Bilateral renal hemorrhage due to polyarteritis nodosa wrongly attributed to blunt trauma

Ihab El Madhoun, Niall G. Warnock, Anu Roy and Colin H. Jones

Background. A 36-year-old, previously healthy man presented to an accident and emergency department with right-sided abdominal pain 7 days after he sustained a trauma to his right flank. He was using no medication other than over-the-counter analgesics since his injury.

Investigations. Complete blood count, serum creatinine measurement, liver function tests, hepatitis B and C screening, abdominal CT, renal angiography, surgical exploration and histology of kidney samples.

Diagnosis. Polyarteritis nodosa with Page kidney causing bilateral perirenal hematoma, severe hypertension and renal failure.

Management. The patient was severely anemic, and his bleeding was investigated. A 15×13×12 cm retroperitoneal hematoma was found in the region of the right kidney and the patient underwent unilateral right nephrectomy. 3 weeks after discharge the patient was readmitted with a left-sided perirenal hematoma. Steel-coil embolization of the kidney stopped the bleeding but the patient developed hypertension and renal failure, and antihypertensive agents and dialysis were started. Microaneurysms and vessel-wall necrosis were discovered on re-examination of the angiogram and histology, respectively, so immunosuppressive therapy was started, comprising intravenous methylprednisolone daily for 3 days and oral prednisolone and intravenous cyclophosphamide for 4 weeks. Page kidney, resulting from the bleeding into the solitary kidney, caused stretching of the renal artery and deterioration of renal function, which required hemodialysis treatment.

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The case

A 36-year-old, previously healthy man presented to an accident and emergency department with severe abdominal pain 7 days after being kicked in his right flank by a cow. Pain had developed gradually after the trauma, and, despite the use of simple, over-the-counter analgesics, had become so severe that the patient decided to visit hospital.

The patient's medical, surgical and family history was unremarkable, and he had not been taking any medication before the accident. He was an ex-smoker and occasionally drank alcohol. Complete blood count revealed anemia (hemoglobin level 86 g/l; normal range 140–175 g/l). The patient's serum creatinine level was elevated (147 μmol/l; normal range 53–106 μmol/l), but liver function test results were normal. Screening for hepatitis B and C was negative. Because of the nature of the clinical presentation and the marked anemia, intra-abdominal bleeding was suspected. Abdominal CT showed a 15×13×12 cm retroperitoneal hematoma in the region of the right kidney (Figure 1). The patient was admitted to the urology department.

Because of the worsening hypotension and falling hemoglobin level, the treating urologist decided to perform surgical exploration, which revealed the hematoma and severe distortion of the right kidney. The affected kidney was deemed unsalvageable and right nephrectomy was performed. The patient made an uneventful recovery and was discharged home 7 days after surgery.

3 weeks later, the patient was readmitted through the accident and emergency department with left-sided abdominal pain and collapse associated with hypotension. He also complained of severe headache. Repeat abdominal CT showed a new left-sided subcapsular, perirenal hematoma (Figure 2). During renal angiography, a bleeding point was selectively embolized with a fibered steel coil, which appeared to stop the bleeding. The patient required two units of blood transfusion as part of the initial resuscitation treatment. The next day, he developed severe hypertension, with a diastolic blood pressure ~130 mmHg, and a further deterioration in kidney function. A nephrology consultation was requested.

The renal angiogram was re-examined, which revealed the presence of multiple microaneurysms suggestive of polyarteritis nodosa (PAN) (Figure 3). Antineutrophil cytoplasmic antibodies were not detected. Further detailed histopathological examination of multiple sections from the right nephrectomy specimen showed focal areas of coagulative necrosis and infarction.

Competing interests
The authors declare no competing interests.

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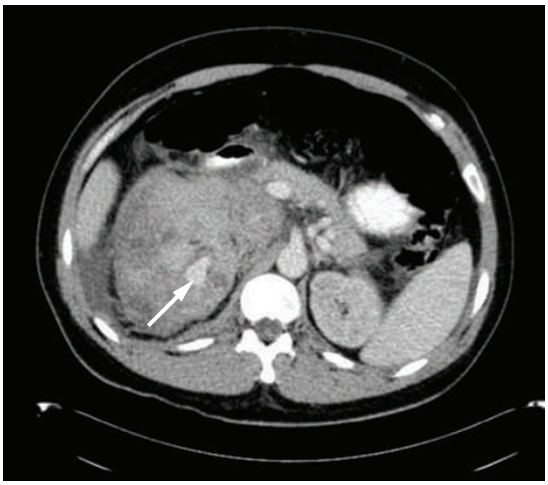

Figure 1 | Abdominal CT performed at the patient's first presentation. The image shows retroperitoneal bleeding around the right kidney (arrow).

