Sarcomatoid Type of Paratesticular Malignant Mesothelioma in a Dry-Cleaning Worker Exposed to Asbestos and Diagnostic Value of WT-1

Asuman Kilitci*, Nesrin Uygun†, Mustafa Levent Emir‡

Of the 3 major histologic types of malignant paratesticular mesothelioma (MPM) (epithelial, sarcomatoid, and biphasic), many cases of epithelial and biphasic mesothelioma have been reported in the literature. Pure sarcomatoid MPM is the least common but the most aggressive of the 3 major histologic types of mesothelioma cells. It is limited to only 2 cases in the literature The sarcomatoid type of MPM can be confused clinically and histologically with true sarcomas because it is rarely seen. We present a case who had been exposed to asbestos for years due to his involvement in the dry-cleaning industry and who was diagnosed with the sarcomatoid type of MPM but had a relatively prolonged survival not usually seen with this tumor. This report also emphasizes the significance of an immunohistochemical examination, focusing especially on the diagnostic role of WT-1. [*P R Health Sci J 2020;39:39-44*]

Key words: Paratestis, Sarcomatoid malignant mesothelioma, Dry cleaner, Asbestos

Malignant mesothelioma (MM) is a rare tumor that develops commonly in the pleural membrane. It occurs less frequently in the peritoneum and very rarely in either the pericardium or the paratesticular regions such as the epididymis, tunica albuginea, tunica vaginalis, and spermatic cord structures (1). Malignant paratesticular mesothelioma (MPM) corresponds with 0.3 to 1.4% of all cases of malignant mesothelioma (2). Of the 3 major histologic types of MPM (epithelial, sarcomatoid, and biphasic), many cases of epithelial or biphasic mesothelioma have been reported in the literature. Pure sarcomatoid MPM is the least common but the most aggressive of the 3 major histologic types of mesothelioma cells. It is limited to only 2 cases in the literature (2).

We present a patient with a past history of asbestos exposure in a dry-cleaning facility. He was diagnosed with the sarcomatoid type of MPM. His prognosis was believed to be good. Our paper emphasizes the relevance of an immunohistochemical examination for a correct diagnosis, focusing in particular on the diagnostic role of WT-1.

Case report

A 60-year-old male was admitted due to swelling in the left scrotum. He had worked in the dry-cleaning business for 37 years. He had no past history of surgery or trauma. His physical examination revealed a mass in the left scrotum. The right testis was unremarkable. The LDH levels were slightly elevated, at 232 U/L, and the serum hCG and AFP levels were normal. He had a normal hemogram and routine biochemistries. An abdominal CT scan examination showed that there was a conglomerate lymphadenopathy (LAP), with the largest diameter measuring 10 cm, that was compatible with metastasis and arose from the root of the mesentery and extended to the bladder and had a heterogeneous hypodense nature and a lobulated surface. A thoracic CT scan revealed nodules compatible with metastasis under the skin of the chest wall and lytic lesions suggesting metastasis in the posterior left 8th and 9th ribs. An upper abdominal CT scan revealed implants—with the largest diameter measuring 2.8 cm—in the liver capsule and on adjacent serosal surfaces. There were skin thickenings of up to 2 cm in the thickest part at the level of the kidney, on the left lateral side.

A testicular tumor was suspected preoperatively. A left radical inguinal orchiectomy was performed. On a postoperative PET/CT scan, abnormal FDG uptake in a large soft-tissue mass (10 cm in diameter) located in the paraaortic area was observed. This was felt to represent the conglomerate LAP. The tumor markers CA125, CA19-9, CA15-3, PSA, and CEA were within normal limits.

