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Eosinophilia and Platelet Derived Growth Factor Receptor A Overexpression in Juvenile Polyps

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ABSTRACT

Background: Although a juvenile polyp is the commonest pediatric polyp, little is known regarding its pathogenesis.
Objective: We aimed to study the role of eosinophils and platelet-derived growth factor receptor A (PDGFRA) expression in juvenile polyps. This could help in understanding the possible mechanism of polyp formation.
Material and methods: This was a retrospective study that included 63 cases of juvenile polyps that were divided into three groups according to the number of polyps. Peripheral and tissue eosinophilia was evaluated. An immunohistochemical study of mothers against decapentaplegic homolog 4 (SMAD4) and PDGFRA was conducted.
Results: The majority (82.5%) of the juvenile polyps were solitary, 11.1% were multiple, and 6.4% of them were cases of juvenile polyposis syndrome. There was an increased number of blood eosinophils (a median value of 2×10^3 cells/μL) and tissue eosinophils (a median value of 30/HPF). In addition, PDGFRA was overexpressed in 66.7% of cases. The expression of PDGFRA was significantly associated with tissue eosinophilia ($p = 0.008$). Tissue eosinophilia and PDGRA overexpression were significantly observed in patients with maintained SMAD4 expression.
Conclusions: Tissue eosinophilia and PDGFRA overexpression were observed in majority of juvenile polyp cases. Juvenile polyps could share histopathological and molecular similarity to inflammatory fibroid polyp. The pathogenesis of juvenile polyp could be influenced by allergic or neoplastic factors.
Keywords: Eosinophilia, Juvenile polyp, PDGFRA, SMAD4.

INTRODUCTION

A juvenile polyp is the commonest pediatric polyp and mainly presents as painless rectal bleeding [(1)]. They are characterized by cystically dilated colonic glands filled with mucus in an inflamed, edematous stroma rich in eosinophils. Approximately half of all children with juvenile polyps have more than one polyp that is usually located on the left side [(2)]. The mechanism of juvenile polyp formation has not yet been well elucidated. However, existing theories include the non-neoplastic, allergy, vascular abnormalities, inflammatory response, or neoplastic theories [(3)].

Juvenile polyposis syndrome (JPS) is a rare autosomal dominant (AD) disease. The clinical criteria include >5 gastrointestinal (GI) polyps, polyps throughout the GI tract, or any number of polyps in a patient with a family history of JPS [(4)]. This disorder is most frequently caused by mutations in mothers against decapentaplegic homolog 4 (SMAD4) [(5, 6)].

JPS with the *SMAD4* mutation could have associated with hereditary hemorrhagic telangiectasia (HHT) syndrome. HHT is characterized by arteriovenous malformations (AVM) of the liver, brain, lung, and GI tract. This syndrome is associated with a higher rate of anemia and early-onset colon cancer [(7)]. In addition, alterations of SMAD4 were reported in different human cancer [(8)].

Patients with solitary juvenile polyp (SJP) do not have an increased risk of GI cancer [(2)]. However, patients with JPS carried a 50% risk of developing GI cancer. A challenge occurs when managing a patient with three or four juvenile polyps because it is unclear whether the patient will develop the JPS phenotype [(9)].

Platelet-derived growth factor receptor A (PDGFRA) is a receptor tyrosine kinase that showed no/low normal colonic mucosal expression [(10)]. Mutations in *PDGFRA* have been reported in different types of cancer [(11)].

In addition, *PDGFRA* gene mutations have been shown to be oncogenic in the subset of gastrointestinal stromal tumor and a significant proportion of inflammatory fibroid polyps (IFPs) [(12)].

Therefore, we aimed to study the role of eosinophils and PDGFRA protein expression in juvenile polyps. This could help in understanding the possible mechanism of polyp formation.

MATERIAL AND METHODS

This was a retrospective study performed on formalin-fixed, paraffin-embedded specimens that included 63 juvenile polyps during the 2015–2020 period. All patients underwent colonoscopy until the terminal ileum to assess the number (solitary, multiple (up to five polyps), or syndrome > 5 polyps) of polyps, the distribution of polyps, and the status of the background colon. Polypectomy was conducted. The clinical, family, and laboratory data were obtained from patients' medical records. Laboratory data included the hemoglobin level and eosinophil count.

