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Diabetic Ketoacidosis Revealing a Delayed New-Onset Diabetes after Renal Transplantation

Mohit Raj Singh[1], Asha Sarkar[2] and Debmalya Sanyal[3*]

[1,2]*Department of Medicine, NHRTIICS, Kolkata, India*

[3]*Department of Endocrinology, NHRTIICS and KPC Medical College, Kolkata, India*

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***Corresponding author:** Debmalya Sanyal, Department of Endocrinology, NHRTIICS and KPC Medical College, Kolkata, India

Abstract

Background: New-Onset Diabetes After Transplantation (NODAT) is a recognised metabolic complication of solid organ transplantation, occurring in up to a quarter to a third of renal allograft recipients within the first three years. While NODAT typically follows an indolent, type 2-like course, it can rarely present acutely as Diabetic Ketoacidosis (DKA), an insulin-deficient emergency more characteristic of type 1 diabetes.

Case Presentation: We report a 43-year-old woman with Autosomal Dominant Polycystic Kidney Disease (ADPKD) who had undergone live-donor renal transplantation four years earlier and was maintained on tacrolimus-based triple immunosuppression. She presented with a seven-day history of generalised weakness and was found to have severe hyperglycaemia. Evaluation revealed high anion-gap metabolic acidosis, ketonuria, and elevated blood β-hydroxybutyrate, confirming DKA in a patient with no prior history of diabetes. She was managed with intravenous fluids and an insulin infusion, transitioned to a subcutaneous basal-bolus regimen, and started on long-term thyroxine replacement for pre-existing hypothyroidism. A supratherapeutic tacrolimus trough level prompted dose reduction. Concurrent hypovolaemic hyponatraemia and hypokalaemia were corrected. She improved clinically and biochemically and was discharged in stable condition on a basal-bolus insulin regimen with structured glucose self-monitoring.

Conclusion: This case highlights that NODAT, although usually a chronic, type 2-like phenomenon driven by calcineurin inhibitor exposure, can occasionally have a delayed presentation as a life-threatening insulin-deficient crisis. Awareness of this atypical presentation, prompt biochemical screening for ketoacidosis in any hyperglycaemic transplant recipient, and close coordination between transplant nephrology and endocrinology are essential to good outcomes.

Keywords: New-onset diabetes after transplantation; NODAT; Diabetic ketoacidosis; Renal transplantation; Tacrolimus; Calcineurin inhibitor; Post-transplant diabetes mellitus

Introduction

New-onset Diabetes After Transplantation (NODAT), also termed post-transplant diabetes mellitus (PTDM), refers to diabetes mellitus diagnosed for the first time after solid organ transplantation in a previously non-diabetic individual. It is among the most common metabolic complications of renal transplantation, with reported incidence ranging from roughly 10–20% at one year to 25–35% by three years post-transplant, depending on the diagnostic criteria and immunosuppressive regimen used.

The pathogenesis of NODAT closely parallels that of type 2 diabetes, involving a combination of insulin resistance and impaired beta-cell insulin secretion. However, in the transplant setting this process is strongly accelerated by immunosuppressive therapy. Calcineurin inhibitors, particularly tacrolimus, are the most consistently implicated agents: by inhibiting calcineurin-dependent NFAT signalling in pancreatic beta cells, tacrolimus suppresses insulin gene transcription, promotes nuclear translocation of FoxO1 and cytoplasmic sequestration of MafA, and reduces beta-cell proliferation and survival. Corticosteroids compound this effect by increasing hepatic gluconeogenesis and peripheral insulin resistance. Traditional risk factors for type 2 diabetes - older age, obesity, family history, non-white ethnicity, hepatitis C or cytomegalovirus infection - further increase susceptibility.

Because NODAT typically mirrors type 2 diabetes, it usually develops gradually and is detected on routine post-transplant glucose surveillance rather than presenting acutely. Diabetic ketoacidosis, an insulin-deficient state classically associated with type 1 diabetes, is a distinctly uncommon initial presentation of NODAT, with only a small number of cases described in the literature. We describe a patient who developed DKA as the presenting manifestation of NODAT several years after renal transplantation, in the context of supratherapeutic tacrolimus levels, and discuss the mechanisms, diagnostic approach, and management considerations this scenario raises.

