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Liver enzyme elevation after ^{177}Lu-PSMA radioligand therapy for metastasized castration-resistant prostate cancer

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ABSTRACT

^{177}Lu-PSMA radioligand therapy (^{177}Lu-PSMA-RLT) is a promising new therapeutic option for patients with metastasized castration-resistant prostate cancer (mCRPC). The spectrum of adverse events with this treatment has to be evaluated. Here, we describe the case of a mCRPC patient with M1c disease (mediastinum, lungs, bones and liver) who presented with elevated liver enzyme levels after ^{177}Lu-PSMA-RLT administration. Pre-treatment ^{68}Ga-PSMA PET/CT showed at least 4 liver lesions with low uptake. Overall, the liver uptake was inhomogeneous. Liver biopsy was performed subsequently.

PART 1

INTRODUCTION

Therapy of metastasized castration-resistant prostate cancer (mCRPC) remains a challenge. A promising approach is the local delivery of radiation to tumor cells by systemic application of radioisotopes bound to the prostate-specific membrane antigen (PSMA). ^{177}Lu-PSMA radioligand therapy (^{177}Lu-PSMA-RLT) has been shown to be safe and effective in mCRPC (*1*). With increasing implementation of this novel therapy modality, the spectrum of adverse events must be evaluated. Therefore, we report a rare, potentially lethal complication after ^{177}Lu-PSMA-RLT and the diagnostic and therapeutic management.

CASE STUDY

A 59 years old male with mCRPC with extensive metastases (including mediastinum, lungs, bones and liver) received ^{177}Lu-PSMA-RLT in our institution after progression following multiple lines of prostate cancer-directed therapies.

Initially, the patient was diagnosed with localized prostate cancer (pT3a, pN0, V0, L1, R1, Gleason 9) and treated with radical prostatectomy and adjuvant radiotherapy. Subsequent relapses were treated with androgen deprivation therapy, gamma knife surgery, and a second-generation anti-hormonal therapy with enzalutamide. Checkpoint inhibition and poly(adenosine diphosphate-ribose) polymerase inhibition in a clinical trial was discontinued 4 months and re-challenge with enzalutamide 6 weeks prior to ^{177}Lu-PSMA-RLT. Of note, the patient did not receive any chemotherapy as per the patient´s decision.

Pre-therapeutic ^{68}Ga-PSMA PET/CT confirmed the previously known mediastinal, hilar, pulmonal and bone metastases. It further revealed at least 4 new liver lesions with low level PSMA uptake (SUVmax(mean) unaffected liver 3.1 (2); SUVmax(mean) metastases 5.8 (3.7), 4.9 (3.9), 5.5 (3.4), and 5.3 (2.2) respectively), suggesting hepatic tumor burden below <10%.The liver metastases had an uptake just slightly above the healthy liver and below the salivary glands (miPSMA2). Liver MRI confirmed these metastases and further revealed metastases that showed no uptake in the PET/CT, i.e. were dedifferentiated. (Figs. 1A-D). The pre-RLT diagnosis according to the miTNM-classification was miT0N0M1a(RP, SD)b(diss)c(hepatic) (*2*).

One course of ^{177}Lu-PSMA-RLT with 6.2 GBq ^{177}Lu-ITG-PSMA-1, a generic preparation of ^{177}Lu-PSMA-I&T, was applied. The post-therapeutic whole-body-scans

confirmed low uptake in hepatic lesions (Fig. 1B). Serological control after ^{177}Lu-PSMA-RLT showed a dramatic increase in liver enzyme levels, which were within normal levels at baseline. Aspartate transaminase peaked at 2105 U/L, Alanine transaminase at 2307 U/L. Serum creatinine was normal. The patient reported neither abdominal pain, discomfort, vomiting nor nausea. He had no history of liver disease and did not report a change in body weight. No new medication had been prescribed.

The patient was referred to the gastroenterology department for further workup. Serology for hepatitis A, B, C and E was negative. Liver ultrasound showed normal liver configuration, size and regular parenchyma texture. It confirmed low tumor burden and normal liver blood flow (Figs. 1F-G). Furthermore, free abdominal fluid was ruled out.

Due to massively elevated transaminases after ^{177}Lu-PSMA-RLT without explanation at this point, a transcutaneous liver biopsy was performed. Histology revealed intact architecture of the liver lobules. However, multiple areas showed severe dystrophy of parenchyma in Rappaport zone 3 with dilatation of the sinusoids, containing deposits of hyaline material, and often highly narrowed central veins, but unaltered portal fields (Fig. 1H).