Histopathological evaluation

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The cases were reviewed by two pathologists to confirm the diagnosis and to assess the following parameters: polyp size, density of inflammatory infiltrate, and tissue eosinophilia (tissue eosinophilia was defined as an eosinophil count of >20 eosinophils/HPF) (3). The cases were further subdivided into the following two groups based on the crypt–stroma ratio: a group A of classic juvenile polyps with prominent stromal compartments and a group B of polyps with a predominantly epithelial component. A cut-off point of 1.00 described equal counts of stroma and epithelium and was chosen to highlight the predominant feature. In addition, dysplasia was graded as absent, indefinite, and positive according to standard criteria [(13)].

Immunohistochemistry (IHC)

A rabbit monoclonal (SMAD4) antibody (Ref, A19116; dilution, 1:100) was obtained from ABclonal, and a rabbit polyclonal (PDGFRA) antibody (Ref, bs-0231R; dilution, 1:200) was obtained from Bioss. Antigen retrieval using high-pH Tris-EDTA solution (Dako, Ref K8000, Glostrup, Denmark) was done for 20 min of heating, followed by cooling for another 20 min. The primary antibodies were incubated overnight at 4°C. Immunostaining detection was carried out by utilizing the Envision™ FLEX/HRP detection system (Dako A/S, Glostrup, Denmark) with 3-diaminobenzidine (Dako) as a chromogen. In addition, positive and negative controls were used for each run.

IHC assessment of SMAD4 and PDGFRA

Positive SMAD4 expression was considered if any brownish nuclear and cytoplasmic staining of epithelial cells was observed. SMAD4 expression was then assessed as diffuse positive, focal loss, and negative [(14)]. PDGFRA was assessed in both epithelial and stromal cells as brownish cytoplasmic staining [(15)]. PDGFRA scores were calculated by multiplying the intensity of staining, which could be negative (0), weak (1), moderate (2), or strong (3), by the percentage of positive staining score, that is, 1 for <25%, 2 for 25%–50%, 3 for 51%–75%, and 4 for >75%. The final score was divided into high (≥3) and low (<3) scores[(16)].

Radiological imaging in patients with JPS

Three out of four patients with JPS underwent further radiological imaging to rule out associated HHT. These included magnetic resonance imaging (MRI) studies on the brain, electrocardiogram (ECG), abdomino-pelvic ultrasound (US), and barium studies to demonstrate additional GI polyps or associated vascular malformations.

Ethical consent:

An approval of the study was obtained from Menoufia University Academic and Ethical Committee. The patients' parent signed an informed written consent for acceptance of participation in the study. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis

Data were analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp). Kolmogorov–Smirnov test was used to verify the normality of the distribution of variables. Comparisons between groups for categorical variables were assessed using chi-square test (Fisher's exact test). Mann–Whitney and Kruskal–Wallis tests were used for continuous variables whose distributions were skewed. The Spearman correlation coefficient was used to assess the correlation between quantitative variables. The threshold for statistical significance was set at $p < 0.05$.

RESULTS

Clinicopathological characteristics of the studied cases

All cases of juvenile polyps presented with bleeding per rectum. The patients that we included were between 2 and 12 years old, with a median age of 5 years. The majority (61.9%) of cases were males. The median hemoglobin level was 11 g/dL, and the median serum eosinophil level was 2×10^3 cells/μL. Approximately 80% of cases were of type B, with a median polyp size of 1 cm. The median eosinophil count within polyps was 30/HPF, (Figs 1 a, b, c).

There was a positive correlation between blood and tissue eosinophilia ($p = 0.057$, $r = 0.656$).

The cases were allocated into three main groups based on the number of polyps: Group 1: 52 patients with SJP (82.5%), Group II: seven patients with multiple juvenile polyps (MJPs) but less than five polyps and without any family history or other GI polyps (11.1%), and Group III: four patients with JPS (6.4%).

There was no statistically significant difference in clinicopathological data between the three groups. However, patients with JPS showed an equal gender distribution and tended to have more severe anemia than those in the other groups ($p = 0.058$). The clinicopathological characteristics of each group are illustrated in Table 1.

