

**CASE REPORT**

# Spurious elevation of Prostate-specific antigen associated with shingles in a prostate cancer patient undergoing active surveillance

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**Key Clinical Message**

Spurious PSA increase in prostate cancer associated with shingles reactivation should be considered under the right clinical scenario to avoid unnecessary investigations or treatment.

**KEYWORDS**

active surveillance, prostate cancer, shingles, spurious PSA elevation

## 1 | INTRODUCTION

A 69-year-old man was followed on active surveillance for low-risk prostate cancer. His PSA was followed serially. His values displayed a transient elevation in association with shingles reactivation and returned to baseline over the next few months and remained at baseline for more than 2 years.

Prostate-specific antigen (PSA) test is a frequently utilized blood test in prostate cancer screening and is a standard of care for patients on active surveillance and for post-treatment monitoring.<sup>1</sup> Falsely elevated PSA levels can raise concerns over disease progression or treatment failure, and may result in unnecessary investigations and interventions, as well as psychological trauma for the patient. A small number of studies present contexts in which PSA elevations may occur due to infectious phenomena, rather than true progression of disease. One such infectious agent is shingles, which is a reactivation of latent varicella-zoster virus (VZV), usually in a dermatomal distribution. A causal relationship between shingles and PSA elevation has not been studied, although there is one case study describing a spike in PSA in two prostate cancer patients during VZV reactivation.<sup>2</sup>

We present the case of a man with a known T1c Gleason 6 adenocarcinoma of the prostate who was being monitored on active surveillance. His PSA value was found to be elevated

during one of the routine follow-ups. This sudden rise in PSA coincided with shingles (VZV) activation in this man. Thereafter, his PSA eventually returned to baseline.

## 2 | CASE

In August 2012, a then 69-year-old patient was diagnosed with a T1c Nx Mx, Gleason 6 prostate adenocarcinoma. That biopsy revealed two microfoci of Gleason 6 disease, 2/13 cores positive, with <1% of the gland involving carcinoma. His PSA on May 2013 was 3.38. Given his low-volume, low-risk disease, he was managed on an active surveillance program.

On 30 May 2013, the patient was seen at our institution, referred for consideration of a clinical trial. At the time of consultation, the patient had mild lower urinary tract symptoms (International Prostate Symptom Score 2/35) and mild sexual dysfunction (International Index of Erectile Function Score 20/25). His past medical history was remarkable for GERD and arthritis. His medications consisted of aspirin, lorazepam, prevacid, and celebrex.

The patient was enrolled in a clinical trial (ASIST) and was randomized to MRI-assisted TRUS biopsy arm. He was continued on active surveillance. He had a PSA blood test

every 3 months (Figure 1) and was seen clinically every 6 months. His PSA values were as follows: 3.38 (May 2013), 3.15 (July 2013), 1.71 (October 2013), 3.15 (January 2014), 2.72 (Apr 2014), 2.05 (June 2014), 2.40 (October 2014), 2.43 (December 2014); his PSA velocity had been flat (Figure 1). In April 2015, his PSA value was markedly elevated at 7.61. Review of systems revealed that the patient was recently diagnosed with shingles. His PSA test was repeated in one week to rule out a laboratory error; the PSA was confirmed at 4.63. His PSA continued to trend down to 3.57 (July 2015), then to 3.15 (September 2015), and to 2.69 (May 2016). It remained stable at 4.1 (November 2016), then 2.9 (May 2017), 3.6 (November 2017), and most recently, at 3.1 (March 2018). He had an MRI prostate study performed that showed a nodule, and a biopsy was repeated, showing Gleason 7 disease. He was then treated with radiotherapy with curative intent in April 2018. Even though he did eventually receive radical treatment in this fashion, his treatment took place 3 years following the spurious rise of his PSA, and he avoided potential side effects of investigations and treatment for that duration.

