

## IMAGING THORACIC MANIFESTATIONS IN HIV INFECTED PATIENTS



**Medicine**

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### ABSTRACT

Acquired Immunodeficiency Syndrome (AIDS) was first recognized as a clinical entity in 1981. Since then, many changes have been noted in the dographics, complications, and treatment of this worldwide epidemic. HIV infected patients suffer from a number of infectious and non-infectious complications through their life span due to their immune compromised state. Pulmonary disorders, particularly respiratory infections, remain an important cause of morbidity and mortality among HIV-infected individuals, even in the current era of potent antiretroviral therapy. Chest radiography is usually the first imaging test obtained for the assessment of an HIV-infected individual with respiratory symptoms followed by chest CT that is highly sensitive in detecting and characterizing various infectious and non-infectious conditions that afflict an HIV positive individual. The spectrum of imaging findings varies with the etiology and patient's immune status. We studied the various thoracic manifestations in HIV-infected patients by chest radiography and CT with special emphasis on imaging pattern recognition in order to facilitate early diagnosis and treatment of these conditions.

### INTRODUCTION

Despite the development of effective antiviral therapy and better prophylaxis of opportunistic infections, pulmonary complications of HIV/AIDS still remain an important cause of mortality and morbidity. A wide spectrum of disease conditions affects HIV positive patients depending on the level of their immune compromise (1,2). These include both infectious and non-infectious conditions with considerable overlap in their clinical and radiological manifestations. In this study we evaluated the spectrum of thoracic imaging findings in HIV infected patients by radiography and CT with special emphasis on pattern recognition in early identification of the disease process (3-5).

### AIMS AND OBJECTIVES

To evaluate the imaging spectrum of thoracic manifestations in HIV infected patients and to identify disease specific imaging patterns using chest radiography and CT.

### MATERIALS AND METHODS

This prospective observational study was conducted over a period of 12 months (June 2015 to May 2016) following approval by the institutional, ethical and scientific committees. Thirty-one adult HIV positive cases with clinical suspicion of thoracic disease, referred to the radiology department from various clinical specialties were included in the study. A written informed consent of the patients was obtained for their inclusion in the study and imaging workup.

Chest radiographs were obtained for all cases followed by Contrast enhanced CT/HRCT of chest performed on 16-slice MDCT (Brilliance16, Philips Medical Systems, Cleveland, USA). The chest radiographs and CT images were analyzed based on the imaging patterns observed in each case. The diagnosis was finally confirmed by clinical and laboratory (microbiology, pathology, biochemical) findings wherever possible.

### OBSERVATIONS AND RESULTS

A total of 31 HIV positive patients with thoracic manifestations were included in the study. Of these 21 were males and 10 females with ages ranging from 24 years to 67 years.

The chief presenting complaints were fever in 74% of cases, cough in 45%, dyspnea in 61% of cases and chest pain and reduced appetite in 9.6% each.

A number of infectious and non-infectious conditions manifesting as thoracic disease were observed in our study. (Table-1)

**TABLE/FIG -1 SPECTRUM OF THORACIC MANIFESTATIONS IN HIV PATIENTS**

DISEASES	NUMBER (N=31)
INFECTIONS	17
PULMONARY TUBERCULOSIS	5
BACTERIAL PNEUMONIA	4
PNEUMOCYSTIS PNEUMONIA	1
FUNGAL INFECTION	
NEOPLASTIC	
CARCINOMA	2
LYMPHOMA	2
MISCELLANEOUS	2
EMPHYSEMA	2
BRONCHIECTASIS	

The spectrum of infections observed in our study group varied with different levels of immune compromise as reflected by the CD4 counts of patients. (Table - 2)

**TABLE/FIG -2 INCIDENCE OF VARIOUS INFECTIONS AT DIFFERENT CD4 COUNTS**

CD4 COUNT	PULMONAR Y TB	BACTERIAL PNEUMONI A	PCP	FUNGAL	DISSEMINATE D TB
>500					
200-499	4	1			1
100-199	7	2	1	1	4
50-100	2	1			
<50	4	1	3		2

Tuberculosis was the commonest infection in our study group with the following imaging findings as seen on chest radiography and CT (Table-3&4)

