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Infectious Diseases Causing Diffuse Alveolar Hemorrhage in Immunocompetent Patients: A State-of-the-Art Review

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Abstract Diffuse alveolar hemorrhage (DAH) represents a syndrome that can complicate many clinical conditions and may be life-threatening, requiring prompt treatment. It is recognized by the signs of acute- or subacute-onset cough, hemoptysis, diffuse radiographic pulmonary infiltrates, anemia, and hypoxemic respiratory distress. DAH is characterized by the accumulation of intra-alveolar red blood cells originating most frequently from the alveolar capillaries. It must be distinguished from localized pulmonary hemorrhage, which is most commonly due to chronic bronchitis, bronchiectasis, tumor, or localized infection. Hemoptysis, the major sign of DAH, may develop suddenly or over a period of days to weeks; this sign may also be initially absent, in which case diagnostic suspicion is established after sequential bronchoalveolar lavage reveals worsening red blood cell counts. The causes of DAH can be divided into infectious and noninfectious, the latter of which may affect immunocompetent or immunodeficient patients. Pulmonary infections are rarely reported in association with DAH, but they should be considered in the diagnostic workup because of the obvious therapeutic implications. In immunocompromised patients, the main infectious diseases that cause DAH are cytomegalovirus, adenovirus, invasive aspergillosis, *Mycoplasma*, *Legionella*, and *Strongyloides*. In immunocompetent patients, the infectious diseases that most frequently cause DAH are influenza A (H1N1), dengue, leptospirosis, malaria, and *Staphylococcus aureus* infection. Based on a search of the PubMed and Scopus databases, we review the infectious diseases that may cause DAH in immunocompetent patients.

Keywords Diffuse alveolar hemorrhage · Infectious disease · Hemoptysis · Pulmonary disease

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Introduction

Diffuse alveolar hemorrhage (DAH) represents a syndrome with various presentations that can complicate many clinical conditions and may be life-threatening, requiring prompt treatment [1]. DAH is recognized by the signs of acute- or subacute-onset cough, hemoptysis, diffuse radiographic pulmonary infiltrates, anemia, and hypoxemic respiratory distress. This clinicopathologic syndrome is characterized by the accumulation of intra-alveolar red blood cells (RBCs) originating most often from the alveolar capillaries and, less frequently, from precapillary arterioles or postcapillary venules [2]. DAH must be distinguished from localized pulmonary hemorrhage, which is most commonly due to chronic bronchitis, bronchiectasis, tumor, or localized infection [3, 4].

The treatment of DAH is directed at establishing the underlying diagnosis, providing respiratory support, and preventing the progression of microcirculation damage, typically with corticosteroids and immunosuppressive agents [1, 5]. However, such treatment is potentially harmful when DAH is due to nonimmune causes such as infection [6]. In immunocompetent patients, pulmonary infections are rarely reported in association with DAH, but they should be considered in the diagnostic workup because of the obvious therapeutic implications [7]. This review presents the infectious diseases that most frequently cause DAH in immunocompetent patients [influenza A (H1N1), dengue,

leptospirosis, malaria, and *Staphylococcus aureus* infection] and summarizes the clinical, pathologic, and imaging features of DAH in infectious diseases. We focus on the primary diseases that cause DAH according to the number of cases described in the literature, determined using the PubMed and Scopus databases.

Initial Considerations

Etiology

The causes of DAH can be divided into infectious and noninfectious, the latter of which can affect immunocompetent and immunodeficient patients. Pulmonary infections include those caused by viruses, bacteria, fungi, and parasites [1, 8, 9]. In immunocompromised patients, the main infectious diseases that cause DAH are cytomegalovirus (CMV) [10, 11], adenovirus [12], invasive aspergillosis [13], and *Mycoplasma* [14], *Legionella* [15], and *Strongyloides* [16] infections. In immunocompetent patients, the most important infections that cause DAH include influenza A (H1N1), dengue, leptospirosis, malaria, and *S. aureus* infection.

