Chemotherapy-induced Raynaud's phenomenon

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■ **BACKGROUND** Various antineoplastic agents can cause Raynaud's phenomenon, as can malignant diseases themselves.

■ **OBJECTIVE** To review the clinical characteristics of chemotherapy-induced Raynaud's phenomenon and compare them with those of malignancy-associated Raynaud's phenomenon.

■ **SUMMARY** Chemotherapy-induced Raynaud's phenomenon most commonly occurs in patients with testicular cancer who receive bleomycin either as a single agent or as part of a multiple-drug chemotherapeutic regimen. It tends to resolve spontaneously, especially after discontinuation of the inducing antineoplastic agent, and rarely causes significant functional impairment. However, it tends to recur with subsequent administration of the drug. In contrast, malignancy-associated Raynaud's phenomenon is rarer, causes more severe symptoms, and usually occurs in older patients with more advanced cancer.

■ **CONCLUSIONS** As more patients with cancer undergo chemotherapy, physicians should be aware of the potential delayed toxic effects of antineoplastic drugs.

■ INDEX TERMS: RAYNAUD'S DISEASE; BLEOMYCIN; VINBLASTINE; CISPLATIN; TESTICULAR NEOPLASMS
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ADVANCES in chemotherapy, especially in multi-drug regimens, are making it possible for an increasing number of patients with malignant diseases to live longer or even be cured. However, as more patients live longer, several delayed side effects of chemotherapy are appearing, including acute myelogenous leukemia and other secondary malignancies,[1] anemia with cardiomyopathy,[2,3] chronic mucocutaneous reactions,[4–10] gonadal dysfunction,[11] peripheral neuritis,[2] pulmonary fibrosis,[2] renal insufficiency,[12] and vascular sequelae.[13] Raynaud's phenomenon is the most common vascular side effect.[14–16] This article will review the features of chemotherapy-induced Raynaud's phenomenon and the agents that can cause it, discuss the treatment of this condition, summarize the postulated mechanisms of its pathogenesis, and compare its characteristics with those of Raynaud's phenomenon caused by malignant diseases themselves.

HISTORY

The onset of Raynaud's phenomenon following treatment with bleomycin and vinblastine was first described in 1977[17] and

TABLE 1
ANTINEOPLASTIC AGENTS THAT INDUCE RAYNAUD'S PHENOMENON

Single-agent regimens
Bleomycin[18,19]
Multiple-agent regimens
Bleomycin and vinblastine[1,17,20-23]
Bleomycin, cisplatin, and etoposide[24]
Bleomycin, cisplatin, and vinblastine[1,13,15,16,25-32]
Bleomycin, cisplatin, and vinca alkaloid[14]
Nitrogen mustard, vincristine, procarbazine, prednisone or doxorubicin, bleomycin, dacarbazine, and vinblastine (along with radiotherapy)[2]

TABLE 2
ORGANS OF TUMOR ORIGIN IN CHEMOTHERAPY-INDUCED RAYNAUD'S PHENOMENON

Endothelium (Kaposi's sarcoma)
Floor of the mouth (carcinoma)
Lymph nodes (Hodgkin's disease)
Pharynx (carcinoma)
Testicle (carcinoma)

TABLE 3
TREATMENTS FOR CHEMOTHERAPY-INDUCED RAYNAUD'S PHENOMENON

Conservative
Additional clothing to involved site
Discontinuation of chemotherapy
Medical
Corticosteroids
Guanethidine
Ketanserin
Nitroglycerine (topical)
Phenoxybenzamine
Tolazoline hydrochloride
Surgical
Dorsal sympathectomy
Transcutaneous nerve stimulation

subsequently was observed in patients with cancer who received bleomycin alone or in combination with other antineoplastic drugs (*Table 1*).[1,2,13–32] Interestingly, Raynaud's phenomenon has also been noted in two cancer-free individuals with idiopathic uveitis who received immunosuppressant therapy with cyclosporine.[33] Because cyclosporine is frequently used to prevent or manage graft-vs-host disease, Raynaud's phenomenon may also occur in cyclosporine-treated patients who undergo bone-marrow transplantation as well as in patients who receive organ transplants.

