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Cluster of acute hemorrhagic appendicitis among high school students in Wuhan, China

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Abstract

Background: Features of a cluster of acute appendicitis that occurred among a high school student population in China were investigated.

Methods: Epidemiologic data, medical records, and histologic slides of resected appendices were examined.

Results: During a period between April 10, 1997, and June 11, 1997, 11 cases occurred in a high school, with 10 cases among 290 students enrolled at the time. From the end of the initial cluster until June, 2000, 20 additional cases were encountered. Female cases (6.5%) are more frequent than male cases (1.9%). There was a clustering pattern. Many patients had a history of mutual contact before the onset of symptoms. Pathologically, the resected appendices exhibited diffuse or focal hemorrhages in the lamina propria or within hyperplastic lymphoid follicles, and infiltration by eosinophils and by lymphocytes. Appendical tissues were examined using immunohistochemistry, but no etiologic agent was identified.

Conclusions: This cluster of acute appendicitis represented a special kind of appendicitis, with features of an infectious disease in epidemiology. © 2004 Excerpta Medica, Inc. All rights reserved.

Keywords: Appendicitis; Cluster; Hemorrhage

Acute appendicitis is the most common acute surgical abdominal condition. Based on the pathologic processes, acute appendicitis is classified into early acute appendicitis, acute suppurative appendicitis, and acute gangrenous appendicitis [1]. Other than an obstructive process in some cases [2], the exact cause of appendicitis is largely unknown. Possible factors include low dietary fiber and high sugar intake [3], bacterial [4–6] and viral infections [7–11], parasite infestation [12], and allergy [13]. Epidemiologic studies have shown that appendicitis is most common in the 10- to 29-year-old age group [14–16], and that the male-to-female ratio is approximately 3 to 2 [15,17]. A reported seasonal variation [18] and two reported clusters of acute appendicitis seem to support an infectious etiology [19,20].

Between April and June, 1997, we encountered a cluster of acute appendicitis at a high school in the city of Wuhan, Hubei Province, China. We investigated the initial cluster and conducted a follow-up survey of students in the school for additional cases for another 3 years. The unique epidemiologic and pathologic features of the cases led us to consider this to be a special kind of acute appendicitis, which may have resulted from a potential infectious agent. We tentatively call this special kind of appendicitis “acute hemorrhagic appendicitis,” owing to the hemorrhages seen microscopically.

Patients and Methods

Epidemiologic, clinical, and pathologic investigations

The study subjects included all patients with acute appendicitis from the high school during the period from April

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1997 to June 2000. Data collected included person and time distributions of cases during the initial cluster between April and June 1997, and new cases after that, up to June 2000. Case history, physical examination, laboratory tests, pathology examination, and exposure history were also recorded. Patients were identified by reviewing hospital records. Exposure history was obtained by interviewing the patients. Twenty-nine of the 31 patients operated on were from one hospital, from which clinical and laboratory data were obtained for the study; the other 2 patients, who were operated on but whose clinical and laboratory data were not obtained, were not hospitalized at the collaborating hospital. Routine blood tests were performed before surgery for all patients. All histologic slides from the appendectomies were reexamined in the Department of Pathology and World Health Organization Collaborating Center for Tropical Diseases, University of Texas Medical Branch, Galveston, Texas. The pathologic examination in the paper was approved by the patients and by the Scientific Section, Medical school, Wuhan University, which is a designated review board.

