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Is Pulmonary Thromboembolism due to Inflammatory Or Hereditary Condition?

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Editorial

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EDITORIAL NOTE

This article built upon the recent paper to deepen the discussion related to the relationship between Venous Thromboembolism (VTE), Toxoplasmosis, and inflammation. The aim is to expand and update knowledge on the subject, covering some new important information recently published. This will lead to suggest an enrichment of perspective from a sole suspicion of infection causing VTE toward a much more imbricated relationship between immune response and direct pathological effect of the parasite.

Analysis of historical toxoplasmosis outbreaks an *Toxoplasma gondii* virulence

There is an ongoing debate in the medical literature on whether these different clinical manifestations could be due to the *T. gondii* strain or its infective form. Meirelles, et al. have performed a systematic procedure of 38 from 437 reported out-breaks in an attempt to provide evidence to end this debate. They concluded that de-spite symptomatology being related to the parasitic burden and the virulence of infecting strains, the proportions of symptomatic cases and symptoms themselves were similar regardless of the form of transmission. In this analysis, no VTE-related events were reported [1]. A recent study has confirmed Meirelles, et al. conclusions.

Dubey, et al. who has worked on outbreaks of clinical toxoplasmosis in humans for the past 55 years (1966-2020), evidenced that in most of the outbreaks, usual toxoplasmosis symptoms (non-tender cervical lymphadenopathy and mild flu like syndrome of fever, malaise, myalgia, hepatosplenomegaly) were the most prevalent. Once again, no thromboembolic events were described [2].

It is possible, regarding this data, that 2 individuals of same family were infected by a high parasite burden from an atypical virulent strain, since it has been reported, In both studies, cases of severe complications with multi-visceral life-threatening outcomes in immunocompetent patients from South America [1,2].

Effect of *T gondii*

Effect of *T gondii* on inflammation biomarkers and its role in the creation of an hypercoagulable state in association with a possible infection by an "unusual" strain of *T gondii*, another possible explanation for the difference in clinical manifestation is patient intrinsic susceptibility and immune response. It is well known that differences in immune response increase infectious risks and alter the symptomatology of infections. During the acute stage of infection, Tumor Necrosis Factor Alpha (TNF-α), a proinflammatory cytokine, and interleukin-12 (IL-12) are major factors of the immune response in the control of *T. gondii* infection. Some parasitic strains have shown the ability to inhibit the production of IL-12 by macrophages and then limit innate immunity against themselves and others, causing severe systemic infection with a massive release of inflammatory cytokines [3]. In relation specifically to TNF-α, there is evidence that it promotes the formation of pathological fibrin as well as fibrin associated adhesions, a fact that might have contributed to thrombus formation in both patients described in the previous paper [4].

Focusing on the direct effect of *T. gondii* in host organisms during severe systemic infection, it is reasonably established that the main effects of this protozoan on vascular injury are a reflection of the release of bradyzoites during acute infection [5]. In immune competent individuals, this activates immune system which releases adhesion molecules like Vascular Cell Adhesion Protein 1 (VCAM-1) and Intercellular Adhesion Molecule 1 (ICAM-1) into circulation by Endothelial Cells (EC) in response to inflammation [6]. Adhesion molecules are part of the formation of the inflammatory response and also are related to thrombus formation. A complex interaction between leukocytes, platelets, and the coagulation cascade leads to the formation of a thrombin-rich thrombus. One of the key steps in this scenario is the expression of Tissue Factor (TF) by activated monocytes that initiates the extrinsic pathway of the coagulation cascade [5].

Von Bruhl, et al. have demonstrated in a murine model of VTE-inflamed endothelium increased expression of a wide range of adhesion molecules that attach leuko-cytes to the vessel wall, as an initial step in the formation of thrombus [7]. Moreover, findings from Mosevoll, et al. have suggested that TF expression by monocytes appears to be more important than the endothelial expression of TF in triggering the co-agulation cascade in VTE [8]. Egorov et al. have corroborated these findings in humans by showing that *T. gondii* IgG seropositivity was significantly associated with increased serum levels of soluble VCAM-1, ICAM-1, and C-Reactive Protein (CPR), which also enhances the thrombotic response to vascular injury [9].

Another prothrombotic effect of the acute release of bradyzoites is the creation of a persistent yet transient hypercoagulable state secondary to EC injury. It is manifested by the presence of high levels of D-dimers, and thrombin-antithrombin III complexes which reflect an activated clotting system increased expression of tissue factor, and increased activation of mutated factor V (FVL). Al-Marsomy, et al. have found a significant association between Toxoplasmosis and high blood levels of CRP and D-Dimer in infected women who have aborted [10].

Inflammation, toxoplasmosis, fvl mutation, and thrombosis

Given the large amount of information recently made available in the literature and the countless pathophysiological possibilities, what concrete do we have about the hypotheses made for the patients? An *in vitro* study performed by Mullarky, et al. has stated that it is the immune response to the pathogen, not the pathogen itself that primarily regulates coagulation during infection [10]. Interestingly, it has been established that coagulation leading to fibrin deposition is a protective mechanism during infection to prevent bacterial growth restriction and dissemination and tissue repair [11].

In brief, it is safe to assert that severe infection seems to play a crucial role in the pathogenesis and outcome of VTE-related events. Concerning the accountability of FVL mutation in this context, despite theoretically having a significant role in the pathophysiology of their clinical condition, both experimental and clinical studies show inconsistent results as to a difference in thrombus formation in carriers of the factor V Leiden mutation during sepsis or severe infection [12]. In a population-based study, it was suggested that the FVL mutation might be associated with infectious disease susceptibility and an increased risk of mortality from sepsis, but further studies need to be performed to establish this link between FVL, inflammation, and infection [13].

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