Hyper-elevated prostate-specific antigen levels are not always carcinoma

Introduction

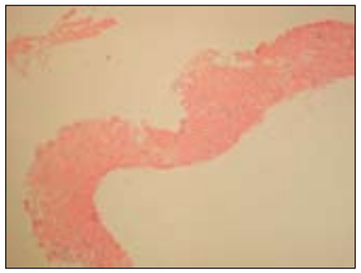
Serum prostate-specific antigen (PSA) testing is becoming more widespread in the community as a result of a variety of patient- and clinician-driven factors. The primary reason relates to the potential for early diagnosis of prostate carcinoma. As a consequence, abnormal PSA results are more likely to be encountered by clinicians. It is imperative that those ordering and interpreting PSA testing are aware of the possible aetiology of a raised serum PSA and are also aware that an extremely elevated serum PSA does not only indicate prostate carcinoma.

Discussion

PSA testing continues to be controversial, particularly regarding prostate cancer screening, yet it remains one of the best tumour markers available in clinical medicine (Crawford, 2005). PSA has well-defined roles in prostate cancer including diagnosis, staging, planning of and response to treatment. However, clinicians must remember that PSA is organ rather than tumour-specific (*Table 1*).

Further, age-adjusted levels of PSA and free:total ratios only help guide clinicians and still require investigation. For example, the role of free:total PSA (carcinoma has more PSA bound) in the setting of a raised PSA may only prevent biopsies being done once one is satisfied that there is no carcinoma (Ciatto et al, 2004). Also, performing a digital rectal exam at a different time to the PSA test may be advisable to avoid a falsely elevated result.

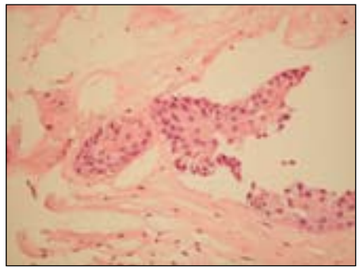
Figure 1. Needle-core biopsy of the prostate demonstrating coagulative necrosis of prostatic glands and stroma (100x, haematoxylin and eosin). The ghost outlines of pre-existing glandular structures can faintly be identified.



As more patients request and clinicians order measurement of serum PSA, results outside the normal range (0–4 ng/ml) will increasingly be found. Clinicians must place a raised PSA in context, or there is a danger of creating anxiety and assuming cancer is the diagnosis. This has often occurred where PSA levels are just above normal, but is probably important in the context of any level.

The absolute cut-off point used to determine the need to evaluate a patient for prostate cancer by biopsy is not clear and detection rates for a PSA level between 2.5–4.0 ng/ml have been found to be similar (around 30%) to those for the PSA range of 4.0–10.0 ng/ml. This indicates that 2–2.5 ng/ml may be a more appropriate cut-off point than 4.0 ng/ml (Crawford, 2005). Against this, some have suggested that serum PSA may be more related to benign prostatic hyperplasia (BPH) than cancer in the modern era and that there is an urgent need for serum markers that more accurately reflect malignancy (Stamey et al, 2004).

Figure 2. Higher magnification (400x) from the edge of infarcted tissue from* Figure 1 *demonstrating nests of squamous metaplasia. These may be mistaken for carcinoma.



Case Report

An 81-year-old man with a past history of diabetes, hypertension, ischaemic heart disease and cerebrovascular disease was admitted to hospital with hypotension and bradycardic collapse. Owing to persistent hypotension and a low urine output, an indwelling catheter (IDC) was inserted per urethra and a cardiac pacemaker was placed the following day. A serum prostate-specific antigen (PSA) level was back-ordered on initial bloods taken before IDC insertion, as passing the catheter was difficult and he was noted to have an enlarged prostate. A trial of void without catheter was successful 24 hours after initial insertion, leading to discharge that evening.

He represented to the emergency department in acute urinary retention the day following discharge and gave no past history of significant lower urinary tract symptoms. An IDC was again inserted draining 700 ml and notes were obtained from his previous admission indicating that he had a PSA of 933 ng/ml (Immulite 2000, Diagnostic Products Corporation, Los Angeles, USA) on admission. The plan was for staging of prostate cancer and needle biopsy in the future to confirm the diagnosis. On examination, his prostate was enlarged and firm with no obvious nodular change.

A bone scan was negative for metastatic prostate cancer. Prostatic needle biopsies (18 gauge) were undertaken revealing benign glands and also the edge of coagulative necrosis (*Figure 1*). The necrosis involved both stroma and glands, and was surrounded by a zone of immature fibrous tissue containing nests of metaplastic squamous epithelium (*Figure 2*). Findings were consistent with prostatic infarction and there was no evidence of malignancy. A repeat serum PSA demonstrated a rapid descent to 9.3 ng/ml. The patient was discharged after a successful trial of void and is now catheter free.

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Table 1. Aetiology of a raised prostate-specific antigen level

Prostate cancer
Benign prostatic hyperplasia
Urinary tract infection
Prostatitis
Prostatic infarction
Trauma
Urological instrumentation and/or catheter insertion
Recent lower urinary tract surgery (including prostate biopsy)
Prostate massage
Radiation (external beam, brachytherapy)
Ejaculation (for 48 hours)
Cryotherapy
Normal variation (up to 15% daily)

Prostatic infarction may result in death of prostatic tissue and typically occurs in large prostates often resulting in sudden serum PSA rises (Milord et al, 2000; Kiran, 2001). Such PSA elevations have been reported only as high as around 300 ng/ml, even in cases diagnosed on needle biopsy and are more often around often around 100 ng/ml (Milord et al, 2000; Kiran, 2001). To the authors' knowledge a PSA of 1000 ng/ml is an exceptional finding for prostatic infarction.

Prostatic infarcts are well-described in the setting of transurethral resection of the prostate (Kiran, 2001). This may indicate that the transition zone of the prostate (region closest to the urethra and the site of BPH) has infarcted and may explain why needle biopsies have rarely revealed infarction. The predominant region of interest in prostatic biopsy for carcinoma is the peripheral zone, where most malignancies are located (Milord et al, 2000). An association between prostatic infarction and acute urinary retention has been reported but was not an issue in this case (Kiran, 2001).

Prostatic infarction is a potential source of misdiagnosis for the pathologist. In particular, immature reactive squamous metaplasia commonly occurs at the edge of prostatic infarcts and may be confused with squamous, urothelial and prostatic carcinoma, as well as other types of inflammation (Milord et al, 2000; Kiran, 2001). Furthermore, benign prostatic glands in areas of inflammation may acquire atypical nuclear changes such as enlargement and nucleolar prominence, so mimicking the features of adenocarcinoma. Problems with interpretation are more likely to occur with needle core biopsy, where the context of infarcted tissue may be more difficult to appreciate than with larger fragments from TURP specimens.

Conclusions

Serum PSA remains a useful test in the context of prostate carcinoma. However PSA is organ- rather than tumour-specific with many differential diagnoses potentially responsible for a raised serum level. For clinicians faced with a raised PSA, it is important to exclude such diagnoses. Where appropriate, referral to an urologist for consideration of a needle biopsy performed transrectally under ultrasound guidance, should be initiated. Histopathology should always be obtained before commencing treatment and counselling patients regarding prostate adenocarcinoma. **BJHM**

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