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Juvenile polyposis of infancy in a child with deletion of *BMPR1A* and *PTEN* genes: Surgical approach

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Abstract Juvenile polyposis of infancy is the most severe and life-threatening form of juvenile polyposis. This disease typically presents in the first two years of life with gastrointestinal bleeding, diarrhea, inanition, and exudative enteropathy. In very few reports concerning this entity, a large deletion in the long arm of chromosome 10 (10q23), encompassing the PTEN and BMPR1A genes, was found. The authors report a case of delayed diagnosis of juvenile polyposis of infancy at 6 years of age. A 3.34 Mb long de novo deletion was identified at 10q23.1q23.31, encompassing the PTEN and BMPR1A genes. The disease course was severe with diarrhea, abdominal pain, inanition, refractory anemia, rectal bleeding, hypoalbuminemia, and exudative enteropathy. A sub-total colectomy, combined with intraoperative endoscopic removal of ileal and rectal stump polyps, was required for palliative disease control.

Juvenile polyposis is a rare condition, defined as the occurrence of multiple juvenile hamartomatous polyps in the gastrointestinal tract [1,2]. It includes a clinically and genetically heterogeneous group of conditions and more often presents in older children and young adults [2].

The association of juvenile polyposis and multisystemic involvement is now designated as "*PTEN* Hamartoma Tumor Syndrome" and encompasses several clinically distinct syndromes associated with germline mutations in the tumor suppressor gene *PTEN* located at chromosome 10q23: Cowden disease, Lhermitte–Duclos disease, Bannayan–Riley–Ruvalcaba Syndrome and Proteus/Proteus-like Syndrome [2].

In the absence of extra-intestinal features consistent with *PTEN* Hamartoma Tumor Syndrome, the diagnosis of Juvenile Polyposis Syndrome (JPS) is made when the following criteria are met: more than five juvenile polyps in the colorectum or multiple juvenile polyps throughout the gastrointestinal tract or any number of juvenile polyps in an individual with a family history of juvenile polyposis

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[1,3]. This disease affects 1 in 100,000 to 1 in 160,000 individuals and 20% to 50% of cases have a positive family history [3]. The mechanism of inheritance is autosomal dominant and has been associated with mutations in the *SMAD4* (18q21.1) or *BMPR1A* (10q23.2) genes [2,3].

According to clinical presentation and clinical course, JPS is categorized into three different entities: juvenile polyposis coli (colonic involvement only); generalized juvenile polyposis and juvenile polyposis of infancy [3]. Juvenile polyposis coli presents at 5–15 years of age, whereas generalized juvenile polyposis presents at a younger age [3].

Juvenile polyposis of infancy (JPI) constitutes an exceptionally rare disease and very few cases have been reported in the international literature. Unlike other types of juvenile polyposis, JPI manifests early in life, with a severe clinical course and reduced life expectancy [1,2,4]. The hallmarks of JPI are early onset of disease (usually within the first 2 years of life), with severe gastrointestinal symptoms, including diarrhea, severe intestinal bleeding, protein-losing enteropathy, intussusception, rectal or polyp prolapse and inanition, leading to death in early childhood [1–3]. JPI is not associated with a family history and has been associated with a *de novo* germline deletion of a chromosomal region encompassing the *PTEN* and *BMPR1A* genes [1,5]. External stigmata (macrocephaly, mental retardation, mucocutaneous lesions, genital pigmentation) may mimic other *PTEN* Hamartoma Tumor Syndrome, such as Cowden syndrome and Bannayan–Riley–Ruvalcaba syndrome [5]. Facial dysmorphisms, digital clubbing, heart defects and generalized hypotonia are other associated features [2].

1. Case report

A 3-year-old male patient with mild mental and motor retardation, macrocephaly (head circumference above the 97th percentile) and minor facial dysmorphisms was referred for genetic consultation. The patient was the second child of a healthy nonconsanguineous couple and had been diagnosed with interatrial communication and patent ductus arteriosus, both corrected in the first year of life. Short stature and digital clubbing were noted but no skin abnormalities were detected at physical examination. Chromosome analysis, subtelomeric and 22q11.2 FISH analysis, molecular testing for Fragile X syndrome and metabolic studies did not identify any anomalies. The skeletal x-ray films showed only minor alterations: hypoplastic clavicles, eleven pairs of ribs, rectified femoral head and mild posterior plagiocephaly. Magnetic resonance imaging of the brain was normal.

Iron-deficiency anemia was then diagnosed, with hemoglobin level of 9.1 g/dL, and iron supplementation was started and achieved good initial response.

The child was consulted by a surgeon at the age of 3 years, because of a little umbilical hernia and recurrent "rectal" prolapse. There were previous complaints of multiple loose bowel movements per day and recurrent episodes of bloody stools, which were attributed to the rectal prolapse.

At 5 years of age the patient was diagnosed with bilateral inguinal hernias. At the time of inguinal herniorrhaphy, significant abdominal distension was noticed and three rectal suction biopsies were performed. Immunohistochemical staining of biopsy specimens was not suggestive of Hirschsprung's disease, but did not exclude intestinal neuronal dysplasia.

The rectal prolapse became more frequent at 6 years of age, complicated by rectal bleeding and persistent anemia. The patient's general condition worsened, with progressive abdominal distension and episodes of foul-smelling diarrhea, with mucus and blood, and colicky abdominal pain and tenderness, attributed to enterocolitis that improved after conservative treatment (bowel rest, enemas, bowel decontamination and blood transfusion). During an appendicostomy, performed for colonic decompression and for antegrade enemas, rectal polyps were seen protruding from the anus which were excised. Histopathological examination of the resected specimens revealed juvenile polyps.

Colonoscopy identified further very large polyps throughout the colon, which were highly exudative and hemorrhagic. Magnetic resonance enterography performed for surgical planning revealed additional small bowel polyps, in lesser number and dimensions (Fig. 1).

The patient underwent further genetic testing and array-based comparative genomic hybridization (Affymetrix 250K SNP array) identified two gains (at 6q and 8q) of maternal and paternal origin, respectively, and a *de novo* deletion at 10q23.1q23.31, 3.34 Mb long, encompassing the *PTEN* and *BMPR1A* genes. Genetic counselling of the family was given accordingly to the results.

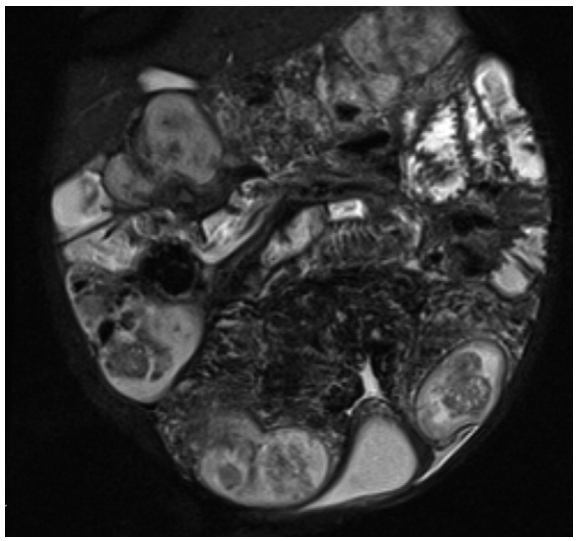

Fig. 1 The magnetic resonance enterography identified large and small bowel polyps.