

Case report

Acute ischaemic stroke following cisplatin-based chemotherapy for testicular cancer

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SUMMARY

Cisplatin is a widely used chemotherapeutic agent for many cancer types. Its toxicity profile includes drug-induced vascular damage. Clinicians should be aware of its varied presentation, including acute and chronic vascular events involving the arterial and venous system. This is a case of an otherwise well 32-year-old man with testicular cancer who received bleomycin/etoposide/cisplatin, and presented following two cycles of chemotherapy with homonymous hemianopia secondary to acute stroke. Acute arterial complications are rare, but clinicians should maintain a high index of suspicion for such events, even in a patient who otherwise has no vascular risk factors. Primary and secondary prevention measures including lifestyle modifications (smoking cessation, diet and exercise), blood pressure and cholesterol management, and antiplatelet therapy should be considered in patients exposed to cisplatin, during and following their treatment.

BACKGROUND

Testicular germ cell tumours are potentially aggressive malignancies which are curable with surgery and cisplatin-based chemotherapy. The patient demographic is typically a young, otherwise healthy male, in whom treatment-related toxicity can have a profound and long-lasting impact. Cisplatin is a key component in combination chemotherapy for testicular tumours, achieving a cure rate of over 95%. Cisplatin has numerous potential toxicities, including nephrotoxicity, neurotoxicity and myelosuppression. Cisplatin can also induce vascular injury, even in the testicular cancer patient population with no or minimal vascular risk factors (such as smoking, hypertension, hypercholesterolaemia or history of vascular disease). While long-term management of blood pressure is a well-recognised part of testicular cancer survivorship, clinicians should also be cognisant of the potential for acute vascular injury with cisplatin-based chemotherapy in this patient population.

CASE PRESENTATION

A 32-year-old man underwent a left orchidectomy for a 50mm non-seminomatous germ cell tumour (NSGCT) of the testis, with risk features of a predominant (90%) embryonal component and presence of lymphovascular invasion. He had elevated tumour markers namely beta-human

chorionic gonadotropin (beta-hCG) of 227 IU/L (normal range (NR) <5) and alpha fetoprotein (AFP) of 69 kU/L (NR <10), although there was a normal lactate dehydrogenase (LDH) level of 201 U/L (NR 120–250). There were no distant metastases on staging positron emission tomography (PET) scan. Postoperatively his tumour markers normalised with beta-hCG <5 IU/L and AFP of 3 kU/L. The patient declined adjuvant bleomycin, etoposide and cisplatin (BEP) chemotherapy and opted to undergo surveillance.

Two months following initial diagnosis he had a rise in beta-hCG level to 232 IU/L. The other tumour markers remained in normal range (AFP 5 kU/L and LDH 180 U/L). CT imaging showed retroperitoneal lymphadenopathy (maximum dimension 21 mm). The patient was diagnosed with good-risk stage IIB NSGCT.

He consented to three cycles of BEP chemotherapy, consisting of bleomycin (30 000 IU on days 1, 8 and 15), etoposide (100 mg/m² on days 1–5) and cisplatin (20 mg/m² on days 1–5) in a 21-day cycle. Following cycle 2 day 8 chemotherapy the patient presented with an acute left homonymous hemianopia, associated with a frontal headache. He had otherwise been systemically well.

The patient had an otherwise unremarkable medical history. He is a non-smoker, and was on no regular medications. Surgical history included previous vasectomy and right inguinal hernia repair.

INVESTIGATIONS

On presentation the patient was normotensive with ECG showing normal sinus rhythm. A CT followed by MRI of the brain confirmed acute ischaemia in the right occipital lobe and right posterior thalamus, consistent with a posterior cerebral artery territory ischaemic stroke (figures 1 and 2). The patient had a normal transthoracic echocardiogram, and carotid Doppler ultrasound demonstrated normal flow in the carotid and vertebral arteries. Cardiac monitoring did not reveal any arrhythmias. A vasculitic workup and testing for hypercoagulability were negative. Specifically, the patient had a negative lupus anticoagulant, negative antiphospholipid antibodies, normal antithrombin, protein C, S and serum homocysteine levels. Factor V Leiden and prothrombin gene mutations were negative. There were no antinuclear antibodies detected.



