

Intussusception and COVID-19 in Infants: Evidence for an Etiopathologic Correlation

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Nonrespiratory conditions related to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections have been largely described. Ileocolic intussusception has been reported in association with SARS-CoV-2 infection in 10 children, raising the possibility of an etiopathologic role for the virus, but none of these cases documented tissue pathology that would have supported SARS-CoV-2 intestinal inflammation. We report 2 cases of intussusception in patients with SARS-CoV-2 infection who were treated at different pediatric tertiary centers in Europe and provide evidence of the presence of the virus in mesenteric and intestinal tissues of the patients.

As severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections continue to spread worldwide, investigators have reported many nonrespiratory manifestations of infection. In the pediatric population, a multisystem inflammatory syndrome develops in a small percentage of children weeks after the acute infection.¹ In addition, children infected by SARS-CoV-2 may also exhibit gastrointestinal symptoms.²

An association between adenovirus and intussusception has been documented.³ It has been hypothesized that hyperplasia of gut-associated lymphoid tissue, secondary to infection, may act as the lead point for intussusception.⁴

At present, ileocolic intussusception has been reported in association with SARS-CoV-2 infection in 10 children, raising the possibility of an etiopathological role for the virus,^{5,6} but none of these cases included documented direct tissue involvement.

We report 2 cases of intussusception in SARS-CoV-2-positive patients treated at different pediatric tertiary centers in Europe.

PATIENTS

A 1-month-old infant girl infected by SARS-CoV-2 presented to the emergency department after a 5-day history of constipation and several episodes of postprandial milky emesis for the previous 24 hours. On admission, the patient was moderately lethargic and dehydrated and developed rectal bleeding after a digital rectal examination. An abdominal ultrasound scan revealed ileocecal intussusception that extended to the sigmoid colon in the left iliac fossa. Before any intervention, a fast antigenic rhinopharyngeal test for SARS-CoV-2 yielded positive results. Due to a deterioration in clinical condition that did not allow an attempt at fluoroscopy guided hydrostatic reduction, the infant was transferred to the operating theater for urgent vascular access and laparotomy. Laparotomy confirmed an ileo-caecal

abstract



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Drs Scottoni and Giobbe conceptualized and designed the study, drafted the initial manuscript, and contributed to subsequent revisions; Dr Zambaiti collected data, conducted the initial analyses, and reviewed and revised the manuscript; Mrs Khalaf conducted the laboratory analyses, provided initial interpretation of the results, participated in conceptualizing and designing the paper, and assisted with the initial draft and subsequent revisions; Prof Sebire participated in conceptualizing and designing the study, coordinated and supervised the laboratory analyses, finalized the interpretation of the results, and critically reviewed and revised the final manuscript; Mr Curry, Prof De Coppi, and Dr Gennari conceptualized and designed the study, coordinated and supervised data collection, and critically reviewed and revised the final manuscript; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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intussusception that was manually reduced. A large lymph node measuring 1.5 cm in diameter was noted within the mesentery, in proximity to the ileo-caecal valve. The lymph node was excised for histologic evaluation (Supplemental Fig 2).

On postoperative day 1, oral feeding was started, and the patient achieved full enteral feedings by the end of day 2. The patient remained hospitalized for 5 more days for isolation and monitoring. At the 1-month follow-up, the patient demonstrated full resolution of all gastrointestinal signs.

A five-and-a-half-month-old infant boy presented with a history of lethargy, poor feeding, and nonbilious vomiting. His medical history was notable for hyperinsulinism that required diazoxide treatment. He had been feeding orally and his blood sugars had been stable. On admission, he tested positive for SARS-CoV-2 but had no signs of respiratory illness. After 2 days, he was transferred to a tertiary center for evaluation of new findings of bilious vomiting and fresh blood in his stool. At that stage, an abdominal radiograph revealed a prominent loop of dilated bowel in the right iliac fossa.

He underwent an abdominal ultrasound scan, which revealed ileocolic intussusception. Pneumatic reduction was attempted but was complicated by an intestinal perforation that required emergent laparotomy. The perforation was identified in the colon adjacent to the ileocecal intussusception, and intestinal necrosis was present from the terminal ileum to the splenic flexure. An extended right hemicolectomy and ileo-colic anastomosis were performed. The resected sample underwent histologic examination. Postoperatively, he was admitted to

