

The Appendix and Aganglionosis. A Note of Caution—How the Histology Can Mislead the Surgeon in Total Colonic Hirschsprung Disease

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Abstract

We present the case of a child with presumed total colonic Hirschsprung disease (HD) to highlight the problems the surgeon is likely to encounter if he/she relies on the appendix alone for histopathologic diagnosis. A newborn male infant, who was presumed to have total colonic aganglionosis when the appendix was found to be aganglionic at the time of initial exploratory laparoscopy, was managed with an ileostomy in the newborn period; however, at the time of his planned pull-through procedure, the rectal biopsy revealed normal ganglion cells. The child was subsequently managed with ileostomy closure and observed for normal feeding and stooling prior to discharge home. We discuss the histopathologic findings of the appendix in separate cases of confirmed total colonic HD seen in our center, and review the normal histopathologic findings of the appendix.

Keywords

- ▶ appendix
- ▶ histopathology
- ▶ Hirschsprung

New Insights and the Importance for the Pediatric Surgeon

Aganglionosis of the appendix has long been considered to be an important finding and diagnostic for total colonic Hirschsprung disease, but the reliability of this pathological finding has seldom been discussed. We present a case in which the finding of an aganglionic appendix misled the surgeons in terms of diagnosis and had severe implications with regards to the management of the child. We identified other case reports in the pediatric surgical and pathologic literature reporting similar findings to ours. We have reviewed the literature in this article and would encourage all pediatric surgeons to be familiar with the current histopathological guidelines with regards to making the diagnosis of Hirschsprung disease.

Case History

A newborn male infant (born at term) presented with abdominal distension and failure to pass meconium in the first 24 hours of life. Hirschsprung disease (HD) was suspected; however, the contrast enema failed to demonstrate a transition zone and was read as normal by radiology. The child was

treated with rectal irrigations but remained persistently distended. All laboratory values were normal. Because of this, the infant underwent a diagnostic laparoscopy. No anatomic obstruction was noted. The appendix was then sent for histopathologic examination and found to be aganglionic, and the case was therefore determined to be total

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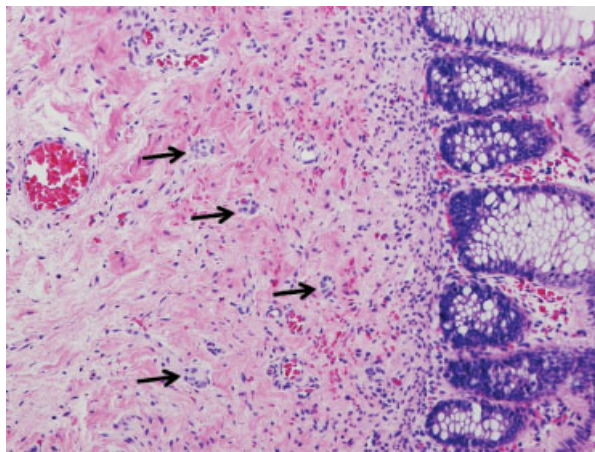


Fig. 1 H&E stain ($\times 100$). Representative example of a normal suction rectal biopsy with several groups of ganglion cells seen in the submucosa.

colonic HD. Based on this finding, the surgeons felt they had confirmed HD and a total colonic type, and thus did not perform a rectal biopsy. An ileostomy was fashioned.

The child thrived after the ileostomy and did not have any episodes of Hirschsprung-associated enterocolitis (HAEC). No further evaluation was done. The child was then referred to our institution for ongoing care and for undergoing the pull-through procedure. The referral center was advised that further surgical intervention should be delayed until the child was potty-trained for urine and the ileostomy output had thickened.

At the visit for the planned ileoanal pull-through, a contrast enema revealed no obstruction, and a colon that was a little narrowed but consistent with the fact that it was defunctionalized for the preceding 2 years. A rectal biopsy was sent to reconfirm the diagnosis as a matter of routine (**Fig. 1**). To our surprise, the rectal biopsy revealed normal ganglion cells and no evidence of hypertrophic nerves. The decision was made then to proceed with closure of the ileostomy. The ileum was flushed in the operating room and no obstruction was noted, and the colon was also flushed and shown to have no anatomic obstruction. The child had normal stools postoperatively and 2 years later remained asymptomatic, with normal stooling and growth.

Discussion

Aganglionosis of the appendix has long been considered to be an important finding in a patient in whom total colonic aganglionosis (TCA) is suspected, but its reliability for diagnosis has seldom been discussed.¹ Our literature review has revealed several cases where surgeons have been misled by the histopathology.^{1,2}

A similar case to ours was reported by Shih et al¹ in 1998, where the diagnosis of total colonic HD was made, on the basis of the appendix histopathology, in a premature infant (30 weeks' gestation) with a birth weight of 1,140 g. The infant was reported to have had an "easy passage of meconium" and to have "tolerated initial feeding," but developed pneumoperitoneum on day 6 of life. At the time of laparoto-

my, the infant was found to have an ileal perforation, 15 cm proximal to the ileocecal valve. Another finding that the surgeon felt supported the diagnosis of total colonic HD was a small-caliber colon distal to the perforation. The appendix was resected and found to be aganglionic, which was felt to support the presumed diagnosis of total colonic HD. No colonic biopsies were taken and an ileostomy was formed. At the time of definitive surgery, as with our presented case, the distal colon was found on repeat rectal biopsies to be ganglionic in its entirety.

