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Biochemical Recurrence in Prostate Cancer and Temporal Association to Bone Metastasis

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Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Case series
Patient: Male, 78 • Male, 65
Final Diagnosis: Bone metastasis from prostate cancer recurrence
Symptoms: Joint pain
Medication: —
Clinical Procedure: —
Specialty: Uro-Oncology

Objective: Rare presentation

Background: Prostate cancer is a common cancer in men. Radical prostatectomy, i.e., the surgical removal of the entire prostate, is a frequently used option. Biochemical recurrence (BCR), i.e., detectable prostate specific antigen (PSA), is common in some men following such treatment. The timing of BCR to metastatic spread of disease in bones is usually a few years. If the biochemical failure occurs after a longer duration from the time of curative intent, it is generally believed to lead to local recurrence.

Case Report: We report on two cases. A 78-year-old male was diagnosed with Gleason 7, prostate cancer in 2001. He subsequently underwent an open radical prostatectomy. Serial post-operative PSA's were undetectable (<0.01 ng/mL) up to 2016. He was diagnosed with a detectable PSA for the first time with a value of 0.3 ng/mL, that year. The PSA continued to rise to a level of 1.1 ng/mL. This rise in the PSA was within a 12-month interval. Subsequent bone scan and bone biopsy detected prostate cancer metastasis in multiple bones. Our second case was a 65-year-old male who underwent a laparoscopic radical prostatectomy in the year 2006 for a biopsy proven prostate cancer with Gleason 3+4=7. Serial post-operative PSA's were undetectable up to 2017. Within a span of 8 months, the PSA rose from 0.3 ng/mL to 1.52 ng/mL. A positron emission tomography scan demonstrated pubic bone lesion indicative of prostate cancer metastasis.

Conclusions: BCR can occur a decade after curative intent treatment of prostate cancer. The duration from BCR to detectable metastasis can be shorter. We demonstrated here that the site of recurrence, in such scenarios, can be distant metastasis and not local recurrence alone. Better imaging modalities are needed to identify the spread of prostate cancer at low levels of PSA.

MeSH Keywords: Diagnostic Imaging • Neoplasm Metastasis • Prostatic Neoplasms

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/918569

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Background

Prostate cancer is the second most common cancer in males in the United States. Annually 174 650 new cases are diagnosed in the United States [1]. Mortality from prostate cancer is predicted to be in the range of 31 620 deaths for the year 2019 [1]. Surgery and radiation therapy are some of the most common, standard of care treatments for prostate cancer. Most cases (77%) of prostate cancer are localized at the time of the diagnosis [2]. The 5-year overall survival rates for men who have undergone curative treatment for localized prostate cancer are high [3]. However, a significant number of men who are treated primarily with curative intent will fail primary treatment. Failure of primary treatment is usually diagnosed by a detectable or a rising PSA which is termed biochemical recurrence (BCR). It is estimated that 40% of the patients undergoing radical prostatectomy may experience BCR [2]. Metastasis, which may occur subsequently, is involvement of a distant organ, typically bone or lymph node by prostate cancer. The transition from BCR to metastasis has been described to be a prolonged duration, extending over years [4]. Detection of this metastasis to bone generally requires the presence of a high level of PSA [5]. The fundamental question remains whether the rise in the PSA is indicative of local recurrence or metastatic disease. Patients experiencing this clinical scenario seek a clear understanding of likely future events. Clinicians managing these situations should be aware of a multitude of possible situations other than those previously described in literature.

We describe 2 clinical scenarios which demonstrate that this period from BCR to detection of bone metastasis may be shorter than has been earlier described in literature [4]. We also demonstrate that the spread of cancer to bone in this setting may occur at very low levels of PSA.

Case Reports

A 63-year-old African American male was diagnosed with an elevated PSA of 6.7 ng/mL in the year 2001. He underwent a prostate biopsy and was diagnosed with Gleason 3+4=7, prostate cancer the same year. Following a negative metastatic workup that included a computerized tomography (CT) of the abdomen and pelvis, he subsequently underwent an open radical prostatectomy (ORP) in 2001. TNM stage, post radical prostatectomy (RP) was T2cN0M0, with a Gleason 3+4=7. Prostate specific antigen (PSA) readings post radical prostatectomy were undetectable (<0.01 ng/mL) until 2016. In 2016 (now aged 78 years), his PSA was detectable for the first time, value being 0.3 ng/mL. From our chart review, no active monitoring or recommendations seem to have been made at this time. In September 2017 he complained of low back and knee pain. He presented to the emergency department and had spine and knee x-rays, which were essentially normal. He was referred to a urologist as part of follow-up.

He was seen and evaluated by the urologist. Following a clinical evaluation, repeat blood work (PSA) and bone scan were ordered. His PSA had increased to 1.1 ng/mL in October 2017. He underwent a technetium 99 m medronate bone scan (26.1 mCi intravenous) (Figure 1) which demonstrated multiple lesions in the spine, sacrum, and pelvic bones.

