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# Pulmonary embolism in a young male with tuberculosis and factor V Leiden

## Zatorowość płucna u młodego mężczyzny z gruźlicą i mutacją czynnika V Leiden

The authors declare no financial disclosure

### Abstract

There is no doubt that venous thromboembolism (VTE) is a complex and multicausal disease. Tuberculosis (TB) itself is found to have thrombogenic potential. There is an association between tuberculosis and VTE. We present a case of a 31-year-old male diagnosed with TB after a 2-month delay. He was treated with an anticoagulant for pulmonary embolism (PE) complicated by pulmonary infarction, and with antibiotics for presumed bacterial pneumonia. The patient did not improve despite in-hospital treatment. Finally, TB was diagnosed with positive sputum smear for acid fast bacilli and subsequent culture of *Mycobacterium tuberculosis*. Antituberculous therapy was uneventful and the patient was discharged home. Thrombophilia screening revealed a heterozygous factor V Leiden mutation. This case report emphasises that although there is a steady decline in active cases of TB, it should be still placed high on the list as a differential diagnosis in non-resolving lung infection or pulmonary infarction. This is especially relevant in cases with typical radiological findings located in the upper lobes. On the other hand, definitive diagnosis may be challenging in a case of concurrent TB, bacterial pneumonia and pulmonary infarction. Thromboembolic events may develop in TB patients without any clinical VTE risk factors. Therefore, thromboprophylaxis should be cautiously considered in this group of patients.

**Key words:** tuberculosis, pulmonary embolism, factor V Leiden, diagnosis

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### Streszczenie

Żylna choroba zakrzepowo-zatorowa jest jednostką o złożonej i wieloczynnikowej etiologii. Gruźlica jako proces zapalny posiada potencjał prozakrzepowy. W literaturze opisywane jest współwystępowanie gruźlicy płuc i żylnej choroby zakrzepowo-zatorowej. W pracy przedstawiono przypadek 31-letniego mężczyzny z zatorowością płucną powikłaną zawałem płuca oraz z rozpoznaną z dwumiesięcznym opóźnieniem gruźlicą płuc. U pacjenta zastosowano leki przeciwkrzepliwe oraz dodatkowo antybiotyki z powodu podejrzenia bakteryjnego zapalenia płuc. Stan kliniczny pacjenta nie poprawiał się pomimo hospitalizacji i zastosowanej terapii. Rozpoznanie zweryfikowano na podstawie dodatniego badania bezpośredniego plwociny, a następnie pozytywnej hodowli prątków gruźlicy (*Mycobacterium tuberculosis*). Leczenie przeciwprątkowe przebiegło bez powikłań. Badania w kierunku trombofilii potwierdziły heterozygotyczną mutację Leiden czynnika V. Mimo stałego spadku zachorowań, aktywna gruźlica powinna być nadal rozpoznaniem różnicowym w sytuacji niepoddających się leczeniu zmian zapalnych w płucach lub zawału płuca. Dotyczy to zwłaszcza przypadków ze zmianami radiologicznymi o typowej lokalizacji i charakterze. Z drugiej strony, ustalenie ostatecznego rozpoznania może sprawiać poważne trudności diagnostyczne przy współistnieniu gruźlicy, bakteryjnego zapalenia płuc oraz zawału płuca. Epizody zakrzepowo-zatorowych u pacjentów z gruź-

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licą mogą wystąpić bez klinicznych czynników ryzyka. W związku z tym profilaktykę przeciwzakrzepową należy wcześnie rozważyć w tej grupie chorych.

**Słowa kluczowe:** gruźlica, zatorowość płucna, mutacja Leiden, diagnoza

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## Case report

Despite a steady decline in TB incidence in Poland in recent years, this slightly underestimated disease should be always taken into account in differential diagnosis in cases of non-resolving lung infection. In Poland TB incidence fell by 12% in 2012, compared with the previous year [1].

There is some evidence that pulmonary tuberculosis is associated with VTE [2]. Besides the well-recognised fact that respiratory infections raise the risk of VTE, TB itself is linked with hypercoagulability [3, 4].

