

Angiosarcoma of the Hand Associated with Chronic Exposure to Polyvinyl Chloride Pipes and Cement

A CASE REPORT*

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Angiosarcoma of the liver has been reported to be causally related to chronic exposure to polyvinyl chloride^{7,14,15,25}. Skin contact with products that contain polyvinyl chloride is known to cause a spectrum of vascular dysplasias^{8,21}.

We report the case of a patient who had angiosarcoma of the hand after having been exposed to polyvinyl chloride over a period of eleven years. The patient had lesions involving the nail-folds of three digits (the thumb and the long and ring fingers) as well as several soft-tissue masses in the palm. He also had metastases to the lungs. The treatment included amputation through the distal third of the forearm followed by chemotherapy. The metastatic lesions in the lungs were excised. Six years after treatment, the patient was alive with evidence of recurrent disease.

We believe that angiosarcoma of the hand can result from chronic skin contact with pipes and cement containing polyvinyl chloride. The use of gloves to minimize skin contact with the material is recommended for those who work with these products on a routine basis. Otherwise healthy individuals who are found to have angiosarcoma of the hand should be questioned about exposure to products containing polyvinyl chloride.

Case Report

A thirty-six-year-old right-hand-dominant man was seen because of mild, persistent pain in the region of the metacarpal of the little finger. He apparently had been injured during a game of softball. He had not noted the presence of any mass.

The patient had worked in the landscaping business for eleven years. His job involved the installation of watering systems that employed pipes and cement containing polyvinyl chloride. During the first three years of his employment, he spent approximately twenty hours per week handling pipes, cement, and primer. After he was promoted to the position of foreman, his direct exposure decreased to ten hours per week for the next five years and then to less than two

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hours per week during the most recent three years. The patient stated that he never wore gloves when working.

The patient had a history of moderate-to-excessive consumption of alcohol (two to eight drinks per day), beginning when he was



FIG. 1

Anteroposterior radiograph of the right hand, showing a well marginated lytic tumor in the distal part of the fifth metacarpal and a lytic lesion in the distal phalanx of the thumb.

eighteen years old and continuing to the time of presentation. He had intermittently smoked cigarettes and marijuana. His mother had multiple lipomatosis, and his father had died at the age of fifty-seven years as a result of complications associated with alcohol-related cirrhosis of the liver. There was no personal or family history of cancer. There also was no history of risk factors such as Raynaud phenomenon, exposure to radiation, lymphedema, or vasculitis.

Physical examination revealed hypervascular tissue in the nail-folds of the thumb and the long and ring fingers as well as diffuse soft-tissue masses in the thenar and hypothenar eminences. Radiographs of the wrist and hand showed a pathological fracture through



FIG. 2

Anteroposterior radiograph of the fingers of the right hand, showing lytic lesions in the distal phalanges of the long and ring fingers secondary to erosion caused by the tumors in the nail-folds.

a well marginated lytic tumor located in the distal part of the fifth metacarpal and multiple erosions in the distal phalanges of the thumb and the long and ring fingers (Figs. 1 and 2). Magnetic resonance imaging demonstrated a sharply circumscribed soft-tissue mass that extended to the fifth metacarpophalangeal joint as well as a circumscribed lesion between the third and fourth metacarpals distally (Fig. 3). The lesion between the third and fourth metacarpals distorted the adjacent volar interosseous muscles and was intimately related to the volar surface of the fourth metacarpal. Magnetic resonance imaging also demonstrated a third lesion, measuring 2.5 centimeters in diameter, within the thenar muscles. A total-body bone scan revealed increased uptake in the right hand and wrist.

The patient was screened for metastases with use of computerized tomography. The scans of the lungs showed multiple nodules bilaterally. No lesions were seen on the scans of the abdomen. Liver-function studies, performed because of the history of increased alcohol intake, revealed normal findings. Biopsy specimens were obtained from two soft-tissue masses in the right arm in order to rule out regional metastasis; histological examination confirmed that both masses were benign lipomas.

