

HEPATIC ANGIOSARCOMA FROM VINYL CHLORIDE.
REPORT OF A NEW ITALIAN CASE

HUMAN
CLINICAL

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« Angiosarcoma epatico da cloruro di vinile. Un nuovo caso italiano ». - Viene descritto un caso di angiosarcoma epatico in un uomo di 43 anni che aveva lavorato per 21 anni esposto a cloruro di vinile. Viene brevemente ricostruita la sua storia lavorativa, iniziata nel 1959 e svolta quasi esclusivamente in un reparto di produzione di PVC, e la storia clinica che dopo modesti prodromi nell'aprile 1980 si è progressivamente evoluta a partire dal dicembre dello stesso anno in maniera rapidamente progressiva. La morte è intervenuta tre mesi dopo la diagnosi per un massivo emoperitoneo. Vengono descritti in dettaglio i reperti macroscopici e microscopici ottenuti dopo esame autoptico. Dalla loro discussione si ricava che la rara neoplasia ha avuto verosimilmente origine policentrica e che alla sua altissima malignità locale non fa riscontro alcuna capacità metastatizzante. Inoltre l'insorgenza dell'angiosarcoma è stata preceduta da lesioni epatiche di natura sclerogena. Il caso è il quarto descritto in Italia e comparso tra i lavoratori esposti a cloruro di vinile e il novantatreesimo comunicato nella registrazione mondiale.

The reports collected up to today in all countries are amply sufficient to confirm the experimental data (6, 16) demonstrating the carcinogenic action of vinyl chloride monomer (VCM) and its peculiar capacity to provoke, other than brain, lung and lymphatic tumors (9, 15, 17), angiosarcomas with a peculiar hepatic localization (4, 5, 7) with a similar effect to that of thorotrast (3) and arsenic compounds (12).

It is important, however, an accurate identification of all cases of VCM hepatic angiosarcoma and for each, a uniform collection of all possible information with the intent

of better understanding aspects which are fundamental in carcinogenesis. One must in fact wait for clarifying information from the in-depth study of the behaviour of tumors like occupational angiosarcoma, whose pathogenesis is influenced demonstrably less than others by a multifactorial etiology. For example, the relationships between type, entity and/or duration of the exposure to the agent and the latency period and, more in general, the complex relationships existing in the system agent-man-neoplasm can, at least in part, be better defined.

After the first reports in the literature all the cases of hepatic angiosarcoma of ascertained occupational origin were registered by the NIOSH: up to October 1977 the record comprised 64 cases (13) observed in Belgium, Canada, Czechoslovakia, West Germany, France, Great Britain, Italy, Japan,

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Norway, Sweden, the United States and Yugoslavia and appeared for the most part in the period 1973-77, after extremely variable latency periods: from the beginning of the exposure to VCM to the clinical evidence of neoplasm, there were intervals of between 9 and 38 years.

The most recent and up to date record of cases of hepatic angiosarcoma in workers exposed to VCM was made by (14) and updated to the end of August 1981, 91 cases, of which 41 occurred in the period 1975-1978.

For 67 of the 77 cases for which the working history was known, the occupational exposure took place in the course of PVC manufacture: among them 29 were also exposed during autoclave cleaning operations. The mean latency between the beginning of exposure and the diagnosis was about 21 years.

Up to now, in Italy, 3 cases have been diagnosed, respectively in 1971, 1972 and 1975 (2, 6): the first had worked in 1965 for about a year as a PVC extruder in bag production, the second from 1953 to 1961 in PVC manufacture, and the third from 1953 for eight years in cleaning autoclaves and then for 12 years checking the polymerization reactions. The first of the Italian cases was not included in the international registration because it was considered atypical and not homogeneous with the others in its clinical history (uncertainty of the primary site of the neoplasm): aside from that it is the only case appearing among workers who were not in production but in PVC utilization: if this also is taken into consideration, the total cases collected amount to 92.