Table (1): The clinicopathological characteristics of SJP, MJP and JPS

Data	Variables	SJP 52 (82.5%)	MJP 7 (11.1%)	JPS 4 (6.4%)	p-value
Clinical	**Age (years)** Mean ± SD Median (min-max)	5.12 ± 2.56 4.25 (2.00–12.00)	5.78 ± 2.51 5.0 (4.00–11.00)	5.75 ± 1.71 5.5 (4.00–8.00)	**0.387***
	Sex Male Female	34 (65.4%) 18 (34.6%)	3 (42.9%) 4 (57.1%)	2 (50.0%) 2 (50.0%)	**0.453****
Laboratory	**Blood Eosinophils** Mean ± SD	1.71 ± 0.51	1.96 ± 0.678	1.72 ± 0.55	**0.646***
	Hemoglobin (g/dL) Mean ± SD	10.97 ± 0.94	11.41 ± 0.39	10.25 ± 0.31	**0.058***
Pathology	**Polyp size (cm)** Mean ± SD	1.07 ± 0.46	0.9714 ± 0.36	1.17 ± 0.24	**0.579***
	Polyp type Type A Type B	12 (23.1%) 40 (76.9%)	1 (14.3%) 6 (85.7%)	0 (0.0%) 4 (100.0%)	**0.496****
	Dysplasia Absent Indefinite	35 (67.3%) 17 (32.7%)	4 (57.1%) 3 (42.9%)	2 (50.0%) 2 (50.0%)	**0.702****
	Tissue Eosinophilia Mean ± SD	30.82 ± 19.32	31.43 ± 8.99	35.0 ± 10.0	**0.863**

SJP: Solitary juvenile polyp, **MJP:** Multiple juvenile polyps, **JPS:** Juvenile polyposis syndrome,
*** Kruskal-Wallis Test ** Fisher exact test**

