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UNUSUAL OCCURRENCES AS CLUES TO CANCER ETIOLOGY

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Vinyl Chloride-induced Hepatic Angiosarcoma

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Abstract: In early 1974, an alert plant physician reported the occurrence of several cases of the otherwise rare hepatic angiosarcoma (HAS) at a single polyvinyl chloride (PVC) production facility in Louisville, Kentucky (U.S.A.). Upon further investigation, the relative risk for HAS at this plant appeared to be approximately 5,000, strongly indicating a causal relationship with some factor at the plant. Epidemiologic studies at this and other PVC polymerization plants identified vinyl chloride monomer (VCM) as the causative agent. Experimental studies reported in early 1974 confirmed VCM as a hepatic carcinogen capable of producing HAS and other tumors.

Follow-up epidemiologic studies revealed that: 1) HAS is the end stage of a progressive liver disease consisting of hepatocytic and sinusoidal cell hyperplasia, sinusoidal dilatation, and hepatic fibrosis; 2) over 100 cases of VCM-induced HAS have occurred worldwide; and 3) an increased risk of lung cancer has been reported in some cohort studies of PVC polymerization workers, although this outcome may be related to PVC dust or factors other than VCM.

A national study of HAS in the United States identified 3 other causes of HAS: Thorotrast, inorganic arsenic, and androgenic-anabolic steroids. Of 168 cases found to occur during 1964 through 1974, 42 cases (25%) were associated with the 4 known etiologic agents, while 126 cases (75%) were of unknown etiology.

In early 1974, John Creech and Maurice Johnson, Louisville plant physician and corporate medical director, respectively, of the B. F. Goodrich Company, reported the first cluster of hepatic angiosarcoma (HAS) cases in polyvinyl chloride (PVC) polymerization workers (*1*). Because of the rarity of this tumor in the general population (approximately 27/year in the United States at that time), this alert clinician noted the first case with interest, sensed concern when the second case appeared, and understood quickly that something important had happened when the third case in several years was diagnosed. In his words, it was like seeing several patients in a row with red, white, and blue spots on their nose—whatever the cause,

which was still uncertain, the problem was hard to miss. Indeed, a rough relative risk calculation very early in the investigation, based on the first 4 cases of hepatic angiosarcoma that had occurred, suggested a relative risk of approximately 5,000, an almost astronomical figure.

Within several weeks, investigations undertaken by the U.S. Public Health Service and others confirmed the diagnosis of HAS, showed that a non-malignant liver disease consisting of hepatic fibrosis and portal hypertension was also occurring among the same workers, and identified vinyl chloride monomer (VCM) as the cause (*2*). Dr. Creech, the alert physician, or surgeon in this case, had also noticed the strawberry-like appearance of the liver capsule, caused by irregular, patchy fibrosis, in the PVC polymerization workers, yet another clue that something unusual had happened.

The impact of this discovery on the public and the scientific community was dramatic. 1) A seemingly innocuous substance to which hundreds of thousands of workers had been exposed over a period of several decades was suddenly transformed into an apparently potent carcinogen producing a rapidly fatal (usually within 3 months) malignancy. 2) Convincing evidence of the carcinogenicity of VCM arrived so swiftly from both human epidemiologic and animal experimental data that emergency regulations were enacted with minimal delay. 3) The widespread uses of VCM in consumer products and its general release into the environment were abruptly stopped as the general public became fearful of potential long-term effects. 4) Scientific investigations proceeded rapidly to unravel the pathogenesis and other aspects of the disease.

Vinyl Chloride-induced Liver Disease and Angiosarcoma

There are three phases in PVC production: VCM production, PVC polymerization, and PVC fabrication. The largest number of workers is in the multitude of PVC fabricating plants, while historically exposures to VCM were dramatically higher (up to levels effectively producing anesthesia) in the PVC polymerization process. Occasional case reports, or small clusters of cases, in VCM production or PVC fabrication workers have been reported (*3*), but in the most recent review of occupational cases worldwide the great majority of cases are still in polymerization workers (*4*, *5*). Cases of HAS from environmental exposures have also been sporadically reported, but no sustained increase has yet been noted. The worldwide register of VCM-related cases maintained by Stafford and Bennett of ICI Chemicals (England) suggests that cases may have peaked in the mid to late 1970's (maximum of 11 HAS deaths/year) and may be declining by the mid 1980's, with 125 VCM-related HAS deaths worldwide by the end of 1986. Of 130 incident cases in this register, the U.S.A. had 36, West Germany 31, France 21, UK 12, Canada 10, and the remainder distributed mainly among other European countries. Two were reported from Japan.

