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The Great Mimicker: Chronic Thromboembolic Pulmonary Hypertension

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Abstract
Chronic thromboembolic pulmonary hypertension (CTEPH) is a sub-category of pulmonary hypertension that is unique from other forms of pulmonary hypertension with regards to its pathogenesis, patient characteristics and management. By definition, CTEPH is precapillary hypertension with a minimum of one segmental perfusion abnormality on scintigraphy or a CT pulmonary angiogram having typical findings of CTEPH. Despite advancement in awareness, diagnosis and treatment of CTEPH, its prevalence has remained a question of concern in the field of medicine majorly contributed by its clinical presentation that mimics common cardiorespiratory diseases. This has largely been contributed by misdiagnosis and under-reporting of the incidence. Available data suggest an incidence of 0.56% for early diagnosis and 3% for late diagnosis/survivors. The commonest risk factors associated with CTEPH include unprovoked pulmonary embolism, recurrent pulmonary embolism and antiphospholipid syndrome. In this case report, we present a 24yr old female who presented to our outpatient clinic with features of heart failure and deep venous thrombosis initially being followed up for heart failure. The only clue towards CTEPH was the chronic leg swelling that was more pronounced on the left side otherwise a systemic inquiry was non-contributory. A Doppler ultrasound of the left lower limb demonstrated chronic deep venous thrombosis involving the femoral system of veins. Consistent with CTEPH was an echocardiogram that showed tricuspid regurgitation and elevated pulmonary pressures whereas a CT Pulmonary angiogram showed a dilated pulmonary artery trunk, dilated right ventricle and atrium, and pulmonary oligaemia.

Keywords: *Chronic thromboembolic pulmonary hypertension, venous thromboembolism, Computed Tomography Pulmonary Angiogram, Ventilation/Perfusion mismatch*

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I. Introduction

Chronic thromboembolic pulmonary hypertension is precapillary hypertension with a minimum of one segmental perfusion abnormality on scintigraphy or CT pulmonary angiography having typical findings(Delcroix et al., 2016). It is in the 4th category of Nice pulmonary hypertension classification. Etiologically, it follows incomplete resolution of pulmonary embolism that later gets organized into fibrous material within the large pulmonary vasculature and manifests with features of elevated pulmonary artery pressures(Mahmud et al., 2018). The epidemiology of CTEPH is poorly documented in medical literature because of under-reporting which is majorly contributed by its non-specific clinical presentation and its limited armamentarium more-so in resource limited countries(Delcroix et al., 2016). In this case report, we present a case of CTEPH in a 24year old female who developed chronic deep venous thrombosis and complicated to CTEPH.

II. Patient Information

A 24yr old para 1+0 female with a last delivery 3 years ago presented to the outpatient clinic with complains of difficulty in breathing, chest pain, orthopnea and left lower limb swelling in New York Heart Association class 3. The patient had been unwell prior to this date and was being managed in another facility for heart failure. Clinical examination on the day of presentation revealed a blood pressure of 102/69mmHg, pulse rate 71beats/minute, respiratory rate 23breaths/minute, temperature 36.4^{o}C and sPO_2 of 95% on room air. There was bilateral, pitting non-tender edema more marked on the left leg, jugular venous distension and auscultation

