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Dramatic recurrence of cancer in a patient who underwent kidney transplant – an analysis of post-transplant cancer recurrence and case report

Nawrót choroby nowotworowej o dramatycznym przebiegu u pacjentki po przeszczepieniu nerki – analiza problemu nawrotu nowotworu po transplantacji i opis przypadku

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Key words

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Słowa kluczowe

transplantacja, wywiad nowotworowy przed transplantacją, śmiertelność zależna od nowotworu

S u m m a r y

Beside cardiovascular diseases and infections, cancers are the main cause of death in patients after transplantation of a vascularised organ. After transplantation, usually *de novo* cancers develop. Recurrence of cancers which had been diagnosed and treated before transplantation is much rarer. In exceptional cases, cancer is transferred with the donor's organ. The epidemiology and the course of post-transplant *de novo* neoplasia is relatively well known. However, the issue of recurrence of pre-transplant cancer, which is significantly rarer and its course more individualised and difficult to predict, poses a challenge to contemporary transplantation.

This paper presents an unexpectedly rapid recurrence of rare cancer – endometrial stromal sarcoma – which occurred shortly after transplantation of a kidney from a deceased donor to a patient who had undergone cancer treatment 7 years earlier. The dramatic course of the disease, complicated with recurrent massive thrombosis of the inferior vena cava and the right cardiac cavities as well as pulmonary embolism and serious infectious complications illustrate the difficulties related to qualifying patients with a history of malignancy for transplantation. The scale of the problem will most likely increase as older recipients are being put on transplant waiting lists and cancer treatment is becoming more effective.

The authors of this paper, based on the case report presented and the review of literature, attempt to find an answer to the question about the risk of cancer recurrence in patients receiving immunosuppressive therapy and find out how it can be minimized. Answering these questions is particularly important if the recurrent cancer is substantially more aggressive, cancer treatment options are limited and the prognosis is poor due to lack of immunocompetence.

S t r e s z c z e n i e

Choroby nowotworowe są obok chorób układu sercowo-naczyniowego i zakażeń główną przyczyną zgonów pacjentów po przeszczepieniu narządu unaczynionego. Po transplantacji najczęściej rozwijają się nowotwory *de novo*, znacznie rzadziej jest to nawrót choroby nowotworowej rozpoznanej i leczonej przed przeszczepieniem; wyjątkowo zdarza się przeniesienie nowotworu z narządem dawcy. O ile epidemiologia i przebieg choroby nowotworowej powstającej *de novo* po przeszczepieniu są stosunkowo dobrze zbadane, to problem nawrotu nowotworu sprzed transplantacji, jako znacznie rzadszy i wykazujący bardziej indywidualny, trudny do wcześniejszego przewidzenia przebieg, jest wyzwaniem dla współczesnej transplantologii.

Praca jest opisem nadspodziewanie szybkiego nawrotu rzadkiego nowotworu, mięsaka podścieliskowego macicy, który wystąpił w krótkim czasie po przeszczepieniu nerki od dawcy zmarłego, u pacjentki po leczeniu onkologicznym zakończonym 7 lat przed transplantacją. Dramatyczny przebieg choroby, powikłany nawracającą masywną zakrzepicą żyły głównej dolnej, jam prawego serca i zatorowością płucną oraz ciężkim powikłaniami infekcyjnymi, jest przykładem trudności w kwalifikowaniu pacjentów z wywiadem onkologicznym do transplantacji. Skala problemu będzie prawdopodobnie narastała w związku z akceptacją na listach oczekujących na przeszczepienie biorców w starszym wieku oraz coraz skuteczniejszym leczeniem chorób nowotworowych.

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Autorzy pracy na kanwie opisywanego przypadku i analizy piśmiennictwa próbują znaleźć odpowiedź na pytanie o ryzyko nawrotu nowotworu u pacjenta poddanego leczeniu immunosupresyjnemu oraz określić możliwości jego minimalizowania. Odpowiedź na te pytania jest szczególnie istotna w sytuacji znacznie bardziej agresywnego przebiegu nawrotu nowotworów, ograniczonych możliwości leczenia onkologicznego oraz gorszego rokowania u pacjentów nieimmunokompetentnych.