Described here is a case of hepatic angiosarcoma which appeared after occupational exposure to VCM, observed at the Milan « Clinica del Lavoro », which appears as the fourth in Italy and the ninety-third in international records.

CASE REPORT

Male born in 1937; psycho-somatic development normal, never smoked, occasional wine at meals, no hard liquor; no major illness up to 1980.

Work history

In April 1959 he begins work at ANIC in Ravenna in charge of the refrigeration cycle in the department for VCM production (acetylene-HCl method) for 8 months; successively in the department for PVC production (polymerization in suspension) with duties in reaction control and recovery (not in cleaning the insides of the reactors) up to 1963; then, as foreman, he was present at all production phases (polymerization, autoclave discharge, filtration, drying) up to 1975 and as supervisor, but always with duties involving direct control of the diverse production phases, up to December 1980.

Clinical features

April 1980: right-side abdominal pains of brief duration appeared, attributed to ureteral colic. December 1980: because of the reappearance of abdominal pains apart from meals, localized prevalently in the epigastrium and the left hypochondrium, radiating backwards and associated with nausea and vomiting, he was admitted to the Division of General Surgery at the Faenza Hospital. Among others, the following examination were done:

Hematochemical tests: Gamma GT = 145 UI/l (n.v. 6-35).

Alkaline phosphatase = 551 UI/l (n.v. 50-220).
AST, ALT = within the norm.

Liver Scan: liver lightly enlarged, vast cold area occupying the right lobe partially and the left almost completely. Spleen lightly enlarged.

Liver-Pancreas Ultrasound Scan: hepatic echostructure altered by the presence in the left lobe and in the anterior region of the right lobe of a vast area of non-homogeneous echo-structure with less reflective zones next to highly reflective areas.

Laparoscopy: liver modestly enlarged, some rare scars, colored red-brown with obvious yellow tones on the surface.

Needle biopsy: « Endothelial cells with striking atypical cytonuclear characteristics ... typical appearance of malignant angioendothelioma » (dr. Tison). « ... single or grouped hepatocytes, sometimes intermingled with fibroblasts, lined with strongly atypical cells in endothelial position.



Fig. 1 - Liver in toto: a vast dark subcapsular area corresponding to the neoplastic localization in the left lobe, bleeding next to the falciform ligament (raised and moved towards the right); some superficial nodules on the right lobe.

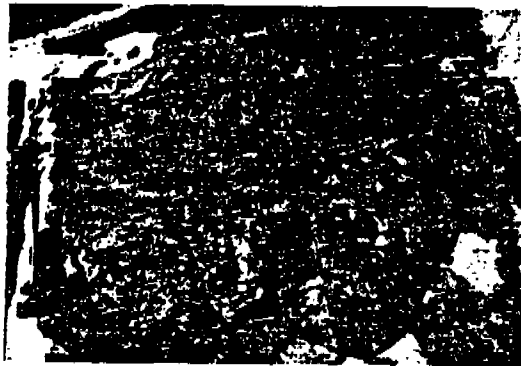


Fig. 2 - Macroscopic features of neoplasm at the cut: two ample and distinct neoplastic masses are evident, located in the right and left lobes.

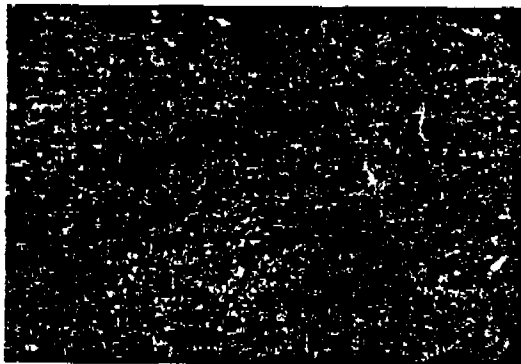


Fig. 3 - Greater enlargement of the preceding figure: spongy hemorrhagic aspect of the intra-hepatic neoplastic mass.

