

Renal Transplantation in a Patient with Catastrophic Antiphospholipid Syndrome and Heparin-Induced Thrombocytopenia

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Antiphospholipid antibody syndrome is a clinical coagulation disorder characterized by vascular thrombosis due to the production of antibodies against antiphospholipid. When APS manifests as multiple vascular occlusions involving multiple organs and systems, it is termed catastrophic APS. CAPS accounts for less than 1% of all cases of APS [1].

Owing to the high recurrence rate of CAPS, survivors are usually treated with anticoagulation therapy for life. Infections, surgery, and anticoagulation withdrawal are all considered potential triggers for further events. If surgery is necessary, low molecular weight heparin or unfractionated heparin is administered for a few days before the procedure, withdrawn right before it, and reinitiated immediately after it.

Heparin-induced thrombocytopenia is an immunologically mediated reaction to heparin and LMWH [2]. Although the thrombocytopenia is rarely severe enough to pose a bleeding risk, thrombosis with organ damage can occur. This state is

termed heparin-induced thrombocytopenia with thrombosis. The clinical presentation of HITT includes deep venous thrombosis, pulmonary emboli, arterial thrombosis, or stroke. Both heparin and LMWH are contraindicated in patients with HITT, who are prescribed an alternative anticoagulant such as sodium warfarin. If surgery is required, the warfarin is stopped and patients must either forego anticoagulation and risk thrombosis or receive another anticoagulation treatment.

In this report we describe, to the best of our knowledge, the first attempt to perform renal transplantation with bivalirudin (Angiomax[®], The Medicines Company, Parsippany, NJ, USA) instead of heparin for anticoagulation in a patient with both APS and HITT. Our use of bivalirudin, a reversible direct thrombin inhibitor, was prompted by reports of its successful application in other surgical scenarios, including heart and liver transplantation [3,4].

PATIENT DESCRIPTION

A 28 year old woman with end-stage renal failure on hemodialysis presented for evaluation for renal transplantation. Her past history revealed an atrophied kidney, possibly from birth. At age 16 she was diagnosed with APS that manifested as a DVT in her left calf. Two years later, multi-organ CAPS developed while the patient was on warfarin treatment with a

target international normalized ratio of 2–3. One sequela of this event was loss of the remaining kidney. The patient began hemodialysis, and as part of the preparation to establish an arteriovenous fistula for continued hemodialysis she was treated with LMWH. Thereafter, severe thrombocytopenia developed, together with a DVT in her arm and grand mal seizures. According to the results of functional laboratory assay studies, these signs/symptoms were attributed to HITT.

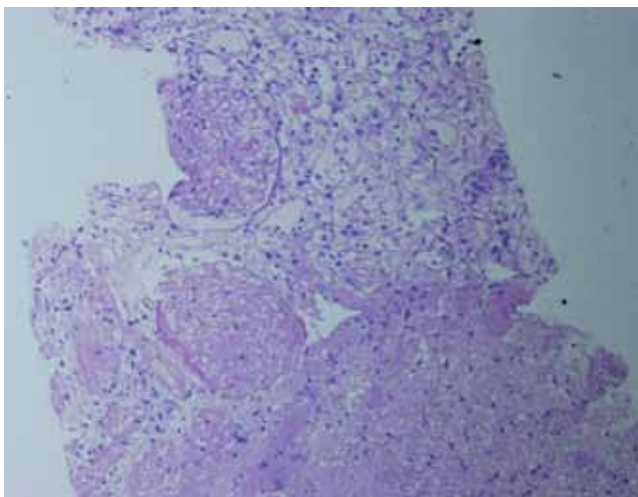
Although the patient’s mother was well-matched as a donor for renal transplantation, this option was initially ruled out because the surgery posed a potential risk of causing catastrophic APS but with no possibility of using heparin for prevention. In addition, the patient had a known sensitivity to iodine-based radiographic contrast, ofloxacin and vancomycin. However, on reconsideration 2 years later, we decided to attempt the procedure using a novel anticoagulant agent, bivalirudin (Angiomax[®]) as an alternative to heparin.

