# Digital Ischemia as a Manifestation of Malignancy

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**The association of malignancy with thrombotic disorders of the arterial and venous systems is well described. To date, however, there are only 23 published case reports of digital gangrene associated with malignancy. During a prospective evaluation of over 700 patients with finger ischemia, there were five patients with finger gangrene associated with malignancy. Detailed clinical and laboratory evaluation, including detailed immunologic survey and hand angiography, allowed establishment of the precise mechanisms responsible for vascular occlusions in each patient. Three mechanisms were identified: arteritis, hyperviscosity, and hypercoagulability. Digital gangrene associated with malignancy is a rare condition, the mechanism for which can be deduced by careful diagnostic evaluation.**

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THE OCCASIONAL ASSOCIATION of diseases of the vascular system with systemic neoplasia has been recognized for over a century. The earliest reported paraneoplastic syndrome involving the vascular system was Trousseau's description in 1865 of femoral vein thrombosis, which he termed phlegmasia alba dolens, and occult carcinoma.[1] Venous thrombosis associated with carcinoma has been reported subsequently, frequently being termed "thrombophlebitis migrans."[2-4]

Descriptions of the remote effects of neoplasms on the arterial system have increased in frequency and variety in the past several decades.[5,6] Hairy cell leukemia has been associated with classic polyarteritis nodosa.[7] Symptoms of central nervous system granulomatous angiitis have preceded the diagnosis of Hodgkin's disease in at least several patients.[8,9] Johnson et al.[10] have described vasculitis involving nutrient arteries of nerves, which may explain the frequently observed relationship of mononeuritis monoplex with small cell carcinoma and lymphoma. Ischemic tissue necrosis, possibly caused by hyperviscosity, has been reported in a patient with chronic granulocytic leukemia.[11] Cryoglobulinemia and multiple myeloma associated with Raynaud's syndrome were reported as early as 1933.[12,13]

The coexistence of digital ischemia and carcinoma was first reported in 1884 by O'Connor. He described a middle-aged woman with breast cancer and presumed left supraclavicular metastases who had gangrenous fingertips.[14] Seven years later, Fagge and Pye-Smith described a young woman with digital ischemia who was found to have a locally infiltrating tumor mass involving the first dorsal sympathetic nerve at necropsy. The patient died within 1 year of onset of symptoms. The authors hypothesized that the digital ischemia was caused by local tumor invasion or metastases to the cervical sympathetic trunk.[15]

To our knowledge there have been 23 published case reports linking digital ischemia and malignant disease. The ischemic changes have been generally bilateral, symmetric, and have involved the upper extremities. Most of the reports have described single patients, with variable, usually sparse, accompanying laboratory data. These reports are summarized in Table 1.

In the past 15 years during a prospective evaluation of over 700 patients with upper extremity ischemia, we found five patients to have finger gangrene occurring in association with systemic malignancy. Each of these patients had detailed evaluation, including magnification

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TABLE 1. *Case Reports Associating Digital Ischemia with Malignancy*

