CASE REPORT

Sirolimus-induced lymphoedema

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Sirolimus is an inhibitor of the mammalian target of rapamycin (mTOR), used as an immunosuppressant for solid-organ transplant recipients and patients with autoimmune disorders. We report a case of lymphoedema, a rare complication of sirolimus, and discuss the mechanism of drug action, the adverse effects and the challenges of treating a kidney transplant recipient with this complication in a resource-limited environment. Lymphoedema is a rare complication of sirolimus, and the mechanisms are not completely understood; however, early recognition can prevent permanent disfiguration. This case highlights the need for early recognition of adverse drug effects and further research into their pathophysiology and management.

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Sirolimus, an inhibitor of the mammalian target of rapamycin (mTOR), is used as an immunosuppressant for solid-organ transplant recipients and patients with autoimmune disorders. We report a case of lymphoedema, a rare complication of sirolimus, and discuss the mechanism of drug action, the adverse effects and the challenges of treating a kidney transplant recipient with this complication in a resource-limited environment.

Case report

A 42-year-old black South African (SA) man received a cadaveric kidney transplant for end-stage renal disease secondary to type 1 diabetes mellitus. Before the transplant, he had been receiving haemodialysis via a left brachiocephalic arteriovenous fistula for 3 years and peritoneal dialysis for 2 years before that.

After the transplant, the patient received basiliximab, methylprednisolone and byclosporine for induction immune suppression and then triple therapy with cyclosporine, prednisone and myclophenolate mofetil (MMF) for maintenance immune suppression. In August 2009, he developed biopsy-proven mild calcineurin renal toxicity, and the cyclosporine was replaced with sirolimus. The mean sirolimus dose was 2 mg daily, with blood trough levels ranging between 3.8 and 11.3 ng/mL (mean 4.5, therapeutic range 4 - 11).

The patient first complained of progressive painful bilateral lower limb swelling, the left leg being more affected than the right, in September 2010, 13 months after the initiation of sirolimus. Despite the graft being in the right iliac fossa and multiple previous central venous catheterisations of both femoral veins, Doppler ultrasound assessments excluded a venous cause for the leg swelling. Graft function remained stable, with a mean creatinine level of 125 µg/mL. Lymphangiography showed almost complete obstruction of the deep lymphatic system of the lower limbs with back-diffusion into the peripheral superficial lymphatic system, the left leg more affected than the right.

In the absence of a significant family history and other causes for lymphatic obstruction, the patient was diagnosed with sirolimus-induced lymphoedema. Initially the treatment was continued because he had excellent graft function despite the physical disfigurement. Low-dose loop diuretics did not result in any notable improvement.

The lymphoedema worsened, and sirolimus treatment was stopped in April 2015 when the patient was unable to cope with the pain and the disfigurement impacted on his quality of life. He is currently receiving tacrolimus, MMF and prednisone for immune suppression, and his graph function has remained stable. There has been slight improvement in the lymphoedema with physiotherapy and cone compression bandaging.

Discussion

The prevalence of chronic kidney disease (CKD) has increased significantly over recent decades. It is currently estimated to be 6 - 18% worldwide.[1] The burden of disease is highest in low-income settings such as sub-Saharan Africa, where the incidence is estimated to be three to four times higher than in developed countries.[2] In SA, there was a 67% increase in deaths due to CKD from 1999 to 2006.[3] In the black African population, malignant hypertension is the most common cause, followed by diabetes mellitus and glomerulonephropathies. [4] Part of the challenge in managing CKD is late presentation of patients, a lack of adequate screening programmes and risk factor control, and the high cost of renal replacement therapy.

Organ transplantation is the treatment of choice for end-stage renal failure, but it carries a high burden of cost to both the patient and the healthcare system because patients require lifelong immune suppression to prevent acute and chronic rejection.

Sirolimus (also known as rapamycin) is a macrocylic lactone immunosuppressive agent produced by *Streptomyces hygroscopicus*. It inhibits T-lymphocyte activation and proliferation due to antigen and cytokine stimulation, and reduces antibody production. It binds to the immunophilin FK binding protein-12 (FKBP-12) and forms an immunosuppressive complex within the cell. The sirolimus/FKBP-12 complex binds to and inhibits activation of the regulatory kinase, the mammalian target of rapamycin (mTOR), thus inhibiting the progression from G_1 to the S phase of the cell cycle.

Sirolimus is currently used in patients with organ transplants and some autoimmune diseases. As with other immunosuppressive agents, adverse effects such as a predisposition to infections, cytopenias and poor wound healing may limit its use. However, compared with calcineurin inhibitors, it is associated with lower rates of nephrotoxicity, hypertension and malignancy, all of which have an impact on long-term graft function. The most common side-effects of sirolimus are dyslipidaemia, anaemia, arthralgia, gastrointestinal

disturbances, skin abnormalities, stomatitis, electrolyte abnormalities, pneumonitis and peripheral oedema.[5]

Patients with lymphatic obstruction can present with lymphoceles (12 - 13%), eyelid oedema, angio-oedema, pleural/pericardial effusions and lymphoedema.[6] Bilateral limb oedema is commonly associated with mTOR inhibitors, more commonly in patients on sirolimus than in those on evarolimus,[7] but the recent literature has indicated an increase in lymphoedema related to the drug, which is often permanently disfiguring.[8-10] According to previous case reports, it occurs between 7 months and 2 years on treatment and does not have a gender predisposition.[9]

Various mechanisms for the development of lymphatic obstruction in patients on sirolimus have been proposed. Most theories arise from the fact that mTOR is a downstream signal in the vascular endothelial growth factor pathway that mediates lymphatic survival, proliferation and passage. As a result, inhibition of the kinase disrupts lymphangiogenesis.[11]

Making the decision to stop treatment with sirolimus in our patient was challenging. Owing to the cost of drugs and problems with reliable supply, the treating facility did not have many options, and the patient also had good, stable graft function on sirolimus. However, his painful and disfiguring lymphoedema was affecting his quality of life. In view of his past history of calcineurin toxicity, the decision to change immunosuppressants could not be made lightly because of the possibility that his graft function would be compromised. Nonetheless, we needed to consider the psychological effect of his deformity and the effect it might have on compliance with treatment. Non-adherence would ultimately also have resulted in graft failure.

The patient's lymphoedema partially subsided after sirolimus was discontinued. His graft function remains stable on tacrolimus, MMF and prednisone.

This case highlights the importance of early recognition of drug complications, which may prevent permanent disfiguration and discomfort. However, in a resource-limited environment where treatment options are few, drugs are expensive and drug supply is sometimes unreliable, clinicians may be faced with the difficult task of deciding between the lesser of two evils – cessation of life-saving treatment, and irreversible deformities.

Conclusion

Lymphoedema is a rare complication of sirolimus, and the mechanisms are not completely understood. However, early recognition can prevent permanent disfiguration. This case highlights the need for early recognition of adverse drug effects and further research into their pathophysiology and management.

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