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Short Communication (Pages: 13203-13211)

Presentation of Sonographic Features of Pulmonary Invasive Fungal Disease in Six Children with Leukemia

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Abstract

Background

The early diagnosis of invasive fungal diseases is important because the therapeutic outcome depends on the prompt initiation of appropriate interventions. In this study, we present the feature of ultrasound of pulmonary fungal infection in six children with leukemia.

***Method and Patients*:** Between June and November 2020, this cross-sectional study was conducted in the radiology department at Dr. Sheikh Children's Hospital, Mashhad, Iran. During this period, we reviewed imaging findings of fungal lung infections in six patients with leukemia (ages 5-11 years old) who were referred for chest ultrasound and CT-scan. High-resolution computed tomography (HRCT) of patients showed multiple nodular lesions with/without ground-glass opacity (halo sign or reverse halo sign), and wedge-shape consolidations. In some patients, there were thick wall cavitary lesions with intra-cavitary fungus ball and the air-crescent sign. Ultrasound findings of the lung included the target lesion, the cavitary lesion, wedge-shape consolidation, and extra-pulmonary invasion to the chest wall or sub-diaphragm. The galactomannan test or debridement of para-nasal sinuses confirmed fungal infections; Aspergillosis or Mucormycosis.

Conclusion

Four characteristic features of pulmonary invasive fungal disease on ultrasound can help in faster diagnosis and monitoring of treatment response in these patients.

***Key Words*:** Aspergillosis, Children, Pulmonary fungal disease, Mucormycosis, Ultrasound.

*Please, cite this article as: Alamdaran SA, Heidarzadeh H, Zavvar SN, Badiee Z, Jaberi M, Ghasemi A. Presentation of Sonographic Features of Pulmonary Invasive Fungal Disease in Six Children with Leukemia. Int J Pediatr 2020; 9(2): 13203-211. DOI: **10.22038/IJP.2021.52657.4172**

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Received dateNov.20, 2020; Accepted date: Jan.12, 2021

1- INTRODUCTION

Delayed diagnosis of invasive fungal diseases is associated with significant morbidity and death in immune-compromised children (1). Clinical signs and symptoms of the pulmonary fungal disease are not specific and patients often present with cough, fever, dyspnea, pleuritic chest pain, variable sputum production, and or unresolved pneumonia. The most common causes of delayed diagnosis are the simultaneous presence of viral or bacterial infections, lack of suspicion of disease, and difficulty in reproducing fungi by conventional methods (2, 3). Early detection of them is very important because the outcome of treatment strongly depends on the rapid start of appropriate interventions. Direct histological examination of tissue collected in biopsy or thin-needle aspiration remains the gold standard in diagnosis, however, the biopsy is an invasive procedure that is not always practical (4). Therefore, diagnostic imaging can be critical in assessing or establishing the diagnosis. Radiologic imaging in children can help to define the extent of infection and monitor the response to anti-fungal therapy. Radiographic and CT-scan manifestations of the pulmonary fungal disease include consolidation, cavitation, abscess formation, nodules, masses, halo sign, and air-crescent sign. However, these signs have been found in a spectrum of diseases (infectious and non-infectious) (5). There are few reports of the usefulness of ultrasound in diagnosing invasive fungal infection of the lungs in the available literature. In this study, we present the specific features of transthoracic ultrasound of fungal lung infection in six children with leukemia.

2- METHOD AND PATIENTS

This cross-sectional study was conducted between June and November 2020 in the radiology department at Dr. Sheikh Children's Hospital (Mashhad University of Medical Sciences, Mashhad, Iran). During this period, we reviewed imaging findings of fungal lung infections in six patients (5-11 years old) with leukemia who were referred for an ultrasound and CT-scan exam of the thorax. The patients developed fever, respiratory distress, and/or pleuritic chest pain in a neutropenic state. **Table.1** summarizes demographic, clinical, and imaging data of our patients.

Table-1: Summary of demographic, clinical and imaging data of our patients.

