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COMEDONECROSIS REVISITED: STRONG ASSOCIATION WITH INTRADUCTAL CARCINOMA OF THE PROSTATE

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Abstract

From the advent of the Gleason grading system for prostate cancer, cancer displaying intraluminal necrotic cells and/or karyorrhexis within cribriform/solid architecture, a phenomenon termed ‘comedonecrosis’, has been assigned pattern 5. Intraductal carcinoma (IDC-P) shows morphologic overlap with high-grade cribriform/solid adenocarcinoma architecturally and cytologically and may also show central necrosis, yet due to the presence of basal cells at the duct periphery is not currently assigned a grade in clinical practice. Based on observations from routine clinical cases, we hypothesized that comedonecrosis was more significantly associated with IDC-P than invasive disease. From a large series of mapped radical prostatectomy specimens (n=933), we identified 125 high grade (Gleason score 4+3=7), high volume tumors with available slides for review. All slides were examined for the presence of unequivocal comedonecrosis. Standard immunohistochemistry for basal cell markers was performed to detect basal cell labeling in these foci. 19 of 125 (15%) cases showed some ducts with comedonecrosis – nine cases with one focus and 10 cases with 2 foci; in all, a total of 73 foci of true comedonecrosis were evaluated. Immunohistochemical stains revealed labeling for basal cell markers in a basal cell distribution for at least some comedonecrosis foci in 18/19 (95%) cases, 12 with IDC-P exclusively and 6 with a mix of IDC-P and invasive carcinoma comedonecrosis foci. These results suggest that comedonecrosis is strongly associated with IDC-P and hence, the routine assignment of pattern 5 to carcinoma exhibiting comedonecrosis should be reconsidered.

INTRODUCTION

Modern prostate cancer (PCa) grading has undergone significant evolution over the past four decades, following the seminal descriptions by Donald F. Gleason and colleagues (1–2). In the past 1.5 decades, two consensus conferences, held under the aegis of the International Society of Urologic Pathology (ISUP), have attempted to codify the most updated knowledge and practice in the field of PCa grading (3–4). Overall these changes have resulted in a more uniform and narrower definition for pattern 3 carcinomas and an expansion in the number of carcinomas being graded as pattern 4, including those with poorly formed, fused and cribriform glands. The spectrum of morphologies that has seen the least change has been pattern 5, which includes single cells, cords, sheets and solid nests of

carcinoma, as well as the finding of comedonecrosis within large solid nests and/or large cribriform structures.

In parallel with ongoing developments in PCa grading, there has been increased recognition of the phenomenon known as intraductal carcinoma (IDC-P). IDC-P is thought by many authors to represent a manifestation of otherwise high-grade PCa involving large ducts and acini. Occasional cases showing: a) IDC-P only at radical prostatectomy, b) IDC-P in the context of microscopic foci of acinar type carcinoma or c) foci of IDC-P which seem to transition from high grade prostatic intraepithelial neoplasia (HGPIN), have also been noted (5–13). Accurate identification/recognition and reporting of IDC-P has been discussed (4, 6–8, 14), with the most well-accepted and reproducible architectural findings being lumen-spanning neoplastic proliferations arranged in dense cribriform to solid patterns. In cases with borderline (loose cribriform/micropapillary) architecture between IDC-P from HGPIN, atypical/pleomorphic nuclei and comedonecrosis are considered the most definitive findings favoring IDC-P (4, 7, 15). Although the association of comedonecrosis and IDC-P is well-known, no study has specifically attempted to identify the incidence with which comedonecrosis represents a finding of IDC-P. Given that comedonecrosis has classically been assigned pattern 5 and current ISUP recommendations (4) advise not grading IDC-P, we aimed to better understand the morphologic backdrop in which comedonecrosis is identified. Specifically, due to overlapping histologic features between PCa with comedonecrosis and some IDC-P, we postulated that comedonecrosis is more commonly seen in intraductal than in invasive disease and investigated the associations between comedonecrosis and IDC-P v. invasive PCa in a large series of mapped radical prostatectomy specimens.

