Successful Renal Transplantation in a Patient with Behcet Disease and Hodgkin Lymphoma in Remission

Remisyonda Hodgkin Lenfoma ve Behçet Hastalığı Olan bir Hastada Başarılı Böbrek Nakli

ABSTRACT

Behcet's disease (BD) is an inflammatory multisystemic disease characterized by perivascular inflammation and generally presents with recurrent oral and genital ulcers and uveitis. It is known that BD may also involve the kidneys. Amyloidosis, glomerulonephritis (crescentic, proliferative), IgA nephropathy, interstitial nephritis are commonly described renal lesions which may lead to end-stage renal disease (ESRD) in BD. Immunosuppressive therapies used for the treatment of BD may cause malignant diseases (lymphoma, skin and solid organ malignancies, etc). The risk with azathioprin is especially high after 10 years of treatment. Cyclosporine, another immunosuppressive agent frequently used for treatment of BD, also has tumorigenic potential and is associated with renal toxicity and renal failure. Renal transplantation may be performed in patients with malignancies after a 2-5 year complete remission period, although it may differ according to the type of tumor. We report a case of end-stage renal disease and Hodgkin's lymphoma occurring after treatment with immunosuppressive medicine for BD. The patient was successfully treated with renal transplantation.

KEY WORDS: Renal transplantation, Behcet disease, Malignancy, İmmunosuppression

ÖZ

Behçet hastalığı (BH), tekrarlayan oral ve genital ülserler, üveit ve perivasküler inflamasyonla karakterize enflamatuvar bir çok sistemi tutan bir hastalıktır. Amiloidozis, glomerülonefritler (kresentik, proliferatif), IgA nefropatisi ve interstisyel nefrit BH'da görülen böbrek tutulum şekilleri olup son dönem böbrek yetmezliğine neden olabilmektedirler. BH tedavisinde kullanılan immünosupresifler malign hastalıklara (lenfoma, deri ve solid organ tümörleri gibi) sebep olabilirler. Azatioprin 10 yıldan fazla kullanıldığında bu risk belirgin olarak artmaktadır. BH'nda yaygın olarak kullanılan siklosporin ise tümör gelişimini kolaylaştırıcı etken olmakla birlikte nefrotoksisite ve böbrek yetmezliği yapma riski de bulunmaktadır. Tümörün tipine göre değişmekle birlikte malignitesi olan hastalara 2-5 yıllık tam düzelme sürecinden sonra böbrek nakli yapılabilir. Çalışmamızda, Behçet Hastalığı tanısıyla immünosüpresif tedavi almış, sonrasında Hodgkin Lenfoma ve son dönem böbrek yetmezliği gelişmiş hastaya yapılan başarılı bir böbrek nakli olgusu sunulmuştur.

ANAHTAR SÖZCÜKLER: Böbrek nakli, Behçet hastalığı, Malignite, Immünosupresyon

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INTRODUCTION

Behcet's disease (BD) is an inflammatory multisystemic disease characterized with perivascular ınflammation and generally presents with recurrent oral and genital ulcers and uveitis. Renal involvement in Behcet's disease was first described by Oshima et al. in 1963 in a case with hematuria and proteinuria. Renal involvement in BD (RB) includes amyloidosis (AA type), glomerulonephritis (GN) and vascular involvement. The clinical spectrum is highly variable, ranging from asymptomatic proteinuria and hematuria to end-stage renal disease (1-2). Amyloidosis (AA type) and glomerulonephritis (GN) are the most commonly observed renal lesions in the course of BD. Diffuse proliferative GN, focal segmental glomerulosclerosis, focal proliferative GN, membranoproliferative GN, immunoglobulin-A nephropathy, crescentic GN and membranous GN are described renal pathologies in BD. However, vascular involvement is also an important complication of BD that leads to renal artery aneurysms, renal artery stenosis, renal vein thrombosis and microscopic vascular disease. Nevertheless, all types of renal involvement may lead to chronic renal failure in BD (2-7).

