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Angiographic and Radionuclide Characteristics of Hepatic Angiosarcoma Found in Vinyl Chloride Workers¹

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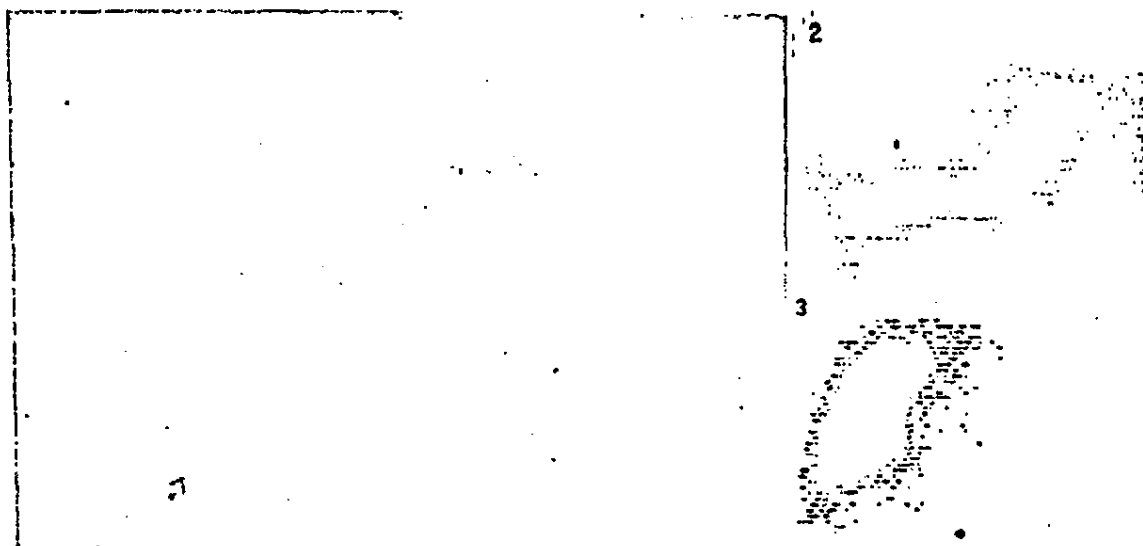
Hepatic angiosarcoma, recently discovered in a large series of vinyl chloride workers, demonstrates characteristic angiographic and radionuclide changes. Tumors exhibiting central hypovascularity with puddling are usually surrounded by a peripheral stain. A negative peripheral defect is demonstrated on hepatic scan. Healing hepatic infarction secondary to wedged hepatic venography creates a false-positive lesion on angiography similar to angiosarcoma. Splenomegaly and systemic venous hypertension develop in a number of these patients.

INDEX TERMS: Liver, infarction • Liver neoplasms, angiography • Liver Neoplasms, radionuclide diagnosis • Sarcoma • Spleen, hypertrophy • Vinyl Chloride

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SINCE 1964, 8 cases of hepatic angiosarcoma have been found in Louisville, Ky. among workers associated with the polymerization of vinyl chloride, a material essential to the production of plastics. In 1973, Creech and Johnson (1) reported the first case of angiosarcoma of the liver in vinyl chloride workers. Sub-

sequent investigation of records of employees from two vinyl chloride plants in Kentucky who died between 1947 and 1973 revealed an elevenfold higher incidence of death from cancer of the liver and biliary tract than expected when compared to the same age group and sex (14) of other workers in the country. Other nonma-



1. Case I. Hepatic arteriogram, 8 seconds. A peripheral stain surrounds a large tumor within the dome of the right hepatic lobe (central hypovascularity is present containing large areas of contrast puddling). Changes of periportal hepatitis are present throughout most of the lobe.

2. Case I. ^{99m}Tc-sulfur colloid liver-spleen scan, anterior view, 1 September 1972. A bilobular mass is present within the right lobe and the left lobe of the liver.

3. Case II. ¹⁹⁷Au liver scan, anterior view. A large defect is present within the entire left lobe and medial right lobe.

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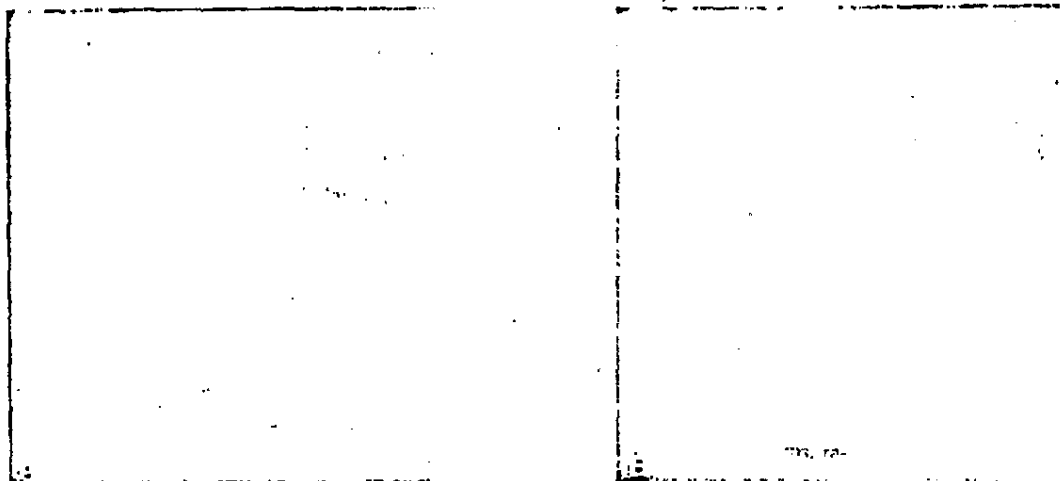


