Measles-Related Appendicitis
Differing Histologic Findings According to the Stage

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Owing to the characteristic Warthin-Finkeldey giant cells found in hyperplastic mucosa-associated lymphoid tissue, it has been emphasized that pathologists can make a diagnosis of measles from appendectomy specimens even in the prodromal stage before diagnostic rashes develop. However, to date, those reported cases of measles-related appendicitis have dealt with the histologic features of the prodromal stage and we found no reports in the English literature describing the histopathologic findings of appendicitis during the full-blown stage of measles. Here, we describe 2 cases of measles-related appendicitis that show contrasting histologic features according to stage, one discovered during the prodromal stage and the other occurring during the full-blown stage. This report describes heretofore unreported histopathologic findings of measles-related appendicitis observed during the full-blown stage of the infection and highlights histopathologic changes caused by replication of the virus in different compartments of the same organ during the course of infection.

Measles is an acute febrile viral disease caused by the measles virus, an enveloped virus that contains a single-stranded RNA genome of 16,000 nucleotides. The condition’s main manifestations are upper respiratory symptoms, fever, and a maculopapular skin rash. Participation of the appendix in measles infection has already been established in several sporadic case reports. However, many clinicians and pathologists, particularly those in countries where measles itself has become a rare disease, are unaware of this fact, and surgical pathologists seldom have a chance to review the pathologic changes caused by measles because the clinical diagnosis is usually apparent. During a recent large measles outbreak in Korea, we experienced 2 cases of measles-related appendicitis. In contrast to previously reported cases in the English literature, one of our cases underwent appendectomy during the full-blown stage of measles. We noted that the histopathologic findings in this patient were different from those discovered during the prodromal stage.

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Figure 1. A, Case 1. Low-magnification view showing hyperplastic mucosa-associated lymphoid tissue with scattered Warthin-Finkeldey cells (hematoxylin-eosin, original magnification ×40). B, Case 1. Medium-magnification view showing characteristic Warthin-Finkeldey cells within the germinal center (hematoxylin-eosin, original magnification ×200). C, Case 2. Medium-magnification view showing cytopathic changes of covering epithelium (hematoxylin-eosin, original magnification ×200). D, Case 2. Low-magnification view showing mucosal ulceration and transmural inflammation (hematoxylin-eosin, original magnification ×40).
Therefore, we report these 2 cases of measles-related appendicitis and compare the contrasting histopathologic features and immunohistochemical staining results for measles antigen according to the stage of infection.

REPORT OF CASES

Case 1

A previously healthy 12-year-old boy presented with a 24-hour history of nausea and vomiting associated with right lower quadrant abdominal pain. His temperature on admission was 38°C. The patient's eyes, ears, and tongue were normal, and there was no lymphadenopathy or rash. Abdominal examination revealed right lower quadrant tenderness. The white blood cell count was 7.22 × 10³/mm³ with segmented neutrophils, 86.2%; lymphocytes, 6.2%; and monocytes, 4.5%. A clinical diagnosis of acute appendicitis was made, and the patient was operated on the same day. The slightly edematous and hyperemic appendix was removed by laparoscopic surgery. Postoperatively, the patient continued to show a low-grade fever. Microscopic examination of the appendectomy specimen demonstrated numerous characteristic Warthin-Finkeldey giant cells in hyperplastic mucosa-associated lymphoid tissue (MALT). Otherwise, the appendix was unremarkable. On the day following the pathologic diagnosis of "histologic findings consistent with prodromal stage of measles," a typical erythematous maculopapular rash began on the child's face and spread to his trunk and limbs. The patient's younger brother also became infected with measles following the uneventful discharge of the patient.

Case 2

A 10-year-old girl with known measles previously diagnosed at a private clinic was admitted with both high fever and sudden severe right lower abdominal pain. Her temperature on admission was 39°C. A maculopapular rash was noted on her face. Oral examination revealed typical Koplik spots. Cough, coryza, and conjunctivitis were also present. Abdominal examination revealed right lower quadrant tenderness with guarding and rebound. The patient's white blood cell count was 5.9 × 10³/mm³ with segmented neutrophils, 80.3%; lymphocytes, 11.7%; and monocytes, 7.7%. Under the impression of acute appendicitis, an appendectomy was performed on the same day. An inflamed retrocecal appendix was removed during surgery. The day following the operation, the patient's rash was noted to have spread to the trunk and extremities. On the fifth postoperative day, the patient was discharged in satisfactory condition.

