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Research Article

P63 Expressing Adenocarcinoma of The Prostate Gland, A Rare Neoplasm Which Tends to Pose Diagnostic Dilemma Sometimes: Review and Update

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Abstract:

It has been documented that prostate cancer is the world's leading cause of cancer and also the second commonest cancer in men which does tend to pose challenges in its diagnosis. It has been iterated that immunohistochemistry studies utilising tumour markers like high molecular weight cytokeratin, p63 aid in the diagnosis of prostate cancer. It has been known for some time that the absence of immunohistochemistry staining of prostate lesion for p63 and high molecular weight cytokeratin and presence of p504s in the biopsies indicate malignant lesions. Nevertheless, it had also been pointed out as well as documented that some rare cases of adenocarcinoma of prostate variants do demonstrate evidence of the tumour cells exhibiting p63 immunohistochemistry staining and this does pose a diagnostic dilemma that may make the unfamiliar pathologist mis-diagnose such a malignant tumour as a benign prostate lesion. p63-positive adenocarcinoma of the prostate gland is a major diagnostic pitfall. There is a danger of interpreting malignant glands as benign and arriving at a false-negative diagnosis. This can be prevented by the understanding of the pattern of immunohistochemistry staining expression related to this variant of prostate cancer. The major points that favour the diagnosis of carcinoma in these cases include: non-basal p63 staining and negative HWMCK and positive p504s staining. The biological behaviour of this particular rare variant of prostatic carcinoma is not certain and requires to be studied further into more detail. Considering the rarity of p63 expressing prostate cancers and the fact that most clinicians including pathologists, urologists, and oncologists would not have encountered a case of p63 expressing prostate cancer before in order to update all clinicians regarding this rare tumour, the ensuing article has been extensively written and divided into two parts: (A) Overview which has discussed general overview aspects of p63 expressing neoplasms and (B) Miscellaneous Narrations and Discussions from Some Case Reports, Case Series, and Studies Related to Primary p63 Expressing Adenocarcinomas of the Prostate Gland. A high-index of suspicion as well as knowledge of the histopathology examination features as well as immunohistochemistry examination features of this rare tumour is required from all clinicians. Knowledge of the treatment options, biological behaviour as well as outcome following treatment of the tumour has been extensively discussed as updating information. The update has clearly pointed out that further studies are required to determine the role of p63 overexpression in prognostication.

keywords: p63 expressing prostate cancer; prostate biopsy; histopathology examination; immunohistochemistry staining; ultrasound scan; computed tomography scan; magnetic resonance imaging scan; diagnostic dilemma; biological behaviour; further studies

Introduction

It has been iterated that with regard to men, carcinoma of the prostate gland represents the second most common cancer, after lung cancer. [1] It had also been documented that carcinoma of the prostate gland is also the world's leading cause of cancer [1] as well as that carcinoma of prostate gland is associated with advanced age, genetics factor smokers, obese individuals, and due to endogenous factors. [2] Prostate-specific antigen (PSA) levels are essential in elderly patients to identify the risk of prostate cancer. Though it is not very specific, high levels are concomitant with prostate cancer. Diagnosis of prostate cancer purely on the foundation of the clinical and morphological features is difficult. Here

comes the role of the tumour markers and immunohistochemical markers. [3] Immunohistochemical markers such as p63, high molecular weight cytokeratin (HMWCK), and p504s aid in the appropriate diagnosis of prostatic cancers.

p63, an analogue of p53, is a tumour suppressor gene which encodes for isotypes which either act as p53-dominant negatives or transactivate p53 reporter genes, whose presence aids apoptosis and reduces the progression of cancer. [4] It comprises 15 exons and codes for 6 different mRNA isoforms which have a common DNA-binding domain. [3] [5] p63 is required for nourishing a basal-cell population, maintaining a prostate epithelial stem cell population, and is also essential for prostate development. [4] Markers like p53 and p63 are expressed on the nuclei of the normal basal cells. Usually, adenocarcinomas are devoid of basal cells, whereas benign lesions are encircled by the same. Hence, prostate adenocarcinoma can be differentiated from benign prostate lesions and hyperplasia by the absence of p63 staining in the basal cells in prostate carcinoma. Hence, p63 and HMWCK, and basal-cell immunohistochemistry markers turn out to be beneficial to distinguish benign and malignant conditions. [6] [7] Yet, there are few adenocarcinomas which retain the basal cells and have partial p63 and HMWCK staining, and there are a small number of Benign prostatic hyperplasia (BPH) and adenocarcinoma mimickers which don't express the basal-cell makers. [7]. Considering that p63 expressing adenocarcinomas of the prostate gland are rare, it would be envisaged that majority of clinicians working globally including Urologists, Oncologists, and pathologists may so far not have encountered this type of kidney neoplasm before. In view of this the ensuing article on primary p63 expressing carcinoma of the prostate gland has been written in two parts: (A) Overview which has discussed general overview aspects of p63 expressing neoplasms and (B) Miscellaneous Narrations and Discussions from Some Case Reports, Case Series, and Studies Related to Primary p63 Expressing Adenocarcinomas of the Prostate Gland.

Aims

To review and update the literature on primary p53 expressing carcinomas of the kidney.

Methods

Internet data bases were searched including: Google; Google Scholar; Yahoo; and PUBMED. The search words that were used included: p63 expressing adenocarcinoma of prostate; p63 expressing prostatic cancer; p63 expressing primary malignant neoplasm of prostate gland; and p63 expressing primary prostatic malignant neoplasm. Forty-four (44) references were identified which were used to write the article which has been divided into two parts: (A) Overview which has discussed general overview aspects of p63 expressing neoplasms and (B) Miscellaneous Narrations and Discussions from Some Case Reports, Case Series, and Studies Related to Primary p63 Expressing Adenocarcinomas of the Prostate Gland.

Results

[A] Overview [8]

Definition / general statement [8]

- It has been iterated that a small sub-set of prostatic acinar carcinoma is typified by strong p63 nuclear immunohistochemistry staining expression, which is a distinctive morphology feature of the neoplasm and molecular phenotypes had been described in these cases. [8]

Essential features [8]

The essential features of p63 expressing prostate cancer tumours had been summated as follows: [8] [9] [10]

- It has been pointed out that p63 protein is normally present within basal cells of benign acini but p63 is absent in usual type acinar or ductal cancers of the prostate gland.
- Despite the aforementioned iteration; nevertheless, it had been documented that commencing in 2008, a rare sub-set of cancers of the prostate gland that is associated with diffuse p63 positivity has been described
- It has been documented that atrophic and basaloid phenotype of the afore-iterated p63 expressing tumour had been noted upon pathology examination of haematoxylin and eosin (H&E) slides of some prostate cancers.
- It has been iterated that in the process of pathology examination of prostate cancers, immunohistochemistry staining for cytokeratin 34 beta E12 (negative) and AMACR / P504s (positive) could be helpful for the resolution of problematic foci of the prostate cancer.

Epidemiology

- With regard to the epidemiology of p63 expressing prostate cancer, it has been iterated that demographically the tumour is identical to adenocarcinoma of the prostate gland in general [8] [9]
- Diagnosis
- It has been iterated that with regard to the establishment of the diagnosis of p63 expressing carcinoma of the prostate gland, immunohistochemistry staining studies tends to be undertaken utilising either the triple immunohistochemistry stain (high molecular weight cytokeratin, p63 and p504S) or with p63 alone [8]

Laboratory tests [8]

- It has been documented that serum prostate-specific antigen (PSA) elevation is a usual feature of p63 expressing adenocarcinoma of prostate gland. [9] [11]

Prognostic factors

The factors of prognostication, had been summated as follows: [8]

- It has been documented that the first description of this p63 expressing prostate cancer entity had consisted of all organ confined prostate cancer cases [9]
- It had also been iterated that a subsequent report had described 76% of the prostate cancer as organ confined, with relatively low Gleason scores, even though 38% of the prostate cancer tumour cells were Gleasson Grade 3 + 5 = 8 [10]
- Nevertheless, it had furthermore, been pointed out that one case of p63 expressing prostate cancer which had manifested in association with metastasis had been reported [12]
    - Hence it had been iterated that majority of p63 expressing adenocarcinomas of the prostate gland would appear to be associated with favourable or good pathology outcome and features
    - It has furthermore, been pointed out that the long-term of p63 expressing primary prostate cancer outcome had not been studied yet
- It had been documented that parenthetically, p63 staining can assume predominant cytoplasmic reactivity in prostate cancer (unlike its strong nuclear staining in basal cells) but this is a separate matter
    - It has been iterated that aberrant immunohistochemistry expression of p63 within the cytoplasm had been noted to be associated with increased tumour proliferation and apoptosis as well as with more prostate cancer specific mortality up to

