

High-Resolution Computed Tomography Chest Findings and Correlation with CD4 Cell Counts among Human Immunodeficiency Virus-Infected Children Presenting with Digital Clubbing, Chronic Cough and Crackles in Chest

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Abstract

Background: Digital clubbing is an important presentation in the human immunodeficiency virus (HIV) infected children especially with the chronic invasive fungal lung diseases. High-resolution computed tomography (HRCT) chest plays an increasing important complementary role in establishing an accurate diagnosis when chest X-ray (CXR) findings are equivocal or non-specific.

Materials and Methods: Three hundred HIV-infected children enrolled for the present study and the children presenting with digital clubbing, chronic cough, and crackles in chest were selected. The retrospective analysis of all the CD4 cell counts, before and during antiretroviral therapy (ART) of the selected patients was done. All the selected children were referred for CXR, HRCT chest and sputum for fungal element staining and culture.

Results: Eight (2.66%) children out of the 300 HIV-infected children were presenting with digital clubbing, chronic cough, and extensive crackles in the chest. A definitive microbiological diagnosis of fungal infections was made from the sputum fungal element staining and cultures in 7 (87.5%) patients out of the selected 8 patients, which included *Aspergillus fumigatus* in 3, *Cryptococcus neoformans* in 2 and *Candida albicans* in 2 patients. The mean of lowest CD4 cell counts, before and during ART up to the time of examination of the selected 8 children was 137.87 cells/ μ l (\pm 76.53). The means of lowest CD4 cell counts of 3 cases of pulmonary aspergillosis, 2 cases of pulmonary cryptococcosis, and 2 cases of pulmonary candidiasis were 93.6 cells/ μ l (\pm 5.03), 114 cells/ μ l (\pm 14.14), and 137 cells/ μ l (\pm 24.04), respectively. The HRCT chest images of all the above selected 8 children were showing with findings suggestive of fungal lung infections.

Conclusion: Digital clubbing, chronic cough, and extensive crackles in chest were the strong clinical findings suggestive of invasive fungal lung infections among HIV-infected children. HRCT chest findings of pulmonary fungal infection were diverse, but some characteristic HRCT chest findings were highly suggestive of pulmonary fungal infections in immunocompromised patients.

Key words: Acquire immunodeficiency syndrome, Clubbing, Human immunodeficiency virus, Imaging lung, Lung diseases-fungal

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INTRODUCTION

Many children were infected with human immunodeficiency virus (HIV). The majority of them were transmitted through parents to child transmission. As of now, with the advances in the knowledge of the disease and its management including antiretroviral therapy (ART), many

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of the HIV-infected children on ART are living longer in good health as chronic manageable diseases. Some of them who are having low CD4 cell counts due to delay in starting of ART as per guideline or who are getting resistance to ART especially due to poor adherence to ART are having high risk for HIV-related opportunistic infections, like chronic fungal infections of lung. Opportunistic fungal infections still remain a problem in HIV-infected children. These fungal infected patients have increased morbidity and mortality as any other chronic disease. Necropsy studies in acquire immunodeficiency syndrome (AIDS) patients have confirmed an incidence of fungal infection of 20-49%.^{1,2} However, these patients are subjected to wide spectrum of pathogens; fungal infections play an important role. As these infections differ in different geographical boundaries, knowledge about the spectrum of them is crucial for clinicians.^{3,4} Invasive fungal infections are common opportunistic infection and the risk of invasive fungal infection varies with host immunity, as well as environmental exposure.⁵ Improved skills and availability of fungal diagnostic tests would improve the outcome in the management of opportunistic infections. Knowledge regarding the opportunistic fungal infections will be useful as timely recognition and treatment of opportunistic infections are the only option. Digital clubbing is an important presentation in the HIV-infected children especially with the chronic invasive fungal lung diseases. Computed tomography (CT) has advantages over chest radiology as it is more sensitive and specific for a variety of conditions affecting the pulmonary parenchyma. High-resolution CT (HRCT) examination of chest was more sensitive (could detect abnormalities when the chest radiography was normal); showed greater accuracy in characterizing disease into interstitial, airway and air space process; and gave a more accurate depiction of the extent of disease. The radiation dose is an important consideration in children; therefore, CT does not have a role in the investigation of a single, uncomplicated lower respiratory tract infection in an immunocompetent child. HRCT chest plays an increasing important complementary role in establishing an accurate diagnosis when chest X-ray (CXR) findings are equivocal or non-specific. So in view of such a situation, this present study was conducted to know the HRCT chest findings and correlation with CD4 cell counts among HIV-infected children presenting with digital clubbing, chronic cough and crackles in chest, at the Department of Pediatrics, Jawaharlal Nehru Institute of Medical Sciences (JNIMS), Manipur, India.