MATERIALS AND METHODS

We evaluated 933 digital tumor maps, created from entirely submitted and whole-mounted radical prostatectomy specimens from a three-year period at a tertiary cancer care center. In each tumor map, areas of pattern 3 tumor and patterns 4/5 tumor were differentially annotated. Of the 933 cases, 135 displaying large high-grade tumors with a predominance of patterns 4/5 were selected, of which 125 had all available slides for review. These 125 cases were examined for the presence of unequivocal comedonecrosis. Comedonecrosis was defined as intraluminal necrotic cells and/or karyorrhexis within cancer displaying cribriform or solid architecture (3). Careful examination was undertaken to exclude foci with dense pink secretions, foamy macrophages and/or crush/cautery artifact. All foci initially identified as comedonecrosis were further reviewed by a group of 6 urologic pathologists for diagnostic confirmation and further study. Immunohistochemistry [IHC] was performed on each lesional area with comedonecrosis-containing foci with antibodies to basal cell markers: high molecular weight cytokeratin (HMWCK) (mAb 34βE12; Roche) and p63 (mAb 4A4; Roche) using standard techniques on an automated platform. IHC stains were evaluated for the presence of basal cells in the consensus foci.

RESULTS

The results are summarized in Table 1. Of the 125 cases with high-volume high-grade (predominance of Gleason patterns 4/5) cancers, 19 (15%) displayed one or more consensus foci of comedonecrosis. Nine of these cases contained one focus of comedonecrosis, 5 contained 2 foci and 5 contained more than 2 foci [Figure 1]; two cases from the latter group displayed numerous foci of comedonecrosis in the context of massive tumors. In total, 73 consensus foci of comedonecrosis were evaluated in this study. Aside from foci of comedonecrosis, Gleason score (GS)/Grade group (GrdGrp) for the 19 tumors were: GS 4+3=7/GrdGrp 3: eight cases (three with a minor/tertiary pattern 5), GS 4+4=8/GrdGrp 4: four cases (two with a minor/tertiary pattern 5), GS 9-10/GrdGrp 5: seven cases. In five cases initially identified, some/all foci were deemed by consensus to not represent true comedonecrosis and these foci were excluded from the final analysis.

On H&E sections, 17 of 19 cases displayed at least some foci of comedonecrosis with a clearly identifiable basal cell layer [Figure 2]. Eleven of these 17 cases showed a basal cell layer in the focus/all foci of comedonecrosis, while 6 cases showed a mix, with some foci containing a clearly identifiable basal cell layer and others showing a flattened/crushed layer of hyperchromatic cells at the periphery of the comedonecrosis focus [Figure 3]. In the remaining 2 of 19 cases, only a flattened/crushed layer of hyperchromatic cells was seen at the periphery of the comedonecrosis focus/foci in which differentiating a basal cell layer from tumor cells with artifact was challenging.

IHC staining of cases with comedonecrosis revealed that twelve of 19 (63%) showed exclusively IDC-P, with both HMWCK and p63 labeling basal cells in all comedonecrosis foci. Six (32%) cases showed a mixture of comedonecrosis foci in both intraductal and invasive carcinoma [Figure 4A-B], ranging from 1 to 7 foci of IDC-P and 1 to 5 foci of invasive carcinoma-associated comedonecrosis. In these 6 'mixed' cases, 3 each showed more intraductal than invasive foci or the opposite. In 3 of these 'mixed' cases, some comedonecrosis foci were seen in conjunction with perineural invasion [n=2] or seminal vesicle invasion [n=1], clearly invasive phenomena. Finally, 1 (5%) case showed comedonecrosis exclusively in invasive carcinoma, with an absence of both HMWCK and p63 labeling in the focus; deeper levels from a recut section revealed that the comedonecrosis was present in an area of extraprostatic extension, further supporting its lack of IDC-P association.

Among the 17 cases with identifiable basal cells on H&E in at least some comedonecrosis foci, IHC basal cell marker labeling perfectly paralleled the H&E finding of basal cells; among 8 cases showing at least some comedonecrosis foci with a peripheral flattened/crushed layer of hyperchromatic cells, 5 cases lacked basal cells in the focus/foci by IHC and represented invasive carcinoma, while 3 showed at least one focus with IHC basal cell marker labeling, representing IDC-P.

DISCUSSION

A finding of comedonecrosis in the context of PCa has been near-universally associated with high-grade disease (3, 8, 16). Yet, this morphology is uncommonly seen, even in radical prostatectomy series with IDC-P (16) and consecutive needle biopsy series with pattern 5 disease (17–18). In the current study, a selected series, in which there was an active attempt to identify high grade and volume tumors from mapped radical prostatectomy specimens with PCa, comedonecrosis was likewise detected in only 15%. This was after careful examination to exclude morphologic mimics. Employing IHC, we demonstrate that comedonecrosis foci are strongly associated with IDC-P, with 63% (12/19) of cases with identifiable comedonecrosis foci being classified as exclusively IDC-P-associated comedonecrosis and 95% (18/19) of cases showing at least one focus of IDC-P-associated comedonecrosis.

