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Treatment approach for pulmonary alveolar echinococcosis

Pulmoner alveoler ekinokok için tedavi yaklaşımı

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ABSTRACT

Background: In this study, we present cases with pulmonary alveolar echinococcosis who were treated in our clinic.

Methods: This single-center, retrospective study included 12 patients (6 males, 6 females; mean age 49.2 years; range 25 to 68 years) diagnosed with pulmonary alveolar echinococcosis between January 2008 and May 2015. Data including age and gender of the patients, the location, number, and size of the cyst, and spread to other organs outside the lungs were recorded.

Results: Of the patients, eight had bilateral diffuse metastatic lesions, while the others had solitary or a few pulmonary lesions. One patient had an endobronchial lesion in the right lower lobe, one had a cystic lesion in the right lung and three lesions in the left lung, one had pulmonary invasion through neighborhood, and one had an endobronchial lesion in the right lower lobe. Initially, wedge resection was applied to the patient who had a solitary pulmonary nodule in the right lung and, then, liver transplantation was performed. Liver transplantation, wedge resection of the lung, and diaphragm resection/reconstruction were simultaneously applied in the patient who had pulmonary invasion through neighborhood. Bilateral thoracoscopic wedge resection with one-month interval was applied in the patient with cystic lesions, one in the right and three in the left lung, and liver resection was planned. Recurrence was not observed in any patients operated.

Conclusion: Surgical treatment can be applied on carefully selected patients with pulmonary alveolar echinococcosis. The decision of surgery should be assessed according to the diffusivity of the lesion, liver functions, and general condition of the patient.

Keywords: Echinococcus alveolaris; lung; management; surgery.

ÖZ

Amaç: Bu çalışmada kliniğimizde tedavi edilen pulmoner alveolar ekinokok olguları sunuldu.

Çalışma planı: Bu tek merkezli, retrospektif çalışmaya Ocak 2008 - Mayıs 2015 tarihleri arasında pulmoner alveoler ekinokok tanısı konmuş 12 hasta (6 erkek, 6 kadın; ort. yaş 49.2 yıl; dağılım 25-68 yıl) dahil edildi. Hastaların yaşı ve cinsiyeti, kistin yeri, sayısı ve büyüklüğü ve akciğerler dışında diğer organlara yayılımına ilişkin veriler kaydedildi.

Bulgular: Hastaların sekizinde iki taraflı yaygın metastatik lezyonlar, diğerlerinde soliter veya birkaç pulmoner lezyon vardı. Bir hastada sağ alt lobta endobronşiyal lezyon, birinde sağ akciğerde kistik lezyon ve sol akciğerde üç lezyon, birinde komşuluk yoluyla akciğer invazyonu ve birinde sağ alt lobta endobronşiyal lezyon izlendi. Sağ akciğerde soliter pulmoner nodülü olan hastaya ilk olarak kama rezeksiyon ve ardından karaciğer nakli yapıldı. Komşuluk yoluyla akciğer invazyonu olan hastaya eş zamanlı olarak karaciğer nakli, akciğer kama rezeksiyonu ve diyafragma rezeksiyonu/rekonstrüksiyonu uygulandı. Sağ akciğerde bir, sol akciğerde üç adet kistik lezyonu olan hastaya bir ay arayla iki taraflı torakoskopik kama rezeksiyonu uygulandı ve karaciğer rezeksiyonu planlandı. Ameliyat edilen hastaların hiçbirinde nüks gözlenmedi.

Sonuç: Dikkatlice seçilmiş pulmoner alveoler ekinokok hastalarında cerrahi tedavi uygulanabilir. Cerrahi kararı lezyonun yaygınlığına, karaciğer fonksiyonlarına ve hastanın genel durumuna göre değerlendirilmelidir.

Anahtar sözcükler: Alveoler ekinokok; akciğer; tedavi; cerrahi.