MATERIALS AND METHODS

This present study was conducted at the Department of Pediatrics, JNIMS, over a period of 4 years from September

2010 to August 2014. The study was approved by the Institutional Ethical Committee of JNIMS.

As inclusion criteria, all the HIV infected children of both sexes with or without ART in the age group of 18 months to 15 years attended the outpatient department (OPD) of pediatrics; JNIMS were enrolled in the present study.

As exclusion criteria, all the HIV infected children of both sexes below 18 months and above 15 years of age were excluded. A written informed consent was obtained from the parents or caregiver of each child before enrollment in the present study. The confidentiality of all the children was maintained.

The HIV status of all the patients was confirmed by the three antibody tests at the integrated counseling and testing centers approved by the National AIDS Control Organization (NACO), Ministry of Health and Family Welfare, Government of India.

All the CD4 cell counts of all the patients enrolled in our study were determined by the CD4 machines, approved by the NACO. Three hundred HIV positive children were evaluated by a pre-designed protocol covering the patient's particulars, relevant past history, clinical conditions before and during ART, adherence to ART, high-risk behavior, presenting complaints and clinical examinations, duration of cough, extension of crackles in chest. Those children presenting with digital clubbing, chronic cough and crackles in chest were selected from the 300 HIV-infected children after thorough clinical examinations. All the CD4 cell counts before and during ART of the selected patients were analyzed retrospectively. The selected patients were referred for CXR, HRCT chest at the Department of Radiodiagnosis, JNIMS. Early morning expectorated sputum samples of the selected patients were collected with complete universal precautions for direct microscopic examinations using Gram- and Giemsa-staining, KOH mounts, India ink preparations and fungal culture at the Department of Microbiology, JNIMS. The samples were subjected to direct microscopy using Gram- and Giemsa-staining, KOH mounts and India ink preparations. Relevant methods were used for fungal culture, isolation and diagnosis which included a battery of tests as per standard procedures.

RESULTS

Three hundred HIV-infected children of both sexes with or without ART in the age group of 18 months to 15 years attended the pediatrics OPD of JNIMS were enrolled in the present study over a period of 4-year.

Eight (2.6%) children out of the 300 HIV-infected children presented with digital clubbing, chronic cough, and extensive crackles in chest.

The male:female ratio of the selected eight patients was 1:3 (Table 1).

A definitive microbiological diagnosis of fungal infections was made from the sputum fungal element staining and cultures in 7 (87.5%) patients out of the selected 8 patients, which included *Aspergillus fumigatus* in 3, *Cryptococcus neoformans* in 2 and *Candida albicans* in 2 patients. The mean of lowest CD4 cell counts, before and during ART up to the time of examination of the selected 8 children was 137.87 cells/ μ l (\pm 76.53) (Table 2). The mean of lowest CD4 cell counts of 3 cases of pulmonary aspergillosis, 2 cases of pulmonary cryptococcosis, and 2 cases of pulmonary Candidiasis were 93.6 cells/ μ l (\pm 5.03), 114 cells/ μ l (\pm 14.14), and 137 cells/ μ l (\pm 24.04), respectively, (Table 2 and Figures 1-8).

One patient out of the selected 8 children shows negative fungal result in the sputum of fungal element staining and culture. The CD4 cell count of the patient was 320 cells/ml (Table 2).

The HRCT chest images of all the selected 8 children were showing with findings suggestive of fungal lung infections.