Clinical Presentation

Hemoptysis, the major sign of DAH, may develop suddenly or over a period of days to weeks. However, this sign is initially absent in up to one-third of patients, in which case diagnostic suspicion is established after sequential bronchoalveolar lavage (BAL) reveals worsening RBC counts. Some patients present with severe acute respiratory distress requiring mechanical ventilation [1, 4]. DAH may present with a course of variable severity and should always be considered an imminently life-threatening condition. DAH is associated with several clinical entities and histologic subtypes. Its pathophysiology is alveolar microcirculation injury, and the cause might be generalized (as in systemic vasculitis) or lung-specific disease [as in diffuse alveolar damage (DAD) or infection] [17, 18].

Diagnostic Studies

DAH may impair oxygen transfer, which might result in hypoxemia. In this setting, the diffusing capacity of the lung for carbon monoxide (DLCO) may be increased, and serial increases in the DLCO may indicate progressive alveolar hemorrhage. After recurrent episodes of DAH, interstitial fibrosis and restrictive changes may develop. Less commonly, patients may exhibit spirometric changes indicating airflow obstruction.

Diagnostic imaging consists primarily of chest radiography showing diffuse alveolar opacities, but recurrent episodes of hemorrhage may produce reticular interstitial opacities due to pulmonary fibrosis [1, 4]. High-resolution computed tomography (HRCT) findings are nonspecific and consist of bilateral areas of ground-glass opacity and/or consolidation [1, 4].

Once the diagnosis of DAH is made, the underlying cause must be established in order to initiate treatment [4]. In addition to the patient's history, other data useful for establishing the underlying diagnosis can be collected by physical examination; flexible bronchoscopy with BAL fluid analysis; chest imaging; routine laboratory studies (to detect anti-neutrophil cytoplasmic antibodies, among others); directed serologic testing for connective tissue disease, systemic vasculitis, and infectious diseases; and biopsy with histologic and immunofluorescence analyses [1, 19]. An exhaustive search should be performed for signs of systemic disease such as sinusitis, cutaneous leukocytoclastic vasculitis, iridocyclitis, synovitis, and glomerulonephritis [9]. BAL specimens should be subjected to routine stains and cultures for bacterial, mycobacterial, fungal, and viral organisms [1].

Histopathology

The histopathology of DAH is characterized by intra-alveolar RBCs and fibrin, with the eventual accumulation of hemosiderin-laden macrophages (siderophages) [4, 9, 20]. Surgical lung biopsy may be required to establish the cause of DAH if serologic testing and/or clinical history is unrevealing [1]. For lung sections, besides hematoxylin and eosin, Grocott, Brown-Hopps, and Ziehl-Neelsen staining may be performed for the identification of fungi, bacteria, and acid-fast bacilli, respectively. Specific immunostaining should also be performed; it may provide information about possible viral inclusions such as those found in CMV, adenovirus, herpesvirus, influenza, and respiratory syncytial virus. Immunohistochemical techniques, such as immunofluorescence, can provide information about immune deposits, and a polymerase chain reaction (PCR) assay can be performed in doubtful cases [9, 19, 21].

Influenza A (H1N1)

Influenza A (H1N1) virus infection causes a broad spectrum of clinical syndromes, ranging from afebrile upper respiratory illness to fulminant viral pneumonia [22]. Most patients presenting for care have a typical influenza-like illness with fever and cough, sometimes accompanied by sore throat, rhinorrhea, and other common systemic viral symptoms [23]. Signs and symptoms such as dyspnea

(or tachypnea in children), chest pain, hemoptysis or purulent sputum, altered mental status, and manifestations of dehydration indicate progression to more severe disease or complications [24]. Underlying conditions associated with complications from seasonal influenza are also risk factors for complications from influenza A (H1N1) virus infection. Pregnant women, those less than 2 weeks postpartum, and patients with immunosuppression or neurologic disorders have also been overrepresented among those with severe influenza A (H1N1) infection [24]. Several other risk factors for severe or fatal cases of this infection, particularly in patients younger than 5 years and older than 65 years, include severe obesity, cardiovascular disease, diabetes, chronic lung disease, metabolic disorders, chronic renal or hepatic disease, immunosuppression, hemoglobinopathy, a long history of smoking, and long-term aspirin therapy [25]. Several laboratory diagnostic tests can be used to detect the presence of influenza viruses in respiratory specimens, including direct antigen detection tests, virus isolation in cell culture, and detection of influenza-specific RNA by real-time reverse-transcriptase polymerase chain reaction (rRT-PCR). RT-PCR has the highest sensitivity and specificity; rapid antigen and immunofluorescence tests, albeit very useful as initial screening tests, are considerably less sensitive [26].

