Cancer Arising After Pancreas and/or Kidney Transplantation in a Series of 99 Diabetic Patients

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OBJECTIVE — Recipients of solid organ transplants have an increased risk of developing certain types of malignancies as compared with the general population. The majority of the literature has reported on neoplasms in kidney and heart transplant recipients.

RESEARCH DESIGN AND METHODS — We describe 9 neoplasms occurring in 7 out of 73 IDDM patients after simultaneous pancreas and kidney transplantation. No cases were recorded among 26 IDDM recipients of kidney transplantation.

RESULTS — Among the neoplasms found were 2 cases of posttransplant lymphoproliferative disorder (PTLD), malignant melanoma, basal-cell and squamous-cell carcinoma of the skin in the same patient, squamous-cell carcinoma in situ of the vulva, hepatocarcinoma, small-cell lung cancer, and ductal carcinoma of the breast. Four patients died. Among immunological risk factors, over-immmunosuppression for steroid-resistant kidney rejection was administered only in the 2 cases of PTLD.

CONCLUSIONS — Increased dosage of immunosuppressive agents may be necessary in some patients to prevent or treat rejection in view of their reduced survival on hemodialysis.

Recipients of solid organ transplants have been reported to have an increased risk of developing some histological types of malignancies (1,2). The majority of the literature has reported on neoplasms in kidney and heart transplant recipients. We describe 9 neoplasms arising in 7 IDDM patients after transplantation in a series of 73 recipients of simultaneous pancreas and kidney transplantation performed between July 1985 and December 1994 at a single institution.

RESEARCH DESIGN AND METHODS

Patients

Seventy-three IDDM uremic patients received a simultaneous kidney and pancreas transplant from a cadaveric ABO-matched donor. One patient received a second kidney and pancreas transplant, and 26 uremic patients received a kidney graft from a cadaveric ABO-matched donor. Among the kidney-graft recipients, two of the cases had pancreatic islets transplanted simultaneously to a first kidney graft, while 10 patients received a second transplant (islet, 5 cases; pancreas, 4 cases; islet plus kidney, 2 cases; heart, 1 case), and two patients received a second kidney graft, together with a pancreas transplant. All pancreas and kidney transplants and kidney transplants performed between July 1985 and December 1994 were included in the study without selection. The "kidney alone" group is smaller because, at our institution, only diabetic patients are transplanted and all of our patients were candidates for simultaneous kidney and pancreas transplantation in the absence of contraindications. In a few cases, the patient asked for a kidney transplant alone.

Mean age at transplantation and diabetes and dialysis duration were, respectively, 38.8 ± 0.8 years, 25.0 ± 0.6 years, and 23.9 ± 1.8 months for the kidney and pancreas transplant group and 38.3 ± 1.9 years, 23.9 ± 1.4 years, and 21.6 ± 4.0 months for the kidney transplant group.

All patients had been admitted to a waiting list after careful evaluation of general conditions. Exclusion criteria were the presence of cancer, severe cardiomyopathy, and peripheral or cerebral vasculopathy. All patients were affected by long-term diabetic complications.

Methods

Twenty-three patients received a segmental neoprene-injected pancreas transplant according to Dubernard (3); 50 patients received a whole bladder-diverted pancreas transplant according to Sollinger (4). Kidney transplantation was performed in the conventional way.

Immunosuppression was the same in the kidney and pancreas transplant and the kidney transplant groups and was based on a prophylactic regimen of antilymphocytic globulin (ALG; 4,250 lymphocytotoxic U · 10 kg^{-1} body wt · day^{-1} on days 1–14), 1 bolus of 500 mg of methylprednisolone on day 1, then 1 mg · kg^{-1} · day^{-1} (24 kidney and pancreas transplant patients, 6 kidney transplant patients) or 0.25 mg · kg^{-1} · day^{-1} (49 kidney and pancreas transplant patients, 20 kidney transplant patients), tapered to 10 mg/day; 150 mg/day azathioprine, adjusted according to leukocyte count; and 7.5–9.0 mg · kg^{-1} · day^{-1} cyclosporin A at ALG withdrawal, adjusted on whole blood levels. The antirejection protocol consisted of 3–5 methylprednisolone boluses (500 mg) as a first-line treatment, unless it occurred during ALG treatment, in which case antithymocyte globulin (ATG; before September 1990) or OKT3 (murine monoclonal anti-CD3 antibodies) was administered; in steroid-resistant cases, ATG (before 1990) or 5 mg/day OKT3 was given for 10

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ALG, antilymphocytic globulin; ATG, antithymocyte globulin; EBV, Epstein-Barr virus; HPV, human papilloma virus; OKT3, murine monoclonal anti-CD3 antibodies; PTLD, posttransplant lymphoproliferative disorder.

