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Cisplatin induced acute mesenteric ischaemia: A case report and review of the literature



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ABSTRACT

INTRODUCTION: Cisplatin is a platinum-based chemotherapeutic agent, widely used in cancer therapies for numerous solid tumours. It is becoming more recognised that a potentially life-threatening complication of cisplatin is accelerated arterial and venous thrombosis.

PRESENTATION OF CASE: We describe a case of a 62 year-old with no risk factors for vascular disease who presented with thromboembolic acute mesenteric ischaemia of the small bowel during treatment with cisplatin for head and neck cancer.

DISCUSSION: We review the literature on the incidence and pathogenesis of cisplatin induced arterial thrombosis and discuss current treatment options of acute mesenteric ischaemia detailing our management of this case.

CONCLUSION: Cisplatin increases the risk of arterial thrombosis and this case report details acute mesenteric ischaemia secondary to its use. We hope to raise clinician awareness of this sequelae which can occur even in patients in the absence of other identifiable risk factors.

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1. Introduction

Cisplatin is a platinum-based chemotherapeutic agent used in the treatment of bladder, lung, ovarian, testicular, gastrointestinal and head and neck cancers. It acts by crosslinking purine residues preventing cell division and increasing oxidative stress inducing apoptosis. Recognised complications include nausea and vomiting, nephrotoxicity, hepatotoxicity, cardiotoxicity, myelosuppression, and allergic reactions [1]. However, recent retrospective analyses have suggested accelerated venous and arterial thrombosis is an under-recognised but common life-threatening side effect of cisplatin, which can occur in up to 18.1% of patients during or shortly after treatment [2].

Mesenteric ischaemia is a life-threatening condition caused by reduced splanchnic perfusion. It can be acute or chronic in onset; arterial or venous in aetiology and pathogenesis is occlusive or non-occlusive. If not promptly identified, it can have 90% morbidity and mortality [3].

Abbreviations: AMAE, acute mesenteric arterial embolism; AMAT, acute mesenteric arterial thrombosis; CTA, computed tomography angiogram; ECG, electrocardiogram; LMWH, low molecular weight heparin; MDT, multidisciplinary meeting; SMA, superior mesenteric artery; TTE, transthoracic echocardiogram; UHI, unfractionated heparin infusion.

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We present a case whereby cisplatin induced multiple arterial thrombi, in a patient without any other identifiable risk factors, resulting in life-threatening mesenteric ischaemia. By doing so we wish to raise awareness amongst clinicians of this sequelae from a commonly used chemotherapeutic agent.

This work has been reported in line with the SCARE criteria [4].

2. Presentation of case

2.1. Clinical presentation

The index case underwent concurrent chemo-radiotherapy with primary curative intent for a right sided T_xN_{2b}M₀ well-differentiated keratinising squamous cell carcinoma of unknown head and neck primary.

6 days after his second chemotherapy cycle, he self-presented to the emergency department with severe, intermittent right-sided abdominal pain and loose stools. The pain was acute in onset, non-radiating, and 9/10 in severity with associated nausea. Stool contained no blood or mucus. There was no concomitant history of intestinal angina. The patient had no past medical history. Social history revealed he was a lifelong non-smoker with 2–3 units of alcohol consumption per week. On examination, he was alert and haemodynamically stable but subjectively appeared unwell. Airway was patent, and there were no problems with breathing. The patient was clinically dehydrated, but of normal habitus with no signs of cachexia. The pulse was regular but of thready character, heart sounds were regular with no added sounds.

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Table 1
Haematological and Biochemical Parameters of Index Case at time of Initial Presentation.

Parameter	Value	Normal Range	Parameter	Value	Normal Range
Haemoglobin (g/L)	152	135–180	Amylase (U/L)	134	70–300
Leucocyte Count ($\times 10^9/L$)	11.02	3.4–11.0	Alkaline Phosphatase (U/L)	31	40–129
Platelets ($\times 10^9/L$)	283	150–450	Bilirubin ($\mu\text{mol/L}$)	27	<21
Serum Creatinine ($\mu\text{mol/L}$)	116	60–120	Aspartate Transaminase (IU/L)	29	4–40
Serum Sodium (mmol/L)	136	132–146	Serum Calcium (mmol/L)	2.2	2.1–2.6
Serum Potassium (mmol/L)	3.5	3.5–5.4	Serum Magnesium (mmol/L)	0.4	>1.0
C-Reactive Protein (mg/L)	140	<5	Activated Partial Thromboplastin Time (seconds)	26	24–37
Serum Lactate (mmol/L)	3.5	0.5–2.2	Prothrombin Time (seconds)	15	11–15

His abdomen was non-distended with a previously prophylactically inserted, freely-flushing percutaneous gastrostomy in situ. A Lanz incision was noted from previous appendectomy. The abdomen was exquisitely tender centrally and in the right iliac fossa but soft with no rebound, guarding or organomegaly. Bowel sounds were scanty. Digital rectal examination was normal.

Haematological and biochemical investigations were performed of which a raised lactate of 3.5 mmol/L was noted (Table 1). An erect chest radiograph did not reveal any free subdiaphragmatic air. The ECG showed normal sinus rhythm.