Cases	Gender, Age, year	Clinical symptoms	CT- scan findings	Sonographic signs	Diagnostic method	Type of fungus
1	Male, 9	Fever	Nodule Halo sign, Reverse halo sign, Crescent sign, Wedge shape opacity	Hyper-echoic nodule with a hypo-echoic rim. Hypo-echoic center with a hyper-echoic rim. Cavitary lesions. Invasion to diaphragm and spleen. Wedge shape consolidation	Para-nasal sinuses Debridement	Mucur-mycosis
2	Male, 5	Fever Respiratory distress	Nodule Halo sign, Wedge shape opacity	Hyper-echoic nodule with a hypo-echoic rim. Hypo-echoic center with a hyper-echoic rim.	Para-nasal sinuses Debridement	Aspergillosis
3	Male, 5	Fever Respiratory distress	Nodule Crescent sign, Wedge shape opacity	Hypo-echoic center with a hyper-echoic rim. Wedge shape consolidation	Galactomannan test	Aspergillosis
4	Male, 11	Fever Pleuritic pain	Nodule Halo sign, Wedge shape opacity	Hypo-echoic center with a hyper-echoic rim. Wedge shape consolidation.	Para-nasal sinuses Debridement	Aspergillosis

5	Female, 7	Fever	Nodule Halo sign, Wedge shape opacity	Hypo-echoic center with a hyper-echoic rim. Hyper-echoic nodule in center. Hypoechoic consolidation.	Target lesions in liver US	Aspergillosis
6	Male, 6	Fever	Cavitary consolidation	Wedge shape consolidation. U-shape consolidation.	Galactomannan test	Aspergillosis

The first case was a 9-year-old boy who was admitted with fever and neutropenia after the second course of acute myeloid leukemia (AML) chemotherapy. The broad-spectrum antibiotic regimen began. On the first day, chest X-ray (CXR) was normal. These symptoms persisted, so CXR was repeated and thoracic ultrasound and abdominopelvic ultrasound were performed. Lung ultrasound findings included the following: 1. The target lesions as a hyper-echoic central nodule with a hypo-echoic rim or hypoechoic center with a hyper-echoic rim; 2. The cavitary lesions and intra-cavitary rounded hyperechoic masses (fungus ball) with air extension at the hypoechoic rim (**Figure.1**); 3. Extra-pulmonary invasion to diaphragm and spleen; and 4. No evidence of vascularity was seen inside the mass in the Doppler study. Antifungal therapy with liposomal amphotericin was added and pulmonary high-resolution computed tomography (HRCT) was requested. High-resolution computed tomography on the 5th day of hospitalization showed multiple nodular lesions with/without ground-glass opacity (halo sign). There were thick wall cavitary lesions with an intra-cavitary fungus ball and the air crescent sign (**Figure.1**). The debridement of the para-nasal sinuses confirmed Mucormycosis.

