Extensive Deep Venous Thrombosis Associated with Chemotherapy for Testicular Cancer: A Case Report with Review of the Literature

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Citation

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Abstract

The authors report a case of an extensive deep venous thrombosis occurring as a complication of chemotherapy with cisplatin, bleomycin and etoposide for a testicular germ cell tumour. During the first cycle of chemotherapy, the patient developed a dramatic picture of deep venous thrombosis, extending from the popliteal and iliofemoral veins up to the thoracic vena cava, close to the right atrium. Progression of thrombosis to the renal veins resulted in acute renal failure requiring dialysis. There are no reports in the literature of such an extensive thrombosis associated with this regimen. Of note, the remarkable results obtained with the early institution of thrombolytic therapy with streptokinase. Thromboembolic events are potentially life-threatening complications that seem to occur more frequently than expected in patients receiving chemotherapy for germ cell tumours, in spite of young age. Preventive measures should not be overlooked in this setting.

LIST OF ABBREVIATIONS

GCT= germ cell tumours
CMF= cyclophosphamide, 5-fluorouracil, methotrexate
CMF/tam= cyclophosphamide, 5-fluorouracil, methotrexate, tamoxifen
DVT= deep venous thrombosis
BEP = bleomycin, etoposide, cisplatin
TT= thrombolytic therapy
DHL= lactate dehydrogenase
-hCG= human chorioninc gonadotropin -subunit
AFP= alphafetoprotein
IV= intravenously
RP= Raynaud phenomenon
SH= systemic hypertension
PVB= cisplatin, vinblastin, bleomycin
FSH= follicle stimulating hormone
LH= luteinizig hormone
PTE= pulmonary thromboembolism

INTRODUCTION

Thromboembolism as well as other vascular phenomena have been associated with cancer. Such events may result in considerable morbidity and impaired quality of life and, in some instances, may be life-threatening. This is a particularly relevant problem in some malignant diseases such as the germ cell tumours (GCT), in which cure or long term survival is expected in most patients ([1]).

The association of anticancer chemotherapy with thromboembolic phenomena was first reported in patients with breast cancer treated with the combination of 5-fluorouracil, methotrexate, cyclophosphamide and tamoxifen (CMF/tam) and in patients with head and neck cancer treated with cisplatin and bleomycin ([1,2,3]). Ever since, similar events have been reported with a variety of anticancer agents and regimens ([4,5,6,7,8,9,10,11,12,13,14]). In GCT, local factors may also contribute to the increased incidence of vascular complications observed in this disease ([5,15]).

We report the case of a patient with a testicular GCT, who developed an extensive deep venous thrombosis (DVT) during cisplatin, bleomycin and etoposide (BEP) chemotherapy. This patient had a favourable outcome with the proposed treatment – namely thrombolytic therapy (TT) with streptokinase.

CASE REPORT

The patient was 18 years old and had had a diagnosis of a nonseminomatous GCT of the right testicle of mixed histology (60% of embryonal carcinoma, 30% of mature teratoma and 10% of immature teratoma). Pulmonary and hepatic metastases were present, as well as massive involvement of retroperitonial lymph nodes. The latter was responsible for extrinsic compression of the inferior vena cava and renal veins. Tumour markers were elevated: lactate dehydrogenase (DHL)=1023 mU/ml, human chorionic gonadotropin -subunit (hCG)=45050 mU/ml and alphafetoprotein (AFP)=3077 ng/ml (TNM: pT3N3M1BS2, AJCC stage: IIIC). Radical orchiectomy was performed and 8 days later chemotherapy according to the protocol BEP (cisplatin 20 mg/m2 IV day 1-5, bleomycin 30 UI IV days 1,8,15 and etoposide 100 mg/m2 IV days 1-5) was started. On day 4 of the first cycle, the patient developed pain and oedema of the lower limbs and an echodoppler diagnosed a DVT (figure 1), extending from both popliteal veins up to the thoracic segment of the inferior vena cava, close to the right atrium. TT with streptokinase was immediately started (250000 u IV in 1 hour as a loading dose, followed by 100000 u/h as a continuous infusion). On day 2, acute renal failure developed (rise in BUN and creatinine from 21 mg/dL and 0.9 mg/dL, at baseline, up to 76 mg/dL and 3.0 mg/dL, respectively) and was attributed to extension of the thrombosis to the renal veins, as demonstrated by echodoppler.

