Multiple Unrelated Malignancies Following Renal Transplantation: An Evaluation of Four Cases

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Abstract

The risk of de novo malignancy is significantly higher in patients who have undergone organ transplantation than in the general population. Long-term immunosuppressive treatment, in addition to age, genetic predisposition and infectious agents, plays a major role in the development of malignancy. Although skin and hemopoietic system cancers are common, atypical presentations of malignancies may occasionally be seen during long-term follow-up in patients with functioning allografts. In this report, four cases, each with more than one different primary malignancy (one patient with three malignancies and three patients with two malignancies), are presented.

Key words: multiple primary neoplasia, malignancy, renal transplantation

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Introduction

The development of de novo malignancy is one of the most serious complications of organ transplantation (1). The incidence of cancer in renal transplant (RT) patients has significantly increased in comparison with that observed in the general population and dialysis patients (2, 3). Due to the genetic and geographical distributions of different types of cancers, differences can be seen in cancer incidence (4, 5). Demographic factors (age, geographical features), conventional risk factors (smoking, sun exposure), oncogenic viruses (Epstein-Barr virus, human herpes virus 8, hepatitis B and C viruses and papilloma viruses), chronic immunosuppressive treatment and genetic familiarity are the known risk factors of malignancy development (6, 7).

The most frequently observed malignancy in RT patients is skin cancer (8, 9). Meanwhile, the incidences of malignant lymphoma, Kaposi’s sarcoma, carcinoma of the vulva or vagina, in situ carcinoma of the uterine cervix, urinary system and liver malignancies and malignant melanoma have also increased significantly (10). In addition, unrelated multiple tumors occurring in the same patient are seen occasionally (1, 5). In this study, the cases of four RT patients who developed more than one unrelated malignancy during follow-up are discussed.

Case Reports

Case 1

A 41-year-old man received a RT from his sister in 1988. His post-transplant clinical course was uneventful. At the 14th year post-transplantation, he was admitted due to a newly developed black-colored skin lesion on his left external ear. The immunosuppressive regimen had consisted of 5 mg/day of prednisolone (Pred) and 100 mg/day of azathioprine (AZA). The patient’s graft function was excellent with a serum creatinine level of 1.09 mg/dL. A microscopic examination of an incisional biopsy specimen revealed lentigo maligna melanoma. An excisional biopsy was performed, and the surgical margins were found to be tumor free. The AZA dose was reduced to 50 mg/day. At 15 years post-transplantation, whole-body positron emission tomography...
(PET)-CT performed to screen for melanoma revealed increased activity in the left lower lobe of the thyroid. Thyroid ultrasonography showed multiple nodules with diameters ranging from 6 to 13 mm and bilateral cervical lymphadenopathy measuring less than 1 cm in diameter. The nodules were hypoactive on thyroid scintigraphy. Total thyroidectomy was performed, and papillary carcinoma with follicular variants within two foci (one in the right lobe measuring 1.3 cm in diameter and one in the left lobe measuring 0.5 cm in diameter) was observed (Fig. 1A).

After thyroidectomy, there were no signs of metastasis on an I-131 whole-body scan. Radioactive iodine treatment was administered to the patient, and the graft function remained stable. At the 16th post-transplant year, an abdominal ultrasound examination revealed the presence of an anechoic mass measuring 14 mm in diameter at the lower pole of the right kidney. Abdominal MR imaging showed a solid mass lesion (exophytic growth) located adjacent to the posterior side of the right kidney. Bilateral native nephrectomy was performed. Both kidneys were found to be atrophic. A microscopic examination of the material revealed renal papillary adenocarcinoma with multiple foci as well as changes associated with dialysis-induced cystic disease (Fig. 1B). The ensuing examinations did not reveal any findings suggestive of recurrence or metastasis. The patient remains alive and is taking 5 mg/day of Pred and 25 mg/day of AZA with a creatinine level of 1.2 mg/dL.

