Adenocarcinoma of the prostatic duct: Association of clinical and pathological features with its biological behaviour

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Abstract

The vast majority of prostatic carcinomas are acinar adenocarcinomas. Unusual histological types account for the remaining 5 - 10% of cancers primarily arisen from the prostate gland. Among the unusual histological variants, ductal carcinoma is the most common histological variant. It arises either from the large primary periurethral ducts or the smaller secondary ducts within the peripheral zone. It shares common architectural patterns with the common acinar adenocarcinoma and similarly to it produces PSA. The general consensus about prostatic duct adenocarcinomas is that they have a rather aggressive biological behaviour however due to its relative rarity no definitive information exists. This paper describes the clinicopathological features of ductal adenocarcinoma and discusses its biological behaviour.

Key words
prostate cancer; ductal carcinoma; biological behavior

Introduction

The vast majority of prostatic carcinomas are acinar adenocarcinomas. Unusual histological types account for the remaining 5 -10% of cancers primarily arisen from the prostate gland. Among the unusual histological variants, ductal adenocarcinoma is the most common histological variant since its prevalence -in its pure form- is estimated that accounts for 0.2% to 0.8% (or more) of all prostatic adenocarcinomas. It has both embryological interest and therapeutic importance.

The origin of this subtype of prostatic adenocarcinoma has provoked discussion ever since its first description in 1967. It was initially named “endometrioid” adenocarcinoma of the prostate since it was originally found to be originated from the uterus masculinus on the verumontanum region which develops in the embryo from the lower part of the müllerian duct. Although it was mainly diagnosed during the histologic examination of prostatic adenomas since it shares several histological characteristics with the adenocarcinoma of the uterus it was considered of müllerian origin. For this reason it was thought that it not responds to androgen ablation. It was not until the middle 90es when was finally recognized that this tumour is a variant of primary duct prostatic carcinoma and so it is concluded that the term endometrioid carcinoma is of descriptive value only. Following the introduction of PSA in the clinical practice and the subsequent increase of prostatic needle biopsies, a rising number of ductal carcinomas from the smaller secondary ducts within the
peripheral zone were reported. Currently it is clear that these tumors demonstrate immunohistochemical features consistent with an origin from prostatic tissue and they share common architectural patterns with the acinar adenocarcinoma. Despite progress in the understanding of the origin of the adenocarcinomas of the prostatic duct their biological behaviour still remains enigmatic. This paper describes the pathological features and discusses their clinical relevance in an attempt to improve our understanding of the biological behaviour of prostatic ductal cancer.

Materials and Methods
A database and a manual search were conducted in the MEDLINE database of the National Library of Medicine, Pubmed, Cochrane Library and other libraries using the key words “prostate”, “carcinomas”, “acinar”, “ductal” “endometrioid”, “prostate cancer” “adenocarcinoma” in various combinations. Bibliographic information in the selected publications was checked for relevant publications not included in the initial search.

Results
We identified 65 studies published from 1978 onwards by using the initial search terms “endometrioid adenocarcinoma of the prostate” and 184 studies published from 1976 onwards by using the initial search terms “ductal adenocarcinoma of the prostate”.

According to the specific literature, ductal adenocarcinoma is composed of tall columnar cells with abundant cytoplasm, which form a single or pseudostratified layer, reminiscent of endometrial carcinoma. The cytoplasm of these cells is often amphophilic and might occasionally appear clear. In most cases, they exhibit a marked cytologic atypia and a high mitotic count consistent with their growth rate. In other cases, nuclear pseudostratification is displayed in absence of cytological atypia. In most of the cases the surrounding stroma appears altered or fibrotic. Ductal adenocarcinoma is found in four district architectural patterns: Cribriform, papillary, solid and invasive glandular. As mentioned in the introduction section, ductal adenocarcinoma develops on both the periurethral region and peripheral zone of the prostate and therefore occurs with two patterns of disease. Centrally occurring cancers appear as exophytic polypoid or papillary masses protruding into the urethra around the verumontanum. This pattern consists of tumors of primary ducts, arising from large, central periurethral prostatic duct spaces that are lined with a distinct basement membrane. Typically, these tumors exhibit papillary fronds supported by branching fibrous connective tissue cores that are usually lined with a single layer of tall, columnar epithelial cells. When deeply invasive, they usually grow as a single gland. Peripherally occurring cancers typically show a white-grey firm appearance similar to acinar adenocarcinoma. They consist of tumors arising from more peripheral or secondary periurethral ducts that show a histologic similarity to the invasive portion of the central prostatic duct carcinomas. Adenocarcinomas of secondary prostatic ducts denote multicentric involvement and are characterized by areas in which growth is contained within intermediate and small ducts. Small papillary projections are common and many of the lumina are filled with eosinophilic debris. Notably, involvement of the secondary ducts is mostly characterized by an extensive invasion of the prostatic gland.

