CASE REPORT

Gross Hematuria Rapidly Deteriorated Renal Function in a Patient with Polycystic Kidney Disease and Klippel-Trenaunay-Weber Syndrome

Shogo Kurebayashi*, Kunihiko Hashimoto, Fumie Maki, Youichi Shiotsuka*, Yukito Kokado* and Masafumi Koga

Abstract

A case of polycystic kidney disease (PKD) associated with Klippel-Trenaunay-Weber syndrome is described. A 58-year-old man with chronic renal failure experienced urinary retention following gross hematuria. Intermittent drainage was necessary for significant urination for five days. Thereafter his urinary retention was relieved, but renal failure progressively developed and hemodialysis was started. Right hydronephrosis and hydroureter disappeared one month later. In spite of relief of obstruction, of which the cause was likely blood clots, renal function was not restored. Obstructive nephropathy was most likely explicable for notable deterioration in renal function. Our case might have susceptibilities to PKD development in terms of angiogenesis.

Key words: massive hematuria, renal hemorrhage, obstructive nephropathy, hemodialysis, angiogenesis

Introduction

PKD is a renal disease characterized by the growth of numerous cysts in the kidneys. Cysts slowly replace much of the mass of the kidney, reducing renal function and leading to renal failure. PKD is one of the frequent causes of end-stage renal disease (ESRD) (1). Indeed, approximately 50% of all PKD patients result in ESRD and need dialysis or kidney transplantation (2). Gross hematuria is highly frequent in PKD. Kaehny and Gabow (3) and Gabow et al (4) have reported that 37 and 42%, respectively, of autosomal dominant PKD (ADPKD) patients experience gross hematuria at some time. Not only is gross hematuria the event which triggers the diagnosis of PKD, but it also occurs during the course of the disease. Previous studies showed that episodes of gross hematuria represent one of the high risk factors affecting the progression of ESRD in ADPKD as well as a gene type of ADPKD1, gender, younger age at diagnosis and developed hypertension and number of pregnancies (5, 6). It is suggested that episodes of gross hematuria have an unfavorable impact on long-term renal function.

Klippel-Trenaunay-Weber syndrome (KTWS), first described in 1900 (7), is one of important vascular disorders, but it is quite rare in daily clinical practice. Patients with KTWS have anomalies with the triad of capillary nevus, varicosities and hemihypertrophy of the extremities. KTWS has been described by several authors (8–10) as a congenital disorder of angiogenesis.

Here, we describe a case of renal failure with acute exacerbation associated with PKD triggered by the gross hematuria. Gross hematuria in our patient contributed to urinary tract obstructions, followed by notable deterioration on short-standing renal function. To our knowledge, this is the first full case report of PKD associated with KTWS. Therefore, we address etiological discussions on the link between PKD and KTWS in terms of angiogenesis.

Case Report

The patient was a 58-year-old man with a past medical history of KTWS and an abnormality in urinary analysis. His medical history included neither hypertension nor diabetes mellitus. No history of KTWS was noted in his family. He had previously received several operations of reduction of venous varicosities and orthopedic procedure for overgrowth of his right limb. His attending physician had followed his continuous proteinuria and renal insufficiency for these years. He had been in stable clinical condition with a serum creatinine level of around 4 mg/dl for these years. He suddenly had massive hematuria with mild flank pain and subsequent urine retention on No-
November 30, 2001. When a ureter catheter was inserted at the clinic, his urine was drained. Intermittent drainage with a ureter catheter were necessary for urination since the patient complained of the inability to urinate for the subsequent five days. On December 7, although he was again able to urinate naturally, he was referred to our hospital due to an increase in the serum level of creatinine (7.0 mg/dl); he was admitted to our hospital on December 10, 2001. On admission we observed multiple simple hemangiomas in the right flank and leg, complicated venous varicosities in the right leg (Fig. 1) and an operation scar in the femur for osteotomy. His blood pressure was 140/76 mmHg. He had no complaints of urination. Biochemical examination showed that serum creatinine was elevated to 9.6 mg/dl and blood urea nitrogen, sodium, potassium, chloride, calcium, inorganic phosphate and uric acid were 90 mg/dl, 137 mEq/l, 5.2 mEq/l, 104 mEq/l, 8.3 mg/dl, 6.8 mg/dl and 9.5 mg/dl, respectively. Arterial blood gas analysis revealed metabolic acidosis: pH 7.286, PO2 90.7 mmHg, PCO2 29.2 mmHg, HCO3⁻ 13.5 mmol/l, base excess –13.8 mmol/l and sO2

Figure 1. A picture of the present patient with Klippel-Trenaunay-Weber syndrome. Multiple hemangiomas and venous varicosities were shown in the right leg.

Figure 2. Clinical course of this patient with deterioration of renal function triggered by gross hematuria.

Figure 3. Abdominal CT scan showed hydronephrosis and ureter dilatation (arrow) with complicated cysts. (A) CT obtained on December 17, 2001 after admission (left side) and (B) CT on January 25, 2002 (right side).
PKD Case Associated with KTW Syndrome

94.2%. These laboratory data indicated rapid exacerbation in renal failure. Although the volume of urine output returned to the normal range of more than 1,000 ml a day after his admission, serum creatinine reached a peak of 9.9 mg/dl in the second day of his admission (Fig. 2). Thus, hemodialysis (HD) was started to improve his uremic state on Day 2 of admission. Maintenance HD has been performed at a frequency of twice to three times a week (three times initially and then twice a week) afterwards.

