Spectrum of Respiratory Involvement in COVID 19 Era; An Overview

Ayushi Jain[1], DhruvTalwar[2], Sunil Kumar[3]

Medical Intern[1], Post Graduate Resident[2], Professor and Head[3], Department of Medicine, Jawaharlal Nehru Medical College, Datta Meghe Institute of Medical Sciences (Deemed to be University), Wardha, Maharashtra, India

Abstract

Introduction: COVID 19 is novel coronavirus which first struck the world 5 months ago and became pandemic in such a short time. China suffered first and then this virus spread to more than 180 countries. Primary organ involved is lungs and the commonest cause of fatality is respiratory failure[1]. Although, its new virus, related to two earlier deadly viruses e.g. SARS and MERS but has already caused tremendous morbidity and mortality in nations heavily affected by it. This short review highlights about lung involvement due to this virus and to make our healthcare professionals aware about what to expect by learning from the experience of the countries where it has already affected thousands of civilians.

Methodology: This review article was written with systematic literature review with the help of data search machine like Pubmed, Scopus, Web of Sciences and google scholar. In this article observational study wand case reports were included. Most of the data were taken from China, Italy and Spain.

Review Findings: COAVID 19 affects lung parenchyma in moderate to severe disease causing pneumonia which starts as unilateral lower lobe, commonly on right side, peripheral ground glass infiltrates and rapidly spreads to involve both lungs with bilateral, multifocal consolidations[2]. Pleural effusion and pericardial involvement may occur. In severe cases the disease progresses to Acute Respiratory Distress Syndrome accounting for >90% of mortality. Pathology of lungs showed diffuse alveolar damage with organization and fibrosis as disease progresses.

Conclusions: COVID 19 a novel coronavirus which is presently a pandemic has affected the world in manner reminiscence of 1918 Spanish flu. Lung involvement as community acquired pneumonia is determinant of mortality, which spreads exponentially to develop sever respiratory failure.

Keywords: *COVID 19, Lymphopenia, Pneumonia, Respiratory failure,Acute lung Injury, Diffuse alveolar damage.*

Introduction

Since December 2019, in Wuhan province of China there was spate of cases of community acquired pneumonias where no etiological agent could be identified. Later, a novel enveloped RNA betacorona virus was isolated currently labelled as SARS CoV2 (Severe Acute Respiratory Syndrome Coronavirus -2) being ~80% similar in structure to earlier seen during Severe Acute Respiratory Syndrome(SARS CoV 2) with mortality ~ 25% in 2002. Clinical presentation mimicked creating a public health emergency followed by WHO declaring it as a pandemic on March 11,2020. Disease though appears to have better survival as compared to SARS CoV-2 (now called COVID 19: Corona Virus Disease 2019) but respiratory involvement & failure

Corresponding Author:
Ayushi Jain
Medical Intern, Department of Medicine, Jawahalal Nehru Medical College, Datta Meghe Institute of Medical Sciences (Deemed to be University), Wardha, Maharashtra, India
e-mail: jaayushi1013@gmail.com

appears to be the driver for mortality and significant residual effects[1].

COVID 19 has swept various nations over a short span of 3 months. In this pandemic, various countries are at different parts of the epidemic curve. Some has seen the worst while other are at the beginning of the curve. India is still at early part with < 10,000 positive cases and fewer than 300 deaths (at the time of going to print), our physicians need to be aware of the implications of the disease which is driven by lung involvement. Review of this nature would not only enhance our medical professionals but also help them to enhance their skills to manage these patients better, translating into less poorer outcomes of this disastrous illness.

Methodology

We review available literature on lung involvement in COVID 19 available on Medline and PubMed data search engines, but little is reported so far considering that its new virus and has crippled the healthcare system of most of the countries where it has reached in significant numbers. More data will emerge when clinicians get time to publish their experiences but at present only few research papers from China and Italy formed source of this review.

