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CASE REPORT

Patient with recurrent paratesticular malignant mesothelioma and multiple primary neoplasms

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Abstract

Paratesticular malignant mesothelioma (MM) is a rare tumor frequently associated with asbestos exposure. Therefore, we present an even rarer case of a 78-year-old male patient diagnosed with multiple primary neoplasms, including prostate cancer, lung cancer, paratesticular MM, and upper tract urothelial carcinoma. The patient initially presented with a painless testicular mass and had a notable medical history of prostate and lung cancers. Following physical examination and an ultrasound evaluation, he underwent radical right inguinal orchiectomy, which revealed paratesticular MM. The patient's lung cancer recurrence and subsequent treatment coincided with periods of no MM recurrence. However, after the lung cancer treatment, the MM recurred multiple times within short intervals. This unique case indicates that systemic treatments for lung cancer, specifically cisplatin-based chemotherapy and atezolizumab immunotherapy, might also have an anti-tumor effect on paratesticular MM. Although MM combined with multiple primary neoplasms is challenging to treat and frequently recurs, treatments for other malignancies, as evidenced in this case, may have suppressive effects on the recurrence and metastasis of MM.

Keywords

Malignant mesothelioma; Multiple primary neoplasm; Testicular tumors

1. Introduction

Paratesticular malignant mesothelioma (MM) is a rare tumor accounting for approximately 0.3–1.4% of all MM cases and typically manifests as an inguinoscrotal mass [1]. Occupational or environmental asbestos exposure is a major risk factor for MM development, with a latency period of up to 60 years [2, 3]. Multiple primary neoplasms are two or more synchronous or metachronous tumors in the same patient [4]. The frequency of multiple primary neoplasms reportedly accounts for 2–17% [4]. Furthermore, the treatment of multiple primary tumors is challenging and frequently causes medical dilemmas [4]. The reported cases of multiple primary neoplasms, including localized paratesticular MM, are exceedingly rare. To our knowledge, only one of these cases is available in the medical literature [5]. Here, we report the diagnosis and 12-year follow-up of a male patient with four histologically distinct malignancies: prostate cancer, lung cancer, paratesticular MM and urothelial carcinoma.

2. Case presentation

A 78-year-old male patient presented with a painless palpable mass in the right testis in February 2018. On physical examination, the right testicular mass was approximately 4 × 3 × 2.5 cm in size, non-tender, globular and firm. An ultrasound (US) scan revealed 3.5 × 2.8-cm sized nodular mass with heterogeneous echogenicity and high vascularity alongside complicated fluid in the right tunical sac (Fig. 1).

The patient had medical history of prostate and lung cancers, hypertension, epididymo-orchitis, bladder stones, had never smoked and did not have apparent asbestos exposure. In 2011, the patient underwent laparoscopic radical prostatectomy and was diagnosed with pT3a prostate cancer with a Gleason score of 7 (3 + 4). In 2015, the patient underwent right upper lobectomy with mediastinal lymph node dissection for abnormal nodular lung lesions that had increased in size on serial computed tomography (CT) scans. Well-differentiated adenocarcinoma of the lung at the T2a stage was diagnosed. After these major surgeries, prostate-specific antigen levels remained stable at an undetectable level, and no metastatic lesions in the lymph nodes or distant organs occurred. Given the patient's medical history of prostate and lung cancer, physical and US findings, testicular cancer, lymphoma and rare metastatic tumor were considered differential diagnoses for the scrotal mass. In March 2018, radical right inguinal orchiectomy with high ligation of the spermatic cord was performed, and severe adhesion between the mass and Dartos fascia was identified during the surgery. According to the pathological report, the mass was 4.5 × 3.3 × 2.7-cm sized MM of the testis without evidence of germ cell neoplasia and lymphovascular tumor emboli. Epithelioid tumor cells infiltrated paratesticular soft tissue and presented

