Dear reviewers;

Thank you for evaluating the case report we submitted. The respective corrections are made according to the review.

We have changed some of the old references; unfortunately since the article features a very rare neoplasm most of the documented cases are old yet they hold great prominence for the sake of articles integrity and I wasn't able to change those.

I have added the keywords to the text but I am unable to upload it to the revision system as a word document; nevertheless, I have made the entry to the revision form.

I have also added legends to the figures and arranged them in a pptx files; unfortunately since they were organized as clustered figures in original article I am unable to present the figures as a whole in the revision system.

Lastly, I have reconstructed the abstract by removing some grammatical mistakes. I am adding the original form of the article as I intend it to be at the end of this letter.

Yours Sincerely

Epithelioid Malignant Peripheral Nerve Sheath Tumor of the Bladder and Concomitant Urothelial Carcinoma: A Case Report and Review of the Literature

Sami Berk Ozden[1], Muhammed Fatih Simsekoglu[1], Ipek Sertbudak[2], Cetin Demirdag[1], Iclal Gurses[2]

[1]Department of Urology, Istanbul University-Cerrahpasa, Cerrahpasa School of Medicine

[2]Department of Pathology, Istanbul University-Cerrahpasa, Cerrahpasa School of Medicine

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CORRESPONDING AUTHOR:

Sami Berk Ozden

Telephone: +905398244997

e-mail: s.berkozden@gmail.com

Abstract

Epithelioid malignant peripheral nerve sheath tumor (EMPNST) of bladder is a rare entity with devastating features. They are thought to originate from malignant transformation of pre-existing schwannomas of pelvic autonomic nerve plexuses and unlike the conventional MPNST's are not encountered in association with neurofibromatosis. The tumor has distinctive morphological, immunohistochemical and molecular features. Additionally; tends to be more aggressive and have a higher mortality. In this case report we present the detailed clinical course of a 71-year-old patient with EMPNST of bladder alongside with a review of the literature.

Introduction

Malignant peripheral nerve sheath tumors (MPNSTs) are sarcomas which originate from peripheral nerves, from a pre-existing benign nerve sheath tumour, or seldomly from a neurofibroma on a patient with neurofibromatosis type 1 (NF1) (1). In the absence of these settings, particularly in sporadic de novo or radiotherapy-associated tumours, the diagnosis is based on the histological and immunohistochemical features suggesting Schwannian differentiation.(2) The incidence of the neoplasm had been known as 0.001 percent in general population (3). Epithelioid variant of the MPNST (EMPNST) is a rare subtype of MPNST with distinctive morphological, immunohistochemical and molecular changes (4). Among the subtypes of MPNST, EMPNST occurs for about 5 % and only reported as case series (4). There are no high-volume studies that could report the disease characteristics clearly due to low patient volume. Although it is hard to make solid statements regarding the course of the disease there are strong clinical opinions supported by observation. In contrast to conventional MPNST, EMPNST is not associated with neurofibromatosis, also they are thought to originate from malignant transformation of pre-existing epithelioid schwannomas of the deep neural tissues with loss of genes like SMARCB/INI1 (5,6). They rarely have genetic alterations in the neurofibromin (NF1), p16/p15 (CDKN2A/CDKN2B), and PRC2 pathways. EMPNST typically shows diffuse strong staining with S100 and SOX10 in contrast to conventional MPNST (5,7). SMARCB1 gene inactivation resulting in SMARCB1 loss by immunohistochemistry is observed in approximately 75% of cases (6). In addition, they tend to be more aggressive and have higher mortality (5,7).

The first case published on this specific neoplasm was described to have a non-neoplastic bladder mucosa and occurred as an isolated EMPNST (8). Our case is unique; hence it is the

first case that presents with a synchronous urothelial carcinoma of the bladder and the epithelioid variant of the MPNST in the literature. It also is the second EMPNST case reported originating from the bladder wall.

Case Presentation

A 71-year-old elderly patient presenting with 1 month long painless intermittent macroscopic hematuria, and a history of the frequency with intermittency was admitted to our outpatient clinic. The patient was an ex-smoker (50 pack/year), also had diabetes and chronic kidney disease. He was on routine surveillance for an incidental tubulo-villous adenoma found on sigmoid colon by our general surgery department. Patient had no history of a previous radiotherapy or neurofibromatosis disease.