| Case # | Date | Author | Sex | Age | Malignancy Type | Symptoms | Course |
|---|---|---|---|---|---|---|---|
| 1 | 1866 | Fagge and Pye-Smith[15] | F | "young" | CNS metastases, 1st dorsal nerve and sympathetic trunk metastases | Blue, cold, painful fingers | Died within 1 year |
| 2 | 1884 | O'Connor[14] | F | "middle aged" | Breast carcinoma | Gangrene: fingertips | Left supraclavicular metastasis |
| 3 | 1901 | Pasteur and Price-Jones[33] | M | 61 | Gastric carcinoma | Cold, blue extremities, Raynaud's | ? |
| 4 | 1920 | Hamilton[34] | M | 54 | Esophageal carcinoma | Typical Raynaud's syndrome | ? |
| 5 | 1928 | Bennett and Poulton[23] | M | 61 | Occult gastric carcinoma | Raynaud's syndrome | Died during cervical sympathectomy |
| 6 | 1961 | Domz and Chapman[27] | F | 56 | Adenocarcinoma right lung, myelofibrosis, cryoglobulins | Digital ischemia, gangrene fingertips | Symptoms resolved with tumor resection |
| 7 | 1963 | Nielson and Petri[24] | F | 77 | Colon carcinoma, cervical sympathetic and stellate ganglion metastasis | Symmetrical gangrene: fingers | Died |
| 8 | 1959 | Hawley et al. (1967)[35] | F | 59 | Anaplastic carcinoma of maxillary antrum | Painful, numb, gangrene digits | Died in 4 months |
| 9 | ? | Hawley et al. (1967)[35] | F | 54 | Hypernephroma | Cold, numb, painful fingers | Return of pulses, healing of lesions, died within months |
| 10 | 1964–1965 | Hawley et al. (1967)[35] | F | 45 | Rectal/colon carcinoma, cystic ovarian tumor | Raynaud's syndrome | Died within 11 months of symptoms despite tumor resection |
| 11 | 1957 | Hawley et al. (1967)[35] | F | 45 | Adenopapillary ovarian carcinoma with metastasis | Numb, cold hands | Radiation therapy, symptoms resolved |
| 12 | 1965–1966 | Hawley et al. (1967)[35] | F | 58 | Pancreatic/ovarian carcinoma | Pain, numb, pallor: fingers | Died in 8 months |
| 13 | 1953–1954 | Hawley et al. (1967)[35] | F | 42 | Hodgkin's disease | Pain, tingling, blue fingers | Chemotherapy, radiation |
| 14 | 1965–1967 | Friedman et al.[25] | F | 32 | Epidermoid carcinoma, cervix, stage 1, ankylosing spondylitis | Raynaud's syndrome, right leg gangrene upper extremity | Symptoms improved with excision and radiation therapy |
| 15 | 1966 | Friedman et al.[25] | F | 57 | Anaplastic breast carcinoma with nodes | Ischemia and gangrene fingers and feet, bilateral thigh amputation | Symptoms resolved 22 months after mastectomy |
| 17 | 1970 | Powell (1973)[36] | M | 7 | Acute lymphocytic leukemia | Raynaud's syndrome | Remission of symptoms after chemotherapy and radiation therapy |
| 18 | 1974 | Palmer and Vedi[6,37] | F | 62 | Reticulum cell sarcoma | Finger cyanosis, bilateral splinter hemorrhages | Death months after onset of symptoms |
| 19 | 1974 | Palmer and Vedi[6,37] | F | 74 | Intra-abdominal carcinoma | Numbness, tingling and cyanosis bilateral fingers | Death months after onset of symptoms |
| 20 | 1974 | Palmer and Vedi[6,37] | F | 66 | Gastric carcinoma | Cold, blue fingers | Symptoms resolved after resection |
| 21 | 1976–1977 | O'Donnell et al. (1980)[28] | M | 9 | Acute myelocytic leukemia | Foot necrosis 9/76 | Died 11/77: right main pulmonary artery thrombus |
| 22 | 1978–1977 | O'Donnell et al. (1980)[28] | M | 52 | Poorly differentiated adenocarcinoma, Buerger's disease | Claudication, great toe necrosis, brachial artery thrombosis | Died 1/79 |
| 23 | 1983 | Wytock et al.[38] | F | 59 | Adenocarcinoma of ileum | Digital ischemia | Resolution of symptoms, resection × 5 years |

hand arteriography and skin biopsy in three of the five patients and detailed laboratory screening for collagen vascular disease and coagulation abnormalities in all five patients. Our experience with the diagnosis and management of these patients forms the basis for this report.

TABLE 2. *Laboratory Tests for Patients with Severe Digital Ischemia*

| | |
|---|---|
| Complete blood count | Platelet count |
| Prothrombin time | Serum triglycerides |
| Partial thromboplastin time | Serum cholesterol |
| Sedimentation rate | Blood viscosity |
| Hepatitis B antigen/antibody | Urine protein |
| Serum protein electrophoresis | Cold agglutinins |
| Immunoglobulin electrophoresis | Cryoglobulin |
| Rheumatoid factor | Cryofibrinogen |
| Antinuclear antibody | Anti-DNA |
| Extractable nuclear antigen | |
| Raji cell immune complex assay* | |
| Complement (C3, C4, C19 binding assay) | |
| Anticardiolipin antibody* | |

* Not routinely obtained.

