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Mesothelioma as second primary tumor detected in ^{68}Ga-PSMA PET/CT

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Abstract
Prostate-specific membrane antigen (PSMA) is a glycoprotein highly expressed in prostate cancer cells and increasingly recognized in the neovasculature of various solid tumors. This case report describes a 71-year-old male with prostate adenocarcinoma who underwent ^{68}Ga-PSMA PET/CT for staging. Incidental PSMA uptake was observed in the pleura, which was diagnosed as epithelioid malignant mesothelioma via biopsy. Despite the primary focus on prostate cancer, this highlights the potential of PSMA PET/CT to identify non-prostatic tumors exhibiting PSMA expression. The case underscores the importance of interpreting PSMA PET/CT findings beyond prostate cancer, considering other malignancies such as mesothelioma. Although rare, mesothelioma may demonstrate PSMA uptake, reflecting neovascularization. Recognizing this phenomenon may influence diagnostic and therapeutic strategies, including the potential for radioligand therapy targeting PSMA in non-prostatic tumors. This report emphasizes the expanding role of PSMA PET/CT in oncologic imaging and the need for awareness of incidental findings that could impact patient management.

Keywords: PSMA PET/CT, mesothelioma, prostate cancer, nuclear imaging, incidental findings, tumor neovasculature, radioligand therapy, oncologic imaging

Introduction
Type II membrane glycoprotein was discovered in 1986 in mice and was subsequently isolated in prostate epithelial cells, thus receiving the name prostate-specific membrane antigen (PSMA). Due to its high expression in prostate cancer cells, this molecule is currently widely used in nuclear medicine for the acquisition of PET/CT studies for initial staging, restaging of biochemical recurrence, evaluation of response to treatment and as a prognostic factor for prostate carcinoma [1].
In recent years, a high expression of this molecule has been documented in the endothelial cells of the neovasculature in many other solid tumors, such as renal cell carcinoma, bladder transitional cell carcinoma, well-differentiated thyroid carcinoma, hepatocellular carcinoma and colorectal carcinoma, breast cancer, lung cancer and gastric cancer, gliomas, salivary gland tumors and some sarcomas such as Ewing's sarcoma [1, 2]. To date, there is not much literature available on PSMA uptake in mesotheliomas. We present a case of incidental finding of a mesothelioma in a ^{68}Ga-PSMA PET/CT.

Case description
A 71-year-old white-skinned male patient who worked in automotive painting and is currently retired. History of osteoarthritis treated with cannabis extract and benign prostatic hypertrophy treated with tamsulosinm, former smoker of 2 cigarettes a day for 5 years until 40 years ago. No other significant personal or family history.
He was evaluated by the urologic oncology service at our institution for presenting decreased caliber and strength of the stream and post-micturition dribbling; with normal blood count, creatinine at 0.72 mg/dl, negative urine culture, elevated prostate-specific antigen (30.4 ng/ml), multiparametric prostate magnetic resonance PIRADS 5 and transrectal prostate biopsy reporting acinar adenocarcinoma of the prostate in the right lobe, Gleason grade 3 (Gleason 4+3, score 7) in approximately 90% of the material examined and left lobe negative for malignancy; bone scan without evidence of lesions suggesting metastatic bone disease and chest x-ray with nodular images in the left lung and pleural effusion, findings suggesting metastatic disease.

Physical examination showed no significant findings in the chest and abdomen, genitourinary tract with a normal penis, wide urinary meatus, testicles in the scrotal sac of normal size, shape and consistency, and digital rectal examination with a 60-gram prostate with a nodular lesion in the right lobe, normal left lobe and free recesses. Additional studies were requested for initial staging with a chest CT and ^{68}Ga-PSMA PET/CT.

The chest CT revealed multiple nodular lesions in the pleura of the left lung, and the ^{68}Ga-PSMA PET/CT documented abnormal PSMA expression in the primary tumor located in the right lobe of the prostate and in the pleura of the left lung (Figures 1 and 2).

The biopsy and immunohistochemistry study of the left pleura reported a malignant tumor favoring malignant mesothelioma, epithelioid subtype, high grade (atypia 3, mitosis 2, summation: grade II), with necrosis.

With these new results, he was presented at the urology oncology medical board, where it was decided to start prostate cancer management with leuprolide acetate and a consultation was made with the clinical oncology service. The patient died two months later.

