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Review Article

A Characteristic Radiological Finding in COVID-19 - New Disease Accounting for Vats Reverse Pulmonary Edema Sign

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Abstract

COVID-19 (coronavirus disease 2019) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), as of 29th May, 2020 the total global numbers of corona virus are 5,991,938 with death toll of 365,343 and increasing day by day with as such no sign of slowing till now.

Objective of current article is to share experience of a large tertiary care center hospital where a significant numbers of Chest X rays are showing bilateral middle and lower lung zones patchy air space shadowing predominantly peripheral in location suggestive of dense pneumonic changes/thrombotic obliteration of micro vessels in the periphery with sparing of apex and the CP angles. CT scan done for these patients usually shows multiple bilateral ill-defined areas of ground glass opacities, predominantly peripheral in location. Denser in the peripheral areas and with bilateral basal infiltrates and atelectatic bands and reticular infiltrates.

Possible hypothesis for the VATS reverse pulmonary edema pattern of COVID-19 pts:

1. Endothelial injury: Pulmonary micro thrombi, and wedge infarcts, thrombotic obliterative micro and major vasculitis and capillaritis.
2. V/Q dependence: Causing lesion to remain localized in the infra hilar region or sparing the apex as exemplified as relative more perfusion in the mid and lower zone and less perfusion in the upper zone hence the primary site of insult remains in the mid and lower lung zone, however is the in just is significant then it may involve entire lungs however then also in majority of cases the apex are usually relatively spared
3. More small and micro vessels capillaries in the peripheral region and secondary to significant microvascular thrombosis, it presents as peripheral infiltrates/consolidation occupying primarily mid and lower zones. These pathological findings are further supported by the increases in oxygenation after putting the patient in prone position, the ventilated patients because after proning the blood gets diverted to the areas where there is free perfusion with resultant better V/Q matching and improvement in hypoxemia.

Conclusion: These findings are reasonably sensitive and specific that's with the characteristics history and risk factors viz (sick contact or travel history) diagnosis could be made with very good certainty and the treatment could be started empirically pending the RT PCR reports which usually takes 1 - 2 days hence saving the time for the initial treatment and favourable outcomes.

Keywords: *COVID-19 (Coronavirus Disease 2019); Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)*

Introduction

COVID-19 (coronavirus disease 2019) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), as of 29th May, 2020 the total global numbers of corona virus are 5,991,938 with death toll of 365,343 and increasing day by day with as such no sign of slowing till now [1].

From February 2020, onwards, I personally have encountered more than 1700 cases of confirmed or highly suspected COVID-19 and all patients were investigated by routine labs, CXR and COVID testes were done by RT PCT swab assay. When we retrospectively analyses the CXR findings, we found that out of these patients approximately 29% were having no or minimal infiltrates, approximately 52% of patients had moderate infiltrates involving less the 50% of the lung parenchyma, however around 19% patients had severe disease involving almost all the lobes radiologically defined as extensive disease or ARDS.

The most striking finding we observed that majority of severe disease patients had CXR findings of Photonegative pulmonary edema with classical sparing of the perihilar region and airspace opacities, described as consolidation or ground glass opacities (GGO) [2,3]. The distribution of infiltrates are most often bilateral, and mid and lower zone predominant, peripheral, Sparing the central part and para cardiac part and apex and basal areas and CP angles classical of reverse pulmonary edema (Photonegative pulmonary edema).

As per the available literature, chest radiographs are typically the first-line imaging modality (although less sensitive or less specific than chest CT) used for patients with suspected COVID-19.

Many studies have revealed that Chest radiographs may be normal in early or mild disease. Of patients with COVID-19 requiring hospitalization, 69% had an abnormal chest radiograph at the initial time of admission, and 80% had radiographic abnormalities sometime during hospitalization [3]. Findings are most extensive about 10 - 12 days after symptom onset with worsening to ARDS [3]. The most frequent findings are airspace opacities, whether described as consolidation or less commonly, GGO [2,3]. The distribution is most often bilateral, peripheral, and lower zone predominant [2,3]. In contrast to parenchymal abnormalities, pleural effusion is rare (3%) [3].

