Acute pyelonephritis with renal vein and inferior vena cava thrombosis and pulmonary emboli in poorly controlled type 2 diabetes and HHS

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Abstract
Renal vein thrombosis is a rare complication of acute pyelonephritis. We report a case of a 56-year-old woman with poorly controlled type 2 diabetes mellitus who presented with acute pyelonephritis and hyperglycaemic hyperosmolar state (HHS), complicated by thrombosis of the renal vein extending into the inferior vena cava. She was managed with intravenous antibiotics, intravenous fluids and insulin and with therapeutic low molecular weight heparin, despite which she developed pulmonary emboli two days after the diagnosis of renal vein and inferior vena caval thrombosis. Following optimisation of the dalteparin dose with factor Xa monitoring and a prolonged course of antibiotics, she made a full recovery. Two months post-treatment there was resolution of the renal vein thrombosis and pulmonary emboli with improvement of inflammation of the right kidney on repeat computer tomography scanning.

This case highlights the need to recognise renal vein thrombosis and pulmonary emboli as complications of acute pyelonephritis, especially in combination with poorly controlled diabetes mellitus, which further increases the hypercoaguable state. Copyright © 2016 John Wiley & Sons.

Key words
pyelonephritis; renal vein; thrombosis; pulmonary embolism; diabetes

Introduction
Renal vein thrombosis is most commonly seen in association with nephrotic syndrome or thrombosis.1,2 Renal vein thrombosis as a complication of acute pyelonephritis is rare and poorly recognised.3 The literature is confined to a few case reports.3–8 Acute pyelonephritis and sepsis can cause a hypercoaguable state which may predispose to thrombosis of the renal vein.3 Combining this with hyperglycaemia in uncontrolled diabetes may cause the hypercoaguable state to increase further.9

As renal vein thrombosis in acute pyelonephritis can extend into the inferior vena cava and be complicated by pulmonary emboli, it is important to recognise and treat this complication promptly.

Here we report a case of renal vein thrombosis that developed in association with acute pyelonephritis in a patient with poorly controlled type 2 diabetes mellitus.

Case history
A 56-year-old female presented with a one-week history of vomiting, abdominal pain and general malaise. There were no other positive symptoms. She had a past medical history of type 2 diabetes mellitus, poorly controlled on an oral hypoglycaemic agent (metformin), and of hypertension treated with amlodipine 10mg and ramipril 10mg daily. Body mass index was 35.6.

Vital signs on admission included a temperature of 38.7°C, pulse of 112/min, blood pressure of 188/96mmHg, respiratory rate of 23/min, and oxygen saturations of 97% on room air. Cardiopulmonary, abdominal and neurological examinations were unremarkable.

Initial laboratory data showed a white cell count of 33.2x10^9/L, neutrophils 30.59x10^9/L; sodium 121mmol/L, potassium 6.7mmol/L, urea 25.6mmol/L; creatinine 151μmol/L (calculated creatinine clearance 49.7ml/min); C-reactive protein 161.4mg/L; haemoglobin 124g/L, platelets 344 x10^9/L; blood ketones 3.7mmol/L; calculated plasma osmolality 324mOSM/kg by JBDS criteria; HbA1c 124mmol/mol. Liver function tests were normal. Urinary dipstick was positive for ketones, glucose and blood, but negative for nitrates and leucocytes. Blood cultures were taken on admission. Chest and abdominal
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Case report

X-rays were normal; electrocardiogram showed sinus tachycardia.

The patient was treated for mild hyperglycaemic hyperosmolar state (HHS) with ketosis and for systemic inflammatory response syndrome with the source of potential sepsis unknown. Seven hours after treatment was initiated blood glucose had fallen to 17 mmol/L and calculated osmolality to 297 mosm/kg. Six litres of intravenous fluids and 1.5 litres of oral fluids were given within the first 24 hours, achieving a positive balance of 4.5 litres. Broad-spectrum intravenous antibiotics and prophylactic dalteparin were instituted.

The patient was seen by the consultant the next day. She did not complain of abdominal pain but on examination her abdomen was obese and a large, tender mass was felt in the right flank. The patient underwent a computer tomography (CT) scan of abdomen and pelvis (Figure 1) which found the right kidney to be remarkably abnormal with multiple foci of low density plus surrounding inflammatory change, in keeping with acute pyelonephritis. A right renal vein thrombosis was also found, extending into the inferior vena cava. The patient was therefore started on weight-based therapeutic dalteparin. Initial blood cultures subsequently grew E. coli and intravenous Tazocin was continued. Further investigation ruled out nephrotic syndrome (urine protein 0.65g/L).

On day 4 the patient developed chest tightness and shortness of breath. A CT pulmonary angiogram showed acute bilateral pulmonary emboli with no right heart strain. It also identified focal lingular and left hilar consolidation representing infection or infarction; a follow-up CT was advised after eight weeks. The case was discussed with haematology colleagues and the dose of dalteparin was increased to 10 000 units twice daily with anti Xa monitoring (therapeutic range for twice-daily dosing 0.5–1.0 U/ml). An inferior vena cava filter was not inserted as therapeutic anticoagulation was not contraindicated and the dose of dalteparin was now optimised and monitored by anti Xa levels; in light of the sepsis there was also the potential risk of infection of the filter.