20 years pursuant to the initial diagnosis of the prostate cancer. [13] [14]
    - It had been documented that the same trend had been observed in dogs [15]

Microscopic (histologic) description

The microscopy histopathology examination features of p63 expressing prostate cancer had been summated as follows: [8]

- It had been iterated that the first series of p63 expressing prostate cancer had been reported in 2008 by Osunkoya et al., [9] who had described 21 cases diagnosed based upon pathology examination of needle biopsy, including 8 with matched prostatectomy in which > 70% of cancer cells were p63 positive
    - Distinctive, atrophic-like morphology was noted
- It had also been iterated that 21 matched biopsy / prostatectomy cases were characterized in a published article. [10]
    - Besides atrophic-like change, salient features that have been described include a basaloid appearance and high N:C ratio, with multilayered and sometimes spindled nuclei
    - Notably, at prostatectomy, 86% of cases had coexisting usual type p63 negative adenocarcinoma while 14% were pure

Immunohistochemistry staining

The immunohistochemistry staining features of p63 expressing prostate cancers had been summated as follows: [8]

Positive stains

- It has been iterated that a strong immunohistochemistry staining exhibiting a strong-nuclear positivity for p63 is required to confirm the diagnosis of **p63** expressing prostate cancer. [8]
- It has been pointed out that immunohistochemistry staining studies, utilising AMACR (P504S) is the most useful staining study that can be used to establish the diagnosis of p63 expressing prostate cancer. [8]
- It has been iterated that in cases of p53 expressing primary prostate cancer, positivity for markers of luminal cells is present, including: CK8, and CK18, androgen **receptor, NKX3.1**, and prostein [5]

Negative stains

The negative immunohistochemistry staining features of p63 expressing prostate cancers had been summated as follows: [8]

- High molecular weight cytokeratin **34 betaE12** is the most useful [5]
- It has been iterated that in p63 expressing prostate cancer, immunohistochemistry staining is or tends to be negative for other basal markers such as **CK14 and CK15** [5]
- It has been pointed out that in cases of p63 expressing prostate cancers, immunohistochemistry staining for CK5/6 has tended to be negative in most cases, even though weak and focal positivity was noted in 4 out of 11 cases [5]

Molecular / cytogenetics description

The molecular and cytogenetics study features of p63 expressing carcinoma of the prostate gland had been summated as follows: [8]

- It has been iterated that 37 p63 positive cancer cases were compiled to investigate the molecular phenotype [5]
    - These tumours were almost all positive for ΔNp63 isoform by immunofluorescence and p63 mRNA by in situ hybridization
    - 100% of these tumours lacked ERG rearrangement at the molecular level by FISH and the protein level by immunostaining; moreover, 100% lacked PTEN loss
        - These 2 features are found in ~50% and 33% of usual acinar carcinomas, respectively
    - Tumours frequently express GSTP1 (14/19; higher than usual)
- It had been iterated that in one case report, 5 tumour foci in a prostatectomy were present, of which one was p63 positive; this focus did not show a TMPRSS: ERG translocation by FISH, while the other foci did [11]
- It had been iterated that ETS2 tumour suppressor gene was highly expressed in 95% (18/19) of p63 expressing prostatic carcinomas and benign prostate basal cells, with lower to undetectable expression in luminal cells and primary usual type adenocarcinomas [16]

Differential diagnoses

The differential diagnoses of p63 expressing prostate cancer had been summated as including the ensuing: [8]

- **Benign acini:**
    - Lack of atypia and **AMACR (P504S)** while cytokeratin **34 beta E12** is positive [6] [9],
- **Atypical basal cell proliferations (adenoma, carcinoma):**
    - These stain diffusely for cytokeratin **34 beta E12** but are negative for **prostate specific antigen (PSA)**
    - Conversely, **p63** positive prostate cancer will be negative for cytokeratin **34 beta E12** while positive for PSA
- **Prostatic carcinoma of usual type:**
    - It is not uncommon for a few nuclei to have weak p63 positivity in usual cancers but this is in contrast to the special type discussed here
- **Urothelial carcinoma with a glandular morphology:**
    - This should be **p63** positive
    - Negative **PSA** or **NKX3.1** staining should raise the possibility of a non-prostatic tumour

[B] Miscellaneous and Discussions from Some Case Reports, Case Series, And Studies Related to P63 Immunonogistochemistry Expressing Carcinoma of The Prostate Gland

Osunkoya et al. [9] stated that aberrant diffuse immunohistochemistry expression of p63 in prostate carcinoma cells is a rare and poorly understood phenomenon.

Osunkoya et al. [9] studied 19 cases of prostate cancer with aberrant diffuse expression of p63 which were diagnosed based upon pathology examination of specimens of prostate needle biopsy and they reviewed the subsequent radical prostatectomies in 6 cases. They reported on 19 out of 21 cases, and they reported that 100% of the cancer nuclei had stained intensely for p63, with 70% staining in the remaining 2 cases. Two additional radical prostatectomies with aberrant p63 staining with no needle biopsies available for review were also analysed by

Osunkoya et al. [9]. On the hematoxylin and eosin-stained slides, 19 out of 21 cases that amounted to 90.5% of the cases had demonstrated a distinctive morphology composed predominantly of glands, nests, and cords with atrophic cytoplasm, hyperchromatic nuclei, and visible nucleoli. Osunkoya et al. [9] also reported the following results:

- Needle biopsy cases had ranged from Gleason patterns 3 to 5 with tumour identified on one or more cores, ranging from a minute focus to 80% of the core.
- In all 8 radical prostatectomies p63 positive cancer was found to be present, with in 2/8 cases both p63 positive cancer and usual p63 negative acinar prostate cancer.
- In all 8 cases, the tumours were found to be organ confined with negative margins and there was no seminal vesicle involvement or lymph node metastasis.
- The presence of p63 positive expressing atypical glands with an infiltrative pattern and perineural invasion on radical prostatectomy had confirmed the needle biopsy diagnosis of carcinoma.
- Rarely, prostate cancer could aberrantly express diffuse p63 staining in a non-basal cell distribution leading to the erroneous diagnosis of atrophy or atypical basal cell proliferation.
- The diagnosis of prostate cancer is based upon the morphology and confirmed by the absence of high molecular weight cytokeratin staining and positivity for alpha-methylacyl-CoA racemase in the atypical glands. Pathologists need to be aware of this rare and unusual phenomenon, which is a potential pitfall in prostate cancer diagnosis.

Giannico et al. [10] stated that prostatic adenocarcinoma with aberrant diffuse expression of p63 (p63-PCa) had been a recently described variant of adenocarcinoma of prostate gland. Giannico et al. [10] undertook a study to investigate the clinical and pathological features of p63-PCa at radical prostatectomy (RP). Giannico et al. [10] reviewed 21 cases of p63-PCa diagnosed based upon needle biopsy at subsequent RP. Giannico et al. [10] undertook immunohistochemical analysis for PIN4 and Ki-67 in all RP cases. Giannico et al. [10] reported the following results:

- p63-PCa had demonstrated a distinctive morphology consisting of atrophic, poorly formed glands, with multilayered and often spindled nuclei.
- Gleason grading was 3+3=6 in 28.5%, 3+5=8 in 38%, 3+4=7 in 14.3%, and 4+3=7, 5+3=8, and 5+4=9 in 9.5%.
- The usual-type acinar carcinoma had coexisted in 85.7% with only p63-PCa present in the remaining cases.
- The usual-type carcinoma was Gleason grade 3+2=5 in 4.7%, 3+3=6 in 57%, 3+4=7 in 19%, and 4+3=7 in 4.3%.
- Overall, p63-PCa had represented 65% of the total cancer volume (median 80%).
- The tumour was organ-confined in 16 cases that amounted to 76.2% of the cases.
- In the remaining 5 cases, 2 had p63-PCa which had extended to the margin within areas of intra-prostatic incisions, 2 had the usual-type acinar adenocarcinoma which had extended to the margin and extra-prostatic tissue, respectively, and 1 had p63-PCa with an unusual cribriform morphology involving the bladder neck. Ki-67 was low, <5% in all cases of p63-PCa, with similar expression in the coexisting acinar-type carcinoma.

Giannico et al. [10] summated that they had recommended that these tumours should not be assigned a Gleason score and their favourable findings at RP should be noted.