Contrast-enhanced computed tomography showed thrombosis of the inferior mesenteric artery but good distal vascular enhancement. Serial blood gases over the initial 24 hours showed a falling lactate which normalised at 1.2 mmol/L.

However, over the subsequent 24 hour, our patient began to experience brisk, fresh rectal bleeding therefore a CT Angiogram (CTA) was requested (Fig. 1A). CTA showed a new, large thrombus in the aorta and another causing 85% occlusion of the superior mesenteric artery (SMA) with poor distal enhancement. Urgent transthoracic echocardiography (TTE) excluded any mural or endocardial thrombosis or fibrillation.

2.2. Differential diagnosis

The sudden onset of acute, severe abdominal pain warranted immediate clinical assessment. In a patient undergoing chemotherapy with these symptoms, visceral perforation needs to be ruled out, particularly in the presence of a high lactate. Acute mesenteric ischaemia was lower on our differential due to absence of typical risk factors. Another rare but potential diagnosis would be drug induced acute pancreatitis, however, the amylase was normal. When Computed Tomography identified an inferior mesenteric artery thrombus a diagnosis was made – however there remained clinico-radiological discordance as there was no evidence of fulminant bowel ischaemia radiologically, such as pneumatosis intestinalis or pneumatosis portalis, which was what we expected. The development of frank rectal bleeding, however, was suggestive of disease evolution and as such CTA was conducted.

2.3. Management

Initial management adopted a conservative approach comprising of fluid resuscitation with crystalloids and intravenous antibiotics (gentamycin, metronidazole and meropenem). However, with onset of brisk rectal bleeding, further aggressive resuscitation was required with crystalloids and blood products. This was when the decision to perform a CTA was made and the results noted.

After discussion with our supraregional vascular centre, the thrombosis was deemed too advanced distally for intervention and a multidisciplinary team (MDT) decision was made for exploratory laparotomy after 24 hours of intravenous unfractionated heparin infusion (UHI). Laparoscopy was avoided due to anaesthetic risk associated with pneumoperitoneum.

Laparotomy showed dusky bowel in the region of the mid-jejunum but it was warm and felt to be viable thus left in situ. The patient was admitted to the intensive care unit and continued on UHI for a further 48 hours. During this time he was initiated on parenteral nutrition via central venous catheter and bowel rest commenced.

Relook laparotomy was conducted at 48 hours. All segments of the bowel were warm and showed peristaltic activity (Fig. 2). After discussion with haematology specialists, the patient was initiated on subcutaneous divided dose therapeutic low molecular weight heparin (LMWH).

After laparotomy, the patient recovered well with no post-operative or anaesthetic complications. He experienced some small volume episodes of PR bleeding which we attributed to sloughing of bowel mucosa from the intermittent ischaemia. Repeat CTA on day 7 showed complete resolution of the aortic thrombus and majority resolution of the SMA thrombus with downstream filling of its branches (Fig. 1B).

Three weeks after discharge, he resumed his pre-event chemoradiotherapy but was maintained on a daily weight based treatment dose of LMWH. At 18 months the patient remains disease free.

3. Discussion

Occlusive arterial causes of mesenteric ischaemia can be subdivided into Thrombotic (AMAT) or Embolic (AMAE) aetiology [3]. AMAE tends to occur in relation to cardiac emboli – mural thrombosis post-infarction, endocardial vegetations or due to atrial fibrillation. All of these were ruled out by TTE in our patient. AMAT is most commonly related to atherosclerotic disease. In our case the patient had no risk factors, no past history or family history of vascular disease, a fasting lipid and glucose profile within normal limits, was normotensive and was a non-smoker. AMAT also typically occurs in patients with a background of chronic mesenteric ischaemia, however, our patient had never experienced symptoms consistent with intestinal angina previously.

It is well documented that cancer predisposes to the development of venous thrombi, however, in patients treated with cisplatin for a variety of tumours, retrospective analysis suggests an incidence of developing arterial thrombi within 4 weeks of treatment cessation of 2.03% [2]. It is also reported in prospective trials that cisplatin has as significantly greater risk of inducing thromboembolic events when compared to other platinum-based chemotherapeutics [5]. There are cases reporting vasospasm and aortic thrombi with potentially fatal distal embolisation in patients undergoing chemotherapy, but AMAT is rare (Table 2) [6–11]. However, it seems that the apparent contribution of cisplatin to arterial thrombosis seems underappreciated amongst clinicians.

The pathogenesis of this accelerated arterial thrombosis is not well understood but may relate to induction of von Willebrand Factor production or due to hypomagnesaemia inducing vasospasm [12,13].



Fig. 1. Computed Tomography Angiogram of Aorta, Superior Mesenteric Artery and Jejunum arteries. (A) At diagnosis. (B) 7 days after heparinisation.

Treatment of AMAT depends on clinical and radiological findings on CTA. Suspicion of peritoneal irritation necessitates urgent laparotomy and assessment of bowel viability. More increasingly revascularisation, either open or endovascular is being used to augment laparotomy. Open techniques include surgical embolectomy and aortomesenteric bypass-grafting whereas endovascularly they consist of aspiration and stenting [3]. However, these techniques require facilities and physicians trained in their use.