In 1986, Anderson and Chandra reported a case of a newborn infant, who was managed as total colonic HD, after the appendix was found to be aganglionic.² At the time of definitive surgery, further biopsies were taken, with the descending and transverse colon being aganglionic; however, the ascending colon was found to be ganglionic, suggesting that the child had long-segment HD. Following this case, the group attempted to clarify the histopathologic findings of the appendix in children with HD, by studying the appendix of 36 children with a known diagnosis of HD. The number of ganglion cells (per $\times 10$ power field) was compared with a control group of children without HD. No ganglion cells were seen in the appendix of children with total colonic HD. Children with rectosigmoid HD were found, however, to have on average 3.0 ganglion cells per high-power field (hpf) (range 0.5–5.1) in the appendix and those with longer-segment disease had 2.2 cells/hpf (range 1.4–5.9). Their report supported the presumption that children with total colonic HD have an aganglionic appendix.

There is little published work, looking at ganglion histopathology of the normal appendix. Over 40 years ago, Kamoshita and Landing recognized that it is often difficult to find myenteric plexus nerve cells in sections of the appendix, in which the muscle is thin and the size of the nerve population is proportionally small.³ **Figs. 2** and **3** are both representative examples of a normal appendix and demonstrate that ganglion cells may be seen in the myenteric plexus or in the submucosa alone. Another paper concluded that the myenteric plexus in the human appendix consists of several distinct networks, and appears to be unique in comparison with the other parts of the intestine.⁴ Therefore the histopathology of the appendix cannot be assumed to be representative of the small bowel and colon. Further attempts have been made to clarify the histopathologic findings of the appendix; however, appendiceal specimens available for research purposes tend to be those resected due to acute appendicitis in which the inflammatory process itself can alter the histopathology.⁵

In 2000, Xiong et al⁶ published a study, looking at the status of the enteric nervous system in normal and inflamed appendices. They looked at 10 appendices in those with histologically proven appendicitis, 10 in those with clinically suspected but histologically normal appendices, and 10 from patients undergoing elective abdominal surgery. This study group identified an increased number of nerve fibers, Schwann cells and enlarged ganglia widely distributed in the muscularis externa and submucosa in all 10 patients with acute appendicitis, and in 4/10 of those with clinically

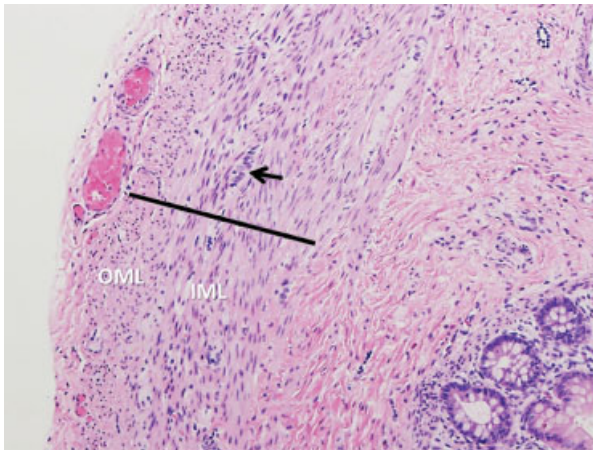


Fig. 2 H&E stain (×100). Appendix of a 5-week-old infant—normal appendix removed during Ladd procedure. Ganglion cells in the myenteric plexus shown by the arrow. The muscularis propria is indicated by the solid line. IML, inner muscular layer; OML, outer muscular layer.

suspected appendicitis. The number and size of ganglia in the muscularis externa and in the submucosa of appendices with acute appendicitis were significantly larger when compared with the control appendices.

In 2008, Singh et al⁵ looked at the eosinophils, mast cells, nerves, and ganglion cells (in the mucosa, submucosa, and muscularis propria) in a total of 329 appendices. In this study they were able to examine the histopathologic features of the appendix in patients with acute appendicitis (group A), clinically acute but histologically normal appendix (group B), elective appendectomy (group C), and normal controls from medicolegal autopsies (group D). They found a significantly higher number of mast cells and eosinophils in the mucosa, submucosa, and muscularis propria in groups A and B compared with C and D. The number of nerves and ganglion cells was significantly higher in group A when compared with B, C, and D. This may suggest that the mast cells and eosinophils cause pain in those with clinically apparent, but “histopatho-

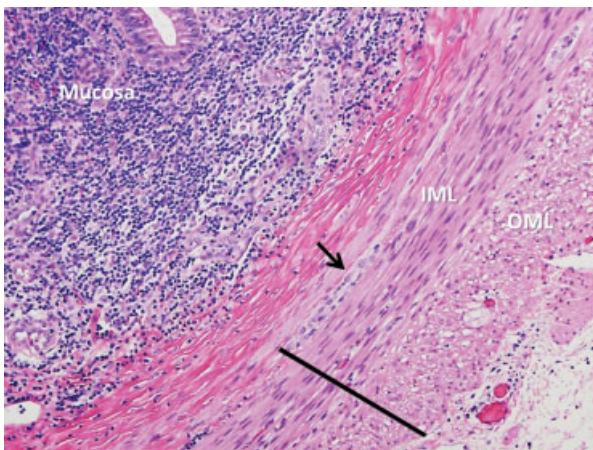


Fig. 3 H&E stain (×100). Appendix—ganglion cells along the outer submucosa shown at the arrow. The muscularis propria is indicated by the solid line. IML, inner muscular layer; OML, outer muscular layer.