This findings led to a diagnosis that prompted specific treatment.

DISCUSSION

Two approaches have to be considered in this case. First, ^{68}Ga-PSMA PET/CT in the liver can be positive in different diseases. Second, elevated liver enzymes have a broad differential diagnosis themselves.

Regarding the positive ^{68}Ga-PSMA PET/CT, further possible differential diagnoses are PSMA-expressing tumors other than prostate cancer, such as hepatocellular carcinoma (*3*), hepatocellular cholangiocarcinoma (*4*), or liver hemangioma (*5*). Hepatocellular carcinoma in patient without evidence of hepatitis or cirrhosis is rare. Hepatocellular cholangiocarcinoma often presents with cholestasis and elevated bilirubin, which were not present in this case. Liver hemangioma would be diagnosed by CT or MRI and not lead to elevated transaminases.

Concerning elevated transaminases, the differential diagnosis is broad and includes tumor progress, viral or alcoholic hepatitis, drug toxicity, toxins (mushrooms), ischemic liver disease, Budd-Chiari syndrome, and sinusoidal obstruction syndrome/veno-occlusive disease (SOS/VOD). Tumor progress was initially diagnosed by PET, but tumor burden was low, as confirmed by liver ultrasound after elevation of transaminases occurred. Viral hepatitis was ruled out by serology. Alcohol, changes in medication, mushroom poisoning were ruled out by history. Liver ultrasound showed no signs of alcoholic/non-alcoholic fatty liver disease or vascular abnormalities, rendering ischemic hepatitis or Budd-Chiari syndrome less likely differential diagnoses. SOS/VOD typically occurs after high-dose chemotherapy, but can also occur after radiotherapy. However, the patient never received any chemotherapy and current SOS/VOD diagnosis scores underline the importance of bilirubin elevation, weight gain, ascites and painful hepatomegaly. Notably, none of these signs were present in our patient.

Therefore, all diagnostic considerations did not lead to a clear diagnosis supported by history, serology and imaging. Consequently, we recommended ultrasound-guided liver biopsy at this point.

Figure 1 (PART 1)

