



Shell Development Company

Interoffice Memorandum

SEPTEMBER 14, 1981

FROM: V. L. KIRKLAND

TO: R. E. JOYNER, M.D.

SUBJECT: VINYL CHLORIDE (VC) - LIVER ANGIOSARCOMA REGISTRY

A copy of the August, 1981, update of the Registry, compiled by Dr. J. Stafford of ICI Ltd. and received via Dow Chemical U.S.A., is attached for your information.

VLK/fcs

Attachment

cc - w/o attachment

M. B. Slomka, M.D.

C. D. Kary

C. B. McCullough

Manager, HS&E Support-Base Chemicals

HS&E-1S(2)

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Shell Oil Company
Interoffice Memorandum

JUNE 26, 1981

TO: P. F. DEISLER, JR.
FROM: R. D. MULLINEAUX
SUBJECT: EXTENDED MEDICAL SURVEILLANCE

Based on the attached Task Force report, the DEPT recommends that epichlorohydrin and vinyl chloride be reviewed with the appropriate Corporate Officers as candidates for extended medical surveillance. The Task Force has determined that these two compounds, and at this time only these, fulfill the first two criteria given in the Guidelines for Extended Medical Surveillance. Shell has the need for additional epidemiologic data on these compounds to increase the probability that we can establish the presence or absence of health effects related to workplace exposure. Such knowledge will enhance our ability to protect current and future employees by better defining the necessary exposure limits.

The estimated cost of the program, as shown in the Task Force report, ranges from \$2,000 to \$3,000 in the first year of implementation to \$18,000 to \$20,000 in the tenth year. We believe the value of these programs far exceeds these costs.

The vast majority of employees in existing medical surveillance programs for VC and ECH are in Operations (1,327 out of a total of 1,354). Therefore, the guidelines require the joint approval of yourself, the Vice President Operations, the Vice President Chemical Products, and the Vice President Employee Relations.

Although on the basis of current knowledge none of the other medical surveillance programs meet the criteria of need for additional epidemiology information or value to current and future employees, this evaluation will be reexamined as new data becomes available. In addition, dibromochloropropane is being evaluated by HS&E, Agricultural Chemicals Business Center, and Legal as to the applicability of Category 3, "Potential liability exposure should the program not be continued".

RDMullineaux

Attachment 01-CC-116

cc: EMS Task Force Members
DEPT Members
DEPT File



Shell Development Company

Interoffice Memorandum

MAY 6, 1981

FROM: V. L. KIRKLAND, SR. RESEARCH TOXICOLOGIST
PRODUCT & PROCESS TOXICOLOGY

TO: R. E. JOYNER, M.D.
~~M. B. SLOMKA, M.D.~~

SUBJECT: VINYL CHLORIDE (VC) - LITERATURE REPORT

The attached clinical report (Ghandur-Mnaymeh, L. and Gonzales, M.S., Angiosarcoma of the Penis with Hepatic Angiomas in a Patient with Low Vinyl Chloride Exposure, Cancer 47:1318-24, 1981) may be of interest.

To this reader, any association between this individual's cancer and "vinyl chloride exposure" seems very shaky, at best. Unfortunately the spectre has been raised.

Attachment

VLK:jf

w/o Attachment

C. D. Kary
C. B. McCullough
R. W. Fortenbach

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Angiosarcoma of the Penis with Hepatic Angiomas in a Patient with Low Vinyl Chloride Exposure

LATIFA GHANDUR-MNAYMNEH, MD, AND MARIO S. GONZALEZ, MD

A case of angiosarcoma of the penis associated with two hepatic angiomas in a 61-year-old man is presented. The patient had worked in a polyvinyl chloride factory as an accountant for ten years. The relationship of this low vinyl chloride exposure to the development of the vascular lesions is discussed with a review of the experimental and epidemiologic data on this subject.

Cancer 47:1318-1324, 1981.

ANGIOSARCOMA of the penis is an extremely rare lesion. About 32 cases have been reported up until the present.^{1,2,6-8,18,26,32} Its occurrence in a patient who worked on the premises of factories handling vinyl chloride (VC) and the presence of two hepatic angiomas is a unique and most unusual association.

