REVIEW ARTICLE

CONTENTS

Diffuse familial adenomatous intestinal polyposis in childhood: current state of the problem and case report

Tetiana Shatynska, Iryna Lembryk, Orysia Tsytsiura, Oleksandra Zhyliak, Anastasiya Stefanyshyn, Nataliia Kostyrko, Yuliia Bodnarchuk

IVANO-FRANKIVSK NATIONAL MEDICAL UNIVERSITY, IVANO-FRANKIVSK, UKRAINE

ABSTRACT

Aim: To explore the prevalence, clinical characteristics, and diagnostic aspects of diffuse familial adenomatous polyposis in childhood. This objective is accomplished through an extensive review of recent literature, and the presentation of case report from our clinical practice.

Materials and Methods: We analyzed 75 scientific papers, the findings of which have been documented in the PubMed database. Our search criteria included keywords such as «diffuse familial adenomatous intestinal polyposis,» «children,» and «diagnosis.» Then we conducted a second-stage analysis that involved a detailed review of a practical case – the medical records of inpatient Kh.V. who had been diagnosed with familial adenomatous polyposis.

Conclusions: The analysis of the literature data is consistent with the findings from our clinical observations of familial adenomatous polyposis in a patient with complicated family anamnesis. It is worth noting that clinical features do not significantly differ across various types of polyposis. In cases of suspected familial adenomatous polyposis in adolescents, genetic testing is crucial.

KEY WORDS: Child, polyps, diagnosis, therapeutics

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INTRODUCTION

Diffuse FAP is a rare hereditary systemic disease that predominantly impacts children [1]. This condition is characterized by the formation of numerous polyps and microadenomas in the large intestine [2, 3]. Notably, diffuse familial adenomatous polyposis plays a pivotal role in carcinogenesis among adult patients, warranting close attention from clinicians, including pediatricians and family doctors, to closely monitor the disease progression [4, 5].

In the literature, there are references to the cumulative impact of various environmental and genetic factors on patients with FAP. This interplay is believed to contribute to significant inter- and intra-family variations in the colorectal phenotype during the tumor development process [6]. It is worth noting that research in this field is ongoing despite the sporadic nature of this pathology.

AIM

This study aims to explore the prevalence, clinical characteristics, and diagnostic aspects of diffuse familial adenomatous polyposis in childhood. This objective is accomplished through an extensive review of recent literature and the presentation of the case report from our clinical practice.

MATERIALS AND METHODS

In pursuit of our research objectives, we meticulously analyzed 75 relevant scientific papers, the findings of which have been documented in the PubMed database. Our search criteria included keywords such as «diffuse familial adenomatous intestinal polyposis,» «children,» and «diagnosis.» Additionally, we conducted a second-stage analysis that involved a detailed review of a practical case – specifically, the medical records of inpatient Kh.V. who had been diagnosed with the condition mentioned above.

REVIEW AND DISCUSSION

The study of familial adenomatous polyposis has a rich history, dating back to 1726 when it was initially described by Menzelio. In 1882, B. Gripps further contributed to the understanding of this disease and established its familial nature. A significant milestone occurred in 1925 when St. Mark's Hospital in London

created a registry of 1238 individuals from 510 families with a preliminary diagnosis of diffuse familial polyposis [7].

In 1975, H. Bussey conducted more in-depth research on the disease, offering a detailed description of the clinical and pathomorphological aspects [7]. The year 1986 marked a breakthrough when researchers first described the genetic basis of familial adenomatous polyposis. In 1991, the APC gene responsible for the development of intestinal familial adenomatous polyposis was identified [7].

Some researchers have also investigated the rare hereditary forms of polyposis, including familial adenomatous polyposis, Cowden syndrome, Li-Fraumeni syndrome, MUTYH-associated polyposis, juvenile polyposis syndrome, and Peutz-Jeghers syndrome [2]. However, it is important to note that there is still a shortage of comprehensive data on this topic, indicating a need for further research in this area.