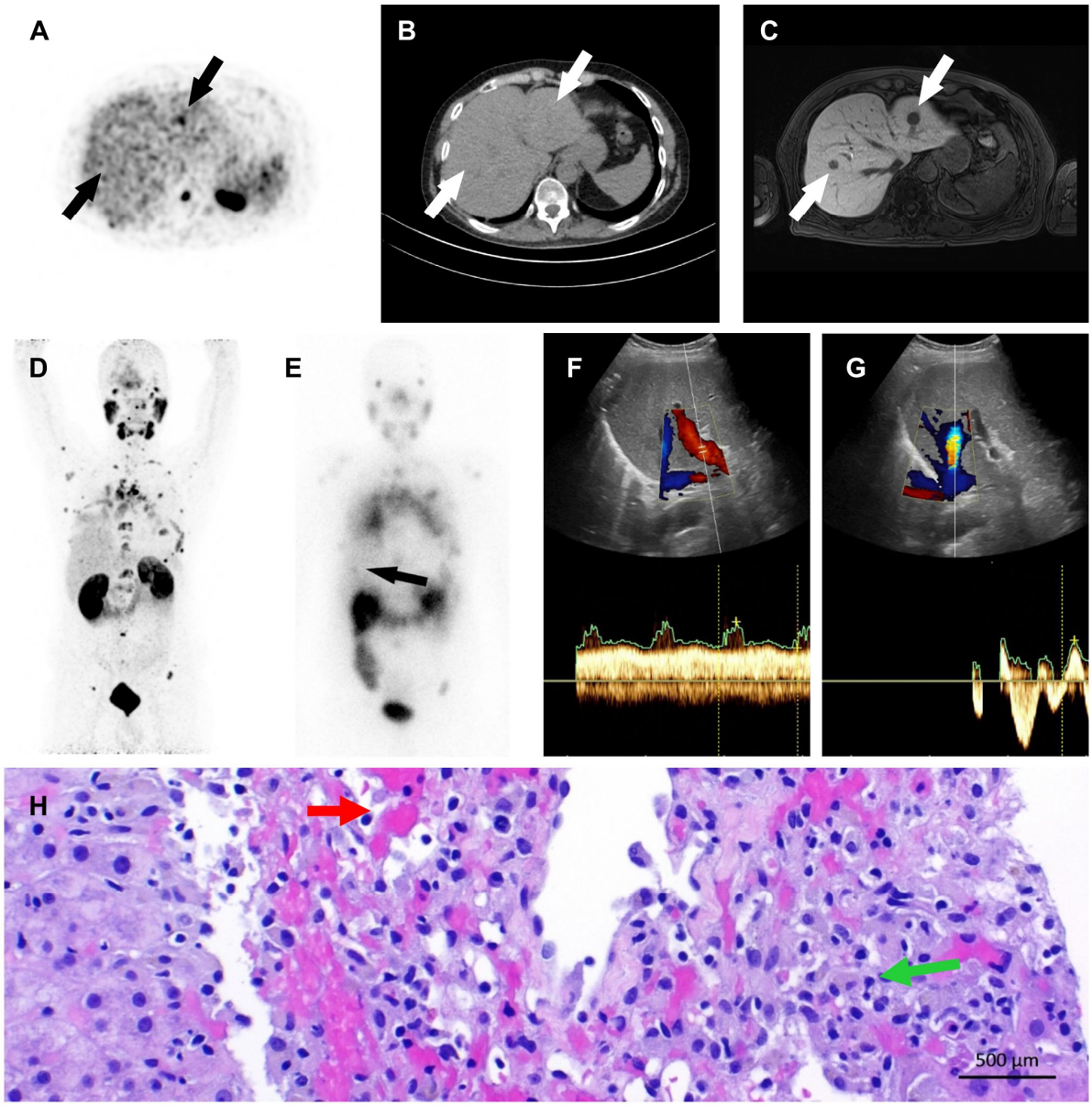

Figure 1. (A)-(C): Axial views of liver lesions: ^{68}Ga-PSMA PET/CT, contrast enhanced CT and MRI (T1flash 20 min. after 7ml Gadoxetate disodium iv.) (from left to right). Arrows indicate liver metastases. The liver metastasis in the left lobe has very low PET-uptake (miPSMA2) while the other metastasis in the right lobe showed no uptake above the liver (miPSMA1). (D) 3D MIP of ^{68}Ga-PSMA PET/CT. (E): Post-therapeutic whole-body-scan in anterior view, black arrow is pointing to very low focal uptake within hepatic

lesions as shown in the ^{68}Ga-PSMA PET/CT. (F) and (G): Normal liver blood flow in ultrasound. (H): Representative area of the liver biopsy. Green arrow: dystrophy of liver parenchyma. Red arrow: sinusoids with deposits.

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PART 2:

TITLE: HEPATIC SINUSOIDAL OBSTRUCTION SYNDROME/VENO-OCCLUSIVE DISEASE AFTER ^{177}LU-PSMA RADIOLIGAND THERAPY FOR METASTASIZED CASTRATION-RESISTANT PROSTATE CANCER

FINAL DIAGNOSIS

The histologic findings lead to the diagnosis of sinusoidal obstruction syndrome/veno-occlusive disease (SOS/VOD). SOS/VOD is a typical, potentially fatal complication of high-dose chemotherapy in the context of hematopoietic stem cell transplantation (HSCT). Classical clinical signs are jaundice, hepatomegaly, right upper quadrant pain, ascites, and weight gain. These are incorporated in established diagnostic scores for SOS, but sensitivity and specificity are not optimal. Risk factors include transplantation-specific as well as patient-, disease- and liver-specific factors, of which especially abdominal/liver irradiation and pre-existing liver disease are relevant here. In HSCT, chemotherapeutic drugs are metabolized in the liver by hepatocytes and toxic metabolites are secreted to the liver sinusoids, damaging and activating sinusoidal endothelial cells. This leads to impaired sinusoidal integrity with accumulation of blood cells and debris in the space of Disse, inflammation, thrombosis formation, reduced fibrinolysis and ultimately sinusoidal narrowing and reduced sinusoidal blood flow (Fig. 2A). SOS/VOD therapy aims to reduce inflammation and clotting and improved fibrinolysis (*1*). SOS/VOD-related mortality is high, although current treatment protocols markedly decrease mortality.

