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CASE REPORT

Thromboembolic complications of COVID-19 leading to Chronic Thromboembolic Pulmonary Hypertension (CTEPH)

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A middle-aged woman was diagnosed with Covid 19. Two months later she was referred to respiratory outpatients in view of worsening shortness of breath and decreased functionality. Investigations including a Computed Tomography pulmonary angiogram (CTPA) lead to the diagnosis of an acute right- sided pulmonary embolism, COVID-19, and bacterial pneumonia. Physical examination and echocardiogram revealed associated right heart strain. Further investigations at follow up confirmed the diagnosis of chronic thromboembolic pulmonary hypertension (CTEPH).

The early diagnosis of the underlying CTEPH has allowed the patient to undergo bilateral pulmonary endarterectomy without undue delay. This was followed by intensive physical and respiratory rehabilitation. In turn the patient improved significantly, so much so that on follow up she was asymptomatic, and she was eventually able to regain her previous functional status.

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Chronic thromboembolic pulmonary hypertension (CTEPH) is a complication of pulmonary embolisation with thrombosis in the microvasculature of pulmonary arteries with development of scarring and eventual pulmonary hypertension. It may lead to right ventricular failure, which not only causes impaired functionality but is also associated with a high mortality.[1]

A connection was found between CTEPH and COVID-19 infection. Both conditions are characterised by endothelial dysfunction with subsequent ventilation/perfusion mismatch, vasoconstriction, thrombosis and inflammation.[2] This case emphasises on how CTEPH can and does occur in patients who have tested positive for COVID-19 and how a high index of suspicion is important for early diagnosis and prompt management to prevent long term complications.

CASE PRESENTATION

A middle-aged lady presented with a three-day history of worsening shortness of breath with sudden deterioration. This was associated with an intermittent non-productive cough. The patient also suffered from hypothyroidism and hypertension and was taking thyroxine and amlodipine as treatment. She had denied any hormonal therapy use. Before the symptoms developed, she had lived an active life and was able to carry out strenuous activities effortlessly.

On examination, the patient was found to have a raised jugular venous pressure 5cm above the sternal angle (upper limit-4 cm above sternal angle), a loud pulmonary component of second heart sound, a few fine crepitations at the right base and mild left lower limb oedema. She was able to maintain good oxygen saturations at rest but desaturated down to 85% upon walking a 50m distance.

Investigations

She had tested positive for COVID-19 at home prior this admission. Initial chest x-ray showed a right upper lobe consolidation as well as cardiomegaly for which a course of intravenous antibiotics was given. In view of a D-Dimer of 2672 ng/mL (0-500ng/ml) this was followed by a computed tomography pulmonary angiogram (CTPA). This showed a right sided pulmonary embolism, as well as findings which were highly suggestive of COVID-19 pneumonia concomitant with bacterial pneumonia in the right upper lobe.

In view of cardiomegaly noted on chest x-ray an NT-proB-type Natriuretic Peptide (BNP) blood test was taken which was found to be 9,060pg/mL (5-125pg/ml).

She was treated with antibiotics, oral steroids and was anticoagulated initially with heparin, then switched to rivaroxaban. She improved and was eventually discharged.

Three months later the patient was reviewed at outpatient and noted to still be suffering from shortness of breath and decreased functionality despite being on anticoagulation therapy.

As part of the work-up spirometry, plethysmography and diffusing capacity of the lungs for carbon monoxide were carried out results illustrated in Table 1, Table 2.

This was followed up with an echocardiogram which showed a pulmonary pressure of 93mmHg (8 - 20mmHg), severely dilated right ventricle and right atrium and a D-shaped left ventricle, in keeping with right sided heart strain. Moreover inferior vena cava was noted to be dilated and was able to collapse less than 50%. An echocardiogram in 2018 had shown normal left ventricular dimensions and global systolic function as well as normal valvular function.

