Case Report

Isometric Tubular Vacuolization in Renal Transplant Recipient: The First Case Report in Thailand

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Cyclosporine can cause acute and chronic nephrotoxicity. Renal biopsy is a reliable tool for the diagnosis of cyclosporine nephrotoxicity. The authors report a 56-year-old Thai female with a history of end-stage renal disease who underwent cadaveric renal transplantation. A transplanted kidney biopsy was performed on day 9 post-transplant to identify the cause of delayed graft function. Light and electron microscopic findings revealed widespread (> 50% involvement) numerous tubules filled with uniformly-sized vacuoles in cytoplasm (isometric vacuolization). Serum cyclosporine trough level was 534 ng/mL. Neither acute rejection nor acute tubular necrosis was seen. Diagnosis of acute cyclosporine nephrotoxicity was made. Isometric vacuolization in more than 50% involvement of the tubules is rare (3%) in biopsy specimens. The tubular isometric vacuolization might not have the strong impact to the long term graft outcome. This is the first case report of isometric tubular vacuolization due to cyclosporine toxicity in renal transplant recipient in Thailand.

Keywords: *Cyclosporine nephrotoxicity, Isometric vacuolization*

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Cyclosporine can cause acute and chronic nephrotoxicity. The serum cyclosporine level does not correlate well with the extent of renal damage. Renal biopsy is a reliable tool for the diagnosis of cyclosporine nephrotoxicity. It can produce lesions which may be focal in nature and overlooked. Acute toxicity is characterized histologically by necrosis and early hyalinosis of individual smooth muscle cells in the afferent arterioles (arteriolopathy) or isometric vacuolization of the proximal straight tubules or tubular microcalcification or thrombotic microangiopathy.

Case

The authors report a 56-year-old Thai female with a history of end-stage renal disease secondary to chronic glomerulonephritis who had been on chronic hemodialysis for 8 years underwent cadaveric renal transplantation from a 21-year-old donor. The cold ischemic time was 31 hours.

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The warm ischemic time was 35 minutes. HLA A-B-DR mismatch was 1-2-0. She received the induction medication with basiliximab. The patient developed anuria and required hemodialysis in the first week postoperatively. Cyclosporine was started on day 6 postoperatively at the dose of 225 mg twice daily. She did not receive any medication that might interfere with cyclosporine metabolism such as diltiazem, verapamil, or azole group. The laboratory investigation revealed complete blood count: hemoglobin 12.3 g/dL, white blood cell 8,700 cells/mm^3, platelet 129,000 cells/mm^3; fasting blood sugar 136 mg/dL, serum sodium 135, potassium 4.3, chloride 98, bicarbonate 21 mEq/L, blood urea nitrogen 89 mg/dL, creatinine 8.1 mg/dL, total protein 6.4 g/dL, albumin 3.7 g/dL, total bilirubin 0.6 mg/dL, SGOT 31 U/L, SGPT 4 U/L, alkaline phosphatase 88 U/L. Ultrasonography of the transplanted kidney was done and the result was unremarkable. A transplanted kidney biopsy was performed on day 9 post transplantation to identify the cause of delayed graft function. Light and electron microscopic findings (Fig. 1 and 2) were as the following: glomeruli showed normal mesangial cells and matrix. No endocapillary proliferation, splitting of capillary basement membrane

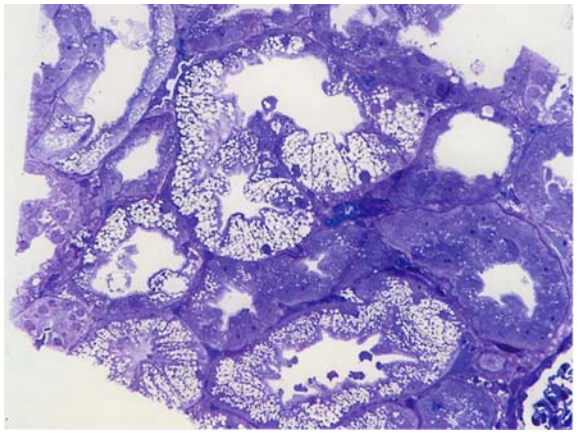

Fig. 1 Light microscopic finding revealed widespread (> 50% involvement) numerous tubules filled with uniformly-sized vacuoles in cytoplasm (isometric vacuolization)

