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Case Report

The successful treatment of renal-vein thrombosis by low-molecular-weight heparin in a steroid-sensitive nephrotic patient

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Introduction

Patients with nephrotic syndrome frequently have renal-vein thrombosis (RVThromb) without overt clinical manifestations. At the onset of the condition only 10% of these patients have acute signs and symptoms such as flank pain, haematuria, proteinuria and a rapid decline of renal function [1]. Patients experiencing severe flank pain, a rapid deterioration of renal function and concomitant pulmonary emboli or multiple thrombi have been successfully managed with thrombolytic agents [3], despite the fact that the risk associated with thrombolytic therapy seems to be greater than that of anticoagulant therapy, which would appear to be a more appropriate choice of treatment. Since low-molecular-weight heparins (LMWHep) have a longer half-life and better bioavailability than unfractionated heparin, they are widely used for treating many clinical conditions [4]. This case report confirms that LMWHep can be used successfully to treat the RVThromb of a nephrotic patient. It also suggests that such therapy may be applied even when thrombolytic or other anticoagulation therapy has previously failed.

Case

A 24-year-old woman had experienced severe left flank pain for about a week before admission to our hospital. She reported that she had noticed bilateral leg oedema for about a month prior to admission, and had had an episode of acute gastroenteritis 2 days prior to experiencing the left flank pain.

Initial physical examinations revealed an acutely ill-looking young woman with bilateral leg oedema (2+ pitting) up to mid-foreleg. Blood pressure was 114/78 mmHg and temperature 35.9°C. Laboratory tests revealed a serum creatinine of 1.4 mg/dl, sodium 128 mEq/dl, albumin 1.7 g/dl and cholesterol 365 mg/dl. A complete blood count revealed white blood cell count of 23 900 cells/mm^3, haemoglobin 17.2 g/dl and platelet count 223 000/mm^3. Urinalysis disclosed protein 500 mg/dl, blood 4+, RBC 50–55/HPF, and WBC 1–3/HPF. Creatinine clearance was 69 ml/min. The patient's daily protein excretion measured 18.8 g/24 h. Anticardiolipin, rheumatoid factor, protein C, protein S and anti-thrombin III levels all were within normal ranges. The patient had taken oral contraceptives during the preceding four years and diuretics for 2 weeks prior to the admission.

With the working diagnosis that the patient was suffering from nephrotic syndrome associated with left RVThromb, selective thrombolysis was performed via the left renal vein using 600 000 units of urokinase on day 1. Following thrombolytic therapy, a loading dose of unfractionated heparin (5000 U) and a maintenance infusion was administered in an attempt to maintain an active partial thromboplastin time of between 1.5 and 2.0 times the control value. The left renal venogram taken some 4 h later, however, revealed a persistent thrombus extending to the inferior vena cava (Figure 1).

The unfractionated heparin administered initially was replaced by warfarin on day 5. A cortical defect and reduced blood flow and glomerular filtration rate in the left kidney were observed after the administration of ^{99m}Tc dimer-captosuccinate (^{99m}Tc DMSA) plus ^{99m}Tc diethylene triamine tetraacetic acid (^{99m}Tc DTPA) on day 5. Magnetic resonance angiography (MRA) performed on day 7 revealed persistent left

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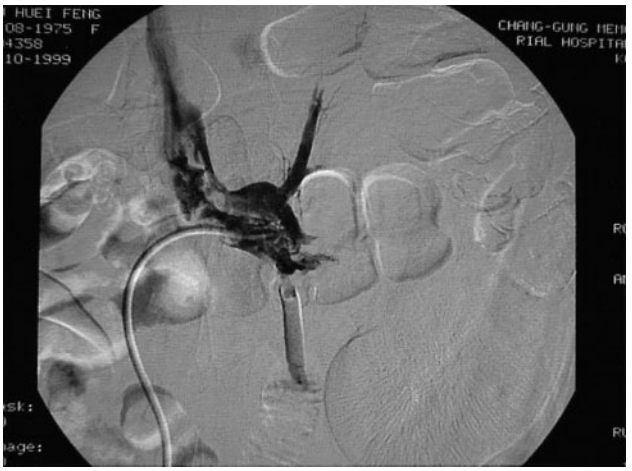

Fig. 1. A left renal venogram following thrombolytic therapy, revealing persistent thrombosis.

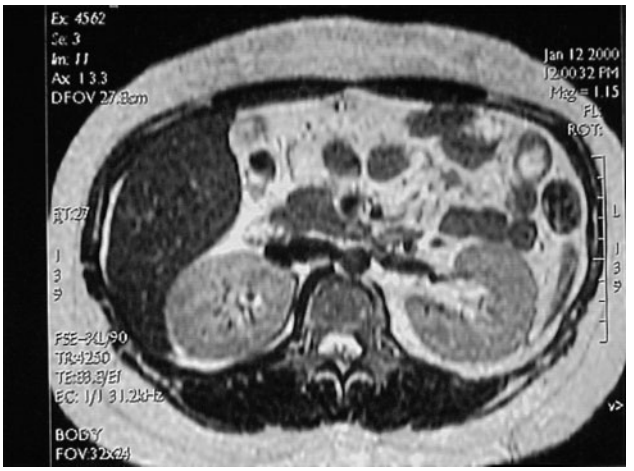

Fig. 2. A magnetic resonance image taken 2 months after the initiation of treatment with LMWHep, showing total resolution of the left renal-vein thrombus.