Case Report

Clinical History: P.L. (NCCH#96929)

The patient was a 61-year-old man who was initially seen in the private clinics of the University of Miami Hospitals and Clinics in December 1977. At that time he presented with generalized weakness and gross hematuria. The only positive finding on physical examination was a hard 1 x 1 cm nodule on the shaft of the penis said not to have been present previously. Laboratory data showed no abnormality except for an elevated alkaline phosphatase. A cystogram showed a lesion in the lateral wall of the urinary bladder and a liver scan showed a filling defect in the right lobe. The patient underwent a cystoscopy and biopsy of the bladder, which showed an angiosarcoma infiltrating muscularis. Past medical history was negative except for the removal of a bluish nodule from the cheek five months earlier (August 1977). The material was reviewed and showed similar tumor infiltrating the dermis. With the diagnosis of an angiosarcoma and the presence of a filling defect in the liver, the possibility of a primary liver angiosarcoma was entertained and the patient's occupational history was investigated. The patient worked in data processing and was employed in factories for the manufacture of plastic products for ten years: between 1955 and 1958 he worked in a Plastic Tapes Factory in New York and between 1963 and 1970 he worked for a company that manufactured plastic goods in Miami, Florida.

The patient's tumor was considered to be primary in the liver and he was treated with a combination of cyclophosphamide, Adriamycin, and methotrexate. He was followed at weekly intervals as an outpatient until May 26, 1978, when he was admitted to the University of Miami Hospital, National Children's Cardiac Hospital, because of weakness, painful penis, and intermittent priapism. On physical examination the liver was palpable at 12 cm below the right costal margin in the anterior axillary and midclavicular lines. There were multiple nodules at the base of the penis. Laboratory data showed the following: hematocrit 31%, white blood cell count 2250, platelet count 67,000, total serum protein 6.2 g/ml (albumin 1.6 g, globulins 4.6 g); total bilirubin 4.2, blood urea nitrogen 10, calcium 7.4, phosphorus 3.5, uric acid 2.5, creatinine 1.9, cholesterol 288 mg/100 ml; alkaline phosphatase 324 U; serum glutamic oxalacetic transaminase 166 U; serum sodium 140, and potassium 3.6 mEq/liter. Urinalysis showed 2-9 white cells/HPF. Bone and brain scans with Technetium 99 m MPD did not show any areas of increased radionuclide concentration to suggest metastatic disease. Liver scan following the intravenous injection of technetium sulfur colloid showed a normal-sized liver with a questionable area of decreased uptake in the porta hepatis. The spleen was enlarged to twice the normal size.

In the hospital, the patient's condition deteriorated and he complained of severe pain at the base of the penis; he required sedation. There was increasing urinary obstruction necessitating instrumentation for the delivery of urine: elevation of the blood urea nitrogen was 47 mg/100 ml. The patient also complained of double vision and cerebellar symptoms. Gradually he lapsed into coma and died on June 14, 1978, 22 months after initial manifestations.

Pathologic Findings

Autopsy Findings

Gross: The skin was jaundiced with a 3-cm well-healed scar over the right cheek. There was no fluid in the body cavities. The heart was unremarkable.

From the Department of Pathology, University of Miami School of Medicine, Miami, Florida.

Address for reprints: L. Ghandur-Mnaymneh, MD, Department of Pathology, University of Miami School of Medicine, 1611 N.W. 12th Avenue, Miami, FL 33136.

Accepted for publication March 25, 1980.

The lungs were heavy, weighing 1020 (right) and 950 (left) g. On cut section, both exhibited multiple 2–3-cm reddish ill-defined foci of induration and 0.5–1 cm similar but greyish foci. The liver weighed 1160 g. Its cut surface was bile-stained and finely nodular with nodules less than 0.5 cm in diameter. In the right lobe, there were two subcapsular reddish purple areas, roughly quadrangular in shape, with ill-defined borders, one about 4 cm and the other 2 cm in diameter. Their cut sections were fleshy-red and honey-combed; the larger had a central 1 cm in diameter area of greyish discoloration (Fig. 1). The spleen was enlarged to 230 g. The gastrointestinal tract was intact with no esophageal varices appreciated. The kidneys weighed 150 and 160 g and showed slight dilatation of the pelvicalyces. In the pelvic cavity, there was extensive replacement of the prostate, seminal vesicles, and periurethral tissues by greyish and reddish fleshy tissue extending into the lateral pelvic walls. The same tissue infiltrated the bladder neck and the posterior wall producing thickening with mucosal ulcerations. There were three diverticula in the posterior wall of the bladder varying between 2 and 5 cm in diameter. The neck of the bladder was surrounded by tumor that extended to and deformed the base of the penis. The proximal penis was markedly deformed with an increase in the diameter to about 6 cm, which was due to an enlargement of the right corpus cavernosum penis (Fig. 2). Both corpora cavernosa were replaced by the same fleshy red tissue, the right more than the left. This also involved the corpus spongiosum with narrowing of the penile urethra. The brain showed a 2 × 2 × 3.6 cm circumscribed hemorrhagic lesion in the right occipital lobe.

