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Impact of Low Prostate Specific Antigen on Prostate Cancer – A Rare Case Report

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Abstract
This article presents a rare case of a common disease, prostate cancer. A 57 year-old patient undergoing annual check-up for prostate cancer presents with a prostate specific antigen (PSA) level as low as 0.64 ng/ml. This patient was revealed to suffer from prostate cancer pT2c pNx pMx. This article assesses the implications of low prostate specific antigen for prostate cancer and discusses the controversial viewpoints as to the cutpoint of prostate specific antigen reviewing recent literature.
Key words: low prostate specific antigen- prostate cancer- threshold

Introduction

In men, prostate cancer is the most common cancer and the second most common cause of cancer mortality [1]. Prostate Specific Antigen (PSA) was discovered during the late 1970s [2] and was introduced as a serum test in 1980 [3]. Like no other serum tumor marker PSA has shown a major impact on diagnosis, treatment and monitoring of prostate cancer. PSA testing is generally considered the primary method by which prostate cancer is diagnosed. For men with abnormally elevated PSA screening results, needle biopsy of the prostate is used to diagnose the tumor. Once malignancy is biopsy confirmed, the PSA level is combined with clinical stage and grading to guide the choice of treatment. PSA has therefore been described as the ideal serum tumor marker [4]. National societies usually recommend screening with PSA and digital rectal examination annually beginning at age 50 for average-risk men [5, 6, 7].

Case Presentation

We present the case of a 57 year-old Caucasian male showing a PSA level of 0.64 ng/ml at annual check-up. A suspicious digital rectal examination was followed by transrectal ultrasound-guided prostate biopsy detecting malignancy. After nerve-sparing prostatovesiculectomy at our department it was revealed that this patient was suffering from prostate cancer pathologically staged as pT2c pNx pMx L0 V0 Pn0 R0.

Discussion

Little is known about the incidence of prostate cancer in the context of a low PSA level [8]. Furthermore, there is no consensus as to what the PSA cutpoint should be [9]. The Prostate Cancer Prevention Trial showed a prostate cancer prevalence of 15.2 % in 2950 men with PSA levels generally considered normal (≤ 4 ng/ml) [10]. Pelzer and co-workers revealed a cancer detection rate of 21% among 1522 patients with a PSA value of 2-3.9 ng/ml [11]. Accordingly, Catalona and his group presented a study of 332 volunteers having PSA levels ranging from 2.4 to 4.0 ng/ml and a benign prostate examination. Cancer was detected in 22% of men who underwent biopsy [12]. These results are similar to a prostate cancer detection rate of 19.4% with PSA ranging from 3.1-4 ng/ml observed by Kanno [13]. In Korea, a country assumed to have a low incidence rate, among 144 Asians with PSA ranging from 2-4 ng/ml cancer was detected in 24 (16.7%) cases [14]. Thompson reported that among 2950 men who had a PSA level of 4 ng/ml or less prostate cancer was diagnosed in 449 (15.2%). In addition, he showed that the prevalence of prostate cancer among those with values of 0.6 to 1.0 ng/ml – as was the case for our patient – was 10.1% [10]. Based upon his analysis of data from 875 patients, Berger observed the proportion of prostate cancers diagnosed in patients with PSA levels below 4 ng/ml rise from 14% to 39.2% within five years [15]. Overall, the incidence of biopsy-detected prostate cancers with PSA values between 2.5 and 4 ng/ml is approximately 20-30% [10, 16, 17, 18, 19]. This would imply that a biopsy threshold of 4 ng/ml would fail to detect a substantial proportion of prostate cancers arising in the context of PSA levels below this limit.

In contrast to the aforementioned studies, Dyche and colleagues presented the results of a group of 98 patients showing a PSA range of 0.1-4 ng/ml all of whom underwent biopsy. None of the patients was diagnosed with prostate cancer [20]. A study from Taiwan examinating 220 patients with a PSA level ranging from 0-4 ng/ml detected only 6 (2.7%) cases of cancer. Therefore, the authors discuss raising the cutoff within a country known for a low incidence of prostate cancer [21]. The German Urological Guidelines estimates that for PSA levels ranging between 0-1 ng/ml- as was the case in our patient- it would be necessary to biopsy 47 men in order to detect one prostate cancer [7]. Furthermore, Welch and his group predict that lowering the PSA cutoff to 2.5 ng/ml would increase the number of men aged 70 and older with abnormal test results by 1.2 million in the United States alone. If referred for biopsy this would require

