Cisplatin induced mesenteric ischemia

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Abstract

Background: Cisplatin is a platinum-based chemotherapeutic agent with wide complications including life-threatening acceleration of venous and arterial thrombosis. Cisplatin associated thrombosis occurs through triggering platelet activation.

Objectives: The aim of this study is to present a case of non-keratinizing undifferentiated nasopharyngeal cancer who had cisplatin chemotherapy.

Methods: We present a 56 year old male admitted to Al-Hada emergency department complaining of diffuse severe abdominal pain associated with nausea at the onset of the pain and constipation one day ago. He was diagnosed with non-keratinizing undifferentiated nasopharyngeal cancer and started chemotherapy of 2 doses of Cisplatin and 12 doses radiotherapy.

Results: On abdominal examination there was generalized guarding and tenderness and the abdomen was distended. There was no organomegaly, bowel sound was scanty, and empty rectum in digital examination. Abdominal X-ray revealed distended small bowel and no air fluid level. There was sinus rhythm on ECG. His WBC count was 19 x 10 3/ µL, and lactic acid level was 9.6 mmol/L. Abdominal contrast enhancement computed tomography showed a large filling defect at the proximal part of the superior mesenteric artery with dilated bowel and porto-mesenteric gas pneumatosis intestinalis. The filling defect seen was obliterating the superior mesenteric artery's lumen denoting acute arterial obstruction distally to its terminal branches. Exploration laparotomy showed heavily necrotic bowel from 30 cm distal to duodenojejunal junction down to 50cm proximal to ileocecal valve, with an area of engorged bowel proximal to that (~ 50 cm, more toward ischemic). After immediate resuscitation with D5 normal saline and intravenous ceftriaxone the patient became oliguric and tachycardic. The patient was admitted to the ICU and labelled as Do-Not-Resuscitate (DNR) and arrested after 6 hours.

Conclusion: In this study, thromboembolic events (TEEs) occurred within the first 100 days of starting cisplatin. TEE prophylaxis is advisable for patients receiving cisplatin-based chemotherapy.

Key words: Cisplatin, induced, mesenteric, ischemia, Hada, Saudi Arabia

Introduction

Cisplatin is a platinum-based chemotherapeutic agent that was licensed in 1978 and is now listed on the World Health Organization's list of essential medicines. It is widely used, alone or in combination, to treat several cancers, including testicular, ovarian, cervical, bladder, head and neck, lung, esophageal and gastric cancers (1,2). It acts by crosslinking purine buildups preventing cell division and expanding oxidative pressure actuating apoptosis (3).

Cisplatin has known complications like nausea and vomiting, nephrotoxicity, hepatotoxicity, cardiotoxicity, myelosuppression, and hypersensitive responses (4). But common life-threatening side effects of cisplatin, which can occur in up to 18.1% of patients during or shortly after treatment is the acceleration of venous and arterial thrombosis (5).

Many hypotheses exist pertaining to the mechanisms associated with Cisplatin associated thrombosis including direct damage to the vascular endothelium, increased procoagulant activity, reduced anticoagulation synthesis, platelet activation and aggregation and vascular inflammation (6,7).

Khorana risk score is used to predicate risk of thrombosis in cancer patients (8). Khorana risk score was used in studies as predictor of thromboembolic events (TEEs) in patients treated with cisplatin based chemotherapy with other predictors like underlying primary malignancy, stage of disease, age, Karnofsky performance status (KPS), and presence of central venous catheter and were significant by multivariate analysis (9).

Thromboprophylaxis for patients treated with cisplatin-based chemotherapy is not included in any guideline but recent studies recommend it if there is no contraindication (10).

Case presentation

History of present illness

After 3 days of last chemotherapy 56 years old male self-presented to Al-Hada emergency department and complained of diffuse severe abdominal pain. The pain started suddenly one day ago, and was progressive, diffuse (mainly epigastric), no radiation, no aggravating or relieving factor. The pain was associated with nausea at the onset of the pain and constipation one day ago, with no history of vomiting, and bleeding per rectum.

On his past medical history, he was a known case of DM, HTN. He was diagnosed 3 weeks ago with non-keratinizing undifferentiated nasopharyngeal cancer and started chemotherapy (received 2 doses of Cisplatin and 12 doses of radiotherapy). Social history revealed that he was a lifelong nonsmoker, and had no history of alcohol consumption.

