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CASE REPORT

Gemcitabine-induced peripheral vascular disease and prolonged response in a patient with metastatic pancreatic adenocarcinoma: A case report

Moinard-Butot Fabien, Poprawa Elodie, Schohn Anna, Pietro Addeo, Benabdelghani Meher

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Abstract

BACKGROUND

Gemcitabine is an antimetabolite used in the treatment of pancreatic cancer. One of the side effects of gemcitabine is vascular toxicity. Here, we report the case of a patient treated with gemcitabine who had peripheral vascular disease concomitant with a prolonged antitumor response.

CASE SUMMARY

A 75-year-old man was diagnosed with locally recurrent pancreatic cancer. Partial response was achieved after 9 mo of gemcitabine. At the same time, the patient reported peripheral vascular disease without necrosis. Chemotherapy was suspended, and after one month the Positron Emission Tomography (PET) scan showed locoregional tumor recurrence. Gemcitabine was resumed and partial response was obtained, but peripheral vascular disease occurred.

CONCLUSION

Our results suggest that the appearance of peripheral vascular disease may be related to a prolonged response to gemcitabine.

Key Words: Gemcitabine; Pancreatic cancer; Peripheral vascular disease; Prolonged tumor response; Case report

Core Tip: Gemcitabine is known for vascular side effect. In this case, we report a vascular acrosyndrome that occurred during first-line with Gemcitabine for pancreatic adenocarcinoma. In this case, the patient experienced prolonged tumor response. Immunological phenomena could be responsible for this double effect.

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INTRODUCTION

Gemcitabine is a nucleoside metabolic inhibitor. This antimetabolite drug has displayed significant antitumor activity in pancreatic adenocarcinoma[1]. Gemcitabine causes often myelosuppression, influenza-like syndrome and vascular toxicity[2]. Among toxic vascular effects of gemcitabine, we find venous and arterial events, digital ischemia and necrosis, vascular inflammation, and thrombotic microangiopathy. We report a case of locoregional recurrent pancreatic adenocarcinoma in a patient treated with gemcitabine who experienced severe peripheral vascular disease and prolonged antitumor response.

CASE PRESENTATION

Chief complaints

A 75-year-old man presented with a diagnosis of borderline adenocarcinoma of the pancreatic body in April 2019.

History of present illness

In July 2021, during Gemcitabine, the patient reported the appearance of Raynaud's phenomenon-like symptoms.

History of past illness

For borderline adenocarcinoma of the pancreatic body, he underwent neoadjuvant chemotherapy by FOLFIRINOX (12 cycles) with stable disease. He underwent pancreaticoduodenectomy in January 2020 (ypT2N2R1). A PET scan showed locoregional recurrence during a follow-up in August 2020 (Figure 1). In accordance with ESMO guidelines, chemotherapy with gemcitabine was initiated. Partial objective response was observed after 9 mo and gemcitabine was continued as maintenance therapy (Figure 1).

Personal and family history

A 75-year-old man had a history of smoking (15 pack-year), and stopped in 1976. He was treated with verapamil for hypertension and with tinzaparine for a deep vein thrombosis of the lower left extremity since 2019.

Physical examination

The symptoms consisting of loss of sensitivity and cold-induced cyanosis of the left middle finger matching with a typical syncopal phase of the Raynaud's phenomenon. Other arguments in favor of this phenomenon were sparing of the thumb and absence of digital pulp ulceration. Allen's test showed pathological results at the radial and ulnar levels. There were no megacapillaries or flame hemorrhage, cupuliform ulceration, or rectangular telangiectasia. There was no toe involvement.

Laboratory examinations

Laboratory analyses showed normal hemogram, electrolytes, creatinine, liver function, and hemostasis. C3- and C4-complement, cryoglobulin, ANCA and CPK did not show any abnormality. Anti-extractable nuclear antigen antibodies and antinuclear antibody (ANA) were negative. The specific absence of anti-Scl70 or anti-centromere antibodies was noted. Other antiphospholipid antibodies were not detected either.

