

Alternative Medicine and Oncology: Erroneous Biochemical Failure Following Herbal Supplementation in Early-Stage Prostate Cancer

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Prostate-specific antigen (PSA) levels are routinely surveilled after oncologic intervention in patients with prostate cancer. Occasionally, PSA levels are elevated because of factors unrelated to disease recurrence, such as herbal supplement use. False-positive PSA elevations may confound the clinical picture and subsequent decision-making processes, potentially leading to unnecessary diagnostic and therapeutic interventions. In this case report, a patient with low-risk prostate cancer who was treated with low-dose-rate interstitial brachytherapy presented several years after treatment with an erroneously elevated PSA level after taking an herbal supplement. This case highlights the importance of a holistic approach to patient care, whereby tactful assessment of the psychosocial and spiritual aspects of health led to the identification of an uncommon but potentially morbid entity.

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Prostate adenocarcinoma is the most commonly diagnosed malignant tumor in US men, accounting for nearly one-fifth of all cancer diagnoses.¹ Like most cancers, treatment approaches are dependent on both disease and patient characteristics. One commonly used treatment modality in the setting of low- and intermediate-risk cancer is interstitial brachytherapy, also known as prostate seed implantation.

Interstitial brachytherapy involves the direct insertion of multiple radioactive sources into the prostate gland, thus allowing for the creation of a steep dose gradient between the target and adjacent normal tissue. After the procedure, patients are monitored for therapeutic complications and tumor recurrence. Surveillance efforts involve both clinical and biochemical assessment with laboratory measurements of prostate-specific antigen (PSA).^{2,3} Influenced by androgenic stimulation, PSA is a glycoprotein produced by both normal and malignant prostatic tissue. In cases of biochemical recurrence (defined as an increase in the serum PSA ≥ 2.0 ng/mL above the posttreatment nadir), further diagnostic (eg, repeated prostate biopsy) and therapeutic strategies are often used.^{4,5} To avoid unnecessary workup and treatment, physicians must be aware of the complex relationship between interstitial brachytherapy and PSA levels. The postradiation decline in PSA is usually gradual and reaches a nadir at approximately 18 months.⁶ Occasionally, the PSA level transiently increases following the posttreatment nadir, yet the patient is disease free. Described as a PSA “bounce,” these benign PSA increases are typically

distinguished from true biochemical failure by the post-treatment time interval (15-18 months for benign increases, >24 months for true recurrence) in which the PSA increase is observed.⁷⁻⁹

In addition to surveillance, physicians should also regularly assess patients for radiation-related complications. Common complications of therapy correspond to the anatomic proximity of the rectum, bladder/urethra, and penile bulb/neurovascular bundles to the prostate and include diarrhea, urinary dysfunction, and sexual dysfunction, respectively. Since 10-year survival rates for early-stage disease exceed 95%, treatment complications can negatively affect the patient's quality of life.¹ Specifically, sexual side effects are often very troubling for survivors, with erectile dysfunction being reported in 50% to 70% of patients treated with interstitial brachytherapy.^{10,11} Considering the sensitive nature of the problem, many patients feel uncomfortable discussing these symptoms with their physician.¹² Complicating matters further, patients will occasionally seek assistance through alternative therapies, including unregulated herbal remedies and supplements. Many of these supplements lack data supporting their efficacy and/or evaluating their safety profile. As a result, the actual ingredients and downstream biological effects are often unknown, thus creating a potentially dangerous situation.¹³ Highlighting these dangers, we present the case of a patient with early-stage prostate adenocarcinoma who had an apparent biochemical failure after initiation of a Chinese herbal supplement.

Report of Case

In February 2014, 30 months after undergoing interstitial brachytherapy for adenocarcinoma of the prostate, a 59-year-old Asian man presented with an increase in PSA from 1.1 to 3.4 ng/mL. He had a history of hypercholesterolemia managed with simvastatin and Peyronie disease with subsequent erectile dysfunction refractory to tadalafil. In the interval since interstitial brachytherapy treatment, the patient denied having any new medical conditions and specifically denied any

new or worsening urinary, constitutional, or musculoskeletal symptoms. Vital signs and physical examination findings were grossly unremarkable, including benign digital rectal examination findings.

In November 2011, the patient underwent a transrectal biopsy after 2 consecutive PSA increases were observed. Ultimately, the biopsy results were positive for Gleason 3+3=6 adenocarcinoma of the prostate involving 2 of 12 total core samples. The positive core biopsy specimens were derived from the right prostatic apex (20% of core) and left prostatic base (10% of core). On initial consultation, his baseline Sexual Health Inventory for Men score was 21 of 25. The patient denied any current supplement use and also denied having a history of tobacco or alcohol use. The patient's family history was significant for papillary thyroid cancer in his sister at age 57 years.

