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Case Report

Complications of Renal Transplant and Immunosuppressive Therapy

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SUMMARY

Renal transplantation is the treatment of choice for end stage renal failure. Quality of life is much improved but the patient is at an increased risk of developing complications as a result of continued immunosuppressive therapy. This is a case report of a patient who developed multiple and life threatening complications of immunosuppressive therapy after renal transplantation, like acute pancreatitis lead to diabetic ketoacidosis, fungal infection of the skin, hypertension, gingival hypertrophy hypertrichosis and bilateral cataracts. Patient was successfully managed. The case is discussed and a review of the literature is presented.

INTRODCTION

Chronic renal failure leading to end stage renal disease is being increasingly recognized in our country. Every year more and more patients with end stage kidney disease are receiving kidney transplants. Immunosuppressive therapy is a double-edged sword, which is necessary to prevent rejection of the transplanted kidney on one side but leads to many side effects on the other. We present here a case of renal transplant who not only developed severe pancreatitis and diabetic ketoacidosis but also other complications of immunosuppression

CASE REPORT

Mr. A.R 40 years old man was admitted in Shaikh Zayed Medical Complex, Lahore with shortness of breath, epigastric pain, nausea and vomiting for 12 hours duration. In the past he suffered from renal failure of unknown cause and developed end stage renal disease for which he was on haemodialysis for 1 year. There was no history of diabetes mellitus, pulmonary tuberculosis, alcoholism or acid peptic disease. He received a live related renal transplant in 1995 and was started on anti rejection triple drug therapy. He developed mild transplant dysfunction in 1997. Renal biopsy of the transplanted kidney showed evidence of rejection, which responded to steroid therapy. He was taking cyclosporin 100 mg twice a day, prednisolone 20 mg daily, azathioprine 50 mg twice daily allopurinol 300 mg once a day and antihypertensive medication consisting of nifedipine 20 mg thrice a day and metoprolol 50 mg twice a day.

Physical examination

On physical examination, pulse was 100/minute, blood pressure 120/80 mmHg; respiratory rate was 30/minute, temperature 98.4°F. No edema, jugular neck veins were not engorged, he had bilateral cataracts (Fig. 1). There was a hypopigmented rash all over the chest due to fungal infection (Tinea Versicolor) (Fig. 2), hypertrichosis and marked gum hypertrophy was noted (Figs. 3, 4). Chest was clear and cardiovascular system was unremarkable. Examination of abdomen revealed marked tenderness in the epigastrium. Operation scar in right iliac fossa was seen. There was no tenderness over the graft. Renal bruit was present. He was confused and restless but having no focal neurological deficit.

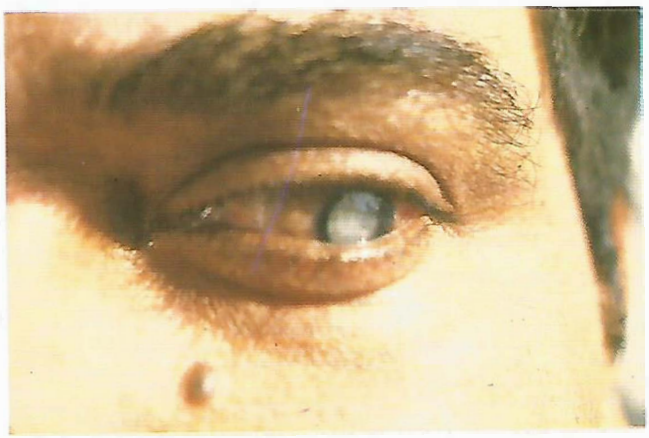

Fig. 1: Mature cataract due to steroid therapy.

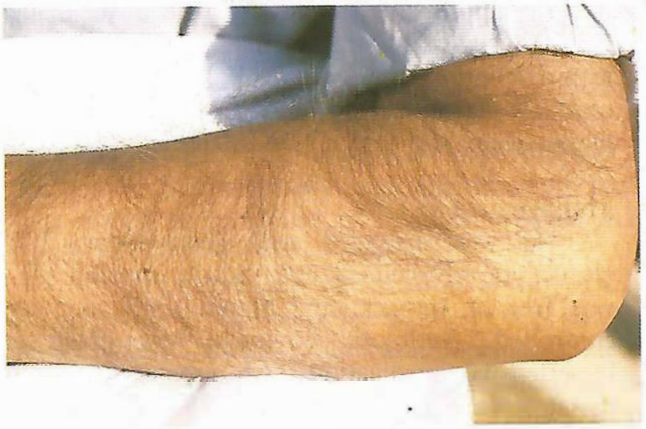

Fig. 3: Forearm showing hypertrichosis due to cyclosporine toxicity.