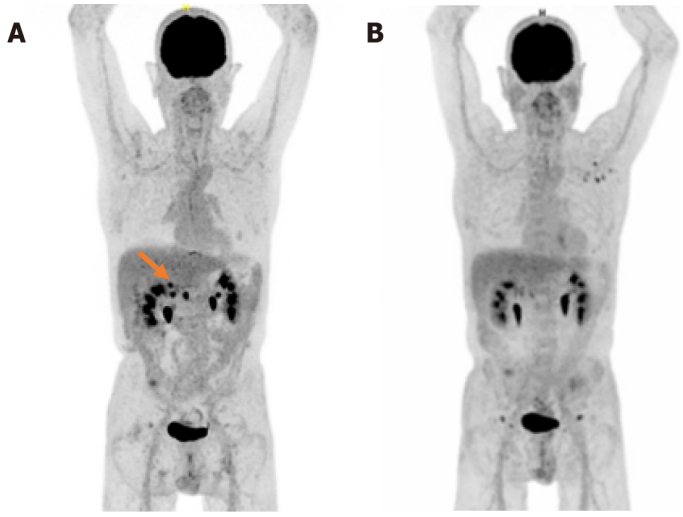

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Figure 1 A positron emission tomography scan with fluorodeoxyglucose F 18. A: Locoregional recurrence in August 2020; B: Partial response in May 2021.

Imaging examinations

An arterial and venous Doppler ultrasound found no abnormality.

FINAL DIAGNOSIS

At the patient's request, chemotherapy was suspended for 4 wk after the onset of symptoms. Paraneoplastic syndrome was initially suspected. PET scan in August 2021 showed locoregional tumor recurrence coincident with an elevation of CA 19-9 blood level at 893 ng/mL. Weekly gemcitabine chemotherapy was consequently resumed, and partial response was obtained after 3 mo of chemotherapy. CA 19-9 blood levels gradually decreased to 380 ng/mL. Gemcitabine was eventually interrupted in December 2021 after 13 cycles because of resurgence of the vascular acrosyndrome (permanent cyanosis and pain) then affecting the distal phalanx of both left and right 2nd and 3rd fingers (Figure 2) and causing great repercussions on daily activities. Symptoms showed little to no improvement after 2 mo with the appearance of ulceration of the 3rd digits (Figure 3). A Doppler echocardiography showed no macrovascular abnormalities but capillary microscopy revealed impaired microcirculation.

TREATMENT

The patient was then referred to the cardiovascular department where a treatment with iloprost (prostacyclin analog) was introduced for a duration of 28 days.

OUTCOME AND FOLLOW-UP

We noticed clinical improvement after 1 mo of treatment, and the disappearance of the ulceration (Figure 3). Gemcitabine was not resumed and disease progression was observed on the March 2022 CT scan. The patient died in June 2022.

DISCUSSION

In the present study, we report a case of metastatic pancreatic adenocarcinoma in a patient presenting with peripheral vascular disease that occurred during first-line chemotherapy. The vascular symptoms improved after discontinuation of gemcitabine. In this case, the patient experienced prolonged tumor response. The median survival time was 5.6 mo in historical studies using gemcitabine. Here, the patient showed no sign of progressive disease 17 mo after treatment initiation. Cases of Raynaud's

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Figure 2 Peripheral vascular disease affecting distal phalanx of both left and right, second and third fingers.

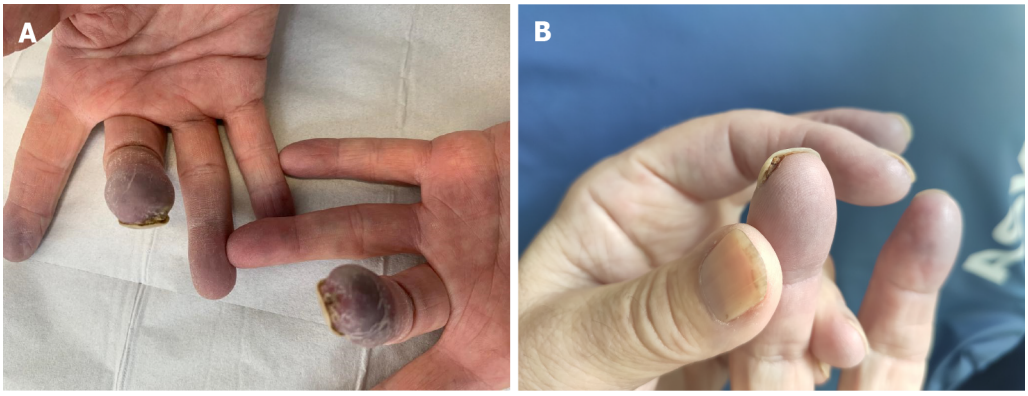

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Figure 3 Evolution of ulcerations with treatment. A: Ulceration of the third digits on both hands; B: Clinical improvement after treatment with iloprost.

