

# Renal cell carcinoma and malignant peritoneal mesothelioma after occupational asbestos exposure: case report

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## KEY WORDS

Asbestos; immunohistochemistry; kidney cancer; mesothelioma; occupational cancer; peritoneum

## PAROLE CHIAVE

Asbesto; immunoistochimica; carcinoma renale; neoplasia professionale; peritoneo

## SUMMARY

**Background:** *Asbestos is the main causal factor for malignant mesothelioma (MM), a relatively rare and aggressive malignancy. Some epidemiological evidence suggests a role of this agent also in the etiology of renal cell carcinoma (RCC), the most common form of kidney cancer. Case report:* After 7 years of asbestos exposure, a 76-year-old asbestos-cement worker came to our notice with left flank pain. Diagnostic imaging disclosed a neoplasm in the upper two thirds of the left kidney, without evidence of metastases. After surgery (nephrectomy with para-aortic lymphadenectomy), histopathology revealed clear cell RCC. One year later, the patient was hospitalized for abdominal pain. Laparoscopy showed diffuse neoplastic infiltration of the peritoneum and liver. Histological and immunohistochemical examination of the bioptic samples led to the diagnosis of biphasic MM. The subject died 2 months later. Autopsy disclosed ascites and diffuse infiltration of the abdominal wall and viscera, without evidence of RCC relapse. **Conclusions:** This is the second reported case of association between RCC and peritoneal MM in the scientific literature. Asbestos might be involved in the causation of both malignancies.

## RIASSUNTO

**«Carcinoma renale e mesotelioma maligno del peritoneo dopo esposizione occupazionale ad amianto: descrizione di un caso».** **Introduzione:** *L'amianto è il principale fattore causale per il mesotelioma maligno (MM), neoplasia relativamente rara e assai aggressiva. Alcuni studi epidemiologici suggeriscono un ruolo di questo minerale anche nell'eziologia del carcinoma a cellule renali (RCC), la neoplasia del rene più comune. Descrizione del caso:* Un uomo di 76 anni, che aveva lavorato per 7 anni nell'industria del cemento-amianto, giunse alla nostra osservazione per dolore al fianco sinistro. La diagnostica per immagini rivelò una neoplasia ai due terzi superiori del rene sinistro, senza evidenza di metastasi. Eseguita nefrectomia sinistra, con linfoadenectomia para-aortica. Diagnosi istopatologica di RCC a cellule chiare. Un anno dopo, nuovo ricovero per dolore addominale. La laparoscopia mostrò infiltrazione

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*neoplastica diffusa del peritoneo e del fegato. L'esame istologico e immunohistochimico dei campioni biotici condusse alla diagnosi di MM bifasico. Il soggetto morì due mesi più tardi. L'autopsia rivelò ascite e infiltrazione diffusa della parete addominale e dei visceri, senza evidenza di recidiva del tumore renale. Conclusioni: Questo è il secondo caso d'associazione tra RCC e MM riportato nella letteratura scientifica. L'amianto potrebbe essere implicato nell'eziopatogenesi di entrambe le neoplasie.*

## INTRODUCTION

Renal cell carcinoma (RCC, renal adenocarcinoma) is the most common form of kidney cancer, accounting for 3-4% of adult malignancies. The peak incidence occurs in the sixth decade of life, with a male to female ratio of 3/2. Knowledge about its etiopathogenesis is limited. Established risk factors include genetic predisposition, smoking, obesity, and arterial hypertension. Additionally, some epidemiologic studies found an association with exposure to a number of industrial chemicals (e.g., organic solvents) (8, 19, 35), including asbestos (31).

Malignant mesothelioma (MM) is a relatively rare and aggressive neoplasm, arising from the mesothelial cells of serous membranes (most frequently, pleura or peritoneum). Asbestos is the principal causal agent, and MM is regarded as an epidemiologic marker of exposure to this carcinogen. The disease is more common in men (due the higher male occupational exposure which occurred in the past), however, in the last 30 years, its incidence has increased in both sexes. On average, MM appears 40-45 years after the beginning of asbestos exposure, usually after retirement (20, 26, 28).

