CASE REPORT

Impaired Lower Extremity Wound Healing Secondary to Sirolimus After Kidney Transplantation

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Introduction

Abstract

PURPOSE: Sirolimus is an immunosuppressive drug used as part of the drug regimen after kidney, liver, and heart transplantation. There have been numerous reports of transplant surgical wound healing complications secondary to sirolimus. The authors present a case of impaired wound healing in the lower extremity after kidney transplantation for a patient on sirolimus. This is one of the few reported cases that we are aware of that demonstrates the effects of sirolimus on wound healing at a nontransplant site.

METHODS: A case highlighting aggressive limb-salvage modalities for a kidney transplant patient on sirolimus is presented. The subject was informed that data concerning the case would be submitted for publication. A brief review of the literature shows the wound healing problems previously associated with sirolimus.

RESULTS: Despite all salvage techniques employed, including aggressive early debridement, forefoot offloading, IV antibiotics, negative pressure wound therapy, and hyperbaric oxygen therapy, the patient eventually went on to failure and a transtibial amputation.

CONCLUSION: Physicians specializing in wound care and limb salvage must be aware of the effects of sirolimus on wound healing and should consider modifications to these patients' immunosuppressive regimens.

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Diabetes is a complex disease affecting many people worldwide. Studies report the population-based incidence between 1.0% and 4.1%.¹ The sequelae of diabetic disease are complex and difficult to manage and include

neuropathy, peripheral arterial disease, and complications due to diabetic foot disease. Diabetics with peripheral neuropathy are at an increased risk of lower extremity ulceration, infection, and amputation. These patients have a 30% lifetime risk of lower extremity complications, leading to amputation rates 10 to 30 times that of the general population.^{1,2} Infections resulting from lower extremity

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ulcerations can involve soft tissue, bone, or both. Infection combined with common diabetic comorbidities, such as coronary artery disease and renal insufficiency, are predictably associated with poor prognosis.³ The management of osteomyelitis typically includes long-term IV antibiotics, surgical resection of bone, and balancing of tendons to address the altered biomechanics of the affected limb.⁴ Failed limb-salvage efforts commonly result in below-knee amputation.

Wound healing can be compromised in diabetic patients because of many factors, including poor glycemic control, protein energy malnutrition, obesity, peripheral arterial vascular disease, and/or organ failure. Diabetic patients who are candidates for organ transplant surgery are at significant risk for accentuation of comorbidities due to the requirement for posttransplant immunosuppression and antirejection pharmacotherapy. Immunosuppressive medications can make glycemic control difficult, further potentiating diabetic complications such as an adverse outcome for wound healing.⁵ The purpose of this case study is to discuss the effects of sirolimus, an immunosuppressive medication, and its affects on wound healing on a lower extremity wound.⁶

Case Report

A 59-year-old male with a chief complaint of a non-healing surgical wound on his left foot was admitted to the hospital for wound care and surgical management. The patient had a history of type 1 diabetes, end stage renal disease with prior kidney transplantation, and right eye blindness. The patient had had 3 previous uncomplicated surgeries on his right eye, including laser photocoagulation and 3 vitrectomies. In addition, the patient had required a right fifth toe amputation approximately 20 years prior and a left second toe amputation 1 year prior, both of which healed uneventfully. A kidney and pancreas transplantation was performed in 1988, and the patient was insulin free for 11 years, with immunosuppression maintained with prednisone. In 1999 a second kidney transplant was performed and was maintained with a regimen of sirolimus and tacrolimus, while diabetic control was achieved with insulin lispro injection (Humalog) and insulin glargine injection (Lantus).

Two weeks prior, the patient had required a left partial fourth metatarsal resection due to an infected fourth metatarsal plantar ulcer. The patient was informed of the potential wound healing complications associated with sirolimus and was recommended to change to a different immunosuppressive therapy. The patient refused discontinuation of sirolimus; however, the daily dose was changed from 4 mg to 2 mg. The procedure was complicated by postoperative infection and ischemia with tissue necrosis (Figures 1A and 1B), and the patient was started on amoxicillin/clavulanate and ciprofloxacin.

Figure 1 A, Debridement Consisted of Open Partial Amputation of the Second Through Fifth Rays, Followed With Aggressive Wound Care. B, Intraoperative Radiograph Prior to Debridement Showing Fourth Metatarsal Head Resection.

Because of cellulitis and ischemia with progressive tissue necrosis, the patient was admitted for aggressive care. Surgical amputations of digits and partial resection of metatarsals 2 through 5 were performed and left open. Furthermore, an intraoperative radiograph was performed (Figure 2). A percutaneous Hoke tendo-Achilles lengthening was also performed. The hallux was left intact as consent for a transmetatarsal amputation could not be obtained from the patient.