Baydar et al. [11] iterated that prostate carcinomas exhibiting aberrant diffuse-nuclear p63 expression were extremely rare, and there was only 1 article in the literature reporting a series of 21 such cases by the time of publication of their article in 2011. Baydar et al. [11] iterated that they had documented an additional case of p63-positive prostatic adenocarcinoma in a 60-year-old man, whose diagnosis was difficult. They reported that the patient was found to have an elevated serum prostate-specific antigen (PSA) level at a general health check-up and he was then referred to the hospital. His serum PSA was 4.2 ng/mL. He underwent digital rectal examination and transrectal ultrasound scan which did not demonstrate a lesion. He underwent trans-rectal needle biopsy of the prostate gland and pathology examination of the biopsy specimens identified atypical, small prostatic glands which were suspected for adenocarcinoma at 2 cores. Nevertheless, immunohistochemistry staining studies of the biopsy specimens had demonstrated nuclear p63 expression within the suspicious glands. Repeat biopsy of the prostate lesion upon pathology examination had demonstrated only high-grade prostatic intraepithelial neoplasia. In the third transrectal biopsy, finding of the same atypical glands demonstrating perineural invasion had facilitated the diagnosis of malignancy. The patient underwent a radical prostatectomy. Five different small tumour foci were identified within the prostate after pathological evaluation, one of which was p63 positive staining and the others p63 negative staining. The largest of the classic p63-negative tumours had shown a TMPRSS2-ERG translocation by fluorescent in situ hybridization while the p63-positive tumour did not. Baydar et al. [11] had iterated that this subtype (p63-positive prostate adenocarcinoma) should be listed among the recognized rare variants of adenocarcinoma of the prostate gland.

Khalid et al. [12] stated the following:

- It had been stated that metastasis to the jaw accounts for 1-2% of oral malignancies, with the mandible being the commonest location for jaw bone metastasis, mainly occurring within the molar region [17].
- Almost 75% of patients who are afflicted by advanced prostate cancer do manifest with distant metastasis, mainly to the lumbar spine, ribs, and pelvis [18]
- Nevertheless, it had been stated that metastasis to the oral cavity, however, is not common in prostate cancer, with only 4% of patients having oral metastases emanating from the prostate gland [17].
- Patients who develop oral metastases commonly manifest clinically with fast-growing swelling, pain, and numbness. It had been generally understood that the prognosis of prostate cancer with distant metastasis is unfavourable or poor [17] [19].
- P63 is a reliable immunohistochemistry staining marker to differentiate benign from malignant lesions of prostate origin, with benign lesions staining positive and malignant lesions such as prostate adenocarcinoma staining negative.
- Nevertheless, it had been iterated that there are rare instances, where malignant prostate lesions had exhibited aberrant staining with p63 [20].
- Their reported case had highlighted a rare incidence of metastasis of prostate adenocarcinoma to the oral cavity and exhibiting an aberrant staining with p63.

Khalid et al. [12] reported a 76-year-old Chinese man, who had attended the clinic with a manifestation of swelling over his right buccal mucosa with on and off pain and numbness at his right chin in December 2017. His symptoms had commenced two months preceding his attendance at the clinic. It was found upon his examination that clinically his buccal mucosa was smooth, and a well-defined firm mass could be palpated over his normal overlying buccal mucosa (see Figure 1). He was completely edentulous with no restriction of his mouth opening.

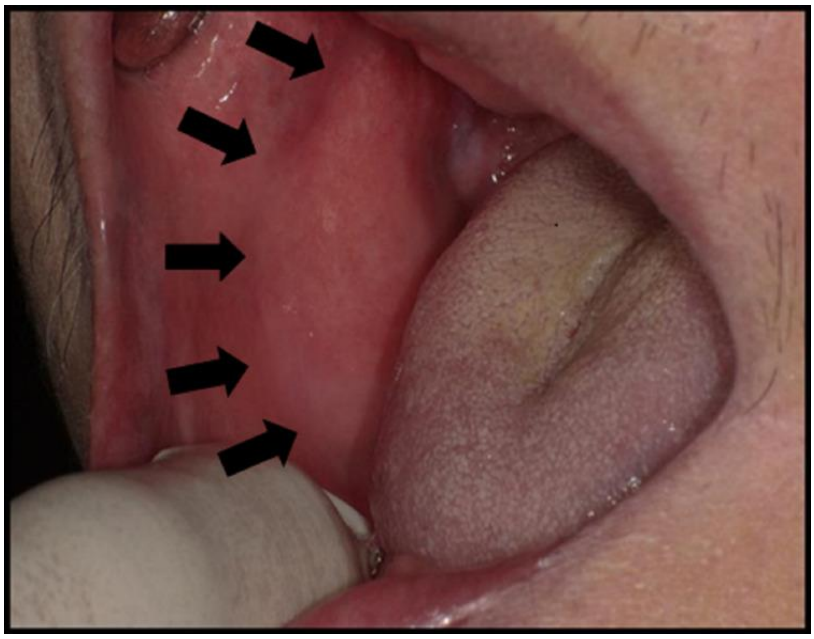

Figure 1: Intraoral photograph showing smooth, well-defined, firm mass over the right buccal mucosa with normal overlying mucosa. Reproduced from: [12] Under the Creative Commons Attribution License.

The patient was documented to be a known case of end-stage prostate cancer. He was initially diagnosed with adenocarcinoma of the prostate gland in June 2014 via pathology examination of specimens of his trans-urethral resection of his prostate (TURP) gland. The Gleason score of his prostate cancer was 4+5 = 9, and his serum prostate-specific antigen (PSA) was high (65 ng/mL). he had an isotope bone scan in July 2014 which had demonstrated multiple bone metastases involving his left 4th rib, 4th lumbar spine, sacrum, and left pubic bone but which had not involved his mandible. He was treated with androgen deprivation therapy (Lucrin) until December 2015, and his treatment was followed by seven months of antineoplastic agents (Abiraterone acetate) from December 2016 to July 2017 due to his persistent high baseline of serum PSA value >100 ng/mL. His prostate cancer disease had progressed and the patient was treated with non-steroidal antiandrogen (Enzalutamide) from July 2017. His serum PSA value did not respond to the treatment he had. By October 2017, his serum PSA level was 120 ng/mL, which had coincided with his first clinical symptom of numb chin syndrome. He underwent a cone-beam computed tomography (CBCT) scan which had demonstrated erosion of bone within the anterior part of his ascending ramus and retromolar region (see Figure 2). An incisional biopsy of the lesion was then undertaken for pathology examination.

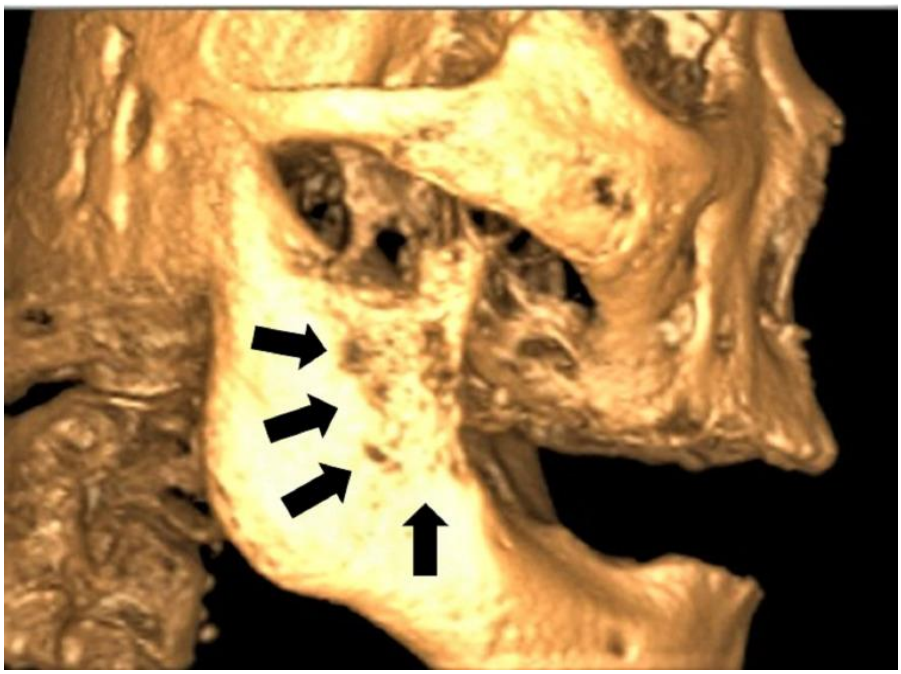

Figure 2: CBCT image showing erosion of bone at the anterior part of right ramus of mandible and retromolar region. Reproduced from: [12] Under the Creative Commons Attribution License.