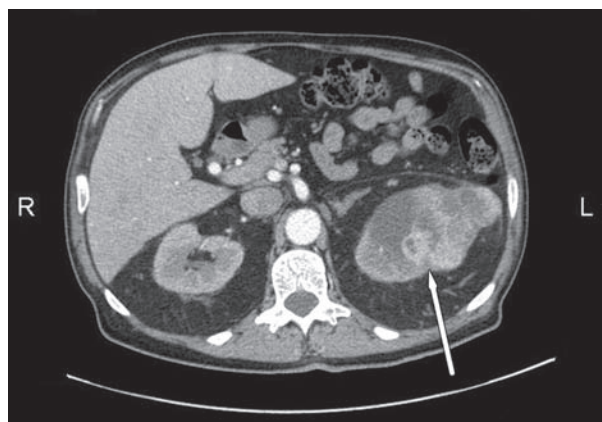
We report the exceptional association of RCC and peritoneal MM in a former asbestos-cement worker.

## CASE REPORT

The patient was a 76-year-old male, former smoker (5 cigarettes a day until age 56), with a history of arterial hypertension and HCV-related chronic hepatitis, who had worked in his youth (22-29 years old) in an asbestos-cement factory in Broni (a small town near Pavia, Northern Italy). His duties included mixing raw materials and cutting asbestos-cement panels with an electric saw. The plant uti-

lized both chrysotile ("white asbestos") and crocidolite ("blue asbestos"), as well as small amounts of amosite ("brown asbestos"). No data on workplace asbestos fibre concentration (in the years of patient's employment) were available, however the patient reported bad industrial hygiene conditions, and lack of protective respiratory devices. This was confirmed by a recent judicial investigation (29). In addition, the man lived about 500 m from the factory where he worked. Besides smoking and asbestos, anamnesis did not disclose other significant exposures to occupational or environmental carcinogens.

At the age of 76, the patient was investigated for left flank pain with abdominal ultrasonography and computerized tomography (CT), which revealed an expansive mass in the upper two thirds of the left kidney (figure 1). Total body positron emission-tomography (PET) showed no evidence of metastases. Left nephrectomy with para-aortic lymphadenectomy was performed. Histopathologic examination of the surgical samples led to a diagnosis of clear cell RCC, moderately differentiated (G2), without renal capsule and lymph nodal invasion (post-operative staging: T2, N0, M0). No adjuvant therapy



**Figure 1** - Abdominal CT scan showing a non-homogeneous substitutive lesion in the left kidney (arrow)

was administered, and the patient was followed up (physical examination, blood/urine analysis, and abdominal echography 4 weeks after surgery, and then every 6 months).

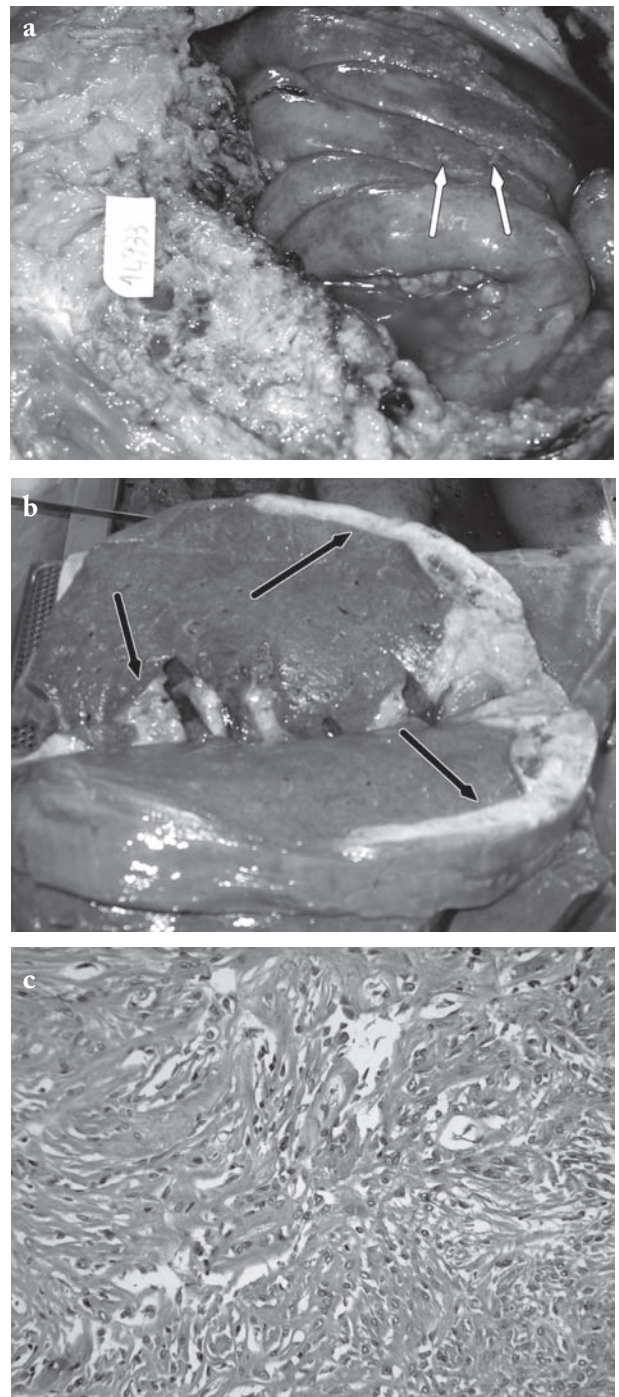
Approximately one year later (just before the third scheduled follow up), the patient was hospitalized for continuous, slowly worsening abdominal pain. Laparoscopy revealed diffuse neoplastic infiltration of the peritoneum and liver, with a carcinomatous aspect. Several bioptic samples were collected. Standard microscopic examination demonstrated neoplastic proliferation with a mixed (epithelioid and sarcomatoid) pattern. Immunohistochemical staining for epithelial markers [carcinoembryonic antigen (CEA), thyroid transcription factor-1 (TTF-1)] was negative, whereas results for the mesothelial markers cytokeratin 7, calretinin, human bone marrow endothelial 1 (HBME-1), and epithelial membrane antigen (EMA) were positive, leading to a diagnosis of (poorly differentiated) biphasic mesothelioma. Chemotherapy with carboplatin (at AUC 2) and etoposide (100 mg/m<sup>2</sup>) was initiated. Both drugs were administered intravenously on days 1, 2 and 3 of each cycle. One cycle of the regimen was defined as a 3-weeks interval. This therapy was interrupted after three cycles due to haematological toxicity. The subject died 2 months later at the age of 79.

