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Two of a kind: Analyzing Juvenile polyps in a 5-year-old boy

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ABSTRACT

Background. Juvenile polyps are most common benign lesions of the gastrointestinal tract predominantly affecting children. Occasionally, they can also be found in adults. These come under the group of Hamartomatous polyps. Sporadic juvenile polyps generally occur singly, common in the rectum, also the most common cause for gastrointestinal bleeding in children.

Case Report. Here, we present a case of 5-year-old male child with the complaints of constipation for past 2 months and bleeding per rectum for past one month. Polypectomy was done post which he was diagnosed with two synchronous non syndromic juvenile polyps which is not very common as most cases will present with either a solitary or multiple polyps (usually more than five in number).

Conclusions. This article discusses about the clinical presentation, histopathological features, pathogenesis, molecular alterations, prognosis and recent diagnostic advances of the juvenile polyps. Despite their innocuous nature, understanding their pathological characteristics is crucial for their timely diagnosis, management and for predicting clinical outcomes. Even with a lower risk of malignancy, regular surveillance is of utmost importance in case of patients with more than one juvenile polyp due to the increased risk of recurrence and neoplastic transformation.

Keywords: Juvenile polyps, Gastrointestinal pathology, Histopathology, Colorectal lesions, Juvenile polyposis syndrome, Hamartomatous polyps

Abbreviations:

JPS – Juvenile Polyposis Syndrome

SMAD4 – Mothers against decapentaplegic homolog 4

BMPR1A – Bone morphogenetic protein receptor, type 1A

TGF – Transforming growth factor

NGS – Next Generation Sequencing

FC – Fecal Calprotectin

IRA – Ileorectal anastomosis

INTRODUCTION

Juvenile polyps represent one of the most common benign lesions of the gastrointestinal tract in the pediatric age group. Sporadic juvenile polyps generally occur singly, most common in the rectum. Grossly, these polyps are highly variable in size (5-50mm), with a globular appearance often with surface erosion. These polyps tend to undergo autoamputation. Histologically, these polyps are characterized by specific features such as cystically dilated glands with no dysplasia and abundant edematous lamina propria with dense inflammatory cell infiltrate that distinguish them from other types of colorectal polyps. However, it's difficult to distinguish it from inflammatory polyp. The current consensus is that non syndromic juvenile polyps entail minimal to no risk of malignant transformation but there are, however, isolated case reports of malignant transformation in young children and several case reports in older individuals. In this article, we discuss about a case of dual synchronous non syndromic juvenile polyps in a 5-year-old male child exploring the histopathological findings and molecular mechanisms to provide a comprehensive understanding of their pathology for further management.

CASE REPORT

A previously healthy 5-year-old male child came to the surgical outpatient department with the complaints of constipation for past 2 months and bleeding per rectum for past one month. There was no significant past history or family history for colonic polyps or carcinoma. On physical examination, he had mild conjunctival pallor but no koilonychia or icterus. The abdomen was soft and non-tender on palpation, bowel sounds were present. Per rectal examination revealed two polypoid masses in the distal rectum, with blood stain on the examining finger. Complete hemogram showed microcytic hypochromic anemia with hemoglobin of 9.2 g/dl. WBC count and other laboratory parameters were within normal range. Colonoscopy was done which revealed two sessile rectal polyps in the distal rectum, one measuring 1x0.5 cm located at the 3'o clock position and other measuring 1x1 cm located at the 5'o clock position. Hot snare polypectomy was done for both the polyps and the sample was sent for histopathological examination

(Figure 1). Post fixation, the sample was bisected and all embedded. After routine processing, the sections were examined microscopically. The sections showed a polypoidal mass consisting of rectal mucosa with focal surface ulceration and granulation tissue formation. The polyp is composed of cystically dilated glands filled with secretions separated by edematous stroma with dense mixed inflammatory cell infiltrate (Figure 2). There was no evidence of cytological atypia. Based on the above findings, the diagnosis of juvenile polyps was given and in association with the history, it was labelled as Sporadic/ Non syndromic Juvenile Polyps. The patient's postop period was uneventful and post discharge, he was put on routine colonoscopic surveillance at regular intervals.