Fig. 4. CASE III. Hepatic arteriogram. A. Arterial phase: 6 seconds. The hepatic artery is of normal size. Circumferential hypervascularity is present. The intrahepatic arteries are small and tortuous suggesting cirrhosis. B. Arterial hepatogram phase: 10 seconds. Note circumferential tumor stain and puddling of contrast agent with a central area of hypovascularity. The stain persisted for 34 seconds. [Reproduced with permission of JAMA (9)]

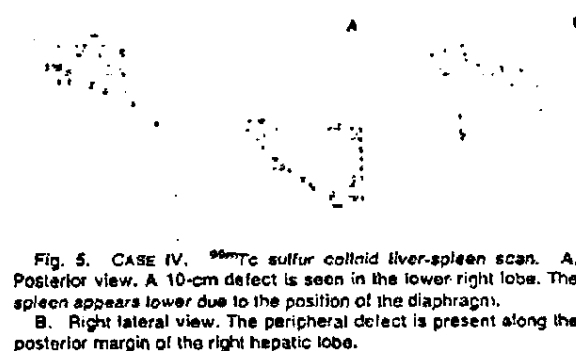


Fig. 5. CASE IV. ^{99m}Tc sulfur colloid liver-spleen scan. A. Posterior view. A 10-cm defect is seen in the lower right lobe. The spleen appears lower due to the position of the diaphragm. B. Right lateral view. The peripheral defect is present along the posterior margin of the right hepatic lobe.

- Malignant diseases of the liver and spleen have recently been described (4, 29) and most of these changes have been detected through a systematic screening program (2, 9).

All 1,180 workers of a Louisville vinyl chloride polymerization plant have had liver scans; 50 of these individuals were subsequently followed with hepatic and splenic angiography, transjugular hepatic venography, venous pressure studies and liver biopsies. Four men were found to have hepatic angiosarcoma.

We will describe the angiographic and radionuclide characteristics of hepatic angiosarcoma found in these workers.

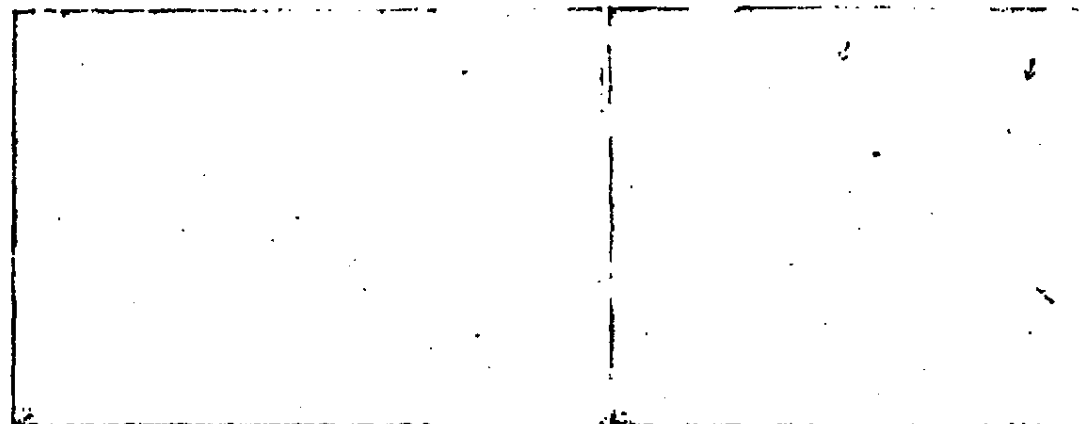


Fig. 6. CASE IV. Hepatic angiogram. A. Arterial phase: at 4 seconds, there is no evidence of neovascularity. Minimal displacement of intrahepatic arterial branches of the right lobe is seen. A stricture is suggested in one branch (arrow), above the area of tumor. B. Venous phase: at 14 seconds the peripheral stain is identified (arrows) lasting through the entire phase. Scattered areas of pooling are also present. Note central hypovascularity.

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MATERIALS AND METHODS

The radiologic screening procedure for vinyl chloride workers consists of a routine 6 ft. posterior-anterior and left lateral chest x ray, a ^{99m}Tc -sulfur colloid liver-spleen scan, panangiography of the liver and spleen as described by Viamonte *et al.* (30), transjugular hepatic biopsy as described by Hanafee (6) and Rosch (27), and portal pressures and venograms.

If the liver-spleen scan is abnormal, or if there are persistent abnormal biochemical liver studies, panangiography is done, including a selective hepatic and celiac angiogram. The spleen is included in the celiac injection. A superior mesenteric angiogram is obtained if there is an accessory or replaced right hepatic artery or if the portal vein is not visualized. In selective hepatic angiography, films are obtained at 2/second for 3 seconds, 1/second for 4 seconds, and 1 film every 4 seconds up to 35 seconds. Initially, the hepatic pressure studies and venography were performed via the femoral route. Later, the transjugular route was used in order to include a liver biopsy. Three to five biopsies were obtained from each patient.