**TABLE/FIG -3 IMAGING PATTERNS IN PULMONARY TUBERCULOSIS**

PATTERN	RADIOGRAPHY	%	CT	%
CONSOLIDATION	3	17.6	4	23.5
FOCAL	1	5.9	2	11.8
DIFFUSE				
CAVITATION	2	11.8	5	29.4
GROUND GLASS OPACITIES			6	35.3
NODULES	5	29.4	10	58.8
LYMPHADENOPATHY	5	29.4	15	88.2
FIBROSIS	5	29.4	6	35.3
BRONCHIECTASIS	3	17.6	6	35.3
PLEURAL EFFUSION	4	23.5	8	47.1

**TABLE/FIG -4 HRCT PATTERNS IN TUBERCULOSIS AT DIFFERENT CD4LEVELS**

HRCT PATTERN	CD4 <50	CD4 50-100	CD4 100-199	CD4 200-499
CONSOLIDATION	1(5.9%)		1(5.9%)	1(5.9%)
FOCAL	2(11.8%)			
DIFFUSE				
NODULES	1(5.9%)		3(17.6%)	1(5.9%)
CENTRILOBULAR		2(11.8%)		2(11.8%)
PERILYMPHATIC				
RANDOM	1(5.9%)			
TREE IN BUD				
CAVITATION		2(11.8%)	2(11.8%)	
GROUND GLASS DENSITY	2(11.8%)	2(11.8%)	2(11.8%)	
LYMPHADENOAPHTHY	4(23.5%)	1(5.9%)	4(23.5%)	2(11.8%)
PLEURAL EFFUSION	1(5.9)		1(5.9%)	2(11.8%)

**IMAGING PATTERN IN PNEUMOCYSTIS INFECTION**

A total of 4 cases of Pneumocystis Pneumonia were observed in our study group. Presence of ground glass opacities was the most common pattern seen on radiographs (50%). On CT the most common pattern seen was ground glass density in all 4 patients (100%), followed by lymphadenopathy (50%)and cystic change in one patient (25%)

**IMAGING PATTERN IN BACTERIAL INFECTIONS**

A total of five cases of bacterial pneumonias were encountered in our study. At radiography, focal consolidation was the most common pattern seen (60%) followed by nodules and lymphadenopathy (40 % each) and pleural effusion in 20% of cases. On CT the most common pattern seen was nodules in 80% of cases, followed by consolidation, lymphadenopathy and pleural effusion in 60 % each.

**IMAGING PATTERN IN FUNGAL INFECTION**

Only one case with fungal infection of the lung (proven as aspergillosis) was seen. This case presented with multiple nodules on radiography as well as CT. A few of the nodules on CT showed cavitation and presence of 'halo sign' resulting from ground glass attenuation around the nodules.

**NON-INFECTIOUS MANIFESTATIONS IN HIV PATIENTS**

These included 2 cases of biopsy proven adenocarcinoma of the lung. One case presented with a thick walled cavity lesion and the other with a peripheral lung mass and adrenal metastasis. In addition, in addition, two cases of Non-Hodgkin's lymphoma were observed and these presented with mediastinal and axillary lymphadenopathy.

Non-infectious non-neoplastic conditions were also observed in a few cases and these included centriacinar /paraseptal emphysema in 2 cases and cystic bronchiectasis in 2 patients. (Table-5)

**TABLE/FIG -5 IMAGING SPECTRUM IN VARIOUS DISEASE CONDITIONS**

Pattern	TB (17)	Bacteri al (5)	PCP (4)	Fungal (1)	Carcino ma (2)	Lympho ma (2)	Total (31)
Consolidati on	4	2	3	-	-	-	9
CXR	8	4	3	-	-	-	15
CT							
Cavitation	2	-	-	-	1	-	3
CXR	2	-	-	-	1	-	3
CT							
Nodules	4	1	-	-	-	-	5
CXR	6	3	-	1	-	2	12
CT							
Nodule with halo	-	-	-	-	-	-	-
CXR	-	-	-	1	-	-	1
CT							
Tree in bud pattern	-	-	-	-	-	-	-
CXR	3	-	-	-	-	-	3
CT							
Ground glassing	-	-	2	-	-	-	2
CXR	6	2	4	-	-	-	12
CT							
Lymphaden opathy	5	2	0	-	1	0	8
CXR	15	3	2	-	2	2	24
CT							
Pleural effusion	4	2	0	-	1	-	7
CXR	9	4	1	-	1	-	15
CT							
Fibrosis	5	-	-	-	-	-	5
CXR	7	-	-	-	-	-	7
CT							
Bronchiecta sis	2	-	-	-	-	-	2
CXR	6	-	-	-	-	-	6
CT							

