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Divergent differentiation and variant morphology in invasive urothelial carcinomas – association with muscle-invasive disease

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Abstract

Introduction: To evaluate the frequency of divergent differentiations / variant morphology in urothelial carcinoma, and their association with muscle-invasive disease at diagnosis.

Methods: All consecutive cases of invasive urothelial carcinoma from a busy pathology laboratory were reviewed. Clinical and pathological data were recorded including data on divergent and variant morphologies and their percentage within the invasive component.

Results: Among 91 cases, 46 (51%) showed some form of divergent/variant morphology. The most common divergent morphology was squamous which was present in 18/46 (39% of cases with some divergent or variant morphology) followed by micropapillary (28%), plasmacytoid (20%) and poorly differentiated (17%). Only squamous differentiation was associated with higher rate with muscularis propria invasion.

Conclusions: Although common, squamous differentiation should be still recognized as a feature of aggressive disease.

Keywords: Urologic neoplasms, Bladder Cancer, Pathology

Introduction

Invasive urothelial carcinoma commonly shows divergent differentiation and variant morphology. Current WHO classification of urothelial carcinoma requires subclassification based on presence or absence of divergent differentiation and variant morphology. Urothelial carcinoma may show divergent differentiation (such as squamous, glandular, trophoblastic) and variant morphologies include nested, micropapillary, microcystic, lymphoepithelioma-like, plasmacytoid, sarcomatoid, giant cell, lipid-rich, clear cell (glycogen-rich) and poorly differentiated. The WHO recognizes micropapillary, plasmacytoid, sarcomatoid and poorly differentiated morphologies as associated with more aggressive behavior. Due to some reports that correlate percentage of micropapillary and plasmacytoid variants with prognosis, international guidelines recommend that some or all divergent differentiation or variant morphology should be quantified (Moch et al. 2016; College of American Pathologists 2018; International Collaboration on Cancer Reporting (ICCR), n.d.).

Data from institutions with mandatory central pathology review suggest that up to 44% of all divergent/variant morphologies may be under-recognized and the most commonly overlooked variants are lymphoepithelial, plasmacytoid, nested, micropapillary and - not a variant but a concomitant tumor - small cell neuroendocrine carcinoma (Shah et al. 2013).

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The NCCN and some institutional guidelines (e.g. MD Anderson) suggest early cystectomy for T1 tumors with micropapillary, plasmacytoid and sarcomatoid morphologies (National Comprehensive Cancer Network Clinical (NCCN), n.d.; MD Anderson Cancer Center, n.d.). The European Association of Urology states that micropapillary, plasmacytoid, nested, sarcomatoid, microcystic variants; and squamous and glandular (adeno) divergent differentiations are associated with poorer prognosis (Babjuk et al. 2017).

We evaluated the frequency of divergent differentiation / variant morphology in urothelial carcinoma, and their association with muscle-invasive disease at diagnosis in a busy Pathology Laboratory in the light of the currently adopted WHO classification (2016).

Methods

All consecutive cases of invasive urothelial carcinoma from a private Laboratory of Pathology - Imagepat Laboratory (Salvador Bahia) - were included. All cases from January 2017 to October 2019 were reviewed. All cases were signed or reviewed by a senior Urologic pathologist. Clinical and pathological data were recorded including data on divergent differentiation / variant morphology and their percentage within the invasive component. Small biopsies were defined as cases resected without intention to remove the entire tumor – that did not include muscularis propria and, therefore, were not analyzed for the association with muscle-invasive disease. All cases defined as TURB had adequate sampling of muscularis propria (in the same sample or in a re-biopsy within few weeks). Qualitative variables were analyzed using Fisher's exact test. This study was approved by the Human Research Ethics Committee of the Faculty of Medicine, Federal University of Bahia (approval number: 3.709.215).