DISCUSSION

Juvenile polyps come under hamartomatous type of polyps with low malignant potential. The term 'Juvenile' refers to the type of polyp and not the age of onset of the polyp in a patient [1], hence it is a misnomer. Typically, these polyps occur in the colorectum and are the most common cause of GI bleeding in children, since they tend to develop a stalk and they prolapse during increase in intra-abdominal pressure as in defecation. Torsion of the stalk can also occur in < 10% of cases. Only 25% of these polyps are sessile. It has a rich blood supply in the stroma hence, it is also considered the most common cause for painless hematochezia in children under 10 years. It can occur in sporadic form or as a part of Juvenile Polyposis Syndrome (JPS). The sporadic form peaks at the ages between 2 to 6 years.[2] Sporadic solitary colorectal juvenile polyps occur in approximately 2% of the pediatric age group. The most common type of polyp seen in pediatric gastroenterology is an isolated juvenile polyp [2] but multiple juvenile polyps may also occur in young individuals in case of Juvenile polyposis syndrome (JPS), a rare autosomal dominant disorder defined by any one of the three findings (Jass diagnostic criteria):

(1) The presence of multiple (>5) juvenile polyps in the colorectum or

(2) Juvenile polyps throughout the entire gastrointestinal tract or

(3) A single juvenile polyp in a person with a positive family history of juvenile polyposis syndrome [3].

The importance of a thorough family history cannot be over emphasized in this scenario. The incidence of JPS in children has found to be 1:100,000 to 1:160,000 [4].

Clinically, juvenile polyp usually presents with abdominal pain, bleeding per rectum and anemia depending on the size and location of the polyp within the gastrointestinal tract [5]. These patients can also present with a prolapsing mass per rectum or as mucopurulent fecal matter [1]. Solitary larger polyps in a more distal location are the common phenotype of a nonsyndromic juvenile polyp [6] and adenomatous transformation within juvenile polyp is suggestive of syndromic juvenile polyp, which indicates as an intermediate stage of dysplastic evolution in the progression to colorectal carcinoma. However, the significance of adenomatous change in non-syndromic juvenile polyps is not known. While most juvenile polyps have no malignant potential when single and also rarely recur, when there are multiple polyps, they have higher risk of recurrence (10 – 20 % of cases) [7] and they may also cause neoplastic transformation and they can also lead to complications such as intussusception or obstruction, also there is a high risk of bleeding and mucosal prolapse necessitating prompt removal, diagnosis and management. These polyps can be removed by sigmoidoscopic snare polypectomy or trans anal excision. Infantile juvenile polyposis often presents with failure to thrive, abdominal pain and is considered fatal before 2 years of age owing to complications like protein losing enteropathy, gastrointestinal bleeding and anemia [8]. These complications can also occur in patients in their late adolescence and adulthood.

Grossly, the polyp appears round, smooth, reddish with a glistening surface; No fissures or lobulations seen. These polyps are mostly present with a stalk (90% pedunculated), with its appearance similar to a bright red cherry and measures around 1 to 3 cm in greatest dimension. But very few cases can even be small and sessile. On cut surface, we can appreciate cystic spaces filled with greyish mucin.

Characteristic chicken skin appearance of mucosa is due to aggregation of lipid in lamina propria, which is a very common finding in larger polyps in rectosigmoid region [2]. Histologically, juvenile polyps come under the group of Hamartomatous polyps and is defined by their unique features, resembling Swiss cheese (Swiss cheese appearance) including tortuous cystically dilated glands lined by columnar epithelium with abundant goblet cells filled with mucous secretions. This is why they were called previously as "Mucus retention cysts". The lamina propria often shows loose connective tissue infiltrated by acute and chronic inflammatory cells predominantly composed of lymphocytes, eosinophils and occasional plasma cells. In some cases, there is denudation or ulceration of the mucosa with underlying inflammatory granulation tissue formation in the stroma, also in some cases, lymphoid follicles can be appreciated. Crypt branching and occasional epithelial tufting may also be noted. The polyps are typically covered by intact mucosa with preserved architecture with no dysplasia, distinguishing them from dysplastic lesions such as adenomatous polyps. The histology of these polyps closely mimics the hyperplastic and inflammatory polyps. In the absence of clinical history, this can be reported in a broad term as "Hamartomatous polyp, not otherwise specified" or "Inflammatory/ Juvenile type polyp". Around 5% of juvenile polyps in children have focal areas exhibiting adenomatous changes. These are not frank adenomas but they are alarming because such polyps may be predisposed to transformation to colorectal carcinoma. The differential diagnosis of juvenile polyps include: Juvenile polyposis syndrome, Meckel's diverticulum, Arterio-venous malformation, Inflammatory bowel disease, Infectious colitis [2].

