Ten Cases of Angiosarcoma of the Liver in Shawinigan, Quebec

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Ten cases of angiosarcoma of the liver have been diagnosed in Shawinigan, Quebec since 1955. All have occurred in men who worked in a vinyl chloride polymerizing plant. Cigarettes and alcohol do not seem to be associated with this tumor. The amount of vinyl chloride to which these people were exposed, according to information obtained through questionnaires, appears elevated. Angiosarcoma of the liver is accompanied by a fibrosis of the liver which may precede its appearance. In describing the Canadian cases of angiosarcoma, this study attempts to shed more light upon the causal relationship between vinyl chloride monomer and angiosarcoma of the liver and thus to provide some clues to understanding the pathogenesis of this disease.

In January 1974, three cases of angiosarcoma of the liver were discovered among workers of a chemical plant.[1] This finding appeared abnormal and the agent suspected of being responsible for the disease was identified as vinyl chloride monomer (VCM). Since then, many reports on the occurrence of this cancer among vinyl chloride workers have appeared around the world[2-5] and the United States Occupational Safety and Health Administration has enacted a new threshold limit value for concentration of this chemical in the air of the working environment.[6]

Ten cases of angiosarcoma of the liver were diagnosed among workers of a vinyl chloride polymerizing plant in Shawinigan, Quebec. This is the largest number of cases ever to take place in a single plant. The present study describes occupational history, drinking and smoking habits and some histological features of these Canadian cases. Data on some of these Canadian cases jointly with cases of angiosarcoma from the United States have already been described in another article by one of the authors.[7] Since more accurate and complete information was retrieved on the Canadian cases, it is being presented separately in the present article.

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Methods

Case Finding. — A search of cases of angiosarcoma of the liver beginning as far back as 1955 and extending over two decades was carried out by scrutinizing records at the regional hospital in the Shawinigan vicinity. All cases of primary tumors of the liver were collected and the histological material (slides, biopsy reports, autopsy reports) were reviewed for the presence of angiosarcoma. To confirm the diagnosis of angiosarcoma in the ten cases were submitted to consultants from the United States familiar with this disease.

Occupational History. — The questionnaires used to obtain a detailed occupational history of each case called for information concerning past and present residence, medical history, smoking and drinking habits along with past occupations and employers in chronological order. The answers to most questionnaires were given by spouses of the men who died from the disease. In one instance, however, the answers were given by the sister and brother-in-law and in another by the worker himself. Two former co-workers of the men who died of an angiosarcoma of the liver confirmed and completed the information obtained through the families.

Plant Description. — The Shawinigan vinyl chloride plant started operating in 1943. At that time it produced and polymerized vinyl chloride monomer. Later in the 1950s it stopped producing VCM and kept operating the polymerization unit. The workforce varied from 100 to 350 workers. At the moment it comprises 250 men. Production of PVC has fluctuated with time. Present production is estimated at 50 million pounds annually. Exposure to VCM in the working atmosphere, though not documented, is believed to have been very high in the past. Sharp improvement has taken place in recent years and it is estimated at less than 5 ppm at the moment.

Results

Table 1 shows the age at death, the smoking habits and alcohol consumption for the ten cases of angiosarcoma of the liver diagnosed in the Shawinigan region over the last two decades. All

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OLI 7016

Table 1 — Sex, Age at Death, Smoking Habits and Alcohol Consumption of Ten Cases of Angiosarcoma of the Liver in a Canadian Community

Case No	Sex	Age at Death	Smoking Habits			Estimation of Cigarette Consumption		Alcohol Consumption	
			Smoker	Exsmoker	Nonsmoker	No of Cigarettes per Day	No of Years Smoked	No Bottles of Beer Per Week	No of Years Drinking
1	male	41	x			20	22	4	4
2	male	43	x			12	27	4	25
3	male	42				—	—	4	25
4	male	48	x			10	30	—	—
5	male	56	x			10	42	4	40
6	male	51	x			40	33	4	5
7	male	52	x			25	34	24	27
8	male	53	x			25	35	28	29
9	male	53	x			20	35	4	10
10	male	61		x		25	43	—	—
$\bar{x}$		50.5							

were males, the age at death ranging from 41 to 61 years with an average of 50.5 years.

