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Unexpected discovery of hepatic cancer via 68Ga-PSMA PET/CT in the staging of prostate cancer

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ABSTRACT

PSMA PET/CT (prostate-specific membrane antigen-based positron emission tomography) measures the overexpression of PSMA with the highest sensitivity in prostate cancer, offering a feasible pathway for detecting primary tumors, metastasis, and recurrences. Several cases reported a PSMA uptake in other solid tumors including also cholangiocarcinoma, broadening its potential utility. Thus, PSMA PET/CT's primary value lies in enhancing prostate cancer diagnostics, but it also aids in detecting other malignancies. Here, we present the case report of an 82-year-old man initially diagnosed with high-risk prostate cancer with unusual PSMA accumulation in the liver at PSMA PET/CT, later identified as a cholangiocarcinoma.

Introduction

Prostate cancer is one of the most common types of cancer in men worldwide, with an estimated 1.4 million new cases and over 375,000 deaths in 2020 (Sung et al., 2021). Conventional imaging modalities such as CT and bone scans have limitations in detecting small and/or low-risk prostate cancer metastases, particularly in the early stages of the disease (Hofman et al., 2020). The introduction of PSMA PET/CT imaging has improved the diagnosis and staging of prostate cancer by providing highly sensitive and specific detection of prostate cancer metastases (Hofman et al., 2018; Lopci et al., 2023). PSMA PET/CT uses a radiolabeled ligand that targets prostate-specific membrane antigen (PSMA) overexpression on prostate cancer cells — quantified by the maximum standardized uptake value (SUVmax), which reflects the intensity of tracer uptake. This enables the detection of even small metastases, leading to more accurate staging and treatment planning (Hofman et al., 2018). Nonetheless, unspecific PSMA uptake in non-prostatic lesions is described in many cases, questioning the specificity of PSMA PET/CT results (Malik et al., 2018). Typically, physiological uptake of PSMA in different degrees of intensity is seen in many organs, accumulated in a very comprehensive way by Lisney and coworkers, as shown in Table 1 (Lisney et al., 2022).

Materials and methods

A 82-year-old patient with lower urinary tract symptoms and bladder catheter due to urinary retention, otherwise healthy, was referred to our department with a PSA elevation of 6.8 ng/ml, a 31 ccm prostate volume and a suspicious digital rectal examination of the apex and, as shown in Fig. 1, an unclear lesion of the whole peripheral zone of the prostate (a PIRADS classification was not possible due to a strong differential diagnosis of prostate inflammation). A transperineal ultrasound-MRI fusion prostate biopsy revealed an adenocarcinoma (Gleason score 4 + 5 = 9 in 8 from 15 cores with a maximum infiltration of 95 %). In a 68Ga-PSMA PET/CT no lymph node- and bone metastases were detected. However, a lesion in liver segment IVa (SUVmax 49.12), which was deemed suspect for a secondary malignancy was revealed (shown in Fig. 1). Following this, an MRI of the liver was conducted with a suspicion of cholangiocellular carcinoma.

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Tab 1
PSMA uptake in different organs and pathologies adapted from Lisney et al. 2022.