The aim of the treatment in BD is the control of disease burden especially in the initial years of the disease. Local steroids with or without antibiotics, and/or colchicine can be used for oral and genital ulcers. Thalidomide is an option in patients with persistent mucocutaneous lesions. Systemic involvement may necessitate treatment with chlorambucil, azathioprine, cyclosporine and methotrexate, especially in steroid resistant patients. Sulfasalazine and azathioprine are effective treatments for gastrointestinal involvement. Cyclosporine is recommended in patients with eye involvement especially in steroid resistant disease. Nephrotoxicity, hyperuricemia, hypertension, diabetes mellitus, hirsutism are some of the important adverse effects associated with cyclosporine use. Long-term use and combination with azathioprine may increase the malignancy risk. Acute nephrotoxicity due to cyclosporine use has been associated with vasoconstriction at the afferent arteriole resulting with reversible functional loss. Acute CsA toxicity is caused by increased vasoconstrictor factors (endothelin, thromboxane, renin-angiotensin-aldosterone system activation, sympathetic nervous system), decreased vasodilator factors (prostacyclin, prostaglandin-E2, NO), endothelial dysfunction and increased free radicals (8, 9). Tubular toxicity is together with isometric vacuolization at the tubule cytoplasm, endoplasmic reticulum enlargement and increased number of lysosomes (10). Chronic nephrotoxicity due to CSA is characterized by irreversible functional loss, arteriolar hyalinosis (generally at the afferent arteriole and irreversible), glomerulosclerosis (thickening, fibrosis, focal and global sclerosis at Bowman capsule) and tubulointerstitial injury (tubular atrophy, interstitial fibrosis) (10). The result is local tubulointerstitial hypoxia and ischemia with free radical formation. Moreover, calcineurin inhibitors cause renal injury by increasing TGF-β expression in tubule epithelial cells (11-15). These mechanisms may lead to acute and chronic renal failure. Therefore, patients treated with CsA should be closely monitored for renal functions and serum levels of CsA.

It is well accepted that renal transplantation is the preferred renal replacement therapy in patients with end-stage renal diseases with different etiologies including BD. Renal transplantation is also possible in patients with malignant diseases in remission.

Immunosuppression has a carcinogenic potential and may increase the risk of relapses in malignant diseases. The risk of malignant disease occurrence is 20% after ten years of immunosuppressive drug therapy; the etiology is multifactorial and there is a positive correlation with the dose of medicines (16-18). Various waiting periods for transplantation are recommended to patients with malignant diseases, but the general tendency is five years. Patients must be monitorized for the relapse of malignant disease after transplantation (19). Azathioprine and cyclosporine are frequently used in the treatment of Behcet's disease and carry a long-term risk of malignancies such as lymphoma, squamous cell carcinoma of the skin, basal cell carcinoma, Kaposi sarcoma, hepatocellular carcinoma, multiple myeloma, prostatic adenocarcinoma and other solid organ tumors (16, 17, 20-22).

A living-unrelated renal transplantation was performed for our patient who had BD and Hodgkin lymphoma, both in remission. No vascular complication, recurrence of disease or graft function loss was observed during 30 months of follow up. We report a rare case of end-stage renal disease (ESRD) with both Behcet's disease and Hodgkin's lymphoma in remission. The patient was successfully treated with renal transplantation.

CASE REPORT

A patient with Hodgkin's lymphoma (HL) in remission and Behcet's disease (BD) with a five-year history of hemodialysis treatment for end-stage renal disease applied to our center for renal transplantation. He had been diagnosed as Behçet's disease in 1988 with oral and genital ulcers, pathergy positivity and uveitis. He had been treated with prednisolone therapy starting with a 1mg/kg/day that was tapered in six months to 15mg/day. After six months of treatment, the patient received three pulse steroid doses (1gr/day for three days) for exacerbation of disease and cyclosporine A and azathioprine were started (Table I shows the doses and intervals of the treatment). After eight years of immunosuppressive treatment his renal functions began to deteriorate and serum creatine level increased to 2.5mg/dl from 1 mg/dl. This treatment scheme was maintained for three years with reduced doses of CsA. After eleven years of concomitant use of CsA and azathioprine, CsA was stopped because of renal failure, but azathioprine treatment was administered for eight more months more at a dose of 150 mg/day. Routine controls of the patient revealed inguinal lymphadenopathies

Table I: Doses and intervals of the medicine used for BH.

