CASE REPORT

In the nick of time: arterial thrombosis on starting combination chemotherapy in metastatic gastric adenocarcinoma

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SUMMARY

A 70-year-old man newly diagnosed with metastatic gastric adenocarcinoma was started on standard first-line palliative chemotherapy with anthracycline (epirubicin), platinum (oxaliplatin) and fluoropyrimidine (capecitabine); EOX combination chemotherapy. 5 days after the first cycle of chemotherapy, he presented with tachycardia with associated severe abdominal and lumbar pains. Initial investigations confirmed life-threatening metabolic acidosis with serum lactate of 9.7 mmol/L (normal range 0.5–2.2 mmol/L). CT angiogram identified acute arterial thrombosis within the abdominal aorta, lumbar and right common iliac artery, which was absent on staging contrast CT scan 6 weeks prior. The patient was immediately anticoagulated and chemotherapy discontinued. Urgent oncology and surgical opinions advised conservative management. The patient responded well to early treatment and survived this acute episode. He was subsequently started on life-long treatment dose enoxaparin and second-line single agent chemotherapy with docetaxel (taxotere), with no reported complications.

BACKGROUND

Stage 4 gastric adenocarcinoma has a poor prognosis of less than 5% overall survival at 5 years.¹ Acute arterial thrombosis in patients with metastatic gastric cancer is uncommon,² but associated with a high mortality.³

Patients on cytotoxic chemotherapy presenting with severe, acute abdominal pains, should immediately raise concerns of acute thrombosis as a differential diagnosis. Awareness of arterial thrombosis allows early recognition and treatment, which can be life saving.

Cytotoxic chemotherapy is associated with increased risk of vascular thrombotic events.⁴ Cisplatin is associated with higher risk of vascular adverse events compared with oxaliplatin.² Acute thrombosis is more commonly reported during initial cycles of chemotherapy.⁴ Granulocyte colony-stimulating factor (G-CSF) has also been linked to arterial thrombosis via the platelet aggregation pathway.⁵

CASE PRESENTATION

A 70-year-old man presented with a 3-month history of weight loss and early satiety. He had previously been fit and well with a WHO performance status of 0. His medical history included quiescent diverticular disease, gout, dyslipidaemia and

cholecystectomy. He had no previous cardiovascular event or thromboembolism. There was no family history of cancer or thromboembolism. He had no known drug allergies and his regular medications included simvastatin and allopurinol. He was a never-smoker.

Oesophagogastroduodenoscopy revealed a circumferential tumour starting from the gastro-oesophageal junction extending circumferentially all the way up to the incisura, which gave this patient a type 3 Siewert classification of gastric adenocarcinoma. Histology of a biopsy taken was later proven to be poorly differentiated adenocarcinoma. Immunohistochemical stains of the tumour samples were negative for human epidermal growth factor (HER2) overexpression.

Staging CT with contrast, of the thorax, abdomen and pelvis, confirmed a locally advanced gastric tumour with peritoneal and retroperitoneal nodal metastases therefore giving a TNM staging of T4a N3a M1, overall stage 4 gastric cancer (figure 1). There was neither visible liver nor bone metastasis.

The patient was started on anthracycline (epirubicin) intravenous 50 mg/m², platinum (oxaliplatin) 130 mg/m² and fluoropyrimidine (capecitabine) 625 mg/m²—EOX combination chemotherapy—which is a first-line treatment for metastatic gastric cancer. As EOX is a high-intensity chemotherapy with predicted incidence of neutropaenia above 20%, G-CSF was administered postchemotherapy infusion as primary prophylaxis to prevent febrile neutropaenia.^{6 7}

Five days after the first cycle of chemotherapy, the patient presented to the local acute oncology unit with sudden severe central abdominal pain and bilateral lumbar pains. He had neither nausea nor diarrhoea episodes.

Physical examination revealed tenderness in the upper and middle abdominal region radiating into the flanks. The patient's vital signs recorded a temperature of 35.7°C, tachycardia with a pulse rate of 100 bpm and supine blood pressure of 162/92 mm Hg. Pulse oxygen saturation measurements were maintained at 100% without oxygen supplementation.