The predominant HRCT findings in influenza A (H1N1) infection consist of bilateral areas of ground-glass opacity and/or consolidation. The crazy-paving pattern has also been described. These abnormalities have a predominantly peripheral and subpleural distribution [27–29]. Although HRCT findings of influenza A (H1N1) pneumonia frequently overlap with those of other diseases, a pattern of extensive or diffuse ground-glass opacities and consolidations with a primarily peribronchovascular or subpleural distribution can be strongly related to influenza A (H1N1) infection [28].

Most reports describing pathologic findings have been related to autopsy series. The most important pathologic finding is focal to extensive DAD, often associated with marked hyaline membrane formation, pulmonary edema, and various degrees of acute pulmonary hemorrhage. Another important finding is focal necrotizing bronchiolitis. Autopsy evidence of acute pneumonia has usually been observed in association with bacteria [21, 30].

Superimposed bacterial infections of the respiratory tract are not only extremely common in severe influenza, but also complicate the histopathologic appearance. A clear distinction between lesions produced by the virus of the epidemic disease and those attributable to complicating organisms may be very difficult [31].

DAH is a serious complication among patients with influenza A (H1N1) with or without other risk factors (Fig. 1). Pulmonary hemorrhage is a known complication of influenza-related pneumonia. Although DAH has been reported in other influenza epidemics [32], in this review we discuss only influenza A (H1N1), which is the viral serotype of influenza currently considered to be related most closely to DAH. Gilbert et al. [30] suspected that severe cases of influenza A (H1N1) pneumonia had a higher incidence of alveolar hemorrhage than previously reported. This suspicion was supported by Mauad et al. [21], who found an intense hemorrhagic component in 5/21 autopsied patients with influenza A (H1N1) infection. These histopathologic features were also reported by other authors, who noted the frequent association of alveolar hemorrhage with DAD in influenza A (H1N1) pneumonia [33–35]. Some other case reports related DAH to influenza A (H1N1) infection, in which HRCT scans showed diffuse bilateral ground-glass opacities [7, 36]. A retrospective chart analysis of 15 fatal cases of influenza A (H1N1) showed that 80 % had intra-alveolar hemorrhage; the most common radiologic findings were fluffy infiltrates, followed by confluent opacities [33].

Dengue

Dengue fever (DF) is an acute infectious disease caused by the dengue virus, an arthropod-borne RNA virus belonging to the family Flaviviridae with four distinct serotypes (DENV 1–4) [37]. Dengue virus causes disease in humans, including DF and dengue hemorrhagic fever (DHF), in which increased vascular permeability is the main pathology leading to shock [37]. The virus is transmitted to humans by the bite of an infected female mosquito of the genus *Aedes*. Its prevalence has grown dramatically in

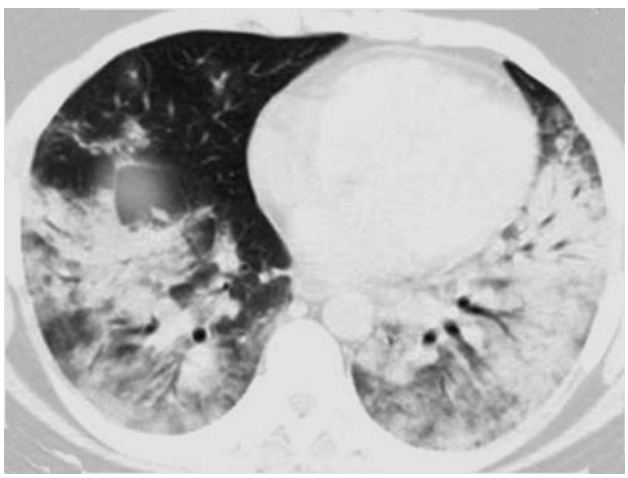

Fig. 1 A 28-year-old woman with influenza A (H1N1) virus–associated pneumonia and diffuse alveolar hemorrhage. High-resolution computed tomography exhibits consolidations and ground-glass opacities in both lower lobes

recent decades, and the disease is now endemic in more than 100 countries in Eastern and Western Africa, Central and South America, the Eastern Mediterranean, Southeast Asia, and the Western Pacific [38].

