

Plague Masquerading as Gastrointestinal Illness

HARRY F. HULL, MD, and JEAN M. MONTES, Santa Fe, New Mexico, and
JONATHAN M. MANN, MD, MPH, Geneva

In clinical descriptions of human plague, fever and tender lymphadenitis are emphasized and gastrointestinal manifestations are rarely mentioned. A review of 71 human plague cases showed that gastrointestinal symptoms occurred commonly (57%). Vomiting (39%) was the most frequent symptom, with nausea (34%), diarrhea (28%) and abdominal pain (17%) occurring less often. Physicians treating patients who reside in or have recently visited plague-endemic areas should include plague in the differential diagnosis in the presence of gastrointestinal symptoms and fever.

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Human plague cases classically present with fever and tender lymphadenitis. Although gastrointestinal symptoms are not prominently mentioned in discussions of the clinical manifestations of plague, we have recently seen a number of patients with laboratory-confirmed plague who had gastrointestinal symptoms as the predominant or sole clinical manifestation of their *Yersinia pestis* infection. Because of the unusual presentations of these cases, we will discuss three instructive cases as an aid to differential diagnosis. In addition, we have reviewed records of cases of plague originating in New Mexico for the five-year period 1980 to 1984 to determine the prevalence of gastrointestinal symptoms in plague.

Patients and Methods

The New Mexico Health and Environment Department (NMHED) records clinical and environmental information for every case of plague that originates in New Mexico. Reporting of cases is likely to be complete because only two laboratories do fluorescent antibody testing and only one laboratory does serum antibody tests for plague. Satisfactory clinical records included any of the following: a complete copy of the hospital chart, a hospital discharge summary, an extract of the hospital records prepared by NMHED personnel according to protocols in use at the time of the case investigation and a death record from the Office of the Medical Investigator. A case of plague was defined as a person who had a clinical illness consistent with *Y. pestis* infection and who had one of the following: identification of *Y. pestis* from culture material, bacteria seen on fluorescent antibody stain for *Y. pestis* on nonviable clinical material, a fourfold difference between acute and convalescent passive hemagglutination (PHA) titers taken at least ten days apart or a single convalescent PHA titer of 1:16 or greater. A case of bubonic plague

had a bubo or swollen, tender lymph node noted on physical examination. A case of septicemic plague had a blood culture positive for *Y. pestis* but no adenopathy noted on physical examination. NMHED records were reviewed for all patients with plague with the onset of their illness between January 1, 1980, and December 31, 1984. Records were reviewed to determine the presence or absence of nausea, vomiting, diarrhea or abdominal pain and other relevant clinical information.

Statistical tests used were the χ^2 and Fisher's exact test for 2×2 tables.

Reports of Cases

Case 1

A 13-year-old boy became ill at 3 AM with fever, nausea, vomiting and diarrhea. He was seen that morning by a physician. On physical examination he had a temperature of 38.9°C (102°F) and no lymphadenitis. He was treated with prochlorperazine and released. At 5 PM the next day, the patient returned to his physician. Physical examination at that time showed a temperature of 40°C (104°F), right lower quadrant pain and tender right inguinal lymphadenitis. His leukocyte count was 25,900 per μl with 39% polymorphonuclear leukocytes (PMNs) and 39% band forms. Bacteria were noted on the peripheral blood smear. Liver function tests showed a serum aspartate aminotransferase (AST, formerly glutamic-oxaloacetic transaminase) level of 709, alkaline phosphatase level of 244 and a lactic dehydrogenase (LDH) level of greater than 1,846 units per liter. Despite treatment with a regimen of gentamicin sulfate and tetracycline given intravenously, the patient rapidly became delirious, went into shock and died. On postmortem examination, the bacteria noted in the peripheral smear were fluorescent antibody positive for *Y. pestis*.

From the Epidemiology Office, New Mexico Health and Environment Department, Santa Fe. Dr Mann is now with the World Health Organization, Geneva. Reprint requests to Harry F. Hull, MD, New Mexico Health and Environment Department, PO Box 968, Santa Fe, NM 87504-0968.

ABBREVIATIONS USED IN TEXT	
AST	= aspartate aminotransferase
GI	= gastrointestinal
LDH	= lactic dehydrogenase
NMHED	= New Mexico Health and Environment Department
PHA	= passive hemagglutination
PMN	= polymorphonuclear [leukocyte]

Case 2

A 61-year-old woman became ill with chills and myalgias. That night she had the onset of nausea, vomiting, diarrhea, abdominal cramping, fever and headache. The next afternoon she went to an emergency room with additional complaints of tiredness, weakness and myalgias. On taking the history, it was noted that a daughter had had diarrhea one week previously. On physical examination she had a temperature of 40.4 °C (104.7°F), hypoactive bowel sounds and diffuse, mild abdominal tenderness. A leukocyte count was 13,700 per μ l with 56% PMNs and 33% band forms. Liver function tests showed an AST level of 18 units per liter and an alkaline phosphatase value of 84 units per liter. Cultures were done of blood and stool specimens. The patient was treated empirically with a regimen of gentamicin and cefazolin sodium and her condition improved slowly. An admission blood culture was positive for *Y. pestis* on the second day in hospital.