In October 2017, he underwent a bone biopsy. This demonstrated metastatic involvement of the bone from poorly differentiated carcinoma, suspicious for prostate cancer (Figure 2).

He is on androgen deprivation therapy because of the symptomatic nature of the bone metastasis.

The second case was a 52-year-old male who was diagnosed with Gleason 3+4=7, prostate cancer after undergoing a biopsy for a PSA of 5.4 ng/mL in the year 2006. He then underwent a laparoscopic radical prostatectomy in 2006, after a negative metastatic workup, which included a CT scan of the abdomen and pelvis. TNM stage post radical prostatectomy was T3aN0M0, with Gleason 3+4=7. Post radical prostatectomy PSA readings were undetectable until 2017. His PSA was detectable, in the BCR range, in October 2018 to a value of 0.3 ng/mL. In April 2019 (now aged 65 years) the PSA had risen to a value of 1.52ng/mL. A technetium 99m medronate (26.1 mCi intravenous) bone scan was negative for metastasis. However, a fluciclovine (9.8 mCi intravenous) positron emission tomography (PET) scan (Figure 3) demonstrated a lesion indicative of metastasis on the pubic bone.

After discussion of all the treatment options, the patient elected to be on androgen deprivation therapy.

In summary both men had Gleason 3+4=7 prostate cancer. Both men had radical prostatectomy, with curative intent, for prostate cancer. These men had an undetectable PSA (≤0.2 ng/mL) for at least over a decade. After the PSA had reached BCR detectable levels, there was an acute rise in the PSA values. Both men were detected with bone metastasis at low PSA levels.

Discussion

Although BCR is a well-accepted pathophysiological phenomenon, the PSA value at which it is considered BCR has been varied, too. Following surgical removal of the prostate, the definition of BCR has been a rise of or equal to 0.2 ng/mL [6]. Some institutes have described BCR as a value of 0.4 ng/mL [2]. For men with a rising PSA after radiation therapy the ASTRO-Phoenix definition of BCR is the nadir value + 2 ng/mL [7].

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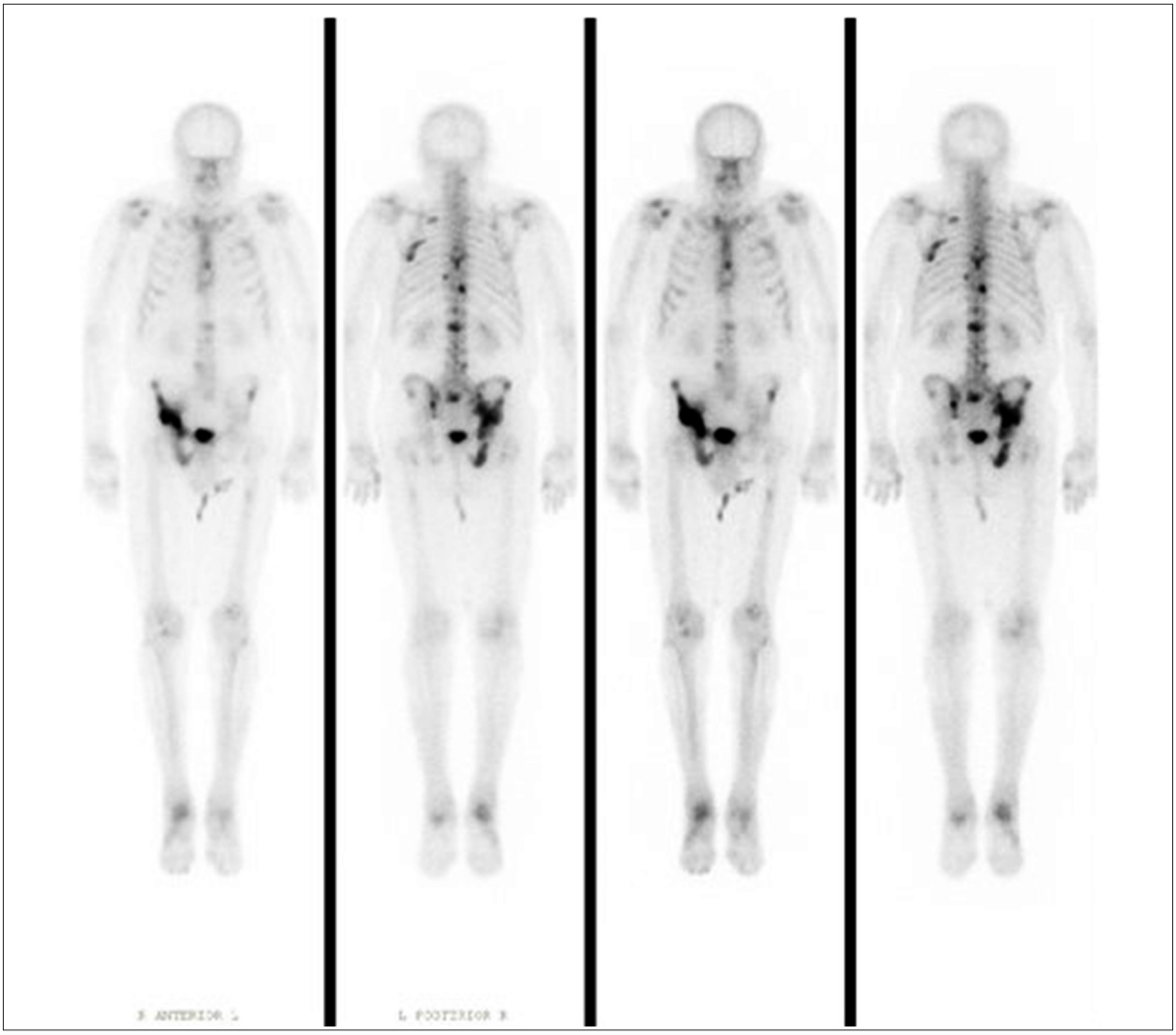