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Alveolar echinococcosis (AE) is a malignant, progressive disease which is primarily seen in the liver and caused by *Echinococcus multilocularis (E. multilocularis).* The structure, behavior, and evolution process of e*chinococcus alveolaris (E. alveolaris)* are similar to *Echinococcus granulosus (E. granulosus).*[1,2] The intermediate hosts of AE are farm mice, while the intermediate hosts of *E. granulosus* are sheep and cattle.[3] It is transmitted to humans by contacting with foxes, dogs, cats which eat infected rodents and importing helminth eggs by eating food which are contaminated with their feces.[3] The disease is more common in the central Europe, northern parts of the Europe, Asia, and near territories to the North Pole, Mongolia, Canada and Japan. In Turkey, it is particularly reported in the East Anatolia region.[4]

There is a limited number of case reports of pulmonary AE in the literature.[5,6] In addition, there is no consensus on the treatment approaches for pulmonary AE. In this study, we present 12 cases with pulmonary AE who were treated in our clinic.

PATIENTS AND METHODS

This single-center, retrospective study included 12 patients (6 males, 6 females; mean age 49.2 years; range 25 to 68 years) diagnosed with pulmonary AE between January 2008 and May 2015.

Medical histories of all patients were obtained and physical examination findings were recorded. Complete blood counts, biochemical parameters, and coagulation tests were done in all cases. Diagnosis was based on the posteroanterior chest radiographs and thoracic computed tomography (CT) findings in all patients. Additionally, magnetic resonance imaging (MRI) was performed in three patients to confirm the diagnosis. Age and gender of the patients, location, number, and size of the cysts, and spread to other organs outside the lungs were noted.

Indirect hemagglutination test result was found to be positive in seven patients. In 11 patients, histopathological diagnosis was confirmed with percutaneous liver biopsy. In one patient, histopathological diagnosis was confirmed with bronchoscopy.

RESULTS

Eight patients presented with respiratory distress, and four patients were asymptomatic for pulmonary symptoms. In these patients, pulmonary alveolar cysts were detected incidentally during radiological examination. In all patients, an alveolar cyst was present in the liver. There was no involvement of organs other than the lungs and liver in any of the cases. While the disease was in the form of bilateral diffuse metastatic lesions in eight patients, it was in the form of solitary or a few pulmonary lesions in the others. One patient had an endobronchial lesion in the right lower lobe, one had a cystic lesion in the right lung and three lesions in the left lung, one had pulmonary invasion through neighborhood, and one had an endobronchial lesion in the right lower lobe. Albendazole treatment (10 mg/kg/day) was administered to the patients with bilateral diffuse metastatic lesions, surgical treatment was avoided. Initially, wedge resection was applied in the patient with a solitary pulmonary nodule in the right lung and, then, liver transplantation was performed. Liver transplantation, wedge resection of the lung, and diaphragm resection/reconstruction were simultaneously applied in the patient with pulmonary invasion through neighborhood. Bilateral thoracoscopic wedge resection with one-month interval was applied in a patient with cystic lesions, one in right and three in the left lung, and liver resection was planned. One patient with an endobronchial lesion refused surgical treatment. Albendazole treatment was initiated after surgery for prophylactic purposes in patients who underwent surgery. Recurrence, morbidity, and mortality were not observed in any patients operated (Table 1, Figures 1-4).

DISCUSSION

While *E. granulosus* is responsible for common echinococcal infections, *E. alveolaris* is the cause of only 3% of all liver echinococcus lesions and even less of the lung lesions.[7,8] The mean age of diagnosis was reported as 55 years.[8] Although primary location is liver, metastases in other abdominal organs, muscles, bones, lymph nodes, lungs, and brain have been reported.[9] Metacestode spreads from the liver to other organs by infiltration and metastasis. Metastasis of *E. alveolaris* from the liver occurs primarily through blood circulation.[6] In a study including 117 patients with AE, Bresson-Hadni et al.[9] reported 20% pulmonary metastasis and 1% cerebral metastasis. In our patients, primary involvement site was the liver. Pulmonary AE was detected through hematogenous spread in 10, neighborhood in one, and through endobronchial spread in one patient. The mean age at the time of diagnosis was 49.2 years in our study.