Case 3

The patient, a 71-year-old woman, had fever, vomiting and right flank and hip pain. On physical examination she had a temperature of 38.2°C (100.8°F) and deep right flank and costovertebral angle tenderness. A leukocyte count was 17,100 per μ l with 66% PMNs and 27% band forms. The AST level was 27, the LDH concentration 208 and alkaline phosphatase level 43 units per liter; a total bilirubin value was 0.5 mg per dl. Urinalysis showed 10 to 15 erythrocytes, few leukocytes and few bacteria per high powered field. She was admitted to hospital for further evaluation. Blood and urine cultures were done and she was treated with ampicillin given intravenously. On the second hospital day, a blood culture was growing a Gram-negative rod. An ultrasound examination showed cholelithiasis. A cholecystectomy was done and gentamicin added to the therapy. The patient recovered uneventfully. Twelve days after admission, the organism was identified as *Y. pestis*.

Results

In all, 71 cases of human plague were recorded in New Mexico during the study period. Satisfactory records noting the presence or absence of gastrointestinal (GI) symptoms were available for 65 (92%) of these cases. Of the 65 cases, 47 (72%) were bubonic and 18 (28%) were septicemic. The frequency of gastrointestinal symptoms is shown in Table 1. Gastrointestinal symptoms were more common in septicemic cases than in bubonic cases. Only the increased frequency of abdominal pain, however, is statistically significant. Fever was usually the first symptom of illness. Abdominal pain, diarrhea and vomiting began on a mean of 1.2, 1.3 and 1.4 days after the onset of illness, respectively. There were no significant differences between cases with and without GI symptoms in regard to age, sex, race, case-fatality rate,

month of onset, prevalence of secondary plague pneumonia or time of onset to first physician visit or admission to hospital.

Other associated constitutional symptoms were fever, chills, malaise and headache. Fever was universal and malaise was reported in 40% of all cases. Chills and headache were noted more frequently in cases with GI symptoms (60% and 54%, respectively) than in cases without GI symptoms (39% and 25%, respectively). Gastrointestinal symptoms preceded node pain in 7 of the 18 (39%) cases of bubonic plague with GI symptoms for whom time of onset was known. Analysis of physical signs at hospital admission showed there were no significant differences in temperature, pulse, respirations or systolic or diastolic blood pressure between cases with or without GI symptoms. None of the patients were noted to have hepatomegaly or splenomegaly. When compared with cases without gastrointestinal symptoms, cases with gastrointestinal symptoms had higher total leukocyte counts (16,700 versus 12,900 per μ l), percent band forms (26% versus 18%) and total percentage PMNs plus PMN precursors (87% versus 79%) on differential leukocyte count. When a blood culture was done, *Y. pestis* was found in the blood more often in patients with GI symptoms (28 of 33, 85%) than in patients without GI symptoms (17 of 24, 71%). Gastrointestinal symptoms occurred more often in bubonic cases with a positive blood culture (15 of 27, 56%) than in bubonic cases with a negative blood culture (5 of 11, 45%). An AST level was recorded for 28 cases. The mean AST concentration for 16 cases with GI symptoms was 115 units per liter, with a range of 12 to 709 units per liter. For the 12 cases without GI symptoms, the mean AST level was 40 units per liter with a range of 10 to 124. Elevated AST levels were found in 44% of cases with GI symptoms and 33% of cases without GI symptoms. Although suggestive, none of these differences in laboratory findings reached statistical significance.

Discussion

Plague is a rare bacterial zoonosis caused by *Yersinia pestis*, a Gram-negative bipolar staining bacillus. Plague is widely distributed in rodents throughout the American West, but two thirds of human cases in the United States have originated in New Mexico. The vast majority of human plague cases are bubonic, presenting with a swollen, tender lymph gland in the groin, armpit or neck. When a physician is alert for the disease, the diagnosis of bubonic plague is straightforward. Prompt and proper treatment then results in low fatality rates. A smaller percentage of plague patients have septi-

TABLE 1.—Frequency of Symptoms in 65 Plague Cases in New Mexico, 1980-1984

Symptom	Septicemic Cases, N = 18 Patients		Bubonic Cases, N = 47 Patients		Total Cases, N = 65 Patients	
	Number	Percent	Number	Percent	Number	Percent
Nausea	8	44	14	30	22	34
Vomiting	9	50	16	34	25	38
Diarrhea	7	39	11	23	18	28
Abdominal pain . . .	7	39	4	9	11	17*
Any gastrointestinal symptom	13	72	24	51	37	57

*P = .007—Fisher's exact test.

emic plague and present with fever and no bubo. Because of the nonspecific presentation of septicemic plague, the diagnosis can be quite difficult and the case-fatality rate is higher.

