

Arterial thrombosis after cisplatin-based chemotherapy for metastatic germ cell tumors

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To the Editor

Although germ cell tumors (GCTs) make up only 1% of all human malignancies, they are the most common cancers among men aged 15 to 34 [1]. Since the introduction of cisplatin-based chemotherapy in the 1970s, long-term survival rates of 80% are achieved even in metastatic settings [2]. This has placed greater emphasis on minimizing therapy-related side effects as they significantly impact the quality of life of long-term survivors. Here we present two cases of cisplatin-induced arterial thrombosis in patients receiving chemotherapy for metastatic good prognosis GCTs. We then review the incidence and consider possible mechanisms of this phenomenon.

Case 1

A 58-year-old male was diagnosed with a classic seminoma with retroperitoneal metastases (Stage IIc). Remarkable past medical history includes malignant melanoma treated surgically 15 years earlier. The patient presented with a three month history of left testicular enlargement with an elevated beta fraction of human gonadotrophic hormone (β HCG) of 49 IU/L (normal = <2 IU/L). An abdominal computed tomography (CT) scan showed enlarged retroperitoneal lymph nodes including a mass encasing the renal arteries and half of the abdominal aorta. The patient underwent an inguinal orchiectomy and was scheduled for four courses of etoposide and cisplatin chemotherapy (EP). After the first cycle, the patient experienced mild symptoms suggestive of intermittent claudication in the distal right lower extremity. After the second cycle of treatment these symptoms worsened and he was diagnosed with acute ischemia secondary to thrombosis in the right external iliac artery. No smoking history or cardiovascular risk factors were identified and investigations ruled out heart disease

as the precipitating cause. A balloon angioplasty of the right common iliac artery, right common femoral artery thrombectomy, and patch angioplasty of the right femoral artery were performed. On discharge, the patient was prescribed clopidogrel and low-dose aspirin for thrombosis prophylaxis. Following resolution of the ischemic episode, the patient resumed chemotherapy and completed four cycles of treatment as initially planned, achieving a complete response. On further follow-up his only complaint is mild bilateral residual neuropathy in the feet. The patient remains free of disease 12 months after the initial diagnosis.

Case 2

A 37-year-old male was diagnosed with good prognosis, stage III testicular cancer of mixed seminoma and non-seminoma histology (95% embryonal carcinoma, 5% seminoma). The past medical history was unremarkable. The patient initially presented with a left testicular mass; scrotal ultrasound revealed a large left testicular lesion and a 4.9 cm mass in the left inguinal region. The alpha-feto protein and β HCG were elevated at 17 IU/L (normal = <5) and 155 IU/L, respectively. The patient underwent an orchiectomy and started chemotherapy with bleomycin, etoposide, and cisplatin (BEP). After the first cycle he developed a painful, swollen, and cyanotic right foot with significantly decreased blood flow and was diagnosed with an acute arterial thrombosis. The patient was admitted to hospital and treated with thromboembolic therapy with tissue plasmin activator (tPA), followed with low molecular weight heparin. After discharge he continued on chemotherapy with prophylactic heparin, and the second cycle of BEP was well tolerated. However, during the third cycle the patient developed a recurrence of arterial embolic disease in the right leg. Despite many interventions including

thrombolysis and tPA, the leg remained ischemic and required amputation below the knee. At this time, tumor markers that were previously elevated had normalized and CT scan evaluation post-treatment showed residual disease with two para-aortic lymph nodes. A nerve-sparing retroperitoneal lymph node dissection was subsequently performed, revealing teratoma histology. No further treatment was implemented and the patient remained free of recurrence 18 months following diagnosis.

Discussion

Thromboembolic events (TEE) represent a frequent cause of morbidity and mortality in cancer patients. Laboratory evidence of hypercoagulation is observed frequently in these patients, although the pathogenesis has not been completely elucidated. Mechanisms involved include defects in blood flow due to local tumor growth, an activation of the coagulation cascade by pro-coagulant factors, and thrombogenic properties of the tumor-related neovascularization [3]. Treatment with chemotherapy is also a well established independent risk factor for TEE in cancer patients, and recent reports have described TEE in a variety of malignancies and many different treatment regimens [4].