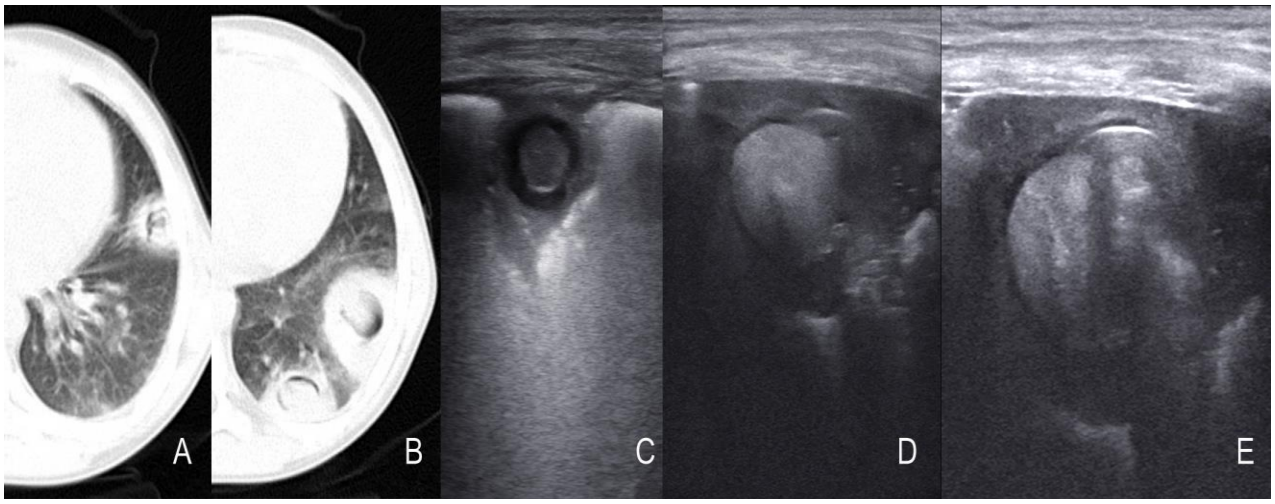

Fig.1: HRCT and Ultrasound images of Mucormycosis infection. A & B) Multiple nodular lesions with peripheral ground-glass opacity or halo sign, reverse halo sign, and air crescent sign. C) The target lesions; a hyper-echoic central nodule with a hypo-echoic rim. D) A hyperechoic nodule (fungus ball) within consolidation. E) Hyper-echoic fungus ball with air extension at the peripheral hypoechoic rim.
(HRCT: High-resolution computed tomography).

The second patient was a new case of acute lymphoblastic leukaemia (ALL), a 5-year-old boy who had developed fever, respiratory distress, and neutropenia since starting chemotherapy. HRCT showed multiple nodular lesions with ground-glass opacity (halo sign) without an air crescent sign. On ultrasound exam, two target lesions

were found as a hyper-echoic central nodule with a hypo-echoic rim and as a hypoechoic center with a hyper-echoic rim (**Figure.2**). Antifungal therapy was added. The debridement of the para-nasal sinuses confirmed Aspergillosis. In low-dose HRCT follow-up, an air crescent sign has occurred within a nodular lesion (**Figure.2E**).