Table 1—*Summary of patient and transplant characteristics, risk factors for cancer arousal, and relevant clinical notes*

Case	Age at transplant	Transplant date	Transplant type	Risk factor(s)	Notes
1	56	May 1987	KP SEGM	HBV, HCV chronic aggressive hepatitis	Normal transaminase levels 3 months before death from hepatoca
2	38	June 1987	KP SEGM	Cigarette smoking	Normal chest film 3 months before mediastinal syndrome
3	36	April 1989	KP SEGM	—	—
4	53	July 1989	KP SEGM	—	Previous thyroid and bladder papillary cancer
5	47	Feb. 1990	KP BD	—	Negative mammography 7 months before breast carcinoma diagnosis
6	45	June 1992	KP BD	OKT3	—
7	34	May 1993	KP BD	OKT3	—

BD, whole bladder-diverted; KP, kidney and pancreas transplant; SEGM, segmental duct-injected.

days. ATG or a second course of OKT3 was used in unresponsive cases.

When islets (n = 5) or pancreas (n = 4) were transplanted after the kidney, another course of ALG was administered during days 1–10, together with 1 bolus of methylprednisolone on day 1. Maintenance immunosuppression was unchanged.

Kidney rejection was suspected in cases of diuresis reduction, creatinine increases, fever, local signs, or ecographic changes and was confirmed by either cytology or histology.

RESULTS — One-year patient and kidney actuarial survival rates were, respectively, 94 and 83% in the kidney and pancreas transplant group and 89 and 88% in the kidney transplant group (2 patients died with a functioning kidney). The one-year pancreas actuarial survival rate was 78%. Posttransplant follow-up was 47.6 ± 32.4 months (range, 1–125) in the kidney and pancreas transplant group and 43.1 ± 39.6 months (range, 1–128) in the kidney transplant group. Two patients in each group died within 1 month after surgery; except for these two patients, the shortest follow-up was 12 and 8 months in the kidney and pancreas transplant and the kidney transplant groups, respectively.

Nine neoplasms occurred in 7 of 73 (12%) kidney and pancreas transplant patients, whereas no neoplasms occurred in the kidney transplant group; neoplasms occurred 1.5–73.0 months after transplant. Cancer-free actuarial survival rates were 97, 95, 92, 90, 85, and 79.6% at 1, 2, 3, 4, 6, and 6.5–10 years, respectively, in the kidney and pancreas transplant group versus 100% up to 10 years in the kidney transplant group. Histological types were posttransplant lymphoproliferative disorder (PTLD; two cases), malignant melanoma, basal-cell and squamous-cell carcinoma of the skin in the same patient, squamous-cell carcinoma in situ of the vulva, hepatocarcinoma, small-cell lung cancer, and ductal carcinoma of the breast. Four patients died.

Patients' characteristics, type of transplant, risk factors for cancer, and relevant observations are summarized in Table 1. Antirejection therapy, type of neoplasm, date of its appearance after transplant, treatment, and clinical outcome are summarized in Table 2.