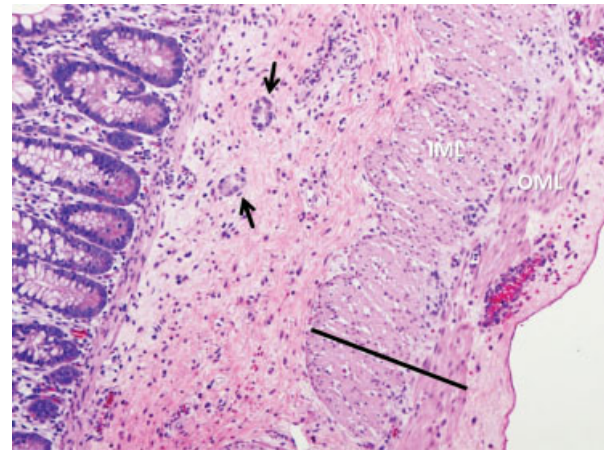


Fig. 4 H&E stain (×100). Appendix of a 4-day-old infant with total colonic Hirschsprung disease (HD). Despite absence of ganglion cells in the entire colon, there were ganglion cells in the submucosa of the appendix as shown by the arrows. The muscularis propria is indicated by the solid line. IML, inner muscular layer; OML, outer muscular layer.

logically normal” appendicitis. Interestingly, however, the changes seen in the number of ganglion cells in those with histopathologically proven appendicitis (group A) make the use of the appendix (in children with appendicitis) undergoing appendectomy, for assessment of ganglion cells in the appendix, problematic as this study suggests that inflammation may change the histopathologic findings. Miller et al⁷ have studied the distribution of enteric nerve cells and interstitial cells of Cajal (ICC) in the normal human appendix and in type 1 diabetics (a group known to have gastrointestinal motility disorders), and concluded that the appendix, a readily available source of human tissue, may be useful in the study of human motility disorders. In a subsequent review article, however, Knowles and De Giorgio acknowledge the ongoing concerns about the reliability of the appendix histopathology being useful “in the heterogeneous” repertoire of systemic diseases affecting the gut, and suggest that the any histopathologic changes observed in idiopathic gastrointestinal motility

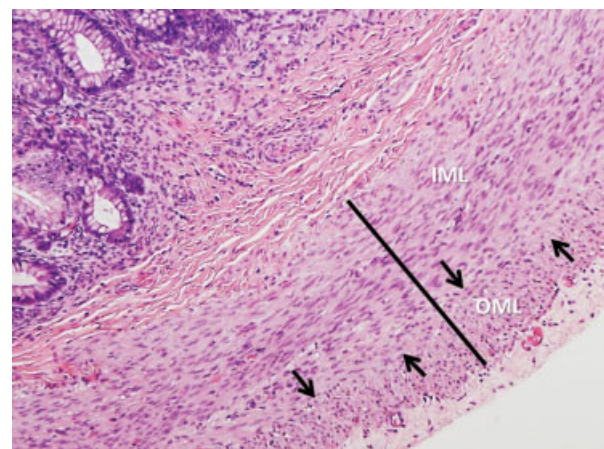


Fig. 5 H&E stain (×100). Appendix of a 3-day-old infant with total colonic Hirschsprung disease (HD). No ganglion cells in the appendix. The normal location of the myenteric plexus is designated by arrows. The muscularis propria is indicated by the solid line. IML, inner muscular layer; OML, outer muscular layer.

disorders will be subtle and probably not identifiable in the appendix,⁸ although this has not been formally tested.

Previous studies have established that the appendix is a site at which aganglionosis may be diagnosed. Appendiceal aganglionosis does not, however, equate with TCA in all patients^{9,10} as demonstrated in ▶Figs. 4 and 5. ▶Fig. 4 is the histology from a child with confirmed TCA, and ganglion cells are seen in the submucosa of the appendix specimen, whereas ▶Fig. 5 is a representative example of a child with TCA and aganglionosis of the appendix.

To standardize the histopathologic methodology and reporting of specimens in gastrointestinal neuromuscular pathology, an international working group published explicit histopathologic guidelines for diagnosis in certain gastrointestinal diseases, including HD.¹¹ The guidelines stipulate that the appendix should not be used for the diagnosis of total colonic HD, and that serial colonic biopsies should be examined before TCA is histopathologically reported. Our case report is intended to reaffirm these guidelines, although we support the notion that further research is required in the field.

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