

Concurrent Malignant Mesothelioma of the Pleura and Hepatocellular Carcinoma in the Same Patient: A Report of Five Cases

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Abstract: Five cases are reported in which malignant mesothelioma of the pleura and hepatocellular carcinoma co-existed in the same patient. The group included four men and one woman, aged between 58 and 86 years. The diagnosis was established at necropsy. In one case the association was clinically suspected. All mesotheliomas were asbestos-related. Liver cirrhosis co-existed in four cases, two of them positive for HCV markers. A lot of elements suggest that the above association is not a fortuitous coincidence. In particular, asbestos could favour liver cancerogenesis by inducing immune impairment.

Key words: Mesothelioma, Pleura, Liver carcinoma, Multiple malignancies, Asbestos, Immune impairment

Introduction

The association between malignant mesothelioma and other primary malignancies has repeatedly been described^{1–26}. Multiple tumors may be a source of serious difficulties in the diagnosis. In addition, the association of more types of cancer is of interest from the etiologic point of view. When the two tumors are metachronous, the hypothesis has to be considered that the treatment adopted for the former malignancy, has induced/or favoured the development of the latter^{13, 21–23}. But the most relevant point is that the development of different cancers in the same subject could indicate that such tumors share some etiopathogenetic factors. We report five cases of pleural mesothelioma associated with hepatocellular carcinoma, and we discuss the possible relationships between these two types of cancer.

Cases

The principal characteristics of the cases are summarized in Table 1.

Case 1

A 86-year-old man had been treated for recurrent right pleural effusions during the last eight months. The patient died for heart failure in February 1994. The necropsy disclosed a malignant mesothelioma of the right pleura (histological type mixed). Right lung, chest wall, pericardium, and peritoneum were involved by the neoplasia. Metastases were found in mediastinic and peripancreatic lymph nodes. Left pleura showed large pleural plaques. The liver showed macro- micronodular cirrhosis and a 2 cm large hepatocellular carcinoma. The patient had worked for 30 years (1937–67) in the shipyards of Monfalcone. Isolation of lung asbestos bodies after chemical digestion following Smith-Naylor method²⁷ showed 88,000 bodies/g dried tissue. Data about hepatitis markers were not available.

Case 2

A 72-year-old man was admitted in January 1996 for a right pleural effusion. Cytological examination of pleural fluid showed the presence of neoplastic cells. Liver ECT showed hepatomegaly and a 2 cm node. Other relevant findings were AFP 1,200 ng/ml, and negative HBV and HCV markers. A diagnosis of liver cell carcinoma was made,

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Table 1. Concurrent malignant mesothelioma of the pleura and hepatocellular carcinoma. Main features in five cases

Case N°	Sex	Age	Asbestos exposure data			Liver cirrhosis	HCV	
			Occupational history	A. b.	P. p.			L. p.
1	M	86	Shipyards worker	88,000	+	56	+	?
2	M	73	Shipyards worker	v.	+	46?	+	-
3	M	71	Sailor, various industries	n. v.	+	?	+	+
4	M	77	Shipyards worker	v.	+	59	+	+
5	F	58	Domestic exposure	70	-	46	-	?

A. b. = asbestos bodies; body amounts/gram of lung dried tissue; v. = visible in routine lung sections; n. v. = not visible in routine lung sections; P. p. = pleural plaques; L. p. = latency period.

and the patient was treated with Tamoxifene and intrapleural Bleomicin. The general conditions remained relatively good for one year. In September 1997, AFP level showed a dramatic increase (88,400 ng/ml). In the following months progressive deterioration occurred, and the patient died with gastroenterorrhagy in November 1997. A diagnosis of probably primary liver neoplasm with pleural metastases was made. At necropsy major findings were malignant mesothelioma of the right pleura (histologically epithelial type), large hepatocellular carcinoma in micronodular cirrhosis, small carcinoma of the urinary bladder, pulmonary asbestosis. The patient had worked as a shipwright at the Monfalcone shipyards for about 25 years after 1950.

Case 3

A 71-year-old man was admitted for left pleural effusion in March 1997. A biopsy of the pleura showed an undifferentiated neoplasia. Chronic liver disease co-existed with positivity for HCV marker. The patient died in June 1997 with diagnosis of pleural mesothelioma and HCV-related liver cirrhosis. The necropsy confirmed the clinical diagnosis; in addition a hepatocellular carcinoma, and large pleural plaques were observed. Mesothelioma, histologically mixed type, had metastasized at several sites (lymphnodes, liver, peritoneum, large bowel, adrenal, kidney). The lungs were involved by severe fibrosis, partly peribronchial and peribronchiolar in pattern, partly with large fibroelastotic scars substituting the parenchyma. Severe anthracosis co-existed. Asbestos bodies were not seen on routine lung sections. The patient had served as an engineer in the Navy for some years. Moreover he had worked in various industries.

