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Case Report

Intra-abdominal hypertension triggered by portal vein thrombosis postoperatively: an ignored, but potential, cause of acute kidney failure in patients with cirrhosis

Jun Lu[1], Zhong Jia[1]*,Guoqiong Liu[2]

[1]Department of General Surgery, Hangzhou First People's Hospital, Affiliated to Nanjing Medical University, Huansha Road 261, Hangzhou 310006, China
[2]Hangzhou First People's Hospital, Affiliated to Nanjing Medical University, Huansha Road 261, Hangzhou 310006, China

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***Correspondence:**
Dr. Zhong Jia,
E-mail: jiazhong20058@hotmail.com

ABSTRACT

Intra-abdominal hypertension (IAH), even abdominal compartment syndrome, resulting from major stem portal venous thrombosis (MSPVT) postoperatively can lead to acute kidney failure (AKF). However, few physicians consider this clinical presentation, which is rarely reported in the literature. IAH often induces a few obvious clinical presentations, such as oliguria, anuria, and abdominal distension, etc., even in cases with normal liver function. Many doctors consider that AKF is due to hepatorenal syndrome (HRS), while postoperative development of portal vein thrombosis (PVT) may be another important factor inducing AKF, which appears to have been ignored in recent years. In fact, devascularization surgery and/or shunt placement for treatment of portal hypertension are known to easily induce PVT, especially during devascularization procedures because of the rapid accumulation of platelets. In addition, the risk of hypercoagulability increases because of the use of hemostatic agents. Also, PVT may lead to gastro-intestinal congestion and tissue edema, which can contribute to the development of IAH. Abdominal distension became very obvious because collateral circulation could not be restored in time due to MSPVT after ligamentectomy surrounding the liver. Thus, it was difficult to arrive at a diagnosis of PVT at an earlier stage by B-type ultrasound and/or measurement of D-dimer levels. To achieve an early diagnosis, it is very important to actively incorporate the methods mentioned above. However, these methods are not recommended unless the diagnosis of HRS is definitive. The effective treatment is to administer anticoagulants, such as low-molecular-weight heparin, and to discontinue hemostatic agents in time. AKF will not benefit from Terlipressin if HRS was not considered as the major cause of AKF, especially in cases of IAH. It is well known that peritoneal dialysis and/or hemodialysis should be adopted to sustain kidney function postoperatively.

Keywords: Portal hypertension, Portal venous thrombosis, Acute kidney failure, Abdominal hypertension

INTRODUCTION

Intra-abdominal hypertension (IAH), even abdominal compartment syndrome, resulting from major stem portal venous thrombosis (MSPVT) postoperatively can lead to acute kidney failure (AKF).[1] However, few physicians consider this clinical presentation, which is rarely reported in the literature. IAH often induces a few obvious clinical presentations, such as oliguria, anuria, and abdominal distension, etc., even in cases with normal liver function.

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portal vein thrombosis (PVT) may be another important factor inducing AKF, which appears to have been ignored in recent years.

CASE REPORT

A 62-year-old man with cirrhosis due to a 25 year history of hepatitis B virus infection was admitted to our hospital because of cirrhosis, portal hypertension, hypersplenia, and upper gastrointestinal hemorrhage. His most recent laboratory test results showed the following: alpha-fetoprotein, 424.7 μg/L (0~20 μg/L); fibrinogen, 1.31 g/L; prothrombin time (PT), 12.6 s; albumin (ALB), 30.8 g/L; glutamic pyruvic transaminase (GPT), 19 mg/dL; and glutamic oxaloacetic transaminase (GOT), 28 mg/dL. Routine urine and stool parameters were normal. B-type ultrasonography suggested the patient had cirrhosis with widening of the inter-diameter of the portal vein and splenomegaly. Simultaneously, a malignant tumor with diameter of 1.5 cm was found in the right hepatic lobe as shown in Figure 1A.

