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A case of bladder enteric-type adenocarcinoma in cytology

Bladder enteric-type adenocarcinoma is a rare primary malignancy of the urinary bladder, that is predominantly observed in males and accounts for up to 2% of all bladder cancers[1]. It is characterized by histological and molecular features that closely mimic those of colorectal adenocarcinoma. These include its enteric-type glandular architecture and the frequent expression of intestinal markers such as CDX2 and CK20, as well as the variable CK7 expression[2]. Intestinal metaplasia and villous adenoma are considered potential precursor lesions, especially when dysplasia is present, that warrant close clinical follow-up due to the risk of progression to carcinoma. However, most cases of intestinal metaplasia without dysplasia do not progress to malignancy[3]. Cytologic diagnosis for bladder enteric-type adenocarcinoma is challenging due to its overlapping features with secondary adenocarcinoma and urothelial carcinoma. In urine cytology, malignant glandular cells may be present, but the cytomorphology is not always highly distinctive. Features may include, but not systematically, columnar cells, mucin production, background of abundant necrosis and sometimes signet ring cells. The diagnostic yield of urine cytology for primary bladder adenocarcinoma is therefore limited, with a significant proportion of cases yielding false negatives or non-specific atypia[4]. In the Paris System for Reporting Urinary Cytology (2022 Paris System), primary bladder adenocarcinoma is classified under the heading "Other Malignancy" (OM). This category is reserved for malignant tumors in the urinary tract that are not of urothelial origin, including adenocarcinoma, squamous cell carcinoma, and small cell carcinoma[5]. We would like to report a clinical case of Bladder enteric-type adenocarcinoma with its cytological work-up and follow-up after transurethral resection of bladder.

Case presentation

A 59-year-old patient with a history of post-void dribbling was referred to the urology clinic by his general practitioner following an episode of acute urinary retention requiring the insertion of an indwelling urinary catheter. The patient's medical history is notable for active cigarette and cannabis smoking as well as aviremic HIV infection. The results of the cystoscopic examination revealed the presence of a trabeculated bladder and numerous diverticula. One of the diverticula contained a centimeter-sized lesion that proved difficult to characterize endoscopically. Cytological examination obtained via intradiverticular lavage showed a low epithelial cell count with a high bacterial load (**figure 1, panel A**). High-magnification analysis revealed a contingent of non-atypical superficial urothelial cells (umbrella cells) distributed

primarily in clusters (**figure 1, panel B**). Rare clusters of atypical epithelial cells were also found, characterized by a vague glandular architecture, enlarged nuclei but a nucleocytoplasmic ratio that fell below the threshold of 0.7, non-hyperchromatic nuclei with irregular nuclear contours and conspicuous to prominent nucleoli (**figure 1, panel C D**). No abundant background necrosis nor mucin deposit was observed. The final cytological diagnosis was "atypical urothelial cells," as defined by the 2022 Paris System. Endoscopic resection of the bladder was warranted due to the high index of suspicion for malignancy and the identification of atypical cells on cytological examination.

Intra-operative endoscopic evaluation revealed an intradiverticular papillary lesion associated with peripheral flat velvety patches, highly suggestive, of a high-grade papillary urothelial carcinoma with foci of urothelial carcinoma in situ. Histological evaluation of fragmented bladder resection material (**figure 2, panel A**) showed the extensive intestinal metaplasia of the urothelial mucosa associated with areas of intestinal type high-grade dysplasia (**figure 2, panel B**). Finally, a pure glandular malignant carcinoma resembling colonic adenocarcinoma with a pseudostratified columnar epithelium and central dirty necrosis was observed (**figure 2, panel C**). Immunochemistry ancillary techniques showed no GATA-3 expression, along with diffuse and strong expression of CK20, and partial expression of CK7 (**figure 3, panels A-C)**. Final histological diagnosis was "well-differentiated infiltrating adenocarcinoma with enteric immunophenotype, having developed from adenoma on intestinal metaplasia." A few weeks later, the diagnosis was confirmed on a radical cystoprostatectomy and revealed a single locally advanced tumor with macroscopic infiltration of the perivesical adipose tissue (AJCC 8th edition: pT3b).

Discussion

This case illustrates the complexity of the diagnostic approach to primary bladder adenocarcinoma in cytology. Compared to conventional high grade urothelial carcinoma, the cytomorphology of primary bladder adenocarcinoma is not as easily characterized as shown by a study from the late 1990s where they found that cytologic examination failed to lead to a diagnosis of malignancy in up to 18% of cases[4]. The primary objective of the 2022 Paris System is to distinguish high-grade urothelial carcinoma, with a false-negative rate of less than 5%[6,7]. The OM category is used when cytomorphologic features are sufficiently diagnostic for a non-urothelial malignancy[5]. In addition to incorporating the patient's clinical history when handling cytological material, the use of ancillary techniques such as direct immunohistochemistry on smear could be considered in certain selected cases. This approach can be used to support or clarify cytological findings, especially in cases with equivocal cytology in absence of typical morphology[8], such as the present case. Early detection of this type of tumor is essential in order to provide appropriate medical care. In conclusion, although rare, primary adenocarcinoma of the bladder should be systematically considered and investigated by the cytopathologist in the clinical context of high-grade bladder tumor that does not meet the cytological criteria for high-grade urothelial carcinoma according to the 2022 Paris System. Future studies will need to be conducted in order to further clarify and refine the minimal diagnostic criteria of this rare primary malignancy of the urinary bladder in order to improve diagnostic accuracy and reduce misclassification.