INTRODUCTION

Beside cardiovascular diseases and infections, cancers are one of the three main causes of death after renal transplantation. At present, the risk of death from cancer developing after transplantation of a vascularised organ is estimated at 7-12%, and in recent years it is systematically increasing (1). It results from the fact that mortality from other causes, i.e. cardiovascular diseases and infections, is decreasing. Increasingly better knowledge of risk factors for cardiovascular diseases, prevention programmes and availability of effective treatment modalities, as well as quick and usually effective treatment of infections, result in cancers being an increasingly more common cause of death in patients with an active graft. Equally important are older age of transplant recipients, longer survival of post-transplant patients and increasingly more effective immunosuppressive drugs, which at the same time interfere with the recipients' immune system to a greater extent. It is estimated that within the next 20 years cancers will become the main cause of death after transplantation (2). This results from not so well defined risk factors for neoplasia, frequently ineffective screening programmes and considerably more limited cancer treatment options compared with non-transplant patients.

The risk for post-transplant cancer increases 3-5 times compared with the general population of the same age and sex (3). After transplantation, usually *de novo* cancers develop. Recurrence of cancers which had been diagnosed before transplantation is much rarer. Sporadically, cancer is incidentally transferred with the donor's organ. Epidemiology of *de novo* post-transplant cancers is relatively well known. The aim of this paper was to analyse the incidence, contributing factors and the feasibility of preventing recurrence of cancers which had been diagnosed and treated before transplantation.

Most information about cancer patients undergoing organ transplant comes from large transplant registers and medical data bases from individual countries. Their review shows that the percentage of patients with a history of malignancy and undergoing kidney transplant compared with all the patients undergoing transplantation is relatively low: in the study by Kauffman et al. (4), based on data from the Organ Procurement and Transplantation Network/United Network for Organ Sharing (OPTN/UNOS) database, it was 2.1% (1358 of the total of 65 999 patients undergoing renal transplant); in the analysis by Chapman et al. (5), based on the Australia-New Zealand Dialysis and Transplant Registry (ANZDATA), it was 1.8%; and in the study by Brattström et al. (6) it was 4% (210/11 894 and 416/10 448 patients with a pre-transplant history of cancer compared with all the patients undergoing transplant, respectively). However, it should be expected that on the transplant waiting lists the number of patients from this population will grow: accepting older transplant recipients and increasingly more effective cancer treatment must inevitably result in an increased number of patients with a history of cancer becoming candidates for transplantation. Even more than recipients of kidneys, the problem concerns patients who require transplantation of life-saving organs such as the heart, lungs and liver whose irreversible damage paradoxically may result from aggressive treatment of cancer.

The fact that immunosuppressive therapy plays a role in the development of post-transplant cancer is indisputable. It is evidenced by a significant increase in cancer risk in immunosuppressed patients compared not only with the general population but also with patients placed on renal transplant waiting lists, who are at an increased risk of oncogenesis compared with patients who do not develop renal failure. Based on the analysis of the ANZDATA register data, Vajdic et al. (7) have ascertained that the standarized incidence ratio (SIR) for all cancers is 1.35 in the case of dialysed patients and 3.46 in the case of patients after renal transplant. The obvious effect of immunosuppression on oncogenesis is also supported by anecdotal reports of the regression of cancer transferred with a transplanted kidney once the the kidney was removed and the immunosuppressive therapy was discontinued (8, 9).

The effect of immunosuppressive drugs on the process of oncogenesis is complex: it results from the inhibition of inborn mechanisms of immune surveillance over cancer cells, direct anthropogenic effects of the drugs, as well as increased risk of developing viruses with oncogenic potential (Epstein-Barr Virus [EBV], Human Herpes Virus 8 [HHV8], Human Papilloma Virus [HPV], Hepatitis B Virus [HBV] and Hepatitis C Virus [HCV]).

Particularly with respect to calcineurin inhibitors (CNI) – cyclosporin a and tacrolimus, both *in vitro* and experimental animal studies showed an increased risk of cancerogenesis and angiogenesis as well as tendency to metastasise (10). It was postulated that the influence on oncogenesis might be connected with increased expression of cytokines regulating tumour growth, such as

transforming growth factor beta (TGF-β), and tumour growth promotion by increased expression of the vascular endothelial growth factor (VEGF). On the other hand, clinical studies comparing the risk for tumour growth in patients either treated or untreated with CNI did not show significant differences in the long-term assessment (11).

Rather than the effect of individual immunosuppressive agents, the cumulative effect of immunosuppression, dependent on the intensity and duration of immunosuppressive therapy, appears to play a greater role. It is clearly evidenced by the fact that cancer risk increases with the time elapsing from transplantation: according to data from the USRDS (United States Renal Data System) database, in the first year after transplantation the risk for cancer is 3.2%, and after 20 years it reaches 40% (12).