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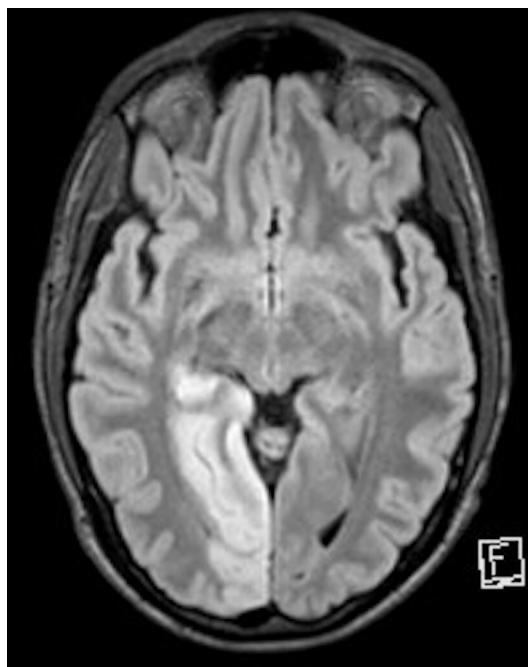


Figure 1 MRI brain (diffusion weighted images) showing occipital ischaemic stroke.

TREATMENT

The patient was managed on a stroke unit, with attention to blood pressure and blood glucose control. He was commenced on dual antiplatelet therapy with aspirin and clopidogrel under a consultant neurologist. He had persistent neurological deficit and the patient was discharged with a referral to Vision Australia to aid in rehabilitation.

A repeat CT scan shortly following the stroke presentation showed treatment response with halving of the size of para-aortic adenopathy (maximum dimension 10 mm). His tumour markers had normalised with hCG <5 IU/L and AFP 3 kU/L. The patient's oncological management was re-discussed at the genito-urinary multidisciplinary meeting, with consultation from interstate and international experts in the field. The options of continuing with completion of chemotherapy under dual antiplatelet cover versus retroperitoneal lymph node dissection (RPLND) were considered.

A key issue was balancing the risk of developing treatment resistant and metastatic disease through suboptimal chemotherapy, versus the risk of further ischaemic complications and subsequent neurological deficits. Given residual lymphadenopathy on imaging, the patient had a significant risk for cancer relapse with metastatic disease which is associated with poor survival. The risk with pursuing completion of BEP chemotherapy was precipitating a further ischaemic event with additional neurological deficit. However, this risk could potentially be ameliorated with concurrent aspirin and clopidogrel administration.

The surgical approach with RPLND was also considered. If there was viable tumour found at surgery, the patient would require further chemotherapy and again be exposed to the risk of cisplatin-associated vascular event. If no viable tumour was present at RPLND, the patient can be spared of further chemotherapy. However, a major surgery such as RPLND would require withholding of antiplatelet therapy for a week prior and up to 3–4 days post-operatively, posing a considerable risk of an intraoperative ischaemic event. Therefore, there

remained a thrombotic risk even in the absence of further chemotherapy.

The patient proceeded with completion of the final cycle of chemotherapy, following an informed discussion of the risk of recurrent stroke, with continuation of aspirin and clopidogrel therapy to minimise this risk.

OUTCOME AND FOLLOW-UP

Three cycles of chemotherapy were completed without a recurrent vascular event, with the patient remaining on dual antiplatelet therapy during treatment. A repeat CT chest/abdomen/pelvis scan 1 month later was clear for any disease and the latest tumour markers remain normal at 4 months following chemotherapy. However, the patients' neurological deficits remain, and he is unable to drive nor return to his former employment as a guard. Repeat MRI brain 2 months following the stroke demonstrated expected evolutionary changes with haemorrhagic transformation of the right occipital lobe infarct and residual gliosis in right posterior thalamus.