Histological observations

Histological material was available in all cases but one (case 1). All biopsies from pleura and lung in case 2 had features of small-cell carcinoma, both of oat cell and polygonal cell type. In case 3, a series of 11 biopsies performed over a 2-year period from the anogenital area and vulva revealed prominent koilocytosis from human papilloma virus (HPV) infection with mild or severe dysplasia [VIN (vulvar intraepithelial neoplasia) II, VIN III]. In two not-consecutive biopsies, two areas of bowenoid squamous cell carcinoma were observed. Cytological studies of the vagina and cervix were always positive only for HPV infection. HPV DNA detection was not performed. Case 4 had an association of head and face skin malignancies. The most serious neoplasm was a malignant nodular melanoma (five millimeters deep of Breslow, Clark level V) with a recurrence 2 years after complete surgical removal. Other skin lesions were basal-cell carcinoma and warts. Case 5 had a segmental mastectomy for invasive ductal carcinoma with areas of mucinous carcinoma (approximately one tenth of the neoplasm). Staging was pT2, G3, and pN1bIII, and <10% of the neoplastic cells were positive for estrogen and progesterone receptors. Case 6 and 7 developed PTLD. In patient 6, the diagnosis was made on the basis of microscopic findings on autopsy material. Previous biopsies from the transplanted kidney had signs of mild rejection that disappeared after therapy in the second specimen. PTLD affected (listed in decreasing intensity) allograft and native kidneys and pancreas, liver, duodenum and antrum (with several ulcers causing severe bleeding), spleen, heart, and brain. Histological features revealed extensive infiltrative processes, consisting of both mature lymphocytes and immature forms resembling immunoblasts infiltrating the perineural space and surrounding small and medium vessels. Necrosis was massive in some areas. Immunoperoxidase studies revealed null phenotype for immature cells; mature lymphocytes were both CD20 and CD3 positive, in different proportion from area to area. In patient 7, the diagnosis was made from axillary lymph node biopsies and liver minicore biopsy; kidney allograft minicore biopsy was suspicious but not diagnostic. Bone marrow biopsy was negative. In lymph node and liver specimens, large lymphoblastic cells with a background of small monomorphic lymphocytes, both with B phenotype, could be seen. Southern blot gene analysis after polymerase chain reaction on frozen lymph node tissue showed two distinct clonal bands, suggesting an oligoclonal PTLD. When a kidney acute rejection occurred 6 months after immunosuppression withdrawal, a liver biopsy confirmed that the portal spaces were free from inflammatory infiltrate, and a kidney biopsy showed an evident lymphocytic tubulitis.

Table 2—*Summary of immunosuppressive treatment, type of neoplasm, time of appearance after transplant, treatment, and patient's outcome*

Case	Antirejection	Type of neoplasm	Appearance (months after transplantation)	Treatment	Outcome (months after cancer)	Graft function
1	—	Hepatoca	73	—	Dead at 1 month	Functioning KP
2	—	Small-cell lung	67	CT	Dead at 21 months	Functioning KP
3	MP 3 boluses	Squamous-cell carcinoma vulva	40	Surgery	Alive at 38 months	Functioning KP
4	MP 8 boluses	Melanoma skin	28	Surgery	Dead at 40 months	Functioning KP
		Basal-cell carcinoma skin	44	Surgery		
		Squamous-cell carcinoma skin	57	Surgery		
5	—	Breast carcinoma	47	Surgery plus CT	Alive at 21 months	Functioning KP
6	MP 5 boluses OKT3 70 mg	PTLD	2	—	Dead at 2 months	Functioning KP
7	MP 3 boluses ATG 10 days OKT3 90 mg	PTLD	1.5	Discontinuation of IS	Alive at 29 months	Functioning KP*

CT, chemotherapy; IS, immunosuppression; KP, kidney and pancreas transplant; MP, methylprednisolone. *One acute kidney transplant rejection episode occurred 6 months after immunosuppression withdrawal and was successfully treated with steroids. Triple immunosuppressive therapy was reinstituted.

CONCLUSIONS — An increased incidence of de novo cancer is a complication of organ transplantation. Only certain types of neoplasms are increased in incidence after transplantation, while tumors occurring commonly in the general population are not. The histological types showing a significantly increased incidence are cutaneous cancers (4- to 21-fold) with a squamous-cell/basal-cell carcinoma ratio of 1.75, non-Hodgkin's lymphoma (28- to 49-fold), and Kaposi's sarcoma (400- to 500-fold) (1,2). In cyclosporin A–treated patients, lymphoma, cutaneous carcinoma, and Kaposi's sarcoma make up the majority of the detected cancers (38, 16, and 10%, respectively). Among risk factors, the Epstein-Barr virus (EBV) is strongly suspected to cause lymphomas in human transplant recipients in the setting of an inhibited T-cell response and the subsequent uncontrolled EBV-induced proliferation of infected B-cells by the use of antilymphocyte antibody preparations (ALG, ATG, and OKT3) (5–8). HPV and ultraviolet radiation, together with immunosuppressive agents, promote skin and genital carcinogenesis (9–12). The role played by immunosuppression in the development of the most common types of cancer occurring after transplantation is well documented by the reversibility of lymphoma and Kaposi's sarcoma after the reduction or withdrawal of immunosuppression (13,14).

