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Case study

DICER1 mutation-positive giant botryoid fibroepithelial polyp of the urinary bladder mimicking embryonal rhabdomyosarcoma☆,☆☆

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Summary Fibroepithelial polyps of the urinary tract are rare lesions. They occur mainly in the upper urinary tract of children. A high disease prevalence has been reported in families with pleuropulmonary blastoma. Here we present a case of a 46-year-old woman who presented with a giant botryoid fibroepithelial polyp of the urinary bladder. Histologically, the lesion showed prominent botryoid features with an embryonal rhabdomyosarcoma-like cambium layer lacking nuclear or cellular atypia. Immunohistochemical analysis ruled out rhabdomyoblastic differentiation. Next-generation sequencing was performed on the polyp tissue and revealed two pathogenic mutations in the DICER1 ribonuclease III (*DICER1*) gene (c.[5439G>T]; p.[Glu1813Asp] and c.[1525C>T]; p.[Arg509*]). Truncating *DICER1* mutations, accompanied by characteristic "hotspot" mutations affecting the RNase IIIB domain of DICER1 are typically seen in DICER1-related lesions. Our findings indicate a role of *DICER1* mutations in the pathogenesis of fibroepithelial polyps of the urinary tract.

1. Introduction

Fibroepithelial polyps (FEP) of the urinary tract are rare and occur mostly in the upper urinary tract of children (approximately 99% in the ureter and renal pelvis, < 1% in the bladder) [1-5]. Hematuria, flank pain, urinary hesitancy, dysuria, enuresis and infections of the urinary tract are the most common symptoms but asymptomatic lesions have been reported as well [1]. Approximately 250 cases of urinary tract FEPs have

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been described since the first half of the 20th century, mainly in urological journals with only four reports describing their pathological features in details - three case reports and one case series of FEPs in adults [2,4-6]. The botryoid variant of FEPs was represented by only two cases (both occurred in children 3 years and 11 years old) indicating its rarity (<1% of all FEPs) [2,6]. Because most botryoid lesions, especially in the bladder, represent embryonal rhabdomyosarcomas, it is essential to recognize other lesions with a botryoid appearance and separate them from embryonal rhabdomyosarcomas [7]. Differential diagnosis is often complicated by the presence of atypical stromal cells occasionally with a cambium-like appearance in FEPs [5,8,9]. In adults the most important differential diagnosis is sarcomatoid transitional cell carcinoma [10].

Here, we describe the case of a 46-year-old woman with a giant botryoid FEP of the bladder associated with pathogenic mutations in a key regulatory microRNA nuclease, the DICER1 ribonuclease III gene (*DICER1*).

2. Case report

In 2010, a 40-year-old woman was diagnosed with a multicentric invasive ductal carcinoma of the breast (ER+, PR+, Her2/neu negative; patient age at breast cancer diagnosis: 40 years). She underwent mastectomy with radical axilla dissection (pT2, pN1mic [1/10], G2 [Elston&Ellis], R0) followed by adjuvant radiation and chemotherapy with Docetaxel, Adriamycin and Cyclophosphamid (TAC). The family history for breast cancer was positive (mother: initial diagnosis at 46 years, local recurrence at 49 years). Despite the probability of familial disposition, genetic counseling was declined by the patient. Nevertheless, bilateral adnexectomy and prophylactic contralateral mastectomy were performed in 2011 at the age of 41. She received tamoxifen which was changed to letrozole in 2013 (according to the patient's request). Until now there was no evidence of local or systemic recurrence of the breast cancer.

In 2016, at the age of 46, she presented with nonspecific urinary symptoms and dysuria. Basic blood and serum markers as well as the urine status were normal (especially no hematuria). Transvaginal sonography revealed a sharply delineated, moderately echogenic and compartmented polypoid bladder tumor, 3 cm in diameter (Fig. 1).

At cystoscopy, a botryoid mass with a narrow stalk was noted at the lower right bladder wall in close proximity to the right ureter ostium. The surrounding mucosa showed no other recognizable pathological findings. The tumor was resected completely.