The Radiological Society of North America (RSNA) has released a consensus statement endorsed by the Society of Thoracic Radiology and the American College of Radiology (ACR) that classifies the CT appearance of COVID-19 into four categories for standardized reporting language as follows [4]:

- **Typical appearance**
    - Peripheral, bilateral, GGO +/- consolidation or visible intralobular lines ("crazy paving" pattern).
    - Multifocal GGO of rounded morphology +/- consolidation or visible intralobular lines ("crazy paving" pattern).
    - Reverse halo sign or other findings of organizing pneumonia.
- **Indeterminate appearance**
    - Absence of typical CT findings and the presence of
        - Multifocal, diffuse, perihilar, or unilateral GGO +/- consolidation lacking a specific distribution and are non-rounded or non-peripheral.
        - Few very small GGO with a non-rounded and non-peripheral distribution.

- **Atypical appearance**
    - Absence of typical or indeterminate features and the presence of
        - Isolated lobar or segmental consolidation without GGO.
        - Discrete small nodules (e.g. centrilobular, tree-in-bud).
        - Lung cavitation.
        - Smoother interlobular septal thickening with pleural effusion.
- **Negative for pneumonia**: No CT features to suggest pneumonia, in particular, absent GGO and consolidation.

In RSNA/ACR statement they concluded that at this time, CT screening for the detection of COVID-19 is not recommended by most radiological societies. However, we anticipate that the use of CT in clinical management as well as incidental findings potentially attributable to COVID-19 will evolve. We believe it important to provide radiologists and referring providers guidance and confidence in reporting these findings and a more consistent framework to improve clarity. Clear and frequent communication among health care providers, including radiologists, is imperative to improving patient care during this pandemic.

In view of the vast limitation and the nonconclusive statement of performing CT scan as screening tool as mentioned above for all suspected or confirmed cases, I would like to throw light on an interesting finding in the CXR.

Objective of current article is to share experience of a large tertiary care center hospital where a significant numbers of Chest X rays are showing bilateral middle and lower lung zones patchy air space shadowing predominantly peripheral in location suggestive of dense pneumonic changes/thrombotic obliteration of micro vessels in the periphery with sparing of apex and the CP angles. CT scan done for these patients usually shows Multiple bilateral ill-defined areas of ground glass opacities, predominantly peripheral in location. Denser in the peripheral areas and with Bilateral basal infiltrates and atelectatic bands and reticular infiltrates. Usually these patients does not have mediastinal lymph nodes and rarely may have minimal pleural effusion and this radiological presentation on CXR could be Highly suggestive of COVID 19 infection along with consideration of the clinical profile/presentation of hypoxia of patient with history of contact and the RT PCR test could be positive or negative.

Discussion and pathophysiology

The typical radiographic pattern of predominantly peripheral consolidation was first described by Gaensler and Carrington as "the photographic negative of pulmonary edema" and is considered to be characteristic of chronic eosinophilic pneumonia (CEP) [5] although later on pulmonary parenchymal opacities with bilateral peripheral predominance were rarely seen in sarcoidosis [6]. Other causes of reverse or photonegative pulmonary edema pattern include bronchiolitis obliterans organizing pneumonia (BOOP), Churg-Strauss syndrome, bronchioloalveolar carcinoma (BAC) and focal radiation injury of the lung. Early bronchoscopy with Bronchoalveolar Lavage and Transbronchial Lung Biopsy helps to differentiate the above conditions.

To my knowledge, after doing extensive search, I am reported first time in these COVID-19 patients typical, dense opacities with ill-defined margins and without lobar or segmental distribution, peripherally closed to the pleura. These opacities are usually in mid and lower zones and lateral locations sparing the periphery and paracardial and central part of the lung and sparing classically the basal and apical lungs hence resembling reverse pulmonary edema, I called this as a VATS reverse pulmonary edema sign.

Figure 1: *Early VATS Reverse pulmonary edema primarily involving right side and less on left side with bilateral infolate however central part of the lung is relatively clear except few basilar ill-defined in-filtrates in right basal area.*

Figure 2: *(A): Early VATS Reverse pulmonary edema primarily involving right side and more on left side with bilateral infiltrtaes however central part of the lung is relatively clear. (B): The peripharal part of pulmonary consolidation has become more dense.*

When the opacities becomes more confluent and extensive then they may spread in both peripheral and central direction with clinical worsening of the patient leaving the perihilar and paracardial areas uninvolved and looks like typical of photonegative pulmonary edema or VATS reverse pulmonary edema sign with simultaneous worsening of hypoxemia and lab parameters.