Hemodialysis was instituted, and on day 3 the patient showed signs of improvement. Recovery of renal function (urea=31 mg/dL and creatinine=0.8 mg/dL one week later, sustained after dialysis was stopped) correlated well with the improvement in blood flow in the renal veins and inferior vena cava. Thrombolytic infusion was stopped on day 6. Clinical signs of DVT continued to improve and follow-up echodopplers, performed on days 14 and 60, respectively, confirmed the favourable outcome. The patient continued anticoagulation with warfarin for the duration of the chemotherapy. Four cycles were given in total, which resulted in a complete clinical and biological response.

Figure 1

Figure 1a: massive thrombosis of the inferior vena cava

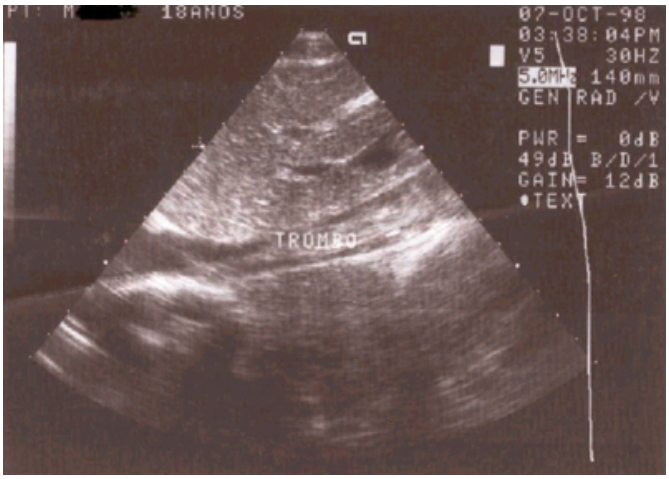


Figure 2

Figure 1b: massive thrombosis of the left common femoral vein

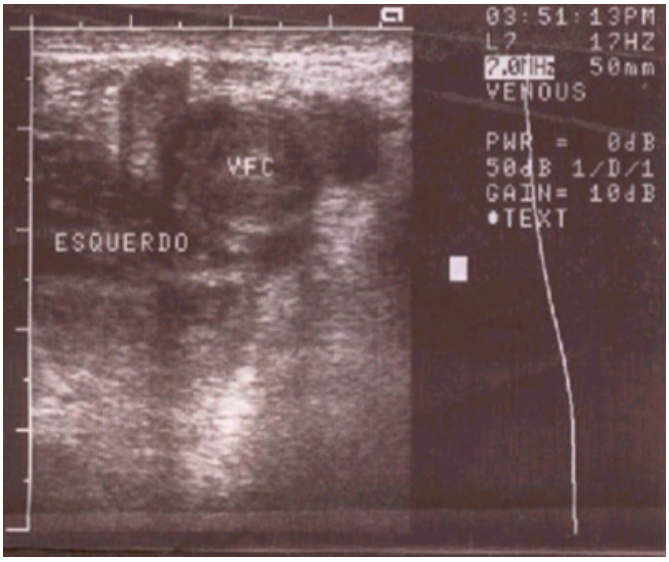
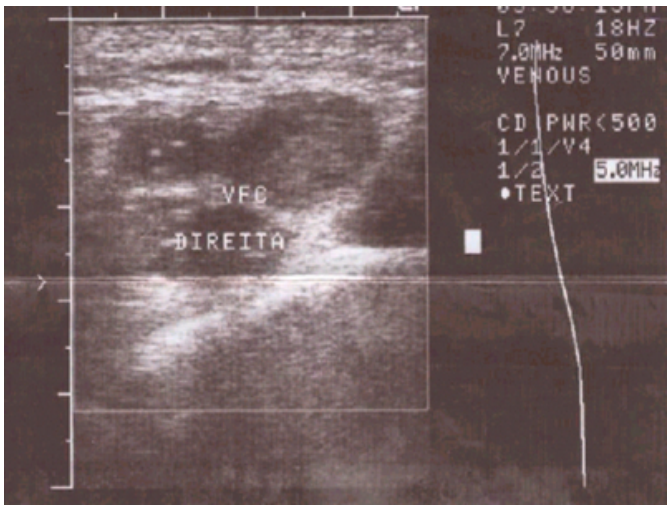


