Ovarian cancer after kidney transplantation

C. Di Berardino, G. Mascaretti

Department of Ostetrics and Gynecology, University of L'Aquila (Italy)

Summary

Malignancies are one of the major causes of morbidity and mortality in transplant patients. The incidence is progressively increasing either because of the increased age transplant patients and the increase of immunosuppressive therapy or the increased follow-up range post-transplantation. The main causes of increased tumor incidence in transplant patients with respect to the general population are the reduced immunosurveillance and the high incidence of infections due to oncogenic viruses. This problem might become more and more serious in the near future due to the introduction of new immunosuppressive strategies that significantly extend allograft survival. A case of ovarian cancer in a kidney transplant patient is described. Attention is focused on the potential dual role of immunosuppressive therapy in the development of malignancies in transplant patients.

Key words: Ovarian cancer; Kidney transplantation; Immunosuppressive drugs.

Introduction

Over the last ten years marrow and solid organ transplants have grown at an exponential rate in Europe and the United States. Furthermore, the prognosis for patients who have a solid organ transplant has been improving over time, with a four-year survival rate for 85-92% of those with a transplanted kidney and 72% of those with a heart transplant [1]. This increase in transplantation activity has been accompanied by an increased frequency of problems related to immunosuppressive activity, which is necessarily applied to reduce rejection risk. Post-transplant problems basically consist of infections and malignancies.

The frequency of neoplastic disease in patients who had a transplant is on the rise (6%) [2, 3], being four to five times higher than among the broader population [4]. This can be linked both to the longer survival of transplanted patients, which results in greater exposure to immunosuppressive therapy, and to the increasingly older age of receivers.

The link between immunosuppression and malignancies became particularly clear at the onset of the transplantation era, in relation to the use of very aggressive and few selective protocols [5-7].

In addition to immunosuppressive therapy, other risk factors have been identified for carcinoma development such as receiver's age, smoke, viral infections and male sex [8].

The most frequent tumors are skin cancer (melanoma, spino- and basocellular carcinoma), Kaposi's sarcoma, lymphoproliferative disorders, anal and genital carcinomas (anus, vulva, penis scrotum), hepatobiliary carcinomas and kidney carcinoma [9].

A case of a kidney transplant patient following chronic kidney failure who underwent immunosuppressive therapy and eventually developed a bilateral ovarian adenocarcinoma ten years after the transplant is presented.

Case Report

A 43-year-old woman came under our observation at the Department of Obstetrics and Gynecology of the University of L'Aquila, where she had been referred from the Transplant Unit of San Salvatore Hospital after being diagnosed with bilateral ovarian neoformation and ascites.

The patient had a kidney transplant in July 1996 following chronic kidney failure and has since been on immunosuppressive therapy: cyclosporin A (150 mg/day) and prednisone (2.5 mg/day).

Family history revealed a predisposition to hypertension and diabetes mellitus type II. The patient had menarche at age 12 and two natural childbirths. She reported that she has been suffering from hypertension for about 12 years. At the time of the examination she was being treated with valsartan (80 mg/day) and felodipine (10 mg/day).

Objective examination showed a good general condition, but there was abdominal extension due to the presence of ascites.

Outcome of the gynecological examination showed outer genitalia typical of a woman who had given birth, a regular vagina, and a well epithelialized uterine neck. Outcome of latest Pap test carried out four months before was normal. The uterine corpus was hard and mobile with increased volume. Adnexa were considerably enlarged with hard and elastic consistency.

The patient underwent hematochemical examinations, tumoral markers, kidney and hepatic functionality assessment, basal and peak cyclosporine treatment, RX thorax, ECG and abdominal CAT scan with and without contrast medium.

Hematochemical examinations showed normal results as well as normal kidney and hepatic functionality.

The patient had high CA125 levels (353.23 IU/ml), CA19-9 was 42.80 IU/ml and CEA within normal range.

