Kidney transplantation in a patient with polycythemia vera

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Abstract
Polycythemia vera (PV) is a clonal over proliferation of hematopoietic stem cells, which increases red blood cell (RBC) mass and hematocrit, and is frequently accompanied with leukocytosis, thrombocytosis, or both. Few cases of renal involvement of PV have been reported to date. We present a case of PV based on JAK2 (Janus kinase 2) mutation that did not need any treatment after unrelated kidney transplantation. According to the rarity of kidney transplantation in PV, more clinical evidence is needed to determine the frequency of its improvement after transplantation.

Implication for health policy/practice/research/medical education:
Few cases of renal involvement of polycythemia vera have been reported to date. We present a case of polycythemia vera based on JAK2 (Janus kinase 2) mutation that did not need any treatment after unrelated kidney transplantation. According to the rarity of kidney transplantation in polycythemia vera, more clinical evidence is needed to determine the frequency of its improvement after transplantation.


Introduction
Polycythemia vera (PV) is a clonal over proliferation of hematopoietic stem cells, which increases red blood cell (RBC) mass and hematocrit, and is frequently accompanied with leukocytosis, thrombocytosis, or both. In PV, colony- and burst-forming units of bone marrow proliferation are formed without erythropoietin. JAK2 (Janus kinase 2) mutation is associated with PV in more than 90% of cases, and it is the most important etiologic factor (1). Phlebotomy is the usual management of PV patients. Hydroxyurea in addition to phlebotomy is prescribed for those with a history of thrombosis or who are more than 60-year old. Renal diseases in PV are rare, and few cases of renal failure with glomerulonephritis have been reported (2,3).

Case Presentation
A 66-year-old Iranian man was referred to the nephrologist for renal replacement. Ultrasonography performed on December 29, 2012, revealed increased renal parenchymal echogenicity and decreased maximal dimension of both kidneys (right, 73 cm; left, 81 cm), with a 30-mm simple cyst in the right and 25-mm simple cyst in the left. Serum analysis revealed a leukocyte count of 18700 × 10^9/L, hemoglobin content of 16.8 g/dL, and platelet count of 967 × 10^9/L. Serum urea nitrogen and creatinine (Cr) levels were 85 and 4.5 mg/dL, respectively. Urine analysis revealed maximum amount of trace proteins and normal white blood cell (WBC) and RBC counts. Serum uric acid was 12.5 mg/dL, and thyroid test revealed high thyroid stimulating hormone (TSH) levels of 19 mIU/L. Serum Na levels were normal, but serum K+ levels were high (5.5 mEq/L). Liver function, serum lipid profile, and glucose levels were in the normal range.

Based on para-clinical data and glomerular filtration rate (GFR) measurement by the modification of diet in renal disease (MDRD) formula, the patient was diagnosed with end-stage renal disease (ESRD). Eight years ago,
Kidney transplantation in polycythemia vera

Polycythemia was diagnosed during routine investigation before coronary artery bypass grafting (CABG). At that time, plasma creatinine was 1.6 mg/dL based on his son’s recall. The patient did not have any nephrology follow-up during that time. PV had been treated by phlebotomy and hydroxyurea. He reported several episodes of gout attack over the past years. Patient’s laboratory data was shown in Table 1.

On examination, the patient was plethoric and his blood pressure was 160/80 mm Hg. The spleen was enlarged, and he had no symptoms and signs of uremia. He was referred to the hematologist for better control of polycythemia. His erythropoietin (EPO) level was 2.9 nm/mL (Reference value: 3.2–31.9), and JAK2 mutation with polymerase chain reaction (PCR) was positive. Polycythemia was controlled with frequent phlebotomy and hydroxyurea. Additional tests revealed intact parathyroid hormone (iPTH) = 182 pg/mL, with electroluminescence study, and 24-hour urine protein test revealed glomerular proteinuria of 1.96 g/d. Secondary workup for proteinuria such as ANA, pANCA, cANCA, dsDNA, C3, C4, CH50, wright, 2ME, coomb’s wright, VDRL, and PPD showed negative results and excluded secondary cause of proteinuria. According to the patient’s refusal for other types of renal replacement therapy, we decided to perform preemptive transplantation. Finally, he received a kidney from an unrelated living donor on May 30, 2014. He had a good graft function after the transplantation, and plasma Cr was just under 2.0 mg/dL. Laboratory data and urinary output during the first 24 hours of transplantation are shown in (Table 2).

Graft ultrasonography and Doppler ultrasonography were normal. Cyclosporine and mycophenolate mofetil was prescribed. Laboratory data at discharge were as follows: HB = 12.7 g/dL, WBC = 14200/µL, PLT = 307 000/µL, Cr =1.1 mg/dL, Na = 137 mEq/L and K = 4.5 mEq/l. During the next 6 months of follow-up, serum creatinine remained in the normal range and phlebotomy was required only once to control polycythemia. Till August 1, 2016 he did not need for special treatment (phlebotomy, hydroxyurea), when his hemoglobin was 16.2 g/dL and phlebotomy was restarted.

Discussion

There are only few studies on PV associated with renal disease in the literature. Jermanovich first reported about a patient who had PV and polycystic kidney on hemodialysis (4). Glomerulonephritis because of PV was reported by Plomely et al in 1938 (5). Previous reports have shown that patients with PV were anemic with ESRD, and EPO was effective in correcting anemia as other ESRD patients (6).