3. Material and methods

3.1. Immunohistochemistry

Immuno-histochemical stains were performed on 2 µm tissue sections using an automated Ventana Benchmark Ultra autostainer (Ventana, Tucson, Arizona, USA). Briefly, tissue sections were deparaffinized, antigens retrieved by heat treatment in a Tris/Borate/EDTA solution pH 8.4 (Ventana) and endogenous peroxidase was blocked with 1% H_2O_2. The following primary antibodies were used for target protein detection: Desmin (clone D33, Dako, 1:50), smooth muscle actin (clone 1A4, SMA, Dako, 1:400), estrogen receptor (ESR1, clone M7047, Dako, 1:40), CD56 (NCAM-1, clone MRQ-43, Cell Marque, 1:100), MyoD1 (clone 5.8A, Dako, 1:50), myogenin (clone F5D, Dako, 1:50), myoglobin (polyclonal, Dako, 1:200), CD34 (clone QBEnd10, Beckman Coulter, 1:500), pancytokeratin (clone AE1AE3, Zytomed, 1:40), protein S100 (clone 4c4.9, Zytomed, 1:3000) and Ki67 (clone MIB1; Dako, 1:80). Revelation was performed using the ultra-VIEW TM DAB systems (Ventana). All tissue sections were counterstained with hematoxylin II/Mayer's hematoxylin (Ventana).

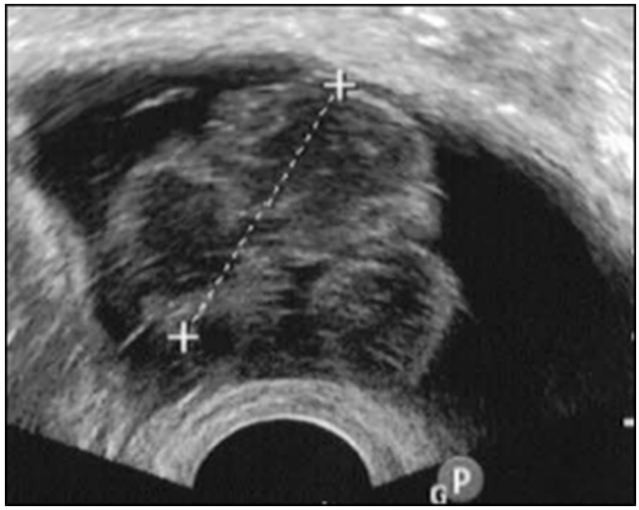

Fig. 1 Ultrasound imaging of the botryoid fibroepithelial polyp (FEP) in the urinary bladder.

3.2. Next-generation sequencing

For comprehensive molecular genetic analysis a 160-gene Next-Generation Sequencing panel (Comprehensive Cancer Panel, Qiagen, Hilden, Germany) was employed. DNA was extracted from paraffin-embedded tissue and DNA quality was assessed by quantitative polymerase chain reaction (PCR) (QuantiFast SYBR Green PCR Kit; Qiagen). The library was prepared using the Comprehensive Cancer Panel (Quiagen). Massive parallel sequencing was performed on a MiSeq instrument (Illumina). Data was analyzed using the CLC Genomics Workbench (Quiagen). All nonsynonymous variants were visually controlled using the genomic viewer function of the CLC Genomics Workbench.

3.3. Ethical aspects

The present study was conducted in accordance with the Declaration of Helsinki and under the guidelines of the institutional board on ethics of the Friedrich-Alexander-University Erlangen-Nuremberg. The patient gave written consent for all the

investigations carried out in this study and for publication. Germline sequencing of blood was declined by the patient.

