

## Gastrointestinal Bleeding During Anticoagulant Therapy for Deep Vein Thrombosis after Simultaneous Pancreas and Kidney Transplantation

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### Abstract

A 46-year-old Japanese woman on dialysis for type 1 diabetes and chronic renal failure underwent simultaneous pancreas and kidney transplantation from a brain-dead donor. On postoperative day 3, ilio-femoral deep vein thrombosis on the side of pancreatic transplantation was diagnosed from swelling of the right leg, an increased D-dimer level, and imaging findings. Anticoagulant therapy was initiated to prevent proximal propagation of the thrombosis and pulmonary thromboembolism. However, gastrointestinal bleeding occurred, which was thought to be due to mucosal bleeding from the duodenal graft. Her anticoagulant therapy was adjusted and hemostasis was conducted, controlling the gastrointestinal bleeding without surgical intervention. Blood flow was maintained to both grafts and graft function was good. When gastrointestinal bleeding occurs during anticoagulant therapy for deep vein thrombosis after combined pancreas and kidney transplantation, bleeding can be controlled by adjusting anticoagulant therapy and other appropriate measures.

**Keywords:** Gastrointestinal bleeding; Deep vein thrombosis; Simultaneous pancreas; Kidney transplantation

### Introduction

Transplantation of the pancreas has been established as a surgical treatment for diabetes. Compared with other organs, pancreatic transplantation is associated with a higher rate of graft loss due to thrombosis [1]. Although the engraftment rate has been increased by improvements to the surgical techniques and immunosuppressive therapy, prevention of graft thrombosis remains a major challenge.

Availability of organs from brain dead donors is lower in Japan than in other countries and there is a high proportion of extended criteria donors according to Kapur's criteria [2] suggesting an elevated risk of graft thrombosis [3].

In a patient undergoing simultaneous pancreas and kidney transplantation, deep vein thrombosis (DVT) developed in the lower limb and gastrointestinal bleeding occurred during treatment of the thrombus. This case is reported with comments on the management of concurrent DVT and gastrointestinal bleeding after organ transplantation.

### Case Report

A 46-year-old woman had a history of type 1 diabetes since age 24, with laser treatment for right fundal hemorrhage at age 37 and initiation of dialysis at age 44 due to chronic renal failure caused by diabetic nephropathy. She was admitted to our hospital for simultaneous pancreas and kidney transplantation. The patient was 168 cm tall, weighed 58.3 kg, and had a body mass index of 20.7 kg/m<sup>2</sup>. Her insulin dose was 28 units/day. Hemoglobin A1c (National Glycohemoglobin Standardization Program) was 7.7%, glycoalbumin was 29.1%, C-peptide was <0.03 ng/mL, insulin antibody was 0.4 U/mL, anti-glutamic acid decarboxylase antibody was <0.3 U/mL, and anti-islet antigen-2 antibody was <0.4 U/mL.

### Donor and surgery

The donor was a 40-year-old woman with subdural hematoma caused by a traffic accident who was determined to be brain dead. A kidney was transplanted into the left iliac fossa and the pancreas was transplanted into the right iliac fossa. Both organs were transplanted retroperitoneally. A Y-limb was created at the terminal ileum by the Roux-en-Y method and was anastomosed to the grafted duodenum for

drainage of exocrine secretions. Using Carrel patches, the celiac artery and superior mesenteric artery were anastomosed to the right external iliac artery, and the portal vein was anastomosed to the right external iliac vein after transecting the right internal iliac vein. After blood flow was resumed, mucosal oozing was observed when the duodenal graft was incised. A 12 Fr catheter was placed for decompression, which was inserted from the ileal Y-limb, advanced beyond the anastomosis, and fixed inside the duodenal graft.

The total ischemic time was 9 hours and 15 minutes for the kidney and 10 hours and 31 minutes for the pancreas. Blood loss was 260 g.

### Post-operative course

Postoperatively, the patient had an adequate urine output and glycemic control, so dialysis and insulin therapy were stopped. (Figure 1) outlines the postoperative course. As induction therapy for immunosuppression, rabbit anti-thymocyte globulin was administered (1.5 mg/kg for 4 days) together with tacrolimus, mycophenolate mofetil, and a steroid. During and after surgery, gabexate mesilate (2000 mg/day) and alprostadil alfadex (prostaglandin E1: 5 µg/kg/day) were administered as antithrombotic therapy. Elastic stockings and intermittent pneumatic compression were used for DVT prophylaxis. Ultrasonography revealed good blood flow to the pancreatic and renal grafts. However, there was marked swelling of the wall of the duodenal graft and a small volume of bloody fluid drained from the intestinal tube, suggesting bleeding from the duodenal graft mucosa. Accordingly, octreotide acetate (300 µg/day) was started on day 2 to control pancreatic secretions. Swelling of the right leg (the side of pancreatic transplantation) was observed, which was considered to be caused by obstruction of venous return.

