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DIAGNOSIS AND CLINICAL MANIFESTATIONS

Dr Jack D. Poland and Dr D. T. Dennis

Yersinia pestis infection in humans occurs in one of three primary clinical forms (1-3). Bubonic plague is characterized by regional lymphadenopathy resulting from cutaneous or mucous membrane exposure. Primary septicaemic plague is an overwhelming plague bacteriaemia usually following cutaneous exposure. Primary pneumonic plague follows inhalation of aerosolized droplets containing Yersinia pestis. Although uncommon, skin or mucous membrane lesions at the point of entry of Y. pestis in humans may be important manifestations, because a local cutaneous ulcer will mimic tularemia when associated with regional lymphadenitis, and plague pharyngitis may be confused with streptococcal or viral pharyngitis. Other clinical forms, such as secondary septicaemia plague, secondary pneumonic plague, meningeal plague, plague endophthalmitis and multiple lymph node involvement result from bacteriaemic dissemination of the plague bacillus. These clinical forms are discussed in detail below.

Bubonic plague

The classic disease in humans, bubonic plague, results from flea bite or direct contamination of an open skin lesion by plague-infected material. Following inoculation a local cutaneous proliferation, not usually clinically evident, ensues. In some cases, a vesicle, pustule, or ulcer develops at the inoculation site (1,3). The infection spreads via the lymphatics to the regional lymph nodes causing inflammation and swelling in one or several nodes (buboes). Buboes may occur in any regional lymph node sites including inguinal, axillary, supraclavicular, cervical, post-auricular, epitrochlear, popliteal or pharyngeal. Deeper nodes (such as intrabdominal or intrathoracic nodes) may also be involved through lymphatic or haematogenous extension.

After an incubation period of 2 to 6 days, patients typically experience a sudden onset of illness characterized by headache, shaking chills, fever, malaise and pain in the affected regional lymph nodes. The nodes may not be clinically enlarged at this stage. Progression of
Symptoms is usually rapid with the regional lymphadenitis becoming excruciatingly tender and painful. Small to moderately enlarged buboes may be masked by an extensive perinodal inflammation and oedema. Within 24 hours after specific therapy has been started, the surrounding erythema clears rapidly. The primary bubo is considerably slower to resolve.

With specific treatment in uncomplicated cases, fever and general clinical symptoms usually resolve over 3 to 5 days. The bubo may, however, remain enlarged and tender for weeks following an otherwise satisfactory clinical recovery. If the bubo becomes suppurative, surgical incision and drainage should be electively performed. Necrotic material from such buboes may contain viable *Y. pestis*.

When a superficial bubo is not found in a patient suspected to be infected with *Y. pestis*, the primary lymph node involvement may be present in deeper areas of the body including mediastinal and intra-abdominal lymph nodes. In this latter circumstance, abdominal pain suggestive of appendicitis, colitis, enteritis or cholecystitis may represent the patient's principal complaint (3-6). In such cases, abdominal tenderness to palpation, rebound tenderness, or localization of pain in the abdomen may be misleading and may result in hazardous exploratory surgery. Primary septicaemic plague is the most serious diagnostic consideration in a patient with suspected plague without evident lymphadenitis or pneumonia.

**Septicaemic plague**

Primary septicaemic plague is a progressive, overwhelming bloodstream infection with *Y. pestis* in the apparent absence of a primary lymphadenopathy (1-3). Without a bubo to prompt a suspicion of plague, the correct diagnosis may easily be overlooked. Septicaemic plague occurs in all age groups, but the elderly appear to be at greatest risk (4).

The presence of rapidly replicating Gram-negative bacilli in the bloodstream initiates a self-perpetuating immunological cascade typically linked to host response to severe injury, in this case the agent inciting injury is bacterial endotoxin (7,8). The host response may result in a wide spectrum of pathological events including disseminated intravascular coagulopathy (DIC), multiple organ failure (MOF), and adult respiratory distress syndrome (ARDS) (2-4, 9-12). Disseminated intravascular coagulation can lead to arteriolar thrombosis, haemorrhage in skin, serosal
surfaces, and organ parenchyma, and sometimes results in acral cyanosis and tissue necrosis (13). Plague septicaemia, whether primary or secondary to bubonic plague, may lead to metastatic infection of other organ systems. Complications include plague pneumonia, plague meningitis, plague endophthalmitis, hepatic or splenic abscesses, or generalized lymphadenopathy (1,3).