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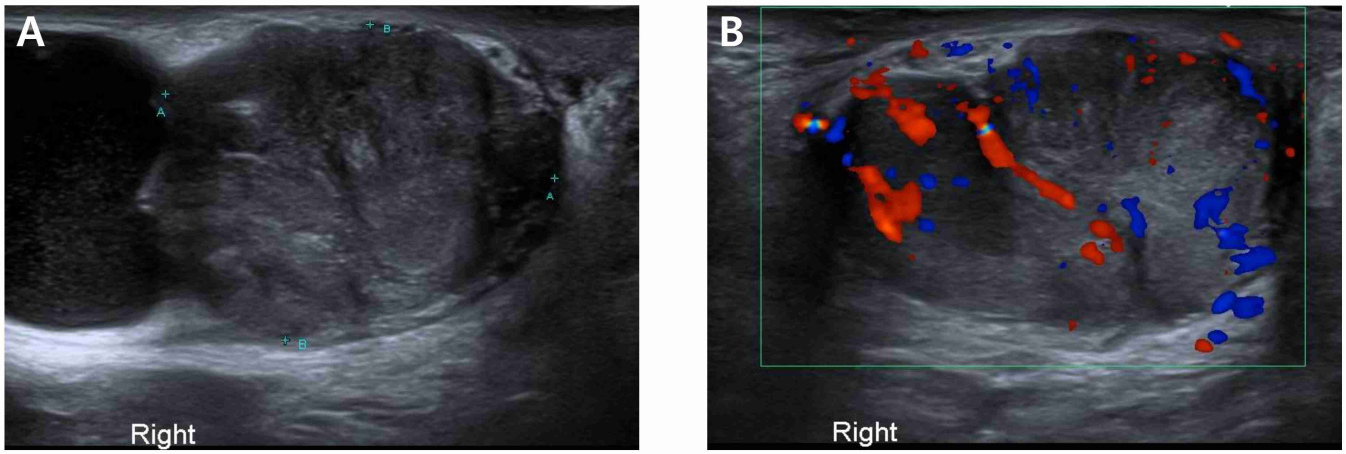

FIGURE 1. Ultrasound scan images. (A) Ultrasound scanning for right testicular mass. (B) Ultrasound scanning with color doppler mode for right testicular mass.

with tubular and micropapillary growth patterns (Fig. 2). Immunohistochemistry showed positive staining for calretinin, cytokeratin (CK) 7, and epithelial membrane antigen (EMA), and negative staining for carcinoembryonic antigen (CEA), CK 20 and inhibin (Fig. 3). Although the radial resection margin was affected by the tumor, the edge of the resected spermatic cord was cancer-free, with a safe margin of 6.5 cm.

During surveillance for lung cancer in June 2018, multiple lung nodules were revealed on chest CT, which were highly suggestive of recurrence. After surgical resection of the lung lesions in the left upper and lower lobes, the recurrence of lung adenocarcinoma was pathologically confirmed. From August 2018 to July 2020, the patient received cisplatin-pemetrexed combination chemotherapy, followed by pemetrexed as maintenance. In August 2020, the patient showed lung cancer progression despite palliative chemotherapy. Therefore, immunotherapy with atezolizumab, which is a monoclonal antibody targeting programmed death ligand 1, was administered [6]. After 1 year of atezolizumab treatment, lung cancer progressed again in August 2021, and a third-line systemic therapy for lung cancer was suggested; however, the patient refused it.

In October 2021, shortly after the systemic treatment for lung cancer, an approximately 4.2-cm sized, non-tender right inguinal mass was identified, which was surgically excised and proved to be recurrent MM of the spermatic cord. After 2 months, the patient underwent left nephroureterectomy for 3.1- and 0.5-cm sized urothelial carcinomas of the renal pelvis and proximal ureter, respectively. Furthermore, he experienced two additional pathologically confirmed recurrences of MM of the spermatic cord in the right inguinal area, which were surgically removed in May and December 2022 (Fig. 4A–C). In February 2023, based on the follow-up CT scan, a newly identified 1.8 cm sized nodular mass was found in the right inguinal region, strongly suggesting another recurrence of MM in the spermatic cord (Fig. 4D). Enlarged lymph nodes in the retrocaval and aortocaval areas and polypoid lesions in the right wall of the bladder were also noted, suggesting lymph node metastasis of undetermined origin and intravesical recurrence of urothelial carcinoma, respectively. Unfortunately, the patient died of aggravated lung conditions in April 2023 after his last visit to our medical center, presenting with burning pain in the chest and a severe cough.

3. Discussion

MM is a treatment-resistant and aggressive tumor that is primarily associated with asbestos exposure [7]. It originates from mesothelial cells that line serosa, such as peritoneum, pleura and tunica vaginalis of the testis. Paratesticular MM represents approximately 0.3–1.4% of all MM cases [1]. Typically, these tumors manifest as inguinoscrotal masses that mimic hydroceles or intrascrotal tumors. More than 55% and 30% of patients present with symptoms of scrotal mass with hydrocele and paratesticular mass, respectively. Additionally, the highest prevalence is observed in individuals aged 55–75 years [8].