Table 1: Demographic profile of the selected 8 patients

Age in months/years	Male	Female	Total number of male and female
18 months-2 years			
>2-5 years		1	1
>5-10 years		2	2
>10-15 years	2	3	5
Total	2	6	8

Table 2: Distribution of various opportunistic fungal infections of chest and mean of lowest CD4 cell counts of the selected 8 children

Opportunistic fungal infection	Total number patients	Mean of lowest CD4 (\pm SD) cells/ μ l	Lowest CD4 cells/ μ l
Pulmonary aspergillosis	3	093.6 (\pm 5.03)	89, 93, 99
Pulmonary cryptococcosis	2	114 (\pm 14.14)	104, 124
Pulmonary candidiasis	2	137 (\pm 24.04)	120, 154
No fungal element isolated	1		320
Total	8	137.87 (\pm 76.53)	89, 93, 99, 104, 124, 120, 154, 320

SD: Standard deviation

HRCT chest findings of the selected 8 patients presenting with digital clubbing, chronic cough and extensive crackles in chest are as follows.

DISCUSSION

In the present study, 3 cases of pulmonary aspergillosis were detected and had a mean of lowest CD4 cell counts of 93.6 cells/ μ l (\pm 5.03). According to one study, patients who had HIV-associated aspergillosis typically have CD4+ counts <100 cells/ μ l.^{5,6} The findings of the present study are comparable to this, in terms of CD4 counts.

One study reported pulmonary cryptococcal infection in 3.3% cases and occurred at mean CD4 count of 144.5 cells/ μ l.⁷ In another study two patients had pulmonary cryptococcosis. The CD4 counts of these 2 patients were 104 and 143 cells/ μ l.⁸ In the present study 2 patients of pulmonary cryptococcal infection were diagnosed and the mean of the lowest CD4 counts was 114 \pm 14.14 cells/ml. The finding of the present study is comparable to this, in terms of CD4 counts.

According to one study *C. albicans* and *Candida glabrata* were isolated from 3 to 1 patient respectively. The mean CD4 cell count was 134.2 cells/ μ l (\pm 66.7).⁸ In the present study 2 patients of pulmonary candidiasis were diagnosed, and the mean of the lowest CD4 counts was 137 cells/ μ l (\pm 24.04). The finding is comparable to this, in terms of CD4 counts.

Angioinvasive disease of aspergillosis is most common, manifest as thick walled cavitory lesions predominating in the upper lobes, with air crescents surrounding areas of desquamated infarcted lung. Less-common patterns include nodules with a peripheral halo of ground-glass attenuation and isolated airway disease or allergic bronchopulmonary aspergillosis, manifesting as bilateral lower lobe consolidation, bronchiectasis, and airway intonation or "finger in glove."^{9,10}

In the present study the HRCT chest images of the three patients of pulmonary aspergillosis show extensive ground glass opacities (GGO) and mosaic pattern, small cystic lesions, cystic and traction bronchiectasis, peribronchial cuffing, branching nodules, multiple small nodules with subtle peripheral halo, well capsulated cavitory lesion with dense nodule with air crescent suggestive of fungal ball.

In the present study, the HRCT chest images of the two pulmonary cryptococcosis show air trapping mosaic and GGO associated with cystic and cylindrical bronchiectasis, peribronchial cuffing with scattered ground glass appearance.