What is also noteworthy is a substantially higher cancer rate in recipients of organs other than kidneys, such as the heart or lung, in whom immunosuppression is usually more potent (13, 14). Gallagher et al. (11) observed an increased cancer risk in patients diagnosed with acute graft rejection within one year of transplantation, who were usually treated with glucocorticosteroid pulses and by way of increasing basic immunosuppression, which meant an increased general "load" of immunosuppression.

In view of the confirmed impact of immunosuppression on the process of oncogenesis, it is particularly important to define the risk for recurrence of the cancer that had been diagnosed and considered cured before transplantation. Many studies suggest that residual, metabolically inactive, "dormant" cancer cells may get activated in the setting of markedly weakened immune system of the recipient, even many years after transplantation (2, 15-17). Regrettably, the contemporary diagnostic modalities do not allow ruling out latent cancer cells with complete certainty or defining their potential for repeat proliferation.

The analyses of transplantation registers show that the post-transplant recurrence risk is 1-25% and is connected mainly with the cancer type and the "grace period" which elapsed from the moment of diagnosis and treatment to the moment of organ transplantation (4-5, 15-16).

In the first historical analyses carried out by Penn et al. based on the Cincinnati Transplant Tumor Registry (CTTR), the overall incidence of cancer recurrence after transplantation of a vascularised organ was 21% (239 recurrences in 1137 patients with a history of cancer undergoing transplantation) (18). Depending on the recurrence risk, Penn et al. classified cancers into three groups:

- cancers with low recurrence risk: < 10% (incidentally discovered renal cancer, testicular cancer, cervical cancer, cancer of the uterine body, thyroid cancer),
- cancers with medium recurrence risk: 11-25% (colorectal cancer, prostate cancer, Wilms tumour, melanoma),
- cancers with high recurrence risk: > 25% (breast cancer, symptomatic renal cancer, urinary bladder cancer, sarcomas, non-melanoma skin cancers, multiple myeloma).

Vast majority of recurrences occurred within 2 years of transplantation (64%); in 24% of patients, cancer recurrence occurred 2-5 years after transplantation, and in the remaining 11% – over 5 years after transplantation.

The recurrence risk was related to the period which elapsed between the time cancer was diagnosed and the time the kidney was transplanted: 54% of recurrences occurred in patients with the "grace period" shorter than 2 years, 33% – in patients with the grace period of 2-5 years, and 13% – when the period between the end of cancer treatment and kidney transplantation was more than 5 years.

Penn's studies became a starting point for producing current recommendations on the mandatory grace period for individual cancers – the time that has to elapse from the end of cancer treatment until the patient is qualified for transplantation. Penn has proposed a two-year period for most low and medium risk cancers and a five-year period for high recurrence risk cancers (invasive renal cancer, breast cancer, lymphomas).

More recent analyses of the post-transplant recurrence resulted in some reservations about the first works by Penn et al. What deserves notice in the first place is unacceptably high overall risk of cancer recurrence, which was over 20% in the analysis presented and which gives rise to some doubts as to whether patients with a history of cancer are eligible for transplantation. It should be taken into consideration that in a patient with cancer recurrence who is subjected to immunosuppressive therapy, sooner and more aggressive malignancy can be expected, which – combined with limited possibilities of cancer treatment (compared with immunocompetent patients) – significantly worsens the prognosis and increases cancer mortality rates.

However, more recent works show significantly lower risk of cancer recurrence. In the analysis by Chapman et al., based on ANZDATA (5) register data, the overall incidence of recurrences was estimated at about 5% (11 recurrences in 210 patients with a history of cancer), and in a study by Kauffman et al. (4), based on the OPTN/UNOS registry data, the recurrence risk amounted to the total of 2.4% (47 cancer recurrences in 1919 patients a pre-transplant history of cancer).

On the other hand, Brattström et al., based on data from the Cancer and Cause-of-Death Register (6), assessed not the incidence of recurrence but the risk of death related to cancer recurrence, which was estimated at 9.4% (39 of 416 patients with pre-transplant history of cancer died).

To account for these considerable differences between the reports by Penn et al. and the more recent papers, varying, specific nature of the presented registers was pointed out: The CTTR register (currently

referred to as IPITTR – Israel Penn International Transplant Tumor Registry) is based on voluntary reporting; reporting for the ANZDATA and OPTN/UNOS registers is mandatory, which increases their credibility and statistical strength of their reviews. What is also of great importance is that fact that most reports in the CTTR register come from an earlier period of transplantation history (40% of the reports were submitted before 1986), which raises hopes that modern diagnostic modalities used for detecting residual pre-transplant cancers are now much more reliable and that some patients who underwent transplantation at that time now would not have been considered eligible for transplantation if the tumour had not been radically removed.

