CLINICS IN CHEST MEDICINE

Clin Chest Med 23 (2002) 479–492

Thoracic amebiasis

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Amebiasis is a protozoan infection caused by *Entamoeba histolytica* [1–3]. It is the third most common cause of death from parasitic diseases after malaria and schistosomiasis, with an annual toll of about 100,000 lives [4]. Although the intestine is the usual site of *Entamoeba* infection most deaths are due to extraintestinal amebiasis, which includes amebic abscess of the liver, pleura, lungs, brain, pericardium, and genitourinary tract. Pleuropulmonary amebiasis is the form of thoracic amebiasis that is the second most common among the extraintestinal amebiasis (after amebic liver abscesses); pericardial amebiasis is a rare form of thoracic disease [5]. Infection of the lung is usually caused by *E histolytica*. Occasional pulmonary infection by another free-living ameba, *Acanthamoeba,* which is associated with amebic meningoencephalitis, also has been reported recently [6–9]. Pleuropulmonary amebiasis is not an uncommon condition in developing countries, but the diagnosis is often missed, mainly due to lack of awareness of the syndrome, which results in prolonged ill health of the patient and sometimes death [5,10]. Once a correct diagnosis is made most patients recover fully with proper treatment [5,10].

Geographic distribution

Amebic infections in humans have been found in all parts of the world, and morbidity and mortality are greatest in the developing countries of the tropics, such as those in Central and South America, Africa, and the Indian subcontinent [11].

Sociodemographic distribution

Amebiasis is common among people of lower socioeconomic classes; poor hygiene, ignorance, crowding, and lack of safe drinking water are the predisposing factors [4]. Malnutrition, chronic alcoholism, and atrial septal defect (ASD) with left to right shunt are contributing factors for the development of pulmonary amebiasis [12,13]. Male homosexuals, travelers, recent immigrants, and institutionalized persons such as prisoners, orphans, children in day care centers, and the mentally ill or retarded are at risk of *Entamoeba* infections in developed countries [14]. The infection is 10 times more common in adult males than in adult females and occurs most frequently in the third and fourth decades of life [7,12,15]. Children rarely develop amebic liver abscesses and pulmonary complications, but the sex distribution is equal among them [16].

Life cycle

Human infection is caused by ingestion of the *Entamoeba* cyst in fecally contaminated food and drink (the feco–oral route). Excystation occurs in the lumen of the small intestine. Multiplication occurs by nuclear division followed by cytoplasmic division, which gives rise to eight trophozoites. The trophozoites then adhere to the mucus and epithelial layers by the D-galactose- or *N*-acetyl-D-galactosamine-(D-gal- or GalNAc-) inhibitable amebic lectin with host-derived glycoconjugates [17–19]. Most infected persons remain asymptomatic and pass the cysts