The patient was alert and hemodynamically stable but subjectively unwell. On abdominal examination there was generalized guarding and tenderness and the abdomen was distended. There was no organomegaly, bowel sound was scanty, and empty rectum on digital examination. An erect chest X-ray was done and there was no pneumoperitoneum. And abdominal X-ray revealed distended small bowel and no air fluid level. There was sinus rhythm on ECG.

Findings of patient's blood analysis

Parameter	value	Normal range	Parameter	value	Normal range
Hemoglobin (g/dl)	16.9	13.0-18.0	Amylase (U/L)	82	25-125
Leucocyte count (x10-3/uL)	19.3	4.00-11.00	Alkaline phosphatase (U/L)	56	40-150
Platelet (x10-3/uL)	265	150-410	Bilirubin (umol/L)	24.4	0.0-20.5
Serum creatinine (umol/L)	85	62-115	Aspartate transaminase (U/L)	24	5-34
Serum potassium (mmol/L)	4.0	3.5-5.1	Serum calcium (mmol/L)	1.99	2.10-2.55
Serum sodium (mmol/L)	138	135-145	Serum magnesium (mmol/L)	0.60	0.66-1.07
C–reactive protein (mg/L)	147.7	0.0-5.0	Activated partial thromboplastin time (sec)	36.8	26.0-40.0
Serum lactate (mmol/L)	9.6	0.5-2.2	Prothrombin time (sec)	15.4	11.5-14.5

Hospital course

The attendant doctor ordered hematological and biochemical investigation that showed that WBC count was 19 x 10 3/μL, and lactic acid level was 9.6 mmol/L. Heparin was given at a 5000 IU dose prophylactically and decision to proceed for CT scan was taken. Abdominal contrast enhancement computed tomography was ordered and results showed large filling defect at the proximal part of the superior mesenteric artery with dilated bowel and porto-mesenteric gas pneumatosis intestinalis. The filling defect seen was obliterating the superior mesenteric artery's lumen denoting acute arterial obstruction distally to its terminal branches.

Air densities were seen within the peripheral branches of the intrahepatic portal tracts mainly in hepatic right lobe pneumoportalis. Dilated small bowel loops reached a diameter of about 3.5 cm with multiple focal areas (mainly ilea loops) of non-enhancing wall showing pneumatosis intestinalis. Small air density was seen at the distal part of the superior mesenteric vein (SMV), and multiple air densities were seen within the peripheral small mesenteric venous branches. Minimal amount of free intraperitoneal fluid was noted. Portal vein was well opacified, and Lower chest cuts were showing minimal right pleural reaction. There was normal enhancement of both kidneys and spleen, and normal CT appearance of the pancreas.

Decision was made for exploration laparotomy, and after immediate resuscitation with D5 normal saline and intravenous antibiotic (ceftriaxone), the patient became oliguric and tachycardic. There was heavily necrotic bowel from 30 cm distal to duodenojejunal junction down to 50cm proximal to ileocecal valve, with an area of engorged bowel proximal to that (~ 50 cm, more toward ischemic). A decision was made with a consultant to close the abdomen, as there was no chance due to his cancer and the status of his bowel. The patient was admitted to the ICU and labelled as Do-Not-Resuscitate (DNR) and arrested after 6 hours. Few case reports have been published about the relationship between cisplatin and acute mesenteric ischemia.

Differential diagnosis

The patient had severe sudden abdominal pain that warranted an immediate clinical care assessment. Visceral perforation needed to be ruled out particularly in a patient who underwent chemotherapy and with the presence of high lactate. Acute pancreatitis was also suspected because the patient also had epigastric pain, however it was ruled out because amylase and lipase were normal. Abdominal x-ray was done and showed no pneumoperitoneum.

The clinical picture was going towards acute mesenteric ischemia, so abdominal computed tomography was requested and showed a large filling defect at the proximal part of the superior mesenteric artery with dilated bowel and porto-mesenteric gas pneumatosis intestinalis. Air densities were seen also within the peripheral branches of the intrahepatic portal tracts mainly in hepatic right lobe pneumoportalis.