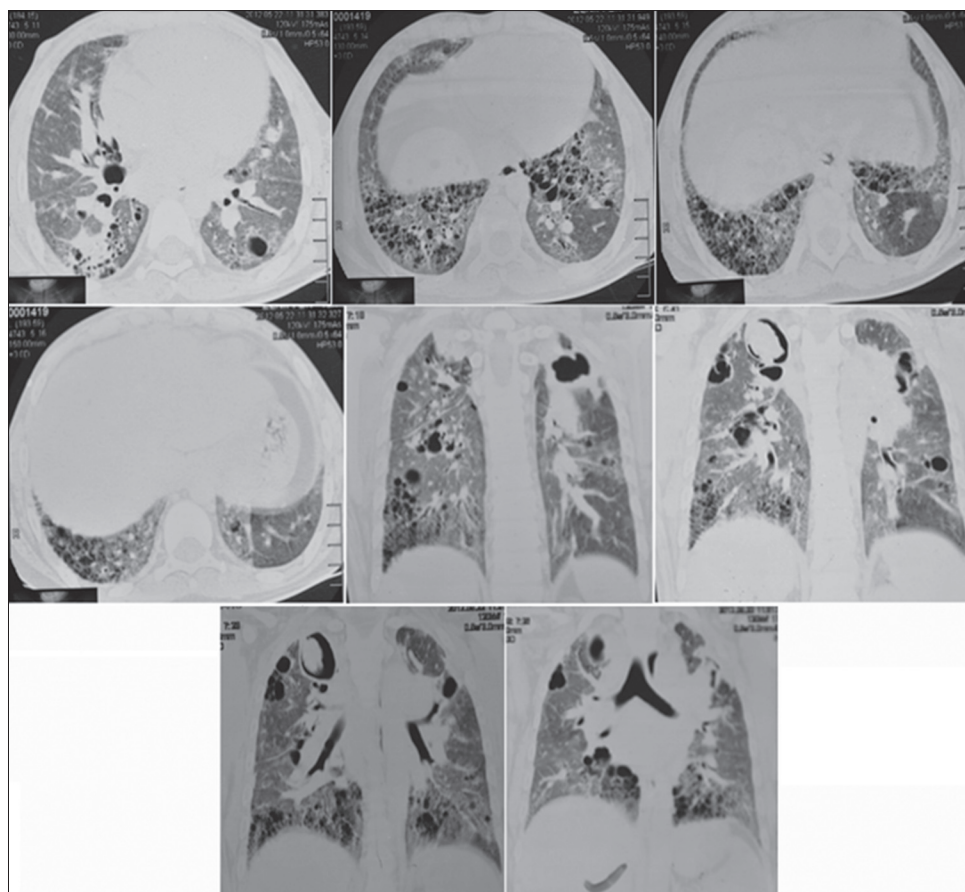


Figure 1: High-resolution computed tomography (HRCT) chest images of a 12-year-old female patient, who had a CD4 cell count as low as 93 cells/ μ l and *Aspergillus fumigatus* was isolated from her sputum. The HRCT chest images show diffused ground glass opacities in bilateral lung fields with multiple cystic bronchiectasis. Well encapsulated cavitory lesion with dense nodules suggestive of fungal ball involving in right upper lobe also seen

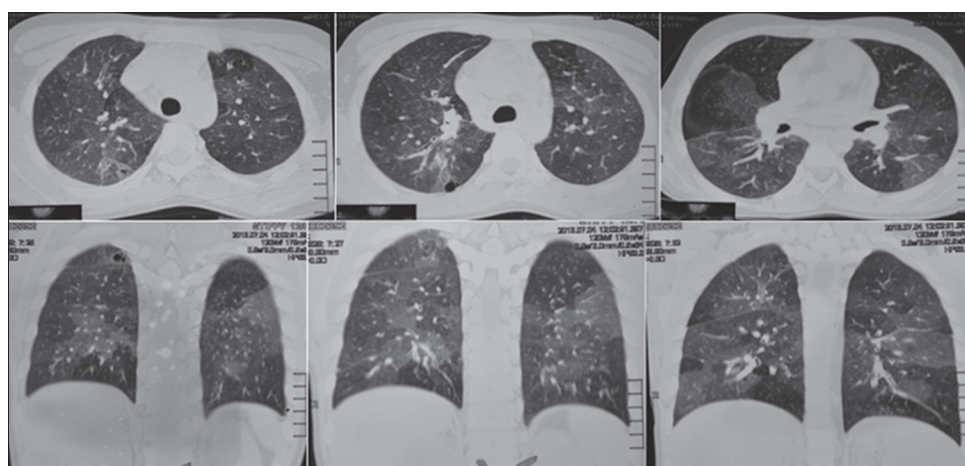


Figure 2: High-resolution computed tomography (HRCT) chest images of a 10-year-old female patient, who had a CD4 cell count as low as 89 cells/ μ l and *Aspergillus fumigatus* was isolated from her sputum. HRCT chest images show extensive bilateral ground glass opacities are seen with scattered areas of normal and less involved lung parenchyma resulting in mosaic pattern. Small cystic lesions are seen in right upper lobe posterior segments