In the past decade, much attention has been focused on the recognition of and diagnostic criteria for IDC-P. Increased recognition may have initially been due to “reflex” performance of IHC stains, such that tumors with complex dense cribriform/solid architecture with or without nuclear pleomorphism/atypia and/or comedonecrosis diagnosed as patterns 4/5 carcinoma in the past, were now identified as IDC-P. In recent literature, comedonecrosis is commonly cited among proposed criteria separating HGPIN from IDC-P (6–7, 11) with the latter typically associated with high-grade high-volume, poor outcome disease. Interestingly, if one examines images published in the 2000 Armed Forces Institute of Pathology fascicle (19) and 2004 World Health Organization Blue Book (20) under the heading “comedonecrosis”, one will find H&E images of carcinoma highly suggestive of containing basal cells. IDC-P with classic features has become well enough recognized that it was recently included as a distinct entity within the 2016 WHO classification of genitourinary tumors. While one might argue that IDC-P is more precisely described as a growth pattern, since both acinar and ductal tumors (21) may exhibit intraductal growth, its frequently reported associations with adverse clinicopathologic outcomes warranted its distinction as a clinicopathologic entity (22).

With increased recognition of IDC-P and its known association with some foci of comedonecrosis, whether to grade comedonecrosis foci has emerged as an area of interest (23). This is in light of recent ISUP grading recommendations, which state a majority consensus opinion that IDC-P is not to be graded (4). It is interesting to note that nearly two decades ago, Wilcox et al suggested that comedonecrosis foci with basal cells, i.e. IDC-P, still be classified as pattern 5 due to typical associations with high grade tumor features (16). However, that study included only 12 cases with IDC-P showing comedonecrosis each of which also contained other IDC-P patterns, including cribriform and solid. Importantly, clinicopathologic findings did not significantly differ between cases of IDC-P with solid and comedonecrosis patterns. Hence, in retrospect, it is difficult to draw definitive conclusions from that study regarding the independent significance of IDC-P with comedonecrosis. Similarly, while Gleason developed his grading system in an era before basal cell IHC stains were routinely employed and therefore, it is likely that all cases of comedonecrosis (invasive or IDC-P) were considered pattern 5, the incidence of comedonecrosis is never provided (1–

2, 24–25). Given the likelihood that any comedonecrosis was associated with aggressive invasive tumors, it is again challenging to know its independent significance.

In the contemporary setting, grading a focus of comedonecrosis as pattern 5 on needle biopsy may significantly alter the grading of cores in which GS 3+4 or 4+3 / GrdGrp 2-3 would otherwise be assigned (3–4). As our present findings were not exclusively observed in a backdrop of the highest grade PCa – over 40% (8/19) of cases with consensus comedonecrosis foci had GS 4+3=7/GrdGrp 3 disease – which is relevant to the needle biopsy scenario above, our results suggest that true comedonecrosis should not be assigned a pattern 5 without IHC work-up, especially in scenarios in which it would change the Grade group (23). We believe that these findings may well have clinical utility in needle biopsy specimens, as a recent survey of 23 experienced European urologic pathologists found that only 17% would perform IHC when detecting comedonecrosis and that 52% would not perform IHC even if H&E basal cell were visualized in a comedonecrosis focus (23). Performing basal cell marker IHC in this setting may be especially relevant, as molecular IHC markers, such as positive ERG labeling and loss of PTEN labeling, which may have utility in the differential diagnosis of HGPIN versus IDC-P (26–28), are less likely to be helpful in dividing invasive from intraductal carcinoma with comedonecrosis.

If a comedonecrosis focus is found to be intraductal in nature, it should be reported along with the GS/GrdGrp due to its clinicopathologic associations, commensurate with ISUP recommendations (4). Importantly, while there have been suggestions that GrdGrp 2-3 with IDC-P show a higher percentage of adverse outcomes (29–31), there is no current evidence that this effect is akin to assigning a pattern 5 to comedonecrosis foci.

