Vinyl chloride-induced liver neoplasms

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History of vinyl chloride monomer (VCM) toxicity

1930’s – 1940’s: Acute effects on man
Narcotic effects (anesthesia)
Central nervous system (euphoria, dizziness, headaches, narcosis)

1950’s – 1960’s: Acroosteolysis (fingers)
Raynaud-like sd, scleroderma-like skin changes, osteolytic bands of distal phalanges

1970’s: Carcinogenicity – liver disease
Experimental carcinogenesis
In exposed workers
Angiosarcoma of the liver (ASL)
Non-cirrhotic portal hypertension
Hepatocellular carcinoma (HCC) rare cases

1987 human carcinogen (group 1) linked to ASL
2007 A causal relationship between VCM and HCC

4. IARC Monographs, Suppl. 6, 566-569, 1987
### History of vinyl chloride monomer (VCM) toxicity

#### Concentrations of VCM measured in manufacturing workshops

<table>
<thead>
<tr>
<th>Year(s)</th>
<th>Concentration of VCM in air (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1945-1955</td>
<td>1,000</td>
</tr>
<tr>
<td>1955-1960</td>
<td>400-500</td>
</tr>
<tr>
<td>1960-1970</td>
<td>300-400</td>
</tr>
<tr>
<td>mi-1973</td>
<td>150</td>
</tr>
<tr>
<td>mi-1974</td>
<td>50</td>
</tr>
<tr>
<td>1980</td>
<td>5</td>
</tr>
<tr>
<td>1985</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

(1 ppm = 2.59 mg/m3)

#### Workers exposed to VCM vapours during autoclave cleaning (tank cleaners)

1. VCM-induced angiosarcoma of the liver (ASL)
2. VCM-induced HCC*
3. VCM-induced liver disease

HCC: hepatocellular carcinoma

Contassot JC. EMC 16541 A25, 9-1990
VCM-induced angiosarcoma of the liver

Morphology

Multicentric tumor

VCM-induced ASL

Morphology

Sinusoidal, papillary, cavernous, massive pattern
Multiple pattern in the same tumour

Scaffolding growth pattern along sinusoids
surrounds hyperplastic hepatocytes
Dilated sinusoids

Sinusoidal growth, with trabecular disarray
(papillary pattern); Hyperplastic hepatocytes
Anatomosing blood filled spaces
**VCM-induced ASL**

<table>
<thead>
<tr>
<th><strong>Morphology</strong></th>
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<tr>
<td>Sinusoidal, papillary, cavernous, massive pattern</td>
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Papillary and cavernous pattern
Peri sinusoidal fibrosis; atrophic hepatocytes
Anastomosing blood channels

**VCM-induced ASL**

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Angiosarcoma cells lining vascular spaces

Massive pattern
The distinction between sarcoma and sarcomatoid HCC is difficult in a small sample
1. VCM-induced angiosarcoma of the liver (ASL)
2. VCM-induced HCC*
3. VCM-induced liver disease: precursor lesions

HCC: hepatocellular carcinoma
VCM-related HCC

Introduction

2007, VCM a human carcinogen causally linked to HCC
Increased risk for HCC is not as great as the risk for ASL
Causal relationship difficult to tease out because of
The high incidence of HCC in non-exposed patients
Some cases were diagnosed as « liver cancer », without histology
Changes in non-neoplastic liver not available in most reported data


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VCM-related HCC

<table>
<thead>
<tr>
<th>HCC number</th>
<th>Fibrosis</th>
<th>“VCM-hepatopathy”</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fox 1977</td>
<td>2\textsuperscript{a}</td>
<td>/</td>
</tr>
<tr>
<td>Pialat 1980</td>
<td>1</td>
<td>/</td>
</tr>
<tr>
<td>Evans 1983</td>
<td>1\textsuperscript{b}</td>
<td>Noncirrh Portal fibr; Hyperplastic hepatocell nodules, 'in some instances, showing malignant transformation</td>
</tr>
<tr>
<td>Langbein 1983</td>
<td>1</td>
<td>Noncirrh Sinusoidal fibrosis, dilatation</td>
</tr>
<tr>
<td>Dietz 1985</td>
<td>2\textsuperscript{c}</td>
<td>Noncirrh Sinusoidal fibrosis (n=1)/ fibrosis NOS</td>
</tr>
<tr>
<td>Lelbach 1996</td>
<td>1</td>
<td>Noncirrh Slight septal and portal fibr</td>
</tr>
<tr>
<td>Saurin 1997</td>
<td>2</td>
<td>Noncirrh Case 1: Mild lobular and portal fibr; sinusoidal dilatation; diffuse steatosis Case 2: Bridging &amp; portal fibr; sinusoidal dilatation; variable steatosis; NHH, hyperpl endoth cells &amp; hepatocytes; Small-cell dysplasia,</td>
</tr>
<tr>
<td>Du and Wang 1998</td>
<td>4</td>
<td>Noncirrh (2 out of 4)</td>
</tr>
<tr>
<td>Weihrauch 2000</td>
<td>18\textsuperscript{d}</td>
<td>Noncirrh 83% interstitial and perivenular fibrosis; sinusoidal dilatation peliosis; moderate pyvesicular steatosis</td>
</tr>
</tbody>
</table>

