

Significance of Tertiary Pattern in a patient with Gleason Score 5a after Radical Prostatectomy: Proposal to increase the grade: A Case Report

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Abstract

Introduction: Present case relates to Gleason histological assessment of adenocarcinomatous tissue of the prostate. Accordingly, malignant tissue may be categorized into 5 different histological grades, lowest grade being 2 and the highest grade being 5 (best-to-least-differentiated). Initially, the most predominant pattern is graded. Subsequently, second most common tissue is graded. Sum of the histological grades of first and second most dominant malignant tissue is reported as Gleason score (GS). Gleason grade 1 may appear normal while Gleason grade 5 either may not show glands or show rudimentary glands. If only a single tumor is detected than double its grade to give a total score. It has been suggested that patient with higher Gleason score may have a worse prognosis as compared to another patient with lower score. In the present case, the first most dominant component of malignant tissue was graded as 3a while the second predominant tissue was graded as grade 2; total Gleason score was $3a+2=5a$. In the present case, another tertiary pattern, consisting of medium-sized malignant glands of higher grade was detected. This pattern was graded as Gleason grade 4. The difference between first and third components was the size of the malignant glands. First major component had irregular small malignant glands while third minor component had irregular medium-sized glands. It was proposed to increase the total Gleason score (GS) either by replacing the second component with the tertiary component ($3a+4=GS$ 7a) or by adding the grade of third component with the original Gleason score ($3a+2+4=GS$ 9a). Thus, Gleason grading appeared to after-effect, lower the grade better the prognosis.

Case report: Current patient was a 70-year-old male. He had bladder obstructive symptoms as dysuria; radical prostatectomy was done. Sections were taken from different areas of prostate. In the current case, tumor appeared to arise from 3 different sites (multicentric). Primary most predominant malignant tissue was graded as 3a [figures B-E] while secondary predominant tissue was graded as Gleason grade 2 [figure A]; total Gleason score being $3a+2=5a$. In addition, present case also had third least-predominant tissue with higher Gleason grade 4 (GG4) [figures F,G].

Discussion: Most prominent feature of the present case was the detection of a third least-differentiated population of prostatic adenocarcinoma. Third population consisted of medium-sized glands with Gleason grade 4 lesion. Difference between primary and tertiary populations was the size of malignant glands. Primary lesion showed small irregular glands while tertiary lesion had haphazard glands of medium size. It was proposed to increase the Gleason score marginally either by replacement of secondary dominant grade of tumor

by tertiary minor tumor (3a+4= GS 7a) or by addition of tertiary grade with original Gleason score (3a+2+4=GS 9a) which appeared much higher than original GS 5a.

Conclusion: Photomicrographs of prostatic tissue showed an additional tertiary population of malignant medium-sized glands. In the current case, a tertiary pattern of grade 4 was identified which might have prognostic significance. Due to rarity of this lesion, it has been proposed to increase the grade of prostatic adenocarcinoma marginally.

Keywords: Tertiary Pattern of Higher Grade may increase Gleason Score

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I. Introduction:

In the current case, 3 components of malignant tissue were seen. At the time of diagnosis, primary most dominant population consisted of small proliferated malignant glands at prostatic anterior zone. According to Gleason histological assessment, it belonged to grade 3a [figures B-E]. Second predominant population comprised of proliferated glands with lower grade, e.g. Gleason grade 2 [figure A]. This population was detected in central zone of prostate. Third component comprised of medium-sized glands which consisted of <10% of total malignant tissue [figure F,G]. In a previous report, it was advised to increase the Gleason grade (GG) if third component was found to be of higher grade than the primary grade. In the present case, primary grade was 3a which was lower than the tertiary Gleason grade 4. Therefore, it was proposed to increase the score marginally. Our findings suggested the possible role of well-differentiated (GS2-4) and moderately differentiated (GS5-7) tumors in deciding the prognosis of prostatic adenocarcinoma. Importance may also be given to the third component of higher grade while deciding GS as in the present case. Findings of this report suggested that nidus for tumorigenesis was at 3 different sites. Earlier, we reported another case of prostatic carcinoma with tertiary pattern of higher grade^[1]. Previously, we also demonstrated the role of high-grade PIN (pre-malignant) in pathogenesis of adenocarcinoma of prostate^[2]. Several other reports on tertiary pattern and its outcome on prostate cancer aggressiveness have been reported^[3,4]. It appeared that prostatic adenocarcinoma may arise either from luminal glandular epithelial cell or from a ductal epithelial cell.

