CASE REPORT

Diagnostic and management dilemma of a pancreas–kidney transplant recipient with aplastic anaemia

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Accepted 8 September 2014

SUMMARY

We report a case of a 57-year-old woman with type 1 diabetes who had received a simultaneous pancreas–kidney (SPK) transplant maintained on tacrolimus, mycophenolic acid (MPA) and prednisolone. Her renal allograft failed 6 years post-transplant but she continued to have a normal functioning pancreatic allograft. Over the course of 5 years, she developed progressive bone marrow failure with repeat bone marrow aspirates demonstrating an evolution from erythroid hypoplasia to hypocellular marrow and eventual aplastic anaemia despite discontinuation of MPA and reduction of tacrolimus. She was transfusion-dependent and had frequent admissions for sepsis. Despite treatment with antithymocyte globulin and cyclosporine for aplastic anaemia, she developed fatal invasive pulmonary aspergillosis within 3 weeks of treatment. Even though the cause of aplastic anaemia is likely multifactorial, this case highlights the difficulty in balancing the need for versus the risk of ongoing immunosuppression in a SPK transplant recipient who continues to have normal pancreatic graft function.

BACKGROUND

This case highlights three important issues in the management of a complicated simultaneous pancreas–kidney (SPK) transplant recipient:

1. Aplastic anaemia is a diagnosis of exclusion in a transplant recipient maintained on chronic immunosuppression.
2. Progressive bone marrow failure can occur even if the intensity of chronic immunosuppression is reduced.
3. There is a fine balance between the need for ongoing immunosuppression to avoid rejection and the need to reduce or stop immunosuppression to prevent complications but at the potential expense of graft failure from rejection.

CASE PRESENTATION

We report the case of a 57-year-old woman with type 1 diabetes and end-stage kidney disease who received an uncomplicated SPK transplant in January 2005. She had received induction with an interleukin-2-receptor antibody and was maintained on tacrolimus, mycophenolic acid (MPA) and prednisolone. Over the ensuing 5 years, there was gradual deterioration in her renal allograft function attributed to biopsy-proven chronic allograft nephropathy with creatinine levels increasing from around 100 µmol/L 1 year post-transplant to

540 µmol/L 6 years post-transplant, associated with the development of progressive proteinuria. She restarted haemodialysis in the same year but remained on low-dose tacrolimus (aiming for trough level of 5 µg/L), mycophenolate mofetil 500 mg twice daily and prednisolone 7.5 mg daily because she continued to have normal pancreatic function. She developed erythropoietin-resistant anaemia 4 years post-transplant requiring 4–6 weekly blood transfusions despite reducing the amount of overall immunosuppression. A bone marrow aspirate and trephine (BMAT) showed a normocellular marrow with isolated erythroid hypoplasia. Her white cell and platelet counts were within normal range during this time. Over the following 2 years, she developed intermittent neutropenia and lymphopenia which progressed to pancytopenia with a repeat BMAT showing a hypocellular marrow. From her seventh year post-transplant onwards her neutrophil and platelet counts remained persistently below 0.9 and 50 G/L, respectively despite discontinuation of antimetabolites. Complicating management decisions, the patient was reluctant to discontinue immunosuppression completely and in fact had often restarted her antimetabolite due to fear of developing rejection in her functioning pancreas. During her seventh year post-transplant, she had six hospitalisations for bacterial, fungal and viral infections ranging from Hickman catheter sepsis to viral and fungal pneumonia. She developed severe cytomegalovirus (CMV) and *Pneumocystis jirovecii* pneumonia (PJP) pneumonia requiring 3 weeks of sulfamethoxazole-trimethoprim and therapeutic dose of ganciclovir/valganciclovir. Five weeks post-discharge, she represented with multiple splenic infarcts and ischaemic toes requiring bilateral fore-foot amputations, presumably related to septic emboli. A source for the thrombus was not found. Her neutropaenia became unresponsive to granulocyte colony stimulating factor (G-CSF) and she remained blood transfusion-dependent. Another BMAT was performed 8 years post-transplant, which showed aplastic anaemia. Despite persistent low-grade CMV viraemia and frequent admissions for sepsis, a decision was made to treat her aplastic anaemia with horse antithymocyte globulin (ATGAM, 15 mg/kg for 5 days) and tacrolimus was replaced with cyclosporin. Three weeks following completion of ATGAM, she developed invasive pulmonary aspergillosis and died soon after despite appropriate antifungal therapy (figure 1).