CAT scans carried out with and without contrast medium revealed presence in the adnexa of a large bilateral cystic formation measuring about 10 cm in diameter, with significant vascularized endocysts which were thicker on the left side,

Revised manuscript accepted for publication June 18, 2007

Fig. 1

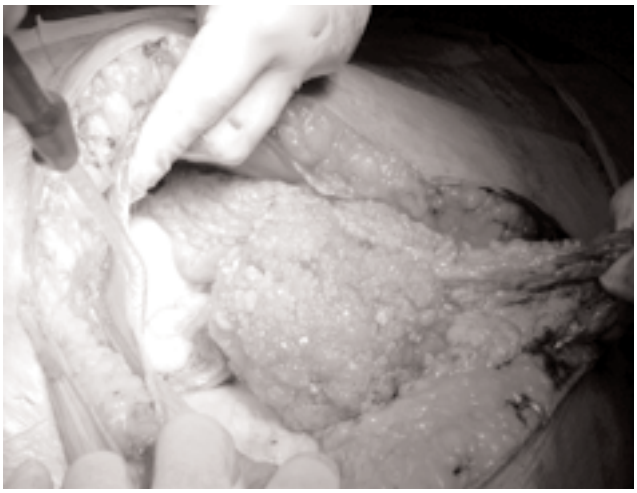

Fig. 2

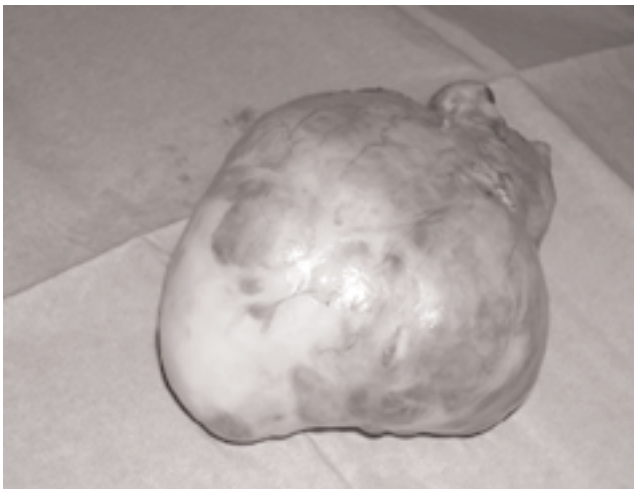

Fig. 3

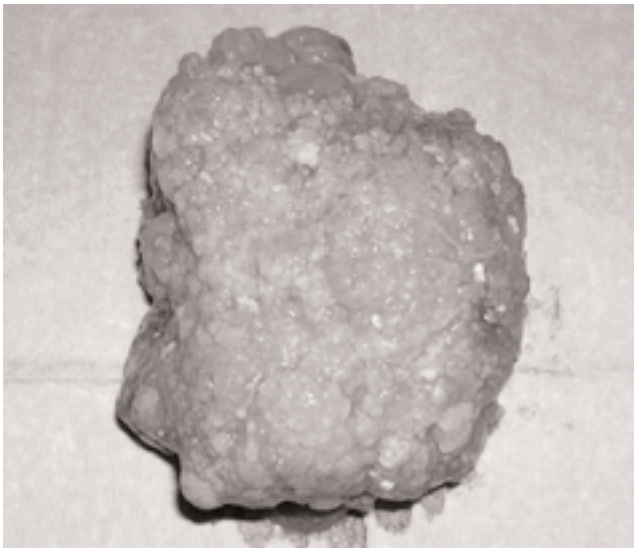

Figure 1. — Image of the left ovary during laporatomy.

Figure 2. — Right ovary showing serous papillary cystoadenocarcinoma.

Figure 3. — Left ovary showing serous papillary adenocarcinoma.

where the solid component reached a diameter of up to 5 cm. Apparent endometrial thickening in the cervical region was linked to irregularities in the left parametrium.