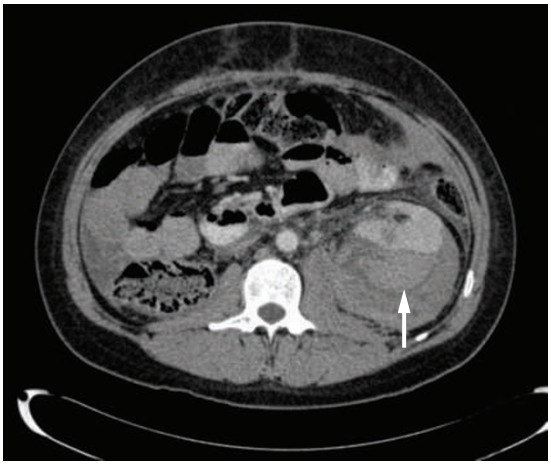

Figure 2 | Abdominal CT performed at the patient's second presentation. The image shows subcapsular and perirenal hematoma around the left kidney (arrow).

Some of the medium-sized arteries showed evidence of fibrinoid necrosis of the vessel walls associated with an inflammatory infiltrate, which included neutrophils, lymphocytes, macrophages and a few eosinophils (Figure 4). The smaller arteries and arterioles did not show necrosis. Some of the vessels showed thrombus formation. The glomeruli displayed minor ischemic changes, but were otherwise normal, and there was no histological evidence of associated glomerulonephritis. The presence of only medium-sized vessel involvement with no histological evidence of associated glomerulonephritis, together with the clinical and radiological findings, was consistent with a diagnosis of PAN.

Over the next 3 days, the patient's hypertension was managed with the sequential introduction of a combination of antihypertensive drugs, including long-acting nifedipine (up to 60 mg per day), atenolol (50 mg per day), hydralazine (up to 50 mg twice daily) and intravenous nitrates. However, despite improvement of his hypertension, renal function worsened and hemodialysis was initiated.

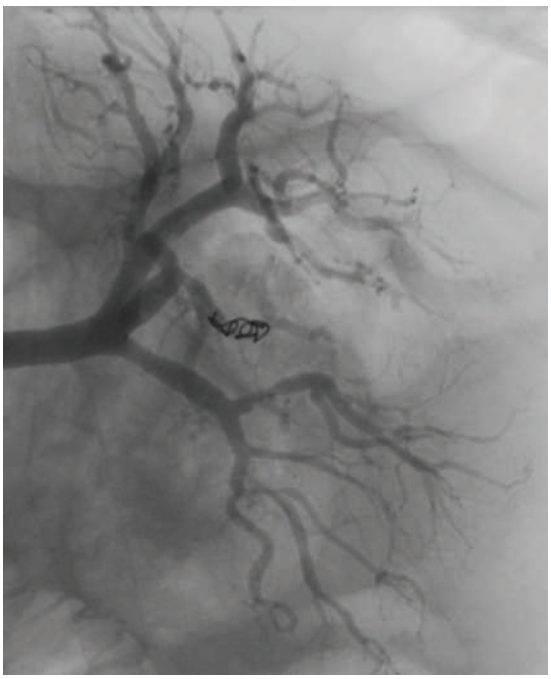

Figure 3 | Left renal angiogram. The image shows multiple small aneurysms and the embolization coil.

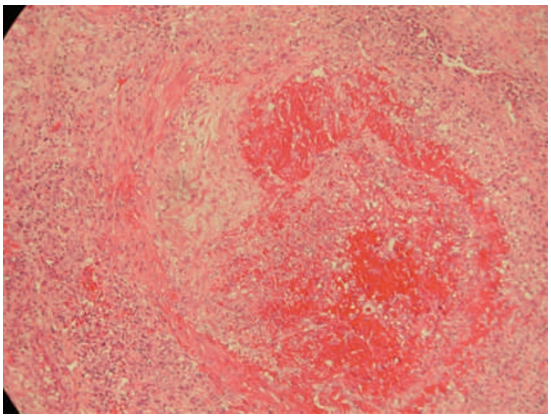

Figure 4 | Photomicrograph of a medium-sized artery. The image shows fibrinoid necrosis of the vessel wall associated with an inflammatory infiltrate, which comprised neutrophils, lymphocytes, macrophages and a few eosinophils. Original magnification ×40; hematoxylin and eosin stain.

Once hypertension was controlled, immunosuppressive therapy comprising intravenous methylprednisolone (500 mg per day for 3 days), intravenous cyclophosphamide (12.5 mg/kg once a fortnight) and prednisolone (initial dose 1 mg/kg, tapered weekly) was commenced. After 4 weeks of treatment, the patient's urine output improved and he regained sufficient renal function to discontinue dialysis and return home.