On physical examination there was no remarkable finding during the inspection. No skin lesions (neurofibromas, café-au-lait spots) were noted. On digital rectal examination, prostate was found to be moderately enlarged with no stiffness or irregularities. On blood samples collected at admission the PSA level was at normal range 2.46 ng/ml (0 to 4) and the patient had elevated BUN and creatinine levels; 69 mg/dl and 1.30 mg/dl respectively. In the collected urine sample patient had microscopic hematuria (33 erythrocyte/hpf).

A urinary ultrasound scan was conducted revealing a diverticulum with a 45x35mm diameter harboring a suspicious papillary projection with a dimension of 30x20 mm on posterior bladder wall. A prompt cystoscopy was performed revealing one papillary lesion with a 30x30 mm diameter on the prementioned diverticulum wall and another 10x10 mm lesion on the right posterolateral bladder wall. TURBT was performed on both lesions. Since one of the lesions was located on the diverticulum wall the resection had been performed superficially. On pathological evaluation, both resection materials were found to be non-invasive low grade papillary urothelial carcinoma (**Figure 1**).

After the initial procedure, patient's hematuria regressed. Patient then underwent a routine control cystoscopy session 3 months after the primary resection. Suspicious papillary projections on both old resection sites and one in proximity to the right ureteric orifice were identified. Complete resection was performed this time with respective deep resection biopsies. On pathological examination both lesions had non-invasive low grade papillary urothelial carcinoma. In addition to this finding, the tissue sample resected near the right ureteric orifice

was found to have atypical mesenchymal cell infiltration in the lamina propria. The cells stained positive with S100, SOX10 and vimentin suggesting these cells can have a neural origin (**Figure 1**). The blood sample was sent to our genetic department for NF-1 mutation analysis but it was not detected on fluorescent in situ hybridization (FISH).

A re-TURBT was planned 2 weeks after for the proper reassessment of the tumor but due to in adherence of the patient, it could have been performed 4 months later. The patient had weight loss and intermittent hematuria with clot passage during the time span. On cystoscopic examination, suspicious bladder wall irregularities including diffuse solid lesions protruding into the bladder lumen were observed in a 5x5 cm area extending from one lateral wall to the other, including the bladder trigone. An incomplete resection could have been performed due to the tumor size. Microscopically, the tumor comprised a relatively uniform but clearly atypical population of epithelioid cells and a smaller proportion of fascicle-forming spindle cells. The epithelioid tumor cell population showed a multilobular growth pattern, with lobules, nests and cords surrounded by fibrous and focal myxoid stroma. The polygonal tumor cells had round vesicular nuclei, prominent nucleoli and abundant palely eosinophilic to amphophilic cytoplasm. Mitotic rate was 42/10 HPF and atypical mitotic figures were seen. Necrosis was present. The background was occasionally infiltrated with neutrophils. The tumor was highly dedifferentiated and was in concordance with grade 3 sarcoma according to FNCLCC (Fédération Nationale des Centres de Lutte Contre le Cancer) sarcoma grading system (8). Immunohistochemically, the tumor cells showed strong and diffuse staining for S100, SOX10, vimentin, p16 and focal staining for CK7, EMA, collagen type 4 (**Figure 2**). There was no expression of the melanocytic markers, Myo-D1, desmin, CD34, SMA, myogenin, CD117, GATA3 or ALK. No loss of INI1 expression was observed. Ki67 proliferative index was determined as 10%. The pathological diagnosis was in concordance with high-grade EMPNST. This time a sample had also been sent to the molecular pathology laboratory for BRAFv600 mutation analysis for evaluating the availability of novel systemic treatment agents, yet it wasn't detected.

