CASE REPORT

Life-threatening Wunderlich's syndrome with concurrent clopidogrel use

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SUMMARY

Spontaneous non-traumatic renal haemorrhage, or Wunderlich's syndrome, is a rare but potentially life-threatening event. We present the case of a 63-year-old man on clopidogrel who became haemodynamically unstable as a result of this condition. Angioembolisation revealed the unusual finding of active bleeding from multiple distinct subsegmental renal vessels, for which haemostasis was successfully achieved by coil placement. The patient remains well and with near-normal renal function on follow-up.

BACKGROUND

Wunderlich's syndrome is an uncommon but dangerous condition, in which spontaneous renal haemorrhage occurs in the absence of trauma. It can be the first presentation of renal malignancy, angiomyolipoma (AML), renal artery aneurysm or arteriovenous malformation (AVM). Conservative management in this case was not successful, and intervention was needed. This revealed interesting pathology, with active haemorrhage from multiple subsegmental renal arteries.

CASE PRESENTATION

A 63-year-old male patient presented with 10 hours of abdominal pain from right loin to right iliac fossa, which developed acutely while carrying heavy baskets at home. He denied trauma or other symptoms.

The patient had a history of right renal colic 9 months prior and had a non-contrast CT scan at that time. This revealed a right renal calculus, subsequently treated endoscopically, with no other abnormalities detected. No contrast-enhanced renal imaging was available.

He also had a history of an appendectomy, thyroidectomy, tonsillectomy, type 2 diabetes mellitus, hypertension, hypercholesterolaemia and treated for iron deficiency due to endoscopically confirmed gastric ulcer. Additionally, he reported asymptomatic coronary artery disease, with one bare metal stent to the right coronary artery placed 4 years prior, using clopidogrel since then. A screening colonoscopy 5 years prior had been unremarkable. The patient was a lifelong smoker of 25 cigarettes per day, reported minimal alcohol use and had neither allergies nor significant family history.

The patient's medications consisted of clopidogrel 75 mg once daily (OD), atenolol 50 mg OD, pantoprazole 40 mg OD, irbesartan 300 mg OD, hydrochlorothiazide 25 mg OD, moxonidine 400 mg OD, tamsulosin 400 mg OD, atorvastatin

40 mg OD and fenofibrate 145 mg OD, as well as metformin 1 g twice daily (BD), lercanidipine 10 mg BD, and thyroxine dose alternating each day between 150 and 200 mg.

On examination, he appeared well, of normal mentation and undistressed. His pulse rate was 73 bpm, blood pressure 128/73 mm Hg, tympanic temperature 36.4°C and saturating 97% on room air per pulse oximetry. Chest auscultation revealed a soft early systolic murmur and decreased air sounds at the right lung base, without adventitious sounds. His abdomen was soft but moderately tender in his right costovertebral angle and right upper and lower abdomen, without rebound or percussion tenderness, visible discoloration or evidence of hernia. The bladder was not distended, and no renal masses were palpable. Genital examination was normal.

INVESTIGATIONS

Initial blood laboratory results showed haemoglobin 136 g/L, white cell count $11.8 \times 10^9/L$ and platelet count of $201 \times 10^9/L$. Urea was 5.6 mmol/L, creatinine 104 micromol/L ($\mu\text{mol/L}$), with an estimated glomerular filtration rate (eGFR) of 65 mL/min/1.73 m². Electrolytes and erythrocyte sedimentation rate were normal. C reactive protein was mildly elevated at 85 mg/L. International normalised ratio was 1.2, and activated partial thromboplastin time was 24 s. Urine dipstick was positive for microscopic haematuria only. Urine microscopy revealed an elevated concentration erythrocytes and no other abnormality. ECG and chest X-ray were normal.

The patient was suspected to have renal colic, given his flank pain and past history of urolithiasis, and a plain CT scan of the abdomen and pelvis was ordered. This revealed a $6 \times 12 \times 10$ cm haematoma in continuity with the right kidney and predominantly in the anterior pararenal space. The ipsilateral collecting system and contralateral kidney appeared normal. All other abdominal viscera were unremarkable, and there was no lymphadenopathy.