On the macroscopic examination of the mass, the outer surface of the specimen had a nodular appearance, and its integrity was partially deteriorated. Tumor nodules, the largest

*Assistant Professor, Ahi Evran University Faculty of Medicine, Dept of Pathology, Kırşehir, Turkey; †Professor, Istanbul University Cerrahpasa Faculty of Medicine, Dept of Pathology, Istanbul, Turkey; ‡Professor, Ahi Evran University Faculty of Medicine, Dept of Urology, Kırşehir, Turkey

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Address for correspondence to: Asuman Kilitci, Assistant Professor, Department of Pathology, Ahi Evran University Faculty of Medicine, Kırşehir-40200, Turkey. Email: dr.asuk@gmail.com

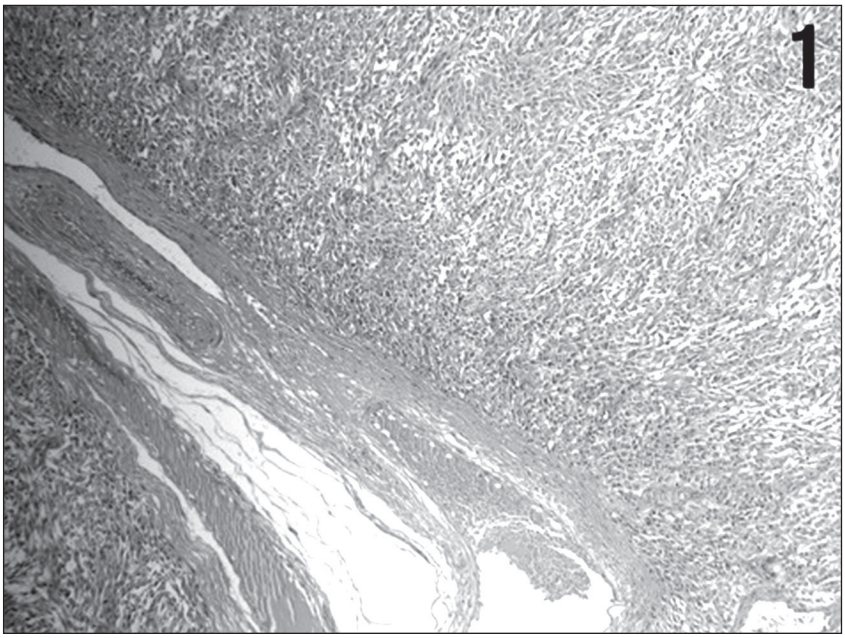

Figure 1. Histopathologic examination demonstrated a malignant tumor which had a multinodular growth pattern (H&E, x50).

one being 5.5x4.2x3.5 cm, were located mostly in the tunica vaginalis and perforated the outermost mesothelial layer of the material. They were dirty white in color and slightly stiff and located around the testis. Tumor nodules were also present in the spermatic cord. The testicular parenchyma, epididymis, and ductus deferens appeared normal. A histopathologic examination revealed a malignant tumor with a multinodular growth pattern in the paratesticular area. The cells were arranged in a fascicular or storiform pattern with both spindle-shaped and polygonal forms. The cells had an eosinophilic cytoplasm and eccentric, oval or round nuclei (Figure 1–3). Central areas of necrosis were observed. Despite examining a large number of slides from different areas of the tumor, we observed no epithelial or other components, except for the sarcomatoid component.

The immunohistochemical examination of the tumor showed that it was diffusely positive for vimentin and WT-1 and was focally positively stained with EMA. However, immunohistochemistry staining showed the tumor to be negative for D2-40, calretinin, panCK, CAM5.2, HBME-1, CK5/6, CD138, desmin, SMA, CD34, CD45, S100, OCT4, AFP, CD30, HCG, CD117, PLAP, CEA, and p53 (Figures 4 [a and b] and 5 [a–f]). The Ki-67 proliferative index was high. There was no tumor in the spermatic cord resection margin or onthe skin of the scrotum or penis. The patient was diagnosed with the sarcomatoid type of MPM. He received 24 cycles of chemotherapy. Although metastases were detected at the time of the patient's diagnosis, he didn't die until 2 years after that diagnosis. This period is greater than the mean survival time reported in the literature.

Discussion

MPM is most commonly seen in patients who are 55 to 75 years old, with a wide distribution in those from 6 to 91 years (1,3). About 10% of the cases are seen in patients under the age of 25, including pediatric cases (3,4). Our case presented at 60 years of age.

