Published in final edited form as:

Hum Pathol. 2009 April ; 40(4): 471–477. doi:10.1016/j.humpath.2008.10.002.

Gleason grading of prostatic adenocarcinoma with glomeruloid features on needle biopsy

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Summary

Glomerulations in prostatic adenocarcinoma are characterized by dilated glands containing intraluminal cribriform structures with a single point of attachment, resembling a renal glomerulus. On prostate biopsy, glomerulations are exclusively associated with carcinoma and not associated with benign mimickers. However, the Gleason grading of carcinoma with glomerulations on needle biopsy remains controversial. We prospectively collected 45 prostate needle biopsies containing carcinoma with glomeruloid features from our consult files for a 9-month period and examined the association between glomerulations and the presence of concurrent high-grade carcinoma. Glomerulations were overwhelmingly associated with high-grade cancer on the same core, composed of either Gleason pattern 4 (n = 36, 80% of cases) or Gleason pattern 5 (n = 2, 4% of cases). Only a minority of glomerulations were surrounded exclusively by pattern 3 cancer (n = 7, 16% of cases) on the same core. Most of the cases with surrounding pattern 4 cancer were scored as 3 + 4 = 7 (n = 24, 66%), whereas a smaller fraction were scored as 4 + 3 = 7 (n = 9, 26%), and only a minority were 4 + 4 = 8 (n = 3, 9%). In most cases, glomeruloid change was present on the same core as the highest Gleason score carcinoma of the case. None of the pattern 3 cases and only a minority of the pattern 4 cancers had higher Gleason score carcinoma on additional cores (n = 5, 14%). Glomeruloid structures are a rare but diagnostic feature of prostatic carcinoma on needle biopsy. Our data indicate that glomerulations are overwhelmingly associated with concurrent Gleason pattern 4 or higher-grade carcinoma. In several cases, transition could be seen among small glomerulations, large glomeruloid structures, and cribriform pattern 4 cancer. These data suggest that glomerulations represent an early stage of cribriform pattern 4 cancer and, until follow-up data are available, are best graded as Gleason pattern 4.

Keywords

Prostatic adenocarcinoma; Glomeruloid; Glomerulations; Gleason grading

1. Introduction

Glomeruloid change in prostate cancer, originally described in 1995, is characterized by dilated glands containing intraluminal cribriform structures with a single point of attachment, resembling a renal glomerulus [1]. Considered one of the few pathognomonic

features of prostatic cancer, glomerulations are never seen in association with benign conditions and are exclusively associated with carcinoma [2–4]. Although these facts concerning glomeruloid structures in prostate cancer are widely accepted, it remains controversial as to what Gleason grade should be assigned to this pattern [5].

To clarify the appropriate Gleason grading of prostatic adenocarcinoma with glomerulations on needle biopsy, we identified 45 cases with this feature in our consult files, comprising the largest series of this rare pattern described to date. In these cases, we studied the Gleason score and predominant architectural pattern of the prostatic carcinoma associated with glomeruloid change.

2. Materials and methods

Forty-five needle biopsy cases of prostatic carcinoma with glomerulations were prospectively collected for a 9-month period from the consultation files of one of the authors from December 2006 to August 2007. An average of 13 needle core biopsies (range, 6–24) were submitted for each case. Glomerulations were defined as dilated glands containing intraluminal cribriform structures with a single point of attachment. Prostatic carcinoma with dilated glands containing intraluminal ball-like clusters of cells without a peripheral point of attachment was considered “telescoped” cribriform glands and was not included in this study. For each case with glomerulations, the total number of cores and percentage of each core containing prostatic carcinoma was recorded. The Gleason score of the carcinoma on the same core as the glomerulations was recorded, as were the Gleason scores for the other cores containing carcinoma in the case. Gleason pattern 4 carcinomas associated with glomerulations were further characterized by predominant architectural pattern (fused/poorly formed glands or large/irregular cribriform glands). In cases with pure Gleason pattern 3 carcinoma associated with glomerulations on needle biopsy, clinical follow-up to obtain the subsequent radical prostatectomy specimen was attempted.