Clinical symptoms of AE are usually silent at the beginning of the disease in many patients. Many symptoms occur by liver parenchymal damage or overgrowth of the cyst. Infestations of AE are similar

Table 1. Characteristics of the patients

No	Age/Gender	Pulmonary symptoms	Lung location and characteristics of the cyst	IHA test	Treatment	Patient follow-up
1	65/M	Asymptomatic	Solitary pulmonary nodule in the right lower lobe	Positive	Liver transplantation after lung wedge resection	Postoperative fourth year without complaint
2	28/F	Asymptomatic	Nodular lesion in the right middle and left lower lobe	Positive	Bilateral thoracoscopic wedge resection was performed. Liver resection is planned	Waiting for liver resection
3	53/M	Dyspnea, cough, sputum	Bilateral diffuse metastatic lesions	Positive	Albendazole	He died six years after the diagnosis of lung alveolar cyst due to respiratory failure
4	69/F	Dyspnea Cough	Bilateral diffuse metastatic lesions	Negative	Albendazole	She died six years after the diagnosis of lung alveolar cyst due to respiratory failure
5	58/F	Dyspnea	Bilateral diffuse metastatic lesions	Positive	Albendazole	She died three years after the diagnosis of lung alveolar cyst due to respiratory failure
6	54/F	Asymptomatic	Right lower lobe invasion by diaphragmatic way	Negative	Simultaneous right lower lobe wedge resection with liver transplantation	Postoperative second year without complaint
7	55/M	Dyspnea Chest pain	Bilateral diffuse metastatic lesions	Negative	Albendazole	In the second year of follow-up treatment Albendazole
8	30/M	Dyspnea Cough	Bilateral diffuse metastatic lesions	Negative	Albendazole	In the second year of follow-up treatment Albendazole
9	59/M	Asymptomatic	Bilateral diffuse metastatic lesions	Positive	Albendazole	He died two years after the diagnosis of lung alveolar cyst due to biliary obstruction and liver failure
10	25/F	Dyspnea Chest pain	Bilateral diffuse metastatic lesions	Positive	Albendazole	In the first year of follow-up treatment Albendazole
11	36/F	Dyspnea Cough	Bilateral diffuse metastatic lesions	Positive	Albendazole	In the sixth year of follow-up treatment Albendazole
12	58/M	Dyspnea Cough	Endobronchial lesion in the right lower lobe	Negative	The patient did not accept liver resection and the right lung lower lobectomy	The patient went to another center

IHA: Indirect hemagglutination test.

to neoplastic diseases, but show a slow progression. Alveolar echinococcosis is mostly encountered with liver lesions. It can spread to the biliary tract, thereby causing biliary obstruction, jaundice, portal hypertension, bleeding, and Budd-Chiari syndrome.[10] Patients may often present with jaundice or portal hypertension.[11] Portal hypertension and secondary biliary cirrhosis are the most common clinical features of the disease. In certain cases, hepatic cysts can be ruptured to the thoracic cavity and can be seen in the bronchial tree, pleural cavity, and mediastinum. Hepatic lesions can invade the vena cava inferior and hepatic veins, thereby, leading to mortality rapidly by parasitic pulmonary emboli through the right atrial metastasis.[8] Lung symptoms typically occur following the liver involvement. In case of pulmonary AE,

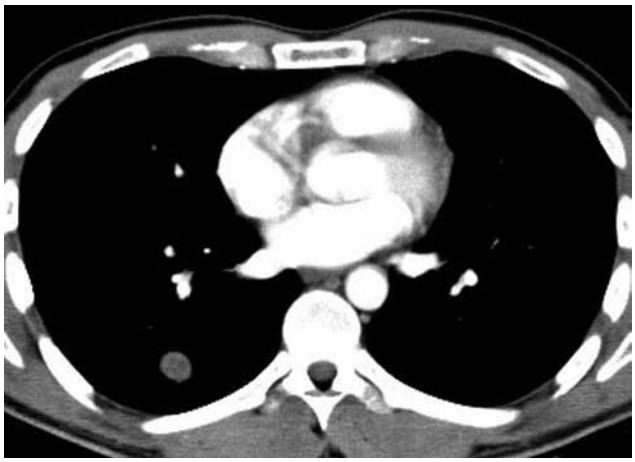

Figure 1. A thoracic computed tomography of a 65-year-old male showing a solitary pulmonary nodule in the right lower lobe *(Case 1).*

hemoptysis, chest pain, cough with expectoration, and exertional dyspnea can be also seen.[12] Hydoptysis is very typical for the lung involvement, and immediate examination is required in these patients.. However, pulmonary AE can be usually asymptomatic for about 10 to 15 years,[13] And can be detected incidentally during radiological examination.[12] Similarly, of our patients, four with asymptomatic pulmonary AE, pulmonary lesions were detected incidentally. In the other patients, respiratory distress was the most common symptom due to multiple metastases and endobronchial involvement.

