Imperial Chemical Industries P L C
Petrochemicals & Plastics Division

TRANSLATION

HEPATOCELLULAR CARCINOMA OF THE LIVER FOLLOWING VINYL CHLORIDE EXPOSURE

For about 50 years vinyl chloride has been used commercially in the production of the most frequently used plastic in the world: Poly-vinyl Chloride (P.V.C.)

The first observations from Russia in 1949 concerning the possible toxicity of vinyl chloride met with no response until the mid 1960's when in both Western Europe and the United States publications appeared which dealt with skin changes similar to dermatosclerosis, acro-osteolyses of the finger ends and fibroses of the liver in workers in firms processing vinyl chloride. Angiosarcoma of the liver was first connected with vinyl chloride in 1974, particularly as in the meantime experiments carried out on animals were able to demonstrate its oncogenic potential. While vinyl chloride induced angiosarcoma of the liver has since been observed in 94 cases all over the world, hepatocellular carcinoma following vinyl chloride exposure, which can also be reproduced in animal experiments is clinically extremely rare.

In 1976 a patient with vinyl chloride induced hepatocellular carcinoma was observed for the first time (9). The following is a report on a further case of hepatocellular carcinoma in a worker who had been exposed to vinyl chloride for many years, in whom evidence of the tumor could be traced in the liver when the patient was still alive.

Case material

Industrial case history: The 54 year old chemical worker worked for 39 years in a large chemical firm. During the last 26 years he worked in various sites within the PVC polymerisation process and was exposed to vinyl chloride concentrations at the place of work estimated to be at least 300 ppm. (The first routine measurements of concentrations at the place of work to be carried out after the middle of the 1970's had shown 300 ppm; no measurements had been carried out in previous years but one must assume that previous levels may well have been substantially higher).

Symptoms: The case history reveals no serious illnesses, in particular no hepatitis and no medicines were taken which would damage the liver. Alcohol consumption amounted to ½-1 litre of beer per day in the last four years and had previously been 1-2 litres per day.

In March 1979, 2½ years before he died, the patient was taken in for examination to try to diagnose uncharacteristic disorders of the epigastrium. The examination revealed a glucose tolerance disorder with adiposity; the liver values were not abnormal.

From the spring of 1980 onwards the patient experienced repeated headaches and a deterioration in sight with double vision. In August 1980 the patient was in a special neurological clinic; electro-encephalography and computer tomography of the skull provided no usable pathological findings.

In September 1980 the patient was again taken in for internal examination due to a general increase in the size of the abdomen.

Findings: Deterioration in general condition, weight 88 kg. height 170 cm. Massive distention of the abdomen, liver 25 cm in the right midclavicular line, noticeably rough with dulled edges, spleen palpable 5 cm below the left costal arch edge.

Sonography and computer tomography: Evidence of intrahepatic claims on space where the lobus hepatis dexter is arched forward by a growth ca 12 cm in diameter of which the boundaries with the liver parenchyma are irregular (fig 1) Sonographically monitored puncture with a fine needle from the centre of the tumor with evidence of carcinoma cells in the cytological smear (fig 2).

Laparoscopy: Massively enlarged lobus hepatis dexter arched forward in a spherical shape, with a smooth surface; no indication of cirrhosis of the liver when examined macroscopically. The lobus hepatis sinister has multiple cysts of ca 1.5 cm on its surface. Clear vascular congestion splenomegaly indicate portal hypertension. Puncture carried out laparoscopically from the centre of the lobus hepatis dexter provides histological as well as cytological evidence of a hepatocellular carcinoma (fig 3).

Skeletal scintigraphy with $^{99}Tc^{22*}$ - MCP focal multiple concentrations in the skullcap as well as in the fifth right ventral rib.

Laboratory values: Blood sedimentation reaction 160 mm in the first hour. Leukocytes 9.9 x 10^9/l, erythrocytes 2.81 x 10^{12}/l, haemoglobin 88 g/l, haematocrit 0.25, MCV 88 fl, MCH, 30.4 pg, MCHC 356g/l.