Discussion

Established guidelines recommend prophylactic anticoagulation for all oncology patients in high-risk settings, such as hospitalization, major surgery, or postoperatively (16).

However, in the ambulatory setting, prophylactic anticoagulation is not currently recommended except for patients with multiple myeloma receiving thalidomide lenalidomide–based combinations. Based on the results of previous studies, TEE prophylaxis may be advisable for patients receiving cisplatin-based chemotherapy (17).

Among platinum agents (cisplatin, carboplatin and oxaliplatin), the highest rate of TEs was found in cisplatin containing regimens followed by carboplatin and oxaliplatin (18). The rate of TEEs increased especially when adding gemcitabine or vinca alkaloids to platinum compounds (cisplatin or carboplatin). Antithrombotic prophylaxis with nadroparin reduced the risk of developing a TE in comparison to placebo in all chemotherapy regimens (18). To improve the risk-benefit ratio of thromboprophylaxis, clinicians should identify patients at higher risk of TEs, who could have more benefit from anticoagulant administration (19).

Khorana Risk Score is a score for predicting the risk of Venous Thrombotic Events for cancer patients depending on type of cancer and other factors (site of cancer, prechemotherapy platelet count, hemoglobin level or use of red cell growth factors, prechemotherapy leukocyte count, and body mass index (BMI)), regardless of the known risk of cisplatin to cause thromboembolic event in many studies. The type of chemotherapy offered is not considered as a risk category in this score (9,20).

The timing of the TEEs in relation to initiation of therapy further suggests a relation between cisplatin administration and TEEs occurrence (21). In this study, 88% of TEEs occurred within the first 100 days of starting cisplatin.

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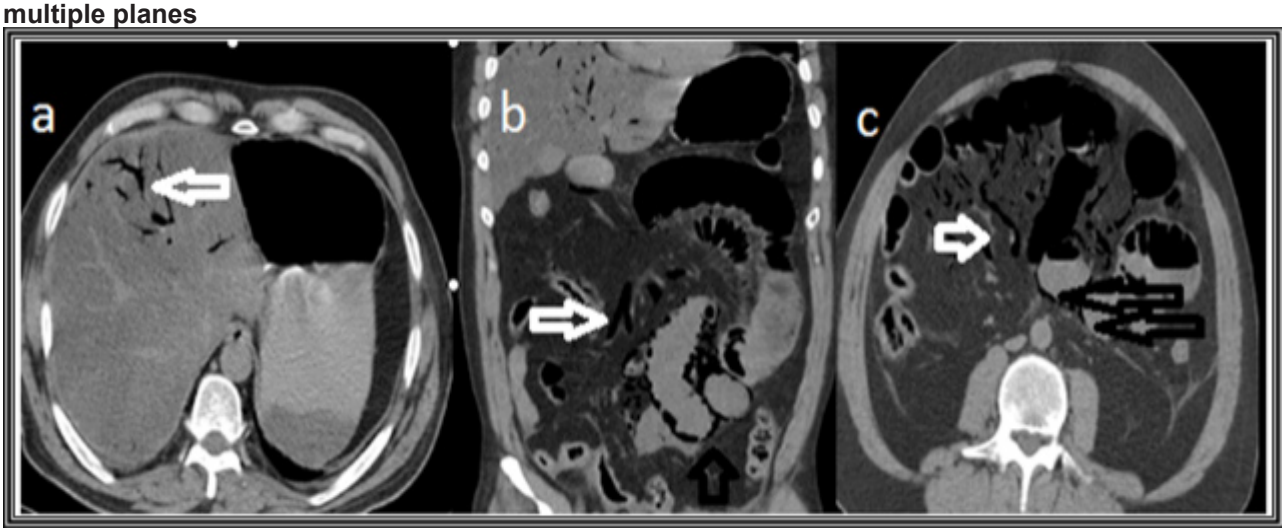
Arterial ischemic events in patients who received cisplatin-based chemotherapy (case reports)

