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Gastrointestinal

Paroxysmal nocturnal haemoglobinuria (PNH) manifesting on CT as a pathologic segment of small bowel

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ABSTRACT

Paroxysmal nocturnal haemoglobinuria, a rare, acquired, life-threatening disease of the blood, is characterised by a triad of haemolysis previously believed to occur mainly at night, bone marrow dysfunction, and thrombophilia. Paroxysmal nocturnal haemoglobinuria is customarily regarded to manifest clinically as haemolytic anaemia and haemoglobinuria experienced as reddened urine in the morning, pancytopenia, and thrombosis.

We describe a case in which an abnormal segment of small bowel as visualised on computed tomography was the principal sign of the disease process on presentation.

Case presentation

The patient, a 40-year-old man of Turkish origin, presented to the emergency department with a 1-day history of abdominal pain and loose stool. Apart from a low-grade fever of 37.6°C and a sinus tachycardia of 129 bpm, his physical observations were normal. Urinalysis was unremarkable. Haemoglobin was 164 g/L and the white cell count 14.5 × 10^9/L. Biochemistry revealed a lactate dehydrogenase of 249 IU/L and a C-reactive protein of 66 mg/L. The remaining parameters were normal. He underwent an emergency abdominal computed tomography (CT) scan, the findings of which are described in the following section.

Over the 3-month interval from his initial attendance at the emergency department until diagnosis, the patient had multiple emergency admissions to hospital with similar presentation on each occasion, the main complaint being severe abdominal pain. The pain, often epigastric but sometimes localised to the left iliac fossa, tended to be episodic, recurring every 3-4 days, and lasting from 2 to 3 hours before settling spontaneously. It was cramping and sharp in nature and was exacerbated by eating. There were no obvious precipitating factors. The pain was occasionally associated with pyrexia and a transient rise in inflammatory markers. Septic screens were repeatedly negative.

The patient also reported feeling hot and sweaty, having a reduced appetite, and loose stools, but no nausea or vomiting, and no dysuria or noticeable change in urine colour.

Other than tachycardia and pyrexia, routine physical observations were within their normal ranges. There was diffuse abdominal tenderness on clinical examination but no other significant findings.

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Investigations

On initial presentation, the patient underwent an intravenous and oral contrast-enhanced CT scan of the abdomen and pelvis, which revealed a grossly abnormal 30-cm segment of jejunum, approximately 50 cm distal to the duodenojejunal flexure (Figs. 1 and 2). This loop of jejunum had moderate concentric thickening, measuring up to 39 mm in diameter, with reduced attenuation of the wall. There was marked regular smooth thickening of the jejunal folds (*plicae circulares*) and localised stranding of the jejunal mesentery. The mesenteric vasculature was prominent with normal opacification of the mesenteric vessels, and small volume but prominent mesenteric lymph nodes measuring up to 7 mm across the short axis. There was no other definite small or large bowel abnormality, and in particular, the terminal ileum appeared normal. The other abdominal organs were unremarkable, and there was no retroperitoneal lymphadenopathy.

The patient was treated with antibiotics for presumed infection, pending a follow-up appointment with gastroenterology. However, over the following 5 weeks, the patient attended the emergency department on 2 more occasions with similar symptoms. A second intravenous and oral contrast-enhanced CT of the abdomen and pelvis was performed (Figs. 3 and 4), 40 days after the initial CT examination. This revealed resolution of the previous jejunal wall thickening and a reduction in the inflammatory changes in the adjacent mesentery, although minimal stranding and smaller mesenteric lymph nodes persisted. Of note, there were new filling defects consistent with

