

# **A case of progressive digital ischemia after early withdrawal of gemcitabine and S-1 in a patient with systemic sclerosis**

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**Running head:** Digital ischemia in systemic sclerosis

## **Abstract**

The safety of chemotherapy for patients with systemic sclerosis (SSc) is unclear, and there are few published reports documenting the side effects of chemotherapy in patients with this condition. Here, we report the case of a patient with SSc who developed severe digital ischemia during combination gemcitabine/S-1 chemotherapy for pancreatic cancer. In spite of aggressive treatment, the digital ischemia progressively worsened and gangrenous changes developed in multiple fingers and toes. In this patient, the SSc had been well controlled, with no digital ischemic symptoms for the previous 6 years, so this progressive clinical course in spite of aggressive treatment strongly suggests that the chemotherapy triggered or aggravated the digital necrosis. To the best of our knowledge, this is only the third reported case of a patient with SSc developing digital necrosis after gemcitabine-based chemotherapy. The incidence of digital necrosis during chemotherapy in patients with SSc is unknown, and the mechanism by which it occurs is unclear, but the three reports published to date, including the present case, suggest that physicians should be very cautious about administering gemcitabine-based chemotherapy to patients with SSc. Any resulting digital ischemia might be refractory to treatment and worsen progressively, even if chemotherapy is withdrawn in the early stages of digital ischemia.

## **Mini-abstract**

A patient with systemic sclerosis who underwent gemcitabine/S-1 chemotherapy developed progressive digital ischemia after a 6-year period

without such symptoms, strongly suggesting that the chemotherapy caused the ischemia.

**Key words:** gemcitabine, necrosis, S-1, systemic scleroderma, toxicity

## **Introduction**

Patients with systemic sclerosis (SSc) are at increased risk of cancer [1], so it seems likely that a not inconsiderable number of SSc patients require and receive chemotherapy in daily clinical practice. Over 90% of SSc patients experience Raynaud's phenomenon, which, in a small number of cases, progresses to digital necrosis [2, 3]. Anti-cancer drugs have the potential to cause vascular toxicity, including digital necrosis [4-9], so patients with SSc may be more susceptible than others to vascular toxicity arising from treatment with anti-cancer drugs. However, the risks for SSc patients of the vascular toxicity associated with chemotherapy are poorly understood.

Here, we report a patient with SSc who developed digital ischemia after gemcitabine/S-1 combination therapy, which became gangrenous in spite of the best available treatment.

## CASE REPORT

A 69-year-old man developed advanced pancreatic cancer with peritoneal dissemination in 2008. He had a history of SSc, which was diagnosed in 1999 and had been well controlled without medication since 2002. He had experienced acute myocardial infarction at the age of 51, and had had diabetes mellitus for 16 years. He had given up smoking 19 years earlier, before which he had had a smoking habit of 22 packs/year. Although there had been no symptoms of digital ischemia over the past 6 years, we were reluctant to treat the pancreatic cancer with systemic chemotherapy because it might increase the risk of digital necrosis. We strongly cautioned the patient about this risk, but he was firm in his wish to receive chemotherapy treatment.

Combination chemotherapy using gemcitabine (400 mg/m<sup>2</sup>, days 1 and 8) and S-1 (80 mg/day, days 1–14) every 3 weeks was started in December 2008. A low dose of gemcitabine was selected given the risk of digital necrosis. The patient's pancreatic cancer was well controlled with chemotherapy and no significant toxicity was observed until June 2009, when he experienced Raynaud's phenomenon. The patient had previously experienced Raynaud's phenomenon, but not for the past 6 years. At this stage, we strongly recommended suspension of chemotherapy; however, the patient refused to discontinue the chemotherapy for fear of the pancreatic cancer progressing. The Raynaud's phenomenon was treated with vasodilators, antiplatelet

drugs and prostaglandin; however, despite the treatment, ischemic changes became evident (Fig. 1A). In July 2009, chemotherapy was discontinued and the patient was hospitalized for treatment of the digital ischemia. Initially, he was treated with prostaglandin, vasodilators, antiplatelet drugs and antithrombin, but these treatments brought about no improvements. Next, bosentan hydrate was administered and a sympathetic nerve block was implemented, but again neither of these treatments yielded any improvement in the digital ischemia. The digital ischemia progressively worsened and in September 2009 gangrenous changes developed in multiple fingers and toes (Fig. 1B). Because the digital ischemia was not complicated with infection, amputation was not performed. The patient died in January 2010 from multiple organ failure.