DISCUSSION

Cisplatin is the chemotherapy most classically associated vascular injury. Late-onset hypertension, coronary artery disease and peripheral artery disease occurring years to decades post treatment are well described. However, there can also be acute presentations with deep vein thrombosis and pulmonary embolism, as well as arterial thrombosis manifesting as cerebrovascular accident (CVA), myocardial infarction and acute limb ischaemia.^{1,2}

In one retrospective analysis of 932 patients, early vascular event during or within 4 weeks of last cisplatin dose occurred in up to 18% of cases.² The majority were deep vein thrombosis (50%), pulmonary embolism (25%) or both (13.6%). Arterial thromboses accounted for about 2% of events in this series, including CVA and myocardial infarction. Another series of patients with germ cell cancer reported thromboembolic complications, between the start chemotherapy

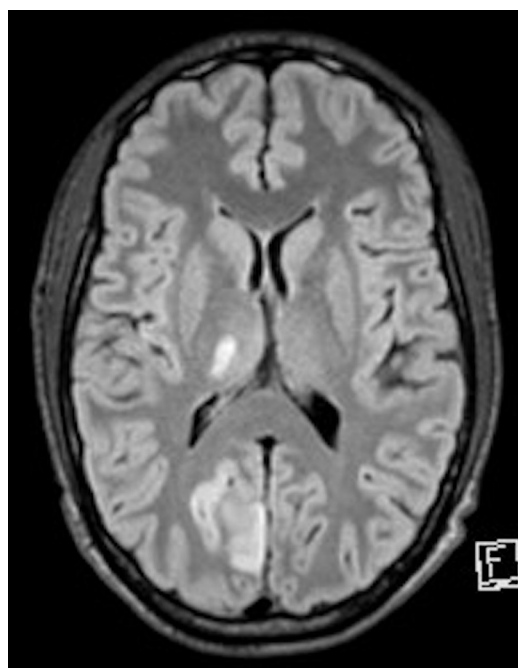


Figure 2 MRI brain (diffusion weighted images) showing thalamic ischaemic stroke.

and 6 weeks after the last dose of chemotherapy, in 8.4% of patients. Similarly, the majority (15/18) were venous events, while a minority (3/18) were arterial thromboembolic events, including two cerebral ischaemic strokes, one of which was fatal. This highlights the importance of acute arterial complications being rare but serious side effects of cisplatin. There are various proposed mechanisms for vascular injury, including elevation of clotting factors (von Willebrand factor, intracellular adhesion molecule-1, plasminogen activator inhibitor-1 and tissue plasminogen activator); platelet activation and direct endothelial damage.

In previous case reports of arterial events associated with cisplatin, the majority of patients had other vascular risk factors such as smoking.¹ The presence of liver metastases and high dose corticosteroids (≥ 80 mg dexamethasone per cycle) were identified as risk factors for thromboembolic complications of patients with germ cell cancer on chemotherapy.³ The dosage of cisplatin may also further influence risk, with highest risk of venous thromboembolism (VTE) occurring with weekly equivalent cisplatin dose >30 mg/m², as used in the BEP regimen for testicular cancer. While other oncological drugs can also be associated with vascular complications, the risk is highest with cisplatin. A meta-analysis found the incidence of VTE was 1.67-fold higher among cisplatin-based compared with non-cisplatin based regimen.⁴ Among the platinum class of chemotherapy, VTE events were more common with cisplatin compared with oxaliplatin (15.1% vs 7.6%, $p < 0.001$), following adjustments for other factors in a multivariate analysis, in a phase III trial of gastro-oesophageal cancer.⁵

Our patient developed an acute CVA following two doses of cisplatin as part of BEP chemotherapy for recurrent testicular carcinoma. This presents a management dilemma. Our patient had no other vascular risk factors, making cisplatin the most likely significant contributor to the cerebrovascular event. This has had a major impact on the patient's livelihood in numerous aspects such as ability to drive and employment prospect. On the other hand, cisplatin is the most important component of testicular cancer chemotherapy, and the standard therapy is three cycles of BEP in patients of low-intermediate risk. Patients who have a CVA are at increased risk for development of a second event, especially in the initial weeks following the first event. Further neurological deficit would have further impaired our patient's functional ability with significant impact on quality of life. All these are factors for consideration against the competing risk of cancer-associated morbidity/mortality. Salvage therapy such as second line chemotherapy and bone marrow-depleting therapy with haematopoietic stem cell transplant for testicular cancer have associated risks and toxicities, and the chance of response and disease cure becomes smaller with each further line of therapy.