3. Results

3.1. Overall clinical/pathologic parameters of cases with glomerulations

Prostatic carcinoma with glomeruloid features was a rare finding in our consult material, present in 0.6% of prostatic adenocarcinoma cases seen in a 9-month period. The clinical/pathologic characteristics of the patient population and biopsies are summarized in Table 1. Average patient age was 66 years (45–86 years). Prostate-specific antigen (PSA) at the time of biopsy was available in 24 cases (53%), and was 7.6 ng/mL on average (range, 2.9–48 ng/mL). In general, prostatic adenocarcinoma with glomeruloid features on needle biopsy was associated with high-grade and high-volume disease. The overall highest Gleason score in this cohort of biopsies was 7 or higher in 84% (38/45) of cases (71% Gleason score 7, 9% Gleason score 8, and 4% Gleason score 9). On average, each case had 3 cores containing tumor (range, 1–10), and tumor constituted an average of 30% of each affected core (5%–95%). In the cases containing high-grade (pattern 4 or 5) disease, the high-grade carcinoma was present on an average of 2 cores (range, 1–8). Five cases (11%) showed perineural invasion; however, no cases demonstrated extraprostatic extension on the needle biopsy.

In general, glomerulations were present only on a minority of cores from each case (1–2 cores). Most glomerulations consisted of relatively small dilated glands containing smooth rounded cribriform structures with only small slit-like spaces (Figs. 1–3), although rare cases showed larger cribriform structures with multiple “punched-out” lumina (Fig. 4). In all cases, a thin stalk-like attachment connected the cribriform gland to the surrounding dilated gland. Rarely, a delicate fibrovascular core was visible at the base of the cellular tuft (Fig. 5).

3.2. Gleason pattern of carcinoma on same core as glomerulations

On the same core, glomerulations were overwhelmingly associated with high-grade cancer composed of either Gleason pattern 4 ($n = 36$, 80% of cases) or Gleason pattern 5 ($n = 2$, 4% of cases). Only a minority of glomerulations were surrounded exclusively by pattern 3 cancer ($n = 7$, 16% of cases) on the same core. Most of the cases with surrounding pattern 4 cancer were scored as $3 + 4 = 7$ ($n = 24$, 66%), whereas a smaller fraction were scored as $4 + 3 = 7$ ($n = 9$, 26%), and only a minority were $4 + 4 = 8$ ($n = 3$, 9%). Pattern 4 cases were evenly divided into those showing predominantly fused poorly formed glands and those showing large or irregular cribriform glands (49% and 51%, respectively) (Figs. 6 and 7). In many cases, a morphological transition could be seen among small glomerulations, large glomeruloid structures, and cribriform pattern 4 cancer (Figs. 8 and 9).

3.3. Gleason pattern of carcinoma on other cores

In most cases, the glomeruloid change was present on the same core as the highest Gleason score carcinoma of the case. None of the cores with only pattern 3 carcinoma and glomeruloid features showed higher score carcinoma on other cores (0/7), and only a minority of the pattern 4 cancers had higher Gleason score carcinoma on additional cores (5/36, 14%).

3.4. Pathologic follow-up on subsequent radical prostatectomy

Follow-up was obtained on all 7 patients with glomerulations present in a background of Gleason pattern 3 carcinoma without associated pattern 4 carcinoma on needle biopsy. Of these patients, 6 (86%) underwent brachytherapy or external beam radiation therapy after the cancer diagnosis. Only one patient underwent a radical prostatectomy, which we reviewed. This specimen, which was not entirely submitted, showed predominantly Gleason $3 + 3 = 6$ carcinoma with tertiary and very focal cribriform Gleason pattern 4 carcinoma.

