Clinique des maladies professionnelles Cluj, Roumania

ETUDE DES MALADIES DUES AU CHLORURE DE VINYLE

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Le développement rapide de l'industrie du polychlorure de vinyle dans notre pays soulève de nouveaux problèmes pour l'hygiène du travail, pour la toxicologie et la pathologie professionnelles. Afin de les étudier un collectif d'hygiènistes et de cliniciens de Cluj ont procédé à l'examen des conditions de travail et des maladies des ouvriers de deux entreprises où l'on fabriquait du polychlorure de vinyle. Les manifestations cliniques que l'on y a rencontrées posent des problèmes d'interprétation étiopathologique d'intérêt pratique et théorique pour la connaissance du tableau clinique et des mesures de prophylaxie et de traitement à instituer. L'étude s'avérait d'autant plus nécessaire que les données de la littérature étaient limitées et lacunaires. surtout relativement aux manifestations cliniques de la maladie. C'est ainsi que DANISEWSKI avait démontré que les monomères qui sont produits au début du processus de fabrication ont une action agressive du point de vue biologique. Ils sont capables de déterminer des modifications destructives dans les téguments et les muqueuses. Certains d'entre eux sont allergisants et ont une action sur les organes parenchymateux où ils déterminent des modifications dégénératives et sur l'appareil hématoformateur étant la source d'anémies de type hémolitique. HERVIEUX et TASSIER rapportent 17 cas de dermatite chimique chez 145 travailleurs occupés dans l'industrie des masses plastiques polyvinyliques. PLESITZER, BONDAR et SMIRNOVA, cités par DANISEWSKI, en étudiant l'action chronique des vapeurs du chlorure de vinyle, mettent en évidence l'apparition, chez l'homme, d'angionévroses toxiques. On voit donc que ces études cliniques disparates n'ont pas encore abouti à l'individualisation d'un tableau clinique de la maladie. Quant aux recherches expérimentales, MASTROMATTEO, FISCHER, CHRISTIE et DANZINGER, en étudiant l'action toxique du chlorure de vinyle sur un lot de 5 souris et 5 cobayes, ont démontré, qu'à doses de 10-20-30 %, cette substance a un effet narcotique. Les expositions répétées déterminent l'apparition de congestions hépatiques et de congestions pulmonaires, qui ont été mises en évidence chez les animaux sacrifiés ou décédés au cours de la période d'exposition; dans certains cas il y a eu aussi une dégénérescence graisseuse du foie.

En ce qui concerne la toxicité, LAZAREEV situe le chlorure de vinyle parmi les substances à faible action narcotique. En poursuivant la dynamique de la symptomatologie clinique et de certaines modifications de laboratoire chez les ouvriers exposés au chlorure de vinyle et aux monomères de celui-ci nous avons constaté que les données obtenues permettent une individualisation du tableau clinique qui aidera les médecins practiciens à

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Hemangioendothelial Sarcoma of the Liver and Hemochromatosis

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A patient who had idiopathic hemochromatosis with cirrhosis, that was treated by multiple phlebotomies, developed hemangioendothelial sarcoma (Kupffer cell sarcoma) of the liver with widespread bony metastases. The possible relationship between hemochromatosis, cirrhosis and this rare tumor is discussed.

An exceptional instance of hemangioendothelial sarcoma occurred in a patient with long-standing idiopathic hemochromatosis. Less than 100 cases of this rare tumor have been reported in adults.[1-14] While the cause of this tumor is unknown, many cases have been associated with cirrhosis or the administration of thorium dioxide suspension (Thorotrast).

Report of a Case

A 46-year-old white man (NYH 77-40-15) was admitted to the New York Hospital-Cornell Medical Center in July 1968 because of diabetes, weakness, impotence, pancytopenia, edema, and hepatosplenomegaly. Past medical history included severe "typhoidal" infectious mononucleosis in 1957, adult onset diabetes mellitus that was diagnosed in 1964, treated initially with oral hypoglycemics and then insulin, and onset of pancytopenia in 1966. Family history included a 37-year-old brother with adult onset diabetes mellitus and obesity who was said to have hemochromatosis, diagnosed after this was established in our patient.