Results

A total of 91 cases of invasive urothelial carcinoma were identified. Frequency of specimens obtained by transurethral resection of the bladder (TURB) and cystectomy were 87 and 3 cases, respectively. Among TURB specimens, maximum extension of tumor was lamina propria in 29 and at least muscularis propria in 41.

Overall, 45 cases had no divergent differentiation or variant morphology while 46 showed some form of them. The most common divergent differentiation was squamous which was present in 18/46 (39% of cases with some divergent/variant morphology) ranging from 5 to 95% of tumor area. The second most common was micropapillary – seen in 13/46 (28%), range < 5–80%. Third, plasmacytoid was observed in 9/46 (20%) (range: 30–90%). These were followed by poorly differentiated 8/46 (17%) (range: 20–100%), glandular 5/46 (11%) (range: 10–50%), giant cell 3/46 (7%) (range: 30–100%), sarcomatoid 2/46 (4%) (range: 30–90%) and one case each had lipid-rich morphology (involving < 5% of the tumor), clear cells (10% involvement) and small cell component (90% involvement). Illustrative images of these cases are shown in Fig. 1. Age and extension of lamina propria invasion did not differ among different variants.

Excluding small biopsy cases, we evaluated the frequency of muscle invasive disease in TURB and cystectomy specimens. The frequency of muscularis propria invasion was 18/36 (50%) in patients with urothelial carcinoma with no divergent differentiation or variant morphology. This rate was lower than the rate seen in patients harboring urothelial carcinomas with squamous component 12/14 (86%) (Fisher's exact Test: $p = 0{,}03$). Although not significant, the rate of muscle-invasive disease was also higher for micropapillary 7/10 (70%) (Fisher's exact Test: $p = 0{,}30$), plasmacytoid 5/6 (83%) (Fisher's exact Test: $p = 0{,}19$), poorly differentiated 4/6 (67%) (Fisher's exact Test: $p = 0{,}18$) and glandular component 3/4 (75%) (Fisher's exact Test: $p = 0{,}60$).

Most common pure forms of divergent/variant morphologies were squamous (11 cases), micropapillary (9 cases), plasmacytoid (5 cases) and glandular and poorly differentiated (4 cases each).

We stratified tumors in groups of papillary and carcinoma in situ (CIS) pathways based on coexistence of such lesions in the sample. Tumors with papillary component most showed the following divergent/variant morphologies: squamous (11/27; 41%; range: 5–100%), micropapillary (8/27; 30%; range: 10–80%), plasmacytoid (6/27; 22%; range: 30–80%), glandular (3/27; 11%; range 30–50%), and poorly differentiated (4/27; 15%; range: 30–100%). Flat/infiltrative tumors associated with CIS showed the following divergent/variant morphologies: squamous (6/13; 43%; range: 5–90%), micropapillary (5/13; 39%; range: < 5 to 20%), glandular (3/13; 23%; range: 10–30%), plasmacytoid (2/13; 15%; range: 80–90%) and poorly differentiated (2/13; 15%; range: 20–90%). Differences on the frequency of divergent/variant morphologies between pathways were not significant.

Most tumors were primarily diagnosed in the specimens included in this series. Among tumors with divergent/variant morphology, only three were recurrent cases. All three had papillary component and they showed squamous (50% extent), plasmacytoid (50% extent) and poorly differentiated morphology (100%).

Follow up were available for a minority of cases. Gastric metastasis was documented in one patient 18 months after the diagnosis of UC with 90% plasmacytoid morphology at TURB specimen. Data of three cystectomy were available: pT0 bladder pT2 prostatic urethra pN0 after a diagnosis of UC with 10% micropapillary