Dengue disease has a wide spectrum of clinical signs and symptoms, ranging from asymptomatic infection to severe and lethal manifestations. DF usually presents as an acute fever with headache, rash, myalgia, arthralgia, retro-orbital pain, prostration, lymphadenopathy, and dry cough. Other findings include petechiae, epistaxis, gingival bleeding, and gastrointestinal bleeding [39]. According to the World Health Organization guidelines, DHF is characterized by four major clinical manifestations: high fever, hemorrhagic phenomena, and often hepatomegaly and circulatory failure. Moderate to marked thrombocytopenia with concurrent hemoconcentration is a hallmark of clinical laboratory findings in DHF [40]. In general, other laboratory findings include neutropenia followed by lymphocytosis, with the presence of atypical lymphocytes [37–40]. The diagnosis is based on serology, RNA detection, and viral isolation in blood specimens. Enzyme-linked immunosorbent assays remain the most widely used technique for serologic diagnosis, but they do not identify the dengue virus serotype responsible for the current infection [8].

Thoracic manifestations such as pleural effusion and pneumonitis are uncommon in DHF, and pulmonary hemorrhage is even rarer (Fig. 2). Hemoptysis has been reported in 1.4 % of dengue infections [41, 42]. The pathogenesis of bleeding in patients with DHF is not well understood. It is thought to be a multifactorial process with abnormalities in the coagulation cascade, thrombocytopenia, platelet dysfunction, disseminated intravascular coagulation, and vascular defects. Increased vascular permeability has been thought to be mediated by histamine release [41, 42]. A histopathologic review of 319 adult patients with dengue showed that pulmonary hemorrhage and DAD were the main features of the infection [43]. Morphologic studies of lung tissues revealed interstitial pneumonia associated with focal or diffuse zones of alveolar congestion and hemorrhage, an increased number of alveolar macrophages, and recruiting of platelets, mononuclear cells, and polymorphonuclear cells [44, 45]. DAH in DHF has been rarely described [41, 42]. HRCT findings in DHF causing DAH may present discrete patchy ground-glass opacities in both lungs [41]. Other features are extensive and bilateral areas of consolidation with air bronchogram and ground-glass opacities associated with small pleural effusions [8].

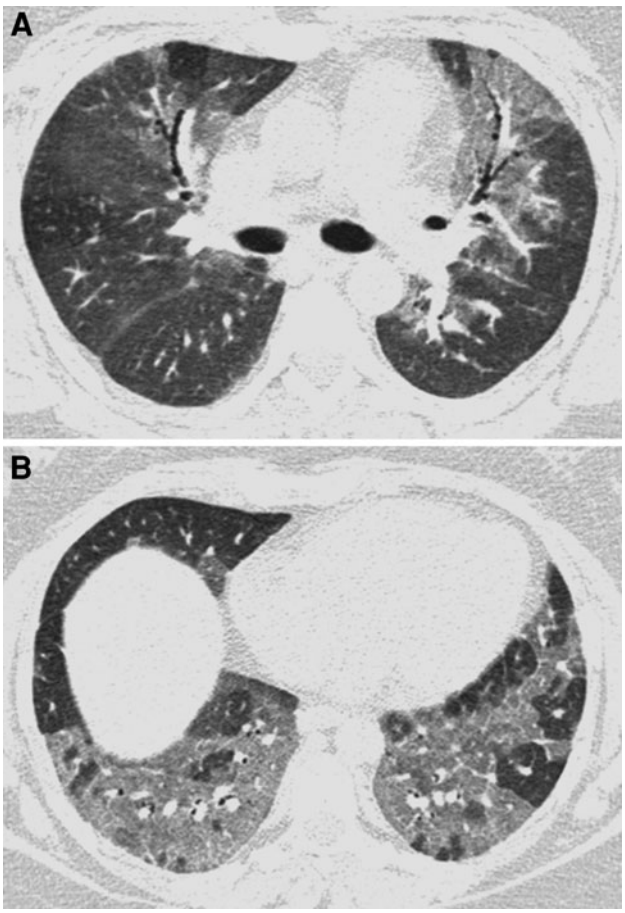

Fig. 2 A 59-year-old man with dengue hemorrhagic fever and diffuse alveolar hemorrhage. High-resolution computed tomography at the levels of the carina (**a**) and lower lobes (**b**) shows extensive areas of ground-glass opacities in both lungs