PSMA Expression	Organ/Pathology
Physiological PSMA Expression	Submandibular glands, normal prostate epithelium, duodenum, colon, proximal tubules of the kidney, sympathetic ganglia, normal transitional epithelium of the bladder, normal breast parenchymal elements, hepatocytes, testis, esophagus, stomach, small intestine, fallopian tube epithelium
Pathological PSMA Expression (Primary Tumor and Metastases)	Prostate carcinoma, renal carcinoma, bladder carcinoma, brain tumors, thyroid tumors, hepatocellular carcinoma, lung carcinoma, squamous cell carcinomas of oral cavity, adenoid cystic carcinoma, salivary duct carcinoma, adrenocortical carcinoma, gynecologic malignancies, high-grade sarcomas, pancreatic carcinoma, colorectal carcinoma, gastric carcinoma, intestinal adenocarcinoma
Pathological Tracer Uptake - Benign Tumors	Elastofibroma dorsi, dermatofibroma, acrochordon, fibromatosis desmoid tumor, intramuscular myxoma, pseudoangiomatous stromal hyperplasia of the breast, thymoma, thyroid adenoma, parathyroid adenoma, adrenal adenoma, meningioma, schwannoma, peripheral nerve sheath tumors, neurofibroma, hemangioma, angiolipoma, hemangiopericytoma
Pathological Tracer Uptake - Granulomatous or Inflammatory Diseases	Pulmonary sarcoidosis, Wegener's granulomatosis, bronchiectasis, anthracosilicosis, berylliosis, pulmonary histoplasmosis, tuberculosis, asbestosis, perianal fistula, renal abscess, post-operative inflammatory processes, Crohn's disease
Pathological Tracer Uptake - Bone Diseases	Fracture, osteophyte, osteoarthritis, Paget's disease, osteomyelitis, fibrous dysplasia, hemangioma
Pathological Tracer Uptake - Various Diseases/Findings	Lymphoma, testicular tumors, thymic carcinoma, polycythemia vera (diffuse bone marrow uptake), atelectasis, amyloidosis of the seminal vesicles, gynecomastia, Barrett's esophagus

Results

A CT-guided liver biopsy was performed, confirming the presence of cholangiocellular carcinoma. Following an interdisciplinary tumor board discussion, and considering the differing levels of tumor aggressiveness, a left hemihepatectomy was recommended as the primary treatment. In parallel, neoadjuvant treatment of the prostate cancer was initiated, due to the anticipated delay in definitive prostate cancer therapy. The patient subsequently underwent a laparoscopic left hemihepatectomy, which confirmed cholangiocellular carcinoma (G2, pT1a, pN0 (0/4), L0, V0, Pn0, R0). After a second interdisciplinary tumor board meeting, treatment options for the prostate cancer included either robot-assisted prostatectomy (preferred due to subvesical obstruction) or radiation therapy. In addition, adjuvant chemotherapy with capecitabine was recommended for the cholangiocellular carcinoma. Given the patient's good general condition and following a thorough discussion of the potential risks and benefits of the available treatment options, a shared decision was made together with the patient to proceed with a robot-assisted prostatectomy. Histopathological evaluation revealed adenocarcinoma of the prostate (pT3b, pN1 (4/21), R1 – focal dorsal margin involvement in the area of the right base, medially over 1 mm). Following the recommendation of our tumor board the patient is on a PSA-triggered follow-up without antiandrogen therapy, and due to the cholangiocellular carcinoma, he began guideline-based adjuvant chemotherapy with capecitabine. At the six-month follow-up, the PSA nadir remained stable at 0.2 ng/mL, indicating an adequate decline in PSA levels following surgery and discontinuation of neoadjuvant androgen deprivation therapy. Imaging studies (CT of the abdomen and thorax) showed no evidence of recurrence of the cholangiocellular carcinoma.

Discussion

PSMA is approximately 100 to 1000-fold overexpressed in nearly all prostate cancer cases (Zhao et al., 2021). The current theory proposes that PSMA plays a central role in folate metabolism. The extracellular component of PSMA functions as a hydrolase and breaks down glutamated folates, which are an additional source of folate and boost proliferation (O'Keefe et al., 2018). PSMA uptake and overexpression have been observed in various non-prostatic malignancies, including glioblastoma, and thyroid, breast, lung, colon, renal, and hepatic carcinomas (Pepe et al., 2024). The degree of tracer uptake, typically measured by SUVmax, reflects PSMA expression and has been strongly correlated with the aggressiveness of the primary prostatic tumor (Zhao et al., 2021; O'Keefe et al., 2018; Pepe et al., 2023). The advent of PSMA PET/CT has highlighted the limitations of conventional imaging modalities such as CT and bone scans in accurately staging prostate cancer. In 2020 a randomized controlled trial revealed PSMA PET/CT outperformed conventional CT and bone scans in identifying lymph node metastasis (92 % versus 65 %), as well as in terms of sensitivity (85 % versus 38 %) and specificity (98 % versus 91 %) (Hofman et al., 2020). PSMA PET/CT scans have a significantly lower rate of indeterminate findings (7 %) compared to CT and bone scans (23 %) (Hofman et al., 2020). However, false-negative results can still occur, particularly in ductal prostate carcinoma (Pepe et al., 2024).