of the heart revealed a split S2. The rest of the systemic examination was unremarkable. At this time, a venous Doppler ultrasound scan of the left lower limb was requested and it demonstrated chronic deep venous thrombosis of the common femoral, deep femoral and superficial femoral veins with mild subcutaneous edema as well as enlarged inguinal nodes. An echocardiogram ordered on the same day showed moderate pulmonary hypertension with severe tricuspid regurgitation (Fig. 1 & 2), dilated right ventricle and atrium in the background of normal left ventricular systolic function. The IVC was dilated with reduced respirophasic activity (Fig. 3). In view of the above findings, a diagnosis of CTEPH was entertained and a Computerized Tomography Pulmonary Angiogram (CTPA) was ordered which demonstrated a main pulmonary artery trunk measuring 2.63cm and relatively larger than the ascending aorta. Central pulmonary arteries were not dilated and had smooth walls with normal thickness. There were no filling defects. The lung parenchyma demonstrated a mosaic pattern of lung attenuation with hypo- and hyper-attenuating patches. Oligaemic foci were noted in the left lower lobe. Scattered centrilobular cystic foci were also noted. With regards to right heart strain, it was reportedly mild and the right atrium appeared dilated. Great vessels together with the central airways were normal. No effusion, consolidation, atelectasis or infarct was noted. ECG showed sinus rhythm, R/S V_1>1, T-wave inversion in leads v_1-V_4 (Fig. 4). In view of the CTPA, echocardiography, Doppler ultrasound scanning and the clinical history, chronic pulmonary microthrombo-embolism with CTEPH as a diagnosis was entertained. Further inquiry from the patient yielded a negative history for prior thromboembolic phenomena, cigarette smoking, use of oral contraceptives or familial history of thromboembolic phenomena. At the time of presentation, the patient was on warfarin 5mg o.d, furosemide 40mg o.d, nifedipine slow release 7.5mg od and digoxin 0.5mg o.d. INR done on the same day was at 2.16 with a prothrombin time index of 49.4% and a prothrombin time of 33secs (Tab. 1). In addition to the above medication, the patient was initiated on sildenafil 25mg tds and torsemide 20mg a.m.

