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Case report:

EXTREMELY LONG LATENCY TIME OF HEPATIC ANGIOSARCOMA IN A VINYL CHLORIDE AUTOCLAVE WORKER

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ABSTRACT

Vinyl chloride is a human carcinogen. The characteristic tumour is the hepatic angiosarcoma, first observed in the 1970s in vinyl/polyvinyl chloride workers, especially in polymerization autoclave workers. Recent epidemiological studies demonstrate a dependence of the tumour incidence on both the duration and cumulative quantity of exposure. However, there is only limited data concerning the possible tumour latency times. Here, a case of hepatic angiosarcoma is presented that had been exposed to vinyl chloride in a very typical way as autoclave worker between 1957 and 1965. The patient was incidentally diagnosed with hepatic angiosarcoma in April 2008. Thus, the tumour latency time, from the beginning of occupational vinyl chloride exposure to clinical diagnosis, was 51 years. This underlines the importance of a continuing medical surveillance of workers exposed to vinyl chloride, at times before its carcinogenicity was recognized and regulatory action could be taken.

Keywords: Vinyl chloride, angiosarcoma, liver, carcinogenicity, latency time

INTRODUCTION AND BACKGROUND

Vinyl chloride has been recognized as a human carcinogen. Case reports of hepatic angiosarcomas (haemangio-epitheliomas) in vinyl chloride-exposed workers (Block, 1974; Creech and Johnson, 1974; Lee and Harry, 1974) and small epidemiological studies (see Kielhorn et al., 2000) were published in the 1970s and 1980s. It was confirmed that occupational vinyl chloride exposures having prevailed until the 1970s were associated with the development of hepatic angiosarcoma. Additional cancer types, particularly hepatocellular carcinoma, have been a matter of discussion.

Within the last 10 years, several cohort studies have demonstrated the increase in the risk of hepatic angiosarcoma with duration of exposure and/or with cumulative exposure to vinyl chloride (Mundt et al., 2000; Ward et al., 2001; Pirastu et al., 2003; Boffetta et al., 2003). In its evaluation of carcinogenicity the International Agency for Research on Cancer (Grosse et al., 2007) arrived at "sufficient evidence" in humans that vinyl chloride causes angiosarcoma of the liver and hepatocellular carcinoma. The relevance of other target sites of carcinogenesis is still debated (Bosetti et al., 2003; Boffetta et al., 2003; Pirastu et al., 2003; Dragini and Zocchetti, 2008).

A large proportion of the angiosarcoma cases observed in the 1970s was among cleaners of vinyl chloride polymerization autoclaves. These employees were regularly exposed to concentrations of 500-1000 ppm vinyl chloride at that time. Soon after introduction of regulatory measures in the late 1970s the numbers of newly diseased cases have dropped rapidly (Gutacker and Lelbach, 1977).

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There are recent indications of geographic/ethnic differences in response to vinyl chloride exposures. In the United States (Mundt et al., 2000; Lewis and Rempala, 2003) hepatic angiosarcoma was strongly associated with vinyl chloride exposure, not with other chemicals used in the production of polyvinyl chloride. The particular focus on hepatic angiosarcoma was also evident in Europe (Hozo et al., 1996, 1997, 2000; Ward et al., 2001; Pirastu et al., 2003; Gennaro et al., 2008). Much in contrast to all studies in "Western" populations, a recent large study on over 3000 workers employed since 1950 in a vinyl chloride polymerization plant in Taiwan failed to demonstrate an increased incidence of hepatic angiosarcoma; instead, an increased risk of hepatocellular carcinoma was found (Wong et al., 2002). By analogy to other industrial chemicals (Bolt et al., 2003), a reason for such a discrepancy could be different toxicokinetics, based on differences in the expression of the key metabolizing enzyme (CYP2E1), between European and East Asian populations. Hence, there is a need of further data from several regions and/or populations.

The hepatic angiosarcoma of the liver caused by vinyl chloride is an officially recognized occupational disease. In Germany, this applies to "BK 1302" of the official list of occupational diseases (Thiess and Frentzel-Beyme, 1975). However, in connection with typical past exposures the range of the associated tumour latency time is still not clear.

Literature data (Kielhorn, 2000) show an overall 5-fold excess of total liver cancer after typical past exposures to vinyl chloride, primarily due to a 45-fold excess risk of angiosarcoma of the liver. The number of vinyl chloride-associated angiosarcoma cases reported up to the end of 1998 was 197 worldwide; the average latency time was 22 years. In 1984, a European angiosarcoma register was established (Hozo et al., 1997).

In Germany, there has been a focus of vinyl chloride-associated angiosarcoma cases in the state of North Rhine-Westphalia, in particular in the area of Cologne/Bonn. Most of these cases were polymerization autoclave workers. From 1975 on, protective measures were introduced that resulted in effective exposure reductions (Gutacker and Lelbach, 1977). Retrospectively, the course of the disease was followed in 21 polyvinyl chloride production workers from this geographical area, covering the period from first exposure to diagnosis and finally to death. In 19 cases death was due to malignant liver tumours, predominantly angiosarcoma, but also cases of hepatocellular and cholangiocellular carcinoma were noted. Two workers died from complications of non-cirrhotic portal fibrosis with portal hypertension. Latency periods in workers with malignant liver diseases in this group ranged from 12 to 34 years; the mean latency time was again 22 years, and a younger age at first exposure (< 27 y) appeared accompanied by shorter latency periods (Lelbach, 1996).