**Pneumonic plague**

Primary pneumonic plague is the most fulminating and fatal form of plague. The incubation period is usually 1-3 days (1,14,15). Disease onset typically manifests by the sudden onset of chills, fever, headache, body pains, weakness and chest discomfort. Cough, sputum production, increasing chest pain, difficulty in breathing, hypoxia and haemoptysis become prominent as the disease rapidly progresses. Death usually ensues if specific antibiotic therapy is not begun within 18-24 hours of disease onset (16). Segmental pneumonitis may progress to lobar pneumonia and then to bilateral lung involvement; pulmonary complications may include localized areas of necrosis and cavitation, pleurisy with effusion, and adult respiratory distress syndrome (14,15,17,18). Concurrent sepsis and endotoxemia may further complicate the patient’s management.

Plague pneumonia occurs in two distinct and epidemiologically significant forms. Secondary plague pneumonia results from haematogenous spread of *Y. pestis* to the lungs. This invasive infection provokes a masked inflammatory response and results in bacterial multiplication in pulmonary tissue. This process then spills over into the alveolar spaces and provides a mechanism for *Y. pestis* to be expelled during coughing episodes (13,14,15). Spread of *Y. pestis* to contacts by the respiratory droplet route can initiate an epidemic of primary pneumonic plague (1,14,15,19,20).

A primary pneumonic plague patient usually has an infectious pneumonitis at the onset of symptoms, often within 24 to 48 hours after exposure. Consequently, physical vigour is largely intact when infection generates an intense cough reflex productive of thin sero-sanguineous expectorate. This is readily aerosolized into fine droplets (<5 µm diameter) which may be inhaled deep into the respiratory tract of close contacts. In contrast, a patient with secondary plague pneumonia has usually been acutely ill for several days prior to lung invasion. Many patients succumb to their infection before they develop a well-advanced pneumonia. Those who do not succumb may be so morbid that their
cough reflex lacks the vigour to produce finely aerosolized droplets. A purulent, thick or tenacious exudate may further limit the patient's ability to produce fine droplets.

Pneumonic plague must be considered highly contagious whenever it occurs, although person-to-person transmission is most likely in cold humid environments coupled with overcrowding (1,14,15,19,20). Since Y. pestis is not truly airborne, person-to-person transmission requires face-to-face exposure within 2 metres of a coughing patient (19,21,22). The organism does not permeate room air where the patient is housed and is not carried through air ducts or vents.

Pharyngeal plague

Pharyngeal plague results from contamination of the oropharynx with Y. pestis-infected material. Recognized sources of exposure include respiratory droplets expelled during coughing by a patient (or animal) with a respiratory plague infection (1,19,23), or ingestion of undercooked or raw tissues of an infected animal (24). It is conceivable that bacteria contaminating the hands or instruments used in skinning an infected animal could be transferred to the mouth.

Asymptomatic colonization of the pharynx has been reported in contacts of pneumonic plague patients (25). Symptomatic pharyngeal pharyngitis is clinically similar to streptococcal or viral pharyngitis although the cervical lymphadenopathy of plague is often more severe and painful. Without epidemiological or historical information to suggest pharyngeal pharyngitis, it is likely that the diagnosis will be missed until there is laboratory identification of Y. pestis in a throat culture (10).

Meningeal plague

Plague meningitis is characterized by fever, headache and stiff neck (nuchal rigidity/meningismus), delirium, confusion, obtundation or coma (1,26,27). Examination of spinal fluid will demonstrate pleocytosis, predominantly polymorphonuclear leukocytes, and often Gram-negative plague bacilli are seen. Meningeal plague may be a primary manifestation, but it usually occurs a week or more after the onset of bubonic or septicaemic plague. It is often associated with delayed, inappropriate or bacteriostatic antibiotic therapy and is more common in patients with axillary (as opposed to inguinal) buboes (27,28).
Plague meningitis has been associated with the use of antibiotics which suppress infection but are not bacteriocidal and which do not readily penetrate the meninges, e.g. the tetracyclines. These agents may not eradicate *Y. pestis* before meningeal invasion occurs, and once the meninges become infected, the organisms there may be protected by the blood-brain barrier. The clinical course is often subacute, and permanent neurological sequelae are rare (26,28).