Review Findings: Clinical presentation of COVID 19 include, fever, cough are common symptoms as in other viral illnesses but GI symptoms though uncommon but indicate propensity of virus to affect gut, makes it distinct from influenza prevailing at this time in most of the countries including India. Lung involvement on CXR was rarely absent in severe cases at the time of presentation (3%) to the hospital but was also present in 18% of patients with non-severe disease and 15% patients admitted with non-severe disease did progress to severe COVID19[1]. However, during hospitalization >91% of COVID 19 patients received physician diagnosis of pneumonia followed by ARDS in 3.4% and shock in 1%. It's also clear from early experience with COVID 19 cases in Wuhan that chances of missing pneumonia diagnosis were higher in cases admitted with non-severe illness. Hence, its recommended to have high suspicion of pneumonia in view of propensity of disease to cause it and fatal outcome associated with it. CT chest done at the time of admission revealed abnormalities in 86% of patients.

Therefore, it's clear that lung involvement in COVID 19 is the denominator for severity of the disease and subsequent mortality and morbidity.

Epidemiological Features of Lung Involvement in COVID 19: Pneumonia is the most common lung manifestation of COVID 19. Classically pneumonia is divided as community acquired vs hospital acquired pneumonia and COVID 19 causes community acquired pneumonia. However, transfer of infection from a case of CAP in hospital to another non-infective patient can occur (unconfirmed reports from Italy & Spain) but still too early to comment on at present. Approximately 24% patients had underlying comorbidities e.g. Diabetes mellitus, Chronic kidney disease, hypertension, stroke, etc. but reached 37% in cases with severe disease. Recent found lesser survivors in hypertensives vs normotensives (34% vs 52%) patients, study postulated that hypertensives on Angiotensin Converting Enzyme (ACE) inhibitors could be the underlying factor predisposing them to higher mortality as ACE-2 receptors besides being vasopeptidase are also coronavirus receptor and hence, are more likely become sicker.

In last 2 decades, there is shift in etiology of community acquired pneumonia, indicating rise in viral infections particularly by the spurt of Influenza infections including H1N1. COVID19 is the next etiological agent where the transmission was initially from animals to human and later human to human by respiratory droplets and direct contact. Potential route of transmission via gut or salivary secretions is under investigation. Interestingly, 8.9% patients of COVID 19 had no pneumonia or did not develop pneumonia later too, raising the role asymptomatic carriers in community.

Clinical Features of COVID 19 Lung Involvement: COVID 19 pneumonia study showed that mean age of patients was 52.8+ 12.2 years with 62% being males. All had symptoms at the diagnosis of disease (this could be due to the study design where inclusion criteria was diagnosis of pneumonia on CT scan). Depending upon clinical presentation, pneumonias are classified as *Typical or Atypical* depending upon whether the presentation is typical with fever, cough, sputum, pleuritic chest pain, breathlessness and blood tinged sputum or atypical with fever, myalgia, headache and minimal or no respiratory symptom, delaying the diagnosis of pneumonia in such cases. The retrospective studies showed that COVID 19 patients with severe disease and pneumonia had presentation with fever, cough with sputum and breathlessness, more like typical

pneumonia but other non-specific symptoms ofmuscle pains and fatigue were also common (1/3rd) and rarely patients had abdominal pain and diarrhea, where early CXR would make diagnosis clear. Worsening vitals and oxygenation at room air predict progression to pneumonia and can be used monitor patients with mild disease.

Laboratory Features of COVID 19 lung Involvement: Patients with COVID 19 pneumonia showed leukopenia in 20%, however, even if total counts are normal or raised, 80% show lymphopenia in differentials while 50% had low percent lymphocytes. ESR was raised in 2/3rd of patients but hs-CRP was elevated in all (100%).

Radiological Features of COVID 19 Lung Involvement: Chest imaging is an essential tool in diagnosis, assessment of severity, clues to etiology, allocating site of care, prognosis and monitoring the progress of pneumonia. CXR is the first imaging modality however can miss about 10% of pneumonia due to poor resolution of bedside films as well as some areas of lung can't be visualized e.g. retro-cardiac and retro-diaphragmatic regions, CT chest is considered better modality to pick up lung infiltrates[2].

Based on lung involvement on chest imaging, pneumonias are labeled as Lobar, bronchopneumonia or interstitial pneumonia. Progression to ARDS(Acute Respiratory Distress Syndrome) leads to development of imaging s/o acute lung injury. COVID 19 pneumonia. Based on CT scan findings in COVID 19 patients, single lesion (lobar/segmental infiltrate) was seen 16% while 84% had multiple lesions (bronchopneumonia). It was observed that multiple lesions were seen when CT scans were done late after the onset of symptoms (6.6+4.0 days vs 2.2+1.8 days), suggesting that it's the evolution of disease and COVID 19 lung disease progresses from single infiltrate to widespread multiple infiltrates in both lungs (Fig 1).