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PII: S0272-5231(01)00008-9

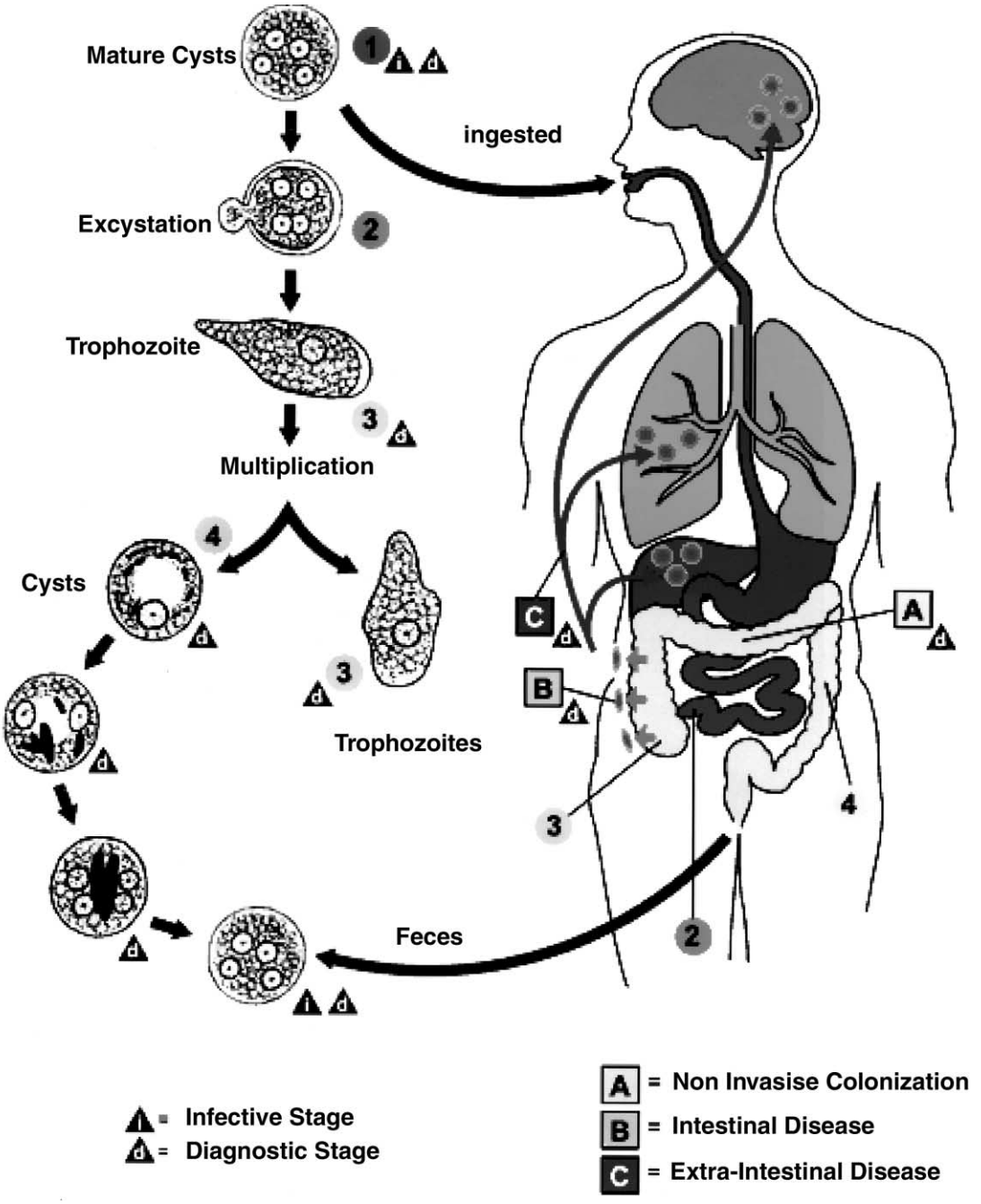

Fig. 1. Life cycle and sites of amebic lesions. Infection by *Entamoeba histolytica* occurs by ingestion of mature cysts (1) in fecally contaminated food, water, or hands. Excystation (2) occurs in the small intestine and trophozoites (3) are released, which migrate to the large intestine. The trophozoites multiply by binary fission and produce cysts (4), which are passed in the feces. In some patients the trophozoites invade the intestinal mucosa (B: intestinal disease) or through the bloodstream to extraintestinal sites such as the liver, brain, and lungs (C: extra-intestinal disease), with resultant pathologic manifestations. (*From internet*, available at: http://www.dpd.cdc.gov/DPDx/HTML/Amebiasis.htm.)

through their stools (re-encystation occurs inside the lumen). Sometimes active trophozoites burrow deep into the mucosal wall and form flask-shaped ulcers in the mucosa with a narrow opening to the gut lumen. Trophozoites may enter the mesenteric veins and reach the liver via portal circulation (Fig. 1). Occasionally amebae enter systemic circulation through venules of the middle and inferior rectal and vertebral veins and are deposited in different organs including the lungs, brain, and genitourinary tract (Fig. 1). The lung is the second most common extraintestinal site of amebic involvement after the liver.

Distribution of *Entamoeba* infection in the chest

The lower and middle lobes of the right lung are usually affected. The lower left lobe or the lingular segment of the left upper lobe may also be sites of amebic lung abscesses. Pulmonary involvement is occasionally bilateral. Amebic empyema constituted 18.5% of the total 200 empyemas of the lung in one series, with a distribution of right-sided (86.49%), left-sided (13.5%), and bilateral (1.7%) [20]. The mortality rate varies from 5.4% to 16.5% in different series [12,20,21]. High mortality is mainly due to poor general condition, age, malnutrition, delayed diagnosis, and inadequate treatment [12]. Both bronchitis and bronchial asthma have been attributed to infestation with *E histolytica* [22]. It is predicted that parasites reach the bronchi by hematogenous spread or their presence in the body constitute an allergen, which may be responsible for these manifestations [20]. Transient pulmonary infiltrates and the subsequent syndromes are described as Loeffler's syndrome [23,24].

Modes of pulmonary involvement

Pulmonary involvement by ameba can occur through various routes (Table 1); it may be described as follows:

Primary

This rare form is contracted through inhalation of dust containing cysts or aspiration of cysts or trophozoites of ameba [25].

Secondary

The secondary form, which is infrequently found, occurs as a result of hematogenous spread from the colon without no liver involvement. The amebae may pass to the pulmonary circulation from the primary intestinal lesion by way of the middle and inferior rectal system or the vertebral system of veins through inferior vena cava and right heart [10,13,26,27].

Table 1
Routes of pulmonary involvement

Routes of involvement	Percent
Abscess extending from liver	37.2
Bronchohepatic fistula	19.6
Empyema extending from liver	17.6
Hematogenous spread without liver involvement	14.3
Hematogenous lung abscess and independent liver abscess	10.4

Tertiary

The most common cause of pleuropulmonary amebiasis is extension from the amebic liver abscess, usually by contiguous involvement. Involvement of the liver occurs in ~3% to 9% of all cases, or 42% of hospitalized patients with intestinal amebiasis [1,28–30]. About 6% to 40% of patients with amebic liver abscess develop pleuropulmonary complications [31–34]. Pleuropulmonary involvement occurs in 2% to 3% of those who have invasive amebiasis [35]. In many cases amebic abscess of the liver near the diaphragm is accompanied by an inflammatory pleural reaction with sterile effusion. Occasionally the necrotic leading edge of the abscess advances to and across the diaphragm. If the hepatic abscess bursts into the pleural space an amebic empyema is formed. As pleuritis frequently precedes diaphragmatic perforation, it causes adhesion between the parietal and the visceral pleura and obliterates the pleural space. Once the pleural space is closed the pleura is protected from further invasion, so empyema is not as common as pulmonary abscesses in thoracic amebiasis [36]. When a liver abscess ruptures to the lung leaving the pleural space unaffected, the usual outcome is the consolidation of the lung or lung abscess. The abscess may burst into the bronchus creating a hepatobronchial fistula or broncho–billiary fistula. Almost all the pus is expectorated by coughing [37]. A liver abscess may burst in both the pleura and lungs simultaneously and cause empyema, consolidation, or a lung abscess. In exceptionally unlucky patients the pus spreads to different lobes and produces multiple lung abscesses. On rare occassions involvement of a part of the lung that is distal to the diaphragm—which is associated with amebic liver abscess—occurs, suggesting that ameba may cross the diaphragm by way of lymphatic channels [38]. Amebic empyema thoracis also may