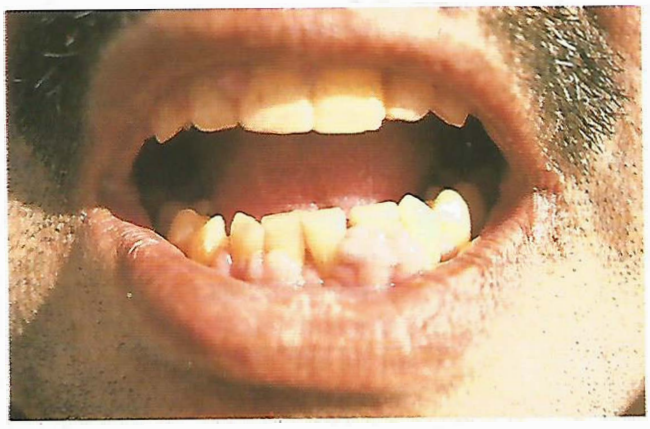

Fig. 2: Hypopigmented rash on chest due to Tinea Versicolor).

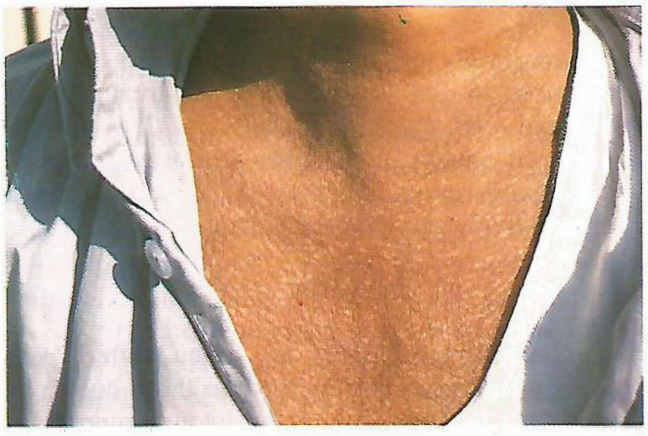

Fig. 4: Gingival hypertrophy due to cyclosporin toxicity.

Investigations

His initial laboratory reports showed hemoglobin 13.7 g/dl, TLC 15800 /cmm, polymorphs 67% lymphocytes 30%, eosinophils 1% monocytes 2%, blood urea nitrogen 61mg/dl, serum creatinine 3.4 mg/dl, serum calcium 9.2 mg/dl, serum phosphorus 5.1 mg/dl, serum uric acid 16.5 mg/dl. Routine urine analysis showed sugar, +++, ketones ++, protein +, blood ++, WBC 4-6/HPF, RBC 10-12/HPF, arterial blood gases revealed, pH 7.03, PaO_2 140 mmHg, $PaCO_2$ 17.3 mmHg, HCo_3 4.6 mmol/l, blood sugar (random) was 580 mg/dl. Serum amylase 2044 U/l Anti CMV (cytomegalo virus) antibodies were negative and whole blood cyclosporin level was 276 ng/dl. Abdominal ultrasound showed transplanted kidney in right iliac fossa which was of normal size and echotexture with no hydronephrosis, liver showed fatty change, spleen and gall bladder were normal, However pancreas was echogenic and swollen.

Final assessment

Live related renal transplantation with chronic graft dysfunction, acute pancreatitis due to immunosuppressive therapy that lead to diabetic ketoacidosis. Cyclosporin toxicity with hypertrichosis and gingival hypertrophy and cataracts due to steroid intake. Additionally he had hypertension and fungal skin infection.

Management

He was managed with intravenous fluids, electrolyte replacement and insulin infusion till he was free of ketones, and blood sugar adequately controlled. Antibiotic coverage was given anti hypertensive medication and immunosuppressive therapy was continued. Topical antifungal cream was applied and dental surgeon performed gingivectomy. Dosage of cyclosporin and azathioprine was reduced to achieve optimal cyclosporin blood level and minimise azathioprine toxicity. Cataract surgery was planned

OUTCOME AND FOLLOWUP

He improved and was discharged in a stable condition. Insulin was added to his treatment. He remained well and asymptomatic for 2 months but developed similar complaints and was readmitted with raised serum amylase (1750 u/l), managed conservatively and improved again.