Figure 3

Figure 1c: massive thrombosis of the right common femoral vein



DISCUSSION

Thromboembolic phenomena occur with increased frequency in patients with cancer. Interestingly, the occurrence of such events has also been associated with the administration of chemotherapy ([1,4,5,6,7,8,9,10,11,12,13,14]).

The pathogenesis seems to be multifactorial, involving local (endothelial lesion) and systemic factors (coagulation abnormalities). Oberhoff et al demonstrated the induction of hypercoagulability by CMF in a group of patients receiving adjuvant chemotherapy for breast cancer ([16]). Similar reports have been presented by others ([17]). Cisplatin is known to induce vasospasm which may lead to vascular abnormalities such as Raynaud phenomenon (RP) and systemic hypertension (SH) or, less commonly, angina, myocardial infarction, mesenteric ischemia, limb ischemia and cerebrovascular accidents ([1,5,6,7,9]). Nevertheless, thrombosis remains the most common cause of ischemic events in this setting. Venous thrombosis is typical but arterial thromboembolism has also been reported ([8,18,19,20]).

The increased incidence of vascular complications observed in GCT is an intriguing finding, as patients tend to be young and fit. Cases of secondary SH, RP and thromboembolism were initially reported with the PVB regimen (vinblastin, cisplatin and bleomycin) ([4,6,8,9,10]). Similar events have been associated with the BEP regimen ([1,20,21]). Of interest, an increased incidence of long term cardiovascular complications has been reported in a group of patients with GCT treated with cisplatin-based chemotherapy. Suggested causes were secondary metabolic and hormonal changes, such as hypercholesterolemia, hypertriglyceridemia, obesity, elevated follicle stimulating hormone (FSH) and luteinizing hormone (LH) ([22]). In a single institution experience, the incidence of major thromboembolic complications reported in a group of 179 patients receiving first-line chemotherapy for GCT was as high as 8.4%, 16.5% of those being arterial events and 83.3% DVT, with 11 pulmonary thromboembolisms (PTE) and one death. The same authors also suggest high dose corticosteroids, presence of liver metastases and anti-emetic therapy as major risk factors ([23]).

Nevertheless, other predisposing factors may also be present and should not be overlooked. In testicular cancer, for instance, local factors such as retroperitonial lymph node metastases may cause vascular compression resulting in stasis ([15,24]). Vascular invasion may result in endothelial damage ([25]). Even HCG, a GCT marker, has already been mentioned as a systemic factor predisposing to thrombosis ([4]). Recent surgery may be an additional factor. In the case of our patient, at least some of these factors may have contributed to the development of DVT, although the temporal relation with the administration of chemotherapy seems clear to us.

In the setting of an extensive DVT, early institution of appropriate anti-thrombotic therapy may prevent complications such PTE and post-thrombotic syndrome ([26]). In such cases, heparin remains the standard treatment, although there is mounting evidence in the literature in favour of TT, followed by anticoagulation ([12,27,28,29,30,31,32,33,34]). In selected cases, novel surgical techniques such as the percutaneous thrombectomy may be life-saving ([35]). Of note, the excellent results obtained in this case with the administration of TT with streptokinase, given as an attack dose and followed by continuous, prolonged infusion, which resulted in complete lysis of the thrombus.

CONCLUSION

Cisplatin-based chemotherapy in GCT should be viewed as highly effective but potentially thrombogenic treatment. We point out that simple preventive measures – such as prophylactic heparin – may be life-saving and should be routinely considered in these patients ([8,27,28]).

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