A physical examination showed blood pressure, 110/60 mm Hg; fair complexion without pigmentation; pretibial edema; splenomegaly; and testicular atrophy. Pertinent laboratory studies disclosed the following values: hemoglobin, 13.6 gm/100 ml; *hematocrit reading*, 42.5%; *white blood* cell count, averaging 3,400 cu mm; platelet count, 40,000 cu mm; serum iron, 228μg/100 ml; total iron-binding capacity, 228μg/100 ml; total serum bilirubin, 1.8 mg/100 ml; serum glutamic oxaloacetic transaminase (SGOT), 52 milli-international units/ml (normal, 10 to 50 m-IU/ml); serum glutamic pyruvic transaminase (SGPT), 40 units (normal, 5 to 40 units); serum alkaline phosphatase, 5.3 Bodansky units (normal, 1.5 to 5.0); fasting blood glucose, 276 mg/100 ml; and +4 glycosuria. There was no evidence of hemolysis. Electrocardiograms showed nonspecific S-T segment and T wave abnormalities. The red blood cell (RBC) agglutination test for antithyroid bodies was positive 1:2,500. Radioactive iodine uptake in 24 hours was 23%.

Percutaneous liver biopsy specimen showed a marked increase in iron deposition, especially in periportal hepatocytes (Fig 1), periportal fibrosis, and glycogen vacuolization of hepatocyte nuclei. The diagnosis of idiopathic hemochromatosis complicated by diabetes mellitus and a diagnosis of hypothyroidism were made. Biweekly phlebotomies were begun.

Two years later, in June 1970, after 63 units of blood (31,500 ml) had been removed by phlebotomy, a liver biopsy specimen showed that iron stores were still present but greatly decreased in comparison to the original specimen. The amount of iron removed by phlebotomy was estimated to be 16 mg; however, serum iron was 200μg/100 ml and total iron-binding capacity was 200μg/100 ml.

Over the next three months the patient lost 5 kg, had a low grade fever, and pain in the left upper quadrant, back, and left shoulder. In September 1970, he was readmitted because of multiple pathologic rib *fractures*. He had developed scleral icterus, lymphadenopathy, and hyperpigmentation of pretibial skin. The serum iron was now 174μg/100 ml and total iron-binding capacity, 164μg/100 ml. Abnormal liver function was now indicated by the following values: SGOT, 103 m-IU/ml; SGPT, 25 units; alkaline phosphatase, 164 m-IU/ml (normal, 30 to 85); and total bilirubin 2.7 mg/100 ml. A biopsy specimen of a soft tissue mass surrounding a pathologic fracture of the sixth rib on the left side of the chest showed metastatic anaplastic malignant tumor. The only clinical evidence of a primary site was a large defect in the right lobe of the liver demonstrated by a liver scan, but a definite diagnosis was not established. The patient was treated with medroxyprogesterone acetate (Depo-provera), cyclophosphamide (Cytoxan), prednisone, and radiation therapy to the fracture site.

Three months later the patient was admitted because of severe generalized bone pain. He had tenderness over multiple ribs, neck vein distention and decreased higher integrative functions. Laboratory data included: serum iron, 122μg/100 ml; total iron-binding capacity, 130μg/100 ml; total bilirubin, 2.1 mg/100 ml; direct bilirubin, 0.6 mg/100 ml; alkaline phosphatase, 269 m-IU/ml; and negative α-feto globulin. Multiple osteolytic metastases were seen

Accepted for publication July 30, 1973.