No jaundice or ascites were apparent and the function of the major internal organs, including the liver and kidneys, were all normal preoperatively. The case was classified as CHILD class A according to the CHILD assessment system. A physical examination revealed the following: blood pressure, 115/57 mmHg; heart rate, 65 beats/min; and mild edema of the limbs, with tenderness of the spleen at a distance of about five fingers below the left ribs. We arrived at a diagnosis of cirrhosis triggered by type b hepatitis infection, portal hypertension, hypersplenia, varicose veins in the esophago-gastric fundus, and primary liver cancer. Liver tissue biopsy, splenectomy, devascularization, and radiofrequency ablation of the liver carcinoma were performed in Dec 2013 as seen in Figure 1B. The surgery was successful with intraoperative blood loss of 250 mL. Postoperative pathological analysis of the resected liver specimen confirmed the diagnosis of middle differential adenocarcinoma in the right liver. An antibiotic Ceftazidime was administered to prevent infection. Hemostasis combined with tranexamic acid, prothrombin complex, and vitamin K1 was administered for possible hemorrhage, while hepatinica and analgesics were administered as usual. The patient felt well within the first 2 days postoperatively. However, on postoperative day 3, the patient developed sudden, severe abdominal distension with tension-induced pain, although no bowel sounds were audible and no abdominal tenderness or abdominal rebound tenderness were found. A diagnosis of portal vein thrombosis (PVT) was suspected by the attending physician, but was not confirmed by emergent B-type ultrasound, which may have been related to gas build-up in the abdominal cavity.[1] Other test results were as follows: serum creatinine (CR), 113 μmol/L (normal range, 1–106 μmol/L); PT, 13.8 s; serum ALB, 29.6 g/L; 24 h urine volume was reduced to 70 mL; urine protein, +; and three red blood cells/high-power field on microscopic examination. These parameters were not relieved by treatment with diuretics and ALB administration. The abdominal distension worsened on postoperative day 4, as 24 h urine volume decreased to 10 mL, bladder pressure increased to 15 mmHg, and biochemical parameters were as follows: ALB, 34.0 g/L; serum CR, 243 μmol/L; white blood cell count, 26.0 ×109 cells/L; and GPT, 88 mg/dL. These results suggested severe kidney damage. Hemodialysis was initiated on postoperative day 5 and performed three times per week to sustain kidney function because the level of CR increased to a peak value of 612 μmol/L, GPT increased to 131 mg/dL, D-dimer level was 5010 μg/L, fibrinogen level was 0.91 g/L, and PT was 13 s.

The D-dimer level rapidly increased from 5010 to15,580 μg/L in 8 h; therefore, administration of hemostatic agents was contraindicated at this time. A diagnosis of PVT was again suspected because of worsening of abdominal distension and kidney function. PVT was confirmed by enhanced abdominal computed tomography (CT) on postoperative day 11 as shown in Figure 1C &1D.

Terlipressin (1 mg, Q8H) was prescribed to increase the renal artery supply for 2 weeks postoperatively. However, kidney function did not improve with Terlipressin. Postoperative changes in liver function, kidney function, and D-dimer levels are shown in Figure 1E. The patient refused further treatment and died of acute kidney failure (AKF) on postoperative day 45.

DISCUSSION

Hepatitis infection continues to be a common cause of cirrhosis in China. Also, among patients with a history of bleeding in the upper digestive tract, up to 50% of cases may be due to portal hypertension. Devascularization surgery is now wildly applied in China for treatment of AKF resulting from hepatorenal syndrome (HRS).[2] An extremely dilated splanchnic arterial bed triggers a marked disturbance in systemic circulation, ultimately leading to kidney failure due to vasoconstriction of the renal arteries. Several studies performed within the past 10 years have shown that HRS may be reversible with appropriate pharmacological intervention. However, some clinical studies have shown that patients with normal liver function may develop severe postoperative complications of AKF, which is thought to contribute to HRS by many physicians. However, there are other possible causes of AKF in HRS that should be considered. For example, the onset of PVT-induced intra-abdominal hypertension (IAH) is very common among patients with portal hypertension, although this phenomenon may be overlooked. AKF is a very important presentation of IAH or abdominal compartment syndrome (ACS). This review provides an overview of the pathogenesis, primary clinical findings, differential diagnosis, and management of AKF resulting from PVT-induced IAH or ACS in patients with postoperative portal

hypertension, with particular emphasis on the benefits of pharmacological treatment and early diagnosis.