There are other case reports of acute vascular event following cisplatin for testicular cancer. However, ours is the first case where the patient was successfully rechallenged with cisplatin under dual antiplatelet cover. Azak *et al* reported on a 17-year-old boy with testicular NSGCT and pulmonary metastases who suffered a haemorrhagic stroke seven days into the fourth cycle of BEP.⁶ Further chemotherapy was postponed and the regimen was switched to paclitaxel and gemcitabine, but the patient ultimately relapsed and died from progression of testicular cancer. On the other hand, Karagoz *et al* described a 34-year-old male with stage IIA NSGCT developed an ischaemic stroke on day 10 of cycle 3 BEP.⁷ The chemotherapy was aborted and the patient remained free of cancer relapse at 6

months follow-up. In the case by Azak *et al* the mechanism for stroke is likely related cisplatin-related vascular injury, hypertension and small vessel vascular damage. This is distinct to Karagoz *et al* and our case, where cisplatin induced an acute thrombotic CVA. Nonetheless, the three cases highlight the spectrum of acute vascular event on cisplatin. Given our report is on an isolated case experience, it should not be perceived as directive on the optimal management, and the decision to rechallenge with cisplatin should be made with consideration of risks and benefits on a case-by-case basis.

The risk for cancer-associated thrombosis is influenced by several factors including those associated with the patient (older age), cancer (primary site, stage, histology), treatment (chemotherapy, anti-angiogenic agents), as well as serum biomarkers (platelet count, leucocyte count, D-dimer). In a predictive model for chemotherapy-associated VTE,⁸ testicular cancer conferred 'high risk', as did lung, bladder, gynaecological cancers and lymphoma; while stomach and pancreas cancers conferred 'very high risk' for a VTE event. Other factors which contribute to the Khorana score include prechemotherapy platelet count $\geq 350 \times 10^9/L$, haemoglobin < 100 g/L or use of red cell growth factors, prechemotherapy leucocyte count $> 11 \times 10^9/L$ and body mass index greater or equal to 35 mg/m².⁸ Our patient would have been categorised as intermediate risk with a Khorana score of 1 (based on tumour type).

The optimal prophylaxis strategy for patients at high-risk for VTE has not yet been identified. Currently, thromboprophylaxis (such as with low molecular weight heparin (LMWH)) is routine only in the inpatient setting and protects against VTE. The majority of patients with cancer receive treatment as outpatients. LMWH such as nadroparin⁹ and semuloparin¹⁰ have been shown to significantly reduce the rate of thromboembolic event in outpatients with cancer. The study¹⁰ assessing semuloparin only included VTE endpoints, whereas the nadroparin study⁹ included both arterial and venous complications.

More recently, oral factor Xa inhibitors have been shown as effective thromboprophylaxis treatments in patients with Khorana score of 2 or higher. Apixaban significantly reduce the incidence of VTE (4.2% in apixaban vs 10.2% in placebo group, HR 0.41), although this was accompanied by a higher risk of majority bleeding (2.1% in apixaban vs 1.1% in placebo group, HR 1.89).¹¹ Rivaroxaban reduced the combined rate of VTE events and death from VTE during the intervention period, and also reduced the composite endpoint which additionally included arterial and visceral thromboembolic events.¹² Arterial thromboembolism occurred in 1% in the rivaroxaban group and 1.7% in the placebo group. Given the rarity of arterial thromboembolic complications on chemotherapy, it is difficult to ascertain the magnitude of impact from these thromboprophylaxis measures. Patient selection also remains challenging, as vascular complications can occur in patients who are not deemed 'high risk', as our patient, and the bleeding risk from anticoagulation, makes it difficult to justify routine prophylaxis in unselected patients.