Differential blood count (%): 13 stab cells, 44 with segmented nuclei, 39 lymphocytes, 2 mono-cytes, 2 metamyelocytes. Thrombocytes 596 x 10^9/l. Total protein 81 g/l, albumins 37.6 rel %. α_1 - globulin 8.1 rel %, α_2 - globulin 22.7 rel %, β - globulin 17.6 rel %, γ - globulin 13.30 rel %. Cholesterine 11.07 mmol/l triglycerides 8.5 mmol/l. Total bilirubin 14.4 μmol/l, alkaline phosphatase 208 U/l, acid phosphatase 12.5 U/l LAP 61 U/l, γ - GT 258 U/l, cholinesterase 2.0 U/l, CK 9 U/l, GOT 21 U/l, GPT 17 U/l, LDH 134 U/l. Copper in the serum 40.4 μmol/l, iron 27.4 μmol/l. α_2 - fetoprotein less than 2 μg/l. IgG 8.38 g/l, IgM 1.44 g/l, IgA 2.84 g/l, IgG less than 14 U/ml, IgE 264 U/ml. No indication that a paraprotein is present. Ferratin 776 μg/l. HBs - antigen negative, anti-HBc negative, anti-HAV (IgG + IgM) positive. Echinococcus - antibodies negative.

* Translator's Note : Possibly 'm' - illegible on copy.

Development of the disease: after his release from hospital, the patient was given simple analgesics and codein exclusively as symptomatic treatment and was thus relatively asymptomatic. In the following months the portal hypertension increased and ascites developed. In April 1981 the patient had to go back into hospital for two weeks because of increasing dyspnea; his system was flushed out by administering aldosterone antagonists. Sonographic check ups revealed a further increase in the size of the liver with progression of the hepatic tumors, both of the lobi hepatis had a completely irregular structure with partly cystic, partly solid unevenly defined areas. The patient died on 29.9.81 with the clinical picture of pneumonia.

Findings from the post-mortem: the autopsy revealed a huge, camerated, extensively sphacelated tumor of the liver (ca 30 cm in diameter in the lobus hepatis dexter) softened by the cyst. In addition, the remaining liver segments were infiltrated with similar tumor nodes with diameters of up to 5 cm. The abdominal cavity was also filled with 2 litres of a haemorrhagic ascites.

Histologically, the tumor proved to have a relatively monomorphous structure with a clear trabecular pattern. The cell nuclei had pronounced atypias in parts, mostly with very prominent nucleoli and numerous mitoses. The cytoplasm was mostly eosinophilic and granular. There was no evidence of gall pigment. There was only slight development of connective tissue septa between the tumor syncytia. For the most part the findings corresponded to those of the biopsy, histology and cystology of one year before the patient's death; the diagnosis was clearly one of hepatocellular carcinoma.

There were no discernible indications of any cirrhotic changes anywhere on the liver segments which were obtained. However, pronounced perisinusoidal fibrosis within the sinus, all of which was clearly enlarged and especially an increase in blood filled vascular fissures in the region of the periportal area were particularly evident.

An orcein pigmentation by the Shikata method indicating hepatitis B artigen proved negative.

An identical picture to that of the primary tumor has shown by the metastases in the skull cap, left parietal, (4 cm in diameter), in the base of the skull in the region of the clinoid plate with enclosure of the nervi optici, in the adrenal glands, in the front wall of the right ventricle of the heart subendocardially, the multiple small nodular metastases in both lungs and in the membrana succingens as well as the lymph nodes metastases on the hilus of the liver, para-aortal-abdominally and on both sides of the hilus of the lung (up to 2 cm in diameter).

In addition, a bilateral bronchopneumonia and the signs of heart circulation failure were found.

Discussion

As late as the end of the 1960's vinyl chloride, a sweet-smelling inflammable, explosive slightly anaesthetic gas, was still considered to be relatively non-toxic (14). Little notice was taken of publications from the Soviet Union dealing with liver damage (29), or of further indications as to the possible toxicity of vinyl chloride from Rumania (27).

Systematic experiments, predominantly in industrial medicine and involving animals were only carried out when, from 1966 onwards, an increasing number of reports appeared concerning symptoms which occurred principally in autoclave cleaners working in VC-processing firms. These workers experienced primarily dermatological changes in the form of cutaneous symptoms similar to dermatosclerosis, Raynaud's phenomenon and band-shaped osteolyses of the finger ends (3, 4, 19, 34). The incidence of a so-called hepatolienal syndrome in workers in a VC polymerisation plant was too high to be put down to coincidence and in 1973 led Marsteller and his colleagues to carry out an extensive clinical, clinico-chemical and morphological analysis of the liver activity, the main feature of which was an unusual type of the diffuse fibrosis, usually connected with portal hypertension.