Medicine	Doses and intervals
Prednisolone	60 mg/day (4 months), tapering to 15 mg/day (2 months)→ total 6 months No response→ metilprednisolone 1gr/day, 3 days→ stopped
Cyclosporine	350 mg/day → 2 months 300 mg/day → 5 years 250 mg/day → 3 years 200 mg/day → 3 years 175 mg/day → 1 month
Azathioprine	175 mg/day → 11 years 150 mg/day → 8 months

and biopsy results were consistent with Hodgkin's lymphoma (HL). Azathioprine was stopped after the diagnoses of HL. The lymphoma was stage 1 and patient was administered four cycles of ABVD (adriamycin, bleomycin, vinblastine, dacarbazine) chemotherapy (last cycle at April 2002). The patient also underwent 33 sessions of radiotherapy to bilateral inguinal and lumbar regions after chemotherapy. Complete remission was achieved by these therapies but the serum creatine level increased to 9mg/dl from 2,5mg/dl following radiotherapy and hemodialysis treatment was initiated. The hemodialysis requirement continued and the patient had three weekly hemodialysis sessions regularly since then. He was in remission for HL and had been on hemodialysis treatment for five years when he came to our center for renal transplantation.

Our patient was 43-year-old male with a height of 167cm and weight of 63kilograms (BMI was 22,6 kg/m^2). On physical examination, blood pressure was 120/70 mm/Hg, pulse 70 beats/minute, body temperature 36,6^{o}C and there was no lymphadenopathy or organomegaly. He had venous collaterals in the cervical, thoracic and upper extremity regions and gynecomastia. Other physical findings were unremarkable. On laboratory evaluation, lymphocyte cross match was negative, there were 5 mismatches (match: HLA A9(24)), the glomerular filtration rate was 10 ml/min and viral hepatitis markers were negative. Additionally, positron emission tomography performed for lymphoma scanning was normal. Extremity doppler ultrasonographies were negative for thrombosis. The donor was the 43-year-old wife of the patient and did not have a hereditary relationship with the patient. The donor was suitable for transplantation. The left kidney was 109mm and the parenchyma was normal on ultrasonography, DTPA scintigraphy showed a glomerular filtration rate of 43ml/min and normal concentration and excretion functions for the left kidney. His blood group type was A Rh (+) and the donor candidate blood group was 0 Rh (+). Eventually, he received a left kidney from his wife. As an induction treatment, we used 20 mg basiliximab at the 0 and 4th days of transplantation and he received cyclosporine (8mg/kg/day) (CsA), mycophenolate mofetil (MMF) (2gr/day) and corticosteroid as the immunosuppressive protocol. CsA and MMF were initiated the day before transplantation. Starting doses of immunosuppression and targeted plasma levels are shown in Table II. The CsA dose was based on the second hour serum level. Valacyclovir 4,5gr/day, trimethoprim-sulfamethoxazol 400mg/day and antifungal drops were used for infection prophylaxis for the first six months. The patient was treated with warfarin and INR was maintained between 2-2,5 because of the BD diagnosis. He was discharged from hospital with a creatine level of 1,3 mg/dl.

Table II: Doses and aimed serum levels of immunosuppressive medicine.

Parameter	MMF (gr/day)	CsA (C2, ng/ml)	Prednisolone (mg/day)	Sirolimus (ng/ml)
Starting dose	2	8 mg/kg/day	See explanation	3 mg/day
Month 0-1	2	1250 - 1350	20	-
Month 1-2	2	950 - 1250	17.5	-
Month 2-3	2	750 - 950	15	-
Month 3-6	2	550 - 750	10	-
Month 6-12	2	400 - 550	7.5	-
Month 12-30	1.5	stopped	5	4-8

Explanation: Metilprednisolone was administered post-transplant at Day 0-5 at doses of 1000-500-250-160-80-40 mg/days IV respectively, and 20 mg/day oral prednisolone was used per oral on the 6th day and later in first month.