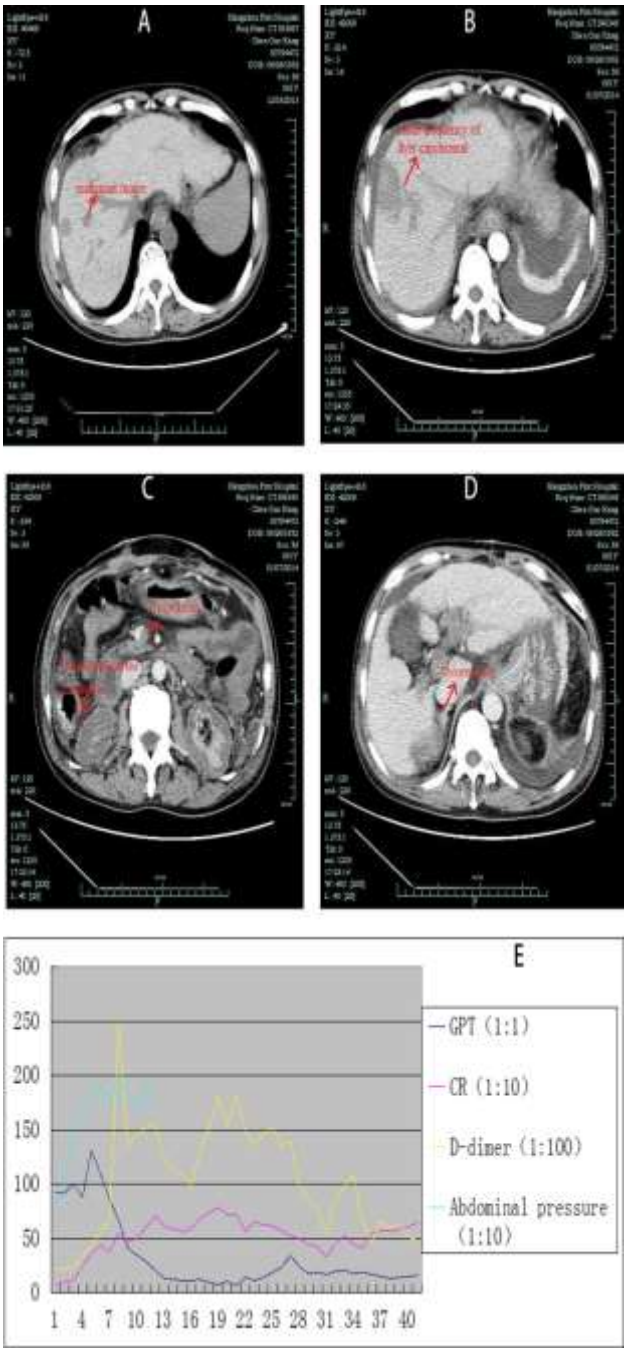

Figure 1A: primary liver carcinoma in right liver preoperatively. 1B: primary liver carcinoma treated by radiofrequency ablation postoperatively. 1C: thrombosis of portal system and ischemia cortex of double kidneys postoperatively. 1D: thrombosis of portal system and ischemia cortex of double kidneys postoperatively. 1E: changes of GPT, CR, D-dimer, and abdominal pressure postoperative.

