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CHARACTERISTICS OF CASES OF
ANGIOSARCOMA OF THE LIVER AMONG
VINYL CHLORIDE WORKERS IN THE
UNITED STATES*

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The relationship between vinyl chloride exposure and human angiosarcoma of the liver (ASL) first received serious attention in December 1973 when a case of this rare tumor was diagnosed at autopsy in a vinyl chloride (VC) worker from the B.F. Goodrich chemical plant in Louisville, Kentucky. At that time, this case represented the third recognized among VC workers at this plant; prior cases had been diagnosed in May 1970 and March 1973. (1) While at first the possibility was considered that case occurrence might be unique to the Louisville facility, the subsequent detection of cases at three other plants has shown the problem to be industry-wide. Ten additional cases have subsequently been identified among other VC polymerization workers in the United States (Table 1). Workers at a total of four different plants have been involved.

The earliest case recorded to date occurred in 1961, the others being scattered over subsequent years, five in the past two years 1973-74. In several instances, the diagnosis of ASL was not specifically made until review of pathologic material during the early months of 1974. Death certificate diagnoses in such cases indicated "primary liver cancer," and in one instance merely "liver cirrhosis." The three most recent cases were diagnosed in the course of systematic medical screening, two at the Louisville plant in February 1974 and one at the South Charleston plant in May 1974. These three patients are the only ones of the thirteen who are currently alive.

All thirteen cases have occurred in white males. About half have been in their 40's with an age range from 36 to 60 years and a mean age at time of diagnosis of 48.2 years. Length of time between first VC work and diagnosis has ranged from 12 to 29 years (mean 20.3 years), mean total duration of VC work being 18.0 years.

Comparison of Observed and Expected Incidence

The reason an etiologic association between VC work and tumor could be so readily inferred on the basis initially of just three cases is because ASL is extraordinarily rare. Based on data from the National Cancer Institute's Third National Cancer Survey (1969-1971), expected annual incidence of this tumor is on the order of 0.0014 case per 100,000, or about 25-30 cases a year in the entire U.S. population. Estimating the total VC worker population past and present in the U.S. at roughly 20,000 persons (an estimate which may be too high), one can calculate that only about 0.03 case of this tumor might be expected in such a population over a decade. Since thirteen cases have thus far been identified (and it is not unreasonable to think that others may yet be found among other VC workers), one arrives at a risk ratio, (a ratio of observed to expected cases), of at least 400 to 1.

Needless to say, had the situation concerned a common tumor such as lung cancer, the picture would have been much less clear cut and would have required many more cases and much more elaborate epidemiologic manipulation to associate tumor with industrial VC exposure.

Clinical Features

Medical and epidemiologic data have been examined in detail for cases at the Louisville plant in particular. The remainder of this presentation summarizes these and other data concerning VC workers at that plant. For each Louisville case, all available medical records have been reviewed. Interviews have been held with each surviving patient and with close relatives of all deceased patients to obtain specific information concerning work history,

toxicologic exposures, and family history. Pathologic material, particularly sections of liver and of tumor, have been reviewed both by local pathologists in Louisville and by Dr. Louis Thomas at the National Cancer Institute and Dr. Hans Pepper at The Fogarty International Center.

In most cases the diagnosis of ASL was reached only with difficulty; three of the five fatal cases were not diagnosed until autopsy. In only one of the two remaining fatal cases was ASL diagnosed unequivocally prior to death (four months). In the other case, a diagnosis of "primary liver cancer" was made five months before death, but ASL was not clearly identified until recent review of autopsy material.

Presenting signs and symptoms varied widely and were relatively non-specific. Abdominal mass was a presenting feature in four cases, GI bleeding in two (diagnosed initially in each instance as peptic ulcer), fatigue and weakness in four, and noticeable weight loss in one. In one case no signs or symptoms referable to cancer or liver disease were present and the diagnosis was made only in the course of workup for another health problem.

Duration of symptoms prior to diagnosis ranged from one to eleven months for five of the six cases displaying symptoms. In the sixth case, symptoms related to liver disease antedated diagnosis of tumor by eight to ten years. In that particular case, a diagnosis of liver fibrosis was made in May 1965 following two episodes of gastrointestinal bleeding in the course of two years. A portocaval shunt operation was performed because of varices, splenomegaly and increased portal vein pressure. Six years later (May 1971) the patient was re-evaluated because of progressive symptoms, and at that time,

liver scans suggested the presence of tumor. ASL, however, was not unequivocally diagnosed until autopsy in March 1973.

At time of tumor diagnosis, physical findings among the seven cases varied considerable. In two cases, no abnormal findings at all were recorded. Three cases presented with liver enlargement, in each instance by splenomegaly. In a fourth case, splenomegaly alone was detected. One additional case presented with severe right upper quadrant tenderness in the absence of clear cut organomegaly. Laparotomy revealed free blood in the peritoneal cavity traced to what was tentatively diagnosed prior to death as "hemangioma of the dome of the liver."