**DISCUSSION**

A total of 31 HIV positive cases with thoracic symptoms were evaluated by chest radiography and CT after careful clinical and laboratory investigations in order to reach a definitive diagnosis. Out of the 31 patients included in our study, 21 were males (67%) and 11 were females (33%). Most of our patients were in the age group of 30-49 years. Kumaraswamy et al (6) have observed a similar age and

gender distribution in their larger study of 549 HIV positive patients from the Indian subcontinent.

Our study comprised of patients with variable levels of immune compromise as assessed by the CD4 count. More than two-thirds of our cases had CD4 counts below 200. Out of the 31 cases in our study, 11 were on ART but no statistically significant difference in the mean CD4 count was observed between this group and the others not receiving ART. This could be attributed either to the recent initiation of therapy or non-compliance by patients.

The commonest presenting symptom in our study group was fever in 74% of cases followed by dyspnea in 61 %, cough in 45 % and chest pain and reduced appetite in 9.6% each.

#### SPECTRUM OF THORACIC MANIFESTATIONS

In our study Tuberculosis was the most common infection, seen in 17 out of the 31 patients (55%), followed by bacterial pneumonias in 5 patients (16%), pneumocystis jirovecii pneumonia in 4 patients (13%) and fungal infection in one patient. Non-infectious conditions included bronchogenic neoplasms and lymphoma in 2 patients each. Chronic lung diseases like bronchiectasis and emphysema were also observed in a few cases.

The incidence of infections and in particular Tuberculosis has been reported with similar incidence in another larger study from India by Kumaraswamy et al (6) in which Tuberculosis was the most common infection seen in about half of their study group. Other workers like Carolyn M Allen et al (7) and Havlir DV et al (8) have also made similar observations from the western world.

#### CORRELATION OF CD4+ CELL COUNTS WITH VARIOUS PULMONARY INFECTIONS

At CD4 counts above 200 we encountered 4 cases of pulmonary tuberculosis and 1 case of bacterial pneumonia.

At CD4 counts between 100-200, 7 cases of pulmonary tuberculosis were seen with disseminated disease in 4 out of the seven cases. Two cases of bacterial pneumonia and 1 case of PCP were also reported.

At CD4 counts between 50-100, 2 cases of pulmonary tuberculosis and 1 case of bacterial pneumonia were noted.

At CD4 counts below 50, there were 4 cases of pulmonary tuberculosis, 1 case of bacterial pneumonia and 3 cases of PCP.

Overall analysis showed a higher incidence of disseminated tuberculosis in cases with CD4 counts below 200 and the incidence of PCP was highest in cases with CD4 counts below 50.

#### IMAGING PATTERNS IN VARIOUS DISEASES TUBERCULOSIS

In the present study a total of 17 cases out of 31 had tuberculosis. Of these 17 patients, 8 were on antiretroviral therapy (ART). The median CD4 count in patients on ART was 150 and in patients not on ART was 158 with no statistically significant difference between the median CD4 counts of the two groups.

In our study nodules was the most common pattern seen in pulmonary tuberculosis (58.8%) followed by consolidation and ground glass attenuation (35.3%) and cavitation (29.4%).

Most cases had multiple small nodules 1-5mm in size. Only one case had larger nodules more than 1cm in size. Nodules were common in upper lobes (in 6 out of 10 cases) and involved both upper and lower lobes (in 4 cases) all of which had disseminated disease. None of the nodular lesions showed cavitation or calcification in our cases.

A centrilobular pattern of distribution of nodules was noted in 4 cases with a tree in bud pattern in 3 cases. Similar observation have been made by Feng et al (9) and Hatipoglu et al (10) in their studies

and they observed that centrilobular nodules and tree in bud sign were common HRCT findings in active pulmonary Koch's. Similar observation have also been made by SS Atwal et al (11) in their study describing HRCT findings of lung spectrum in symptomatic adult HIV positive patients.

Consolidation in tuberculosis was seen in 6 cases (35%) and was focal (unilobar /multilobar) in 4 out of 6 cases and diffuse multilobar in 2 cases.