Pathology examination of the haematoxylin and eosin (H&E) slides of his biopsied lesion demonstrated tumour islands that consisted of central cells with hypo-chromatic and vacuolated nuclei, pale eosinophilic cytoplasm, and this had exhibited pleomorphism. The peripheral basal tumour cells were found upon pathology examination to be spindle-shaped and appeared hyperchromatic (see Figure 3), with areas of extensive comedonecrosis visualised. The central tumour cells had exhibited immunohistochemistry staining positivity for PSA (see Figure 4A) and cytokeratin (CK; weak). The peripheral basal tumour cells were noted to have exhibited immunohistochemistry staining positivity for PSA, CK (weak), and p63 (scattered) (see Figure 4B). Both the central tumour cells and the basal tumour cells had exhibited negative staining for CK7 and CK20. Considering the H&E and immunohistochemistry manifestation of the case, a diagnosis of adenocarcinoma metastasis from the prostate was reported.

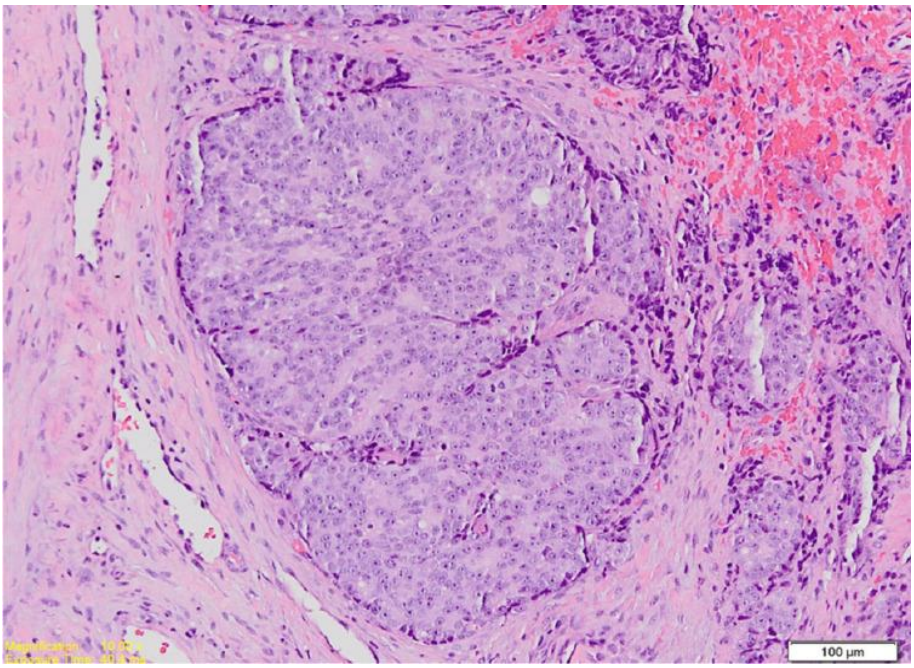

Figure 3: Photomicrograph shows a tumour island consisting of central round cells and peripheral spindle (magnification x100, stain A&E). Reproduced from: [12] Under the Creative Commons Attribution License.

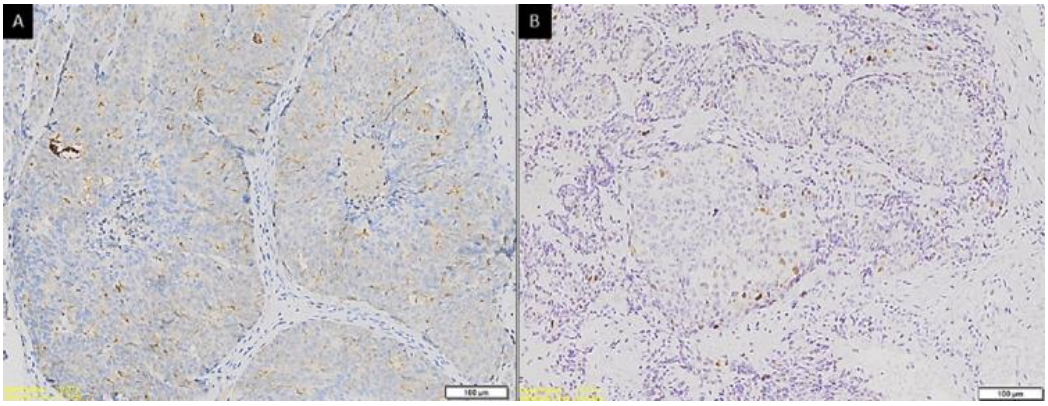

Figure 4: Photomicrographs showing (A) immunopositive cytoplasmic staining of tumour cells with PSA (magnification x100) and (B) scattered immunopositive staining of tumour cells with p63 (magnification x100). Reproduced from: [12] Under the Creative Commons Attribution License.

The attending oncologist was informed of the metastatic finding. Following this, the patient underwent a computed tomography (CT) scan and isotope bone scan (see Figure 5A and 5B) which demonstrated multiple bone metastases to his sternum, ribs, ilium, femur, and vertebrae as well as his mandible. Subsequently, patient received chemotherapy treatment. Nevertheless, three months later, unfortunately, the patient died as a sequel of hi tumour.

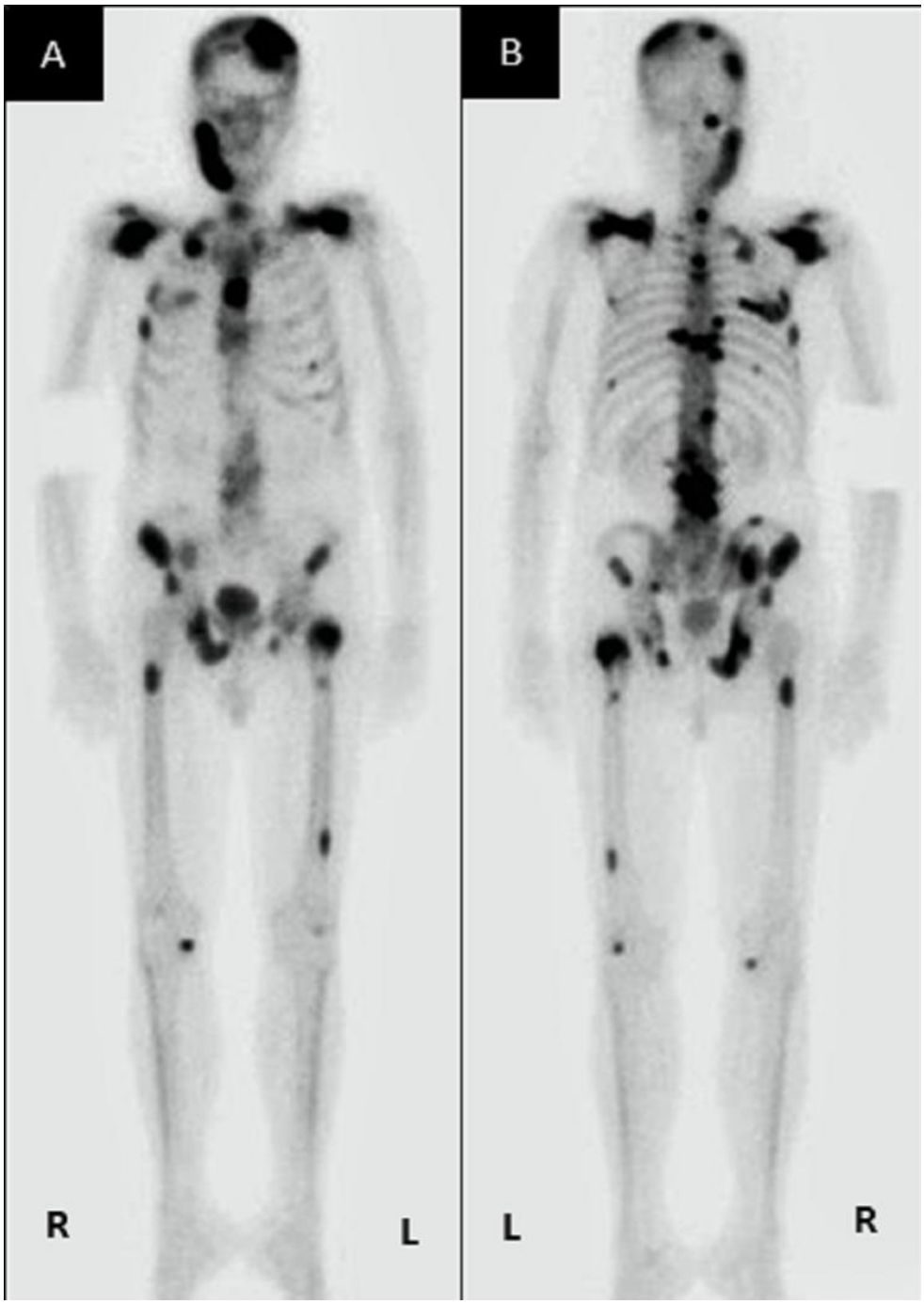

Figure 5: Bone scan images (A) anteroposterior view and (B) posteroanterior view showing multiple distant bone metastases to the mandible, sternum, ribs, ilium, femur and vertebrae. Reproduced from: [12] under the Creative Commons Attribution License.

