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Teaching Case

Local Graft Irradiation for Acute, Medication Refractory Transplant Rejection of a Pancreas Alone Graft: A Case Report

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Introduction

Pancreas transplant is an established surgical treatment for diabetes mellitus, with over 61,000 transplants performed worldwide.[1] Transplant can be used in patients with type 1 or type 2 diabetes with the goal of euglycemia without need for insulin treatment. Historically, transplant was completed with simultaneous kidney transplant in patients with secondary renal complications of diabetes.[2] However, more recently pancreas transplant alone is being used for treatment of brittle diabetes.[3] Patients undergoing transplant require lifelong immunosuppression to prevent rejection. Improvements in immunosuppressive regimens and surrogate laboratory monitoring for acute graft rejection have improved outcomes and graft survival rates in patients undergoing pancreas alone transplants, with 3-year graft survival of 84% for newer sirolimus based regimens compared with 69% for tacrolimus based regimens.[2,4] Pancreas transplant alone has been associated with higher incidence of rejection, with a 1-year rate of 19.2%.[4] Rejection episodes must be managed with increase or change in immunosuppressive medication regimens. However, in patients undergoing immune rejection unresponsive to medical therapy, options remain limited and risk of graft failure is high. Here we report a case of a patient successfully treated with low dose graft irradiation for pancreas transplant rejection unresponsive to medical management.

Case

A 47-year-old woman with long standing history of type 1 diabetes mellitus underwent pancreas-alone transplant 18 months before presentation. She was moderately sensitized to the donor organ, and her initial immunosuppression regimen included antilymphocyte globulin, desensitization with a course of intravenous immune globulin (IVIG), and oral maintenance therapy of mycophenolate, tacrolimus, sirolimus, and prednisone. Her posttransplant course was complicated by gastrointestinal difficulties secondary to immunosuppressive medications. Her immunosuppression regimen was transitioned to Azathioprine, Sirolimus, Belatacept, and prednisone. She later developed tacrolimus induced thrombotic microangiopathy of the kidney with mild diffuse interstitial fibrosis and subsequent development of stage 4 chronic kidney disease. Sirolimus was discontinued secondary to oral ulcers and cyclosporine was initiated. Azathioprine was eventually discontinued because of infectious complications. Her most recent immunosuppressive regimen before admission was cyclosporine, mycophenolate, and prednisone.

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Her pancreatic enzymes (amylase and lipase) rose dramatically over a 4-week course before admission (June2022). Her amylase rose from 95 units per L (normal range, 30-105) to 367 units per L, and her lipase rose from 78 units per L (normal range, 15-100) to 769 units per L. She developed a corresponding rise in her donor specific antibodies concerning for antibody mediated rejection. Her exogenous insulin requirement continued to rise, requiring use of an insulin pump. She was admitted to the hospital for acute antibody-mediated graft rejection. She initially was managed with high-dose dexamethasone, and, given the rising donor specific antibodies, she underwent IVIG infusion and plasmapheresis. Initially, she had a decrease in amylase and lipase levels and improvement in subjective symptoms following IVIG and plasmapheresis. However, these levels began to rise again despite ongoing therapy, and radiation oncology was consulted for consideration of graft irradiation.

She underwent local graft irradiation to a dose of 8 Gy delivered over 4 daily fractions using a 3-dimensional conformal arc plan (Figure 1). Computed tomography simulation planning imaging and recent diagnostic computed tomography imaging with oral contrast were used to generate a local graft internal target treatment volume. A 1-cm uniform expansion was used to generate a planning target volume. She tolerated treatment well with no acute side effects. Her amylase and lipase started down-trending following the second fraction and were within normal limits following her final fraction. She did continue IVIG and plasmapheresis during radiation, receiving 5 treatments of IVIG. She was discharged following her final radiation treatment. Her amylase and lipase labs remain normal (75 and 65 units/L, respectively) 12 weeks following radiation. She continues on cyclosporine and mycophenolate for immunosuppression.

Discussion

Pancreas alone transplant is an increasingly used definitive treatment for diabetes mellitus.[4] However, complications of the immediate surgery, long-term immunosuppressives, and risk of graft rejection continue to cause long-term issues for these patients. Here, we presented the case of a patient receiving low-dose, local graft irradiation for acute antibody mediated pancreas transplant rejection. The patient had normalization of labs and resolution of medication refractory pancreas graft rejection following radiation treatment.

Historically, radiation was investigated as a preparative therapy before transplant. Various regimens and volumes