PATHOLOGIC FINDINGS

On gross examination, the appendix from case 1 showed mild serosal congestion, while the appendix from case 2 showed an obviously dull-appearing, adherent, and thickened serosa. Histologically, case 1 was characterized by diffuse and marked hyperplasia of MALT causing luminal narrowing (Figure 1, A). Numerous Warthin-Finkeldey giant cells were found, predominantly in the germinal centers (Figure 1, B). These cells did not contain any inclusions. Although a few Warthin-Finkeldey cells were found in the upper part of the lamina propria near the epithelium, the crypt epithelium demonstrated no microscopic abnormalities. No inflammation was seen in the muscular and serosal layers of the appendix. The histopathologic findings of case 2 differed significantly from those of case 1. Most interestingly, syncytial giant cells were exclusively located in the surface and glandular epithelium (Figure 1, C). Small numbers of epithelial giant cells were found admixed with acute inflammatory cells in the lamina propria and even among desquamated cells within the lumen of the appendix. Warthin-Finkeldey cells and hyperplasia of the MALT were negligible. Addition-
ally, frank suppurative transmural inflammation as well as sloughing of the degenerated surface epithelial cells associated with mucosal necrosis and ulceration were present (Figure 1, D).

Sections from routinely processed paraffin-embedded tissue were examined immunohistochemically, as previously described for measles, using a 1:50 dilution of monoclonal anti-measles nucleoprotein (Light Diagnostics, Temecula, Calif), the EnVision system (Dako, Glostrup, Denmark), and fast red as the chromogen. Immunohistochemical staining for L26, CD79a, polyclonal CD3, CD21, and CD35 (Dako) was also carried out to determine the phenotype of Warthin-Finkeldey cells using the LSAB kit (Dako) and diaminobenzidine as the chromogen in case 1. Some of the Warthin-Finkeldey cells in case 1 (Figure 2, A) and some of the epithelial cells in case 2 (Figure 2, B) demonstrated positive reactions for measles antigen. None of the epithelial cells in case 1 showed a positive reaction for measles antigen, and no distinct staining of the lymphoid cells was present in case 2. The Warthin-Finkeldey cells within the germinal centers in case 1 were stained by B-cell markers (L26 and CD79a) (Figure 2, C) and were entirely negative for follicular dendritic cell markers (CD21 and CD35).

COMMENT

In 1931, Warthin and Finkeldey were the first to independently describe the appearance of giant cells in tonsillar tissue during the prodromal stages of measles. One year later, these same giant cells were noted in appendectomy specimens by Herzberg and by Davidsohn and Mora. Thereafter, there have been notably few case reports of measles-associated appendicitis in the English literature. This absence is probably due to the decreased incidence of measles in the Western world owing to successful vaccination programs and the uncommon occurrence of symptomatic appendicitis as a complication of measles.

Although the incidence of measles has decreased dramatically owing to the introduction of routine measles vaccination, cyclical miniepidemics still occur worldwide. During a recent, unusually large measles outbreak in Korea, we were able to evaluate 2 examples of measles-related appendicitis with different clinical and pathologic findings. On comparing the clinicopathologic features of these 2 cases with those of previous case reports, we found that case 1 shared nearly identical features with those reports; that is, the patient was inadvertently operated on for acute appendicitis in the prodromal stage before the emergence of diagnostic Koplik spots and rash. The removed appendix showed hyperplasia of MALT and pathognomonic Warthin-Finkeldey giant cells. In actuality, we are uncertain about using the pathologic term appendicitis for this case because there was no inflammatory cell infiltration in the muscle layer. However, the clinicopathologic findings of case 2 differed considerably from case 1 and previous findings. The appendix of case 2 was removed after the clinical diagnosis of measles was established. The severe acute inflammatory changes seen in case 2 may have developed in the course of measles due to bacterial superinfection and/or luminal obstruction of the appendix caused by lymphoid hyperplasia. Other authors have also suggested the same reasons for true granulomatous or suppurative appendicitis developing in the course of measles.

Measles infection begins by the attachment of the virus to respiratory lining cells followed by local replication. Primary viremia causes dissemination of the virus in lymphoid tissues throughout the body. Replication of the virus in the lymphoid tissue then induces lymphoid hyperplasia and formation of characteristic reticuloendothelial giant cells and Warthin-Finkeldey cells. A secondary viremia soon follows, disseminating the virus to other organs by infected lymphocytes and monocytes. Epithelial changes, such as giant cells and intranuclear or cytoplasmic viral inclusion, develop during secondary viremia and are most prominent at the onset of rash when reticuloendothelial giant cells begin to disappear. The appendix is an ideal organ in which to observe these sequential histopathologic changes, owing to its normally existing MALT. The histopathologic findings and immunohistochemical staining results for the measles antigen observed in our 2 cases exactly recapitulate the classic sequential pathologic changes and sites of replication of measles viruses according to the stage. Previous studies have suggested that Warthin-Finkeldey giant cells and epithelial giant cells are formed by a mechanism of fusion. According to our immunohistochemical staining results, the Warthin-Finkeldey cells in the germinal centers of case 1 were B cells, and there were no giant cells that expressed follicular dendritic cell markers, as reported in a previous study.

In conclusion, we demonstrated that measles-related appendicitis can show varying histopathologic findings according to stage. Furthermore, the superimposed frank suppurative inflammation occurring in case 2 reiterates the need for an initial surgical approach in all measles patients with lower quadrant abdominal pain, irrespective of the presence of exanthema.

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References