**Renal cell carcinoma and malignant peritoneal mesothelioma after occupational asbestos exposure: case report /.**

**Carcinoma renale e mesotelioma maligno del peritoneo dopo esposizione occupazionale ad amianto: descrizione di un caso**

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**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 linfadenectomia para-aortica. Diagnosi istopatologica di RCC a cellule chiare. Un anno dopo, nuovo ricovero per dolore addominale. La laparoscopia mostrò infiltrazione neoplastica diffusa del peritoneo e del fegato. L’esame istologico e immunoistochimico dei campioni bioptici 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 life decade, 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 the exposure to a number of industrial chemicals (e.g., organic solvents), including asbestos (8, 19, 31, 35).

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 during youth (22-29 years) in an asbestos-cement factory in Broni (a small town near Pavia, Northern Italy). His duties included mixing first matters, and cutting asbestos-cement panels with an electric saw. The plant utilized both chrysotile (“white asbestos”) and crocidolite (“blue asbestos”), as well as small amounts of amosite (“brown asbestos”). No data on workplace asbestos fibres concentration (in the years of patient’s employment) are available, however the patient reported bad hygienic working conditions, and lack of protective respiratory devices. This was confirmed by a recent judicial investigation (29). Additionally, the man lived about 500 m from the factory where he worked.

At the age of 76, the patient was investigated for left flank pain with abdominal ultrasonography and computed 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 was administered, and the patient was followed up.

Approximately one year later, 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 [carcinoembrionary 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/m2) 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 liters 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 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. However, it is conceivable that RCC and MM share some etiologic factors. While the role of asbestos 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 intratracheal 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 to those inducing carcinomas. Indeed, asbestos is genotoxic on 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 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, like in the patient reported here (noteworthy since, in peritoneal MM, the incidence of biphasic tumors is lower than in pleural disease). As a general rule, immunohistochemistry is required for the differential diagnosis and should include (like 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 (as in the case presented), and may disseminate to lymph nodes and distant organs, such as the lungs (7). The survival is usually of few months from diagnosis, however encouraging results have recently been obtained with cytoreductive surgery plus intraoperative 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. Beginning 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 determining further harm for future generations (30).

Thus, 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, it should be known that peritoneal mesothelioma and renal carcinoma may occur concurrently, though very rarely, 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 seving) as expert (for the judge) or consultant (for the public prosecutor, the plaintiff, or the defendant) in several criminal or civil trials regarding asbestos-related diseases. No remuneration has been received for writing this article.