Figure legend

Figure 1. Pre-operative bladder intradiverticular washing cytology specimen. Panel A: low magnification showing low epithelial cell count intermingled with a background rich in bacterial elements. Panel B: rare population of non-atypical superficial urothelial cells. Panel C: scattered epithelial clusters showing non-high grade urothelial carcinoma type atypia.

Figure 2. Bladder endoscopic resection specimen. Panel A: fragmented bladder diverticular mucosa and submucosa material. Panel B: intestinal metaplasia extensively colonizing the bladder mucosa associated with high grade dysplasia. Panel C: area of transformation into invasive enteric type adenocarcinoma infiltrating the submucosa can be observed in several fragments.

Figure 3. Immunochemistry ancillary techniques. Panel A-C: absence of GATA-3 urothelial related specific transcription factor expression by the malignant component (A). CK20 (B) and CK7 (C) expression pattern suggests a primary adenocarcinoma of the bladder with enteric immunophenotype.

References

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Figure 1

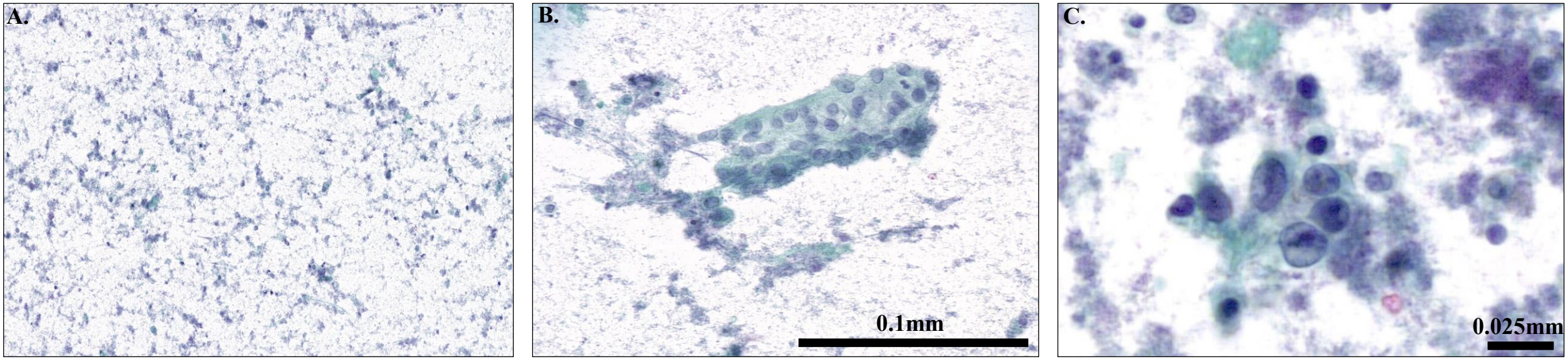

Figure 2

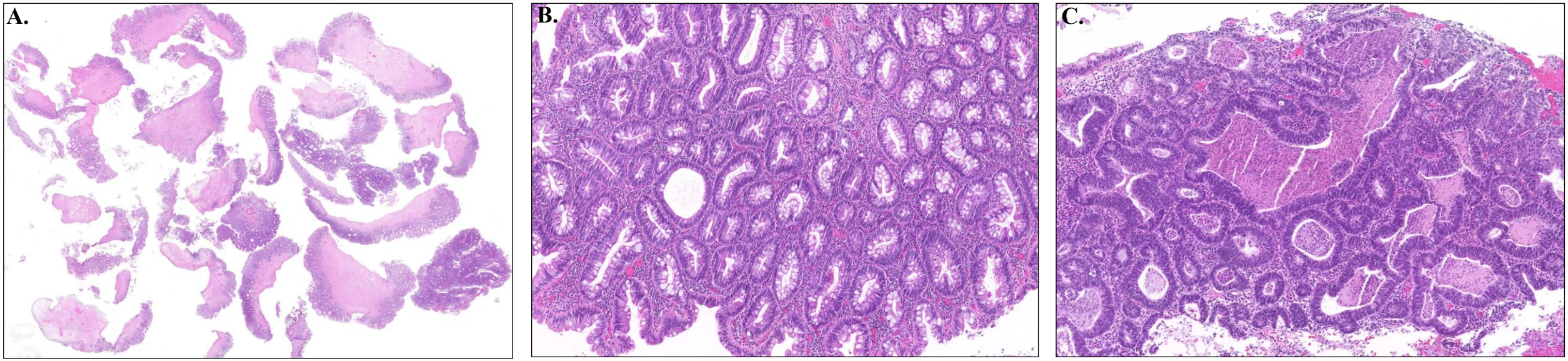

Figure 3