RVThromb. Because of the patient's persistent flank pain and vaginal bleeding, her warfarin was replaced with LMWHep (Fraxiparin 5,700 ICU AXa subcutaneously q12h) on day 14.

Methylprednisolone 24 mg/day was started on day 14 in order to attempt to deal with the patient's nephrotic syndrome. On day 21, the patient's left flank pain subsided and her proteinuria diminished (to 10 g/24 h). The patient was discharged on day 28. Treatment was continued as an outpatient at the nephrology clinic where subcutaneous Fraxiparin 5,700 ICU AXa q12 h and methylprednisolone 24 mg per day were prescribed. A renal biopsy performed on day 60 revealed minimal-change disease, and follow-up MRA revealed patent renal veins bilaterally (Figure 2).

LMWHep was discontinued at that time. The patient's creatinine clearance level was 118 ml/min on day 65.

Discussion

Patients with nephrotic syndrome who have low serum albumin, high rates of protein excretion, high fibrinogen levels, low antithrombin-III levels, and hypovolaemia are more likely to suffer thromboembolic events [1]. RVThromb is one of the more frequent thromboembolic events, and may result in kidney infarction, hypertension, chronic infection and renal failure [2]. Therefore, early diagnosis and optimal treatment for such a condition seems to be crucial.

Since the 1960s, nephrectomy or thrombectomy have been used as the initial treatment for RVThromb [2], although both methods are invasive and may be somewhat risky and drastic. Following a series of published reports on the resolution of renal-vein thrombi with anticoagulant therapy alone, the administration of systemic unfractionated heparin or oral warfarin has replaced nephrectomy and thrombectomy as the treatment of choice [2], although conventional therapy with unfractionated heparin is associated with certain disadvantages such as an unpredictable anticoagulant response or complications that include thrombocytopenia, bleeding and osteoporosis [3]. Over the past two decades, LMWHep, which are fragments of unfractionated heparin with molecular weights ranging from 4200 to 6000 Daltons, have been investigated for the treatment of RVThromb, and have been found to exhibit several advantages over unfractionated heparin. The advantages of therapy with LMWHep include a more predictable anticoagulant response, better bioavailability, longer half-life and fewer complications. In addition, LMWHep may be used alongside many surgical procedures and medical conditions both for prophylaxis or treatment of arterial or venous thrombi, especially pulmonary embolism and deep-vein thrombosis in the outpatient setting [4]. Reports of cases in which RVThromb was treated with LMWHep in an outpatient setting are rare. In 1999, however, Tien *et al.* [5] reported the case of a pregnant woman suffering from nephrotic syndrome complicated with thromboses in the renal vein and inferior vena cava, a condition that was successfully treated using LMWHep. The RVThromb in our patient could have resulted from severe hypoalbuminaemia, her usage of oral contraceptives, and perhaps dehydration as a result of her viral gastroenteritis and the use of diuretics [6,7]. The suboptimal response to urokinase may have been due to the age of the thrombus. We surmised that the vaginal bleeding and persistent flank pain implied an inadequate response to, and complication from, the administration of unfractionated heparin and subsequently warfarin. Based upon these observations and conclusions we elected to utilize LMWHep to treat the patient's RVThromb.

Minimal-change disease has been considered to be a disorder of T-lymphocytes, which release a cytokine, injuring the glomerular epithelial cells and eliciting

reduced synthesis of the polyanion such as heparan sulphate [8]. The corticosteroid therapy referred to above suppressed the T-lymphocytes, and LMWHep, perhaps one might conjecture, increased glomerular basement membrane negative charge density by augmenting heparan sulphate proteoglycan synthesis [9], thus contributing to the subsidence of the patient's proteinuria. In addition, the anticoagulant effect of LMWHep halted the progression of the thrombus of our patient and facilitated the recanalization of the renal vein.

LMWHep obviates the need for substantial laboratory monitoring of patients with RVThromb, reduces hospital stays, and improves the quality of life of such patients [10]. Our case suggests that LMWHep may be a good alternative and an effective outpatient therapeutic agent when treating RVThromb. This group of compounds may also be used in patients with RVThromb for whom alternative thrombolytic therapies are contraindicated pregnant patients, who are taking drugs that may interfere with the action of warfarin, and especially those patients who previously have been unsuccessfully treated with a thrombolytic agent and unfractionated heparin.

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