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Computerized tomography diagnosis of pulmonary fungal infection in patients with acute leukemia after chemotherapy

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► ***Original article***

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ABSTRACT

Background: To explore computerized tomography (CT) imaging features of pulmonary fungal infection (PFI) in patients with acute leukemia (AL) after chemotherapy. ***Materials and Methods***: Totally 116 AL patients who received chemotherapy in our hospital from June 2016 to April 2023 participated into this study, and the pulmonary fungal infection was confirmed by laboratory examination and clinical antifungal treatment. The CT image signs, lesion distribution, CT concomitant signs and main types of fungal infection were analyzed. ***Results***: CT image signs of two main types, nodule/mass type and mixed type were recorded, with76 cases of nodular/mass type and 40 cases of mixed type. There were 372 lesions in nodules/mass cases, mainly in the upper lung (46.24%). In these 372 lesions, 113 micro-tubercle, 138 small nodules, 115 nodules and 6 masses were included. There were 88 cases of halo sign, 26 cases of cavity, and 25 cases of air crescent sign. Candida albicans was the most common pathogenic fungal strain, followed by aspergillus, candida tropicalis, candida glabrata, candida parapsilosis, cryptococcus, candida dubliniensis, mucor, candida krusei and candida rugosa. ***Conclusion***: The CT manifestations of AL complicated with pulmonary fungal infection after chemotherapy were various, most of which had no characteristics, but the "halo sign" and "air crescent sign" had certain specificity. The combined CT and clinical manifestations can narrow the range of differential diagnosis. When the diagnosis still cannot be confirmed, diagnostic therapy or early diagnosis by fungal culture and histological examination can be performed.

INTRODUCTION

Acute leukemia (AL) is a malignant clonal disease of hematopoietic stem cells [1]. It occurs when abnormal primitive cells and immature cells (leukemia cells) proliferate and accumulate in the bone marrow, inhibit normal hematopoietic formation, and infiltrate the liver, spleen, lymph nodes, and other extramedullary organs extensively [2]. Signs such as anemia, bleeding, infection, and infiltration are commonly observed in this process. AL can be divided into acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML) based on the type of cells involved [3]. The incidence of AML is about 162/100 000 and that of ALL is about 0.69/100000 [4]. AML is more common in adults and ALL frequently occurs in children [5]. Without special treatment, the average survival time of AL is only about 3 months, and some cases even die a few days after diagnosis [6]. For AL patients, the most important thing is to control the disease first [7]. Patients were recommended to be hospitalized for chemotherapy, receive high-calorie, high-protein, high-vitamin diet, and pay attention to oral hygiene, intensive care, aseptic isolation, and regular treatment to preventing infection [8].

Patients with AL will experience a significant decrease in the number of granulocytes and gradual reduction in the immune function after receiving chemotherapy, which increases the risk of infection [9]. According to epidemiological analysis, the vast majority of patients with AL will have chest infections during chemotherapy, among which invasive fungal infection of the lung is the most common site and type, and is an important cause of death in patients with AL [10]. Therefore, it is imperative to ensure prompt diagnosis and treatment for AL patients. However, based on the actual clinical diagnosis of pulmonary fungal infection in AL, the misdiagnosis or missed diagnosis rate is high due to the complex and

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changeable imaging manifestations and lack of specific characteristics, and it is difficult to distinguish from other pulmonary comorbidities, which challenges clinical diagnosis and treatment [11].

Computerized tomography (CT) images with extremely high density resolution is highly sensitive to lung lesions, which can basically reflect the pathological changes of pulmonary fungal infection [12]. Herein, we explored the diagnostic effect of CT examination on pulmonary fungal infection in AL patients after chemotherapy. The results of our study are expected to provide novel clues for the clinical diagnosis and therapy of pulmonary fungal infection in AL patients.

MATERIALS AND METHODS

Patient specifications

A total of 116 AL patients who received chemotherapy in our hospital from June 2016 to April 2023 were randomly selected for the study, and the pulmonary fungal infection was confirmed by laboratory examination and clinical antifungal treatment. General information of patients was shown in Table 1. Totally 73 males and 43 females were included and their age ranged from 27 to 75 years old, with the average age of 41.92±10.82 years old. Among the 116 AL cases, 16 cases were ALL and 100 cases were AML.

Inclusion criteria: (1) Patients received chemotherapy, and had pulmonary fungal infection. (2) All patients had fever, cough, and other symptoms of different degrees. (3) The lowest value of neutrophil in laboratory examination was 0.2×10^9/L-1.0×10^9/L. (4) Complete case data. (5) All patients were informed of the research content and signed the informed consent.

