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HISTOLOGICAL CHARACTERISTICS OF UROTHELIAL PAPILLOMA - INSIGHTS INTO A RARE LESION - A REVIEW OF LITERATURES

Histopathology

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ABSTRACT

Urothelial papilloma is a very rare papillary urothelial neoplasm with a benign course, rare recurrence if completely excised. Morphologically shows a delicate fibro-vascular core lined by urothelium of normal thickness & cytology. Its etiology is uncommon but often associated with KRAS/HRAS mutations. Progression to higher grades is extremely uncommon. Complete excision of the tumor with transurethral resection of bladder tumor (TURBT) is often curative with recurrence rate is 0 - 8.8%. The objective of this report is to present our incidental finding of a case with an exophytic Urothelial Papilloma & review the literature for appropriate diagnosis, to discuss & differentiate it from the other non-invasive papillary urothelial neoplasms, treatment of choice, patient follow up & management.

KEYWORDS

Papillary neoplasm, Urothelial papilloma, TURBT, Benign, Diffuse papillomatosis

INTRODUCTION

Rare papillary urothelial neoplasm, synonymous with transitional cell papilloma - characterized by delicate fibro-vascular core & lined by urothelium of normal thickness & cytology & usually follows a benign course. Recurrence is very much uncommon (0 - 8.8%) if completely excised. [1] It is an exophytic tumor composed of thin papillary fronds lined by a patent layer of an umbrella cell layer. No cytological dysplasia, no increase in thickness of the epithelial lining, no invasion into the fibro-vascular core or subepithelial stroma - distinguish it from its morphological differential diagnosis of Papillary Urothelial Neoplasm of Low Malignant Potential (PUNLMP), Urothelial Carcinoma, Polypoid Cystitis & Fibroepithelial Polyp. It comprises less than 1% of papillary bladder neoplasms. Patients are usually younger than the patients of Urothelial Carcinoma. The average age is less than 50 years. It can occur in younger age groups also. A case was reported in a 9-year-old boy who presented with gross & painless hematuria.[2] Male predominance with Male: Female ratio 1.9: 1.[3][4] Urothelial papilloma often presents as a solitary tumor.[3] Can occur independently or in association with other pre-existing urothelial neoplasms.[5] It can occur on any site within the urinary bladder but the most common occurrence is noted on the posterior & lateral walls of the bladder. The aetiology of urothelial papilloma is unknown but targeted new gene sequencing (NGS) and whole exome sequencing (WES) show a common association with KRAS/HRAS mutations.[6]

MATERIAL & METHOD:

Young age patients present with painless hematuria - gross or microscopic[7], may be an incidental finding while routine health check-ups. Ultrasonography & subsequent cystoscopy can reveal a unifocal endo-vesical papillary lesion, a solitary polypoid or lobulated soft tissue mass or an elevated unifocal lesion of variable size. Further work up should be carried out with transurethral resection of bladder tumor for histopathological opinion. These modalities can lead to a definitive diagnosis. Urine cytology would be negative for malignant cells.

Biopsy or TURBT specimens reveal soft, pink, small, isolated growth with delicate papillary structures & is usually pedunculated.

Microscopically predominantly it is an exophytic tumor with discrete papillary structures with central delicate fibro-vascular core with hierarchical branching without fusion of the papilla along with intact core & prominent umbrella cell layer. Mitosis is very & if present then very occasionally at the basal layer. Lymphocytic infiltrate noted in the stroma. It does not reveal any lamina propria or muscularis propria or stromal invasion. Sometimes it can show marked stromal oedema or cystitis cystica like invaginations. Papillae are lined by urothelium of normal thickness & morphologically benign cellular features along with patent umbrella cell layer & no fusion of the papillae. Umbrella cells may display cytoplasmic vacuolation & degenerative type of atypia.

There is no low- or high-grade cellular dysplasia, increased thickness of the epithelium or increased mitotic activity or apoptosis. Rarely bladder mucosa may be replaced by multiple papillomatosis & convert into diffuse papillomatosis.[8]

Immunohistochemistry reveals CK20 positive in the umbrella cell layer. No p53 abnormality detected. Ki67 reveals a very low proliferative index.