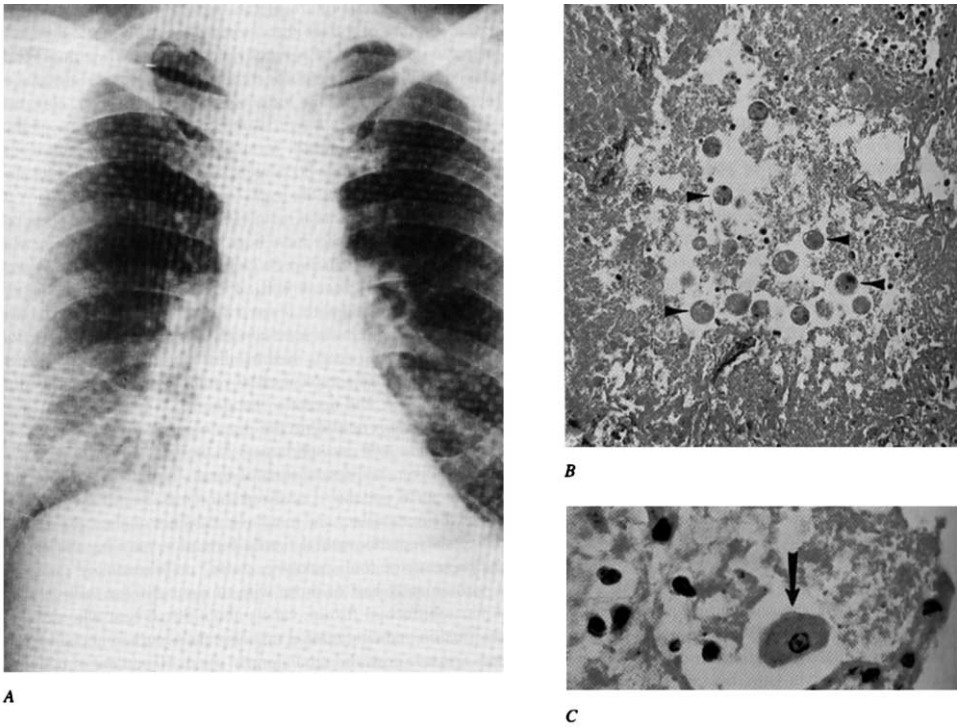

Fig. 2. *Entamoeba histolytica* involving the right lung after rupture of a hepatic abscess through the right hemidiaphragm. (A) Chest radiograph shows elevated right hemidiaphragm, right lower lobe infiltrate, and effusion. (B) Cysts of amebae in lung tissue; (C) Entamoeba trophzoites in pus aspirated from amebic empyema thoracis. (See also Color Plate 3.) (Courtesy of Armed Forces Institute of Pathology. *From* Elias JA, Fishman JA, Grippi MA, Kaiser LR, Senior RM, editors. Fishman's pulmonary diseases and disorders. 3rd edition. vol. 2. NewYork: McGraw-Hill; 1998. p. 2382; with permission.)

result from direct extension of an amebic lung abscess to the pleura [10].

The usual manner of extension is by perforation of a subphrenic or hepatic abscess through the diaphragm and across an obliterated pleural space with pulmonary consolidation or abscess. Sometimes a lesion may develop in an area of the lung remote from the diaphragm, which may be spread hematogenously, or transbronchial spread by aspiration or bronchial embolism in cases of hepatobronchial fistula [20]. In very rare occasions a posterior amebic liver abscess may burst into the inferior vena cava and lead to embolism of the inferior vena cava and thromboembolic disease of the lungs [5] with right ventricular hypertrophy and dilatation followed by congestive cardiac failure or cor–pulmonale [39].

Clinical features

When reactive pleuritis develops keeping the abscess below the intact diaphragm, apparent liver disease may or may not be evident. Liver enzymes usually remain normal [34,35,40]. Frequently, but not invariably, right upper quadrant pain with typical pleuritic chest pain referred to the shoulder or scapula is present. Effusion may be too small or large enough to cause dyspnea. The exudative fluid is sterile and has no distinguishing feature [3,10]. Amebic liver abscess is suspected by observing hemidiaphragm with some atelectasis or haze at the lung base in the chest radiograph (Fig. 2A). It is common to hear a pleural rub in patients with an amebic liver abscess extending to the pleura [20]. After development of a serous fluid or with anti-amebic treatment the rub may disappear.

Table 2
Types of lung involvement

Type of lesion	Percent
Hepatobroncial fistula	47
Pleural effusion and empyema	19
Lung abscess	14
Consolidation	10

Types of lung involvement after rupture of a hepatic abscess are shown in Table 2. Usually development of amebic empyema is insidious in onset and fever, right upper quadrant pain referred to the shoulder, and chest pain with dry cough are the presenting features of these patients. Some patients present with a dramatic onset of severe pain with a tearing sensation, respiratory distress, and shock; sometimes death may occur [3]. Although a history of fever for weeks with pain in the right upper quadrant is common in these cases, clinical enlargement of the liver is observed in about half of patients [41]. Only a few cases have had a history of diarrhea, and less than half have had cysts of *E histolytica* in their stool .The aspirated pus may be of characteristic ''anchovy paste'' color (Fig. 3) and trophozoites of *E histolytica* may be found under the microscope (Fig. 2C). Sometimes pus may be cream-coloured or greenish. Hemophtysis is common; a brisk bout of hemophtysis followed by expectoration of ''anchovy sauce-like'' pus indicates that the pus is of liver origin. The presence of bile indicates establishment of bilio–bronchial fistula [12]. Hemophtysis due to pulmonary infarction may occur as a result of thromboembolism of the lung from the amebic liver abscess [5,39]. Hiccough indicates the involvement of the diaphragm [12]. Constitutional symptoms may be absent in pleuropulmonary amebiasis [42]. In endemic areas amebiasis should be considered as a cause of respiratory distress with tender hepatomegaly in children, especially those >3 years of age [43].

Physical examination may reveal hepatic enlargement and tenderness (if associated with amebic liver abscess), dullness to percussion, and diminished or absent breath sounds. Pleural rub or crepitation may be heard. In chronic cases patients may be severely emaciated and digital clubbing may be prominent [10,44]. Fever may be present in 82% to 100% of patients, chest pain in 50% to 100%, cough in 87% to 100%, hemophtysis in 44% to 50%, hypochondrial pain in 19% to 88%, dyspnea in 23%, digital clubbing in 0% to 40%, signs of consolidation in 62.5% to 100%, and pleural friction rub in 22% of patients [10,45].