A full body FDG-PET CT scan was performed to rule out distant metastases and for local staging. On abdominopelvic cross-sectional images, an intrapelvic mass was bordering the posterior bladder wall and causing compression and distortion of pelvic structures. No distinctive border could be identified between the mass and the bladder wall. Increased FDG uptake on both the right external iliac and right common iliac lymph nodes was noted. An isolated paracaval lymph node just above the right iliac bifurcation also had increased FDG

uptake. On cross-sectional thoracal images a nodular lesion on right upper lobe of the lung with a 14x13mm diameter was observed. The lesion also had nuclear material uptake making it a candidate for metastases of the primary lesion (**Figure 3**).

The patient was discussed in a multidisciplinary uro-oncology meeting with the participation of urology, oncology, pathology, and radiation oncology departments. It had been decided to perform a radical cystoprostatectomy and extended lymph node resection for providing local disease control. The patient underwent radical cystoprostatectomy with ileal loop repair and bilateral ilioinguinal lymph node dissection. During the surgery, no notable adhesions, stiff tissues, or pathologic bodies along the perivesical spaces, rectovesical borders, and retropubic area were noted. These perioperative findings indicated that the tumor anatomically originated from the bladder rather than the pelvic plexuses. There were no operation related complications during the hospital stay. The patient was discharged 7 days after the surgery following the drain removal.

Through the pathologic examination of the cystoprostatectomy specimen, full-thickness infiltrating EMPNST into the bladder wall was seen. There was also a heterologous component (mature bone) in the focal area within the tumor, no other peripheral nerve sheat associated tumor types (schwannoma, neurofibroma or perineuroma) were noted. In addition, acinar adenocarcinoma (Gleason score 3+3=6) was detected incidentally in the prostate. EMPNST metastases were detected in 2 of 11 right pelvic lymph nodes removed. The number of bilaterally excised lymph nodes was 18.

An intravenous contrast-enhanced CT scan was performed 3 months after the cystectomy. The lesion located on the apical portion of the right lung was found to be increased in diameter (13x14 mm) and another nodular lesion with contrast uptake was added to the inferior lobe of the right lung. Patient could not receive any additional systemic therapy due to frailty. The patient passed away 4 months after the cystectomy and 12 months after the initial diagnosis due to emerging type 1 respiratory failure causing cardiac arrest after ICU admission.

Discussion

Mesenchymal tumors comprise %0.04 of all malignant tumors of the whole urinary system (10). Bladder-originating MPNST is a lesser-known entity that originates from pelvic autonomic nerve plexuses. MPNST is only occasionally documented in the case reports in the literature

making the process of diagnosis and treatment harder due to a lack of evidence-based data. Most reported patients are diagnosed with NF-1 disease and are below the age of 40. Published cases mostly presented with hematuria, suprapubic mass, and urinary retention. Most cases were not distinguished form urothelial carcinoma during cystoscopy and transurethral resection (8,11,12).

Even though the entity of EMPNST had been known since 1957, EMPNST alone only constitutes %5 of all MPNST's. Due to the rarity; information regarding the clinical presentation and prognosis remains the same. Yet, the understanding of the tumor's histopathologic features has evolved through the years by the refinement of histopathological diagnostic tools (4,5,6). The EMPNST of the bladder alone is a much rarer entity with aggressive features and a very poor prognosis making it hard to be studied under prospective randomized clinical trials. The known two risk factors for conventional MPNST's in general are radiation exposure and neurofibromatosis type 1 (3). Though in a comprehensive case series none of the EMPNST patients had neurofibromatosis and some had benign schwannoma areas in resected tumor samples which suggests that the tumor originates from a benign neoplasm in contrast to conventional MPNST's (4). They are thought to originate from malignant transformation of pre-existing epithelioid schwannomas of the deep neural tissues.

It is challenging to differentiate EMPNST from urothelial carcinoma by clinical evaluation. Ultrasonography, computed tomography, or magnetic resonance imaging can not differentiate EMPNST from urothelial carcinoma. Therefore, it is important to evaluate the pathology piece in detail with appropriate pathological methods (8, 13).

Typically, EMPNST's are composed of spindle cells growing in a haphazard manner consisting of interlacing sheets and nodules accompanied by atypical round polygonal ovoid cells with eosinophilic cytoplasm (14). More than 50% of tumor cells should be in polygonal morphology. In addition to these features, they present with interstitial infiltration of inflammatory cells namely mononuclear cells, neutrophils, and eosinophils (4).

