

# Liver Enzyme Elevation After $^{177}\text{Lu}$ -PSMA Radioligand Therapy for Metastasized Castration-Resistant Prostate Cancer

Hannes Treiber<sup>1</sup>, Alexander König<sup>2</sup>, Albrecht Neesse<sup>2</sup>, Annika Richter<sup>3</sup>, Carsten Oliver Sahlmann<sup>4\*</sup>, and Arne Strauss<sup>5\*</sup>

<sup>1</sup>Department of Hematology and Medical Oncology, University Medical Center Göttingen, Göttingen, Germany; <sup>2</sup>Department of Gastroenterology and Gastrointestinal Oncology, University Medical Center Göttingen, Göttingen, Germany; <sup>3</sup>Institute of Pathology, University Medical Center Göttingen, Göttingen, Germany; <sup>4</sup>Department of Nuclear Medicine, University Medical Center Göttingen, Göttingen, Germany; and <sup>5</sup>Department of Urology, University Medical Center Göttingen, Göttingen, Germany

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

**Key Words:** genitourinary oncology; radionuclide therapy;  $^{177}\text{Lu}$ -PSMA RLT; PSMA radioligand therapy; prostate cancer; mCRPC

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## PART 1

Therapy of metastasized castration-resistant prostate cancer remains a challenge. A promising approach is local delivery of radiation to tumor cells by systemic application of radioisotopes bound to the prostate-specific membrane antigen (PSMA).  $^{177}\text{Lu}$ -PSMA radioligand therapy (RLT) has been shown to be safe and effective in metastasized castration-resistant prostate cancer (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  $^{177}\text{Lu}$ -PSMA RLT and the diagnostic and therapeutic management.

## Case Study

A 59-y-old man who had castration-resistant prostate cancer with extensive metastases (including the mediastinum, lungs, bones, and liver), and whose disease had progressed after multiple lines of prostate cancer-directed therapies, received  $^{177}\text{Lu}$ -PSMA RLT at our institution.

Initially, the patient was diagnosed with localized prostate cancer (pT3apN0V0L1R1; Gleason score, 9) and treated with radical prostatectomy and adjuvant radiotherapy. Subsequent relapses were treated with androgen deprivation therapy,  $\gamma$ -knife surgery,

and a second-generation antihormonal therapy with enzalutamide. Checkpoint inhibition and poly(adenosine diphosphate-ribose) polymerase inhibition in a clinical trial was discontinued 4 mo before  $^{177}\text{Lu}$ -PSMA RLT, and subsequent rechallenge with enzalutamide 6 wk before  $^{177}\text{Lu}$ -PSMA RLT. Of note, the patient decided not to receive any chemotherapy.

Pretherapeutic  $^{68}\text{Ga}$ -PSMA PET/CT confirmed the previously known mediastinal, hilar, pulmonary, and bone metastases and further revealed at least 4 new liver lesions with low-level PSMA uptake (unaffected liver:  $\text{SUV}_{\text{max}}$  of 3.1 and  $\text{SUV}_{\text{mean}}$  of 2; metastases:  $\text{SUV}_{\text{max}}$  of 5.8, 4.9, 5.5, and 5.3, with  $\text{SUV}_{\text{mean}}$  of 3.7, 3.9, 3.4, and 2.2, respectively), suggesting a hepatic tumor burden below 10%. The liver metastases had an uptake just slightly above the level in the healthy liver and below the level in the salivary glands (molecular imaging PSMA score, 2). Liver MRI confirmed these metastases and further revealed metastases that showed no uptake on PET/CT—that is, were dedifferentiated. (Figs. 1A–1D). The pre-RLT diagnosis according to the molecular imaging TNM classification was mT0N0-M1a(RP, SD)b(diss)c(hepatic) (2).

One course of  $^{177}\text{Lu}$ -PSMA RLT with 6.2 GBq of  $^{177}\text{Lu}$ -ITG-PSMA-1, a generic preparation of  $^{177}\text{Lu}$ -PSMA-I&T, was applied. The posttherapeutic whole-body scans confirmed low uptake in the hepatic lesions (Fig. 1B). Serologic control after  $^{177}\text{Lu}$ -PSMA RLT showed a dramatic increase in liver enzyme levels, which had been within normal limits at baseline. Aspartate transaminase peaked at 2,105 U/L, and alanine transaminase peaked at 2,307 U/L. Serum creatinine was normal. The patient did not report abdominal pain, discomfort, vomiting, or 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 a normal liver configuration and size and a regular parenchyma texture. It confirmed a low tumor burden and normal liver blood flow (Figs. 1F and 1G). Furthermore, free abdominal fluid was ruled out.