Venous pressures are obtained with use of the Menon-Grantbatch² monitor. An average of three pressures are recorded within the inferior vena cava, the right atrium, and the free and wedged hepatic vein positions.

The Cook³ transjugular biopsy needle and catheter have been modified; both were lengthened 1.5 cm because the catheter could not be properly wedged for the necessary pressure data in several patients, and the Teflon catheter was enlarged to 10 Fr to accommodate a 14-gauge biopsy needle to obtain better specimens. Also, the bevel of the needle was reversed to the lesser curve side to allow entrance into more sharply angled hepatic veins and better penetration of the superolateral wall of the right hepatic vein.

CASE REPORTS

CASE I. This 40-year-old man had worked as a chemical operator in vinyl chloride polymerization for 16 years. Since January 1964, he has had recurrent hematemesis and melena. Initial upper gastrointestinal (G.I.) studies were normal. In May 1965, hepatosplenomegaly, esophageal varices, thrombocytopenia, and internal and external hemorrhoids developed. A portacaval shunt was performed and the splenoportogram was normal except for a possible 3-cm defect within the right hepatic lobe. Portal vein pressure measured 25 mm Hg. In October 1970, he underwent surgery for cholelithiasis and the liver biopsy revealed bile duct proliferation, portal fibrosis and Kupffer cell hyperplasia. In May 1971, because of continued symptomaticity, a hepatic angiogram was obtained which revealed a malignant neoplasm (Fig. 1 and TABLE I). Biopsy suggested anaplastic hepatoma. In September 1972 following chemotherapy, a ^{99m}Tc -sulfur colloid liver scan demonstrated a bilobular defect

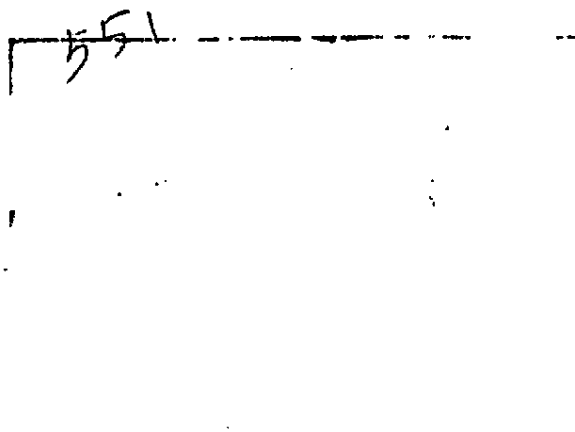


Fig. 7. CASE IV. Splenic arteriogram, 10 seconds. There are two pie-shaped defects on the lateral and inferolateral aspect of the spleen. The spleen is not enlarged.

within the liver (Fig. 2). The patient died in March 1973. Postmortem finding was hepatic angiosarcoma. Earlier liver biopsies also demonstrated subcapsular and periportal fibrosis and Kupffer cell hyperplasia.

CASE II. This 37-year-old man had worked as a chemical operator in vinyl chloride polymerization for 12 years. In September 1966, he presented with internal and external hemorrhoids which were then excised. In January 1970, painless melena occurred for the first time. Several upper G.I. studies were normal. In May 1970, melena recurred and he was found to have hepatosplenomegaly, esophageal varices and thrombocytopenia. An ^{199}Au liver scan revealed a large lesion replacing the left lobe with extension into the right lobe (Fig. 3). Exploratory laparotomy revealed a markedly thickened liver capsule and hepatic angiosarcoma. In spite of ^{60}Co radiation and chemotherapy, massive ascites and liver failure developed and he died in September 1971.

CASE III. This 42-year-old man had worked as a chemical operator in vinyl chloride polymerization for approximately 20 years. In August 1967, he had a sympathectomy for treatment of Burger's disease of the left lower extremity. A femoral angiogram revealed corrugation of the anterior and peroneal arteries. He had also been hospitalized twice for alcoholism.

In February 1974, through the vinyl chloride screening program (9), a ^{99m}Tc -sulfur colloid liver spleen scan detected a superficial 4-cm lesion on the anterior inferior surface of the right hepatic lobe. The spleen was normal. An ^{125}I rose bengal liver scan demonstrated the same defect. Hepatic angiography confirmed a lesion corresponding to the liver scan defect (Fig. 4). The tumor margin was hypervascular and contained a hypovascular center. Puddling and peripheral stain persisted from the early arterial to the late venous phase (TABLE I). Splenic and portal veins were normal. Venous pressures obtained were: wedged hepatic vein (WHV) 15 mm Hg and free hepatic vein (FHV) 10 mm Hg. The free hepatic venogram was normal. The wedged hepatic venogram demonstrated portal vein reflux with hepatopetal flow. On exploratory laparotomy, the tumor could be seen on the surface of the liver. Biopsy revealed angiosarcoma with extensive necrosis, portal fibrosis and moderate cirrhosis. In spite of chemotherapy, there was progressive enlargement of the tumor, massive ascites and liver failure. The patient died in March 1975. Autopsy revealed angiosarcoma, multifocal throughout the liver, as well as direct extension into the diaphragm and grill-bladder. Metastases were found in regional lymph nodes, lungs, scalp and skull.

² Menon-Grantbatch Electronics, Inc., 10123 Main Street, Clarence, N. Y. 10431.

³ Cook, Inc., P. O. Box 489, Bloomington, Indiana 47401.