DIFFERENTIAL DIAGNOSIS

At presentation (day 1), it was felt that this patient's spontaneous non-traumatic renal haemorrhage most likely stemmed from a poorly visualised underlying neoplasm. Other known causes of the syndrome were considered possible, such as ruptured haemorrhagic cyst, renal artery aneurysm or AVM, while inflammatory markers were not consistent with vasculitis. It is possible that heavy lifting at the time of symptom onset may have

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involved an auto-Valsalva manoeuvre, which has been associated with Wunderlich's syndrome previously.¹

TREATMENT

The patient's clopidogrel use was suspended, his blood type determined and cross-matching performed. Given that the patient was initially stable physiologically and biochemically, the decision was made to manage the patient conservatively with fasting, fluid resuscitation, bed rest and repeat haemoglobin testing every 6 hours. However, over the following 12 hours, the patient's condition slowly deteriorated. He reported worsening pain and became tachycardic and hypotensive. Laboratory results 24 hours after initial presentation revealed a haemoglobin decrease to 87 g/L. Serum creatinine had increased to 241 $\mu\text{mol/L}$ prior to the contrast CT scan and has since risen further to 299 $\mu\text{mol/L}$, with eGFR 18 mL/min/1.73 m². CT angiogram, performed 12 hours after the initial scan, showed no increase in haematoma size but did reveal a tiny focus of arterial enhancement with accumulation on delayed imaging at the posterolateral aspect of the right kidney, suspicious for active haemorrhage (figure 1). No causative lesion was seen, nor change in overall haematoma size compared with the plain scan. The patient was assessed as having significant ongoing haemorrhage and evolving acute kidney injury. This was assessed as due mainly to haemorrhagic hypovolaemia with a possible degree of contrast-induced nephropathy.

The decision was made to angioembolise in a low-contrast-dose technique after first transfusing 2 units of packed red cells and 1 unit of platelets, to further resuscitate, aid haemostasis and offer maximum protection against further renal injury. Angiography, on day 2 of admission, revealed active

extravasation from subsegmental vessels in the right renal upper, mid and lower poles, and no other causative lesion. Three 2-mm-diameter Interlock microcoils and two 3 mm-diameter Helical coils (Boston Scientific, Natick, Massachusetts, USA) were deployed, with successful haemostasis (figure 2).

OUTCOME AND FOLLOW-UP

The patient suffered a hyperactive delirium postoperatively, requiring propofol and norepinephrine infusions. He also received further blood product transfusions. During his admission, these totalled 4 units of packed red cells and 2 units of platelets.

Fluid resuscitation was managed carefully. On the day of admission, the patient fasted and had strict fluid balance monitoring. Input over the first 3 days totalled 4082 mL with nil oral, 1880 mL including 290 mL via nasogastric tube (NET) and 2031 mL including 580 mL via NET. These figures include the transfusions mentioned above. The total urine output for the same 3 days was 835, 2960 and 3005 mL, respectively.

On day 3, the patient's mentation returned to normal, and he became asymptomatic, with no further pain. His serum haemoglobin and eGFR improved, and the patient was discharged on day 7 of admission.

Follow-up results 4 days later (day 11) revealed further improvement in serum haemoglobin to 109 g/L, serum creatinine to 90 $\mu\text{mol/L}$, with eGFR at 77 mL/min/1.73 m². The patient shared follow-up with our department and his general practitioner. This includes repeat blood tests, and a contrast CT scan of the abdomen and pelvis 3 months postprocedure to confirm the degree of renal atrophy, haematoma resolution and absence of causative lesion.

Figure 1 Contrast CT scan of the abdomen and pelvis during arterial phase; axial and coronal views. A focus of enhancement is seen posterolateral to the right inferior renal pole within the large subcapsular haematoma, suspicious for active haemorrhage.

Figure 2 Plain films of the right kidney during angioembolisation. On the initial plain film, contrast from the catheter within the right renal artery can be seen extravasating from several points along the lateral renal cortex. The second film taken at the conclusion of the procedure shows five coils within subsegmental arteries of the right kidney, and no further extravasation.

DISCUSSION

Spontaneous non-traumatic renal haemorrhage was first described by Bonet in 1679 and then a German physician Carl Reinhold August Wunderlich in 1856, from whom the syndrome takes its name. The largest systematic review to date comprises only 165 cases.² Approximately two-thirds of cases are due to neoplasms, which are approximately evenly split between benign, usually AMLs, and malignant, usually renal clear cell carcinomas. Other causes include vasculitis, typically polyarteritis nodosa, as well as AVM, renal cystic and calculous disease, nephritis and systemic coagulopathies. No cause is found in up to 7% of cases, as in our patient.