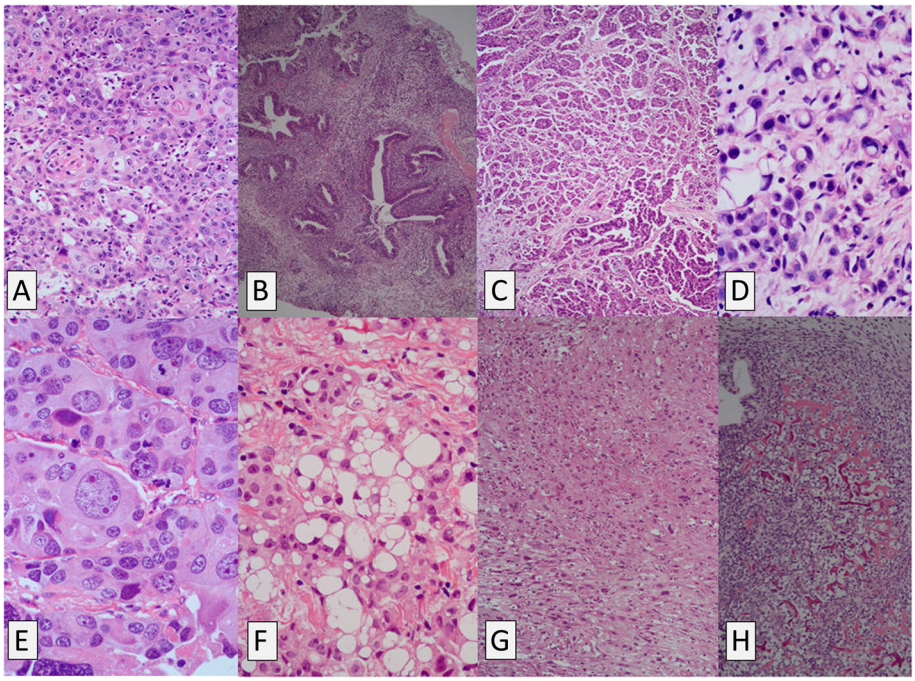

Fig. 1 Divergent differentiation in urothelial carcinoma of cases from the present series. **a** Squamous (HE, 100x); **b** Glandular (HE; 40x); **c** Micropapillary (HE; 40x); **d** Plasmacytoid (HE, 400x); **e** Poorly differentiated (HE, 400x); **f** Lipid-rich (HE, 100x); **g** Sarcomatoid (HE, 40x) and **h**) Sarcomatoid with heterologous osteosarcoma component (HE, 40x)

morphology; pT2 pN0 after diagnosis of UC with 20% squamous morphology; and pT3b pN1a after a diagnosis of UC with 10% micropapillary morphology.

In one case poorly differentiated variant and in one case a small cell component were diagnosed only in consultation after a primary diagnosis of ordinary urothelial carcinoma.

Discussion

The 2016 WHO blue book updated the classification of invasive urothelial carcinoma and discerned tumors with divergent differentiation and variant morphology. Urothelial carcinoma has a broad morphologic plasticity. Some variant morphologies are rare, and the small number of cases restricts the evaluation of the clinical impact of some variants. Squamous and glandular are the commonest divergent differentiations. The 2016 WHO blue books identified the patters of micropapillary, plasmacytoid, sarcomatoid and poorly differentiated as more aggressive variants – and the percentage of each variants should be reported (Moch et al. 2016; College of American Pathologists 2018). The American Joint Committee on Cancer (AJCC) current staging manual states that the prognostic impact of urothelial carcinoma subtypes is a matter of active research, however, it recognizes (AJCC Level of Evidence II) that small cell carcinoma, plasmacytoid and sarcomatoid morphologies are associated with reduced survival (Bochner et al., n.d.). Recognizing divergent/variant morphologies with different clinical behavior is of relevance since, by default, almost all invasive urothelial carcinomas area labelled as high grade (Amin et al. 2015). The International Collaboration on Cancer Reporting (ICCR) dataset for cancer reports recommends that all divergent/variant morphologies in urothelial carcinoma should be described and quantified as percentage of total tumor volume (International Collaboration on Cancer Reporting (ICCR), n.d.).