Two sets of control cases were selected as follows: to examine if there are unique features among the patients in the high school, we selected 8 patients with sporadic acute appendicitis from a college in Wuhan City in 1997 as controls, who were in same hospital; and to explore the causes of the cluster, we designed a case-control study with individual matches. Two normal controls were selected for each case. One control was selected from an adjacent seat in the classroom of the patient, and the other was selected randomly from the same dormitory room as the patient. The matching variables included sex and age. A questionnaire consisted of two parts: (1) clinical history: presence or absence of a cold before the onset of symptoms, stomach disease, typhus fever, dysentery, ascariasis, and schistosomiasis; and (2) exposure factors: presence or absence of unclean or spoiled food intake before the onset of symptoms, type of food intake, dinner party, washing hands before meals, ingestion of water not boiled. To probe why the incidence rate was higher among female students, we also collected gynecologic and menstrual history of the female patients. The female patients were divided into three groups according to the phase of menstrual cycle in which they presented with appendicitis: the menstrual group (day 1 to 5 after the onset of the period), the follicular group (day 6 to 14 after the onset), and the luteal group (day 15 to 28 after the onset). To correct for the different lengths of each phase, the incidence of disease was calculated by dividing the number of instances in each phase by the length of days.

Case definition

The operative cases were defined as those who had typical clinical manifestations of acute appendicitis and who had surgery (appendectomy). Nonoperative cases were defined as patients who had a typical clinical manifestation but were not operated on. New cases were defined as patients

who had acute appendicitis after the initial cluster, ie, cases occurring after June 1997.

Immunohistochemical screening of antigen of enterovirus and adenovirus

To screen for potential infectious agents using immunohistochemistry, we used monoclonal mouse anti-enterovirus clone 5-D8/1 (Dako, Glostrup, Denmark), which reacts with 36 enterovirus serotypes of the Echo, Coxsackie including B2 and B5 and poliovirus groups, and monoclonal anti-adenovirus group (Argene, Varilhes, France), which reacts with most adenovirus strains including type 7. Positive controls consisted of formalin-fixed and paraffin-embedded culture cells that had been infected with the Coxsackie A-9, Echo-6, and Polio-1. Positive controls also consisted of enterovirus positive control slides (Dako, Ely, United Kingdom) and adenovirus positive control slides (Dako). Negative controls were the patient's appendical tissue sections and the above positive controls slides incubated with irrelevant antibodies.

Sections, 5 μ m thick, were prepared from the formalin-fixed, paraffin-embedded tissue blocks of 11 cases in the initial cluster in the high school and 8 cases in the college in 1997. After deparaffinization in xylene and rehydration through a concentration series of alcohol, slides were treated with 3% H₂O₂ for 10 minutes at room temperature to inhibit the endogenous peroxidase activity. That was followed by incubating the section with 1.5% normal goat serum at room temperature for 30 minutes to block nonspecific secondary antibody binding. A heating antigen retrieval step was used by immersing the sections in (10% target retrieval solution; Dako, Carpinteria, California), at 100°C for 10 minutes. The monoclonal mouse anti-enterovirus clone 5-D8/1 and monoclonal anti-adenovirus group, described above and diluted 1:100, was incubated at room temperature for 30 minutes for each section respectively. After a washing step, the Dako LSAB2 peroxidase detection kit (Dako, Carpinteria, California) was used following the manufacturer's instruction; 3-amino-9-ethylcarazole (AEC) was used as chromogen. Positive controls and negative controls were stained using the same methods.

Statistical analysis

Incidence rates were calculated for the operated on patients only. Statistically significant differences in occurrence and exposure factors between patients and healthy controls, and in incidence rates between the male and female students were assessed using 1:2 matched-pair chi-square tests and chi-square tests, respectively. Class clustering of patients was assessed by binomial distribution. Statistically significant differences in clinical manifestations, white blood cell counts (WBC), and differential white blood cell counts, between the cluster group and the college control group, were assessed by Fisher's exact test, *t* test,

Table 1

Dates of onset of appendicitis cases occurring in a cluster, in China, from April 10 to June 11, 1997

Case no.	Dates of onset
1	4–10
2	4–11
3	5–14
4	5–17
5	5–18
6	5–21
7	5–29
8	6–03
9	6–07
10	6–08
11	6–11

During the initial cluster, 9 of the 11 cases clustered in a 28-day period from May 14 to June 11, 1997. Two incidence peaks occurred, one between May 14 and May 21, the other between May 29 and June 11.

and *t* test after arcsine transformation, respectively. A *P* value <0.05 was considered significant for the above statistical methods. SYSTAT software (version 10.0 SPSS, Chicago, Illinois) was used for statistical analysis.