It is somewhat doubtful that smoking has much to do with this type of tumor. Out of the ten cases, one man was a nonsmoker, five were moderate smokers, smoking an average of 20 cigarettes or less per day, and the remaining four smoked one pack of cigarettes per day or more. The tumor appeared earlier in the moderate and nonsmokers ($\bar{x}$ age 47 years) than in the heavy smokers ($\bar{x}$ 54 years).

The men who developed an angiosarcoma of the liver were very light drinkers. Only two men out of ten drank more than one bottle of beer per day. None of the ten men drank wine or liquor regularly. As with cigarette smoking, drinking does not appear to be associated with an angiosarcoma of the liver in vinyl chloride workers.

Past diseases of the liver may also be ruled out as potentiating the development of angiosarcoma of the liver since the medical history of the ten cases showed no previous liver diseases nor hepatic troubles.

Table 2 shows the length of time the men were exposed to vinyl chloride either by working in the polymerization unit or by being directly exposed to vinyl chloride. It also shows the occupations they performed and whether they worked overtime. They worked for periods ranging from 11 to 29 years in the plant with an average of 21 years and 4 months. Direct exposure to vinyl chloride monomer was obviously shorter, ranging from 5 years 3 months to 26 years with an average of 16 years 10 months.

From the job descriptions, it can be seen that most of the men worked either as operators or maintenance workers, or both. Seven men worked as reactor cleaners — an operation which seems to have been the worst in exposing workers to vinyl chloride monomer. One woman said of her husband's exposure, "He went down into the autoclaves many times. Once they had to take him out unconscious."

It is difficult to get a fair idea of the amount of vinyl chloride monomer to which these people were exposed. Many spouses (six out of ten) insisted upon mentioning that their husbands worked overtime.

As shown in Table 3, the time elapsed between the last exposure to vinyl chloride monomer and the diagnosis of the disease ranges from 11 years to 28 years with an average of 20.5 years. This concurs with previous findings that an angiosarcoma of the liver can develop after a minimum exposure of four years but that actual manifestation does not occur for at least ten years.[7]

Residence history revealed that all workers lived within a two-mile radius of the VCM plant since the beginning of their employment at that plant. However, no particular pattern in the residential history could be identified that could lead to finding environmental factors common to everyone.

Past occupational history showed that all these workers spent

Table 2. — Occupational History of Ten Cases of Angiosarcoma of the Liver in a Canadian Community.

Case No.	Time Exposed: Worked in the Plant		Worked in Contact with VC		Occupation in Contact with Vinyl Chloride	Worked Overtime
	Years	Months	Years	Months		
1	11		11		Reactor cleaner, operator polymerization unit	
2	14	2	14	2	Maintenance operator, millwright, pipe fitter	yes
3	20	5	20	5	Operator, foreman	yes
4	22		22		Reactor cleaner, operator, foreman, water cooling unit	yes
5	17	5	5	3	Reactor cleaner, water cooling unit	yes
6	25	4	23	4	Reactor cleaner, maintenance, millwright, reagor	yes
7	26	6	25	6	Reactor cleaner, operator, VCM fabrication and polymerization unit, machine shop	
8	25	8	5	8	Reactor cleaner, maintenance, machine shop	
9	29		26		Furnace operator, pipe fitter, maintenance	yes
10	18	10	14	9	Reactor furnace operator, packaging	
$\bar{x}$	21	4	16	10		

OLI 7017

Table 3. — First Exposure, Year of Diagnosis, Survival Time, Type of Tumor, Accompanying Benign Liver Lesions and Means of Diagnosis of Ten Cases of Angiosarcoma of the Liver in a Canadian Community

Case No.	First Exposure	Disease Found	Survived Months	Type of Tumor: Sinusoidal	Nodulo papillar	Sarcomatous	Cavernous	Other Lesions Accompanying: Thickening of Liver Capsule	Portal Fibrosis	Sclerosis of the Wall of Portal Vein	Perisinusoidal Fibrosis	Dilatation of Sinusoids	Proliferation of Sinusoidal Cells	Reactional Liver Cells	Means of Diagnosis
1	1344	1955	2		x		x	x				x	x		Biopsy
2	1943	1957	1	x	x	x	x	x	x	x	x	x	x	x	Autopsy
3	1941	1962	4				x			x		x	x	x	Autopsy
4	1945	1967	8	x	x		x	x	x	x	x	x	x	x	Biopsy
5	1944	1968	3	Not enough non-tumoral material to appreciate			x								Biopsy
6	1947	1971	2				x	x	x	x	x	x	x	x	Autopsy
7	1946	1972	7	x		x	x	x	x	x	x	x	x	x	Biopsy
8	1961	1973	8				x		x	x	x	x	x	x	Autopsy
9	1946	1974	2				x	x	x	x	x	x	x	x	Biopsy
10	1953	1976	alive 4			x	x	x	x	x	x	x	x	x	Biopsy
$\bar{x}$			4.1												

the greater part of their active lives working for the same employer. The longest period anyone worked outside the plant was four years.