Micropapillary and plasmacytoid variants are important because of the potential implications in prognosis, even in superficially invasive (pT1) tumors (Gaya eta l. 2010; Ghoneim et al. 2011; Kaimakliotis et al. 2014; Spaliviero et al. 2014). In addition, there are reports suggesting that these variants are commonly missed in daily practice – suggesting an impact on care associated with the implementation of central pathology review. Overall, 20% of invasive urothelial carcinomas show divergent/variant morphology and 44% of these were not primarily recognized (Shah et al. 2013).

Micropapillary variant may be difficult to recognize because it shares with ordinary invasive carcinomas the appearance of lacunar spaces with epithelial growth within it, which is attributed to retraction artifact in the latter. True micropapillae are delicate filiform process without true fibrovascular core tightly clustered within lacunar spaces. Features suggested to be distinctive of micropapillary variant are multiple epithelial nests

within a single lacunaor epithelial ring formation (Amin et al. 2015).

Micropapillary morphology has been associated with poor prognosis and the percentage of micropapillary morphology in transurethral resections was reported to predict higher stage (Gaya et al. 2010; Samaratunga and Khoo 2004) and cancer specific death (Samaratunga and Khoo 2004; Comperat et al. 2010). Those findings are the main reason to report the presence and the percentage of micropapillary morphology in pathology reports. The association with poorer outcome led some authors to suggest early cystectomy even in pT1 tumors (Kamat et al. 2006). Since some cases treated with early cystectomy still show advanced stage and nodal metastasis, consideration of neoadjuvant chemotherapy has been suggested (Ghoneim et al. 2011), while a recent study suggested benefit of prior chemotherapy only in muscle invasive disease (Fernández et al. 2017). A recent meta-analysis suggests that although associated with more advanced disease at diagnosis, micropapillary urothelial carcinoma is not associated with poorer outcomes after surgical treatment (Abufaraj et al., 2019).

Plasmacytoid variant is the current term of choice for obsolete terminology of signet ring or diffuse variants of urothelial carcinoma (Moch et al. 2016). It is usually associated with advanced stage at diagnosis and poor survival (Fox et al. 2017). In a trial of muscle-invasive urothelial carcinoma, treated by radical cystectomy and adjuvant cisplatin-based chemotherapy, it was shown that plasmacytoid morphology was an independent predictor of poor survival when compared to ordinary urothelial carcinoma and micropapillary variant (Keck et al. 2013). On the other hand, a recent series did not show the impact of plasmacytoid morphology on outcome (Li et al. 2017). A distinctive clinical feature is the high rate of recurrence with peritoneal spread (Dayyani et al. 2013; Ricardo-Gonzalez et al. 2012). A potential pitfall in cystoscopy is that the tumor may invade muscularis propria without grossly identifiable mucosal tumor (Fritsche et al. 2008). Mirroring the discussion on early cystectomy for the micropapillary variant, some authors also suggest aggressive therapy in pT1 disease with plasmacytoid morphology (Kaimakliotis et al. 2014).

Both micropapillary and plasmacytoid variants commonly show HER2 oncogene alterations including amplification and mutation and, therefore, may be prone to target therapy in the future (Ching et al. 2011; Ross et al. 2014; Schneider et al. 2014; Kim et al. 2016).