## DISCUSSION

To the best of our knowledge, this is only the third reported case in the English-language literature of an SSc patient developing digital necrosis after chemotherapy [5, 6] (Table 1). In all three cases, gemcitabine was included in the chemotherapy regimen, and digital necrosis developed 3, 16 and 27 weeks after chemotherapy began, respectively. All three patients eventually developed gangrenous changes in spite of the best available treatment for the digital ischemia, whereas complete recovery from digital ischemia after chemotherapy has been reported for patients without SSc [6]. Gemcitabine is known to cause digital ischemia in patients without SSc, with the vascular toxicity thought to be due to its causing endothelial damage or a hypercoagulable state [5-7]. We could not find any reports in the literature documenting digital ischemia following S-1 treatment. In the present case it is not possible to conclude which agent played the greater role in the development of ischemia; determining whether gemcitabine is associated with a higher risk of vascular toxicity compared with other anti-cancer drugs in SSc patients requires further study.

In the present case, we cannot rule out the possibility that factors other than chemotherapy were involved in the development of digital ischemia. The patient had a history of smoking and diabetes mellitus, both of which could potentially increase the risk of digital ischemia. However, considering that the patient had experienced no symptoms of digital ischemia over the

previous 6 years, and had undergone a progressive clinical course in spite of aggressive treatment, we strongly suspect that chemotherapy triggered or aggravated the digital ischemia in this patient.

Vascular toxicity is a rare but serious side effect of chemotherapy [4-9]. The precise incidence is unknown, and the mechanism by which chemotherapy causes digital necrosis in patients with SSc remains unclear, but in the light of previous case studies, the present findings strongly suggest that physicians should be very cautious about administering chemotherapy, especially gemcitabine-based chemotherapy, to SSc patients. The resulting digital ischemia might be refractory to conventional treatment and worsen progressively, even if chemotherapy is withdrawn at an early stage in the development of digital ischemia.

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### Figure legend

**Fig. 1** Progression of digital ischemia in a patient with systemic sclerosis, who was undergoing gemcitabine/S-1 combination chemotherapy for pancreatic cancer. (A) Digital ischemia at the time of hospitalization in July 2009. (B) Worsening digital ischemia and development of gangrene in multiple fingers and toes in September 2009.

**A**



**B**



Table 1. Published case reports of digital necrosis following chemotherapy in patients with systemic sclerosis (SSc)

|                                   | Report                                                                                              |                                                                                                      |                             |
|-----------------------------------|-----------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------|-----------------------------|
| Demographic and clinical features | Cloese <i>et al.</i> [8]                                                                            | Marie <i>et al.</i> [9]                                                                              | Present case                |
| Patient age (years)               | 50                                                                                                  | 49                                                                                                   | 69                          |
| Patient sex                       | Female                                                                                              | Female                                                                                               | Male                        |
| Primary disease                   | Lung cancer                                                                                         | Lung cancer                                                                                          | Pancreatic cancer           |
| SSc manifestation                 | Sclerodactyly, Raynaud's phenomenon, sicca syndrome, esophageal involvement, carpal tunnel syndrome | Diffuse cutaneous sclerosis, Raynaud's phenomenon, esophageal involvement, interstitial lung disease | Diffuse cutaneous sclerosis |
| Chemotherapy regimen              | Gemcitabine and carboplatin                                                                         | Gemcitabine and cisplatin                                                                            | Gemcitabine and S-1         |

| Time of onset <sup>†</sup>     | 3 weeks                                                                                | 16 weeks                                  | 27 weeks                                                                                                 |
|--------------------------------|----------------------------------------------------------------------------------------|-------------------------------------------|----------------------------------------------------------------------------------------------------------|
| Treatment for digital ischemia | Calcium channel blocker, prednisolone, cephalexin, gabapentin, stellate ganglion block | Nitroprusside, prostacycline, vasodilator | Prostaglandin, vasodilators, antiplatelet drugs, antithrombin, bosentan hydrate, sympathetic nerve block |
| Outcome                        | Gangrenous changes (amputation)                                                        | Gangrenous changes (surgical debridement) | Gangrenous changes (no amputation)                                                                       |

<sup>†</sup>Time of onset after start of chemotherapy.