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

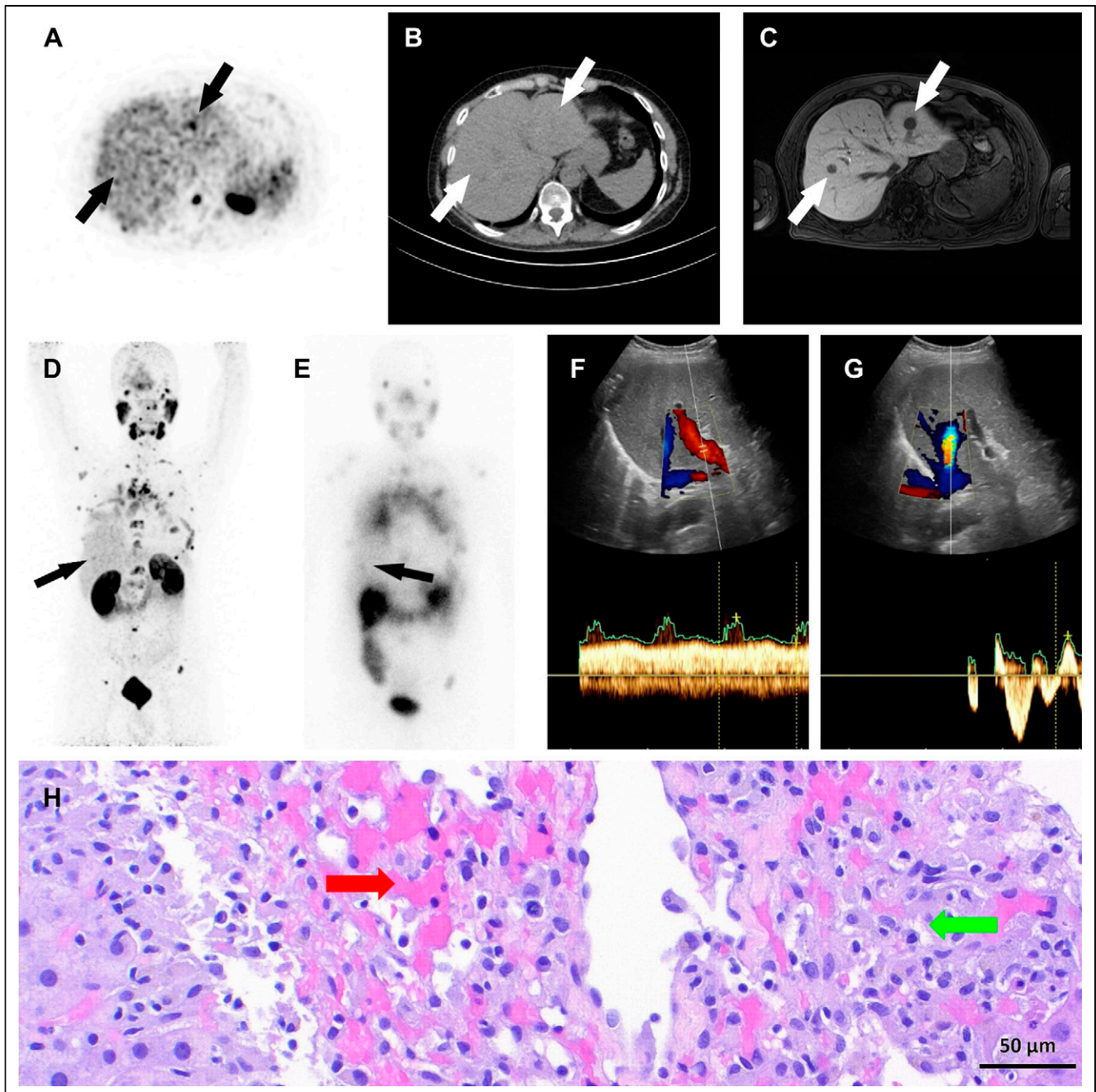
These findings led to a diagnosis that prompted specific treatment.

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For correspondence or reprints, contact Hannes Treiber (hannes.treiber@med.uni).