Paper	Tumor	Chemotherapy regime	Findings
Bayne MC (11)	T1N1M0 Tonsillar squamous cell carcinoma	Cisplatin and Fluorouracil	Saddle embolus at bifurcation of aorta causing bilateral limb ischaemia
Tait CD & Rankin EM (12)	TxN3M0 Small cell lung cancer .2T4N3M0 lung adenocarcinoma .3T4N1M0 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 (13)	Tongue base squamous cell carcinoma	Cisplatin and Radiotherapy	Thrombus occluding descending aorta and left common iliac causing left lower limb ischaemia
Allerton R (14)	T4N1M0 squamous cell nasopharyngeal carcinoma	Cisplatin, 5-Fluorouracil and Vincristine	Thrombus occluding superior mesenteric artery causing complete midgut ischaemia (F)
Doll DC. et al (15)	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

Figure 1: Non-Contrast CT (SOMTOM Definition AS) scan using 128 multi-slice CT of the abdomen at multiple planes

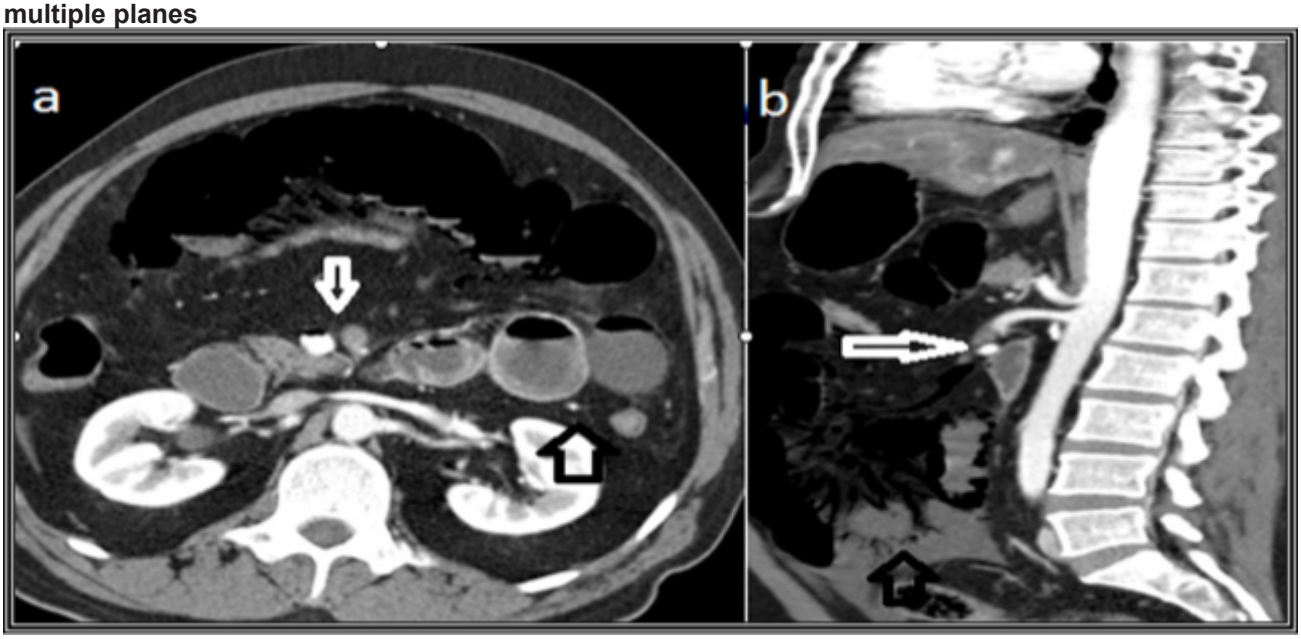


a. Non-contrast axial CT scan at the level of the upper abdomen above the liver hilum with prominent IHBRs with evidence of air densities inside pneumo-bilia (white arrow).

b. Non-contrast coronal CT scan of the whole abdomen with multiple linear shaped air densities seen along the root of the mesenteric vessels (white arrow). Noted dilated small intestinal loops with evidence multiple areas of intra-mural air densities seen inside the dilated bowel (black arrow).

c. Non-contrast axial CT scan at the lower abdominal level with multiple intra-mural air densities seen inside the dilated bowel (pneumo-intestinalis with some of them showing characteristic arc shaped\ (black arrow). Other multiple linear tortuous areas of air densities seen inside the mesenteric fat along the branches of the mesenteric vessels.