Leptospirosis

Leptospirosis is a zoonosis caused by spirochetes from the species *Leptospira interrogans* [46]. It is one of the most widespread zoonoses in the world, occurring mainly in tropical and subtropical regions, and is considered an important public health problem [46]. Humans are infected when mucous membranes or abraded skin come into direct contact with the urine of infected animals (including rats, mice, sheep, cattle, pigs, dogs, raccoons, and goats) or by exposure to contaminated water, soil, or other matter. Clinical manifestations of leptospirosis range from asymptomatic or febrile episodes to severe forms. The clinical findings include fever, muscle tenderness (especially of the calf muscles), headache, conjunctival suffusion, and digestive disorders, with hepatic and renal involvement. Mental status disturbance may also appear [47]. Leptospirosis should be considered in the differential diagnosis of patients with febrile illnesses associated with pneumonitis and respiratory failure, especially when hemoptysis is present [48].

This disease is associated with cardiovascular collapse and significant mortality [47]. Severe disease is estimated to occur in 5–15 % of all human infections, typically

presenting as Weil's syndrome, a triad of hemorrhagic manifestations and hepatic and renal dysfunction. Severe pulmonary involvement in leptospirosis consists primarily of hemorrhagic pneumonitis. The emergence of severe pulmonary hemorrhage syndrome (SPHS) in leptospirosis may present as acute respiratory distress or massive pulmonary hemorrhage, generally associated with hemoptysis [49, 50]. The diagnosis of leptospirosis is based on clinical findings, a history of direct or indirect exposure to infected animals in endemic areas, and positive serologic tests [51].

Radiographic findings commonly accompany pulmonary symptoms but may occur without them; they consist of nonspecific, diffuse, small opacities, which may be disseminated or coalesce into larger areas of consolidation with increasing severity of symptoms [52]. These infiltrates correspond to areas of intra-alveolar and interstitial hemorrhage [52]. The most frequent HRCT findings are extensive, bilateral, ground-glass opacities involving all lobes (Fig. 3). Areas of consolidation, peripheral airspace nodules, and pleural effusions may be present. The abnormalities involve mainly the peripheral and dorsal lung regions and the lower lung zones [48, 53]. Microscopic examination reveals extensive areas of intra-alveolar and interstitial hemorrhage, but other findings, such as pulmonary edema, fibrin deposition, hyaline membrane formation, and proliferative fibroblastic reactions, are frequent [49].