Shih et al investigated the in vitro and in vivo responses of erythroid progenitor cells to EPO effect in sera of patients with ESRD because of PV and reported that autonomous progenitor cell growth persisted during the spent phase of PV and was characteristic of erythroid progenitor after development of end-stage renal failure (7). We presented the patient who needed frequent phlebotomy and hydroxyurea to control polycythemia during the spent phase of ESRD.

Only 23 patients of PV associated with renal disease have been reported in the literature. IgA nephropathy and focal segmental glomerulosclerosis were the most predominant histopathological features (3,5,8-16). Other histopathological features included membranoproliferative glomerulonephritis and rapidly progressive glomerulonephritis (3,17).

In contrast to most reports, our patient had sub-nephrotic proteinuria with 1960 g/d (2,3,5,8-15,16). Microthrombi, glomerular capillary occlusion, and reduction in GFR because of PV associated with increased blood volume and viscosity can be considered to be associated with renal disease. In addition, factors associated with PV such as hypertension and hyperuricemia can affect renal microcirculation (16,18). Thrombocytosis and abnormal activation of megakaryocytes are other pathological factors for glomerular sclerosis (3,19).

Our patient was hypertensive, which is consistent with previous reports (2,3,5,8-10,14,16). He had a good graft function after transplantation, and serum creatinine

Table 1. Laboratory tests before kidney transplantation

<table>
<thead>
<tr>
<th>Date</th>
<th>HB (g/dL)</th>
<th>PLT×10^9/L</th>
<th>WBC×10^9/L</th>
<th>Cr (mg/dL)</th>
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<tr>
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<td>967000</td>
<td>18700</td>
<td>5.5</td>
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<tr>
<td>2012.10.17</td>
<td>16.2</td>
<td>437000</td>
<td>15700</td>
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<td>2012.11.28</td>
<td>16.8</td>
<td>480000</td>
<td>18500</td>
<td>3.9</td>
</tr>
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</table>

Table 2. Clinical status and laboratory tests after kidney transplantation

<table>
<thead>
<tr>
<th>Date</th>
<th>BP (mm Hg)</th>
<th>Urine Output (cc/24 h)</th>
<th>Intake (cc/24 h)</th>
<th>Weight (kg)</th>
<th>WBC (×10^9/L)</th>
<th>HB (g/dL)</th>
<th>PLT (×10^9/L)</th>
<th>FBS (mg/dL)</th>
<th>BUN (mg/dL)</th>
<th>Cr (mg/dL)</th>
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<td>2013.1.6</td>
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<td>13150</td>
<td>13800</td>
<td>68</td>
<td>12300</td>
<td>12.2</td>
<td>558000</td>
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<tr>
<td>2013.6.2</td>
<td>130/80</td>
<td>7400</td>
<td>7000</td>
<td>70.5</td>
<td>10800</td>
<td>12.5</td>
<td>507000</td>
<td>90</td>
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<tr>
<td>2013.6.3</td>
<td>150/80</td>
<td>6600</td>
<td>6500</td>
<td>68.5</td>
<td>8100</td>
<td>10.9</td>
<td>394000</td>
<td>78</td>
<td>20</td>
<td>1.1</td>
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<tr>
<td>2013.6.4</td>
<td>130/80</td>
<td>4500</td>
<td>4650</td>
<td>68.5</td>
<td>8100</td>
<td>11.1</td>
<td>358000</td>
<td>119</td>
<td>21</td>
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<tr>
<td>2013.6.5</td>
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<td>3350</td>
<td>2050</td>
<td>68.3</td>
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<td>2016.2.6</td>
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<td>69</td>
<td>10000</td>
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<td>80</td>
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<td>72</td>
<td>11600</td>
<td>16</td>
<td>696000</td>
<td>74</td>
<td>28</td>
<td>1.3</td>
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</tbody>
</table>

*He had not regular follow up after 2015.3.4.
was below 2.0 mg/dL. 24 hours after transplantation. Graft ultrasonography and Doppler ultrasonography were normal, and he did not develop any thrombotic complications after the transplantation. Despite the necessity to treat polycythemia in the spent phase of ESRD, his hemoglobin was maintained at an acceptable level without the need for special treatment during 26 months after kidney transplantation.

Anemia after kidney transplantation is a known term in nephrology, its etiology may be a common cause seen in general population such as iron deficiency anemia or gastrointestinal bleeding, or may be a specific cause related to transplantation such as immunosuppressive drugs, acute rejection, infection, malignancies and chronic inflammation. Azathioprine, mycophenolate mofetil and specially sirolimus are drugs can suppress bone marrow (20,21). Decreased allograft function is the most important factor for post-transplantation anemia (22).

Post-transplant anemia due to immunosuppressive drugs, iron deficiency and chronic inflammation may be one explanation of good control of polycythemia for several months in the patient.

Conclusion
We report a rare case of PV was underwent renal transplantation with good control of PV during 26 months after transplantation without specific treatment. To the best of our knowledge, the present report is the first case of PV with no necessity for treatment for polycythemia after kidney transplantation. More clinical evidence is needed to determine the frequency of polycythemia improvement after transplantation in PV patients.

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Authors’ contribution
All authors contributed to write the manuscript. All authors read, revised, and approved the final manuscript.

Conflicts of interest
The authors declare no conflict of interest.

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