Fig 1 CXR showing bilateral multifocal airspace shadows

Single lesions were seen in 90% in right side with right lower lobe being the commonest to be involved and left lingular segment was the only case in left lung. When multiple lesions were on imaging, there was no case with central region involvement as all cases showed either peripheral (78%) or combined peripheral and central infiltrates in rest of the cases. CT scan study showed that lower zones as well as posterior areas were more frequently and severely involved in comparison to the rest of the lung fields.

CT patterns of Lung Involvement in COVID 19: CT scan involvement of lungs in COVID 19 may show various changes in lungs but may involve all compartments in thorax except mediastinal lymph nodes[3,4]:

A Lung parenchymal involvement: Air space changes (Fig. 2 A to G).

- Ground glass abnormalities (GGO's) – 40%
- Consolidations – 34%
- Reticular opacities with GGO's
- Vacuolar sign
- Microvascular dilatation sign
- Fibrotic streaks
- Sub pleural line of involvement or sparing

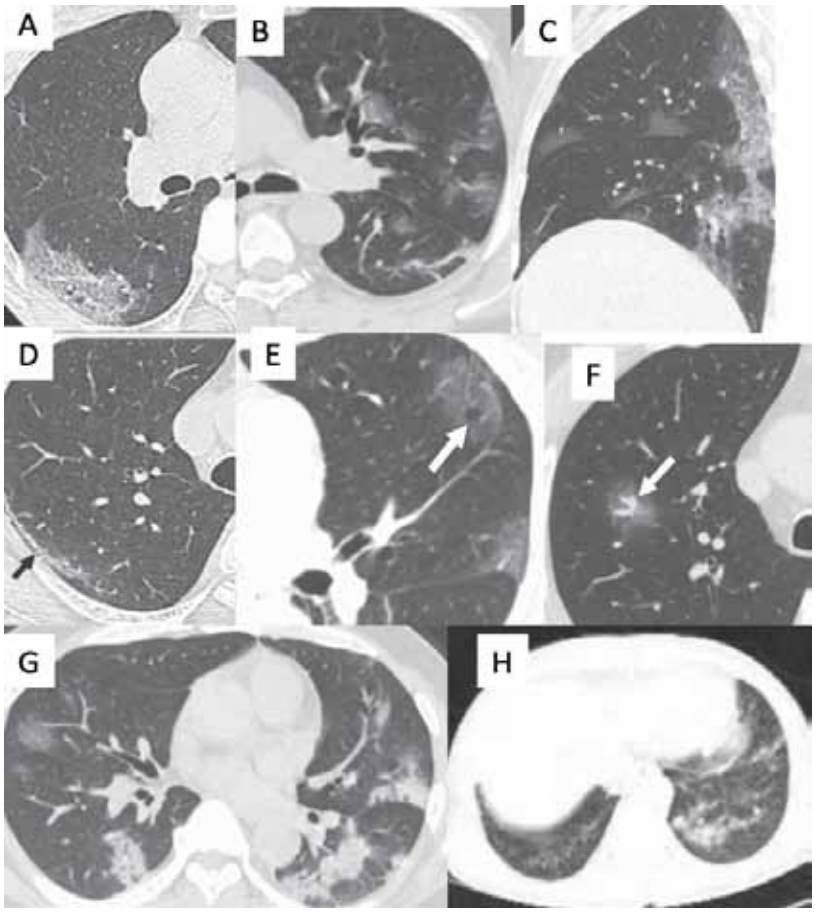

Fig 2: A GGO, B Fibrotic lesion, C Peripheral & posterior distribution, D Sub pleural spared lesions, E Vacuolar sign, F Microvascular dilatation sign, G Consolidation with multifocal widespread lesions H GGO's with linear streaks

B Airway involvement:

Bronchial changes: seen as air bronchogram – 73%

- Dilatation
- Distortion
- Air trapping

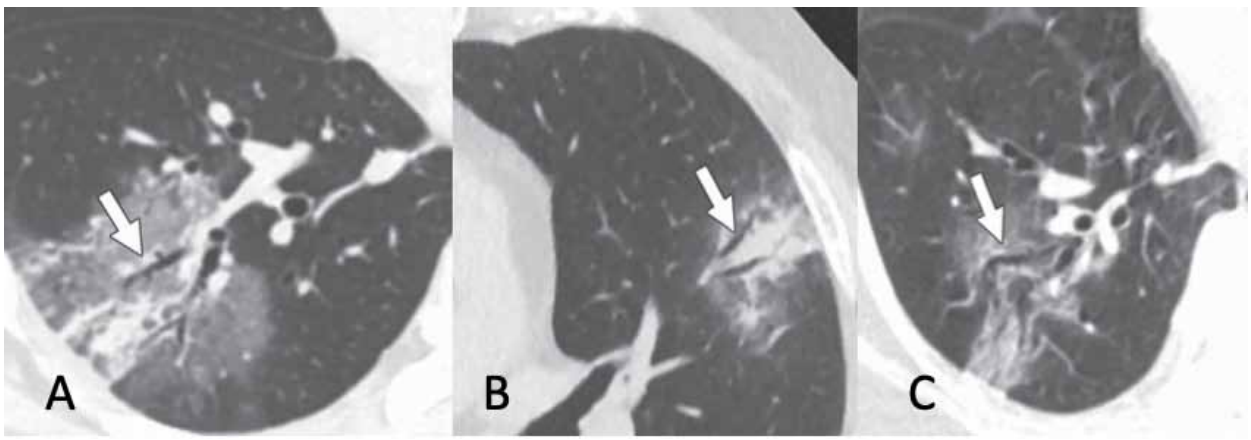

Fig 3 A Airway dilatation, B Air bronchogram, C airway distortion marked with arrow

C Pleural Involvement:

- Pleural effusion – 10%
- Pleural thickening – 48%
- Pleural retraction

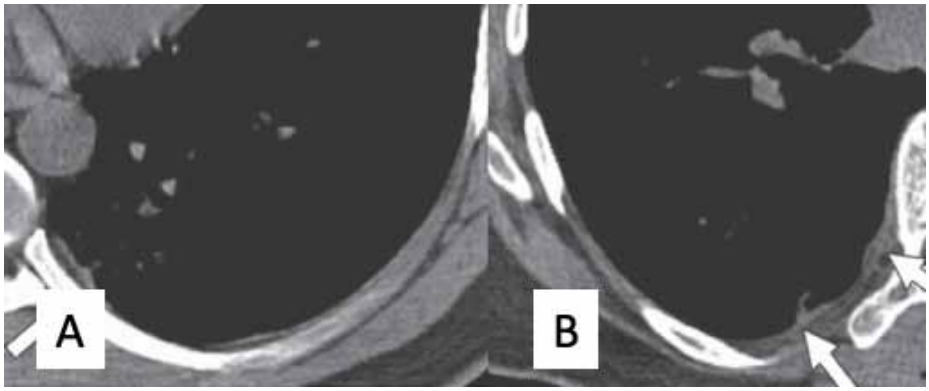

Fig. 4: A pleural effusion, B pleural thickening and retraction marked with arrow

As the disease progresses, it was found that GGO's, airway and pleural abnormalities were less prominent (after 7 days of illness)

CT scans showed that COVID 19 on imaging may show diverse and mixed findings of pneumonia and a clinician needs to be aware of these findings and should realize that such findings are evaluating very fast with time becoming multi focal and diffuse. Bilateral infiltrates or rapidly progressive lung lesions indicate poor prognosis.

Lung Pathological Findings in COVID 19 Pneumonia: Autopsy studies in COVID 19 patients showed features similar to the cases earlier reported with SARA CoV and MERS pneumonias as lungs showed picture of ARDS with desquamation of Type 2 pneumocytes and formation of hyaline membranes (Fig 5). Since, lung may show different stages of ARDS, interstitial mononuclear infiltrates may be seen in early phase while interstitial fibrosis in later stage. Intra-alveolar organization with multinucleated syncytial cells with enlarged atypical pneumocytes showing viral cytopathic changes[5]. In late stage disease, interstitial thickening with intra-alveolar fibroblastic plugs seen. In some casesthrombo-emboli was also detected and Microthrombi were regularly found within small lung arteries, occasionally within the prostate, but not in other organs.[6]