II. Case Report:

A 70-year-old male presented with dysuria, increased urinary frequency and retention. Serum PSA was raised. Per rectal digital examination revealed nodular hard prostate, provisionally, the patient was diagnosed as a case of prostatic adenocarcinoma. Suprapubic radical prostatectomy was done. Later, histological grading was also done. In the current case, most predominant malignant tissue was graded as Gleason grade 3a. Second dominant malignant tissue was graded as Gleason grade 2. Subsequently, Gleason score (GS) was calculated as 3a+2= GS 5a. Clinically, the patient was diagnosed as a case of moderately differentiated adenocarcinoma. Additionally, another tertiary minor pattern (<10%) of grade 4 was detected. The patient was finally diagnosed as a case of adenocarcinoma prostate 3a+2= GS 5a with tertiary grade 4 lesion. If the Gleason grade of second tumor was replaced by tertiary least-differentiated tumor of higher grade, Gleason score would be 3a+4 = 7a. However, if histologic grade of tertiary pattern is added with original Gleason score, then the GS will be 3a+2+4= 9a which is much higher than original GS 5a.

III. Discussion:

Prostatic cancer is the second common cause of cancer-related deaths in men aged >40 years. African Americans appear to have higher incidence of prostatic carcinoma as compared with European Americans, suggesting that genetic factors are involved in pathogenesis of prostatic cancer. Single layer of cuboidal cells, lining irregular haphazard proliferated acini may be an important feature for the diagnosis of adenocarcinoma of prostate. Majority of adenocarcinomas may be acinar or ductal in origin; later arising from high-grade prostatic intraepithelial neoplasia (PIN). Further, nucleomegaly, clumped chromatin near nuclear membrane with 1 or 2 irregular nucleoli may be other features of adenocarcinoma of prostate. Splitting or distortion of smooth muscle fibers may also occur in stroma.

Adenocarcinoma of prostate is known to spread by local invasion. Grading of prostatic adenocarcinoma has been correlated with lymphatic and vascular metastases, prostatic acid phosphatase and PSA levels^[5]. The patient with a Gleason score 2 to 4 may develop asymptomatic or mild disease while a patient with GS 8 to 10 may develop aggressive disease. Rarely, lymphatic spread has been reported in a patient with Gleason score 3+2=5 or 2 + 3 = GS5^[6]. Current patient also had Gleason score of 3a+2=5a. Another feature of current case was detection of a tertiary minor pattern of Gleason grade 4. If the grade of minor pattern is added with original GS, then it might predict a severe disease (3a+2+4 = GS 9a). Genitourinary pathology society (GUPS) and International society of urology pathology (ISUP) meetings were organized to discuss the significance of tertiary

pattern of higher grade. The participants could not reach to consensus. However, it was suggested that pathologists should also mention the Gleason grade of the tertiary pattern while writing the final report [7,8]. Gleason grading criteria were first reported in the year 1966 [9]. Later, tertiary Gleason pattern was introduced in the year 2005 [10]. Since then several studies have described the negative role of tertiary pattern in prognosis of prostatic carcinoma [11]. Moreover, risk of tertiary pattern after radical prostatectomy (RP) was higher than secondary Gleason pattern [12]. In addition, original Gleason score may be modified as Gleason grade grouping model (mGGG). Moreover, Gleason score <6 may suggest asymptomatic cancer while Gleason score of >8 may suggest poorly differentiated tumor with worse prognosis [13,14]. In addition, over expression of Ki 67 may suggest a higher risk of histologic outcome [15]. Moreover, osteopontin expression as well as 'PSA doubling time' may indicate poorer prognosis [16]. Gleason grading system may consider including tertiary Gleason pattern (TGP) to improve the prognostic assessment of patients with adenocarcinoma prostate. For example, Gleason grade 4+3 = 7 with TGP had worse prognosis than Gleason 4+3 = 7 with out tertiary grade [17]. Further, GS of primary tumor as well as of positive surgical margin were predictors of biochemical clinical recurrence (BCR) after radical prostatectomy [18].