Prior to 1974, VCM was treated by many as an almost inert substance; it was in fact used as the proverbial "inert substance" or propellant in aerosol cans (*e.g.*, hair spray). In retrospect, should we have anticipated this problem before its clinical

TABLE 1. Chronology of PVC Production and Health Risks

1942	Start of commercial PVC production in U.S.
1949	Earliest references to AOL and hepatic effects
1966–7	Detailed description of AOL
1960's	Reports of hepatomegaly
1971	First report of experimental carcinogenicity
1972–3	Detailed description of hepatotoxicity
1974	First cluster of HAS

appearance? Should the alert epidemiologist have seen this coming before the alert clinician diagnosed the cases?

VCM has actually caused 2 unusual diseases, HAS and acroosteolysis. Dr. Creech said that people will always remember him for the VCM/HAS association, but that was easy to spot. The more difficult was recognizing the VCM-induced cases of acroosteolysis, which he and his associates had described earlier. The classic appearance of acroosteolysis includes the following triad: Raynaud's phenomenon, scleroderma-like lesions on the hands and forearms, and lytic lesions of the terminal phalanges of the fingers (*6*). Occasionally, systemic manifestations have been observed (radiographic changes in the patella, sacroiliac joint, and terminal phalanges of the feet). More recently vascular changes in the digital arteries of the hand were found to accompany acroosteolysis. For a number of years it was thought that this disease was caused by external, manual contact with VCM/PVC, unrelated to systemic absorption and without systemic effects. In any event, early references to acroosteolysis and vague hepatic effects started over 20 years prior to 1974 (Table 1); and detailed descriptions of acroosteolysis and hepatotoxicity appeared in the late 1960's and early 1970's (*7*). Experimental carcinogenicity, albeit at very high doses, was reported in 1971, but in the skin, lungs, and bones of the rat, rather than in its liver (*8*).

Part of the answer for the delay in recognizing the dangers of vinyl chloride is that investigators underestimated the hepatotoxicity of VCM because it was a different type of hepatotoxin rather than the weak hepatotoxin it appeared to be. Detailed review of liver pathology in vinyl chloride workers by Popper *et al.* elucidated the progression of VCM-induced liver disease (*9*). The earliest stage consists of combined hyperplasia of both the hepatocytes and the sinusoidal cells, with sinusoidal dilatation and excess reticulin surrounding the sinusoids. The hyperplastic sinusoidal cells progress to increasing atypia and ultimately HAS; the sinusoidal dilatation may progress, occasionally to the extent of peliosis hepatis, and increased fibrous deposition leads to hepatic fibrosis and portal hypertension. In VCM-exposed workers hepatocellular carcinoma only rarely develops, but in experimental animals increasing hepatocyte atypia leading to hepatocellular carcinoma is more often seen. What is not seen in workers until late stages and then secondary to the above are the signs of hepatocellular injury measured by the standard liver function tests (Table 2). As a result, the silent progression of serious hepatotoxicity could have been misconstrued as less serious hepatotoxicity.

When the natural course of vinyl chloride-induced hepatotoxicity was fully

TABLE 2. VCM-induced *vs.* Classic Hepatotoxicity

VCM-induced hepatotoxicity:
relatively silent progression
not detected early by standard liver function tests
effective screening tests lacking
least common of all causes of hepatotoxicity
various parts of spectrum seen with VCM, Thorotrast, arsenic, and steroids (androgenic-anabolic and contraceptive)
Classic hepatotoxicity:
clinical signs and symptoms appear early
hepatic effects noted by enzyme changes, and other readily available laboratory tests
many clinical screening tests are used
wide array of hepatotoxins have been identified

described, there were actually no readily available, easily applied, or fully effective screening tests for detecting the early stages of the disease. A variety of approaches have been used, including liver scans, grey-scale ultrasonography, indocyanine green and bile acid clearances, *in vivo* capillary microscopy, and most simply the presence of persistent, multiple liver function test abnormalities.