The classical presentation is Lenk's triad of flank pain, flank mass and hypovolaemic shock. However, patients may display nausea, low-grade fever and acute abdomen mimicking appendicitis, dissecting aortic aneurysm or perforated viscus. The timing and intensity of symptoms will relate to the rapidity, volume and duration of the blood loss. In our patient, hypovolaemic shock took 18 hours to fully develop and responded only transiently to resuscitative efforts, indicating slow persistent haemorrhage.

Giving its rarity and risk, imaging is fundamental to correct diagnosis and management. CT scanning remains the gold standard, with multiple studies reporting 100% sensitivity in detecting perirenal haemorrhage,^{2 3} although with only 60% sensitivity in determining the causative lesion. Ultrasound scanning is barely 50% sensitive in detecting the haemorrhage; however, it has the advantage of being quick, inexpensive and without radiation risk. Angiography is necessary when CT scan fails to find a cause. It is well suited for detecting AVMs but poorly sensitive for neoplasms.³ MRI may be useful in delineating parenchyma from blood but has limitations of cost, availability and again sensitivity.

The last half-century has seen a revolution in the treatment of Wunderlich's syndrome. Authors once deemed nephrectomy as the treatment in all cases, warning 'conservative therapy is uniformly unsuccessful'.⁴ However, more recently, management has evolved to resemble that of renal trauma (table 1). Regardless of the degree of severity and intervention chosen, all patients should receive other staples of renal haemorrhage management such as bed rest and serial serum haemoglobin measurement.⁵

After the incident admission, follow-up care should include CT scans, to assess for the resolution of haematoma and to detect the underlying cause if not initially clear, as in our case. Blood pressure monitoring is also required to monitor for the

development of hypertension secondary to extrinsic compression of renal parenchyma, known as Page kidney.

Haemorrhage may be more severe in the presence of anticoagulation, and so an understanding of anticoagulant medications and their reversal strategies is vital. Clopidogrel irreversibly inhibits ADP's P2Y₁₂ receptor on platelet membranes, hindering activation of glycoprotein GP IIa/IIIb, another membrane receptor integral in platelet degranulation and aggregation via fibrin. Other than suspending administration, optimal reversal therapy is still being defined.⁶

Patient's perspective

'The pain in my side came suddenly. I thought I had colic again, but they said my kidney was bleeding. They gave me some blood on the first night when my numbers got worse. On the second day, they treated the bleeding with tubes through the groin. They tell me I was very sick for a couple days. I only remember some things, and then I was back to normal. Many teams visited during my stay and it was great to see them work together.'

Learning points

- ▶ Wunderlich's syndrome of spontaneous non-traumatic renal haemorrhage is a rare and dangerous differential in patients with flank pain or acute abdomen.
- ▶ Neoplasms and vascular disease are the most common aetiologies, but occasionally no cause is found.
- ▶ Angioembolisation or nephrectomy is necessary for severe symptoms, enlarging haematoma or haemodynamically unstable patients.

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REFERENCES

- 1 Lin HW, Tsao YT, Lin YF, *et al*. In-flight Valsalva maneuver induced life-threatening Wunderlich syndrome. *Am J Emerg Med* 2008;26:732.e5–6.
- 2 Zhang JQ, Fielding JR, Zou KH. Etiology of spontaneous perirenal hemorrhage: a meta-analysis. *J Urol* 2002;167:1593–6.
- 3 Belville JS, Morgentaler A, Loughlin KR, *et al*. Spontaneous perinephric and subcapsular renal hemorrhage: evaluation with CT, US, and angiography. *Radiology* 1989;172:733–8.
- 4 McDougal WS, Kursh ED, Persky L. Spontaneous rupture of the kidney with perirenal hematoma. *J Urol* 1975;114:181–4.
- 5 Shoobridge JJ, Corcoran NM, Martin KA, *et al*. Contemporary management of renal trauma. *Rev Urol* 2011;13:65–72.
- 6 Berndtson AE, Coimbra R. The epidemic of pre-injury oral antiplatelet and anticoagulant use. *Eur J Trauma Emerg Surg* 2014;40:657–69.

Table 1 Current management of Wunderlich's syndrome

Patient severity	Standard treatment
Minimally symptomatic patients	Fluid resuscitation and analgesia
Patient with gradual deterioration, active haemorrhage or enlarging haematoma	Angioembolisation
Patently unwell or unstable patients	Emergent nephrectomy

This table is a guide only. Treatment choice will vary according to patient factors, local resources and experience of the attending surgeon.

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