CASE REPORT

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Multiple malignancies in a renal transplantation patient

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ABSTRACT

Kidney transplantation has been associated with an increased risk of a variety of malignancies. With the introduction of more potent immunosuppressive protocols, the life expectancy of allograft recipients has been extended but there are a greater number of tumours.

We report a case of a 54-year-old man who underwent cadaveric renal transplantation and was submitted to ciclosporin, azathioprine and steroids treatment. Ten years after renal transplantation the patient developed a basal cell skin and local resection was performed. Eleven years posttransplantation a prostate cancer was diagnosed and conversion to sirolimus from calcineurin inhibitor was performed. Two years after conversion a rare and aggressive sarcoma was detected and the patient died.

Posttransplantation malignancies arise from a complex association of many factors including individual genetic predisposition.

Key-Words:
Immunosuppression; malignancy; renal transplantation.

INTRODUCTION

Over the last decade, the use of more potent immunosuppressive agents has dramatically reduced the incidence of acute rejection in kidney transplantation, but posttransplantation malignancy is becoming an important cause of mortality, however. It has been well established that the relative risk of cancer in transplanted patients is increasing over that of the general population[1-3]. The occurrence of malignancies has been estimated at 20% after 10 years of transplantation[4]. With longer graft survival these subjects are exposed to the potential development of multiple primary tumours[5]. It is possible that different factors contribute to the increased incidence of malignancies, such as cumulative exposure to immunosuppression and environmental and genetic factors. With the recent evidence that mammalian target-of-rapamycin (m-TOR) inhibitors have anti-oncogenic effects[6], an efficient immunosuppression and control over the development of cancer may be achieved. We report a case of a long-term renal transplant recipient who had an unusual propensity for malignancies.

CASE REPORT

A 54-year-old man with polycystic kidney disease in haemodialysis underwent cadaveric renal transplantation in August 1995. Initial immunosuppression consisted of ciclosporin (8mg/Kg/day), azathioprine (3 mg/Kg/day) and prednisone (20 mg/day). The patient recovered renal function over the following week (Cr 1.2 mg/dl). One month later the patient presented impaired renal function (Cr 1.9 mg/

dl) and a renal biopsy was performed. The diagnostic of acute cellular rejection IA (Banff) was obtained and treatment with corticosteroids was commenced with recovery of renal function. Six years later, azathioprine was switched to mofetil mycofenolate (2 g/day), with a good tolerance. Ten years after transplantation, the patient developed basal skin carcinoma of the face and a complete resection of the tumour was performed. There was no past history or family history of malignancies. Eleven years after transplantation the patient had a rising PSA level and a localised prostate adenocarcinoma was diagnosed by ultrasonically guided prostatic biopsy. He received hormonal and local radiation treatment with complete resolution. Ciclosporin was switched to sirolimus. The graft function remained stable (Cr 1.4 mg/dl) and sirolimus blood levels were within the range 6 to 10 ng/ml during two years. Thirteen years posttransplantation the patient was admitted to hospital complaining of fever, asthenia, anorexia and painless left inguinal nodes. Laboratory examination results showed elevated C-reactive protein level (10.0 mg/dl), leucocytosis and a stable renal function (Cr 1.5 mg/dl). Epstein-Barr and CMV serology were negative. Computed tomography examination revealed the presence of a 16x15 mm lesion in the lower pole of the right native kidney, an 80x56 mm lesion in the left psoas muscle, a 33x35 mm lesion in right iliac muscle and a conglomerate of left inguinal adenopathies. Excision of muscular lesions and subsequent right nephrectomy were performed and histopathological and immunohistochemical studies revealed the diagnosis of a fusiform high-grade sarcoma compatible with Malignant Peripheral Nerve Sheath Tumour (MPNST). The patient died one month after surgery.

DISCUSSION

The risk of malignancy is known to be related to the overall dose of immunosuppression, type of drugs used and duration of treatment[7,8]. Additionally, older patients receiving a transplant are at a higher risk of developing cancer than younger patients[9]. There is evidence that mean age of recipients has risen 10 years over the last decade[10]. Proposed mechanisms for the increased risk of cancer include impaired immune surveillance, which ordinarily prevents the growth of neoplasms through elimination of tumour cells[11] and depressed antiviral immune activity, with some common posttransplant malignancies being associated with viral infection[12,13]. Epstein-Barr virus is strongly implicated in causing lymphomas, human papilloma virus in causing carcinomas of uterine cervix, vulva and skin and human herpes virus 8 appears to play a role in the development of Kaposi's sarcoma. The types of malignancies encountered in renal transplant patients differ from those encountered in the general population. A higher incidence of relative rare tumours including lymphomas, Kaposi's sarcoma, merkel cell tumour, renal and hepatobiliary carcinomas was noted[14]. Skin cancer is the most commonly encountered malignancy, with squamous cell carcinomas being more common than basal cell carcinomas, in contrast to the distribution in the nontransplant population. The second most common malignancy is lymphoma, with non-Hodgkin's lymphoma the predominant type. This disorder represents the major cause of cancer-related morbidity and mortality.

Recent reports indicates that sirolimus, an mTOR inhibitor, is associated a remission of Kaposi's sarcoma and reduces the risk of malignancies[15]. Also the anti-neoplastic activity of these immunosuppressant agents, including direct inhibition of cancer cell replication, induction of apoptosis and inhibition of tumour angiogenesis, has been demonstrated experimentally[16]. However, m-TOR inhibitor may not protect renal transplant recipients from the occurrence of tumours[17]. Multiple primary malignancies, unrelated to each other, were seen in our patient: skin cancer, prostate carcinoma and sarcoma. He developed the first malignancy after 10 years of chronic immunosuppression and after a treatment of acute rejection, which is also associated with the occurrence of tumours[18]. After the development of the second primary tumour in this patient, conversion to sirolimus from calcineurin inhibitor was performed, with no protective effect on cancer occurrence observed. Two years after conversion, the patient developed a rare and aggressive tumour. MPNST is a variety of soft tissue sarcoma of mesenchymal origin which arises from peripheral nerve branches or the sheath of peripheral nerve fibres. This tumour may arise spontaneously or can be associated with a neurofibromatosis type 1[19]. Multifocality is a frequent feature of this cancer. Furthermore, tumours that occur in transplant patients frequently demonstrate a more

aggressive nature than similar tumours in the general population[20]. This was the first case of MPNST in our centre. The documentation of three solid tumours suggests that genetic predisposition plays a role in the genesis of posttransplant malignancies. It is possible that genetic factors influence susceptibility or resistance to the development of cancer in addition to damage and interference with normal repair mechanisms of DNA caused by immunosuppressive agents. However, the exact mechanisms are not yet established.

In conclusion, success of transplantation has been limited by the high incidence of malignancies. This case suggests that duration and possibly the total dose of immunosuppression, as well as genetic predisposition, were determining factors in the development of multiple malignancies.

Conflict of interest statement. None declared.

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