

## PULMONARY THROMBOEMBOLISM DUE TO METHYLENETETRAHYDROFOLATE REDUCTASE (MTHFR) GENE MUTATION PRESENTING WITH ODDBALL PULMONARY COMPLICATIONS

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### PRESENTATION OF CASE

Pulmonary Thromboembolism (PTE) has customarily been a diagnostic predicament for treating physician despite breakthroughs in diagnosis and treatment of the disease. Hare-footed diagnosis of this entity is crucial to nutshell, the complications and to forestall mortality. Identification of the risk factors of PTE is an equivalently arduous task. Methylenetetrahydrofolate Reductase (MTHFR) gene mutation is subtle cause of PTE with its pathology enrooted in the resultant hyperhomocysteinaemia and pulmonary infarction inciting parenchymal cavitation and pleural complications like hydropneumothorax is a heteroclitic clinical manifestation of the disease. Our case poises unique owing, the dual significance of its rare aetiology and rarer presentation.

Pulmonary Thromboembolism (PTE) is a consequence of embolisation of a thrombus from a distant source like the deep veins of the lower or upper limbs into the pulmonary vasculature. Under physiological conditions, microthrombi are formed and lysed perpetually within the venous circulatory system. However, an imbalance in one of the components of Virchow's triad<sup>1</sup> culminates in aggregation of these microthrombi to form a thrombus. PTE is a multifactorial disease caused due to interplay of various genetic and environmental factors. Hyperhomocysteinaemia is a strong risk factor for thrombosis with Methylenetetrahydrofolate Reductase (MTHFR) gene mutation as a rare underlying cause. Prosaic presentations of PTE include sudden onset breathlessness, chest pain and cardiorespiratory arrest. Patients presenting with offbeat clinical situations due to complications like cavity consolidation and pyopneumothorax are seldom encountered in literature. We herein present a case which is cogent due to its rare aetiology as well as unconventional manifestation.

### CASE SUMMARY

A 37-year-old man presented with complaints of cough with mucoid expectoration associated with streaky haemoptysis, left-sided chest pain, intermittent fever and breathlessness. He was a smoker (10 pack years). He had past history of right leg deep vein thrombosis diagnosed 2 months ago on therapy with warfarin. On examination, the patient was febrile with pulse of 108 beats per minute, blood pressure of 110/80 mmHg, a respiratory rate of 24 cycles per minute with use of accessory respiratory muscles and pulse oximetry showing saturation of 94% with no pedal oedema. There were signs of left hydropneumothorax with decreased respiratory movements, dull note and decreased breath sounds with elicitation of succession splash. Pulmonary component of second heart sound was loud and left parasternal heave was noted. The Chest X-Ray (CXR) showed a left large hydropneumothorax with mediastinal shift to right. The contrast-enhanced computed tomography confirmed the same findings along with cavity consolidation of the left lower lobe (Figure 1). Haemogram showed haemoglobin of 16 gm% with total leucocyte count of 24,000/cu mm. Biochemical investigations were normal. The patient was intervened with a wide bore intercostal drainage (pigtail), which drained pus and air and treated with antibiotic co-amoxiclav. Sputum smear was negative for Acid-Fast Bacilli (AFB). Sputum GeneXpert did not detect mycobacterium tuberculosis. The pleural fluid on routine microscopy showed a neutrophil predominant exudate with normal ADA level. The pleural fluid AFB smear and GeneXpert were negative. The Electrocardiogram (ECG) showed sinus tachycardia. His Well's score was 4, the revised Geneva score was 6 and D-dimer was highly raised suggestive of high clinical probability of PTE. The Computed Tomography Pulmonary Angiography (CTPA) showed bilateral lower lobe PTE with left pyopneumothorax, cavity consolidation and pigtail in situ (Figure 2). On bilateral lower limb Doppler, multiple thrombi were seen in the right common femoral vein, distal femoral vein, superficial femoral vein and popliteal vein. Two-dimensional echocardiography revealed moderate pH of 55 mmHg. In view of absence of acquired risk factors, he was tested for protein C and S deficiency, antithrombin III deficiency, factor V Leiden mutation and antiphospholipid antibodies. MTHFR A1298C mutation was detected with raised homocysteine level. Low molecular weight heparin and cyanocobalamin, folic acid and pyridoxine were added. The pigtail was

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removed after complete lung expansion and drainage. Patient was discharged in stable state and remains symptom free at 4 month follow-up.