4. Discussion

Prostatic adenocarcinoma can assume a wide variety of architectural patterns, many of which were described by the original Gleason grading system some 40 years ago [6]. However, some patterns and variants of prostate cancer were not recognized in Gleason's era, and the grading of these lesions up until relatively recent times was left to the individual pathologist's discretion. In 2005, an updated Gleason grading system was derived with input from 80 urologic pathologists from around the world [5]. Where possible, the updating was based on data; in areas where there was either a lack of data or scant information as to the optimal method of grading, the consensus was based on personal and institutional experience with a large number of cases. The updated Gleason system was not a newly derived system, but rather a codification of what most urologic pathologists were already doing in their contemporary practice.

Although a consensus was reached in the updated Gleason system as to the grading of most variants and patterns of prostate cancer, there remained several lesions where the experts could not agree, in large part because of the absence of any data. The grading of glomeruloid structures was one such lesion. According to some experts, for the rare case of Gleason score $3 + 3 = 6$ admixed with small glomeruloid glands, a grade of $3 + 3 = 6$ was assigned. Larger glomeruloid structures were uniformly accepted by urologic pathologists as Gleason pattern 4. Other experts in the field felt that all glomeruloid structures should be assigned a Gleason pattern 4. Consequently, it was decided that either approach was acceptable for practicing pathologists until future data indicated which method was more accurate.

Until now, the relative rarity of glomeruloid structures in prostate cancer precluded an in-depth analysis of this architectural pattern [7,8]. In the only other series of prostatic carcinoma with glomeruloid features, Pacelli et al [9] reported that glomeruloid features were seen in only 3% of 100 consecutive needle biopsy specimens and 4.5% of 202 entirely embedded radical prostatectomy specimens. Furthermore, in both needle biopsies and prostatectomies, glomerulations made up less than 10% of the total tumor volume on average. In the current study, we took advantage of our extensive consult experience and assembled the largest group of prostate needle biopsies showing adenocarcinoma with glomeruloid features described to date. Ultimately, we found that glomerulations were almost invariably associated with definitive (traditional) Gleason pattern 4 carcinoma showing fused/poorly formed glands or irregularly cribriform glands. When present, the high-grade carcinoma was typically present near the glomerulations (on the same core in every case associated with Gleason pattern 4 carcinoma). In addition, several cases showed a morphological transition among small glomerulations, large glomeruloid structures, and cribriform pattern 4 cancer, suggesting that glomerulations likely represent an early Gleason pattern 4 adenocarcinoma.

Our findings in the present study are in agreement with several previous studies. In the original series, Pacelli et al [9] found that 7 (78%) of 9 cases on radial prostatectomy were associated with Gleason score 7 or 8, and only 2 cases were associated with Gleason score 6 or lower. Given the known association between Gleason score and pathologic stage, it is also consistent that a large number of these cases with glomeruloid change showed high pathologic stage (T3b or T3c) on radical prostatectomy as well (67%).

In addition, although glomerulations in prostate cancer have been likened to those in Wilms tumor (ie, as a primitive attempt of undifferentiated carcinoma cells to recapitulate renal glomerulus development), previous morphological studies support our conclusion that glomerulations are best characterized as an early cribriform Gleason pattern 4 carcinoma. As seen in the current study, Pacelli et al [9] found morphological evidence of a true fibrovascular core in only a minority of the cases they examined. In an ultrastructural study of several cases of prostate cancer with glomeruloid change, Yang et al [10] found that although blood vessels were rarely seen at the base of the glomeruloid tufts, no true fibrovascular cores were present in the tumor cell aggregates in the center of dilated gland. Thus, the resemblance to a primitive renal glomerulus is most likely superficial, and glomerulations in prostate cancer are more similar to small cribriform glandular structures seen in carcinoma.

Much like glomerulations, the grading of small cribriform prostate carcinoma glands has also been controversial, as to whether they represent Gleason pattern 4 or 3 carcinoma. Currently, they continue to be considered Gleason pattern 3 carcinoma by the most recent modification of the Gleason system [5]. However, in a recent study of a highly selected set of images thought to be the best candidates for cribriform pattern 3 that were sent to 10 experts in urologic pathology, most experts interpreted the cribriform patterns as pattern 4 [11]. Moreover, most of the cribriform foci investigated (73%) were associated with more definitive pattern 4 elsewhere on the needle biopsy specimen. It was concluded that most of the small cribriform cancer foci seen on needle biopsy should be interpreted as Gleason pattern 4 and not pattern 3. Given transitions between glomeruloid structures and both small and larger cribriform cancer, the findings and conclusions of both the current study and that of grading small cribriform structures are complimentary and supportive of each other.