Although findings from experiments on animals first provided indications of the oncogenic potential of vinylchloride in 1970 (11, 18, 30, 31), vinyl chloride disease was only given proper consideration when reports were published dealing with malignant angiosarcoma of the liver as a consequence of chronic exposure to vinyl chloride (5, 13, 16, 17).

In the meantime, the National Institute for Occupational Safety and Health has compiled data from all over the world on 68 cases of angiosarcoma (up to 1977) in workers from firms processing vinyl chloride (26); within the same period 16 such cases were registered in the Federal Republic of Germany (23). According to the Professional Association of the German Chemical Industry, there were 21 recognised cases of vinyl chloride induced haemangiosarcoma of the liver in the Federal Republic of Germany up until 1982. World wide this figure stands at 94.

Although both hepatocellular carcinomas from the early stages to fully developed carcinomas, as well as haemangiosarcomas were observed where there had been exposure to vinyl chloride in animal experiments, and although the same result was therefore to be anticipated in humans, publications dealing with hepatocellular carcinomas in humans following vinyl chloride exposure were nevertheless extremely rare. One of the first observations of this type was made in 1976 by Gokel and colleagues (9); this case relates to a further definite observation of a VC-induced carcinoma of the liver in a human. Both cases are essentially identical: a worker who was employed in the same VC-processing firm working on the polymerisation process. It can be proven that for more than 20 years, he had been exposed to a VC concentration which may well have been at least 300 ppm and sometimes much higher.

The patients showed no indication of having suffered from hepatitis; both the serum parameters and the orcein pigmentation by the Shikata method indicating hepatitis B antigen proved negative. Alcohol damage was obviously not an important contributory factor, and neither adiposis hepatica nor cirrhosis was present. There was no indication whatsoever that a medicamentous or any other kind of toxic lesion could have been connected with the development of the hepatocellular carcinoma. It is remarkable that in the remaining liver tissue which was obtained there was evidence of a conspicuous atypical proliferation of vascular walls periportally as well as a clear enlargement of the sinus with fibrosis in parts. In the experimental investigations (22) such changes are described as typical early changes in the development of VC induced angiosarcomas. It must be assumed, therefore, that

in this case, as well as the manifest and fatal, metastasised hepatocellular carcinoma, there already existed early changes which would develop into angiosarcoma. The simultaneous incidence of vinyl chloride induced angiosarcoma and hepatocellular carcinoma is described in four cases in the literature (2, 6, 12, 28). One reason for the significant prevalence of VC-induced angiosarcomas of the liver over hepatocellular carcinomas could lie in a stronger carcinogenic effect of vinyl chloride on the sinusoidal riparian (?) cells; it is not known why this was not the case for the two patients who come from the same VC-processing firm.

After it was discovered that vinyl chloride inhalation and the occurrence of malignant tumors of the liver were connected, industry was relatively quick to take the logical steps by drastically reducing the permissible VC concentrations in the air at the place of work (to 1.0 ppm since 1977). Nevertheless, because of the long lag time, VC damage should still be expected to occur in workers who were at one time exposed to vinyl chloride.

However, the clinical symptoms of both the VC induced angiosarcomas and the hepatocellular carcinomas usually remain untypical up to a very advanced stage, often clinical symptoms only appear with metastases, as in this case. Similarly, the clinico-chemical parameters are unchanged, or are at the most untypically changed up to a very advanced stage of the tumor; there is no correlation with other VC induced changes, eg acro-osteolyses or Raynaud's phenomenon (15, 33). In this case even α_1-fetoprotein - normally a characteristic indication of tumors - was not present in a quantity high enough to indicate a tumor. It is therefore difficult to set up an examination programme for patients at risk from VC processing firms.

Lately, sonography and computertomography have become available as very reliable non-invasive methods which are easy on the patient. Sonography, as well as being inexpensive has the additional advantage of involving no exposure to radiation. Both methods can provide evidence of intrahepatic tumors in the preclinical stages with approximately equally high sensitivity (10, 24, 25) so that it seems advisable when monitoring workers exposed to vinyl chloride to choose sonographic examinations of the liver with additional computertomographic examinations if required. This type of systematic monitoring is justified and encouraged by the results of liver surgery (7) according to which liver tumors, resected by means of conization or resection parts of the liver, have a relatively favourable prognosis with a 5-year survival rate of 25-40%.