Currently, a diagnosis of HRS must meet several criteria, including a minimum serum CR level of 1.5 mg/dL (133 µmol/L), which corresponds to a glomerular filtration rate of <30 mL/min/1.73m2. In patients treated with diuretics, CR should be monitored after diuretic therapy is withdrawn because CR levels may decrease. With no useful or specific laboratory tests to elucidate an actual cause, it is very difficult to arrive at a differential diagnosis of AKF in patients with portal hypertension.[3] Many symptoms of HRS, including hypotension and electrolyte disturbances, can be treated by administration of hypertonic solutions. Therefore, other causes, such as infection-induced hypotension and even shock, should be considered in the diagnosis of HRS. Furthermore, AKF may be caused by glomerulonephritis in patients with cirrhosis. The most recent guidelines of the European Association for the study of the liver (EASL) published in 2010 recommend Terlipressin (1 mg/4–6 h as IV bolus) together with ALB as the first-line treatment for HRS.[4] The aim of treatment is to decrease serum CR levels to <1.5 mg/dL (<133 µmol/L). Modifications to this dosage are guided by changes in serum CR concentrations: if serum CR is decreased by at least 25% after 3 days of treatment, the dose is maintained, if not, then the dose is increased to 2 mg/4–6 h. For recurrence at any time after treatment discontinuation, patients should be re-treated with Terlipressin and ALB. Alternatives to Terlipressin are Noradrenaline and Midodrine plus Octreotide, both in combination with ALB, although information on the efficacy of this regimen is very limited. Patients treated with vasoconstrictors should be followed-up carefully throughout the course of treatment for early detection of side effects. The 2009 guidelines of the American association for the study of the liver recommend Midodrine and Octreotide together with ALB for treatment of type 1 HRS. However, it should be noted that Terlipressin is not currently available in the US.[5]

In the present case, CR levels did not recover to discernable levels with any of the various treatments, which included Terlipressin, ALB, hemodialysis, and Octreotide, among others. The patient finally decided to forgo treatment because of the heavy burden of hospitalization costs. This case clearly indicated that Terlipressin did not benefit AKF, while evidence of normal postoperative liver function during treatment for AKF indicated the possibility of an alternative cause of AKF that may have developed over the past few years.

The first series of paraneoplastic glomerulonephritis was published by Lee et al in 1966. Kidney injury is characterized by pathological changes, membranous nephropathy (MN), membranoproliferative nephritis, focal segmental glomerulosclerosis (FSGS), crescent glomerulonephritis, and mesangial proliferative nephritis. MN is often caused by solid malignant tumors, which can be confirmed by kidney puncture biopsy in 68.7% of cases with solid tumors. Some patients present with earlier abundant proteinuria before the diagnosis of a solid malignant tumor. These findings can be explained by a mechanism of the immune complex in the glomeruli in response to endo or extra antigens combined with anti-tumor-related antibodies or caused by tumor-associated

dysfunction of the immune response. Some studies have reported simultaneous detection of carcinoembryonic antigen (CEA) in the renal tissue, solid tumor, and serum. This finding was consistent with the distribution of CEA, IgG, and C3 by immunofluorescent staining of the prepapillary vascular loops. A possible explanation of this mechanism involves sedimentation of immune factors associated with tumor growth in the circulation or the product of the reaction of tumor antigens combined with antibodies in the glomerular epithelium. Actually, the mechanism of immune complex sedimentation remains unclear and tumor antigens are not detected in the glomerular epithelium in most cases. The prognosis of MN-related tumors is intimately related to the biological behavior of the tumor and the treatment regimen. MN is usually relieved by actively removing the solid tumor. Depending on the treatment regime, many cases of severe kidney injury can achieve effective recovery, although to various extents. However, the curative effect of MN therapies is often hindered by metastasis of the tumor or recurrence of the primary tumor. AKF is also caused by tumor-related proteinuria, with major clinical presentations that include hypoproteinemia, hematuria, proteinuria, and casts found in the urine. Our case was diagnosed with primary hepatic carcinoma secondary to cirrhosis due to B-type hepatitis, and a tumor with a diameter of about 1.5 cm, thus radiofrequency ablation was employed. According to the current understanding of MN, proteinuria should resolve or decrease after removal of the primary tumor, although no proteinuria was observed in our patient preoperatively. Therefore, we excluded a diagnosis of MN-related tumor formation in this case in accordance with the evidence provided above.

