Diversity in polyp pathology and distribution of Familial Juvenile Polyposis Syndrome

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ABSTRACT

Objective: Juvenile polyposis syndrome is a rare autosomal dominant disorder with incomplete penetrance. The aim of this study was to review our experience with juvenile polyposis syndrome with emphasis on the diversity of polyp pathology and distribution and the recommended treatment.

Methods: Over the period January 1994 through February 2001, 10 family members were managed at Princess Basma Teaching Hospital, Irbid, Jordan. Two siblings with juvenile polyposis syndrome are discussed.

Results: The polyps were unusually concentrated in the rectum. In one patient the polyps were purely of the adenomatous type. The father suffered from non-polyposis colon cancer at the age of 35.

Conclusion: Proctocolectomy and ileal pouch-anal anastomosis is recommended as the treatment of choice. Screening of juvenile polyposis syndrome patients and their relatives is emphasized for early detection of malignancy.

Keywords: Juvenile polyposis syndrome, hereditary mixed polyposis syndrome, polyposis, colon cancer.

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Juvenile polyposis syndrome (JPS) is a rare disorder which has been described in families as early as 1964.[1] The disease can occur as an isolated condition or in association with other genetic syndromes.[2] The isolated form is an autosomal dominant disorder with incomplete penetrance, as well as, variable expressivity.[3-5] Germ-line mutations in SMAD4 (DPC4) tumor suppresser gene located on chromosome 18q account for a subset but not all of the JPS cases.[6-7] Some other cases are attributed to mutations in PTEN, another tumor suppresser gene located on chromosome 10q.[8] On the other hand, the hereditary mixed polyposis syndrome (HMPS) can be considered a variant of JPS.[9] This disorder was mapped to a locus on the long arm of chromosome 6 in one large family.[9] However, it is thought that the different identified loci represent an interaction between disease causing-genes, modifier loci and environmental factors. Juvenile polyposis syndrome has been associated with gastrointestinal malignancy in the patients themselves and in relatives, but seems to be unrelated to the polyps.[10-11]

Methods. Over the period January 1994 through February 2001, 10 family members were managed at Princess Basma Teaching Hospital, Irbid, Jordan. Two siblings (individuals V6 and V7, **Figure 1**) were diagnosed as having JPS while their father (individual IV2, **Figure 1**) was diagnosed as having

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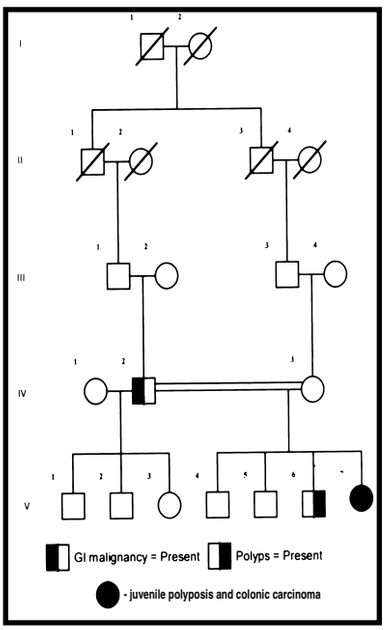

Figure 1 - Five generation pedigree of the family showing individual IV 2 to have gastrointestinal malignancy, V6 to have polyps and V7 to have juvenile polyposis and colonic carcinoma, IV - 4, V- 5.

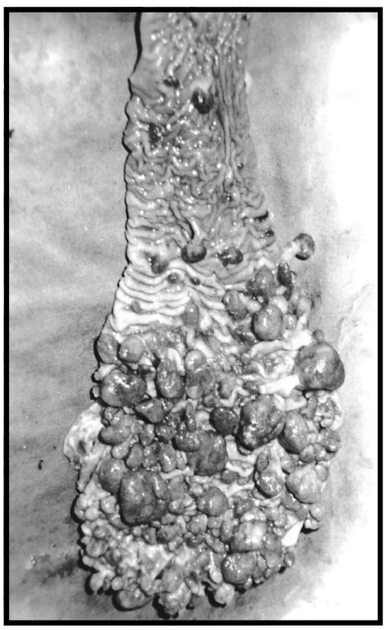

Figure 2 - Photograph from patient 2 showing the rectum (part of total proctocolectomy) stud with polyps.