Differences in the previous papers do not, however, change the basic fact that the overall mortality and the mortality related to cancer recurrence in transplant recipients with a history of cancer are markedly higher. In the current analysis by Brattström et al. (6), all-cause mortality in this group increased by 30% (hazard ratio [HR] 1.3; $p < 0.0005$), and cancer mortality increased over three times in relation to recipients with no history of cancer (HR 3.6; $p < 0.0001$). The authors have not observed any differences in cardiovascular mortality or infection-related mortality in either group, which clearly suggests that the overall mortality increase is a direct result of an increased number of cancer-related deaths.

The same analysis confirmed that the risk of cancer recurrence and the risk of cancer recurrence-related death depend on the type of cancer; as in the paper by Penn et al., breast cancer, symptomatic cancer of the kidney and the urinary bladder, haematological cancers and gastrointestinal cancers comprised the group of higher risk cancers (over 5-fold increase in the risk of cancer-related death). The group of low risk cancers (less than 5-fold increase in the risk of cancer-related death) comprised prostate cancer, cervical cancer and cancer of the uterine body, thyroid cancer and non-melanoma skin cancer.

Special attention needs to be paid to skin cancer classified in Penn's analysis as high recurrence risk cancer (53%), and in the paper by Brattström classified as cancer with low risk of cancer-related death. Non-melanoma skin cancers (NMSC) are the most common de novo cancers developed after transplantation; the risk of developing NMSC rises over 100 times compared with the general population (19-20). Also the post-transplant recurrence risk is high: in the analysis by Hanaway et al. (16), the overall incidence of recurrence of squamous cell carcinoma (SCC) and basal cell carcinoma (BCC) was 73%; at the same time, there was no death related to cancer recurrence. Although on the whole, in immunosuppressed patients skin cancers are more aggressive and tend to infiltrate and metastasise more, they are relatively easy to detect and respond well to treatment. Thus they are not a contraindication for transplantation and according to some authors, if there are no metastases, no grace period is required before placing a patient on the transplant waiting list.

What is of vital importance in assessing the post-transplant prognosis, apart from cancer type, is its staging at diagnosis. Unfortunately, in most transplant registers based on which the analyses referred to were conducted, cancer staging and its histological type are not taken into account, although they are vital for assessing the risk of recurrence. In the analysis by Kauffman et al. (4), the risk of post-transplant recurrence of the urinary bladder cancer is closely connected with its staging: *in situ* cancer or non-invasive papilloma rarely recur after transplantation and do not require a grace period; in the case of stage T1-T2 urinary bladder cancer, the recurrence risk is 15%; in the case of cancer in stage T3-T4 at diagnosis, the risk is almost twice as high (27%). Likewise, cervical cancer confined to the cervix has low risk of recurrence (1.3%), while invasive cancer recurs in 62.5%.

The data presented show that in deciding on organ transplantation eligibility in the case of a patient with a history of cancer, many factors need to be taken into consideration: cancer type, staging, histological type and preferably also the course of treatment and response to treatment. Based on these data, international transplantation bodies develop guidelines specifying mandatory grace periods from the moment cancer is considered cured to the moment when the patient is put on a transplant waiting list (21-25).

In the case of most cancers, the grace period is 2 years; in the case of higher recurrence risk cancers it is 2-5 years; and in the case of most invasive cancers it is not less than 5 years.

Unfortunately, due to high individual variability of the course of malignancy, also the recommendations regarding specific types of cancers are not always coherent and clear-cut. In the collation of various guidelines by Chapman et al. (26), early cervical cancer (*in situ*), according to CARI (Caring for Australasians with renal impairment) guidelines (21) and B&D Bunnapradist and Danowitch (22), does not require any grace period; according to European Best Practise Guidelines (EBPG) (23) and the Canadian Society of Nephrology (CSN) guidelines (24), the grace period should be at least 2 years; and according to the American Society of Transplantation (AST) (25), it should be 2-5 years. This discrepancy renders these uneasy clinical decision even more difficult.

According to the American Society of Transplant Physician Guidelines, the two-year grace period allows avoiding 53% of recurrences, and the 5-year grace period – 87% (27). However, even such long grace periods do not completely eliminate the risk of recurrence. In the analysis by Brattström et al. (6), the risk of death caused by recurrence of cancer from the high risk group, even with a grace period of over 10 years from the diagnosis, was almost four times higher than in transplant patients without a history of malignancy.