Diagnosis

Diagnosis of pleuropulmonary amebiasis is difficult due to a lack of concrete and classical clinical features. In a country where intestinal amebiasis is

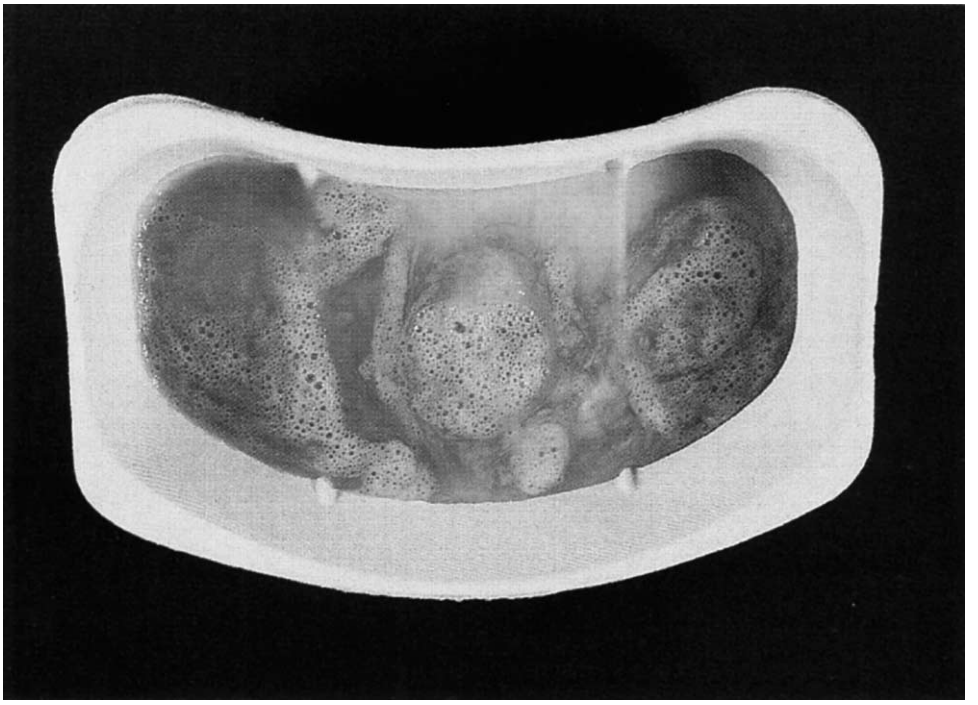

Fig. 3. ''Anchovy sauce'' coughed up when the liver abscess discharged through the diaphragm and the right lower lobe. (See also Color Plate 4.) (*From* Macfarlane JT, Finch RG, Cotton RE, editors. A color atlas of respiratory infections. 1st edition. London: Chapman and Hall; 1993. p. 85. Fig. 8.16; with permission.)

endemic, the possibility that a thoracic lesion may be of amebic origin should be borne in mind. The characteristic roentgenographic feature makes headway in the diagnosis. The radiographic appearance varies considerably depending on the stage of the disease, the location of the abscess, and the extent and degree of hepatic and thoracic involvement. The diagnosis of thoracic amebiasis is suggested by the combination of an elevated hemidiaphragm, hepatomegaly, pleural effusion, and basal pulmonary involvement. Haziness and loss of definition of the hemidiaphragm, usually on the right side, are the earliest radiological findings. These early changes perhaps result from a localized reaction above the fixed and inflamed hemidiaphragm. The patient may complain of chest pain at this stage. As the disease progresses the patient develops marked clinical features with more advanced radiological changes. The involved lung becomes fluffy and irregular, obstructing the diaphragmatic dome and obliterating the costophrenic and cardiophrenic angles. Marked pleural thickening, especially at the lung bases, is the usual end result of amebic empyema. A curative response to anti-amebic therapy confirms the diagnosis indirectly in endemic areas.

Laboratory investigations

Routine hematology and other blood chemistry tests are not especially helpful in the diagnosis of thoracic amebiasis [32]. Erythrocyte sedimentation rate (ESR) is invariably elevated [5,10,40]; neutrophilic leucocytosis (>15,000/mm^3) was observed in 30% and counts >10,000/mm^3 were observed in 50% of the pleuropulmonary amebiasis patients; eosinophilia is not a feature [10]. Normocytic, normochromic anemia is usually present [27]. Liver function tests, with the exception of alkaline phosphatase, are usually normal even if the pulmonary amebiasis is a hepatic complication [40,46]. Presence of bile in the sputum may be an important clue that the lesion is of hepatic origin [12].

Chest radiographs

The following eight radiographic changes are observed in cases of pleuropulmonary amebiasis [10,12,15,20,47,101]:(1) Elevation of the right dome of the diaphragm (Fig. 2A), which may be seen as an upward hump-like prominence on a right lateral view, located either anteriorly (50%), posteriorly (30%), or in the middle (12.5%) of the diaphragm. The hump is produced by the upward progressing liver abscess, and an anterior hump is the most common variety. (2) A triangular area of consolidation with its base against the diaphragm and the apex pointing upwards towards the hilum (65%), consolidated lung may or may not have cavitation, best seen in lateral view. (3) A hazy, crescentic shadow over the right dome of the diaphragm, lighter than a liver shadow, best seen in the posterior–anterior radiograph. This sign may be considered as pathognomonic for liver abscess. (4) Pleural effusion; this sign was observed in 62.5% of cases. Accumulation may be mild, moderate, or massive. A hydropneumothorax may be seen when a broncho–pleural fistula is present. (5) An air-containing cavity, with or without fluid level, may be found under the diaphragm. It may be formed following a hepatobronchial fistula when pus is coughed up and air is accumulated in the empty abscess cavity. This finding was observed in 12.5% cases. (6) Abscesses in either lung resulting from hematogenous spread. It was found in 2.5% cases, and amebic lung abscesses were located in a position of the lung remote from the diaphragm. (7) Bronchography may show nonfilling of the middle lobe or the basal segment of the lower lobe, which was observed in 7.5% patients. (8) Fluoroscopy of the diaphragm may reveal decreased or absent diaphragmatic motility.