Microscopic Examination

Sections of the corpora cavernosa showed a gamut of changes: in some areas, the vascular spaces were lined by normal-appearing endothelial cells with small nuclei and attenuated cytoplasm. In other areas, the lining cells were large and atypical with prominent vesicular nuclei sometimes containing large nucleoli. Further on, the lining cells were definitely anaplastic with clustering and intravascular tufting (Fig. 3). In all the above areas, the fibromuscular trabecula maintained the normal architecture of the corpus cavernosum. In other fields, there was replacement of the normal architecture by large masses of tumor cells with their own fibrous stroma. The tumor cells were either spindly, forming fascicles and sometimes lining small lumens, or round forming large sheets of loose cells separated by fibrous trabecula. In both areas, the



FIG. 1. Cut surface of the right lobe of the liver with the hamangiomas. Both lesions exhibit a spongy or honey-combed surface. The larger one has a central more solid grayish area. The intervening tissue appears fibrotic. The remaining hepatic parenchyma is finely nodular.

neoplastic cells had large vesicular nuclei with very prominent nucleoli and irregular chromatin clumping. Around the corpora cavernosa, tumor nests were seen within vascular structures and in perineural lymphatics. Sections from around the bladder neck and the seminal vesicles showed a poorly differentiated anaplastic sarcoma diffusely infiltrating the tissue; however, there were always attempts at vessel formation by the tumor cells (Fig. 4).

Sections from the red lesions in the liver showed a cavernous hemangioma (Fig. 5). In several sections, the endothelial spaces were filled with clusters of tumor



FIG. 2. Cross-section of the base of the penis showing the markedly enlarged right corpus cavernosum, the foci of involvement with dark and white discoloration of the left corpus, and the compression of the urethra by the surrounding grayish tumor.

FIG. 3. Microscopic section of the corpus cavernosum penis. The endothelial lining cells are hyperchromatic and show tufting and papillary projections (H & E, $\times 625$).

cells growing mainly as round cells with ill-defined borders and prominent nucleoli. In such areas, the lining endothelium was benign in appearance and conspicuously different from the contained tumor cells.

Sections from the remaining part of the liver showed a micronodular cirrhosis consisting of portal fibrosis with bridging of fibrous tissue from one portal area to another. In many fields, the septa extended from portal

area to central vein with obliteration of lobular architecture (Fig. 6). Some portal areas showed a moderate degree of pseudoductular proliferation. A conspicuous number of hepatocytes showed multivesicular fat accumulations scattered throughout the lobule with no zonal preference. There was a moderate degree of intracytoplasmic and canalicular bile stasis. The Kupffer cells were not prominent and no sinusoidal



FIG. 4. Invasive angiosarcoma as seen in pelvic cavity and metastatic foci. The tumor cells are either spindle or polyhedral with hyperchromatic or vesicular nuclei. They form nests and fascicles with cleft formations (H & E, $\times 150$).

FIG. 5. Microscopic appearance of one of the hemangiomata in the liver. Multiple sections of the entire surface area showed all sinusoids to be lined by flat endothelial cells with inconspicuous nuclei. Anaplastic cells with vesicular nuclei and prominent nucleoli are present within two sinusoids mixed with red blood cells (H & E, $\times 625$).



dilatation was noted in the cirrhotic part. One section with overlying capsule did not show subcapsular scarring.

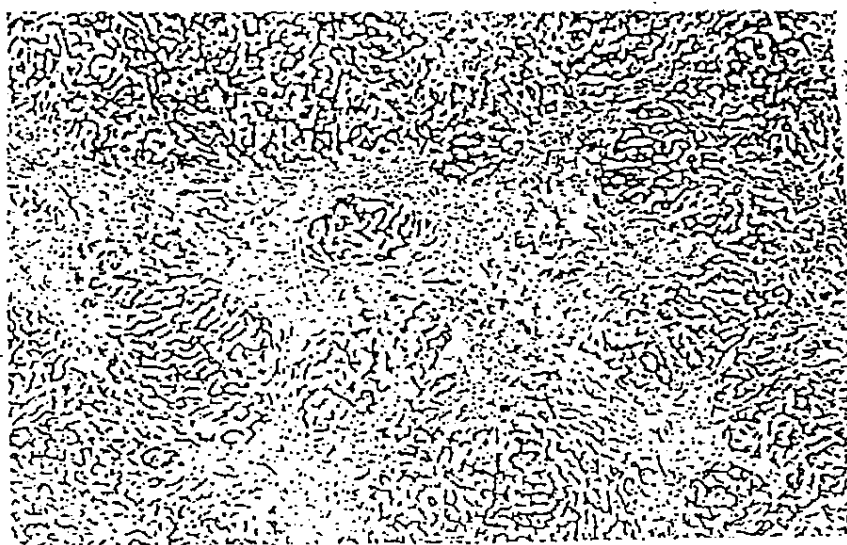
Sections from the spleen showed slight prominence of the sinusoidal endothelial lining with perisinusoidal fibrosis. There was no endothelial cell atypicality. Most of the central arteries were almost naked with marked depletion of lymphoid tissue.