NHH, nodular hepatocytic hyperplasia. EH, endothelial hyperplasia

\textsuperscript{a} one undifferentiated carcinoma, NOS. \textsuperscript{b} another case combined HCC ASL. \textsuperscript{c} previously published by Langbein d). Between 1981-1997
### VCM-related HCC

#### Documented reports of HCC combined HCC ASL

<table>
<thead>
<tr>
<th>HCC-ASL number</th>
<th>Fibrosis</th>
<th>VCM-disease</th>
</tr>
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<tbody>
<tr>
<td>Byren et al. 1975</td>
<td>1</td>
<td>/</td>
</tr>
<tr>
<td>Gokel 1976</td>
<td>1</td>
<td>Noncirrh</td>
</tr>
<tr>
<td>Evans 1983</td>
<td>1</td>
<td>Noncirrh</td>
</tr>
<tr>
<td>Delorme 1978</td>
<td>1</td>
<td>Noncirrh</td>
</tr>
<tr>
<td>Tamburro 1978</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Koischwitz 1981</td>
<td>1</td>
<td>Cirrh</td>
</tr>
<tr>
<td>Leibach 1996</td>
<td>1</td>
<td>Noncirrh</td>
</tr>
</tbody>
</table>

#### Pathologic features

- Multicentric HCC with diffuse intra hepatic spread (autopsy case)
1. VCM-induced angiosarcoma of the liver (ASL)
2. VCM-induced HCC
3. VCM-induced liver disease
Criteria for attributing both cancers to VCM exposure
**VCM-induced liver disease**

**Natural history of ASL**

1970s, Characteristic sequential « tumorogenesis » in ASL

- Focal hepatocellular hyperplasia
- Endothelial cell dysplasia
- Endothelial cell hyperplasia
- Focal mixed hyperplasia
- Sinusoidal dilatation
- Sinusoidal fibrosis (→ Portal hypertension)
- Portal, septal & capsular fibrosis
- Multiple hepatoc nodular hyperplasia
- Small cell change
- Hepatoc dysplasia
- HCC


**VCM-induced liver disease**

**Natural history of ASL**

Irregular dilatation of sinusoids
Peliosis hepatis
Increase in lining cells
Sinusoidal fibrosis
Endothelial cell hyperplasia – dysplasia – angiosarcoma

VCM-induced liver disease
Sinusoidal dilatation
Endothelial cell hyperplasia (→)
Sinusoidal fibrosis (portal hypertension)

Mixed hyperplastic area: hepatocytes in 2-cell-thick plates and excess of sinusoidal cells
Sinusoidal dilatation

Natural history of ASL
<table>
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<th>Natural history of ASL</th>
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<tr>
<td><strong>Endothelial cell hyperplasia – dysplasia - angiosarcoma</strong></td>
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- Irregular dilatation of sinusoids
- Mixed hyperplasia of hepatocytes (in 2-cell-thick plates) and endothelial cells
- Bile plugs in dilated bile canaliculi & Kupffer cells

- Dilated sinusoids lined by dysplastic endothelial cells
- Sinusoids lined by sarcomatous cells
VCM-induced liver disease

Natural history of HCC

Focal hepatocellular hyperplasia

ASL

Sinusoidal cell dysplasia

Sinusoidal cell overgrowth

Focal mixed hyperplasia

Sinusoidal dilatation

Sinusoidal fibrosis

Portal septal & capsular fibrosis

Foci/ nodules of hepatoc hyperplasia

Small cell change

Hepatoc dysplasia

HCC


VCM-induced liver disease

Natural history of HCC

Hepatocyte hyperplasia – dysplasia - HCC

Portal fibrosis

Multiple garland-shaped areas of hepatoc hyperplasia

Mimics cirrhosis, but without annular fibrils
VCM-induced liver disease

Natural history of HCC

Areas of hepatoc hyperplasia

Hepatocytic hyperplasia - Small cell change
Sinus. Dilatation - Sinus. Fibrosis
VCM-induced liver disease

- Portal fibrosis extending into periportal parenchyma with loss of hepatocytes in the limiting plate
- Atrophied hepatic plates surrounded by fibrosis

Hepatocytic hyperplasia
Small cell change

VC-induced liver disease

- Capsular & portal fibrosis
- Nodular hepatocytic hyperplasia

Natural history of HCC
VC-induced liver disease

Hepatocyte hyperplasia – dysplasia – HCC

Small-cell change foci (noncirrhotic liver)
Sinusoidal dilatation – Peliosis hepatis

VCM-induced liver disease

Hepatocyte hyperplasia – dysplasia – HCC

Natural history of HCC
**Conclusion**

VC-induced liver cancers and disease: an exceptional human model of sequential chemical carcinogenesis

They occur in a fibrotic non-cirrhotic liver

3 hepatic target cells

- Peri sinusoidal cells $\rightarrow$ sinusoidal fibrosis
- Endothelial cells $\rightarrow$ angiosarcoma
- Hepatocytes $\rightarrow$ HCC

K-ras codon 13 mutations\(^1,2\)

- in VC-induced ASL (53%) and nontumorous liver (13%)
- In VC-induced HCC (33%) and nontumorous liver (17%)

Workers compensation

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