An open biopsy was performed to obtain tissue from the mass in the fifth metacarpal as well as from the fourth distal phalanx and nail-fold. Gross examination of the specimen from the mass in the fifth metacarpal revealed brownish, mildly hemorrhagic, friable tissue. Histological examination of the material from the fourth distal phalanx and nail-fold led to the diagnosis of a grade-2 angiosarcoma²⁶ (Fig. 4).

The diagnosis of a grade-2 angiosarcoma with metastases to both lungs was made in September 1991. The initial treatment, which was continued for six months, consisted of five cycles of chemotherapy with the MAID regimen (a combination of mesna, Adriamycin [doxorubicin hydrochloride], ifosfamide, and dacarbazine, each administered for three days every four weeks). In November 1991, while the patient was still receiving chemotherapy, an amputation was performed through the distal third of the forearm. The pathological examination confirmed the diagnosis of angiosarcoma of the nail-folds of the thumb and the long and ring fingers, with erosion into the corresponding distal phalanges, as well as the presence of multiple lesions in the soft tissues of the palm.

In March 1992, at the completion of the chemotherapy protocol, forty nodules were excised from the right lung; histological examination of the specimens confirmed the diagnosis of angiosarcoma and showed no evidence of tissue necrosis. The chemotherapeutic agents were changed to etoposide and cisplatin, again administered in three-day cycles with a four-week hiatus. After the completion of two cycles

of treatment, thirty nodules were removed from the left lung; there was no evidence of necrosis of adjacent tissues.

Computerized tomography, performed in August 1992, showed multiple recurrent pulmonary nodules bilaterally. The chemotherapeutic agent was changed to etoposide only (fifty milligrams per square meter of skin), administered for twenty-one days followed by seven days of abstinence from all medication. This regimen was continued for twelve cycles, until July 1993. Computerized tomography at that time demonstrated no change in the size or number of pulmonary lesions.

At the latest follow-up examination, in February 1997, the patient was alive with evidence of disease. He had no additional chemotherapy and had returned to his former job in the landscaping business.

Discussion

Angiosarcoma is an extremely rare vascular neoplasm that has been estimated to account for less than 1 per cent of all sarcomas¹². Of 449 soft-tissue tumors seen at the M. D. Anderson Hospital during a twenty-two-year period, only one was an angiosarcoma⁴. Angiosarcoma of the extremities has been known to arise in the setting of chronic lymphedema^{30,34}. Enzinger and Weiss¹³, in a review of 366 cases of angiosarcoma that were included in the files of the Armed Forces Institute of Pathology, reported that 210 cases involved the skin and soft tissues. Angiosarcoma involving the liver is rare but is known to be caused by exposure to a number of carcinogens¹³. In four studies comprising 273 patients who had a hepatic angiosarcoma, 28 per cent (seventy-seven) of the patients had a history of exposure to one of several carcinogenic agents, including thorium dioxide (Thorotrast) angiographic contrast material (thirty-three patients; 12 per cent), vinyl chloride monomer (twenty-six patients; 10 per cent), arsenic (fourteen patients; 5 per cent), and anabolic steroids (four patients; 1 per cent)^{5,6,14,32}. Popper et al.²³ compared fifty patients who had a hepatic angiosarcoma that had been induced by exposure to vinyl chloride, Thorotrast, or arsenic with 117 patients who had the same lesion but with an un-

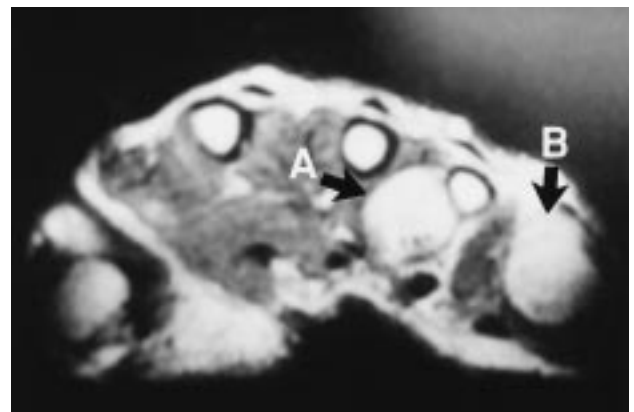


FIG. 3

T2-weighted axial magnetic resonance image showing a lesion in the soft tissues of the interspace between the third and fourth metacarpals (A) and another lesion in the region of the fifth metacarpal (B). (A third lesion, which was located within the thenar muscles, was seen on a different magnetic resonance image.)

