De novo malignant melanoma occurred in renal allograft: DNA typing to determine the origin of the tumour

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Abstract: Malignant diseases are considered as great challenges in clinical transplantation. It is well known that the incidence of malignancy is higher in the transplanted population if compared with the normal population. It is important to distinguish between neoplastic diseases originating from pre-existing lesions in the transplanted organs and de novo graft tumours. Post-transplant malignancy of donor origin is a rare complication of organ transplantation, most likely transmitted as micrometastases within the parenchyma of the donor organ or from circulating tumour cells contained within the organ. Malignant melanoma, although its incidence is rather low, is one of the most common donor-derived tumour inadvertently transplanted, comprising 28% of donor transmitted tumours. Malignant melanoma in the graft without dermatological localisation is extremely rare. We report a case of de novo melanoma occurring in the allograft, where transmission from the donor was excluded by DNA (desoxyribonucleic acid) investigation. We did not find any data in the literature where a malignant melanoma occurred after transplantation in the transplanted kidney without any skin lesions and the donor origin was excluded. We draw attention to the importance of the DNA typing in case of tumours occurring in immunosuppressed patients.

Keywords: melanoma, de novo, kidney transplantation, tumour, transmission, DNA, typing

Introduction

Tumour development is an increasingly recognized problem in kidney transplanted patients. The incidence of malignancy in transplanted patients is higher than in the general population. Since the development of immunosuppressive therapy transplanted patients live longer, however, have greater chance to develop malignant diseases. Length and intensity of immunosuppressive therapy are related to the risk of post-transplant malignancy. The risk of developing malignancy is 14% at 10 years and 40% at 20 years after transplantation [1, 2]. The leading cause of death in kidney transplant recipients with a functioning graft are cardiovascular complications. Malignant tumours are the second most common cause of death after kidney transplantation [3, 4].

Malignant diseases are considered as great challenges in clinical transplantation [5, 6]. Skin tumours are frequently seen after organ transplantation, in particular, squamous cell carcinoma. The incidence of malignant melanoma is less extensively reviewed in the literature [7, 8].

In patients followed for 20 years after solid organ transplantation post-transplant malignancies occurred in up to 50%. Post-transplant malignancies are expected to be the leading cause of death within the next 20 years in kidney transplant recipients. Cancer will surpass cardiovascular complications as the leading cause of death in transplant patients within the next 2 decades. It is important to distinguish between neoplastic diseases originating from pre-existing lesions in the transplanted organs and de novo graft tumours. An understanding of the underlying pathobiology and knowing how to minimize cancer risks in transplant recipients are essential. The etiology of post-transplant malignancy is believed to be multifactorial and involves impaired immunosurveillance of neoplastic cells as well as depressed antiviral immune activity with a number of common post-transplant malignancies being viral-related. Although calcineurin inhibitors and azathioprine have been linked with post-transplant malignancies, newer agents such as mycophenolate mofetil and sirolimus may even have antitumor properties [9, 10]. Long-term data evaluation is needed to determine
whether the use of these agents will ultimately diminish the mortality due to malignancy for transplant recipients. Early diagnosis and management of de novo malignant disease in transplant patients is crucial for the prognosis of graft function and patients survival [11–15].

Post-transplant malignancy of donor origin is a rare complication of organ transplantation, most likely transmitted as micrometastases within the parenchyma of the donor organ or from circulating tumour cells contained within the organ. The incidence of tumour transmission is reported to be 0.02–0.2%, with a mean time to diagnosis of 14.2 months [16–18]. Once a post-transplant malignancy is diagnosed, differentiation of the malignancy is of recipient or donor derivation significantly influences the treatment algorithm. In addition to the withdrawal of immunosuppression, explantation and retransplantation may be the treatment protocol for donor transmitted malignancies. Malignant melanoma is one of the most common donor transmitted malignancy, comprising 28% of donor transmitted tumours [19–21].