Occupational or environmental asbestos exposure is a major risk factor for MM development, with a latency period of up to 60 years [2, 3]. Despite the association between asbestos exposure and MM, spontaneous or idiopathic MM and non-asbestos mineral-induced MM have also been reported [9–11]. Therefore, the absence of a medical history of asbestos exposure does not rule out the possibility of developing MM.

The accurate diagnosis of MM of the spermatic cord is crucial but rarely achieved preoperatively, posing a challenge for patient management [12, 13]. Most cases of MM of the spermatic cord are determined intraoperatively and present with papillary excrescences or fibrotic thickening of tunica vaginalis with or without hemorrhagic hydrocele fluid [8]. Radiological modalities, such as CT, magnetic resonance imaging, and positron emission tomography, are important in MM diagnosis and monitoring [14]. However, final confirmed diagnosis of MM was based on pathological report after surgical excision. Pathological diagnosis of MM can be made by demonstrating mesothelial, epithelial or sarcomatous differentiation in tumor cells [14]. On microscopic examination, a paratesticular MM predominantly appears as a pure epithelial or mixed type [15], and its growth pattern is frequently papillary or tubulopapillary, similar to that of peritoneal and pleural

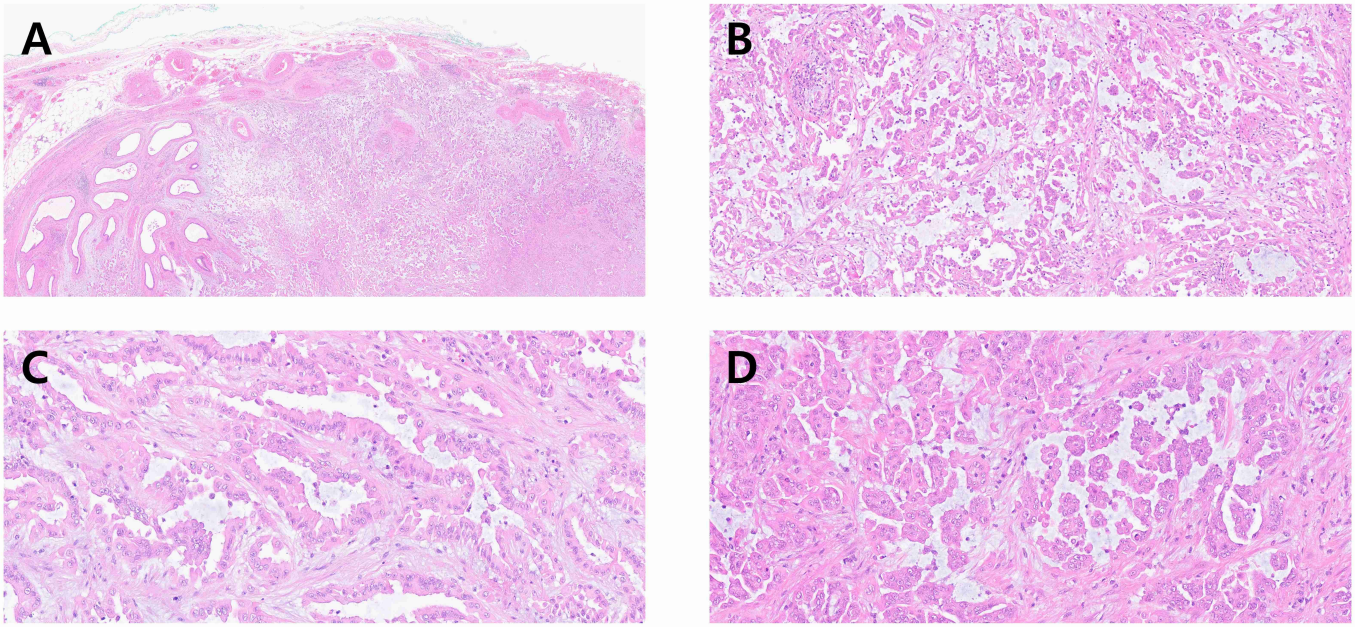

FIGURE 2. Representative pathological images. (A) Tumor cells infiltrating paratesticular soft tissue (hematoxylin and eosin staining (H&E), ×40). (B) Epithelial cells with eosinophilic cytoplasm showing micropapillary growth pattern (H&E, ×200). (C,D) Large polygonal epithelioid cells with fair amounts of cytoplasm and round to oval nuclei showing tubular and micropapillary architectural patterns (H&E, ×400).