After 14 days of intravenous Tazocin, antibiotics were changed to oral ciprofloxacin. A repeat CT renal showed appearances consistent with pyelonephritis, a well-defined thrombus in the right renal vein extending into the inferior vena cava, and no new changes. Urology advised that no surgical intervention was required.

The patient was discharged 17 days after admission. She had no pyrexia for 48 hours and her white cell count and C-reactive protein level had improved. It was advised that she complete four weeks of ciprofloxacin (six weeks of antibiotics in total) and have a repeat CT renal one week prior to completion. On discharge, dalteparin was changed to once-daily dosing with anti Xa monitoring; it was subsequently changed to oral anticoagulation with warfarin.

The patient’s blood glucose was controlled quickly during insulin infusion and, once eating and drinking, on a twice-daily insulin mixture. Subsequently, it was possible to wean the insulin and achieve excellent glucose control on low-dose gliclazide and metformin. The patient’s HbA1c two months post-discharge had fallen to 58mmol/mol.

Repeat CT imaging of the chest, abdomen and pelvis two months after discharge showed resolution of the renal vein thrombus and pulmonary emboli previously noted, and significant improvement of the inflammatory stranding around the right kidney.

Discussion

Renal vein thrombosis is an uncommon complication of acute pyelonephritis. In adults, nephrotic syndrome (especially membranous nephropathy) is the most common cause. This results from a hypercoagulable state, due to heavy proteinuria leading to acquired anti thrombin deficiency and decreased osmotic pressure. Other potential causes include renal malignancy, renal transplantation, other hypercoagulable states, and antiphospholipid syndrome.

It is striking that previous case reports of renal vein thrombosis secondary to acute pyelonephritis have frequently documented newly diagnosed or poorly controlled diabetes mellitus. Our patient had severe hyperglycaemia and mild HHS on a background of poorly controlled diabetes and significant obesity. Her renal mass was not detected on abdominal examination until day 2 of her admission, suggesting that...
either her obesity made the mass difficult to detect or that the thrombosis occurred or extended after her admission. She had no symptoms to suggest renal vein thrombosis and there were no clinical indications to start therapeutic anticoagulation on admission. Although significantly dehydrated she was treated aggressively with intravenous fluids during the first 24 hours; occurrence or extension of renal vein thrombosis during this time cannot therefore be attributed to inadequate fluid resuscitation.

Diabetes is associated with an increased risk of venous as well as arterial thrombosis. It is likely that the prothrombotic effect of diabetes is due to a combination of the pathophysiological mechanisms described by Virchow: damage to the vessel wall (endothelial damage), reduction of blood flow (stasis) and hypercoagulability of the blood. Poorly controlled type 2 diabetes is associated with high levels of plasminogen activator inhibitor-1 (PAI-1) resulting in reduced fibrinolysis. In the laboratory, procoagulant effects of both hyperinsulinaemia and hyperglycaemia have been demonstrated: levels of tissue factor procoagulant activity (TF-PCA), plasma factors VII, VIII and thrombin-antithrombin (TAT) complexes in people with diabetes were raised independently by increasing glucose and insulin levels and were reduced by normalising glucose levels. Hyperglycaemia also has a procoagulant action by affecting the glycocalyx in the vascular endothelium, promoting platelet-endothelial cell adhesion and releasing coagulation factors. Furthermore, hyperglycaemia causes increased glycation of proteins, including clotting factors, which may also contribute to the prothrombotic effect by causing denser fibrin clots and reduced fibrinolysis.

It is likely therefore that this patient’s acute severe hyperglycaemia and chronically poorly controlled diabetes were contributory factors to the development of renal vein thrombosis in the context of pyelonephritis. She also had sepsis with Gram-negative bacteraemia, features which have been associated with renal vein thrombosis in pyelonephritis. Endotoxins released from Gram-negative bacteria can cause disruption of the endothelial lining of blood cells predisposing to thrombosis. It has also been reported that acute pyelonephritis may be associated with renal vein thrombophlebitis, again predisposing to thrombosis. In our patient, the raised BMI was another general risk factor for thrombosis.

Extension of thrombosis into the inferior vena cava and pulmonary emboli have both been reported previously as complications of renal vein thrombosis. Management is by anticoagulation alongside treatment of the underlying cause. The recurrence rate after anticoagulation has been discontinued is less than that for patients with deep vein thrombosis, suggesting renal vein thrombosis is a distinct clinical entity associated with its underlying cause.

**Conclusion**

This is an unusual case of renal vein and inferior vena cava thrombosis secondary to acute pyelonephritis in a patient with poorly controlled type 2 diabetes and acute severe hyperglycaemia. The patient developed pulmonary emboli despite therapeutic anticoagulation with low molecular weight heparin. This case highlights the need to recognise renal vein thrombosis and pulmonary embolism as complications of acute pyelonephritis, particularly in patients with diabetes. Finally, it illustrates that full recovery with resolution of renal vein thrombosis and pulmonary emboli can occur with conventional medical treatment, including optimisation of low molecular weight heparin treatment by factor Xa monitoring.

**Declaration of interests**

There are no conflicts of interest declared.

**References**


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