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**FIGURE 1.** (A–C) Axial views of liver metastases (arrows). From left to right are shown  $^{68}\text{Ga}$ -PSMA PET/CT, contrast-enhanced CT, and MRI (T1-weighted fast low-angle shot sequence 20 min after 7 mL of intravenous gadoxetate disodium). Liver metastasis in left lobe has very low uptake (molecular imaging PSMA score, 2), and other metastasis in right lobe shows no uptake above level in liver (molecular imaging PSMA score, 1). (D) Three-dimensional maximum-intensity projection of  $^{68}\text{Ga}$ -PSMA PET/CT with focal uptake in the liver (arrow). (E) Posttherapeutic  $^{177}\text{Lu}$ -PSMA-whole-body scan in anterior view, showing very low focal uptake (arrow) within hepatic lesions seen on  $^{68}\text{Ga}$ -PSMA PET/CT. (F and G) Ultrasound showing normal liver blood flow. (H) Photomicrograph of representative area of liver biopsy showing dystrophy of liver parenchyma (green arrow) and sinusoids with deposits (red arrow), 200 $\times$ , HE.

### Discussion

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

Regarding the positive findings on  $^{68}\text{Ga}$ -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 patients 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 the 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/venoocclusive disease. 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, and mushroom poisoning were ruled out by history. Liver ultrasound showed no signs of alcoholic or nonalcoholic fatty liver disease or of vascular abnormalities, rendering ischemic hepatitis or Budd–Chiari syndrome less likely differential diagnoses. Sinusoidal obstruction syndrome/venoocclusive disease typically occurs after high-dose chemotherapy but can also occur after radiotherapy. However, the patient never received any chemotherapy, and current scores for diagnosing sinusoidal obstruction syndrome/venoocclusive disease underline the importance of bilirubin elevation, weight gain, ascites, and painful hepatomegaly. Notably, none of these signs were present in our patient.

Because none of the diagnostic considerations led to a clear diagnosis supported by history, serology, and imaging, we recommended ultrasound-guided liver biopsy at that point.

## PART 2

The case study was described and discussed in part 1 of this article (1).

### Final Diagnosis

The histologic findings lead to the diagnosis of sinusoidal obstruction syndrome/venoocclusive disease (SOS/VOD). SOS/VOD is a typical, potentially fatal complication of high-dose chemotherapy in the context of hematopoietic stem cell transplantation. Classic 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 abdominal/liver irradiation and preexisting liver disease are especially relevant here. In hematopoietic stem cell transplantation, 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 process 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. 1A). SOS/VOD therapy aims to reduce inflammation and clotting and improve fibrinolysis (2). 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 to patient doses during external irradiation of a hepatocellular carcinoma. Between 6% and 66% of the patients who received doses of 30–35 Gy developed SOS/VOD (3). Furthermore, external irradiation differs from irradiation with open radionuclides. In the literature to date, SOS/VOD has practically never been described for nuclear medicine therapies with open radionuclides. The only example, to our knowledge, is a case of myeloablative therapy for a neuroblastoma in which <sup>131</sup>I-metaiodobenzylguanidine was administered with high-dose chemotherapy

The final diagnosis will be revealed in part 2 of this article.

## DISCLOSURE

Arne Strauss received fees from AstraZeneca, Bayer, BMS, Eisai, Ipsen, Merck, MSD, Pfizer, and Roche for speaker engagements and for an advisory role. No other potential conflict of interest relevant to this article was reported.