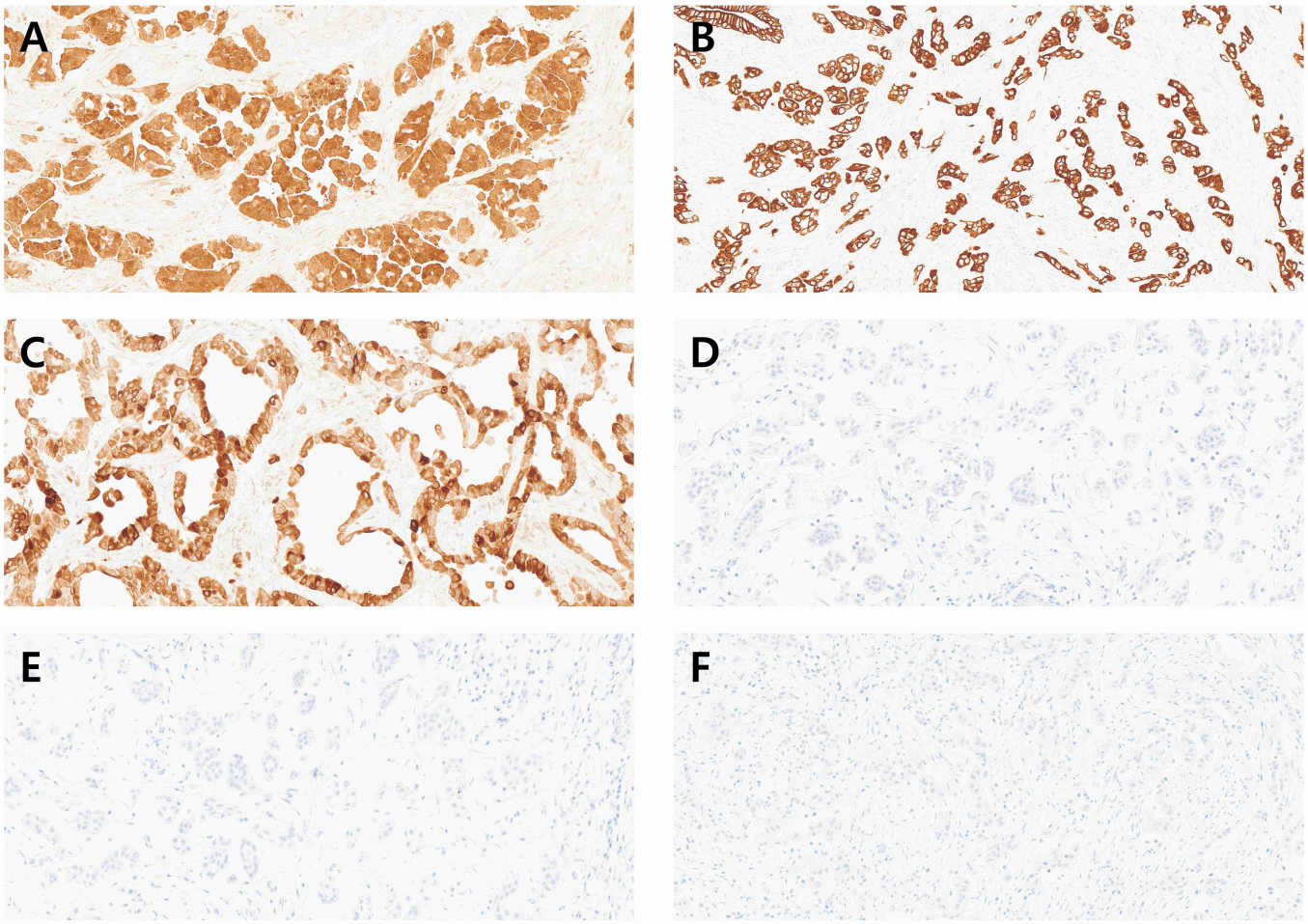

FIGURE 3. Representative immunohistochemical images. Positive for (A) calretinin, (B) CK 7 and (C) EMA Negative for (D) CEA, (E) CK 20 and (F) inhibin (immunohistochemistry staining, ×400).