At our institution, kidney transplantation in nondiabetic recipients is not performed, so we do not have a nondiabetic transplanted series to compare the incidence of cancer. Cancer cases were detected only in kidney and pancreas transplant patients and not after kidney transplant alone. The incidence of cancer arising after simultaneous kidney and pancreas transplantation was 9 out of 73 (12%), which is higher than has been reported in the literature. In particular, we observed an incidence of non-Hodgkin's lymphoma of 2.6%. The incidence of non-Hodgkin's lymphoma in a multicenter study of 45,141 kidney transplants and 7,634 heart transplants was 0.22 and 1.21%, respectively (6). Recently, Gruessner et al. (15) described three cases of EBV-associated B-cell lymphoma after pancreas transplantation in patients treated prophylactically with FK 506 (an incidence of 3.6%). Our two cases of PTLD had both received high doses of antilymphocytic sera for steroid-resistant kidney rejection: one course of ALG plus two courses of OKT3, which resulted in a cumulative dose of OKT3 of 70 mg in patient 6 and 90 mg in patient 7. A cumulative OKT3 dosage >75 mg has been associated with an increased risk for the development of PTLD (16). In case 7, EBV DNA could be detected in the lymphocytic infiltrate. Both cases of PTLD developed within 2 months after transplantation, and in one case, the recognition of the disease and the discontinuation of immunosuppression led to the disappearance of lymphoma, as already described in the literature (13). Overall, seven of nine cancers were of histological types whose incidence is increased after transplantation (3 skin, 2 lymphomas, 1 anogenital, and 1 hepatocarcinoma). By contrast, lung cancer (case 2) and carcinoma of the breast (case 5) are not histological types typically associated with immunosuppression, although immunosuppressive treatment may have accelerated their evolution. For cases 1 (hepatocarcinoma) and 2 (lung cancer), well-known risk factors were present (chronic aggressive hepatitis B and C viruses and cigarette smoking, respectively).

Some authors have reported a higher incidence of acute kidney rejection after combined kidney and pancreas transplantation than has been observed after kidney transplantation alone (17,18), the subsequent antirejection treatment being possibly implicated in the arousal of cancer. Transplantation centers performing kidney and pancreas transplantation adopt heavier immunosuppressive protocols, compared with kidney transplantation alone, leading to over-immunosuppression to preserve kidney function (19). Nevertheless, this is not the case in our patients who were not over-immunosuppressed, except for the two PTLD cases. In fact, case 3 had two mild rejection episodes treated with low-dose methylprednisolone (two boluses plus one), and case 4 had two antirejection treatments based on methylprednisolone boluses alone (three plus five); in the other three patients, no rejection occurred. At our institution, basic immunosuppression is a quadruple regimen both after kidney and pancreas transplantation and kidney transplantation alone. This regimen in kidney transplantation is definitely heavier than that adopted in

many centers performing kidney transplantation in nondiabetic patients. Curiously, no cancer was detected in 26 recipients of kidney transplant alone at the same institution, 10 of whom received a second transplant together with a reinforcement of immunosuppression. As the length of post-transplant follow-up in the two groups was the same, it may be that the small number of patients in the kidney transplant group was cancer-free by chance.

In conclusion, it is difficult to say if the heavy immunosuppressive regimen can be incriminated for cancer arousal in our series. Nevertheless, in our opinion, the policy of a heavy immunosuppressive treatment in IDDM patients undergoing kidney or kidney plus pancreas transplantation may be justified. The most important consideration is that the life expectancy of diabetic uremic patients on hemodialysis is remarkably reduced, compared with patients affected by end-stage renal disease of other causes, and is good after pancreas and kidney transplantation: the 5-year diabetic and nondiabetic patient survival rate on hemodialysis (for patients started on dialysis at 25–44 years of age) is ~40 and 75%, respectively (20). Conversely, the 5-year diabetic patient survival rate after pancreas and kidney transplantation is as high as 89% (21), and the one-year survival rate of the patient and of the kidney transplanted into the diabetic patient is as high as in nondiabetic individuals (91.6 and 79% vs. 94 and 80%, respectively) (19,22). Therefore, once the diabetic patient is submitted to kidney transplantation, the maximum effort must be made to preserve kidney function, because the patient's risk of death while on a waiting list is very high; that is to say, nondiabetic patients can survive for a long time on dialysis, while diabetic patients cannot. Last, the incidence of cancers in dialysis patients may be higher than in the general population (23). Any further increase in the incidence of cancer caused by immunosuppressive therapy given for renal transplantation is more than offset by the better 5-year survival rate of diabetic renal transplant recipients, compared with that of diabetic dialysis patients. An increased dosage of immunosuppressive agents may be necessary in some patients to prevent or treat rejection. The development of new immunosuppressive drugs with reduced side effects while retaining antirejection potential is warranted. Until then, special care is needed for the early diagnosis and monitoring of treatable immunosuppression-associated cancers.

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