## Diagnostic Evaluation

Our approach to the diagnostic evaluation of patients with severe finger ischemia is standardized and has been previously reported.[16-19] Each patient has had pharmacodynamic magnification hand arteriography and/or noninvasive digital vascular examinations to identify and quantitate digital arterial obstruction and/or vasospasm. Biopsy specimens of affected tissue were obtained for routine histologic examination and immunofluorescent staining. In addition, a standard panel of laboratory tests as outlined in Table 2 was obtained.

## Case Reports

### *Case 1*

This 53-year-old woman had a history of 11 years of episodic digital color changes with cold exposure. There was a family and personal history of neurofibromatosis, with multiple skin lesions having been removed. There was no history of collagen vascular disease. She was found to have a large fixed breast mass and had modified radical mastectomy with postoperative irradiation. Pathologic examination showed an infiltrating ductal carcinoma with 15 of 21 nodes positive. The patient's digital ischemic symptoms worsened and gangrenous lesions of multiple fingers developed. Complete serologic evaluation including antinuclear antibody, rheumatoid factor, immunoglobulin electrophoresis, complement determination, cold agglutinins, and cryoglobulins were normal. Arteriography showed numerous digital artery occlusions with associated cold-induced vasospasm. Treatment with guanethidine gave some symptomatic relief. She had persistent digital ischemia for 2 years at which time she was found to have abdominal metastatic disease and was treated with hormonal therapy and chemotherapy. She died 7 months later of metastatic disease.

### *Case 2*

A 49-year-old woman noted the onset of bilateral finger pain and cyanosis at the time of a modified radical mastectomy for infiltrating ductal carcinoma. No axillary lymph node involvement was present. The symptoms continued for 6 months, associated with progressive digital dysesthesia and fingertip gangrene. An arteriogram showed occlusion of most named palmar and digital arteries with associated vasospasm. The digital ischemia improved slightly after brachial artery injections of tolazoline and reserpine. Chest x-ray showed pulmonary metastases, and chemotherapy was begun. The digital ischemia persisted but did not worsen. Serologic tests showed a low-titer antinuclear antibody and nonspecific mild immunoglobulin elevations. Upper extremity nerve conduction showed diffuse neuropathic changes. The patient died 2 months after the initiation of chemotherapy. At necropsy she was found to have extensive metastatic carcinoma to the viscera. Pathologic examination of the radial artery and involved skin showed no evidence of inflammatory vasculitis, immune deposits, or thrombosis.

### *Case 3*

This 75-year-old man with a life-long history of mild, stable Raynaud's syndrome was found to have chronic lymphocytic leukemia (CLL) in 1977. He received chemotherapy and was in remission. Five years later he had an abrupt onset of blanching of both hands and feet, followed in several days by gangrenous changes of most toes and fingers. These lesions persisted despite treatment with antibiotics, corticosteroids, and pentoxifylline. A skin biopsy specimen showed lymphocytic infiltration, believed to be secondary to his CLL. He was treated with Leukeran® for 6 months and the digital lesions healed. Four months later ischemic finger lesions again developed. Evaluation revealed an exacerbation of the leukemia, with a leukocyte count of 120,000/$\mu$L and gangrene of multiple fingertips. Digit plethysmography showed decreased pulsatile flow to the affected digits. The only abnormal laboratory finding was a small amount of plasma cryofibrinogen. His evaluation is summarized in Tables 2 and 3. The digital lesions improved somewhat with the initiation of leukemia chemotherapy, but the patient died 3 weeks later of septic complications.

### *Case 4*

A 63-year-old woman noted the precipitous onset of cold-induced tenderness and blanching of her fingers followed by cyanosis and rubor. Within 3 weeks, small ulcerations and gangrenous changes of the tips of the thumbs, index, and middle fingers of the right hand and the index and middle fingers of the left hand developed. Magnification hand angiography showed widespread palmar and digital arterial obstruction (Fig. 1). The abnormal findings of her evaluation are summarized in Table 3, and included a striking elevation of IgG to 2,800 mg/dL. Hematuria led to renal angiography, which revealed an avascular mass in the upper pole of the left kidney. A radical nephrectomy was done and the mass was found to be a sarcomatoid renal adenocarcinoma, with metastasis to hilar, periaortic, and mesenteric nodes. After operation the digital ischemia improved with healing of the lesions over the next 2 months, associated with a decrease of IgG to normal levels. She received a short course of chemotherapy. Over the next 3 years she continued to have Raynaud's attacks and recurrent digital ulcerations. She had no evidence of metastases at this time, although the carcinoembryonic antigen (CEA) remained elevated. She was treated medically for her Raynaud's syndrome. She returned 3 months later with a large epigastric mass and died soon thereafter of recurrent tumor.