Abnormalities of one or more liver function tests were present in every case at or around the time of diagnosis. In most instances, however, these abnormalities did not become clear-cut until the terminal phases of illness. SGOT values were at least mildly increased in all seven cases, total bilirubin in six and alkaline phosphatase in five. LDH was increased in four of six cases tested and BSP in one of two.

Diagnoses were made with the help of liver-spleen scanning in six cases and hepatic angiogram in two. Esophageal varices were demonstrated in two cases, one by x-ray, the other by endoscopy. Efforts at tissue diagnosis were made by open liver biopsy in all seven cases and by needle biopsy in three; autopsies were performed in four of the five deceased cases. Open liver biopsy provided a diagnosis of tumor in four cases while in the remaining three cases, diagnosis was made only at autopsy.

Recent review of pathologic material in all seven cases has shown evidence of portal fibrosis as well as of tumor. In addition, discrete subcapsular fibrotic areas were described at time of open liver biopsy in one of the two cases diagnosed in 1974. In two cases, angiosarcoma was present in tissues other than liver. In one the picture was that of local tumor spread.

Epidemiologic Features

The B.F. Goodrich Louisville plant employs about 1,200 persons of whom about 270 or 20 per cent are engaged in VC polymerization activities. The plant first began polyvinyl chloride (PVC) production in 1942 after pilot operations dating from 1937. The present polymerization work force size was reached in the late 1950's. All seven patients had worked in jobs directly related to VC polymerization, and in this capacity all seven can be assumed to have had direct exposure to vinyl chloride monomer (VCM). Initial involvement in VC work occurred from 12 to 28 years prior to tumor diagnosis (mean 20.0 years) (Table 1). Involvement was essentially continuous during these years (mean duration of VC work 17.0 years). Dates of initial industrial VC exposure ranged from 1944-45 soon after the plant began production (two cases), to as recently as 1957 and 1961. Ages at initial exposure ranged from 23 to 33 years (mean age 27.6 years).

Although the data are far from conclusive, they do suggest a possible dose-response relationship when one tries to compare intensity of VC exposure with latent period. Virtually everyone entering VC polymerization work at the Louisville plant starts as a "helper," a job which includes cleaning the interiors of polymerization vats and hence involves a maximum exposure to VCM

When duration of work as a "helper" (a rough measure of VC¹ exposure) is correlated with interval between first exposure and diagnosis, an inverse relationship is suggested. For three cases averaging only 5.3 months as "helpers," exposure-to-diagnosis intervals averaged 22.0 years; for the four remaining cases averaging 36.5 months as "helpers," this interval was 14.5 years.

No evidence was found that exposure to other potentially hepatotoxic materials outside the work place played any consistent role in these particular cases. Only two patients had a history of increased alcohol intake, and in one the increase was borderline. One man gave a history of exposure to arsenic insecticides for several years as a teenager. In none was there any suggestion of thorium dioxide exposure. Acroosteolysis, past or present, was not observed in any case.

Non-malignant Liver Disease

Because two of the three tumor cases which were initially recognized in Louisville had shown evidence of hepatic fibrosis antedating or coexisting with tumor, medical records at the Louisville plant were reviewed for cases of non-malignant liver disease. A total of four such cases have been identified to date, again all among VC workers.

The clinical and epidemiologic features of these four cases closely resemble those of the seven tumor cases (Table 2). All were white males, average age 46.5 years at time of first diagnosis. One was diagnosed in 1968, one in 1972, and two in 1973. VC work began on the average 20.8 years prior to diagnosis and in every instance was continuous. One patient, however, a 26-year-

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old man, had worked at the plant for only six years. Duration of illness prior to diagnosis ranged from 0 to 7 months. While three of the four patients presented with significant splenomegaly (one with hepatomegaly in addition), in one case physical examination was entirely negative. A variety of liver function tests showed abnormalities although none were severe and no consistent patterns were evident. In two cases esophageal varices were demonstrated, and in both instances, splenorenal shunt operations were performed. All three patients with splenomegaly underwent splenectomy.

Open liver biopsies were performed in all four cases. In each instance, a picture of portal fibrosis was seen accompanied by the observation in three cases of discrete nodules of subcapsular fibrosis. The latter feature was indistinguishable pathologically from the subcapsular lesions observed in one of the seven tumor cases.

Discussion

In light of recent animal experiments (2) and of clinical observations reported in European VC workers (3), it seems likely that exposure to VCM in the course of VC polymerization work is responsible for malignant and non-malignant liver disease in these cases. Epidemiologic features further suggest that either prolonged exposure and/or a long interval from initial exposure is required before liver disease becomes apparent. While the length of time involved seems quite variable (6 to 29 years), in all but one case the interval was twelve years or longer.