After the emergent amputation was performed to rid the leg of infection, the patient's vascular status was assessed.

Figure 2 Intraoperative Radiograph Showing Metatarsal Resection. Debridement Was Carried Back to Viable, Bleeding Tissue.

Ankle-brachial index testing showed noncompressable vessels with monophasic waveforms and sluggish velocity at the dorsalis pedis and tibialis posterior arteries. Transcutaneous oximetry at the level of the foot showed air-breathing baseline values of 17 and 11 mm Hg at 2 separate locations on the dorsal distal foot, rising to 30 and 22 mm Hg breathing 100% oxygen at 1 atmosphere absolute (ATA). Transcutaneous oximetry during an initial hyperbaric treatment revealed an augmentation to 135 mm Hg at 1.5 ATA. The treatment was prematurely aborted because of otic barotrauma, and a result at 2.4 ATA could not be determined. However, the rise at 1.5 ATA was encouraging and suggestive of potential benefit of hyperbaric oxygen therapy.⁷

Magnetic resonance angiogram showed the abdominal aorta, bilateral iliac, femoral, and popliteal arteries to be free of significant arterial disease. The trifurcation vessels were diseased, however, with extensive occlusion of the tibialis anterior and peroneal arteries without significant reconstitution (Figure 3). There was blood flow from the posterior tibial artery to the foot (Figure 4). Consultations were made to an interventional radiologist specializing in revascularization and 2 separate vascular surgeons all yielded the opinion that the patient had no endovascular or bypass revascularization options.

Hyperbaric oxygen therapy (HBOT) was initiated as a limb-salvage effort because the patient had failed to heal despite aggressive local measures, control of his diabetes, and his poor baseline tissue oxygenation. The patient progressed well with wound care, which included the use

Figure 3 Magnetic Resonance Angiogram Reveals Complete Occlusion at the Trifurcation of the Tibialis Anterior and Peroneal Arteries on the Left; There Is Flow to the Tibialis Posterior Artery.

of the Vacuum Assisted Closure (VAC; KCI, San Antonio, TX). A flap closure was performed 4 days after the initial debridement (Figure 5). The patient was discharged from the hospital 8 days after the initial debridement, after having received 12 HBO treatments and maintaining a stable wound.

The patient was followed on an outpatient basis for wound care and HBOT. At approximately 1 month following the initial debridement, the wound began to rapidly deteriorate (Figure 6). The patient was readmitted to the hospital, and a surgical debridement of the necrotic flap was performed. Intraoperative VAC therapy was started, and HBOT was restarted postoperatively. A nephrologist who is a transplant specialist was consulted for management of the patient's immunosuppression regimen. The sirolimus was discontinued, and the tacrolimus was decreased to 1.5 mg twice daily. Also, the patient was put on mycophenolate mofetil 720 mg twice daily and prednisone 10 mg daily. Despite aggressive surgical and medical care, the patient deteriorated, with progressive tissue ischemia and necrosis, and a transtibial amputation was recommended. Two weeks after his readmission and discontinuation of sirolimus, to allow for clearance of the sirolimus, the patient underwent a transtibial amputation with an uncomplicated postoperative course. The patient was discharged home well.

Figure 4 Magnetic Resonance Angiogram of the Feet Showing Tibialis Posterior Artery Flow to the Forefoot on the Left After the Open Resection of the Metatarsals.

Discussion

Sirolimus (Rapamune, Rapamycin, RAPA, AY-22989; Wyeth Research, Philadelphia, PA) was first isolated from a strain of fungus called *Streptomyces hygroscopicus* in 1969 by Dr. S. Sehgal in the soil of Easter Island. It was found to

Figure 5 Clinical Picture Showing Flap Closure of Second Through Fifth Partial Ray Resection with Healthy Wound Edges, No Signs of Infection, and No Ischemic Changes; Patient Was Discharged From the Hospital in This Condition.