Today, it is firmly established that diffuse familial adenomatous polyposis primarily exhibits an autosomal dominant mode of inheritance and accounts for approximately 1% of colorectal cancer cases within the population [2]. This disease is closely linked to mutations in the highly penetrant tumor suppressor gene (TSG) known as the Adenomatous Polyposis Coli (APC gene), responsible for regulating cell proliferation in the gastrointestinal mucosa. The APC gene is located on the 5th chromosome (5q21-22; OMIMNM_000038.5), and there are over a thousand known mutations in this gene, all of which are documented in the international database of genetic mutations – the Human Gene Mutation Database [2].

It's essential to note that individuals carrying mutations in the APC gene face a near 100% risk of developing diffuse familial polyposis and colon cancer [8]. Furthermore, these patients also have an elevated risk of other tumor processes, particularly gastroblastoma, duodenoblastoma, and hepatoblastoma. This underscores the significance of close clinical monitoring and intervention in these cases [9].

Undoubtedly, comprehensive genetic testing and health monitoring for adolescents with FAP are crucial for early diagnosis and the prevention of malignancy resulting from detected pathomorphological changes. However, it's worth acknowledging the challenge of precisely identifying the genetic subtype of this pathology. This difficulty arises from the fact that approximately 30% of children either lack a family history burdened by the condition or possess spontaneous de novo mutations in the APC gene [10].

It is essential to emphasize that the identification of specific pathogenic APC variants and understanding the correlations between genotype and phenotype play a vital role in monitoring the health and managing family members who may be at risk due to a compromised immune system or a history of colorectal cancer.

CASE REPORT

A boy named Kh. V., born in 2006, was admitted to the specialized department of the CNE "Ivano-Frankivsk RCCH IFRC". He reported experiencing periodic cramping, spastic abdominal pain, which tended to occur more frequently after meals. This pain was often associated with defecation, did not radiate, and was accompanied by occasional heartburn. He also mentioned experiencing episodes of nausea, unstable bowel movements occurring 6 to 8 times a day, severe bloating, decreased appetite, fatigue, weakness, nasal congestion, and conjunctivitis.

MEDICAL HISTORY

These complaints had been troubling him for the past 2 months and had gone untreated, which led to his admission to the Ivano-Frankivsk Regional Children's Clinical Hospital for further examination and treatment.

LIFE HISTORY

The boy's growth and development were by his age. He was born full-term via normal delivery and was up to date with his vaccinations. He had no known allergies and had a notable family history on his paternal side, with both his grandmother and father having a history of familial adenomatous polyposis.

OBJECTIVE FINDINGS

The boy's body weight was 69 kg, and his general condition was moderately severe. His constitution was normosthenic. His skin appeared pink and clean, with atopic dermatitis observed on the cheeks and dryness noted on the elbows. Normal skin turgor was observed, and his sclerae were normal. In the oral cavity, the tongue was thickly coated with white-grey plaque and appeared dry. Submandibular, and anterior cervical lymph nodes were palpable. Respiratory examination revealed vesicular breathing without wheezing, with a respiratory rate of 18 breaths per minute. In the pharynx, there was hyperaemia of the posterior wall, and nasal breathing was slightly difficult.

Cardiovascular assessment revealed audible, rhythmic, and clear heart sounds, with a heart rate of 78 beats per minute. The heart limits were within the