The bridging treatment protocol involved cessation of warfarin treatment and administration of 5 mg intravenous vitamin K. The patient’s baseline activated partial thromboplastin time was determined and continuous intravenous bivalirudin therapy, 0.15 mg/kg/hr, was initiated. The aPTT was measured every 4 hours and the bivalirudin dosage was titrated to an aPTT 1.5–2 times the baseline value. Because bivalirudin has a very short half-life (approximately 25

APS = antiphospholipid antibody syndrome
CAPS = catastrophic APS
LMWH = low molecular weight heparin

HITT = heparin-induced thrombocytopenia with thrombosis
DVT = deep vein thrombosis

aPTT = activated partial thromboplastin time



Transition between infarct and viable tissue on a kidney biopsy performed 8 days after transplant (periodic acid-Schiff, x 10)

minutes) it was stopped immediately before surgery and reinstated directly after. The patient was then kept on bivalirudin until warfarin was reinstated and an INR of ≥ 2.5 was achieved.

The postoperative course was complicated by a delay of several days before cessation of bivalirudin treatment, which was administered for a total of 7 days. Immediately after transplantation, severe thrombocytopenia developed, with the platelet count reaching a nadir of 10,000/dl on postoperative day 3. It resolved spontaneously by postoperative day 6. In addition, 2 days after transplantation, the arteriovenous fistula through which dialysis was administered became occluded followed by an abrupt reduction in urine output.

Hemodialysis was deemed necessary and an intravenous dialysis catheter was inserted. Because of continued non-function of the graft despite the improved diuresis, renal biopsy was considered. In the interval, on the assumption that the patient was undergoing acute rejection, we started anti-rejection therapy with pulse steroids (500 mg intravenous methylprednisolone daily for 3 days). On the evening before the renal biopsy, warfarin was stopped and 0.5 mg vitamin K was

administered intravenously; normal aPTT levels were achieved.

Renal biopsy, performed on postoperative day 8, showed acute tubular necrosis with areas of infarction [Figure]. C4-d immunofluorescence staining was negative. Subsequent scintigraphic studies demonstrated a well-perfused organ with very poor function. A regimen of hemodialysis three times a week was begun. The serum creatinine level began to decrease gradually, reaching below 4 mg/min/1.73 m² at 5 weeks. Hemodialysis was then stopped and the patient was discharged. Renal function continued to improve with every follow-up visit. Currently, 42 months after transplantation, the patient's creatinine level is 2.3 mg/dl.

COMMENT

This case report demonstrates the feasibility of attempting renal transplantation in a patient with both CAPS and HITT using bivalirudin (Angiomax[®]) as an alternative to heparin. Although the half-life of bivalirudin is prolonged by renal failure (from about 25 minutes to 50 minutes), it is still sufficiently short for this setting and is relatively unaffected by variability in kidney function.

The kidney transplant was successful and there was no significant bleeding.

However, there was a prolonged period of graft non-function after transplantation. This might have been due to a form of acute tubular necrosis occasionally seen in transplantations or, more reasonably, to activation of the patient's APS. The latter possibility was supported by findings of a renal infarct on biopsy study and the development of thrombocytopenia immediately after the transplantation procedure. The postoperative occurrence of APS would indicate that bivalirudin anticoagulation is insufficient to prevent thrombosis. At the same time, patients with APS have been known to exhibit acute thrombotic events even when receiving adequate oral anticoagulation [5]. Thus, it remains unclear if the thrombotic event in our patient was preventable. Marked thrombocytopenia associated with thrombosis of an arteriovenous fistula 2 days after transplantation might indicate the need for earlier reinstatement of warfarin.

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References

1. Espinosa G, Cervera R. Antiphospholipid syndrome: frequency, main causes and risk factors of mortality. *Nat Rev Rheumatol* 2010; 6: 296-300.
2. Otis SA, Zehnder JL. Heparin-induced thrombocytopenia: current status and diagnostic challenges. *Am J Hematol* 2010; 85: 700-6.
3. Simsir SA, Schwarz ER, Czer LS, Hamburg SL. Heart transplantation using bivalirudin as anticoagulant. *Interact Cardiovasc Thorac Surg* 2010; 10: 150-1.
4. Anderegg BA, Baillie GM, Uber WE, et al. Use of bivalirudin to prevent thrombosis following orthotopic liver transplantation in a patient with Budd-Chiari syndrome and a history of heparin-induced thrombocytopenia. *Ann Clin Lab Sci* 2008; 38: 277-82.
5. Ruiz-Irastorza G, Khamashta MA, Hunt BJ, Escudero A, Cuadrado MJ, Hughes GR. Bleeding and recurrent thrombosis in definite antiphospholipid syndrome: analysis of a series of 66 patients treated with oral anticoagulation to a target international normalized ratio of 3.5. *Arch Intern Med* 2002; 162: 1164-9.

INR = international normalized ratio