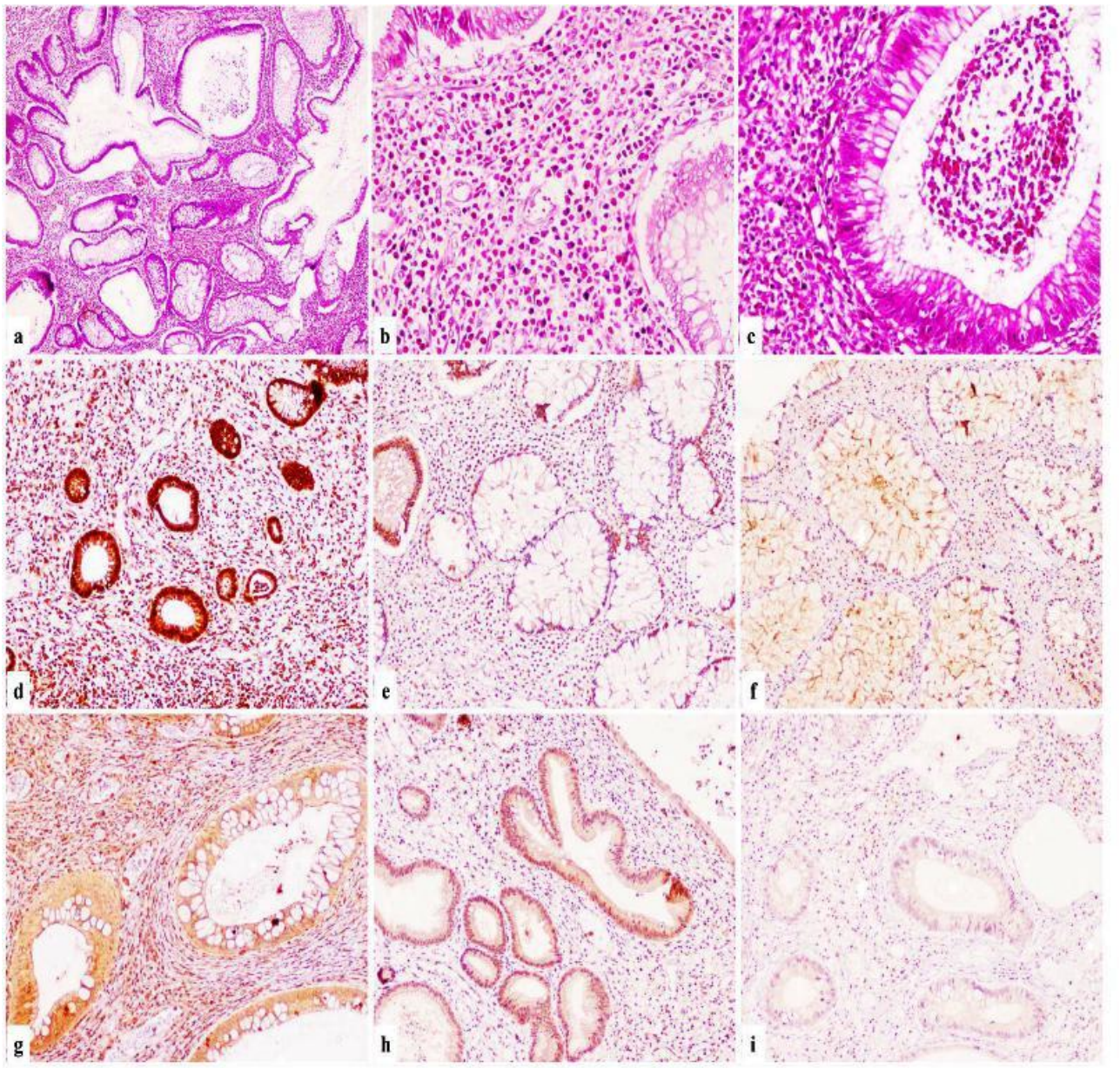

Fig. (1): Tissue eosinophilia, SMADE4 and PDGFRA expression in juvenile polyp: a) Juvenile polyp formed of cystically dilated colonic glands within an inflamed stroma (H&E 40x), b) Stroma with rich eosinophilic infiltrate (H&E 100x), c) Colonic gland showing eosinophilic abscess formation (H&E 200x), d) Diffuse maintained SMAD4 expression (IHX 40x), e) Focal loss of SMAD4 expression (IHX 100x), f) Complete loss of SMAD4 expression (IHX 100x), g) High PDGFRA expression in both epithelial and stroma (IHX 100x), h) Low PDGFRA expression in both epithelial and stroma (IHX 100x), i) Negative PDGFRA expression in both epithelial and stroma (IHX 100x).

Expression of SMAD4 and PDGFRA in the studied cases

The expression of SMAD4 was diffusely maintained in 55.7% of cases, focal loss in 39.4% of cases, and completely negative in 4.9% of cases (two cases of SJP and one case of MJP), (Figs 1d, e, f). In addition, PDGFRA showed high epithelial expression in 66.7% of cases and high stromal expression in 54.1% of cases, (Figs 1g, h, i). The detailed expression was illustrated in table 2A.

There was no statistically significant difference in SMAD4 ($p = 0.757$) and PDGFRA expression ($p = 0.35$) between the three groups. There was a significant association between SMAD4 expression and PDGFRA epithelial expression ($p = 0.004$) as demonstrated in Table 2B.

Table (2): The immunohistochemical expression of SMAD4 and PDGFR in the studied cases:

A- The expression of SMAD4 and PDGFRA in the studied groups						
Variable	Frequency (%)					
SMAD4 expression Negative Focal loss Diffuse positive	 3 (4.9%) 24 (39.4%) 34 (55.7%)					
PDGFRA epithelial expression Low High	 20 (33.3%) 40 (66.7%)					
PDGFRA stromal expression Low High	 28 (45.9%) 33 (54.1%)					
B- The association between SMAD4 and PDGFR expression in the studied cases						
	PDGFR epithelial expression			**PDGFR stromal expression**		
SMAD4	**Low**	**High**	**Test P-value**	**Low**	**High**	**Test P-value**
Negative **Focal loss** **Diffuse**	3(15.0%) 11(55.0%) 6(30.0%)	0 (0.0%) 13(32.5%) 27(67.5%)	0.004**	3 (10.7%) 13 (46.4%) 12 (42.9%)	0 (0.0%) 11 (33.3%) 22 (66.7%)	0.057**

PDGFRA: Platelet derived growth factor receptor alpha, **** Fisher exact test**

Association between SMAD4 and PDGFRA expression and the clinicopathological data

There was a significant association between both blood and tissue eosinophilia and the diffuse maintained SMAD4 expression (p = 0.027 and p = 0.005, respectively). In addition, SMAD4 expression was significantly associated with type A juvenile polyps (p = 0.017), Table 3.