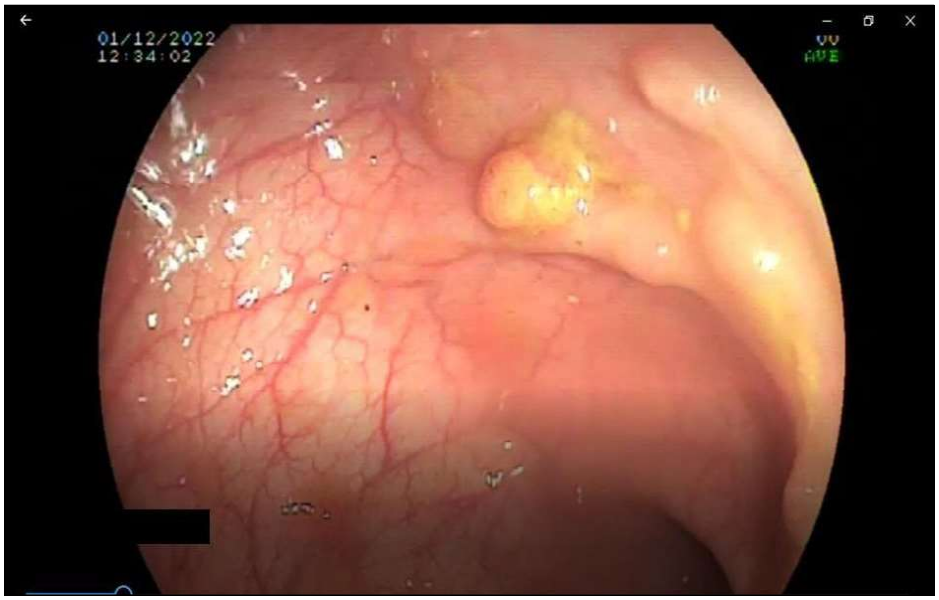

Fig. 1. Colonoscopy of the patient Kh.V.

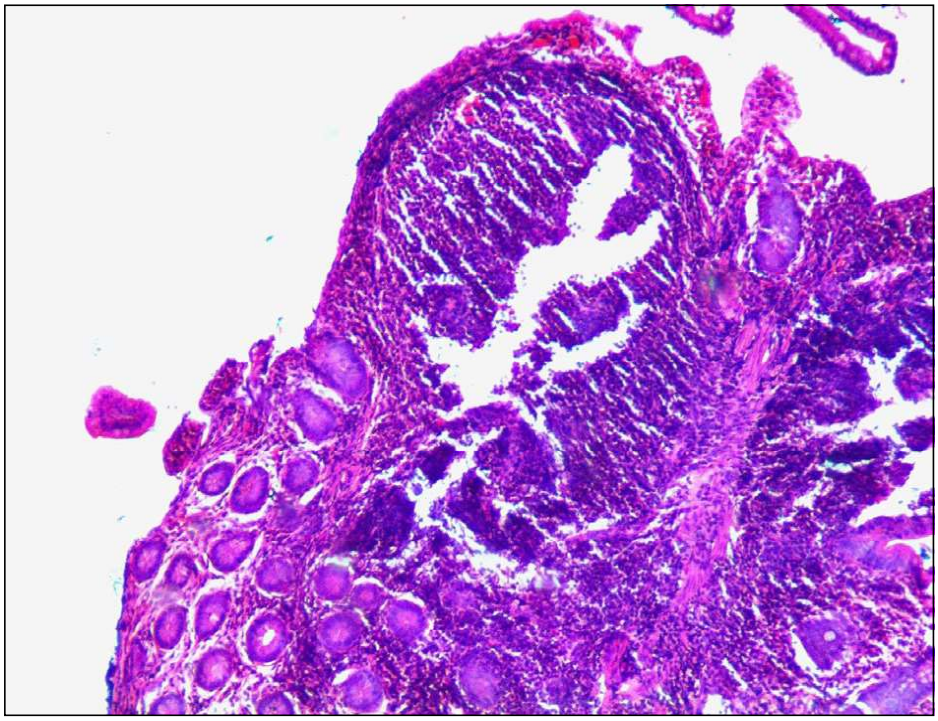

Fig. 2. Biopsy findings in the intestinal mucosa of the patient Kh.V. (H&E stain, x 100 magnification).

age-appropriate range. Upon abdominal examination, the abdomen was soft upon palpation, but tenderness was noted in the epigastric, and umbilical regions, as well as both retroperitoneal areas. The abdomen was distended. The liver, and spleen were not palpable. Segments of the intestine were distended, and spasmodic in both the ileum. Stools occurred 6 to 8 times a day, and they were hard and lumpy.

LABORATORY TESTS AND INVESTIGATIONS

Complete blood count: Hb -158 g/l, erythrocytes 5,23x10^{12}, CI 0,91, leukocytes 7,86x10^{9}, eosinophils 2%, bands 4%, segmented 64%, lymphocytes 20%, monocytes 10%, platelets 214x10^{9}, ESR 4,76.

Biochemical blood assay: ALT 32 U/l, AST 69 U/l, TSB 19.42 µmol/l, direct bilirubin 3.49 µmol/l, indirect bilirubin 15.93 µmol/l, thymol test 1.43 U, total protein 70.0 g/l, BUN 5.2 mmol/l, creatinine 93 µmol/л, amylase 54 (normal range 0–90), glucose 4.7 mmol/l.