sigmoid colon adenocarcinoma. The affected 2 siblings were evaluated by full blood count, colonoscopy and multiple polyp biopsies, and barium follow through. They have been follow-up for the last 7 and 5.5 years following their surgical management. The affected father has been under follow-up for the last 5 years including clinical examination and repeated colonscopy. the remaining siblings (individuals V1-5, **Figure 1**) were evaluated by colonoscopy once followed by clinical follow-up over the last 5 years. The mother (individuals IV1 and IV3, **Figure 1**) refused colonoscopy or radioloical evaluation.

Results. In this report, we describe 2 siblings with JPS whose father suffered from non-polyposis colon cancer at an early age (**Figure 1**). The distribution of the polyps was unusually concentrated in the rectum and the pathology of the polyps in one patient which was unusual in being of the adenomatous type. Patient one (individual V6, **Figure 1**) is a male product of a 2nd cousin marriage. He was seen in January 1994 at the age of 6 years, because he started to pass blood during and after defecation. He gave a history of the passage of sloughed polyps and severe anemia at 7 gm/dl (normal range 12-16gm/dl) necessitating multiple blood transfusions. Colonoscopy revealed multiple polyps involving the whole colon. Barium follow through did not reveal any small intestinal polyps. The patient underwent endoscopic excision of the rectal polyps, total colectomy and ileorectal anastomosis. Gross pathological examination revealed 2 clusters of polyps one in the cecum where 70 polyps were counted ranging between 0.2 and 1.5 cm in size. The other cluster was in the distal colon were 20 polyps were counted some of them very near to the resection margin. The pathological diagnosis was juvenile polyposis coli. Rectal follow up was planned but the patient was lost to follow up. The patient was referred to our hospital 3 years later, September 1997, at the age of 9 years with recurrence of bleeding, frequent bowel motions (>7 times/24 hours), anemia and growth retardation. Proctoscopic evaluation revealed a rectum studded with polyps. The patient underwent restorative proctectomy and J ileal pouch-anal anastomosis. Pathology confirmed the previous diagnosis. Follow up showed good pouch function with 2-3 bowel motions/24 hours, normal hemoglobin and growth profile. At 7 months follow-up there is no evidence of polyps elsewhere in the remaining gastrointestinal tract.

Patient 2 (individual V7, **Figure 1**) is the sister of patient one. She came to our care in June, 1995 at the age of 13 years with a 5 month history of passing blood and mucous per rectum along with headache and dizziness. Examination revealed a pale patient and multiple polyps were felt by rectal examination. Her hemoglobin was 9 gm/dl (normal range 12-16 gm/dl). Colonoscopy revealed that the rectum and lower sigmoid were studded with polyps of different sizes both sessile and pedunculated with scattered

polyps in the remaining colon. The patient underwent restorative proctocolectomy and J ileal pouch-anal anastomosis and a covering ileostomy that was closed 10 weeks later. Follow up showed dramatic improvement in the general health. She passes 1-2 bowel motions per day with no soiling, complete control of defecation and full discrimination between flatus and stool. Gross pathology revealed multiple different sized polyps with up to 110 counted, both sessile and pedunculated concentrated in the rectum and to a lesser extent in the cecum, the largest polyp was 3x2.5x1.5 cm (**Figure 2**). Pathology revealed adenomatous polyps, the majority with mild dysplasia. In some polyps severe dysplasia was seen and in fewer polyps carcinoma in situ was noticed. To date, there is no evidence of polyps elsewhere in the gastrointestinal tract.

Family history revealed that the father of patients one and 2 (Individual IV2, **Figure 1**) underwent high anterior resection for a moderately differentiated sigmoid colon adenocarcinoma at the age of 35 years. He is still doing well more than 5 years after surgery. Follow up colonoscopy and barium follow through did not reveal any colonic or extracolonic polyps.