The most common referral complaints of patients are a painless palpable unilateral scrotal mass, swelling, pain, hydrocele, and scrotal tension (5). Even when a complete physical examination is made, there may be a delay in making a definitive diagnosis due to the absence of specific tumor markers, the presence of non-specific symptoms, the wide age range, recurrent hydrocele, epididymo-orchitis, or the misdiagnosis of inguinal hernia (1,3). For these reasons, in only a very few cases has a correct preoperative diagnosis been made (6). Our patient also presented with swelling.

Most of the time, MPMs arise from the tunica vaginalis as well as, less frequently, from the spermatic cord and epididymis (7). Although the developmental mechanism of MPM is not well understood, exposure to asbestos or material containing asbestos is the best-known risk factor. Studies have suggested

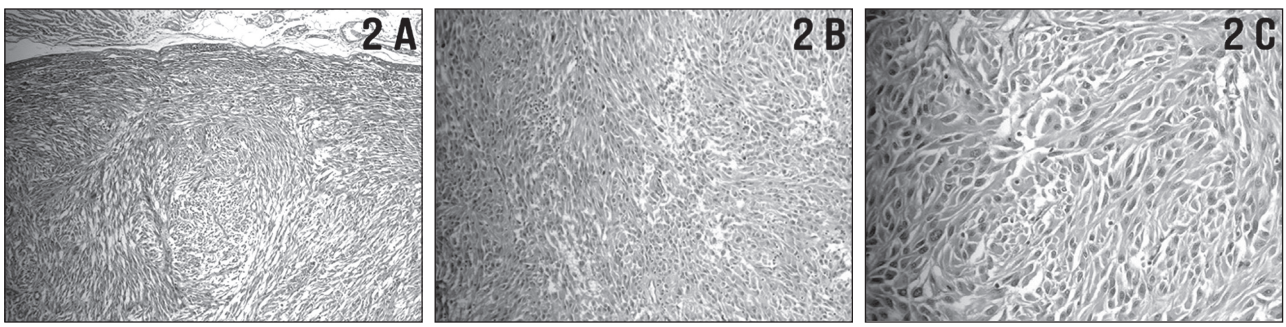

Figure 2A–2C. Neoplastic cells were arranged in a fascicular or storiform pattern with both spindle-shaped and polygonal forms (H&E, x100; H&E, x200; H&E, x200).

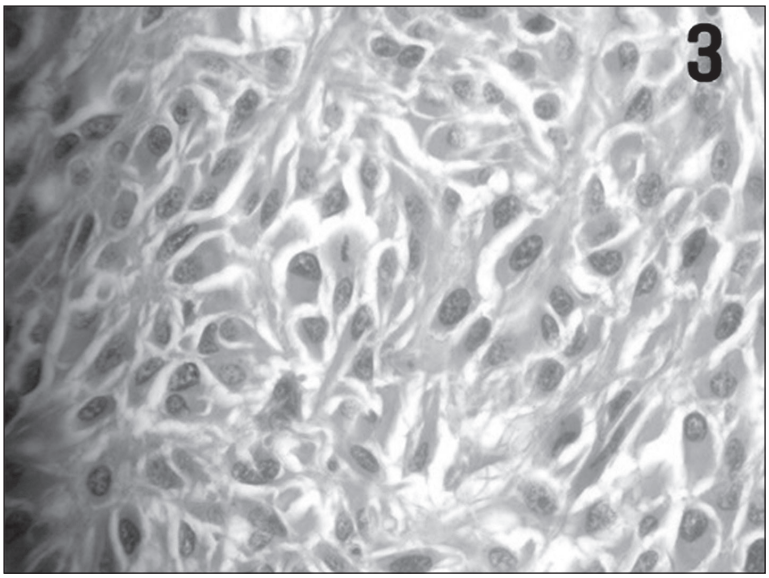

Figure 3. Atypical mesothelial cells with eosinophilic cytoplasm and eccentric oval or round nuclei (H&E, x400).

that chronic hydrocele and trauma as well as radiation, radiotherapy, chromosome anomalies, and viral infections are risk factors in the development of testicular mesothelioma. The disease can also occur in the absence of any risk factor. The association of MPM with asbestos exposure was first proposed by Fligiel and Kaneko in 1976 (8). Although the incidence of asbestos exposure in MPM is underestimated due to insufficient clinical knowledge, such exposure is reported to be present in 23 to 41% of subjects (1). The diagnosis of mesothelioma is based directly on occupational asbestos exposure, but there are individuals who are indirectly exposed via the environment (e.g., at home) and have no direct occupational exposure (8). The long latency period, which ranges from 15 to 60 years from the onset of asbestos exposure to the onset of MM, explains the increase in mesothelioma mortality rates (6).