A 31-year-old lean (BMI 20 kg/m$^2$) male smoker was admitted to a general medical ward with a history of two-week long productive purulent cough, intermittent haemoptysis, night sweats and weight loss of 10 kg. He was febrile (axillar temperature 38$^0$C), without dyspnea, fatigue or anorexia. One day before admission he reported a sharp central chest pain exacerbated by respiration. As an out-patient he received a course of amoxicillin for supposed community-acquired pneumonia (CAP). He worked as a logistics manager with unremarkable medical history. There was no history of contact with TB source or any other socio-demographic risk factor for TB transmission except for smoking. He did not report any recent trauma, surgery or long-distance travel. On examination, he was normotensive (blood pressure — 110/70 mm Hg), non-tachycardic (85/min), non-tachypnic with bronchial breathing over the right upper lobe. His oxygen saturation was 93% in air. His legs were both non-tender and without oedema. His chest X-ray showed a large wedge-shaped consolidation in the upper right lobe abutting the horizontal fissure and parietal pleura with irregular infiltrations in the middle and lower lobe of the right lung (Fig. 1). Doppler ultrasound examination of his legs was negative. Regarding his symptoms and chest X-ray, pulmonary infarction was suspected and computed tomographic pulmonary angiography (CTPA) was ordered. It showed numerous emboli in a division of the right pulmonary artery, in all right upper lobe branches as well as the left lower lobe artery (Fig. 2). There were also infiltrations in peripheral parts of the right upper lobe with extensive air bronchogram and thickwalled cavity measuring 2 cm in the second right segment (Figs 3, 4). The inflammatory markers were raised (erythrocyte sedimentation rate (ESR) — 58 mm/hour, C-reactive protein (CRP) 119 mg/L). At that time the working diagnosis was large pulmonary infarction associated with CAP. Accordingly, he was treated with heparin and antibiotics (amoxicillin with clavulonic acid and ciprofloxacin). Given no evident risk factors and his young age, thrombophilia screening was performed. Among the investigated panel, including antiphospholipid antibodies and the prothrombin G20210A mutation, heterozygous factor V Leiden mutation was the only positive finding. After moderate clinical improvement with a moderate decrease in CRP (36 mg/L), the patient was discharged to continue on oral anticoagulation.

After a month the patient was readmitted with non-resolving fever, cough and sharp right-side chest pain. Inflammatory markers were still elevated (CRP 65 mg/L, ESR 70). CT showed

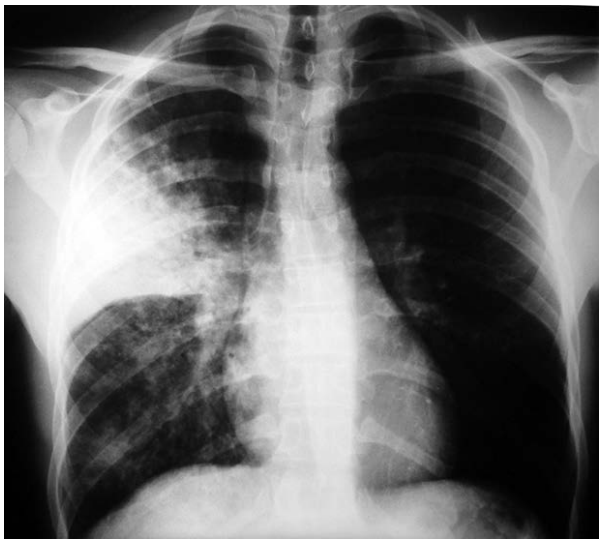

**Figure 1.** Chest X-ray on admission. Consolidation in the upper right lobe with irregular infiltrations in the middle and lower lobe of the right lung

**Rycna 1.** Zdjęcie RTG klatki piersiowej przy przyjęciu. Naciek w górnym płacie oraz nieregularne zmiany zapalne w środkowym i dolnym płacie płuca prawego

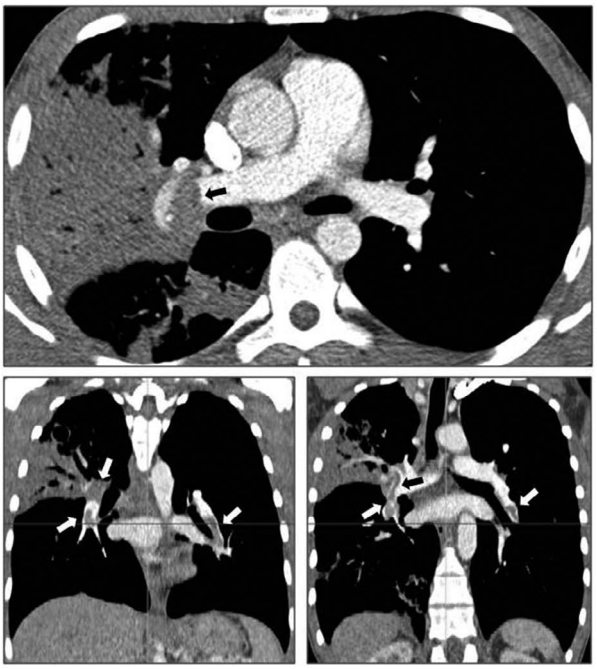

**Figure 2.** Computed tomography (pulmonary angiography) with multiplanar reconstruction. Bilateral emboli mainly in the right pulmonary artery and its branches (arrows). Large consolidation in the right upper lobe