Causal Agents of Hepatic Angiosarcoma

The discovery of VCM-induced HAS raised many new questions. For example, vinyl chloride was actually the third identified cause of HAS. German vintners in the 1940's and 1950's who had previously been heavily exposed to inorganic arsenical pesticides had been reported to have high rates of HAS. In addition, Thorotrast recipients in Portugal and other parts of the world (*e.g.*, Denmark, Germany, Japan) had been shown to have high rates of HAS, as well as hepatocellular carcinoma and cholangiocarcinoma. (Thorotrast is a colloidal suspension of thorium dioxide, used primarily in the late 1920's and 1930's for liver-spleen scans; it unfortunately remains in the liver and radioactively decays, releasing alpha particles, well beyond the life span of the recipient.) An intriguing question was whether this rare tumor with three known causal agents, but the bulk of cases still considered as idiopathic, had other identifiable etiologies.

A case-finding effort utilizing a variety of methods (Table 3) identified 168 cases in the U.S. during the years 1964–1974 (*10*). An interesting observation for those who study rare tumors was that in addition to the large number of cases of HAS not identified on the death certificate as HAS, 50% of cases reported on the death certificate as HAS turned out to be misdiagnosed, *i.e.*, false positives. HAS cases occurred at a younger age than other reported sarcomas of the liver, and even in the non-VCM, non-apparently occupational-induced cases a striking male preponderance was seen starting in the 30–39 year old age group. Extensive case investigations showed 7% related to VCM, 12% to Thorotrast, 4% to arsenic (mostly in the form of large doses of Fowler's Solution for the treatment of asthma or other conditions), and 4 cases (2%) associated with the use of androgenic-anabolic steroids. A matched death certificate case-control study did not reveal any other occupational factors associated with HAS; 75% of the cases were still considered idiopathic.

TABLE 3. HAS Case Solicitation Methods 1964–1974, U.S. (CDC)

A mailing to all U.S. pathologists
Separate mailings to State epidemiologists, tumor registries, and tumor referral centers
Death certificate review of Code 197.8
Files of Armed Forces Institute of Pathology (AFIP)
Studies of VCM/PVC plants
Medical journal announcements
Previously published cases

Detailed pathology review showed the pathologic appearance of cases for the different causal agents and for the idiopathic cases to be identical.

The relatively large number of Thorotrast-induced cases was surprising, since almost none had previously been reported in the U.S. The review of 26 U.S. cases showed that most had received the Thorotrast during carotid arteriography (54%) or hepatolienography (35%). Of interest was the apparent rising number of cases related to low-dose procedures occurring after prolonged latent periods (*11*). This suggested the possibility of a second, and larger, wave of VCM-induced cases among workers with lesser exposures at some time in the future; so far there is no evidence that this is happening.

Most intriguing were the 4 cases of HAS associated with androgenic-anabolic steroids (*12*). Limited FDA data on androgenic-anabolic steroid use suggested a very low probability of even 1 such case occurring. We postulated as a result that these cases served as a link between the type of hepatic disorders seen after VCM (or arsenic and Thorotrast) exposure and that seen after exposure to contraceptive and anabolic steroids. The common feature would be the precursor stages, usually not recognized by clinical laboratory tests and consisting of areas of hyperplasia of hepatocytes and sinusoidal cells and of sinusoidal dilatation. This common precursor lesion could then lead potentially to hepatic adenoma, carcinoma, peliosis, and angiosarcoma, with the frequency of these outcomes differing for each of the causal agents. The androgenic-anabolic steroids served as the link, because they had been reported to induce all of these outcomes, *i.e.*, adenoma, carcinoma, peliosis, and, with our report, HAS. Since our report in 1979, occasional cases of VCM-associated hepatocellular carcinoma (*13*) and oral contraceptive-associated peliosis and, rarely, HAS have been reported (*14*). The clinical overlap, however, is not impressive even if there is conceivably a single spectrum for these hepatic disorders.

PVC Polymerization Worker Cohort Studies

Another question that arose with the discovery of VCM-induced HAS was whether VCM-exposed workers would turn out to be similar to experimental animals in whom a variety of tumors, including non-hepatic angiosarcomas as well as tumors of other organs, develop. To answer this question a number of cohort studies of PVC polymerization workers have been conducted in different parts of the world. The National Institute of Occupational Safety and Health (NIOSH), Centers for Disease Control (CDC) conducted one such study in four PVC polymerization plants, following workers through 1973 (*15*).