Exclusion criteria: (1) Fungal parasitism and allergy caused bronchial pulmonary fungal infection. (2) Infection of other pathogens including mycoplasma, bacteria, viruses or tuberculosis infection at the present stage).

Table 1. Clinical characteristics of AL patients.

Characteristics	All patients (n=116)
Age (years)	41.92±10.82
Gender	
Male	73
Female	43
Disease	
ALL	16
AML	100
Chemotherapy	
First induction	92
Consolidation	12
Re-induction/salvage therapy	12

Diagnostic criteria of pulmonary fungal infection

(1) Sputum smear and culture were positive for 3 consecutive times (and it was the same fungus). The sputum smear was added with Gram's stain (Baso, China) and directly observed under a microscope (Olympus CX31RTSF, Japan). (2) Positive blood culture and pleural effusion culture. Three blood cultures were performed using the BD System (BACTEC FX, USA). GM serum detection was conducted using ELISA method (Xinuo, China). The pleural effusion samples were collected and cultured in the BD System (BACTEC FX, USA) and identified by MALDI-TOF (Merieux，France). (3) Pulmonary biopsy confirmed fungal infection. (4) The results of smear test with brush solution of fiberoptic bronchoscope were also positive.

CT method

All patients underwent dual-source 64-slice spiral CT scanner (Siemens, Germany). During the scan, patients were maintained in supine position, and inspiratory scan was performed on the conventional cross section with the range from lung tip to diaphragmatic roof. The relevant scanning parameters were set as follows: voltage 120 kV, current 100 mA, layer thickness 5mm, layer spacing 5mm, image reconstruction 1.25 mm,. Coronal multiplane scans were performed.

CT image analysis

CT signs were analyzed and recorded by two senior thoracic diagnostic radiologists. In case of disagreement, consensus was reached through consultation and recorded. Representative CT images of patients were shown in figure 1.

CT manifestations: (1) Nodule/mass: defined as small nodule diameter <5 mm, small nodule diameter 5-10 mm, nodule diameter 10 mm-30 mm, mass diameter ≥30 mm. (2) Consolidation: distributed in the lung segment or lobe uniform dense shadow, with blurred or clear edge (3) Ground-glass Opacity (GGO): opacity within the lung but did not cover the original background of the blood vessels and trachea in the area. (4) Pleural effusion: unilateral or bilateral pleural effusion. (5) Mediastinal lymph node enlargement: defined as short diameter of one or more mediastinal lymph nodes >10 mm.

Lesion distribution: (1) Unilateral and bilateral distribution: single occurrence in single lung, multiple occurrence in single lung and multiple occurrence in both lungs. (2) Distribution of lung lobes: upper (including the upper lobe of the left lung and the upper lobe of the right lung), middle (middle lobe of the right lung), lower (including the lower lobe of the left lung and the lower lobe of the right lung), random (any two or more lesions distributed in the upper, middle and lower lobe of the lung).

CT concomitant signs: (1) Halo Sign (HS) was defined as dense shadows oozing from ground glass around nodules or masses. (2) Reversed Halo Sign (RHS) was defined as focal ground glass shadow in the center and solid lung tissue shadow surrounding

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the reversed halo sign. (3) Voids/cavities were defined as gas-containing components presented in nodules, masses, or consolidated lesions. (4) Air crescent sign was defined as crescent shaped space of gas density formed between the microsphere and the cavity wall. (5) Air bronchial sign was defined as air bronchial branch shadows that could be seen in lung consolidation.

Statistical analysis

Results were analyzed using the SPSS 22.0 software (SPSS Inc, Chicago, IL, USA). The absolute number was presented as the mean ± standard deviation, and the relative number was presented as the rate and ratio. The chi-square test was used for comparisons of enumeration data. $P<0.05$ indicated statistical significance.

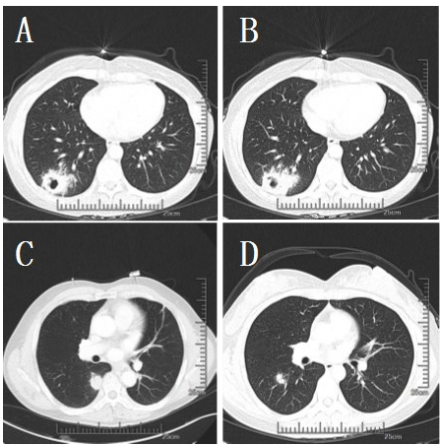


Figure 1. CT images of AL patients after chemotherapy. **(A-B)** Patients with cavities. **(C)** A patient with air bronchial sign. **(D)** A patient with halo signs and air bronchial sign. **(B-D)** A patient with multiple occurrence.

