

The British Hepatic Angiosarcoma Register

by Peter J. Baxter*

A register of British cases of primary hepatic angiosarcoma (HAS) was established in 1974 to monitor the occurrence of cases from 1963 onwards. Details of cases dying in 1963-77 have been obtained. Thirty-five cases were agreed as HAS by a panel of liver pathologists, and occupational and medical information was obtained in the majority of these. Two cases were attributable to VCM exposure, and eight others had received intra-arterial Thorotrast. In 1978-79, two more cases were confirmed in VCM polymerization workers.

Introduction

In 1974, the Health and Safety Executive embarked upon a mortality study of all workers in Great Britain who had been exposed to vinyl chloride in the manufacture of vinyl chloride (VCM) or poly(vinyl chloride) (PVC), and a register of British cases of primary hepatic angiosarcoma (HAS). The mortality study embraced over 7000 people, and an analysis of deaths up to the end of 1974 has been published (1). The main finding was four certified cases of liver cancer, two of which were histologically confirmed HAS. An update of this analysis has been postponed while, with the collaboration of the factories concerned, exposure data are being refined to take into account job changes and exposure to PVC dust. A mortality study of PVC fabricators was considered, but remains in the planning stage. The register is also the basis for a case-control study of occupation for those cases occurring from 1974 onwards (2).

To determine the annual occurrence of HAS and to monitor its incidence, cases dying in 1963-73 were reviewed as well as those occurring after this period. Information on cases for the 15 years 1963-77 has now been obtained and will be outlined here. Further details may be found elsewhere (3, 4).

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Methods

Cases were identified by a search of death certificates in seven appropriate categories of the International Classification of Diseases for a diagnosis of HAS (or one of its synonyms). Hospital pathologists and cancer registries were requested to report cases, as were the medical departments of factories manufacturing VCM or PVC. Some cases were identified from publications. When available, histological material was sought for all the reported cases and submitted to a panel of three liver pathologists (Drs. P. P. Anthony, R. N. M. MacSween and P. J. Scheuer), who reviewed the slides independently and without knowledge of the prior diagnoses. For control purposes, histological material from other liver cancers was included. For those cases agreed by the panel as HAS, the full medical records were sought and further information, for example, occupational histories and alcohol consumption, was obtained when possible by interview with the next of kin.

Results and Discussion

Eighty-eight cases were reported from all sources. The panel agreed the diagnosis in 32 cases and three more were agreed from among the controls. In half of the confirmed cases the diagnosis had been recorded on the death certificate, but the remainder would have been missed if reliance had been placed upon death certificates as the sole method of ascertainment. At least some clinical and

necropsy details were obtained in all but two patients. Occupational histories were obtained in 91%, the occupation recorded on the death certificate being accepted for the remainder.

The annual numbers of both reported cases and those agreed by the panel increased after 1975, so that in 1977, 12 cases were reported, 10 of which were agreed by the panel. Between 1968 and 1977 an average eight cases per annum were reported and three per annum were agreed by the panel, the population of Britain during this period being about 50 million. The observed increase in incidence was almost entirely due to 10 cases of known etiology; eight were patients who had received intra-arterial Thorotrast (a colloidal suspension of thorium dioxide), and two others had been VCM polymerization workers. Plotting on a map the last places of residence of all 35 agreed cases revealed a cluster of six Thorotrast cases in or around Edinburgh, where the use of Thorotrast in neurological diagnosis had been greater than at any other British center. One hundred and nine patients who had received intra-arterial Thorotrast in Edinburgh during 1933-48 have been followed up in detail (5): about three quarters of these patients have died, 13 (17%) from liver tumors. Histological material for review by the panel was available in nine of these. In those cases dying in earlier years, the tumors were predominantly cholangiocarcinomas, but later cases were all HAS, confirming that the recent emergence of Thorotrast-induced HAS in Britain is a real increase in incidence and not an artifact due to under-reporting of cases occurring in the past.

Twenty-eight of the 35 cases were males; one female infant died aged 8 months. For idiopathic cases, the male:female ratio was 4:1. Adult cases were assigned to one of the Registrar General's five social classes according to the occupation on the death certificates. The social class distribution was unremarkable, except that the only cases in social classes one and two were four men, all of whom were designated as electrical engineers. In fact, six out of the 28 males had worked in the electrical industry at some time, a figure in excess of any other industry. Three other men had been employed in workplaces where PVC was fabricated, but the occupational histories were inadequate to confirm that these men had worked with PVC. One other male case had lived for six years before his death within a half mile of a plant manufacturing PVC. Occupational exposure to arsenic did not appear to be a factor in any of these cases. Arsenical drugs were commonly prescribed in Britain in the past and, in a few areas, even until the

early 1960's. However, one case only was suspected to have clinical evidence of chronic arsenical intoxication, but nail and hair analyses for arsenic were negative and the medical records were inadequate for verifying the use of arsenical drugs. None of these cases was recorded to have taken androgenic steroids (6), but one woman had taken an estrogen preparation for several years. Alcohol did not appear to be an important factor in the majority of cases, only four men having a history of heavy consumption.

In its age distribution, clinical presentation and prognosis, HAS resembled primary liver carcinoma (4). Upper abdominal pain and a hepatic mass were the commonest presentation, and extrahepatic metastases were found in 23% of cases only. Excluding the Thorotrast cases, and for men only, the median interval between the onset of symptoms and death was six months for those aged under sixty years, and only six weeks for those aged sixty and over, a difference which was statistically highly significant. Hemochromatosis was not evident in any of the cases.

In 1978-79, two more cases of HAS have been confirmed in polymerization workers, and another case has led to speculation that hydrazine derivatives, such as phenelzine, may induce angiosarcoma in man (7). It is too early to predict the full impact of past industrial exposure to VCM in Britain and at least until the picture becomes clearer the monitoring of HAS should continue.

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