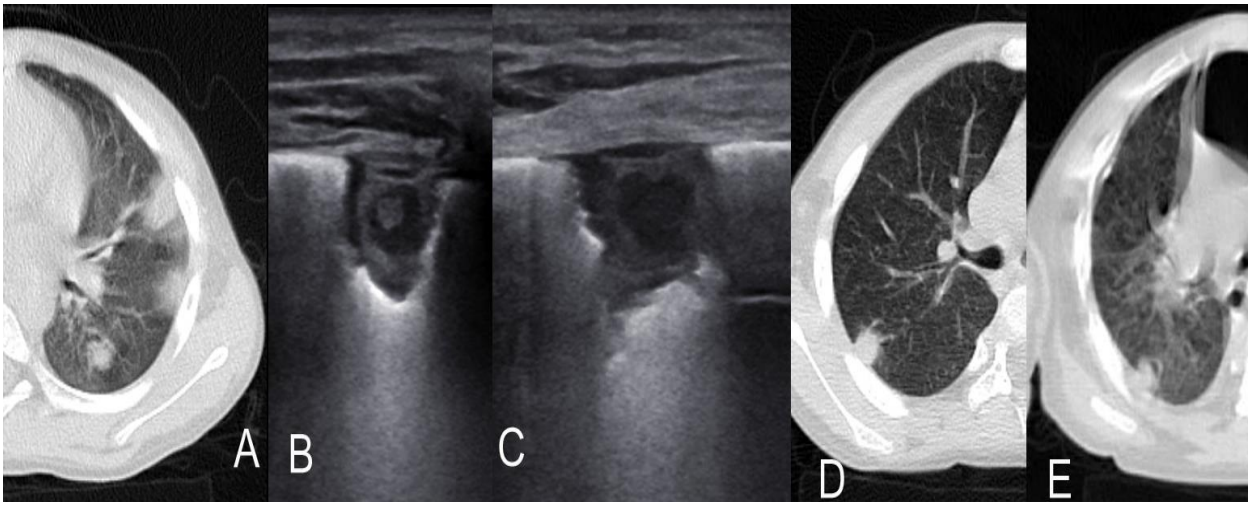

Fig.2: HRCT and ultrasound images of Aspergillosis infection. A) Multiple nodular lesions with ground-glass opacity (halo sign) without air crescent sign. Two target lesions in ultrasound. B) hyper-echoic central nodule with the hypoechoic rim. C) Hypoechoic center with a hyper-echoic rim. D&E) a nodular lesion of the right lung that has developed an air crescent sign in control HRCT. (HRCT: High-resolution computed tomography).

A relapsed patient of ALL (7-year-old boy) with fever, respiratory distress, and pancytopenia was our third case. HRCT showed multiple nodular lesions with an air crescent sign, but without ground-glass opacity (halo sign). The ultrasound exam shows wedge shape consolidation associated with the target lesions as a hypo-echoic center with a hyper-echoic rim (**Figure.3**). The galactomannan test was positive (possible Aspergillosis).

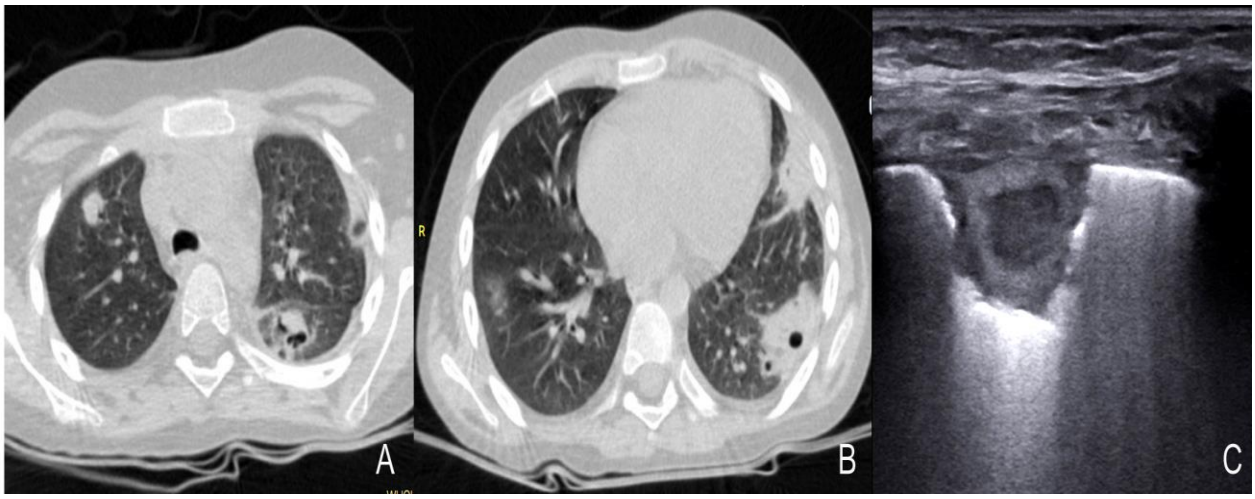

Fig.3: HRCT and ultrasound images of Aspergillosis infection. A & B) Multiple nodular lesions with cavitation. C) The target lesion in ultrasound a hypo-echoic center with the hyper-echoic rim. (HRCT: High-resolution computed tomography).

The next patient was an 11-year-old boy with relapsed ALL who had presented with pleuritic chest pain and fever during a pan-cytopenic state. HRCT showed multiple nodular lesions with ground-glass opacity (halo sign), but without an air crescent sign. On ultrasound examination, the target lesions were found as a hypo-echoic center with a hyper-echoic rim (**Figure.4**). The debridement of the para-nasal sinuses confirmed Aspergillosis. Imaging modalities were repeated 10 days later; the low dose HRCT showed multiple cavitary lesions with a fungal ball and air crescent sign. On ultrasound examination, in addition to wedge-shape consolidation and the target lesions, we found hypoechoic U-shape consolidation, which demarcated with lung air and the central cavity.