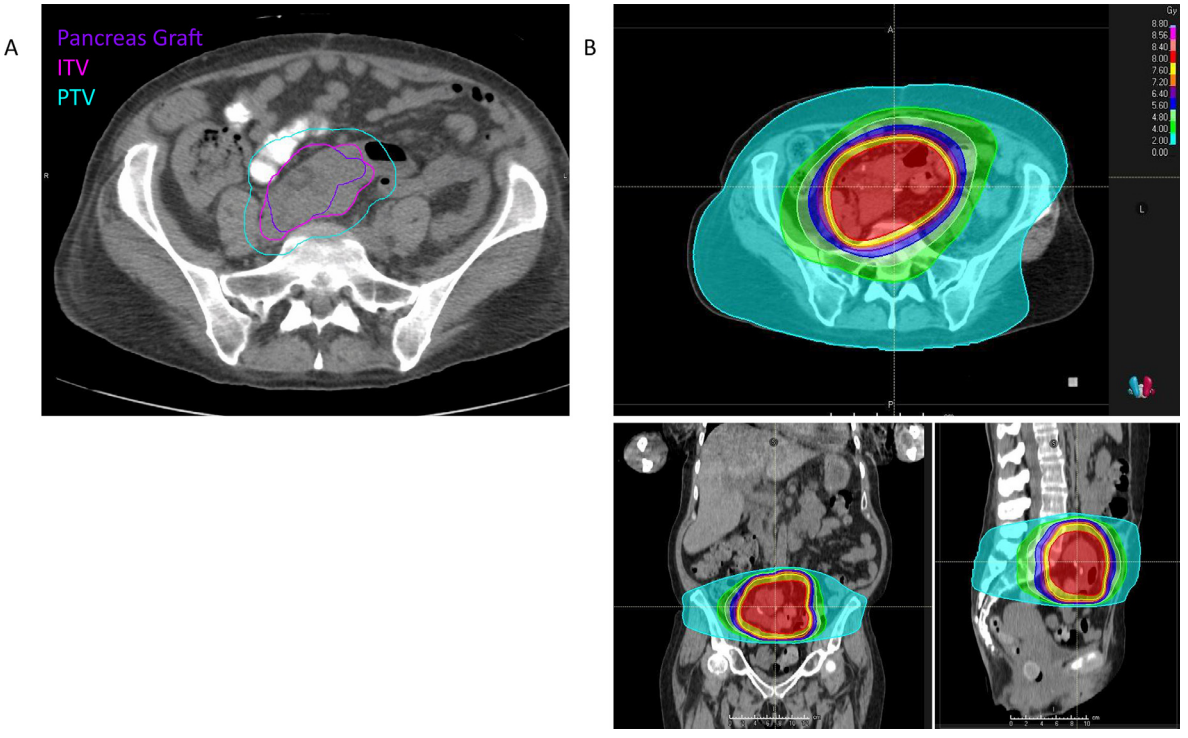

Figure 1 Representative computed tomography images of A, local graft radiation treatment volumes and B, total treatment isodose lines. A, Contours represent pancreas graft on planning image set (purple), internal target volume (ITV) accounting for motion seen on corresponding diagnostic imaging (pink), and planning target volume (PTV, aqua), representing a 1-cm expansion from ITV. B, Isodose color wash representing total dose coverage, with red representing 8 Gy and blue representing 2 Gy.

have been investigated, including total body irradiation, total lymphoid irradiation, and local graft irradiation.[5-11] However, these studies produced no benefit or inferior results to newer immunosuppressive agents, and the role of radiation in the peri-transplant period has been replaced by medical management. Nevertheless, radiation may still play a role in management of acute rejection unresponsive to medical management. Indeed, radiation remains the only possible salvage treatment option for patients failing all chemical immunosuppression. Multiple single institution retrospective studies in renal transplant patients have shown response to radiation in medication refractory transplant rejection. Response to radiation varies in these studies from 35 to 60%. Overall, 1-year graft survival ranges from 20 to 60% following radiation, with a mean dose of 4.5 to 8 Gy.[8,12-16] One study reported an 80% response rate with long-term graft survival of 50% following 4.5 Gy in 3 fractions.[14] While these response rates remain poor, the radiation is well tolerated, typically without any acute or long-term side effects given the low total dose, making it an attractive final salvage option for patients with few other options.

As the use of radiation for acute graft rejection has fallen out of favor with improved pharmaceutical based immunosuppression, the exact mechanism for preventing or salvaging acute rejection is not fully understood. Successful salvage likely reflects a multifactorial response in the local graft environment restoring an immunosuppressive state. Prior studies have identified both T and B lymphocytes present in rejected tissue.[17,18] These lymphocytes are exquisitely sensitive to radiation, and, thus, radiation likely works, in part, by eliminating these lymphocytes responsible for immune mediated rejection.[19] However, additional possible mechanisms may be extrapolated from the effects of radiation on the microenvironment in cancer literature.[20] Following low-dose total body radiation, CD4+ CD25+ Foxp3 + T regulatory (Treg) cells show increased survival compared with other lymphocytes, suggesting radiation resistance of Tregs.[19,21] Additionally, low-dose radiation has been shown to recruit Tregs to the local microenvironment.[22] Tregs help mediate immune homeostasis and down regulation of immune response. Low-dose radiation can upregulate Treg CTLA-4 expression, leading to T cell downregulation.[23] Moreover, Treg expression and function have been correlated with allograft survival.[24-26] It is possible that radiation helps restore an immunosuppressive microenvironment by eliminating activated lymphocytes while promoting immunosuppressive cellular states, though more research outside of cancer immunology and within this specific patient population are needed to further elucidate the mechanism of action.

In the case presented, our patient had an excellent laboratory response at time of her final fraction of radiation. While the effect may be a delayed response to IVIG and plasmapheresis, her initial response to these therapies followed by worsening of rejection laboratory markers indicates a potential response to the radiation therapy. To our knowledge, this is the first report of salvage radiation for acute rejection of a pancreas only graft. In similar pancreas transplant patients with medication refractory graft rejection, low-dose local graft irradiation may serve as a final salvage option.

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