## REFERENCES

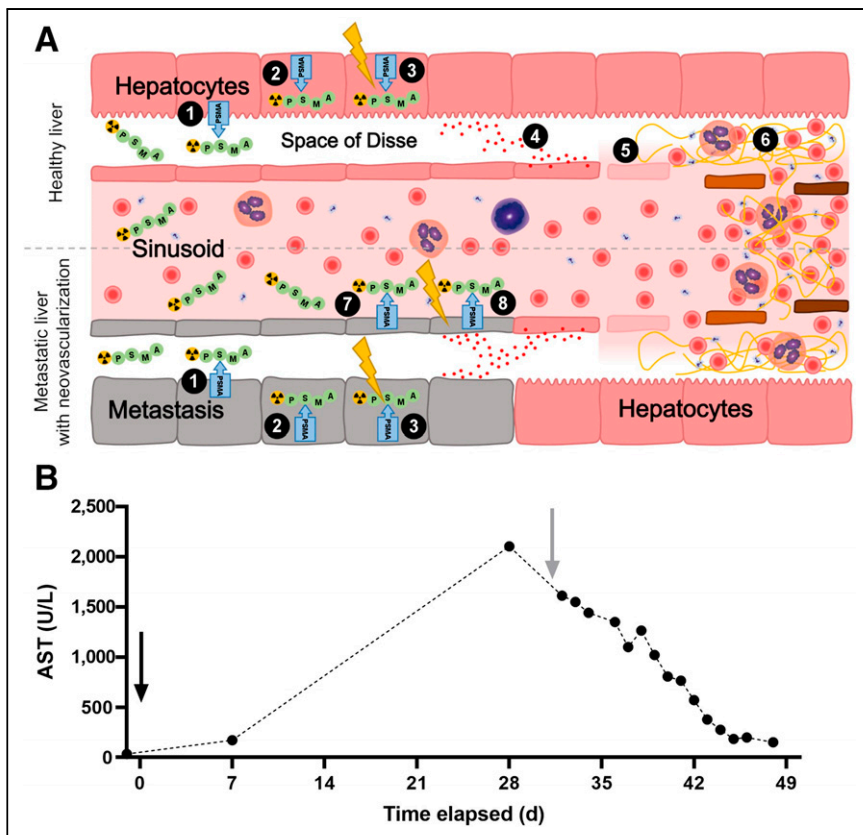
1. Heck MM, Tauber R, Schwaiger S, et al. Treatment outcome, toxicity, and predictive factors for radioligand therapy with <sup>177</sup>Lu-PSMA-I&T in metastatic castration-resistant prostate cancer. *Eur Urol*. 2019;75:920–926.
2. Eiber M, Herrmann K, Calais J, et al. Prostate cancer molecular imaging standardized evaluation (PROMISE): proposed mITNM classification for the interpretation of PSMA-ligand PET/CT. *J Nucl Med*. 2018;59:469–478.
3. Shetty D, Patel D, Le K, Bui C, Mansberg R. Pitfalls in gallium-68 PSMA PET/CT interpretation: a pictorial review. *Tomography*. 2018;4:182–193.
4. Alipour R, Gupta S, Trethewey S. <sup>68</sup>Ga-PSMA uptake in combined hepatocellular cholangiocarcinoma with skeletal metastases. *Clin Nucl Med*. 2017;42:e452–e453.
5. Rowe SP, Pienta KJ, Pomper MG, Gorin MA. Proposal for a structured reporting system for prostate-specific membrane antigen-targeted PET imaging: PSMA-RADS version 1.0. *J Nucl Med*. 2018;59:479–485.

including autologous stem cell transplantation (4), whereby the SOS/VOD was traced back to the whole-body irradiation from the <sup>131</sup>I-metaiodobenzylguanidine. Dosimetry data are available neither for this study nor for the patient discussed here. The mechanism of induction of SOS/VOD at low doses remains unclear. So far, too few data have been available on the induction of SOS/VOD by radionuclide therapies; the mechanism could be different from that of external radiation. In our case, at least 3 putative mechanisms might be considered. First, treatment in the presence of liver metastases is a potential trigger, but tumor burden and uptake in the liver were low in this case. Second, prostate-specific membrane antigen (PSMA) is physiologically expressed in healthy liver (5), leading to a diffuse liver irradiation dose in the particular context of PSMA-targeted treatment. Third, neovascularization of prostate carcinoma metastases can also express PSMA and thus could trigger the damage cascade (6). It remains unclear what the exact cause of SOS/VOD induction in this patient was. The cause may or may not have been the <sup>177</sup>Lu-PSMA radioligand therapy (RLT).

We hypothesize that one of these mechanisms or a combination of them could have played a role in triggering SOS/VOD in our patient (Fig. 1A). Induction by chemotherapy can be ruled out because the patient was chemotherapy-naïve. However, the severity of this complication with therapeutic consequences should be known to physicians using <sup>177</sup>Lu-PSMA RLT to treat patients with metastasized castration-specific prostate cancer.

The patient was hospitalized and received defibrotide, the internationally approved treatment for SOS/VOD, intravenously for 22 d. There were no treatment-related toxicities. Liver enzymes steadily declined to an aspartate transaminase level of 196 U/L and an alanine transaminase level of 130 U/L before discharge. In subsequent outpatient visits, liver enzymes were within normal limits (Fig. 1B). The maximum total bilirubin level, a serologic marker for SOS/VOD and a cornerstone of current diagnostic scores, was normal at histologic diagnosis and treatment initiation and reached a level of only 2.1 mg/dL in the course of the disease.