Ductal adenocarcinomas can be found alone or in association with the typical acinar carcinoma. Coexisting ductal and acinar adenocarcinomas are much more common than pure ductal adenocarcinomas, but the actual incidence is not well established. Rotterdam and Melicow reported a high rate for adenocarcinomas of the prostatic duct that contain additional components of acinar adenocarcinoma of the prostate. Millar et al. however, reported that only half of the prostatic duct cases in their clinicopathological study contained mixed ductal - acinar carcinomas. Dube et al. reported that real dual primary lesions are relatively rare and account for only close to 5% of all cases of ductal prostatic carcinoma. Other researchers report an incidence of mixed ductal - acinar adenocarcinoma as high as 4.8%.

The immunophenotype of prostatic ductual adenocarcinoma is similar to that of acinar adenocarcinoma: Immunostains for PSA and PSAP are almost always positive while α - methylacyl CoA racemase can be also detected in DA but at a reduced level. Other researchers however reported a high percentage of ductal adenocarcinomas which overexpress α - methylacyl CoA. Tumour cells are typically negative for basal cell - specific highmolecular weight cytokeratins although in some of them a basal cell layer can be seen, which is
probably due to tumor growth into preexisting ducts.14.

Although the histologic diagnosis is generally not difficult, atypical and underrecognized features may occasionally occur and may result in diagnostic problems. The main differential diagnoses are intraductal prostate cancer, high-grade PIN, and acinar adenocarcinoma.15. Of the above, the most challenging differential consideration—in case of solitary/small focus of ductal adenocarcinoma or when the amount of carcinoma in needle biopsy tissue is minimal or limited and more importantly, in cases of ductal adenocarcinomas with flat and tufted morphology closely resembling HGPIN—is high grade PIN.16,17. In such a case the absence of immunohistochemical reaction of basal cell may facilitate the diagnosis. The differential diagnosis includes two more considerations. In TUR material from the urethra and in biopsies taken from the bladder trigone the papillary architecture can suggest urothelial carcinoma. In addition, when the tumor is solid and diffusely invading can suggest rectal adenocarcinoma invading the prostate. In both cases PSA and PAP immunostaining is usually diagnostic.

Following the two patterns of disease, clinical manifestation may include obstruction and haematuria (when the tumor is exophytic, protruding into the urethra at or near the verumontanum) or may be asymptomatic (when the tumor arises from the peripheral zone). In several cases symptoms of metastatic disease occur. Men with prostatic ductal adenocarcinoma are typically aged 63–72 years (range 41–89). Due to its relative rarity no definitive information exists regarding the biologic behaviour however the general consensus about prostatic duct adenocarcinomas is that they have a rather aggressive biological behaviour. The main differential diagnoses are intraductal prostate cancer, high-grade PIN, and acinar adenocarcinoma.15. Of the above, the most challenging differential consideration—in case of solitary/small focus of ductal adenocarcinoma or when the amount of carcinoma in needle biopsy tissue is minimal or limited and more importantly, in cases of ductal adenocarcinomas with flat and tufted morphology closely resembling HGPIN—is high grade PIN.16,17. In such a case the absence of immunohistochemical reaction of basal cell may facilitate the diagnosis. The differential diagnosis includes two more considerations. In TUR material from the urethra and in biopsies taken from the bladder trigone the papillary architecture can suggest urothelial carcinoma. In addition, when the tumor is solid and diffusely invading can suggest rectal adenocarcinoma invading the prostate. In both cases PSA and PAP immunostaining is usually diagnostic.

Discussion

Similar to the common acinar adenocarcinoma, most ductal adenocarcinomas have a serum PSA level of > 4ng/ml. A substantial minority—comparable to that of the standard acinar adenocarcinoma—can present with ‘metastatic’ levels of serum PSA. The DRE findings are also consistent with the stage of the disease and there is no difference between ductal and acinar adenocarcinoma in the immunostaining reaction for prostatic-specific antigen and prostate-specific acid phosphatase. However, several authors associated ductal origin with more aggressive natural history and worse prognosis. In fact they reported that the clinical stage is more often advanced in presentation, with poorly differentiated and distant disease and. According to other ductal adenocarcinoma has a tendency to spread to regional lymph nodes, axial skeleton, and visceral organs.8,9,11,18,19. For this reason it was a priori considered high grade in the modified Gleason grading system (as happens for aggressive tumours). Evidence from the reported case series and case reports offers controversial information. Stajno et al. reported on a 90-year-old man presented with acute urinary retention and gross hematuria that was diagnosed with ductal carcinoma after suprapubic transvesical adenectomy and remained progression free during two years months of follow-up.20. Similar behavior was reported by Dohan et al. in a four years’ follow-up of a single case of locally advanced pure ductal adenocarcinoma.21. Notably, the finding of prostatic ductal adenocarcinomas among autopsy material, as well as some favourable histological features exhibited by these tumours may also suggest a similar biological potential as prostatic acinar cancer.22. Although other researchers reported better prognosis for this pattern than that of the acinar carcinomas, it is probably similar stage for stage and grade for grade.23.