Results

Epidemiologic findings

Location and population: the school is a boarding high school, located in an urban district of Wuhan, Hubei Province, which is in central China, by the Yangtze River. Students of this school come from all over the country. During the period of April 1997 to July 2000, 704 students (364 male and 340 female) were enrolled. The students' ages ranged from 16 to 18 years. During the initial cluster period, 290 students (149 male and 141 female) were enrolled. All students and 81 staff used the same water source and dining hall. About 50 students who were from the city lived at home. During September 1997 to June 2000, 618 students (321 male and 297 female) were enrolled. Students lived in a seven-story dormitory building with seven rooms on each floor. The building was partitioned by wall on each floor with one side having four rooms (for female students) and another side having three bedrooms (for male students). In general, there were 6 to 7 students in each room.

The characteristics of occurrence in the initial cluster were as follows. Thirty-one operative cases of acute appendicitis (29 students operated on) occurred in this high school from the onset for the initial cluster (April 1997) to the end of this study (June 2000), among a total of 42 patients who had clinical manifestations of the disease. Among the operated on cases, 11 occurred during the initial cluster (from April 10 to June 11, 1997), with 9 of the 11 cases clustered in a 28-day period from May 14 to June 11, 1997 (Table 1). Two incidence peaks occurred, one between May 14 and

Table 2

Date of onset of new appendicitis cases from the end of the initial cluster to June 2000

Case no.	Dates of onset
1	09-29-97
2	10-01-97
3	12-15-97
4	12-25-97
5	03-30-98
6	04-04-98
7	10-21-98
8	10-22-98
9	10-26-98
10	10-31-98
11	11-1-98
12	03-30-99
13	08-?-99*
14	09-19-99
15	09-30-99
16	01-02-00
17	04-03-00
18	04-10-00
19	04-20-00
20	06-?-00*

* Exact dates are unknown because the patients were not hospitalized in a collaborating hospital. With the exception of 4 cases (cases 12, 13, 16, and 20), all cases occurred in clusters, and the longest interval between cases in each cluster was 11 days, with 5 of the 20 cases clustered in a 11-day period from October 21 to November 1, 1998.

May 21, the other between May 29 and June 11. Among the 11 cases, only 1 staff member (a 21-year old man) had appendicitis during the cluster; he had a high level of contact with student patients. Five additional cases (4 female and 1 male) presented with clinical manifestations of acute appendicitis, but were not operated on (data not shown).

During the initial cluster, the incidence rate of acute appendicitis among students was 3.8% (10 of 290), with 3 male and 7 female students. The incidence rates between male students and female students were 2.0% and 5.0%, respectively. Among nonresident students who had meals at home, the incidence rate was 5.0% (2 of 40). A history of mutual contact was found in these patients. In Table 1, cases 4 and 5 were roommates, as were cases 7 and 8. In addition, cases 7, 8, 9, and 10 were also classmates.

A case-control analysis did not show correlation between disease occurrence and the exposure factors described before. In 1996, there were only 2 sporadic cases with acute appendicitis in the school.

The characteristics of occurrence of the disease after the initial cluster were as follows. Summer vacation for the students was from mid-July to September 1 of each year. From September 29, 1997, to June, 2000, 20 operative cases of acute appendicitis were encountered, as shown in Table 2. With the exception of 4 cases (case 12, 13, 16, and 20), all cases occurred in clusters, and the longest interval between cases in each cluster was 11 days. Only 1 staff member (a 40-year-old woman) suffered from acute appendicitis during this period; she had the same clinical and

histologic features. Six additional cases presented with clinical manifestations of acute appendicitis, but were not operated on (not shown). Among all the new cases, 15 patients operated on and 5 patients not operated on were students enrolled in the school after the initial cluster.