Table (3): The relation of SMAD4 expression with the clinicopathological data

Variables	**Negative No = 3**	**Focal loss No = 24**	**Diffuse No = 34**	**P-value**
Age (years) Mean ± SD Median (min-max)	 4.33 ± 1.53 4.0 (3.00–6.00)	 5.39 ± 2.60 4.75 (3.00–12.00)	 5.26 ± 2.56 5.0 (2.00–12.00)	**0.845***
Sex Male Female	 1 (33.3%) 2 (66.7%)	 13 (54.2%) 11 (45.8%)	 23 (67.6%) 11(32.4%)	**0.357****
Hemoglobin level (g/dL) Mean ± SD	 10.73 ± 0.21	 10.94 ± 0.87	 11.02 ± 0.93	**0.886***
Eosinophils Mean ± SD	 1.83 ± 0.21	 1.52 ± 0.46	 1.91 ± 0.55	**0.027***
Polyp size Mean ± SD	 1.47 ± 0.50	 1.09 ± 0.41	 0.99 ± 0.45	**0.205***
Tissue eosinophilia Mean ± SD	 10.67 ± 9.02	 26.54 ± 15.94	 37.85 ± 16.57	**0.005***
Polyp type Type A Type B	 2 (66.7%) 1 (33.3%)	 7 (29.2%) 17 (70.8%)	 3 (8.8%) 31 (91.2%)	**0.017****
Dysplasia Absent Indefinite	 3 (100.0%) 0 (0.0%)	 18 (75.0%) 6 (25.0%)	 20 (58.8%) 14 (41.2%)	**0.201****
Number of polyps SJP MJP JPS	 2 (66.7%) 1 (33.3%) 0 (0.0%)	 20 (83.3%) 2 (8.3%) 2 (8.3%)	 28 (82.4%) 4 (11.8%) 2 (5.9%)	**0.757****

SJP: Solitary juvenile polyp, **MJP:** Multiple juvenile polyps, **JPS:** Juvenile polyposis syndrome, *** Kruskal-Wallis Test ****

Fisher exact test

Regarding PDGFRA, there was a statistically significant association between PDGFRA epithelial overexpression, and the tissue eosinophilia (p = 0.008) as can be seen in Table 4.

Table (4): The relation of PDGFR expression with the clinicopathological data

	PDGFR Epithelial expression			**PDGFR Stromal expression**		
Variables	**Low No = 20**	**High No = 40**	**p-value**	**Low No = 29**	**High No = 33**	**p-value**
Age (years)	4.72 ± 2.18 4.0 (3.00–12.00)	5.57 ± 2.67 5.0 (2.00–12.00)	**0.241***	5.22 ± 2.56 5.0 (2.00–12.00)	5.32 ± 2.47 5.0 (2.00–12.00)	**0.820***
Gender Male Female	 10 (50.0%) 10 (50.0%)	 27 (67.5%) 13 (32.5%)	**0.189****	 17 (58.6%) 12 (41.4%)	 21 (63.6%) 12 (36.4%)	**0.686****
Eosinophils	1.68 ± 0.43	1.78 ± 0.28	**0.481***	1.68 ± 0.44	1.79 ± 0.61	**0.595***
Hemoglobin (g/dL)	10.85 ± 0.822	11.01 ± 0.89	**0.683***	10.89 ± 0.91	11.08 ± 0.87	**0.484***
Polyp size	1.12 ± 0.45	1.03 ± 0.44	**0.557***	1.04 ± 0.46	1.067 ± 0.42	**0.648***
Polyp type Type A Type B	 4 (20.0%) 16 (80.0%)	 7 (17.5%) 33 (82.5%)	**0.813****	 4 (13.8%) 25 (86.2%)	 8 (24.2%) 25 (75.8%)	**0.299****
Dysplasia Absent Indefinite	 15 (75.0%) 5 (25.0%)	 25 (62.5%) 15 (37.5%)	**0.333****	 20 (69.0%) 9 (31.0%)	 21 (63.6%) 12 (36.4%)	**0.658****
Tissue eosinophilia	24.15 ± 3.40	36.57 ± 5.46	**0.008***	29.10 ± 19.03	33.85 ± 16.345	**0.276***
Number of polyps SJP MJP JPS	 15 (75.0%) 4 (20.0%) 1 (5.0%)	 34 (85.0%) 3 (7.5%) 3 (7.5%)	**0.355 #**	 26 (89.7%) 2 (6.9%) 1 (3.4%)	 25 (75.8%) 5 (15.2%) 3 (9.1%)	**0.358 #**