68Ga-PSMA, widely regarded as the radiotracer of choice for staging and recurrence detection in prostate cancer, has also demonstrated potential in other solid tumors due to its association with angiogenic pathways and endothelial proliferation (Uijen et al., 2021). Mechanistically, PSMA facilitates endothelial cell invasion during angiogenic sprouting, thereby promoting neovascular formation and contributing to tumor progression by enhancing the supply of oxygen and nutrients (Chen et al., 2020). In highly vascularized malignancies such as hepatocellular carcinoma and cholangiocarcinoma, PSMA expression has been predominantly observed in the tumor neovasculature rather than in the tumor cells themselves (Chen et al., 2020). A large-scale analysis of 203 primary cholangiocarcinoma cases further demonstrated that

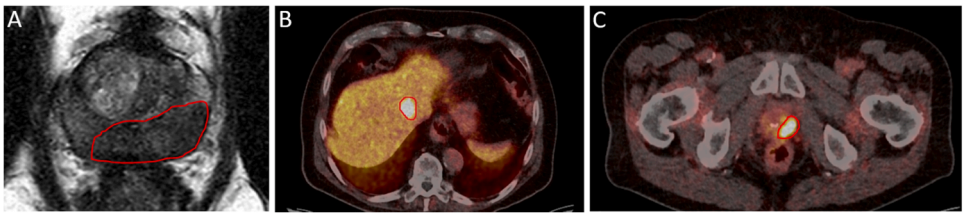

Fig. 1. A) mpMRI of the prostate before the biopsy - extensive radiological changes of the prostate in the peripheral zone (red outline), making it hard to distinguish between severe inflammation (prostatitis) and potential prostate cancer; B) 68Ga-PSMA PET/CT – a soft, well-supplied liver lesion in segment IVa (red outline) (confirmed as cholangiocellular carcinoma); C) 68Ga-PSMA PET/CT - malignancy-typical hypermetabolism (red outline) of the known primary prostate tumor.

79.3 % exhibited PSMA positivity within the tumor-associated neovasculature, supporting its relevance as an imaging and potentially therapeutic target in cholangiocarcinoma as well (Chen et al., 2020). The study also found a positive correlation between PSMA expression and both tumor grade and stage in hepatocellular carcinoma and cholangiocarcinoma, with significantly higher expression observed in stage III and IV disease compared to earlier stages (Chen et al., 2020).

Interestingly, in our case, the tumor exhibited markedly elevated PSMA expression (SUVmax 49.12) on PET/CT imaging, despite histopathological findings indicating an early-stage cholangiocarcinoma. This striking discrepancy highlights the potential of PSMA PET/CT to reveal possible biologically aggressive features that may not yet be apparent on conventional pathology, underlining its value in comprehensive tumor assessment and therapeutic decision-making. However, given the limited data available, especially in non-prostatic tumors such as cholangiocarcinoma, further studies are needed to better understand the clinical significance of PSMA expression and its correlation with tumor biology and outcomes.

Conclusion

Altogether, PSMA PET/CT has emerged as a significant advancement in the diagnosis and staging of high-risk prostate cancer due to its superior sensitivity and specificity compared to conventional imaging methods. The overexpression of PSMA in nearly all prostate cancers offers a unique strategy for detection and recurrence tracking. Nevertheless, the utility of PSMA PET/CT extends beyond prostate cancer, as it shows promise in identifying other solid tumors. This is illustrated by studies indicating PSMA uptake in other cancers like cholangiocarcinoma. While using PSMA PET/CT as staging examinations in high-risk prostate cancer, it is important to be cautious regarding the incidental detection of other malignancies. Careful consideration of the various disease possibilities detected through this imaging modality is essential for accurately determining an appropriate treatment sequence.

Patient consent statement

Written informed consent was obtained from the patient for publication of the details of his medical case and the accompanying images. This study protocol was reviewed and approved by the Center for Translational & Clinical Research of RWTH Aachen, approval number CTC-A 23–382.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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