The liver, suprarenal glands, spleen, and pancreas were all normal. A normally vascularized kidney that has been transplanted into the left iliac fossa was seen as well as ascitic fluid.

Radiography of the thorax did not reveal any signs of ongoing pleuroparenchymal infiltration processes, there was normal distribution of lung vascularization, and heart shade was within normal values.

The patient underwent total hysterectomy with bilateral salpingo-oophorectomy, appendectomy, right pelvic and lumbar aortic lymphadenectomy (left pelvic lymphadenectomy had been performed during the kidney transplant) and omentectomy.

No problem occurred in the postoperative period. Kidney functionality has been checked regularly but no changes have been noted. The patient carried on with immunosuppressive therapy throughout her stay in the hospital with slightly lower dosages (cyclosporin, 75 mg/day and prednisone 2.5 mg/day every second day).

Histological examination revealed well and moderately differentiated left ovarian serous papillary adenocarcinoma all over the ovarian surface, with psammoma bodies. Neoplastic infiltration of fatty tissue adhering to the ovary was noted. The left tube was free of infiltration. There was well differentiated serous papillary cystoadenocarcinoma in the right ovary, not appearing on the ovarian surface. The right tube was free of neoplastic infiltration. The lymph nodes examined were found to be free of infiltration. Cytologic analysis of the peritoneal washing revealed some clusters of adenocarcinomatous cells.

The patient was discharged on the tenth day in good general condition while still on immunosuppressive therapy.

She has undergone outpatient checks at the Transplant Unit of San Salvatore Hospital in L'Aquila, which as yet have not revealed any changes in kidney functionality, nor any second offense with regard to neoplastic disease.

Discussion

For many years transplants have been a concrete and effective therapeutic approach for terminal diseases of many organs such as the kidney, heart, liver and lungs. In the United States 300,000 new transplants are performed every year [10]. As for Italy, the latest estimates show that 250,000 organ transplants were carried out between 1992 and 2003 [11].

Survival has also considerably increased for transplanted patients due to improvements in surgical methods as well as, most importantly, to the advancement of immunosuppressive therapy.

It is a fact that immunosuppressive therapy increases the risk for infections and malignancies in patients with transplanted organs compared with the general population due to its very operational mechanism.

Most reports on post-transplantation malignancies have been limited by a small number of relevant cases. Kasiske *et al*. [12] studied the frequency of tumors in kidney transplants carried out in various centers in the period 1995-2001, examining a total of 35,756 patients. For the most common tumors, such as those affecting the colon, lung, stomach, esophagus, pancreas, ovary and breast, the incidence after kidney transplant was found to be twice as high as among the general population. Melanoma, leukemias, hepatobiliary tumors, tumors of the uterine neck and vulvovaginal tumors all turned out to be five times as common, with kidney cancer being 15 times as common. Testicular and vesical neoplasty were about three times as frequent, with kidney cancer 15 times as frequent. Kaposi's sarcoma, non-Hogkin lymphomas and skin tumors other than melanoma were 20 times as frequent as among the general population. Hence the incidence of most forms of neoplasty after kidney transplant is found to be higher than among the general population.

Transplant patients as well as other groups of patients with different immunodeficiency conditions (congenital or HIV) are not at high risk of developing the most common forms of malignancies such as breast, prostate or colon carcinoma. On the contrary, the tumors most frequently developing in transplant patients are seldom found in the broader population and are often etiologically associated with viral infections such as lymphomas that are often associated with infections caused by the Epstein-Barr virus (EBV) and Kaposi's sarcoma, which is invariably associated with infections caused by human herpes virus 8 (HHV-8) [13].

Reduction of immunosuppressive treatment is the first therapeutic option which, while effective in causing a remission of tumor in some cases, almost invariably leads to the organ being rejected. Some types of treatment, including those based on adoptive cell immunotherapy, are either still in the trial stage or have come into use in medical practice only recently.

