early re-transplantation, close follow-up without re-operation is certainly an alternative, especially for low-grade, local tumors. The risk of tumor transferral should be studied by analyzing the outcome of large series, using the databases of Eurotransplant or the United Network for Organ Sharing. Such a study could lead to a rational scientific approach to the management of recipients of hepatic allografts harvested from donors with undiagnosed malignancy.

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