Imaging findings of *Cryptococcus* infection of the chest are varied and non-specific. Reticular or reticulonodular infiltrates are the most common pattern.^{9,10} Solitary or multiple nodules, often up to 4 cm in diameter, are seen

in around 30%. A biopsy is usually required for diagnosis. Cavitations occur less frequently in AIDS-related disease compared to immune competent hosts, usually appearing early in the course of the illness, when the level of immune

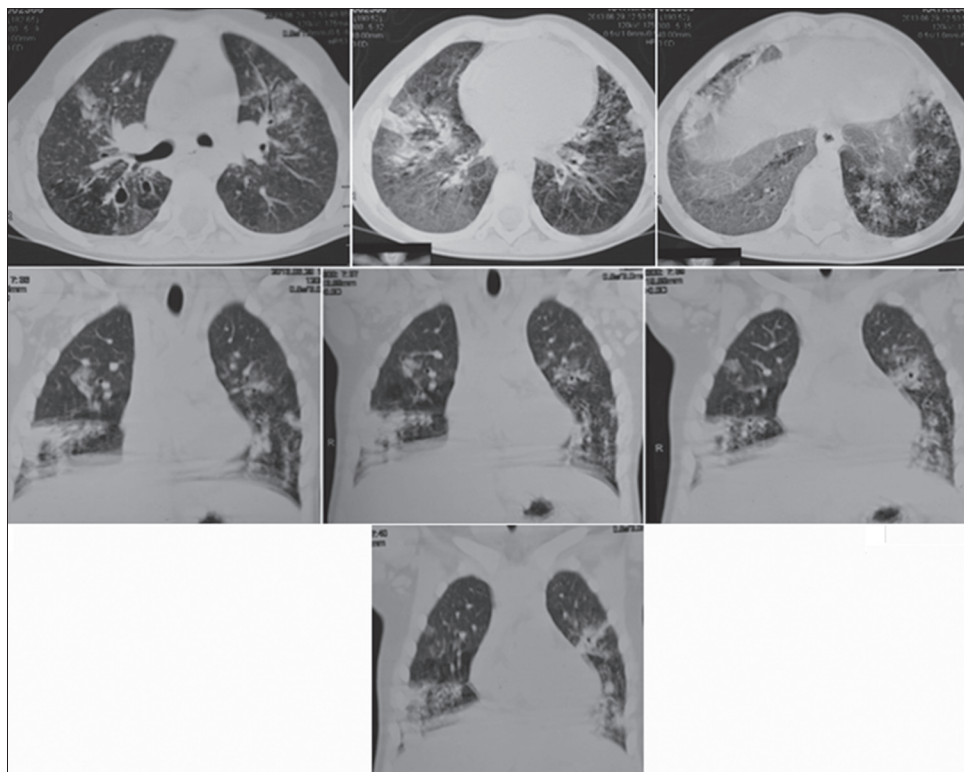


Figure 3: High-resolution computed tomography (HRCT) chest images of a 5-year-old female patient, who had a CD4 cell count as low as 99 cells/ μ l and *Aspergillus fumigatus* was isolated from her sputum. HRCT chest images show cystic and traction bronchiectasis, peribronchial cuffing, branching nodules and ground glass appearances are seen in the bilateral upper lobes predominantly in the anterior segments. Similar lesions are seen in the posterior basal segment of bilateral lower lobes. Multiple small nodules with subtle peripheral halo are seen in bilateral upper lobes. Intra and interlobular septal thickening with ground glass appearance is seen predominant in lateral basal segments bilaterally. No significant lymphadenopathy is seen