On the other hand Brinker et al. reviewed 20 cases originally diagnosed in needle biopsy and treated with radical prostatectomy and they found extraprostatic spread in 63%, positive margins in 20%, and seminal vesicle invasion in 10% of cases.6. In contrast, researchers of the same institution, in a study of 10 patients with ductal adenocarcinoma on needle biopsy who underwent radical prostatectomy, found extraprostatic spread and positive margins in only 10% of the reported cases.15. Similarly, Randolph et al., reported that > 50% of patients with ductal adenocarcinoma have metastasis at the time of diagnosis while according to Brinker et al., the median rate of metastases at presentation was less than 30%.24,6.

Recently, Meeks et al., compared clinical features and cause of death from men with ductal and acinar histological types and found that ductal adenocarcinomas are more likely to be diagnosed at advanced disease (30% T3 with ductal, compared with 7% with acinar). Moreover they showed that men with ductal carcinomas had a significantly greater rate of death from prostate cancer (12% vs 4%)25.
Generally speaking, survival and response to treatment appear to be related to stage which is more often advanced for ductal adenocarcinoma than that of microacinar adenocarcinoma.

It is not known whenever and if intrinsic characteristics of ductal histological type contribute to the above-mentioned controversial findings. Is there any difference in terms of pathologic stage at diagnosis and clinical progression between the primary and secondary duct tumours? Does the presence of acinar element play any role in the biologic behaviour of mixed acinar - ductal tumours? Is it possible that the aggressiveness of the mixed acinar - ductal tumours derives from the additional components of acinar carcinoma?

Actually, the central location of tumours from the primary ducts probably does not allow tumours’ invasion of the prostatic stromal tissue. It is notable that most transition zone tumours are noninvasive, even when they are large or have an advanced cancer grade. If invasive, they show much less capsular penetration than peripheral zone cancers of comparable possible volume; this is due to the transition zone boundary, which provides a barrier to tumor spread through the peripheral zone. In confirmation to the above, Aydin et al. reported ductal tumors presented as a small periurethral tumour with no concomitant acinar PA, which were fully eradicated by the initial biopsy/TURP alone. A larger study by Seipel et al. on radical prostatectomy specimens wasn’t able to confirm the above.

Tumours from the secondary ducts are usually mixed with standard acinar carcinoma, and they often lack a urethral component. Patients with this pattern of disease usually have advanced disease and are more likely to be diagnosed with metastatic disease at presentation. Importantly, in the study of Christensen et al. the incidence of positive margins in specimens with carcinoma of secondary ducts was reported to be higher than in acinar carcinomas. Similarly, the incidence of capsular penetration in clinical stage T3 ductal carcinomas was reported to be much higher than in acinar carcinomas of the same clinical stage. Moreover, the prognosis for patients with prostatic cancer is greatly influenced by histological grade and multifocality. These characteristics are most likely determined by the acinar tumor components, since acinar tumours are often more aggressive than the coexistent ductal carcinoma.

Recently Jardel et al. analyzed the expression of molecules involved in either hormonal signalling or androgen independent pathways, in ductal carcinomas compared to high grade acinar carcinomas and accordingly to their findings suggested that the hormone related molecular pathways that drive cancer progression might be different. Of note, a large contemporary population - based study between patients with ductal and acinar carcinomas of the prostate presented with lower prostate - specific antigen showed more favourable pathological features in the cohort of ductal carcinomas. Finally Morais et al. based on PTEN and ERG, suggested that ductal adenocarcinomas and their concurrent acinar carcinomas may be clonally related in some cases and show important molecular differences from pure acinar carcinoma. The above findings are highlighting the role of acinar carcinoma component of mixed ductal - acinar carcinomas of the prostate.