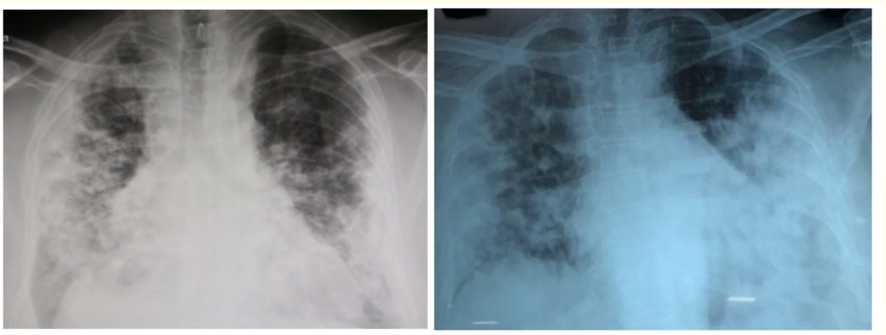

Figure 3: *(A): VATS Reverse pulmonary edema primarily involving right side and less on left side with bilateral infiltrates however, central and apical part of the lung is relatively clear. (B): VATS Reverse pulmonary edema primarily involving left side and less on right side with bilateral infiltrates, however central and apical part of the lung is relatively clear.*

However, if the disease remains uncontained then these may worsen to present like ARDS picture with significant refractory hypoxemia. These opacities take times to resolve unlike CEP which responds dramatically to steroids with clinical and radiological improvement.

Figure 4: *VATS Reverse pulmonary edema primarily involving left side and less on right side with advanced bilateral infiltrates partly sparing the mid central zone and the apical areas of lungs central and apical part of the lung.*

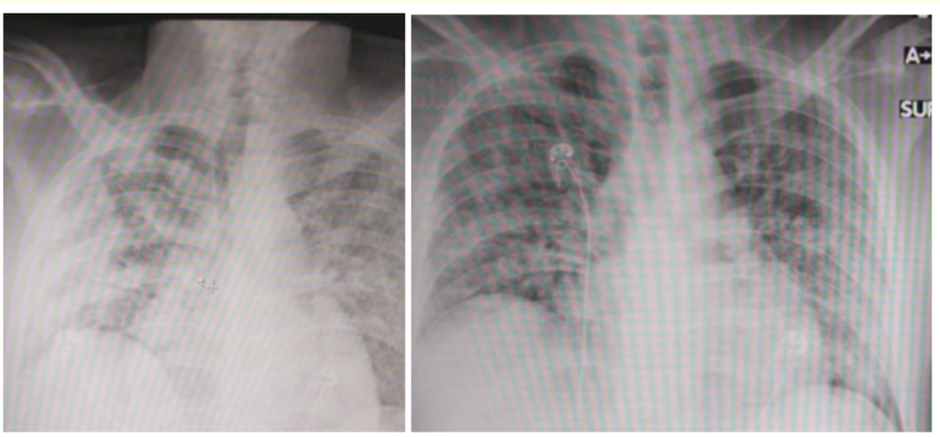

Figure 5: *(A): VATS Reverse pulmonary edema primarily involving right side and less on right side with advanced bilateral infiltrates, partly sparing the mid central zone and the apical areas of lungs and central and apical part of the lung. (B): Same patientt improving after 3 weeks of treatmnet and the consolidation is being replace by fine fibrosis and realtively preservation of lung parenchyma.*

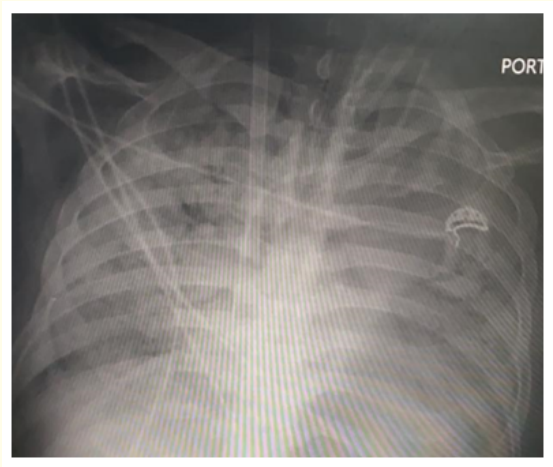

Figure 6: *Severe bilateral infiltartes with hypoxia consistent with ARDS.*

In COVID-19 patients these opacities persist and takes few days to resolve with clinical and lab improvement. This typical radiographic pattern is virtually highly suspicious, reasonably sensitive and specific considering the characteristics history and risk factors viz (sick contact or travel history), labs (high ferritin, high LDH, high Dimer, lymphopenia with normal WBC, hypoxia and RT PCR results even if negative) diagnosis could be made with very good certainty and the treatment could be started empirically pending the RT PCR reports which usually takes 1 - 2 days, Hence I strongly recommend to start empiric treatment based on the available guidelines even pending the RT PCR reports in these in clinically suspected patient having classical photonegative pulmonary edema and thus saving the time for the initial treatment and this could save many lives.