DISCUSSION

Complications that are seen after renal transplantation can be divided into those due to the renal graft itself or due to the immunosuppressive therapy given to the patient for the prevention of graft rejection (Table 1). New anti-rejection drugs with greater safety profile and efficacy are being developed (Table 2). The host is more susceptible to develop not only bacterial but also viral and fungal infections.

Complications related to transplant itself include:

1. Acute and chronic transplant dysfunction
2. Hypertension
3. Polycythemia
4. Hypercalcemia
5. Hypophosphatemia
6. Transmission of HBV, HCV, CMV and other viruses

Table 1: Side Effects of Immunosuppressive Drugs

Name of Drug	*Common side effects*
Cyclosporin	Gingival hypertrophy, hypertrichosis hepatic and neurotoxicity, skin & R.E. system malignancy, nephrotoxicity intravascular hemolysis, pancreatitis, hypetension.
Azathioprine	Pancreatitis bone marrow suppression brain lymphoma, hepatotoxicity, alopecia, tumors.
Steroids	Pancreatitis, cataract, hypertension, acid peptic disease, osteoporosis, cushingoid facies, acne, growth retardation.

Table 2: Drugs Used for Immunosuppression

Older drugs	*Newer Drugs*	*For Acute Rejection*
Azathioprine	Mycophenolate	OKT3
Cyclosporin	FK 506	ATG
Corticosteroids	Rapamycin	ALG
Cyclophosphamide	Brednin	
	Brequinor Sodium	

Acute and chronic transplant dysfunction

Acute and chronic transplant dysfunction may result from acute or chronic episodes of rejection, due to obstruction to the urinary outflow, renal vein thrombosis or renal artery stenosis of the transplanted kidney[1,2].

Hypertension

Hypertension is either due to native kidneys or renal artery stenosis of transplanted kidney. Drugs like cyclosporin and steroids may also contribute towards hypertension[3]. There is convincing evidence that cyclosporin acts as a vasoconstrictor[4]. With steroids sensitivity of arterioles to circulating vasoconstrictors is increased. Weight gain during

prednisolone administration is associated with increased post transplant hypertension[5,6]

Polycythemia

Also known as post transplant erythrocytosis occurs in few patients due to increased renal mass, renal ischaemia or from effects of steroids on the bone marrow.

Hypercalcemia

Parathyroid glands may become autonomous in some transplant recipients due to previous hyperparathyroidism and cause hypercalcemia and hypophosphatemia; they may require parathyroid surgery[7].

Infections

Incidence of infections remains a major hazard for the transplant patients, especially in the early months after the procedure[8] CMV is the most important viral infection occurring in transplant recipients[9] Hepatitis B and C infection may be present before the transplant or may be introduced at the time of transplantation. Progressive liver disease due to Hepatitis B or C infection may lead to chronic liver failure[10].

Bacterial and fungal infections are not all that uncommon. Tuberculosis and infections with Pneumocystis carini, Nocardia, Blastomycosis, Coccidoiodomycosis, Aspergillosis, Candida, Herpes simplex and Zoster, Cryptococcus, Listeria, Giardia, Clostridium deficile, Strongyloides stercoralis and Schistosoma are frequently seen in transplanted patients due to the depressed-immune response.

Malignancies

The incidence of cancer in transplant recipients varies considerably from region to region, ranging from a low figure of 1.6% of patients developing cancer after transplantation in Europe to as high as 24% of patients in Australia[11]

Pancreatitis

The incidence of pancreatitis in renal transplant recipients varies from 2% -5.6%. Nogueira & Freedman (1972) reported series of patients who developed pancreatitis after receiving azathioprine and had recurrent disease after the drug was restarted. Further convincing evidence comes from the National Cooperative Crohn's Disease Study. This study found that 6.2% of 116 patients receiving azathioprine alone developed acute pancreatitis. Azathioprine toxicity may not be dose related[12]. The mortality of acute pancreatitis is high and upto 70% patients may die of it. Cyclosporin has also been implicated in the etiology of acute Pancreatitis[13]

Steroids also precipitate acute pancreatitis It is recognized that relatively high incidence of acute pancreatitis in recipients of renal transplants may partly be due to the use of steroids[14].

In our patient acute pancreatitis developed as a complication of immunosuppressive therapy and the most likely cause was azathioprine toxicity precipitated by allopurinol, however steroid and cyclosporin could have contributed. This patient had marked hyperurecemia and was taking allopurinol. Co-administration of this drug increases the toxicity of azathioprine. The mechanism is the blockage of conversion of mercaptopurine to its inactive metabolites by xanthine oxidase which is inhibited by Allopurinol. About 65-75% reduction in dosage of azathioprine is recommended for patients who are on allopurinol[15].