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CASE REPORTS

CASE I. This 46-year-old man had worked as a chemical operator in vinyl chloride polymerization for 16 years. Since January 4, he has had recurrent hematemesis and melena. Initial upper gastrointestinal (G.I.) studies were normal. In May 1965, hepatosplenomegaly, esophageal varices, thrombocytopenia, and internal and anal hemorrhoids developed. A portacaval shunt was performed; the splenoportogram was normal except for a possible 3-cm defect within the right hepatic lobe. Portal vein pressure measured 11 mm Hg. In October 1970, he underwent surgery for cholelithiasis; the liver biopsy revealed bile duct proliferation, portal fibrosis, Kupffer cell hyperplasia. In May 1971, because of continued splenomegaly, a hepatic angiogram was obtained which revealed a large neoplasm (Fig. 1 and Table I). Biopsy suggested anaplastic hepatoma. In September 1972 following chemotherapy, a ^{99m}Tc -sulfur colloid liver scan demonstrated a bilobular defect

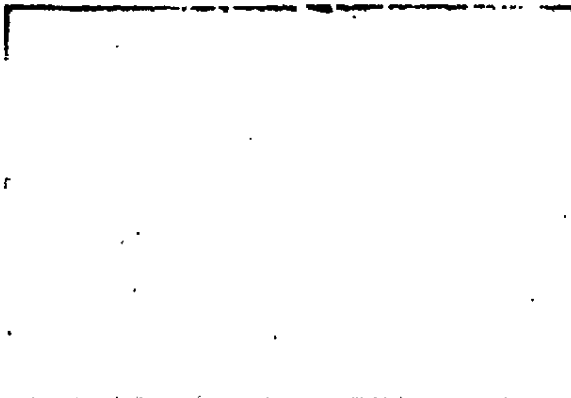


Fig. 7. CASE IV. Splenic arteriogram, 10 seconds. There are two pie-shaped defects on the lateral and inferolateral aspect of the spleen. The spleen is not enlarged.

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CASE II. This 37-year-old man had worked as a chemical operator in vinyl chloride polymerization for 12 years. In September 1966, he presented with internal and external hemorrhoids which were then excised. In January 1970, painless melena occurred for the first time. Several upper G.I. studies were normal. In May 1970, melena recurred and he was found to have hepatosplenomegaly, esophageal varices and thrombocytopenia. An ^{187}Au liver scan revealed a large lesion replacing the left lobe with extension into the right lobe (Fig. 3). Exploratory laparotomy revealed a markedly thickened liver capsule and hepatic angiosarcoma. In spite of ^{60}Co radiation and chemotherapy, massive ascites and liver failure developed and he died in September 1971.

CASE III. This 42-year-old man had worked as a chemical operator in vinyl chloride polymerization for approximately 20 years. In August 1967, he had a sympathectomy for treatment of Buerger's disease of the left lower extremity. A femoral angiogram revealed corrugation of the anterior and peroneal arteries. He had also been hospitalized twice for alcoholism.

In February 1974, through the vinyl chloride screening program (9), a ^{99m}Tc -sulfur colloid liver spleen scan detected a superficial 4-cm lesion on the anterior inferior surface of the right hepatic lobe. The spleen was normal. An ^{113}Ba rose bengal liver scan demonstrated the same defect. Hepatic angiography confirmed a lesion corresponding to the liver scan defect (Fig. 4). The tumor margin was hypervascular and contained a hypovascular center. Puddling and peripheral stain persisted from the early arterial to the late venous phase (Table I). Splenic and portal veins were normal. Venous pressures obtained were: wedged hepatic vein (WHV) 15 mm Hg and free hepatic vein (FHV) 10 mm Hg. The free hepatic venogram was normal. The wedged hepatic venogram demonstrated portal vein reflux with hepatopetal flow. On exploratory laparotomy, the tumor could be seen on the surface of the liver. Biopsy revealed angiosarcoma with extensive necrosis, portal fibrosis, and moderate cholestasis. In spite of chemotherapy, there was progressive enlargement of the tumor, massive ascites and liver failure. The patient died in March 1975. Autopsy revealed angiosarcoma, multifocal throughout the liver, as well as direct extension into the diaphragm and gall bladder. Metastases were found in regional lymph nodes, lungs, and bone.

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Fig. 8. CASE IV. Free hepatic venogram. The hepatic vein is markedly displaced cephalad by tumor with amputation of tributary branches (arrow). This is the "thorn sign" as described by Doehner (Radiology 90:1124-1131, Jun 1968).

Fig. 9. CASE IV. Operative portal venogram. The exposure is made at the completion of a hand injection of 40 ml of Fenografin-76. The intrahepatic portal veins are markedly displaced by tumor, almost completely compressing the left branch. The area of tumor is hypovascular with no evidence of tumor stain or puddling.



Fig. 10. ^{99m}Tc -sulfur colloid liver scan, anterior view. A peripheral 2.5-cm defect is present on the dome of the right hepatic lobe (single arrow). A defect from the confluence of hepatic veins appears more medial (double arrows).