In their absence, laparotomy and anticoagulation are recommended in first instance with a view to inpatient transfer. In patients without an acute abdomen, reperfusion should be attempted before damage control surgery [3].

In our case, the absence of local revascularisation facilities and thrombosis not amenable for thrombolysis or thrombectomy,

laparotomy and UHI was the most suitable treatment modality. After relook laparotomy, the entire bowel was still viable and heparinisation has successfully begun to treat the thrombosis thereby giving our patient the optimal outcome.

This case does pose the question as to whether prophylactic anticoagulation should be used in patients undergoing cisplatin chemotherapy. Current *meta-analysis* does suggest a statistically significant reduction in symptomatic venous thromboembolic events when parenteral heparin-based treatments are given to patients undergoing chemotherapy for a variety of cancers but with an increased risk of minor bleeding events [14,15]. However, further research is required to elicit their benefits in reducing incidence of arterial embolic events and to specifically look at patients on platinum-based agents in isolation.

Table 2
Case Reports identifying Arterial Ischaemic Events in patients undergoing Cisplatin-based Chemotherapy. F – Fatal events.

Paper	Tumour	Chemotherapy regime	Findings
Bayne MC. ⁶	T ₁ N ₁ M ₀ Tonsillar squamous cell carcinoma	Cisplatin and 5-Fluorouracil	Saddle embolus at bifurcation of aorta causing bilateral limb ischaemia
Tait CD. & Rankin EM. ⁷	1. TxN ₃ M ₀ Small cell lung cancer 2. T ₄ N ₃ M ₀ lung adenocarcinoma 3. T ₄ N ₁ M ₀ lung adenocarcinoma	1. Cisplatin and etoposide 2. Cisplatin and Docetaxel 3. Cisplatin and Pemetrexed	1. Non-occlusive thrombus of subclavian artery causing ischemic right hand 2. Occlusive thrombi in lower limb bilaterally and non-occlusive thrombus in thoracic aorta 3. Occlusive thrombus of distal aorta causing bilateral lower limb ischaemia (F)
Rishi A. & Ghoshal S. ⁸	Tongue base squamous cell carcinoma	Cisplatin and Radiotherapy	Thrombus occluding descending aorta and left common iliac causing left lower limb ischaemia
Allerton R. ⁹	T ₄ N ₁ M ₀ squamous cell nasopharyngeal carcinoma	Cisplatin, 5-Fluorouracil and Vincristine	Thrombus occluding superior mesenteric artery causing complete midgut ischaemia (F)
Doll DC. et al ¹⁰	Testicular germ cell: 1. IIB Yolk Sac Tumour 2. IIA Embryonal Cell 3. III Embryonal Cell 4. III Embryonal Cell	All: 1. Cisplatin, 2. Vinblastine and 3. Bleomycin	1. Myocardial Infarction 2. Cerebrovascular Accident 3. Myocardial Infarction 4. Cerebrovascular Accident

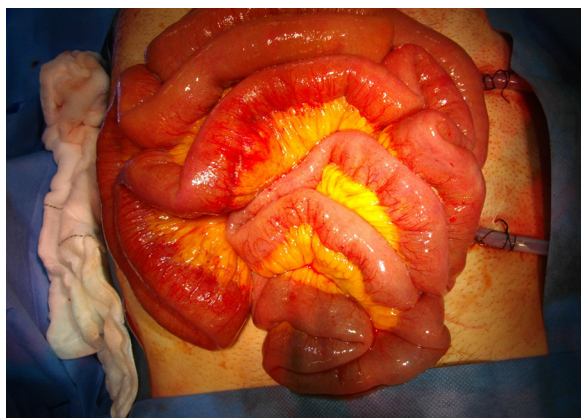


Fig. 2. Intraoperative photograph of Small Bowel during relook laparotomy.

4. Conclusion

Acute mesenteric artery thrombosis is a life-threatening condition. Cisplatin increases the risk of arterial thrombosis and thus can precipitate this condition, even in patients who may not have other risk factors for AMAT, and we hope to have raised awareness amongst clinicians of this. From our experience, in a patient with thrombosis not amenable to revascularisation therapies, a combination of laparotomy with a secondary relook and heparin infusion is an excellent management strategy with the benefit of targeting other unidentified thrombi. However, work is required to identify the benefit of prophylactic LMWH in mitigating arterial embolic events in patients undergoing chemotherapy with platinum-based agents.

Consent

Written, informed consent was obtained from our patient prior to submission of this manuscript.

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Authors contribution

Study Design: Yasser Abdulaal

Data Collection: Shivun Khosla, Lauren Kennedy
 Manuscript Preparation: Shivun Khosla
 Manuscript Editing and Review: Shivun Khosla, Lauren Kennedy, Yasser Abdulaal

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Ethical approval

This was not a research study.

Registration of research studies

This was not a research study.

Guarantor

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Conflict of interest

The authors declare no conflicts of interest.

Conflicts of interest

No conflicts of interest.

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