Two weeks later, the patient attended a consultation at the radiation oncology clinic to discuss treatment options. On presentation, his vital signs were as follows: blood pressure, 130/80 mm Hg; pulse rate, 76 beats/min; and respiratory rate, 16/min. Physical examination findings were grossly unremarkable, with no evidence of prostatic mass or asymmetry, bone pain, lymphadenopathy, or tissue texture changes in the lumbar spine or iliotibial band. As the patient's life expectancy would likely extend beyond 10 years, several suitable treatment options were discussed, including active surveillance, external beam radiation therapy, interstitial brachytherapy, or radical prostatectomy. The patient elected to pursue treatment with interstitial brachytherapy, because he was not comfortable with the approach of active surveillance. He found the logistics of external beam radiation therapy to be cumbersome and wished to avoid the temporary period of incontinence following prostatectomy.

In February 2012, he underwent treatment with ultrasound-guided interstitial brachytherapy with implantation of 97 I-125 seeds. The perioperative course was uncomplicated, and the postoperative dosimetric parameters were favorable, with a D90 (dose covering 90% of the prostate volume) of 165.5 Gy and a

V100 (volume of the prostate receiving 100% of prescribed dose) of 91.67%. During the next 18 months, the patient's PSA level declined and eventually reached a nadir of 1.1 ng/mL in August 2013 (Figure). His only complaint was of occasional loose bowel movements. He denied worsening of urinary or sexual functions.

At the current February 2014 visit, the patient denied starting any new prescription medication; however, on further questioning, the patient stated that he was seeing an acupuncturist who recommended that he take an herbal supplement by the name of Jin Gui Shen Qi Wan. He was taking one 750-mg tablet per day but was unable to recall why he was taking the supplement. Nevertheless, he was encouraged to discontinue use, and he complied with this request. Follow-up PSA levels were reassessed at 1 and 3 weeks after supplement discontinuation and found to be 2.3 ng/mL and 1.0 ng/mL, respectively. By September 2014 (6 months after

supplement discontinuation), the patient's PSA level fell to 0.7 ng/mL. At the last follow-up in August 2018, the patient's PSA level was 0.1 ng/mL, and he clinically showed no evidence of disease.

Discussion

More than 50% of oncologic patients use herbal or dietary supplements as alternative or supplementary therapy to conventional medical treatment.¹³ However, two-thirds of patients taking herbal supplements do not disclose use to their physician.¹³ Both patient- and physician-related factors, including age, sex, race, culture, socioeconomic status, and frequency of health care exposure likely contribute to nondisclosure of herbal supplement use. Additionally, patients with genitourinary complications secondary to prostate cancer therapy are likely more reluctant to discuss

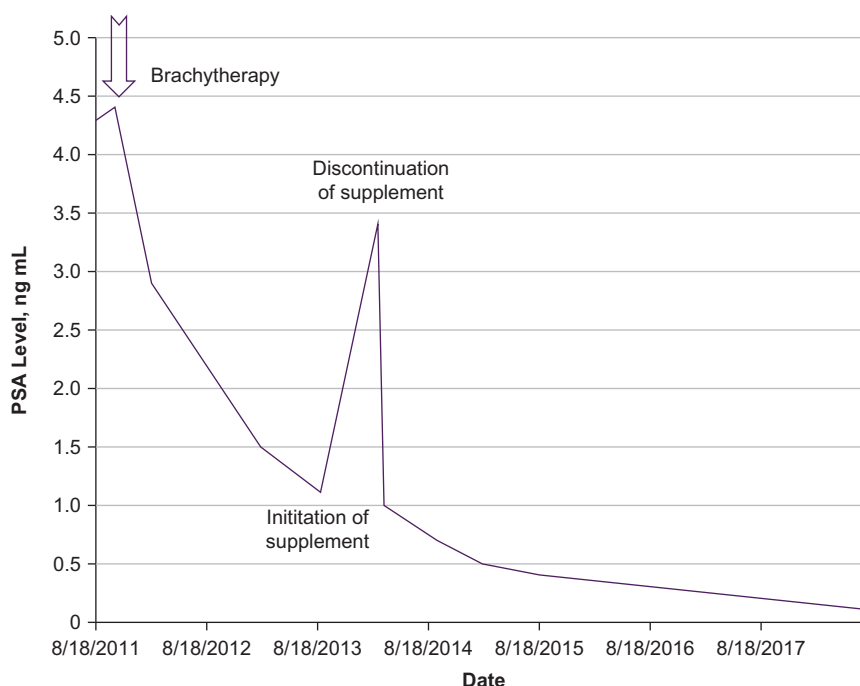


Figure.