Plain radiography is the first-line imaging method for the evaluation of patients in whom the presence of pulmonary AE is suspected. The plain chest radiograph is a valuable diagnostic technique in pulmonary AE. On chest radiography, lesions of uncomplicated pulmonary AE are typically homogeneous and round or oval masses with smooth borders.[12]

Computed tomography and MRI are also helpful for preoperative evaluation. The first is the primary imaging modality for morphological assessment of AE lesions, and it allows identification of the number, size, and location of the lesions in the lungs. It also enables a comprehensive preoperative evaluation of the vascular and extra-pulmonary extensions. On CT, pulmonary lesions appear as masses with irregular contours and low attenuation. This imaging modality

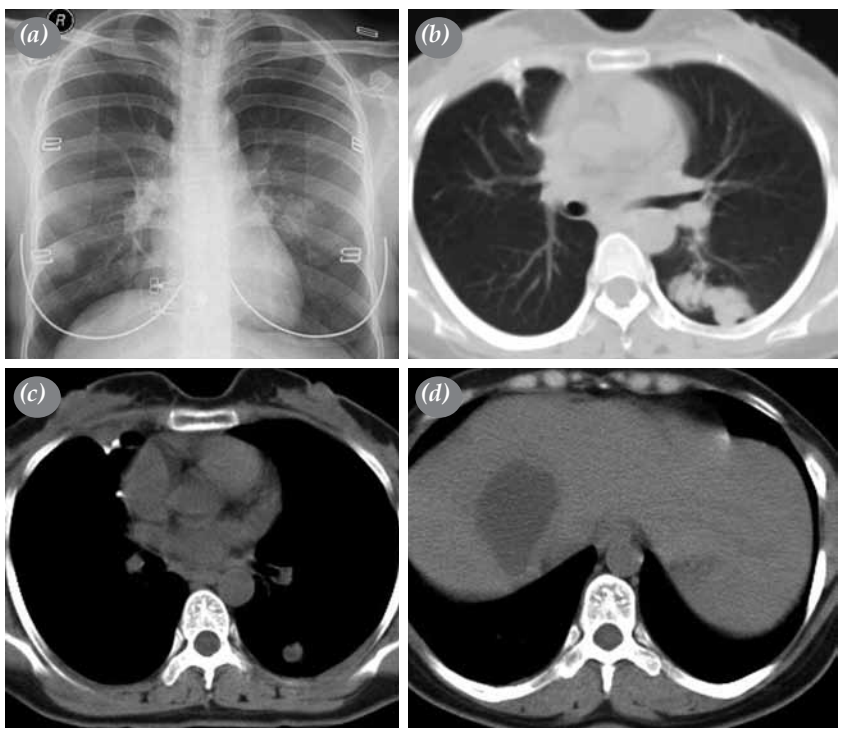

Figure 2. A thoracic computed tomography and conventional radiography of a 28-year-old female showing multiple nodules. **(a)** Chest radiography showing multiple alveolar echinococcosis lesions in the right lower and left middle zone. **(b-d)** Computed tomography scans showing lesions in the right middle lobe and superior segment of the left lower lobe with an alveolar echinococcosis lesion of the liver *(Case 2).*