### *Case 5*

A 43-year-old man was found to have gastric adenocarcinoma with extension to regional nodes and hepatic metastases. He was treated with chemotherapy with 5-fluorouracil and developed lower extremity deep vein thrombosis. He was anticoagulated with heparin followed by warfarin. Six months later while therapeutically anticoagulated with warfarin, right axillary vein thrombosis developed followed by the rapid onset of hand ischemia progressing to gangrene of the right thumb, index, middle, and ring fingers. Digit plethysmography confirmed absent arterial flow in these four fingers with preservation of normal pulsatile flow in the fifth finger and normal palpable radial and ulnar pulses (Fig. 2). Ten days later despite heparin treatment, deep

TABLE 3. *Summary of Clinical Courses of Described Patients*

| Case Number | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|
| Malignancy | Breast, infiltrating ductal | Breast, infiltrating ductal | Chronic lymphocytic leukemia | Renal adenocarcinoma | Gastric carcinoma |
| Metastases | 15 of 21 axillary nodes, ovarian, iliac, mesenteric nodes | 0 of 14 axillary nodes, pulmonary metastasis | Remission 1977–1982 | Recurrent peritoneal nodes | Mediastinal and lymphatic metastases |
| Treatment | L MRM 1969<br>XRT 1969<br>Oophorectomy 1976<br>XRT/CTX 1976 | R MRM 1983<br>CTX 1984 | Chlorambucil CTX-1977<br>Chlorambucil 1982–1985<br>CTX 1985 | L radical<br>CTX 1974 | Laparotomy, CTX |
| Smoking history | 80 pack years | Moderate, none 1980 | 80 pack years, none since 1966 | Unknown | >100 pack years |
| Associated diseases | Neurofibromatosis | None | None | None | None |
| Previous Raynaud's syndrome | 11-year history cold-induced pain and cyanotic changes | None | Cold-induced pain and blanching since adolescence | None | None |
| Digital lesions | Ulcerations, cyanosis and gangrenous changes over multiple fingers (bilateral) | Dysesthesias and punctate ulcerations and several gangrenous areas over 7 fingertips | Purpura, ulcerations with gangrenous lesions over 19 fingers and toes | Ulcerations and gangrenous changes over 5 fingers (bilateral) | Gangrene of fingers and distal palm |
| Angiography | Multiple digital artery occlusions, marked vasoconstriction with ice immersion, relieved with reserpine | Bilateral radial artery occlusion with multiple digital artery occlusions; some improvement with tolazoline | Not done | Left hand multiple arterial irregularities with narrowing, no improvement with reserpine | Not done |
| Skin biopsy | Not done | No cutaneous vasculitis or inflammation (at autopsy) | 1. Vasocentric lymphohistiocytic infiltrate<br>2. Discoid lupus V. chilblains | Mild leukocytoclastic angiitis | No arteritis, widespread venous and arterial thrombosis |
| Treatment of digital lesions | Good response to reserpine orally and intra-arterial | Some relief with intra-arterial reserpine/ tolazoline/ dextran IV; mild relief with nifedipine and prednisone | Initial relief with chlorambucil, local wound care and CTX with recurrence | Increased symptoms following initial slight relief with guanethidine and phenoxybenzamine with recurrence | Amputation |
| Outcome | Died with extensive metastases 1976 | Died of septic complications of CTX for pulmonary metastasis 1984 | Died of septic complications of CTX 1985 | Died with recurrent tumor 1977 | Died 2 months after diagnosis |
| Autopsy | Extensive abdominal metastases | Metastases to lung and liver, radial artery patent, no evidence of vasculitis | Not done | Not done | Not done |
| Outcome of digital lesions | Acrocyanosis and several ulcerations at time of death | Acrocyanosis, petechiae, and single gangrenous ulcer | Great improvement and healing of ulcerations | Painful red hands with minimal ulcerations | No new lesions |

MRM = modified radical mastectomy.
XRT = radiation therapy.
CTX = chemotherapy.