The molecular pathogenesis of juvenile polyps is not fully elucidated but may involve alterations in signaling pathways associated with inflammation and mucosal proliferation. Before making a diagnosis of juvenile polyp, the possibility of juvenile polyposis syndrome (JPS) should always be considered. About 60% of patients with JPS harbors a germline mutation in the SMAD4 or BMPR1A gene which plays a vital role in the TGF-beta signaling pathway like cellular proliferation, cellular differentiation and apoptosis. This form of polyposis syndrome carries a lifetime risk of colon carcinoma of 39% and a relative risk of

34. Almost all patients who test positive for SMAD4 mutations, also have hereditary hemorrhagic telangiectasia, which also has to be kept in mind. Most mutations are either point mutations or deletions which can be identified by gene sequencing studies like NGS. About 40% of patients with JPS does not have a germline mutation for which the pathogenesis is unknown [9]. Immunohistochemistry for the SMAD4 protein is shown to be a specific marker for cases with SMAD4 germline mutation. Selective loss of SMAD4 dependent cell signaling in the T cells causes a Juvenile polyposis syndrome – like phenotype. It is also believed that juvenile polyps with SMAD4 germline mutation have a higher crypt density regardless of the status of dysplasia and juvenile polyps with BMPR1A defect has a prominent stromal component with a low crypt density. Ki67 immunostaining can be done to confirm it. Specific driver mutations or genetic markers for distinguishing juvenile polyps from other types of polyps remain as areas of ongoing research.

Recently, Fecal calprotectin (FC) has been discovered to be useful in the screening of juvenile polyps. The increase in fecal calprotectin levels in juvenile polyp is due to the presence of dense inflammatory cell infiltrate within the polyp [10]. Calprotectin is an antimicrobial protein, which constitutes up to 60% of the proteins in the cytoplasm of neutrophils and is distributed in the cytoplasm of monocytes, macrophages, and granulocytes. This has the potential to be the main screening tool for patients with juvenile polyps making the surveillance easy but it is still in its early phases of research.

A challenge occurs when managing a patient with two to four juvenile polyps, because it is unclear whether the patient will develop juvenile polyposis syndrome and therefore be at significant risk of carcinoma. [1] Predictive genetic testing for pediatric patients must be done only when familial mutation has been identified in a parent or sibling. If not, then there's no need to perform genetic testing, only surveillance is sufficient. Predictive testing in a patient can be delayed until 12 to 15 years of age unless it is necessary to investigate for a non-colonic clinical manifestation of juvenile polyposis or to differentiate it from other causes of

juvenile polyps.[5] Genetic testing is essential in these cases to differentiate it from other entities like Cowden syndrome and Bannayan – Riley – Ruvalcaba syndrome. When a disease-causing phenotype is identified in a patient with juvenile polyposis, other close family members must undergo genetic testing to identify its presence. [11]

When these polyps are present, they must be removed by snare polypectomy and regular colonoscopic surveillance with repeat polypectomies has to be done for polyps > 5mm until the colorectum is completely free of the polyps or until the patient is free of symptoms. If there is a strong family history but no polyps are found in the colonoscopy, surveillance must be continued at regular intervals until the patient attains 45 years of age. If the polyps are restricted to colon or if any of the polyp exhibits high grade dysplasia or malignant transformation or if polyposis cannot be controlled via endoscopic removal, the treatment of choice is a total abdominal colectomy with IRA. The polyps may still arise in the remaining rectum hence, surveillance of the remnant pouch is necessary. If multiple polyps present throughout the rectum along with a foci of carcinoma rectum, then a total proctocolectomy with ileoanal reservoir must be considered. Regular surveillance of the entire gastrointestinal tract is recommended in these patients especially when symptomatic [11] It is essential for the clinician to communicate to the patient with juvenile polyposis syndrome that their offsprings or siblings may be at the risk of developing it too. Hence, genetic testing by DNA sequencing/ NGS is always recommended for their family members presenting with similar complaints.[1]

The prognosis for patients with juvenile polyps is generally favorable, especially with early detection and appropriate management. The lifetime relative risk of carcinoma colon in patients with juvenile polyposis has been found to be around 38.7% [3].

Fox et al. has suggested that children who present with even a single polyp may continue to form more polyps over time [12].

Ibrahimi et al has also observed that neoplastic transformation in nonsyndromic juvenile polyps may be more common than appreciated and is a significant observation [6].

Gupta et al reported dysplasia in 1 out of 184 children with juvenile polyps. The patient was a 12-year-old boy with a single polyp containing a focus of high-grade dysplasia diagnosed as adenocarcinoma in situ. These findings when taken together with other case reports of advanced neoplasia arising within a juvenile polyp suggests that children who form even small numbers of juvenile polyps are at increased risk for adenocarcinoma [13].

Brennan et al also reported a young patient with juvenile polyps diagnosed with colonic adenocarcinoma. Hence, regular follow-up is crucial to monitor for its recurrence or complications, although the risk of malignant transformation in isolated or sporadic juvenile polyps is rare, regular surveillance with colonoscopy is advised due to an increased risk of recurrence and neoplastic transformation [14].

Fox et al. also recommends a starting interval of 1 to 3 years after the initial polypectomy adjusting according to the polyp burden and presence of dysplasia during the index colonoscopy [12]. In the absence of family history and presence of less than 3-5 synchronous juvenile polyps, these are considered as nearly benign entities [15].