The direct role of divergent/variant morphology on treatment decision is controversial. Some authors propose a treatment algorithm with early cystectomy in non-muscle invasive bladder cancer (T1) with micropapillary, plasmacytoid and sarcomatoid morphologies (Willis and Kamat 2015). Although an early surgical treatment is not explicitly recommended in the MD Anderson practice algorithm, patients with micropapillary and sarcomatoid variants may be followed as T2 tumors. Early cystectomy should be considered in variant morphologies demonstrating concurrent carcinoma in situ (MD Anderson Cancer Center, n.d.). The National Comprehensive Cancer Network (NCCN) guideline for bladder cancer states that non-muscle invasive bladder cancer with micropapillary, plasmacytoid and sarcomatoid morphologies are at higher risk of progression and more aggressive approach should be considered (National Comprehensive Cancer Network Clinical (NCCN), n.d.). The American Urological Association (AUA)/ Society of Urologic Oncology (SUO) Guideline mentions that an experienced genitourinary pathologist should review the pathology of a patient with any doubt in regards to variant or suspected variant histology (e.g., micropapillary, nested, plasmacytoid, neuroendocrine, sarcomatoid), extensive squamous or glandular differentiation, or the presence/absence of angiolymphatic invasion. (Moderate Recommendation; Evidence Strength: Grade C). Presence of variant histology requires restaging transurethral resection within 4–6 weeks when a bladder sparing approach is considered, or consideration of early cystectomy due to high risk of upstaging (Expert Opinion) (Chang et al. 2016). The European Association of Urology (EAU) guidelines on Non-muscle-invasive Bladder Cancer mentions micropapillary, nested, plasmacytoid, sarcomatoid, microcystic, squamous and adeno divergent/variant morphologies as associated with poor prognosis (Babjuk et al. 2017). For muscle-invasive disease, the EAU acknowledges that neoadjuvant chemotherapy may be beneficial for patients with micropapillary, plasmacytoid, sarcomatoid, and mixed variants, and especially for patients with neuroendocrine tumours (Veskimäe et al. 2019).

In our experience, only squamous morphology was associated with a higher rate of advanced (muscle-invasive) disease. Squamous morphology is the most common divergent differentiation observed in urothelial carcinoma and occurs in 20–40% of all cases (Lopez-Beltran et al. 2019). Several reports have associated squamous differentiation with more advanced stage disease at presentation (Krasnow et al. 2017; Gofrit et al. 2016; Liu et al. 2017). However, it is controversial if such morphology is an independent predictor of poor prognosis (Moch et al. 2016).

Awareness of proper variant histology classification will probably gain additional importance since recent data suggest that squamous and lymphoepithelioma -like morphologies may predict pathological response of neoadjuvant *anti*-PD-1 immunotherapy (Necchi et al. 2020).

In our study, the frequency of divergent/variant morphologies did not differ between tumors from the

papillary or CIS (flat/infiltrative) pathways. Few cases were diagnosed as recurrent disease precluding analysis of the relationship between primary vs recurrent diagnosis (length of disease) with frequency of divergent/variant morphology. A major limitation of this study was the lack of clinical follow-up.

Conclusion

Divergent/variant morphologies in invasive urothelial carcinomas is common in routine practice of a busy Pathology Laboratory. They have clinical implications and should be cautiously searched. Central pathology review should be considered in large institutions dedicated to treat urothelial carcinomas. In our almost three-year experience after new WHO classification of urologic tumors, only squamous differentiation is associated with higher rate of muscle invasive disease. Although common, squamous differentiation should be still recognized as a feature of aggressive disease.

Abbreviations

AJCC: American Joint Committee on Cancer; AUA: American Urological Association; CAP: College of American Pathologists; EAU: European Association of Urology; ICCR: International Collaboration on Cancer Reporting; NCCN: National Comprehensive Cancer Network; TURB: Transurethral resection of the bladder; WHO: World Health Organization

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Adherence to national and international regulations

Not applicable.

Authors' contributions

DAA conceived the idea. DAA was the major contributor to the writing of the manuscript. MFS, MEPA, DAA diagnosed all cases. MFS, MEPA, SCC were major contributors for critically revising the manuscript for important intellectual content. All authors read and approved the final manuscript.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Ethics approval and consent to participate

This study was approved by the Human Research Ethics Committee of the Faculty of Medicine, Federal University of Bahia (approval number: 3.709.215).

Consent for publication

The authors declare that they have no competing interests.

Competing interests

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