Cavitation was noted in 4 patients and was thick walled in all patients. All patients with cavitation had CD4 count less than 200. This observation differs from those made by Atwal et al (11) in their study where all patients with cavitation had CD4 > 200.

In our study lymphadenopathy was seen in mediastinal and/or hilar location in 88% cases of tuberculosis on CT and out of these nearly half of the cases showed central necrosis. R. Prasad et al (12) in their study have made similar observations.

Conglomerated necrotic lymph nodes were seen in mediastinum and upper abdomen in 2 patients both of which had disseminated disease with CD4 counts below 50 in both cases.

Disseminated tuberculosis was seen in 7 of our patients and most of these cases with disseminated infection had CD4 counts less than 200.

Fibrotic lesions were seen in 6 cases (35.3%) suggestive of old healed infective process in addition to active pathology. Bronchiectasis was noted in 2 cases (11.8%) with presence of bronchial wall thickening in both.(Figs 6-9)

#### BACTERIAL PNEUMONIAS

In our study 5 out of 31 cases (16%) had bacterial pneumonias.

Chest radiography showed focal consolidation as the most common finding (60%) in bacterial pneumonias followed by nodules and lymphadenopathy (40% each) and pleural effusion in 20% of cases.

On CT, the most common pattern seen was nodules in 80% of cases, followed by consolidation, lymphadenopathy and pleural effusion in 60% each.(Fig 10)

The CD4 count in these patients varied from 27 to 250 cells/mm<sup>3</sup>, with a mean count of 140 cells/mm<sup>3</sup>. The findings of our study correlate well with other studies by Brecher CW et al (13), Magnenat et al (14) and Boiselle PM et al (15) as regards the spectrum of imaging findings in bacterial pneumonias in HIV positive patients.

#### PNEUMOCYSTIS PNEUMONIA (PCP)

A total of four patients in our study were diagnosed to have Pneumocystis pneumonia. All of these patients were severely immunocompromised with a mean CD4 count of 38 cells.

On CT, the most common pattern seen was ground glass density in 4 patients (100%),(Fig 11) followed by lymphadenopathy (50%) and cystic change in one patient (25%). Strangely one case showed extensive ground glass densities with reverse halo sign. In 2 cases with PCP multiple small sub centimeter size lymph nodes were also noted in mediastinum. Findings of our study are similar to those reported by James F Gruden et al (16), Phillip M. Boiselle et al(15) and many others in existing literature.

#### FUNGAL INFECTION

We encountered one case with fungal pulmonary infection. This was a 57 year old male with a CD4 count of 130 and radiographic findings of multiple nodular opacities in both lungs. CT in addition demonstrated cavitation within the nodules and 'halo sign' in majority of nodules.(Fig 12) The findings in this case are consistent with those described by Aquino et al (17) and Carolyn M. Allen et al (7). They observed that all morphologic forms might coexist in the

same patient.

### BRONCHOGENIC CARCINOMA

Two cases of bronchogenic carcinoma were seen in our study, one patient was a 65-year-old male with CD4 count of 158 and radiographic evidence of an ill defined pleural-based mass lesion in left lower lung field. CT confirmed a heterogeneously enhancing mass lesion abutting pleural surface in left lower lobe with an enhancing nodule in left upper lobe with nodular enhancing lesions in both adrenal glands suggestive of metastatic deposits.(Fig 13) The second case was a 55yr old male with a CD4 count of 238, with evidence of a thick walled cavity in right lower lobe seen on chest radiograph. CT demonstrated an irregular thick walled cavity with rim enhancement. (Fig 14)

In both cases the diagnosis of bronchogenic carcinoma was confirmed by CT guided biopsy. The findings of our study are similar to those made by White CS et al (18), Sigel K et al (19) and Fishman JE et al (20) in their study of thirty HIV-positive individuals with bronchogenic carcinoma. Eighteen of these patients (60%) had peripheral lung tumors and Most of these tumors were adenocarcinomas.

