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Case Report

# A Case of Colo-Colic Intussusception Revealing a Constitutional Mismatch Repair Deficiency

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## Abstract

A 15-year-old boy presented with asthenia, dyspnea, and dizziness. He had no rectal bleeding and passed gas and stools. He had multiple café-au-lait spots and no abdominal pain or palpable mass. The hemoglobin rate was 28 g / l. Ultrasound and CT scan found a right colic intussuscepted tumor. A laparoscopic-assisted right hemicolectomy was performed. Histology showed a colonic adenocarcinoma in situ and several polyps. Genetic analyses revealed a maternal transmitted heterozygous deleterious constitutional bi-allelic mutation on the exon 7 in the PMS2 gene. Methylation tolerance test and ex vivo microsatellite instability assay cells confirmed a Constitutional Mismatch Repair Deficiency Syndrome.

## Introduction

Intestinal intussusception is a common surgical problem in children. Ninety percent are idiopathic[1,2] with peak incidence between five and ten months of age.[2] In older children, principal causes for intestinal intussusceptions include polyps and tumors.[1,2] Constitutional Mismatch Repair Deficiency (CMMRD) is an autosomal recessively hereditary childhood cancer susceptibility syndrome caused by biallelic germline mutations in one of the four major Mismatch Repair (MMR) genes, with patients presenting with café-au-lait spots reminiscent of neurofibromatosis type 1 (NF1).[3-6] The most frequently implicated gene is PMS2, followed by MSH6, and more rarely, MLH1 and MSH2.[7] Lacking a functional DNA MMR system in all tissues enhances the risk of tumorigenesis in several organ systems, such as the nervous, gastrointestinal, and immune systems, mostly during childhood[6] with the median age at diagnosis of the first tumor is 7.5 years.[3,7] Family history is most often non-contributive unless the parents are inbred.[3-7] Diagnosis requires germline genetic testing,[6] completed with methylation tolerance test and ex vivo microsatellite instability assays on the patient's lymphoblastoid cells.[3] Management of CMMRD patients consists of extensive preventive screening associating clinical examination, laboratory tests, imaging, and endoscopy.[3,4,6,7] We are reporting a case of CMMRD, presenting as intussception, highlighting to look for CMMRD as a possible cause of intussception.

## Case Report

A 15-year-old boy presented to our OPD for asthenia, dyspnea, and dizziness. Heart rate was 100 beats / minute, respiratory rate was 20 breaths / minute, and oximetry was 98% in ambient air. He had a good appetite, no nausea or emesis, and passed

gas and stools. He did not complain of rectal bleeding. His parents were not related, and there was no familial history of cancer or congenital malformation. On inspection, he had many café-au-lait spots (Figure 1A). On palpation, there was no abdominal pain, guarding, or palpable mass. The rest of the clinical examination was normal. We admitted him for further evaluation. Blood tests revealed severe iron deficiency anemia at 28 g/l and blood transfusion was given.

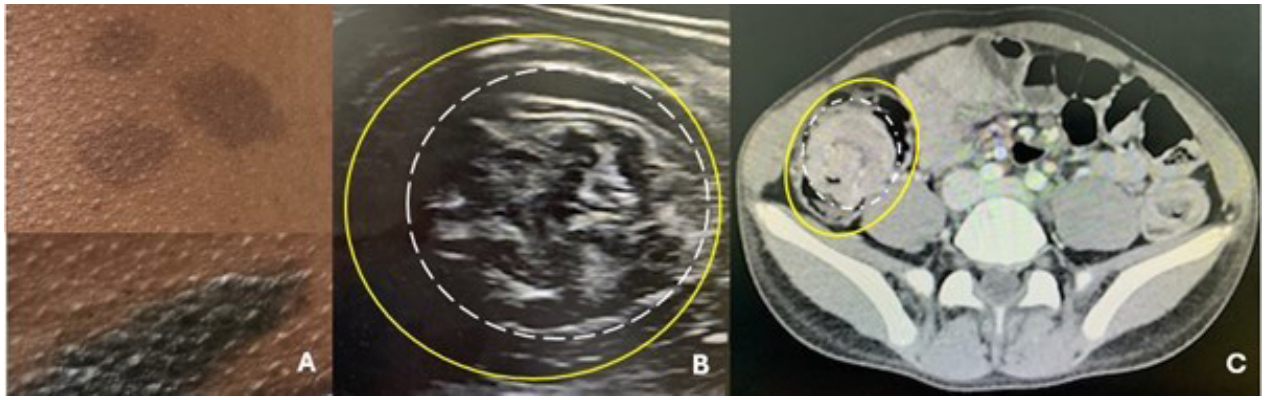


**Figure 1:** A) Café-au-lait spots. B) Abdominal ultrasound demonstrating a hypoechoic edematous outer loop of bowel (yellow ellipse) and a hyperechoic compressed loop of bowel telescoping within (dotted white ellipse), C) and CT scan confirming the diagnosis of colo-colic intussusception.

Abdominal ultrasound (Figure 1B) showed a 'target sign' in the transverse orientation, representing layers of intestine within the intestine, and a 'pitchfork' in the longitudinal orientation, near a 61-millimeter-long mass in the right upper quadrant, whereas a cervico-thoraco-abdomino-pelvic CT scan (Figure 1C) demonstrated a sausage-shaped mass with a target sign in the right colon, both exams confirming a right colo-colonic intussusception of neoplastic origin. We performed a laparoscopic-assisted right hemicolectomy. (Figures 2A and 2B) The postoperative outcomes were favorable. He was discharged home on postoperative day 10.

