Case Report

Discrepancy between Biochemical and Radiological Response in Metastatic Hormone-Sensitive Prostate Cancer: A Case Report and Literature Review

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Abstract

Background: Here we expose a case of a 59-years-old patient with hormone-sensitive metastatic low-volume prostatic cancer with an inconsistency between the PSA data and the detection of new lesions by the PSMA PET/CT.

Case Report: In April 2021, a 59-years-old man was diagnosed with prostatic adenocarcinoma with lymph nodes and bone (sacrum, iliac wing, and ischium) metastases (cT3b N1 M1b) which classified him in a stage IV low-volume according to CHAARTED criteria. At diagnosis, he presented a PSA of 59 ng/ml. Androgen deprivation therapy with LHRH analogue agonist was started. After 5 months, PSA decreased to 8.01 ng/ml and a prostate MRI demonstrated a partial response, therefore radiotherapy to the prostate was considered. However, a restaging with PSMA PET/CT was also prescribed to better define the local treatment planning. New PSA assay [18F]F-PSMA-1007 PET/CT showed a mixed response, with reduction in number and uptake of known lymph nodes lesions, with the appearance of four new highly PSMA-avid bone lesions defining a disease progression.

Discussion: The explanation of the discordance of PSA values and PSMA PET/CT images is still unclear and under investigation. PSMA expression and PSA secretion may be independently regulated with different behaviour after treatment with anti-hormones. Other hypotheses concern a mixed response to treatment, with a general decrease in PSA for an overall volumetric reduction of the lesions, although the newly ones secrete PSA, with preserved PSMA expression. Anyway, an unequivocal answer to the reasons besides this discordance is not possible and other studies are necessary.
Keywords: Hormone; Sensitive; Metastatic; Low-Volume; Prostatic Cancer; PSMA PET/CT; PSA

Key Messages: In about twenty per cent of cases PSA trend is discordant with the outcome of PSMA PET/TC, the most sensitive and specific radiological examination. The aim of this paper is to assess its causes and how to manage it in clinical practice.

Introduction

De novo metastatic hormone-sensitive prostate cancer (mHSPC) represents about 5-10% of all cases of prostate cancer and is related to a poor prognosis [1]. In the last seven years, many studies have evaluated different strategies of combination treatment (docetaxel, new hormonal agents, radiotherapy) with androgen deprivation treatment (ADT) in mHSPC demonstrating a statistical and clinical benefit in overall survival (OS) with respect to ADT monotherapy. In particular, the CHAARTED trial has introduced the concept of the extension of disease as a new prognostic and predictive factor for mHSPC: high-volume disease is defined as the presence of visceral metastases or four or more bone metastases with one or more outside the vertebral bodies or pelvis; all other cases are defined as low-volume disease [2]. Alongside this recent definition of disease volume, the only serum biomarker validated for the management of prostate cancer is the Prostate Specific Antigen (PSA). PSA is a prostate-specific, not cancer-specific, serum biomarker. It is typical to notice an increase of it in the prostatic neoplasms, but also in other conditions such as prostatic hyperplasia, prostatitis, and recent instrumentation of the urinary tract, urinary tract infection, and even ejaculation [3]. In clinical practice a PSA increase, which lasts throughout time and does not cover the terms above mentioned, may reveal a prostatic tumour presence. When PSA is strictly (o directly) related to the prostatic cancer presence, it becomes a prognostic factor and a response marker (regardless of treatment type among surgery, radiotherapy, and chemotherapy). Indeed, a PSA increase, after or during the treatment, often correlates with disease progression (PD) [4-6]. In the last years, alongside the PSA, new very sensitive imaging techniques have emerged in the detection and monitoring the prostatic disease. Prostate-specific membrane antigen positron emission tomography/computed tomography (PSMA PET/CT) has demonstrated to be more sensitive, specific and accurate compared to other conventional methods in the initial staging of the patient and in the restaging setting, even with low PSA serum levels (e.g. < 1 ng/ml) [7-11]. PSMA is a transmembrane glycoprotein highly expressed in the majority of prostate cancers and its expression is generally positively correlated to the PSA value and to a lesser extent to other factors such as PSA doubling time, Gleason Score and hormonal status [12-16]. However, during treatment, an inconsistency between PSA value (decreased) and disease status (PD) detected by PSMA PET/CT is possible. Here we expose a case of a 59-years-old patient with a low-volume de novo mHSPC with an inconsistent biochemical and radiological response to ADT.