4. Results

4.1. Pathology

Grossly, the tumor presented as a polypoid mass 3 cm in maximum diameter with a botryoid configuration attached to a narrow vascular stalk and had a tan soft jelly-like cut surface. Microscopically, the tumor was covered by a hyperplastic layer of urothelium with regular stratification and slight reactive changes (but no dysplasia). Focally, a cystitis cystica-like prominent pseudoglandular urothelial metaplasia accompanied by mild chronic inflammation was present. The stromal cores showed prominent edema, scattered ectatic vessels and few stromal cells arranged into narrow cords with a dendritic-like morphology lacking cellular atypia (Fig. 2B). In close proximity to the urothelial layer and the pseudoglandular

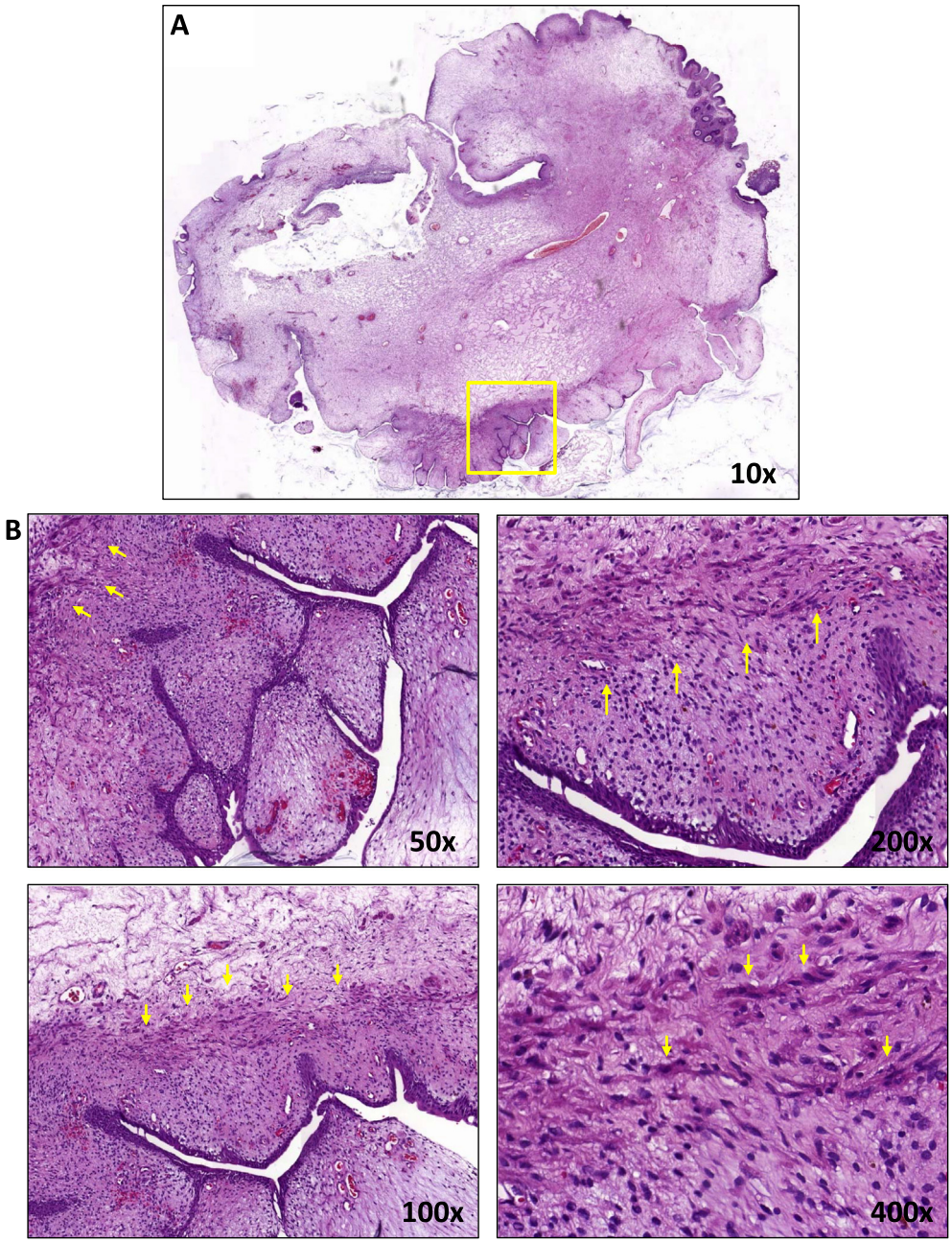

Fig. 2 A, Complete overview of the Hematoxylin Eosin (HE) staining of the polyp (10x magnification). B, The polyp shows a dense, continuous cambium-like layer in the underlying stroma beneath the urothelium (yellow arrows, 50-200× magnification). The cells were small and showed only mild to moderate nuclear atypia. Scattered throughout the layer a few larger cells were noted with prominent eosinophilic cytoplasm but no significant atypia (HE, yellow arrows, ×400 magnification).