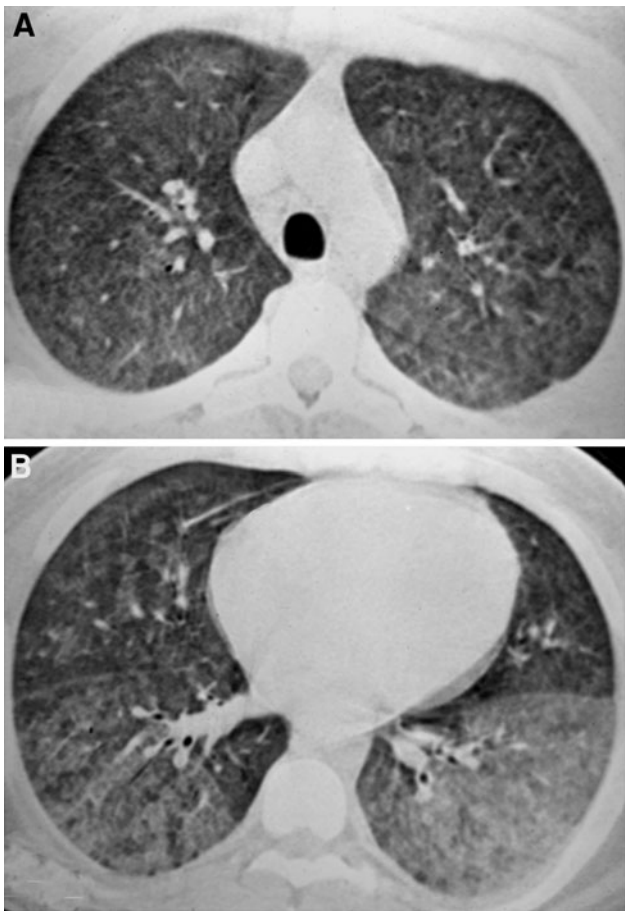

Fig. 3 A 41-year-old man with leptospirosis and diffuse alveolar hemorrhage. High-resolution computed tomography at the levels of the upper (**a**) and lower (**b**) lobes shows bilateral ground-glass opacities in both lungs

Bernardi et al. [54] found increased expression of C3aR, toll-like receptor 2, and intercellular and vascular cell adhesion molecules in the lungs of patients who died of leptospirosis. These data indicate that innate immune receptors and adhesion molecules contribute to the pathogenesis of lung hemorrhage in leptospirosis. Croda et al. [55] suggested that the linear deposition of immunoglobulins (IgA, IgG, and IgM) and complements on the alveolar surface may play a role in the pathogenesis of pulmonary hemorrhage in human leptospirosis. Thus, leptospirosis pulmonary hemorrhage syndrome seems to have unique pathologic features not seen in other pulmonary hemorrhagic syndromes. These results are important because no treatment other than supportive respiratory care is currently available for this syndrome. A better understanding of the pathogenesis can contribute to the development of treatment strategies for this devastating manifestation of leptospirosis [54, 55].

Surveillance between 2003 and 2005 identified 47 (10 %) SPHS cases among 474 patients whose diagnosis met the clinical definition of severe leptospirosis [56]. All of these cases presented with the onset of massive hemoptysis, and 24 showed alveolar or interstitial bilateral infiltrates on chest radiographs [56]. In one series, 74 % of 89 fatal cases of leptospirosis had clinically detected pulmonary involvement, which was the strongest risk factor [57]. Autopsies performed on 43 of these patients showed pulmonary hemorrhage in 72 % of cases [57]. The treatment of leptospirosis is based on antibiotics and supportive care. Some studies have reported success in the treatment of DAH caused by leptospirosis using hemostatic agents such as desmopressin [58] and recombinant activated factor VII [59].

Malaria

Malaria remains a significant global public health problem, especially in tropical and subtropical regions where temperature and rainfall are most suitable for the development of the malaria agent, the *Plasmodium* parasite, in *Anopheles* mosquitoes, which transmit malaria through their bites. Malaria has a devastating socioeconomic impact on

affected countries. More than two billion people are exposed to the risk of acquiring malaria [60].

Whereas patients with uncomplicated malaria usually present with fever and nonspecific symptoms, severe and complicated malaria is characterized by multiorgan involvement, including acute lung injury and acute respiratory distress syndrome (ARDS). Pulmonary symptoms such as cough with or without expectoration and dyspnea have been described in patients with malaria [60, 61]. The clinical manifestations of malaria have shown a paradigm shift in the last two decades; multiorgan failure is encountered much more frequently than previously, likely due to the high transmission rate of falciparum malaria and drug resistance to commonly used antimalarial agents [62]. In patients living or having traveled in endemic areas, malaria should be considered as a possible cause of ARDS of obscure etiology. ARDS is increasingly reported in falciparum malaria and malaria caused by species formerly considered benign (*Plasmodium vivax*, *P. ovale*, and *P. malariae*) [60]. Parasites can be detected on thick and thin peripheral blood smears. Thick smear examination facilitates the quantification of parasitemia [60, 61].

ARDS is considered to be the most severe form of lung injury in malaria and is frequently associated with cerebral malaria. In patients with falciparum malaria, ARDS can develop at the time of initial presentation or after several days of treatment, when patients appear to be improving and parasitemia is reduced [60, 61]. Pregnant women with severe falciparum malaria are particularly prone to the development of ARDS and have a high rate of mortality [61]. Adequate supportive management is considered to be an essential component of treatment to reduce mortality in patients with severe complicated malaria, and the early administration of specific antimalarial treatment can be lifesaving [60–62].