Figure 6 Clinical Picture of Wound 2 Weeks After Discharge From the Hospital Revealing Rapid Deterioration of Wound With Complete Flap Failure With Necrotic Center, Nonhealing Edges, Infection, and Increased Wound Size; Patient Was Taken Off of Sirolimus for 2 Weeks and Was Given a Below-Knee Amputation.

be a lipophilic microcyclic lactone with powerful immunosuppressive effects. Sirolimus binds the intracellular receptor called FK binding protein 12 and forms a complex (SRL-FKBP-12) that acts on the mammalian target of rapamycin (mTOR). The complex inhibits mTOR-mediated pathways during G0-G1 transition and during G1 progress. It also inhibits the IL-2 and IL-4-dependant proliferation of T and B cells, which leads to suppression of new ribosomal protein synthesis and arrest of the G1-S phase of the cell cycle. Finally, it inhibits responses and pathways mediated by basic fibroblast growth factor, platelet-derived growth factor, vascular endothelial cell growth factor, and transforming growth factor. This leads to the inhibition of fibroblasts, endothelial cells, hepatocytes, and smooth muscles. The half-life is between 57 and 63 hours, and excretion is mostly fecal.^{8,9}

Sirolimus has found its place in immunosuppression after transplant for several reasons. It has been found to increase the potency of immunosuppression when added with other drug regimens. It has a synergistic effect with cyclosporine, a calcineurin-inhibiting immunosuppressant that is widely used in transplant surgery. It has been shown to protect against chronic rejection and also contributes to a reduction in malignant changes in transplanted organs. It has been shown to be an option in steroid and calcineurin-inhibitor-sparing transplant drug regimens. Inhibition of fibroblast activation has been hypothesized to lead to a less fibrogenic intra-graft environment, which causes congestion and eventual graft failure. Finally, it does not have some of the more common side effects of other transplant drugs, such as nephrotoxicity, neurotoxicity, diabetes mellitus, and hypertension.¹⁰

Sirolimus is also known for certain disadvantages. Therapeutic monitoring is difficult in large part because

of its metabolism control through P-glycoprotein and CYP3A4, each of which has interindividual variations. Sirolimus can cause hyperlipidemia, and this can be potentiated when used in patients with renal insufficiency or when combined with cyclosporine or steroids. Myelosuppression has been reported, particularly when the trough reaches supratherapeutic levels (>16 ng per ml). Finally, impaired wound healing with sirolimus use is commonly reported.¹⁰

Wound complications related to sirolimus have been reported since early trials. Specific wound healing issues include sternal instability, pleural effusion and pericardial tamponade after heart transplant, and urine leaks and lymphoceles after kidney transplants. Superficial and deep wound infection, cellulitis, seroma formation, fascial dehiscence, and incisional hernias have all been linked to sirolimus.^{11,12,13,14,15,16,17} The medical and surgical team caring for the patient must assess the risk–benefit ratio of sirolimus with close attention to the vast array of side effects in order to minimize potential complications. Various strategies have been employed to avoid potential problems. Avoiding use in obese patients, delaying use until after the wounds have healed, decreasing the dose, or withdrawing concomitant steroids from the immunosuppressive regimen have all been recommended.¹¹

Wound healing compromise in patients receiving sirolimus is multifactorial. Oftentimes patients receiving transplants are in poor health or obese and thus are intrinsically at relatively high risk for complications. All immunosuppressive regimens including sirolimus can contribute to compromised wound healing.⁵ Wound healing inhibition due specifically to sirolimus largely relates to the mechanism of action. Sirolimus inhibits platelet-derived growth factor and basic fibroblast growth factor, slowing proliferation of many cell types, including endothelial cells, fibroblasts, and smooth muscle cells. These cell lines are all essential to the formation of granulation tissue and propagation of the wound healing cascade.^{11,12,16} One report reviewed a case of a clinically healed incision that was reopened 9 months later and revealed minimal degradation of absorbable suture material and a lack of mechanical strength of the fascial layer.¹¹

Wound healing compromise due to sirolimus has been frequently reported in acute surgical wounds following transplantation. Our review of the literature failed to find an abundance of reports of failed healing in lower extremity wounds not related to the transplant procedure. However, 1 study reports the effects of sirolimus on wound healing in dermatologic surgery. This was a retrospective study that looked at 2 groups of patients that had undergone dermatologic procedures, 1 group taking sirolimus and the other not. The study reports the incidence of postoperative infections and wound dehiscence was greater in the sirolimus group, but the difference was not significant. The author states that the limitations of this study are the small sample size ($N = 63$) and the retrospective nature of

the study.¹⁸ In general, the transplant population is at high risk for foot and ankle wounds due to complications of comorbid disease states such as diabetes and arterial occlusive disease. The management of these patients must include attention to all transplant-related medications. This case illustrates this issue in a renal transplant patient who required long-term immunosuppression that included sirolimus. The patient received excellent wound care, including HBOT and VAC treatments,^{19,20,21} as well as prompt, aggressive surgical debridement and tendon balancing.⁴ Despite this, the patient went on to unexpected deterioration of his wound and eventual transtibial amputation. We believe that despite his other medical issues, the wound healing issues found in this patient can be at least partially attributed to the known side effects of sirolimus.