Figure 1. Technetium 99 m bone scan demonstrating metastasis in the spine and pelvic bones.

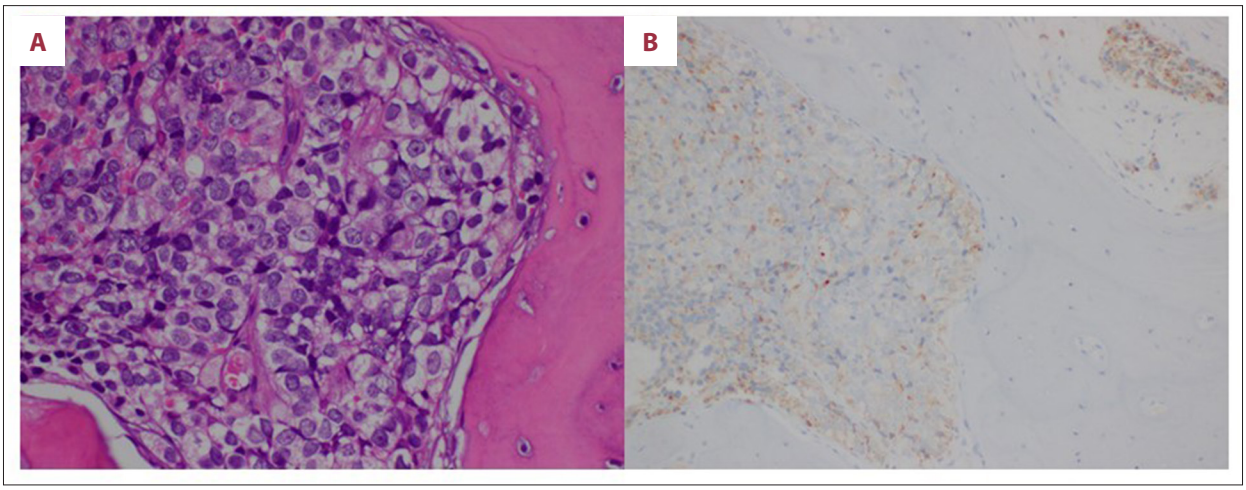

Figure 2. (**A**) Bone biopsy showing cohesive sheets of tumor cells with prominent nucleoli (hematoxylin and eosin [H&E] 40× magnification). (**B**) Tumor cells are positive with prostate specific acid phosphatase (PSAP) immonostains.

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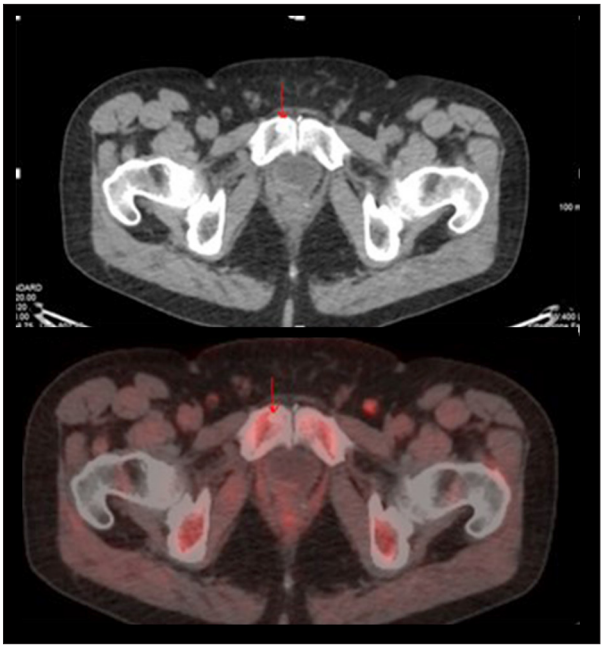

Figure 3. Fluciclovine positron emission tomography (PET) scan demonstrating presence of metastasis in right pubic bone.