Case Report

A 59-years-old man was diagnosed in April 2021 with an adenocarcinoma of the prostate (Gleason score 4+4 in 2/12 biopsies, GS 4+3 in 8/13 biopsies e GS 3+4 in 1/13 biopsies). He performed a Multiparametric Magnetic Resonance Imaging (mpMRI), a computerized tomography (CT) scan and a bone scan: the clinical stage was cT3bN1M1b, defined as low-volume disease, according to CHAARTED criteria, for the presence of metastases to regional lymph nodes and three bone metastases all located to the pelvis (sacrum, iliac wing, ischiium). This stage was confirmed with a [68Ga]Ga-PSMA-11 PET/CT for staging purposes. The PSA value at diagnosis was 59 ng/ml. The treatment strategy chosen for the patient was ADT + Radiotherapy (RT) to the prostate as for the STAMPEDE trial [17]. Note that androgen receptor signalling inhibitors (ARSI) such as abiraterone, apalutamide and enzalutamide were not yet available in Italy at that moment. The patient started treatment with ADT (LH-RH analogue agonist). After 5 months of treatment with ADT, overall well tolerated, PSA decreased to 8.01 ng/ml (with concomitant suppression of the testosterone value) and the multiparametric prostate MRI revealed a partial response (RP) of the primary lesion. However, a restaging with PSMA PET/CT was also prescribed to better define the local treatment planning. Although performed with [18F]F-PSMA-1007, the restaging PSMA PET/CT clearly showed a mixed response compared to the baseline. In particular, a reduction in number the uptake of regional lymph nodes metastases and the appearance of new highly PSMA-avid bone lesions to the anterior arch of V rib, D9, right sacrum and pubic symphysis [Figure 1]. Although validated for the castration-resistant phase of prostate cancer, if the PSMA PET progression (PPP) criteria were applied, it resulted in PD [18,19]. The patient, subsequently, underwent a new PSA test showing a further slight reduction, reaching the value of 6.75 ng/ml. Given the radiological progression of the disease, radiotherapy of the prostate was not performed and a first-line treatment for the metastatic castration-resistant setting with Enzalutamide was started. In May 2022, after 3 months from the beginning of treatment, the patient appeared in good condition at clinical examination, reported excellent tolerance to the drug and the PSA value decreased to 1.01 ng/ml. A further [18F]F-PSMA-1007 PET/CT performed in July 2022 revealed a radiological response with the PSMA uptake uniformly decreased in all metastatic sites, without the appearance of new lesions. PSA value in July 2022 was 0.45 ng/ml. The patient continued the treatment, which is still in progress.
Discussion

PSA values are related to disease trend in patients affected by prostatic cancer: their reduction indicates an active response and a consequent benefit related to the medical, radiotherapy or surgical treatment used, instead their increase correlates with the progression of the disease. In castration-resistant tumours it has already been demonstrated that in about a quarter of cases PSA trend and imaging results are discordant, mainly manifesting with a decrease in PSA value with a concomitant progression of disease detected by PSMA PET/CT [7-9,18,20,21]. A similar situation likely extends to the hormone-sensitive setting, but there are no data from the literature about this condition. The reasons underlying the discordance between PSA values and PSMA PET/CT findings are still unclear and under investigation. The expression of PSMA can be very heterogeneous [22-24]. Many in vitro and in vivo studies showed that PSMA expression and PSA secretion are independently regulated with different behaviour after treatment with anti-hormones [25,26]. It seems that in men with hormone-sensitive cancers, androgen deprivation leads in most cases to a decrease in maximum and mean standardized uptake value (SUV) at PSMA PET/CT as well as PSA secretion. On the contrary in men with castration-resistant prostate cancer, androgen deprivation leads to increased SUVs at PSMA PET/CT, but PSA response can be variable or delayed [26,27]. Nevertheless, a flare phenomenon of expression of PSMA has been reported when starting hormone therapy both in castration-sensitive and in castration-resistant setting [28]. Another explanation of this discordance is that different prostate cancer cell clones may develop during tumour progression or under treatment with different expression of PSMA or PSA secretion [29]. An emblematic example is the progressive neuroendocrine dedifferentiation of some advanced prostate cancers that is associated with poor PSA secretion and heterogeneous and inconstant PSMA uptake [30-33]. Finally, a mixed response to treatment may justify the biochemical and PSMA PET/CT discordant findings, with a general decrease in PSA for an overall volumetric reduction of the lesions, although the newly ones secrete PSA, with preserved PSMA expression [34,35]. This hypothesis is further supported by the high percentage of patients who do not benefit from the ADT treatment for a long time: in patients considered low-volume in the STAMPEDE study the failure-free-survival rate was about 80% [17]. In this scenario, medical oncologists will be faced with the question of how to deal with this significant proportion of patients, in the absence of studies with sufficient case series and the resulting indications. The main options are to continue the current treatment or to switch to a subsequent line of therapy, whether in the hormone-sensitive or castration-resistant setting. Until the role of the new lesions, their nature and possible evolution over time are not clear, giving an unequivocal answer to what is the correct way to proceed is not possible. Other studies are necessary to investigate the prognostic role and the clinical guidance of PSMA PET/CT in these contexts. In the strong suspicion that, despite a satisfactory overall response to treatment, the new foci are clones resistant to therapy, indicating a real progression of the disease, it was decided in this case to move to the next line of therapy. The new line of treatment with ARSI resulted in a biochemical and radiological response. New studies are warranted to identify the correct strategy to apply in terms of biochemical and radiological follow-up during treatment for mHSPC and the best treatment choice in patients with discordant radiological PD and biochemical response.
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References