formations in the underlying stroma the stromal cells formed a dense, continuous cell layer which presented as a cambium-like layer reminiscent of botryoid rhabdomyosarcoma of the bladder (Fig. 2B). The majority of the cells within the layer were predominantly small and showed only mild to moderate nuclear atypia, however also noted throughout the cell layer were a few large cells with prominent eosinophilic cytoplasm lacking high grade nuclear atypia and a. Mitotic figures were not found (Fig. 2B). The stromal component of the polyp lacked other heterologous elements, in particular no fat or cartilage tissue was seen.

By immunohistochemistry, the stromal cells within the cambium-like layer and the stromal cores were strongly positive for desmin (Fig. 3C), SMA (Fig. 3B), estrogen receptor (ER) and CD56. They were negative for MyoD1 (Fig. 3E), myogenin (Fig. 3D), myoglobin, CD34, pancytokeratin (Fig. 3F) and protein S100. The dendritic-like cells in the stromal core showed the same immunoreactive profile, especially a strong positivity for CD56. The superficial urothelial layer was strongly positive for pancytokeratin. Ki67 immunohistochemistry revealed a very low proliferative activity in the stromal cells (<1%). Cells within the cambium-like cell layer showed a slightly increased proliferative activity. The urothelial layer showed no increased proliferation.

After exclusion of embryonal rhabdomyosarcoma and other differential diagnoses, the above findings are consistent with a diagnosis of a botryoid FEP of the bladder with myofibroblastic stroma.