### LYMPHOMA

In our study group, 2 cases had Non Hodgkin's lymphoma. One patient had mediastinal widening on chest radiograph and CT confirmed significant mediastinal and axillary lymphadenopathy. The other patient had no significant abnormality on the chest radiograph but CT showed significant axillary lymph nodes and small centrilobular nodules in lower lobe of the left lung.(Fig 15) Both these patients also had hepatosplenomegaly. Eisner MD et al (21) in their retrospective study involving 38 patients of HIV with NHL involving lungs or pleura observed that pulmonary nodules, lobar infiltrates and lung mass were the most common parenchymal abnormalities along with pleural effusion and thoracic lymphadenopathy. Thoracic lymphadenopathy is much more common than previously believed. Lee KS et al (22) also describe that pulmonary nodules are the most common radiographic or CT finding in AIDS related lymphoma (ARL).

When adenopathy is the sole finding in a patient with AIDS the major diagnostic consideration should be ARL with HIV adenopathy as an alternative consideration. Furthermore, ARL should be considered when axillary adenopathy is present regardless of associated findings. Histopathology gives a definite diagnosis.

### NON- INFECTIVE, NON-NEOPLASTIC CONDITIONS

We encountered 2 cases each of COPD (emphysema and bronchiectasis) in our study. The 2 cases with emphysema showed features of hyperinflation on chest radiographs and presence of centriacinar and paraseptal emphysematous changes in both lungs on CT. Both these patients had past history of smoking.

Bronchiectatic changes were seen in 2 cases with bilateral cystic bronchiectasis in one patient and early tubular bronchiectasis in the second case. Both patients had CT findings of bronchial wall thickening and centrilobular nodules with significant mediastinal lymphadenopathy in one case. The case with early tubular bronchiectasis and centrilobular nodules was confirmed to have opportunistic bacterial infection whereas the other case with mediastinal lymphadenopathy was confirmed as tubercular in etiology. Clausen E et al (23) in their Cross-sectional study of 121 HIV infected patients found that radiographic chest abnormalities remain common in HIV-infected individuals with emphysema, nodules, and bronchiectasis being the most common.

### CORRELATION OF CHEST RADIOGRAPHIC FINDINGS WITH CT

A comparative evaluation of chest radiographic and CT findings in our study reveals that CT is both more sensitive and more accurate in evaluation of HIV positive patients with thoracic symptoms as it not

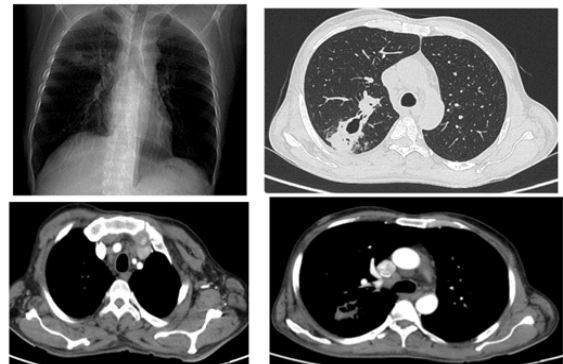
only detects lesions that are occult on radiography but also helps in etiological diagnosis based on CT imaging patterns. Furthermore CT has a high negative predictive value in excluding active pulmonary disease.

Nodules were detected in 16 ( 51%) cases by CT and 10 (32 %) cases by radiograph ,consolidation was detected by CT in 12 cases ( 38.7%) and by radiograph in 10 cases (32%), Lymphadenopathy was detected by CT in 21 patients and by radiograph in 9 patients, Pleural effusion was detected by CT in 13 cases and by radiograph in 6 cases, Cavitation was detected by CT in 7 cases and by radiograph in 3 cases, Fibrosis was detected by CT in 6 cases and by radiograph in 5 cases. Bronchiectasis was detected by CT in 7 patients and by radiograph in 3 patients. Tree in bud appearance, halo and reverse halo signs and cystic change in lung parenchyma were findings picked up exclusively on CT. Overall CT was found to be much more informative than plain radiographs in most of our cases.

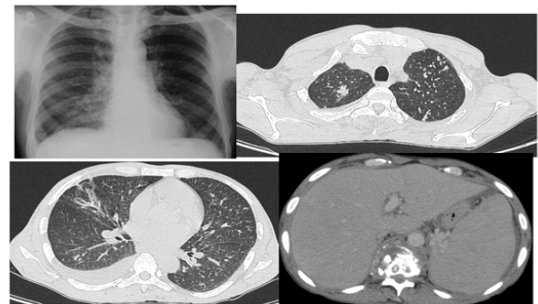
Results of our study were consistent with other series in literature including one by Im JG et al (24) which also describes CT as more sensitive over chest radiography in the detection and characterization of both subtle localized or disseminated parenchymal disease and mediastinal lymphadenopathy.

