CASE REPORT

Peripheral obstructive arterial disease worsened by use of gemcitabine for the treatment of pancreatic cancer: case report and review of the literature

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ABSTRACT

We report a case of lower limb critical ischemia associated with chemotherapy with gemcitabine. This report presents a case of a 68-year-old man who underwent pancreatoduodenectomy due to pancreas tumor. One month later, the patient was submitted to four chemotherapy sessions with gemcitabine for 1 month. In addition, 30 days later he developed symptoms of peripheral arterial obstructive disease, and critical ischemia of the right lower limb 2 weeks later. An imaging study showed diffuse arterial disease associated with femoropopliteal occlusion and poor distal bed. The patient was submitted to a revascularization procedure, which was unsuccessful due to local conditions, resulting in above-knee amputation.

Keywords: Chemotherapy, thrombosis, neoplasms.

RESUMO

Este estudo tem por objetivo relatar um caso de isquemia crítica de membro inferior associada a quimioterapia com gemcitabina. O relato descreve o caso de um paciente de 68 anos submetido a duodenopancreatectomia devido a tumor no pâncreas. Um mês depois da operação, o paciente realizou quatro sessões de quimioterapia com gemcitabina, durante um mês. Após 30 dias, o paciente desenvolveu sintomas de doença arterial obstrutiva periférica, e duas semanas depois,

isquemia crítica do membro inferior direito. O exame por imagem demonstrou doença arterial difusa associada à oclusão femoropoplítea com reenchimento distal precário. O paciente foi submetido a uma tentativa de revascularização que, devido às condições locais, foi malsucedida, resultando na amputação do membro no nível da coxa.

Palavras-chave: Quimioterapia, trombose, neoplasias.

Introduction

Distal arterial ischemia is a rare complication caused by chemotherapy and probably associated with preexisting organic diseases.[1] The chemotherapeutic agents used for the treatment of cancer have been associated with three forms of vascular toxicity: hepatic and pulmonary venoocclusive disease,[2] venous and arterial thrombosis[3] and brain, myocardial and limb ischemia.[4] There is a large number of drugs causing vascular toxicity (Table 1).[1,5,6] The exact pathogenesis of vascular lesions has not been completely cleared so far.[1] Other causes of vascular disease should be studied, since neoplasms alone can cause vascular toxicity. In addition, previous vascular diseases associated with tobacco are frequent.[1,5]

Gemcitabine is an active nucleoside analogue that acts against a wide range of solid tumors. Toxicity is low, and the most frequent complications are myelosuppression and nausea.[7-10] Thrombotic microangiopathy is a reported, although rare complication.[1]

Table 1 - Vascular toxicity associated with anticancer drugs

Hepatic venoocclusive disease	BCNU, cisplatin, busulfan, cyclophosphamide, cytarabine, dacarbazine, urethane, azathioprine, etoposide, mitomycin, 6-thioguanine, gemcitabine, pulse therapy
Pulmonary venoocclusive disease	Bleomycin, mitomycin, BCNU
Budd-Chiari syndrome	Dacarbazine, 6-thioguanine, cytarabine, methotrexate
Raynaud phenomenon	Polychemotherapy based on cisplatin, combinations of bleomycin, combinations of Vinka alkaloids, doxorubicin
Ischemia and myocardial infarction	Vinka alkaloids, bleomycin, combination cisplatin-bleomycin-vinblastine, 5-fluorouracil
Thrombotic microangiopathy	Mitomycin, cisplatin, carboplatin, bleomycin, gemcitabine
Thrombotic and thromboembolic events	Cyclophosphamide, methotrexate, 5-fluorouracil, vincristine, prednisone, doxorubicin, tamoxifen, combinations of cisplatin-gemcitabine

BCNU = bischloroethylnitrosourea.
Adapted from Barceló et al.[1]

This report aims at presenting a case of peripheral arterial disease worsened by use of gemcitabine and demonstrating the association potential of chemotherapeutic drugs with arterial ischemia of the lower limbs.

Case description

A 68-year-old male patient with diagnosis of pancreatic adenocarcinoma. He reported being a sporadic smoker and hypertensive for long time, and denied diabetes mellitus or other diseases.

Over the 3 months previous to diagnosis, the patient developed asthenia and lost 11 kg. He did not have cachexia, only weight loss. In addition, he reported abdominal discomfort over the past 3 weeks. On vascular examination, the patient had present and full femoral and popliteal pulses and reduced, but present distal pulses. Computed tomography showed a 2-cm tumor in the pancreas head. The patient was submitted to duodenopancreatectomy with good surgical and oncological outcome. In the following month, he was submitted to four sessions of chemotherapy with gemcitabine for 30 days. Two weeks after the last chemotherapy session, the patient had right lower limb cooling and pain. Critical ischemia with rest pain was diagnosed three weeks after the end of chemotherapy. Popliteal and distal pulses were not palpable, and the foot was cold and pale. The patient had normal coagulogram and slightly increased inflammatory markers (globular sedimentation velocity = 32). Arteriography showed diffuse arterial disease associated with femoropopliteal occlusion with ankle recanalization (Figure 1). The patient was then submitted to exploratory surgery with the aim of revascularizing the lower limb, but the limb had no local conditions to perform the procedure. He was then submitted to right lower limb amputation at the thigh level. The arteries, through the whole femoropopliteal and distal extension, had much adherence, significant inflammatory process, thickening and lumen thrombosis.