**Rycina 2.** Angio-KT tętnic płucnych. Rekonstrukcja wielopłaszczyznowa. Obustronne skrzepliny głównie w prawej tętnicy i jej gałęziach (strzałki). Duże zagęszczenia w górnym prawym płacie

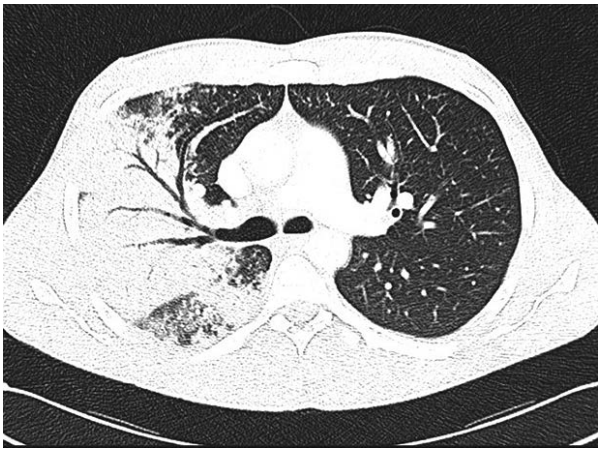

**Figure 3.** Chest computed tomography (CT). Massive infiltrations in peripheral parts of the right upper lobe with prominent air bronchogram of all segmental bronchi

**Rycina 3.** Tomografia komputerowa. Masywne zmiany zapalne w prawym płacie górnym z bronchogramem oskrzeli segmentowych

progressively larger consolidation in the upper right lobe and more cavities but with no emboli in arteries (Figs 5, 6). The patient was transferred to a respiratory ward in another hospital. Sputum microscopy was found to contain acid-fast bacilli (AFB+). Anti-tuberculous treatment (ATT) was