## DISCUSSION

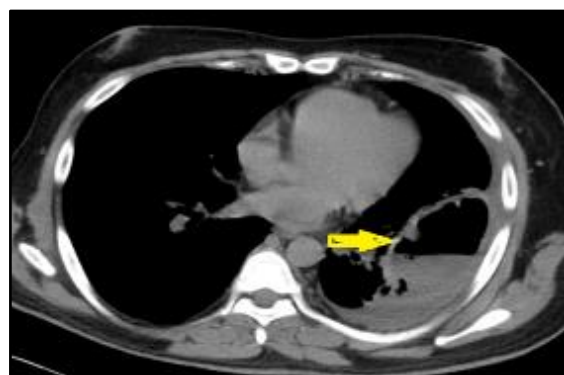
PTE is a bourgeois yet potentially calamitous disease. It can have a gamut of presentations. These depend on a multitude of factors such as the size of the embolus, the degree of vascular obstruction, the location and extent of lung parenchymal damage and the degree of cardiac compromise. Pulmonary infarct<sup>2</sup> tends to occur only in 10% of pulmonary thromboembolism due to dual blood supply. Patients harbouring an underlying cardiopulmonary disease are essentially predisposed to the development of pulmonary infarction.<sup>3</sup> However, our patient did not have any underlying cardiopulmonary disease. Among the multitudinous manifestations of PTE, cavitation with or without pneumothorax/hydropneumothorax associated with pulmonary infarction is scarcely reported in literature. Cavitation results from superadded infection of infarct or aseptic liquefaction.<sup>4</sup> The incidence of pneumothorax or hydropneumothorax secondary to pulmonary infarction has not been precisely estimated in literature. However, it is undeniably picayune with smattering reported sporadically. Our case is one of the caboodle. Due clinical suspicion coupled with timely application of scoring systems like Wells and Geneva aid the diagnosis and risk stratification in cases of PTE especially in unorthodox circumstances.

The aetiologies of PTE are amalgamate. In the last decades, multiple inherited aetiologies have been catalogued as the causative factors for PTE. These include<sup>5</sup> protein C deficiency, protein S deficiency, antithrombin III deficiency, factor V Leiden mutation and hyperhomocysteinaemia. Hyperhomocysteinaemias, an entrenched cause of systemic thromboembolic events. Mouravas et al<sup>6</sup> found high level of homocysteine as a rare risk factor for deep vein thrombosis. Radovanovic et al reported hyperhomocysteinaemia in PTE compared with healthy individuals. Ringwald et al<sup>7</sup> documented homozygous or combined heterozygous status of MTHFR C677T and A1298C mutation with higher frequency of deep vein thrombosis.

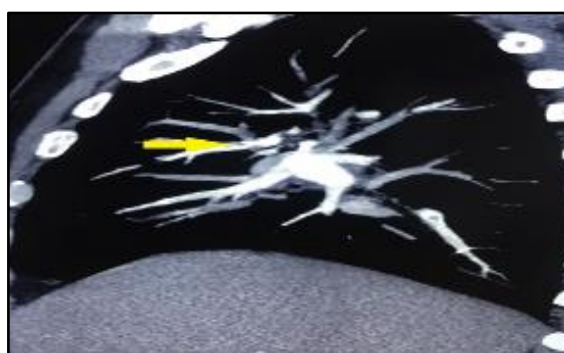
The increased level of homocysteine (hyperhomocysteinaemia) is a strong risk factor for thrombosis and it is influenced by genetic factors. MTHFR is an important enzyme that regulates folate metabolism due to affect DNA methylation and nucleic acid synthesis.<sup>8,9</sup> MTHFR catalyses the reduction of 5, 10-Methylenetetrahydrofolate (5, 10-MTHF) to 5-methyltetrahydrofolate (5-MTHF). 5-MTHF is a methyl donor for the homocysteine-to-methionine re-methylation and circulatory form of folate. The reduction of MTHFR activity causes hyperhomocysteinaemia.<sup>10</sup> The gene for MTHFR is located on chromosome 1 at 1p36.3 and consists of 11 exons. MTHFR gene includes two common polymorphisms - C677T (ALA222VAL) and A1298C (GLU429ALA) polymorphisms.<sup>11</sup> These polymorphisms are correlated with reduction on MTHFR enzyme activity. With this way, these

polymorphisms play a role on pathogenesis of thrombosis. There are several studies that present influence of MTHFR polymorphisms on diseases such as ischaemic stroke, obstetrical pathologies, arterial and venous thrombosis and metabolic diseases.<sup>12</sup> The occurrence of thromboembolism due to hyperhomocysteinaemia can be elucidated by various hypothesis such as the toxic effect of homocysteine on vascular endothelium and an abnormal methionine metabolism due to aberration in methylation of DNA and cell membranes.<sup>13</sup> The noteworthy aspect of this cause of PTE is that it is substantially rectifiable with supplementation of high doses of multivitamin, including folate, vitamin B6 and vitamin B12.<sup>14</sup> Hence, this cause of PTE stands out amongst the other causes of PTE owing to its salvageable aftermaths. To the best of our knowledge in literature, the effects of MTHFR polymorphisms in PTE were shown mostly in case reports and thus, there is limited information. In our case, single heterozygous state of MTHFR A1298C mutation predisposed to elevated homocysteine level and endothelial injury. This caused deep vein thrombosis from where embolisation lead to PTE, whereas cavitation and pyopneumothorax was secondary to pulmonary infarction and super-added infection.

PTE is a diagnostic quandary given the prodigious presentations particularly in the emergency departments. It can masquerade and camouflage a throng of clinical situations. Our case reiterates that PTE should be kept as one of the differentials in incidences of cavitation with or without pneumothorax/hydropneumothorax and hyperhomocysteinaemias, one of the rarefied, yet salient and corrigible causes of this cataclysmic disease.



**Figure 1. Left Lower Lobe Cavity with Air-Fluid Level s/o Hydropneumothorax**



**Figure 2. Partial Filling Defect in Distal Part of Right Lower Lobe Pulmonary Artery**

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