In the radiotherapy context, SOS/VOD has been investigated in animal models, but the corresponding administered doses of external irradiation are not comparable with

patient doses during external irradiation of an HCC. 6-66% of the patients who received doses between 30-35 Gy developed the picture of a SOS/VOD (*2*). Furthermore, it should be considered that external irradiation differs from irradiation with open radionuclides. In the literature to date, SOS/VOD has practically not been described for nuclear medicine therapies with open radionuclides. The only example is a myeloablative therapy of a neuroblastoma with ^{131}Iodine-metaiodobenzylguanidine (^{131}I-mIBG) and high-dose chemotherapy including autologous stem cell transplantation (*3*), whereby the SOS/VOD was traced back to the whole-body-irradiation of the ^{131}I-mIBG. Dosimetry data is neither available for this study nor the patient discussed here. The mechanism of the induction of a SOS/VOD at low doses remains unclear. So far too little data are available on the induction of a SOS/VOD by radionuclide therapies; this could be a different mechanism than with external radiation. In our case, at least three putative mechanisms might be considered. First, the treatment in the presence of liver metastases is a potential trigger, however, tumor burden and uptake in the liver was low in this case. Second, PSMA is physiologically expressed in the healthy liver (*4*). This leads to a diffuse liver irradiation dose in the particular context of PSMA-targeted treatment. Third, neovascularization of prostate carcinoma metastases can also expresses PSMA and thus could trigger the damage cascade (*5*). It remains unclear what the exact cause of SOS/VOD induction in this patient was, this may or may not be due to ^{177}Lu-PSMA-RLT.

We hypothesize that one of these mechanisms or a combination of them could have played a role in the triggering of the SOS/VOD in our patient (Fig. 2A). Induction by chemotherapy can be ruled out as the patient was chemotherapy-naïve. However, the

severity of this complication with therapeutic consequences should be known to physicians treating mCRPC patients with ^{177}Lu-PSMA-RLT.

The patient was hospitalized and received defibrotide, the internationally approved treatment for SOS/VOD, intravenously for 22 days. There were no treatment-related toxicities. Liver enzyme levels steadily declined to Aspartate transaminase 196 U/L and Alanine transaminase 130 U/L prior to discharge. In subsequent outpatient visits, liver enzymes where within normal levels (Fig. 2B). Of note, the maximum total bilirubin levels, a serologic marker for SOS/VOD and cornerstone of current diagnostic scores, were normal at histologic diagnosis and treatment initiation and only reached 2.1 mg/dL in the course of the disease.

The patient did not receive further ^{177}Lu-PSMA-RLT, but instead systemic chemotherapy, on which liver metastasis regressed but bone metastases progressed quickly, underscoring the general need for further therapeutic options in mCRPC.

CONCLUSION

To the best of our knowledge, this represents the first description of SOS/VOD occurring after ^{177}Lu-PSMA-RLT for mCRPC. Importantly, SOS/VOD developed despite low hepatic tumor burden. Possibly this side-effect is dose-independent. Liver metastases and/or constitutive PSMA expression in healthy liver may contribute to SOS/VOD occurrence. With high SOS/VOD-related mortality and specific treatment available, the diagnosis should not be missed. Our patient did not meet the established clinical SOS/VOD diagnostic criteria at the time of histological diagnosis.

The ongoing VISION Phase III trial will assess toxicity for a similar compound. After ^{177}Lu-PSMA-RLT, liver enzyme levels might be included in the follow-up and

clinicians be aware of this SOS/VOD case and recommend further workup in patients with elevated liver enzymes until further safety data are available.

In case of elevation, we recommend a workup for acquired transaminase elevation. SOS/VOD should be suspected when right upper quadrant pain, weight gain, ascites, hepatomegaly, bilirubin ≥ 2 mg/dL or transaminases ≥ 2x normal occur. This should lead to clinical evaluation using established scores and a serologic control in a reasonable interval. If no SOS/VOD and no other cause can be determined and robust bilirubin (≥ 5 mg/dL) or transaminases (≥ 5x normal) elevations compatible with a severe VOD/SOS are detected, a liver biopsy might be discussed as established clinical criteria for diagnosis of SOS/VOD may be negative in the nuclear medicine setting as demonstrated by this case. To that end, physicians must be aware of the putative differential diagnosis of SOS/VOD when caring for patients presenting with elevated liver enzymes in a critical period of even more than 21 days (late onset SOS/VOD) after ^{177}Lu-PSMA-RLT. SOS/VOD should be treated according to established protocols.