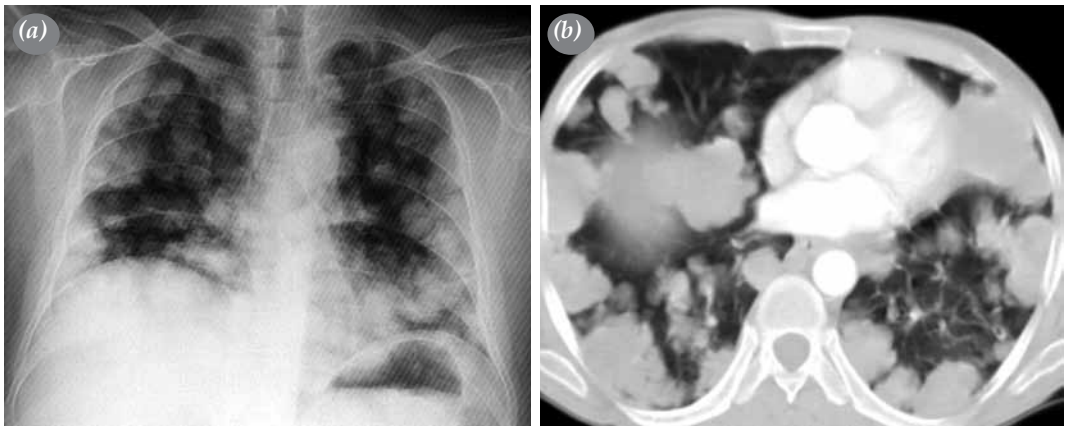

Figure 3. (a) Thoracic conventional radiography and **(b)** computed tomography scans of a 53-year-old male showing multiple alveolar echinococcosis lesions presenting as metastatic lung lesions *(Case 3).*

may also show wall calcifications and intralesional calcifications. The parasitic lesions may present as multiple nodules and masses on chest radiography and CT. Multiple bilateral pulmonary lesions are, however, difficult to distinguish from pulmonary metastases and granulomatous diseases affecting the lungs.[12]

On the other hand, MRI is the excellent modality for characterizing the components of AE lesions. It reveals the multi-vesicular structure of the lesions. On MRI, AE lesions typically show low-to-intermediate signal intensity on T_1-weighted images and heterogeneous signal intensity on T_2-weighted images.[12]

Pulmonary AE diagnosis is mostly based on previous primary liver lesion findings, clinical history, endemic geographic location, and laboratory evidences.[6] The diagnosis can be also done with combination of radiological imaging and serology. Of note, serology is more sensitive and specific.[8] Specific *E. multilocularis* antigens such as Em2 and Em18 are frequently used in serodiagnostic identification. It is reported that these antigens can reveal the difference between *E. granulosus* and *E. multilocularis* with a success rate of 95 to 97%.[8] In 11 patients, AE diagnosis in the liver was histopathologically confirmed by percutaneous biopsy, while histopathological diagnosis was confirmed with bronchoscopy in one patient. Histopathological diagnoses were identical in all three patients who underwent lung surgery. In the remaining eight patients who were not operated, radiological imaging findings were suggestive of pulmonary AE. In addition, indirect hemagglutination tests were found to be positive in seven patients.

The main treatment strategy is early detection, careful evaluation of the location and dissemination of the lesion.[11] Early diagnosis and treatment are also essential to prevent complications. Guidelines for the treatment of human AE have been available since 1996,[14] and were most recent updated in 2011 by the World Health Organization Informal Working Group on Echinococcosis.[13] Total resection with radical surgery is the first-line treatment in all eligible cases. In addition, radical resection is recommended, if the involvement is less than three segments of the liver, residual liver functions can allow surgery; vena cava, portal vein, hepatic artery, and bile ducts are suitable for repair, distal metastases are suitable for resection and do not pose life-threatening complications in patients aged below 75 years.[15] If total resection is not possible, palliative surgery, such as percutaneous bile or abscess drainage and endoscopic dilatation of the bile duct strictures, following plastic stent placement are recommended.[12,16] In the treatment, several hepatectomy types are also advocated. Liver transplantation can be considered in patients with severe esophageal variceal bleeding caused by portal hypertension, ascites, symptomatic secondary biliary cirrhosis, or spread lesions.[12] Continuing chemotherapy at least two years after surgery is recommended.[8,14] Patients who are not eligible for radical resection need resection, as much as possible, and liver transplantation and constant chemotherapy for years. Long-term chemotherapy can extend survival even in inoperable patients.[8,9,12] The most extensive surgical treatment study was reported by Koch et al.[17] in the literature. In this study, 16 of 45 patients were treated with transplantation. Five-year survival rate was found to be 71% and disease-free survival rate was found to be 58%.[17] However, there is a limited number of data in the literature on surgical treatment of patients with pulmonary involvement. In the present study, we