Molecular NGS & WES assays reveal common alterations in MAPK / ERK Pathways in particular KRAS/HRAS gene mutations. KRAS/HRAS mutations are very common than HRAS mutations. Mutations in common modifiers - which are commonly associated with urothelial papillary carcinoma are rare with papillary urothelial neoplasm of benign category.

APOBEC - Apolipoprotein B mRNA editing catalytic polypeptide like mutational signatures are negative in case of urothelial papilloma, while positive in case of 70% muscle invasive urothelial carcinomas. FGFR3 mutations are detected in 75% cases.[9] TERT Promoter mutations are detected in 46% cases.[10] However these findings have not been replicated in the newer studies with NGS & WES.

DISCUSSION:

Grading of Non-Invasive Papillary Urothelial Neoplasms:

Papillary Urothelial Neoplasm of Low Malignant Potential (PUNLMP): It is having complex papillary architecture with branching & fusion along with increased cellular proliferation which lead to increased thickness of the urothelium. It also lacks the prominence of the umbrella cell layer. It does not display much architectural abnormality with maintained polarity of the lesion & no nuclear atypia.

Non-Invasive Papillary Urothelial Carcinoma - Low Grade: Displays complex papillary architecture with branching & fusion of the papillae. Increased thickness of the urothelium with cytological low-grade dysplasia. Cases of papillary carcinoma without increased thickness show marked cytological & architectural abnormalities. Umbrella cell layers may not be prominent & show fusion of the papillae at places.

Polypoid Papillary Cystitis: This lesion is usually associated with a history of urothelial irritation by stones, radiation or stents. [11][12] Microscopically it reveals nonbranching broad base fronds with oedematous, fibrotic stroma & associated with inflammation. It can be evaluated at low power microscopy. Lining urothelium displays reactive atypia & loss of prominent umbrella cell layer.

Fibroepithelial Polyp: Usually it is seen in children but can be detected in adults also. It can be present as a polypoid mass or a papillary lesion. May have broadened stalks with dense fibrous cores. Lacks prominent umbrella cell layer.

Inverted Urothelial Papilloma: Shows minimal or no exophytic component, as this lesion is endophytic. Predominantly displays anastomosing cores, trabeculae or glandular subtype without any

stromal invasion.[13]

Grading & classification of non-invasive papillary urothelial neoplasm is of particular importance as they all are having different clinical outcomes. Urothelial papillary neoplasm or PUNLMP has favourable prognosis than non-invasive high grade papillary carcinomas which have unfavourable prognosis as they express biologic properties of high level of genetic instability similar to invasive urothelial carcinoma.[14]

On endoscopic evaluation urothelial papilloma are identical to PUNLMP or low grade papillary urothelial carcinoma. TURBT is the treatment of choice. [2][15]

Urothelial Papilloma has a favourable clinical outcome. It can recur & can recur multiple times after initial diagnosis & a very occasionally progression to carcinoma.[1] Rare cases of disease progression are described in association with immunosuppressive therapy.[3]

In view of a very rare but factual risk of recurrence & disease progression, some authors suggest a two year follow up of the patient with cystoscopy every six months, while other authors propose clinical examination & USG carrying out at 3, 6 & 12 months & then annually. If the two years of period is event free then follow up of the patient with urinalysis, USG & cystoscopy guided biopsy (TURBT) of the ex-tumor site after two years also recommended by some authors to confirm complete resection & no local recurrence. Consecutive follow up will take place annually.[4] [16]

CONCLUSION:

Urothelial papilloma is an accidental finding while regular routine check-up or follow up of gross or microscopic painless hematuria. Diagnosis of such rare lesions is mainly dependent on histopathological morphology. Though the lesion usually proceeds with the benign course usually but the single or multiple recurrence & disease progression to high grade disease or invasive carcinoma is also documented. Regular close follow up of the patient after first occurrence is advisable to make watch on recurrences & of disease progression to higher grade. We have tried to establish the mentioned features of the tumor - Rarity, Benign Course, Risk of Recurrence or multiple recurrences & the disease progression to a higher grade, importance of skillful histopathological diagnosis, grading system, follow up of the patient, treatment & prognosis.

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