Sections of the lungs showed foci of broncho-

pneumonia and multiple metastases. Neoplastic cells similar to those described above were present within alveoli, in vascular lumens, and infiltrating perivascular tissues. The hemorrhagic lesion in the occipital lobe of the brain showed a recent hematoma with no tumor cells, macrophages, or glial response.

Review of the cheek and the bladder biopsies showed an angiosarcoma similar in all respects to that present in the other organs.

FIG. 6. Microscopic appearance of liver. The fibrous septae have completely disrupted the lobular architecture. The fatty change in the hepatocytes and pseudoductular proliferation is not apparent at this magnification (H & E, $\times 150$).



Discussion

With the history of vinyl chloride exposure, the presence of a filling defect in the liver and the histologic diagnosis of angiosarcoma in cheek and bladder biopsies, it stands to reason that the primary tumor was assumed to be in the liver. The gross and microscopic autopsy findings leave no doubt that the primary tumor was in the corpus cavernosum penis: the lining endothelial cells of the residual cavernous spaces showed premalignant changes and an *in situ* angiosarcoma progressing into an invasive sarcoma in and around that structure. The tumor in the bladder biopsy represents a direct extension and that in the cheek a metastasis. The primary tumor, evident locally as a nodule on the penis, was not noted by the patient until after it had produced metastases and was associated with priapism and dysuria. The tumor had infiltrated locally extensively and metastasized mainly to the lungs. In the liver, metastatic angiosarcoma was found only within the hemangiomas with sparing of the remaining cirrhotic liver. The brain lesion was grossly thought to be metastatic. Although microscopic sections showed only a hematoma with no tumor cells, it is believed to represent a metastatic focus with hemorrhage.

Could the angiosarcoma of the penis be related to vinyl chloride? Was the exposure of sufficient magnitude to have been significant etiologically? To elucidate these points one has to review briefly some of the pertinent data related to VC carcinogenesis.

The carcinogenic effects of VC were first recognized in experimental animals in 1971²⁰ and later confirmed on a larger scale by Maltoni and Lefemine.¹⁶ These authors noted that animals exposed to VC gas developed a variety of tumors, including sebaceous gland carcinomas, hepatic and extrahepatic angiosarcomas, angiomas, fibromas, neuroblastomas, lung adenomas, and hepatic and mammary carcinomas. The extrahepatic angiosarcomas developed in kidney, subcutaneous tissue, lips, lung, uterus, and intra-abdominally diffusely. The angiomas occurred in the liver, cecum, heart, subcutaneous tissue, and in the peritoneum.

In 1974, Creech and Johnson⁴ described the first case of angiosarcoma of the liver in a worker exposed to occupational vinyl chloride. Review of the death certificates and the institution of screening tests on all workers at the same plant revealed six additional cases.²¹ All seven instances occurred in employees of unit 62 where polyvinyl chloride (PVC) is produced

