Thrombosis of Internal Carotid Artery after Cisplatin-Based Chemotherapy

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Dear Sir,

The role of a malignant disease as a risk factor for cerebrovascular disorders is established and mechanisms are well determined [1]. Less commonly, the increased risk may also be due to vascular toxicity of chemotherapy [2]. The past sporadic case reports of acute cardiovascular events in young men receiving chemotherapy containing cisplatin for testicular cancer have raised concern that these events may be treatment-related complications and impugn the safety of such treatment [3–7]. Particular association was suggested between cisplatin-based chemotherapy and ischemic stroke [8–10]. Nevertheless, although such cases are rare, they may appear occasionally [7]. Today, about 80% of metastatic testicular cancer patients can be cured by 3–4 cycles of chemotherapy containing cisplatin, etoposide and bleomycin [11]. This treatment of testicular cancer is definitely effective, but occasional reports of complications speak in favor of the need of supporting the continued research of strategies to minimize toxicity in patients with favorable prognosis [12].

Case Report

A 44-year-old right-handed locksmith was admitted to the Neurology Department after a sudden onset of diminished consciousness and right-hand side hemiparesis. His wife had spoken with him that morning, when he had felt well. Four hours

later, she found him lying by the bed unable to communicate and unable to move his right limbs. On admission 3 h later, he was somnolent, globally aphasic, and he had central paresis of the facial nerve and spastic hemiplegia with brisk reflexes and extensor plantar response on the right side. There were no clinical signs of deep venous thrombosis. A few months earlier, he had been diagnosed as having testicular seminoma. A day prior to the admission, he had finished the second cycle of chemotherapy – etoposide and bleomycin regimen (bleomycin 15 mg/day continuous infusion over 3 days, etoposide 100 mg/m²/day over 5 days, cisplatin 20 mg/m²/day over 5 days), which he had received after orchiectomy on the right because of retroperitoneal metastases. He had no other diseases or risk factors for cerebrovascular diseases and was taking no other medications. He had not had any abdominal surgery for retroperitoneal metastases either.

On admission he was hemodynamically stable with a blood pressure of 150/102 mm Hg, normal body temperature and laboratory results that showed signs of early inflammation [C-reactive protein (CRP) <5 mg/l, leukocytes 10.3×10^9 /l, 90% segmented neutrophils]. A day later, the body temperature increased (38.3°C), and the blood pressure dropped (104/77 mm Hg). We found no other clinical signs of infection. However, laboratory measures

confirmed an ongoing inflammation [CRP: 116 mg/l, procalcitonin: 3.85 µg/l, sedimentation rate (SR): 48, leukocytes: 8.5×10^9 /l, 89.5% of segmented neutrophils], but cultures from aspirate, urine and blood were sterile. Pulmonary X-ray was performed and showed a normally sized heart and aorta, and no signs of metastasis or other pathological infiltrates in pulmonary parenchyma. He was prescribed antibiotics (cefotaxim 2 g/8 h and garamycin 240 mg/24 h), and after 5 days, the body temperature dropped to normal. During the next few days, normocytic anemia (erythrocytes 2.92×10^{12} /l, hemoglobin 88 g/l, hematocrit 0.251) and later leukopenia gradually developed (leukocytes 1.7×10^9 /l). He received transfusion. The general condition improved within a week after admission.

On the day of admission, CT of the head showed a cortico-subcortical ischemic lesion in the territory of the left medial cerebral artery. The subsequent CT of the head a few days later showed thrombosis of the left medial cerebral artery. Color Duplex sonography of the neck arteries showed hypoechoic masses that occluded the left internal carotid artery. Ultrasound examination of the heart revealed patent foramen ovale. Except for the increased levels of fibrinogen (4.53 g/l) and D-dimer (1,811 µg/l), the tests for thrombophilia were normal. Antinuclear

antibodies, extractable nuclear antigens, cardiolipin antibodies and homocystein concentrations were within normal limits. Magnesium concentration was also within normal limits (0.83 mmol/l). Control ultrasound of the abdomen showed complete regression of the retroperitoneal metastases and diffuse liver parenchyma damage.

Supportive treatment for ischemic stroke with physical therapy and logopedic management was introduced. When the patient was discharged from hospital, he was still suffering from right-sided hemiparesis and motor aphasia. He was then hospitalized at the Institute for Rehabilitation in Ljubljana, and after the rehabilitation program, he was able to walk around his apartment.

Six months later, he was readmitted to the Neurology Department because of 2 epileptic attacks. CT scan of the head revealed atrophy after ischemic stroke. He was prescribed anticonvulsive treatment and returned to home care.

Discussion

Cisplatin is an effective and widely used antineoplastic agent used for the treatment of solid tumors. Occasional case reports suggest that vascular damage is an important, although less well-known side effect of this drug [13]. The first report of stroke following cisplatin-based chemotherapy was described in 1983 [14]. Later, 3 cases of young patients with cerebrovascular accidents, despite a normal 4-vessel cerebral angiography, were reported [4, 15]. The frequency of this complication is lower than 1 in 2000 treated patients [10]. Several mechanisms for cisplatin early toxicity were postulated. The possibility of direct endovascular damage was suggested [10, 14]. Moreover, cisplatin may increase platelet aggregation [7, 14, 16], and both factors may lead to intra-arterial thrombus formation. In addition, cisplatin can cause changes in coagulation factors, abnormality of thromboxane-prostacyclin homeostasis, autonomic dysfunction, vasculitis and stimulation of fibroblasts [14]. An acquired deficiency of anticoagulant protein C and elevated plasma von Willebrand factor levels were also observed [17, 18]. A possible mechanism of stroke is vasospasm caused by cisplatin-induced hypomagnesemia [7, 10]. However, there has been no in vivo evidence for cisplatin-induced vasospasm so far.

In our case, we failed to find any known pathophysiological mechanisms that had been suggested as a consequence of malignant disease or consequent chemotherapy. The time interval between the chemotherapy and the thrombosis of the internal carotid artery with subsequent ischemic stroke suggested a cisplatin-related cause (such adverse effects are unknown with bleomycin and etoposide). Although we could not exclude occult sepsis according to elevated body temperature and inflammatory parameters 1 day after admission, the patient initially had no clinical or laboratory signs of inflammation. Therefore, the inflammation was probably not the cause, but rather the consequence of stroke. Although all other tests for thrombophilia were normal, the increased levels of fibrinogen and D-dimer raised the suspicion of deep venous thrombosis/pulmonary embolism/paradoxical embolism as a possible mechanism of stroke. In a patient with malignancy and a patent foramen ovale, such a mechanism would be extremely rare but not impossible. It could also explain the fever. However, there were no clinical signs of deep venous thrombosis or pulmonary embolism, and the chest X-ray and ultrasound of the heart showed no signs of that either.

In conclusion, chemotherapy was the most likely cause of carotid thrombus and stroke in our patient. However, currently, there is not enough evidence to recommend prophylactic anticoagulation, and studies are needed to clearly identify the risk factors for stroke in cisplatin-based chemotherapy.

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