Translated by: Miss D Johnston

DJ/MB

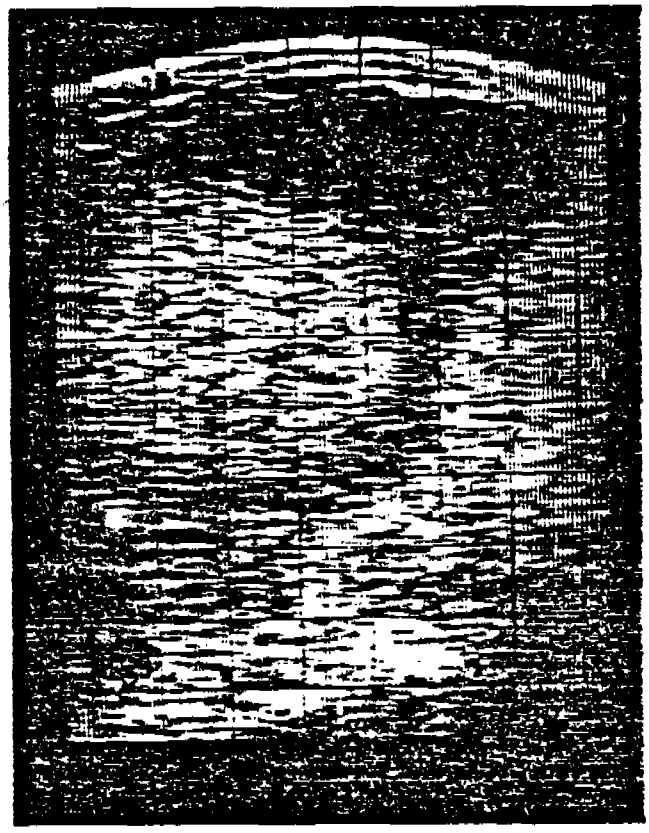

Fig 1. Sonographic longitudinal section through the liver at the level of the right mid-clavicular line. Solid tumor of around 10cm in diameter.

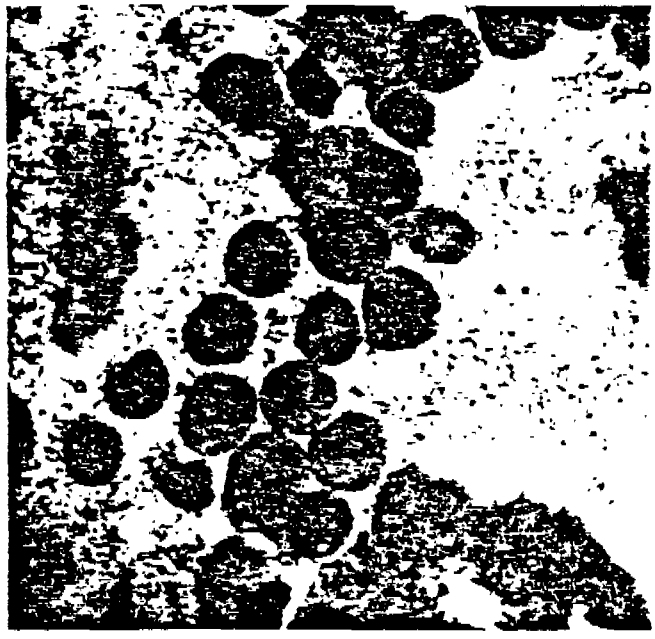

Fig 2. Cytological smear obtained by puncturing with a fine needle the hepatocellular carcinoma with medium, hypochromatic cell nuclei, which had extremely large nucleoli. Pappenheim pigmentation. Magnification: 400 : 1.

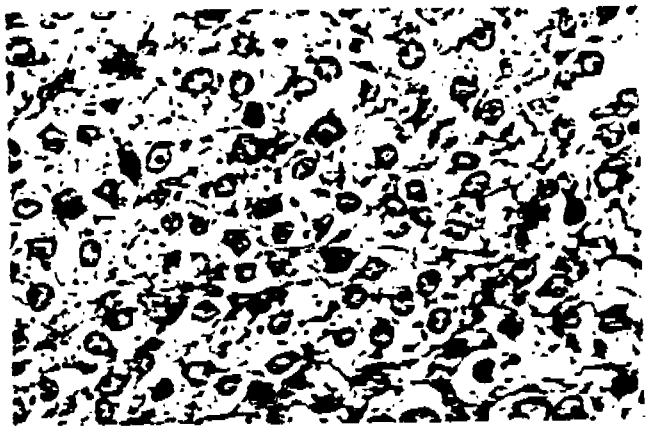

Fig 3. Histological section of a liver punch cylinder from the carcinoma of the liver (one year before death with [illegible] metastases closely packed, coarse cells