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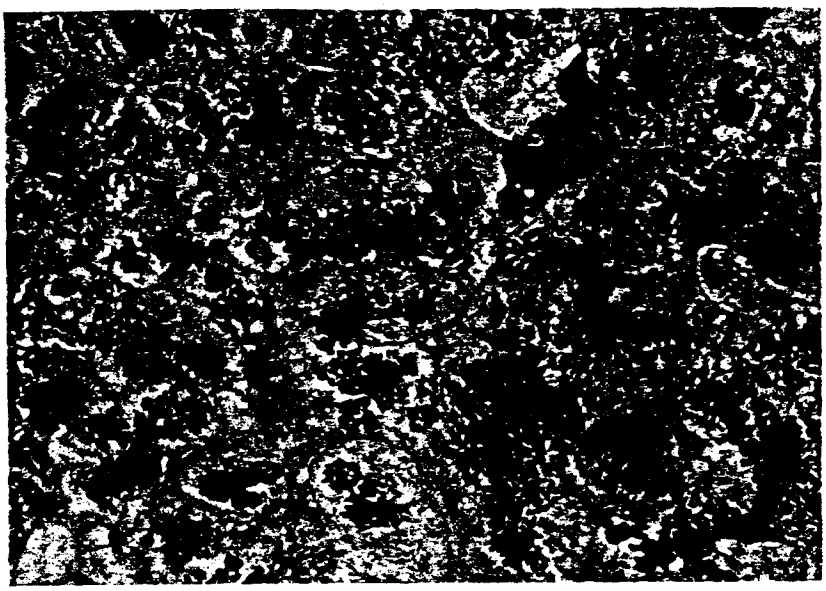
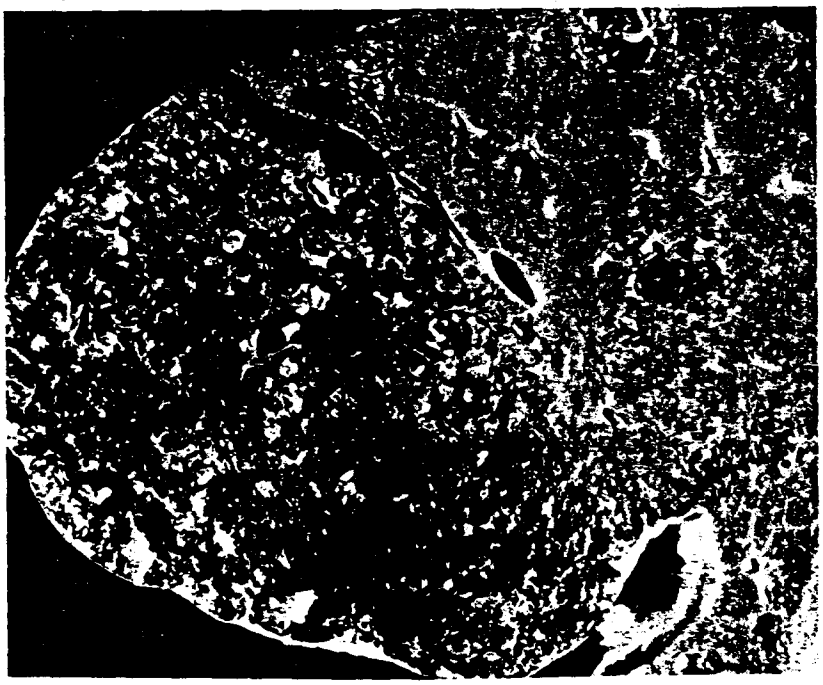


Fig 1.—Pretreatment percutaneous liver biopsy showing marked increase in iron deposition in hepatocytes and Kupffer cells (hematoxylin-eosin, original magnification ×400).

Fig 2.—Hemangioendothelial sarcoma in liver. Hemorrhagic and necrotic mass replacing a large portion of right lobe of liver. Multiple smaller tumor nodules are scattered throughout remainder of the cirrhotic liver.



in roentgenograms of ribs, cranial vault, long bones, clavicles, scapula, and pelvis. Liver scan showed hepatosplenomegaly with a grossly irregular distribution of radioactivity in the liver. A regimen of fluorouracil was added to his therapeutic program but he developed hepatic failure and hypotension and died.

The final clinical diagnoses were metastatic malignant tumor of unknown primary site and hemochromatosis with diabetes mellitus and mild hypothyroidism.

Autopsy Findings

The liver weighed 1,600 gm and was chocolate-brown with diffuse, firm, 0.3- to 1.0-cm nodules separated by thin bands of connective tissue. Microscopically, there was a pigmentary cirrhosis with hemosiderin deposits at approximately the same level as seen on the last antemortem liver biopsy specimen. Glycogen vacuolization of hepatocyte nuclei, bile stasis, and scattered foci of necrosis in regenerating nodules were seen. The pancreas, submandibular glands, and lymph nodes were also dark brown and the testes and thyroid were atrophic. Iron deposits were most marked in the pancreas, submandibular salivary glands, lymph nodes, zona glomerulosa of the adrenals, choroid plexus of the brain, testes, thyroid, and the kidneys.

A largely necrotic and hemorrhagic 11 × 10 × 8-cm tumor was found in the posterior portion of the right lobe of the liver (Fig 2). Multiple 0.5- to 2.0-cm hemorrhagic nodules were scattered throughout the remainder of the right and left lobes of the liver, primarily in and around portal veins. Microscopically, the tumor consisted of large, plump, spindle-shaped cells with large, vesicular nuclei with coarse, clumped chromatin (Fig 3). Mitoses and tumor giant cells were numerous. Reticulin stains showed that the tumor cells lined anastomosing vascular channels containing RBC. The tumor diffusely infiltrated between hepatocytes and, in some areas, bore a striking resemblance to hyperplastic Kupffer cells. A few tumor cells contained hemosiderin granules and some also showed erythrophagocytosis. Extramedullary hematopoiesis within the tumor or remaining liver was not seen. Identical

tumor tissue was found in many ribs and adjacent soft tissue, vertebra, and the cranial vault. This lesion was interpreted as being hemangioendothelial sarcoma.