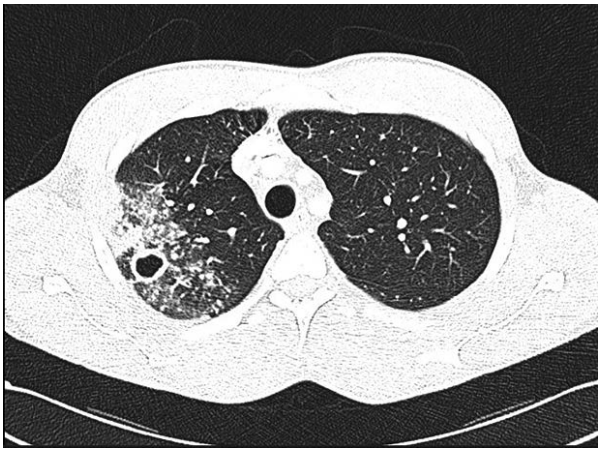

**Figure 4.** Chest CT. Thick-walled cavitary lesion in the second right segment

**Rycina 4.** Tomografia komputerowa. Grubościenna jama w segmencie drugim płuca prawego

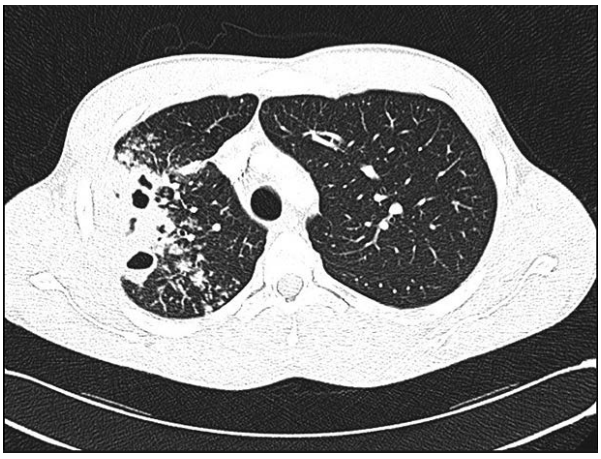

**Figure 5.** Chest CT. New cavitary lesions in the second right segment

**Rycina 5.** Tomografia komputerowa. Rozpady z utworzeniem nowych jam w drugim prawym segmencie

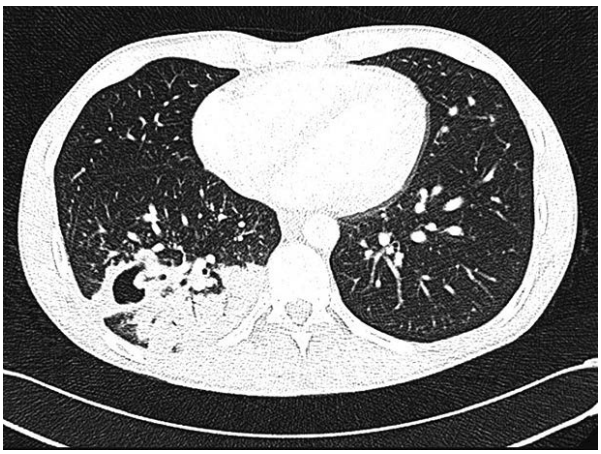

**Figure 6.** Chest CT. Cavities in the lower right lobe

**Rycina 6.** Tomografia komputerowa. Jamy w płacie dolnym prawym

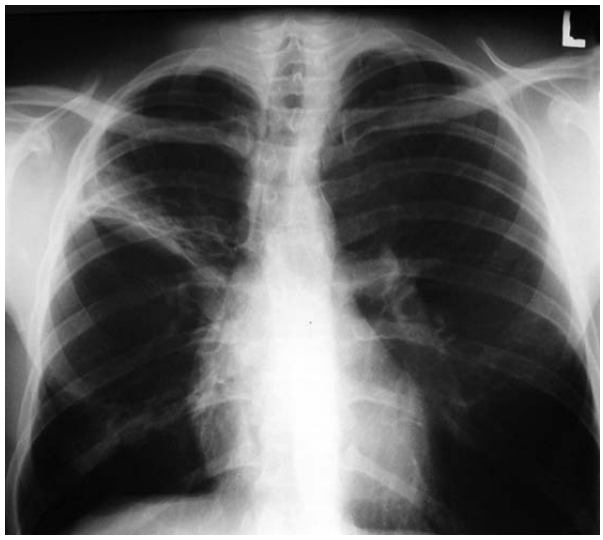

**Figure 7.** Chest X-ray in the follow-up (the 5th month of ATT). Remarkable resolution of the consolidation in the right lung

**Rycina 7.** Zdjęcie kontrolne w 5. miesiącu leczenia przeciwprątkowego. Znaczna regresja zmian w prawym płucu

started with rifampicin (R), isoniazid (H), ethambutol (E) and pyrazinamide (Z) and piridoxine. Consequently, after 15 days, *Mycobacterium tuberculosis* was cultured with the MB/BacT system and later identified with MGIT (*Mycobacteria* Growth Indicator Tube). Drug susceptibility testing (DST) showed sensitivity to first-line drugs, except for streptomycin. The patient improved with resolution of his general symptoms. There were no adverse affects. In order to avoid an interaction between rifampicin and warfarin he was anticoagulated with low-molecular-weight heparin. His sputum samples were negative for AFB after 2 months of ATT. Subsequently, after 2 months of in-hospital treatment he was discharged with a good clinical response but very slow radiological one. After that he was treated as an out-patient with HR as a continuation phase for the next 4 months. In the 5th month there was a substantial resolution on the chest X-ray (Fig. 7).

## Discussion

We report a case of pulmonary tuberculosis diagnosed after a delay and complicated by thromboembolism. That delay in TB diagnosis may indicate that despite typical radiological features, such as cavities and upper lobe location, TB might nowadays be slightly forgotten.

The absolute number of TB cases has been falling since 2006 and has dropped by 2.2% between 2010 and 2011 [5]. The incidence worldwide is 125/100,000 whereas in Poland it has recently fallen (in 2012, 19.6 cases per 100,000 population) [1]. Interestingly, we could hardly find any predisposing risk factors for TB as well as PE in the history. The only well-established risk factor for TB was smoking (RR = 2.3–2.7) [6]. Likewise, Sharif-Kashani et al. found that the majority (n = 28) of TB patients with coexisting VTE (n = 46) did not have any evident VTE risk factor [7].