Disseminated intravascular coagulation (DIC) is also a common cause of AKF. Although the criteria for DIC vary among countries, the following criteria have been adopted in China: (1) basic diseases causing DIC are regarded as the precondition of diagnosis; (2) related lab test results, including (2A) platelet (PLT) count (× 109/L) (>100, score = 0; <100, score = 1; <50, score = 2), (2B) markers of fibrosis (D-dimer) (normal, score = 0; small increase, score = 1; mid-range increase, score = 2; remarkable increase, score = 3), (2C) delay in PT (<3 s, score = 0; 3–6 s, score = 1; >6 s, score = 2), and (B4) FBG (>1.0 g/L, score = 0; <1.0 g/L, score = 1); and (3) A sum of scores ≥5 is regarded as significant DIC, although the score should be recalculated daily to arrive at a correct result.[6] In general, DIC causes ischemia of the kidney cortex, as the microvessels of the kidney cortex form micro-thrombi to various degrees. In our case, the D-dimer level on postoperative day 3 was about 2300 μg/L, which indicated a slight increase according to the criteria mentioned above, PLT was 30 × 109/L, PT was normal, and FBG was 0.53 g/L, for a total score of 4, so the criteria of a diagnosis of DIC was not met and, meanwhile, the patient exhibited no tendency of hemorrhage characteristic of DIC. In short, ischemia of the kidney cortex was not indicative of DIC, even if we assessed the patient's DIC score actively. Furthermore, no thrombosis formation was observed in the micro-vasculature, but rather the major portal venous system, thus it is very difficult to explain the observed ischemia of the kidney cortex. Therefore, we were left with the question: What was the actual cause of the injury to the kidney cortex.

Abdominal surgery, especially devascularization and shunt placement for portal hypertension, often leads to the development of thrombi of the large vessels, such as in PVT, which is often ignored by many surgeons because it is speculated that PVT is not detrimental to patient prognosis. However, our study indicated that IAH rapidly increased due to PVT, which can cause AKF, although these associations have not been previously reported in patients with postoperative portal hypertension. Acute postoperative PVT can produce congestion, tissue edema, and gas accumulation in the digestive tract, which will induce acute IAH. Abundant ascites emerges suddenly in most cases with normal ALB at that time point. Many doctors administer combinations of hemostatic agents to prevent capillary hemorrhage at the wound surface. As a result, the risk of thrombosis in the major vessels increases in the portal venous system. Furthermore, compliance of the abdominal wall was remarkably reduced in our patient due to the large incision. Therefore, acute IAH cannot be easily avoided because of the various above-described factors, which differed from those that cause the slow accumulation of ascites. During the devascularization procedure, the ligaments surrounding the liver, the short gastric vein, splenic vein and so on are all cut off, so the collateral circulation could not rebound in the short amount of time that the major trunk of the portal vein developed a thrombosis. Based on these findings, acute IAH appears to be closely associated with PVT and may be a potential cause of AKF. However, the response of the kidney is very sensitive to a rapid increase in intra-abdominal pressure, thus kidney function is actually damaged first even if there are no observable change in kidney morphology on a CT scan. However, once the kidney cortex is no longer visible on a CT scan, the kidney damage may be too severe to achieve functional recovery. Many factors play roles in PVT formation, including (1) rapid PLT accumulation after splenectomy, which increases the risk of thrombosis formation in the large vessels, (2) the overuse of combined hemostatic agents, which promotes blood coagulation, (3) reduced blood flow because of the patient's limited movement after surgery, which may avoid hemorrhage, and (4) IAH resulting from PVT.[7]

The bladder is an inter-peritoneal organ that can reflect abdominal pressure because of its good compliance, thus detection of bladder pressure is now regarded as the gold standard to measure intra-abdominal pressure.[8] In our patient, bladder pressure increased to >15 mmHg on postoperative day 3 and maintained a relatively high level, peaking at 20 mmHg. Therefore, we narrowed our