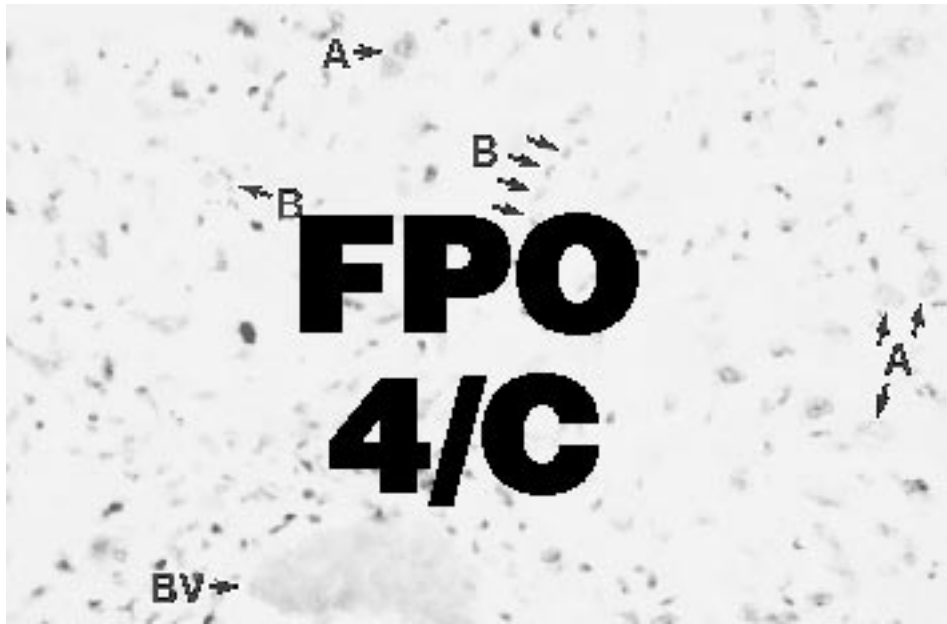


FIG. 4

Photomicrograph of a specimen of tissue from the nail-fold, showing a grade-2 angiosarcoma²⁶ with epithelioid features (hematoxylin and eosin, $\times 100$). Note the characteristic fibroreticular pattern (A) separating aggregates of oval cells (B). A blood vessel (BV) also is seen.

known etiology. Those authors concluded that exposure to polyvinyl chloride plays a role in the development of this lesion. Wong et al.³³ performed an industry-wide epidemiological study of 10,173 workers who had been exposed to vinyl chloride between 1942 and 1982 and came to similar conclusions with regard to the association between exposure to vinyl chloride and angiosarcoma. Baxter⁵ reported on thirty-five patients who were managed for hepatic angiosarcoma between 1963 and 1977. Two of these patients had been exposed to vinyl chloride, and eight others had received Thorotrast intra-arterially. Brady et al.⁶ performed a case-control study of twenty-six patients who had an angiosarcoma. Three patients had been exposed to vinyl chloride; two, to arsenic; and two, to Thorotrast. Those authors concluded that exposure to any of these three agents was causally related to the development of angiosarcoma; this association was significant ($p < 0.02$). Falk et al.¹⁴ identified 168 patients who had a hepatic angiosarcoma; twelve had been exposed to vinyl chloride.