General radiographic and HRCT findings in malaria are consistent with noncardiogenic pulmonary edema. Pleural effusion, diffuse interstitial edema, and lobar consolidation may also be seen [63].

Malaria causing DAH may show progressive refractory hypoxemia and diffuse infiltrates on radiographs and pathologic findings of scattered hemorrhage and alveolar septal thickening, leading this complication to resemble ARDS [64]. Corne et al. [65] reported the occurrence of intra-alveolar hemorrhage during *P. falciparum* malarial crisis. Brooks et al. [66] described five patients who developed fatal pulmonary edema with normal central venous pressure in which histopathologic specimens showed alveolar hemorrhage and hyaline membrane formation. Autopsy studies in patients with severe falciparum malaria revealed heavy edematous lungs, congested pulmonary capillaries, thickened alveolar septa, intra-alveolar hemorrhage, hyaline membrane formation, and serous pleural and pericardial effusions [60].

Staphylococcus aureus Pneumonia

Staphylococcus aureus is recognized as an extremely successful human pathogen that may colonize patients in the hospital or community, potentially causing a variety of clinical entities such as cutaneous infections, pneumonia, and sepsis [67]. *Staphylococcus aureus* is estimated to cause 1–10 % of community-acquired pneumonias and 20–50 % of nosocomial pneumonias [68]. Pneumonia often occurs after influenza infection, particularly in elderly patients with preexisting chronic diseases such as chronic obstructive pulmonary disease and cardiovascular diseases. It has an abrupt clinical scenario, with pleural chest pain, cough, purulent sputum, and sometimes hemoptysis. The prevalence of methicillin-resistant *S. aureus* (MRSA) is well known as a cause of hospital-acquired infections, and the frequency of community-onset MRSA (CO-MRSA) infections has increased substantially in the past decade [69]. Methicillin resistance is determined by the presence of a penicillin-binding protein with decreased affinity to penicillin [56]. Methicillin-sensitive *S. aureus* (MSSA) and MRSA may produce Panton-Valentine leukocidin (PVL) and cause necrotic hemorrhagic pneumonia, but the majority of publications have been related to CO-MRSA or mixed patient groups [70, 71]. Whether methicillin resistance plays a role in the pathogenesis of CO-MRSA has not been well established. One study compared outcomes between MSSA and MRSA strains and found no significant difference. Mortality rates are not higher among patients with MRSA-related PVL-positive pneumonia than among those with MSSA-related PVL-positive pneumonia [71].

The main feature of *S. aureus* pneumonia on HRCT is bronchopneumonia with segmental consolidations, which tend to be multilobar and typically affect the lower lobes. Nodular opacities can also be seen on radiographs or HRCT. Lung abscesses are present in about 15–30 % of patients; they are usually solitary, but may be multiple. Pneumatoceles occur in ~50 % of children and 15 % of adults, generally in the first week of pneumonia, and often disappear spontaneously within weeks or months. Pleural effusions are found in 30–50 % of patients [72].

The role of CO-MRSA infection as a causative agent of serious pneumonia in children and healthy young adults was previously reported. Frank hemoptysis occurs in about one-third of patients and the outcome is fatal in about 50 %, illustrating the lethal potential of CO-MRSA pneumonia [69, 70, 73, 74]. In one series, hemoptysis was found in 6/16 (38 %) patients with severe pneumonia associated with *S. aureus* strains carrying PVL genes compared with 1/33 (3 %) PVL-negative patients [70]. Lina et al. [75] screened 23 cases of CO-MRSA pneumonia with PVL genes; 14 (61 %) of these cases were fatal, and autopsies revealed diffuse, bilateral necrotic

hemorrhagic pneumonia. Moreover, Francis et al. [69] reported four cases of severe necrotizing MRSA pneumonia in previously healthy patients, which presented as an influenza or influenza-like prodrome. Two of the patients had evidence of concomitant influenza A infection. The association between influenza and severe staphylococcal pneumonia is well recognized [69]. In a cohort of 112 patients with criteria for DAH, the most infectious cause was *S. aureus*, which was present in five cases, including two methicillin-resistant and three PVL-producing strains [6].