Recently with the ongoing pandemic of COVID-19, we have frequently observed classic pattern of VATS reverse pulmonary edema pattern varying from faint infiltrates to the extensive consolidation at presentation or worsening during the hospital stay from mild, moderate and severe and then lending to ARDS and severe refractory hypoxia.

In our experience of cases of confirmed or very highly suspicious COVID cases approximate prevalence of photonegative pulmonary edema pattern was around 7 - 8% (or may be more, studies are on the way to precisely estimate the CXR findings) in those patients who had radiographic abnormalities at admission, Majority of patients had faint, ill defined, infiltrates primarily in mid and lower zones (approximately 77% of pts) and sometimes moderate or severe consolidation (approximately 15% of pts).

CT scan was done only in minority (only in case where we suspected massive pulmonary embolism or any other coexisting etiology) of our patients because of following reasons (unless absolutely indicated) primarily we focused on the clinical picture + Labs + CXR and COVID test to diagnose pt with COVID-19.

The use of CT as a primary screening tool is discouraged, not least because these studies tended to suffer from selection bias [7-11] with a recent (April 2020) meta-analysis reporting a pooled sensitivity of 94% and specificity 37% [12]. In low prevalence (< 10%) countries, the positive predictive value of RT-PCR was ten-fold that of CT chest [12].

According to a Fleischner Society consensus statement published on 7 April 2020 [13]:

- Imaging is not indicated in patients with suspected COVID-19 and mild clinical features unless they are at risk for disease progression.
- Imaging is indicated in a patient with COVID-19 and worsening respiratory status.
- In a resource-constrained environment, imaging is indicated for medical triage of patients with suspected COVID-19 who present with moderate-severe clinical features and a high pretest probability of disease.

Moreover performing CT routinely for large cohorts of patients carries additional risks [11] like depletion of finite resources, especially PPE due to excessive usage, increased risk of viral transmission (to staff, patients and carers) as COVID-19 positive and negative patients come into close proximity in the radiology department, additional ionizing radiation exposures [11].

The most important pathophysiology of COVID-19 leading to radiological abnormalities although not very clear but based on the knowledge available till now it has 2 steps as follows.

There are 3 sequential phases of COVID-19 clinical and pathophysiology process:

- **Stage 1:** Asymptomatic state (initial 1 - 2 days of infection): The inhaled virus binds to the nasal cavity epithelial cells and starts replicating. Best Diagnosis tools: nasal swap (than oral ones) or both pharyngeal and nasal Although the viral burden may be low, these individuals are infectious.
- **Stage 2:** Upper airway and conducting airway response (next few days): Virus migrates down the lower respiratory tract initiating innate immune response to contain and kill virus by human body (present clinical manifestations).
- **Stage 3:** Hypoxia, ground glass infiltrates, ARDS: virus infects alveolar type II cells: Making diffuse alveolar damage with fibrin rich hyaline membranes mostly in peripheral as I mentioned, lead to more severe scarring and fibrosis, desquamation of pneumocytes and hyaline membrane formation making intrapulmonary shunting. This explains that why deep BAL has a more sensitivity than swabs in stage 2 and especially in stage 3 (hypoxia patients) And more peripheral GGOs in step 3.

Possible hypothesis for the VATS Reverse pulmonary edema pattern of COVID-19 pts

1. Endothelial injury: Pulmonary microthrombi and wedge infarcts, thrombotic obliterative micro and major vasculitis and capillaritis.
2. V/Q dependence: Causing lesion to remain localized in the infra hilar region or sparing the apex as exemplified as relative more perfusion in the mid and lower zone and less perfusion in the upper zone hence the primary site of insult remains in the mid and lower lung zone, however is the in just is significant then it may involve entire lungs however then also in majority of cases the apex are usually relatively spared.
3. More small and micro vessels capillaries in the peripheral region and secondary to significant microvascular thrombosis, it presents as peripheral infiltrates/consolidation occupying primarily mid and lower zones. These pathological findings are further supported by the increases in oxygenation after putting the patient in prone position, the ventilated patients because after proning the blood gets diverted to the areas where there is free perfusion with resultant better V/Q matching and improvement in hypoxemia.