CASE IV. A 45-year-old man had worked as a chemical operator in vinyl chloride polymerization for 12 years. During a screening test in February 1974, he was found to have a persistently elevated lactic acid dehydrogenase. A ^{99m}Tc -sulfur colloid liver spleen scan revealed a large defect on the posterior periphery of the right lobe of the liver (Fig. 5). Hepatic angiography demonstrated a multilobular tumor corresponding to the liver scan defect (Fig. 6). The angiographic features are described in TABLE I. Two pie-shaped defects were present within the spleen (Fig. 7). Venous pressures obtained were: right atrium (RA) 14 mm Hg; inferior vena cava (IVC) 16 mm Hg; WHV 20 mm Hg, and FHV 14 mm Hg. One hepatic vein branch was partially compressed by tumor (Fig. 8). On wedged venography, there was portal vein reflux with some portal stagnation. Exploratory laparotomy and biopsy revealed hepatic angiosarcoma, capsular fibrosis, sinusoidal dilatation and portal fibrosis. The spleen was normal to palpation. A portal venogram demonstrated marked displacement by tumor (Fig. 9). Portal vein pressure measured 20 mm Hg.

In spite of ^{60}Co radiation and chemotherapy, the tumor progressed. Massive ascites and liver failure developed and the patient died in July 1975. At postmortem, the angiosarcoma was multifocal throughout the liver and extended into the diaphragm. There were extensive metastases to regional, retroperitoneal and mediastinal lymph nodes, lungs, adrenal glands and cerebellum. The spleen was normal and free of metastasis in spite of the angiographic findings.

CASE V: *false-positive angiosarcoma*. This 50-year-old man had been a chemical operator in vinyl chloride polymerization for 18 years. In May 1974, through the vinyl chloride screening program, a

^{99m}Tc -sulfur colloid liver spleen scan was done which suggest defect on the dome of the right hepatic lobe (Fig. 10), that was in the anterior and right lateral views. Initial hepatic angiogram was unsuccessful. The following day, transjugular hepatic venostudies and biopsy were performed. A wedged hepatic venogram demonstrated portal vein reflux with hepatopetal flow (Fig. 11). Day later, a repeat hepatic angiogram via the transaxillary route revealed a 3.5 X 4.5-cm oval lesion within the superior right hepatic lobe consisting of a peripheral stain with a central hypovascular area (Fig. 12).

Seven days later, a right hepatectomy was performed because the angiographic pattern resembled that of angiosarcoma. On gross examination, the lesion appeared as a 2-cm pyramidal lesion at the base on the liver capsule. This was found to be a healing infarct which corresponded to the exact configuration and area of wedged venogram. In addition, there was some degree of portal fibrosis.

PATHOLOGY

Hepatic angiosarcoma is a tumor believed to arise from the endothelial cells lining the sinusoids. The tumor is also referred to as malignant hemangioendothelioma, or Kupffer cell sarcoma. The histologic characteristics have recently been well described (22, 29), and the spread of this tumor is mainly by direct invasion and by the coelomic route (22). Metastatic tumor has been found within portal veins, bone marrow and peritoneal cavity, lung, spleen and the thyroid (10, 22, 29). Edmundson reported that up to 50% of these tumors have pulmonary metastases (3).

Seven of the 8 vinyl chloride workers had tumors outside the liver. Three of these directly invaded the diaphragm, one extended into the duodenum and another had reached the posterior abdominal wall on follow-up exploration. There is no histologic evidence of splenic involvement in any of these cases.

Subcapsular fibrosis, portal fibrosis, sinusoidal dilatation and atypical sinusoidal lining cells have been found to coexist with this tumor (2, 4, 10, 22, 29). It is presently felt that the lesions of portal fibrosis, sinusoidal dilatation, and atypical lining cells may represent a pre-

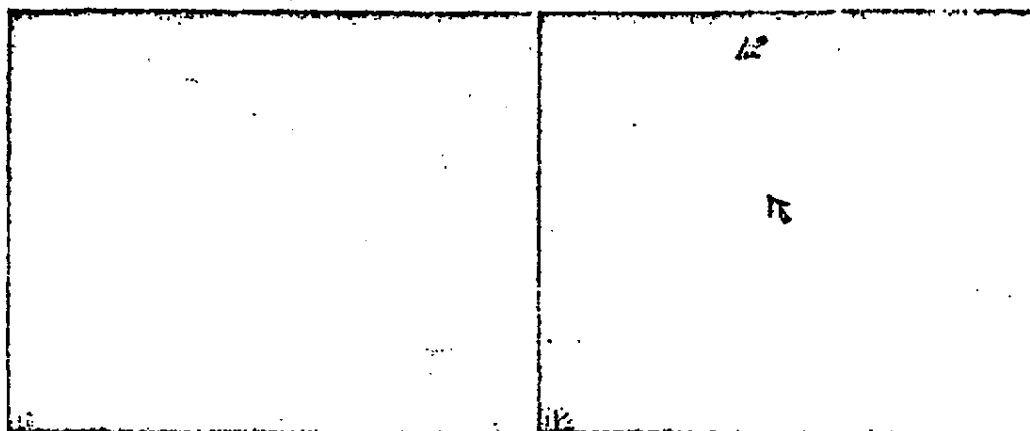


Fig. 11. Transjugular wedged hepatic venogram: 8 ml of Renografin-76 injected at 2 ml per second. There is portal vein reflux with hepatopetal flow.