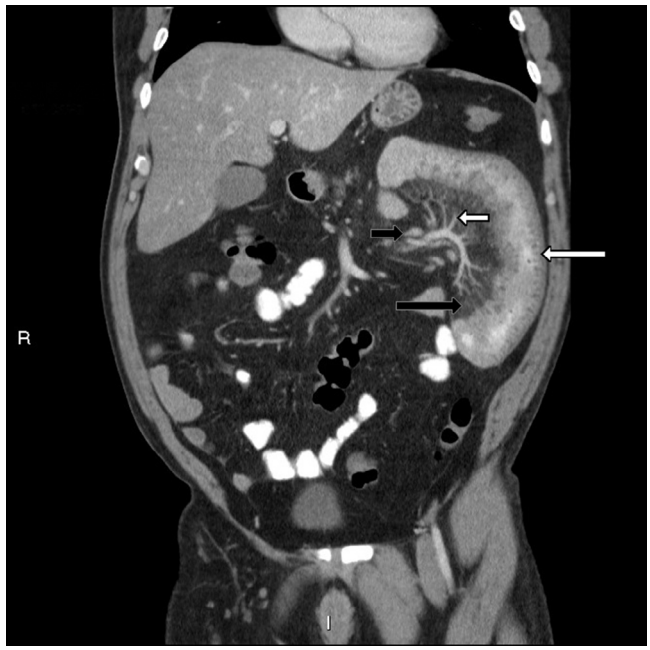

Fig. 2 – Coronal reformat of a computed tomography (CT) of the abdomen with intravenous and oral contrast, in the portal venous phase, showing marked thickening of a 30-cm loop of proximal jejunum. There is regular smooth jejunal fold thickening (long white arrow), and stranding of the mesentery (long black arrow) with engorgement of the draining veins (short white arrow) and prominent mesenteric lymph nodes (short black arrow).

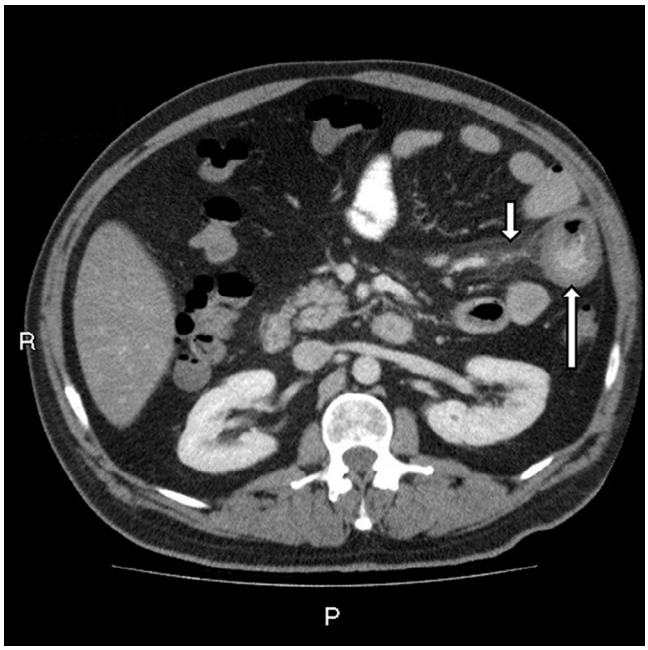

Fig. 1 – Axial image of a computed tomography (CT) of the abdomen with intravenous and oral contrast, in the portal venous phase. Marked concentric thickening of a proximal jejunal loop with reduced attenuation of the wall (long arrow), and localised stranding of the jejunal mesentery (short arrow).