Other Infections Rarely Presenting with DAH in Immunocompetent Patients

CMV is considered a member of the family Herpesviridae and can cause severe symptomatic and life-threatening pulmonary disease in immunocompromised patients [76]. Although CMV infections are prevalent in the general population, symptomatic pneumonia in immunocompetent hosts is rarely reported [77]. In severe cases, massive hemorrhage with frank hemoptysis may occur [78]. Magro et al. [10] described four previously healthy adults who developed subacute onset of respiratory symptoms temporally associated with serologic or culture evidence indicative of acute CMV infection. Biopsies showed vascular injury involving the lungs or other organs. Open lung biopsies showed extensive hemorrhage and hemosiderin deposition. Another report [11] described a fulminant lethal case of DAH in an immunocompetent patient with CMV pneumonia, whose HRCT demonstrated bilateral perihilar consolidation with air bronchograms. In patients with CMV pneumonia, the diagnostic histologic feature is cellular enlargement combined with intranuclear and intracytoplasmic inclusions [79].

Humans are infected by hantaviruses after inhalation of aerosolized virus particles from rodent urine, saliva, or dried excreta [80, 81]. Several antigenically distinct viruses throughout the world have been found to cause two clinical symptom complexes: hantavirus hemorrhagic fever with renal syndrome and hantavirus fever with pulmonary and cardiovascular syndrome [82]. Hantavirus pulmonary syndrome (HPS) has a high case-fatality rate and characteristically presents as respiratory distress from noncardiogenic edema, although alveolar hemorrhage may be present [83, 84]. The pathogenesis of HPS is believed to be related to the immune response to the virus, which is responsible for increased capillary permeability leading to pulmonary edema. Although the virus antigen is present in microvascular endothelial cells, the disturbance is basically functional and no alveolar damage occurs in most patients [85]. Based on clinical suspicion and epidemiologic history, the etiologic diagnosis is made by serologic tests and detection of the viral genome by RT-PCR [85].

Radiographically, HPS presents as interstitial edema with or without rapid progression to airspace disease; the distribution is central or bibasilar and lacks the peripheral pattern usually seen in the acute phase of ARDS [86]. On HRCT, HPS may present with bilateral areas of ground-glass attenuation, thickened interlobular septa, poorly defined small nodules, and bronchial wall thickening. These findings are nonspecific and the differential diagnosis should consider other pulmonary infectious and noninfectious diseases [87]. Histopathologic examination of the lungs may reveal interstitial and alveolar edema, alveolar hemorrhage, and mild interstitial pneumonia characterized by infiltrates of immunoblasts and mononuclear cells [88].

Although pulmonary tuberculosis (TB) is a very common infectious disease, it is rarely associated with DAH. TB is usually diagnosed using Ziehl-Neelsen staining for acid-fast bacilli, which is nonspecific, or by culture. Keung et al. [89] reported a fatal case of pulmonary TB infection masquerading as DAH after autologous stem cell transplantation. Marruchella et al. [90] reported a case of culture-proven pulmonary TB presenting as DAH in an immunocompetent man. HRCT showed bilateral areas of ground-glass opacity, focal areas of consolidation, and scattered nodules. Traditional findings of pulmonary TB, such as upper-lobe nodules or cavities, were not found. BAL showed a progressively bloodier return, and its culture revealed *Mycobacterium tuberculosis*. The patient showed progressive clinical improvement after receiving a drug regimen to treat TB.

A fatal case of miliary TB causing DAH has also described [91]. Radiography and HRCT showed bilateral pulmonary infiltration and diffuse ground-glass opacities, but disseminated nodules were not identified. BAL was bloody, leading to the suspicion of DAH, and its culture revealed *M. tuberculosis*. An autopsy showed abundant necrotizing epithelioid granulomas in both lungs and other organs. Marked alveolar hemorrhage and hyaline membrane were also found in both lungs [91].

Conclusions

In conclusion, infectious diseases should be considered in the differential diagnosis of DAH syndrome because early, adequate, targeted therapy in combination with supportive treatment and, possibly, corticotherapy will improve survival. The most frequent infections causing DAH in immunocompetent patients are influenza A (H1N1), dengue, leptospirosis, malaria, and *S. aureus* pneumonia. Hantaviruses, CMV, and TB may also cause DAH, although such cases are rare.

Conflict of interest None.

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