Once the tumor is diagnosed, the survival period is very short. In the present study, the longest survival period was eight months, the average 4.1 months.

It must be pointed out that angiosarcoma is not the only liver pathology found in vinyl chloride monomer workers.[3] There are two types of benign lesions — sclerosis and cellular transformation. Sclerosis manifests itself by a thickening of the capsule of the liver, a portal fibrosis with proliferation of the bile ducts and lymphocytic infiltrate, a sclerosis of the wall of the portal vein and centrolobular veins and a perisinusoidal fibrosis with sinusoid dilatation. Cellular transformation shows a sinusoidal cell proliferation with atypic, dysplasic and reactional liver cells. The tumor itself is a malignant angiosarcoma type tumor appearing in four definite histological patterns, a cavernous pattern, a sinusoidal pattern, a nodulo-papillar pattern and a sarcomatous pattern. In our experience, the cavernous pattern is the most constant and frequent one (Table 3).

Discussion

The present study is an epidemiological and a histological description of the ten cases of angiosarcoma of the liver found in the region of Shawinigan, Quebec. Although the selection of cases was made from hospital records, it happened that all were men who worked in the same factory — a vinyl chloride polymerization plant. This type of tumor being very rare, a causal relationship between the exposure to vinyl chloride and the development of an angiosarcoma of the liver is established.

The present study reveals that the exposure necessary to develop the cancer must be relatively high. Cleaning reactors and operating production units were occupations carried out in an environment with a high concentration of vinyl chloride monomer. Furthermore, it is possible that in the 1940's, the men worked more than 40 hours a week. To this, one must add overtime work, another contributing factor. It will be necessary to assess with as much accuracy as possible the exposure of these people to vinyl chloride monomer to discover a dose-response relationship between the chemical and the disease.

It seems that benign non-tumoral reactions are the first response of the liver to the chemical. Eventually they give way to malignant transformations.[3] Obviously more research will be necessary to discover whether the benign and malignant lesions are two steps of a unique phenomenon or [illegible].

References

1. Creech JL and Johnson MN. Angiosarcoma of the liver in the manufacture of polyvinyl chloride. J Occup Med 16: 150-151, 1974.
2. Du Plan J, Harris DS, Angiosarcoma [illegible]
3. Black A, Bruyn I, Angiosarcoma [illegible] 229: 1367-1368, 1974.
4. Rösch, Savage, Angiosarcoma [illegible] 331: 555-12 déc. 1975.
5. Centers for Disease Control. Angiosarcoma [illegible] 25 8: 342-343, 1976.
6. Department of Labor. Occupational Exposure [illegible] 39 [illegible] Oct. 4, 1974.
7. Maiseiu, Deforme, Angiosarcoma in vinyl chloride workers 37 [illegible]
8. Laszlo M, Deforme, Hepatic angiosarcoma in vinyl chloride workers 37 [illegible]
9. Deforme F and Maiseiu, Angiosarcoma [illegible] cirrhose cardiaque prolongée [illegible] Sem. des Hôp. 104 [illegible]
10. Deforme F and Maiseiu, Angiosarcoma [illegible] cirrhose cardiaque prolongée [illegible] Sem. des Hôp. 119 [illegible]
11. Thomas LB and Popper H. Pathology [illegible] among vinyl chloride-polyvinyl [illegible] 246: 268-277, 1975.
12. Thomas LB, Popper H, [illegible] New Engl J Med 292: 17-22, 1975.
13. Gedigk P, Maller R, et al. Morphology [illegible] vinyl chloride production workers. A report on 37 [illegible] 246: 278-285, 1975.
14. McDonald RB. Primary carcinoma of the [illegible] 99: 26-279, 1957.
15. Popper H and Thomas LB. Alterations of liver [illegible] workers exposed to vinyl chloride. Ann NY Acad Sci 246: [illegible]

OLI 7018