Khalid et al. [12] made the ensuing educative summative iterations:

- The ability to metastasize is one of the inherent properties of malignancies.
- This process is somewhat regulated to be site-specific.
- The "seed and soil" postulate had mentioned that the metastatic tumour (seed) will only grow in an organ which provides a suitable environment (soil).
- The metastatic process is complex; the tumour cells need to be detached from the primary tumour and they should invade adjacent tissues and enter the vascular or lymphatic vessels prior to their lodging at a distant site.
- These tumour cells then survive by the processes of angiogenesis, tumour dormancy, and evading apoptosis [17].
- The distant spread of tumour from the prostate gland to the maxillofacial region might occur through a Batson's plexus. During a transient increase in intraabdominal pressure, this route enables the retrograde spread of tumours through the valveless prevertebral veins [21]. This was

evident in the bone scan of their reported patient, and had demonstrated metastasis along the vertebra as well as to the maxillofacial region and skull.

- In their reported case, the patient was a known case of end-stage prostate cancer, as in cases that had been reported previously in the literature. [22] [23] [24]
- The time interval between the diagnosis of prostate cancer and the occurrence of metastasis to the mandible has ranged from 2 months [24] to 120 months [22]. It was 45 months in their reported case. Nevertheless, in many other reported cases, oral lesions were visualised as the first lesions to have manifested before the diagnosis of prostate cancer, [25] [26] [27] thus helping to find the primary cancer.
- It had been iterated that clinically, oral metastatic lesions from the prostate cancer do manifest as a fast-growing swelling with pain and/or paraesthesia (numbness) within the chin area (numb chin syndrome) if the mandible is involved [17].
- In their reported case, the patient had reported having swelling, pain, and paraesthesia (numb chin syndrome) within his right chin region, which had indicated the involvement of the mandible. Nevertheless, the swelling was also not found present within his right buccal mucosa, which had suggested that the lesion had involved not only the mandible but also the oral soft tissue, which was similar to a case that had been reported by Mohamed and Suleiman [24].
- The other clinical manifestations that had been reported in oral metastasis of prostate cancer are trismus or limited mouth opening [23]and necrotic bone due to medication-induced osteonecrosis [28].
- The molar region of the mandible had been reported as the most commonly affected hard tissue site in the maxillofacial skeleton, and the attached gingiva (only two cases) was the most commonly involved soft tissue site for the development of oral metastases from the prostate [17].
- A review of the literature had reported that the most commonly affected sites for metastasis of the mandible were the molar and premolar regions, followed by the ascending ramus, angle of the mandible, and mental region [29].
- In their reported case, the metastases were to the anterior part of the ascending ramus and the retromolar region, as seen in the CBCT and extending into the oral soft tissue of the right buccal mucosa.
- Majority of the cases of prostate metastasis to the mandible had osteolytic lesions [26] such as in their reported case; nevertheless, some cases had reported osteoblastic lesions with a sunburst [25] [27] appearance as is visualised in osteosarcoma.
- Histopathology, utilisation of CK7 and CK20 markers in tandem might be undertaken to aid in the diagnosis of prostate carcinoma. A negative stain for both CK7 and CK20 would indicate prostate carcinoma [30] and had been reported in many cases [25] [31]
- A study had concluded that the PSA marker, which is highly sensitive in prostate cancer, could be used to distinguish prostate carcinoma from other forms of carcinoma [32].
- In their reported case, utilisation of CK was undertaken to verify a neoplasm of epithelial origin.
- With regards to the case under discussion, both CK7 and CK20 were negative, whereas PSA was strongly positive, which had indicated adenocarcinoma of prostate gland.
- In previous studies, using high molecular weight cytokeratin (HMWCK) markers had also been demonstrated to enable differentiation between carcinoma of prostate gland from benign prostate lesions, whereby there is a loss of staining of the basal cells in cases of prostate carcinoma [33].
- Utilisation of HMWCK would therefore also be a helpful option for the confirmation of the diagnosis of adenocarcinoma of prostate gland.
- Furthermore, alpha-methylacyl-CoA racemase (AMACR) might also be used as a viable option to diagnose adenocarcinoma of prostate gland [31].
- AMACR is a carcinoma stem cell marker which had emerged as a prostate cancer marker [34] but it is also highly expressed in other cancers such as renal cancer, liver cancer, and colon cancers [35].
- It has been demonstrated over the years that p63 is a reliable marker to differentiate benign from malignant lesions of prostate origin, with benign lesions staining positive and malignant lesions such as prostate adenocarcinoma staining negative [20] [25].
- Nevertheless, it had also been iterated that there are instances, even though uncommon, where even malignant prostate lesions had shown aberrant staining with p63 [6] [36], such as in their reported case.
- Utilisation of p63 must also be interpreted with caution in lesions which occur within the oral cavity, as certain salivary gland tumours such as basal cell adenocarcinoma, polymorphous adenocarcinoma, and adenoid cystic carcinoma tend to exhibit immunohistochemistry positive staining to p63, which is a known myoepithelial marker. These salivary gland tumours also often have ductal structures that are similar in pattern to those seen in adenocarcinoma of prostate gland. Nevertheless, in their reported case, utilisation of PSA had excluded a salivary gland tumour.
- It was also worth noting that comedonecrosis, as reported in their case, had also been associated with high-grade disease [37], which had explained in part the aggressiveness of the disease in this patient.
- Metastasis of prostate cancer to the mandible is regarded or understood to occur at an advanced stage and the prognosis is poor, with survival being as low as three weeks [25].
- In their reported case, the patient died three months after his development of his oral metastasis.

Khalid et al. [12] made the ensuing conclusions:

- p63 is not exclusively expressed in benign lesions of the prostate gland, as the aberrant expression may also be evident in malignant lesions such as prostate adenocarcinoma.
- Therefore, the determination of benign or malignant lesions of the prostate utilising only p63 should be interpreted with caution.
- The expression of proteins demonstrated through immunohistochemistry should be used as an adjunct diagnostic tool in the context of the presence or absence of histopathology examination features in a tumour.

Ferronika et al. [13] stated the following:

- Prostate cancer in Indonesia was the 3rd ranking cancer among males and the 5th rank for their cancer mortality.

- Prognostic markers that could identify aggressive prostate cancer in early stages and help select appropriate treatment to finally reduce the mortality are therefore urgently needed.
- It has been postulated that stem cells within the prostate gland do have a role in the commencement, progression, and metastasis of cancer, even though controversy had continued to exist.
- Maintenance of normal stem cell or reserve cell populations in several epithelia including prostate gland had been demonstrated to be regulated by p63 and alteration of p63 expression has been considered to have an oncogenic role in prostate cancer.
- They had postulated that the immunohistochemistry expression of cytoplasmic aberrance of p63 is associated with high ALDH1A1 expression as a cancer stem cell marker, thus leading to progression of prostate cancer.

Ferronika et al. [13] reported that they had utilised a cross-sectional study during two years between 2009 and 2010, and they had investigated a total of 79 paraffin embedded tissues of benign prostatic hyperplasia, PIN prostatic intraepithelial neoplasia, low and high Gleason score prostate cancer by means of immunohistochemistry staining studies. Ferronika et al. [13] also analysed the associations between cytoplasmic p63 and ALDH1A1, as well as with pathological diagnosis, by undertaking Chi-Square test using SPSS 15.0. Links of both markers with cell proliferation rate (KI-67) and apoptotic rate (cleaved caspase 3) were also analyzed by Kruskal-Wallis test. Ferronika et al. [13] summated their results as follows:

- The mean age of patient at the time of initial diagnosis is 70.0 years.
- Cytoplasmic aberrance of p63 was found to be associated with ALDH1A1 expression ($p<0.001$) and both were found to have significant relationships with pathological diagnosis (including Gleason score), ($p=0.006$ and $p<0.001$ respectively).
- Furthermore, it was also found that higher levels of cytoplasmic p63 were significantly associated with the frequency of proliferating cells and cells undergoing apoptosis in prostate cancers ($p=0.001$ and $p=0.016$ respectively).
- Ferronika et al. [13] made the ensuing conclusions:
- p63 cytoplasmic aberrance is associated with high ALDH1A1 expression.
- These components had been suggested to have an important role in prostate cancer progression and may be used as molecular markers.