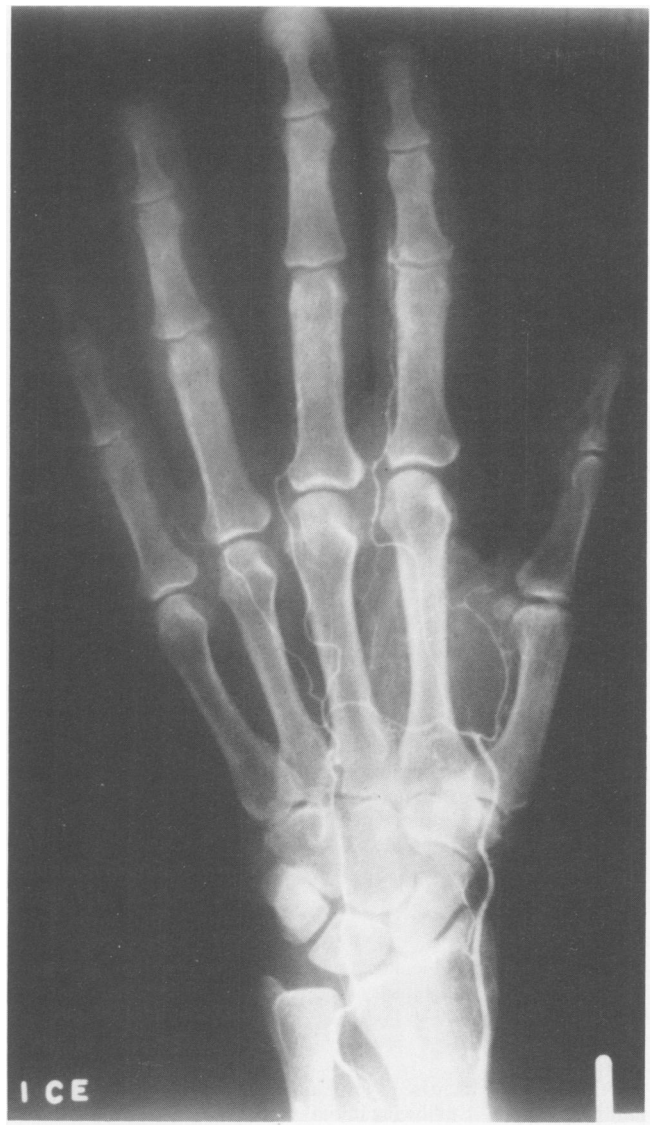


FIG. 1. Magnification hand arteriogram demonstrating widespread palmar and digital arterial obstruction (Case 4).

vein thrombosis recurred in the right leg. The patient died 2 months after limited hand amputation. Pathologic examination of the involved arteries showed no evidence of vasculitis. The details of the case histories are summarized in Table 3.

## Discussion

Patients with episodic digital ischemic syndromes have been classically said to have Raynaud's disease if the condition exists alone and Raynaud's phenomenon if the ischemic symptoms exist in the presence of an associated disease process, frequently collagen vascular diseases.[20] Since neither of these terms describes a specific diagnosis, many authorities have abandoned them in favor of the term Raynaud's syndrome, used to describe the symptom complex of episodic digital ischemia in response to cold or emotional stimuli.[16] Fixed digital ischemic symptoms including gangrenous changes do not constitute Raynaud's syndrome as currently defined. Clearly, however, patients with severe digital ischemia may also have episodic symptoms that are properly termed Raynaud's syndrome. The patients described in this report all reported symptoms of Raynaud's syndrome accompanying their severe digital ischemia, and in two of the patients (Cases 1 and 3) these symptoms preceded the development of severe digital ischemia by years. The relationship between fixed digital arterial obstruction and Raynaud's syndrome has been described previously.[16]