The cumulative incidence rate for cases after the initial cluster was 3.1% (19 of 618). Again, there was a female preponderance (female 5.1%, 15 of 297; male 1.3%, 4 of 321). As with the patients in the initial cluster, many of the patients had a history of close contact. During this period, three classes each contributed 2 cases operated on sequentially, eg, cases 8 and 10, cases 14 and 15, and cases 18 and 19. In addition, cases 8, 9, and 10 lived on the same floor of the dormitory of building. They had a contact history and suffered from acute appendicitis sequentially. Case 18 had onset of acute appendicitis after caring for case 17.

For the cases operated on, the total incidence rate in students was 4.1% (29 of 704), and there was a statistically significant difference (chi-square = 10.6, $P < 0.01$) between incidence rates in male (1.9%, 7 of 364) and female students (6.5%, 22 of 340). There was a clustering of cases among classes ($P < 0.05$, binomial distribution). Appendicitis patients were in 11 of 19 classes; 3 classes contributed 4 patients each, 3 classes contributed 3 patients each, and another 3 classes contributed 2 patients each. The remaining 2 classes had only 1 patient each. Mean age of the patients was 16.6 years (range 15 to 19).

A follow-up study did not find frequent exposure factors with new patients in the high school (data not shown).

The control patients were 8 college students who had acute appendicitis (7 male and 1 female student) and had their illness in 1997. All the patients underwent urgent appendectomy. They ranged in age from 19 to 23 years (mean 20.4). A total of 2,499 students (1,812 male and 687 female) were present at the college during that time; the incidence rate for these sporadic cases was thus calculated as 0.32%.

Clinical and laboratory data

The 29 patients who were operated on had right lower quadrant pain or pain migrating to the right lower quadrant, and tenderness at or near McBurney's point. Twenty had rebound tenderness, 5 had involuntary muscle spasm, and 3 had diarrhea. None of the patients had blood in stool. Microscopic stool examination was performed on 5 patients, and no red blood cells were found. Four patients had axilla temperatures more than 37°C (37.1°C, 37.3°C, 37.8°C, and 37.8°C). White blood cell counts (WBC) were found to be mildly elevated in 6 cases (range $11.3 \times 10^9/L$ to $12.5 \times 10^9/L$) and neutrophil level in the differential WBC was found to be elevated in 12 cases (range 72% to 85%). Platelet counts and prothrombin times (PT) were within the normal range in all 29 patients. Physical examination did not show hemorrhagic symptoms or signs. The mean length of time between onset of symptoms and operation was about

Table 3

Comparison of white blood cell (WBC) count ($10^9/L$) and neutrophils in differential WBC count (mean $\pm$ SE) between patients at the school and controls

Groups	WBC	Neutrophils*
Patients at the school (n = 29)	8.5 $\pm$ 0.5	58.4 $\pm$ 1.3
Control patients (n = 8)	12.1 $\pm$ 1.1	66.7 $\pm$ 1.9
t	3.3822	3.0683
P	0.0018	0.0041

* Neutrophil counts were processed into continuous variables with arc-sine transformation. Continuous variables are reported as mean $\pm$ SE. There were significant differences in WBC count and neutrophils in differential WBC between patients at the school and controls.

50 hours. Among 21 female patients with regular menstrual period, 2 cases occurred in the menstrual phase (0.41 person/day); 11 occurred in the follicular phase (1.2 person/day); and 8 occurred in the luteal phase (0.57 person/day).

All 8 control patients from the college had right lower quadrant pain or pain moving to the right lower quadrant and tenderness at or near McBurney's point. Seven patients had rebound tenderness, 4 had involuntary muscle spasm, and 3 had axilla temperature more than 37°C (37.2°C, 37.2°C, and 37.7°C). White blood cell counts were elevated in 5 of 8 cases (range $10.6 \times 10^9/L$ to $16.2 \times 10^9/L$) and neutrophil level in the differential WBC was elevated in each case (range 75% to 94%). The mean length of time between onset of symptoms and operation was about 23 hours. Comparisons of WBC and differential WBC between the two groups of patients are shown in Table 3.