Figure 2: Non-Contrast CT (SOMTOM Definition AS) scan using 128 multi-slice CT of the abdomen at multiple planes

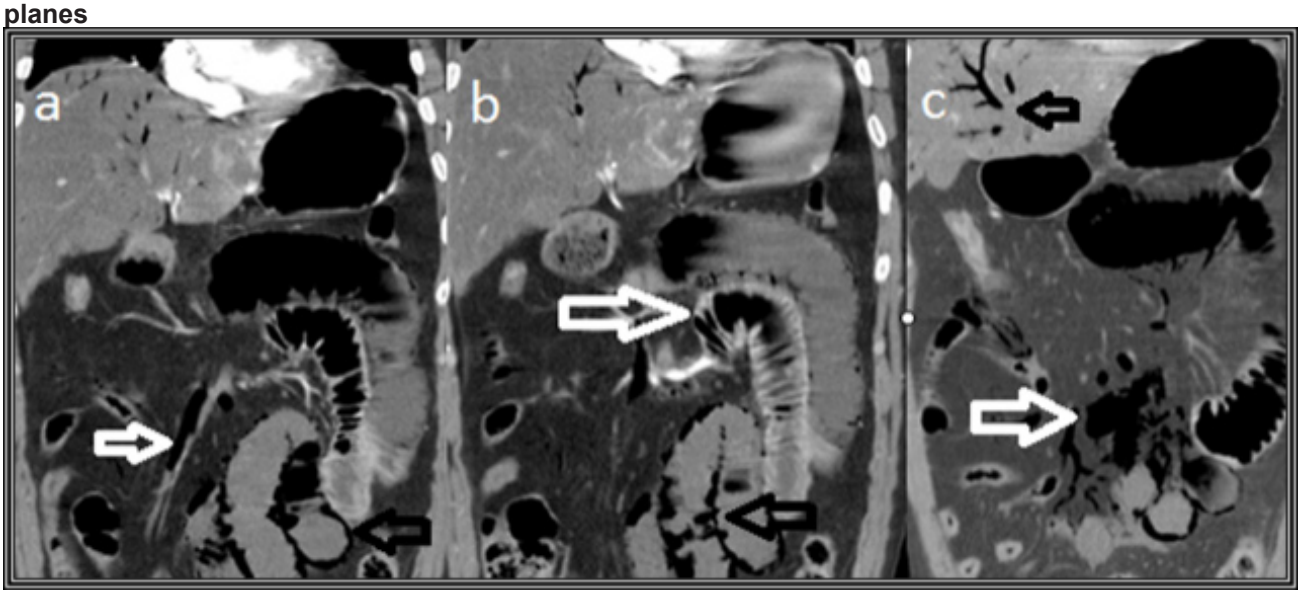


a. Non-contrast axial CT scan at the level of the upper abdomen above the liver hilum showing prominent IHBRs with evidence of air densities inside pneumo-bilia (white arrow).

b. Non-contrast coronal CT scan of the whole abdomen shows multiple linear shaped air densities seen along the root of the mesenteric vessels (white arrow). Note dilated small intestinal loops with evidence of multiple areas of intra-mural air densities seen inside the dilated bowel (black arrow).

c. Non-contrast axial CT scan at the lower abdominal level show multiple intra-mural air densities are seen inside the dilated bowel (pneumo-intestinalis with some of them showing characteristic arc shape (black arrow). Other multiple linear tortuous areas of air densities are seen inside the mesenteric fat along the branches of the mesenteric vessels.

Figure 3: Post-Contrast CT (SOMTOM Definition AS) scan using 128 multi-slice CT of the abdomen at multiple planes



Multiple shapes and distribution of air densities in abnormal areas inside the abdominal cavity with:
a. Linear air densities seen along the root of the mesenteric vessels (white arrow). Multiple linear and curvi-linear shaped areas of pneumo-intestinalis seen at the lower abdomen (black arrow).

b,.The proximal segments of the jejunal loops still shows wall enhancement with multiple linear areas of intra-mural air densities giving the appearance of saw teeth sign (white arrow). Other focal globular shaped areas of pneumo-peritoneum seen at the distal jejunal loops with absence of its wall enhancement (black arrow).

c. Linear air densities seen inside the prominent IHBRs pneumo-bilia (black arrow). Focal area of collected air densities seen at the central part of the peritoneum cavity suggested of large pockets of pneumo-peritoneum (white arrow).

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