Before describing this study, let me point out some of the limitations of our study, which apply to many of the other studies as well (*16*). 1) The PVC polymerization industry was born in the 1940's; most of the new workers started while still very young. Even in 1973, most had hardly lived into their 50's and, therefore, still had not passed through the age of peak cancer occurrence. It is perhaps too early to see the full spectrum of disease that may occur in these groups. 2) Most of the cohort studies have a relatively small number of deaths among workers with prolonged exposure and latency. This diminishes the ability to detect findings. 3) Most studies have had difficulty, due to lack of past measurements, in precisely quantifying past exposure to VCM, PVC dust, and other chemicals used in the polymerization process (*e.g.*, other monomers used with VCM to make copolymers).

In the NIOSH/CDC study a total of 1,294 workers with at least 5 years of exposure and 10 years since last exposure to VCM were studied. Thirty-five malignant neoplasms were observed with only 23.5 expected (SMR=149; $p<0.05$). No other statistically significant increases were seen. When all malignant neoplasms were subdivided by site, the only statistically significant increase was for biliary and liver cancer (7 Obs. *vs.* 0.6 Exp.; SMR=1,155; $p<0.01$). This increase was entirely due to HAS. Nonsignificant increases were seen for brain and CNS cancer (3 Obs. *vs.* 0.9 Exp.), respiratory system cancer (12 Obs. *vs.* 7.7 Exp.) and lymphatic and hematopoietic system cancer (4 Obs. *vs.* 2.5 Exp.). At a higher cut-off for latency ($\geq$15 years), brain and CNS cancer (3 Obs. *vs.* 0.6 Exp.) and respiratory system cancer (11 Obs. *vs.* 5.7 Exp.) became statistically significant at $p<0.05$.

In summary, the cohort studies are definitive with regard to increases in HAS; there are enough inconsistencies between studies and difficulties from small numbers that more investigation is needed before definitive conclusions are reached on the other tumor types mentioned. In our study (NIOSH/CDC) we became intrigued by the lung cancer increase for two reasons: 1) among the initial cases there appeared to be an altered histologic distribution with a greater than expected proportion of large cell undifferentiated cases, and 2) the lung cancer cases appeared to have worked more heavily in areas with exposure to PVC dust rather than VCM (*17*). Subsequently, cases of pneumoconiosis secondary to PVC dust exposure were reported. Nevertheless, this association is still tenuous, and needs further study in groups whose exposures to VCM, PVC dust, and other chemicals are clearly defined.

Toxicology

Toxicologic studies indicate that 1) HAS is linked to the amount of VCM metabolized rather than to the VCM concentration, 2) reactive intermediates, particularly the epoxide (chloroethylene oxide) formed by oxidative metabolism of the carbon/carbon double bond, are most likely the carcinogenic agent, 3) the short-lived metabolites are formed in the hepatocytes but are carcinogenic in the adjacent sinusoidal cells to which they migrate presumably because these cells have less detoxification potential, and 4) the reactive metabolites covalently bond to macromolecules such as DNA.

Another series of questions stimulated by the discovery of VCM-induced HAS

related to the carcinogenic potential of the array of chemicals structurally similar to VCM. Many experimental and epidemiologic studies have since been initiated to study compounds such as vinyl bromide, acrylonitrile, chloroprene, vinylidene chloride, trichloroethylene, and tetrachloroethylene.

Surveillance of Rare Tumors

To go back to my earlier question, what could the alert epidemiologist have done to anticipate or detect this problem before it was diagnosed by the alert clinician? First, surveillance of rare, or marker, tumors such as HAS (or mesothelioma) is most useful when the system covers the entire population—otherwise, important geographic patterns or clusters may be missed. Second, it is extremely time-consuming and requires too much effort to consider national reporting or surveillance individually for each of these marker tumors; it would be ideal to have a single system which would simultaneously collect data on a broad variety of rare, marker tumors. It is not inconceivable to think of such a system. CDC is currently instituting a pilot surveillance system to collect computerized pathologic information and other data from all cases seen by selected medical examiners—eventually this pilot system will be expanded to provide broad coverage of cases seen by medical examiners. Sooner or later, similar computerized data should probably exist for all autopsies and biopsies and surveillance of data from pathologists should be conceivable. Third, a systematic approach to analyzing epidemiologic and experimental data should identify rare tumors of interest to study. HAS, *e.g.*, would have been of interest even before the association with VCM was known for the following reasons: a) the higher male: female ratio and earlier age of appearance than that for all other hepatic sarcomas; b) the previously noted human causative agents (Thorotrast and arsenic); and c) the large number of experimental chemicals that induce HAS in animals. In summary, surveillance for rare, marker tumors might provide unique opportunities for epidemiologic and pathogenetic studies of occupational and environmental carcinogens. Setting up such a systematic or centralized approach will not be easy.