During surgery, hyperemia and edema were observed on the appendix of each patient from the study group; no surface exudates were identified except for 1 case, in which the appendix had a trace of purulent exudate. Fluid was present in the abdominal cavity of 11 cases; 2 had hemorrhagic fluid (1 had 300 mL of hemorrhagic fluid). In contrast, among the control cases from the college population, gross examination revealed obvious purulent exudates as well as hyperemia and edema on the surface of appendices in 7 of 8 cases. Perforation was found in 1 control case. Fluid existed in the abdominal cavity in 3 patients, 1 of whom had purulent fluid. There was a statistically significant difference in the frequency of purulent exudates between the two groups ($P < 0.0004$).

Histologic findings and immunohistochemistry results

Microscopic examinations of the appendices revealed that, of the 29 cases in the study group, 17 had diffuse hemorrhages and 6 had focal hemorrhage in the lymphoid follicles and lamina propria (Fig. 1A). A large number of lymphocytes and red blood cells were found in the lumen of the appendix of 20 cases with hemorrhage. Lymphocytic infiltration of the epithelium in both the luminal surface and the crypts is focally evident (Fig. 1B). Eosinophils were

Fig. 1. Histologic features of hemorrhagic appendicitis, as shown by hematoxylin and eosin stain. (A) Hemorrhages in a lymphoid follicle in the wall of the appendix (original magnification, $\times 40$). (B) Infiltration of the lamina propria by scattered eosinophils, in addition to the lymphocytes and plasma cells. The epithelium is infiltrated by lymphocytes. (C) Eosinophilic infiltration of a germinal center of a lymphoid follicle (original magnification, $\times 200$) (D) Eosinophilic transmural infiltration of the muscle layers (original magnification, $\times 400$).

found in 14 of the 29 cases, infiltrating the lamina propria, submucosa, lymphoid follicles (Fig. 1C), and transmurally in the muscle layers (Fig. 1D). In 5 cases there was evident lymphocytic infiltration in the serosa, and in 2 cases there was hemorrhage in the subserosal layer. Parasite eggs were not identified in appendices. Two cases revealed characteristics of acute suppurative appendicitis. In contrast, among the 8 control patients, microscopic examination revealed characteristics of early acute appendicitis in 2 cases and characteristics of acute suppurative appendicitis in 6 cases, with infiltration of neutrophils in various layers of the appendices without hemorrhage and without eosinophils (not shown).

Immunohistochemistry tests for enteroviruses and adenoviruses were positive for relevant positive controls and negative for appendiceal tissue sections from all 11 cases from the high school and 8 control cases from the college, and negative controls (data not shown).

Comments

Epidemiology plays an important role in the discovery of new disease patterns, particularly when there is an outbreak

of cases, clusters, or abnormal increases in incidence rates. In recent years, many newly emerging infectious diseases were first identified because of clusters or abnormal increases in incidence rates (eg, *Escherichia coli* O157:H7 infection, Legionnaires' disease, Ebola hemorrhagic fever, hantavirus pulmonary syndrome, Lyme disease, severe acute respiratory syndrome, and so forth).

Two articles concerning clusters of acute appendicitis have been reported previously. Martin and Gustafson [19] described a cluster in a town of 8,000 people in the United States. Thirteen cases of appendicitis occurred during a 3-month period. A case-control study of these patients indicated that sweets in the diet and consumption of local farm eggs may have been associated with the appendicitis. They hypothesized that a group of young male patients who were susceptible to appendicitis because of the high sugar content of their diets were exposed to a bacterium or virus that precipitated this cluster of appendicitis. About the cluster, the Centers for Disease Control [21] published an editorial note that the cluster of appendicitis offered a unique opportunity to identify possible risk factors and to search for precipitating infectious agents. The CDC encouraged reporting such clusters to the Enteric Disease Branch, Center

for Infectious Diseases. Andersson et al [20] described “three outbreaks” that occurred in a city of Sweden during a 22-year period. On three occasions, a significantly increased number of cases were observed in 60 days, as compared with expected cases, with a range of 1.6 to 2.2. That did not represent a typical cluster. The incidence rates in this city were lower than those Martin reported. Our study reports an incidence rate more than 10 times higher than those reported in the above two reports.