from VC. This part of the plastics industry is referred to as PVC production or polymerization and it is the section with the highest concentration of VC. It is to be distinguished from PVC processing wherein the already manufactured PVC plastic, in powder form, is mixed with stabilizers, colors, and other materials and processed into the different shapes (sheets, tubings cables, etc.) and consistency (rigid or flexible) in which it will be used.^{14,17} Vinyl chloride is the toxic gas with the carcinogenic effect whereas PVC is the inert plastic end product. Because most of the hepatic angiosarcomas related to VC exposure were observed in workers involved with PVC production, i.e., in the stage of polymerization of the toxic VC gas into the inert PVC resin, the impression was that PVC processing entails no toxic or carcinogenic risks, inasmuch as this step involves handling of inert PVC and does not utilize VC gas. According to Marsteller *et al.*,¹⁷ PVC processing is listed as harmless (erroneously) in many occupational bulletins and standard textbooks. However, during processing, the PVC is heated to temperatures of 100–300 C to give it the hardness and the shape required for the particular need. This results in the liberation of VC, trapped within the PVC during its polymerization, with escape of fumes, gases, and smoke into the surrounding atmosphere.^{14,17} Prior to 1974 the trapped VC monomer in the PVC averaged about 500–1000 ppm, sometimes reaching 7000 ppm.²² The presence of the characteristic sweet odor of VC in such areas indicates a high atmospheric concentration. This characteristic odor is also noted in closed storage areas of PVC sheets.¹⁰ Measurements made by Jaeger in factories in the Boston area detected 1/2–1 ppm of VC in a non-polymerization factory.¹¹ Schweitzer²³ noted a concentration of 1–2 ppm in air outside the B.F. Goodrich Plant in Louisville, Kentucky.

Workers in PVC processing show abnormalities of liver function tests, blood counts, platelet numbers, and in size of the spleen.¹⁴ Furthermore, of five cases of death from cancer in a group of 257 workers, two were not involved in PVC production, but were maintenance employees.²⁰ Data by Creech and Makk⁵ indicate that minimal exposures are associated with significant biochemical changes. These authors divided the workers in a PVC production plant into five categories representing decreasing areas of exposure to VC: (1) PVC production, representing the highest exposure; (2) other areas of production; (3) maintenance personnel for PVC production; (4) all other maintenance employees; (5) all other employees, including administration, plant protection, secretarial

services and the like, representing the population least exposed to VC. Their studies revealed that each of the five categories showed almost the same percentage of individuals having abnormal SMA-12 profiles, with elevation of alkaline phosphatase, total bilirubin, and serum glutamic oxalacetic transaminase. This indicated that workers far removed from the VC-PVC production area exhibit biochemical manifestations of altered liver function. However, no pre-employment tests are available for comparison. Although hepatic angiosarcomas related to VC-PVC production have occurred in workers in the immediate production area, recent observations show that remote exposures may also be significant. In an epidemiologic study of 26 cases of angiosarcoma of the liver in New York State, Brady *et al.*³ found 19 patients in whom no direct exposure to VC-PVC, arsenic, or thorium dioxide could be documented. Of these 19 patients, five lived nearer to VC processing or polymerization plants than did their matched controls, supporting an indirect mode of exposure. Thus, the hazards of VC are not limited to individuals with high exposures, but include those with low exposures as well; such low exposures would be incidental to working in PVC factories as nonproduction personnel or to living in the vicinity of such plants. Experimentally, animals exposed to low VC concentrations develop the same tumors as those exposed to high concentration but less frequently.^{13,16} In a hypothetical discussion of the relationship of carcinogen to frequency of induction of cancer, Peto²¹ showed that lowering the dose decreases the number of induced cases but does not eliminate the risk altogether. Nicholson¹⁹ states that two cases of angiosarcoma of the liver have occurred in nonproduction workers, one in a processing employee and the other in an accountant working in a PVC processing plant.

Experimentally there are other synergistic factors that affect the metabolic pathway of VC and the frequency of VC tumor induction.^{10,11,29,31} Radlike *et al.*²⁴ have shown that the latent period for the development of angiosarcoma in rats fed 5% ethanol and exposed to 600 ppm VC was 38 weeks compared with 58 weeks in rats not fed ethanol.

In the patient under discussion, the portal fibroblastic changes described to be typical for VC effect by Popper and Thomas²² and others^{9,13,23,28} were not observed. This could have been masked by the already existing cirrhotic changes. The endothelial changes of the hepatic sinusoidal cells, also considered typical for VC,²² were absent in the liver but similar changes were observed in the corpus cavernosum,

suggesting that these could be the result of VC effect. The lymphoid hyperplasia in the spleen described in VC-exposed individuals²² was conspicuously absent in this patient and not unexpectedly: the patient was receiving chemotherapy until his demise and hence lymphoid depletion is expected.

Although hepatic and extrahepatic angiosarcomas and hepatic and extrahepatic angiosarcomas have been induced experimentally by VC exposure, there is no indication at this time that the extremely common cavernous hemangioma of the liver in man is related to vinyl chloride exposure. Likewise, extrahepatic angiosarcomas related to VC exposure have not been reported in man. The role of VC in the tumorigenesis of the present case cannot be unequivocally proven, nor can it be easily dismissed.

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