There was also cytomegalic inclusion virus pneumonia of the middle and lower lobes of the right lung.

Comment

Hemangioendothelial sarcoma of the liver is a rare tumor. Only one instance was found in 52,000 autopsies at the Los Angeles County Hospital[1] and this lesion constituted only 3% of primary malignant tumors of the liver at Memorial Hospital for Cancer and Allied Diseases in New York during a 25-year period.[2] Less than 100 cases of hemangioendothelial sarcoma of the liver have been reported in adults,[1-14] but the exact number of cases is uncertain because of the proliferation of names resulting from uncertainty of the cell of origin. Designations have included hemangioendothelial sarcoma of the liver, malignant vascular tumor of the liver, Kupffer cell sarcoma, hemangioendothelioma, hemangioblastoma, angiosarcoma, endothelioblastoma, reticuloendothelioma, angioplastic sarcoma, primary hepatic sarcoma, angioblastic sarcoma, endothelioma, hemangiosarcoma, and malignant hemangioma.

Hemangioendothelial sarcomas may arise in a variety of sites including liver, bone, spleen, breast, and subcutaneous tissue. The exact primary site is sometimes difficult to determine because of rapid spread and possible multicentric origin. Hemangioendothelial sarcomas are occasionally difficult to distinguish from extremely vascular spindly hepatocellular carcinomas or vascular metastases, particularly of adenocarcinoma of the kidney and leiomyosarcoma. The differential diagnosis also includes Kaposi sarcoma and choriocarcinoma.

Two distinct age peaks in the distribution of the reported cases of hemangioendothelial sarcoma of the liver have been noted by Videbeck,[3] one at 8 months and the other at 49 years. The tumor in infants is different from that seen in adults in clinical and morphologic presentation, and prognosis.[15-17] In adults, males are affected approximately three times as frequently as females.

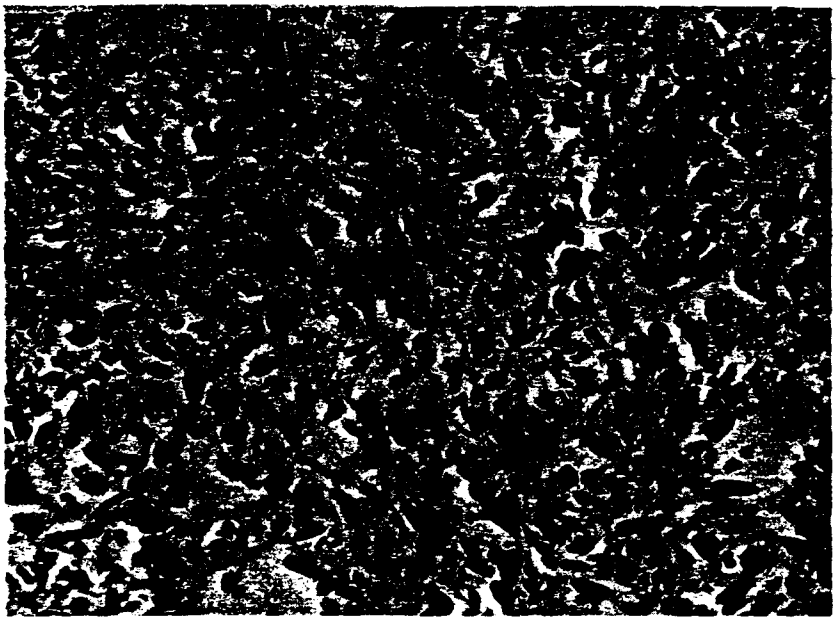


Fig 3.—Hemangioendothelial sarcoma consists of multiple anastomosing vascular channels lined by plump endothelial-like cells with pleomorphic nuclei and bizarre mitotic figures (hematoxylin-eosin, original magnification ×250).