The illustrative cases described here had gastrointestinal symptoms that were unusually prominent. This study indicates, however, that GI symptomatology is quite common in plague, affecting more than half of the patients. Gastrointestinal symptoms previously described in plague include abdominal pain, nausea, vomiting and initial constipation followed by diarrhea.^{1,2} The diarrhea material may be bloody and melanic stools have also been described. A series from the United States describes abdominal nausea or vomiting in 13 of 19 (68%) plague patients.² In one series of 500 patients from Vietnam, vomiting and diarrhea or abdominal pain (or all) were present in 7% of patients with buboes, 14% of patients with bubo and bacteremia and 20% of patients with septicemia (Nguyen NT, Nguyen DT: Clinical considerations and therapeutics on 500 confirmed plague patients in Cho-Quam Hospital, unpublished data, Aug 1970). Another series from Vietnam found that "more than 50%" of 88 plague patients presented with vomiting.³ In an outbreak of plague in Nepal,⁴ 12 (46%) and 18 (69%) of 26 patients had vomiting and diarrhea, respectively. The findings of these studies concur with our findings and suggest that gastrointestinal symptomatology is common in plague.

Gastrointestinal symptoms associated with plague are thought to be a general response of the body to serious illness and stress rather than resulting from a specific gastrointestinal pathologic process.¹ Vomiting and diarrhea are common symptoms of Gram-negative septicemia caused by organisms other than *Y pestis*. McCabe and Jackson noted nausea and vomiting in 43% and diarrhea in 21% of their patients with Gram-negative septicemia.⁵ Diarrhea has also been described as occurring in patients with meningococemia⁶ and those with *Streptococcus pneumoniae* bacteremia.⁷ Abdominal pain, such as described in case 3, might be caused by intra-abdominal buboes. Lymphadenopathy of mesenteric or retroperitoneal nodes has been found in patients with plague in both the presence and the absence of associated inguinal node involvement.⁸⁻¹⁰ The frequency with which this occurs remains unknown, and the role of intra-abdominal buboes in causing abdominal pain remains speculative. An alternative explanation of abdominal pain in plague could be enlargement of the liver or spleen. Hepatosplenomegaly and liver dysfunction have been observed in cases of plague.^{11,12} Although 44% of patients with GI symptoms in our study had an abnormal AST level, this was not substantially different from patients without GI symptoms. None of the patients in this study were noted to have hepatosplenomegaly.

Gastrointestinal symptoms occurred frequently in patients with confirmed plague in this study. The onset of GI symptoms occurred early in the course of the illness, sometimes preceding the appearance of lymphadenopathy or lymph node pain in bubonic plague. Additionally, GI symptoms occurred more frequently in septicemic plague, in which no bubo was

present. Physicians who are treating patients who reside in or have recently traveled to plague-endemic areas should, therefore, not be reassured by the presence of symptoms suggesting that illness originates in the gastrointestinal tract. A careful history and physical examination of patients with GI symptomatology may yield important epidemiologic clues or reveal node pain or lymphadenopathy. A differential leukocyte count may be helpful because virtually all plague patients have an elevated blood count and percentage of PMNs plus PMN precursors. Antibiotic therapy may be warranted for patients with suggestive findings on physical or laboratory examination. The use of streptomycin, tetracycline and chloramphenicol is recognized to be effective against plague. Trimethoprim/sulfamethoxazole may also be used for the treatment of plague when all of the above drugs are contraindicated. The administration of gentamicin is probably effective treatment for plague although controlled trials have not been conducted.¹³ In patients who are treated empirically with antibiotics a blood culture or acute and convalescent titers, or both, should be done to provide laboratory confirmation of the cause of the illness.

In summary, physicians practicing in the American West and physicians elsewhere treating patients who have been in the West within the past week should consider plague in the differential diagnosis of patients presenting with fever and gastrointestinal symptoms. These patients should be queried about residence in rural areas, outdoor activities and possible exposure to plague vectors, including wild rodents and free-roaming domestic dogs and cats. A differential leukocyte count may be helpful in raising the possibility of plague. Because of the high fatality rate of untreated plague and public health concerns related to secondary spread of the infection, prompt antibiotic therapy and appropriate isolation are warranted for patients who may have plague.

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