Asbestos is generally used in industrial areas, such as building and housing construction (including the manufacture of insulation and wall paneling), automotive assembly and repair (e.g., brake pads), ship building and repair, cement production, injection molding, casting, and the maintenance and demolition of asbestos-containing materials. Dry-cleaning workers are in a very high-risk group due to their exposure to asbestos-containing materials in their work environments. Our patient owned a dry-cleaning business for 37 years and therefore was exposed to asbestos-containing materials for this duration. We have been unable to document dry cleaning–linked occupational exposure in the literature as a risk factor for sarcomatoid MPM.

When we investigated the relationship between asbestos exposure and dry-cleaning employees, it was observed that there are several ways in which dry-cleaning employees are exposed to asbestos products. The boiler-fueled steam presses are a cause of exposure to asbestos; there is also some asbestos in some parts of the equipment used in large laundry facilities. In the past, asbestos was used to cover the boilers and steam pipes; the surface pads of the pressing machinery were also made from asbestos in the past. Dry-cleaning employees were thus exposed to asbestos due to their frequent use of the steam-press pads. The large washers and dryers that were used for commercial purposes were also made with asbestos (9,10).

On macroscopic examination, various presentations may be seen, from diffuse thickening of the tunica vaginalis to numerous, hard, dirty-white nodules on or around it (1). MPM is usually unilateral and rarely bilateral and may invade the paratesticular areas such as the testes, epididymis, and spermatic cord. A histopathological examination is essential to establish the correct diagnosis (11).

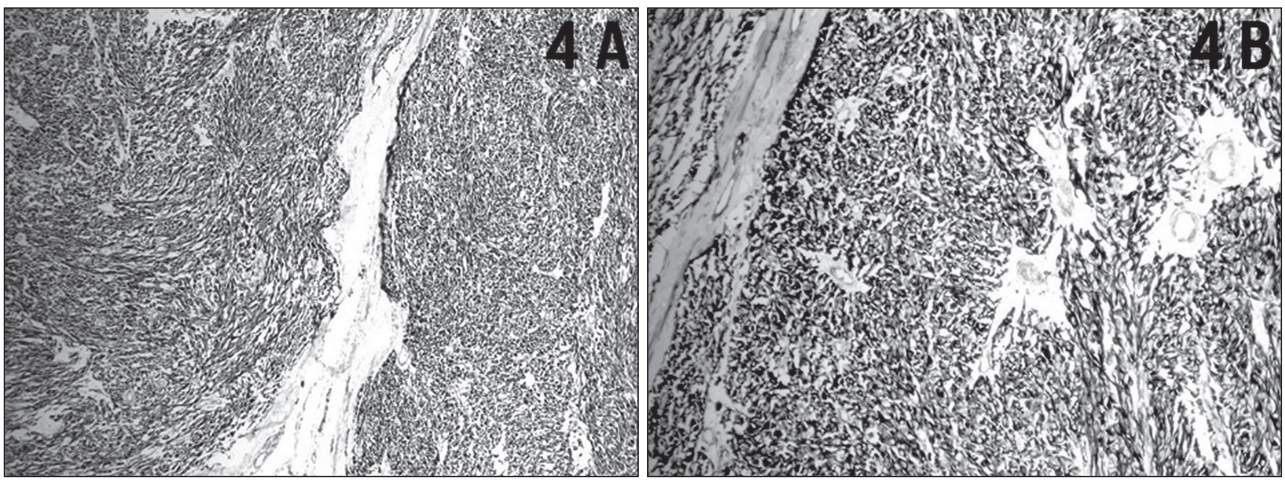

Figure 4A–4B. Immunohistochemical examination of sarcomatoid malignant mesothelioma; the tumor was diffusely positive for WT-1 (x50, x100).