**References**

1. Attanoos RL, Thomas DH, Gibbs AR: Synchronous diffuse malignant mesothelioma and carcinomas in asbestos-exposed individuals. Histopathology 2003; *43*: 387-392.
2. Auerbach O, Conston AS, Garfinkel L, et al: Presence of asbestos bodies in organs other than the lung. Chest 1980; *77*: 133-137.
3. Barlow CA, Lievense L, Gross S, et al: The role of genotoxicity in asbestos-induced mesothelioma: an explanation for the differences in carcinogenic potential among fiber types. Inhal Toxicol 2013; *25*: 553-67.
4. Bianchi C, Bianchi T, Ramani L: Malignant mesothelioma of the pleura and other malignancies in the same patient. Tumori 2007; *93*: 19-22.
5. Boor P, Casper S, Celec P, et al: Renal, vascular and cardiac fibrosis in rats exposed to passive smoking and industrial dust fibre amosite. J Cell Mol Med 2009; *13*: 4484-4489.
6. Browne K: A threshold for asbestos related lung cancer. Br J Ind Med 1986; *43*: 556-558.
7. Cao S, Jin S, Cao J, et al: Advances in malignant peritoneal mesothelioma. Int J Colorectal Dis 2015; *30*: 1-10.
8. Chow W-H, Dong LM, Devesa SS: Epidemiology and risk factors for kidney cancer. Nat Rev Urol 2010; *7*: 245-257.
9. Cook PM, Olson GF: Ingested mineral fibers: elimination in human urine. Science 1979; *204*: 195-198.
10. Edelman DA: Does asbestos exposure increase the risk of urogenital cancer? Int Arch Occup Environ Health 1992; *63*: 469-475.
11. Enterline PE, Hartley J, Henderson VL: Asbestos and cancer: a cohort followed up to death. Br J Ind Med 1987; *44*: 396-401.
12. Finn MB, Hallenbeck WH: Detection of chrysotile asbestos in workers’ urine. Am Ind Hyg Assoc J 1985; *46*: 162-169.
13. Gibel W, Lohs K, Horn KH, et al: Experimental study on cancerogenic activity of asbestos filters [in German]. Arch Geschwulstforsch 1976; *46*: 437-442.
14. Guillemin MP, Litzistorf G, Buffat PA : Urinary fibres in occupational exposure to asbestos. Ann Occup Hyg 1989; *33*: 219-233.
15. Huang J, Hisanaga N, Sakai K, et al: Asbestos fibers in human pulmonary and extrapulmonary tissues. Am J Ind Med 1988; *14*: 331-339.
16. Husain AN, Colby T, Ordonez N, et al: Guidelines for pathologic diagnosis of malignant mesothelioma: 2012 update of the consensus statement from the International Mesothelioma Interest Group. Arch Pathol Lab Med 2013; *137*: 647-667.
17. Kawakita M, Kamoto T, Okabe T, et al: Renal cell carcinoma with malignant peritoneal mesothelioma: report of a case [in Japanese]. Hinyokika Kiyo 1992; *38*: 937-940.
18. Lauriola M, Bua L, Chiozzotto D, et al: Urinary apparatus tumours and asbestos: the Ramazzini Institute caseload. Arch Ital Urol Androl 2012; *84*: 189-196.
19. Lipworth L, Tarone RE, Lund L, et al: Epidemiologic characteristics and risk factors for renal cell cancer. Clin Epidemiol 2009; *1*: 33-43.
20. Magnani C, Bianchi C, Chellini E, et al: III Italian Consensus Conference on malignant mesothelioma of the pleura: epidemiology, public health and occupational medicine related issues. Med Lav 2015; *106*: 325-332.
21. Mandel JS, McLaughlin JK, Schlehofer B, et al: International renal-cell cancer study. IV. Occupation. Int J Cancer 1995; *61*: 601-605.
22. Mattioli M, Truffelli D, Baldasseroni A, et al: Occupational risk factors for renal cell cancer: a case-control study in Northern Italy. J Occup Environ Med 2002; *44*: 1028-1036.
23. McCredie M, Stewart JH: Risk factors for kidney cancer in New South Wales. IV. Occupation. Br J Med 1993; 50: 349-354.
24. Mellemgaard A, Engholm G, McLaughlin JK, et al: Occupational risk factors for renal cell carcinoma in Denmark. Scand J Environ Med 1994; *20*: 160-165.
25. Mirarabshahii P, Pillai K, Chua TC, et al: Diffuse malignant peritoneal mesothelioma – An update on treatment. Cancer Treat Rev 2012; *38*: 605-612.
26. Mossman BT, Shukla A, Heintz NH, et al: New insights into understanding the mechanisms, pathogenesis, and management of malignant mesotheliomas. Am J Pathol 2013; *182*: 1065-1077.
27. National Toxicology Program: NTP toxicology and carcinogenesis studies of chrysotile asbestos (CAS No. 12001-29-5) in F344/N rats (feed studies). Natl Toxicol Program Tech Rep Ser 1985; *295*: 1-390.
28. Neumann V, Löseke S, Nowak D, et al: Malignant pleural mesothelioma - incidence, etiology, diagnosis, treatment, and occupational health. Dtsch Arztebl Int 2013; *110*: 319-326.
29. Oddone E, Ferrante D, Cena T, et al: Asbestos cement factory in Broni (Pavia, Italy): a mortality study [in Italian]. Med Lav 2014; *105*; 15-29.
30. Ogunseitan OA: The asbestos paradox: global gaps in the translational science of disease prevention. Bull World Health Organ 2015; *93*: 359–360.
31. Pascual D, Borque A: Epidemiology of kidney cancer. Adv Urol 2008, Article ID 782381, 7 pages, doi: 10.1155/2008/782381. Available on line at: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2581742/>. (last accessed 27-10-2015)
32. Patel-Mandlik KJ: Asbestos fibers in normal and cancerous human kidneys. Arch Environ Contam Toxicol 1981; *10*: 41-54.
33. Pesch B, Haerting J, Ranft U, et al: Occupational risk factors for renal cell carcinoma: agent-specific results from a case-control study in Germany. Int J Epidemiol 2000; *29*: 1010-1024.
34. Pollice L, Molinini R, Paoletti L, et al: Asbestos fiber count in extra-pulmonary tissues [in Italian]. G Ital Med Lav Erg 1997; *19*: 39-41.
35. Ridge CA, Pua BB, Madoff DC: Epidemiology and staging of renal cell carcinoma. Semin Intervent Radiol 2014; *31*: 3-8.
36. Ron IG, Ron H, Lerman Y: Extrapulmonary neoplasms among asbestos-exposed power plant workers. Int Occup Environ Health 1999; *5*: 304-306.
37. Sawazaki H, Yoshikawa T, Takahashi T, et al: Renal cell carcinoma with malignant pleural mesothelioma after asbestos exposure: a case report [In Japanese]. Hinyokika Kiyo 2007; *53*: 805-808.
38. Sali D, Boffetta P: Kidney cancer and occupational exposure to asbestos: a meta-analysis of occupational cohort studies. Cancer Causes Control 2000; *11*: 37-47.
39. Schlehofer B, Heuer C, Blettner M, et al: Occupation, smoking and demographic factors, and renal cell carcinoma in Germany. Int J Epidemiol 1995; *24*: 51-57.
40. Selikoff IJ, Seidman H: Asbestos-associated deaths among insulation workers in the United States, and Canada, 1967-1987. Ann NY Acad Sci 1991; *643*: 1-14.

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**Figure legends**

**Figure 1 –** Abdominal CT scan showing a disomogeneous substitutive lesion in the left kidney (arrow).

**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).