Dhillon et al. [14] stated the following:

- Protein expression of p63 is utilised to distinguish prostate cancer from benign mimickers.
- Recent studies had indicated that p63 protein expression might also differentiate aggressive prostate cancer with down-regulated expression occurring in men with more advanced disease.
- Dhillon et al. [14] undertook a prospective study among 298 men, whose ages had varied between 51 years and 84 years, who had been diagnosed as having prostate cancer in the Physicians' Health Study in 1983 to 2004 and whose tissue was available for immunohistochemical staining. Dhillon et al. [14] used Cox proportional hazards regression to evaluate the association of p63 protein expression with fatal prostate cancer. Dhillon et al. [14] correlated p63 expression with tumour cell proliferation (Ki-67) and apoptosis (TUNEL staining). They reported the following:
- Predominant location of tumour p63 staining occurred in the cytoplasm, an uncommon departure from the strong nuclear staining usually which is observed in nonneoplastic basal cells.
- Increasing expression of cytoplasmic p63 (tertiles) was found to be associated with prostate cancer mortality (n = 19 deaths); the hazard ratios (95% confidence intervals) were 1.0 (reference), 4.0 (0.9-18.9), and 5.9 (1.3-27.5; P(trend) = 0.03).
- The positive trend had remained significant (P = 0.047) after multivariable adjustment for age, year of diagnosis, and Gleason score.
- Higher tertiles of cytoplasmic p63 were also found to be associated with reduced levels of apoptosis (P(trend) = 0.0408) and increased cellular proliferation (P(trend) = 0.0026).
- Dhillon et al. [14] made the ensuing concluding summating iterations:
- They had found aberrant expression of p63 within the cytoplasm to be associated with increased prostate cancer-specific mortality up to 20 years pursuant to the initial diagnosis of the prostate cancer.
- The mis-localized expression was noted to be associated with reduced apoptosis and higher proliferative activity and might indicate an oncogenic role in prostate cancer progression and survival.
- Fonseca-Alves et al. [38] stated the following:
- An unusual variant of prostate adenocarcinoma (PC) expressing nuclear p63 in secretory cells instead of the typical basal expression had been reported in men.
- Nevertheless, the biological behaviour as well as the clinical significance of this phenomenon was not known.
- In dogs, this unusual PC sub-type had not been described.

Fonseca-Alves et al. [38] reported that in their study, p63 immunohistochemistry staining expression was investigated in 90 canine PCs and 20 normal prostate tissues (NT). Fonseca-Alves et al. [38] also reported that the p63 expression pattern in luminal or basal cells was confirmed in a selected group of 26 PCs and 20 NT by immunohistochemistry and/or Western blotting assays. They had compared eleven canine PC samples aberrantly expressing p63 (p63+) in secretory cells with 15 p63 negative (p63-) cases in the context of several molecular markers (high molecular weight cytokeratin-HMWC, CK8/18, CK5, AR, PSA, chromogranin, NKX3.1, PTEN, AKT and C-MYC). Fonseca-Alves et al. [38] summarised their results as follows:

- P63+ samples had exhibited positive staining for CK5, HMWC and CK8/18 and negative for PSA, NKX3.1, PTEN and chromogranin.
- Five p63+ PCs were negative for AR, and the remaining six samples had low AR expression.
- On the contrary, p63- PC had demonstrated AR and PSA positive expression in all 15 samples.
- Only five p63- PCs had exhibited positive staining for CK5.
- Both p63+ and p63- PC samples had demonstrated higher cytoplasmic AKT expression and nuclear C-MYC staining in comparison with normal tissues. Metastatic (N = 12) and non-metastatic (N = 14)
- PCs had demonstrated similar immunohistochemistry staining expression for all markers tested.

- In contrast to human PC, canine PC aberrantly expressing p63 had shown higher expression levels of HMWC and CK5 and lower levels of NKX3.1.

Fonseca-Alves et al. [38] made the ensuing conclusions:

- Canine p63+ PC is a very rare PC group demonstrating a distinct phenotype compared to typical canine PC, including AR and PSA negative expression.
- Even though in a limited number of cases, p63 expression was not associated with metastasis in canine PC, and cytoplasmic p63 expression was observed in animals with shorter survival time, similar to human PC cases.

Wu et al. [6] reported a case of adenocarcinoma of prostate gland that showed diffuse aberrant p63 expression within the secretory cells and they reviewed the literature and differential diagnosis. Wu et al. [6] made the ensuing iterations:

- p63-positive prostatic adenocarcinoma is rare and is typically encountered when working up an atypical focus with basal markers and α-methylacyl coenzyme A racemase.
- These carcinomas do have unusual morphology features such as atrophic cytoplasm and basaloid morphology.
- The differential diagnosis includes basal cell hyperplasia and basal cell carcinoma; morphologic features such as the presence of small, infiltrative acini with nuclear atypia, lack of high-molecular-weight cytokeratin expression, and positive α-methylacyl coenzyme
- A racemase and prostate-specific antigen expression could help differentiate a p63-positive prostatic adenocarcinoma from atypical basal cell proliferations.
- Current controversies regarding the grading, prognosis, and molecular profile of p63-positive prostatic adenocarcinomas also do exist to be discussed.

Tan et al. [5] described a rare group of prostate adenocarcinomas that had exhibited an aberrant expression of p63, a protein strongly which is expressed in prostatic basal cells and absent from usual-type acinar prostate cancers. Tan et al. [5] stated the following:

- The partial basal-like immunophenotype of these tumours is intriguing in light of the persistent debate surrounding the cell-of-origin for prostate cancer; nevertheless, their molecular phenotype was not known.
- Tan et al. [5] collected 37 of these tumours on radical prostatectomy and biopsy and they assessed subsets for a diverse panel of molecular markers. Tan et al. [5] reported their results as follows:
- The majority of p63-expressing tumours had exhibited positive staining for the ΔNp63 isoform (6/7) by immunofluorescence and p63 mRNA (7/8) by chromogenic in situ hybridization.
- Despite p63 positivity, these tumours uniformly had expressed luminal-type cytokeratin proteins such as CK18 (13/13), CK8 (8/8), and markers of androgen axis signalling commonly seen in luminal cells, including androgen receptor (10/11), NKX3.1 (8/8), and prostein (12/13).
- Conversely, basal cytokeratins such as CK14 and CK15 were found to be negative in all cases (0/8) and CK5/6 was weakly and focally positive in 36% (4/11) of cases. Pluripotency markers including β-catenin, Oct4, and c-kit were negative in p63-expressing tumours (0/11).
- Despite nearly universal expression of androgen receptor and downstream androgen signalling targets, p63-expressing tumours had lacked ERG rearrangements by fluorescence in situ hybridization (0/14) and ERG protein expression (0/37).
- No tumours had expressed SPINK1 or had shown PTEN protein loss (0/19).
- Surprisingly, 74% (14/19) of p63-expressing tumours had expressed GSTP1 protein at least focally, and 33% (2/6) entirely had lacked GSTP1 CpG island hypermethylation by bisulfite sequencing.

Tan et al. [5] made the following conclusions:

- In contrast to the usual adenocarcinomas of the prostate gland, prostate tumours with p63 expression had demonstrated a mixed luminal/basal immunophenotype, uniformly lack ERG gene rearrangement, and frequently express GSTP1.
- These data had strongly indicated that p63-expressing prostate tumours do represent a molecularly distinct subclass and further study of this rare tumour type might yield important insights into the role of p63 in prostatic biology and the prostate cancer cell-of-origin.

Torres et al. [39] stated the following:

- Rare prostate carcinomas aberrantly do express p63 and have an immunophenotype intermediate between basal and luminal cells.
- They had undertaken gene expression profiling on p63-expressing prostatic carcinomas and compared them to usual-type adenocarcinoma.
- They had identified ETS2 as highly expressed in p63-expressing prostatic carcinomas and benign prostate basal cells, with lower expression in luminal cells and primary usual-type adenocarcinomas.