There is no doubt that VTE is a life-threatening disease with a significant clinical burden. Although it is difficult to assess its frequency accurately due to its vague manifestations, the incidence of VTE among acute in-hospital patients in Europe varies from 3.65% to 14.9% [8]. Respiratory infections in general are reported to raise that risk [3].

Unfortunately, studies examining the coexistence of TB and VTE are scarce in the literature. In a study from South Africa it was reported that up to 3.4% of adult patients with TB were diagnosed with deep vein thrombosis (DVT) [2]. Patients treated with rifampicin had more that 4.5-times raised relative risk of DVT compared to those without it. Intriguingly, in the majority of these patients the diagnosis was made during the first 2 weeks of therapy and in winter months. While rifampicin is well known for its enzyme-inducing effects, which complicate anticoagulant therapy, there is no clear explanation of that increased DVT risk.

In Italy, the prevalence of VTE in TB patients was much lower (0.6%) compared with that reported by White et al. from South Africa in 1986 [9]. That difference may be influenced by various epidemiologies of TB in these two countries as well as advances in VTE prevention. In addition, in the latter, DVT was not confirmed in some cases objectively and there were no data on comorbidities. In a more recent retrospective study from Iran, the precise incidence of VTE was 1.3% [7]. What is interesting, the vast majority of these patients were admitted initially for TB therapy and later developed VTE. Again, these patients with in-hospital VTE did not have any risk factor for PE, except TB itself.

Although VTE may be a presenting first manifestation of TB, it can be difficult to diagnose due to its non-specific symptoms. It was reported that only 10% of all VTE cases are thought to be apparent [10]. On the one hand, such a symptom as haemoptysis is regarded as a complaint attributed to both PE and TB. In a large study of patients with confirmed PE, it was found only in the minority (9%) of patients [11]. Sudden onset dyspnea, chest pain and fainting were much

more frequently reported. On the other hand, systemic features such as fever, sweats and weight loss with chronic cough are very suggestive of TB. Nonetheless, in a UK prospective study of confirmed pulmonary TB, up to 25% of patients did not report any of these [12]. Moreover, in a prevalence survey from South Africa, symptom screening was less sensitive for detection of TB than chest radiographic screening [13]. The former, including symptoms like cough longer than 2 weeks, haemoptysis, night sweats, fever and weight loss, did not reveal any extra TB cases.

Due to substantial delay in TB diagnosis, our patient was treated with several courses of antibiotics including quinolone and amoxicillin/clavulanate. These drugs are found to have a degree of anti-mycobacterial activity. It has been suggested that it is quinolone treatment which may indeed cause a delay in diagnosis and therapy of TB [14]. That observation may be related to late TB diagnosis in the presented case. Likewise, in a European country with low TB burden, patients receiving various antibiotics experienced a significant delay in therapy [15]. However, that delay was not associated with any type of antibiotic or clinical improvement, but it was more due to prolongation of care. What is interesting, in 94% of cases the initial chest X-ray image was indicative of TB infection.

Gender and socio-cultural determinants of delay to TB diagnosis were also identified. In countries with high TB burden, such as India, Malawi and Bangladesh, female sex, status of married woman, housewife and non-specific symptoms like chest pain and breathlessness were associated with the longest delay of over 90 days from initial symptoms to final diagnosis [16]. Cough in India, as a common TB symptom, was related to timely diagnosis.

Diagnostic delay could also have been caused by radiological findings, which to some extent shared common qualities both with TB and pulmonary embolism. In one-third of patients with PE but without infarction (90% of all patients) there is no evident imaging abnormality [17]. The remaining two-thirds were found to have some abnormal radiological features. The most frequent non-specific findings were plate-like atelectasis, areas of consolidation, a pleural effusion and vascular changes (focal oligaemia, local widening of a vessel). Whereas in half of patients with infarction, chest X-ray shows consolidation, which classically is a truncated cone with a pleural base (Hampton's hump). The most frequent radiological findings in acute PE were cardiac enlargement (27%), normal chest X-ray (24%) and pleural effusion (23%) [18]. In the radiographic scoring system for TB, the most frequent features were upper-lobe opacity (adjusted odds ratio [aOR] 4.2; 95% CI 2.1, 8.3), cavity of any location (aOR 4.0; 95% CI 2.0, 7.6), adenopathy of any location (aOR 3.8; 95% CI 1.7, 8.2) and unilateral pleural effusion (aOR 2.1; 95% CI 1.5, 4.2) [19]. Besides, it was reported that patients with recurrent PE requiring inferior vena cava ligation may develop lung abscess [20]. This phenomenon was also confirmed in at least 2 case-reports describing relatively high incidence of aseptic cavitations of a sterile pulmonary infarction [21, 22]. Although lung abscess following PE seems rather unusual, this possible aetiology of a cavitary lesion other than TB may be considered in a patient with pulmonary infarction.

