Chemotherapy-induced Raynaud's phenomenon

EUGENIA TOUMBIS-IOANNOU, MD, AND PHILIP R. COHEN, MD

■ **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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From the Department of Dermatology, The University of Texas Medical School at Houston.
Address reprint requests to P.R.C., Department of Dermatology, The University of Texas Medical School at Houston, 6431 Fannin, Suite 1.186, Houston, TX 77030.

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.

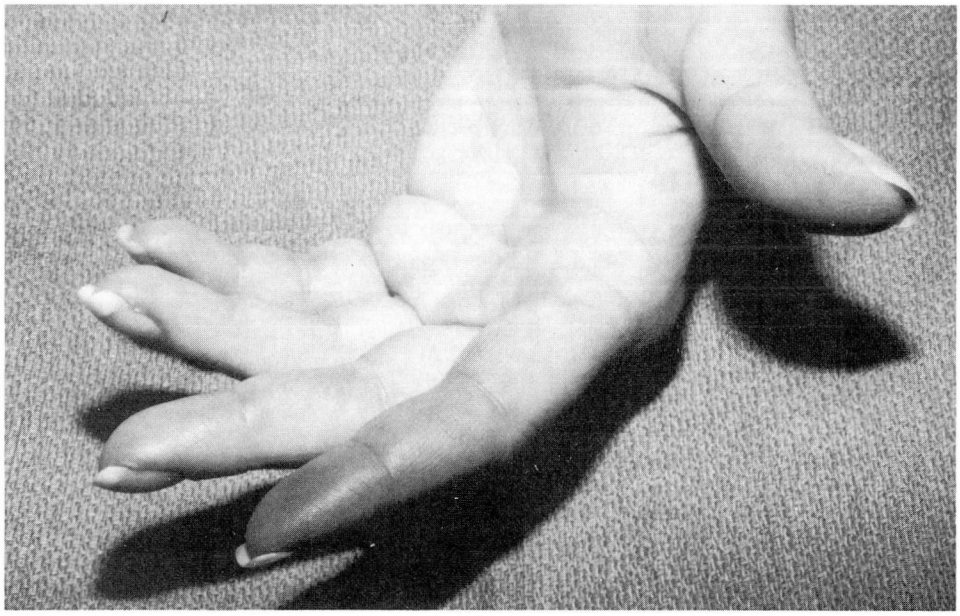

FIGURE. Discoloration of the distal fingers due to Raynaud's phenomenon.

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.