Case 4

A 77-year-old man has been treated for HCV-related chronic hepatitis since 11 years. In August 1998 a liver

biopsy showed a hepatocellular carcinoma. The neoplasia was treated by radiofrequency and chemoembolization. In October 1998 a thoracic CT showed a mass involving the soft tissue of left hemithorax associated with left pleural effusion. In the following months several left thoracenteses were performed, and intrapleural bleomycin was given. The patient died in September 1999 with the diagnosis of "HCV-related hepatocellular carcinoma, suspected mesothelioma of the left pleura". At necropsy, the co-existence of the two tumors was confirmed. In addition, micronodular liver cirrhosis, small pleural plaques of the right pleura, and pulmonary asbestosis were observed. Histologically mesothelioma was classified as mixed. The patient had worked as a welder at the Monfalcone shipyards in the period 1939-79.

Case 5

A 58-year-old woman underwent left pleurectomy for malignant pleural mesothelioma (epithelial type) in August 2000. Some months later the patient showed evidence of recurrence, and signs of peritoneal involvement. She died in April 2001, seven months after surgery. At necropsy, mesothelioma involved pleura of both sides as well as peritoneum. The liver showed a small whitish nodule, some millimeters in diameter, with microscopic features of hepatocellular carcinoma. Asbestos bodies were not found on routine lung sections. A small amount of bodies (70/g dried tissue) were detected after isolation.

The patient had a definite history of asbestos exposure, since during the childhood she had cleaned the work clothes of her family members, the father and the uncle, both employed in the shipyards. She had worked in various workplaces, including a small factory in which transistor radios were carried out. It could not be ascertained if asbestos exposure has or not occurred in such place.

Discussion

In the past one of the basic criteria followed in the diagnosis of mesothelioma was to exclude the existence of other primary malignancies. In such a way the possibility of identifying the association of mesothelioma with other types of cancer was eliminated *a priori*²⁸. Nevertheless, it is undoubtful that mesothelioma, like all the other varieties of tumors, may co-exist with other malignancies, and this occurrence has been documented by several researchers. Recently, Suzuki reported 32 cases of double tumor, observed in a very large series of mesotheliomas²⁶.

The current cases illustrate adequately the difficulties of the diagnosis. The co-existence of the two tumors was established at necropsy. However, the double malignancy was clinically suspected in one only of the five cases.

The development of two different primary tumors in the same subject raises the question if some relationship exists between the two types of cancer.

From the etiological point of view it is clear that in the present group all pleural mesotheliomas were asbestos-related. All the patients had histories of not trivial exposure to asbestos, with four of them showing objective signs of such an exposure (pleural plaques and/or high numbers of lung asbestos bodies). Liver carcinoma was related to viral infection at least in two cases, and possibly in the others. Asbestos-related mesothelioma is generally a tumor with a very long latency period²⁹. In the present cases latency periods ranged between 46 and 59 years. Regarding liver carcinomas, the incubation period in the present cases cannot be calculated with precision. However, it is known that in hepatitis C virus-related liver carcinoma, the time interval elapsing between infection and the development of cancer is longer than 20 years³⁰. This means that in the current cases the incubation periods of both tumors elapsed during the same decades. The tumors developed in different organs, but in the same years and on the same background.

A role of virus infection in the genesis of liver carcinoma is well recognized³⁰. On the other hand a possible role of viruses has also to be considered for malignant mesothelioma: SV-40 has frequently been detected in mesothelioma tissues³¹, the development of mesothelioma has been described in some patients with AIDS³²⁻³⁵, and mesothelioma has been reported in association with malignancies, certainly or possibly virus-related, such as Kaposi sarcoma^{14, 25}, and lymphoproliferative disease^{3, 7, 8, 12, 24}.

Various data suggest that immunosurveillance plays a role in the genesis of cancer. Recent findings show that cytotoxic activity of peripheral-blood lymphocytes is inversally

correlated with cancer risk³⁶. As far as hepatocellular carcinoma is concerned, less recent researches indicated that patients with liver cirrhosis and with low natural killer cell activity were at increasing risk of hepatocellular carcinoma³⁷. On the other hand it has been shown that exposure to asbestos is associated with reduced effectiveness of natural killer cells³⁸. This suggests that in four of the present cases immune impairment, induced by asbestos, could have had a role in facilitating the evolution from liver cirrhosis to hepatocellular carcinoma.

The possible role of asbestos in the etiology of liver carcinoma has been proposed^{39, 40}. This hypothesis did not receive attention. Nevertheless, various clues may be found in the literature, suggesting such a role. The classic studies of Selikoff and coworkers on the cohort of insulators of US and Canada, showed high mortality for various types of malignancy, including liver cancer⁴¹. This finding, observed when the death certificates were considered, disappeared when only selected cases investigated more in depth, were included. However, it has been emphasized⁴² that the more suitable term of reference in these studies was the death certificate. In addition, some large studies on linkage of occupation and cancer incidence showed significant associations between primary liver carcinoma and some occupations characterized by heavy asbestos exposure⁴³. Moreover, other researchers have reported significant increase of liver cancer⁴⁴, or increase of liver and biliary passages cancer⁴⁵, among asbestos workers.

In conclusion, some data suggest that the association between malignant pleural mesothelioma and hepatocellular carcinoma does not represent a simple coincidence. Clearly, the available epidemiological data are not sufficient to admit an etiologic role of asbestos in liver cancerogenesis. However, given the high incidence of liver carcinoma in the world and the widespread use of asbestos many countries had, the idea that asbestos might favour liver cancer deserves further attention.

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