A rise in the PSA after definitive treatment is none the less, considered evidence of recurrent disease.

BCR provides the earliest evidence that there is recurrent or residual disease. The clinical use of BCR as a surrogate end point for intervention to alter the subsequent natural history of cancer thereof has been questionable [8]. A detectable PSA after definitive treatment may imply either local recurrence or distant recurrence. Distant recurrence is cancer spreading to bones or soft tissue, e.g., lymph nodes and solid organs. Local recurrence is generally recurrence of disease in the prostatic fossa if the prostate was removed or in the prostate, if the initial treatment was radiation therapy. There are different treatment implications for treating men with BCR who have failed locally or distant. Local recurrence may still be amenable to salvage radiation or salvage radical prostatectomy [9]. Distant metastasis generally would require systemic therapy like androgen deprivation therapy [10].

The implications on developing a BCR are not definitive. Detection of BCR does not necessarily indicate a terminal outcome. Frazier et al. [11] demonstrated that about 93% of the patients with BCR had not failed clinically, i.e., no evidence of detectable metastasis. Jhaveri et al. [12] demonstrated that the difference in overall survival in men with BCR and no BCR at 10 years was minimal.

The timing of BCR from the definitive treatment has been considered important for differentiating between local and distant recurrence. Studies [2] indicate the shorter the duration of BCR from surgery, PSA detection indicates "occult distant metastasis". Whereas longer intervals imply a local recurrence [13]. In our case reports though, the duration from curative intent surgery to BCR was over a decade; the recurrence seems to be associated with distant bone metastasis and not local recurrence.

The rate at which the PSA rises has been used to predict the location of recurrent disease. Partin et al. [14] also demonstrated that local recurrence is more common when the PSAV was <0.75 ng/mL per year. When the PSA doubling time was >12 months Patel et al. [15] showed that the recurrence was more likely to be local. Generally, PSA doubling time of <6 months implies a likelihood of distant recurrence [16]. Faster rise of PSA appears to be associated with distant metastasis. This seems to be the case in our 2 case reports.

Detection of spread to bone has significance in the algorithm of decision-making. However, detecting the spread to bones has long been a diagnostic challenge. Bone scans yield lower sensitivity in patients with low PSA values. Oesterling et al. [17] thought that any BCR value which was lower than 2 ng/mL did not benefit from a bone scan. Cher et al. [5] demonstrated that the lowest PSA associated with a positive bone scan was 46 ng/mL in their series. In PSA only recurrence, Moul et al. [2] felt that bone scan had limited value unless the PSA exceeds 30 to 40 ng/mL. Even with lower PSA value, our cases had the presence of bone metastasis.

The duration between BCR and detecting distant metastasis has been reported earlier [4]. The median actuarial time from BCR to metastasis was reported to be 5 years (mean 8 years) according to Pound et al. [4]. This was a seminal paper describing the natural history of BCR. This paper also demonstrated that the time from metastasis to death was approximately 5 years. Our case scenarios seem to demonstrate that the duration from detection of BCR to bone metastasis was much shorter than described in this paper.

The presence and natural history of BCR has been studied for a long time. There has been some evidence [4] to suggest that the predictors of location and metastasis are related to the timing of the recurrence from the initial definitive therapy. The duration of BCR and time to detectable metastasis was described to be multiple years [4]. The 2 cases presented in this report demonstrated that the duration from BCR to metastasis can be short. Even at low values of PSA, there can be metastatic involvement of bone. In Case 1, the bone metastasis was proven by a bone biopsy and a bone scan. In Case 2, the involvement was not detected on technetium 99m bone scan but was positive on fluciclovine PET scan. This could also imply that the duration from BCR to metastasis may not be as definitive as previously implied. Clinicians need to have a high level of suspicion for detecting the presence of metastasis even with

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low PSA values. Traditionally used imaging modalities like technetium bone scans have a lower sensitivity to detect metastasis at low PSA levels. Newer technology like fluciclovine [18] PET scan may help in scenarios wherein the traditional imaging techniques are not sensitive enough to detect metastasis.

Conclusions

Delayed BCR is possible in prostate cancer. The timing of BCR from the initial definitive treatment of prostate cancer may not definitively indicate the location of disease failure. The time interval from detectable PSA to development of metastasis may be shorter in certain scenarios. Distant bone metastasis can occur in prostate cancer even with low PSA values. Sensitive imaging techniques are required for precise early detection of the site of BCR in prostate cancer.

Conflict of interest

None.

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