RESULTS

CT image signs of patients

Totally 116 AL patients with pulmonary fungal infection enrolled in this study received CT scan. CT image signs in the nodule/mass type (CT signs were simple nodule or mass) and mixed type (CT signs included two or more types) were recorded. Totally 76 cases were nodular/mass type, with an incidence of 65.52%, and 40 cases were mixed type with an incidence of 34.48%. The mix types included 20 cases of atelectasis (17.24%), 4 cases of ground glass (3.44%), 8 cases of interstitial inflammation (6.9%), and 8 cases of tree bud sign (6.9%) (table 2).

Table 2. Types and incidence of CT image signs in AL patients.

CT image signs	Cases	Incidence rate
Simple nodule or mass type	76	65.52%
Mixed type	40	34.48%
Atelectasis	20	17.24%
Interstitial inflammation	8	6.90%
Tree bud sign	8	6.90%
Ground glass	4	3.44%

CT, computerized tomography; AL, acute leukemia.

Lesion distribution of patients

As displayed in table 3, there were 372 lesions in 76 nodules/masses type of cases, and these lesions mainly distributed in the upper lung (46.24%), followed by the lower lung (36.29%), and in the middle lung (17.47%).

Table 3. CT lesion distribution location of AL patients with pulmonary fungal infection.

Main distribution area	Number of nodules (n=372)	Incidence rate
Upper right	80	21.51%
Middle right	65	17.47%
Low right	69	18.55%
Upper left	92	24.73%
Low left	66	17.74%

CT, computerized tomography; AL, acute leukemia.

CT concomitant signs of patients

In patients with nodular/mass type of CT signs (n=76), totally 372 lesions were identified, including 113 micro-nodules, 138 small nodules, 115 nodules and 6 masses. There were 88 cases of halo sign, 26 cases of cavity, and 25 cases of air crescent sign. The CT nodular/mass type lesions showed statistical significance in the lesion size and concomitant signs (table 4).

Table 4. CT lesion seize and concomitant signs in AL patients.

Nodule size	Cases	Halo sign	Cavity	Air crescent sign
Micro-nodules (<5 mm)	113	2	1	0
Small nodules (5-10 mm)	138	42	6	1
Nodules (10-30 mm)	115	40	15	20
Masses (>30 mm)	6	4	4	4
P value		<0.001	<0.001	<0.001

CT, computerized tomography; AL, acute leukemia.

Main types of fungal infection

As displayed in table 5, *candida albicans* was the most common pathogenic fungal strain, accounting for 43.97% of all bacterial strains in the lung fungal infection of AL patients, followed by *aspergillus* (24.14%), *candida tropicalis* (10.34%), *candida glabrata* (5.17%), *candida parapsilosis* (4.31%), *Cryptococcus* (4.31%), *candida dubliniensis* (3.45%), *mucor* (2.59%), *candida krusei* (0.86%) and *candida rugosa* (0.86%).

Table 5. Main types of bacterial strains in the lung fungal infection of AL patients.

Bacterial strain	Cases	Incidence rate
Candida albicans	51	43.97%
Candida tropicalis	12	10.34%
Aspergillus	28	24.14%
Candida dubliniensis	4	3.45%
Candida parapsilosis	5	4.31%
Candida krusei	1	0.86%
Candida glabrata	6	5.17%
Candida rugosa	1	0.86%
Mucor	3	2.59%
Cryptococcus	5	4.31%

AL, acute leukemia.

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DISCUSSION

Granulocytopenia is common in patients with AL, especially after chemotherapy [13]. Infection is the most common complication and the main cause of death in AL patients [14]. Pulmonary fungal infection includes endogenous and exogenous infections and secondary infection, and common pathogenic bacteria include *aspergillus*, *candida albicans* and *cryptococcosis* [15]. Consistently, in our study, we revealed that candida albicans was the most common pathogenic fungal strain, which accounted for 43.97% of all bacterial strains in the lung fungal infection of AL patients, followed by *aspergillus*, *candida tropicalis*, *candida glabrata*, *candida parapsilosis*, *cryptococcus*, *candida dubliniensis, mucor, candida krusei* and *candida rugosa* (table 5). After chemotherapy in AL patients, intense chemotherapy results in severe neutropenia and severe bone marrow suppression, which is an important factor in inducing opportunistic fungal infection [16]. The use of immunosuppressants in AL chemotherapy further decreases the immune function of the body [17]. Combined with the application of broad-spectrum antibiotics, the balance of flora in the body is changed, and the chance of fungal proliferation is increased, leading to secondary pulmonary fungal infection [18].