Autopsy (figure 2) revealed ascites (approximately 2 litres of serohaematic fluid), and subtotal, coat-like neoplastic infiltration of the abdominal wall, with involvement of the liver, spleen, intestine, and right kidney/adrenal gland. Histological and immunohistochemical examination confirmed the diagnosis of biphasic malignant mesothelioma. No evidence of RCC relapse was found.

Both the Italian Judicial Authority and the National Institute for Insurance against Accidents at Work (INAIL) recognized the occupational origin of the mesothelioma.

## DISCUSSION

The development of renal carcinoma and peritoneal mesothelioma in the same patient is utterly exceptional. Another case (apparently in the absence of asbestos exposure) was previously observed in a



**Figure 2** - Autopsy findings. a: Diffuse neoplastic invasion of the abdominal wall, ascites, and nodular infiltration of the small intestine (arrows). b: Neoplastic tissue coating and infiltrating the liver (arrows). c: Microscopic section of neoplastic tissue showing both epithelioid (oval) and sarcomatoid (fusiform) cells (liver sample; original magnification, x480; hematoxylin-eosin staining)

41-year-old Japanese man (17). The association of RCC with pleural MM is also extremely rare, with only five reported cases: four of them in male subjects with former occupational exposure to asbestos (mostly in shipbuilding) (4, 37), one in a woman with a history of domestic exposure (4).

These observations could be coincidental. In the case described here, smoking and arterial hypertension could have played a role in the development of RCC, but not of MM. It is nevertheless conceivable that the two malignancies share some etiologic factors. Asbestos is the most likely candidate. While the role of this agent in the causation of mesothelioma is well established (20, 26, 28), evidence for a carcinogenic effect on the kidney is conflicting, as discussed below.

The possibility of adverse effects of asbestos on the urinary tract is suggested by the presence of fibres in the urine both of exposed workers (12, 14) and of subjects who had drunk contaminated water (9). Fibres were also found in the renal parenchyma (15, 34), even after environmental, low level exposure (32). Additionally, asbestos bodies were observed in 75% of the kidneys of heavily exposed patients (2).

A significant increase in the incidence of renal tumours was observed in rats orally treated with chrysotile (13, 27). However, in a more recent study, no neoplastic lesions were found in rat kidneys after intra-tracheal instillation of amosite fibres, though glomerulosclerosis and interstitial tubule-fibrosis were observed (5).