REFERENCES

1. **Vogelzang NJ, Bosl GJ, Johnson K, Kennedy BJ.** Raynaud's phenomenon: a common toxicity after combination chemotherapy for testicular cancer. Ann Intern Med 1981; **95**:288–292.
2. **Straus DJ, Myers J, Passe S, et al.** The eight-drug/radiation therapy program (MOPP/ABDV/RT) for advanced Hodgkin's disease: a follow-up report. Cancer 1980; **46**:233–240.
3. **Von Hoff DD, Layard MW, Basa P, et al.** Risk factors for doxorubicin-induced congestive heart failure. Ann Intern Med 1979; **91**:710–717.
4. **Bronner AK, Hood AF.** Cutaneous complications of chemotherapeutic agents. J Am Acad Dermatol 1983; **9**:645–663.
5. **Kerker BJ, Hood AF.** Chemotherapy-induced cutaneous reactions. Semin Dermatol 1989; **8**:173–181.
6. **Hood AF.** Cutaneous side effects of cancer chemotherapy. Med Clin North Am 1986; **70**:187–209.
7. **Adrian RM, Hood AF, Skarin AT.** Mucocutaneous reactions to antineoplastic agents. CA Cancer J Clin 1980; **30**:143–157.
8. **Dunagin WG.** Clinical toxicity of chemotherapeutic agents: dermatologic toxicity. Semin Oncol 1982; **9**:14–22.
9. **Cohen PR.** Cancer chemotherapy-associated mucocutaneous reactions. In: Medical oncology: a comprehensive board review. (from the University of Texas M.D. Anderson Cancer Center). New York: PRR (publishers of Oncology), 1993:491–500.
10. **Cohen PR.** Cutaneous manifestations of internal malignancy. In: Callen JP, Bone R, editors. Dermatology volume of current practice of medicine. Philadelphia: Current Medicine (in press).
11. **Schilisky RL, Lewis BJ, Sherins RJ, Young RC.** Gonadal dysfunction in patients receiving chemotherapy for cancer. Ann Intern Med 1980; **93(Part 1)**:109–114.
12. **Einhorn LH, Williams SD.** The role of cis-platinum in solid-tumor therapy. N Engl J Med 1979; **300**:289–291.
13. **Doll DC, List AF, Greco FA, Hainsworth JD, Hande KR, Johnson DH.** Acute vascular ischemic events after cisplatin-based combination chemotherapy for germ-cell tumors of the testis. Ann Intern Med 1986; **105**:48–51.
14. **Bissett D, Kunkeler L, Zwanenburg L, et al.** Long-term sequelae of treatment for testicular germ cell tumors. Br J Cancer 1990; **61**:151–155.
15. **Aass N, Kaasa S, Lund E, Kaalhus O, Heier MS, Fossa SD.** Long-term somatic side-effects and morbidity in testicular cancer patients. Br J Cancer 1990; **61**:151–155.
16. **Fossa SD, Aass N, Kaalhus O.** Testicular cancer in young Norwegians. J Surg Oncol 1988; **39**:43–63.
17. **Teutsch C, Lipton A, Harvey HA.** Raynaud's phenomenon as a side effect of chemotherapy with vinblastine and bleomycin for testicular carcinoma. Cancer Treat Rep 1977; **61**:925–926.
18. **Adoue D, Arlet P.** Bleomycin and Raynaud's phenomenon [letter]. Ann Intern Med 1984; **100**:770.
19. **Cohen IS, Mosher MB, O'Keefe EJ, Klaus SN, DeConti RC.** Cutaneous toxicity of bleomycin therapy. Arch Dermatol 1973; **107**:553–555.
20. **Scheulen ME, Schmidt CG.** Raynaud's phenomenon and cancer chemotherapy [letter]. Ann Intern Med 1982; **96**:256.
21. **Rothberg H.** Raynaud's phenomenon after vinblastine-bleomycin chemotherapy [letter]. Cancer Treat Rep 1978; **62**:569–570.
22. **Soble AR.** Chronic bleomycin-associated Raynaud's phenomenon [letter]. Cancer Treat Rep 1978; **62**:570.
23. **Chernicoff DP, Bukowski RM, Young JR.** Raynaud's phenomenon after bleomycin treatment [letter]. Cancer Treat Rep 1978; **62**:570–571.
24. **MacLeod PM, Tyrrell CJ, Bliss B.** Raynaud's phenomenon following cytotoxic chemotherapy successfully managed by dorsal sympathectomy. Eur J Surg Oncol 1989; **15**:79–81.
25. **Hansen SW, Olsen N.** Raynaud's phenomenon in patients treated with cisplatin, vinblastine, and bleomycin for germ cell cancer: measurement of vasoconstrictor response to cold. J Clin Oncol 1989; **7**:940–942.