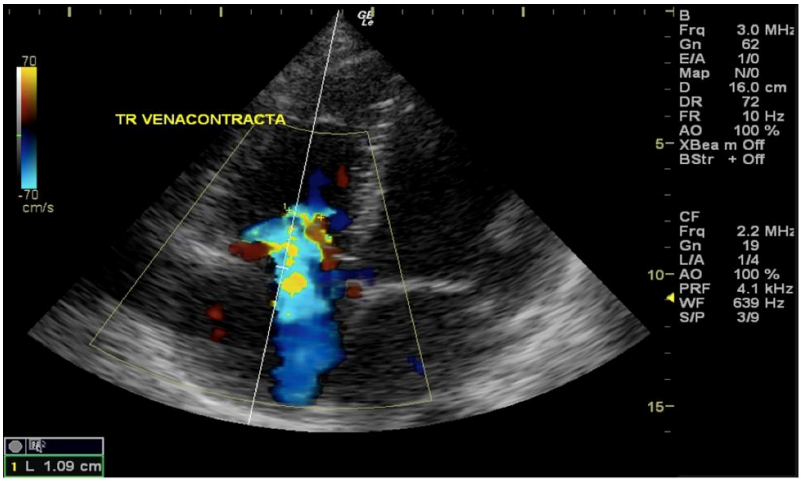

Figure 1

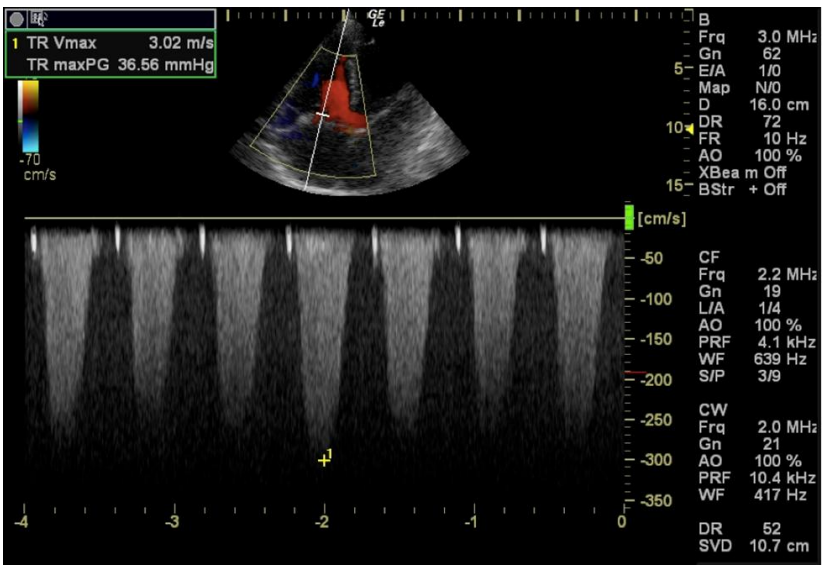

Figure 2

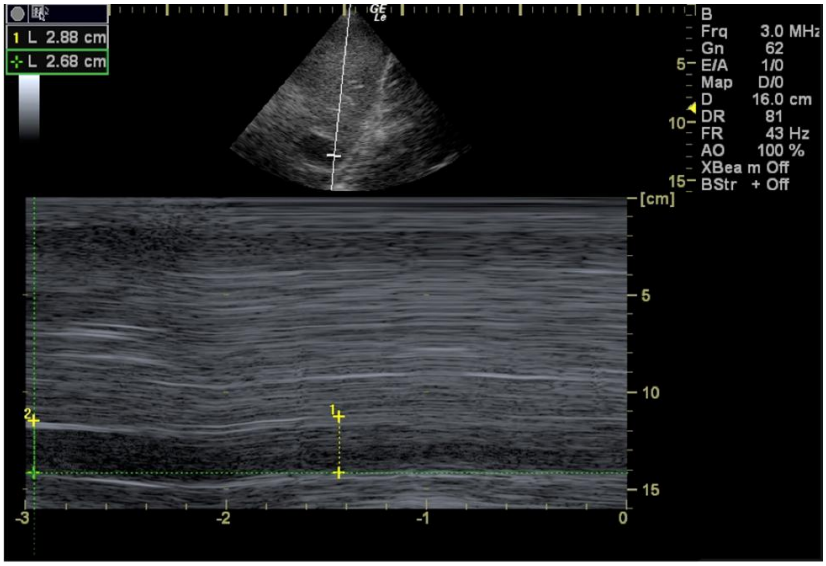

Figure 3

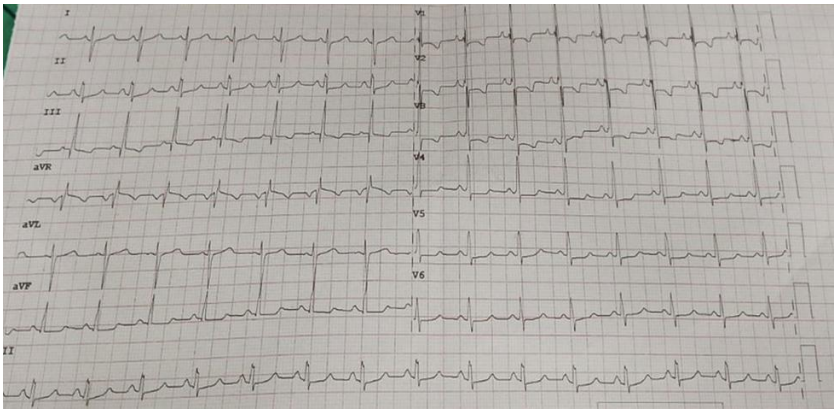

Figure 4.

Table 1: Diagnostic assessment, therapeutic intervention, follow-up and outcomes

	Date	Interpretation/diagnosis	Intervention	Follow-up/outcomes
Laboratory				
Prothrombin time	13/11/2023	33secs	-	
Prothrombin time index		49.4%	-	
INR		2.16	Warfarin	
Radiological				
Doppler ultrasound scan left lower limb	13/11/2023	Left chronic DVT of the femoral system of veins	Treatment for CTEPH initiated Sildenafil 25mg tds	Clinical improvement noted.
Echocardiogram		Severe tricuspid regurgitation, severe pulmonary hypertension		
CT pulmonary angiogram		Dilated pulmonary artery trunk, dilated right atrium, pulmonary oligaemia		
Electrocardiogram	13/11/2023	T-wave inversion in leads V_4 and V_5	-	-

III. Discussion

Chronic thromboembolic pulmonary hypertension(CTEPH) is a sub-category of pulmonary hypertension that is unique from other forms of pulmonary hypertension with regards to its pathogenesis, patient characteristics and management(Wilkens et al., 2018). By definition, CTEPH is precapillary hypertension with a minimum of one segmental perfusion abnormality on scintigraphy or a CT pulmonary angiogram having typical findings(Delcroix et al., 2016). The hallmark of CTEPH is chronic thrombi in the pulmonary arterial bed that eventually leads to progressive vascular remodeling resulting in an increase in pulmonary vascular resistance which manifests as an increase in pulmonary artery pressures (Klok et al., 2018).