An ultrasonograph and a computed tomographic (CT) scan of the abdomen revealed enlarged kidneys and multiple cysts with right side predominance. These features were consistent with the diagnosis of PKD. The CT scan obtained after admission, also showed hydronephrosis in the right kidney and dilated ureter in the right side (Fig. 3A). These findings were diminished in another CT scan obtained one month after admission (Fig. 3B). These alterations in CT scans indicated the previous presence of reversible obstructions, which were presumably due to blood coagulations formed from renal bleeding. Bladderscopy and cytology study showed sign of neither tumor nor stone.

He was discharged on Day 58 following an operation for right inguinal herniation and an examination of brain magnetic resonance angiography (MRA). MRA showed no abnormal findings in cerebral arteries. Serum creatinine level did not return completely and remained around 6.0 mg/dl on discharge.

Discussion

The previous medical practitioner had noted that the present patient continued to have microscopic hematuria and proteinuria and also had renal insufficiency. This case, however, had never been diagnosed with PKD before he was referred to our hospital. Abdominal ultrasonograph on admission revealed multiple cysts with complicated cysts in both kidneys. These findings are compatible with the criteria for PKD (11), even there was no information of PKD inheritance in his family history.

It was the first time for the present patient to exhibit massive hematuria 7 days before his admission. No examination after admission suggested the presence of tumor or stone. The CT scan showed hyperdense cysts among numerous cysts (data not shown), which indicated renal hemorrhage. Massive hematuria in this case must be due to renal hemorrhage. Gross hematuria is one of the potential complications for KTWS. In KTWS patients, renal hemangioma (12, 13), upper urinary tract hemangioma (14) and bladder hemangioma (15) were identified as the cause of the massive hematuria. No finding of hemangioma was detected as far as we examined. Therefore, we speculated that the gross hematuria was probably due to PKD. Angiography or MRA could have supported this speculation certainly. Bello-Reuss et al observed an extensive capillary network in the cyst wall of ADPKD kidney and vascular malformations (16). Their protein analysis demonstrated expression of vascular endothelial growth factor (VEGF) in the cyst cells and VEGF receptor in endothelial cells. VEGF is reported to be one of the growth factors which stimulates angiogenesis (17). These findings indicate that the process of angiogenesis occurs in ADPKD and this process may be necessary for cyst cells to grow. It is well known that several complications are associated with PKD, such as renal hemorrhage, hypertension, liver cyst, herniation and vascular abnormalities including cerebral aneurysm (18). In addition to the growth of cysts, renal bleeding and the formation of aneurysm might result from the angiogenesis process (16).

The present case of PKD was previously diagnosed with KTWS because hypertrophy of tissues and bones, hemangiomas and venous varicosities of the affected right lower limb were present. These manifestations are comparable to those of the first case reported by Klippel and Trenaunay (7). It is generally thought to occur sporadically, although a few studies (19–21) have reported familial occurrence in extensive evaluations of relatives of KTWS patients. In most cases of KTWS, somatic findings of the triad are distributed, suggesting somatic mutation of an as-yet-unknown gene. One candidate site of gene localization could be on chromosome arm 5q or 11p. Whelan et al (22) demonstrated a case of KTW syndrome associated with reciprocal translocation t(5;11)(q13.3;p15.1). Two studies have shown a clue to elucidate a part of the etiology of KTWS. Klessinger and Christ (23) demonstrated that the notochord acts as a barrier to keep endothelial cells from crossing the midline of the embryo. Their results could be of significance to explain the patterning of vascular anomalies, which generally appear in one-half side of the body of KTWS. The present case showed the KTWS triad in the right side. It is noteworthy that enlargement and cysts of the kidney were dominant in the right side. These findings may possibly support the association with PKD in the present case of KTWS. Moreover, Sumoy et al (24) demonstrated that blood vessel formation had defects in zebrafish mutant for notochord formation. These two reports suggest that the genetic alteration responsible for KTWS may be located in endothelial cells altered in the process of vessel formation. Thus, KTWS is described as “a congenital disorder of angiogenesis and vasculogenesis” (8–10), also called “asymmetric vascular syndrome” (25). As described above, angiogenesis is also fundamental to the pathological process in ADPKD (16). Therefore, we suppose that a factor critical to angiogenesis and vasculogenesis in KTWS might contribute to PKD development including the growth of renal cysts and the renal bleeding in the present case.

Disappearance of hydronephrosis and the dilated ureter indicated that the obstruction in the right ureter was reversibly relieved. We found no evidence of stone or tumor. The cause of urinary obstruction must be blood coagulation in the right upper urinary tract. It is possible that abnormal coagulopathy might be in part involved in the formation of blood clots in the urinary tract. In fact, cases with KTWS were reported to complicate coagulopathy sequential to hemorrhage after routine gynecologic procedure (9) and after cesarean delivery (26). Obstructive nephropathy is a term commonly used to describe obstruction of the urinary tract and its consequences (27). Several derangements occur in long-term obstructive nephropathy, including decreased renal blood flow, abnormalities in tu-
bular function and renal increased fibrosis (27, 28). It was reported that an array of growth factors, vasoactive peptides and cytokines are involved in obstructive nephropathy (29). An obstruction persisting longer than two weeks could mainly explain the progressive deterioration of renal failure. The renal insufficiency in the present case prior to incident of massive hematuria is suspected to be susceptible to the notable deterioration of renal function due to obstructive nephropathy.

In summary, we presented a case with PKD and KTWS, in which gross hematuria had discernable impact on the rapid progression of renal failure. We speculate that blood clots consequent to gross hematuria resulted in obstructive nephropathy. It is important to pay close attention to an insidious obstruction of the urine tract in cases of progressive renal dysfunction after gross hematuria even if urine output is not decreased.

References