Laboratory results of the patient at posttransplant 30th month were as follows: MDRD based glomerular filtration rate 63 ml/min, proteinuria in 24h was 120 mg/day, hemoglobin 14 gr/dl, albumin 4.5 mg/dl, LDL cholesterol 120 mg/dl, triglyceride 195 mg/dl.

We planned to switch CsA to sirolimus and decrease the dose of MMF at the 6th month of the treatment because of the HL history and to avoid chronic toxicity and chronic allograft nephropathy due to CsA. However, the social conditions of the patient, his residence that was very far away from our center, and the impossibility of the patient accommodating in a close area precluded close monitorization of the serum levels of the drug and did not allow us to make these changes at that time. The patient's condition became suitable one year after transplantation so we switched CsA to sirolimus and made a 25% decrease in the dose of MMF. The sirolimus plasma level was maintained between 4-8 ng/ml. There were no treatment-related complications during the last 30 months.

During follow up in outpatient clinic, he did not develop delayed graft function, post-transplant diabetes mellitus, hypertension, CMV infection or any acute rejection. We also did not detect lymphoma recurrence in clinical, biochemical and radiological examination during the post-operative 30 months of follow-up. The patient is still under follow-up with stable renal function and both BD and HL in remission.

DISCUSSION

We performed living-unrelated donated renal transplantation in a patient with end-stage renal disease who had both Behcet's disease and Hodgkin's lymphoma in remission and we did not observe any problems during 30 months of follow-up. Behcet's disease is a chronic, relapsing, inflammatory disease. The basic histopathological lesion is perivascular inflammation. Renal involvement is usually due to amyloidosis, glomerulonephritis or vascular problems. Renal transplantation has been rarely performed in patients with renal Behcet. Two patients with BD and end-stage renal disease due to glomerulonephritis were reported to have successful transplantation and long-term follow up (2, 23). This is the first case describing successful transplantation for an ESRD patient with both BD and HL in remission.

CsA has both acute and chronic nephrotoxicity, and may therefore cause functional loss in either the native or transplanted kidney. Close monitoring of renal functions is crucial in patients treated with CsA. In case of renal failure, the dose must be diminished or the treatment must be stopped and a switch made to another agent. Chronic renal insufficiency may develop if a prompt medical approach is not used.

CsA was held responsible for renal failure during BH treatment in our patient. The CsA dose was stopped when the creatine level was 2.5mg/dl, but the patient's renal functions continued to deteriorate during radiotherapy for HL. The serum creatine level reached 9mg/dl and hemodialysis was started. This progressive renal failure was postulated to be associated with the poor health status of the patient during radiotherapy, decreased oral intake and possibly fibrosis during radiotherapy. Therefore, rgw patient had renal failure while being treated with CsA and end-stage renal disease during radiotherapy for HL. The patient's treatments and follow-up for BH and HL were performed at another center and the lack of a biopsy during this period makes it impossible to reveal the exact cause of renal failure.

Immunosuppressive therapies for BD may cause malignancies. Azathioprine has an especially higher risk with long-term treatment (>10 years). Combination of azathioprine with cyclosporine increases the risk of malignancy (21). Epstein-Barr virus is an important etiological agent for lymphoma in patients treated with immunosuppressive medicine. Immunosuppression-related cancers include skin cancers (basal cell CA, squamous cell CA), solid organ cancers, lymphomas, bone tumors and rarely multiple myeloma. The malignancy risk increases with increased doses and periods of immunosuppressive medicine. Our patient had also long-term treatment with azathioprine and cyclosporine and this may be the etiology of HL in our patient.

Recipient and donor evaluation did not reveal any contraindication for transplantation. During recipient evaluation, we especially focused on lymphoma scanning and vascular complications of BD. It was an important decision to perform renal transplantation in a patient with lymphoma history that was possibly related to immunosuppressive therapy as transplantation follow-up would again include long-term immunosuppressive therapy. We did not observe any operation-related complication. During thirty months of follow up, we did not observe any complication related to immunosuppressive drugs or BD. More importantly, lymphoma recurrence was not detected. We did not come across any reported ESRD case with BD and remitted lymphoma that underwent successful renal transplantation.

Our case suggests that renal transplantation can be performed in ESRD patients with BD and remitted malignant disease.

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