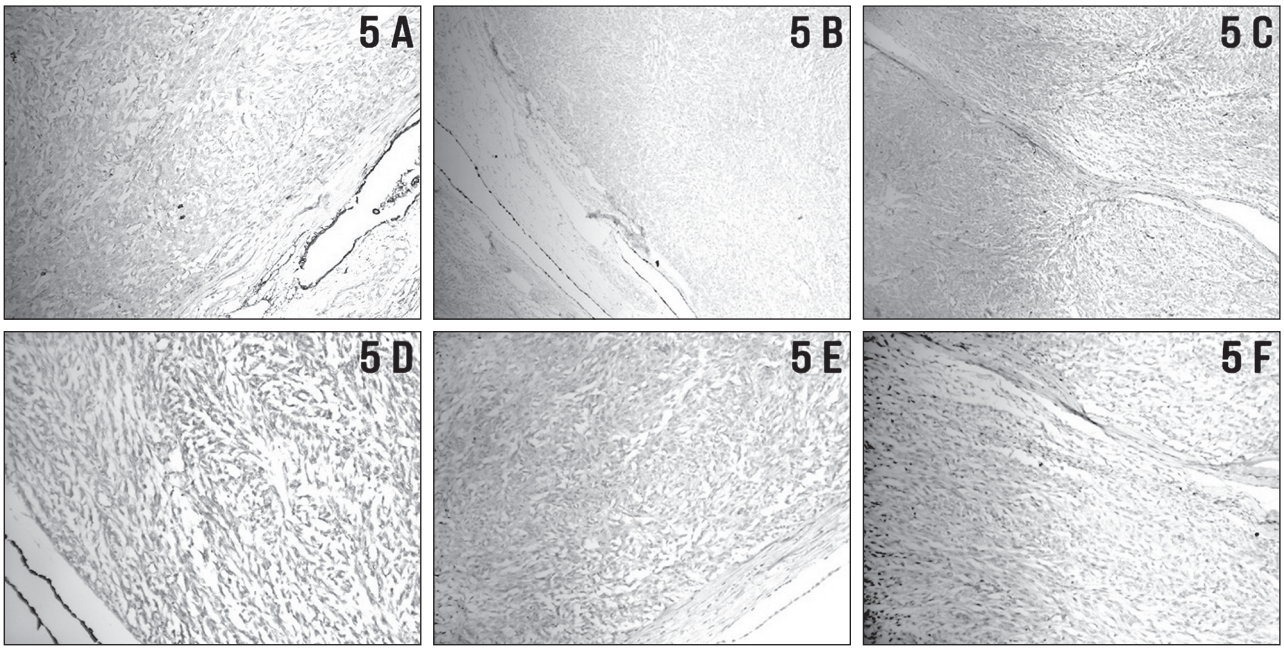

Figure 5A–5F. Sarcomatoid tumor cells were non-immunoreactive to HBME-1 (5A), x100; calretinin (5B), x50; CD68 (5C), x50; PanCK (5D), x100; D2-40 (5E), x100; and CD138 (5F), x100.