**Clinical presentations relative to the source of exposure**

The location of the primary bubo suggests the source of infection. Inguinal buboes in adults and older children indicate that infection was transmitted by the bite of an infective flea on the lower extremities. Axillary buboes suggest upper extremity inoculation through handling of infected animal tissues, including cuts incurred while skinning an animal or contamination of open sores, abrasions, or other breaks in the skin.

In circumstances where patients are exposed to flea bites while sleeping, such as when plague-infected rats and rat fleas have invaded residences, localizing a bubo to the upper or lower torso does not serve to differentiate flea bite from exposure to contaminated material.

**Differential diagnosis**

Bubonic plague may be confused with streptococcal or staphylococcal lymphadenitis, infectious mononucleosis, cat-scratch fever, lymphatic filariasis, tick typhus, tularemia and other causes of acute lymphadenopathy. Involvement of intra-abdominal lymph nodes may mimic appendicitis, acute cholecystitis, enterocolitis or other intra-abdominal surgical emergencies (5,10). Inguinal buboes have been mistaken for an inguinal hernia. Involvement of intrathoracic lymph nodes and deep cervical lymph nodes also presents diagnostic dilemmas. In the case of severe deep cervical adenitis, displacement of the trachea threatening an airway obstruction may constitute a medical emergency.

Septicaemic plague also constitutes a medical emergency which, unless the clinician has good reason to suspect the specific etiology, the working diagnosis is often a non-specific sepsis syndrome, or a Gram-negative sepsis. Fortunately, some empiric antibiotic regimens for Gram-negative sepsis, e.g. aminoglycosides or fluoroquinolones are effective against *Y. pestis*, but increasing use of advanced generation cephalosporins is problematic. As in other sepsis syndromes, gastrointestinal complaints of abdominal pain, nausea, vomiting and diarrhoea may be prominent and
misleading (1,4,5). Perhaps the most serious point of confusion in the differential consideration of plague sepsis may come from the laboratory. For example, an improperly decolorized Gram-stain examination of a blood smear or lymph node aspirate may result in the interpretation of Y. pestis bipolarity as a Gram-positive diplococcus; also, automated bacterial identification devices may not code for Y. pestis and may result in misidentifications (29).

Pneumonic plague may be confused with other causes of acute, severe community-acquired pneumonia, such as pneumococcal, streptococcal, H. aemophilus influenzae, anthrax, tularemia, Legionella pneumophila, leptospiral, hantavirus pulmonary syndrome, and influenza virus pneumonia. Regional lymphadenitis may indicate plague or tularemia pneumonia arising secondary to a cutaneous infective exposure.