This entitiy has a distinct immunophenotypic characteristic. Unlike conventional MPNSTs, EMPNSTs show strong and diffuse staining for S100 and SOX10, alongside with the absence of melanoma markers. They may also be positive for keratin and retain expression of H3K27me3 (4,5,8). Molecular distinction of EMPNSTs from conventional MPNSTs can be further elaborated. SMARCB1 gene inactivation resulting in SMARCB1 loss by immunohistochemistry is observed in approximately 75% of cases (6). They rarely have genetic

alterations in the neurofibromin (NF1), p16/p15 (CDKN2A/CDKN2B), and PRC2 pathways (4,7). In addition, they tend to be more aggressive and have higher mortality than MPNSTs (4-6).

Sarcomatoid urothelial carcinoma, leiomyosarcoma, epithelioid angiosarcoma, melanoma and perivascular epithelioid cell tumors (PEComas) falls into pathological differential diagnosis of this neoplasm. The first tumor to be considered in the differential diagnosis of our case had been sarcomatoid urothelial carcinoma. No macroscopic or microscopic relationship was identified between the urothelial tumor in the bladder mucosa and the tumor in the bladder wall. Furthermore; the mucosal tumor consisted entirely of non-invasive low grade papillary urothelial carcinoma, no high grade foci or lamina propria invasion was observed. The EMPNST in the bladder wall was diffusely positive for SOX10 and S100 while urothelial tumors stained negative for these markers. Epithelial markers (EMA, CK7) were found to be focally positive, in contrast to anticipated diffuse staining in urothelial carcinomas. GATA3 was also negative in tumor whereas positive in specimens containing urothelial carcinoma. The presence of lobular growth pattern in the epithelioid component and the presence of myxoid stroma, albeit focal in the periphery, were other microscopic findings supporting the diagnosis of EMPNST.

The patient has no history of melanoma and no in situ melanocytic lesion in the bladder was observed. It was noted that some nuclei were wavy in the spindle areas of the tumor and no pigment (melanin) was detected. In melanoma, positivity of epithelial markers is not expected, whereas focal positivity can be seen in EMPNST, as in our case. In addition to morphological findings, leiomyosarcoma and angiosarcoma were ruled out due to negative muscle and vessel markers. PEComas are composed of epithelioid and/or spindled cells with clear to eosinophilic granular cytoplasm. Epithelioid cells are arranged in dyscohesive nests surrounded by delicate thin-walled vessels and/or in sheets whereas spindled cells often form fascicles. Radial/perivascular distrubition of tumor cells is a valuable finding. Conventional PEComas express HMB45, melan A and smooth muscle markers with variable intensity and extent. HMB45 is a more sensitive marker, being positive in nearly all PEComas whereas melan A is a more specific marker, being positive in at least half of the tumors (15). Melanocytic markers were exclusively negative in the tumor within the bladder wall.

Primary treatment modality for conventional MPNST's is surgical resection if no gross solid organ metastases are present. Adjuvant radiotherapy can be given to provide local disease control after resection. Unfortunately, the distant metastases are almost always present or may

become evident within two months after initial diagnosis. Although the effectiveness is still controversial; patients with unresectable tumors on trunk or extremities may benefit from anthracycline regimens containing doxorobucin, ifosfamide, etoposide regimen (16,17). Furthermore, since the sarcoma deploys from a neural crest originated stem cell it may express BRAFv600E mutation which may response to targeted systemic therapy with vemurafenib (18,19). There are some continuing molecular and invitro cell culture studies conducted to identify tumor vulnerability in advance for a potential targeted therapy (19-21).

As for the MPNST of the bladder, the data regarding the disease stems from cases reported at different clinics around the globe and there is no high-volume study covering the patient demographics, prognosis, clinical data such as overall survival or disease-free survival after undergoing different treatment modalities.

