Allochronic Overlapping Malignancies After Renal Transplantation in a Patient with p53 Gene Mutation: Report of a Case

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Abstract
We report a rare case of the development of various tumors over a 16-year period after renal transplantation. A 56-year-old woman underwent renal transplantation using a US kidney. Immunosuppressive treatment consisted of a triple regimen of methylprednisolone, azathioprine, and mizoribine. Left breast cancer was diagnosed 9 years after the renal transplantation, then colon cancers and meningeal epidermal menigioma were diagnosed, 10 years and 12 years post-transplant, respectively. During the investigations for the breast and colon cancers, a p53 gene mutation was detected. A deterioration of renal function was found 16 years after the transplant and graft biopsy confirmed chronic rejection. We suggest that the effects of the immunosuppressive drugs combined with the p53 gene abnormality accelerated tumor development in this patient.

Key words Renal transplantation · Allochronic overlapping tumor · p53 gene mutation · Immunosuppression

Introduction
There are many reports of allochronic overlapping tumors developing after renal transplantation, most of which are progressive and associated with a poor prognosis. We report the case of a patient in whom various tumors developed over a 16-year period after renal transplantation, until renal failure occurred due to chronic rejection, but whose post-transplantation course was good because the tumors were detected early. We also discuss the possible association of p53 mutation, with references to the literature.

Case Report
The patient was a 56-year-old woman who had undergone a renal transplantation, using a US kidney, at our hospital when she was 37 years old. She had been diagnosed as having chronic glomerulonephritis when she was 22 years old and commenced on hemodialysis when chronic renal failure was confirmed at the age of 29 years old. Her family history was unremarkable. Immunosuppressive treatment consisted of a triple regimen of methylprednisolone 6mg, azathioprine 50mg, and mizoribine 100mg daily. The patient had a history of blood transfusion and was positive for hepatitis C virus antibodies. Her postoperative course after renal transplantation was uneventful. She noticed a nodule under her left breast 8 years later when she was 44 years old, and ultrasound showed a single low-echoic-mass lesion, about 0.8 cm, under the skin (Fig. 1). Aspiration biopsy cytology confirmed class V left breast cancer (T1aN0M0 stage I), and a modified radical mastectomy was performed. The pathological diagnosis was invasive ductal carcinoma. Abnormal computed tomography (CT) performed at the same time to check for possible metastasis in the liver showed a space-occupying lesion, about 5 cm in diameter, in the lateral region of the liver, which was diagnosed as a benign liver hemangioma based on its nature and appearance on the CT images. This hemangioma started to grow, but is now becoming smaller. At the age of 48 years, 4 years later, a regular checkup examination detected occult blood in the stool, and she underwent colonoscopy. The colonoscopy showed a translucent image, about 1 cm in diameter, in the sigmoid colon, and the total colonoscopy showed a...
subpedunculated polyp, located about 25 cm on the oral side of the anal verge (Fig. 2). About 3 months later, colonoscopic polypectomy was performed. The final pathological diagnosis was adenocarcinoma in adenoma. Furthermore, immunostaining of paraffin-embedded sections prepared from previously resected specimens using the p53 gene revealed mutations of the p53 gene in both the left breast cancer and sigmoid colon cancer (Fig. 3). No residual cancer was detected in the cut end, and no further resection has been performed. The dosages of the immunosuppressive drugs were reduced 3 years later, following the detection of cryptococcosis in the left lung. About 5 months later, at the age of 52 years, she felt weakness in her left lower leg and experienced difficult walking. She was admitted to the Department of Orthopedic Surgery in our hospital where CT and magnetic resonance imaging examinations were done. These examinations showed a subdural tumor in the extraspinal at Th5–6 (Fig. 4). The tumor was resected and the pathological diagnosis was meningeal epidermal meningioma, but no malignant change was found. Deterioration of renal function became evident about 2 years later and graft biopsy confirmed chronic rejection reaction. Hemodialysis was recommenced 2 months later.

Discussion

The development of malignant tumors after renal transplantation is common. In 1993, Penn reported the incidence to be about 100 times higher than that of the age-matched general population, with an overall 3- to 4-fold increased incidence of cancer in transplant patients compared with age-matched controls. Moreover, malignant tumors are the major cause of death (26% of cases) in patients whose transplanted kidney has remained functional for more than 5 years. The possible reasons for this include:
1. Suppression of immunological surveillance by the lymphatic reticuloendothelial system as a result of immunosuppressive therapy
2. Direct oncogenous action of the immunosuppressive drugs themselves on cells
3. Strengthening of the effects of carcinogenic substances in the body by drugs
4. Promotion of tumor virus infection by drugs
5. Weakening of the activity of sensitized lymphocytes attacking a tumor by immunosuppressive therapy
6. Chronic immunologic stimulation by antigens
7. Reduction in immunity due to renal failure before the transplantation