In a recent study from Italy analyzing the postmortem findings of COVID-19 patients found that. The predominant pattern of lung lesions in COVID-19 patients is Diffuse alveolar damage (DAD), as described for the other two coronavirus that infect humans, SARS-CoV

and MERS-CoV. Hyaline membrane formation and pneumocyte atypical hyperplasia are frequently found. The main relevant finding is the presence of platelet-fibrin thrombi in small arterial vessels; this important observation fits into the clinical context of coagulopathy which dominates in these patients and which is one of the main targets of therapy [14]. And these platelet-fibrin thrombi in small arterial vessels; clearly explains the predominant pattern of the VATS reveres pulmonary edema causing obliteration of the micro vessels in the peripheral parts of lung and on CXR presenting as consolidation or VATS reverse pulmonary edema due to thrombotic obliterative micro and major vasculitis and capillaritis.

Biopsy photo published in an Italian study clearly found DAD, hyaline membranes, micro thrombosis, luminal organizing fibrosis, advanced proliferative phase, with interstitial myofibroblastic reaction and residual scattered hyperplastic type II pneumocytes, clearly shows intense inflammatory, prothrombotic, procoagulant and well organized thrombosis in the micro vessels.

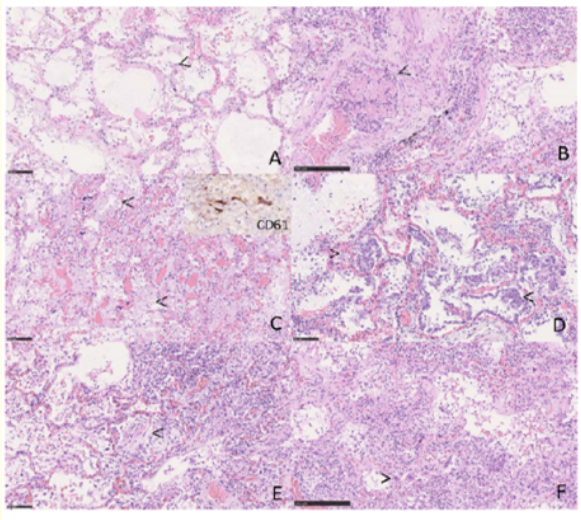

Figure 7: *Lung parenchyma with diffuse alveolar damage [14]. Panel A: Exudative phase with hyaline membranes (arrow); Panel B: Organizing microthrombus (arrow); Panel C: Entrapped megakaryocytes in alveolar capillaries (arrow), high lightened by CD61 (inset); Panel D: Early proliferative phase with many hyperplastic, seldom atypical, type II pneumocytes (arrows); Panel E: Intermediate phase with luminal organizing fibrosis (arrow); Panel F: Advanced proliferative phase, with interstitial myofibroblastic reaction and residual scattered hyperplastic type II pneumocytes (arrow). Hematoxylin-Eosin, OM 10x 14.*

A recent study suggested that COVID-19 is associated with the classical syndrome named disseminated intravascular coagulation (DIC) and the subsequent consumption coagulopathy. Moreover, it has been shown that heparin, beside its anticoagulant effects, also displays an anti-inflammatory action, various immunomodulatory properties, and protects glycocalyx from shedding [15,16].

I strongly suspect that we are dealing with a COVID-19 infection are the ground glass patterned areas, which, even in the initial stages, affect both lungs, in particular the lower lobes and especially the posterior segments, with a fundamentally peripheral and subpleural distribution. These findings are present on chest CT in practically 50% of patients in the first two days; For this, in China, CT is being used as a screening or diagnostic method.

These lesions progress in the following days until they become more diffuse. If they associate with septal thickening, they will present with a crazy paving pattern. In general, they progress in extension and towards the consolidation that is done concomitantly with

the ground glass pattern, which can present a rounded morphology. It is very rare that it is associates lymphadenopathy or cavitation or pneumothorax, as the Middle East respiratory syndrome coronavirus (MERS-CoV) did.

Conclusion

These findings are reasonably sensitive and specific that's with the characteristics history and risk factors viz (sick contact or travel history) diagnosis could be made with very good certainty and the treatment could be started empirically pending the RT PCR reports which usually takes 1 - 2 days hence saving the time for the initial treatment and favourable outcomes.

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