### CONCLUSION

Imaging plays a pivotal role in management of HIV patients with thoracic diseases. Interpretation of imaging studies is based on pattern recognition and must be read in conjunction with demographic clinical and laboratory data. Chest radiography remains the mainstay of thoracic imaging but CT plays an important role in establishing accurate diagnosis when radiographic findings are equivocal or non-specific. HRCT is a highly sensitive tool for detecting lung parenchymal and interstitial lesions and allows better characterization of the lesions. By developing a practical approach based on various imaging patterns radiologists can generate a clinically relevant and succinct diagnosis thereby improving patient care. Despite the development of effective antiviral therapy and better prophylaxis of opportunistic infections, pulmonary complications of HIV/AIDS remain an important cause of mortality and morbidity



TABLE/FIG-6 45 Y.M. A CASE OF PULMONARY TUBERCULOSIS WITH CD4 COUNT OF 174 CHEST RADIOGRAPH SHOWS CONSOLIDATION WITH BREAKDOWN IN RIGHT UPPER ZONE. CT SHOWS CAVITATION AND MEDIASTINAL LYMPHADENOPATHY



TABLE/FIG 7 48Y/M WITH DISSEMINATED TUBERCULOSIS AT A CD4 COUNT OF 109 CHEST RADIOGRAPH SHOWS LINEAR OPACITIES IN RIGHT MID ZONE WITH PROMINENCE OF RIGHT HILUM AND CT SHOWING CENTRILOBULAR NODULES AND BRONCHIECTATIC CHANGES IN RIGHT MIDDLE LOBE WITH POTT'S SPINE SEEN AS DESTRUCTION OF VERTEBRAL BODY AND ASSOCIATED PRE AND PARAVERTEBRAL ABSCESS.

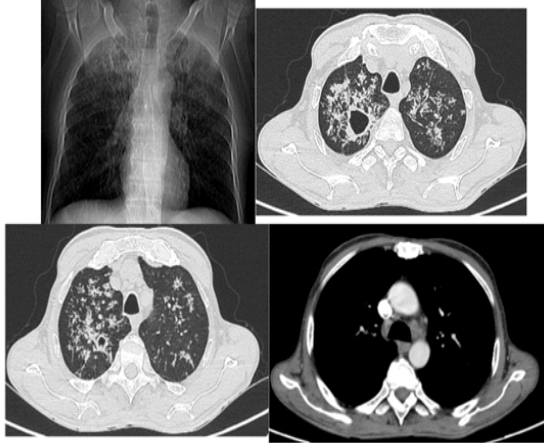




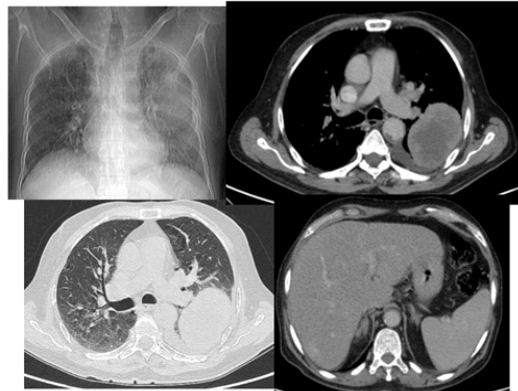
TABLE/FIG 8- 35 Y/M WITH CD4 196. CHEST RADIOGRAPH REVEALS NO SIGNIFICANT ABNORMALITY. CT SHOWS FINE CENTRILOBULAR NODULES AND MULTIPLE CONGLOMERATED NECROTIC ABDOMINAL LYMPH NODES IN A CASE OF DISSEMINATED TUBERCULOSIS



TABLE/ FIG 12- 57Y/M WITH CD4 130 TOPOGRAM SHOWING MULTIPLE NODULAR OPACITIES IN THE LEFT LUNG. CT SHOWS MULTIPLE NODULES IN LEFT LUNG, FEW OF THEM SHOWING CAVITATION AND HALO SIGN IN A CASE OF ASPERGILLUS INFECTION



TABLE/FIG 9- 65Y/M WITH CD4 COUNT OF 78. CHEST RADIOGRAPH SHOWS RETICULONODULAR OPACITIES IN BILATERAL UPPER ZONES. CT SHOWS MULTIPLE CENTRILOBULAR NODULES WITH A 'TREE- IN- BUD' APPEARANCE AND A CAVITY IN RIGHT UPPER LOBE IN A CASE OF ENDOBRONCHIAL TUBERCULOSIS.