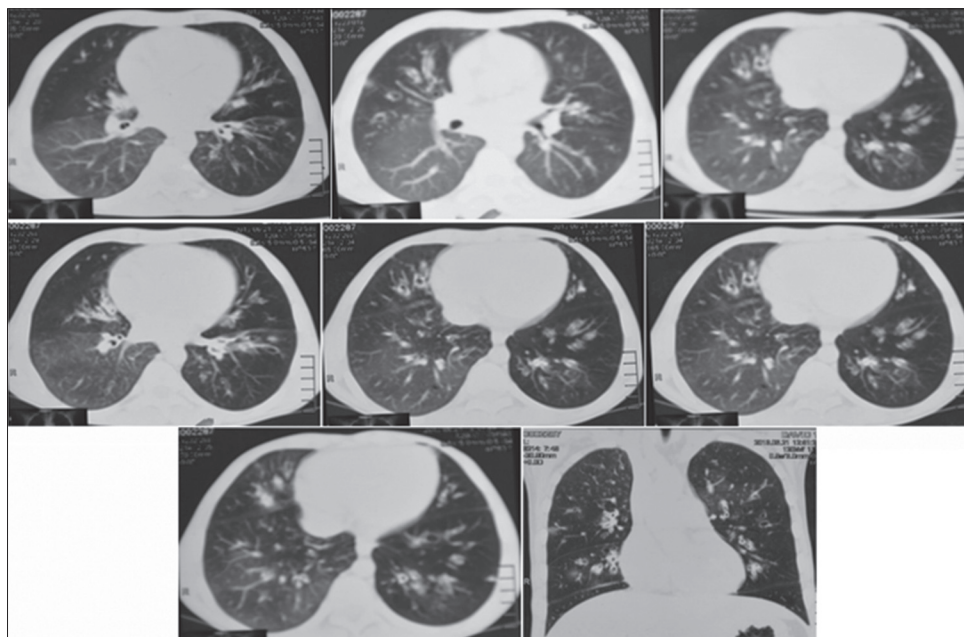


Figure 4: High-resolution computed tomography (HRCT) chest images of a 5-year-old male patient, who had a CD4 cell count as low as 124 cells/ μ l and *Cryptococcus neoformans* was isolated from his sputum. HRCT chest images show cystic and cylindrical bronchiectasis with peribronchial cuffing predominantly involving in the bilateral lung upper and lower lobes with scattered ground glass appearance in the bilateral lung fields