substantial resources [22]. Moreover, such a lowering of the PSA cutoff to 2.5 ng/ml in all men, regardless of their age, might presumably increase the number of early – stage, non-life threatening prostate cancers [16, 23, 24, 25]. In turn, it is suspected that such overdiagnosis might induce treatment of insignificant cancers but result in significant complication rates [6, 26]. In addition, Vis concludes from a study of 117 prostate cancer patients that a high proportion of the cancers in men with low PSA levels (0.0-3.3 ng/ml) and in whom a biopsy was prompted by a suspicious digital rectal examination were detected fortuitously [27].

As a matter of fact, the preoperative prediction of an insignificant tumor remains a difficult task, because prostate cancer is a multifocal disease, and the biopsy technique provides only a limited amount of tissue. Thus, it is not surprising that the correlation between biopsy and final pathology, tumor volume and Gleason grade might be considered rather poor, and the potential aggressiveness of a small lesion can be underestimated [16]. Additionally, a recent update of studies showed when 2.5 ng/ml was used as the PSA threshold fewer than 10% of the cancer cases detected were insignificant at any time during a 12-year period [28]. Furthermore, it is difficult to label with certainty any carcinoma as "insignificant" as, by definition, the growth of a malignant lesion remains unpredictable. Accordingly, Horninger, evaluating the results of prostate cancers detected at a PSA level of 1.25-3.25 ng/ml, demonstrates that small cancers with low PSA levels and low tumor volumes exhibit all the malignant characteristics of cancers with higher tumor volumes [19]. Biopsy-detected prostate cancers, including high-grade cancers, are not rare among men with PSA levels of 4.0 ng/ml or less, generally thought to be in the normal range [8, 10, 29, 30]. Finally, even a small cancer may be clinically relevant in a 40-year-old man with a long life expectancy [31].

Following from these considerations, Oesterling and colleagues recommended a reference range for men aged 40-49 years to be 0.0 to 2.5 ng/ml and for 50-59 year-old men a range from 0.0 to 3.5 ng/ml according to data from 2119 healthy men at the Mayo Clinic. They concluded that the serum PSA concentration is directly correlated with patient age and prostatic volume, the latter of which also being directly related to age. They propose, therefore, that it is more appropriate to have an age-specific reference range rather than relying on a single reference range for men of all age groups. These age-specific ranges would potentially render the serum PSA a more discriminating tumor marker for detecting clinically significant carcinomas in older men (increasing specifity) and to find more potentially curable cancers in younger men (increasing sensitivity) [32]. A population screening study from Austria confirms that cancer detected at lower PSA levels was, in a statistically significant way, more likely to occur at earlier stages and in younger patients compared with cancer detected at PSA levels of 4 to 10 ng/ml which is in optimal candidates for treatment with curative intent [11].

Overall, these data suggest that 2.5 ng/ml might be a more appropriate cutoff point than 4.0 ng/ml, particularly in younger men (i.e. less than 60 years old) in whom prostatic hyperplasia does not contribute significantly to elevated PSA levels [16]. Additionally, on the basis of evidence published since 2000, Catalona and his group recently recommend that screening for prostate cancer begin at age 40 [33]. Accordingly, the recent guidelines of the National Comprehensive Cancer Network in the U.S. recommend considering biopsy in men with PSA levels in the range of 2.6 -4.0 ng/ml as well as a baseline testing at age 40 for all average-risk men [34] whereas the United Kingdom´s National Health Service Executive has issued extensive guidance stressing the importance of adequate counselling prior to performing the PSA screening test [35].

CONCLUSION

Although its benefit in the detection of prostate cancer cannot be denied, screening for prostate cancer with serum PSA remains a controversial topic requiring further investigation and validation. Therefore, this article assesses the impact of low PSA on prostate cancer. Our case indicates that the decision to perform a biopsy should not be determined solely by a PSA threshold. Furthermore, our case of clinically significant cancer and the review of recent data suggest that lowering PSA to age-specific reference ranges would be desirable since in general, this screening continues to provide the only method to identify consistently life-threatening cancers at a stage when cure is possible.

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