INVESTIGATIONS

Admission venous blood gas revealed metabolic acidosis with a pH of 7.29 (normal range 7.35–7.45), serum bicarbonate of 19.2 mmol/L (normal range 22.0–28.0 mmol/L) and base excess of –7.0 (normal

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Figure 1 Staging contrast CT of the abdomen and pelvis showing abnormal gastric appearances on the left—evidence of locally advanced gastric tumour.

range -2.0 to $+2.0$). Serum lactate was elevated to life-threatening levels at 9.7 mmol/L (normal range 0.5 – 2.2 mmol/L).⁸

Full blood results revealed elevated white cell counts ($26.4 \times 10^9/L$, normal range 4.0 – $11.0 \times 10^9/L$) and neutrophilia (neutrophils $25.9 \times 10^9/L$, normal range 2.5 – $7.5 \times 10^9/L$). The patient was also mildly anaemic with haemoglobin of 114 g/L (normal range 135 – 180 g/L) and had slightly raised platelet levels of $473 \times 10^9/L$ (normal range 140 – $400 \times 10^9/L$). Serum electrolytes, liver function tests and calcium levels were within normal range.

ECG revealed normal sinus rhythm, and erect chest radiograph showed no evidence of free air under the diaphragm to indicate perforated bowels (figure 2). Plain abdominal film showed constipation but no evidence of bowel obstruction or perforation (figure 3).

Urgent CT angiogram revealed extensive acute arterial thrombosis within segments of the abdominal aorta, starting from the

Figure 2 Erect chest radiograph showing a normal anatomical variant of bowels interposed with the liver in the right upper quadrant in keeping with Chilaiditi's sign. There was no free gas below the diaphragm to suggest bowel perforation. There was no lung collapse and no consolidation.

coeliac axis and extending to the level of bifurcation (figures 4 and 5). The arterial thrombosis extended into the lumbar and right common iliac arteries (figure 6), explaining the patient's back pain. This thrombosis was absent on his staging contrast scan carried out 6 weeks prior. There were no visible mesenteric thrombi nor was there evidence of established bowel ischaemia. There was also no evidence of ascites nor of free air within the abdominal cavity to suggest perforated viscus.

DIFFERENTIAL DIAGNOSIS

Patients with cancer presenting with sudden severe abdominal pain and back pain following chemotherapy should raise the suspicion of mesenteric ischaemia, perforated viscus, bone metastasis, metastatic compression of nerve bundles and acute arterial thrombosis.

In a patient with raised inflammatory markers, sources of sepsis should be sought out using a septic screen including blood culture, urine culture and chest X-ray. In this patient, the raised white cell count and neutrophil count were likely due to G-CSF administration.

There is a list of other causes of acute abdomen that also ought to be considered. Important surgical causes to be considered include acute appendicitis, acute pancreatitis and ruptured aneurysm of the abdominal aorta. Non-surgical causes to be considered include diabetes ketoacidosis, myocardial infarction and lower lobe pneumonia.

TREATMENT

On recognition of his acute arterial thrombosis, the patient was anticoagulated using treatment dose low molecular weight heparin, enoxaparin 130 mg (1.5 mg/kg). Chemotherapy was discontinued and the patient was started on intravenous fluids and adequate subcutaneous analgesia. He was kept on strict bowel rest. Intravenous broad spectrum antibiotics were started empirically.

Urgent oncology and surgical specialty opinions were sought to guide further treatment. The patient responded well to conservative management without requiring any surgical intervention. Once he had recovered from the acute stage and was deemed safe to restart oral intake, inpatient dietician team input was sought. A rectal enema was given to prevent the adverse effects related to the high dose opiates he had been taking.

OUTCOME AND FOLLOW-UP

The patient responded well and survived to be discharged from hospital. He was instructed to continue on life-long anticoagulation with daily subcutaneous injection of enoxaparin 130 mg (1.5 mg/kg).

He was followed up in the outpatient clinical oncology clinic 3 weeks later. He remained well and was extremely keen to continue on chemotherapy. Owing to his acute thrombosis, we explained the increased risk of complications with further chemotherapy to the patient. We would not challenge him further with platinum-based chemotherapy. Single-agent second-line chemotherapy, docetaxel, was offered to the patient.

After 6 weeks from his acute thrombosis, he was started on single-agent docetaxel chemotherapy, 75 mg/m². He was monitored closely, showed no complications and remains well.