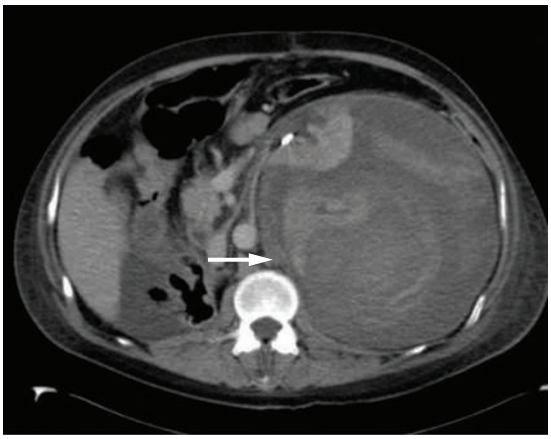

Figure 5 | Abdominal CT performed at the patient's third presentation. The image shows the expanded left subcapsular and perirenal hematoma and stretching of the left renal artery (arrow).

Box 1 | American College of Rheumatology criteria for the classification of PAN[8]

- Weight loss ≥4 kg
- Livedo reticularis
- Testicular pain or tenderness
- Myalgias
- Mononeuropathy or polyneuropathy
- Diastolic blood pressure >90 mmHg
- Elevated blood urea nitrogen or serum creatinine levels
- Presence of hepatitis B reactants in serum
- Arteriographic abnormality
- Presence of granulocyte or mixed leukocyte infiltrate in an arterial wall on biopsy

The presence of three criteria is required for a diagnosis of PAN. Abbreviation: PAN, polyarteritis nodosa.

2 weeks after discontinuation of dialysis, the patient presented again with further left-sided abdominal pain, hypertension, anuria and acute-on-chronic renal failure. Abdominal CT revealed expansion of the left subcapsular hematoma with compression of the renal parenchyma and stretching of the renal artery (Figure 5), suggesting a diagnosis of Page kidney.[1] This was the probable cause of the further deterioration of renal function: at this presentation, his creatinine level was very high (~600 μmol/l). The patient required a further 2 weeks of hemodialysis, after which his creatinine level was 272 μmol/l without dialysis support. The patient continued to receive daily oral prednisolone and intravenous cyclophosphamide, with the intention of switching to oral azathioprine once clinical remission had been achieved.

Diagnosis

PAN, which was first described in 1866 by Kussmaul and Maier, is a systemic disease characterized by necrotizing inflammatory lesions that predominantly affect medium-sized blood vessels. The disease can involve various organs, including the skin, kidneys, gastrointestinal tract, peripheral nervous system and joints, but has a tendency to spare the lungs. The prevalence of PAN varies geographically from 2–33 per million population, and affects adults and children and is more frequent in males than females (ratio approximately 3:2).[2–4] Most cases of PAN are idiopathic, but an association with hepatitis B infection has been described; in one French retrospective study, one-third of patients with PAN also had hepatitis B infection.[5] PAN can develop secondary to other conditions, such as connective tissue diseases (for example, systemic lupus erythematosus[6]) and hairy cell leukemia.[7]

The pathological mechanisms by which PAN affects blood vessels are poorly understood. An immune-complex mechanism is thought to be involved in some cases, but how the immune stimulus precipitates disease is not clear. The inflammation of blood vessel walls and intimal thickening can lead to luminal narrowing, causing ischemia and infarction of the affected areas. The effects on the vascular wall can also lead to microaneurysm formation. At the renal level, localized infarction and ischemia can result in activation of the renin–angiotensin system, causing hypertension, and aneurysm rupture can lead to bleeding and hematoma formation, as we saw in the patient we report.

Variability in the presentation and the multisystemic nature of symptoms can make differentiation of PAN from other forms of vasculitis difficult. The American College of Rheumatology created a set of 10 criteria for the classification of PAN (Box 1). The presence of three of these criteria (the minimum number required to make a diagnosis) has 82.2% sensitivity and 86.6% specificity for a diagnosis of PAN.[8]

Laboratory testing is often unhelpful in the diagnosis of macroscopic PAN. While the presence of an active urinary sediment (hematoproteinuria and red cell casts) and positivity for anti-neutrophil cytoplasmic antibodies are characteristic of small vessel vasculitides (including Wegener granulomatosis and microscopic polyarteritis), these investigations are often negative in patients with macroscopic PAN. The demonstration of aneurysms of the medium-sized arteries of the affected tissues is considered diagnostic. A tissue-based diagnosis is considered essential for small vessel vasculitis, but is not routinely performed in the diagnostic work-up of PAN. This is because angiography is usually diagnostic; needle biopsy is often unhelpful because the disease affects medium-sized arteries rather than small vessels and is highly focal. Anecdotally, needle biopsy is associated with a higher risk of postbiopsy hemorrhage in patients with PAN owing to the risk of rupturing an aneurysm.