We have no assurance, however, that the actual latency required for development of liver disease (as opposed to latency in relation to clinical recognition) may not be considerably shorter. Unfortunately, if one can judge by the clinical features of the Louisville cases, manifestations of liver disease are quite variable, and in most instances were not detected until the process of hepatic fibrosis was so far advanced that splenomegaly and increased portal pressure had already been produced. Furthermore, if one envisions angiosarcoma as a late manifestation of the same pathologic process, then it seems even more likely that clinical detection of liver disease lags considerably behind actual disease onset. At present, therefore, a major concern is to develop more sensitive means for detecting liver disease, not in its late malignant phase (if in fact a single pathologic spectrum is involved), but in the early stages when fibrotic reaction first sets in.

Eventually, non-malignant liver disease, not ASL, may prove to be the most prominent disease problem associated with VCM exposure in terms of numbers of persons affected. One must also consider the possibility, however, that VCM may produce angiosarcoma at sites other than liver or that tumors of other kinds may also be induced. At present, animal experiments suggest that a wide spectrum of tumors may be involved (1), although as yet there is no clear human evidence to support the concept. In addition, no human cases of liver disease, whether fibrosis or frank angiosarcoma, have yet been strongly linked to VC exposure outside the industrial setting. While this may mean that risk of disease is greatly reduced or even non-existent at very low levels of

VC exposure, it is obviously too early to draw any conclusions. In view of past experience with other oncogenic chemicals, it will be prudent, until much more data have been assembled, to view any exposure to VCM as potentially harmful.

SUMMARY

A total of 13 cases of ASL have been documented to date among VC workers in four different plants in the U.S. In this particular industrial population, this number of cases represents at least a 400-fold increase over expected incidence for this extremely rare tumor. The first case occurred in 1961. Average age at diagnosis is 48.2 years. Average length of time between initial VC work and diagnosis has been 20.3 years.

A detailed review of seven cases associated with one plant revealed that clinical features varied from little or no overt illness prior to diagnosis to advanced liver disease with portal hypertension and marked splenomegaly. Portal fibrosis was present in all seven of these ASL cases as well as in four additional cases with non-malignant liver disease among VC workers at the same plant. These findings suggest that exposure to VCM in industrial settings can produce hepatic fibrosis with angiosarcoma as a late manifestation. Conventional liver function tests may not be sensitive indicators of such liver impairment, at least in its early stages.

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Table 1. Cases of Angiosarcoma of the liver (ASL)
among vinyl chloride workers in the United States

Name of Company	Location of plant	Age at diagnosis, race, sex	Month and year of			Number of years between first vinyl chloride work and ASL diagnosis	Total years in vinyl chloride work
			first vinyl chloride work	diagnosis	death		
D.F. Goodrich	Louisville, Ky.	52 WM	6-44	4-64	4-64	19	18
"	"	43 WM	7-52	8-67	1-68	15	15
"	"	36 WM	11-55	5-70	9-71	14	13
"	"	49 WM	12-48	3-73	3-73	24	16
"	"	58 WM	11-45	12-73	12-73	28	28
"	"	45 WM	1-62	2-74	---	12	12
"	"	43 WM	5-45	2-74	---	28	17
Goodyear	Niagara Falls, N.Y.	40 WM	10-46	4-61	8-61	14	14
"	"	54 WM	6-51	5-68	5-68	16	16
"	"	60 WM	10-46	3-70	3-70	23	23
Union Carbide	S. Charleston, W. Va.	45 WM	8-44	3-68	3-68	23	18
"	"	52 WM	8-44	4-74	---	29	29
Firestone	Pottstown, Pa.	50 WM	9-49	5-69	5-69	19	15

Table 2. Cases of non-malignant liver disease among
Louisville vinyl chloride workers

Age at diagnosis, years	Month and year of diagnosis	Number of years between first VC work and diagnosis	Clinical features			Pathologic features	
			<u>enlarged spleen</u>	<u>liver</u>	<u>abnormal liver function tests*</u>	<u>Portal fibrosis</u>	<u>Subcapsular fibrosis</u>
48 WM	12-63	24	+	-	AP, BSP, SGOT	+	+
28 WM	1-72	6	+	+	TB, SGOT	+	+
58 WM	9-73	24	+	-	TB, AP	+	-
56 WM	9-73	29	-	-	TB, LDH, SGOT	+	+

*AP = alkaline phosphatase

BSP = bromsulphalein clearance

SGOT = serum glutamic oxaloacetic transaminase

TB = total bilirubin

LDH = lactic dehydrogenase

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