Nevertheless, disease had mostly been recorded in patients younger than the fourth decade of their lives. Majority have type 1 neurofibromatosis with exception of a few sporadic cases (14). The youngest patient reported in the literature had neurofibromatosis type 1 disease and was 9 years old at the time of diagnosis. Patient undergone cystectomy and treated with systemic therapy (22). The disease may present with painless hematuria, abdominal mass, weight loss or nonspecific irritative urinary symptoms. No clinically significant tumor specific centricity has been noted in the literature and the neoplasm may arise from the trigone, dome, or the lateral walls of the bladder. Although long term follow ups are not disclosed in case reports it is known that prognosis is poor, and disease is at an advanced stage at the time of diagnosis (8,9,23-25). Despite there is a single case reported to be cured with transurethral resection of the tumor the patients long term follow up is unknown. Moreover, the epithelial variant of the tumor had only been reported once in the literature and not much is known regarding the prognosis of the reported patient (9). Our case is unique hence the patient presents with a synchronous EPMNST and urothelial carcinoma being the first to be reported in the literature. The patient was initially diagnosed with non-invasive bladder carcinoma and the EPMNST was identified 7 months after the admission. Cystectomy was performed at the 8 months after the initial admission. During the pathological evaluation of the cystoprostatectomy material it had been found that patient also had a metachronous Gleason score (3+3) 6 prostate adenocarcinoma in addition to the EPMNST and urothelial carcinoma. The patient passed away 12 months after diagnosis due to respiratory failure related to lung metastases. It is unknown whether tumor would have had any response to systemic therapy since the patient was unable to receive any treatment.

Our presented case is unique; hence it is the first case that presents with a synchronous urothelial carcinoma of the bladder and epithelioid variant of the MPNST in the literature. It is the second reported case that presents bladder EMPNST.

Conclusion

In conclusion, during the management of EMPNST cases, offering aggressive treatment modalities such as radical cystectomy to the patient is appropriate for the chance of contenting the disease regardless of the tumor stage and the extent of local disease at the initial diagnosis. There is no oncological consensus or evidence-based data on the use of systemic therapy for MPNST originating from the urogenital system. It is not known whether performing radical surgery has any effect on prognosis and it should be further investigated on studies with higher patient volume.