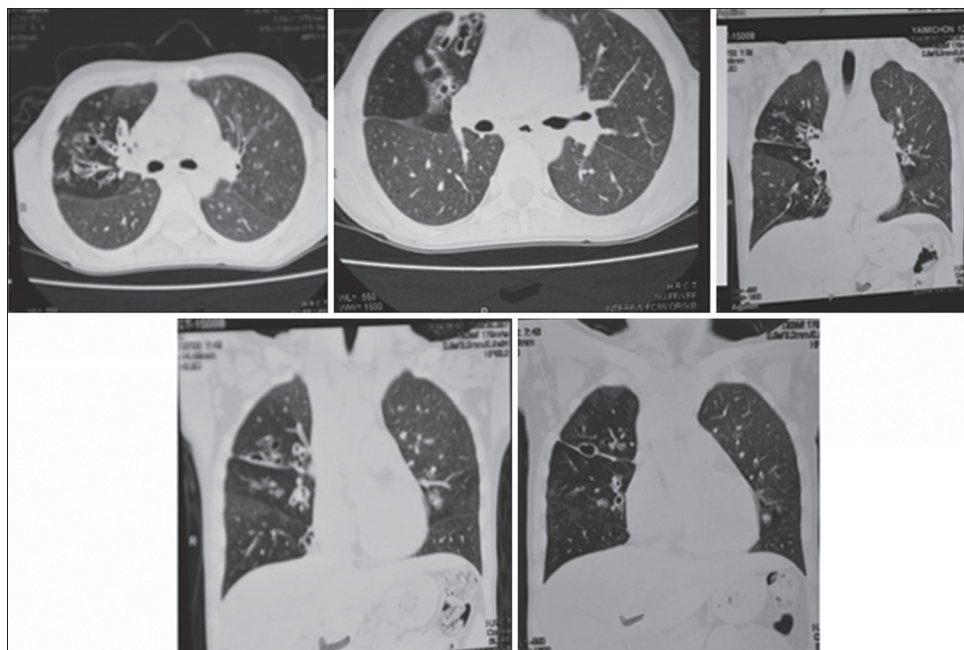


Figure 5: High-resolution computed tomography (HRCT) chest image of a 12-year-old female patient, who had a CD4 cell count as low as 104 cells/ μ l and *Cryptococcus neoformans* was isolated from her sputum. HRCT chest images show air trapping mosaic and ground glass opacities attenuation associated with cystic and cylindrical bronchiectasis predominantly in the upper lobes of right lung. Subpleural interstitial thickening pulmonary fibrosis also noted in the right apical-posterior segment. Left lingual subsegmental cystic bronchiectasis is seen with air trapping mosaic attenuation

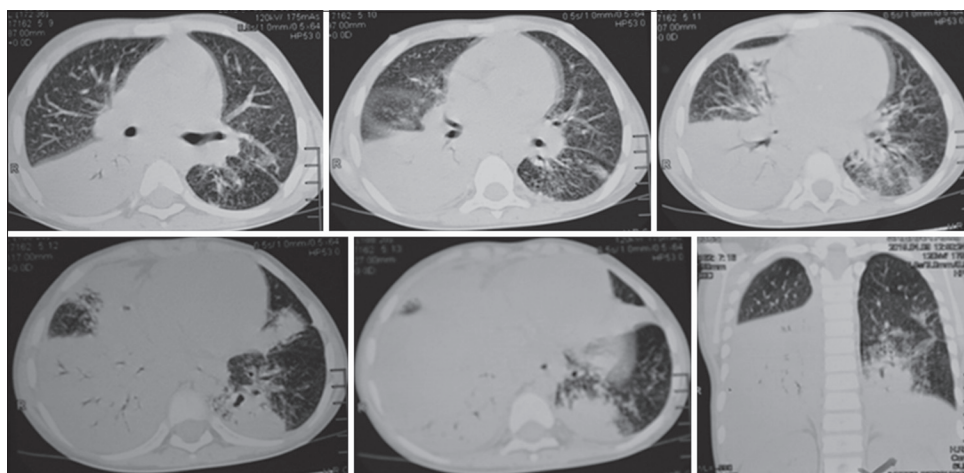


Figure 6: High-resolution computed tomography (HRCT) chest image of a 7-year-old female patient, who had a CD4 cell count as low as 154 cells/ μ l and *Candida albicans*, *Aspergillus* was isolated from her sputum. HRCT chest images show lobar consolidation with the presence of air bronchogram in right lower lobe of the lung. Segmental areas of consolidation are seen in the medial segment of middle lobe, inferior lingual segment and posterior basal segment of left lower lobe. Diffused ground glass opacity of the visualized lung field with patchy normal areas is seen

suppression is mild.^{6,9,10} Less frequent manifestations of *Cryptococcus* infection of chest include adenopathy effusion, consolidation, millary nodularity and GGO and chest wall abscess.^{6,9} The classic appearance is of bilateral symmetric perihilar or diffuse interstitial opacification, which may be reticular, finely granular or ground-glass in appearance. If left untreated, this may progress to alveolar consolidation in 3 or 4 days. Infiltrates clear within 2 weeks but in a proportion, infection will be followed by coarse reticular

opacification and fibrosis.¹¹ The presence of large nodules and visualization of halo-sign are most suggestive of fungal infection.

The HRCT images of two pulmonary candidiasis in this study show lobar consolidation, dense attenuating parenchymal lesions with air bronchogram, traction bronchiectasis, ground glass appearances (GGO), and centrilobular nodules.

