

Angiosarcoma of the Liver: A Signal Lesion of Vinyl Chloride Exposure

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Vinyl chloride (VCM) induced angiosarcoma of the liver (ASL) is a rare vascular tumor which might be associated with a wide range of disease states. The possibility that this tumor might be a signal lesion is supported by mortality studies suggesting that cancers of the digestive, respiratory, neurological and lymphatic systems have occurred more often than expected in VCM workers. There is also evidence that certain non-neoplastic disorders, such as pneumoconiosis and excess fetal deaths, may be associated with this chemical.

It has been suggested that a gradual increase in the incidence of ASL might have occurred in recent years. This could be a reflection of the long latency period and/or the increased recognition of this entity. Several cases of ASL have occurred in people living in the vicinity of VCM plants. This raises the possibility that low-level exposure to this chemical over a long period might induce ASL.

Angiosarcoma of the liver (ASL) is an unusual vascular tumor (1) that has been associated with exposure to ThO₂ (2, 3), arsenic (4, 5) and most recently vinyl chloride (VCM) (6-8). The latter agent is a colorless gas used in the production of vinyl chloride resins and methyl chloroform (9, 10). Historically, VCM has been used as a refrigerant, as an extraction solvent for heat-sensitive materials, and in the production of chloroacetaldehyde, an intermediate in the synthesis of sulfa drugs (9, 10). Until 1974 VCM had been used as a propellant of pesticides and hairsprays (9, 10).

Epidemiologic and clinical studies have suggested that the frequency of angiosarcoma of the liver (ASL) might be increasing and the spectrum of disorders associated with VCM exposure might be greater than initially appreciated. This report reviews the literature concerning these observations and presents observations in New York State relating to them. We suggest that angiosarcoma of the liver might be an important signal lesion of vinyl chloride exposure. That is, despite its rarity, the occurrence of ASL might be indicative of a wide range of other more common disease states.

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Estimating the Frequency of Angiosarcoma of the Liver

In England and Wales there were 32 ASL adult deaths (males 21, females 11) from 1963 through 1973 (11). In the United States, a total of 68 deaths (males 46, females 22) due to this tumor were identified for the period 1966 through 1973 (12). It has been estimated that in the United States 25 to 30 cases (13) and in England and Wales three to four cases occur each year (11). Hammond and Selikoff (14) make reference to the fact that in 52,000 autopsies at Los Angeles County Hospital, only one case has been identified. The rarity of ASL would therefore appear to be established.

More recent reports have suggested that a gradual increase in the frequency of ASL might have occurred during the past two decades (15). This possibility gains some support from a registry based study in New York State (excluding New York City) which indicated that the annual incidence rate for patients (8 males and 8 females) whose ASL was diagnosed from 1970 through 1975 was 0.25 per million population (16). Table 1 lists the 24 cases of histologically confirmed ASL (13 males, 11 females) diagnosed among residents of New York State (excluding New York City) from

1970 through 1978. The annual incidence rate for this period was also 0.25, almost double the expected rate of 0.14 per million in the United States (8). There are several possible explanations for these observations. New York is more industrialized than many other states, and it is possible that the exposed cohort might be larger. Increased recognition and reporting of this entity might also be a factor. Finally, relatively few workers have been exposed for a long time to high levels of vinyl chloride monomer.

As Fox and Collier (17) point out, more than half of the people who have ever been exposed to VCM in the manufacture of PVC in Great Britain are currently employed in the industry; approximately 75% of men who have been employed in the industry have been employed for less than 10 years; only 8% have been employed for 20 years or longer; approximately half the persons who have been exposed to VCM have been intermittently exposed; and only 10% of those who have been constantly exposed have been exposed to high concentrations.

Thus it is possible that we are only beginning to see the full impact of industrial exposure to VCM. This suggestion is supported by the observation of Monson et al. (18) that the relative frequency of all cancers appears to be increasing with time in vinyl chloride workers.

Other factors must also be considered in examining the frequency of ASL in our society. Working conditions in the manufacture of PVC have undoubtedly been influenced since the early 1940s. This was largely due to the recognition after 1957 that exposure to high concentrations of VCM can cause acro-osteolysis (19) and Raynaud-like phenomena, and in the early 1970s that high concentrations of this chemical increase the risk of dying from ASL (6). A reasonable assumption is that earlier workers were probably exposed to higher concentrations of VCM than those who entered this industry during the last decade. Interestingly, it has recently been suggested that the age at diagnosis and latency period for ASL might be increasing (15). If verified, these preliminary observations

Table 1. Angiosarcoma of the liver (ASL) in residents of New York State (excluding New York City), 1970-1978.

Case	Age	Race ^a	Sex	Year of ASL diagnosis	Exposure history ^b	Metastatic site	Other tumors		
							Type	Site	Year of diagnosis
1	60	W	M	1970	Direct, VC	Adrenal, omentum	---		
2	45	W	F	1970	Possible, VC	Kidney, scalp, dura	---		
3	45	W	M	1970	---	Bone, adrenal	---		
4	18	B	F	1970	---	Spleen, lymph nodes	---		
5	55	W	F	1971	---	Spleen, omentum, adrenals, lymph nodes	---		
6	68	W	M	1971	---	---	Lymphosarcoma	Ileum	1955
7	4/12	W	F	1971	---	Lungs, adrenals, skin	---		
8	31	O	F	1972	Possible, VC	Heart, brain, lungs, adrenals	---		
9	77	W	M	1972	---	Spleen, marrow, lymph nodes	---		
10	64	W	F	1973	Direct, AS	---	Fibromyxoliposarcoma	Knee	1969
							Mesenchymoma	Liver	1973
11	47	W	M	1973	Direct, ThO ₂	Brain, lymph nodes	---		
12	62	W	F	1973	Possible, VC	Spleen	---		
13	63	W	M	1973	---	Spleen, pancreas, adrenals, brain, bone, lungs, lymph nodes	Transitional cell carcinoma	Bladder	1973
14	59	W	M	1973	---	---	---		
15	31	W	F	1974	Possible, VC	---	---		
16	45	W	M	1974	---	---	---		
17	62	W	F	1974	---	---	---		
18	65	W	M	1975	Direct, VC	---	---		
19	73	W	M	1975	---	---	---		
20	43	W	M	1977	---	Spleen, brain, lungs, duodenum	---		
21	54	W	F	1977	---	---	---		
22	68	W	M	1977	---	---	---		
23	83	W	F	1978	---	---	---		
24	46	W	M	1978	---	---	---		