We report a case of kidney transplanted patient who developed malignant melanoma in the transplanted kidney and the donor derived origin of tumour was excluded by DNA HLA typing.

Case report

The 23-year-old male with end stage renal failure due to focal segmental sclerosis was treated with regular haemodialysis until 1997, when a cadaveric donor kidney became available. The donor, a 45-year-old male had died of a massive intracerebral haemorrhage. The donor had no history or clinical evidence of melanoma or any other tumour, as confirmed by the donor procedure. Autopsy was not performed since no signs of malformation were known at the time of the kidney transplantation. There was a 1A, 1B and 1DR HLA (human leukocyte antigen) antigen match between the donor and recipient. DNA samples of the donor were stored (at minus 80 centigrade in liquid nitrogen). Both the donor and the recipient were CMV (cytomegalovirus) negative. The patient received cyclosporine and steroid-based immunosuppression. The postoperative course was uneventful, there were no rejection episodes and renal function was satisfactory.

![Fig. 1.](image-url)
(creatinine clearance of 80 ml/min) at discharge from hospital (18 days after transplantation). Thirteen months after the renal transplantation he was admitted to the hospital because of fever and weight loss. Renal function was unchanged; there were no signs of rejection. Ultrasoundography of the graft showed a hyperdense, irregularly shaped tumour, with a diameter of 10 centimetres. Chest X-ray and CT (computer tomography) scan revealed multiple nodules, involving both lungs highly suspicious to be metastatic in origin (Fig. 1). The biopsy of the kidney graft showed a low-grade malignant mesenchymal tumour. Immunosuppression was withdrawn and surgery was planned. During the operation a large mass, infiltrating the whole kidney allograft, as well as the iliac vessels, the ureter and the abdominal muscles was found. The transplanted kidney was removed and a regional block dissection of the inguinal lymph nodes were performed. Regular haemodialysis was re instituted.

Upon macroscopic inspection the graft kidney showed several round foci of lobulated, partly necrotic tumour, the largest measuring 105 mm in maximum dimension. The tumour invaded the renal pelvis as well as other hilar structures.

On microscopic examination an invasive solid tumour could be identified (Figs 2 to 4). The cells showed remarkable atypical characteristics with frequent mitotic figures, swollen nuclei, prominent eosinophilic nucleoli, coarsely granulated chromatin pattern and occasionally vacuolated cytoplasm. Scattered multinucleated giant cells could also be demonstrated.

The immunohistochemistry was positive for vimentin, S-100 protein (Fig. 3), CEA (carcinoembryonic antigen), HMB-45 (Fig. 4) and was negative for LCA (leucocyte common antigen), CD31, cytokeratin, EMA (epithelial membran antigen), AFP (alpha fetoprotein) and HCD. The examined lymph nodes showed the same characteristics.

To determine whether the tumour was of donor- or recipient origin DNA typing was performed on the removed tumour and compared with the DNA of the donor. DNA was obtained by trypsin digestion of the tumour tissue followed by the salting-out method. DNA typing was performed by PCR-SSP (sequence specific primer) [22, 23] and the key-reactions were repeated by the more sensitive nested PCR (polymerase chain reaction) technique [24–26]. The result of DNA typing on the basis of HLA mismatches excluded the donor origin of the tumour. We concluded that the tumour represented a de novo malignancy and was not transmitted by the donor (Fig. 5).