26. **Vogelzang NJ, Torkelson JL, Kennedy BJ.** Hypomagnesemia, renal dysfunction, and Raynaud's phenomenon in patients treated with cisplatin, vinblastine, and bleomycin. Cancer 1985; **56:**2765–2770.
27. **Stefenelli T, Kuzmits R, Ulrich W, Glogar D.** Acute vascular toxicity after combination chemotherapy with cisplatin, vinblastine, and bleomycin for testicular cancer. Eur Heart J 1988; **9:**552–556.
28. **Stoter G, Koopman A, Vendrik CPJ, et al.** Ten-year survival and late sequelae in testicular cancer patients treated with cisplatin, vinblastine, and bleomycin. J Clin Oncol 1989; **7:**1099–1104.
29. **Fossa SD, Borge L, Aass N, Johannessen NB, Stenwig AE, Kaalhus O.** The treatment of advanced metastatic seminoma: experience in 55 cases. J Clin Oncol 1987; **5:**1071–1077.
30. **Fossa SD, Aass N, Kaalhus O, Klepp O, Tveter K.** Long-term survival and morbidity in patients with metastatic malignant germ cell tumors treater with cisplatin-based combination chemotherapy. Cancer 1986; **58:**2600–2605.
31. **Heier MS, Nilsen T, Graver V, Aass N, Fossa SD.** Raynaud's phenomenon after combination chemotherapy of testicular cancer, measured by laser doppler flowmeter. A pilot study. Br J Cancer 1991; **63:**550–552.
32. **Kukla LJ, McGuire WP, Lad T, Saltiel M.** Acute vascular episodes associated with therapy for carcinomas of the upper aerodigestive tract with bleomycin, vincristine, and cisplatin. Cancer Treat Rep 1982; **66:**369–370.
33. **Deray G, LeHoang P, Achour L, Hornych A, Landault C, Caraillon A.** Cyclosporin and Raynaud phenomenon [letter]. Lancet 1986; **2:**1092–1093.
34. **Bellmunt J, Navarro M, Morales S, et al.** Capillary microscopy is a potentially useful method for detecting bleomycin vascular toxicity. Cancer 1990; **65:**303–309.
35. **Olsen N, Hansen SW.** Vasomotor functions of skin microcirculation in vasospastic Raynaud's phenomena. Acta Physiol Scand 1992; **143(Suppl 603):**101–107.
36. **DeCross AJ, Sahasrabudhe DM.** Paraneoplastic Raynaud's phenomenon. Am J Med 1992; **92:**571–572.
37. **Hawley PR, Johnston AW, Rankin JT.** Association between digital ischaemia and malignant disease. Br Med J 1967; **3:**208–212.
38. **Hamilton WF.** Carcinoma of the oesophagus and Raynaud's disease. Can Med J 1920; **10:**665–671.
39. **Bennett TI, Poulton EP.** Raynaud's disease associated with cancer of the stomach. Am J Med Sci 1928; **176:**654–657.
40. **Friedman SA, Bienenstock H, Richter IH.** Malignancy and arteriopathy: a report of two cases. Angiology 1969; **20:**136–143.
41. **Wilmalaratna HSK, Sachdev D.** Adenocarcinoma of the lung presenting with Raynaud's phenomenon, digital gangrene and multiple infarctions in the internal organs [letter]. Br J Rheumatol 1987; **26:**473–475.
42. **O'Connor B.** Symmetrical gangrene. Br J Med 1884; **1:**460.
43. **Field J, Lane IF.** Carcinoma of the lung presenting with digital ischaemia. Thorax 1986; **41:**573–574.
44. **Spitell JA Jr.** Raynaud's phenomenon and allied vasospastic disorders. In: Juergens JL, Spittell JA Jr, Fairbairn JF II, editors. Peripheral vascular diseases. 5th ed. Philadelphia: WB Saunders, 1980:554–583.
45. **Powell KR.** Raynaud's phenomenon preceding acute lymphocytic leukemia [letter]. J Pediatr 1973; **82:**539–540.
46. **Andrasch RH, Bardana EJ Jr, Porter JM, Pirofsky B.** Digital ischemia and gangrene preceding renal neoplasm. An association with sarcomatoid adenocarcinoma of the kidney. Arch Intern Med 1976; **136:**486–488.
47. **Domz CA, Chapman CG.** Pseudo-Raynaud's: cryoglobulinemia secondary to occult neoplasm. Calif Med 1961; **95:**391–393.
48. **Wytock DH, Bartholomew LG, Sheps SG.** Digital ischemia associated with small bowel malignancy. Gastroenterology 1983; **84:**1025–1027.
49. **Stavem P, Rorvik T, Brandtzaeg P, Brosstad F, Nordhagen R, Grabner P.** Gastric lymphoma causing granulocytopenia and cold intolerance, with recovery after treatment. J Intern Med 1991; **229:**193–196.
50. **Schwartz TB, Jager BV.** Cryoglobulinemia and Raynaud's syndrome in a case of chronic lymphocytic leukemia. Cancer 1949; **2:**319–328.

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