Patients with Raynaud's syndrome may be conveniently divided into two groups, which we have termed spastic and obstructive with the differential point being the presence of fixed obstruction to flow in the palmar and digital arteries. Patients with spastic Raynaud's syndrome have symptoms as a result of an exaggerated vasospastic response to cold or emotional stimuli. Patients with obstructive Raynaud's syndrome have symptoms

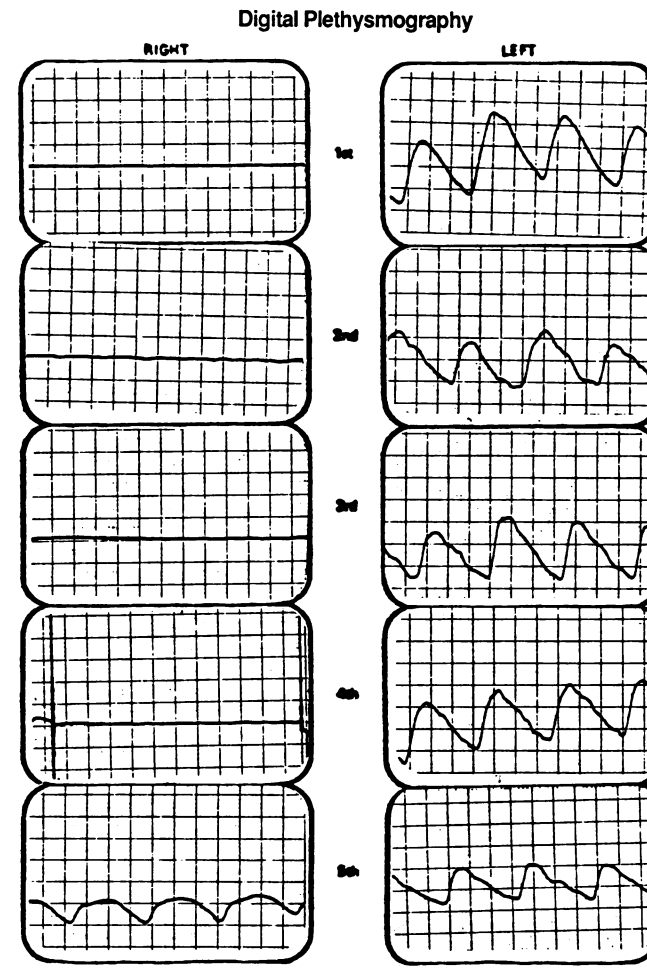


FIG. 2. Digital plethysmography demonstrating absence of pulsatile flow in right hand fingers 1–4 with normal pulsatile flow in left hand fingers (Case 5).

from digital artery closure caused by a normal vasoconstrictive response acting on an obstructed vessel.[21] Although spastic Raynaud's symptoms may be symptomatically severe, it has never in our experience caused digital gangrene. The latter has occurred only in the presence of diffuse palmar and digital arterial fixed obstructive disease.[17] The five patients with digital gangrene described in this report all had extensive fixed arterial obstructive disease in the hand and finger arteries as demonstrated by arteriography in three patients and digital plethysmography in the remainder. Three patients had a history of Raynaud's syndrome before the development of digital gangrene, and each patient had moderate improvement of ischemic symptoms after intra-arterial injection of vasodilators. Spastic Raynaud's syndrome preceding by years the development of fixed arterial obstruction and digital gangrene has been repeatedly noted by us and by others.[16,17,22]

Previous observers have postulated multiple mechanisms to explain the digital vasospasm and the digital artery obstruction producing digital ischemic symptoms in association with malignancy. Vasospasm has been attributed to sympathetic hyperactivity and to arteritis. Arterial obstruction has been attributed to arteritis, to hyperviscosity caused by elevated levels of a variety of serum proteins or of the formed elements of the blood, and to hypercoagulability associated with malignancy.

The earliest reports of digital ischemia associated with malignancy hypothesized vasospasm caused by metastatic tumor invasion of sympathetic nerves. Bennett and Poulton described in 1928 the case of a 61-year-old man with an occult gastric carcinoma who died during a cervical sympathectomy for relief of digital ischemic pain.[23] In 1963, Nielson and Petri reported a 77-year-old woman with bilateral digital gangrene and occult colon cancer with metastases to the cervical sympathetic chain and stellate ganglion.[24] None of the five patients described in this report had metastases detected to the sympathetic nerves to the upper extremity. The existence of bilaterally symmetrical symptoms in four of our five patients and in 22 of the 23 patients listed in Table 1 likewise mitigates against a local infiltrative process as the cause of this syndrome.