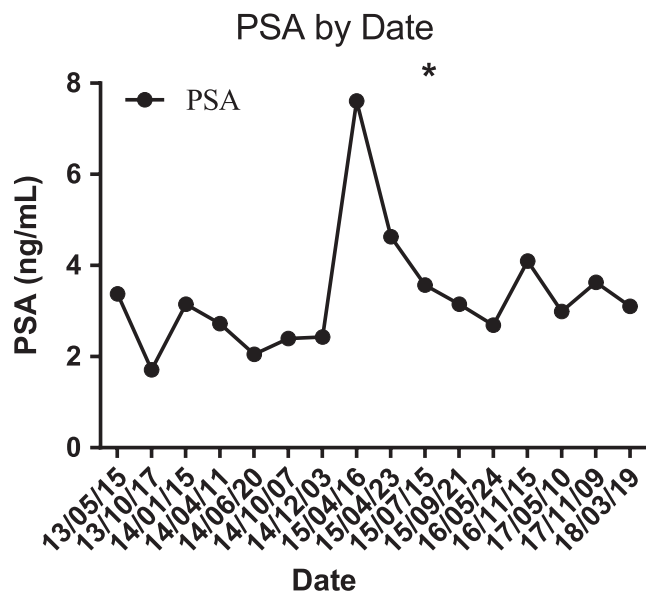
### 3 | DISCUSSION

Elevation in PSA values defines treatment failure and disease progression, and thus, recognizing spurious elevations is crucial to avoid unnecessary investigations and interventions. To our knowledge, the rate of spurious PSA elevation in prostate

cancer patients is not well documented. In the surveillance population, we had previously described the variability of PSA blood tests and the peril of using the last PSA value as a trigger for treatment.<sup>1</sup> This case report is the second report<sup>2</sup> to describe this phenomenon in association with shingles, and the first report to describe it in the context of active surveillance. Nonetheless, the mechanism by which the PSA increase occurs during shingles remains unexplored. In addition to shingles, other possible causes of spurious PSA rise have only begun to be appreciated, and there are few studies that address this issue.

A small number of studies demonstrate a correlation between other infectious causes and an increase in PSA. For instance, Epstein-Barr virus (EBV), a herpes family virus and the causative agent of infectious mononucleosis (IM), has been associated with a PSA rise as well.<sup>3</sup> One case-control study of a population of US military recruits with or without IM found a statistically significant increase in the probability of large PSA increase (defined as an increase by 20 ng/mL or 40% or greater rise) in those diagnosed with IM compared to controls. As with shingles, the mechanism of this increase is unknown. One report presented the case of one male with a diagnosis of acute Hepatitis A who had an elevated PSA level (28.6 ng/mL)<sup>4</sup>; whether this PSA rise reflected an involvement of the prostate gland by the virus or a separate phenomenon was not addressed by the authors. Similarly, there is one case report of a 64-year-old man with Gleason 6 disease on active surveillance, who contracted an infection with chikungunya virus, resulting in a transient increase in PSA.<sup>5</sup> The increase in PSA was also confirmed in this case by an independent laboratory and is thought by the authors to have occurred due to a subclinical prostatitis caused by the virus. Other studies have combined the results of two longitudinal studies of men with sexually transmitted infections (STIs) in clinics in Baltimore, Maryland (USA).<sup>6,7</sup> In this study, the PSA values of men with STIs were more likely to increase by 40% or more during an acute STI. In case of an STI, direct inflammation of the prostate is postulated to cause the increase in PSA.

Benign causes of PSA elevation such as sexual activity, exercise associated with perineal trauma (bicycle or horse riding), and passage of kidney stones are well established. However, spurious PSA elevation due to infectious causes may represent a more common phenomenon than currently appreciated. Although the cellular mechanism for an increase in PSA after infection has not been definitively established, it is believed that prostatic inflammation and disruption of epithelial integrity result in release of PSA extracellularly.<sup>8</sup> The inflammatory cascade may involve proinflammatory cytokines such as IL-6 and IL-8, which have been implicated in benign prostatic hypertrophy (BPH), chronic prostatitis, and prostate cancer development (reviewed in<sup>9</sup>). One study measured the levels of C-reactive protein (CRP) in young males



**FIGURE 1** Serum prostate-specific antigen values by date in our patient. The values were obtained in community laboratories, except for the value dated 23 April 2015 (asterisk), which was obtained in Sunnybrook Health Sciences Centre laboratories. Values show a peak in 16 April 2015, which is when the patient had shingles, with return to baseline by 24 May 2016

in the military in the context of sexually transmitted illness and also tested a correlation with PSA.<sup>10</sup> However, the rise in CRP was only significant during gonorrhea compared to controls, and CRP levels correlated poorly with PSA. When faced with an unexplained rise in PSA, clinicians should maintain a high level of vigilance for non-prostate cancer conditions including viral infections that may have resulted in a spurious elevation of PSA in order to avoid subjecting patients to unnecessary investigations, interventions, and psychological distress.

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