Published studies have indicated that the expected incidence rate of appendicitis is about 1.5 cases per 1,000 persons [15,22]. It is generally accepted that appendicitis is a sporadic, noncommunicable disease process more frequently found in males than females. The majority of the patients have elevated WBC and differential WBC. Pathologic examinations usually reveal purulent inflammation with neutrophils. In this study, the control patients had the above features of classic acute appendicitis, whereas the patients from the high school cluster exhibited an obviously different pattern. On the basis of the epidemiologic and pathologic features, we hypothesize that the patients from the high school had a special kind of appendicitis, which might have been caused by an infectious agent. Our reasons are as follows: (1) the occurrence of outbreak and clustering are usually characteristics of infectious diseases, and classic appendicitis does not occur in this pattern; (2) female patients were more common than male patients, in contrast to classic appendicitis in which males predominate; (3) many patients had a history of mutual contact before the onset of symptoms, suggesting person-to-person transmission; (4) with the exception of 4 cases, all of the postcluster patients were students enrolled right after the cluster; (5) only a minority of the patients had mildly elevated WBC or differential WBC; and (6) gross pathologic examination of the appendices revealed only minimal purulent change, and microscopic examination revealed hemorrhagic features mainly with infiltration and exudation of lymphocytes as well as infiltration of eosinophiles. In addition, the average lag time between onset of symptoms and surgical intervention was more than twice that of control patients. Therefore, the unique features of the patients from the high school cluster are not early manifestations of classic acute appendicitis; instead, they seem to represent a special kind of appendicitis process. The absence of parasite eggs in the students' appendices and the negative history of intestinal parasites excluded parasitic infection. Tobe [7] reported that Coxsackie virus B2 and B5 and adenovirus type 7 were demonstrated in appendiceal tissues of the cases with appendicitis. We were not able to find positive results using monoclonal mouse anti-enterovirus clone 5-D8/1 and monoclonal anti-adenovirus group.

A common source of clustering caused by food- or water-borne transmissions can also be excluded. This exclusion is based on the following: the staff and students used one canteen and water source, and none of the staff suffered from the disease except for 1, who lived with the students;

the students did not have a dinner party (single common exposure) before the cluster; and incidence rates between resident students and nonresident students having meals at home were very similar. As the students were in close contact with each other without exposure to suspected physical or chemical factors, it is postulated that the cluster probably resulted from person-to-person transmission.

Why there were more female patients than male patients may be related to close contact among the female students, or possibly to the former's higher susceptibility to potential infections. Because only 2 female patients had appendicitis during menstruation and hemorrhage also occurred in the appendices of the male patients, menstruation probably did not account for the higher incidence rate among female students.

There was no record of stool hemorrhage in the patients' charts, and microscopic examination of stool samples from 5 patients did not find red blood cells in their stools. In addition, platelet counts and prothrombin times were normal in the 29 patients. Physical examination did not show hemorrhagic symptoms and signs. These results suggest that hemorrhagic appendicitis is neither a manifestation of other intestinal hemorrhagic diseases nor a local manifestation of general hemorrhagic diseases.

In summary, we examined the clinical, epidemiologic, laboratory, and pathologic features of a group of patients in a cluster of acute appendicitis from a high school in central China. All features suggest that this cluster represents a special kind of acute appendicitis, with clinical features of classic acute appendicitis but also with unique pathologic findings, namely, hemorrhage in the lamina propria and hyperplastic lymphoid follicles. Epidemiologic features also suggest that this condition may be caused by an infectious agent. We tentatively name this condition “acute hemorrhagic appendicitis.” Investigations to identify an infectious agent from these cases are ongoing.

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