Fig. 12. Hepatic arteriogram 2 days following the wedged hepatic venogram. A 3.5 X 4.5-cm oval lesion containing a peripheral stain and hypovascular center persisted into the late venous phase. This corresponds to the area of the wedged hepatic venogram which was histologically proved to be an infarct.

rsor stage in the development of angiosarcoma (4).
I groups of vinyl chloride workers with tumors have

had varying degrees of portal and subcapsular fibrosis.
Up to 40% of these tumors have been reported to have

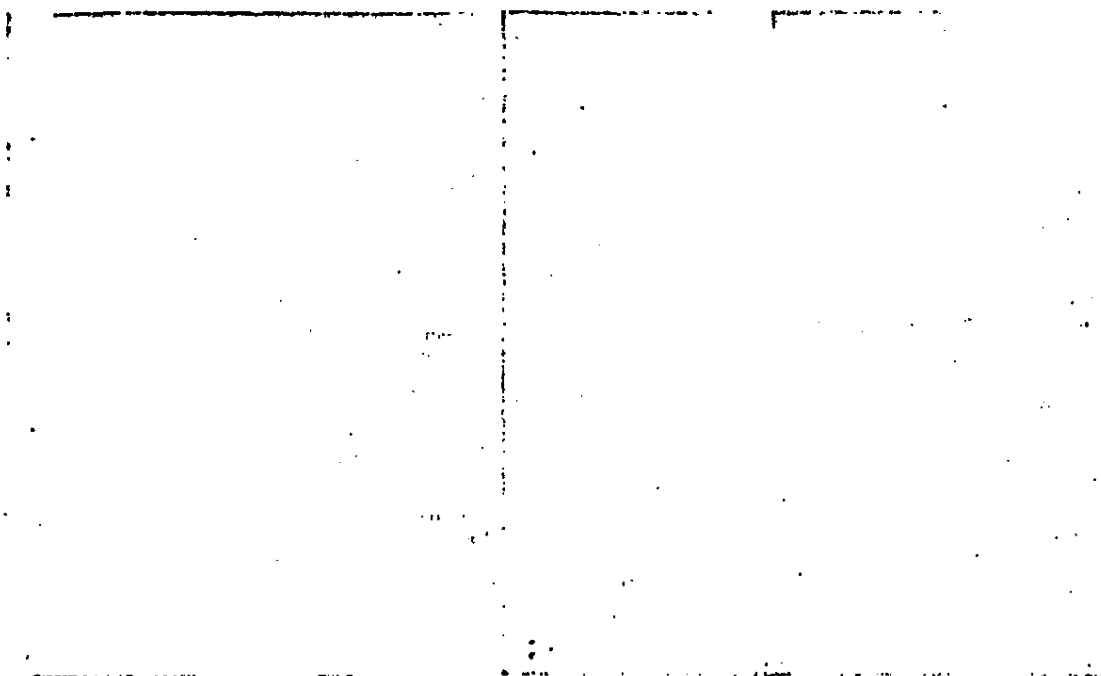


Fig. 13. A 28-year-old vinyl chloride worker with abnormal liver function studies and normal liver scan. A. Hepatic arteriogram, hepatogram phase, 28 Aug. 1974. Distribution of contrast agent is normal.

B. Hepatic wedged venogram, 29 Aug. 1974. A uniform subcapsular peripheral stain is present with portal vein reflux and hepatopetal flow.

C. Repeat hepatic arteriogram, hepatogram phase, 30 Aug. 1974. A peripheral stain appears at 5 seconds and persists up to 31 seconds. A reticular pattern of pooling appeared simultaneously throughout the central area of hypovascularity, corresponding to the area of hypovascularity.

Table I: Angiographic Features of Hepatic Angiosarcoma

	Case I	Case III	Case IV
Arterial			
Hepatic artery size (to tumor)	Normal	Normal	Normal
Encasement	No	No	No
Displacement	Yes	No	Yes
Hypervascularity	Yes (2 sec)	Yes (2.5 sec)	No
Central vascularity	Hypovascular	Hypovascular	Avascular
A. V. shunts	No	No	No
Peliosis hepatis	Yes (left lobe)	No	No
Tumor stain			
Central	No	No	No
Peripheral	Yes	Yes	Yes
Time	4-15 sec*	5-34 sec*	6-30 sec
Maximum stain	8 sec	10 sec	6 sec
Puddling time	2-15 sec*	5-14 sec	6-40 sec*
Venous			
Portal	Not demonstrated (portacaval shunt); splenic vein; 11 sec	10 sec	13 sec

*Last film in series

coexisting cirrhosis (22). The relationship of cirrhosis to this tumor is not determined. Only 2 of the 8 vinyl chloride workers with tumor had cirrhosis.

DISCUSSION

Liver and Spleen Scans

Angiosarcoma appears as a negative defect on liver scan with use of either ^{198}Au , ^{131}I -rose bengal, or $^{99\text{m}}\text{Tc}$ -sulfur colloid. Sufficient ^{67}Ga studies have not been performed to be conclusive. Although most lesions appear initially as a single focus, one patient presented with two separate lesions. At serial scans and autopsy, the tumor is seen to progress to multifocal lesions throughout the liver. Even though most lesions, when detected, were rather large, they appeared peripheral in location. This was also found to be true at surgery. In the tangential view, there is no radioactivity surrounding the defect and no activity within the defect itself. We used the camera technique to view the studies of 2 other patients with this tumor. These also appeared as peripheral lesions. Without the history of vinyl chloride exposure, it would be difficult to differentiate this lesion from an extrahepatic contiguous lesion (24). It is also difficult to differentiate from normal anatomical defects such as portahepatis, gallbladder fossa, confluence of hepatic veins, or rib and xiphoid. Peripheral development of this tumor is possibly related to the subcapsular fibrosis found in these workers (7, 29). Their peripheral location is also the most likely reason that these tumors show early direct extension through the liver capsule.