The current patient had decreased renal function, indicated by raised creatinine levels, hypertension and microaneurysms detected on angiography. Histological analysis of the removed right kidney showed necrosis

and inflammation of the medium-sized blood vessels and the presence of an inflammatory infiltrate. These findings were consistent with a diagnosis of PAN. The cause of the patient's renal failure on his third presentation was identified as Page kidney. This condition occurs when the kidney is compressed, usually by a subcapsular hematoma (as was the case in the current patient) or, more rarely, a cyst or tumor, with a consequent decrease in renal blood flow, hyper-reninemia, hypertension and acute renal failure. John *et al.*[9] reported a case of Page kidney resulting in acute failure of the solitary kidney in a patient who had undergone partial nephrectomy for renal cell carcinoma. It has also been reported as a complication of percutaneous antegrade endopyelotomy[10] and after allograft kidney biopsy.[11]

The presentation and clinical course of the current patient was remarkable for two reasons. Firstly, his recent history of abdominal trauma led the treating surgeon to believe that this was the cause of the bleeding. This presumed etiology was not initially questioned during his second admission with left-sided perinephric hemorrhage. The subsequent development of hypertension and severe renal impairment, however, prompted review of the case and PAN was suspected on the basis of microaneurysms seen on the renal angiogram. Secondly, bilateral perirenal hematoma is an unusual presentation of PAN. Perirenal hematoma can have several other potential causes, including familial Mediterranean fever,[12] sudden relief from a severely enlarged bladder (for example, following urinary catheterization),[13] eclampsia,[14] tetralogy of Fallot,[15] angiomyolipoma,[16] renal tumors,[17] previous lithotripsy,[18] Wegener granulomatosis[19] and Waldenström disease.[20] The patient's renal histology, however, showed no evidence of these other causes.

Treatment and management

Untreated PAN has high associated mortality, with survival at 1 year being only 50%.[21] The prognosis improves substantially when immunosuppressive therapy is administered: Phillip *et al.*[22] reported survival of 75–80% at 5 years. The core of therapy for PAN includes glucocorticoids and cyclophosphamide, and treatment regimens vary according to which organs are involved and the degree of disease severity. Glucocorticoids have been used as monotherapy in cases of mild disease, such as in patients with normal renal function and no gastrointestinal or neurological involvement. Cyclophosphamide can be used as an additional treatment, or as initial therapy in combination with steroids. The duration of treatment also varies according to the presentation and disease severity; a period of 6–18 months is usually sufficient. In a series of 260 patients, all patients requiring cytotoxic therapy were treated for 1 year.[23] However, some patients may require long-term, low-dose maintenance immunosuppression. In the current patient, we decided to use cyclophosphamide as part of the initial treatment. We aimed to induce rapid disease remission, maintain the remission for as long as possible and prevent other major organs from becoming affected. The patient tolerated immunosuppressive therapy well.

Plasma exchange has been advocated in the management of small vessel vasculitides complicated by severe renal failure.[24] However, a prospective, multicenter, randomized trial of 62 patients with macroscopic PAN showed that this approach in addition to glucocorticoids and cyclophosphamide was not superior to treatment with glucocorticoids and cyclophosphamide alone.[25] Plasma exchange is associated with a significant risk of bleeding complications, and given our patient's presentation and the lack of good evidence for benefit, plasma exchange was not initiated.

Conclusion

This case highlights a number of important points. Firstly, clinicians are taught to take a careful history and to listen to and value the opinion of their patients. In this case, the acceptance of a temporally remote trauma as an explanation for the patient's symptoms led to the erroneous diagnosis of a traumatic renal hemorrhage. Secondly, when a patient re-presents with new or worsening symptoms, the initial diagnosis needs to be re-examined in the context of this new information. If the diagnosis no longer fits, then all the available information needs to be reviewed and re-evaluated with the benefit of hindsight. Thirdly, macroscopic PAN is a focal disease. Initial examination of the nephrectomy specimen was interpreted in the context of the clinical history of trauma. Once PAN had been diagnosed on the basis of the renal angiogram, further examination of additional sections of renal tissue revealed the characteristic findings of PAN. These are rarely seen in the modern era of needle biopsy. Finally, Page kidney is an unusual finding in clinical practice. In our patient, this condition was well delineated on CT.

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