The present report describes a new case from the Cologne/Bonn area, occupationally exposed to vinyl chloride in the 1950-1970s. He contracted a hepatic angiosarcoma in 2008.

CASE DESCRIPTION

The worker was a male person, born 1927, of German descent.

Working history: The person had different jobs (without particular chemical exposure) between 1941 and 1957.

From 1957 to 1987 he was employed in the chemical industry in the Cologne/Bonn area. From 1957 to 1976 he has been worker and foreman in the polyvinyl chloride producing plant. Thereafter, from 1976 to 1986, he was committed with office/administration work (without relevant exposure to chemicals).

Specifically, from 1957 to 1961 he worked in the "autoclave room", where vinyl chloride was polymerized to polyvinyl chloride. From 1961 to 1962 he worked in "polyvinyl chloride drying". From 1962 to 1976 he was foreman in the entire polyvinyl chloride producing department.

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Within the total time since 1957, he was regularly involved in autoclave cleaning between 1957 and 1965 (between 1961 and 1965 to a lesser extent than before).

According to investigations by industrial hygienists of the responsible German Social Accident Insurance (*Berufsgenossenschaft der chemischen Industrie*), the working conditions in general were characterized by frequent transitions of the former airborne concentration limit for vinyl chloride of 100 ppm.

Medical history: In March 2008 the patient became dyspnoeic and was admitted to his local hospital. An embolization of the lung artery was diagnosed, caused by thrombosis of the left *V. poplitea* and the *V. tibialis posterior.* In the course of the diagnostic procedures, computer tomography (CT) revealed two areas within the right lobe of the liver that were considered suspect of metastatic processes. Initially, an abdominal primary tumour was considered, but only non-specific colitis could be found, without any indication of malignancy. On April 2, 2008, a CT-driven punction of one of the suspicious areas in the right caudal liver lobe was performed. Light microscopy revealed necrotic areas with fibroblastic and pseudo-bile duct proliferations, as well as angioma-like changes. Additional immunohistochemistry revealed many parenchymal areas containing CD34-expressing vascular elements. These sinusoids also showed atypical expression of CD105, and cell nuclei were intensively marked by P54-antibody staining. Additional Ki67 immuno-histochemistry stained nearly exclusively the sinusoidal nuclei. This led to the final histological and clinical diagnosis of a hepatic angiosarcoma.

DISCUSSION

There is a remarkable consistency in the organotropism of the carcinogenicity of vinyl chloride between experimental animals and humans (Bolt, 2005). In principle, the compound presents itself as a pluripotent carcinogen, in first instance directed towards endothelial cells (angiosarcoma), secondly towards parenchymal cells of the liver (hepatocellular carcinoma). The active metabolite (Kappus et al., 1975), chloroethylene oxide, is formed in hepatocytes by CYP2E1 (El Ghissassi et al., 1998) and may leave these cells to act on adjacent sinusoidal (endothelial) cells (Ottenwälder and Bolt, 1980).

The occurrence of angiosarcoma of the liver in persons occupationally exposed to vinyl chloride is very specific. This type of tumour is very rare on a sporadic basis. Besides vinyl chloride, known exposure-related causes are arsenicals (Roth, 1957) and the i.v. administration of thorium dioxide (Thorotrast®) as an x-ray contrast medium (Becker et al., 2008). The high specificity of this malignancy was the reason why the causality with vinyl chloride exposure was evident after the first consistent case reports (*vs.*).

The case reported here had a typical working history with high vinyl chloride exposures, specifically upon autoclave work, from 1957 to 1965. He had worked in the polyvinyl chloride producing plant from which the first series of cases of “vinyl chloride disease” in Germany was reported (Jühe and Lange, 1972; Jühe et al., 1973). Sclerodermia-like skin changes, as part of the “vinyl chloride disease”, had been seen in these cases after working periods of 3¼ to 11¾ years. *Raynaud’s* syndrome was observed even earlier, in one case after just 1¾ years of working under these conditions (Lange and Veltman, 1977).

In our present case, the latency time from the beginning of (autoclave) work with vinyl chloride (1957) until the clinical angiosarcoma diagnosis (2008) was as long as 51 years. Against the background of reported data (*vs.*), this is the case with the longest latency time of a vinyl chloride-associated hepatic angiosarcoma ever described. There can be no doubt concerning causality, in view of the specific working history and the rareness and specificity of the tumour.

It therefore appears necessary that all workers exposed to vinyl chloride under respective working conditions (up to the

late 1970s) should be kept under continuous medical surveillance, such as by the „ODIN" system established in Germany (Radek, 1998).

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