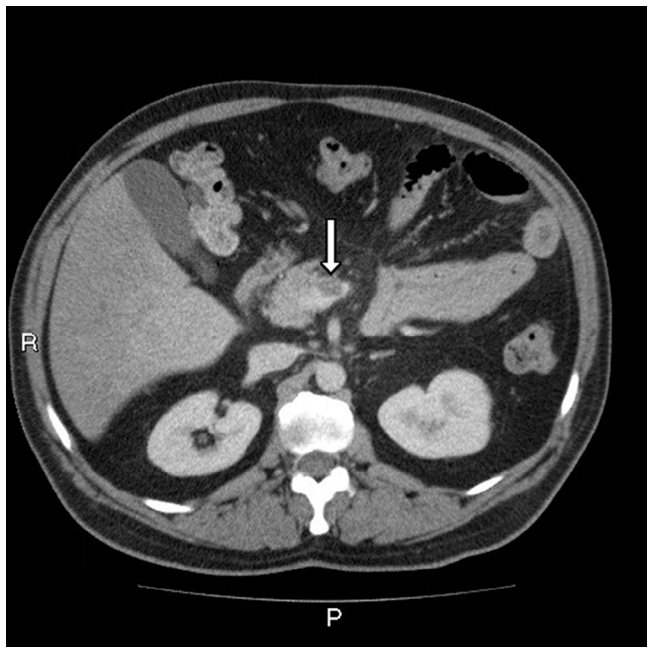

Fig. 3 – Axial image of a computed tomography (CT) of the abdomen with intravenous and oral contrast, in the portal venous phase. A non-occlusive thrombus can be seen within the superior mesenteric vein at the level of the pancreatic head (shown by the arrow).

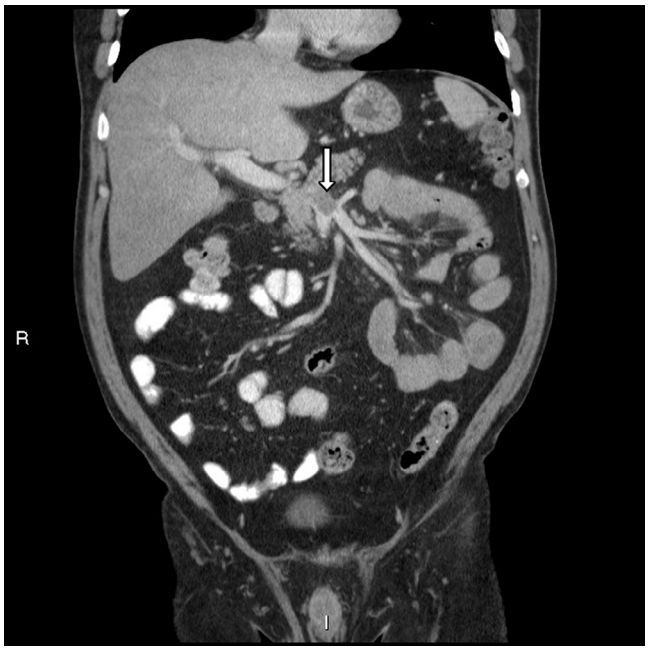

Fig. 4 – Coronal reformat of a computed tomography (CT) of the abdomen with intravenous and oral contrast, in the portal venous phase. Thrombosis can be seen at the confluence of the superior and inferior mesenteric veins (shown by the arrow).

thrombosis in the splenic vein adjacent to the splenic hilum, in the superior mesenteric vein at the junction of the superior mesenteric and portal veins, in the main portal vein, and in the left portal vein. The liver demonstrated a heterogenous attenuation with poorly defined hypodensities in the right and left lobes. No other abnormalities were evident.

Over the ensuing weeks, and after further admissions, additional investigations were performed, including capsule endoscopy, which showed the presence of isolated areas of ulceration in the jejunum, not typical of inflammatory bowel disease, although at the distal ileum there were small ulcers and erosions thought possibly to represent inflammatory bowel disease. Colonoscopy was unremarkable.

A positron emission tomography-CT revealed low-grade metabolically active nodal disease above and below the diaphragm, with marrow involvement. The uptake in the marrow suggested either marrow activation or infiltration. Metabolic activity within the vasculature was within normal limits, and there was no evidence of vasculitis.

Subsequently, a bone marrow biopsy was completed to rule out lymphoma.

Differential diagnosis

Based on the first CT scan, the differential diagnoses included vasculitis on account of the prominent mesenteric vasculature, and ischaemia resulting in thickening of the bowel wall with reduced attenuation. Lymphoma and infective causes such as giardiasis, which often show thickening of small bowel folds, and is usually restricted to the duodenum and jejunum [1], were also considered. Other potential causes of thickening of the bowel wall, such as Crohn disease, were felt less likely given the apparent limited distribution of the pathology, with no involvement of the terminal ileum.