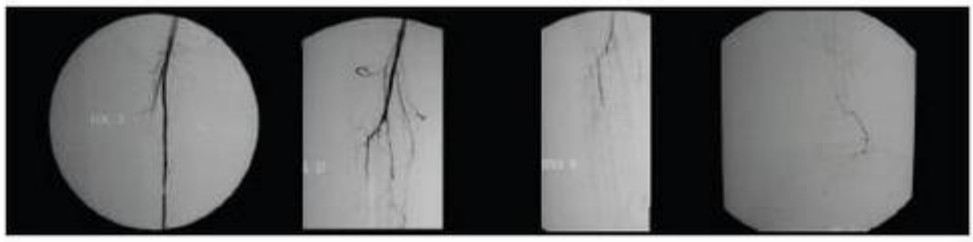

Figure 1 - Preoperative arteriography showing femoropopliteal occlusion with distal recanalization and diffuse arterial disease

The anatomopathological examination of the right lower limb showed diffuse atherosclerosis, fibrous plaques, arterial lumen thrombosis and arterial thickening due to the inflammatory process of the medial layer.

Discussion

Ischemic complications of the lower limbs in oncological patients are rare. Vascular disease is more frequently associated with smoking, dyslipidemia, hypertension and diabetes mellitus.[1] Vasculopathy is also related to tumors that produce mucin or not, as well as to anticancer treatment.[1,5,6,10] Arterial complications related to pancreatic neoplasia are rare and more frequently microangiopathic.[1] It is hard to attribute the genesis of vascular disease to only one factor when all factors are present.[1,11] However, differently from venous thromboembolic complications, arterial thromboses are rare.

The only treatment with healing potential for neoplasia in the pancreas head is

duodenopancreatectomy. However, even in that procedure survival is low. Adjuvant chemotherapy is used in most cases, especially in more advanced stages. Gemcitabine is one of the chemotherapeutic drugs used in adjuvant treatment.[12,13]

Arterial thrombotic complications have been described in cisplatin-based chemotherapeutic regimes for the treatment of germinative cell tumors. Vos et al. described three cases complicated due to arterial occlusion and one due to silent myocardial infarction. These events occurred 10 days after the beginning of chemotherapy and improved with treatment cessation.[6] There are many reports describing thromboembolic complications related to chemotherapy for germinative cell tumors.[11,14-16]

Chemotherapy for breast neoplasia has a 1.3% incidence of arterial thrombosis during the treatment. Use of tamoxifen and reduction in levels of C and S protein seen during the treatment seem to be factors related to arterial complications, but their mechanisms remain unknown.[1,15]

Gemcitabine, which is an analogue of the antimetabolite ara-C, has not been associated with arterial ischemia, thrombosis or vascular spasm. However, thrombotic microangiopathy is one of the arterial complications related to gemcitabine.[1] It is a drug with few collateral effects, such as pulmonary toxicity with alveolar lesion, venoocclusive disease with hepatic failure, changes in glomerular filtration and hemolytic uremic syndrome.[18-22]

Barceló et al. reported four cases of patients who developed distal ischemic complications associated with combined chemotherapy with cisplatin and gemcitabine. Two of these patients were submitted to infracondylar amputation, one to thrombectomy, and the last was treated with platelet antiaggregating agents and vasoactive drugs. In those four cases, distal ischemia was attributed to chemotherapy. It is important to stress that all patients had history of smoking.[1]

In the present case, the patient had few risk factors for vascular disease before the chemotherapeutic treatment. Sporadic smoking and hypertension, when under control, do not generally cause sudden arterial occlusive events, but atherosclerosis and chronic vascular disease with insidious evolution. Therefore, diffuse atherosclerosis demonstrated in arteriography could be attributed to smoking and hypertension. The likely association between ischemic alterations and treatment using gemcitabine is due to the sequence of events and period of symptom occurrence. Mechanism and pathogenesis remain unexplained. In addition, the inflammatory process of the arterial wall diagnosed by anatomopathological examination indicates an inflammation that could have its origin in chemotherapeutic drugs.

Critical ischemia of the lower limbs in oncological patients is a rare event. Peripheral ischemic symptoms, especially when associated with chemotherapy with gemcitabine, should be strictly followed. As a result of democratization of chemotherapeutic treatments, ischemic alterations should always be considered due to risk of evolution for critical ischemia and limb amputation. Further studies are needed to confirm this association and its respective impact on clinical practice.

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