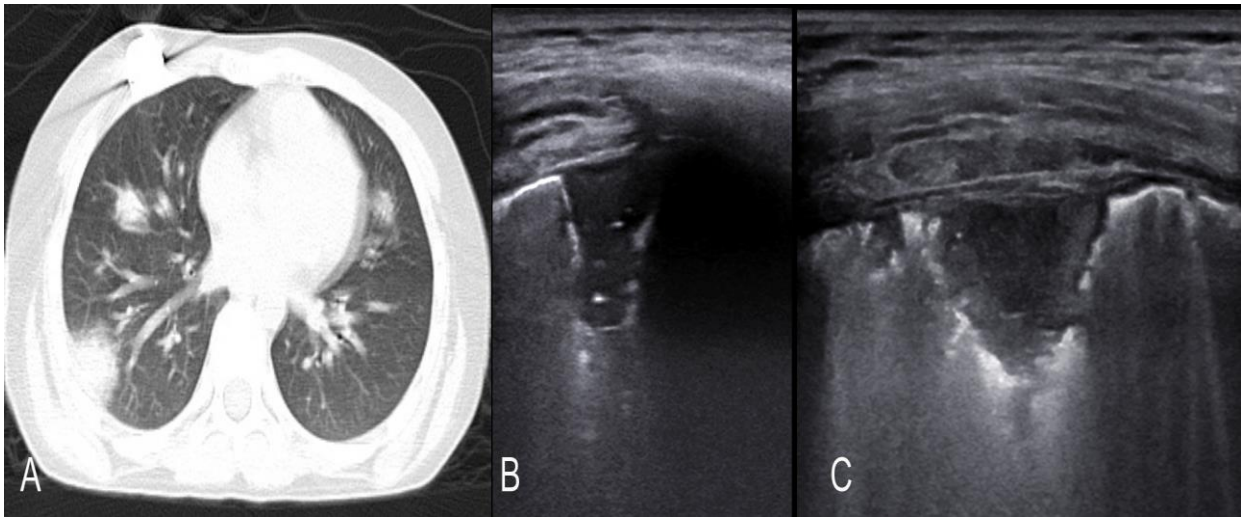

Fig. 4: HRCT and ultrasound images of fungal infection. A) Multiple nodular lesions with ground-glass opacity and without air crescent sign. B) The target lesion in ultrasound a hypo-echoic center with a hyper-echoic rim. C) Wedge shape consolidation. (HRCT: High-resolution computed tomography).

The invasion on the chest wall and pleural adhesion were found, which can justify the patient's pleuritic chest pain (**Figure.5**). The target lesion with central hyperechoic nodule appeared in some lesions. The fifth patient was a 6-year-old boy with a history of ALL from 4 years ago who presented with fever during a neutropenic state. HRCT showed a cavitary lesion. The ultrasound exam showed the wedge-shaped consolidation with central cavitation. The air in the lungs and the air in the central cavity enveloped the consolidation and formed a U-shaped configuration (**Figure.5c**). The galactomannan test was positive (possible Aspergillosis). Two drug antifungal therapies (amphotericin and Voriconazole) were started, and the patient was discharged after significant improvement. Our latest patient was a 7-year-old boy with Down syndrome and ALL who developed fever, lethargy, and neutropenia during the last course of chemotherapy. HRCT showed wedge shape opacities and multiple nodular lesions with ground-glass opacity (halo sign), without an air crescent sign. On lung ultrasound examination, the target lesions were found as a hyper-echoic central nodule with a hypo-echoic rim and as the hypoechoic center with a hyper-echoic rim. Similar target lesions were found simultaneously in the liver (**Figure.6**). Two anti-fungal drugs (Amphotericin and voriconazole) were started. In follow-up ultrasound, the lesions were obscured without cavity formation.