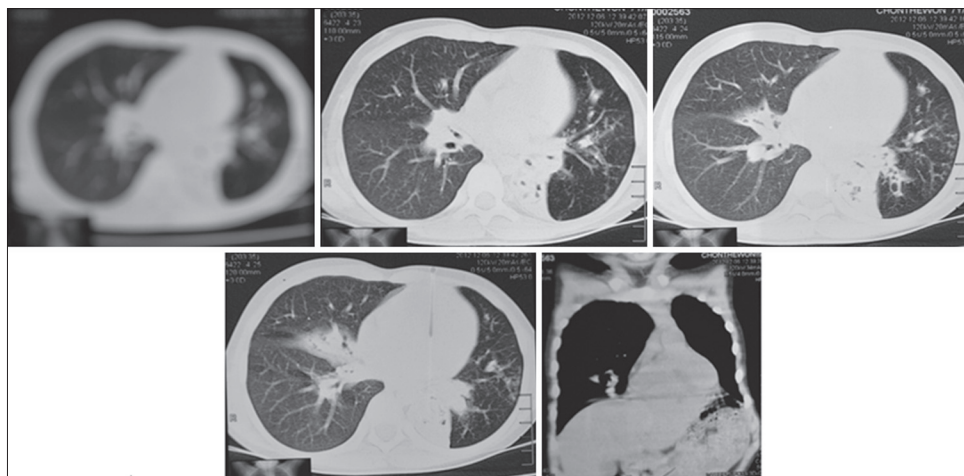


Figure 7: High-resolution computed tomography (HRCT) chest images of a 7-year-old female patient, who had a CD4 cell count as low as 120 cells/ μ l and isolated *Candida albicans Aspergillus* from sputum. HRCT chest images show parenchymal dense attenuative lesions with air-bronchogram involving the superior segment of the left lower lobe. Another wedge shaped dense attenuating parenchymal lesion is also seen in medial segment of right middle lobe

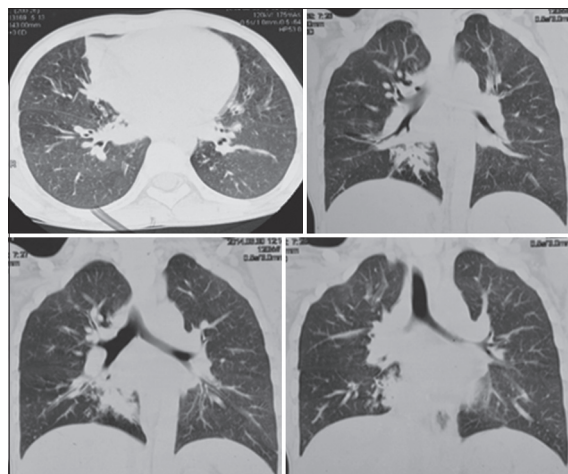


Figure 8: High-resolution computed tomography (HRCT) chest images of a 13-year-old male patient, who had a CD4 cell count as low as 320 cells/ μ l and fungal element was not isolated from his sputum. HRCT chest images show a wedge shaped parenchymal lesion in medial segment of right middle lobe seen suggestive of consolidation

In some studies, the HRCT chest typical findings of pulmonary candidiasis are nodules with halo sign. This feature is almost identical to that of invasive pulmonary aspergillosis (IPA), and it is often difficult to distinguish. The nodules of pulmonary candidiasis are usually smaller than those in IPA. In the endobronchial spread, centrilobular nodules, tree-in- bud pattern and peribronchial consolidation are seen.

The HRCT image of a 13-year-old male patient out of the selected 8 children shows a wedge shaped parenchymal lesion in medial segment of right middle lobe seen suggestive of consolidation but fungal element cannot be isolated from the sputum of the patient.

CONCLUSION

Digital clubbing, chronic cough and extensive crackles in chest were the strong clinical findings suggestive of invasive fungal lung infections among the HIV-infected children. HRCT chest may be considered for these patients with high index of suspicion for fungal chest infections. HIV-positive children with fungal infections of the lung were significantly associated with low CD4 cell counts below 200 cells/ μ l, the mean of lowest CD4 cell counts was 137.87 cells/ μ l (± 76.53). This may be due to either delay in starting ART as per the latest national ART guideline of CD4 cell count which was increased from 200 to 350 cells/ μ l or getting resistance to ART during treatment, especially with poor adherence to ART. HRCT chest findings of pulmonary fungal infection were diverse but some characteristic HRCT chest findings were highly suggestive of pulmonary fungal infections in immunocompromised patients. Regular pre ART CD4 cell count every 6 months, early initiation of ART, strict adherence to ART and early diagnosis of treatment failure of ART as per the national ART guideline will be one of the best options for prevention of fungal chest infections.

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