Case 2

A 43-year-old man received a RT from his sister in 2000 due to end-stage kidney disease caused by AA amyloidosis secondary to ankylosing spondilitis. The patient had no history of rejection or infection and maintained a strong graft function during routine therapy. He had received consultation in the 6th post-transplant year for a dark-colored lesion under the right eyelid. On an excisional biopsy, nodular-type basocellular carcinoma was diagnosed. At the time of diagnosis, the serum urea level was 47 mg/dL, the creatinine level was 1.29 mg/dL and the patient was taking Pred at a dose of 5 mg/day, AZA at a dose of 75 mg/day and cyclosporine A (CsA) at a dose of 150 mg/day as maintenance therapy. The Pred and AZA treatment was continued at the same dosage, while the CsA dose was decreased to 100 mg/day. No relapse of basocellular carcinoma occurred during follow-up. On a complete blood count obtained at 8.5 years post-transplant, the white blood cell, hemoglobin and platelet counts were determined to be 18,230/mm³, 9.4 g/dL and 429,000/mm³, respectively. The serum ferritin, vitamin B12 and folic acid levels were normal. On a bone marrow aspiration and biopsy performed to evaluate the etiology of the hematological disorder, findings compatible with large granular cell leukemia were found. The maintenance dose of CsA was decreased to 50 mg/day, AZA was discontinued and Pred was continued at 5 mg/day. Twelve cycles of chlorambucil and steroid treatment were administered. No relapse or metastasis occurred during follow-up. At the 11th post-transplant year, the patient is still being followed in our outpatient clinic and continues to have a well-functioning allograft.

Case 3

A 26-year-old woman had received a RT from her 47-year-old mother 14 years previously. The patient had no history of rejection or infection and maintained a good graft function for the first six months post-transplant. However, at the 6th post-transplant month, hemophagocytic histiocytic syndrome developed together with an exacerbation of...
chronic hepatitis C virus infection, and the AZA and CsA treatments were interrupted. In the 1st post-transplant year, the serum urea level was 19 mg/dL, the creatinine level was 1.09 mg/dL, the aspartate aminotransferase (AST) level was 114 mg/dL, the alanine transaminase (ALT) level was 96 mg/dL, and the total bilirubin level was 1.05 mg/dL. The maintenance treatment was adjusted to Pred at a dose of 10 mg/day and AZA at a dose of 75 mg/day. During follow-up, the patient’s graft and liver function tests were stable. In the 7th post-transplant year, asymptomatic hyperglobulinemia (globulin: 4.6 g/dL) was detected. The serum levels of IgG, IgA and IgM were found to be 2.280 mg/dL (650-1.600), 96 mg/dL (40-350) and 134 mg/dL (50-300), respectively. The lambda and kappa light chain levels were 717 mg/dL (93-242) and 207 mg/dL (138-375), respectively. On a bone marrow aspiration and biopsy, 15% atypical plasma cells were observed, thus myeloma was diagnosed (Fig. 2A). No hypercalcemia or lytic defects in the bone were observed. The patient was taken under observation with a smoldering multiple myeloma diagnosis, and the AZA dose was decreased to 50 mg/day.

Upper gastrointestinal endoscopy was performed in the 13th post-transplant year due to dyspeptic complaints. On a biopsy, an epithelial malignant tumor of the stomach was diagnosed (Fig. 2B). During surgical exploration, peritoneal spreading of the tumor was observed, and peritonitis carcinomatosa was confirmed histologically. Eight cycles of cisplatin and capecitabine chemotherapy was applied. The patient died one year after receiving the gastric carcinoma diagnosis.

Case 4

In 1994, a 52-year-old man received a RT from his 50-year-old wife. The patient had no history of rejection or infection and maintained a good graft function. An excisional biopsy was performed following the formation of purple lesions on the left front arm and palate in the 2nd post-transplant year, and Kaposi’s sarcoma was diagnosed. At the time of diagnosis, the patient had a serum urea level of 67 mg/dL and a creatinine level of 1.84 mg/dL. He was taking Pred at a dose of 10 mg/day, AZA at a dose of 125 mg/day and CsA at a dose of 250 mg/day as maintenance therapy, and his serum cyclosporine peak blood level was 313 ng/mL. The CsA treatment was withdrawn. Concomitantly, bronchoscopy was performed due to the presence of suspicious areas on chest X-ray and tomography. An appearance conforming to Kaposi’s sarcoma was observed in the trachea, and the bronchoalveolar lavage samples revealed a benign cytology. Because the patient’s creatinine level had progressed from 1.5 mg/dL to 2.2 mg/dL in the 3rd post-transplant year, he was assessed as having chronic rejection and it was decided to continue Pred at a dose of 10 mg/day and AZA at a dose of 125 mg/day. In addition, 1 g of IV methyl prednisolone was administered for three days. The patient’s graft function was stable during the follow-up.

In the 7th year of follow-up, the patient was admitted for purple skin lesions on the internal side of both legs. He was considered to have a relapse of Kaposi’s sarcoma based on a context of histopathologic confirmation. The serum creatinine level was 2.65 mg/dL at the time of relapse. Pred was continued at a dose of 10 mg/day, while the dose of AZA was decreased to 75 mg/day. On routine chest X-ray imaging performed at the 10th post-transplant year, an irregular, homogenous density measuring 3 cm in diameter was observed at the right perihilar area. The mass was confirmed by tomography. A bronchoscopic biopsy revealed squamous cell carcinoma of the lungs, and the patient died due to respiratory insufficiency two months after receiving the lung cancer diagnosis.