A causal role of occupational asbestos exposure in the genesis of kidney cancer is supported by several case-control (21-23, 33) and cohort (11, 40) studies, as well as by case reports (18, 36). On the other hand, other epidemiological investigations yielded negative results (10, 24, 39), and a meta-analysis of occupational cohort studies pointed towards the lack of an association, concluding that high asbestos exposure might entail only a slight increase in risk (38).

In any case, the infrequency of reported synchronous MM and RCC (or other malignancies, such as lung carcinomas) (1) suggests that the pathogenic mechanisms by which asbestos induces MM are different from those inducing carcinomas. Indeed, asbestos is genotoxic for the mesothelial cells, mainly acting (as an initiator) during the early stages of the

oncogenic process, even at very low doses (3). On the other hand, in inducing carcinomas, asbestos probably behaves as a promoter with a threshold-dependent mechanism, acting synergistically with tobacco smoke and other carcinogens (6).

The patient described had been exposed to asbestos several decades before the appearance of the two neoplasms. Such a long latency is common for malignant mesotheliomas (20). Our case suggests the possibility of a similar delayed development also for asbestos-related renal carcinomas, in accordance with previous observations (18).

The diagnosis of peritoneal mesothelioma is usually difficult, due to the rarity of the tumour, its non-specific clinical manifestations (abdominal discomfort or pain, ascites, abdominal masses), and its non-specific histological appearance. With hematoxylin-eosin staining, epithelial (or epithelioid) MM (the most common histopathological subtype) often presents the same morphology as carcinomas, suggesting metastatic invasion of the peritoneum. Sarcomatous (or sarcomatoid) MM may in turn simulate sarcomas originating from connective tissue (e.g., fibrosarcoma). Besides MM, a variety of other abdominal and pelvic malignancies (e.g., gastrointestinal or genitourinary cancer) may in fact present with peritoneal seeding. The only pathognomonic histotype is the mixed (or biphasic) mesothelioma, where epithelioid and sarcomatoid tissues coexist, as in the patient reported here (noteworthy since, in peritoneal MM, the incidence of biphasic tumours is lower than in pleural disease). As a general rule, immunohistochemistry is required for the differential diagnosis and should include (as in the present case) positive and negative markers (7, 16).

Peritoneal MM is a highly aggressive neoplasm, poorly responsive to systemic chemotherapy. The tumour usually invades the abdominal wall and viscera (sometimes in a few weeks, as in the case presented), and may disseminate to lymph nodes and distant organs, such as the lungs (7). Survival is usually a few months from diagnosis, however encouraging results have recently been obtained with cytoreductive surgery plus intra-operative hyperthermic chemotherapy (7, 25).

Besides MM and carcinomas, occupational and environmental asbestos exposure may cause benign

pleural abnormalities and asbestosis (interstitial lung fibrosis), with a risk proportional to the duration and intensity of exposure. Starting in the 1970s, the European Community, USA and Japan progressively introduced restrictive laws concerning the sale and use of asbestos, which was present in a variety of industrial processes. Italy definitively banned its extraction, import/export and use in 1992. However, asbestos continues to represent a major public health concern, since asbestos-induced disease (especially MM) may develop several decades after exposure. Indeed, a mesothelioma epidemic is currently occurring in the industrialized world. Moreover, a large portion of the asbestos utilized in the past is still present in the general environment, and inevitably causes the release of fibres into the air, due to aging and disintegration. Removal of pre-existing asbestos, as well as maintenance, renovation and demolition of old buildings or structures, are current sources of exposure. Worryingly, asbestos is still produced and used in a large number of countries, thus causing further harm for future generations (30).

Therefore, physicians should be aware of the possibility of malignant mesothelioma occurring among workers previously exposed to asbestos. In such cases, careful occupational anamnesis may disclose a causal link between exposure and disease, which is important in the case of legal issues and occupation-related compensation claims. In addition, there should be greater awareness that peritoneal mesothelioma and renal carcinoma may occur concurrently, though very rarely, and is an event with potential clinical and medical legal implications. The presence of MM may in fact prevent accurate recognition of the concomitant kidney neoplasm, and vice versa. Moreover, the presence of RCC in patients with occupational peritoneal mesothelioma requires the second tumour to be assessed as whether or not it is also asbestos-related, and its impact on life expectancy.

#### CONFLICT OF INTEREST

S.M. Candura, Yao Chen and F. Scafa served (and are serving) as experts (for the judge) or consultants (for the public prosecutor, the plaintiff, or the defendant) in several criminal trials or civil proceedings regarding asbestos-related diseases. No remuneration has been received for writing this article.

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