EPIDEMIOLOGY

Most patients with chemotherapy-induced Raynaud's phenomenon are men in their early to middle 30s with testicular cancer (*Table 2*).[1,13–17,19–31] Most of the other individuals who acquire Raynaud's phenomenon after receiving chemotherapy are also men; their neoplasms include Hodgkin's lymphoma,[2] oral epidermoid carcinoma,[19] and pharyngeal carcinoma.[32] Chemotherapy-induced Raynaud's phenomenon has also been observed in a woman with Kaposi's sarcoma.[18]

CLINICAL CHARACTERISTICS

The appearance of chemotherapy-induced Raynaud's phenomenon is similar to that of Raynaud's phenomenon in cancer-free individuals (*Figure*). The symptoms are usually mild, mainly involve the fingers, and typically develop within 1 year after the patient has completed antineoplastic treatment. Most patients receive at least four courses of chemotherapy before symptoms arise, although Raynaud's phenomenon has occurred during or immediately after chemotherapy in some individuals.[17,18,23,27,32]

TREATMENT

Chemotherapy-induced Raynaud's phenomenon can be treated conservatively, medically, or surgically (*Table 3*).[1,17,18,20–24,31] It rarely causes any significant functional impairment,[14] but a 69-year-old man with epidermoid carcinoma of the floor of the mouth acquired gangrene after receiving bleomycin.[19] The clinical symptoms of Raynaud's phenomenon eventually improve in most patients[1,17,18,20–24,27,30,32]; rarely, they remain unchanged or progress.[1,19,30]

PATHOGENESIS

How chemotherapy induces Raynaud's phenomenon is unclear. Most patients who have acquired this condition have received multiple antineoplastic agents; hence, it has been suggested that Raynaud's phenomenon is caused by synergistic drug toxicity.[1,17,20,24,27,31,32] Alternatively, bleomycin,[17–19,31,32] vinblastine,[1,21] and cisplatin[1,26] have each been considered the causative agent.

Bleomycin likely has an important etiologic role, either by itself or in concert with the other agents, because this condition has occurred in patients who

received only this drug.[18,19] Whether the incidence of Raynaud's phenomenon is related to the total dose of bleomycin is controversial.[1,14,20,34] Although some authors have not observed a direct relationship between the quantity of drug received and the occurrence of Raynaud's phenomenon, one group of investigators found that every patient who received more than 200 units of bleomycin acquired vascular abnormalities.[34] However, Bellmunt et al[34] also noted that these abnormalities were present in a patient who received only 60 units of bleomycin.

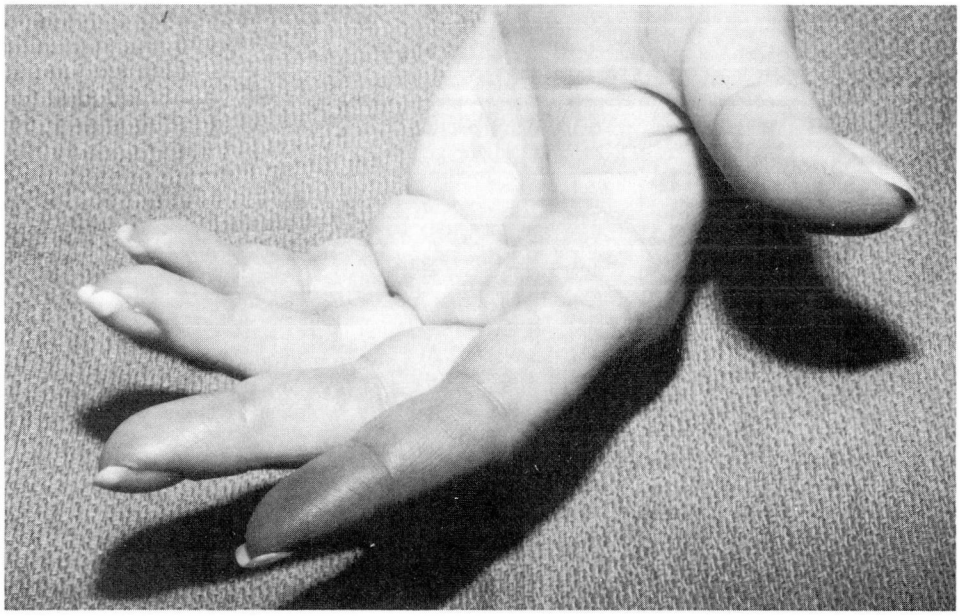

FIGURE. Discoloration of the distal fingers due to Raynaud's phenomenon.