In view of the recurrent severe abdominal pain with accompanying pyrexia and the patient's Turkish heritage, familial Mediterranean fever was also considered as a differential.

Following the second CT scan showing multiple venous thromboses, pathology of haematological aetiology became the prime suspect. With the positron emission tomography-CT showing nodal disease and bone marrow involvement, haematological investigations were carried out, including flow cytometry of peripheral blood, as well as bone marrow aspirate and biopsy.

Outcome and follow-up

The patient was thrombolysed with low molecular weight heparin, which was continued prophylactically.

Following flow cytometry, a diagnosis of PNH was made. The bone marrow aspirate showed erythroid hyperplasia, consistent with PNH.

The patient was referred to a specialist PNH centre where he went on to be treated with eculizumab, as is now the standard treatment for the disease [2].

Discussion

PNH is a type of acquired haemolytic anaemia in which red blood cells break down with release of haemoglobin, which is excreted in the urine. It is now believed that the haemolysis is not nocturnal, rather occurring throughout the day, but the characteristic reddening or darkening of the urine is particularly evident in the morning when urine and its solutes are at their most concentrated. However, many of those afflicted do not report this symptom [3].

In terms of aetiology, a sub-population of red blood cells lacks the complement regulatory surface proteins CD59 and CD55, rendering the cells vulnerable to complement-mediated haemolysis. Such red blood cells are produced by a clonal expansion of hematopoietic stem cells that have acquired a somatic mutation of the phosphatidylinositol glycan anchor (PIGA) gene. PIGA is necessary to anchor CD59 and CD55 to the cell surface. Thus, the progeny of affected stem cells that are deficient in functioning PIGA also lack CD59 and CD55, as well as other proteins that depend on PIGA for anchoring [3].

Diagnosis of PNH can be made by flow cytometry of peripheral blood showing red blood cells with reduced expression of CD59 and CD55, as well as granulocytes with reduced expression of CD16 and fluorescein-labeled aerolysin (FLAER), or other PIGA-anchored surface proteins [4]. In the case reported here, it was found that 46.8% of red blood cells were negative for both CD55 and CD59, and 90.3% of granulocytes were negative for both CD16 and fluorescein-labeled aerolysin (FLAER), thus confirming the diagnosis of PNH.

From a radiological point of view, our finding of thromboses in the splenic, superior mesenteric, and portal veins is an important sign pointing to PNH. Indeed, occurrence of thromboses in unusual venous sites such as the hepatic, mesenteric, cerebral, and dermal veins is characteristic of PNH [3]. This may be of particular value in cases such as that reported here, where other signs and symptoms typical of PNH, such as anaemia, pancytopenia, and haemoglobinuria, are not present or not reported.

Of note is that thromboses were not directly evident in the initial CT examination. Nevertheless, the pathologic appearance of a section of jejunum, with bowel dilation and bowel wall thickening [5], thickening of the small bowel folds [6], and mesenteric oedema with fat stranding [7] is typical of bowel ischaemia, and this would raise the suspicion of occult thromboses in the mesenteric vasculature. Indeed, recurrent small bowel ischaemia has previously been reported in a patient with PNH, with similar findings [8].

Incidentally, it is also of interest to note that, 2 months after his first presentation, the patient's haemoglobin level had dropped from its initial value of 164 g/L to 99 g/L, showing that anaemia did eventually emerge as a sign during the progression of the disease.

Learning points

(1) Multiple thromboses in the typical venous distribution as evidenced on cross-sectional imaging may provide an important spur toward consideration of PNH as a differential diagnosis, especially when other features such as anaemia and pancytopenia, or overtly discoloured urine, are not present.

(2) Venous thromboses are a characteristic occurrence in PNH, and should be evident on contrast-enhanced CT scans in the venous phase. However, as in the case presented here, the consequences of ischaemia in the affected viscera may be a more conspicuous feature on CT.

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