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Sustainable positive response to sirolimus in juvenile polyposis of infancy

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Juvenile polyposis of infancy (OMIM 612242)

ACCEPTED

Juvenile polyposis of infancy (OMIM 612242) is a hamartomatous polyposis including macrocephaly, facial dysmorphism, hypotonia, developmental delay; rectal bleeding occurred during the first 2 years of life (1, 2). It results from a microdeletion of chromosome 10q23 involving *PTEN* (phosphatase and tensing homolog) and *BMPRIA* (bone morphogenetic protein receptor type 1A) tumour-suppressor genes (1, 2). A protein-losing enteropathy can lead to colectomy in the first years of life (1, 2) and to an early death (2). Later on, there is an increased risk of colorectal cancer (2).

In mice, the conditional deletion of *Bmpr1a* induces the development of numerous polyps mimicking human juvenile polyposis (3). BMP signalling promotes cell differentiation and thus balances the intestinal stem cell renewal under the control of the Wnt/Apc/ β -catenin pathway. In adenomatous polyposis coli (*Apc*) deficient mice, the inducible loss of *Pten* leads to an increased tumorigenesis because of an increased activation of PI3K/Akt/mTOR (phosphatidylinositol 3 kinase/Protein kinase B/mammalian target of rapamycin) pathway (4).

mTOR is a downstream effector of the PI3K negatively regulated by PTEN. Its expression is increased in intestinal polyps of *Apc* deficient mice; its inhibition reduced the number of polyps and their size (5), and also delayed the apparition of dysplasia (6). The wider use of the mTOR inhibitor sirolimus in clinical trials of cancer therapy and the severity of the phenotype of our young patient led us to consider this drug as a new therapeutic option.

An 11-year old girl was followed since birth for macrocephaly (+5 SD), mild hypotonia, motor and developmental delay. When she was 18 months old, she had rectal bleeding. Her colonoscopy revealed numerous juvenile polyps, up to 3 cm of diameter (Figure 1 A, B). Genetic analysis found a *de novo* germline deletion encompassing *PTEN* and *BMPRIA*. Follow-up

endoscopies confirmed a severe form of polyposis with 30 to 50 polyps, mainly located in the colon but also in the stomach and the small bowel. She had a failure to thrive, mild anaemia and protein-losing enteropathy. A colonic perforation occurred after resection of large polyps when she was 5 years old. In emergency, a transient ileostomy was performed.

Instead of performing a colectomy, which could exacerbate watery and stool losses and increase the risk of dehydration, we decided to start a treatment with sirolimus when she was 6-year-old, targeting a blood concentration of 5 ng/mL. We found a decrease in number and size of polyps during yearly endoscopic follow-up (Figure 1 C, D). After more than 4-year of follow-up, she showed a weight improvement and normal serum albumin level without recurrence of anaemia or adverse event. When she was 11-year-old no polyp was detected, even in the rectum where few small polyps were previously present.

Importantly, an immunostaining of phospho-S6 ribosomal protein, a target of mTOR, showed a marked decreased expression after sirolimus initiation (Figure 2).

In conclusion, this report suggests that sirolimus is effective in the treatment of severe juvenile polyposis of infancy and could be considered as a therapeutic option, instead of colectomy.

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Figure 1: Juvenile polyps under sirolimus treatment. Prior to treatment, there were large pediculated or sessile polyps with exudative loss on their heads (A, B). The number and size of polyps decreased after 1 and 3 years of treatment (C and D respectively).

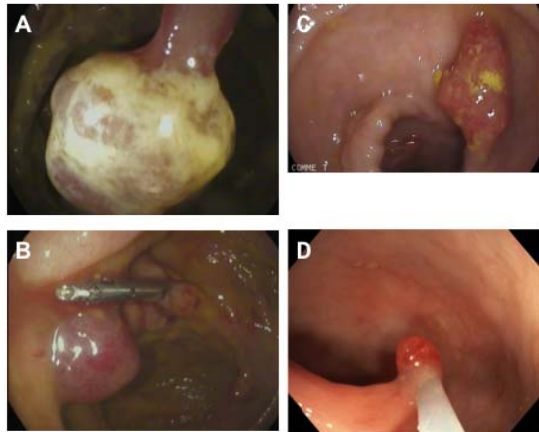


Figure 2: mTOR activity in sirolimus-treated polyps.

Immunostaining of phospho-S6 ribosomal protein (left panels) was performed to measure mTOR activity under sirolimus treatment. Nuclei staining (DAPI, right panels) and the whole sections (boxes) of the polyps are shown. Despite a strong and large decrease in phospho-S6 ribosomal protein labelling, demonstrating mTOR inhibition, some polyps areas remained positive (see box).