^aW = White; B = black, O = oriental.

^bVC = vinyl chloride, PVC = poly(vinyl chloride), As = arsenic, ThO₂ = thorium dioxide; possible = lived within one mile of VC or PVC factory.

might be of great importance in evaluating the possibility that lower doses of VCM might be associated with ASL after a prolonged latency period.

Apart from the risk of ASL associated with industrial exposure to VCM, the possibility exists that nonoccupational exposure might also be associated with ASL. Block (20) has suggested that this disorder might result from chronic low level exposure to this chemical. Landrigan and Heath (21) found cases of ASL among workers at two poly(vinyl chloride) fabrication plants and in residents living nearby. A study in New York State (16) found that five individuals with ASL (but no apparent occupational exposure to VCM) lived in closer proximity to polymerization and fabrication plants than their matched controls. In a study of 10 patients with ASL in Wisconsin (22), one patient lived near a chemical company that made plastics and resins. These observations might be fortuitous and must be tempered by the preliminary evidence suggesting that no excess of ASL is found among PVC fabricators (11). At present there is no conclusive evidence associating this tumor with nonoccupational exposure to VCM. However, this issue and a closely related one—that chronic low dose exposure might be associated with an increased risk of ASL—require further evaluation. To fully appreciate the potential magnitude of this issue, one must consider both residential proximity to plants and other potential sources of public exposure. Estimates have been made that 4.6 million people live within five miles of United States monomer and polymer production facilities (23). During the years of uncontrolled emissions, it was calculated that the average exposure level to this population was approximately 17 PPB (23). Household use of aerosol products in enclosed spaces, even in short 30-sec bursts, could result in air concentrations of VCM as high as 400 ppm which can persist several hours after spraying (9, 10).

The Biologic Spectrum of Vinyl Chloride

Reference has already been made to the association between VCM and acro-osteolysis, Raynaud-like disorders and ASL. It is also clear that this agent can induce nonmalignant liver disease. In Russia a form of chronic hepatitis was found in approximately 25% of VCM workers (24). In addition, Thomas et al. (25) documented the occurrence of portal hypertension associated with hepatic fibrosis (Banti's syndrome) in a study of the hepatic tissues obtained from 20 workers with industrial exposure.

Of great concern is the growing evidence suggesting that the spectrum of disorders associated with VCM might include certain other neoplastic diseases, pneumoconiosis and possibly excess fetal loss. Several mortality studies have been conducted in recent years. Monson et al. (18) found an apparent excess of lung and brain cancers. A slight excess of digestive tract, lymphatic and hematopoietic tumors was also observed. A historical prospective mortality study of 8384 men who had at least one year of occupational exposure to vinyl chloride demonstrated that cancers of the digestive system (primarily ASL), respiratory system and brain and lymphomas occurred more often than expected in those members with the greatest estimated exposure (26). Similar results were observed by Waxweiler et al. (27) in a retrospective cohort study of workers from four plants engaged in the polymerization of vinyl chloride for at least 15 years. Although observed numbers in each of these studies are quite small, the strength of these observations lie in their consistency. In addition inhalation studies by Viola et al. (28), Maltoni (29) and Neplinger et al. (30) have demonstrated that this chemical induces adenomas and adenocarcinomas of the lung, neuroblastoma of the brain, lymphoma and various other tumors in a variety of animal species. Two other studies are notable for the different results obtained. A mortality study of over 4000 deaths among current and former employees of 17 PVC fabricators from 1964 through 1973 found an excess of cancers of the breast and urinary organs among white females (31). Fox and Collier (17) studied 7000 men who were at some time between 1940 and 1974 exposed to VCM and found no evidence to support the hypothesis that cancers other than those of the liver are associated with this agent.

Vinyl chloride inhalation or PVC might cause abnormalities of pulmonary function and chest x-rays (32, 33). Szende et al. (34) was the first to describe pneumoconiosis due to PVC. Although PVC dust appears to be the major offender, Lilis et al. (32) showed that inhalation of this agent induced less severe respiratory function abnormalities than simultaneous inhalation of VCM and PVC. In a more recent study of 1216 PVC production workers, 20 cases of pneumoconiosis were found. Duration of exposure was about 12 years, on the average, and never less than five years (35). This study also suggests that pulmonary changes are directly related to PVC dust, while VCM exposure alone fails to cause these changes (35).

Available evidence also suggests that VCM is mutagenic (36), and workers appear to have an excess of chromosomal aberrations in lymphocytes

when compared to nonexposed controls (37). Selikoff (38) found that fetal death rates among wives of VCM workers ranged from seven to 14 per 100 pregnancies. Infante et al. (39) conducted a case-control study of the pregnancy outcome among wives of workers exposed to VCM and found a significant excess of fetal loss in the exposed group. While suggestive, these observations require verification, particularly in view of the many factors known to influence pregnancy outcome.

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