The role of immunosuppression in tumor development has been documented by the comparison between patients with a transplanted kidney and patients on kidney transplant waiting lists. This analysis has highlighted that transplantation, while reducing the overall death risk for the patient, significantly increases the chance of death from maligancies, especially among older patients [14].

Obviously, intense immunosuppression, needed to curb immune response to the transplanted organ, inevitably limits the body's ability to eliminate the cells transformed as a result of tumor.

However, many believe that the significant immune response reduction in transplanted patients alone cannot fully explain the increased post-transplant incidence of neoplastic disease. Among the responsible factors a role has been suggested for chronic antigenic stimulation due to external antigens found in transplanted organs and to frequent infections. Indeed, this condition may cause excessive stimulation of the already depressed immune system, thereby further "diverting" it from its surveillance of neoplastic cells [4, 15].

The direct oncogenous potential of immunosuppressive drugs should also be considered. Indeed, it is a well known fact that these drugs can cause direct damage to DNA by strengthening the effects of other carcinogenic factors [4, 15]. Nevertheless, recent studies suggest that not all immunosuppressive drugs lead to the development of tumors in transplanted patients, with some of them having potentially antineoplastic properties [16].

In our particular case we ought to consider the role played by cyclosporine in the onset of ovarian tumors. Its introduction in immunosuppressive transplant therapy has significantly improved the short- and long-term outcome of organ transplants; this result can be ascribed to the drug's powerful immunosuppressive effect [17]. In contrast, the development of malignant neoplasia with an unusual aggressive phenotype has been linked to immunosuppression by cyclosporin, through the drug's direct action on the phenotype of neoplastic cells. The latter, under exposure to the effect of cyclosporin, show an increase in proliferation and migration speed [18, 19].

An additional mechanism that may be behind the carcinogenic effect of cyclosporin is thought to result from inhibition by this drug of the molecular mechanisms responsible for DNA repair processes [20].

However, cyclosporin's pro-neoplastic effect is complemented by the inhibiting action of neoplastic cells on the production of glycoprotein p, a membrane pump which enables cells to eliminate anti-neoplastic drugs [21].

Since tumors are one of the main morbidities and causes of death among transplant patients, it seems advisable to adopt a set of preventive treatment measures in an attempt to reduce tumor incidence within this category of patients: careful anamnestic history and accurate clinical and laboratory analyses, avoidance of heavy immunosuppressive therapies, careful and regular clinical surveillance of transplanted patients, limiting exposure to cancerogenic agents, and prophylaxis of viral infections.

Conclusion

The introduction of immunosuppressive therapies has considerably improved survival after kidney transplantation but, at the same time, it causes profound changes in the immunological surveillance mechanism that plays a vital role in restraining tumor growth [22].

Tumors are indeed a major cause of death and morbidity among patients receiving a kidney transplant, not least because the natural history of neoplastic diseases shows greater aggressiveness in transplanted patients compared with the general population [23].

It would be advisable to use a careful monitoring protocol for patients on the transplant list as well as for transplanted patients – one that allows diagnosis of tumors at an early stage.

Tumor management in transplanted patients requires a multidisciplinary approach, aggressive treatment, and involves modifying immunosuppressive treatment according to the histotype and natural history of the tumor.

The emergence of new types of immunosuppressive drugs offers an opportunity to take advantage of the neoplastic action of some of them, thus ensuring good immunological protection in combination with the oncologic protocol.

References

[1] Bower M.: "The management of lymphoma in the immunosuppressed patient". *Best Pract. Res. Clin. Haematol.,* 2002, *15,* 517.

[2] Winter P., Schoeneich G., Miersch W.D., Klehr H.U.: "Tumor induction as a consequence of immunosuppression after renal transplantation". *Int. Urol. Nephrol*., 1997, *29*, 701.

[3] Baccarani U., Adani G.L., Montanaro D., Risaliti A., Lorenzin D., Avellini C. *et al*.: "De novo malignancies after kidney and liver transplantations: experience on 582 consecutive cases". *Tranplant. Proc*., 2006, *38,* 1135.