Torres et al. [39] compared a total of 8 p63-expressing prostate carcinomas at radical prostatectomy to 358 usual-type adenocarcinomas by gene expression profiling performed on formalin fixed paraffin embedded tumour tissue using Affymetrix 1.0 ST microarrays. Correlation between differentially expressed genes and TP63 expression was performed in 5239 prostate adenocarcinomas available in the Decipher GRID. For validation, ETS2 in situ hybridization was undertaken on 19 p63-expressing prostate carcinomas and 30 usual-type adenocarcinomas arrayed on tissue microarrays (TMA). Torres et al. [39] summarised the results as follows:

- By gene expression, p63-expressing prostate carcinomas had demonstrated low cell cycle activity and low Decipher prognostic scores, but were predicted to have high Gleason grade compared to usual-type adenocarcinomas by gene expression signatures and morphology.
- Among the genes over-expressed in p63-expressing carcinoma relative to usual-type adenocarcinoma were known p63-regulated genes, along with ETS2, an ETS family member previously implicated as a prostate cancer tumour suppressor gene.

- Across several cohorts of prostate samples, ETS2 gene expression was found to have correlated with TP63 expression and was significantly higher in benign prostate compared to usual-type adenocarcinoma.
- By in situ hybridization, ETS2 gene expression was noted to be high in benign basal cells, and low to undetectable in benign luminal cells or usual-type adenocarcinoma. In contrast, ETS2 was highly expressed in 95% (18/19) of p63-expressing prostate carcinomas.
- Torres et al. [39] made the ensuing conclusions:
- ETS2 is a predominantly basally-expressed gene in the prostate, with low expression in usual-type adenocarcinoma and high expression in p63-expressing carcinomas.
- Given this pattern, the significance of ETS2 loss by deletion or mutation in usual-type adenocarcinomas, was not certain.

Lokesha et al. [1] iterated the following:

- In men, carcinoma of the prostate gland is the second most common cancer, after pulmonary cancer.
- Prostate cancer is also the world's leading cause of cancer.
- It has been documented that Prostate cancer is associated with advanced age, genetics factor smokers, obese individuals, and due to endogenous factors [2]
- Prostate-specific antigen (PSA) levels are essential in elderly patients in order to identify the risk of prostate cancer.
- Even though serum PSA is not very specific, high levels have tended to be concomitant with prostate cancer.
- The diagnosis of prostate cancer purely upon the foundation of the clinical and morphological features could be difficult and for this reason, the role of tumour markers and immunohistochemical markers had been pointed out as a means by which diagnosis of prostate cancer has tended to be confirmed upon. [3]
- Immunohistochemistry staining tumour markers such as p63, high molecular weight cytokeratin (HMWCK), and p504s do aid in the appropriate diagnosis of carcinomas of the prostate gland.
- p63, which is an analogue of p53, is a tumour suppressor gene that encodes for isotypes which either act as p53-dominant negatives or transactivate p53 reporter genes, whose presence does aid apoptosis and helps in reducing the progression of cancer. [4]
- It has been stated that it comprises 15 exons and codes for 6 different mRNA isoforms which have a common DNA-binding domain. [3] [5]
- p63 is needed for nourishing a basal-cell population, maintaining a prostate epithelial stem cell population, and it is also essential for the development of the prostate gland [4]
- Tumour markers like p53 and p63 are expressed upon the nuclei of the normal basal cells.
- Usually, adenocarcinomas are devoid of basal cells, whereas benign lesions are encircled by the same. Hence, adenocarcinoma of the prostate gland could be distinguished from benign prostate lesions and hyperplasia by the absence of p63 staining within the basal cells in prostate carcinoma.
- Hence, p63 and HMWCK, and basal-cell immunohistochemistry markers have turned out to be beneficial to differentiate benign and malignant conditions. [6] [7]
- There are few adenocarcinomas which do retain the basal cells and do exhibit partial p63 and HMWCK staining, and there are a small number of benign prostatic hyperplasia (BPH) and adenocarcinoma mimickers which do not express the basal-cell makers.[7]

Lokesha et al. [1] reported an 87-year-old, diabetic, as well as a known hypertensive gentleman who had manifested with incomplete voiding, increased urinary urgency, and frequency of micturition, together with bilateral pitting type of oedema which was confined to his feet and dull and deep generalized pain within his lower abdomen which appeared following his voiding of urine. The result of his serum PSA level had significantly increased to 213.3 ng/ml. Upon digital rectal examination, a Grade 3 prostate enlargement and hard prostate were felt. He underwent trans-rectal prostate biopsies which were obtained for histopathology examination. Pathology examination of his prostate biopsy tissue cores demonstrated a tumour which had comprised of back-to-back arranged small glands without basal-cell layer. The epithelial lining had demonstrated enlarged hyperchromatic nuclei with prominent nucleoli (see figure 6 and 6 b).

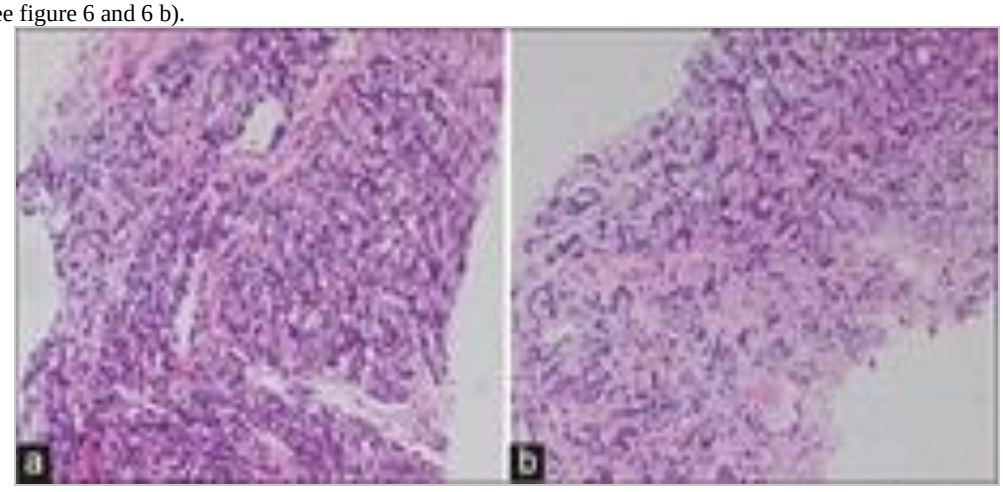

Figure 6: (a and b) Hematoxylin and eosin staining of the prostatic tissue exhibiting tumour composed of back-to-back arranged small glands without basal cell layer and epithelial lining showing enlarged hyperchromatic nuclei with nucleoli [200 × magnification] Reproduced from [1] under the Creative Commons Attribution License.

Immunohistochemistry staining study analysis was undertaken to evaluate the biopsy for the presence of basal cells with HMWCK and p63. A positive tumour marker p504s was also undertaken.

To the surprise of the authors, the nuclei of the tumour cells had exhibited positivity with p63 causing confusion [see figures 7 a and b]. The HMWCK study demonstrated negative staining within the cancerous glands [see figure 8] and p504s was diffusely and strongly positive [see figures 9 a and b].

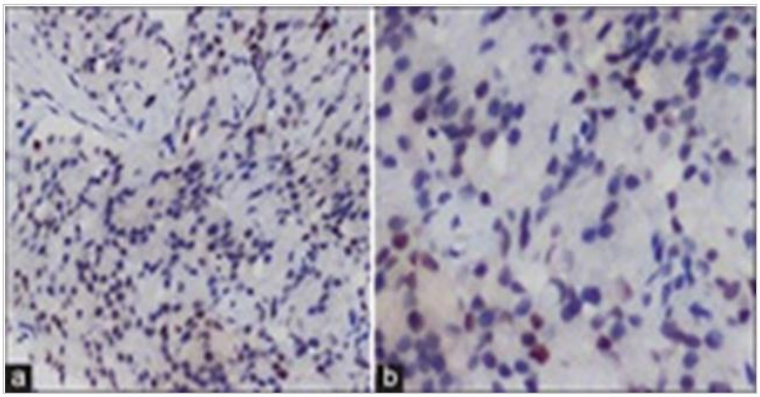

Figure 7: (a and b) Photograph of the prostatic tissue [1b showing a magnified image] where nuclei of the tumour cells demonstrate p63 positivity [immunohistochemistry, 100 × magnification].