More than 30% patients with renal transplant will have at least 10-15% elevation in their baseline blood pressure[15]. In our patient hypertension was due to multiple reasons. Chronic graft dysfunction, Cyclosporin toxicity and excessive use of steroids were important causes. Since mechanism of hypertension due to cyclosporin is vasoconstriction, use of calcium channel blockers was justified here.

It has been mentioned in the literature that 30-40% patients on steroids develop posterior subcapsular cataracts and 5% may be symptomatic and require surgery[15]. Our patient had bilateral mature cataracts due to prolonged administration of corticosteroids in maintenance dose and higher doses used for control of previous rejection episode.

Gingival hypertrophy due to cyclosporin may lead to loss of teeth if it goes unchecked. Plaque control is crucial to avoid this complication Erythromycin has been recommended for it. One should be aware of the fact that it interferes with the P-450 cytochrome system it may further enhance cyclosporin levels.

CONCLUSION

Patient's with renal transplantation due to a persistent immuno compromised state are at an

increased risk of developing life threatening complications. Symptoms may be masked and delay in diagnosis may lead to high mortality. Extreme care shold be taken to interpret clinical data and patient's condition. Drug toxicity is potentially reversible and should be suspected in every case. Judicious use and close monitoring is recommended to maintain balance between side effects and transplant rejection. Drug interaction are common and new drugs should be added cautiously keeping in mind their pharmacokinetics.

REFERENCES

1. Belzer FO. Glass N, and Sollinger, H. Technical complications after renal transplantation. In P.J.Morris (ed) Kidney transplantation: Principles and Practice (2nd ed). Newyork:Grune and Stratton, 1984, pp. 407-426.
2. Tilney NL, Rocha A, Strom TB, et al. Renal artery stenosis in transplant patients. Ann Surg 1984; 199: 454.
3. Bennett WM, McDonald WJ, Lawson RK, et al. Postransplant hypertension, Studies of cortical blood flow and the renal pressor system. Kidney Int 1974; 6: 99.
4. Curtis JJ, Luke RG, Jones P, Dubovsky EV, Whelchel JD, Diethelm AG Cyclosporine in therapeutic doses increases renal allograft vascular resistance. Lancet 1986; 2: 477-479.
5. Rudnik MR, Basti CP, Narins RG, Diagnostic approaches to hypertension, Contemp Issues Nephrol (Hypertension) 1981; 8: 270-339.
6. Curtis JJ, Gall JH, Woodford SY, Saykaly RJ, Luke RG, Comparison of daily and alternate day prednisone during chronic maintenance therapy: A controlled crossover study. Am J Kidney Dis 1981; 1: 166-174.
7. Jullian BA, Quarles LD, Nieman KMW, Musculoskeletal complications after renal transplantation. Am J Kidney Dis 1992; 2: 99-120.
8. Winnearls CG, Lane DJ, Kurtz J. Infectious complications after renal transplantation In. Morris P.J (ed) Kidney Transplantation, Principles and practice (2nd ed) New York: Grune and Stratton, 1984; pp. 427-467
9. Rubin RH. The problem of Cytomegalovirus infection in transplantation. In P.J. Morris and N.L. Tilney (eds) Progress in Transplantation, Newyork, Churchill Livingstone 1984; pp. 89-114.
10. La Quaglia MP, Tolkoff-Rubin NE, Dienstag JL, et al. Impact of hepatitis on renal transplantation. Transplantation 1981; 32: 504.
11. Penn I. The incidence of malignancies in transplant recipients. Transplant Proc 1975; 7: 323.
12. Nogueira J, Freedman M. Acute Pancreatitis as a complication of Imuran therapy in regional enteritis. Gastroenterology 1972; 62: 1042.
13. Allen RDM, Chapman JR. A manual of renal transplantation. 1994 Edwadr Arnold, London.
14. Nakashima Y, Howard JM. Drug induced pancreatitis. Surgery Gynaecology and Obstetrics 1977; 145: 105-109.
15. Handschumacher RE. In: Drugs used for immunosuppression. Goodman & Gillman The Pharmacologic Basis of Therapeutics 1264-1276 Gilman AG, Rall TW, Nies AS, Taylor P (eds) 1991, Pergamon Press New York.

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