More recently, authors have highlighted the notion that cancer foci with cribriform and/or intraductal carcinoma may represent “bad actors” that have associations with more adverse pathologic and clinical outcomes when compared with other pattern 4 architectures (32–36). One might argue therefore, that the current findings are less significant, if in fact invasive and intraductal cribriform proliferations may be grouped together. Nonetheless, as evidenced by a substantial portion of prostatectomy cases in our series, comedonecrosis is not only seen in the setting of the highest grade PCa. Again, this is most relevant in needle biopsy specimens, where under current recommendations, in the case of three patterns, the first and highest are summed (4, 22). As such, GS 4+3=7/GrdGrp 3 would be scored as GS 4+5=9/GrdGrp 5 if a focus of comedonecrosis was called invasive, rather than IDC-P, which may lead to significantly different management strategies depending on the center. The emerging findings regarding cribriform morphology and specifically its relationship to/ interchangeability with IDC-P await further study.

Fortunately, our findings reveal that the intraductal nature of comedonecrosis-bearing carcinoma may be readily evident on H&E, with the finding of clearly identifiable basal cells in histologic sections showing perfect correlation with IHC basal cell marker staining. On a practical level, when one encounters a focus of true comedonecrosis, a careful evaluation of the duct/acinar periphery to detect basal cells will often point to an IDC-P diagnosis. However, in cases in which comedonecrosis foci show crushed blue cells at the periphery, this determination may be challenging. The phenomenon of crushed blue cells,

which has been previously described and felt to represent necrotic compression of tumor cells due to expansile tumor growth (37–38), has less specificity in the differential diagnosis of invasive-v. IDC-P-associated comedonecrosis. Indeed, in three of 8 cases in this study with at least some foci displaying crushed blue cells, as opposed to clearly identifiable basal cells on H&E, IDC-P comedonecrosis foci were diagnosed after IHC basal cell labeling. In the occasional case with comedonecrosis surrounded by crushed blue cells alone, our findings suggest that IHC is mandatory to determine the invasive v. intraductal nature of the focus.

In conclusion, in a cohort of radical prostatectomy cases selected for large high grade tumors, comedonecrosis remains an infrequent event. In nearly two-thirds of cases with comedonecrosis foci detected on H&E, all comedonecrosis foci identified exclusively intraductal in nature. Intraductal carcinoma-associated comedonecrosis was present in 95% of cases, including all but one case also associated with invasive comedonecrosis foci. Due to its strong association with intraductal carcinoma, routine grading of comedonecrosis as pattern 5 should be reconsidered.

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Figure 1.
Carcinoma with multiple foci of comedonecrosis in expanded cribriform glands.

Figure 2.
Enlarged duct with central comedonecrosis and calcification showing a patchy, yet clearly evident basal cell layer.

Figure 3. Multiple ducts with comedonecrosis showing a crushed layer of hyperchromatic cells at the periphery, in which differentiating basal cells from flattened tumor cells is challenging on H&E staining.

Figure 4.

Case containing multiple ducts with comedonecrosis on H&E section (A); IHC stain for basal cells (high molecular weight cytokeratin; 34βE12) reveals invasive pattern 5 carcinoma with comedonecrosis on the right and IDC-P with comedonecrosis on the left (B).

Table 1

Pathologic and Immunohistochemical Features of 19 Cases with Consensus Foci of Comedonecrosis

Case #	Grade Group	Number of Comedonecrosis Foci	Basal Cells / Crushed Blue Cells in Comedonecrosis Foci	After IHC: Comedonecrosis Foci Represent IDC-P / Invasive
1	3	1	Basal cells	IDC-P
2	5	2	Basal cells	IDC-P
3	3	2	Basal cells	IDC-P
4	5	1	Basal cells	IDC-P
5	3	1	Basal cells	IDC-P
6	5	>2	Both	Both (IDC-P: 7; Invasive: 2)
7	5	1	Basal cells	IDC-P
8	3	1	Basal cells	IDC-P
9	4	>2	Both	Both (IDC-P: 2; Invasive: 1)
10	3T5 [*]	1	Basal cells	IDC-P
11	4	1	Basal cells	IDC-P
12	3T5 [*]	2	Basal cells	IDC-P
13	5	>2	Both	Both (IDC-P: 1; Invasive: 3)
14	4T5 [*]	2	Both	Both (IDC-P: 1; Invasive: 1)
15	5	1	Crushed blue cells	Invasive
16	3	1	Basal cells	IDC-P
17	3T5 [*]	2	Both	IDC-P
18	4T5 [*]	>2	Both	Both (IDC-P: >10; Invasive: >10)
19	5	>2	Crushed blue cells	Both (IDC-P: 1; Invasive: 4)

IHC: immunohistochemistry; IDC-P: intraductal carcinoma

^{*} indicates a tertiary (minor) component of pattern 5 was also present