Sarcomatoid mesothelioma is defined as the presence of a predominantly sarcomatoid component in a given patients biopsied material with no epithelial components or the epithelial tissue less than 10%. (12).Microscopically, there are spindle-shaped neoplastic mesothelial cells with eosinophilic cytoplasm that are arranged in a fasciculus and storiform pattern. A histological diagnosis of sarcomatoid mesothelioma is more problematic than other types due to its resemblance to malignant spindle-cell neoplasms along with the presence of limited or incompatible expression of mesothelial immune markers (12). The World Health Organization classifies malignant mesothelioma as epithelial, mesenchymal/sarcomatoid, and biphasic/mixed types, each of which can be subdivided further (12). This classification has implications for both diagnosis and prognosis (12). The most common subtypes of MPM are the epithelial (60–70%) and biphasic (30–40%) types. The sarcomatoid type is rarely seen and is limited to 2 cases in the literature (13). Klebe et al. identified several histological subtypes in 326 cases of sarcomatoid mesothelioma originating from the pleura and peritoneum. These subtypes were desmoplastic, osteosarcomatous and/or chondrosarcomatous mesothelioma, sarcomatoid mesothelioma showing desmoplastic features, sarcomatoid mesothelioma with lymphohistiocytoid histology and conventional sarcomatoid malignant mesothelioma of no special subtype. The most common tumor type was conventional sarcomatoid malignant mesothelioma of no special subtype, with a rate of 44% (12). The immunohistochemical profile of MM includes the positivity of CK7, CK5/6, calretinin, EMA, D2-40, HBME-1, and thrombomodulin and the negativity of CK20, CEA, BerEP4, and MOC32, B72.3. Calretinin positivity distinguishes mesothelioma from adenocarcinoma (8). The negativity of immunohistochemical markers such as PLAP, OCT4, SAL-4, and CD30 and the absence of intratubular germ cell neoplasia distinguish MPM from germ cell tumors such as seminoma and embryonal carcinoma (11). Vimentin immunoreactivity varies from negative to diffusely positive according to the sarcomatous component (2). The current literature reports on the positive expression of WT1 and CD138 in malignant mesothelioma of the tunica vaginalis (8).

Differentiating between sarcomatoid mesothelioma and sarcomatoid tumors, which both involve the pleura, peritoneum, pericardium, and tunica vaginalis, has a crucial significance for optimal clinical management, in terms of making a diagnosis. This last is quite difficult to do with only a routine exam with light microscopy. Recently, a few immunohistochemical markers have been added to the spectrum of markers, but there are many used to differentiate epithelial mesothelioma from adenocarcinoma. A limited number are present to define sarcomatoid mesothelioma.

Moreover, the accuracy of immunohistochemistry in distinguishing sarcomatoid carcinoma from other sarcomatoid tumors is unclear (14). Kushitani et al. have suggested that an immunohistochemical panel consisting of a combination of CAM5.2, AE1/AE3, and WT1 antibodies is most useful for distinguishing sarcomatoid mesothelioma from sarcomas. They have also reported that there is currently no useful marker for distinguishing sarcomatoid mesothelioma from sarcomatoid carcinoma. Unlike epithelial mesothelioma, which shows nuclear positivity for calretinin and WT1, sarcomatoid mesothelioma mainly shows cytoplasmic positivity for calretinin and WT1 (14). Chirieac et al. indicated that D2-40 and podoplanin were

immunohistochemical markers which had a high sensitivity for sarcomatoid pleural mesothelioma and had a high specificity and sensitivity for epithelial pleural mesothelioma, and that few cases were positive for calretinin (about 20%) or WT-1 (about 30%). Moreover, they also stated that a negative stain did not exclude sarcomatoid mesothelioma (15). Klebe et al. reported that the positive expression of CK, vimentin, and calretinin was quite characteristic for sarcomatoid MM. They found that 93% of the 280 patients with pleural and peritoneal tumors were positive for CK and 31% were focally positive for calretinin (12). Although we applied a broad immunohistochemical panel to this specimen, the diffuse positivity of WT1 and vimentin led to the definitive diagnosis.

Elevated levels of testicular tumor markers, including AFP, beta-hCG, and LDH, help in the diagnosis of testicular tumors. In MPM, testicular tumor markers are usually within normal limits (16). On scrotal ultrasound, MM is usually characterized by a hypoechoic hydrocele containing echogenic, heterogeneous masses at the periphery (5). At the time of diagnosis and in approximately 15% of cases, thoracic and abdominal CT scans are generally used for clinical staging, determining the presence (or absence) of distant organ metastasis, and the detection of retroperitoneal lymph node metastasis (16). Positron emission tomography (PET) is useful for differential diagnosis and follow-up.

The absence of a testicular intraparenchymal mass in the gross examination is a significant finding. In our case, the testicular parenchyma and size were normal.