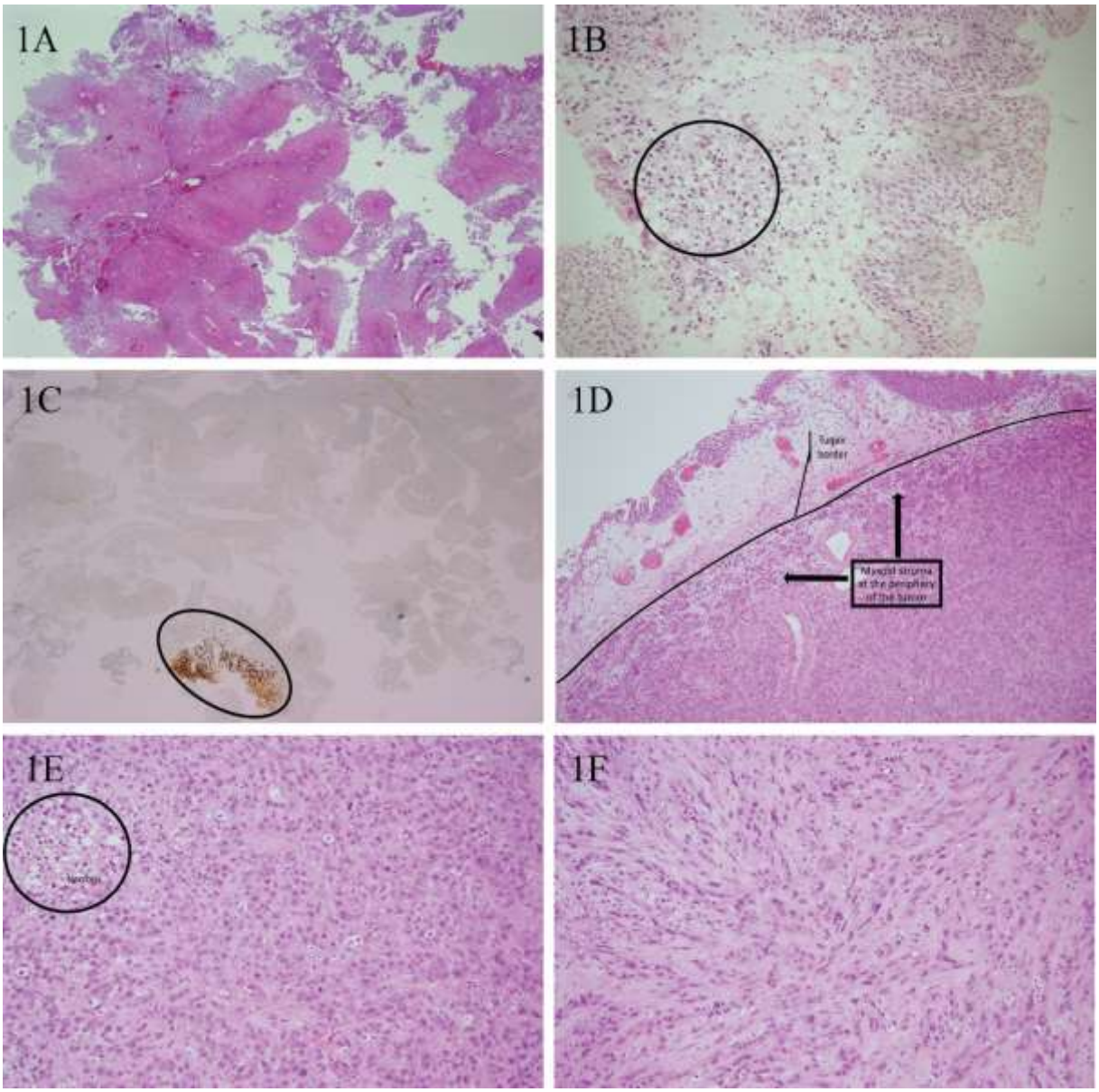

Figure 1: Epithelioid malignant peripheral nerve sheath tumor of the bladder. **1A:** Non-invasive low grade papillary urothelial carcinoma seen on initial biopsy. **1B:** Non-invasive low grade papillary urothelial carcinoma and atypical mesenchymal cell infiltration in the lamina propria(the area within the circle) determined on second biopsy. **1C:** SOX-10 immunopositivity in atypical mesenchymal cells (the area annotated with ellipse) located in the lamina propria in one of the tissue fragments representing the non-invasive papillary urothelial carcinoma **1D:** Focal myxoid stroma at the periphery of the tumor with a lobular growth pattern. (an arc is used to distinguish normal urothelium from tumoral tissue) **1E:** Epitheloid tumor cells with round vesicular nuclei, prominent nucleoli and abundant eosinophilic cytoplasm; necrosis in the upper left corner. **1F:** Spindle tumor cells with fascicular growth (H&E, SOX10, x40, x100 and x200).