Ultrasonography and imaging

Ultrasonography and imaging techniques are used widely to diagnose and monitor the response of extraintestinal amebiasis to treatment in addition to radiological examinations [48,49]. Neither of these techniques can distinguish between pyogenic and amebic abscesses, which should be interpreted by clinical features, serology results, and physical and microscopic pictures of aspirated pus or sputum [49]. These procedures have some advantages over radiological examinations, however. The pleural space contains 3 to 7 mL of transudative fluid with a low concentration of lymphocytes (< 1500 cells/μL) [50]. Up to 200 to 500 mL of pleural fluid is required to cause obliteration of the costophrenic angles. Moreover, a considerable amount of fluid may be collected in the subpulmonic regions without obvious radiographic findings [51]. Accumulation of such fluid can be diagnosed by ultrasonography and imaging.

Unlike bacterial empyemas, which proceed through three stages such as early exudative stage, second fibrinopurullent stage, and the final organizing stage [51], amebic empyemas do not have these stages. This is why loculations and sepatations are rarely found in amebic empyemas. Ultrasonography and chest CT imaging are important investigations in patients with loculated effusions. Ultrasonography

can detect as little as 5 mL of pleural fluid, define the presence of loculations (which is common in bacterial effusions), and estimate fluid viscosity [23]. Pleural fluid collections beneath the scapulae, adjacent to the mediastinum, or within the fissure may not be detected by ultrasonography. In some settings ultrasonography may have better capabilities than CT imaging to detect sepatations within loculations that appear to be monolocular on CT images.

Chest CT imaging can detect and define intrapleural fluid anywhere in the thorax [51]. Moreover, CT imaging can guide interventional procedures, image the airways to detect obstructing lesions, detect loculations with large effusions that appear monolocular by standard radiographs, and differentiate an empyema with a broncho–pleural fistula from a lung abscess [51–53]. Although MR imaging can differentiate exudative from transudative pleural effusions, it is not ideal for diagnosing parapneumonic effusions due to its poor ability to image parenchymal lesions. MR imaging is usually reserved for patients who cannot undergo a chest CT image due to hypersensitivity [51].

Stool examination

Microscopy of stool samples have limited value in the diagnosis of extraintestinal amebiasis because only ~35% of patients with amebic liver abscess with or without pleuropulmonary amebiasis have a history of dysentery symptoms [54]. Cysts or trophozoites of amebae have been detected in 15% to 33% of the stools of extraintestinal amebiasis [50,55–57]. On the contrary, the presence of ameba in stool does not signify that the extraintestinal lesion is secondary to the intestinal lesion because both pathogenic (*E histolytica)* and nonpathogenic (*Entamoeba dispar)* forms of *Entamoeba*, which are morphologically indistinguishable, are present in the gut [58–61]. Moreover, it may be a mere association in endemic areas as many normal inhabitants of endemic countries are asymptomatic carriers [62]. Pathogenic and nonpathogenic ameba may be distinguished by zymodeme analysis [59,62], monoclonal antibody-based Enzyme-linked immunosorbent assay (ELISA) [63], and genomic DNA differences and restriction fragment length polymorphism techniques [7].

Culture is a more sensitive method for detecting *E histolytica* than microscopic detection [64]. *Entamoeba* grows in Robinson's medium when a stool culture is done [100]. An ELISA method has been developed to detect and differentiate pathogenic (*E histolytica)* and nonpathogenic (*E dispar*) *Entamoeba* antigen directly from stool samples [64].

Examination of pus or sputum

Amebic pus can be diagnosed by observing the classical characteristics and colors such as thick, opaque, and reddish brown, resembling "anchovy paste" or "chocolate sauce" (Fig. 3). The color can vary from pink to red and pale yellow to dark brown, however, and it might be mistaken for frank blood on first inspection [1,2]. Expectorated pus may be of "anchovy sauce" color in heptobronchial fistula and dark yellow in broncho–billiary fistula due to presence of bile [37]. Aspirated pus is usually sterile and expectorated pus contains surprisingly few organisms with a limited number of cells for its purulent appearance—until superinfection ensues. Diagnosis of amebiasis should not be excluded on the basis of gross characteristics of pus because atypical pus is common [1,65,101].

The detection rate of active trophozoite under a microscope varies from 0% to 100% in different series (Fig. 2C) [3,12,41,66]. Both over-diagnosis and under-diagnosis are common due to technical difficulties in demonstrating the trophozoites [65,67]; such demonstration of *E histolytica* from sputum or pleural pus can easily be confused with a morphologically similar and common oral commensal, *Entamoeba gingivalis* [68]. The differentiating feature between these two amebae is that *E histolytica* engulfs only erythrocytes but no leucocytes, but *E gingivalis* engulfs both erythrocytes and leucocytes [69]. Saline wet mount on a warmed microscope stage is perhaps the most sensitive diagnostic test [3]. Sometimes cysts of amebae can be detected (Fig. 2B) The specimen should be refrigerated at 4°C if microscopic examination is delayed for more than two hours. If it is needed for subsequent confirmation it may be preserved in polyvinyl alcohol [65]. Culture of the pus in Robinson's medium may yield growth of *E histolytica.*