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However, the D-dimer level increased progressively (4.0 µg/ml on day 1, 23.9 µg/ml on day 2, and 55.2 µg/ml on day 3), so ultrasonography of the lower limbs was performed on day 3, revealing DVT of the right leg. Contrast-enhanced computed tomography (CT) was performed immediately and identified widespread DVT of the right lower limb extending near to the anastomosis of the portal vein with the iliac vein (Figure 2). Right ilio-femoral DVT was diagnosed.

### Management of concurrent DVT and bleeding

Heparin (3000 units) was immediately administered intravenously and continuous infusion was started at 10000 units/day (200 units/kg/day). Administration of warfarin (2 mg/day) was initiated simultaneously. Melena occurred from the night of starting anticoagulation and gradually increased. Drainage of bloody fluid from the intestinal tube also increased, suggesting that melena was related to mucosal bleeding from the duodenal graft. Anticoagulant therapy was continued to prevent proximal propagation of the thrombus and pulmonary thromboembolism, while blood transfusion was also performed for anemia targeting a hemoglobin > 10 g/dl and a hematocrit > 30%.

The activated partial thromboplastin time (APTT) was monitored and heparin infusion was adjusted targeting an APTT 1.5 times the standard level. The warfarin dose was adjusted targeting a prothrombin time -international normalized ratio of (PT-INR) from 1.5 to 2.0. On day 6, both APTT (49 seconds) and PT-INR (3.03) were increased and melena was worse, so infusion of heparin was reduced to one quarter

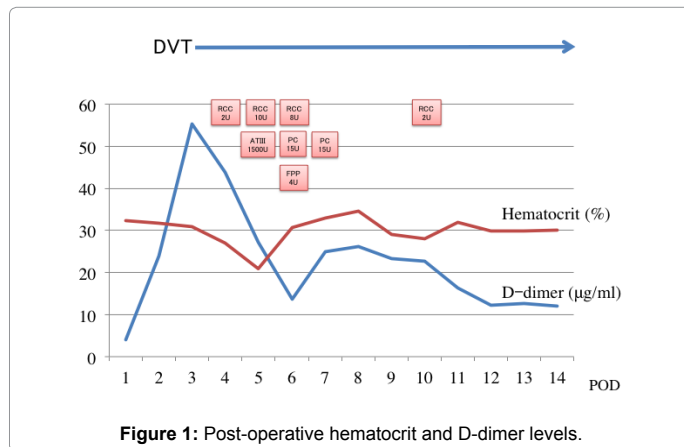


Figure 1: Post-operative hematocrit and D-dimer levels.

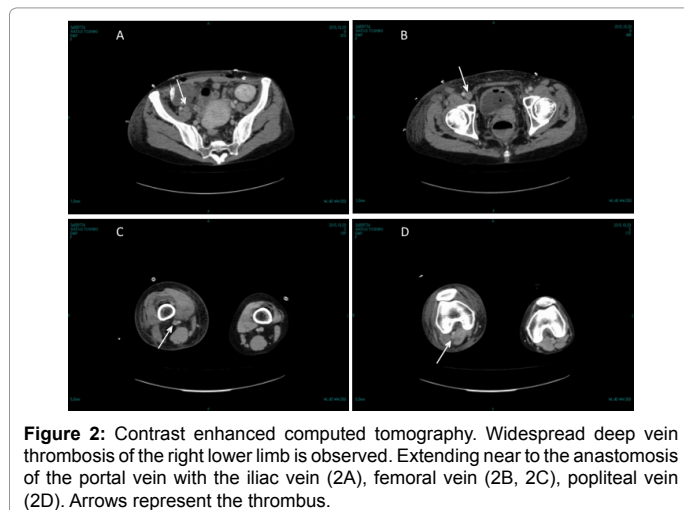


Figure 2: Contrast enhanced computed tomography. Widespread deep vein thrombosis of the right lower limb is observed. Extending near to the anastomosis of the portal vein with the iliac vein (2A), femoral vein (2B, 2C), popliteal vein (2D). Arrows represent the thrombus.



Figure 3: Recovery from deep vein thrombosis of the right lower limb. The circumference of the right thigh is 48 cm and that of the left thigh is 40 cm.

of the previous dose and warfarin was suspended. Intravenous vitamin K (5 mg) and fresh frozen plasma (4 units) were given. The platelet count fell to 68,000/µl, so platelet transfusion was performed. Melena decreased on day 7 and resolved on day 10. Warfarin started again on day 7 because PT-INR was decreased to 0.97 on day 7. After peaking on day 3, D-dimer decreased to 13.7 µg/ml on day 6. The circumference of the left thigh was 40 cm and that of the right thigh increased to 54 cm, but swelling started to improve on day 7.

Administration of valganciclovir was started to prevent cytomegalovirus infection one week after surgery. The cytomegalovirus antigenemia assay and quantitative PCR for were consistently negative. Although low-dose insulin was needed immediately after transplantation, blood glucose soon became stable without insulin.

Heparin was discontinued on day 10, but warfarin was continued. Resolution of duodenal graft wall swelling was revealed by ultrasonography. From day 20, dipyridamole (300 mg/day) and cilostazol (100 mg/day) were added. Ultrasonography demonstrated recanalization of the deep veins in the right lower limb on day 52, when the circumference of the right thigh was reduced to 48 cm (Figure 3).