Four of the 8 vinyl chloride workers with tumor had splenic enlargement, demonstrated in one patient after the tumor was detected. Three of these patients presented with Banti's syndrome. Watson and Baltaxe (31) attributed splenic enlargement to massive replacement of liver parenchyma, or invasion of the portal vein by tumor. Splenic enlargement occurred in one of our pa-

tients (CASE I) prior to massive tumor involvement. In 3 others, portal venograms did not demonstrate occlusion or invasion. On postmortem examination in CASES III and IV, no tumor was demonstrated within the portal veins. We have found, in fact, approximately 10% of the 1,180 employees screened to have splenic enlargement without evidence of tumor. Splenic enlargement may be due to stimulation of splenic cells by chronic exposure to vinyl chloride, thus producing an increase in splenic blood flow. Further hemodynamic studies are currently being conducted.

Angiographic Characteristics

TABLE I contains a summary of the angiographic features in CASES I, III and IV. The hepatic arteries are of normal size with some displacement by tumor in CASES I and IV, and of increased size of the left hepatic artery not supplying the tumor in CASE I. Hypervascular changes were present in CASES I and III around the periphery of the tumor but not in CASE IV in which the number of terminal vessels decreased. No true tumor vessels were demonstrated. Changes of peliosis hepatis as, described by Pliskin (19), were present within the left lobe in CASE I. The central portion of tumors in these patients has some degree of hypovascularity, most likely secondary to necrosis as was found in the biopsy of CASE III. A peripheral tumor stain was present in all 3 cases, appearing in the midarterial phase and extending up to approximately 34 seconds. The stain in CASE I was faint at 15 seconds (the last film obtained in that series). The hemodynamics of the hepatic circulation may have been altered in this case due to the previous portacaval shunt. Puddling within the hypovascular portion of the tumor appeared for the same period of time. The amount of puddling seemed to increase with the increased size of the tumor, again, probably related to the amount of necrosis. Maximum stain and puddling occurred prior to the portal vein phase; these changes appeared closer to the portal vein phase in the smaller

Table II: Vascular Lesions of the Liver

Lesions	Vessel Size (N) Normal (D) Increased (E) Created	Vessel Position (N) Normal (D) Displaced (E) Embedded	Tumor Vessels	Hyper-vascular	Stain				Puddling or Laking	Hypo-vascular	Partial Vein		Scar tissue	Refractile
					(D) Diffuse (P) Peripheral (I) Irregular	Arterial Phase	Venous Phase	(D) Discluded (N) Normal			(P) Preserved (N) Negative			
Angiosarcoma	N	D	(-)	(+)	P	(+) 5 sec	(+) 40 sec	(+)	(+)	Due to necrosis	D	P	Widespread	
Hepatoma														
(a) Hepatocellular (well-differentiated)	I	D	(+)	(+)	D	(+) 5 sec	(+) 10 sec	(+)	(+)	Due to necrosis	O	P	(2)	(16, 20)
(b) Multicentric	D	D	(-)	(+)	(-)	(-)	(-)	(-)	(-)	(-)	O	P	(20)	
(c) Anaplastic	N, D	D	(-)	(+)	I	(+)	(+)	(-)	(-)	(-)	D	P	(2)	(7, 8)
(d) Cholangio-carcinoma	N, D	E	(+)	(+)	I	(-)	(-)	(-)	(-)	(-)		P	(18)	(24)
Liver cell adenoma	N	D	(+)	(+)	(-)	(-)	(-)	(+)	(+)	Reticular septoids		P	(18)	(24)
Cavernous hemangiomas (large and small)	N, D	D	(-)	(-)	(-)	(-)	(-)	(+)	(+)	Due to fibrosis		P	(11, 21)	
Metastatic lesions	I	D	(+)	(+)	D	(+) 5 sec	(+) 10 sec	(-)	(-)	Due to fibrosis		P	(15, 20)	
Hemangioma	N, D		(-)	(+)	D	(+) 5 sec	(+) 10 sec	(-)	(-)	(-)	D	P	(13)	(25)
Macronodular regeneration of cirrhosis			(-)	(+)	D	(+) 5 sec	(+) 10 sec	(-)	(-)	(-)		P	(13)	(25)
Focal nodular hyperplasia	I	(-)	(+)	(+)	D	(+) 5 sec	(+) 10 sec	(-)	(-)	(-)		P	(13)	(25)
Peliosis hepatis	N	(-)	(-)	(-)	D	(+) 5 sec	(+) 10 sec	(-)	(-)	(-)	N	P	(13)	(25)
Healing infarct	N	N	(-)	(+)	Numerous nodules	(+) 5 sec	(+) 34 sec	(+)	(+)	Due to necrosis	N	N	Widespread	

(+) Present.
(-) Absent.

tumor in CASE III. No stain or puddling could be demonstrated in the portal venogram in CASE IV during surgery. The tumor, therefore, appears to receive its major blood supply from the hepatic artery. Even though the peripheral stain persists well into the venous phase, little of this appears to be due to the portal circulation. The peripheral stain in these cases probably represents sinusoidal dilatation (2, 29). The portal and hepatic veins in these cases are displaced but have not been obliterated.