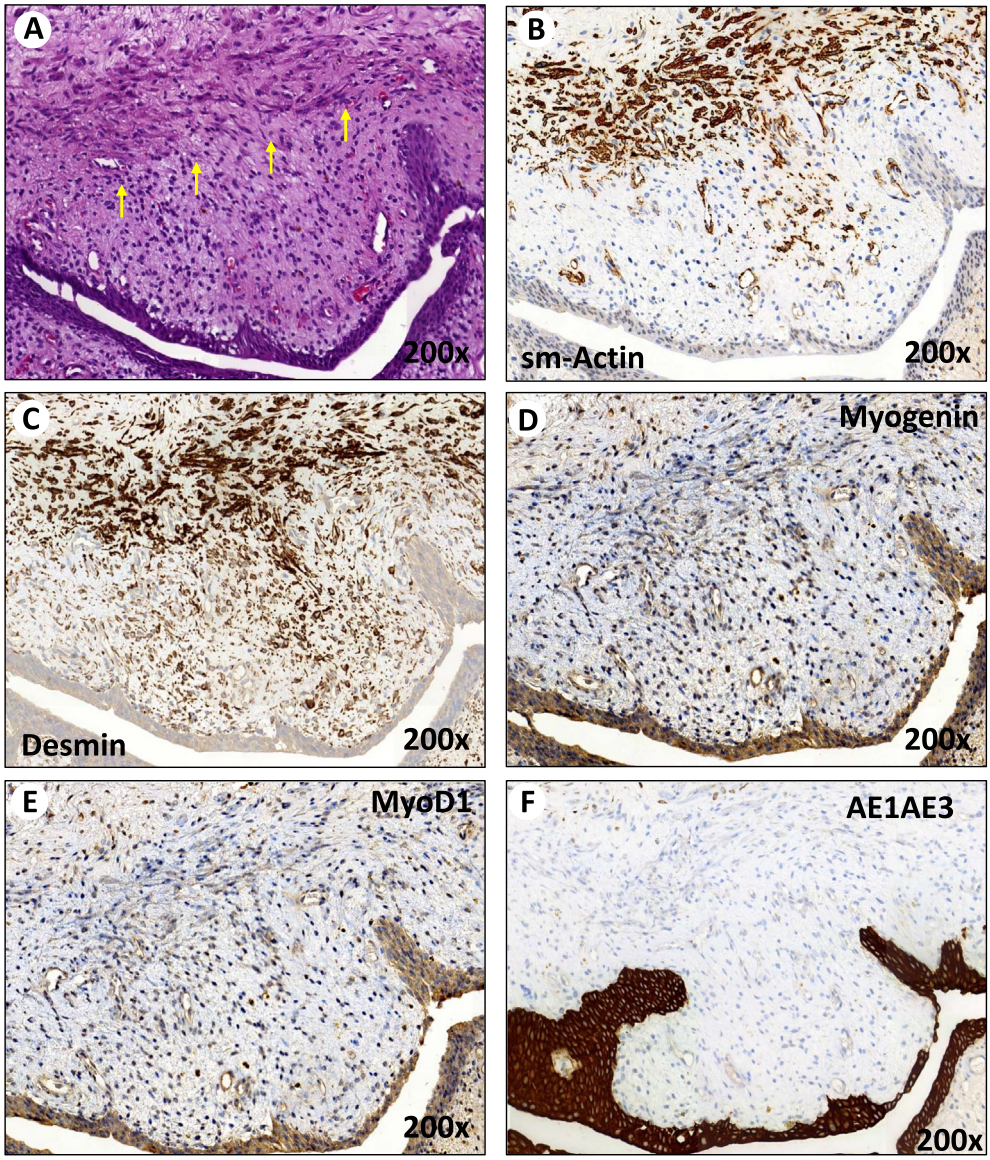

Fig. 3 Immunohistochemical staining of the FEP (200x magnification). A, HE stained corresponding area. Cells in the cambium-like layer exhibit strong cytoplasmic expression of smooth muscle Actin (B) and desmin (C) while they are completely negative for myogenin (D) and MyoD1 (E). F, Pancytokeratin staining exclusively stained the urothelial layer.

4.2. Next-generation sequencing

We identified a "hotspot" missense mutation in the *DICER1* gene (c.[5439G>T]; p.[Glu1813Asp]) in the FEP, which had been previously described as a recurrent pathogenic missense mutation ("*DICER1* syndrome") in numerous DICER1-related lesions [11,12]. Additionally, we identified a second pathogenic *DICER1* missense mutation, creating a premature translational stop signal, predicted to result in a truncated protein (c.[1525C>T]; p.[Arg509*]). Similar truncating mutations have been seen numerous times in DICER1 syndrome families. None of the *DICER1* mutations were found in the breast cancer tissue from this patient, thus indicating that the two *DICER1* variants we found in the bladder tumor are likely to be somatic events. Additionally, a *BRCA1* missense mutation (c.[5005G>T]; p.[Ala1669Ser]) was detected in both the FEP and the breast tumor, however. This mutation has been previously classified as "benign" or "likely benign" (single nucleotide polymorphism) [13]. No further variants were detected in the FEP or the breast tumor.

5. Discussion

Fibroepithelial polyps (FEPs) occur in several anatomical locations [3,14,15], but are quite rare in the bladder [1-5]. In spite of their rarity, they are a clinically well-known disease entity especially in children. Until today, the etiology of FEPs is unknown [4]. It has been discussed that these polyps are true neoplasms [3], but some authors favored a reactive genesis analogous to similar lesions in other locations such as the anal canal [4,14], the nasal cavity [16], and the female genital tract [8,15,17,18]. Regardless of their etiology, FEPs behave clinically benign and do not recur [2-5].

In a series of FEPs published in 2005, Tsuzuki and Epstein defined three different histomorphological FEP patterns that carry resemblance to florid cystitis cystica et glandularis, polypoid/papillary cystitis and (inverted) urothelial papilloma as the main differential diagnoses [4]. Some of the evaluated cases were interpreted in outside institutions as (inverted) papilloma. Both, FEPs and urothelial papillomas are considered benign and usually are curable by complete excision. However, papillomas may recur occasionally and even exhibit progression [19], which may then necessitate life-long clinical follow up [20-22]. In contrast, FEPs are not associated with urothelial carcinoma and usually do not recur pointing to the importance of correct diagnosis.