Discussion. Juvenile polyposis is a rare condition characterized by the development of multiple juvenile polyps in the gastrointestinal tract.[12] The malignant potential was only recognized in 1981.[3-4,13-14] Malignant predisposition involves the colon and other parts of the gastrointestinal tract.[15] It also involves other relatives who are at risk for the development of colon cancer. This calls for screening of the relatives including those who do not develop polyposis. The father of our 2 patients is a clear example as he developed non-polyposis colon cancer at the age of 35 years. This malignant predisposition differentiates this condition from solitary juvenile polyps, which do not change malignancy and do not require further follow up of investigations of the patients or their relatives.[16] The mode of inheritance of this disorder in this family is clearly conforming to the previously reported autosomal dominant pattern with incomplete penetrance. It seems that the father who suffered from the gastrointestinal malignancy is the transmitting parent, a fact that puts his offspring at risk for developing polyposis or malignancy. The half siblings and the full siblings of the 2 affected sibs (patient one and patient 2) are at risk and should be followed periodically.

Juvenile polyps originate in the lamina propria.[8] The lesion is characteristically non-neoplastic which is distinct from the neoplastic lesion of adenomatous polyposis.[17] They are regarded as hamartomatous whether occurring in familial syndrome or sporadic settings.[18] Dysplasia was reported in 31% of syndromic juvenile polyps but not in sporadic juvenile polyps.[18] More genetic alterations that are usually involved in colorectal neoplasia were found in JPS polyps compared to sporadic ones.[18] Neoplastic changes frequently occur in juvenile polyps of the familial variety ranging from focal to extensive adenomatous changes to adenocarcinoma.[14] The pathology of the polyps in patient one was typical of juvenile polyps. However, those in patient 2 were of the classical adenomatous variety with dysplasia and carcinoma in situ which is unusual for JPS. Hereditary mixed polyposis syndrome is a variant form of juvenile polyposis where bizarre mixtures of different sorts of polyps adenomatous, hyperplastic and hamartomatous occur in the same patient.[19] This does not fit the condition of our 2 patients where the pathology in each is quite distinct but different from each other.

Three forms of the disease have been described:[20] 1. Juvenile polyposis of infancy, which affects the whole gastrointestinal tract. 2. Generalized juvenile polyposis, and 3. Juvenile polyposis of the colon. Presentation is usually by bleeding, anemia, prolapse or intussusception. Juvenile polyposis of infancy presents early and may lead to death in the first 2 years of life, the other 2 forms usually present in the first or 2nd decades of life or even later. Our 2 patients fit the juvenile polyposis of the colon variety as judged from the site of pathology and the time and type of presentation. Extra-colonic abnormalities were reported in 11-20% of the patients;[21] none of these abnormalities were present in our patients.

Diagnosis is made in the presence of more than 10 colonic juvenile polyps, diffuse gastrointestinal juvenile polyps or any number of juvenile polyps in a patient with a family history of juvenile polyposis.[20] Fewer then 10 polyps may also suggest the diagnosis.[4,22] Polyps in the colon and rectum in this syndrome were reported as being evenly distributed through the large bowel,[23] or more numerous in the right colon fewer in the descending and none in the rectum.[24] Contrary to that, our 2 patients showed clustering of the polyps in 2 sites, the rectum and the cecum.

The treatment alternatives range between colonoscopic polypectomy followed by colonoscopic surveillance, colectomy with ileorectal anastomosis and proctocolectomy and ileal pouch anal anastomosis.[22-25] Any treatment less than total proctocolectomy could not be looked at as being reasonable in our 2 patients. The systemic manifestations of anemia and malnutrition were severe and the number of polyps particularly in the rectum were beyond endoscopic capacity. As important, the adenomatous type of pathology puts the patient at a high risk of malignancy as seen by the dysplasia and carcinoma in situ in many polyps of patient 2.

In conclusion, our 2 patients with JPS showed different types of pathology compared to each other,

different distribution of polyps from what is known, and severe symptoms necessitating early proctocolectomy and ileal pouch-anal anastomosis which resulted in cure. The development of early non-polyposis colon cancer by the father emphasizes the need for the evaluation of the relatives including those who do not have the disease manifested by polyp development.

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