PDGFRA: Platelet derived growth factor receptor alpha, **SJP:** Solitary juvenile polyp, **MJP:** Multiple juvenile polyps, **JPS:** Juvenile polyposis syndrome, *: Mann Whitney, #: Fisher exact test**, **:** Chi square**.**

Radiological imaging of patients with JPS

Thorough examinations of the three JPS cases showed no AVM or intracranial hemorrhage during MRI studies of the brain. Similarly, ECG and abdominal US revealed neither associated congenital heart disease nor AVM of the liver or abdominal lymphangioma, respectively. Barium meal follow-through revealed no associated gastric or small bowel polyps or intestinal malrotation.

Barium enema revealed a residual non-excised small sessile polyp 7 cm from the anal verge, whereas the other patient refused the examination, Fig. 2.

The third JPS case underwent subtotal colectomy and was advised to comply with regular follow-up by colonoscopy.

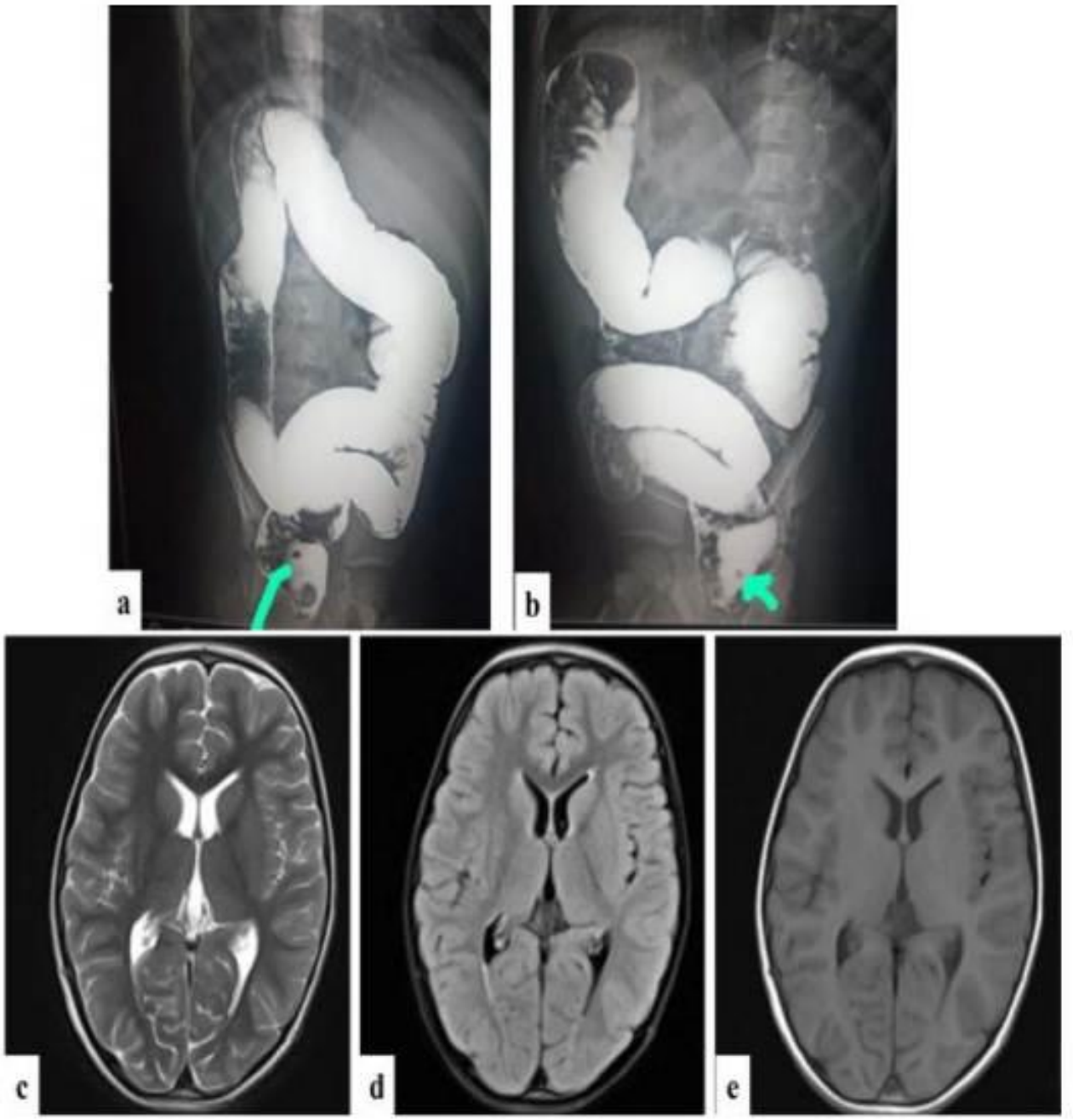

Fig. (2): Radiological imaging on patient with juvenile polyposis syndrome: a) and b) Double contrast barium enema shows small sessile 5 mm polyp at the sigmoid colon 7 cm from the anal verge, c), d) and e) Magnetic resonance imaging examination of the brain axial T2, FLAIR and T1 shows no evidence of arteriovenous malformations.

DISCUSSION

The pathogenesis of juvenile polyps is not well established. Different hypotheses point to the microenvironmental rather than neoplastic process. The present study showed a potential role of PDGFRA and tissue eosinophilia in the pathogenesis of juvenile polyps. To our knowledge this is the first study explore the histopathological and genetic similarity between juvenile polyps and IFP. The pathogenesis of juvenile polyp could require a crosstalk between allergy and genetic changes that necessitates further studies.

The current study showed prominent blood and tissue eosinophilia in all groups of juvenile polyps, which is consistent with the findings of previous studies [(3)]. Increased mucosal eosinophilia induced an inflammatory response, which contributes to mucosal overgrowth [(17)]. Two theories of the role of mucosal eosinophilia in colonic polyps were reported. The first was reported by **Alexander *et al.* [(18)],** who found patients with family or individual histories of allergy-developed juvenile polyps. The role of allergy is supported by a study performed by **Roma-Giannikou[(3)],** who found increased tissue eosinophilia in both the polyp and adjacent colonic mucosa. The positive association of blood and tissue eosinophilia in our study could support this hypothesis. The second theory was put forward by **Moezzi *et al.* [(19)],** who found stromal eosinophilia in early preneoplastic colonic lesions. However, no strong evidence validates this theory. Therefore, we aimed to link tissue eosinophilia with the expression of both SMAD4 and PDGFRA to highlight a possible neoplastic association.