Hemangioendothelial sarcoma of the liver is a rapidly progressive fatal disease in adults. Clinical findings frequently include rapid hepatic enlargement, hemorrhagic ascites and jaundice. Occasionally, a vascular bruit is heard over the hepatic region.[5] Microangiopathic hemolytic anemia[6] and hypercalcemia[7] have also been reported in association with this tumor. Distant metastases are present in approximately 50% of cases at autopsy, most commonly in portal lymph nodes, lungs, bones, and spleen. Death may follow intraperitoneal hemorrhage secondary to rupture of the tumor or from hepatic coma.

Several associations of possible etiologic importance have been noted with these tumors. MacMahon et al[18] reported the development of this tumor after the administration of a thorium dioxide suspension, and Da Silva Horta et al[19] found 22 cases of hemangioendothelioma in 1,107 patients exposed to a thorium dioxide suspension. This suspension is also associated with other malignant tumors including hepatocellular carcinoma and cholangiocarcinoma.[14] The latent period between the administration of the thorium dioxide suspension and the clinical onset of hemangioendothelial sarcoma was often as much as 20 years. Further support for the role of thorium dioxide suspensions came with the experimental induction of this tumor in animals injected with colloidal solutions of thorium dioxide.[20] Another implicated iatrogenic agent is arsenic, according to a report by Regelson et al[21] concerning hemangioendothelial sarcoma of the liver in a patient who had received Fowler solution. There was no history of or morphologic evidence of exposure to either thorium dioxide suspension or arsenic in our patient.

Cirrhosis was present in approximately one third of the reported adult cases of hemangioendothelial sarcoma of the liver.[9] The types of cirrhosis included alcoholic, postnecrotic, and pigmentary. Ansari and Weigent[4] have explained the association of cirrhosis and hemangioendothelial sarcoma of the liver in two ways: one, that cirrhosis plays a role in the genesis of this tumor as it does in hepatocellular carcinoma; two, that the tu-

mor itself may initiate fibrosis and nodular regeneration. The latter explanation seems less likely, since in cases like the one reported here, diffuse cirrhosis was demonstrated prior to any evidence of existence of the tumor.

Only two cases of hemangioendothelial sarcoma in hemochromatosis have been previously reported.[5,9] In one instance,[5] hemochromatosis was suspected only at autopsy because of pigmentary cirrhosis and iron deposition in pancreatic acini; however, other causes of hemosiderosis were not ruled out clinically and iron was not identified within tumor cells. In the second instance,[9] the antemortem diagnosis of pigmentary cirrhosis was made only a few weeks before death and was not treated. Iron was found in many of the tumor cells. In three of the four cases of hemangioendothelioma of the liver reported by Alpert and Benisch,[6] hepatic siderosis was noted and the authors suspected that this was a consequence of microangiopathic hemolytic anemia due to the tumor.

In the case reported here, the presence of diabetes 1½ years before hemochromatosis was diagnosed, suggests that the latter condition may have been present at least four years antemortem. The patient was treated with multiple phlebotomies that resulted in decreasing serum iron levels and diminution of liver iron load as seen on the biopsy specimen. Nevertheless, he went on to develop a hemangioendothelial sarcoma of the liver, a situation analogous to an instance of hepatoma arising in treated hemochromatosis as reported by Hines et al.[22] It would, therefore, appear that the removal of iron does not prevent the development of either hepatoma or hemangioendothelial sarcoma once cirrhosis has developed.

Kupffer cell origin of these tumors is suggested by the tendency to form anastomosing vascular elements lined by prominent endothelial-like cells. The presence of hyperplastic Kupffer cells in areas of the liver remote from frank tumor as described by Baker et al[5] also supports a Kupffer cell origin of this tumor. Phagocytosis of a thorium dioxide suspension and hemosiderin by tumor cells mimics the activity of Kupffer cells, but does not prove Kupffer cell origin, since other tumors may demonstrate phagocytic activity including erythrophagocytosis. The significance of extramedullary hematopoiesis within the tumor is unknown.

Many of the clinical features seen in patients with hemangioendothelial sarcoma of the liver are shared with patients having hepatocellular carcinoma. Because of the extremely vascular nature of this tumor, aspiration or needle biopsy is contraindicated and may result in fatal hemorrhage. Early diagnosis and partial hepatectomy might offer some hope of increased survival but unfortunately nearly all lesions in adults are diagnosed at an advanced stage and characterized by a rapidly progressive course leading to death within six months.

Nonproprietary Name and Trademark of Drug

Fluorouacil—*Efudex, Fluoroplex.*

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