phenomenon and digital necrosis after receiving gemcitabine for bladder cancer and lung cancer have been reported[3-6]. Three cases of Raynaud's phenomenon and/or digital ischemia have also been described in patients with pancreatic cancer[6-8]. Peripheral vascular disease is a rare and painful condition that impairs the patient quality of life. The most frequent etiologies are connective diseases, vasculopathies, hematological diseases, paraneoplastic syndromes, drugs, infectious diseases, and embolic diseases. They can all be complicated by secondary vasospasm[9]. In this case, we discuss the multifactorial mechanisms underlying peripheral vascular disease, aggravated by the administration of antimetabolites, and the relationship to the associated better outcomes.

Antimetabolites can have cumulative toxicity leading to endothelial dysfunction and hypercoagulability. Several chemotherapies can induce endothelial lesions or cause thromboembolic events[10-15].

Many vascular side effects have been reported in the literature as related to gemcitabine treatment. We note venous and arterial events, vasculitis with necrosis, thrombotic microangiopathy, severe capillary leak syndrome, and digital necrosis[5,6,16,17]. Here, chemotherapy was stopped, resulting in the improvement of symptoms despite cancer progression. The occurrence of peripheral vascular disease in patients with cancer can also be considered a paraneoplastic disorder, natably in the case of adenocarcinoma, squamous cell carcinoma or hematological diseases[18]. Several mechanisms have been proposed to explain peripheral vascular disease associated with cancer. It is suggested hypothesis a peripheral vasospasm or larger production of vasoconstrictor substances by tumor cells following neoplastic involvement of the cervical sympathetic trunk[19]. A thromboembolic mechanism with either migration of tumor fragments or hyperviscosity, hypercoagulability and spontaneous platelet aggregation has also been suggested[20]. In many case-report of patients with paraneoplastic peripheral vascular disease, vasospastic complications improve after initiation of suitable anticancer treatment[21]. For our patient, this etiology was unlikely to be the cause of the patient's digital manifestations, as he had an radiologic response at the time of symptoms worsening.

The hypothesis immunological's mechanism has also been suggested. In fact, cancer diseases can promote autoimmunity by generating autoantibodies against different autoantigens, leading to the activation of the complement upon contact with the arterial wall[22].

The association between toxicity and treatment efficacy has long been a concern in cancer patients. Better outcomes associated with immune-related adverse events is well described in cancer patients treated with immunotherapy. For example, vitiligo is significantly correlated with a better outcome to ICI in melanoma[23].

The restoration of antitumor immunity during treatment with immunotherapy leads to multiples manifestations, including vasculitis of the medium and large vessels but rarely of the small vessels[24]. Several recent studies have described the development of acral vascular necrosis with immunotherapy, without history of autoimmune disease[25,26]. The mechanism of action of immunotherapy could lead to a disturbance of immune tolerance with stimulation of T population of lymphocytes or to the formation of autoantibodies against many antigens such as endothelial cells and be at the origin of the disorder's vascularization. Additionally, an autoimmune etiology of digital ischemic symptoms during treatment of immunotherapy is supported, as a steroids treatment might improve acral necrosis[27,28].

One study postulated that antimetabolites induced both vascular and immunological adverse effects and prolonged response as shown with ICI[29]. Gemcitabine has the capacity to activate the immune system and create an inflammatory tumor microenvironment[30,31]. In particular, it depletes regulatory T lymphocytes and selectively kills immunosuppresive cells, thereby alleviating immunosuppression and enhancing cytotoxic T-cell-dependent anti-cancer immune responses[32].

CONCLUSION

Peripheral vascular disease is a rare complication of antimetabolite chemotherapeutic drugs. This is the second study to report the case of peripheral vascular disease and prolonged response with gemcitabine. Immunological phenomena could be responsible for this double effect.

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FOOTNOTES

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