We found five studies in which hepatic angiosarcoma was diagnosed in individuals who had been exposed to high levels of polyvinyl chloride monomers while working in polymerization plants.^{1,11,15,16,28} There was a long latent period before the onset of the disease: the average interval between the time of the first exposure and death was more than twenty years. The Agency for Toxic Substances and Disease Registry¹ reported fifteen deaths due to angiosarcoma among the 10,173 workers who were listed in its database. Doll¹¹, in a review article that included data from studies performed in Italy, Canada, and the United Kingdom, reported one death due to angiosarcoma among 1256 Italian workers, eleven

deaths among 451 Canadian workers, and seven deaths among 5498 workers in the United Kingdom. The clinical characteristics of latency and the risk of mortality were summarized in that article¹¹. Hayashi et al.¹⁵ studied the relationship between malignant cells and the sinusoids and vascular channels of the liver and concluded that metastasis could occur easily through access to the vascular system. In a study by Hollstein et al.¹⁶, four patients who had an angiosarcoma after exposure to vinyl chloride were tested for mutations in the p53 tumor-suppressor gene. Two of the patients had A:T to T:A missense mutations, which were absent from non-tumorous tissues. Simonato et al.²⁸, in a multicenter study, reviewed the records of 14,351 workers who had been exposed to polyvinyl chloride and found documentation of twenty-two deaths due to hepatic angiosarcomas and two deaths due to other hepatic tumors. This rate was almost threefold higher than the expected rate. Those authors pointed out that the prevalence of this tumor appears to have decreased since the 1970s because of the drastic reduction in the level of exposure to toxic agents. It is an accepted fact that exposure to high concentrations of vinyl chloride during the manufacturing process causes angiosarcoma of the liver, with inhalation being the most likely route of exposure²⁴.

Our patient had routinely been exposed to pipes and cement containing polyvinyl chloride while installing sprinkler systems during an eleven-year period. He had handled, cut, and glued pipe fittings together, primarily with the right hand, resulting in repeated direct skin contact with newly cut pipe shavings. He also had had frequent and prolonged direct skin contact with the glue and had accumulated the residue in the nail-folds. The

outdoor nature of his job presumably reduced his level of exposure through inhalation, which is the primary route of exposure among factory workers. Therefore, in the absence of any other known risk factors, chronic exposure to vinyl chloride monomer through direct skin contact could have resulted in the development of angiosarcoma in our patient.

Although we were unable to find any reports of angiosarcoma of the hand in association with exposure to polyvinyl chloride, there have been several reports of non-malignant pathological changes associated with direct skin contact. Chronic skin exposure to polyvinyl chloride among workers who scrape autoclave production vessels by hand has been found to produce a constellation of clinical signs and symptoms known as vinyl chloride disease^{1,18}. The clinical features include hepatosplenomegaly, patchy scleroderma of the dermis, acro-osteolysis (distal phalangeal resorption), microvascular abnormalities, and Raynaud phenomenon^{10,21}. These clinical features were noted in a laborer who had cut polymerized polyvinyl chloride plastic sheets for four years, in whom multiple histiocytoid hemangiomas developed in the skin, subcutaneous tissue, and bones of the forearm and hand⁸.

Maricq et al.²¹ used wide-field capillary microscopy to examine the hands of 152 individuals who worked in vinyl chloride polymerization plants and of fifty manual laborers who had no history of exposure to vinyl chloride. This non-invasive screening technique allows for the detection of microvascular patterns such as the presence of dilated and deformed microvessels. Twelve standard sites, including the nail-fold, the dorsal aspect of the distal and middle phalanges, the proximal interphalangeal joint, and the finger-pad, were evaluated. Thirty-eight of 108 workers who had had no previous evidence of abnormalities associated with a history of exposure to polyvinyl chloride had abnormal, dilated capillaries compared with three of the fifty manual laborers who did not have a history of exposure. Thirteen of seventeen workers who had reported signs and symptoms that possibly were related to exposure to polyvinyl chloride were found to have abnormalities such as dilated capillary loops in the nail-folds, pale avascular areas, papular skin lesions, and hemorrhages under the nail-plate. These pathological changes were observed almost exclusively on the hands in the areas of chronic contact. Only four of twenty-seven workers who had no abnormalities on liver-function tests or who had minor non-specific rashes, healed acro-osteolysis, or only Raynaud phenomenon had abnormal capillaries as seen on microscopy. Maricq et al. concluded that capillary abnormalities were more frequent in asymptomatic workers who had been exposed to vinyl chloride than in the control group; this difference was significant (chi square = 15.50, $p < 0.001$).