In the present study, SMAD4 was expressed in most cases of juvenile polyps and specifically in all JPS cases. Patients with focal loss of SMAD4 shared the same clinicopathological criteria of diffuse SMAD4 expression. In addition, nearly two-thirds and half of juvenile polyp cases showed PDGFRA overexpression in the epithelia and stroma, respectively. In addition, the expression levels did not differ significantly with the number or type of polyps. We did not find any previous studies to which we could compare this finding. PDGFRA promotes epithelial proliferation and induces tumor stromal growth and vasculature through the downregulation of several pathways [(20)].

Moreover, we observed a significant association between tissue eosinophilia and PDGFR overexpression in all groups of juvenile polyps. IFP and juvenile polyps shared some histological features, which include vascular proliferation and inflammatory stroma rich in eosinophils [(21)]. *PDGFRA* mutation was established in the pathogenesis of IFP [(22)]. In addition, eosinophilia was reported in several hematological malignancies that showed *FIP1L1-PDGFRA* gene fusion [(23, 24)]. These neoplasms were combined with multisystem infiltration by neoplastic eosinophils that produce several pro-inflammatory cytokines and induced tissue damage [(25, 22)].

Therefore, *PDGFRA* expression could play a dual role in enhancing both the epithelial and stromal elements in juvenile polyps. In addition, PDGFRA and eosinophilia could participate in the pathogenesis of juvenile polyps, independent of SMAD4. Neoplasia of the epithelial cells was proposed to be either induced by the microenvironment or induced through genetic background [(26, 27, 28)]. This could raise questions regarding the neoplastic nature of polyps. Further studies and genetic analyses are recommended to validate our results and to highlight the nature of mutations. We concluded that tissue eosinophilia and PDGFRA overexpression are commonly observed in juvenile polyp in cases maintained SMAD4 expression. Their role is independent of the type or number of polyps. The pathogenesis of juvenile polyp could be a crosstalk between allergic and genetic mechanisms.

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