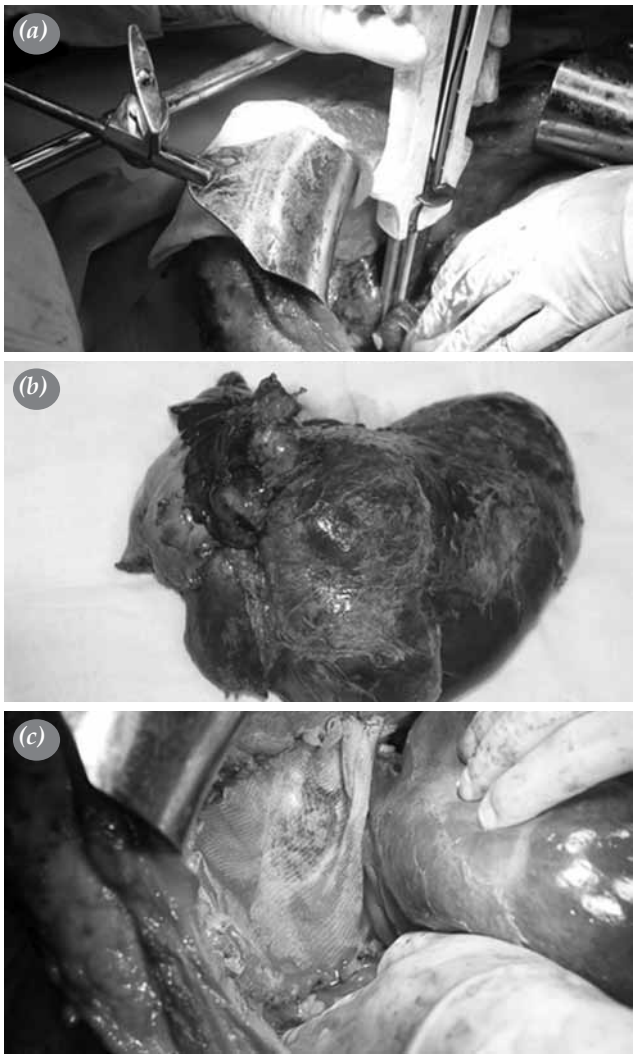

Figure 4. View of lung invasion through diaphragm in a 54-year-old female. **(a)** Wedge resection from the lung through abdomen incision, **(b)** gross visualization of the resected liver, lung and diaphragm, **(c)** liver transplantation and reconstruction of the diaphragm with a prolene mesh *(Case 6).*

evaluated all patients with general surgery specialists and applied pulmonary resection in three patients with limited pulmonary involvement. Two of these patients underwent liver transplantation, and hepatic resection was planned in one patient.

Benzimidazole derivatives are used in the medical treatment of alveolar hydatic disease. However, it does not cure the disease, but only suppresses the development of larvae.[15] Study findings on mebendazole and albendazole are promising. Albendazole is the most effective drug based on animal experiments.[18] It is usually used at a dose of 10 mg/kg.[8] Albendazole absorption increases with liposomal application.[18] Synergistic effects were observed with the application of albendazole and cimetidine.[16,18] In about 48% patients who were treated with high-dose mebendazole, the liver lesion significantly diminished, and clinical course improved with and extended survival rates.[19] Albendazole is absorbed better than mebendazole with improved tissue penetration.[11] On the other hand, controversial opinions about chemotherapy benefits have been reported. In particular, re-evaluation has been advocated following chemotherapy in non-resectable lesions.[17,18,20] Similarly, in our study, the patients with non-resectable lesions were followed with high-dose albendazole (usually 800 mg daily).

In conclusion, pulmonary alveolar echinococcosis is a malignant, progressive parasitic disease which typically presents with liver involvement. Pulmonary alveolar echinococcosis and treatment decision should be evaluated together with the liver lesions. Surgical treatment should be considered primarily, when pulmonary metastasis is resectable and liver lesion is suitable for resection or transplantation. We also suggest that benzimidazole treatment should be given after surgery and inoperable patients.

Declaration of conflicting interests

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