Case Presentation

A 43-year-old woman presented with a seven-day history of generalised weakness and was found on outpatient testing to have markedly elevated random blood glucose (763 mg/dL). She had no personal history of diabetes mellitus prior to this presentation.

Relevant Medical History

The patient had end-stage renal disease secondary to Autosomal Dominant Polycystic Kidney Disease (ADPKD) and had undergone renal transplantation four years prior to this admission. She was maintained on tacrolimus-based immunosuppression. Other known comorbidities included systemic hypertension, primary hypothyroidism, and β-thalassaemia trait. Her surgical history included internal fixation for a trimalleolar right ankle fracture, a ligasure haemorrhoidectomy for bleeding haemorrhoids, and a prior lower-segment caesarean section. There was no significant family history of diabetes, and no known drug allergies.

Examination Findings

On admission, the patient was hypertensive (blood pressure 160/80 mmHg) with tachycardia and clinical signs of dehydration, including a dry tongue. Capillary blood glucose was unrecordably high on the bedside glucometer (reading as "High").

Investigations

Arterial blood gas analysis demonstrated a high anion-gap metabolic acidosis. Urine ketones were positive, and blood β-hydroxybutyrate was elevated, confirming diabetic ketoacidosis. Tacrolimus trough level was supratherapeutic at 7.72 ng/mL. Serum sodium and potassium were both reduced, consistent with hypovolaemic hyponatraemia and hypokalaemia. Glutamic Acid Decarboxylase (GAD) and islet-cell antibody testing were not performed in this admission (Table 1).

Diagnosis

On the basis of new hyperglycaemia, high anion-gap metabolic acidosis, ketonuria, and elevated β-hydroxybutyrate in a patient with no prior diabetes, a provisional diagnosis of New-Onset Diabetes After Transplantation (NODAT) presenting with diabetic ketoacidosis was made. Associated dyselectrolytaemia (hypovolaemic hyponatraemia and hypokalaemia, the latter likely insulin-related) was also identified.

Management and Course in Hospital

The patient was managed jointly by the transplant nephrology and endocrinology teams. Initial treatment followed standard DKA protocol with intravenous fluid resuscitation for rehydration and an intravenous insulin infusion to control hyperglycaemia and resolve ketoacidosis. Electrolyte derangements were corrected concurrently. As glucose levels improved, she was transitioned from the insulin infusion to a subcutaneous basal-bolus insulin regimen, comprising thrice-daily prandial short-acting human insulin and once-daily basal insulin degludec.

Given the supratherapeutic tacrolimus trough level, the dose was reduced from 3 mg to 2.5 mg twice daily in consultation with the transplant nephrology team, balancing the competing risks of nephrotoxicity/diabetogenicity against graft rejection. Pre-existing hypothyroidism was managed with once-daily levothyroxine 50 mcg taken before breakfast. Capillary glucose was monitored closely, and insulin doses were progressively optimised under endocrinology guidance.

The patient showed steady clinical and biochemical improvement: hydration status normalised, she became haemodynamically stable, and oral intake was re-established. She was discharged on a basal-bolus insulin regimen with structured self-monitoring of capillary blood glucose four times daily (pre-meals and bedtime), education on recognising and managing hypoglycaemia, dietary counselling for a diabetic diet, and advice on foot care. Outpatient follow-up was planned with renal function tests, urine albumin-creatinine ratio, HbA1c, lipid profile, and thyroid function tests, alongside continued glucose surveillance.

Discussion

New-onset diabetes after transplantation occurs in a substantial proportion of renal allograft recipients and is associated with worse graft survival, higher cardiovascular morbidity, and increased mortality compared with non-diabetic recipients [1-3]. Diagnostic criteria mirror those used for type 2 diabetes in the general population: fasting plasma glucose ≥126 mg/dL, random glucose ≥200 mg/dL with symptoms, an oral glucose tolerance test 2-hour value ≥200 mg/dL, or HbA1c ≥6.5% [4,5].