Our case illustrates a much rarer fourth FEP pattern, the "botryoid pattern", which can closely mimic embryonal botryoid rhabdomyosarcoma (eRMS) of the bladder, both cystoscopically and histologically [2,6]. Although degenerative stromal cell atypia is not uncommon in FEPs of the bladder and analogous lesions [5,8,9], the most interesting characteristic feature noted in our case was the presence of a subepithelial cambium-like cell layer with atypical stromal cells along with scattered large eosinophilic cells, which could be mistaken as a feature of a botryoid eRMS. As mentioned previously, the *DICER1* p.[Glu1813Asp] missense mutation observed in the FEP has been observed in numerous DICER1-syndrome related lesions [11,12]. Thus in addition to the similar *DICER1* mutation, FEPs, cervical embryonal rhabdomyosarcomas and pleuropulmonary blastoma share also the morphologic peculiarity of botryoid appearance. Interestingly, there are frequent bi-allelic *DICER1* mutations, with presumably inactivating "hotspot" missense mutations at one allele and inactivating missense mutations or deletions at the second allele as is the case in our patient which may indicate a key role of sporadic *DICER1* mutations in the pathogenesis of FEPs [23]. FEPs in association with germline *DICER1* variants seem to occur as multiple lesions at different localizations at young age [24]. Accordingly, *DICER1*-associated FEPs might represent index lesions for possible underlying *DICER1* syndrome with the implication for genetic counseling, similar to Gardner fibromas in familial adenomatous polyposis (FAP) [25], in particular if multifocal.

For the very rare botryoid pattern of FEP the most critical differential diagnosis is eRMS and inflammatory myofibroblastic tumor (IMT). RMS of the bladder is a rather frequent sarcoma manifestation in children and more than 90% belong to the embryonal subtype (especially with prominent botryoid appearance) [26-29]. A somatic hotspot DICER1 mutation has been reported recently in a bladder ERMS [30]. In adults, RMS of the urinary bladder is extremely rare [31-38]; to date, only three cases of botryoid eRMS in adults have been reported [39-41].

eRMS is typically composed of primitive spindled to round cells (rhabdomyoblasts) embedded in a variably fibromyxoid stroma. Interestingly, *DICER1* associated RMS (especially of the cervix), pleuropulmonary blastoma and anaplastic renal sarcoma in the spectrum of progression of cystic nephroma share the common occurrence of cartilaginous differentiation which may be a helpful differential diagnostic feature [23,42-46]. Botryoid variants present with a prominent myxoid stroma with only few cells and a subepithelial condensation of tumor cells forming a cambium layer which often contains deceptively bland small rounded to spindled cells. In contrast to botryoid FEPs, the rhabdomyoblastic cells within eRMS show specific expression of Myogenin and myoD1 [47,48]. IMTs with prominent myxoid features may be an important differential diagnosis of FEP, especially if associated with prominent papillary urothelial changes [33]. However, morphologic features arguing for IMT include cellular uniformity, fascicles of myofibroblastic cells, prominent staining for SMA ("tram-track" pattern), desmin, and low-molecular-weight cytokeratin (>50% of cases). Approximately 60% of all IMTs show an expression of anaplastic lymphoma kinase (ALK) which may also be helpful in distinguishing IMTs from other spindle cell neoplasms [49-51].

In summary, this is the first report of giant FEP in the bladder in an adult woman mimicking botryoid rhabdomyosarcoma. Since we did not find any of the two the *DICER1*

mutations of the FEP in the breast cancer tissue both mutations are likely of somatic origin. Similar to our report, somatic *DICER1* mutations have been reported in an adult-onset ERMS of the uterine cervix where a germline variant was excluded. Cervical ERMS is among the prototypical diseases of *DICER1* syndrome [52]. In summary, this might indicate a crucial role for somatic *DICER1* mutations for the tumorigenesis of tumors outside the established *DICER1* syndrome spectrum, arising in the adulthood. This potential involvement of *DICER1* mutations in the molecular pathogenesis of botryoid FEPs of the urinary tract in adults is in line with previous observations on *DICER1* mutations in analogous fibroepithelial (mixed epithelial/stromal) lesions in other organs.

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