TABLE/FIG 13-- 67Y/M WITH CD4 OF 158. TOPOGRAM SHOWING A LARGE ILL DEFINED OPACITY IN LEFT LUNG. CT SHOWED A LARGE HETEROGENOUSLY ENHANCING PERIPHERAL MASS LESION IN LEFT LUNG WITH LEFT PLEURAL EFFUSION AND INVOLVEMENT OF ADRENALS. CT GUIDED BIOPSY CONFIRMED THE LESION AS POORLY DIFFERENTIATED CARCINOMA



TABLE/FIG 10- 60Y/F WITH CD4 COUNT OF 192. CT SCANOGRAM SHOWS MULTIFOCAL CONSOLIDATION IN RIGHT LUNG, CT CONFIRMS CONSOLIDATION WITH AIR BRONCHOGRAM IN RIGHT LUNG IN A CAE OF BACTERIAL PNEUMONIA

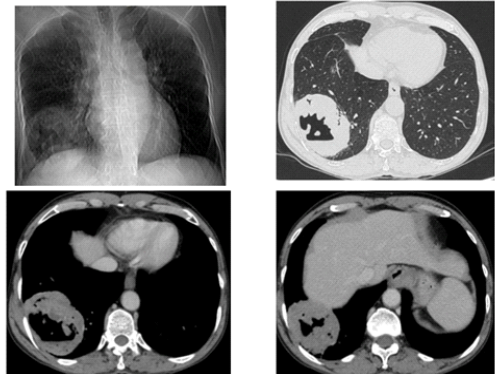
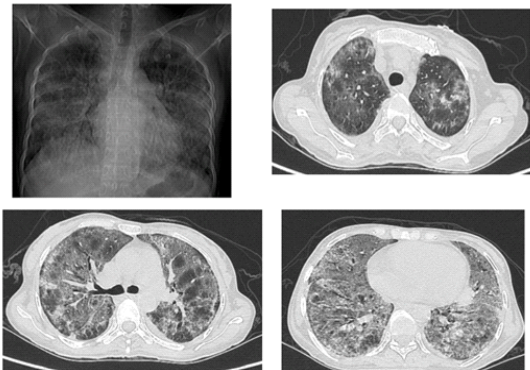


TABLE FIG 14- 55Y M CD4 238. RADIOGRAPH SHOWS A THICK WALLED CAVITY IN RIGHT LOWER ZONE. CT SHOWED A THICK WALLED CAVITY WITH HETEROGENOUSLY ENHANCING RIM AND BIOPSY CONFIRMED THE LESION TO BE AN ADENOCARCINOMA.



TABLE/FIG 11- 44Y/F WITH CD4 COUNT OF 7 AND PNEUMOCYSTIS PNEUMONIA. SCANOGRAM SHOWS ALVEOLAR AND RETICULAR OPACITIES IN BOTH LUNGS IN MID AND LOWER ZONES. CT SHOWS DIFFUSE GROUND GLASS DENSITIES WITH INTERSTITIAL THICKENING IN BOTH LUNGS

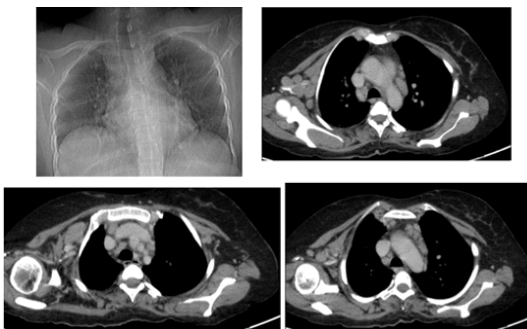


TABLE FIG 15- 45YM WITH CD4 COUNT OF 48. CT SCANOGRAM SHOWING MEDIASTINAL WIDENING. CT CONFIRMED RT AXILLARY AND MEDIASTINAL LYMPH NODES IN A BIOPSY PROVEN CASE OF NON-HODGKIN'S LYMPHOMA

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