In the presented case it is very challenging to elucidate the main cause of the radiological findings. The initial CT scans presented large consolidation in the right lung and extensive filling defects in branches of the right pulmonary artery. These findings suggested the diagnosis of lung infarction. However, from the perspective of completed treatment and its outcomes it appears that it is TB rather than pulmonary embolism and infarction that contributed to the radiological presentation. This is supported by the remarkable improvement on ATT in the $5^{th}$ month. In contrast, there was gradual clinical and imaging progression after only two months of anticoagulation and antibiotics with no anti-tuberculous therapy. Moreover, on the second hospital admission, the consolidation was even larger with more numerous cavities, in spite of complete resolution of extensive embolism in pulmonary arteries.

TB might be also associated with atypical location of thrombosis, such as cerebral venous thrombosis in a heterozygous patient for prothrombin mutation [23]. There may be also a link between extrapulmonary TB, such as gastrointestinal, and DVT [24]. These observations may confirm the thrombogenic potential of tuberculosis.

Undoubtedly, there is firm evidence for the hypercoagulable state in tuberculosis. Robson et al. found that plasma fibrinogen was increased in patients with active TB coupled with lower level of antithrombin III and reactive thrombocytosis [4]. These haemostatic changes improved on ATT. Lang et al. found that plasminogen activator inhibitor and tissue factor antigen were also increased in pulmonary endothelial cells from a patient with pulmonary embolism and TB [25].

One possible explanation is significant secretion of cytokines like tumour necrosis factor alpha (TNF-$\alpha$) and interleukin-6 (IL-6) by monocytes/ /macrophages in TB patients [26]. As a result, they can induce hepatic acute-phase response and a subsequent change in coagulation proteins such as fibrinogen. Finally, the release of these cytokines from peripheral mononuclear cells (PBMC) can be further enhanced by the killing effect of isoniazid and rifampicin.

Our patient was positive for the heterozygous factor V Leiden (FVL) mutation. This most common inherited cause of thrombophilia is present in approximately 15–20% of patients with venous thromboembolism, and its prevalence in the general white population varies between 2% and 15% [27]. While, in heterozygous carriers of FVL, VTE risk is increased moderately (3- to 5-fold), it is estimated that homozygous patients have that risk elevated up to 80 times [28]. Despite this high risk, FVL is recognised as a rather modest thrombophilic defect which still does not cause VTE in all carriers. The thrombotic risk depends very much on the interaction with other mutations or, more frequently, with acquired high-risk situations [28]. Moreover, there is ongoing debate about its routine testing, which is recommended only on an individual basis [29]. However, there is no doubt that this risk of thrombosis is elevated during an inflammatory state. In fact, it has been suggested that the inflammatory response may further increase the thrombotic risk in FVL patients. Damage of the endothelium as well as exposure of adhesion molecules may play a major role in upregulating the thrombophilic state in this group of patients [30]. Last but not least, the risk of PE is only mildly elavated in FVL carriers. On the contrary, the risk with FVL for DVT is much higher (OR 4.5 95% CI 3.8 to 5.3) vs. PE (OR 1.7 95% CI 1.3 to 2.2) [31]. So far there has not been found a clear explanation for this so-called Factor V Leiden paradox. There has not been found a clear explanation for the FVL paradox.

In conclusion, a differential or coexisting diagnosis of pulmonary tuberculosis in a case of non-responsive chest infection as well as large pulmonary infarction should be always considered. Consequently, TB can be the possible diagnosis of presumed bacterial pneumonia. In such cases, appropriate TB-focused investigations such as sputum smear and culture should be performed. On the other hand, a hypercoagulable state secondary to acute inflammation is reported in these patients [32]. Consequently, patients, especially those with no improvement on ATT or with predisposing factors, should be thoroughly monitored for VTE. Patients with TB may develop VTE even without other predisposing conditions. Therefore, prevention should be cautiously considered regardless of any risk factors.

## Conflict of interest

The authors declare no conflict of interest.

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