

## Necrotizing Vasculitis with Polyarteritis Nodosa-Like Pattern in a Patient with Urothelial Carcinoma Treated with Gemcitabine

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### Abstract

This manuscript reports a case of necrotizing vasculitis of the lower limbs in a 73-years-old man with a metastatic urothelial carcinoma after second cycle of chemotherapy with gemcitabine and cisplatin. The exact mechanism by which gemcitabine determinates the development of vasculitis is still unknown and does not appear to be related to the number of doses administered. As soon as the diagnosis of vascular ischemia was made, therapy with gemcitabine and cisplatin was promptly discontinued. The patient's lower limb was initially erroneously attributed to the prothrombotic effect of gemcitabine, and therefore treatment with anticoagulants and prostaglandin analogues did not prevent the amputation of the left leg. The steroid therapy, introduced after the histological diagnosis of vasculitis of small and medium-sized cutaneous vessels, made it possible to limit the ischemic damage to the contralateral limb. In conclusion, gemcitabine-induced necrotizing vasculitis is a rare adverse event, whose early recognition is essential to immediately establish steroid therapy to limit induced toxicity damage.

**Keywords:** Gemcitabine, Cisplatin, Urothelial Carcinoma, Necrotizing vasculitis with polyarteritis nodosa-like pattern

### Introduction

Gemcitabine is a pyrimidine analog that inhibits the synthesis and repair of DNA. It is widely used in the treatment of lung, pancreatic, bladder, breast, ovarian cancer and some hematologic malignancies. Gemcitabine has always been considered a chemotherapy drug well tolerated, having relatively limited toxicity in favor of a good cytotoxic power [1]. The most common side effects are fever, lethargy, myelosuppression, hypertransaminasemia flu-like syndrome, skin rash and peripheral edema. In recent years, however, numerous case reports and case series have shown a higher incidence of thrombotic and vascular events than previously believed. Thromboembolic events are certainly the most frequent, but cases of acute coronary artery disease, digital ischemia and necrosis, necrotizing vasculitis, necrotizing enteritis and hepatic veno-occlusive disease have been reported [2]. We report a case of necrotizing vasculitis of the lower limbs in a patient with metastatic urothelial carcinoma after second cycle of chemotherapy with gemcitabine and cisplatin.

### Case

G.G., an independent 73-years-old-man. In anamnesis: active tabagic habit, arterial hypertension, outcomes of radical prostatectomy for adenocarcinoma. In January 2018 he underwent surgery of left nephroureterectomy and left iliac-obturator lymphadenectomy due to high-grade papillary urothelial carcinoma. In March 2018 confirmed through PET, he was diagnosed of pulmonary metastases, for which he began chemotherapy with cisplatin and gemcitabine. After the second cycle of chemotherapy the patient felt the onset of pain in the lower limbs, greater on the left and worse at night. At the beginning of May he went to the hospital where initial cyanosis of the forefoot and of the left toe were detected with undetectable arterial pulses. The arteriographic study showed the patency of the arteries of both limbs up to the supra malleolar site of the tibialis; reduced the visualization of the whole circle of the left foot, and of the plantar one of the right foot. Hospitalized at our Geriatric ward, the case was discussed with the fellow angiologist and vascular surgeons, and conservative therapy was agreed with low molecular weight heparin associated with clopidogrel and iloprost. At the end of May, due to the lack of improvement of the perfusion and the cyanosis of the left

foot, with progressive worsening of the pain, it was necessary to amputate the leg. Histological examination showed a picture of ischemic/coagulative necrosis of the cutaneous, subcutaneous, aponeurotic and muscular skeletal tissues of the foot, secondary to necrotizing arteritis of the cutaneous and subcutaneous and small caliber arteries, with polyarteritis nodosa-like pattern, and associated multiple thromboses occluding or stenosing the vessel lumen. The investigation of Neutrophil Anti-Cytoplasm (ANCA), anti-cardiolipin and anti-nucleus antibodies was negative. In the meantime, there was a progression of the ischemic suffering of the first toe of the right foot, which appeared cold and cyanotic. In light of the aforementioned histological report, therapy with prednisone was established, obtaining progressive demarcation of the paracellular lesions of the first toe of the right foot and consensual reduction of the painful symptomatology. At the Arterial Echo-Doppler Ultrasound the right femoral-popliteal-tibial axis appeared patent, with a three-phase flow up to the dorsal arteries of the foot, retro malleolar and orthotics. Therefore, the amputation of the right leg was not necessary. Discharged in June with indication of gradual tapering until the suspension of steroid therapy, in August the patient was hospitalized again due to an extension of the necrosis at the level of the first toe of the right foot, which was subjected to disarticulation of the third phalanx. No chemotherapy treatment was performed during the period between the two admission. Long term low-dose steroid therapy was restored and the patient returned home with an indication of oncological re-evaluation and a prosthetic treatment of the lower left limb.

## Discussion

The combination of gemcitabine and cisplatin is the first-line treatment for patients with metastatic urothelial cancer. Necrotizing vasculitis secondary to treatment with Gemcitabine is rare and so far, documented only in isolated case reports. Voorburg, et al. present the case of a patient with non-small lung cancer who, after the first cycle of gemcitabine and cisplatin, developed a picture of leukocytoclastic vasculitis and muscular necrosis of the 4 limbs. Immediate withdrawal of chemotherapy in association with steroid therapy, was sufficient to reverse the symptoms. Birlik, et al. [3], described a patient with recurrent bladder tumor who, after the second chemotherapy cycle with cisplatin-gemcitabine, presented extensive necrotizing vasculitis with muscular necrosis of the upper limbs, effectively treated with cyclophosphamide and prednisone. We consider attributing the peripheral ischemic event to gemcitabine as there are known cases of gemcitabine monotherapy vasculitis [4]; on the other hand, cisplatin induced vasculitis is not reported in the literature. However, it is possible that the combination with cisplatin enhances the vascular toxicity of gemcitabine alone. In this regard Ito, et al. [5] have shown, in a study conducted in rats, that the administration of cisplatin causes severe damage on the endothelium of the superior

mesenteric artery of rodents. The exact mechanism by which gemcitabine determinates the development of vasculitis is still largely unknown and does not appear to be related to the number of doses administered. In the neoplastic patient, vasculitis can be an expression not only of an adverse drug reaction, but also of paraneoplastic syndrome. However, in our case, the latter can be excluded due to the close temporal relationship between the chemotherapeutic cycle and the onset of complication. As soon as the diagnosis of vascular ischemia was made, therapy with gemcitabine and cisplatin was promptly discontinued. Initially, the patient's lower limb ischemia was erroneously attributed to the prothrombotic effect of gemcitabine, and therefore treatment with anticoagulants and prostaglandin analogues did not prevent the amputation of the left leg. The steroid therapy, introduced after the histological diagnosis of vasculitis of small and medium-sized cutaneous vessels, made it possible to limit the ischemic damage to the contralateral limb, which then unfortunately progressed, probably due to a too much early suspension of the therapy itself.

## Conclusion

Gemcitabine-induced necrotizing vasculitis is a rare adverse event, whose early recognition is essential to immediately establish steroid therapy to avoid, or at least limit, induced toxicity damage.

## Compliance with ethical standards

**Conflict of interest:** On behalf of all authors, the corresponding author states that there is no conflict of interest.

**Statement of human and animal rights:** This article does not contain any studies with human participants or animals performed by any of the authors.

**Informed Consent:** For this type of study informed consent is not required.

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