These cells are elongated, ovular or halfmoon endowed with voluminous nuclei, intensely hyperchromatic; the cytoplasm is of variable extent, homogeneous and eosinophilic. This presents the picture of hepatic angiosarcoma with a high degree of cellular atypia (prof. Maltoni).

19 February 1981: admitted to the Clinica del Lavoro of the University of Milan. Inconstant abdominal pains persisting, either piercing or characterized by vague aching prevalently in the left hypochondrium.

From December 1980 weight loss of about 20 kilograms. Among others, the following tests were done.

X-rays hands: no alterations attributable to acroosteolysis.

Digital photoplethysmography: within the norm.

Blood count: hematocrit 29%, hemoglobin 9.3; red cells 4,050,000.

Gamma GT = 108 mU/ml (n.v. = 4-18).

Alkaline phosphatase = 85 mM (n.v. up to 44).

AST, ALT = within the norm.

Ultrasound scan: no significant variations in respect to preceding exam. **Computerized tomography upper abdomen:** expansive hepatic process: pancreas, spleen, kidneys within the norm; no retroperitoneal adenopathies.

Multiple transfusions and symptomatic therapy were done in preparation for chemotherapy.

28 March 1981: the abdominal pain intensifies suddenly involving both hypochondriac zones accompanied by accumulation of fluid in the peritoneal cavity.

30 March 1981: sudden increase of fluid in peritoneal cavity which at the exploratory puncture appears hematic; paleness, sweating, dyspnea. Death

2 April 1981: necropsy.

Gross Pathology

Abdominal cavity contains about 4,000 c.c. of uncoagulated blood; the peritoneum smooth and shiny, some reddish nodules on the anterior face of the omentum.

Liver: shape and size within the norm, diminished consistency, multiple nodules on the surface, some whitish, others of a blueish-red color with hemorrhagic borders. A bleeding nodule near the falciform ligament (fig. 1). Two distinct zones are

observed on the cut surface, respectively in the right lobe and in the left, where the hepatic tissue is substituted by newly-formed tissue, spongy in appearance, partially necrotic clearly defined by the surrounding parenchyma, which presents a brownish yellow colour and with lacunas filled with blood (figg. 2, 3).

Spleen: normal shape, size increased, consistency reduced.

The macroscopic observation shows, in addition, brown myocardiosis, signs of nefrosis and multivisceral regressive changes.

Microscopic features

Liver: the newly-formed tissue in the hepatic site appears constituted of masses of highly atypical cells, sometimes gigantic and multinuclear but tending to be spindle-shaped with elongated and hyperchromatic nuclei, and with acidophilic cytoplasm (figg. 4-5) disposed sometimes in endothelial position lining the pre-existing vascular spaces (fig. 6) or newly formed blood vessels surrounding grouped hepatocytes (fig. 7). In some points, ample cavernous spaces are seen filled with erythrocytes and containing papillary elongations or solid masses of spindle shaped cells; in other points thrombotic or hemorrhagic phenomena are predominant.

Special stains show a notable increase of reticulin fibers: newly formed collagen fibers are also evident (fig. 8). The histological characteristics are those of angiosarcoma. The hepatic parenchyma not involved in the neoplastic proliferation presents microscopic aspects of vacuolar degeneration and a moderate perlobular steatosis. The connective tissue of the portal-biliary spaces is clearly increased and envelops the vascular and biliary branches in areas of compact sclerosis sometimes extending to the interlobular spaces (figg. 9-10).

The microscopic examination of the other tissues confirms the grossly observed impairment. No vascular alterations are found with the exception of slight renal arteriosclerosis with hyalinosis of some glomeruli.

Pathological diagnosis: haemoperitoneum in subject affected by hepatic angiosarcoma, splenomegaly, pulmonary edema, bilateral hydrothorax, myocardiosis, renal arteriosclerosis, nephrosis and multivisceral regressive changes.



Fig. 4 - Microscopic feature: highly atypical elements, tending to be spindle shaped with elongated and hyperchromatic nuclei arranged sometimes in endothelial position (Haematoxylin-Eosin 300 x).