DISCUSSION

Cancer is a hypercoagulable state and strongly associated with venous thromboembolism (VTE). Patients with cancer are seven times more at risk of VTE compared with normal patients.⁴

Figure 3 Plain abdominal radiograph showing multiple gas-filled loops of small bowel noted in the right upper quadrant. Gas and faeces can be seen in the large bowels. There is no evidence of obstruction nor of perforation. Cholecystectomy clips were noted, in keeping with previous cholecystectomy.

A review of the literature shows a lack of data on the incidence and prevalence of arterial thrombosis.² A small number of arterial thrombosis cases in patients with cancer have been

Figure 4 CT angiogram showing the area of the filling defect within the abdominal aorta during the arterial phase, showing evidence of acute arterial thrombosis not present in staging contrast CT 6 weeks earlier.

reported, of complicating cancers such as lung cancer,⁹ oesophageal carcinoma,¹⁰ testicular seminoma¹¹ and others.

A prospective study on thromboembolism in advanced metastatic gastro-oesophageal cancer in platinum-based combination chemotherapy reported the incidence rate of arterial thrombosis at 2.2% (95% CI 1.4% to 3.4%).² Arterial thrombosis occurring in patients with cancer is associated with a high mortality.³ A small study by a UK vascular centre of patients with cancer presenting with arterial thrombosis reported a 50% mortality rate at 3 months from time of presentation and a 83% mortality rate at 1 year from presentation.³

Chemotherapy has been postulated as an independent risk factor for thrombosis by way of cytokine activation, direct toxic effect into blood vessels and disruption of the balance of pro-coagulant and anticoagulant factors.¹²

Different chemotherapy agents have shown to affect thromboembolism differently.² In the platinum-based combination chemotherapy in metastatic gastric cancer, cisplatin is shown to double the incidence of thromboembolism when compared with oxaliplatin.²

A literature search revealed only a handful of similar case reports. One recorded the occurrence of arterial thrombosis of abdominal aorta in a patient with metastatic gastric cancer during treatment with epirubicin, cisplatin and capecitabine, where the patient was warfarinised and continued on

Figure 5 CT angiogram showing extension of the filling defect in the abdominal aorta, confirming segment of acute arterial thrombosis within the abdominal aorta.

chemotherapy after the acute event.¹³ A second case reported development of arterial thrombosis in both popliteal arteries 1 day after starting on combinative chemotherapy with fluorouracil, cisplatin, docetaxel for metastatic gastric cancer.¹⁴ The patient was started on low weight molecular heparin and remained well 1 month after the acute event.

There is no current consensus on the use of thromboprophylaxis in chemotherapy patients.¹⁵ Considering the dismal 5-year survival rate of stage 4 gastric cancer of less than 5%,¹ and the high mortality rate in patients with metastatic gastric cancer who develop arterial thrombosis,³ risk and benefit assessments should be made and patients informed before starting chemotherapy.

Assessment of comorbidities and vascular risk factors prior to starting on chemotherapy is paramount. Important triggers of arterial thrombosis such as atrial fibrillation, sepsis and indwelling catheters must not be missed.

Arterial thrombosis in patients with cancer is often treated with conservative management using anticoagulation and

stopping chemotherapy.³ As such, awareness and early recognition of acute arterial thrombosis can be life saving.

The patient in this case had no previous cardiovascular disease, never smoked and did not use any vascular devices. As such, this patient's arterial thrombosis was likely related to his underlying prothrombotic state from metastatic disease process as well as G-CSF and chemotherapy treatment.^{2 5}

Patient's perspective

I am extremely grateful that I have survived this episode. I know that I could have possibly died during this admission. I am disappointed that my chemotherapy treatment had to be suspended but I am keen to restart on treatment once I see the doctors in the outpatient clinic.

Learning points

- ▶ Acute arterial thrombosis should be suspected in patients with cancer on chemotherapy who present with acute abdomen or back pain.
- ▶ Early recognition and treatment of acute arterial thrombosis with anticoagulation and stopping chemotherapy by clinicians can be life saving, as arterial thrombosis is associated with a very high mortality rate.
- ▶ Arterial thrombosis is uncommon in patients with cancer, likely attributed to a prothrombotic state triggered by metastatic disease process, granulocyte colony-stimulating factor treatment and chemotherapy.

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Competing interests None declared.

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Figure 6 CT angiogram showing extension of the filling defect within the right common iliac artery—evidence of extension of acute arterial thrombosis.

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