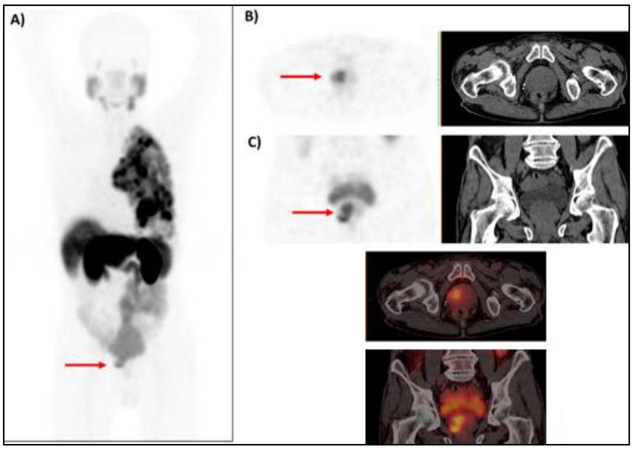

Fig 1: ^{68}Ga-PSMA PET/TC. A: MIP showing PSMA expression in the right lobe of the prostate (red arrow). B: axial and C: coronal images of the PET, low-dose CT and image fusion, respectively, showing diffuse PSMA expression in the base and middle third of the right lobe of the prostate with SUVmax 6.8, due to acinar adenocarcinoma of the prostate. There is no regional lymph node involvement.

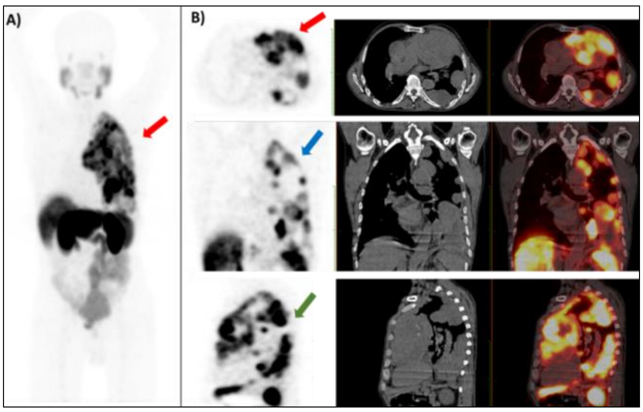

Fig 2: ^{68}Ga-PSMA PET/TC. MIP showing heterogeneous PSMA expression in the left lung field. B: axial (red arrow), coronal (blue arrow) and sagittal (green arrow) images of the PET, low-dose CT and image fusion, respectively, showing nodular thickening of the entire left pleura, some nodules merge to form masses, with heterogeneous PSMA expression with SUVmax 30.1.

Discussion

Malignant pleural mesothelioma (MPM) is a rare tumor that is associated with asbestos exposure in 70-90% of cases, with a latency period of 10 to 40 years between exposure and diagnosis. Its etiology is heterogeneous both at the histological and molecular level, the main pathways involved are the generation of free radicals, alteration in regulation and signaling mediated by kinases, direct cytotoxicity, chronic inflammation and mutations in tumor suppressor genes such as BAP1, CDKN2A/2B, NF2 and TP53, which affect the surface mesothelial cell monolayer in the parietal pleura [3].

MPM is most frequently present in men with a mean age of 70 years, white race and without major comorbidities; 50% of patients are in stage IV at the time of diagnosis. MPM has 3 histological subtypes: epithelioid, sarcomatoid and biphasic. The most common subtype with the best prognosis is epithelioid, with a median survival of less than 10.3 months from diagnosis and up to 19.8 months in patients who are able to be treated with surgery [4].

Our patient had the risk factors most frequently associated with this type of tumor, such as male sex and mean age of 71 years at diagnosis, the most frequent subtype (epithelioid) and a history of exposure to asbestos; asbestos was removed from automotive paints only after 1998 [5] and finally, he had a short overall survival of approximately 6 months.

Clinically, patients may present with dyspnea, chest pain, and weight loss, which may be present for several months, although there may be no symptoms, as in the case of our patient [6].

Currently, diagnosis is based on contrast-enhanced chest CT, pleural fluid cytology in case of pleural effusion, and CT or ultrasound-guided biopsy; in the most difficult cases, thoracoscopy is another option. 18F-FDG PET/CT is recommended for staging in patients who are candidates for surgical management [6]. Although current treatment is based on systemic therapy, radiotherapy or surgery, our patient died quickly without being able to start treatment.

Nuclear medicine, in its wide range of molecular imaging, has other types of PET/CT tracers other than FDG, which have shown uptake in different types of solid tumors including mesothelioma [7-9], one of them being PSMA. In 2012, Denmeade *et al.* demonstrated that at least 30% of the collected mesothelioma paraffin tissue samples showed PSMA binding to the PSMA monoclonal antibody [10].

To our knowledge, only one case of PSMA uptake by mesothelioma in ^{68}Ga-PSMA PET/CT has been published to date [11]. Despite the documented expression of PSMA in the tissues of this tumor, the low incidence of presentation and the aggressive course of the disease make it difficult to perform other tests in these patients that may open the door to other treatment options such as radio metabolic therapies.

Conclusion

^{68}Ga PSMA PET/CT is a nuclear medicine technique for the evaluation of patients with prostate cancer, however, many other solid tumors may present PSMA uptake, and attention must be paid to other uptakes other than the prostate as they could be related not only to possible metastasis but to another type of primary tumor.

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