Immunological tests

Several immunodiagnostic tests have been developed for the diagnosis of extraintestinal amebiasis for detection of antibodies in sera. Some such tests are the indirect haemagglutination test (IHA), ELISA, and the indirect fluorescent antibody test (IFAT) [35,46,63,70,71]. Tests for detection of antibodies in pus are ELISA [46,63] and IFAT [46]. A high antibody titer above the cutoff is necessary to confirm diagnosis by these methods. There are several disadvantages to diagnosing pleuropulmonary and other extraintestinal amebiasis by detecting anti-ameba IgG antibodies. Firstly, detectable antibodies may not

develop in the early stages of the disease or in immunosuppressed patients. Secondly, antibodies may present inside the body in a significant titer for a considerable period of time after treatment of the disease. Thirdly, normal people who live in endemic areas may have antibodies in their blood. Finally, antibodies may be developed in cases of asymptomatic colonization in the intestine. The detection of immunoglobulin M (IgM) antibodies may be more useful in diagnosing acute cases because, unlike IgG, IgM antibodies appear in the body early and persist in the serum for a short period of time. Anti-amebic Gal or GalNAc-inhibitable adherence lectin IgM antibodies were recently detected by ELISA in the sera of patients with intestinal and extraintestinal amebiasis [70]. The potential role of the detection of the amebic lectin antigens in serum for the diagnosis of amebic liver abscess from patients who have intestinal and extraintestinal amebiasis appears promising [58,70]. The role of the ELISA method, which can detect the Gal- or GalNAc-inhibitable amebic lectin antigen (which has already been proven as specific diagnostic test for *E histolytica* in stool samples), still must be proven to detect the same antigen in the serum of extraintestinal amebiasis patients, whose sensitivity appears to be >90% when used before treatment. ELISA sensitivity falls rapidly after the patient has been treated with anti-amebic drugs [8]. Recently developed monoclonal antibodies successfully detected *Entamoeba* Gal or GalNAc-inhibitable lectin antigen in serum and pus of an amebic liver abscess with the TechLab (TechLab, USA) *E histolytica* II Antigen Detection Kit [63]. This kit may eventually facilitate tests for antigen detection in sputum and pleural fluid. Detection of DNA of ameba in pus and pleural fluid by polymerase chain reaction (PCR) may be the most sensitive method for diagnosing pleuropulmonary amebiasis.

Bacterial pathogens that cause superinfections

Although a broad range of pathogens has been isolated, *Streptococcus pneumonae*, *Staphylococcus aureus*, enteric gram-negative bacilli, and anaerobic bacteria cause most pleural infections [72]. Malodorous pus indicates superinfection by anaerobic organisms, although a considerable number of anaerobic empyemas do not have this finding [73]. Gram stain and culture of the frank pus are the only laboratory studies necessary for most patients. Pleural fluid Gram stains can identify pathogens in 55% to 65% patients with established empyemas [51,74]. If uncentrifuged fluid is normal then a centrifuged specimen should be examined. Thoracentesis prior to starting antibiotics and rapidly transporting pleural fluid to the microbiology laboratory increase the diagnostic yield of fluid cultures. An anaerobic transport container is the better way to transport the samples. Refrigeration of the sample before plating inhibits growth of *S pneumoniae, Haemophilus influenzae,* and anaerobes. If the patient has already been started on antibiotics, acridine orange stains may detect bacteria that have been killed [75].

Differential diagnosis

Pleuropulmonary amebiasis is often mistaken for bronchial carcinoma, pulmonary tuberculosis (TB), and lung abscesses. Many patients are diagnosed late after initial treatment with broad-spectrum antibiotics or anti-tubercular drugs [5,10,37,44]. Expectoration of blood-stained sputum over a period of few weeks and the presence of radiological opacity of the right lung, digital clubbing, and emaciation may lead to a mistaken diagnosis of bronchial carcinoma. It is easy to assume as a secondary deposit when the liver is palpable in these cases. Repeated episodes of hemophtysis are commonly mistaken as pulmonary TB. Two cases of pleuropulmonary amebiasis have been reported to have associated pulmonary TB, however [76]. The anterior segment of the right lower base of the lung is rarely infected by *Mycobacterium tuberculosis* and other bacteria, and its involvement is almost always of an amebic origin unless otherwise indicated [10]. Other differential diagnoses are primary and secondary lymphomas, sarcoidosis, and pulmonary hydatidosis.

Treatment

Oral or parenteral metronidazole 800 mg (35 to 50 mg/kg/day for children) three times daily for 5 to 10 days is usually sufficient for treating the extraintestinal amebiasis [32,40]. Within the ameba, the nitro group of metronidazole is reduced to a toxic compound that binds to DNA and blocks the DNA replication [40]. Emetine and dehydroemetine, which are more toxic but less effective, are sometimes used for critically ill patients or those with frequently fatal complications (such as rupture into the pericardium or peritoneum) by some physicians based on the clinical impression that they give a more rapid response than metronidazole [67]. Emetine and chloroquine should be avoided because of the potential cardiovascular side effects of the for-

mer and higher relapse rates with the latter; there is no convincing evidence that combined therapy with two drugs is more effective than the single drug regimen [32]. These drugs are more effective in tissue infections, and metronidazole is the most effective drug to eradicate acute intestinal infections among them. None of these drugs can eliminate an *Entameba* cyst from the gut. To avoid reinfection all patients must be treated with a full course of a luminal amebicidal drug such as diloxanide furoate (Furamide 500 mg three times a day for 10 days; for children, 20 mg/kg/day in three divided doses for 10 days), a drug that can eliminate intestinal cysts of *E histolytica*. Clinical improvement is usually observed in 48 to 72 hours of metronidazole treatment. If no improvement occurs then bacterial superinfection, which occurs in up to one third of patients with pleural amebic lesions, should be suspected [41,77].

No treatment is usually needed for a reactive pleuritis and pleural effusion other than treatment of the liver abscess. If the effusion is large enough to cause respiratory distress, however, a therapeutic thoracocentesis may be performed. Oral amebicidal drugs and postural drainage cure most amebic lung abscesses. Appropriate antibiotics are required in bacterial superinfections.