The intestinal tube was removed on day 54, and the patient was discharged on day 56.

### Discussion

Up to May 2016, 58 patients underwent pancreatic transplantation at our hospital (11 from non-heart beating donors and 47 from brain dead donors). Among 47 patients receiving a pancreas from a brain dead donor, lower limb DVT developed in 4 patients (8.5%), including the present patient. All 4 of these patients underwent simultaneous pancreas and kidney transplantation (4/40 patients: 10%). However, only the present patient developed gastrointestinal bleeding during treatment of DVT. Previous reports on DVT occurring early after pancreatic transplantation include a report by Humar et al [4], of DVT in 50/276 patients (18.1%) undergoing simultaneous pancreas and kidney transplantation and a report by Harish et al. [5] of DVT in 4/287 patients (1.4%) undergoing pancreatic transplantation.

Generally, laboratory tests and imaging studies are used to diagnose DVT, with D-dimer being a useful quantitative parameter [6]. Imaging methods for confirming thrombosis include ultrasonography, contrast-enhanced CT, and magnetic resonance venography [7]. Color Doppler imaging is a standard ultrasonography technique. The extent of thrombosis can be accurately determined by continuous ultrasonographic examination from the groin to the thigh, popliteal

region, and leg. Floating thrombosis is identified by partial loss of blood flow and migration of clots [7,8]. Contrast-enhanced CT can simultaneously evaluate the pulmonary arteries and abdominal /lower limb veins and is often performed when pulmonary thromboembolism is suspected [9]. In the present patient, ultrasonography and contrast-enhanced CT demonstrated DVT extending to the iliac vein with a stable proximal end to the clot.

When lower limb DVT develops, treatment is required to prevent progression of thrombosis and pulmonary thromboembolism, as well as to prevent early and late sequelae. Treatment can include medical therapy, physical therapy, catheter therapy, and thrombectomy. Heparin and warfarin are used for anticoagulation. Since the early relapse rate is high when warfarin is administered alone, combined therapy is essential [10]. Continuous infusion of 40000 units of heparin over 24 hours is recommended after an initial dose of 5000 units to prolong the APTT by 1.5- to 2.5-fold [11]. Because DVT developed 3 days after simultaneous pancreas and kidney transplantation in the present patient, treatment was started with 3000 units of heparin followed by 24-hour infusion of 10000 units. Warfarin was started simultaneously at 2 mg and then adjusted so that the PT-INR was 1.5 to 2.0. In patients with a first idiopathic DVT and unknown risk factors, warfarin is administered for at least 3 months, after which treatment may be continued depending on the risks and benefits [10].

While compression with elastic stockings or bandages is effective for preventing DVT, the usefulness of compression therapy after development of DVT is unknown. Catheter-directed thrombolysis and thrombectomy are useful in some DVT patients [11,12] but should be performed with caution after simultaneous pancreas and kidney transplantation due to the risks of progressive thrombosis and bleeding.

After complete occlusion of a vein by thrombus, the clot usually dissolves over time and the vein is recanalized. It was reported that recanalization occurred in 44% of patients by 7 days after the onset of DVT and in 100% by 90 days [13] or that recanalization was observed in 87% of patients within 6 weeks after complete venous occlusion by thrombosis [14]. In the present patient, ultrasonography demonstrated recanalization after 52 days owing to continuation of anticoagulation therapy despite gastrointestinal bleeding.

In our patient, gastrointestinal bleeding became apparent immediately after initiation of anticoagulant therapy following diagnosis of DVT. Thrombosis involved the iliac vein near the anastomosis of the portal vein with the external iliac vein. Therefore, we focused on preventing propagation of the clot and portal vein thrombosis, along with prevention of pulmonary thromboembolism. Transfusion was performed for gastrointestinal bleeding (assumed to be due to mucosal bleeding from the duodenal graft) while anticoagulant therapy was continued for DVT.

Creation of a duodenoduodenostomy to facilitate endoscopy of the grafted duodenum and as drainage for exocrine secretions has been reported [15]. Bleeding could have been stopped endoscopically if our patient had a duodenoduodenostomy, so this should be considered in the future. However, we found that monitoring the volume of blood discharged from the intestinal tube was a useful index of bleeding without performing endoscopy or angiography.

In our patient, blood flow was maintained to the grafted pancreas and kidney throughout treatment of the DVT. Since portal vein thrombosis is the most important factor related to early graft loss after pancreatic transplantation, avoiding progression to portal thrombosis is very important during treatment of DVT.

## Conclusion

We experienced a difficult patient with gastrointestinal bleeding during treatment of DVT after simultaneous pancreas and kidney transplantation.

Since portal vein thrombosis soon after pancreatic transplantation is an important factor in relation to early graft loss, preventing the progression of DVT with anticoagulant therapy is essential. Careful adjustment of the anticoagulant regimen and close monitoring are required if gastrointestinal bleeding occurs during anticoagulant therapy for DVT in this setting.

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