[4] Penn I.: "Depressed immunity and development of cancer". *Cancer Detect. Prev*., 1994, *18,* 241.

[5] Penn I.: "Second malignant neoplasm associated with immunosoppressive medication". *Cancer,* 1976, *37,* 1024.

[6] Penn I.: "Malignancies associated with renal transplantation". *Urology,* 1997, *10,* 57.

[7] Ramsay H.M., Fryer A.A., Reece S., Smith A.G., Harden P.N.: "Clinical risk factors associated with nonmelanoma skin cancer in renal transplant recipients". *Am. J. Kidney Dis.,* 2000, *36,* 167.

[8] Penn I.: "Post transplan malignancies". *Transplant Pro*., 1999, *31*, 1260.

[9] United Network For Organ Sharing, www.unos.org, 2003.

[10] Penn I.: "Immunosuppression – a contributory factor in lymphoma formation". *Clin. Transplant,* 1992, *6*, 214.

[11] Stallone G., Infante B., Schena A., Grandaliano G., Di Paolo S., Scolari M.P. *et al*.: "Malignant neoplasia and renal transplant". *Italian J. Nefrol*., 2003, *20,* 611.

[12] Kasiske B.L., Snyder J.J., Gilbertson D.T., Wang C.: "Cancer after kidney transplantation in the United States". *Am. J. Transplant,* 2004, *4,* 905.

[13] Boshoff C.: "Kaposi's sarcoma biology". *IUBMB Life,* 2002, *53,* 259.

[14] Meier-Kriesche H., Ojo A., Hanson J., Kaplan B.: "Exponentially increased risk of infectious death in older renal transplant recipients". *Kidney Int*., 2001, *59*, 1539.

[15] Penn I.: "Malignancy after immunosuppressive therapy : how can the risk be reduce?". *Clin. Immunotherapy*, 1995*, 4,* 207.

[16] Infante B., Stallone G., Schena A. *et al*.: "Pro and anti-neoplastic effects of immunosuppressive drug in renal transplantation". *Ital. J. Nefrol.,* 2006, *23*, 389.

[17] Kahan B.D.: "Cyclosporine". *N. Engl. J. Med*., 1989, *321*, 1725.

[18] Masuhara M., Ogasawara H., Katyal S.L., Nakamura T., Shinozuka H.: "Cyclosporine stimulates hepatocyte proliferation and accelerates development of hepatocellular carcinomas in rats". *Carcinogenesis,* 1993, *14,* 1579.

[19] Hojo M., Morimoto T., Maluccio M., Asano T., Morimoto K., Milagros Lagman M. *et al*.: "Cyclosporine induces cancer progression by a cell-autonomous mechanism". *Nature,* 1999, *397*, 530.

[20] Herman M., Weinstein T., Korzets A., Chagnac A., Ori Y., Zevin D. *et al*.: "Effect of cyclosporin A on DNA repair and cancer incidence in kidney transplant recipients". *J. Lab. Clin. Med.,* 2001, *137*, 14.

[21] Twentyman P.R., Fox N.E., White D.J.: "Cyclosporin A and its analogues as modifiers of adriamycin and vincristine resistance in a multi-drug resistent human lung cancer cell line". *Br. J. Cancer,* 1987, *56,* 55.

[22] Veroux M., Pulitati C., Fiamingo P.: "Early de novo malignances after kidney transplantation". *Transplant Proc.,* 2004, *36*, 718

[23] Startzl T.E., Nalesnik M.A., Porter K.A.: "Reversibility of lynphomas and lynphoproliferatuive lesion developig under cyclosporin-steroid therapy". *Lancet*, 1984, *1,* 583.

Address reprint requests to:
G. MASCARETTI, M.D.
Dip. Scienze Chirurgiche
Facoltà Medicina e Chirurgia
Piazzale S. Tommasi, 1
67010 Coppito L'Aquila (Italy)
e-mail: giulio.mascaretti@libero.it