Table 1 *Spirometry*

	Before salbutamol:	After Salbutamol:
FEV	11.96L (72 % predicted)	12.11L (78 % predicted)
FVC	2.79L (83 % predicted)	2.79L (83 % predicted)
FEV1/FVC	87%	94%

Table 2 *Plethysmography and DLCO values*

Parameter	Value
DLCO, mL/mmHg/min	17, 74% predicted
Alveolar volume (VA,) L	4.56
DLCO/VA, mL/mHg/min/L	3.72 (90% predicted)
Total lung capacity, L	5.24 (108% predicted)
Vital capacity, L	2.90 (90% predicted)
Residual Volume, L	2.34 (137% predicted)

Repeat CTPA showed signs of pulmonary arterial hypertension secondary to chronic thromboembolic disease. Pulmonary trunk was dilated to 3.4cm and was larger than the ascending thoracic aorta. A concentric thrombus was lining the right lower lobe pulmonary artery. Subsegmental peripheral pulmonary artery branches manifested sharp cut-off/pruning. These findings were noted to be consistent with chronic thromboembolic pulmonary hypertension (CTEPH).

Patient was then referred to a tertiary centre were CTEPH diagnosis was further confirmed using right heart catheterisation and Ventilation perfusion scanning. Right heart catheterisation showed a severe pulmonary hypertension of the precapillary type with severe increase in vascular resistance.

She was also investigated from a haematological point of view in view of the polycythaemia on blood investigations. Janus kinase 2 V617F (JAK 2V617F) mutation came back as negative. This was followed up by checking for JAK 2 EXON 12 which was also negative. Serum Erythropoietin (EPO) was taken which was normal at 16.3mU/mL (4-26mU/mL), thus not in keeping with polycythaemia Rubra Vera in which case one would expect a suppressed EPO A final impression of secondary polycythaemia in the context of CTEPH was reached.

Treatment

At the time of initial diagnosis of acute pulmonary embolism 3 months ago, the patient was started on rivaroxaban 15 mg twice daily for 3 weeks, which was then switched to 20mg daily thereafter. She was also started on bumetanide at 1mg daily which was later increased to twice daily to control the symptoms of fluid overload because of a right sided heart failure.

The case was discussed with a tertiary centre and it was agreed that the patient would benefit from surgical endarterectomy. Bilateral pulmonary endarterectomy was carried out successfully at a tertiary centre abroad. This involved short intermittent intervals (7-10) minutes of hypothermic circulatory arrest altered with reperfusion periods of at least 5 minutes during which clearance of obstructions in 27 segments on the right and 9 on the left was performed.

After the procedure, she was transferred to the intensive care unit, where she contracted pseudomonas pneumonia which was in turn treated with a course of antibiotics. During her admission at the tertiary centre, she underwent an intense physical and respiratory rehabilitation program.

She was transferred back to the caring hospital and was kept as an inpatient for intense rehabilitation. After the procedure the patient had been started on acenocoumarol which was then changed to warfarin. Novel oral anticoagulants are not yet approved for CTEPH and post- pulmonary endarterectomy, and only vitamin K antagonists are indicated.

Outcome and Follow-up

After physical and respiratory rehabilitation patient was able to maintain oxygen saturations above 94% on exertion without need for supplemental oxygen. Repeat plethysmography was performed which showed a diffusion capacity within normal limits. Patient was deemed fit for discharge with appropriate follow up as well as a scheduled repeat echo in 3 months from procedure.

At the follow up appointment the patient had been doing much better and had seen a significant improvement in functionality, for instance she was now able to walk up a flight of stairs without any shortness of breath. The repeat echocardiogram showed mild dilated right ventricle with normal right ventricular contractility. Moreover the Inferior vena cava was no longer dilated and was now collapsible. In conclusion, there was very significant improvement in right ventricular function.

DISCUSSION

In CTEPH there is an elevated mean pulmonary arterial wedge pressure above 20 mmHg of normal as well as elevated pulmonary vascular resistance above 3 Wood Units. This occurs secondary to the progressive precapillary pulmonary artery remodelling[3]

Chronic thromboembolic pulmonary hypertension is usually known to be a long-term complication of pulmonary thromboembolism. In this patient, the presence of thromboembolism was confirmed by computed tomography which showed a concentric thrombus lining the right lower lobe pulmonary artery. Moreover subsegmental peripheral pulmonary artery branches were shown to manifest sharp cut-off indicating occlusion.