Pericardial amebiasis

In most cases this rare complication occurs in the event of an amebic abscess of the left lobe of liver. It is believed to occur in $<2\%$ of such patients or in 0.2% to 7.5% of patients who have thoracic complications of an amebic liver abscess [78–81]. Amebic pericarditis has two clinical forms: (1) pericardial rub with electrocardiographic and radiographic evidence of pericarditis associated with an amebic liver abscess of the left lobe, or (2) purulent pericarditis from perforation of a left lobar amebic liver abscess into the pericardium [20,80,82,83]. Involvement of the pericardium may also occur from amebic abscesses in the right lobe of the liver or in the lung that communicate with the pericardium; occasionally pneumopericardium may develop [80,82,84,85,102]. An initial accumulation of serous fluid resulting from an inflammatory reaction followed by intrapericardial rupture may produce two different types of clinical symptoms: (1) severe, sudden onset presenting as a cardiac tamponade with thoracic pain, shortness of breath, venous hypertension, and shock; and (2) progressive, suppurative effusion presenting with epigastric and thoracic cage pain, progressive dyspnea, and fever [79,81].

In the early stages diagnosis is difficult until amebic liver abscess, especially of the left lobe, is suspected. Chest radiograph, ultrasound examination, and CT scan usually confirm the presence of a liver abscess in continuity with the pericardium and fluid with an increased echogenicity within the pericardial sac with or without the fistulous tract [86]. Pericardial effusion fluid may also be visible by echocardiography [81]. Early and successful treatment of amebic liver abscesses usually resolves the inflammatory fluid in the pericardial sac if it has not already ruptured. Pericardiocentesis is useful because it confirms the diagnosis and improves the general condition of the patient [87,88]. Aspiration of accumulated fluid should be performed urgently in cardiac tamponade; repeated aspiration may be needed. Surgical drainage should be performed (if needed) as soon as possible. These patients should be managed in ICU, and metronidazole and dihydroemetine should be administered without delay. With appropriate management with specific drug therapy, full recovery without constriction is usual. Secondary bacterial infection has been demonstrated in cases in which pericardial constriction develops [20]. Constriction may also develop in the absence of recognized secondary infections and may resolve without pericardiectomy [89].

Pleuropulmonary amebiasis, host response, and HIV/AIDS

Although high titers of antibodies are developed in persons cured of invasive amebiasis and these patients appear to be resistant to subsequent reinfections, this humoral response during the invasive phase of the disease apparently has little impact on potential re-infections or the healing process. Antibodies to amebae appear to act through activation of classical and alternative complement pathways, but trophozoites purified from invasive lesions are resistant to complement-mediated lysis. Trophozoites found in intestinal lumen are prone to complement-mediated lysis. Similarly, cell-mediated immunity is of some benefit but is not especially protective. The incidence of amebiasis is not as high in AIDS patients compared to HIV-seronegative patients [90]. This phenomenon suggests that a mucosal immune response is not deeply associated with cellular immunity. Fulminant amebic disease may develop in those who have suppressed cellular immunity, however, such as the malnourished, the very young, those who are taking steroids, and pregnant women.

Although the exact incidence of thoracic amebiasis in HIV/AIDS patients is not known, reports have been published regarding identification of HIV in patients who presented with amebic liver abscess; invasive amebiasis including a pleuropulmonary variety is increasing in HIV/AIDS patients in Taiwan [91,92]. In a 5-year study in the United States one third of all patients diagnosed with amebic liver abscess with or without pleuropulmonary complications were HIV-positive, many of whom were found to be HIV infected only after presentation with extraintestinal amebiasis. This finding suggests that in the absence of recognized risk factors the development of amebic liver abscess and its thoracic complications may suggest an immunocompromised host [93]. The incidence of *E histolytica* infection is more common in homosexual men among HIV-positive individuals, suggesting that this group of people contracts both HIV and *E histolytica* through sexual contact [90,94]. Extraintestinal amebiasis is easily treated by metronidazole, even in older AIDS patients who have low CD4 cell counts and are receiving anti-HIV drugs [95]. Invasive amebiasis, including pleuropulmonary amebiasis, is an important infection in HIV/AIDS patients and is increasing in Taiwan [91,92].

Pulmonary infection by free-living amebae

Free-living amebae rarely infect humans, and when it does occur the outcome is almost always fatal. Humans contract infection by contact with these amebae in their natural, free-living state. *Naegleria fowleri* causes primary meningoencephalitis. Humans, usually children, get infection from contaminated water. The ameba enters the central nervous system (CNS) after disruption of the nasal mucosa and pierces the submucosal nervous plexus and cribriform plate.

Acanthamoeba sp, another free-living ameba, causes subacute meningoencephalitis after hematogenous spread from dermal, pulmonary, or other lesions with the same species [96]. These amebae are discussed here because the diagnosis of pulmonary disease with *Acanthamoeba* may allow the administration of life-saving therapy before meningoencephalitis develops. *Acanthamoeba* usually infects those with systemic lupus erythematosus (SLE), AIDS, diabetes mellitus, pregnancy, liver disease, malignancies with or without steroid or chemotherapy, radiotherapy, alcoholism, and organ transplantation [6–9]. *Acanthamoeba* was identified from 38 of 2289 individuals in their pharynx in one series, and in two of 58 children in their nasal and pharyngeal mucus in another series; these findings indicate that more people are infected than are reported [7]. The onset of *Acanthamoeba* disease is insidious. Unless the patient is severely immunosuppressed, as in AIDS patients with low CD4 cell counts, the lesion is granulomatous. The primary lesion site is usually the lung or the skin, and it is present for weeks or months before the CNS disease becomes apparent. Meningoencephalitis by *Acanthamoeba* has been reported in two patients after bone marrow transplantation. These patients presented with fever and nodular pulmonary infiltrates 6 to 9 months after transplantation for leukemia; both patients had a history of sinusitis and were treated with steroids [6]. A chest radiograph showed diffuse interstitial pulmonary infiltrates in a patient who was suffering from meningoencephalitis by *Acanthamoeba* [8]. Trophozoites of *Acanthamoeba* are almost always seen in microscopic examination of lung sections (along with early signs of bronchopneumonia) in autopsy examinations. This finding clearly indicates that the infection spreads from the lung by a hematogenous route [8,9,97]. This amebic disease should be considered in the differential diagnosis of nodular pulmonary infiltrates or for other unusual pulmonary signs in immunosuppressed patients.