In the clinical diagnosis of pulmonary fungal infection after chemotherapy for AL, pathological biopsy of the diseased tissue and in vitro culture of fungi are the most important diagnostic methods [19]. However, in the early stage of pulmonary fungal infection in patients with acute leukemia after chemotherapy, the clinical symptoms are not significant, and the results of body fluid culture are not clear. Thus, the optimal treatment time may be missed, leading to the death of patients [20]. Therefore, how to diagnose pulmonary fungal infection after AL chemotherapy as early as possible and improve the clinical therapeutic effect of leukemia has been paid increasing attention.

The pathological changes of pulmonary fungal infection mainly include allergic reaction, inflammatory exudation, granuloma, hemorrhage, necrosis and abscess, may be combined with pleurisy and lymph node enlargement [21]. With the exception of *aspergillus*, most pulmonary fungal infections lack characteristic features on plain chest radiographs or CT [22]. One of the CT characteristic manifestation of early pulmonary fungal infection was nodular “halo” sign, it means that there is ground glass density shadow around the lesion of pulmonary nodules with blurred edges [23]. The density is lower compared with central nodules or masses, but higher relative to adjacent normal lung tissue, showing a halo-like change [24]. In our study, it was found that 88 patients had “halo” sign, and the CT nodular/mass type lesions were statistically significant in signs such as halo sign (P<0.001, table 4), which was consistent with previous studies [25].

Besides, air crescent sign is the formation of a crescent-shaped fissure between a pulmonary nodule, mass, or solid central necrotic structure and the peripheral bleeding lung parenchyma [26]. Its pathogenesis is due to the invasion of *aspergillus* mycelium into pulmonary vessels, leading to pulmonary hemorrhage and arterial embolism, leading to infarction of corresponding blood supplying lung segments [27]. The appearance of this sign suggests the possibility of pulmonary fungal infection, which mostly appears in the absorption period of infection and the middle and late lesions, generally around 7-14 days after the formation of pulmonary nodules or masses [28].

In this study, we found that 25 patients had air crescent sign, which was consistent with the above literatures, and CT nodular/mass type lesions were statistically significant in air crescent signs (P<0.001, table 4). The appearance of the air crescent sign depends on the recovery of granulocyte function. In patients with granulocytopenia, the air crescent sign appearance suggests a better prognosis for infection because the necrotic material cannot be absorbed [29]. Gaeta *et al.* [30] find that in AL patients, the survival rate of patients with air crescent sign was 67% and 8% higher than that of patients without this sign. The air crescent sign has a high specificity but low incidence.

Pulmonary cavity sign is a complete enclosed air space in one or both lungs with single or multiple lesions [31]. Pathologically, it may be non-supportive exudative/serous alveolitis. The CT results showed that the size of the cavity was different and the thickness of the cavity wall was different. The *aspergillus* pellets formed by the mycelium inside the cavity were generally round or oval, with clear edges and uniform density [32]. They were free in the cavity and could move with the change of body position. Mobile nodule in cavity is not a unique sign of pulmonary a*spergillosis*, sometimes seen in lung abscess necrotic matter, cancerous cavity, tuberculous spherolysis aggregation, cavity or cyst hematoma, but when it appears around the halo sign, fungal infection should be considered first [33]. In this study, we showed that 26 patients had cavity sign, and CT nodular/mass type lesions were statistically significant in cavity sign in AL patients (P<0.001, table 4).

In conclusion, the CT manifestations of AL complicated with pulmonary fungal infection after chemotherapy are various, and most of them have no characteristics. The combined CT and clinical manifestations can narrow the range of differential diagnosis which may provide evidence for the diagnosis and therapy of pulmonary fungal infection in AL patients after chemotherapy.

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***Author contribution*:** D.K.,J.G. and L.S. conceived and designed the study; D.K., Q.L., J.L. and L.S. collected and analyzed the data; D.K. drafted the manuscript and L.S. reviewed and edited the manuscript. All authors read and approved the final manuscript.

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