According to Gleason criteria, first and second grades (best-to-least-differentiated) are considered for calculation of GS. Several reports have suggested prognostic significance of third minor population of malignant cells of higher grade. Addition of numerical number of minor tertiary grade with original Gleason score (3a+2+4 = GS 9a) or replacement of number of second prominent population by third minor component (3a+4 = GS 7a), increased the GS. Another finding of the present case was the detection of higher grade in third tertiary population as Gleason grade 4 [GG4] as compared with first major populations [GG3a]. Moreover, the percentage of third minor population was much less (<10%) as compared to first major malignant cell population (65%). Furthermore, grade of positive surgical margin also appeared to increase the modified Gleason group grade (mGGG). Mosse et al demonstrated that radical prostatectomy (RP) cases with 4+3=GS7 with a tertiary pattern 5 might have worse pathologic behavior than cases with GS of 4+3=GS7 without tertiary pattern. However, radical prostatectomy cases they had a lower incidence of seminal vesicle invasion and lymph node metastasis [19].

IV. Conclusion:

In the current case, a tertiary pattern of higher grade was identified. Tertiary pattern showed medium-sized irregular malignant glands of prostatic adenocarcinoma while primary pattern had small glands of irregular size. It has been proposed to increase the Gleason score either by adding grade of tertiary pattern with original Gleason score (3a+2+4=9a) or by replacing the Gleason grade of secondary pattern by tertiary pattern (3a+4=7a).

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Figures

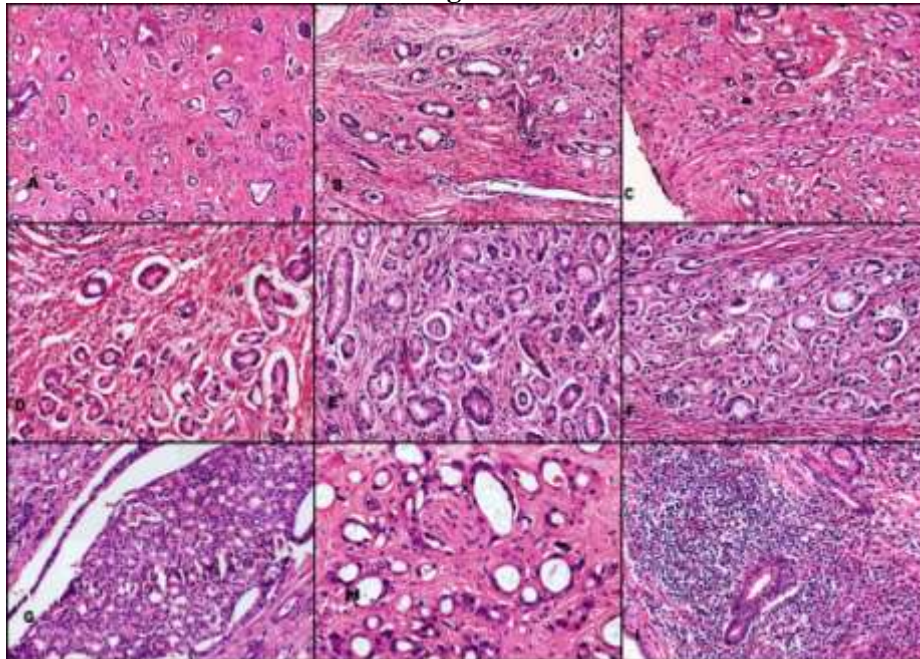


Fig. 1: (A) Photomicrograph shows diffusely scattered irregular glands with intervening stroma, suggesting Gleason grade 2 lesions (HE×100). (B) Photomicrograph shows irregular haphazard glands, lined by single layer of cuboidal cells. Malignant glands show high nuclear cytoplasmic ratio with coarse chromatin, prominent nucleoli and scant eosinophilic cytoplasm (HE×100). (C) Irregular glands with malignant tumor cells are seen near capsule ~0.1 mm from inked margin (HE×100). (D) Photomicrograph shows marked variation in size and shape of glands around which a line may be drawn, suggesting Gleason grade 3a lesion (HE×200). (E) Photomicrograph shows closely packed glands as seen in D (HE×200). (F) Higher magnification shows closely packed glands, suggesting Gleason 4a lesion (HE×200). (G) Lower magnification showed glomeruloid cribriform-like appearance, suggesting a Gleason grade 4c lesion (HE×100). (H) Photomicrograph shows perineural invasion (HE×400). (I) shows focal lymphocytic infiltration around normal Gleason grade 1 glands (HE×400).