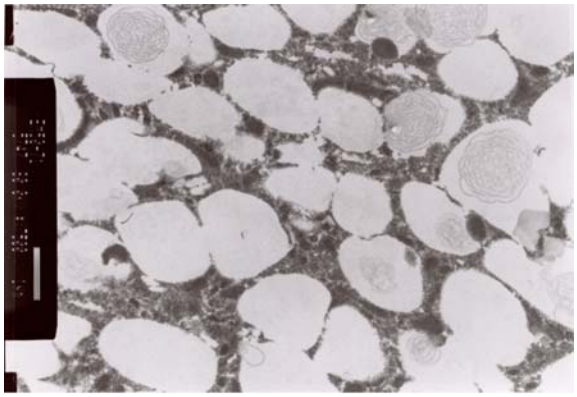

Fig. 2 Electron microscopic finding revealed numerous tubules filled with uniformly-sized vacuoles in cytoplasm (isometric vacuolization)

or spikes was appreciated. There were no glomeruli with segmental sclerosis. There were no crescents or fibrin in Bowman's space. There was no interstitial fibrosis. Interstitial lymphocyte was rarely seen. There were numerous and convoluted tubules with isometric vacuoles in their cytoplasm. It revealed widespread (> 50% involvement) numerous tubules filled with uniformly-sized vacuoles in cytoplasm (isometric vacuolization). Neither acute rejection nor acute tubular necrosis was seen. Arterioles and interlobular arteries were not remarkable. No endothelialitis was seen. At that time, serum cyclosporine trough level was 534 ng/mL.

Diagnosis of acute cyclosporine nephrotoxicity was made. Cyclosporine dosage was then decreased to 150 mg twice daily. Serum creatinine gradually came down to 1.4 mg/dL on the day of discharge. Forty days post transplantation at the clinic, her serum creatinine was 0.9 mg/dL. The serum creatinine has remained at 0.7 mg/dL four years post transplantation.

Discussion

The present patient received cadaveric kidney transplantation of which the cold ischemic time was so prolonged at 31 hours. There was no correlation among serum cyclosporine level, clinical toxicity and kidney pathology in patients with cyclosporine nephrotoxicity. The kidney biopsy was found to be the most reliable method for diagnosing cyclosporine nephrotoxicity[1]. Therefore, the allograft kidney biopsy was performed in the presented patient in order to confirm the diagnosis of cyclosporine nephrotoxicity and to exclude other possible causes such as acute rejection and acute tubular necrosis.

Histopathological features for diagnosing cyclosporine nephrotoxicity varied widely which included arteriolar hyalinosis, isometric vacuolization of tubules, severe tubular microcalcification, global glomerulosclerosis and striped interstitial fibrosis[2-7]. There was no single pathognomonic feature for cyclosporine nephrotoxicity[1,2]. Previous studies demonstrated that arteriolar hyalinosis and striped interstitial fibrosis were indicators of chronic cyclosporine nephrotoxicity, whereas isometric vacuolization of tubules was common histological feature for acute cyclosporine nephrotoxicity and usually found within 1 month after kidney transplantation[1,2,8]. The isometric vacuolization in more than 50% involvement of the tubules is rare (3%) in biopsy specimens done in 91 patients received calcineurin inhibitor. It may occur in other clinical settings, such as renal ischemia or tubular epithelial injury caused by intravenous administration of hyperosmotic fluid including mannitol, radiocontrast agents and in case reports of osmotic nephrosis associated with acute kidney injury after intravenous immunoglobulin (IVIG) treatment. There was a significant association between vacuolization score and blood calcineurin inhibitor level[9,10].

Calcineurin inhibitor toxicity (CNIT) score was proposed to use based on six parameters graded semiquantitatively including tubular isometric vacuoles, interstitial fibrosis, arteriolar medial hyalinosis, glomerulosclerosis, tubular atrophy and mesangial matrix increase[2]. It was shown that the CNIT score

was highly correlated with future graft function. But arteriolar medial hyalinosis seems to be the most important factor contributing to the clinical impact of CNIT score[2].