Urinalysis: specific gravity 1024, protein – scarce, color – yellow, transparent, pH 6.0, mucous +, leucocytes 3 to 4 per high power field, epithelium 7 to 9 per high power field.

C-reactive protein: 32.4 mg/l (normal range <5). Saccharomyces cerevisiae IgA 0.09 (<1.0), Saccharomyces cerevisiae IgG 0.04 (<1.0).

Fecal calprotectin: 738.0 mcg/g (<50).

Blood type: A (II), Rh+ positive.

Coagulation studies: aPTT 28.2, PT 10.9 sec, PTI 101%, QuicK index 89%, INR 0.99, fibrinogen 2.77 g/l.

Ova stool exam: ova are not detected, no blood in stools.

Esophagogastroduodenoscopy No.524: erosive exudative erythematous reflux esophagitis, catarrhal, and stagnant gastroduodenopathy, along with increased acid production. There are small polyps in the sub-cardiac region. Indirect signs of hepatobiliary dysfunction. pH 1–2.0.

Colonoscopy data are shown below (Fig. 1.).

Colonoscopy report No. 26: During the colonoscopy, an examination of the large intestine up to, and including the dome of the cecum, and the terminal ileum was conducted. The intestine was found to be fully passable. Throughout the large intestine, remnants of turbid, yellow-colored flush water were observed, which were subsequently washed, and removed. Peristalsis was noted as preserved.

The folding of the intestine was maintained, and conformed to anatomical norms. The folds were moderately thickened, and could be unfolded by the introduction of air. In the terminal ileum, rounded folds were present, without thickening. The mucous membrane appeared pink, finely villous, and featured multiple rounded polypoid formations, ranging in size from 0.5 x 0.5 to 1 x 1 mm.

Within the cecum, an oval-shaped appendix pupil was observed, and the ileocecal angle was found to be lip-shaped, and closed. The mucous membrane of the examined sections of the large intestine displayed a shiny, elastic, pink appearance throughout, with areas of erythema, predominantly more pronounced in the left parts of the colon. The vascular pattern of the intestine was preserved, with regular contours, although some blurring was noted in the sigmoid colon.

In the colon, with the majority located in the rectum, and sigmoid colon, multiple rounded polypoid lesions were observed. These lesions had a broad base, and varied in size, ranging from 1 x 0.5 x 0.5 mm to 4 to 5 x 3 x 2 mm. Most of these lesions appeared pink in color, while some were bright red. The anal canal was found to be free-flowing, with pink mucosa. Additionally, there were moderately expressed anal papillae.

Abdominal ultrasound: The liver is positioned typically, protruding 1 cm below the costal arch. The liver parenchyma displays normal echogenicity. Hepatic veins are not remarkable. Bile ducts are slightly thickened. The portal vein measures 9 mm, with unobstructed blood flow, and the choledochus is not dilated.

The gallbladder is ovally shaped, with a volume of 29 cm^3 after oral liquid consumption. The gallbladder wall is not thickened, and its content appears heterogeneous with sediment. The pancreas is visible in its entirety, exhibiting a heterogeneous structure with multiple hyperechogenic inclusions. The parenchyma is isoechogenic. The spleen is of normal size, featuring a homogeneous structure and an additional lobe. Kidneys are typically located with even, and clear contours. Differentiation of the cortical, and medullary layers is preserved. The collecting system of kidneys is not widened, and appears thickened. In the stomach, there is a significant amount of residual content, and the stomach wall measures 4.1 mm, with signs of flatulence. Paraumbilical lymph nodes have a diameter of 8 to 10 mm. The bladder has a volume of 40 cc with sediment.

Thyroid ultrasonography: The thyroid gland is normally positioned, and not enlarged. The isthmus width is 4 mm. The right lobe has a volume of 5.4 cm^3, and the left lobe has a volume of 4.3 cm^3. The echo structure of thyroid gland appears heterogeneous due to the presence of small follicles with calcifications. The blood supply exhibits moderate intensity in the Doppler spectral sonography. The total thyroid volume is 9.7 cm^3, which falls within the normal range of 5.58 to 12.44 cm^3.