On the other hand, a too cautious approach to qualifying patients with a history of cancer for organ donation deprives potential recipients of a chance to receive

a transplant, especially if life saving organs such as the heart, lung and liver are needed and long waiting time frequently means death from an underlying disease. Also in the case of patients receiving dialysis, who have other options of renal replacement therapy (apart from transplantation), long participation in the dialysis programme worsens the outcomes of transplantation and frequently renders it altogether impossible due to increasing number of comorbidities. Authors of the guidelines emphasise that the decision on qualifying for transplantation and on the grace period must be made on an individual basis and in consultation with the patient and the patient's oncologist.

By all means, one should aim at ruling out residual cancer using all available imaging examinations and biochemical tests, and the patient must be made aware of the risk of cancer recurrence which cannot be completely eliminated.

CASE REPORT

We present a case of cancer recurrence after renal transplantation in a 54-year-old female who was in the care of the Dialysis Unit and the Department of Transplantation Medicine and Nephrology, Transplantation Institute, Warsaw, from January 2007.

End-stage renal failure necessitating renal replacement therapy resulted from obstructive nephropathy caused by cancer of the uterine body (endometrial stromal sarcoma), which was unusually long-standing and whose treatment was complicated. The patient was diagnosed with sarcoma of the uterine body in 1987, at the age of 29. The cancer treatment was ended in 2004. Over that time, the patient underwent several surgeries and received chemotherapy, radiotherapy and hormone therapy. The course of the disease has been presented in table 1.

Long-lasting cancer treatment and its complications manifested as bilateral hydronephrosis and cirrhosis of the left kidney resulted in chronic kidney disease. In October 2006, creatinine level was 8.4 mg/dl; in November 2006, arteriovenous fistula was made in the left forearm and on 10 January 2007 treatment with repeat haemodialysis was started.

In March 2007, due to a right kidney tumour suspected on imaging examinations, right nephrectomy was performed; on histopathological examination, no neoplastic pattern was found. The nephrectomy was complicated with unintended removal of the right adrenal gland due to surgical difficulties caused by extensive adhesions within the abdominal cavity.

From 2009 onwards, numerous serious episodes of urinary tract infections recurred, which involved the non-functioning left kidney and were accompanied by purulent discharge from urostomy. In March 2010, the cirrhotic kidney with chronic inflammatory infiltrate was removed; despite special carefulness, the left adrenal gland, entangled in numerous postinflammatory adhesions, could not be isolated and spared. Immediately after surgery, hormone replacement therapy with hydrocortisone preparations was started due to iatrogenic insufficiency of the adrenal gland cortex.

Haemodialysis proved very difficult from the very beginning because of problems with venous access and poor tolerance of dialysis.

During 4 years of dialysis therapy, numerous episodes of thrombosis in arteriovenous fistulas occurred, which were reconstructed using also artificial materials. Based on in-depth haematology tests, primary or secondary thrombophilias were ruled out. Catherisation

Table 1. The course of the neoplasmatic disease.

Date	Clinical data
November 1987	Suspected stromal sarcoma based on the examination of scrapings from the uterine cavity
December 1987	Removal of the uterus without the adnexa, partial resection of the right ovary
1987-1988	Hormone therapy with progestagens in high doses
March 1995	A single metastatic lesions in the right lung
30 March 1995	Thoracotomy and enucleation of the right lung tumour
December 1997	Suspected recurrence manifested as infiltration of the anterior vaginal wall
December 1997-January 1998	Teleradiotherapy with Co-60 for the area of the vaginal tumour
March 1998	Fine needle biopsy of residual vaginal lesions – no neoplastic pattern
March 2001	Another surgical collection of specimens from the anterior vaginal wall – no neoplastic pattern
June 2001	Partial surgical resection of the lesion in the anterior vaginal wall – no neoplastic pattern
November 2003	Suspected tumour recurrence within the lesser pelvis infiltrating the urinary bladder on a CT scan Confirmed infiltration of the urinary bladder wall on cystoscopy Creatinine level: 1.3 mg/dl
December 2003-May 2004	Chemotherapy (6 cycles) – cisplatin, adriamycin
28 June 2004	Bilateral excision of adnexa, vaginectomy, cystectomy with Bricker urinary diversion, excision of regional lymph nodes. On histopathological examination, cancer (stromal sarcoma) only within the vagina and the urinary bladder; adnexa and lymph nodes without neoplastic infiltration
August 2004	Diagnosis of bilateral hydronephrosis, unsuccessful attempt at performing nephrestomy Increasing renal failure – creatinine level 3.8 mg/dl. Diagnosis of cirrhosis of the left kidney
7 June 2005	Reimplantation of both ureters to the neobladder due to shunts stenosis and chronic hydronephrosis No improvement in renal function

of central veins was also attempted on many occasions, in order to implant permanent or temporary dialysis catheters. When creating successive arteriovenous shunts proved no longer feasible, the patient underwent dialysis using permanent catheters, which caused other problems, such as recurrent episodes of severe catheter-related sepsis and repeat dysfunction of the catheter.