The incidence of malignant tumors after transplantation in Japan is similar to that in Europe and the United States at about 5%, but the body site-specific incidences are different. In Europe and the United States, skin carcinoma and choriocarcinoma are the most common, occurring in 40% of patients, followed by malignant lymphoma (12%), cervical carcinoma (6%), lung carcinoma (5%), and carcinomas of the digestive system (only 3%). On the other hand, in Japan, carcinomas of the digestive system, including gastric, hepatic, and colon carcinomas, account for about half of these malignancies, according to many reports. This difference is thought to be due to regional variations in the incidences of malignant tumors, with the most common malignant tumors in each region probably also being the most common tumors after transplantation. A notable characteristic in Japan is the high incidence of malignant tumors in young people after renal transplantation, which is thought to reflect the relatively large number young recipients receiving living-related renal transplantations. In the last 20 years, we have performed 169 renal transplantations for renal failure, on 125 men and 44 women, including 142 living-related and 27 cadaveric transplantations. Malignant tumors have subsequently developed in 8 (4.7%) of these patients (Table 1). From the viewpoint of body site-specific incidences, carcinomas of the digestive system, including gastric, hepatic, and colon carcinomas, account for about half of these cases, in accordance with other reports. These malignant tumors were diagnosed after an average period of 109 months, although two patients (nos. 3 and 6) were thought to already have had carcinoma at the time of their operation. According to Barrett et al., it can take 15–20 years before a malignant tumor becomes symptomatic after stimulus by a carcinogenic substance. When this is taken into consideration, it is hard to imagine carcinogenicity being directly caused by immunosuppressive drugs. The p53 gene is involved in suppressing the expression of many genes by binding as a transcription factor to specific base sequences. It has various function such as cell cycle regulation, angiogenesis, and induction of apoptosis. The prognosis of patients with p53 gene mutations is generally poor. It is now widely accepted that p53 gene mutation plays a significant role in the mechanism of onset of carcinoma, but not in tumor growth. Considering previous findings, the most likely explanation for the onset and growth of malignant tumors after renal transplantation is oncogenesis due to immunosuppressive drugs and p53 gene mutation, or a reduction in immunity against tumor antigens during immunosuppressive therapy. These findings are supported by a report that malignancies after renal transplantation grow more rapidly than similar tumors in patients who have not had a transplant. There are also several reports that p53 gene mutation can precipitate tumor growth. However, to our knowledge, no published study demonstrates a relationship between oncogenesis or tumor development after renal transplantation and p53 gene mutation. Further studies will be required to clarify this point. A p53 gene abnormality was detected in our patient (Fig. 3) and thus we speculate that the immunosuppressive drugs and the p53 gene abnormality may have accelerated the tumor onset and development, although we cannot exclude other factors affecting tumor regression and promotion. A quick method of detecting p53 mutation on an outpatient basis would be useful. A recent paper reported that checking for an antibody to p53 would be a potent and useful method of checking for mutation.
In conclusion, we described a case of allochronic overlapping tumors, including two malignant ones, developing after renal transplantation. Since p53 gene abnormality was detected, we suggest that the patient’s immunosuppressive drugs and p53 gene abnormality may have accelerated the tumor development and growth.

References


<table>
<thead>
<tr>
<th>Case</th>
<th>Age (years)</th>
<th>Gender</th>
<th>Organ</th>
<th>Pathology</th>
<th>Years after transplantation</th>
<th>Treatment</th>
<th>Prognosis</th>
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<tbody>
<tr>
<td>1</td>
<td>62</td>
<td>M</td>
<td>Liver</td>
<td>Hepatocellular carcinoma</td>
<td>18 years 3 months</td>
<td>None</td>
<td>Died of multiple liver metastasis</td>
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<tr>
<td>2</td>
<td>37</td>
<td>F</td>
<td>Liver</td>
<td>Hepatocellular carcinoma</td>
<td>21 years 11 months</td>
<td>Microwave</td>
<td>Died of rupture of hepatocellular carcinoma 2 months after diagnosis</td>
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<tr>
<td>3</td>
<td>18</td>
<td>M</td>
<td>Thyroid</td>
<td>Papillary carcinoma</td>
<td>7 years 2 months</td>
<td>Hemithyroidectomy</td>
<td>Surviving after 7 years 2 months</td>
</tr>
<tr>
<td>4</td>
<td>25</td>
<td>M</td>
<td>Throat</td>
<td>Papillary carcinoma</td>
<td>9 years 5 months</td>
<td>Hemithyroidectomy</td>
<td>Died of acute heart failure 3 months after operation</td>
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<td>M</td>
<td>Gallbladder</td>
<td>Adenocarcinoma</td>
<td>3 months</td>
<td>Chemotherapy</td>
<td>Surviving after 5 years 7 months</td>
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<td>6</td>
<td>23</td>
<td>M</td>
<td>Stomach</td>
<td>Adenocarcinoma</td>
<td>7 years 0 months</td>
<td>Orchiectomy</td>
<td>Died of multiple liver metastasis and direct invasion to the stomach 3 months after diagnosis</td>
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<td>7</td>
<td>50</td>
<td>M</td>
<td>Prostate</td>
<td>Papillary adenocarcinoma</td>
<td>8 years 5 months</td>
<td>Mastectomy</td>
<td>Surviving after 3 years 11 months</td>
</tr>
</tbody>
</table>
| 8    | 46          | F      | Breast | Adenocarcinoma | 10 years 1 month | Polypectomy | }

a Age at diagnosis of malignant tumor after renal transplantation
b Time to diagnosis of malignant tumor after renal transplantation
c After commencement of treatment for malignancy