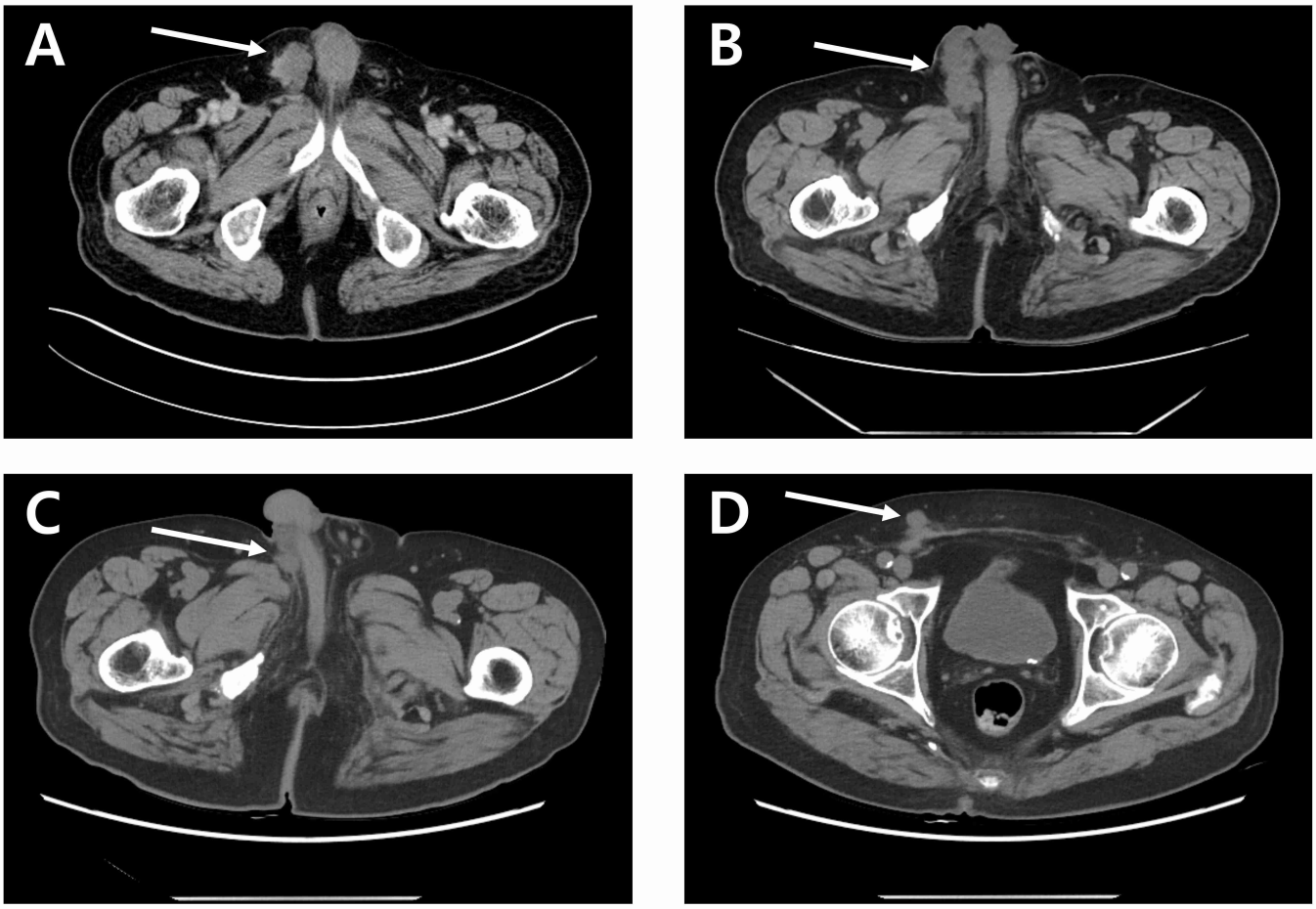

FIGURE 4. Computed tomography scan images. Recurrences of paratesticular malignant mesothelioma in (A) October 2021, (B) April 2022, (C) November 2022 and (D) February 2023.

MM. Invasion into subtunical connective tissue, testis and epididymis has been observed in approximately one-third of cases [15]. Hyaluronidase-sensitive mucin-containing intracytoplasmic vacuoles were identified using Alcian blue histochemical staining. Immunohistochemical analysis revealed that MM tests were positive for CK 7, CK 5/6, EMA, thrombomodulin and calretinin. However, the tumor was negative for CK 20 and CEA [1, 15].