Peritoneal dialysis as an alternative modality of dialysis could not have been taken into consideration as peritoneal failure was highly probable due to adhesions within abdominal cavity after numerous surgeries, radiotherapy and past inflammation, which was evidenced by the course of both nephrectomies.

What was an additional problem from the very beginning was poor tolerance of haemodialysis related to repeated episodes of serious dialysis-induced hypotony associated with consciousness disturbances which were further intensified after bilateral adrenalectomy and which made adequate ultrafiltration impossible. Cardiac examination ruled out damage to the myocardium, and standard methods of preventing intra-dialysis blood pressure drops proved ineffective. Also, the modification of the hormone replacement therapy by way of changing the hydrocortisone dosage and starting a mineralocorticoid (fludrocortisone) failed to bring about an improvement. Frequent episodes of hypotony combined with venous access dysfunction rendered dialysis inadequate in terms of controlling the volume status and uraemic parameters.

In 2011, seven years after cancer treatment was ended, since options of renal replacement therapy were being exhausted, it was decided – in consultation with the patient – to qualify her for a renal transplant. Based on a number of imaging examinations – repeat ultrasound scans, computed tomography scan of the abdominal cavity and pelvis and positron emission tomography (PET-CT), an active neoplastic process was ruled out. In addition, the patient was frequently seen by a gynaecologist and an oncologist, neither of whom saw any contraindications for renal transplantation. The results of other tests and examinations unrelated to cancer and required under the kidney transplant eligibility protocol were normal.

On 19 November 2011, in the Department of General and Transplant Surgery of the Medical University of Warsaw, a kidney from a deceased donor was transplanted. The patient shared two HLA-DR antigens with the donor; on the last test, PRA was 0%. Intraperitoneal kidney transplantation was performed; the ureter was anastomosed to the Bricker's loop which had been formed in 2004; the anastomosis was created using a double J stent. During surgery, also arteries in the donor's kidney were reconstructed (three arteries supplying the kidney).

The patient was qualified for a three-drug immunosupressive regimen: glucocorticosteroids, tacrolimus and mycophenolate mofetil.

The kidney did not start to work immediately after transplantation; delayed graft function (DGF) was observed; after transplantation, the patient required haemodialysis for one week. In the later period, despite an increasing urine output, the graft function was still unsatisfactory – the lowest level of creatinine after transplantation was 2.9 mg/dl.

Potentially reversible causes of abnormal renal function were ruled out: disorder of urine outflow (also after elective removal of the double J catheter no urine retention was observed) and significant disorders of the graft vasculature (on Doppler ultrasound scan, no stenosis in the arteries supplying the graft, although it cannot be ruled out that they were getting entangled with the changing body position); intrarenal flows measured using ultrasound PI and RI indices were also normal. Nephrotoxicity of high blood levels of tacrolimus was also ruled out.

Poor renal function was most probably caused by urinary tract infections recurrent from the early post-transplantation period, presenting with high fever, tenderness in the graft region and further transient worsening of its function, oliguria and elevated markers of uraemia. From the urine, a multi-drug resistant ESBL-producing strain of *E. coli* (+) was grown on several occasions. The patient was treated with antibiotics many times, most frequently with carbapenems, based on antibiograms.

On 20 December 2011, once another urinary tract infection was overcome, a biopsy of the graft kidney was performed and both acute cellular rejection and antibody-mediated rejection (C4d-negative) were ruled out. However, moderately intense chronic interstitial infection with numerous neutrophils in the infiltrate was found, suggestive of bacterial interstitial inflammation of the graft kidney. a prolonged, over 3-week-long therapy with ertapenem was applied, however, the graft function did not improve: creatinine level ranged between 3.2 and 4.3 mg/dl (MDRD eGFR 10-20 ml/min).

From the early post-transplantation period, due to recurrent infections, history of cancer and relatively low immunologic risk, immunosuppression was quickly reduced and the doses of glucocorticosteroids and mycophenolate mofetil were lowered; 12 weeks after transplantation, MMF was discontinued. Also, relatively low blood levels of tacrolimus (5-7 ng/ml), compared with the moment of transplantation, were maintained.

Successive follow-up biopsy of the graft was performed on 17 February 2012 and revealed no signs of interstitial inflammation. However, acute tubular epithelial cell damage and first chronic lesions manifested as focal glomerulosclerosis and IF/TA i were found.