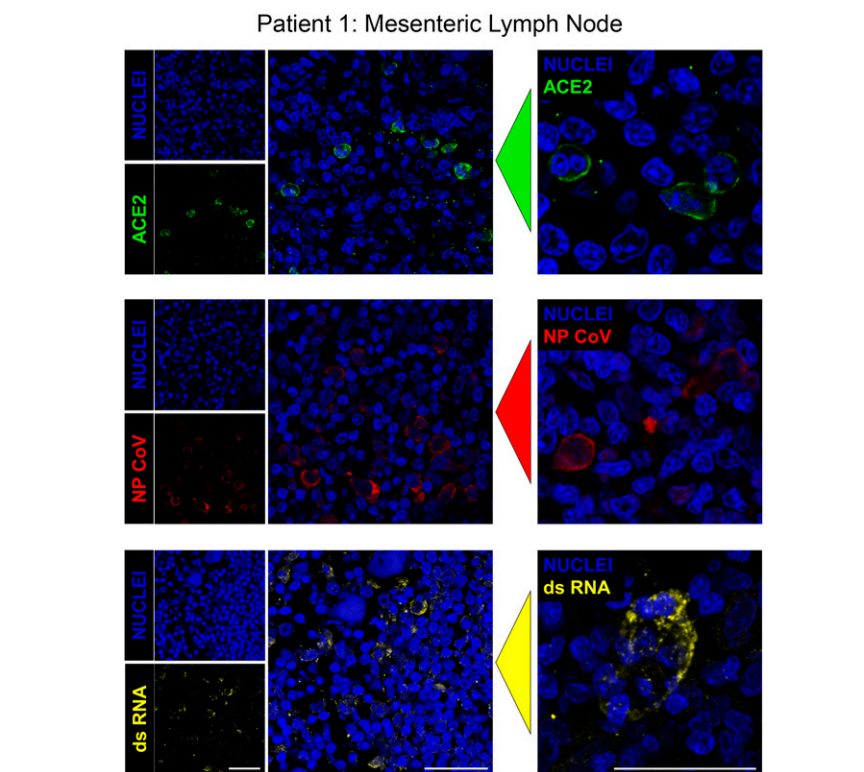


FIGURE 1 Immunofluorescence panels of paraffin-embedded 7 μm tissue sections after antigen retrieval in a mesenteric lymph node isolated from patient 1. ACE2 (R&D Systems AF933) shown in green; SARS-CoV-2 nucleocapsid (NP CoV) (Sino Biological 40143-MM05) shown in red; SARS-CoV-2 double strand RNA (dsRNA) (Scicons J2) shown in yellow; all nuclei are stained in blue (Hoechst 33342) (Thermo Fisher 62249). All scale bars in main images and enlargement panels are 30 μm.

the ICU, where he required high-frequency ventilation and low-dose noradrenaline support for significant respiratory disease. He was extubated on day 9 after surgery and was discharged from the ICU to the surgical ward on postoperative day 11.

After the admission to the surgical ward, the patient progressed to full oral feeds and was discharged in good condition on postoperative day 26.

Both the lymph node from patient 1 and the intestine from patient 2 revealed nonspecific findings on routine histopathologic examination (Supplemental Fig 2). To confirm the role of SARS-CoV-2 as directly contributory, immunofluorescence staining for human angiotensin-

converting enzyme 2 (ACE2, a transmembrane enzyme serving as cell entry point for SARS-CoV-2), NP CoV (SARS-CoV-2 nuclear protein), and dsRNA (viral double-stranded RNA) was performed on both samples. Immunofluorescence staining revealed the presence of SARS-CoV-2 in both the mesenteric lymph node from patient 1 and in the ileum from patient 2 (Fig 1, Supplemental Fig 2).

DISCUSSION

The association between virus and intussusception in children is well known from previous studies.⁴ In addition, ileocolic intussusception has been reported in association with SARS-CoV-2 infection in 10 children, raising the possibility of a

correlation between these conditions.^{5–10} However, these reports did not directly implicate SARS-CoV-2 in intestinal pathology.

In literature, the accepted hypothesis regarding the etiopathology of intussusception and its correlation with viral infection is based on Peyer's patch swelling and lymph node hypertrophy acting as lead points.^{4,11} Theoretically, any virus capable of triggering an enteric inflammatory response could produce an intussusception in a vulnerable host. Notably, ACE2, the most important receptor that mediates intracellular SARS-CoV-2 entry in humans, is densely present

in the membranes near small intestine enterocytes.¹² It is reasonable to hypothesize that inflammation of the small intestine and associated lymphatic hyperplasia from SARS-CoV-2 infection may result in intussusception.

In summary, we have provided histopathologic evidence that supports the role of SARS-CoV-2-mediated intestinal inflammation and lymphoid hypertrophy in the etiopathogenesis of ileocolic intussusception.

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ABBREVIATIONS

ACE2: human angiotensin-converting enzyme 2
SARS-CoV-2: severe acute respiratory syndrome coronavirus 2

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