Postnatal Cytomegalovirus Infection as a Potential Trigger for Very Early-onset Crohn's Disease in an Immunocompetent Infant

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INTRODUCTION

We describe a girl with colitis onset at 2 weeks of age in whom postnatal cytomegalovirus (CMV) infection appears to have been the event triggering Crohn's disease (CD).

BACKGROUND

- Intestinal complications of congenital and postnatal CMV infections include bloody diarrhea, necrotizing enterocolitis, and perforation. [1-3]
- Inflammatory bowel disease (IBD) in infancy is rare, with only about 0.25% of cases reported within the first 3 months of life. [4]
- At this early stage of life, the origin of IBD is typically associated with monogenic pathogenic mutations. [5]
- IBD patients infected with CMV generally have a worse prognosis and are more likely to be refractory to steroids. CMV infection triggering IBD is rarely recognized and most potential cases are reported in adults (>60% ulcerative colitis). [6,7]
- Proposed mechanisms for CMV triggering IBD include alteration of intestinal immunity with viral proteins upregulating inflammation, making CMV positive hosts more susceptible to developing IBD. [8]

REFERENCES

CASE PRESENTATION

Day of Life	Clinical Event
Birth	Born at term via elective repeat c-section after uncomplicated pregnancy to a 36yo G3P3 mother; small for gestational age with non-syndromic features including large anterior fontanelle and low set ears
2	**Urine CMV by PCR negative**; done for ventriculomegaly, sensorineural hearing loss, and secundum atrial septal defect
15	Initially breast-fed and presented with blood and mucous in stool, milk-protein allergy suspected
16-137	Diagnosed with milk-protein allergy and treated with elemental formula, partial improvement in symptoms but bloody diarrhea never ceased
138	Sigmoidoscopy: moderate-to-severe chronic colitis, CMV immuno-stain negative **(Fig. 1)**
139	Methylprednisolone 0.5 mg/kg/dose IV BID started
140	**Urine CMV PCR positive**, CMV IgM 80.9 AU/mL (positive if ≥35) and CMV IgG >10 U/mL (positive if ≥0.70), increased methylprednisolone dose
141	EGD/Colonoscopy: chronic colitis, ileitis, duodenitis, gastritis, rare-CMV positive cells on immunostaining in descending colon and rectum. Terminal ileum showed inflammation **(Fig. 2).** IV ganciclovir started 5 mg/kg/dose BID, continued corticosteroids
150	Oral Valganciclovir started at 16 mg/kg/dose BID
157	Invitae Primary Immunodeficiency Panel (407 genes) and Comprehensive Deafness Panel (203 genes) showed two pathogenic mutations (hemizygous) in *CTNS* and *SLC26A3*, but no other known mutations associated with primary immune deficiency or genes associated with very early IBD
174	Weaning oral steroids while on oral valganciclovir
181	Azathioprine 1 kg/mL day started for IBD
182-228	Moderate improvement in symptoms followed by progressive increase in stool frequency and relapse of bloody diarrhea
229	EGD/Colonoscopy: chronic colitis, increased CMV-positive cells on immunostaining in transverse, descending, and sigmoid colon as well as rectum, weaned steroids, some histological improvement but still mild to moderate inflammation mostly in distal colon
231	IV ganciclovir started for a 6-week course
237	Azathioprine discontinued
246	CMV DNA undetectable in serum
254	TPN for failure to thrive, poor PO intake, and bowel rest; prednisolone restarted, urine CMV by PCR negative
266	Colonoscopy: complete suppression of CMV but chronic inflammation still present, oral valganciclovir started
274	First infliximab infusion 10 mg/kg q3w, continued bowel rest and TPN
292	Gastrostomy for long-term nutrition
321	Third infliximab dose, clinical relapse, oral valganciclovir discontinued
330	Azathioprine restarted to decrease clearance of infliximab; progressive increase in stool frequency
363	Colonoscopy: rectal ulcer with positive CMV cells on immunostaining, improved or absent colitis elsewhere, oral valganciclovir re-started **(Fig. 3)**
386	Symptoms continued to progress, infliximab infusion increased to 15 mg/kg q4w with azathioprine 12mg qd
416	Infliximab level: 24.3 µg/mL (≥7.0 for IBD maintenance IFX targets)
447	Azathioprine level: 340 pmole/8X10E8 RBC (reference range 230-400, indicating higher likelihood of response)
460	Colonoscopy: overall histologic improvement of colitis, but rare CMV still present and increased inflammation in sigmoid colon and rectum
523-527	Admitted for failure to thrive, decreased PO intake and relapsing bloody diarrhea
527	Loop ileostomy and subsequent significant clinical improvement