Damage to DNA following exposure to vinyl chloride and its metabolites was demonstrated by Barbin et

al.², who performed an *in vitro* test with use of three strains of *Escherichia coli* that had been exposed to the final metabolite of polyvinyl chloride, chloroethylene oxide. This metabolite has been shown to produce DNA base-pair mutations in bacteria^{3,20}, yeast¹⁹, and hamster cells¹⁷, and it has been found to be tumorigenic in rodents³⁵. Barbin et al.² provided a succinct description of the widely used *Escherichia coli* multitest system, developed by Toman et al.³¹, which represents a new area of cancer research. The three strains of *Escherichia coli* that are used in this test have specific mutations in a single repressor gene (the λ cI repressor gene). These strains allow the mode of action of the DNA-damaging agents to be identified as mutagenesis, induction of the so-called SOS response, or homologous recombination. This test uses the *gal* operon system, and the metabolism of galactose indicates the presence of mutagenesis. Barbin et al.² found typical dose-response curves for the toxicity and mutagenicity of chloroethylene oxide. The toxicity was decreased in the presence of a functional SOS system; however, this system was not required for mutagenesis. In addition, mutagenesis did not occur by homologous recombination. Those authors concluded that the mutagenicity of chloroethylene oxide arose mainly from miscoding DNA adducts and was mainly SOS-independent.

Factory workers who have been diagnosed with hepatic angiosarcoma after exposure to polyvinyl chloride have been found to have point mutations in the p53 tumor-suppressor gene and other point mutations causing activation of the *c-Ki-ras-2* oncogene^{9,16,22}. Although isolated exposures to polyvinyl chloride may have a low carcinogenic potential, polyvinyl chloride is known to be more soluble in fat than in water, thereby making it possible to have cumulative exposure with repeated contact. The absorbed vinyl chloride and its converted metabolites may then act as a DNA adduct and induce point mutations in either tumor-suppressor genes or cell-proliferation regulatory genes, which in turn may cause various vascular abnormalities ranging from benign dysplasia to frank angiosarcoma. Abnormal tumor-suppressor genes allow uncontrolled growth of cells, which is manifested as metaplasia, dysplasia, or frank carcinoma, depending on the extent of cellular atypia. This progression of changes is most widely understood in relation to the cervical epithelium, where abnormalities progress from dysplasia to invasive carcinoma on a continuum. Maricq et al.²¹ performed a blinded analysis of photographs made with use of a wide-field microscope and described the changes that were seen in association with dysplasia of the vascular system. These changes included abnormal, dilated capillary loops; pale avascular areas; capillary hemorrhages; so-called splinter hemorrhages; abnormal distribution of capillary loops in the tissues; and micropapillary vascular lesions consisting of tangled knots of capillaries.

Inherited mesenchymal disorders, such as osteochon-

dromatosis²⁷ and neurofibromatosis²⁹, have been associated with an increased risk of sarcoma. In addition to the chronic contact with polyvinyl chloride, our patient had other possible risk factors for carcinogenesis, such as familial lipomatosis. We are unaware of any reported association between angiosarcoma and lipomatosis, but it is possible that this underlying mesenchymal disorder may have increased the risk of carcinogenesis in our patient. Consumption of alcohol has been shown to potentiate the effects of exposure to vinyl chloride on the development of hepatic angiosarcoma¹, but it has no known role in the development of angiosarcoma at other

sites of the body. In the case of our patient, excessive alcohol consumption may have enhanced the carcinogenic effects of the brief yet repeated exposures to polyvinyl chloride.

Additional studies are necessary to quantify the risk and specific mechanism of induction of angiosarcoma through direct skin contact. Otherwise healthy individuals who have angiosarcoma of the hand should be questioned about contact with polyvinyl chloride. Direct exposure of the skin to pipes and adhesives containing polyvinyl chloride should be kept to a minimum, and gloves should be worn to decrease any inherent risks.

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