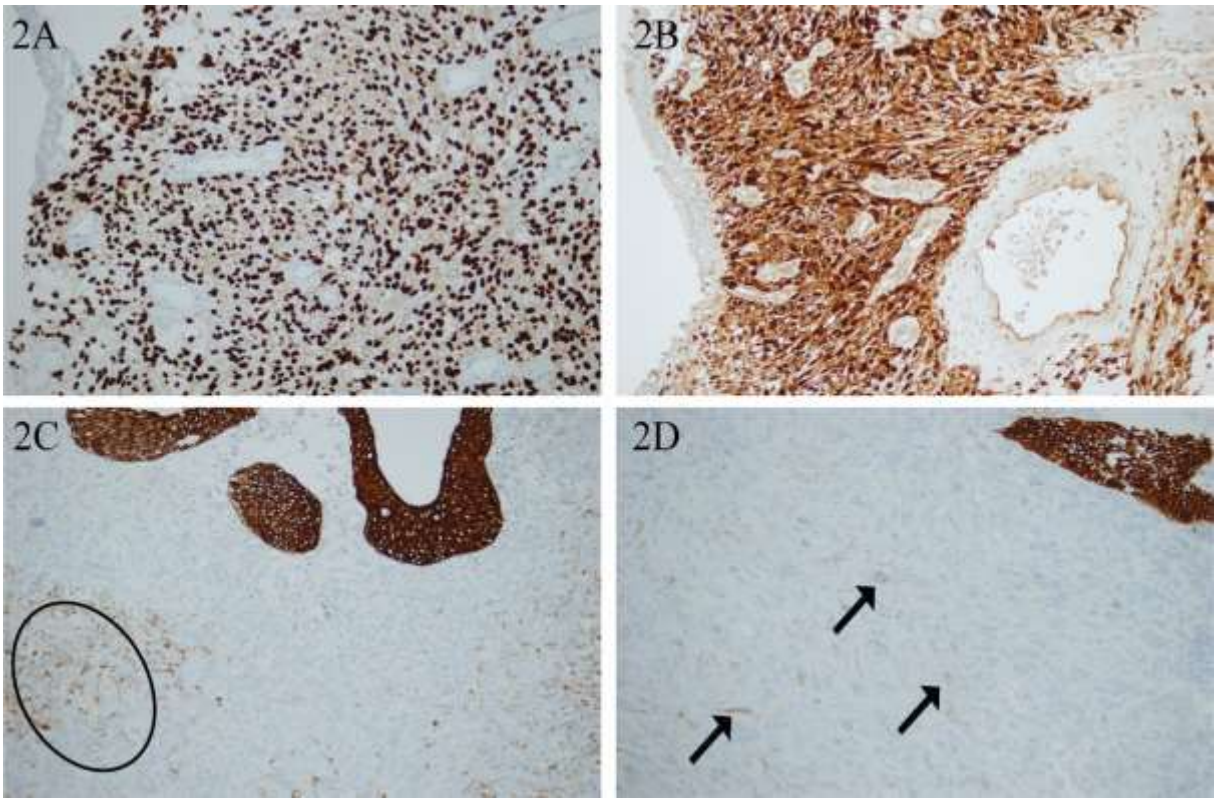

Figure 2: Immunohistochemical findings of epithelioid malignant peripheral nerve sheath tumor. **2A:** Immunohistochemistry for SOX10 showing strong nuclear positivity of epitheloid tumor cells. **2B:** Diffuse and strong immunopositivity for S100. **2C:** CK7 immunohistochemistry shows patchy cytoplasmic positivity.(Staining cells are annotated with an ellipse) **2D:** Occasional cells are positive for EMA (x200). (Arrows used to denote dispersed tumoral cells staining positively)