REFERENCES

1. Creech, J. L., Jr. and Johnson, M. N. Angiosarcoma of liver in the manufacture of polyvinyl chloride. J. Occup. Med., *16*: 150–151, 1974.
2. Thomas, L. B., Popper, H., Berk, P. D., Selikoff, I., and Falk, H. Vinyl chloride-induced liver disease—From idiopathic portal hypertension (Banti's syndrome) to angiosarcomas. N. Engl. J. Med., *292*: 17–22, 1975.
3. Maltoni, C., Clini, C., Vicini, F., and Masina, A. Two cases of liver angiosarcoma among polyvinyl chloride (PVC) extruders of an Italian factory producing PVC bags and other containers. Am. J. Ind. Med., *5*: 297–302, 1984.
4. Forman, D., Bennett, B., Stafford, J., and Doll, R. Exposure to vinyl chloride and angiosarcoma of the liver: A report of the register of cases. Br. J. Ind. Med., *42*: 750–753, 1985.
5. Bennett, B. Personal communication. Feb. 1987.
6. Wilson, R. H., McCormick, W. E., Tatum, C. F., and Creech, J. L. Occupational acroosteolysis—Report of 31 cases. JAMA, *201*: 577–581, 1967.

7. Lange, C. E., Juhe, S., Stein, G., and Veltman, G. So-called vinyl chloride disease: Is it an occupational systemic sclerosis? Int. Arch. Occup. Environ. Health, *32*: 1–32, 1974.
8. Viola, P. L., Bigotti, A., and Caputo, A. Oncogenic response of rat skin, lungs, and bones to vinyl chloride. Cancer Res., *31*: 516–522, 1971.
9. Popper, H., Thomas, L. B., Telles, N. C., Falk, H., and Selikoff, I. J. Development of hepatic angiosarcoma in man induced by vinyl chloride, Thorotrast, and arsenic. Am. J. Pathol., *92*: 349–376, 1978.
10. Falk, H., Herbert, J., Crowley, S., Ishak, K. J., Thomas, L. B., Popper, H., and Caldwell, G. G. Epidemiology of hepatic angiosarcoma in the United States, 1964–1974. Environ. Health Perspect., *41*: 107–113, 1981.
11. Falk, H., Telles, N. C., Ishak, K. G., Thomas, L. B., and Popper, H. Epidemiology of Thorotrast-induced hepatic angiosarcoma in the United States. Environ, Res., *18*: 65–73, 1979.
12. Falk, H., Thomas, L. B., Popper, H., and Ishak, K. G. Hepatic angiosarcoma associated with androgenic-anabolic steroids. Lancet, *ii*: 1120–1124, 1979.
13. Evans, D., Williams, W. J., and Kung, I. T. Angiosarcoma and hepatocellular carcinoma in vinyl chloride workers. Histopathology, *7*: 377–388, 1983.
14. Forbes, A., Portmann, B., Johnson, P., and Williams, R. Hepatic sarcomas in adults: A review of 25 cases. Gut, *28*: 668–674, 1987.
15. Waxweiler, R. J., Stringer, W., Wagoner, J. K., Jones, J., Falk, H., and Carter, C. Neoplastic risk among workers exposed to vinyl chloride. Ann. N.Y. Acad. Sci., *271*: 40–48, 1976.
16. Salmon, A. G. Vinyl chloride: The evidence for human carcinogenicity in different target organs. Br. J. Ind. Med., *42*: 73–74, 1985.
17. Waxweiler, R. J., Smith, A. H., Falk, H., and Tyroler, H. A. An epidemiologic investigation of an excess lung cancer risk in workers at a synthetic chemical plant. Environ. Health Perspect., *41*: 159–165, 1981.