Conclusions
It is generally accepted that prostatic duct adenocarcinomas are in an advanced pathologic stage by the time they are diagnosed, and that compared to acinar cancers, they are linked with much higher short-term treatment - failure rates. However many studies have demonstrated that patient age, symptoms, findings on DRE, and levels of serum PSA, in patients with adenocarcinomas of the prostatic duct are similar to those found in patients with acinar adenocarcinomas. Furthermore, several findings suggest that these two types of carcinoma might have a similar biologic behavior that is related to histological differentiation, volume, location, multifocality and concomitant acinar carcinoma. More research is needed in order to clarify the role of acinar carcinoma component of mixed ductal - acinar carcinomas of the prostate.
Η συντριπτική πλειοψηφία των προστατικών καρκινωμάτων (90 - 95%) είναι αδενοκαρκίνωμα ενώ το υπόλοιπο ποσοστό αφορά σε διάφορους ιστολογικούς τύπους πρωτοπαθών καρκίνων από τον προστάτη αδένα. Μεταξύ αυτών των αυξηθητών ιστολογικών παραλλαγών περιλαμβάνεται και το πορογενές καρκίνωμα που μάλιστα είναι η πιο ποικιλή εκ αυτών. Η συχνότητα εκτιμάται μεταξύ του 0.2% και του 0.8% των αδενοκαρκινωμάτων του προστάτη. Η οντότητα αυτή παρουσιάζει ενδιαφέρον τόσο από εμβρυολογικής και ιστολογικής όσο και από κλινικής άποψης. Η προέλευση αυτού του υποτύπου του πρωτοπαθούς καρκίνου προκαλεί συζήτηση ήδη από την πρώτη περιγραφή της το 1967. Αρχικά είχε το όνομα «ενδομητριοειδές» αδενοκαρκίνωμα του προστάτη, δεδομένου ότι αρχικά βρέθηκε να προέρχεται από την «ανδρική μήτρα», μια περιοχή του σpermατικού λοφίδιου που αναπτύσσεται στο έμβρυο από το κατώτερο τμήμα του αγωγού του Müller. Παρά το γεγονός ότι είχε διαγνωτεί κυρίως κατά την ιστολογική εξέταση χειρουργικών παρασκευασμάτων αδενωμάτων του προστάτη, δεδομένου ότι μοιράζεται πολλά ιστολογικά χαρακτηριστικά με το αδενοκαρκίνωμα της μήτρας θεωρήθηκε Μυλεριανής προέλευσης. Για το λόγο αυτό θεωρήθηκε ότι δεν ανταποκρίνεται στη θεραπεία στέρησης των ανδρογόνων και οι ασθενείς εκείνης της εποχής ακιλούθησαν άλλες θεραπείες. Στα μέσα της δεκαετίας του 90τελικά αναγνωρίστηκε ότι αυτός ο όγκος είναι μια παραλλαγή του πρωτοπαθούς καρκίνου των προστατικών πόρων και σήμερα ο όρος καρκίνωμα ενδομητριοειδές έχει μόνο περιγραφική αξία. Μετά την εισαγωγή του PSA στην κλινική πρακτική και την επακόλουθη αύξηση των προστατικών βιοψιών βελόνας, αναφέρθηκε ένας αυξανόμενος αριθμός διαγνωσμένων καρκινωμάτων από τους μικρότερους δευτερευόντες πόρους της περιφερειακής ζώνης. Επί του παρόντος, είναι σαφές ότι οι όγκοι αυτοί αποδεικνύουν ανοσοϊστοχημικά χαρακτηριστικά σύμφωνα με την ιστική προέλευσή τους (τον προστατικό ιστό) και μοιράζονται κοινά αρχιτεκτονικά πρότυπα με το λοβώδες αδενοκαρκίνωμα. Το πορογενές αδενοκαρκίνωμα αναπτύσσεται τόσο στην περιουρηθρική περιοχή όσο και στην περιφερειακή ζώνη του προστάτη και ως εκ τούτου εκδηλώνεται με δύο μορφές: Μία κεντρική που εμφανίζονται ως εξωφυτικές ή θηλώδεις μάζες που προεξέχουν στον αυλό της ουρήθρας γύρω από το σpermατικό λοφίδιο και μια περιφερική που αναπτύσσεται όπως το συνήθες λοβώδες καρκίνωμα του προστάτη στην περιφερειακή ζώνη του αδένα. Παρά την πρόοδο στην κατανόηση της προέλευσής τους η βιολογική συμπεριφορά τους εξακολουθεί να παραμένει αινιγματική. Αυτό το άρθρο περιγράφει τα παθολογικά χαρακτηριστικά και συζητά την κλινική σημασία τους σε μία προσπάθεια να βελτιώσει η κατανόηση της βιολογικής συμπεριφοράς του πορογενούς καρκίνου του προστάτη.

Περίληψη

Λέξεις ευφημισμού

καρκίνος προστάτη,
pορογενές καρκίνωμα,
bιολογική συμπεριφορά

References