This case serves as an example of a significant vascular event in a patient receiving cisplatin chemotherapy. It is important for emergency physicians, cardiologists and neurologists to be aware of chemotherapeutics serving as a significant vascular risk factor, in an otherwise well young patient with an acute neurological presentation or chest pain. It also serves as a reminder for oncologists to be more vigilant of acute vascular complications, particularly with cisplatin, and work with

Unexpected outcome (positive or negative) including adverse drug reactions

primary care providers to manage any modifiable risk factors such as hypertension and hypercholesterolemia both during and following chemotherapy. Although this does not eliminate the risk, primary prevention measures potentially can mitigate the chance of chemotherapy precipitating a vascular event.

Learning points

- ▶ Vascular complications related to cisplatin chemotherapy can have various manifestations, either acute or chronic, involving the arterial or venous systems.
- ▶ Cisplatin-associated acute vascular events are rare compared with venous thromboembolic events, but can occur in patients without other vascular risk factors.
- ▶ Acute thromboembolic events can be serious, with long-term functional implications on the patient.
- ▶ Thromboprophylaxis with low molecular weight heparin and oral anti-Xa inhibitors can help reduce vascular events in high-risk ambulatory patients with cancer, but the benefit is mostly demonstratable for venous thromboembolism.
- ▶ Rechallenge following a cisplatin-associated acute vascular complication should be considered on a case-by-case basis by a multidisciplinary team, taking into consideration the competing risk of malignancy recurrence, and secondary prophylaxis with antiplatelet agents should be strongly considered.

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REFERENCES

- 1 Tait CD, Rankin EM. Arterial emboli complicating cisplatin therapy. *Case Rep Oncol Med* 2012;2012:1–2.
- 2 Moore RA, Adel N, Riedel E, *et al*. High incidence of thromboembolic events in patients treated with cisplatin-based chemotherapy: a large retrospective analysis. *J Clin Oncol* 2011;29:3466–73.
- 3 Weijl NI, Rutten MF, Zwinderman AH, *et al*. Thromboembolic events during chemotherapy for germ cell cancer: a cohort study and review of the literature. *J Clin Oncol* 2000;18): :2169–78.
- 4 Seng S, Liu Z, Chiu SK, *et al*. Risk of venous thromboembolism in patients with cancer treated with cisplatin: a systematic review and meta-analysis. *J Clin Oncol* 2012;30:4416–26.
- 5 Al-Batran S-E, Hartmann JT, Probst S, *et al*. Phase III trial in metastatic gastroesophageal adenocarcinoma with fluorouracil, leucovorin plus either oxaliplatin or cisplatin: a study of the Arbeitsgemeinschaft Internistische Onkologie. *J Clin Oncol* 2008;26:1435–42.
- 6 Azak A, Oksüzöçlü B, Deren T, *et al*. Cerebrovascular accident during cisplatin-based combination chemotherapy of testicular germ cell tumor: an unusual case report. *Anticancer Drugs* 2008;19:97–8.
- 7 Karagoz B, Bilgi O, Akyol I, *et al*. Cerebrovascular accident after chemotherapy for testicular cancer. *Mil Med* 2009;174): :320–1.
- 8 Khorana AA, Kuderer NM, Culakova E, *et al*. Development and validation of a predictive model for chemotherapy-associated thrombosis. *Blood* 2008;111): :4902–7.
- 9 Agnelli G, Gussoni G, Bianchini C, *et al*. Nadroparin for the prevention of thromboembolic events in ambulatory patients with metastatic or locally advanced solid cancer receiving chemotherapy: a randomised, placebo-controlled, double-blind study. *Lancet Oncol* 2009;10): :943–9.
- 10 Agnelli G, George DJ, Kakkar AK, *et al*. Semuloparin for thromboprophylaxis in patients receiving chemotherapy for cancer. *N Engl J Med* 2012;366:601–9.
- 11 Carrier M, Abou-Nassar K, Mallick R, *et al*. Apixaban to prevent venous thromboembolism in patients with cancer. *N Engl J Med* 2019;380:711–9.
- 12 Khorana AA, Soff GA, Kakkar AK, *et al*. Rivaroxaban for thromboprophylaxis in high-risk ambulatory patients with cancer. *N Engl J Med* 2019;380:720–8.

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