Discussion

The incidence of malignancy has increased in RT patients. Although it varies according to geographical and genetic properties, the most commonly observed type of cancer is skin cancer with an incidence in the 20th year post-transplantation varying between 60% and 80% (8, 9). In addition, in the registry data of various countries, while the incidence of non-skin cancer in the first three years following transplantation ranges between 2.5% and 7.5%, it reaches 20% in the 10th year and 30% in the 20th year (11). This increase in cumulative prevalence during the follow-up period in transplant patients is also associated with increasing incidences of multiple unrelated malignancies. Despite a lack of consensus, several suggestions have been made for cancer screening in RT patients (12). In two of our cases (case 1 and case 4), second malignancies were diagnosed when the patients were asymptomatic.

Among the 1,100 patients who are being followed up in our center, the incidence of hematological malignancy is 1.1% (n : 12), while that of solid cancer is 2% (n : 22). Four of a total of 34 patients with malignancy also have multiple unrelated neoplasias. The time to diagnosis and age at onset of multiple unrelated malignancies among our patients are 7.2±4.9 (case 2-14) years and 47±10 (case 33-55) years, respectively. In other cases, these rates are 8.4±5.1 (case 1-21) years and 46±12 (case 27-66) years, respectively. The patient characteristics are presented in Table.

It is not known whether the incidence of multiple unrelated malignancy in transplant patients increases in association with the rate observed in the general population. As the follow-up period of transplant patients with functioning grafts lengthens, the incidence of malignancy may also increase. Multiple unrelated malignancy cases with extremely different clinical presentations and courses have also been published in the literature (13-19).

Barroso-Vicens reported a fatal case that involved an association between skin carcinoma, non-Hodgkin lymphoma and malignant fibrous histiocytoma in the 12th post-transplant year (13). In an autopsy of a patient who developed larynx carcinoma in the 2nd post-transplant month and
mofetil (5, 22) and the mammalian target of rapamycin is foreseen that the carcinogenic effects of mycophenolate mofetil, which were localized on the skin (16). In addition, Childs reported a case of gall bladder adenoma occurring in the 1st post-transplant year and a nonfunctioning pancreatic islet cell tumor developing in the 5th post-transplant year (17). Motoyama et al. reported Epstein Barr virus-associated malignant lymphoma and thyroid papillary carcinoma in a pediatric RT recipient (18). Lo Monte et al. described a case of double endocrine neoplasia (thyroid papillary carcinoma and adrenocortical carcinoma) in a RT recipient (19).

A review of the published case submissions reveals that the clinical pictures are profoundly heterogeneous. The time period for development of the first malignancy ranges between the 2nd post-transplant month and the 11th post-transplant year. Although both malignancies can be seen at the same time, they can also occur separately at three- to four-year intervals. The tumors may develop from a common origin or as completely unrelated tumors.

In our cases, the occurrence of the first malignancy varied between two and 14 years. The second malignancy developed after one to eight years. The occurrence of malignancy in the late post-transplant stage suggests that chronic immunosuppressive treatment exposure and age also contribute to malignancy. Another remarkable finding is that the first malignancy in three of our four patients was a skin-related malignancy. Skin malignancies were also present in two of the previously published seven cases. Therefore, in patients having any skin malignancies, the risk of developing an unrelated malignancy should be considered and the patient should be closely followed.

Chronic immunosuppressive treatment is an important risk factor for the development of post-transplant malignancy. The carcinogenic effects of AZA and CsA have been shown in various studies (20, 21). In contrast, although unverified, it is foreseen that the carcinogenic effects of mycophenolate mofetil (5, 22) and the mammalian target of rapamycin inhibitor group would be reduced (23). In both our cases and the previously reported multiple primary malignancy cases, conventional immunosuppressive regimens consisting of Pred, AZA and CsA were used. Until now, no reported cases of multiple unrelated malignancy have occurred with the newer drugs, which can be explained by various factors. First, the newer drugs may have less potential for malignancy. Second, dose minimization strategies for immunosuppressive drugs have become popular in recent years. Third, there remain inadequate follow-up periods with the newer drugs.

As a result, multiple unrelated malignancies can occur in RT patients, and it should be noted that new neoplasias can occur in patients with a past history of malignancy. It should be emphasized that close monitoring and screening strategies are essential for the early diagnosis of concomitant malignancies and recurrence.

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