The patient received targeted oncological therapy: dacarbazine (200 mg/m²) for 5 days (with 3 days interruptions) for 1 year. Control ultrasonography showed an 8-cm large recidive mass in the iliac fossa. On control chest X-ray the pulmonary metastases disappeared. Re-operation was performed: a local recurrence was found.
and removed. Histology of the removed tissue and lymph nodes did not reveal signs of malignancy. Reactive changes in the lymph nodes and scar tissue with signs of fibrosis were confirmed. The patient returned to regular haemodialysis treatment, and following 6 (six) tumour-free years after the transplantectomy and 5 (five) years after completing the oncological therapy he was put on the kidney transplant waiting list again. Ten years after transplant nephrectomy he was transplanted with a cadaveric kidney with 1 HLA A, 2 HLA B and 1 HLA DR matches. The donor was CMV positive and the recipient CMV negative, so he received ganciclovir prophylaxis for 3 months. The immunosuppressive therapy consisted of Zenapax, Tacrolimus, Mycophenolate-mofetil and steroids. On the 7th postoperative day clinical signs of rejection appeared, so the patient received steroid pulse therapy for 5 consecutive days. His serum creatinine level decreased.

Because of previous malignant melanoma his immunosuppressive therapy was converted to the combination of Sirolimus, Mycophenolate-mofetil and steroids 2 months after the transplantation. His kidney function is stable, with a serum creatinine 112 µmol/l, GFR: 80 ml/min. The regular screening tests for malignancy did not reveal any abnormalities.

Discussion

Tumour development is an increasingly recognized problem in kidney transplanted patients. The incidence of malignancy is higher in transplanted patients than in the general population. Since the development of immunosuppressive therapy transplanted patients live longer, however, have a greater chance to develop malignant diseases. Length and intensity of immunosuppressive therapy are related to the risk of post-transplant malignancy. The risk of developing malignancy is 14% at 10 years and 40% at 20 years after transplantation.

The leading cause of death in kidney transplant recipients with a functioning graft are cardiovascular complications. Malignant tumours are the second most common cause of death after kidney transplantation [27, 28].
De novo melanoma in a renal allograft without cutaneous localisation

Immunosuppression has been identified as an etiological factor in the increased incidence of malignancies in kidney transplant recipients [28]. Immunosuppression has a non-specific and a direct effect on tumour genesis. Non-specific immunosuppression enhances oncogenic virus replication. Steroids are believed not to be involved in cancer development. Calcineurin inhibitors and azathioprine are relevant risk factors. Azathioprine reduces DNA replication. Steroids are believed not to be involved in kidney transplant recipients [28]. Imunosuppression has a specific immunosuppression enhances oncogenic virus motes B-cell proliferation by increasing T lymphocyte IL-6 secretion, decrease DNA repair ability. They also might be able to promote the spreading of metastases by direct cellular effect that is independent of their effect on the host’s immune cells. Proliferation signal inhibitors are involved in the control of cellular growth and proliferation. Recent articles report that mTOR inhibitors have anti-cancer effects as well as immunosuppressive properties. In vitro and in vivo studies have documented the ability of proliferation signal inhibitors to inhibit primary and metastatic tumour growth, to stop the cell cycle in G1 phase. They decrease the expression of vascular endothelial growth factor (VEGF-A) and the IGF-β expression. The incidence of different tumours varies in different geographical regions [29,30]. Existing studies are not in agreement over the increased risk of melanoma in the transplanted population. Hollenbeak et al. showed that renal transplantation recipients were nearly 3.6 times more likely to develop melanoma than the general population, Le Mire et al. showed that in the studied Oxford transplant population melanomas occurred at approximately 8 times the rate in the general population; this is the highest rate reported in the literature [18,31].

Considering the well-known aggressivity of melanomas this is also an uncommon finding that after multidisciplinary treatment (surgery, oncology) the patient became tumour and metastasis free. Melanomas transmitted from a donor were already reported [32,33] and advanced donor origin was proved by DNA typing as well [34,35]. However, we did not find any report in the literature, where a malignant melanoma occurred after transplantation without any skin lesion and the donor origin was excluded by DNA typing. We highlight the importance of monitoring for de novo tumours in immunosuppressed population, and also the role of DNA typing in the determination of the tumour’s origin. In case of multiorgan donation the importance of donor transmitted tumours is even higher. Tumours have uncommon behaviour in immunosuppressed patients. To achieve good prognosis multidisciplinary treatment is suggested.

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