Monahan et al also suggests that colonoscopic surveillance can be commenced from the age of 15 years or earlier if the patient is symptomatic and the interval should be 1 to 3 yearly depending on the colorectal phenotype of the patient [16]. Also, there are multiple polyposis registries in almost all the countries to promote the identification of patients with high risk for colorectal carcinoma and also to ensure a lifelong participation of these patients in the surveillance programs. These registries offer multiple specialty services like prenatal counseling, patient education and support groups for their patients [1]. All these attempts are for these patients to have a better quality of life in spite of their disease.

CONCLUSION

Colorectal juvenile polyps occur in a wide range of locations and in variable numbers. These polyps are solitary in most patients, but in patients with >1 juvenile polyp as in our case, JPS must be suspected which has to be ruled out by extensive review of patient history and molecular or genetic evaluation as soon as possible. Juvenile polyposis syndrome (JPS) is a rare autosomal dominant disorder with an incidence of 1:100,000 to 1:160,000. Even with a lower risk of malignancy, regular surveillance is of utmost importance in case of patients with more than one juvenile polyp due to the increased risk of recurrence and neoplastic transformation. Hence, being aware of the pathology of juvenile polyps is essential for an accurate rapid diagnosis, effective management and prediction of clinical outcomes. Further research into the molecular mechanisms underlying these polyps may lead to newer diagnostic techniques and targeted therapeutic approaches in the future. Nevertheless, different type of genetic mutations which can be diagnosed by newer techniques are of great significance for disease screening and further treatment.

PATIENT CONSENT

Written informed consent was obtained from the participant/patient(s) for the publication of this case report.

CONFLICT OF INTEREST

Nil

AUTHOR'S CONTRIBUTIONS

ML conceived the idea for the manuscript and provided guidance, JP did the writing of original draft which was reviewed by ML.

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Nil

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FIGURES

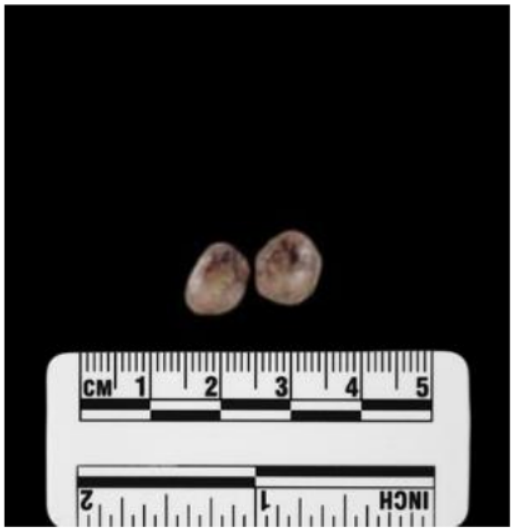

Figure 1. Gross image showing two sessile polypoidal masses

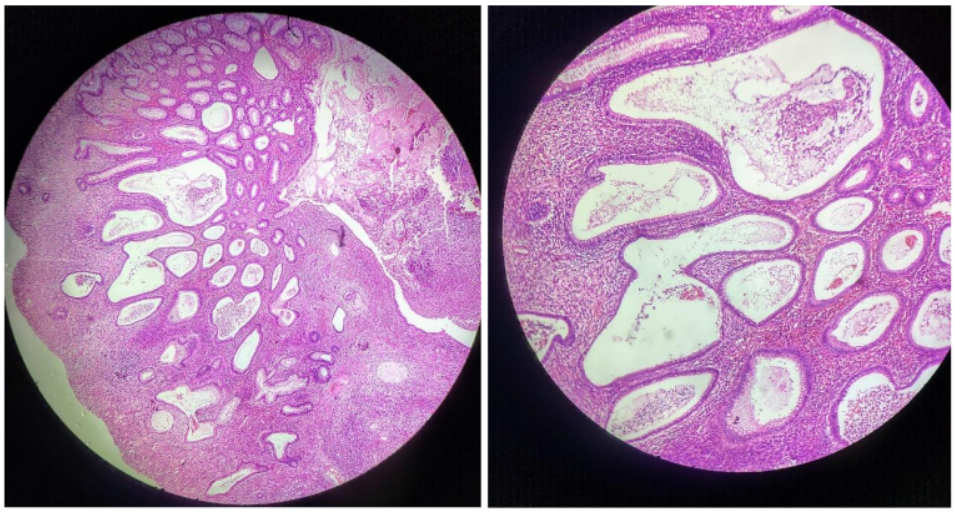

Figure 2. (A) Low magnification image (H&E, 4x) showing varying sized cystically dilated glands; (**B**) High magnification image (H&E, 10x) showing cystically dilated glands filled with eosinophilic secretions and lamina propria showing dense mixed inflammatory infiltrate.

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