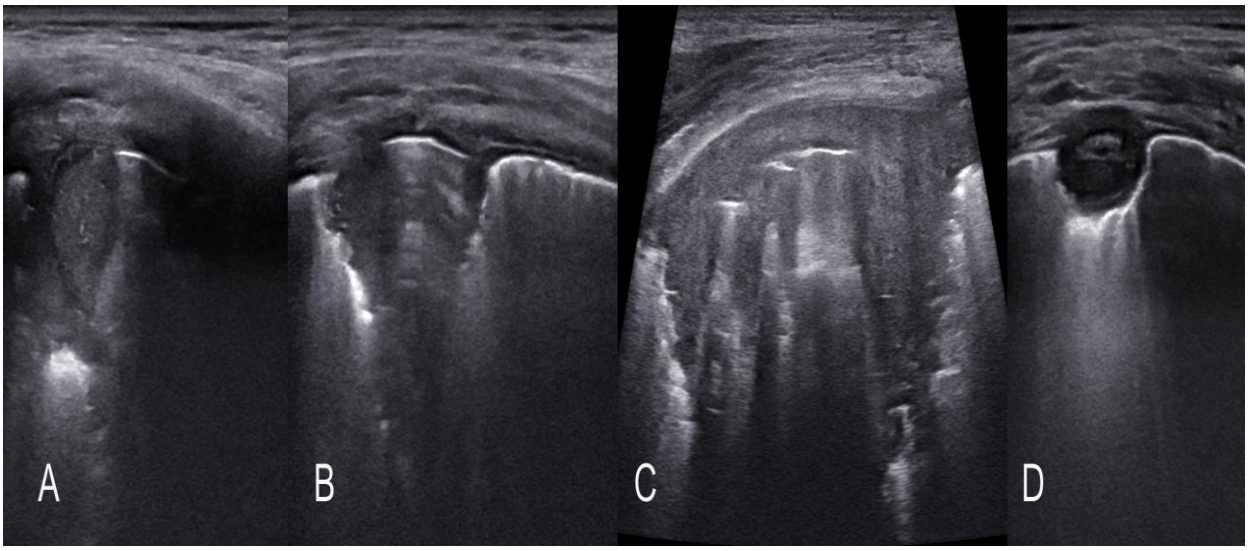

Fig.5: The ultrasound images of the fourth case after 10 days. A) Central hyper-echoic fungus ball with air extension at the peripheral hypoechoic rim as air crescent sign on ultrasound. B & C) Peripheral U-shape consolidation due to central cavitation. D) A target lesion with invasion on the chest wall associated with pleural adhesion.

