Late post-transplant erythrocytosis in a hepatitis C-positive allograft recipient on sirolimus

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ABSTRACT

Hematological complications in renal transplant recipients include anemia, leukopenia, and post-transplant erythrocytosis (PTE). There are numerous causes for these which include immunosuppressive drugs, viral infections, etc. We report here a hepatitis C (HCV)-positive case who developed PTE while receiving rapamycin. As both HCV infection and rapamycin through different mechanisms can produce anemia, this case report highlights the rarity of erythrocytosis.

Key words: Hepatitis C, post-transplant erythrocytosis, rapamycin

Introduction

Hematological complications in renal transplant recipients include anemia, leukopenia, and post-transplant erythrocytosis (PTE). There are numerous causes for these which include immunosuppressive drugs, viral infections, etc. We report here a hepatitis C (HCV)-positive case who developed PTE while receiving rapamycin.

Case Report

A 30-year-old lady underwent cadaveric renal transplantation in June 2000 for end-stage renal disease. She was HCV positive and cytomegalovirus (CMV) IgG positive. She received two doses of 20 mg basiliximab as induction. Maintenance immunosuppression was micro-emulsion form of cyclosporine 175 mg BD and prednisone 35 mg OD. She had a delayed graft function requiring dialysis and biopsy-proven acute cellular rejection, which was appropriately treated. Serum creatinine increased to 2 mg/dl due to cyclosporine toxicity, and as a rescue therapy, she was started on mycophenolate mofetil (MMF) 500 mg BD and cyclosporine dose was reduced. She had good allograft function for the next 2 years, with cyclosporine, prednisone, and MMF. In February 2003, she had another episode of acute cellular rejection and was started on rapamycin 1 mg OD with cyclosporine being tapered and eventually withdrawn. Due to persistently low leukocyte count and hemoglobin, MMF was discontinued. With the above measures, there was gradual rise in hemoglobin, leukocyte counts, and good graft function with stabilization of serum creatinine. Her hemoglobin was 17.5 g/dl, PCV 53.3 fl, MCV 83.2, MCH 26.6, MCHC 31.9. WBC 8300 cells/ mm^3, polymorph 60%, lymphocyte 29%, eosinophil 5.8%, monocyte 3.9%, platelet count 1,54,000 cells/mm^3, blood glucose 91 mg/dl, urea 13 mg dl, creatinine 0.8 mg/dl, SGPT 53 IU, alkaline phophatase 59 IU, urine albumin trace, HCV viral load >17,85,714 IU/ml, serum erythropoietin 20 μu/ml, TSH 0.75, FSH 8.3 mIU/ml, LH 4 mIU/ml, prolactin 22.3 ng/ml. Ultrasound abdomen showed normal transplant kidney of size 11 × 5 cm, left ovarian cyst, and a normal liver. Serum alpha-fetoprotein (AFP) levels were within normal limits. But red blood cell (RBC) count gradually increased beyond the normal level for an adult female to 6.39 × 10^5 cells/mm^3, which is in the range of being defined as PTE. At present, immunosuppressive medications are prednisone 5 mg and 0.5 mg rapamycin. She was started on losartan 25 mg OD. The current hemoglobin level is 12.5 g/dl, WBC 7000 cells/ mm^3 with neutrophil 64%, lymphocyte 31%, monocyte 4%, basophil 0.3%, eosinophil 0.6%, platelet 2, 27,000 cells/mm^3, RBC 4.58 × 10^5 cells/mm^3. Currently the patient is doing well with a good graft function.

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Discussion

PTE is a well-established complication of varied etiology. The incidence ranges from 10% to 15% of patients during the first 2 years.[1] The most common cause for the development of PTE is transplant renal artery stenosis (TRAS). The risk factors include male gender, retention of native kidney and good allograft function in the absence of rejection, and high baseline hemoglobin pre-transplant.[2,3] In our case, erythrocytosis was demonstrated on subsequent follow up with erythropoietin level, which was inappropriately high for the erythrocyte count. There is no literature on the relationship between HCV viral load and PTE. Therefore, we are not able to conclude on the association between active HCV infection and erythrocytosis in this patient. TRAS as a cause for PTE is less likely in this patient due to the absence of graft bruit, significant hypertension, edema, and proteinuria. The other postulated explanation for this late erythrocytosis is rapamycin. The cause for erythrocytosis appears to be related to defective feedback regulation of erythropoietin metabolism.

Rapamycin inhibits erythropoiesis at the level of the erythropoietin receptor[4] and is used as a treatment for PTE. Binding of erythropoietin to its cytoplasmic receptor leads to the activation of a cascade of phosphorylating enzymes, including phosphoinositide 3-kinase (PI 3-kinase) which is responsible for controlling cell survival and cell cycle progression in multiple cell lines, including erythroid precursors.[5] One enzyme downstream form of PI 3-kinase is p70 S6-kinase. Through mTOR inhibition, rapamycin has been shown to block S6 kinase activity and consequently impair cell replication in an erythroid cell line.[6]

Literature review did not reveal any case reports correlating HCV positivity with PTE. There is no clinical evidence of obvious chronic liver disease or hepatocellular carcinoma. However, the exact pathophysiology remains unknown and the association with rapamycin remains unclear. This case report highlights the rare occurrence of late PTE which responded to ARB therapy, in a lady with active HCV virus infection, normal liver, and allograft function on minimum dose of rapamycin as an anti-rejection therapy.

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