Arteritis of diverse etiologies has been clearly associated with digital artery vasospasm, as well as with digital artery obstruction producing finger ischemia and finger gangrene.[16,17,25] Several of the existing reports of tumor-associated digital ischemia have noted changes consistent with arteritis in the affected vessels, occasionally in association with circulating immune complexes.[26] The cause of the arteritis is unknown but may be related to tumor antigen–antibody complexes with subsequent complement activation in contact with the arterial wall.

Viscosity abnormalities have also been proposed as a mechanism of ischemia. An increase in blood viscosity may result from an increase in numbers of circulating blood cells as was noted by Hild and Myers who reported a case of ischemic necrosis of the fingertips, which they attributed to a severely elevated whole blood viscosity (Oswald viscosity: 7.1) in a patient with chronic granulocytic leukemia.[11] This mechanism appears to have resulted in digital ischemia in Case 3 in this series, in whom the granulocyte count was elevated to 120,000/$\mu$L at the time of severe symptoms. Hyperviscosity may also be caused by an increase in circulating blood proteins as was described by Domz and Chapman who related the 1961 case of a 56-year-old woman with adenocarcinoma of the lung who had elevated cryoglobulin levels and "pseudo-Raynaud's disease" progressing to gangrene. Tumor resection and concommitant decrease in circulating cryoglobulin level was associated with healing of the digital lesions and resolution of pain. Cryoglobulins were postulated to produce localized thrombosis and eventual infarction by precipitating prothrombin and accessory clotting factors.[27]

Hyperviscosity caused by cryoglobulinemia and arteritis may coexist.[28] In Case 4 described in this report, cryoglobulinemia was present in association with severely elevated IgG levels during the period of maximal digital ischemia. In this case the ischemia resolved and ulcerative lesions healed after resection of a sarcomatoid renal adenocarcinoma. Elevated gamma-globulin level, IgG immunofluorescence of tumor cells, and electron-dense deposits lining the endothelium of the tumor microvasculature were seen, suggesting the presence of immune complex deposition in vessel walls. Moore and Cupps in their review of the neurologic complications of vasculitis postulate immune complex deposition as the cause of both hypersensitivity vasculitis and systemic necrotizing vasculitis.[8] They cite the isolation of soluble immune complexes in experimental models, microscopic demonstration of immunologically mediated vascular destruction, and resolution of findings with immunosuppressants as justification for their conclusions.

Hypercoagulability in the absence of arteritis or hyperviscosity has been detected in 50–90% of patients with malignant tumors, especially those with metastases.[29,30] In as many as 15% of these patients, thrombotic events may be clinically apparent.[31] Case 5 described in this report had widespread venous and arterial thrombosis that progressed rapidly despite anticoagulant therapy. The relative resistance to treatment of this form of hypercoagulability has been well described.[32]

The fixed digital artery obstruction in these patients appeared to be caused by hyperviscosity in two patients. Arteritis was documented by pathologic findings and presumably caused the obstruction in two additional

patients. In the final patient, diffuse digital artery obstruction resulted from thrombotic occlusion caused by hypercoagulability.

Four of the five patients described in this report had considerable symptomatic improvement after treatment directed at their primary neoplasms, emphasizing the ability of the hands and fingers to recover from severe ischemia, presumably through the development of collateral arterial channels.[17] Although antitumor therapy is of primary importance in treatment of these patients, the administration of vasodilators, currently calcium channel blockers, may result in moderate symptomatic improvement in those patients with an underlying vasospastic component in addition to the fixed arterial obstruction.

Digital gangrene in association with malignancy, although uncommon, is not rare and is being recognized with increasing frequency. The judicious application of angiography and plethysmography, serologic testing, and biopsy should permit accurate definition of which mechanism(s) of ischemia is (are) most important in the individual patient and permit selection of optimal therapy.

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