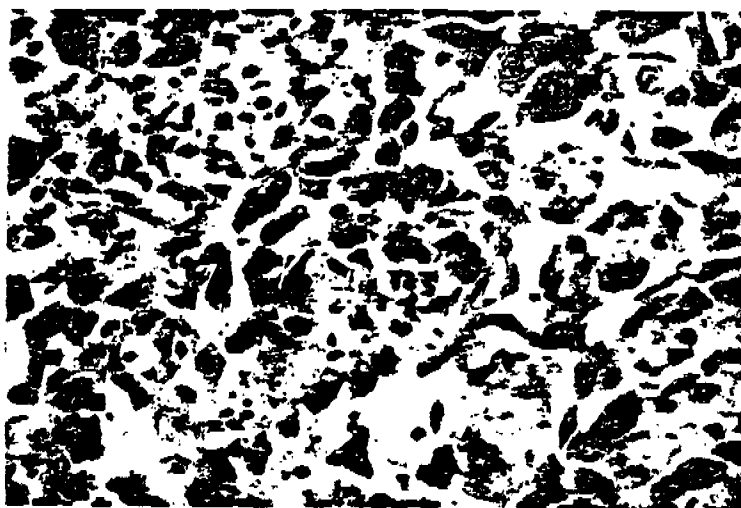


Fig. 5 - Microscopic feature: the characteristics described in the preceding figure are clearly evident (Haematoxylin-Eosin 480 x).

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Fig. 6 - Microscopic feature: tendency to endovasal proliferation (Haematoxylin-Eosin 300 x).

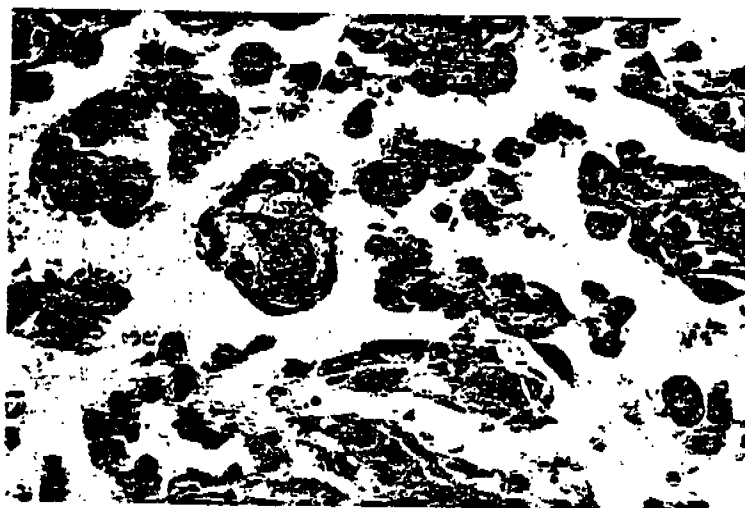


Fig. 7 - Microscopic feature: neoplastic elements surrounding single or grouped hepatocytes, with ample lacunas where red cells are distinguishable (Haematoxylin-Eosin 480 x).

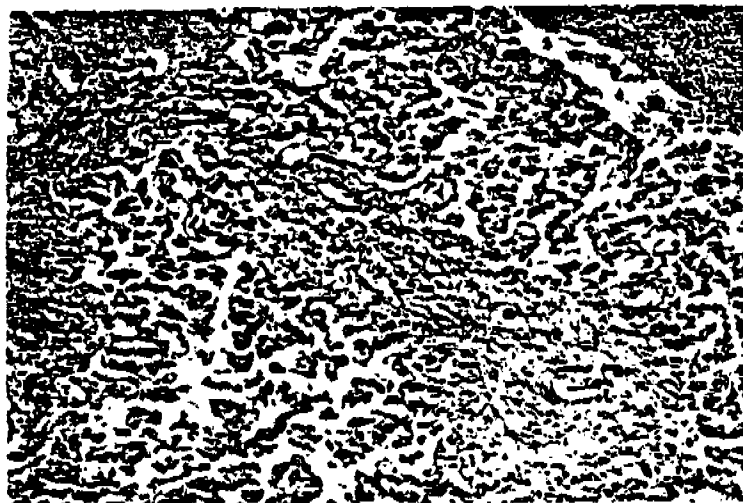


Fig. 8 - Microscopic feature: obvious newly formed connective fibers (Haematoxylin-Eosin 120 x).