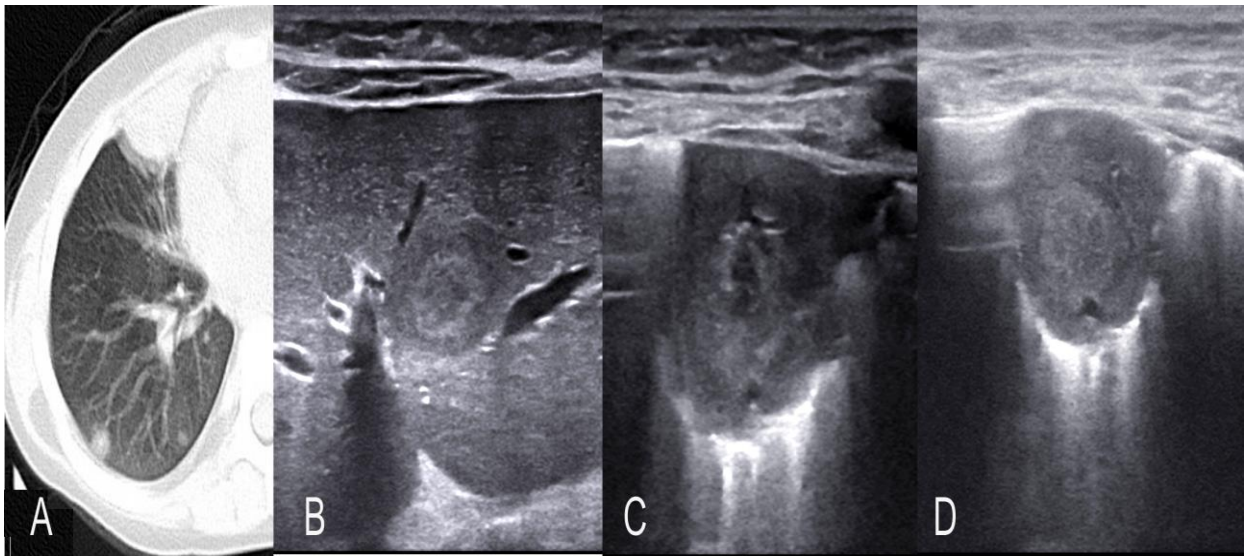

Fig.6: The HRCT and ultrasound images of fifth cases. A) Wedge shape opacity and nodular lesions. B) Typical target lesion of fungal infection in the liver. C) A hyper and hypoechoic lesion in the center of a peripheral pulmonary nodule. D) A hyperechoic nodule in the center of consolidation. (HRCT: High-resolution computed tomography).

3- DISCUSSION

The early diagnosis of invasive fungal diseases is important because the therapeutic outcome depends on the prompt initiation of appropriate interventions. Aspergillus and Candida are two major causes of opportunistic fungal infections. Mucormycosis is much less common than these two, but its mortality rate is much higher (6). Airway or Angio invasive feature of fungi in immunocompromised patients is characterized by fungal invasion to the arterial or bronchial wall that results in infarct-like necrosis with associated inflammatory debris (7). Because lung fungal infections are associated with up to 80% mortality (3), diagnostic imaging can

be crucial in faster diagnosis or assessment. Radiographic imaging can help to diagnose, determine the extent of dissemination of infection and monitor the response to anti-fungal therapy. In this study, we discuss imaging findings of invasive fungal diseases on ultrasound and comparison with CT scan findings in six children with leukemia. The radiologic or CT scan manifestations of invasive fungal disease of the lung are the same and include consolidation, pulmonary infarction, cavitations, abscess formation, nodules, and masses (1, 7). These findings are due to the Airway or Angio invasive feature of fungus and are typically non-specific and cannot help to distinguish invasive fungal infection from other causes. The halo sign and the "reverse-halo" sign are more specific findings of pulmonary fungal infection on CT scan images. The halo sign represents a crescent or complete ring of ground-glass opacity that surrounds a focal rounded area of consolidation. The "reverse-halo" sign represents a focal rounded area of ground-glass opacity surrounded by a crescent or complete ring of consolidation (8).

In the appropriate clinical setting, a halo sign seen with CT is highly suggestive of Angio-invasive Aspergillosis and the reverse-halo sign is suggestive of Mucormycosis (1). Calcium or metal ions in the fungal ball are thought to be the cause of high attenuation in the central nodule and the halo of ground-glass opacity is due to angio-invasive nature of fungal infections and represents a hemorrhagic infarct (7). These two signs are also actually non-specific and could be seen in tuberculosis, pseudomonas, herpes simplex virus, cytomegalovirus pneumonia, Sarcoidosis, Wegener granulomatosis, Kaposi sarcoma, or hemorrhagic metastasis and cannot help to distinguish invasive fungal infection from other causes (1). However, although these signs have been observed in several diseases (infectious and noninfectious), they have been described as an indicator of pulmonary fungal infection in patients with hematologic malignancy (5). Another characteristic feature of pulmonary fungal infection on X-ray or CT scan is the air crescent sign. It was originally described by Monod et al. as a soft tissue mass in a pre-existing cavitary lesion in a normal immunity state, as the characteristic finding of a mycetoma or aspergilloma. The crescent-shaped lucency reflects airspace between the fungus ball and the wall of the cavity. This air crescent sign can also be seen in the improving phase of Angio-invasive Aspergillosis (7, 9, 10). Interestingly, these suggested findings of Aspergillosis, such as the “halo” sign or the “crescent "sign seen in neutropenic patients, do not occur in infants with the chronic granulomatous disease (8).