Diagnosis of free-living amebae is accomplished by detecting *Acanthamoeba* in histological sections. Unfortunately, diagnosis has almost always occurred at autopsy. Both cysts and trophozoites of the organism may be isolated from the cerebrospinal fluid (CSF) of patients who have granulomatous amebic encephalitis. A biopsy from brain, lungs, or skin may be the only way to make the diagnosis during life [7]. A non-nutrient agar overlaid with killed *Escherichia coli* may be used for growth of *Acanthamoeba* when biopsy material is negative. Giemsa, hematoxylin–eosin, Wright, and periodic acid-Schiff stains are used to visualize and identify the cysts and trophozoites of *Acanthamoeba* [98]. Organisms can be seen in biopsy specimens by staining with Calcofluor white, a fluorescent laundry detergent brightener. Antibody detection against *Acanthamoeba* sp has been confirmed, but the usefulness of diagnostic tests for the diagnosis of these infections has not yet been proven. The authors are still undecided regarding the treatment of *Acanthamoeba* meningoencephalitis because trophozoites and cysts of *Acanthamoeba* isolates vary in their sensitivity to antimicrobial agents. Polyhexamethylene biguanide and chlorhexidine are the most successful cysticidal agents, followed by sepazonium and propamidine. Clotrimazole, paromomycine, and

ketokonazole were cysticidal in a few specimens, but only in high concentrations. Neomycin, although found to be effective, was ineffective on cysts in vivo [99]. Usually combination therapy is used. Each clinical isolate should be tested for sensitivities to these drugs along with the diamidine group, the most effective group of drugs, which includes propamidine and pentamidine [7].

Summary

Pleuropulmonary amebiasis is the common and pericardial amebiasis the rare form of thoracic amebiasis. Low socioeconomic conditions, malnutrition, chronic alcoholism, and ASD with left to right shunt are contributing factors to the development of pulmonary amebiasis. Although no age is exempt, it commonly occurs in patients aged 20 to 40 years, with an adult male to female ratio of 10:1. Children rarely develop thoracic amebiasis; when it does occur there is an equal sex distribution. The infection usually spreads to the lungs by extension of an amebic liver abscess. Infection may pass to the thorax directly from the primary intestinal lesion through hematogenous spread, however. Lymphatic spread is one possible route. Inhalation of dust containing cysts and aspiration of cysts or trophozoites of *E histolytica* in the lungs are some other hypothetical routes.

The lung is the second most common extraintestinal site of amebic involvement after the liver. Usually the lower lobe, and sometimes the middle lobe of the right lung, are affected, but it may affect any lobe of the lungs. The patient develops fever and right upper quadrant pain that is referred to the tip of the right shoulder or in between the scapula. Hemophtysis is common. The diagnosis of thoracic amebiasis is suggested by the combination of an elevated hemidiaphragm (usually right), hepatomegaly, pleural effusion, and involvement of the right lung base in the form of haziness and obliteration of costophrenic and costodiaphragmatic angles.

Infection is usually extended to the thorax by perforation of a hepatic abscess through the diaphragm and across an obliterated pleural space, producing pulmonary consolidation, abscesses, or broncho–hepatic fistula. Empyema develops when a liver abscess ruptures into the pleural space. Rarely, a posterior amebic liver abscess can burst into the inferior vena cava and develop an embolism of the inferior vena cava and thromboembolic disease of the lungs with congestive cardiac failure or cor–pulmonale. Diagnosis by finding *E histolytica* in stool specimens is of limited value. In a limited number of cases amebae might be found in aspirated pus or expectorated sputum. "Anchovy sauce-like" pus or sputum may be found. Presence of bile in sputum indicates that the pus is of liver origin. Serological tests are of immense value in diagnosis. Liver enzymes are usually normal and neutrophilic leucocytosis may or may not be found. ESR is invariably elevated. Anti-amebic antibodies can be detected by ELISA, IFAT, and IHA. Amebic antigen can be detected from serum and pus by ELISA. Detection of *Entamoeba* DNA in pus or sputum may be a sensitive and specific method. Pleuropulmonary amebiasis is easily confused with other illnesses and is treated as pulmonary TB, bacterial lung abscesses, and carcinoma of the lung. A single drug regimen with metronidazole with supportive therapy usually cures patients without residual anomalies. Aspiration of pus from empyema thoracis may be needed for confirmation and therapeutic purposes.

The pericardium is usually involved by direct extension from the amebic abscess of the left lobe of the liver, sometimes from the right lobe of the liver, and rarely from the lungs or pleura. An initial accumulation of serous fluid due to reactive pericarditis followed by intrapericardial rupture may develop either (1) acute onset of severe symptoms with chest pain, dyspnea, and cardiac tamponade, shock, and death, or (2) progressive effusion with thoracic cage pain, progressive dyspnea, and fever. Chest radiograph, ultrasound examination, and CT scan usually confirm the presence of a liver abscess in continuity with the pericardium and fluid within the pericardial sac with or without the fistulous tract. Echocardiography may demonstrate fluid in the pericardial cavity. Patients should be cared for in the ICU and ambecides should be started without delay. Pericardiocentesis usually confirms the diagnosis and improves the general condition of the patient. Aspiration of the accumulated fluid should be performed urgently in cardiac tamponade; repeated aspiration may be needed. Surgical drainage should be done if needed.

Acanthamoeba, a free-living ameba, may also infect the lungs in the form of pulmonary nodular infiltration and pulmonary edema in association with amebic meningoencephalitis in immunocompromised patients. It usually spreads to the meninges of the brain by way of the blood from its primary lesion in the lung or skin. Early diagnosis and institution of treatment may be life saving for these patients.

A literature review shows that HIV/AIDS patients are not prone to infection with *E histolytica*. It is now clear that there are an increasing number of HIV-seropositive patients among amebic liver abscess patients, however, which suggests that although the

incidence of intestinal infection is not high among HIV-seropositive or AIDS patients they are more susceptible to an invasive form of the disease.

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