In the WHO categorization of pulmonary hypertension, it has been categorized as category 4 pulmonary hypertension (Leber et al., 2020).

Despite advancement in awareness, diagnosis and treatment of CTEPH, its prevalence has remained a question of concern in the field of medicine. This has largely been contributed by misdiagnosis and under-reporting of the incidence(Delcroix et al., 2016; Mahar et al., 2020). Available data suggest an incidence of 0.56% for early diagnosis and 3% for late diagnosis/survivors(Mahar et al., 2020). The commonest risk factors associated with CTEPH include unprovoked pulmonary embolism, recurrent pulmonary embolism and antiphospholipid syndrome(Mahar et al., 2020). Other risk factors statistically associated with CTEPH include; elevated plasma levels of factor VII and von Willebrand factor, chronic inflammatory diseases as evidenced by high levels of C-reactive protein that declines post thromboendarterectomy, elevated levels of interleukin 10, monocyte chemotactic protein-1, macrophage inflammatory protein-1α, and matrix metalloproteinase 9, splenectomy, ventriculoartrial shunts, malignancies and persons with non-O blood group(Mahmud et al., 2018). Chronic Staphylococcus aureus infection has also been implicated in CTEPH whereby it has been postulated that thrombus infection is a trigger to development of CTEPH(Wolf et al., 2000).(Ogeng'o et al., 2011)(Ngunga et al., 2020)

The pathophysiological mechanisms that result in development of CTEPH are not well documented though several theories regarding its pathophysiology have been fronted. Despite these uncertainties, the hallmark is persistence of thrombi within the pulmonary vasculature that result in vascular remodeling, increase vascular resistance that eventually results in pulmonary hypertension(Mahmud et al., 2018). Amongst the fronted hypothesis include a defective endogenous fibrinolysis, fibrin variants that are resistant to endogenous fibrinolysis and in-situ pulmonary arteriopathy. In addition; a chronic rise in inflammatory markers implies a possible role of inflammation in causation of CTEPH as high levels of C-reactive protein and tumor necrosis factor α have been noted in CTEPH patients. Other rare conditions or states seemingly associated with CTEPH include; presence of a pacemaker, ventriculoartrial shunts, splenectomy and chronic inflammatory disorders like inflammatory bowel disease(Yan et al., 2019).

CTEPH more often than not presents a diagnostic challenge because of its non-specific presentation and that most patients do not have a previous history of pulmonary embolism. Clinically, these patients present with progressive dyspnea, physical activity intolerance and non-specific clinical signs. More often than not patients present in New York Heart Association functional classification class III/IV with signs of right ventricular failure(Xie et al., 2019). A diagnostic work-up for chronic thromboembolic disease is merited in patients who have received antithrombotic treatment for pulmonary embolism for three months and they still have a persistence of symptoms and signs of the same(Kharat et al., 2018). On suspicion of CTEPH, a screening ventilation/perfusion scan is needed for it provides a high sensitivity and a high negative predictive value. As a gold standard, pulmonary angiography is employed for definitive diagnosis and a pre-surgical evaluation tool. Other newer technologies that have been recommended by European Society of Cardiology/ European Respiratory society (ESC/ERS) for CTEPH diagnosis include Dual Energy Computed Tomography angiography as well as Computed Tomography angiography(Albani et al., 2019). These technologies have the advantage of being non-invasive and provided similar information as conventional pulmonary angiography(Tong et al., 2020). In addition to these radiological tests, case based laboratory tests including plasma levels of inflammatory markers, a check for antiphospholid syndrome antibodies, screening for possible malignancies, plasma levels of factors VII and von Willebrand may be done.

IV. Conclusions

From the above findings it is seen that diagnosis and treatment of CTEPH in resource poor settings poses a challenge as initially the patient was on follow up for heart failure only for the suspicion of CTEPH to come later way into complications.

Patient perspective

The patient reports that since the diagnosis of CTEPH was made she has had marked improvement as compared to before when she was being treated for heart failure. Despite the clinical improvement she has not been able to resume her routine activities including work due to limited functional ability. She reports difficulty in breathing with heavy house chores.

Consent

Verbal consent was sought from the patient and anonymity was observed.

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