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To cite: Vieceili A, Hessamodini H, Augustson B, et al. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2014-205076

2009	2010	2011	2012	2013	DEATH
<ul style="list-style-type: none"> ▪ Bone marrow – erythroid hypoplasia ▪ Red cell antibody negative ▪ Low-grade CMV viraemia 	<ul style="list-style-type: none"> ▪ Low-grade CMV viraemia 	<ul style="list-style-type: none"> ▪ Bone marrow – hypocellular marrow ▪ Low-grade CMV viraemia 	<ul style="list-style-type: none"> ▪ CMV viraemia ▪ TOE negative 	<ul style="list-style-type: none"> ▪ Bone marrow – aplastic anaemia ▪ Low-grade CMV viraemia 	
INVESTIGATIONS					
<ul style="list-style-type: none"> ▪ Salmonella enteritis ▪ Actinomyces sepsis ▪ Severe anaemia ▪ Multiple UTIs 	<ul style="list-style-type: none"> ▪ Infected toe ulcers ▪ Pancytopenia (severe anaemia) ▪ Multiple UTIs 	<ul style="list-style-type: none"> ▪ Infected wound sinus in foot (<i>Staphylococcus</i>) ▪ Intermittent pancytopenia ▪ Failed renal allograft 	<ul style="list-style-type: none"> ▪ Pancytopenia ▪ CMV pneumonitis ▪ PJP pneumonia ▪ Multiple febrile episodes ▪ Multiple emboli 	<ul style="list-style-type: none"> ▪ Disseminated aspergillosis ▪ Achromobacter sepsis ▪ Severe pancytopenia 	
INFECTIONS & HOSPITALISATIONS					
<ul style="list-style-type: none"> ▪ Antibiotics ▪ Blood transfusion/EPO ▪ Reduced tacrolimus ▪ Reduced MMF 	<ul style="list-style-type: none"> ▪ Antibiotics ▪ Blood transfusion/EPO ▪ Reduced tacrolimus ▪ MMF ceased, azathioprine started 	<ul style="list-style-type: none"> ▪ Antibiotics ▪ Blood transfusion/EPO/G-CSF ▪ MMF ceased, azathioprine started 	<ul style="list-style-type: none"> ▪ Antibiotics ▪ Blood transfusion/EPO/G-CSF/platelet transfusion ▪ Forefoot amputations ▪ Azathioprine ceased 	<ul style="list-style-type: none"> ▪ ATGAM/cyclosporin ▪ Antibiotics ▪ Blood transfusion/EPO/G-CSF/platelet transfusion 	
TREATMENT					

Figure 1 Timeline of investigations, infections, hospitalisations and treatment. ATGAM, horse antithymocyte globulin; CMV, cytomegalovirus; EPO, erythropoietin; G-CSF, granulocyte colony stimulating factor; MMF, mycophenolate mofetil; PJP, *Pneumocystis jiroveci* pneumonia; TOE, transesophageal echocardiogram; UTIs, urinary tract infections.

INVESTIGATIONS

Investigations of pancytopenia:

- Haematological
 - Bone marrow aspirate/trephine (figure 2).
 - ▶ 2009—normocellular bone marrow with significant erythroid hypoplasia. B and T cells have normal immunophenotype.
 - ▶ 2010—hypocellular bone marrow with reduced erythropoiesis. The granulocytes and erythroid series showed megaloblastoid changes. B and T cells have normal immunophenotypes.
 - ▶ 2013—bone marrow aplasia (aplastic anaemia). There was lymphopenia affecting the CD8+ T cells, natural killer (NK) cells and B cells.
 - ▶ Absence of haemophagocytosis on BMAT
- Viral
 - ▶ Parvovirus
 - B19 IgG-positive (enzyme immunoassay (EIA)).
 - B19 IgM-negative (EIA).
 - B19 DNA PCR not detected.
 - ▶ CMV—peak viral load 1.27×10^5 copies/mL, no CMV detected in the bone marrow.
 - ▶ Epstein-Barr virus (EBV) DNA PCR not detected.
 - ▶ Hepatitis B surface antigen negative.
 - ▶ Hepatitis C antibody not detected
 - ▶ HIV antigen/antibody not detected.
- Immunological
 - ▶ Graft versus host disease—no clinical features or histological evidence in colon biopsies.
 - ▶ Pure red cell aplasia—no red blood cell antibodies present.

DIFFERENTIAL DIAGNOSIS

- ▶ Viral infection—CMV, parvovirus, EBV, hepatitis and HIV.
- ▶ Haemophagocytic lymphohistiocytosis (HPLH).
- ▶ Graft versus host disease (GVHD).
- ▶ Post-transplant lymphoproliferative disorder (PTLD).