Prostate-specific antigen (PSA) levels in a patient who underwent interstitial brachytherapy for prostate cancer, who had a spike in PSA level 2 years after treatment. After learning that the patient was taking the herbal supplement jin gui shen qi wan, his physician advised him to discontinue the supplement, after which his PSA level decreased and continued to decrease in subsequent years.

herbal supplement use, considering the patients' apprehension toward the subject of sexual dysfunction. As demonstrated in the current case, this communication breakdown can have negative consequences.

Considering the hormonally sensitive nature of prostatic tissue, problems may arise if patients (knowingly or unknowingly) experiment with supplements that contain androgens or andromimetics. Exogenous androgen stimulation of prostatic tissue and subsequent elevations of PSA can confound surveillance efforts and possibly lead to unnecessary diagnostic and therapeutic interventions, such as computed tomographic and bone scans, biopsies, hormonal deprivation, or salvage cryosurgery. Even worse, exogenous androgen stimulation of residual malignant tissue may expedite tumor recurrence. Consistent with a biochemical failure, the current patient's most recent PSA increased 2.3 ng/mL above the nadir within a 6-month interval. Additionally, this increase occurred at 30 months' after radiation treatment, outside the typical 12- to 18-month posttreatment window of time during which PSA bounces are usually observed.⁷⁻⁹ However, given the rapid and sustained decline in PSA after discontinu-

ation of the supplement, in conjunction with the absence of clinical evidence of disease recurrence, the increased PSA level was likely mediated by the supplement. The exact mechanism behind the observed PSA increase remains unclear; however, several postulations can be made after reviewing the 12 ingredients in Jin Gui Shen Qi Wan ([Table](#)).

First, a total of 3 of 12 ingredients (Fo-Ti [*Fallopia multiflora*], goji [*Lycium chinense*], and *Schisandra*) are cytochrome P450 inhibitors.¹⁴⁻¹⁸ Since testosterone and other androgens are metabolized through the cytochrome P450 pathway, inhibition of these enzymes, specifically CYP3A4, theoretically could increase the bioavailability of testosterone.¹⁹ As a result of the increased availability of testosterone, prostatic tissue would be stimulated to increase PSA production. A less likely alternative explanation for the increased PSA involves direct androgenic stimulation of the prostatic tissue by a component of the herbal supplement. The 12 herbal components do not appear to have androgenic activity; however, the available body of literature on these substances is limited. Considering the lack of regulation of herbal supplements, it is possible that an

Table.
Jin Gui Shen Qi Wan Herbal Supplement Ingredients

Chinese Nomenclature	Binomial Nomenclature	Common Name ¹⁵
Shu Di Huang	<i>Rehmanniae preparata</i>	Chinese Foxglove
Shan Zhu Yu	<i>Corni officinalis</i>	Cornelian Cherry
Shan Yao	<i>Dioscoreae oppositae</i>	Chinese Yam
Mu Dan Pi	<i>Moutan Radicis</i>	Tree Peony
Fu Ling	<i>Poriae cocos</i>	Poria Mushroom
Ze Xie	<i>Alismatis orientalis</i>	Water Plantain
Rou Gui	<i>Cinnamomi cassiae</i>	Cassia Cinnamon
Zhi Fu Zi	<i>Aconiti Lateralis preparata</i>	Aconite Root
Niu Xi	<i>Achyranthis bidentatae</i>	Achyranthes Root
He Shou Wu	<i>Polygoni multiflori</i>	Fo-Ti
Gou Qi Zi	<i>Lycii chinensis</i>	Goji
Wu Wei Zi	<i>Schisandrae chinensis</i>	Schisandra

unreported androgenic compound was present that could have directly affected the PSA levels. Another alternative postulation is that the metabolism of PSA itself was affected, thus reducing its clearance. Although PSA is predominately metabolized through the liver, the lack of clinical hepatologic signs, symptoms, or laboratory findings makes this explanation less likely.

Competing explanations for the patient's PSA elevation would include a subclinical urinary tract infection, prostatitis, or a delayed presentation of the PSA bounce phenomenon. However, the coinciding temporal relationship between the PSA increase and decrease and initiation and discontinuation of the supplement is less supportive of these 2 competing explanations.

Although the true cause of the PSA elevation will likely be undetermined, the possible complications of the laboratory result are significant. Both diagnostic and therapeutic interventions were imminent, including a repeated biopsy and possibly salvage therapy with leuprolide or radical prostatectomy. These interventions all carry potential unnecessary morbidity risks and were avoided through tactful communication. Although the patient never admitted to worsening of his erectile dysfunction, it is conceivable to believe that this was the root reason for his supplement use. Overall, this case highlights the importance of assessing the entire clinical picture, including psychosocial, cultural, and spiritual factors. These factors contribute significantly to the overall health of individuals, yet tend to be overlooked by physicians, resulting in potentially significant consequences.

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