In the presented patient, the kidney pathology revealed widespread (> 50% involvement) isometric vacuolization of the tubular epithelial cells. Neither acute rejection nor acute tubular necrosis was seen. She received the induction therapy with basiliximab and had never been exposed to mannitol or IVIG. Then the diagnosis was acute cyclosporine nephrotoxicity with low CNIT score based on pathological finding concurrent with serum cyclosporine trough level of 534 ng/mL. Good response was obtained after the cyclosporine dose was decreased. The presented patient has been followed-up for four years post transplantation and serum creatinine currently is 0.7 mg/dL.

Conclusion

This is the first case report of isometric tubular vacuolization due to cyclosporine toxicity in renal transplant recipient in Thailand.

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Potential conflicts of interest

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การตรวจพบ vacuoles ขนาดเท่า ๆ กันในซัยโตพลาสมของเซลล์เยื่อบุท่อไตในผู้ป่วยที่ได้รับการผ่าตัดปลูกถ่ายไต: รายงานผู้ป่วยรายแรกในประเทศไทย

ประเจษฎ์ เรืองกาญจนเศรษฐ์, วีรศักดิ์ แพร่ชินวงศ์, ไพสิฐ เผือกสกนธ์, บัญชา สถิระพจน์, อุปถัมภ์ ศุภสินธุ์, ถนอม สุภาพร

ซัยโคลสปอรินสามารถทำให้มีผลภาวะเป็นพิษต่อไตได้ ทั้งแบบเฉียบพลันและเรื้อรัง การเจาะตรวจชิ้นเนื้อไตเป็นวิธีการหนึ่งที่น่าเชื่อถือในการให้การวินิจฉัยภาวะเป็นพิษต่อไตจากผลของยาซัยโคลสปอริน เราขอเสนอรายงานผู้ป่วยหญิงไทยอายุ 56 ปี ที่มีประวัติโรคไตวายเรื้อรังระยะสุดท้ายที่ได้รับการผ่าตัดปลูกถ่ายไตจากผู้บริจาคที่เสียชีวิตและได้รับการเจาะตรวจชิ้นเนื้อไตในวันที่ 9 หลังการผ่าตัดปลูกถ่าย เพื่อหาสาเหตุของภาวะไตทำงานช้า การตรวจด้วยกล้องจุลทรรศน์และกล้องอิเลคตรอนไมโครสโคป พบว่ามีท่อไตมากกว่าร้อยละ 50 ของท่อไตทั้งหมด ที่ตรวจพบว่ามี vacuoles ขนาดเท่าๆ กันอยู่ในซัยโตพลาสม (isometric vacuolization) พร้อมกับการตรวจพบระดับของยาซัยโคลสปอรินในเลือดที่จุดต่ำสุด (trough level) ได้เท่ากับ 534 นาโนกรัมต่อมิลลิลิตร การเจาะตรวจชิ้นเนื้อไตไม่พบลักษณะของการสลัดไต หรือการตายแบบเฉียบพลันของเซลล์เยื่อบุท่อไตแต่อย่างใด และได้ให้การวินิจฉัยว่ามีภาวะเป็นพิษต่อไตแบบเฉียบพลันจากผลของยาซัยโคลสปอริน ซึ่งการตรวจพบมี vacuoles ขนาดเท่าๆ กันอยู่ในซัยโตพลาสมในท่อไตเกินกว่าร้อยละ 50 พบได้น้อยมาก (ร้อยละ 3) ในชิ้นเนื้อไตที่ได้รับการเจาะตรวจ และไม่ได้ส่งผลต่อหน้าที่การทำงานของไตในระยะยาว รายงานผู้ป่วยฉบับนี้เป็นฉบับแรกที่ได้รายงานการตรวจพบภาวะเป็นพิษต่อไตจากผลของยาซัยโคลสปอรินที่มีลักษณะ isometric vacuolization ที่ท่อไตในผู้ป่วยที่ได้รับการผ่าตัดปลูกถ่ายไตในประเทศไทย