More than 60% of patients experience tumor recurrence within 2 years of follow-up, with approximately 40% mortality rates following disease progression. Only 16% of patients present with local recurrence without definite evidence of distant metastasis [8]. However, the overall prognosis is poor, with median survival of 23 months, which is reduced to 14 months if recurrence occurs [8]. Because of the aggressive and treatment-resistant features, including local recurrence and distant metastasis through lymphatic and hematogenic routes, diverse treatment strategies have been studied and surgery, cisplatin-based chemotherapy, radiotherapy or a combination of these modalities are commonly used [1, 7]. Since inguinal or scrotal orchiectomy demonstrates the best rates of local control, reaching 90%, radical surgical excision should be the primary treatment [8]. Furthermore, postsurgical radiotherapy has been shown to effectively control local recurrence and prevent tumor cell seeding [7].

In this report, we described an exceptionally rare case of a 78-year-old male patient with multiple primary neoplasms, including localized paratesticular MM, for which only one similar case has been reported to date [5]. The patient was diagnosed with four primary neoplasms: prostate cancer, lung cancer, paratesticular MM and upper tract urothelial carcinoma. Here, we focused on the timeline and treatment of lung cancer and paratesticular MM. In March 2018, the patient underwent radical inguinal orchiectomy, which revealed testicular MM. Five months later, he underwent 2 years of cisplatin-pemetrexed chemotherapy for recurrent lung cancer, followed by 1 year of atezolizumab immunotherapy because of its progression. During these 3 years, no recurrence or metastasis of the paratesticular MM was observed. However, after lung cancer treatment, MM recurred three times in the right inguinal area within a short interval of 3–7 months. Therefore, we speculated that systemic lung cancer treatments (cisplatin-based chemotherapy and atezolizumab immunotherapy) had an anti-tumor effect on paratesticular MM in this rare multi-malignancy case. Because of the rarity of paratesticular MM, the effects of chemotherapy and immunotherapy are not well known. However, various strategies, including chemotherapy and immunotherapy, have been explored to manage the aggressive and treatment-resistant MM. Platinum-based regimens, such as platinum-pemetrexed combination

followed by gemcitabine maintenance or cisplatin-pemetrexed combination, have shown moderate response rates and survival benefits in patients with MM [16, 17]. Additionally, immune checkpoint inhibitors, such as nivolumab (anti-programmed death 1 antibody), pembrolizumab (anti-programmed death 1 antibody), avelumab (anti-programmed death-ligand 1 antibody), and ipilimumab (anti-cytotoxic T lymphocyte antigen-4 antibody), have been investigated for their potential roles in MM treatment [18–20]. In this patient, who presented with multiple primary neoplasms without apparent asbestos exposure, germline mutations, including the *breast cancer gene 1-associated protein 1* (*BAP1*) gene, should be investigated. Furthermore, one-third of *BAP1* mutation carriers develop multiple cancers, including mesotheliomas, which was consistent with the clinical features of this case [10, 21]. Unfortunately, the patient died in 2023, and the additional genetic tests could not be conducted.

4. Conclusion

We present a rare case of recurrent paratesticular MM in a patient with multiple primary neoplasms. Although asbestos is a known risk factor for MM, it can arise without exposure. MM frequently recurs and metastasizes, leading to treatment resistance and increased mortality rates. Additionally, the presence of multiple primary neoplasms complicates the treatment. In this case report, we noted the possibility of a common treatment for two distinct malignancies. We speculated that chemotherapy and immunotherapy intended for lung cancer could have an anti-tumor role in paratesticular MM that suppresses recurrence and distant metastasis.

AVAILABILITY OF DATA AND MATERIALS

The data are contained within this article.

AUTHOR CONTRIBUTIONS

KHK, YL, JYK, HKH and HJP—designed the study, completed and supervised the data collection. KHK and HKH—analyzed the data and interpreted the data. KHK—prepared the manuscript for publication. HJP—reviewed the draft of the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Ethical approval was obtained from the Ethics Committee of Pusan National University Hospital (Approval No: 2309-007-131). The informed consent was waived by the ethical approval institution.

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CONFLICT OF INTEREST

The authors declare no conflict of interest. Hyun Jun Park is serving as one of the Editorial Board members of this journal. We declare that Hyun Jun Park had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to AW.

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