Table 1. Chronology of Procedures, Diagnoses and Treatment Modalities
Abbreviations: BID, Twice daily; CMV, Cytomegalovirus; EGD, Esophagogastroduodenoscopy; PCR, Polymerase chain reaction; IBD, Inflammatory Bowel Disease; IV, Intravenous; q3w, Every 3 weeks; q4w, Every 4 weeks; qd, Once daily

ENDOSCOPY IMAGES

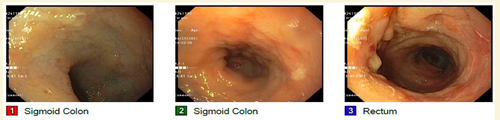

Figure 1. Sigmoidoscopy Prior to Corticosteroid Initiation demonstrates moderate-to-severe chronic colitis.

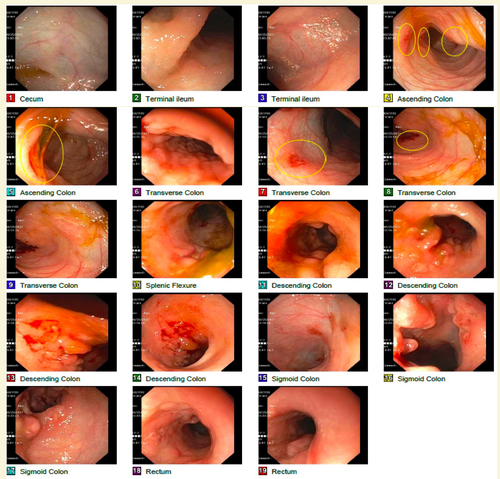

Figure 3. Colonoscopy After Infliximab Infusion demonstrates rectal ulcer with positive CMV cells on immunostaining.

LEARNING POINTS

This case illustrates postnatal CMV infection in a seemingly immunocompetent infant without CD-associated gene mutations can be considered a potential trigger for IBD.

Treatment of CMV colitis is needed in conjunction with immunosuppressive therapy for CD.

The frequency of CMV infection as a possible trigger for infantile CD needs further study.

An unknown immune defect could exist that increases susceptibly to IBD and resistance to CMV treatment.

PATHOLOGY

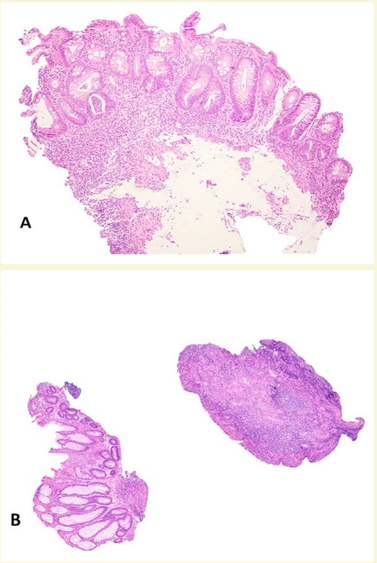

Figure 2. Tissue Histopathology with CMV Immunostaining (A) Crypt architectural distortion, acute cryptitis, and crypt abscess (day 138 of life). (B) Tissue fragment to the left shows some mild crypt architectural distortion and the one to the right shows complete ulceration with granulation tissue and abundant mixed acute and chronic inflammation (day 229 of life). **(C)** High-power images of tissues biopsied on day 229 of life showing on top a small-sized vessel with a cytoplasmic inclusion in an endothelial cell (arrow) and positive CMV staining (brown staining) in tissue.