DISCUSSION

Aplastic anaemia is a rare complication of solid organ transplant recipients, which should be considered as a differential diagnosis of progressive pancytopenia. Unlike the general population whereby up to 50% of cases of aplastic anaemia are idiopathic; all reported cases in solid organ transplant recipients are acquired aplastic anaemia. The reported incidence of aplastic anaemia in liver transplant recipients is 0.7 per million recipients¹ but the incidence in other solid organ transplant recipients including SPK recipients remains unknown. Causes of aplastic anaemia in solid organ transplant recipients other than viral infections and immunosuppression include GVHD and HPLH, which were both unlikely in our patients. Most common clinical presentations of acute GVHD include a maculopapular rash (81%) followed by gastrointestinal (54%) and liver involvement (50%).² In chronic GVHD, multiple organs can be involved including skin, mucous membranes, nails, eyes, muscles, joints, liver, gastrointestinal tract, lungs, kidneys, heart and bone marrow.³ Systemic or bone marrow chimeric studies were not performed to exclude GVHD as our patient did not fulfil the diagnostic clinical criteria for GVHD,⁴ which made the presence of GVHD very unlikely. HPLH is an immune dysregulatory disorder that typically presents with a febrile illness and multiple organ involvement.⁵ Diagnostic criteria require the presence of

Figure 2 Bone marrow aspirates performed between 2009 and 2013.

either molecular identification of a HPLH-associated gene mutation or five clinical features including fever, hyperferritinemia, hypertriglyceridaemia and/or hyperfibrinogenemia, splenomegaly, cytopenia of at least two cell lineages, haemophagocytosis present in BMAT or other lymphoid tissues, low or absent NK

cell activity or elevated soluble CD 25. Our patient did not fulfil these criteria.

This patient is likely to have acquired aplastic anaemia, attributed primarily to chronic immunosuppression, but repeated infections including persistent low-grade CMV viraemia are likely to be contributing. Although there have been multiple reports of immunosuppression-induced pancytopenia in solid organ transplant recipients, aplastic anaemia has never been reported in a SPK patient. Even though we cannot be certain that chronic immunosuppression is the predominant cause of this patient's acquired aplastic anaemia, the systematic exclusion of other causes and the slowly evolving nature of progressive bone marrow failure do suggest the likelihood of a secondary cause of aplastic anaemia. Although antimetabolites have a greater suppressive effect on bone marrow function compared to calcineurin inhibitors, it is likely that the intensity of overall immunosuppression may be more important than any single agent alone. It is possible that complete cessation of all immunosuppressive medications at the expense of the pancreatic graft may have prevented the progression to aplastic anaemia but this management option was refused by the patient. In addition, the efficacy of treating acquired aplastic anaemia with ATG in solid organ recipients is unknown but this was deemed to be a final attempt at keeping the patient alive. Acquired aplastic anaemia is primarily attributed to immune-mediated destruction of the bone marrow. When bone marrow transplantation is relatively contraindicated as a result of advanced age or the presence of significant comorbidities, immunosuppressive therapy with horse ATG combined with cyclosporine is the next preferred treatment option with nearly 70% of patients achieving transfusion-independence by 6 months post-treatment and 96% survival at 3 years following treatment.^{6,7} Other treatment options in the general population include cyclophosphamide combined with cyclosporine,⁸ supportive therapy, alemtuzumab, an anti-CD52 monoclonal antibody⁷ and most recently eltrombopag, a thrombopoietin mimetic which is currently still under investigation in multiple trials.⁶

This case highlights the difficulty in achieving a balance between maintaining adequate immunosuppression and the consideration for withdrawal of immunosuppression in a patient with a functioning organ transplant who has developed progressive bone marrow failure and eventual aplastic anaemia. Acquired aplastic anaemia, likely related to chronic immunosuppression in this case, is largely a diagnosis of exclusion and in the absence of a well-established treatment regimen for acquired aplastic anaemia in solid organ transplant recipients, treatment options comprise of supportive

Learning points

- ▶ Acquired aplastic anaemia is a rare but potentially fatal complication of solid organ transplant recipients maintained on chronic immunosuppression.
- ▶ Acquired aplastic anaemia is a diagnosis of exclusion.
- ▶ Aplastic anaemia can slowly evolve from erythroid hypoplasia over time despite reducing the intensity of immunosuppression.
- ▶ Sacrificing a functioning organ transplant by early discontinuation of all immunosuppression may be the only real prospect of keeping a patient alive.
- ▶ There is no established treatment for acquired aplastic anaemia in solid organ transplants other than supportive care and avoidance of bone marrow toxic agents if possible.

care and avoiding bone marrow toxic agents. Owing to the uncertainty regarding the potential reversibility of the progression from erythroid hypoplasia to aplastic anaemia even with discontinuation of immunosuppression, the decision to sacrifice a functioning graft can be very difficult.

Acknowledgements The authors would like to thank Dr Germaine Wong, Dr Jeremy Chapman and Dr Philip O'Connell from the renal department at Westmead Hospital in NSW for their involvement in this patient's care.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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