ECG: Wandering atrial pacemaker, abnormal ventricular repolarization. Sinus rhythm, with a heart rate ranging from 56 to 68 beats per minute, bradycardia. Increased ECG voltage observed in the left chest leads.

Chest X-Ray No. 16155: not remarkable.

Sinus X-Ray No. 16156: subtotal opacification of paranasal sinuses bilaterally.

The obtained intestinal biopsy data are shown in Fig. 2.

Biopsy of the intestinal mucosa No. 1468-75:

1. The specimen consists of fragments of the small intestine mucosa. Submucosal lymphoid infiltration is evident in certain sections. The crypts remain intact. This finding may be indicative of Crohn's disease, and necessitates clinical correlation and ongoing monitoring of biopsy changes over time.

2. Fragments from the colon mucosa show polypoid hyperemia, and focal proliferation of glandular epithelium, which aligns with familial adenomatous polyposis.

Consultation by a surgeon: No signs of acute surgical condition were observed during the examination.

Consultation by an ophthalmologist: allergic conjunctivitis.

ENT consultation: acute sinusitis. Recommended: antibiotic therapy, glucocorticosteroid nasal sprays (Etacid), nasal decongestant (Nasivin), H1-blockers (Cetrine).

Genetic testing: 19CN003493 mutation of the APC gene was detected.

Treatment: mesalazine, proton pump inhibitors, probiotics, antibiotics, mucolytic drugs, nasal irrigation, hepatoprotective drugs, glucocorticosteroid nasal sprays, H1-blockers.

RECOMMENDATIONS

Follow-up by a paediatric oncologist, gastroenterologist, and surgeon;

Genetic testing of the polyp biopsy specimens (planned visit in the out-patient setting);

Plan for hospitalization one year from now (including esophagogastroduodenoscopy and colonoscopy);

Salofalk 1000 mg three times a day and 500 mg in the evening for one month, with potential long-term use, subject to dose adjustment;

Probiotics (Enterol 250) at a dosage of 1 cap. two times a day for two weeks;

Faecal calprotectin in one month;

Complete blood count, and liver function tests (AST, ALT) in two weeks for follow-up, and once a month thereafter;

Decoction of flaxseed: one tablespoon three times a day before meals for three months;

Hepatoprotective drugs (Ursofalk) 500 mg at bedtime for three months;

Sea Buckthorn Oil: one teaspoon twice a day before meals for three months;

Sanatorium treatment during periods of remission (Morshyn and Myrhorod);

Treatment effectiveness: The patient is discharged with improvement.

As commonly noted in scientific literature, adenomas in the intestine typically manifest during the second decade of life, with clinical symptoms becoming apparent around the age of 16, and their prevalence increases in the third decade [2, 11]. Given the natural progression of intestinal processes, colorectal cancer may emerge in this patient cohort around the age of 40 [2, 11, 12]. It is important to recognize that both the development of colorectal cancer, and the formation of adenomas in the intestine are parallel pathological processes that do not necessarily contradict each other [13].

Recent scientific research has revealed specific correlations between the severity of clinical symptoms in familial adenomatous polyposis and specific mutations in the APC gene. This genetic insight aids in identifying distinct subtypes of FAP [14].

Moreover, more than 70% of FAP patients may exhibit not only intestinal manifestations but also extraintestinal symptoms, which can align with certain syndromes. These include Gardner syndrome, Turcot syndrome, and attenuated FAP [8, 13]. For example, Gardner syndrome presents with intestinal polyposis alongside dental abnormalities, osteomas, and soft tissue tumors. Turcot syndrome is characterized by both: intestinal polyps similar to those in FAP, and central nervous system tumors. Other forms of polyposis share clinical similarities with FAP and attenuated adenomatous polyposis but differ significantly in terms of the number of polyps (ranging from 10 to 100), and the age of symptom onset, which is typically later. Specifically, attenuated familial adenomatous polyposis is characterized by the presence of single intestinal polyps, usually around 30 to 35 in number, with approximately 8% of them occurring in the proximal intestine.