The pathophysiology of NODAT overlaps substantially with type 2 diabetes - insulin resistance combined with impaired beta-cell insulin secretion - but is markedly accelerated by post-transplant immunosuppression [5,6]. Calcineurin inhibitors are central to this process. Tacrolimus, the most commonly used calcineurin inhibitor in contemporary regimens, binds FKBP12 and inhibits calcineurin, a calcium-calmodulin-dependent phosphatase required for nuclear translocation of NFAT, a transcription factor important for beta-cell insulin gene expression and survival [7-9]. Tacrolimus also promotes nuclear

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localisation of FoxO1 and cytoplasmic sequestration of MafA, both beta-cell-enriched transcription factors whose disruption further impairs insulin synthesis and secretion [10]. Compared with cyclosporine, tacrolimus carries a more pronounced diabetogenic effect, an observation reflected in this patient's markedly elevated trough level at presentation [11]. Corticosteroids, also part of most maintenance regimens, add to this risk by increasing hepatic gluconeogenesis and peripheral insulin resistance.

Because this mechanism resembles type 2 diabetes pathophysiology, NODAT typically follows an indolent course and is usually identified through routine post-transplant glucose screening rather than acute presentation. Diabetic ketoacidosis, by contrast, reflects near-absolute insulin deficiency and is the hallmark presentation of type 1 diabetes; it is reported only rarely as the initial manifestation of NODAT [12,13]. Several published cases describe DKA as the presenting feature of tacrolimus-associated NODAT, occurring from weeks to several years after transplantation, sometimes in association with supratherapeutic calcineurin inhibitor levels, as in the present case, and sometimes despite levels within the therapeutic range [12-14]. In some reported cases, subsequent testing has revealed positive GAD or islet-cell antibodies, raising the possibility of unmasked or accelerated Latent Autoimmune Diabetes in Adults (LADA) rather than a purely drug-induced insulin-deficient state [14]. Antibody testing was not performed during this admission, and this remains an important gap; outpatient testing for GAD/IA-2 antibodies and C-peptide would help clarify whether an autoimmune process contributed to this presentation and would inform long-term diabetes classification and management.

This patient's presentation illustrates several recognised contributing factors converging simultaneously: a markedly supratherapeutic tacrolimus level, intercurrent dehydration, and a several-year interval since transplantation, during which the cumulative diabetogenic burden of immunosuppression accrues. The hypovolaemic hyponatraemia and hypokalaemia she developed are well-described accompaniments of DKA, reflecting osmotic diuresis, vomiting, and the intracellular potassium shift driven by insulin therapy, and required concurrent correction alongside glycaemic control.

Management of DKA in a transplant recipient follows the same core principles as in the general population - fluid resuscitation, intravenous insulin infusion, and electrolyte correction - but with added attention to graft function and immunosuppressive drug levels. Tacrolimus dose adjustment, as performed in this case, must balance the competing risks of worsening hyperglycaemia and nephrotoxicity against under-immunosuppression and rejection, underscoring the value of close coordination between endocrinology and transplant nephrology [15]. Once stabilised, most patients with NODAT, including those presenting with DKA, can be transitioned to subcutaneous basal-bolus insulin, with some later able to step down to oral agents depending on residual beta-cell function and the degree of insulin resistance [16].

This case reinforces the importance of considering NODAT, and specifically DKA, in any renal transplant recipient presenting with unexplained hyperglycaemia or non-specific symptoms such as weakness, regardless of how long after transplantation they present or how long they have been clinically stable on immunosuppression. Routine post-transplant glucose surveillance, periodic tacrolimus trough monitoring, and patient education about hyperglycaemic symptoms are key preventive measures. Early recognition and prompt biochemical confirmation of ketoacidosis, rather than assuming a purely type 2-like trajectory, are essential to avoid delays in life-saving treatment.

Conclusion

New-onset diabetes after renal transplantation is usually an indolent, type 2-like metabolic complication of long-term immunosuppression, but it can rarely present as acute diabetic ketoacidosis, as illustrated in this patient several years after transplantation in the setting of supratherapeutic tacrolimus levels. Clinicians caring for transplant recipients should maintain a low threshold for screening any hyperglycaemic patient for ketoacidosis, irrespective of time elapsed since transplantation, and should manage such presentations through close collaboration between endocrinology and transplant nephrology to optimise both glycaemic control and graft outcomes.

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