Figure 2 (PART 2)

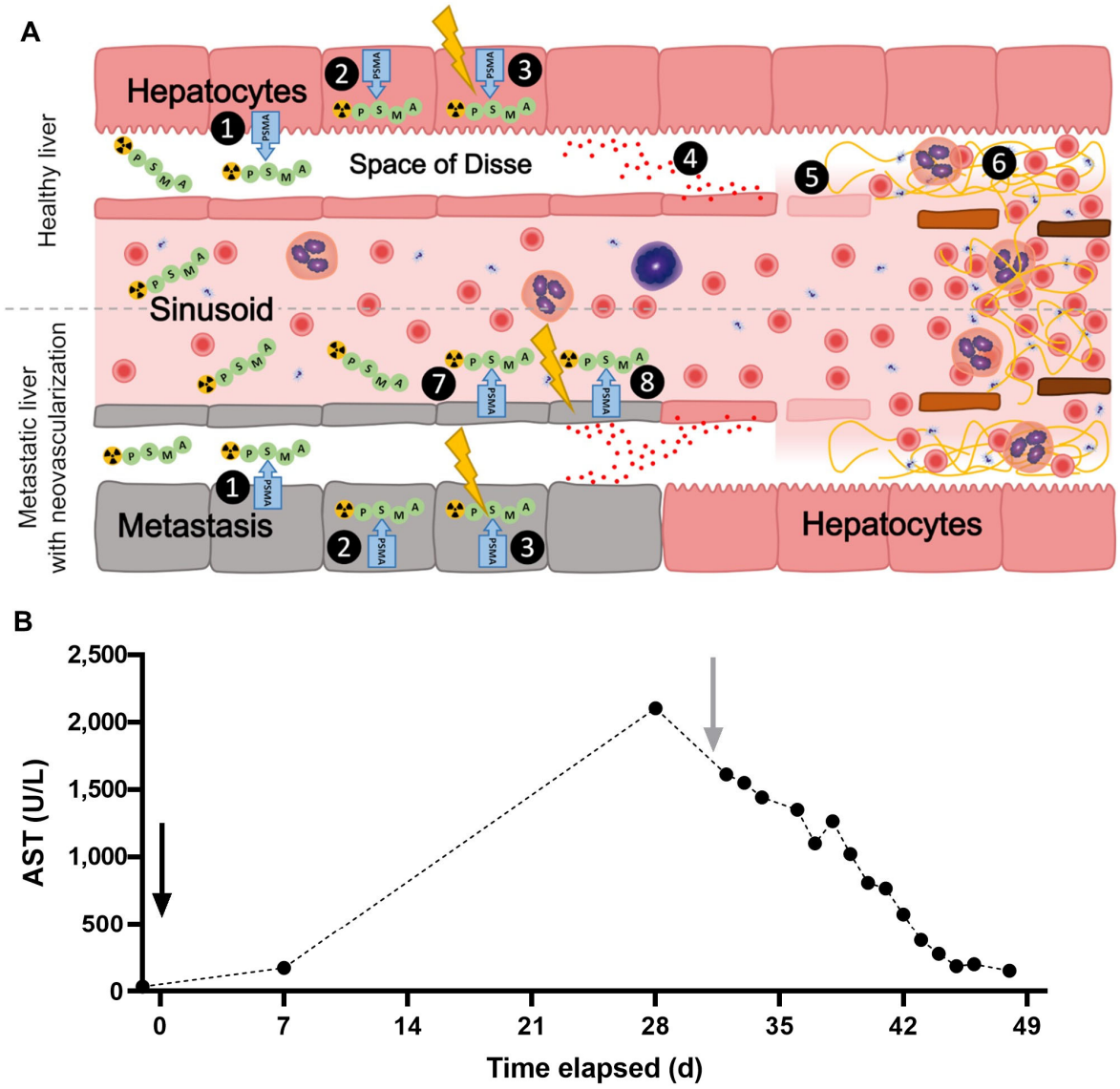

Figure 2. (A): Illustration of putative pathophysiology of SOS/VOD in ^{177}-Lu-PSMA-RLT context. 1: ^{177}Lu-PSMA binds to PSMA physiologically expressed on hepatocytes or to PSMA-expressing metastases. 2: Internalization of the tracer-PSMA-complex. 3: Radiation damage of the hepatocytes or the tumor cells. 4: Release of cytokines into the space of Disse. 5: Cytokine-related damage of the endothelium and leakage of the

sinusoids. 6: Fibrin, blood cells, cell debris and thrombus in the space of Disse and in the sinusoids. 7: ^{177}Lu-PSMA binds to PSMA expressed by the neovascularization of prostate cancer metastases. 8: Radiation damage of the endothelium (B): Course of Aspartate transaminase (AST) levels after ^{177}Lu-PSMA-RLT and initiation of treatment. Black arrow: ^{177}-Lu-PSMA-RLT (Day 0). Grey arrow: Begin Defibrotide treatment.

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DISCLOSURE STATEMENT

AS received for speaker engagements and advisory roles: Amgen, AstraZeneca, Bayer, BMS, EISAI, MSD, Novartis, Pfizer, Roche.

No other potential conflicts of interest relevant to this article exist.