The angiographic characteristics of hepatic angiosarcoma, therefore, appear to be: (a) a normal-size hepatic artery supplying the tumor which becomes displaced as the tumor enlarges; (b) a peripheral tumor stain and puddling appearing during the midarterial phase and persisting as late as 34 seconds; and (c) some degree of hypovascularity of the central portion of the tumor including the smaller tumors.

Angiographic Differential Diagnosis

Multiple vascular lesions of the liver in adults are to be considered with hepatic angiosarcoma (TABLE II). Although some variations exist, this review includes the major description of these lesions. Well-differentiated hepatomas differ from angiosarcoma due to enlarged hepatic arteries with true neovascularity and a rather diffuse stain which lasts only through the early venous phase (8, 16, 20). Multicentric avascular hepatomas (26), anaplastic hepatomas (8), and cholangiocarcinomas (7, 8) are excluded because of their relative avascularity with small scattered areas of stain and lack of puddling. Liver cell adenomas are excluded due to the presence of neovascularity and lack of a peripheral stain (18). This lesion could simulate angiosarcoma if central necrosis develops as in the case described by Sacket *et al.* (28). A large cavernous hemangioma has peripheral puddling of contrast material surrounding a central avascular area of fibrosis (11, 17, 21). However, there is no evidence of peripheral stain. Metastatic lesions (15, 20) and hamartomas are excluded since a stain appears only during the arterial phase. Recently, bile duct hamartomas of the liver have been visualized as clusters of ring-like stains lasting from the arterial to the late venous phase, diffusely involving the liver (12). Angiosarcoma has not presented with this pattern in any of our cases. Macronodular regeneration of cirrhosis can be excluded since the stain appears rather uniform in the venous phase with no evidence of puddling (13, 25) and the scan may also be normal (25). Focal nodular hyperplasia may appear as a diffuse stain in the arterial and venous phases (13, 25); however, there is no evidence of central hypovascularity or puddling of contrast substance. Here, also, the scan may be normal (25).

Angiographic changes of peliosis hepatis have recently been described (19). This may also represent the changes as seen in hepatic vein occlusion (5) and those described by Viamonte *et al.* (30) in longstanding portal

vein obstruction. These lesions, however, tend to be numerous, involve the entire liver, and have a diffuse stain throughout the nodules. The stain does seem to persist into the late venous phase. In 4 of the 50 vinyl chloride workers evaluated, varying degrees of peliosis hepatis have been demonstrated angiographically. This pattern is also suggested within the left lobe in CASE I. Some of these patients are being followed closely since this histologic change may be one of the preliminary findings before the occurrence of angiosarcoma in vinyl chloride workers (2, 4). These nonmalignant changes will be the subject of a future publication.

Hepatic infarction secondary to wedged hepatic venography was found to closely resemble angiographic changes of angiosarcoma and, in fact, led to a right hepatic lobectomy in CASE V. At the time of this discovery, another worker had just been studied by hepatic angiography, followed by wedged venography (Fig. 13, A and B). Repeat angiography confirmed an area of infarction (Fig. 13, C). Serial liver scans failed to detect this lesion. In 3 cases in which the wedged venogram was obtained first, the angiographic pattern was similar.

Hepatic Venography and Venous Pressures

Venography and pressure studies are carried out to evaluate the overall condition of the liver. The free hepatic venogram was normal except when enlarging tumor has caused displacement. No occlusive changes have been demonstrated.

Because of iatrogenic lesions created by wedged venography in 3 patients, this study has been discontinued as part of the routine screening procedure. All vinyl chloride workers were asymptomatic following wedged venography. Serial hepatic scans from 1 day to 7 months postinjection have been negative. The small hepatic infarct is probably insignificant due to the marked regenerative power of the liver. Wedged hepatic venography is still used in cases of nonopacification of the portal vein during angiography to differentiate reverse flow from obstruction. This study, if performed, should follow angiography.

Hepatic venous pressures were elevated in CASES III and IV. In a number of these workers, the free hepatic vein pressure and the inferior vena caval pressure were found to be elevated from 7 to 25 mm Hg. The majority of the corrected sinusoidal pressures have been within the normal range (0-5 mm Hg). Portal pressure, however, may not correlate with the corrected sinusoidal pressure since periportal fibrosis is one of the predominant lesions found among these workers. A more detailed investigation is being conducted to further evaluate the systemic and splanchnic venous beds.

SUMMARY

Isotopic and angiographic studies of hepatic angiosarcoma in vinyl chloride workers are presented. Of the screening procedures included in our project (9), the

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liver scan has been the most useful in detecting the tumor. No single biochemical liver test has, as yet, consistently been found to be abnormal in these patients. The peripheral defect on the liver scan may be difficult to differentiate from a normal anatomical defect or an extrahepatic lesion contiguous with the liver. The angiographic features which are characteristic, if not diagnostic, of this lesion are peripheral tumor stain, puddling of contrast agent extending from the midarterial phase up to 34 seconds, and some degree of central hypovascularity within the tumor. Transjugular hepatic pressures and biopsies are essential procedures since systemic venous hypertension seems to develop in some workers. Subcapsular fibrosis, portal fibrosis, sinusoidal dilatation and endothelial lining cell hyperplasia are associated with the tumors. Follow-up studies will be helpful to determine whether these changes are reversible or can be arrested after removal of these men from vinyl chloride exposure, and the effects of therapeutic and other treatment regimens.

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