At the beginning of March 2012, as improvement in graft function was no longer possible and serious infectious complications recurred, it was decided to discontinue immunosuppressive therapy and perform graftectomy. However, as the graft function temporarily improved (creatinine dropped to 2.7 mg/dl) and the patient was very reluctant to restart dialysis, the procedure was postponed. Finally, graftectomy was performed on 14 May 2012 after another episode of serious urosepsis

caused by *Pseudomonas aeruginosa*. Two weeks earlier, immunosuppressive agents were discontinued, and only replacement therapy with a glucocorticosteroid was continued. The patient was enrolled in a haemodialysis programme.

Two weeks after graftectomy, the patient was again hospitalised due to another episode of sepsis, this time caused by *Staphylococcus epidermidis*. At that time, as part of a diagnostic work-up in search of the source of sepsis, a CT scan of the chest and abdominal cavity was performed which, unexpectedly, revealed two focal lesions in the lungs, 8 and 11 mm in diameter, with morphological features of secondary metastatic lesions, and an extensive thrombus involving almost entire lumen of the lower part of the inferior vena cava. On chest CT, two small thrombi in the superior vena cava and signs of pulmonary embolism manifested as a floating thrombus in the pulmonary trunk, whose margin extended to the right pulmonary artery. Transthoracic echocardiogram (TTE) and trans-aesophageal echo (TEE) also confirmed the presence of thrombi in the right atrium, which protruded into the right ventricle during diastole. However, no signs of infectious endocarditis or any relationship between the thrombi and the dialysis catheter were found.

On 1 June 2012, in the Department of Cardiac Surgery of the Independent Public Central Clinical Hospital (SPCSK) of the Medical University of Warsaw, infected thrombi were removed from inferior vena cava, right cardiac cavities and pulmonary artery, with extracorporeal circulation. Histological examination of the removed thrombi revealed the presence of neoplastic tissue which on immunophenotypic analysis corresponded with stromal sarcoma.

Due to high levels of inflammatory parameters (CRP over 200 mg/l) and febrile episodes resulting most probably from thrombi infection (blood culture revealed *Pseudomonas aruginosa* and periodically *Staphylococcus epidermidis*), the patient received long-term treatment with several successive antibiotics: vancomycin combined with ceftazidime, amikacin and meropenem (on some cultures, only partial sensitivity to carbapenems was found).

The oncologist who has treated the patient for many years did not decide on chemotherapy due to the patient's general condition, end-stage renal failure, high risk for continued prothrombotic effect of cytostatic drugs and slow dynamics of the cancer so far.

On 8 October 2012, due to another episode of sepsis (this time with signs of a septic shock), suspected inflammatory infiltrate in the region of the Bricker loop left after graftectomy and the presence of interloop abscesses found on a CT scan of the abdominal cavity, another surgery was performed to remove the neobladder and perform abdominal lavage.

Computed tomography scan repeated in November revealed recurrence of massive thrombosis of the inferior vena cava and iliac veins as well as small thrombi in the branches of pulmonary vessels, without clinical signs.

Obviously, from the first episode of thrombosis, the patient received anticoagulation therapy with low molecular weight heparin preparation (enoxaparin), and anti-Xa activity was monitored. Maintaining therapeutic levels of the drug was associated with recurrent episodes of bleeding at injection sites as well as gastrointestinal bleeding, even so, recurrences of thrombosis were not prevented. a PET-CT scan performed in December 2012 revealed extensive neoplastic plugs within the inferior vena cava and metastatic lesions in the lungs, which indicated progression compared with previous computed tomography scans.

The consulting cardiac surgeon stated that another surgery to remove thrombi was very risky and that the character of the underlying disease made permanent recovery impossible. Also in the opinion of the oncologist, cancer treatment options had been exhausted. The patient died on 27 April 2013, 15 months after kidney transplantation.

DISCUSSION

We report a case of cancer recurrence soon after starting immunosuppressive therapy following renal transplantation. Cancer recurrence was established six months after transplantation based on a computed tomography scan which revealed extensive, although asymptomatic, thrombi and a neoplastic infiltrate in the inferior vena cava complicated with clinically submassive pulmonary embolism and secondary metastatic lesions in the lungs, without localised primary tumour visible on imaging examinations. However, it is highly probable that theses lesions had developed much earlier but were invisible on repeat chest x-rays and abdominal ultrasound scans.