Although the use of transthoracic ultrasound (TUS) in the diagnosis of disorders such as pleural effusion, pneumonia, and pulmonary masses has been well established (11-13), few texts on the usefulness of TUS in diagnosing invasive fungal infections of the lungs have been reported in the literature. We found few case reports in the available literature on this subject. In Grabala et al.’s case report, transthoracic ultrasonography revealed a subpleural consolidation area of heterogeneous echo-structure with an abnormal air bronchogram, and they suggested an invasive pulmonary fungal disorder. Color-coded Doppler scan revealed no flow within the vessels of the aforementioned consolidation area. Interstitial-alveolar opacities were also revealed bilaterally in the vicinity of the consolidation area (4). Raffaella et al.’s study on ultrasound evaluation of pulmonary invasive fungal diseases after Allogeneic Hematopoietic Stem Cell Transplantation shows consolidations and hypoechoic areas with an inhomogeneous echotexture with blurred margins in 40%

of patients (14). However, their reported findings are non-specific and are seen in other pneumonic states. In the case report of Pinto et al., endoscopic ultrasound was done in a patient with acute myeloid leukemia. They found a characteristic finding as an ill-defined hypoechoic para-esophageal lesion, with a central annular image without vascular flow. The endoscopic ultrasound-guided fine-needle aspiration (FNA) of the lesion was positive for Aspergillus fumigatus (15). In our cases, HRCT revealed classical findings of pulmonary fungal infection; multiple nodular lesions with/without ground-glass opacity (halo sign) and thick wall cavities with intra-cavitary fungus ball, air crescent sign, and wedge-shaped opacities.

But, the trans-thoracic ultrasonography in pulmonary fungal infection showed four types of lesions: the target lesion, the cavitary lesions, wedge-shape consolidation, and extra-pulmonary invasion to the chest wall or sub-diaphragmatic. The target lesions have one of these pictures: 1) A hyper-echoic central nodule with a hypo-echoic rim. 2) A hypoechoic center with a hyper-echoic rim. 3) A hypoechoic nodule in center of consolidation and 4) A hyperechoic nodule in center of consolidation. As the central hyperechoic nodule was constant in the lesions of four cases, it is probably a fungus ball.

The cavitary lesions on ultrasound have two different pictures; 1) The central hyperechoic masses (fungus ball) with air extension at the hypoechoic rim as an air crescent sign and 2) The hypoechoic U-shape consolidation, which demarcated with the air of the lung and central cavity. Sub-segmental consolidation, especially with a wedge-shaped appearance was a usual finding in both HRCT and ultrasound of our patients. The extra-pulmonary invasion to the chest wall or sub-diaphragmatic area was seen in two cases. However, that can be a specific sign of pulmonary fungal infection which can lead to the rapid start of treatment, eliminate the need for tissue diagnosis or other invasive diagnostic procedure, and limit the differential diagnosis of the halo sign. By viewing this specific pattern and the immediate start of treatment with two anti-fungal drugs, these pulmonary nodules disappeared within two weeks without cavity formation. However, the diagnostic value of these signs and especially on differentiation type of fungal infection needs further research.

4- CONCLUSION

In invasive fungal disease, the trans-thoracic ultrasound can show four characteristic appearances; the target lesion, the cavitary lesions, wedge-shape consolidation, and extra-pulmonary invasion to the chest wall or sub-diaphragmatic. These signs on ultrasound can help in faster diagnosis and monitoring of treatment response in these patients.

5- ACKNOWLEDGMENTS

This study was supported by the Deputy for Research of Mashhad University of Medical Sciences, Mashhad, Iran.

6- CONFLICT OF INTEREST: None.

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