**FIGURE 1.** (A) Illustration of putative pathophysiology of SOS/VOD in  $^{177}\text{Lu}$ -PSMA RLT context. (1) Binding of  $^{177}\text{Lu}$ -PSMA to PSMA physiologically expressed on hepatocytes or to PSMA-expressing metastases. (2) Internalization of tracer-PSMA complex. (3) Radiation damage to hepatocytes or tumor cells. (4) Release of cytokines into space of Disse. (5) Cytokine-related damage to endothelium and leakage of sinusoids. (6) Fibrin, blood cells, cell debris, and thrombus in space of Disse and in sinusoids. (7) Binding of  $^{177}\text{Lu}$ -PSMA to PSMA expressed by neovascularization of prostate cancer metastases. (8) Radiation damage to endothelium. (B) Course of aspartate transaminase (AST) levels after  $^{177}\text{Lu}$ -PSMA RLT and initiation of treatment, with black arrow indicating day 0 of  $^{177}\text{Lu}$ -PSMA RLT and gray arrow indicating beginning of defibrotide treatment.

The patient did not receive further  $^{177}\text{Lu}$ -PSMA RLT but instead received systemic chemotherapy, on which liver metastasis regressed but bone metastasis progressed quickly, underscoring the general need for further therapeutic options in metastasized castration-specific prostate cancer.

### Conclusion

To the best of our knowledge, this article represents the first description of SOS/VOD occurring after  $^{177}\text{Lu}$ -PSMA RLT for metastasized castration-specific prostate cancer. Importantly, SOS/VOD developed despite a low hepatic tumor burden. Possibly, this side effect is dose-independent. Liver metastases 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 histologic diagnosis.

The ongoing VISION phase III trial (7) will assess toxicity for a similar compound. Clinicians should be aware of this SOS/VOD case, consider including liver enzyme levels in follow-up assessments

after  $^{177}\text{Lu}$ -PSMA RLT, and recommend further workup in patients with elevated liver enzymes until further safety data are available.

In cases of elevation, we recommend a workup for acquired transaminase elevation. SOS/VOD should be suspected when there is right-upper-quadrant pain, weight gain, ascites, hepatomegaly, a bilirubin level of at least 2 mg/dL or transaminases at least two times the normal level. Such findings should lead to clinical evaluation using established scores and a serologic control at a reasonable interval. If no SOS/VOD and no other cause can be determined and robust bilirubin ( $\geq 5$  mg/dL) or transaminase ( $\geq 5\times$  normal) elevations compatible with severe VOD/SOS are detected, a liver biopsy might be discussed, because the 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 that extends to even more than 21 d (late-onset SOS/VOD) after  $^{177}\text{Lu}$ -PSMA RLT. SOS/VOD should be treated according to established protocols.

### DISCLOSURE

Arne Strauss received fees from Amgen, AstraZeneca, Bayer, BMS, Eisai, MSD, Novartis, Pfizer, and Roche for speaker engagements and for

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### REFERENCES

- Treiber H, König A, Neesse A, Richter A, Sahlmann CO, Strauss A. Liver enzyme elevation after  $^{177}\text{Lu}$ -PSMA radioligand therapy for metastasized castration-resistant prostate cancer: part 1. *J Nucl Med*. 2021;62:1016–1018.
- Richardson PG, Corbacioglu S, Ho VT-V, et al. Drug safety evaluation of defibrotide. *Expert Opin Drug Saf*. 2013;12:123–136.
- Kim J, Jung Y. Radiation-induced liver disease: current understanding and future perspectives. *Exp Mol Med*. 2017;49:e359.
- Yanik GA, Villablanca JG, Maris JM, et al.  $^{131}\text{I}$ -metaiodobenzylguanidine with intensive chemotherapy and autologous stem cell transplantation for high-risk neuroblastoma: a new approaches to neuroblastoma therapy (NANT) phase II study. *Biol Blood Marrow Transplant*. 2015;21:673–681.
- Kinoshita Y, Kuratsukuri K, Landas S, et al. Expression of prostate-specific membrane antigen in normal and malignant human tissues. *World J Surg*. 2006;30:628–636.
- Chang SS, Reuter VE, Heston WD, Bander NH, Grauer LS, Gaudin PB. Five different anti-prostate-specific membrane antigen (PSMA) antibodies confirm PSMA expression in tumor-associated neovasculature. *Cancer Res*. 1999;59:3192–3198.
- Sartor AO, Morris MJ, Messman R, Krause BJ, VISION: an international, prospective, open-label, multicenter, randomized phase III study of  $^{177}\text{Lu}$ -PSMA-617 in the treatment of patients with progressive PSMA-positive metastatic castration-resistant prostate cancer (mCRPC). *J Clin Oncol*. 2017;38:TPS259.