Fig. 9 - Portal biliary space in the hepatic parenchyma distant from the neoplastic mass, with a notable increase of connective tissue (Van Gieson 120 x).



Fig. 10 - Area of connective formation with obvious collagen bundles, which extend into the interlobular space (Van Gieson 120 x).

DISCUSSION

In accord with what has been noted for the majority of cases, this case also is consequent to an exposure to VCM prevalently related to working on polymerization: the period of maximum exposure is that comprised between 1960 and 1963 when concentrations of VCM of thousands of ppm could be present near the autoclaves. In successive years the change of duties (foreman) and the improvement of the equipment probably brought a reduction of the level of exposure. In the opinion of department technicians, the exposure in the decade 1963-1973 had a discontinuous character with frequent peaks however on the order of hundreds of ppm. In 1973, finally drastic technological modifications dramatically reduced the exposure. The latent period between first exposure and detection of cancer was 21 years, with maximum exposure in the first four years. The duration of exposure was also 21 years because the interruption of work coincided with the manifestation of symptoms which led to hospital admittance.

No references to extrahepatic manifestations of « VCM disease » (peripheral circulatory disturbances with acroosteolysis, skin changes, thrombocytopenia) are present in the patient's history: liver damage was instead certainly present, as manifested by the portal-biliary and intralobular sclerosis analogous to those already described (7, 8) and probably preceding the appearance of angiosarcoma: the multivisceral regressive changes histologically observed are instead to be related mostly to recent metabolic changes connected with the neoplasm.

The neoplastic localization in two clearly distinct, main masses, situated in the right and left lobes supports the possibility of a polycentric onset which moreover has been well documented in experiments by intense exposure (6).

The complete absence of metastases, in contrast with the malignancy of the tumor, with its advanced evolution in the liver and with the evident tendency to endovasal proliferation was already noted (7) and seems to be confirmed ever more with the enrichment of the case-studies, as a characteristic

peculiar of VCM angiosarcoma, opposed to other forms unrelated to this toxic substance (1, 11).

In cases involving VCM exposure where angiosarcomas were found in extrahepatic sites, the possibility remains open however of a multifocal origin rather than a metastatic spread, hypothesized in various cases (6, 7, 10) observed also in experiments (6) and related to the vascular toxicity of the substance (18).

In conclusion, the following information emerges from the case described: intense and prolonged exposure, latency period on the order of 20 years corresponding to the average of all the cases described, onset of cancer after liver sclerosis, origin probably polycentric, high histological malignity with a rapid evolution *in loco*, and, in contrast, total absence of metastatizing capacity.

The ultimate significance of some of this information cannot, for now, be clarified: there is no doubt however that the observations of these peculiarities of behaviour of rare tumors which are the ultimate effect of single and well defined noxae like angiosarcoma or, for example, mesothelioma will improve our knowledge more than could the data from the study of high incidence tumors, in whose etiology multiple endogenous and exogenous factors interact in a complex way.

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ABSTRACT

The fourth case of angiosarcoma of the liver among workers exposed to vinyl chloride in Italy is reported. The case was a 43 years old man who worked from 1959 to 1980 in a VCM/PVC production plant, mostly in the polymerization area. He died

in March 1981, four months after diagnosis, for a massive haemoperitoneum. Post mortem examination was performed. According to four independent pathologists the histologic appearance was typical of a highly deviating angiosarcoma. The tumor developed after a sclerotic liver lesions was already present. The angiosarcoma was probably polycentric, had a high degree of malignancy and a rapid local evolution while, in contrast, no metastases were detected.