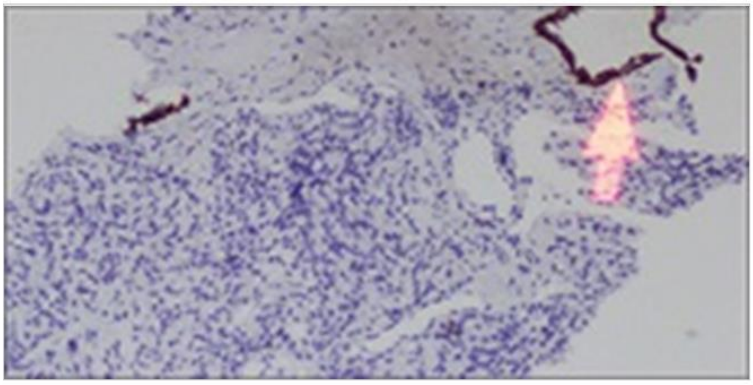

Figure 8: Glands of the tumour cells demonstrating negativity for high molecular weight cytokeratin [100 × magnification].

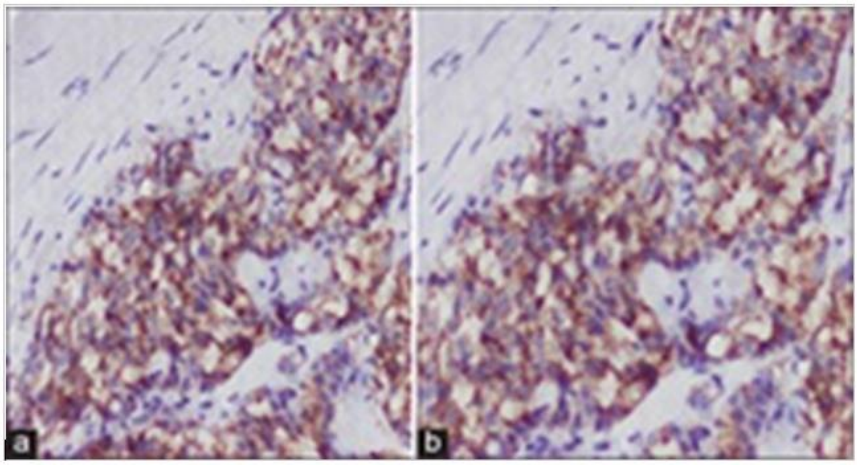

Figure 9: (a and b) Glands of the tumour cells [4b showing a magnified image] showing diffuse positivity for p504s molecular marker [100 × magnification].

Lokesha et al. [1] stated that upon review of literature, it was evident that a rare variant of adenocarcinoma of the prostate gland called p63-positive prostatic carcinoma could exhibit p63 overexpression within the nuclei of the malignant glands. They also found out upon review of the literature that this tumour entity could be distinguished from benign glands by the fact that the expression of p63 is not basal in nature and the glands had exhibited negative reaction with HMWCK. A positive p504s staining also supports the malignant diagnosis. Lokesha et al. [1] iterated that in concordance with the immunohistochemical and histopathological findings, the case was confirmed to be a diagnosed case of p63-positive

adenocarcinoma of prostate gland. The patient was managed mainly by means of chemotherapy, injection pamorelin (11.25 mg, intramuscular), tablet finast, tablet silodac, and tablet tabi for a month. Currently, the patient at the time of publication of his case had been undergoing regular follow-up assessments and he was asymptomatic.

Lokesha et al. [1] made the ensuing educative discussions:

- The incidence of carcinoma of prostate gland had been rising over recent days.
- The number of patients who manifest with obstructive voiding had also been increasing.
- In this scenario, both the clinical and histopathology evaluations do play a major role.
- The prostate biopsies are routinely undertaken in these set of patients.
- It had been iterated that cytology examination features like nuclear atypia, enlarged nucleoli, and so on are indicators of cancer, together with other definite features like infiltrative growth and formation of collagen micronodules.[40]
- But then also, the diagnostic difficulty arises in these biopsies in view of many mimickers of malignancy.
- Atrophy, post-atrophic hyperplasia (PAH), adenosis, prostatitis, and tangentially cut high-grade prostatic intraepithelial neoplasia could be some of the differential diagnoses of this tumour.
- PAH is a non-involuting and proliferative lesion, which demonstrates similar nuclear and architectural characteristics like carcinoma of prostate gland and is therefore, the best-known mimic of adenocarcinoma of prostate gland. It has to be differentiated by the surgical pathologist due to therapeutic consequences.[41]
- It has been stated that even though light microscopy examination findings are the gold standard for the diagnosis of carcinoma of prostate gland, in these suspicious cases, immunohistochemistry is usually sought or relied upon for confirmation of diagnosis. [40]
- p63, HMWCK, and p504s are the routinely utilised tumour markers within their department. p63 and p504s could resolve 93% of the apprehensive lesions of the prostate gland.
- p504s indicates upregulation in the metabolic pathways of the normal glands. Thus, it is upregulated in cancerous glands and is a positive tumour marker for cancer.
- p504s demonstrates an increase in various conditions like high-grade PIN, partial atrophy, some benign glands, and also crowned grands.
- In view of this, it was concluded that p504s is not very specific but very sensitive. [42]
- Because of many false-positive reactions with p504s, the diagnosis mainly relies upon p63 and HMWCK.
- p63 and HMWCK in combination with p504s are utilised to differentiate carcinoma of prostate gland from benign mimickers.
- It has been documented that p63 and HMWCK, nuclear and cytoplasmic antibodies, when used, they do exhibit immunohistochemistry staining for the prostate basal cells. [3]
- It has been pointed out that the absence of the basal cells within the carcinoma but presence of the same within the benign glands does help in the differentiation of the two.
- The expression of p63 and HMWCK together was studied by Zhou M et al. [43]
- It has been iterated that positive staining of p63 and HMWCK is indicative of benign glands and negative indicative is stated to be indicative of malignancy. [44]
- It has been documented that higher levels of p63 within cytoplasm of the tumour cells are significantly associated with increased proliferative activity and decrease of apoptosis. The cytoplasmic staining of p63 might indicate a mis-localized protein, which possibly emanates into an oncogenic function in carcinoma of the prostate gland progression. [14]
- It has been iterated that rarely, some adenocarcinomas of prostate gland do express p63 within the nuclei of the malignant glands and stain positively. This could wrongly be interpreted as benign glands. [9] [10] This does tend to cause diagnostic confusion and a major pit fall. It could be avoided by considering HMWCK staining and p504s staining.[9]
- There are findings of some reports that had iterated that p63-positive prostatic carcinoma has a favourable prognosis.
- It has been iterated that absence of p63 is associated with increased Gleason scores and metastasis with worse prognosis.
- In concordance with few studies, organ confinement and no lymph node metastases are noticed in association with p63-positive tumours. [3] [9]
- Nevertheless, the behaviour of this particular tumour at the time of publication of their article was under investigation.
- The timely diagnosis of this variant without much confusion could enable the patient undergo appropriate treatment.
- The treatment modalities for this particular carcinoma align with the treatment protocol of the usual adenocarcinoma of prostate gland.
- The tumour with Gleason grade 6 is preferably treated with chemical (androgen blockade) or surgical castration and brachytherapy which produce very good results even without radical prostatectomy whose morbidity is very high.

Lokesha et al. [1] made the ensuing conclusions:

- p63-positive adenocarcinoma of prostate gland, is a major diagnostic pitfall.
- There is a danger of interpreting malignant glands as benign and arriving at a false-negative diagnosis. This could be avoided by the knowledge of the pattern of immunohistochemical expression related to this variant.
- The major points that favour the diagnosis of carcinoma in these cases are the non-basal p63 staining and negative HWMCK and positive p504s staining.
- The biological behaviour of this particular rare variant of carcinoma of prostate gland is not certain and needs to be studied further.
- Further studies are necessitated in order to ascertain the role of p63 overexpression in prognostication of the tumour.

Conclusions

- p63-positive or p63 expressing adenocarcinoma of the prostate gland has tended to be a major diagnostic pitfall.
- There has tended to be a danger of interpreting malignant glands as benign and arriving at a false-negative diagnosis and does delay the establishment of the correct diagnosis

as well as delays commencement of the appropriate effective treatment of the prostate cancer.

- This could be avoided by the understanding of the pattern of the immunohistochemistry staining expression related to this variant of p63 expressing prostate cancer.
- The major points or factors that favour the diagnosis of prostate cancer in these cases include: the non-basal p63 staining and negative HWMCK and positive p504s staining.
- The biological and clinical behaviour of this particular rare variant of prostate cancer is not yet certain and hence it does need to be studied further in a more detailed fashion.
- Additional studies are necessitated in order to ascertain the role of p63 overexpression in the prognostication of prostate cancer.

Conflict Of Interest - Nil

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