It should be emphasized that none of the pre-transplantation imaging examinations available, including PET-CT scans, revealed metabolically active cancer cells. However, their presence in the latent stage is, in the light of the course of the disease, unquestionable, which confirms the thesis proposed by Brattström et al. (6) that even the longest grace period from the end of cancer treatment to kidney transplantation does not completely eliminate the risk of recurrence, although it does lower it significantly. In the case presented, the seven-year period free from clinically apparent cancer proved insufficient.

Data from literature on transplantation of vascularised organs in patients with a history of sarcoma are very limited. In the initial analyses by Penn (18), sarcomas were classified as cancers with high recurrence risk: out of the 17 patients included in the CTTR register, cancer recurred in 5 (29%); however, no data on the pre-transplant grace period or cancer staging are provided in the CTTR register. In the available literature, the authors of this paper have not found many reports on transplantation of vascularised organs in patients diagnosed with sarcoma, which is why guidelines usually do not provide for pre-transplant grace

periods for this type of cancers, unlike in the case of more common cancers. Armitage et al. report on a patient after a heart transplant performed due to primary angiosarcoma in whom no cancer recurrence was found during an 18-month follow-up (28). Of fundamental importance is also the fact that sarcomas generally have poor prognosis and high mortality rate, therefore few patients can be considered cured and cancer free with certainty sufficient to qualify them for organ transplantation.

Endometrial stromal sarcoma (ESS) is also one of rare malignancies with poor prognosis: it accounts for 4-9% of all uterine cancers and the overall 5-year survival does not exceed 50% and is dependent on the degree of cancer cell differentiation: high grade endometrial stromal sarcoma (HG ESS) is characterised by very poor prognosis (5-year survivals below 10%), whereas low grade endometrial stromal sarcoma (LG ESS) has better prognosis (29). In the case reported, the degree of cancer cell differentiation was not provided in the histopathological examination reports available. This does not change the fact that the course of neoplasia in the patient presented was atypically chronic and the 7-year cancer symptom-free period gave rise to hoping that recurrence could be avoided.

The decision to qualify the patient for transplantation was also forced by the fact that continued dialysis was gradually becoming less feasible due to lack of venous access. On several occasions, referring the patient for an urgent kidney transplant was considered due to serious difficulties with implanting further dialysis catheters and recurrent severe catheter-related infections. Poor tolerance of dialysis sessions, substantially worsening the patient's quality of life, was also an important factor.

Regrettably, kidney transplant should be considered unsuccessful from the very beginning, regardless of the cancer type. Because of unsatisfactory function of the kidney and recurrent, life-threatening urinary tract infections with episodes of urosepsis, as soon as a dozen or so weeks after transplantation, graft removal and restarting dialysis was considered.

Another problem was the choice of immunosuppressive drugs and their dosage in patients with a history of cancer after organ transplant. The preferred course of action in patients with post-transplant *de novo* cancer is to substitute immunosuppressive drugs with drugs from the class of proliferation signal inhibitors (PSI) which act by inhibiting the mammalian target of rapamycin (mTOR) protein taking part in the regulation of growth and proliferation of various types of cells, cancer cells included. Their anticancer potential has been confirmed in *in vitro* and animal studies (30). There have been many reports on cancer regression, mostly Kaposi sarcoma, after introducing mTOR inhibitors to the immunosuppressive regimen (31).

In accordance with the standards adopted at the authors' Department, substituting drugs from the PSI class for the previous treatment in patients with a history of malignancy is postponed by several or a dozen or so weeks, when postoperative wounds are healed and the graft function is stable. In the case reported, there was an additional problem with chronic thrombocytopoenia observed even before transplantation (periodically 100-120 G/l) and a concern about early thrombosis in the graft vessels connected with pretransplant reconstruction of three arteries in the donor's kidney. Then, due to recurrent serious infections, the doses of immunosuppressants were reduced and 12 weeks after transplantation two immunosuppressants were used (glucocorticosteroids + tacrolimus). After less than six months from transplantation, all immunosuppressants were discontinued. It is noteworthy that the overall potency of immunosuppression in the patient presented was objectively low compared to the post-transplant period, which however resulted in such a potent suppression of the immune system that it lead to very rapid recurrence of cancer which had remained clinically latent for many years.

In any case, immunosuppressive treatment had been discontinued before cancer recurrence was established, and regrettably it did not result in cancer regression.

This case report also confirms the thesis that recurrent cancer is significantly more aggressive than the previous long-lasting disease. The risk of recurrence and poor prognosis in most cancers in transplant patients makes decisions on qualifying for or disqualifying from transplantation exceptionally difficult in this patient population. Regrettably, such difficult decisions will have to be made by nephrologists and transplantologists more and more frequently.

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