Characteristic pathologic findings of diphtheria include mucosal ulcers with a pseudomembranous coating composed of an inner band of fibrin and a luminal band of neutrophils. Initially white and firmly adherent, in advanced diphtheria the pseudomembranes turn gray or even green or black as necrosis progresses. Mucosal ulcers result from toxin-induced necrosis of the epithelium accompanied by edema, hyperemia, and vascular congestion of the submucosal base. A significant fibrinosuppurative exudate from the ulcer develops into the pseudomembrane. Ulcers and pseudomembranes in severe respiratory diphtheria may extend from the pharynx into medium-sized bronchial airways. Expanding and sloughing membranes may result in fatal airway obstruction.

APPROACH TO THE PATIENT: Diphtheria

Diphtheria, though rare in the United States and other developed countries, should be considered when a patient has severe pharyngitis, particularly when there is difficulty swallowing, respiratory compromise, or signs of systemic disease (e.g., myocarditis or generalized weakness). The leading causes of pharyngitis are respiratory viruses (rhinoviruses, influenza viruses, parainfluenza viruses, coronaviruses, adenoviruses; ~25% of cases), group A streptococci (15–30%), group C streptococci (~5%), atypical bacteria such as *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* (15–20% in some series), and other viruses such as herpes simplex virus (~4%) and Epstein-Barr virus (<1% in infectious mononucleosis). Less common causes are acute HIV infection, gonorrhea, fusobacterial infection (e.g., Lemierre's syndrome), thrush due to *Candida albicans* or other *Candida* species, and diphtheria. The presence of a pharyngeal pseudomembrane or an extensive exudate should prompt consideration of diphtheria (Figure 175-1).

FIGURE 175-1 Respiratory diphtheria due to toxigenic *C. diphtheriae* producing exudative pharyngitis in a 47-year-old female patient displaying neck edema and a pseudomembrane extending from the uvula to the pharyngeal wall. The characteristic white pseudomembrane is caused by diphtheria toxin–mediated necrosis of the respiratory epithelial layer, producing a fibrinous coagulative exudate. Submucosal edema adds to airway narrowing. The pharyngitis is acute in onset, and respiratory obstruction from the pseudomembrane may occur in severe cases. Inoculation of pseudomembrane fragments or submembranous swabs onto Löffler's or tellurite selective medium reveals *C. diphtheriae*. *(Photograph by P. Strebel, MD, used by permission. From R. Kadirova et al: J Infect Dis 181:S110, 2000. With permission of Oxford University Press.)*

CLINICAL MANIFESTATIONS

Respiratory Diphtheria The clinical diagnosis of diphtheria is based on the constellation of sore throat; adherent tonsillar, pharyngeal, or nasal pseudomembranous lesions; and low-grade fever. In addition, diagnosis requires the isolation of *C. diphtheriae* or histopathologic isolation of compatible gram-positive organisms. The Centers for Disease Control and Prevention (CDC) recognizes *confirmed* respiratory diphtheria (laboratory proven or epidemiologically linked to a culture-confirmed case) and *probable* respiratory diphtheria (clinically compatible but not laboratory proven or epidemiologically linked). Carriers are defined as individuals who have positive cultures for *C. diphtheriae* and who either are asymptomatic or have symptoms but lack pseudomembranes. Most patients seek medical care for sore throat and fever several days into the illness. Occasionally, weakness, dysphagia, headache, and voice change are the initial manifestations. Neck edema and difficulty breathing are evident in more advanced cases and carry a poor prognosis.

The systemic manifestations of diphtheria stem from the effects of diphtheria toxin and include weakness as a result of neurotoxicity and cardiac arrhythmias or congestive heart failure due to myocarditis. Most commonly, the pseudomembranous lesion is located in the tonsillopharyngeal region. Less commonly, the lesions are located in the larynx, nares, and trachea or bronchial passages. Large pseudomembranes are associated with severe disease and a poor prognosis. A few patients develop massive swelling of the tonsils and present with "bull-neck" diphtheria, which results from massive edema of the submandibular and paratracheal region and is further characterized by foul breath, thick speech, and stridorous breathing. The diphtheritic pseudomembrane is gray or whitish and sharply demarcated. Unlike the exudative lesion associated with streptococcal pharyngitis, the pseudomembrane in diphtheria is tightly adherent to the underlying tissues. Attempts to dislodge the membrane may cause bleeding. Hoarseness suggests laryngeal diphtheria, in which laryngoscopy may be diagnostically helpful.

Cutaneous Diphtheria This dermatosis is characterized by punched-out ulcerative lesions with necrotic sloughing or pseudomembrane formation (Figure 175-2). The diagnosis requires cultivation of *C. diphtheriae* from lesions, which most commonly occur on the lower and upper extremities, head, and trunk.

Infections Due to Non-*diphtheriae Corynebacterium* Species and Nontoxigenic *C. diphtheriae* Non-*diphtheriae* species of *Corynebacterium* and related genera (discussed below) as well as nontoxigenic strains of *C. diphtheriae* itself have been found in bloodstream and respiratory infections, often in individuals with immunosuppression or chronic respiratory disease. These organisms can cause disease manifestations and should not necessarily be dismissed as colonizers.

FIGURE 175-2 Cutaneous diphtheria due to nontoxigenic *C. diphtheriae* on the lower extremity. *(From the Centers for Disease Control and Prevention.)*