Sarcomatoid mesotheliomas can be histologically and clinically confused with other spindle-cell tumors. This variation in the histology may cause confusion with soft-tissue tumors, including primary/metastatic sarcomatoid carcinoma, leiomyosarcoma, rhabdomyosarcoma, pleomorphic sarcoma, a malignant peripheral nerve sheath tumor, and fibrosarcoma (12,14). At this point, it should be noted that the role of immunohistochemistry is more limited for sarcomatoid MM than for epithelial MM because staining for markers is often less positive in sarcomatoid MM than it is in epithelial MM (12).

Although other antibodies may be helpful, WT-1 is the most significant immunohistochemical marker for distinguishing sarcomatoid mesothelioma from sarcomas. Ascoli et al. suggested that the possibility of a given tumor's having a multicentric origin could not be ruled out in a case of MM involving the pleura, peritoneum, and/or tunica vaginalis, but the first affected region might be the pleura, according to the clinical chronological order, possibly spreading to the peritoneum and tunica vaginalis, respectively (17).

The initial management is surgery, with optional postoperative radiotherapy and/or chemotherapy. Despite radical orchiectomy and adjuvant treatment (chemotherapy and/or radiotherapy), recurrence and distant metastasis occurs in about half of the cases (5,11). Local recurrence after orchiectomy is reported in approximately 10% of patients. The necessity of inguinal or iliac lymph node dissection in primary treatment remains controversial. In metastatic or advanced disease, palliative chemotherapy may reduce tumor volume and seems to play a role in increasing the survival of patients (up to 10 months) (8). The chemotherapy regimens of MPM are similar to those used in pleural mesothelioma. Cisplatin and pemetrexed are frequent chemotherapeutic agents (8,16).

MPMs are aggressive neoplasms that have the ability to cause extensive local spread as well as lymphatic and hematogenous tumor spread (6). In a study from Plas et al., the most commonly reported sites of metastasis were the lymph nodes (13.8%), lungs (9.7%), and liver (4.2%), respectively (3). While the pelvic lymph nodes (iliac and obturator) usually become metastatic at an advanced stage, the paraaortic lymph nodes are the most common metastatic site (6). The histological pattern and differentiation of the tumor, presence of lymph node involvement, and age of the patient are the most important prognostic factors (6,18). In general, tumors with a sarcomatoid component have a poor prognosis (19). Patients younger than 60 years of age tend to have better results (6). Recurrence occurs in 60% of cases within 2 years after diagnosis, and in more than 90% of cases within 5 years after diagnosis (8). The mortality rate after mean 2-year survival is around 30% (8).

Of all the mesotheliomas, sarcomatoid MM has the poorest prognosis. In various studies, the mean survival rates have been reported to be 5.5, 5.8, 6.0, or 6.2 months (12). It responds poorly to chemotherapy. Although our case was diagnosed at an advanced stage, he survived longer than did similarly afflicted individuals reported on in different studies.

There are many structures in Puerto Rico, and in many other places, containing asbestos. Recognizing this type of malignancy (and other asbestos-related neoplasias) is important for physicians treating patients with a history of exposure to asbestos. A patient's history of asbestos exposure should be explored in detail. Tumors with a mesothelial origin should be considered in cases with normal tumor markers and having extensive tumor nodules. The sarcomatoid type of MPM can be confused clinically and histologically with true sarcomas because it is rarely seen and requires immunohistochemical methods for its proper diagnosis. The critical importance of WT-1 as a diagnostic tool should not be forgotten.

Resumen

Dentro de los 3 principales tipos histológicos de mesotelioma maligno paratesticular (MMP) (epitelioide, sarcomatoide y bifásico), muchos casos de epitelioide y sarcomatoide han sido reportados en la literatura. MMP sarcomatoide puro es el menos común pero el más agresivo de los tres principales tipos histológicos de células mesoteliales. Está limitado solo a dos casos. El MMP variedad sarcomatoide puede ser confundido clínicamente e histológicamente con un sarcoma puro porque es raramente visto. Nosotros presentamos un caso con exposición a asbestos en una tintorería y fue diagnosticado como MMP variedad sarcomatoide y tuvo relativamente un buen pronóstico, lo cual no ha sido

reportado previamente en la literatura. Este reporte también enfatiza la importancia del examen de inmunohistoquímica, especialmente en el rol diagnóstico de WT-1.

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