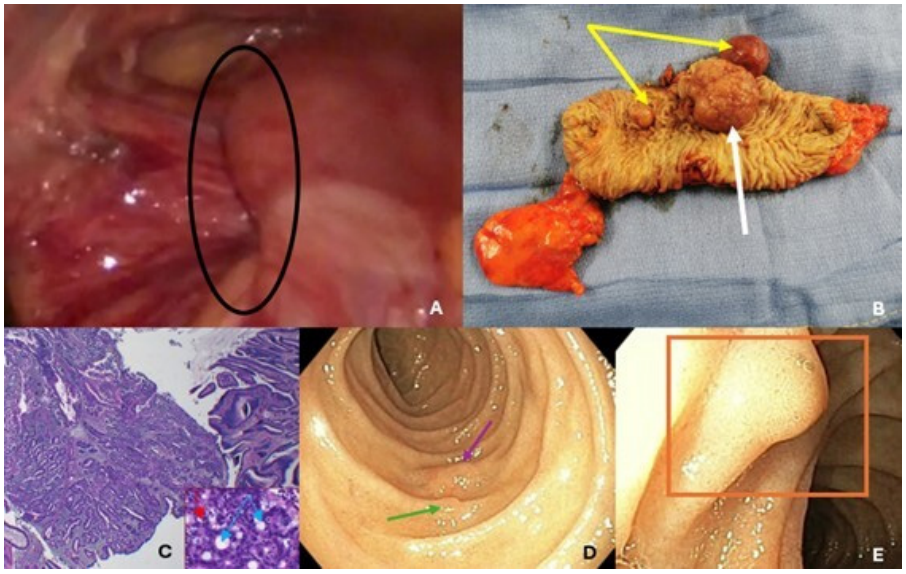


**Figure 2:** A) Laparoscopy showing the colo-colic intussusception (black ellipse). B) The resected specimen revealed a four-centimeter-length lesion (white arrow) and two smaller ones (yellow arrows). C) HES, x 20: Focus of intramucosal adenocarcinoma: tumor cells of low atypicality organized in cribriform masses within the mucosa. D) and E) Gastroscopy revealed a centimeter-sized duodenal polyp (purple arrow) as well as a millimetric sessile polyp (green arrow and orange rectangle). Histological analysis after resection concluded that it was a high-grade dysplastic tubular adenoma without infiltrating tumor cells.

Histology confirmed the existence of a colic intramucosal adenocarcinoma with healthy margins (Figure 2C), and genetic analyses revealed a familial heterozygous deleterious constitutional bi-allelic mutation c.756_757del p.(Cys252*) on the exon 7 in the PMS2 gene, as the patient and his mother display the same mutation. Besides, methylation tolerance test and ex vivo microsatellite instability (evMSI) assays on the patient's lymphoblastoid cells confirmed the CMMRD syndrome. Further genetic explorations, such as transcript studies, are in progress in search of large rearrangements and introns. Two benign duodenal polyps were endoscopically resected three months later. (Figures 2D and 2E) Ten months later, he underwent intestinal adhesiolysis by laparotomy. The patient is presently doing well after a four-year follow-up.

## Discussion

Paediatric colo-colic intussusception is quite common, however, intussception resulted due to malignancy is relatively rare.[2] When a child presents with intussception and also has neurocutaneous markers, then associated tumors should also be considered. Café-au-lait spots associated with paediatric colorectal tumors may represent a CMMRD syndrome.[3,8] Colorectal carcinoma is relatively rare in children. As for the different histological types of colorectal tumors, in children, colocrectal adenocarcinoma is the predominant type.[9,10] Carcinoma in children could have some syndromic association. Hence, in this case also, we tried to look for the syndromic association. The patient was a case of CMMRD with colorectal adenocarcinoma.

The final diagnosis of CMMRD syndrome is based on genetic tests. In our case, a biallelic germline mutation in one of the four major Mismatch Repair (MMR) genes[4,5,7] was noted and functional assays demonstrated that the cells of the patient displayed methylation tolerance and ex vivo microsatellite instability.[3] After genetic counseling, we proposed family members screening. Family screening was done and one parent had the same mutation. In CMMRD, the siblings have a 25% chance of occurrence.[5]

After treating the initial malignancy, multidisciplinary management is necessary. CMMRD is known to affect brain, gastrointestinal, and hematological with malignancies, especially during childhood. Hence, CMMRD patients must annually undergo a gastroscopy, nueroimaging, a video capsule endoscopy, a urinary tests and it is recommended to undergo clinical examination twice a year, along with abdominal ultrasound and a coloscopy.[4,5,7]

## Conclusions

Intussception can be the presenting feature of intestinal tumors. Association of intussception with pathologic colorectal carcinoma should make one suspect for syndromic association. When there is no familial history of cancer, then it should further enhance the suspicion of CMMRD. Clinical and imaging signs may not be adequate, so radical surgery with histologic analysis will confirm the diagnosis of adenocarcinoma. However, only genetic tests can confirm CMMRD and lead to familial counseling and genetic testing. Due to the high risk of occurrence of multiple different types of cancer, surveillance is necessary.

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**Conflict of Interest:** None

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