diagnosis to IAH or ACS, in accordance with the guidelines. Depending on the requirements of a particular case, it may be necessary to perform emergent surgery if the intra-abdominal pressure (IAP) reaches the standard of ACS.[9] However, this option is not correct under special circumstances, such as the situation in our study, in which the patient would not have benefited from a reoperation because the PVT was not reduced postoperatively. Our patient died of AKF less than 1 month later, which may have been the result even if we administered other conservative treatments, such as Terlipressin and dialysis to sustain kidney function. A review of this case indicates that AKF will not improve from the treatments mentioned above if IAH resulting from PVT, which is a very important potential cause of AKF, is ignored. We suspect that the optimal treatment is to remove the thrombosis with anticoagulants, such as low-molecular-weight heparin, although the use of terlipressin is not recommended if HRS is not considered as the major cause of AKF. This conclusion was also reported in a similar case of a 67-year-old female with PVT on postoperative day 5 who developed sudden ascites accumulation from 200 ml to 2000 ml accompanied with abdominal pain. Both B-type ultrasound and abdominal CT showed thrombosis formation in the major stem and left branch. Meanwhile, the 24 h urine volume was 700~800 mL and her bladder pressure was 16 mmHg. Treatment of ALB and diuretics resulted in no obvious reduction in ascites. In this case, low-molecular-weight heparin (12,500 U.ih.Q12H) was administered in time and continued for 2 weeks, resulting in a marked reduction in ascites volume and gradual increase in urine volume. Afterward, low-molecular-weight heparin was replaced with warfarin (3 mg.po.QD), which was continued for 6 months. On follow-up, little ascites was observed and recanalization of the thrombosis was confirmed by B-type ultrasound. The amount of warfarin was halved (1.5 mg.po.QD) because of the adverse effect of diarrhea and continued for an additional 6 months. The patient achieved complete recovery from the timely correct choice of treatment. Based on the findings of these reports, as well as our experience, we believe that it is very necessary and important to maintain balance between the coagulation system and anticoagulation system in order to sustain the stable abdominal pressure. If there is no obvious abdominal bleeding, all hemostatic agents should be discontinued by postoperative day 2 to avoid the risk of PVT. Further studies are needed to develop other methods to ensure balance between the coagulation system and anticoagulation system in order to choose an optimal treatment in the future.

Postoperative PVT formation in cirrhosis is a very common clinical finding, but the impacts of PVT and IAP on kidney function are traditionally ignored. A report by Sugrue suggested that the time between IAH and AKF postoperatively was only 1.7±1.4 days, which was in accordance with the observations in our study. This suggests that a close relationship exists between IAH and AKF, as shown in Figure 1E, which should greatly help to understand these new findings and confirm our views. The direct evidence presented in Figure 1E shows a relationship between IAP, PVT, liver function, and kidney function, which should help us to determine the true cause of AKF according to the characteristics themselves and then choose the most effective treatment regarding the cause of AKF. If the liver function is normal or near normal without hypotension, HRS should be diagnosed discreetly. If no tendency towards hemorrhage emerged, DIC should be excluded from a potential diagnosis. For cases with a rapid increase in ascites without low-ALB, PVT should be considered promptly and a diagnosis can be made earlier by abdominal CT and/or B-type ultrasound. Other direct evidence in our study is shown in Figure 1C, 1D. CT failed to image the kidney cortex, which is seldom observed in most cases, although, simultaneously, the major stem of a PVT was observed. However the size of the renal artery did not decrease, while that of the inferior vena cava increased. Taken together, these findings suggest the IAH resulting from PVT may be a very important potential cause of loss of kidney function, although this possibility is ignored by many doctors. Active monitoring of D-dimer levels is greatly helpful for the early detection of PVT. From our experience, discontinuing hemostatic agents and the use of anticoagulants are very useful to reduce kidney injury once thrombosis of a large vessel is discovered to ensure patient survival.

CONCLUSION

PVT often develops in patients with postoperative portal hypertension, although this occurrence is often overlooked. Actually, IAH or even ACS can be triggered by major stem portal venous thrombosis. Therefore, the cause of AKF can include not only HRS, but also IAH induced by PVT. Also, Terlipressin will not benefit treatment of HRS, if HRS is not considered as the major cause of AKF. It is critical to control the course and the dose of hemostatic agents, and the use of anticoagulants, such as hemostatic agents, low-molecular-weight heparin, and warfarin, to control the development of PVT and for treatment of AKF.

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