Cisplatin is widely used in oncology and represents the cornerstone for the treatment of GCTs; its toxicity profile predominantly includes emesis, myelosuppression, renal, and peripheral nerve damage. Additionally, vascular side effects have been linked to cisplatin use, ranging from vasospasm to acute ischemic arterial thrombosis [5]. In a retrospective review of 271 patients who received cisplatin-based chemotherapy for urothelial transitional cell carcinoma, vascular events occurred in 35 patients (12.9%), of which 7 (20%) were arterial thromboses [6]. Various other publications over the last 20 years have described recurrent peripheral arterial thromboses in patients receiving cisplatin for the treatment of various types of malignancies [7–9].

The molecular mechanisms by which anticancer drugs such as cisplatin induce TEE remain poorly understood and likely involve local and systemic factors. It has been hypothesized that exposure of vascular endothelial cells to chemotherapeutic agents may result in the loss of a thrombo-resistant phenotype and therefore lead to an increased risk of TEE. Other mechanisms possibly involved include cisplatin-induced hypomagnesemia, elevated Von Willebrand factor levels, increased platelet aggregation and the endothelial cell protein C receptor [5,10].

While it is generally known that malignancy and treatment with cisplatin-containing regimens cause patients to be at higher risk for TEE, they appear to

occur more frequently in GCTs. Various case-reports have been supportive, and larger studies have attempted to summarize the incidence of these events [11]. In a cohort of 179 males who received cisplatin-based chemotherapy for GCT, 15 (8.4%) developed TEE, of which 3 (17%) were arterial [10]. Another analysis compared TEE in 100 GCT patients with 100 non-GCT patients who received cisplatin therapy. The former were found to be at a higher risk, and it appeared that TEE was predicted by serum lactose dehydrogenase levels and body surface area [12]. In spite of supporting evidence, at least three publications with retrospective analyses have reported no apparent correlation between acute cardiovascular complications, GCTs, and chemotherapy [13–15].

To our knowledge, no prospective studies have analyzed specific risk factors for arterial TEE in GCTs patients, rendering it difficult to make recommendations about primary prophylaxis. Moreover, guidelines recently published by the American Society of Clinical Oncology advise against routine venous thromboembolism prophylaxis in ambulatory cancer patients, without making any special mention on GCTs or the use of cisplatin [16]. No formal recommendations exist in the literature regarding arterial event prevention in cancer patients. Thus, early recognition of this process and proper therapy are critical.

In order to optimally manage cisplatin-induced arterial TEE in GCT patients, recommendations should be extrapolated from those for the general population. Treatment is dependent on whether the occlusion is caused by an embolism in a healthy or atheromatous artery. Prompt embolectomy through surgical intervention is the conventional technique of removing emboli from healthy arteries; percutaneous thromboembolectomy with the aid of an aspiration catheter or thrombectomy device is a recent alternative. Additionally, guidelines of the American College of Chest Physicians (ACCP) recommend immediate systemic anticoagulation with heparin followed by Vitamin K antagonism to prevent propagation and recurrence in patients undergoing embolectomy. An alternative to surgical revascularization is intra-arterial thrombolytic therapy with agents such as tPA, urokinase, or streptokinase. This option is particularly recommended by the ACCP in patients with short term (<14 days) thrombotic or embolic disease with low risk of myonecrosis and ischemic nerve damage.

In conclusion, although cisplatin-induced arterial TEE in GCT patients represent an overall low incidence phenomenon (~2%), dramatic consequences can occur if they are not detected early and managed properly. While no general guidelines

can be given regarding primary prophylaxis, it is recommended that existing guidelines be adapted to each patient. Consideration should be given to previous cardiovascular risk factors; the volume of disease and its anatomical relation with great vessels is also likely related. Insufficient data exist regarding the relevance of factors such as histology, location of metastasis, or the use of particular medications to include them in formal recommendations. Thus, it is critical that patients with GCTs be managed in centers with extensive experience on the treatment of this disease and their potential complications.

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Long-term progression-free survival in metastatic uveal melanoma after chemoimmunotherapy and consolidation thermoablation

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To the Editor

Uveal melanoma is remarkable for its initially purely hematogenous dissemination and its tendency to metastasize to the liver [1]. At least 40% of patients develop metastases during the first decade [2] and the liver, a “sentinel node” for uveal melanoma, is

involved in about 90% of them [3,4]. Micrometastasis may take place several years before diagnosis of the primary tumor [5], whereas development of clinically detectable metastasis can be delayed for many years or even decades after the primary tumor has been definitively cured [2].

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