REFERENCES

1. ADAM Y.G., HUVON A.G., HAIDU S.I.: Malignant vascular tumors of liver. *Ann. Surg.* 175, 375-383 (1972).
2. BERTAZZI P.A., VILLA A., FOÀ V., SAIA B. et al.: An epidemiological study of vinyl chloride exposed workers in Italy. *Arh. za Hig. Rada i Toksikol.*, 30, (suppl.) 379-397 (1979).
3. DA SILVA HORTA J.: Late effects of thorotrast on the liver and spleen and their efferent lymph nodes. *Ann. N.Y. Acad. Sci.*, 145, 676-699 (1967).
4. LLOYD Y.W.: Angiosarcoma of the liver in vinyl chloride/polyvinyl chloride workers. *J. Occup. Med.*, 16, 809 (1974).
5. MALTONI C., LEFEMINE G., CHIECO P., CARRETTI D.: Vinyl chloride carcinogenesis: current results and perspectives. *Med. Lavoro*, 65, 421-444 (1974).
6. MALTONI C.: Angiosarcoma epatico in operai esposti a cloruro di vinile. Resoconto dei primi due casi riscontrati in Italia. *Med. Lavoro*, 65, 445-450 (1974).
7. MAKK L., DELMORE F., CREECH J., OGDEN L., FADELL H., SONGSTER C., CLANTON J., JOHNSON M.N.: Clinical and morphological feature of hepatic angiosarcoma in vinyl chloride workers. *Cancer*, 37, 149-163 (1976).
8. MARSTELLER H.J., LELBACH W.K., MÜLLER R., JÜKE S., LANGE G.E., ROHNER H.G., VELTMAN G.: Chronisch-toxische Leberschäden bei Arbeitern in der PVC Produktion. *Dtsch. Med. Wschr.*, 98, 2311-2314 (1973).
9. MONSON R.R., PETERS J.M., JOHNSON M.N.: Proportional mortality among vinyl chloride workers. *Lancet*, 2, 397-398 (1974).
10. POLICKOWSKI P., FAURE C., AUBERT M., PAHN M., LATREILLE R., BARRIE J.: Angiosarcome costal lié à une intoxication au chlorure de polyvinyl. *Nouv. Presse Med.*, 8, 2485 (1979).
11. POLLARD S.M., MILLWARD-SADLER G.H.: Malignant haemangioendothelioma involving the liver. *J. Clin. Pathol.*, 27, 214-221 (1974).
12. REGELSON W., KIM U., OSPINA J., HOLLAND J.F.: Haemangioendothelial sarcoma of liver from chronic arsenic intoxication by Fowler's solution. *Cancer*, 21, 514-521 (1968).

13. SPIERTAS R., KAMINSKI R., HYG M.S.: Angiosarcoma of the liver in vinyl chloride/polyvinyl chloride workers. *J. Occup. Med.*, 20, 427-429 (1978).
14. STAFFORD J.: Written communication (1981).
15. TABERSHAW I.R., GAFFEY W.R.: Mortality study of workers in the manufacture of vinyl chloride and its polymers. *J. Occup. Med.*, 16, 509-518 (1974).
16. VIOLA P.L., BIGOTTI A., CAPUTO A.: Oncogenic response of rat skin, lungs and bones to vinyl chloride. *Cancer Res.*, 31, 516-522 (1971).
17. WAXWEILER R.I., STRINGER W., WAGONER J.K., FALK H., CARTER C.: Neoplastic risk among workers exposed to vinyl chloride. *Ann. N.Y. Acad. Sci.*, 271, 40-48 (1976).
18. WILSON R.H., MCCORMIK W.E., TATUM C.F., CREECH J.L.: Occupational acroosteolysis. Report of 31 cases. *J.A.M.A.*, 201, 577-581 (1967).

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