Conclusion

Professionals who treat wounds of the lower extremity, particularly in high-risk, medically unstable patients, have a responsibility to understand the complex issues and adjunctive treatments these patients may be receiving. Practitioners must keep abreast of new pharmaceuticals and device developments and their effects on our patients and our patients' surgical outcomes. The use of sirolimus, an mTOR inhibitor, may have profound effects on these already compromised and high-risk patients. We believe this is one of the few reports in the literature examining the healing complications in a lower extremity wound, caused or contributed to by sirolimus.

References

1. Singh N, Armstrong DG, Lipsky BA: Preventing foot ulcers in patients with diabetes. *J Am Med Assoc.* 2005;293:217–228.
2. Lavery LA, Armstrong DG, Vela SA, Quebedeaux TL, Fleischli JG: Practical criteria for screening patients at high risk for diabetic foot ulceration. *Arch Int Med.* 1998;158:157–162.
3. Armstrong DG, Stacpoole-Shea S, Nguyen H, Harkless LB: Lengthening of the Achilles tendon in diabetic patients who are at high risk for ulceration of the foot. *J Bone Joint Surg Am.* 1999;81:535–538.
4. Armstrong DG, Lavery LA, Harkless LB: Validation of a diabetic wound classification system. *Diabetes Care.* 1998;21:855–859.
5. Banks AS, Downey MS, Martin DE, Miller SJ. *McGlamry's Comprehensive Textbook of Foot and Ankle Surgery.* 3rd ed. Philadelphia, PA: Lippincott, Williams, & Wilkins; 2001.
6. Schaffer M, Schier R, Napirei M, Michalski S, Traska T, Viebahn R: Sirolimus impairs wound healing. *Langenbecks Arch Surg.* 2007;392:297–303.
7. Fife C, Buyukcakar C, Otto G, et al: The predictive value of transcutaneous oxygen tension measurement in diabetic lower extremity ulcers treated with hyperbaric oxygen therapy: a retrospective analysis of 1144 patients. *Wound Repair and Regeneration.* 2002;10(4):198–207.
8. Mehrabi A, Fonouni H, Kashfi A, et al: The role and value of sirolimus administration in kidney and liver transplantation. *Clin Transplant.* 2006;20(suppl. 17):30–43.
9. Physicians' Desk Reference. 61st ed. Montvale, NJ: Thomson PDR; 2007.

10. Kahan BD: Sirolimus-based immunosuppression: present state of the art. *J Nephrology*. 2004;17(suppl 8):32–39.
11. Dean PG, Lund WJ, Larson TS, et al: Wound-healing complications after kidney transplantation: a prospective, randomized comparison of sirolimus and tacrolimus. *Transplantation*. 2004;77:1555–1561.
12. Flechner SM, Zhou L, Derweesh I, et al: The impact of sirolimus, mycophenolate mofetil, cyclosporine, azathioprine, and steroids on the wound healing in 513 kidney-transplant recipients. *Transplantation*. 2003;76:1729–1734.
13. Guilbeau JM: Delayed wound healing with sirolimus after liver transplant. *Ann Pharmacotherapy*. 2002;36:1391–1394.
14. Kuppahally S, Al-Khalidi A, Weisssha D, et al: Wound healing complications with de novo sirolimus versus mycophenolate mofetil-based regimen in cardiac transplant recipients. *Am J Transplant*. 2006;6:986–992.
15. Mehrabi A, Fonouni H, Wents M, et al: Wound complications following kidney and liver transplantation. *Clin Transplant*. 2006;20(suppl 17):97–110.
16. Valente JF, Hricik D, Weigel K, et al: Comparison of sirolimus vs mycophenolate mofetil on surgical complications and wound healing in adult kidney transplantation. *Am J Transplant*. 2003;3:1128–1134.
17. Zakliczynski M, Nozynski J, Kocher A, et al: Surgical wound-healing complications in heart transplant recipients treated with rapamycin. *Wound Repair Regen*. 2007;15:316–321.
18. Brewer JD, Otley CC, Christenson LJ, Phillips PK, Roenigk RK, Weaver AL: The effects of sirolimus on wound healing in dermatologic surgery. *Dermatol Surg*. 2007;34:216–223.
19. Andros G, Armstrong DG, Attinger CE, et al: Consensus statement on negative pressure wound therapy (V.A.C. therapy) for the management of diabetic foot wounds. *Ostomy Wound Manage*. 2006;Jun(suppl 1):32.
20. Niezgoda JA: Combining negative pressure wound therapy with other wound management modalities. *Ostomy Wound Manage*. 2005;51(2A suppl):36S–38S.
21. Tibbles PM, Edelsberg JS: Hyperbaric-oxygen therapy. *NEJM*. 1996;334(25):1642–1648.