Usually resolution of thrombus in the case of acute pulmonary embolism will occur within six to eight weeks. But in the cases where thromboembolism is chronic there is incomplete clot lysis.[4]

Risk factors for thromboembolism involve pro-coagulant conditions which are found to be present in more than 30% of patients with CTEPH[4]In patients with COVID-19 a common abnormality is coagulopathy, and these patients tend to get elevated levels of both D-dimer and fibrinogen. It was found that venous thromboembolism can occur in COVID-19 positive patients even in patients treated with therapeutic anticoagulation as of admission.[5]

Pulmonary embolism in COVID-19 positive patients is thought to be caused secondary to a local thrombo-inflammatory syndrome induced by a severe acute respiratory syndrome rather than by a thromboembolic event.[6]Inflammation is thought to result in enhanced release of procoagulant factors, thus inducing the coagulation cascade and resulting in de novo thrombosis and fibrin deposition within the pulmonary vasculature.[7]

In a study on patients with non-critical COVID-19, it was found that among patients who presented with respiratory deterioration after being admitted with a diagnosis of non-critical COVID-19, about 20% had a confirmed acute pulmonary embolism. In these patients, the best cut-off value of d-dimer was approximately 10-fold the upper limit of normal.[8] In this case d-dimer was found at 2672ng/mL(0-500ng/ml), which is in keeping with this. Despite the D dimer being a good indication of pulmonary embolism, a high index of suspicion is needed for performing CT pulmonary angiogram to exclude or diagnose an acute pulmonary embolism.

Several retrospective studies have indicated that Computed topography scans have a higher sensitivity (86–98%) and lower false negative rates when compared to Reverse transcription polymerase chain reaction (RT-PCR), in diagnosing COVID-19. This has increased the incidence of CT scans being carried out during the pandemic.[9] Therefore one may argue that the increased incidence of pulmonary embolism during the COVID-19 pandemic could be secondary to the use of Computed Topography as part of the workup for COVID-19 rather that the COVID-19 itself.

There are studies that suggest that patients on thyroid hormone replacement are at an increased risk of developing CTEPH Three European multicentre studies concluded that 19.9% of CTEPH patients were on thyroid hormone replacement therapy while 6.2% of CTEPH patients had a history of hypothyroidism.[10] This patient was known to suffer from hypothyroidism, and this might have been a contributing factor to her developing CTEPH.

CTEPH being a progressive vascular disease, will eventually result in an increased right heart load secondary to pulmonary vascular resistance. This then in turn leads to failure of the right heart.[10] Therefore it goes without saying that this condition causes a significant burden on one's quality of life. This makes its early diagnosis and thus management crucial to avoid its advancement.

The pattern of right sided strain secondary to pulmonary hypertension was seen clearly in the patient being discussed as both physical examination and an echocardiogram done were consistent with a right sided heart strain with right sided dilation.

Although patients may have little to no limitation at first, they may get eventual progression to overt limitation on exercise and ultimately right ventricular failure and death.[4] Our patient presented with symptoms of CTEPH about four months after testing positive for COVID-19, thus a high index of suspicion led us to connect the dots and come to the right diagnosis.

Management options for patients with CTEPH involve Pulmonary endarterectomy, balloon pulmonary angioplasty, medical therapy, lung transplantation or a combination of the former.[11]

Pulmonary endarterectomy (PEA) can result in total resolution of pulmonary hypertension in some patients. PEA is usually used as first-line therapy. Whether one goes for surgery or not depends on several factors, mainly including the anatomic extent of obstruction, the degree of microvascular disease as well as taking into consideration the haemodynamic of the pulmonary vasculature and the right ventricular function. The patient's health status and comorbidities also play a role in whether to choose surgery as the management of choice. Saying all this, the decision should be taken at a multidisciplinary level.[4]

In this case surgery was the treatment of choice and the procedure was carried out successfully with the patient gaining better functionality and normalisation of both respiratory and cardiac function.

SUMMARY BOX

- COVID-19 has just recently been recognised as an important risk factor for the development of Chronic Thromboembolic Pulmonary Hypertension (CTEPH).
- More awareness is needed regarding the correlation between COVID-19 and CTEPH
- Early suspicion and investigation for CTEPH, in patient presenting with persistent Shortness of breath after COVID-19 infection is paramount for early diagnosis of CTEPH before functional limitation develops.
- CTEPH associated functional limitations have the potential for reversibility if the condition is caught early and managed in a timely manner, therefore a high index of suspicion is needed.

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