Laboratory diagnosis

When plague is suspected, clinical specimens should be collected immediately, and specific antimicrobial treatment begun. A definitive laboratory diagnosis of Y. pestis infection is based on the isolation and identification of the organism from clinical specimens or by demonstrating a diagnostic change in antibody titre in paired serum specimens. Routine diagnostic specimens for smear and culture include the following: whole blood; aspirates from suspected buboes; pharyngeal swabs, sputum samples or tracheal washes from those with suspected plague pharyngitis or pneumonia; and cerebrospinal fluid from those with suspected meningitis. Since early buboes are seldom fluctuant or necrotic, they usually require aspiration after an injection of 1-2 ml of saline through an 18-22 gauge needle. Suitable microbiological culture media (e.g. brain-heart infusion, broth, sheep blood agar, or MacConkey agar) should be inoculated with a portion of each specimen. Smears should be examined with Wayson or Giemsa stain and with Gram-stain; smears should also be submitted for direct fluorescent antibody testing (anti-F1 antibody). An acute-phase serum specimen should be tested for antibody to Y. pestis; for serological confirmation, a convalescent-phase serum specimen should be collected 4-6 weeks or more later. When a suspected plague patient dies, appropriate autopsy tissues for culture, immunohistochemical staining, and fluorescent antibody testing include lymph nodes, liver, spleen, lung and bone marrow. Materials for culture should be sent to the laboratory either fresh or frozen on dry ice. Cary-Blair or a similar holding medium can be used to transport Y. pestis-infected tissues.
Plague patients typically have white blood cell (WBC) counts of 12,000 to 25,000/µl blood, with a predominance of immature polymorphonuclear cells (PMNs) (7). Leukaemoid reactions sometimes occur. Chest roentgenograms of patients with pneumonic plague usually show patchy bronchopneumonic infiltrates as well as segmental or lobar consolidation with or without confluence; they occasionally show cavitation, or bilateral diffuse infiltrates of acute respiratory distress syndrome (17). Stained sputum specimens usually contain PMNs and may demonstrate bipolar staining Gram-negative bacilli. In Y. pestis septicaemia, the finding of characteristic organisms in a stained peripheral blood smear or a buffy-coat smear is a grave prognostic sign (27). In patients with plague meningitis, cerebrospinal fluid pleocytosis with a predominance of PMNs is typical. The characteristic bipolar appearance is not unique to Y. pestis, and is best seen in Wayson- or Giemsa-stained material.

The diagnosis of plague is confirmed in the laboratory by the isolation of Y. pestis from cultures of body fluids or tissues (30,31). Cultures of three blood samples taken over a 45-minute period before treatment will usually result in isolation of the bacterium. Y. pestis on solid media grows as grey-white, translucent colonies, usually too small to be seen as individual colonies at 24 hours. After incubation at 37°C for 48 hours, colonies are about 1-2 mm in diameter. After 48-72 hours of incubation colonies are raised and have an irregular, A-hammered copper appearance (30,31). Cultures are definitely identified as Y. pestis by specific phage lysis. Automated bacteriological test systems can be used to assist in the identification of isolates as Y. pestis, but such isolates can be misidentified (e.g. as Y. pseudotuberculosis) or overlooked if these systems are improperly programmed (29).

When Y. pestis is not isolated, plague can be confirmed by seroconversion (a four-fold or greater titre change) to Y. pestis F1 antigen by passive haemagglutination testing of paired serum specimens (30,31). The specificity of a positive passive haemagglutination test requires confirmation with the F1 antigen haemagglutination-inhibition test (31). A few plague patients seroconvert as early as 5 days after onset of symptoms. Most seroconvert between 1 and 2 weeks after onset; a few seroconvert 3 weeks or more after onset; and a few (less than 5%) fail to seroconvert (32). Early, specific antibiotic treatment may delay seroconversion by several weeks. After seroconversion, positive serological titres usually diminish gradually over months to years. Enzyme-linked immunosorbent assays (ELISAs) for detecting IgM and IgG antibodies,
Detection of the F1 antigen in tissues or fluids by direct fluorescent antibody testing (or other standardized antigen detection procedures) provides presumptive evidence of plague, as does a diagnostically elevated F1 antibody titer in a single serum sample from a patient with a plague-compatible illness who has not received plague vaccine (30,31). Visualization of bipolar coccobacilli in a Wayson- or Giemsa-stained specimen supports a diagnosis of clinically suspect plague. A summary of laboratory diagnostic categories for human plague is as follows:

**Case definitions**

**Suspect plague:**
- compatible clinical and epidemiological features; and
- suspicious organisms seen or isolated from clinical specimens.

**Presumptive plague:**
- *Y. pestis* F1 antigen detected in clinical materials by direct fluorescent antibody testing, or by some other standardized antigen detection method; or
- isolate from a clinical specimen demonstrates biochemical reactions consistent with *Y. pestis* or PCR positivity; or
- a single serum specimen is found positive for diagnostic levels of antibodies to *Y. pestis* F1 antigen, not explainable on the basis of prior infection or immunization.

**Confirmed plague:**
- isolate identified as *Y. pestis* by phage lysis of cultures; or
- a significant ($\geq$4-fold) change in antibody titre to the F1 antigen in paired serum specimens.
References