Several mechanisms for the pathogenesis of chemotherapy-induced Raynaud's phenomenon have been postulated. Bleomycin may directly alter small blood vessels.[18,24,34,35] Also, a localized lack of the hydrolase that degrades bleomycin in the skin and lungs may account for the increased likelihood of drug-related toxicity in these organs.[8] Antineoplastic agents may promote constriction of the distal arteries and arterioles, subsequently causing Raynaud's phenomenon.[25] Vinblastine may directly increase sympathetic activity, thereby enhancing vasoconstriction.[1] Alternatively, cisplatin-induced hypomagnesemia may also contribute to the development of Raynaud's phenomenon by potentiating the contractile response of the arteries and arterioles to various neurotransmitters and hormones.[1,26]

DIFFERENTIAL DIAGNOSIS

Raynaud's phenomenon has also been reported, although rarely, as a "paraneoplastic syndrome" (*Table 4*).[36–50] The symptoms, which are typically more severe than in chemotherapy-induced Raynaud's phenomenon, frequently include digital gangrene and usually appear when the neoplasm is advanced. Also, whereas chemotherapy-induced Raynaud's phenomenon is exacerbated by antineoplastic agents, malignancy-associated Raynaud's phenomenon has been observed to improve after chemotherapy or tumor resection, or both.[45–50] As in chemotherapy-induced Raynaud's phenomenon, vasoconstriction caused by sympathetic stimulation may also have an etiologic role.[37,39] In addition, the pathogenesis of malignancy-associated Raynaud's phenomenon may be related to tumor-secreted products or to coagulopathy from the precipitation of cryoproteins.[40,46,48–50]

CONCLUSION

Although cure of patients who suffer from malignancy remains of central importance, close attention must also be focused during follow-up to detect delayed adverse sequelae of antineoplastic therapy. Chemotherapy-induced Raynaud's phenomenon may appear not only in patients with testicular cancer who have been treated with cytotoxic agents, but also in patients with other malignancies who have received bleomycin alone or as part of a multiple-agent chemotherapeutic regimen. Malignancy-associated Raynaud's phenomenon must be excluded when the diagnosis of chemotherapy-induced Raynaud's phenomenon is being considered. Both conditions are most commonly observed in patients with testicular carcinoma. Malignancy-as-

TABLE 4
CHARACTERISTICS OF CHEMOTHERAPY-INDUCED RAYNAUD'S PHENOMENON AND MALIGNANCY-ASSOCIATED RAYNAUD'S PHENOMENON

	Chemotherapy-induced Raynaud's phenomenon	Malignancy-associated Raynaud's phenomenon
Epidemiology		
Patients	Mostly men	Men and women equally
Age of onset	Early to middle 30s	Early 50s
Tumor stage	Irrelevant	Advanced
Occurrence	Common	Rare
Clinical features		
Associated symptoms	Mild	Severe
Location	Mainly hands	Mainly hands
Bilateral symmetry	Not mentioned	In ≥50% of patients
Gangrene	Rare	In ≥50% of patients
Etiologic factors		
Associated tumors	Mainly testicular	Mainly testicular; also other genitourinary tumors
Chemotherapy	Bleomycin (single agent or combination therapy)	Not related
Treatment	Conservative, medical, or surgical	Conservative, medical, or surgical

sociated Raynaud's phenomenon is a rare condition with severe clinical manifestations; it primarily occurs in older individuals who have advanced neoplastic disease, and it is not exacerbated by chemotherapy. In contrast, chemotherapy-induced Raynaud's phenomenon is a relatively common disorder with mild symptoms that appear almost exclusively in young men whose previous antineoplastic treatment has included bleomycin.

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