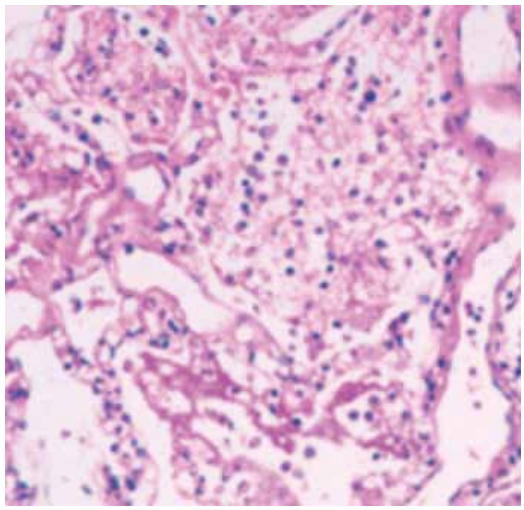

Fig 5: Intra-alveolar organization with lymphocytic infiltration of Interstitium and multinucleate syncytial cells

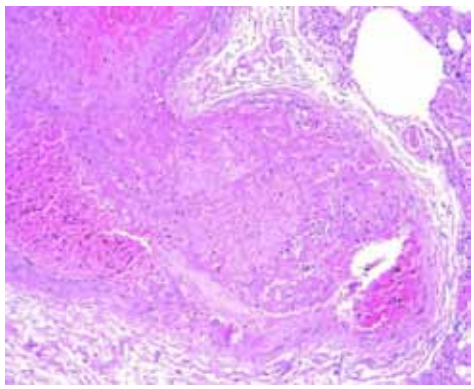

Fig 6 Pulmonary thromboembolism in a patient of Covid 19

Treatment & Outcome with COVID 19 Pneumonias: Follow up data from patients with COVID 19, shows that nearly 50% patients needed oxygen therapy while 6% requires mechanical ventilation. Non-invasive ventilation has been used in less severe cases while systemic corticosteroids have been used mostly in severe cases. Hydroxychloroquine (HCQ) and Azithromycin has been used by some centers to treat severe pneumonia but trails are still ongoing. [7]

Once patient develops ARDS they are managed on standard guidelines for ARDS management. Rarely ECMO (Extra Corporal Membrane Oxygenation) has been used in severe cases with yet undefined success. However, latest communications from Italy suggested to use early mechanical ventilation, low PEEP, prone ventilation in refractory hypoxemia. NIV in contrast led to higher mortality which could be delay in initiation of respiratory support or mechanical injury produced by large volumes of tidal volume in lungs. High frequency nasal cannula for providing higher fiO2 with led to some success in cases with moderate hypoxemia.

Frequentreasons for admittingpatients of COVID 19 to the Intensive Care Unit were hypoxemic respiratory failure leading to mechanical ventilation, hypotension requiring vasopressor treatment, or both.[8]

Melatonin is also being studied as a potential adjuvant treatment due to its anti-inflammatory effects.[9]

Even though physiological models of SARS-CoV infection show a theoretical benefit of using ACEI/ ARB these findings are yet to found in the studies done practically.[10] Research efforts regarding production of vaccine is being conducted increasingly and are already being reported in various distinct studies.[11,12,13.]

Various factors like smoking also effect the progression of the disease as smoking is most likely associated with the negative progression and adverse outcomes of COVID-19.[14]

Rather than specific pattern on CXR or CT scans with CT scans being much more sensitive to diagnose pneumonia·Studies show that More Consolidation in Upper Lungs on Initial CT Increases the Risk of Adverse Clinical Outcome in COVID-19 Patients .[16]Wheras progressive stage on CT is the most common stage with negative co relation with Spo2 and lymphocyte count.[17]Vital signs monitoring is key to early diagnosis of pneumonia and effectively use triage**.** Human CoVs remains a great threat for global public health. However, human beings have not gained enough experience in previous battles with SARS and MERS and thus appropriate measures and studies need to be conducted to control this lethal pandemic with a great destructive potential.[18,19,20]

Conclusions

Pneumonia is the most common determinant of severity and outcome in COVID 19 and at present evidence favors its presentation as typical, community acquired pneumonia with constitutional features suggesting viral etiology. Radiologically it manifests as progressive bilateral, multifocal pneumonia, though may initially begin as localized GGO peripheral infiltrates. Such findings may be non-specific and at present h/o travel or contact with COVID 19 may be more indicative of underlying etiology.

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Conflict of Interest: Nil.

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