It is important to point out, however, that a number of caveats apply to the interpretation of the current study as well as to the previous study by Pacelli. Both are *association* studies, showing the concurrence of high-grade adenocarcinoma in cases of prostate cancer with

glomeruloid change. Ideally, accurate Gleason grading of glomerulations would be determined by a study obtaining clinical follow-up to compare outcomes of pure Gleason score 6 carcinoma with and without glomerulations matched for the typical clinical and pathologic characteristics (age, PSA, stage, etc). For the time being, such a study is not possible because glomerulations are seen in only a small percentage of needle biopsies showing adenocarcinoma. In addition, as our study has demonstrated, the percentage of cases with glomerulations and associated pure Gleason 6 carcinoma is vanishingly small (16%), making the assembly of such a series with clinical follow-up very difficult if not impossible. In lieu of clinical follow-up, we did attempt to obtain pathologic follow-up on this small cohort of patients with glomerulations in a background of exclusive Gleason pattern 3 carcinoma because we would predict that most of these patients would have associated conventional Gleason pattern 4 carcinoma on radical prostatectomy due to sampling issues at the time of biopsy. Unfortunately, however, only one of our patients underwent a subsequent radical prostatectomy; thus, no conclusions could be drawn from these data.

Ultimately, the weight of the current evidence suggests that that glomerulations most likely represent an early stage of cribriform pattern 4 cancer. This is supported by the fact that most glomerulations are associated with traditional pattern 4 carcinoma in the immediate vicinity, as well as by the fact that a number of cases show a morphological transition between small glomerulations and larger cribriform glands. In addition, though they resemble a renal glomerulus superficially, most do not contain a true fibrovascular core. Thus, until extensive follow-up data are available, we propose that prostatic adenocarcinomas with glomeruloid features on needle biopsy are best graded as Gleason pattern 4.

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Fig. 1.
Adenocarcinoma with glomeruloid change (arrow).

Fig. 2.
Adenocarcinoma with glomeruloid change (arrow).

Fig. 3.
Adenocarcinoma with glomeruloid change (arrow).

Fig. 4.
Larger glomerulations with a more complex architecture verging on cribriform structures reminiscent of Gleason pattern 4 carcinoma (arrow).

Fig. 5.

In rare glomerulations, a delicate fibrovascular core was apparent in the “stalk” attaching the glomerulation to the surrounding dilated gland (arrow).

Fig. 6. Glomerulations with adjacent Gleason pattern 4 cancer consisting of poorly formed and fused glands on the same core.

Fig. 7.
Glomerulations surrounded by cribriform grade 4 carcinoma.

Fig. 8.
Transition between glomeruloid structures (arrow) and more complex and cribriform
Gleason pattern 4 carcinoma (arrowhead).

Fig. 9. Transition between glomeruloid structures (arrow) and cribriform Gleason pattern 4 carcinoma (arrowhead).

Table 1

Clinical/pathologic characteristics of carcinoma cases associated with glomerulations on needle biopsy

No. of patients	45
Mean age (range) (y)	66 (45–86)
PSA, n (%)	
<4	2 (4%)
4–9.9	20 (44%)
10	2 (4%)
Unknown	21 (47%)
Overall Gleason score, n (%)	
6	7 (16%)
7	32 (71%)
8	6 (13%)
Number of cores involved by tumor, n (%)	
2	25 (55%)
3–5	13 (29%)
6	7 (16%)
Percent of each core involved by tumor	
Average	30%
Range	5%–95%
No. of cores involved by high-grade (Gleason score 7 or higher) tumor, n (%)	
2	33 (73%)
3–5	9 (20%)
6	3 (7%)