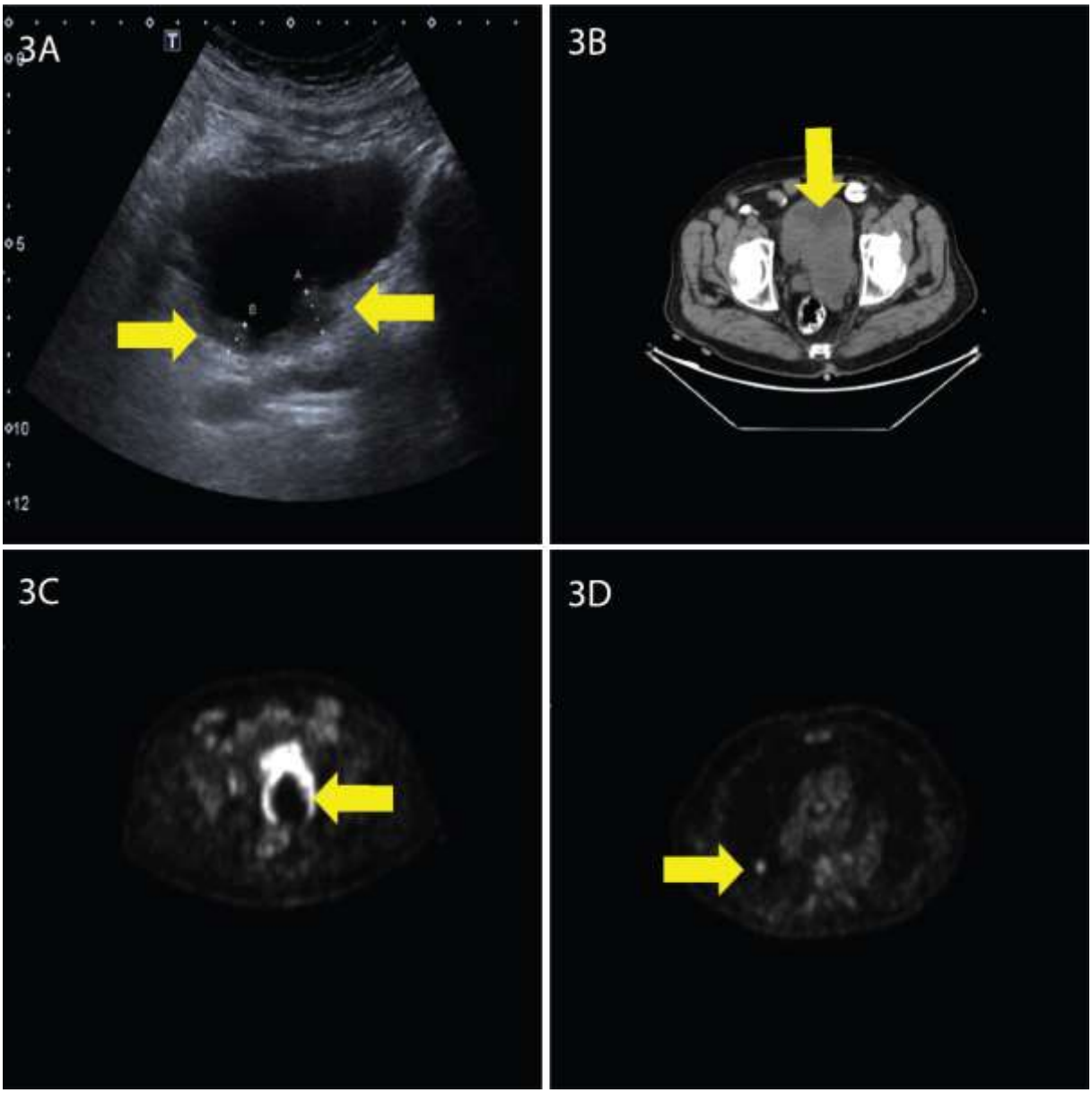

Figure 3: Radiological findings of epithelioid malignant peripheral nerve sheath tumor. **(3A, 3B)** Ultrasonography and computed tomography images of patients; **(3B, 3C)** The PET-CT slices of the patient show a large radiodense mass filling the diverticulum and extending through the posterior wall of the bladder with significant FDG uptake **(3D)** Foci of metastasis on right lung detected on FDG-PET scan. (arrows on Fig 3A,3B,3C and 3D used to annotate the descriptions).

Figure legends:

Figure 1: Epithelioid malignant peripheral nerve sheath tumor of the bladder.

1A: Non-invasive low grade papillary urothelial carcinoma seen on initial biopsy.

1B: Non-invasive low grade papillary urothelial carcinoma and atypical mesenchymal cell infiltration in the lamina propria determined on second biopsy. (the area within the circle)

1C: SOX-10 immunopositivity in atypical mesenchymal cells (the area annotated with ellipse) located in the lamina propria in one of the tissue fragments representing the non-invasive papillary urothelial carcinoma.

1D: Focal myxoid stroma at the periphery of the tumor with a lobular growth pattern. (an arc is used to distinguish normal urothelium from tumoral tissue)

1E: Epitheloid tumor cells with round vesicular nuclei, prominent nucleoli and abundant eosinophilic cytoplasm; necrosis in the upper left corner.

1F: Spindle tumor cells with fascicular growth (H&E, SOX10, x40, x100 and x200).

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(3A, 3B) Ultrasonography and computed tomography images of patients

(**3B, 3C)** The PET-CT slices of the patient show a large radiodense mass filling the diverticulum and extending through the posterior wall of the bladder with significant FDG uptake.

(**3D)** Foci of metastasis on right lung detected on FDG-PET scan. (arrows on Fig 3A,3B,3C and 3D used to annotate the descriptions).

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