A review of the existing literature indicates that patients with FAP exhibit varying phenotypes, and the associated extraintestinal manifestations can significantly differ, with their occurrence observed in about 40% of cases. Our current understanding of this condition aligns with the prevailing notion that colorectal cancer had been the leading cause of mortality in FAP patients for many years. However, this trend is gradually changing due to enhanced surveillance, early diagnosis, and preventive surgical interventions.

Notably, desmoid tumors, and tumors in the upper digestive tract pose greater risks in terms of malignancy and mortality [14, 15].

When examining the spectrum of polyposis syndromes, it becomes apparent that patients with multiple adenomatous polyps are more likely to exhibit signs of FAP or its variants. Less frequently, patients may have attenuated familial adenomatous polyposis or MYH-associated polyposis (MAP) [2, 10].

For individuals suspected of having a polyposis syndrome, genetic testing is recommended. If no APC gene mutation is detected, further evaluation should include MYH gene testing to assess the potential development of MAP. According to the literature, approximately 10 to 20% of patients who do not carry an APC gene mutation exhibit biallelic MYH gene mutations [10]. This particular form of polyposis is extremely challenging to clinically differentiate from FAP or attenuated familial adenomatous polyposis. The condition is characterized by the presence of small intestinal polyps, ranging from 10 to 100. Notably, this variant of polyposis is associated with older age of onset, autosomal recessive inheritance, and typically lacks a family history of colorectal carcinoma symptoms. Duodenal polyps can be detected in approximately one-fifth of patients with this syndrome [7, 8], but there is no heightened risk of developing other cancer types associated with it.

It's important to highlight that the patient under our observation experienced clinical symptoms at a specific age of 16 years, aligning with the data found in the literature [2, 16]. Additionally, the patient had a family history of the condition. Given that the clinical symptoms in both of our cases were relatively mild, and not highly distinctive, the results of colonoscopy and intestinal biopsy played a crucial role in confirming

the diagnosis FAP. As mentioned earlier, other forms of intestinal polyposis generally present with clinical symptoms at a later age, fewer polyps within the intestinal mucosa, or in combination with other syndromes.

When comparing the clinical case we described with similar cases in the literature, we identified both common and distinct features.

All these cases share a common characteristic of being sporadic, and typically presenting with relatively mild clinical symptoms due to their later onset. The age at which symptoms manifest can vary among cases. For example, in contrast to our study, one case reported in the literature involved a 10-year-old boy with an early onset of clinical symptoms at just one year of age. Additionally, some cases have no family history of the disease or colorectal cancer, unlike the cases we observed.

CONCLUSIONS

1. Familial adenomatous polyposis in childhood is a rare hereditary precancerous disease characterized by an autosomal dominant mode of inheritance. It is primarily caused by pathogenic germline variants in the adenomatous polyposis tumor suppressor (APC) gene, which leads to colorectal cancer in 1% of cases.
2. The analysis of the literature data is consistent with the findings from our clinical observations of familial adenomatous polyposis in a patient with complicated family anamnesis. It is worth noting that clinical features do not significantly differ across various types of polyposis, making them insufficient as the primary diagnostic criterion.
3. In cases of suspected FAP in adolescents, genetic testing is crucial to confirm the diagnosis of familial polyposis, and to refine diagnostic and therapeutic strategies.

FUTURE RESEARCH PROSPECTS

Addressing the feasibility of laparoscopic prophylactic colectomy in the examined patient.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

CORRESPONDING AUTHOR

Tetiana Shatynska
Ivano-Frankivsk National Medical University
132 Konovaltsia, 76014, Ivano-Frankivsk, Ukraine
e-mail: tetjanaua16@gmail.com

ORCID AND CONTRIBUTIONSHIP

Tetiana Shatynska: 0009-0002-9932-0145 D
Iryna Lembryk: 0000-0001-7584-7407 A
Orysia Tsytsiura: 0009-0004-9962-2690 B
Oleksandra Zhyliak: 0000-0003-0152-6277 B
Anastasiya Stefanyshyn: 0000-0001-8258-9477 D
Nataliia Kostyrko: 0009-0007-7676-2764 E
Yuliia Bodnarchuk: 0000-0001-8031-5368 F

A – Work concept and design, B – Data collection and analysis, C – Responsibility for statistical analysis, D – Writing the article, E – Critical review, F – Final approval of the article

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