Venous thromboembolism and sarcoidosis: co-incidence or coexistence?

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Abstract

The association between venous thromboembolism (VTE) and sarcoidosis has been reported recently, nevertheless the true incidence of co-incident sarcoidosis and VTE is unknown. Sarcoidosis as a chronic disease of immune dysregulation might be associated with an increased risk of VTE. The mechanisms responsible for VTE development are not clear and may be influenced by several factors: activity of inflammation, clinical characteristics of sarcoidosis and comorbidities. Pulmonary embolism (PE) as a potentially fatal condition should be considered in all of the patients with sarcoidosis in whom worsening of the respiratory status is diagnosed. A high plasma D-dimers (DD) level may be suggestive of VTE, nevertheless elevated plasma DD should be interpreted with caution, in the context of the active inflammatory process. If sarcoidosis appears to be one of risk factors for VTE development, further investigations are needed to define the pro-thrombotic phenotype of this disease.

Key words: sarcoidosis, inflammation, venous thromboembolism.

Introduction

Sarcoidosis is a systemic disease of unknown etiology with systemic inflammation leading to formation of granulomas. Lung parenchyma and/or mediastinal lymph nodes are affected in > 90% of patients [1]. Macrophages and activated lymphocytes, an immunological hallmark of sarcoidosis, are also involved in the process of thrombin activation and fibrin formation [2, 3]. The association between sarcoidosis and venous thromboembolism (VTE) has been reported recently [4, 5], nevertheless it is still not clear if sarcoidosis is a risk factor for VTE. Thus, the aim of the present study was to describe possible mechanisms that could be responsible for the increased occurrence of VTE in sarcoidosis.

Epidemiology

A higher risk of pulmonary embolism (PE) in sarcoidosis patients has been reported recently, according to data from the UK, with a risk ratio of 2.0 (95% CI: 1.1-3.4), in patients under 65 years of age, comparing to a reference cohort [4]. Swigris et al. found PE in 2.5% of US dece- dents with sarcoidosis, regardless of gender, race or age [5]. In the retrospective analysis of clinical outcome and comorbidities among 798 sarcoidosis patients who have been hospitalized in the 2nd Pulmonary Department of our Institution between 2004 and 2014, 8 symptomatic cases of PE (one fatal case), were found.

Possible mechanisms involved

The mechanisms that could predispose sarcoidosis patients to the development of VTE may be related to several factors: activity of inflammation, clinical picture of sarcoidosis or comorbidities.

Inflammatory profile

A close anatomic relation between the site of active sarcoidosis and thrombus formation was described in the literature: mural thrombus in myocardial sarcoidosis [6], cerebral vein thrombosis in neurosarcoidosis [7-9], thoracic vein thrombosis in mediastinal sarcoidosis [10-12], portal vein hypertension in hepatic sarcoidosis [13], suggesting the local hypercoagulability status as the cause of thrombosis. Local hypercoagulability might have been the consequence of active granulomatous inflammation with an increased concentration of inflammatory markers [14-19]. We have found recently features of disease activity: elevated CRP, ESR, and ACE, monocytosis and hyper-gammaglobulinemia in our patients with sarcoidosis who developed VTE (unpublished data). Nonspecific hypergammaglobulinemia reflecting the B cell activation, which is
observed in the active disease may indicate a more generalized inflammatory process, although the definitive role for humoral immunity in the pathogenesis of sarcoidosis is not established [20].

The regulatory influence of cytokines produced by local mononuclear phagocytes results in granulomatous inflammation in sarcoidosis patients [3, 21, 22]. Cermak et al. demonstrated that peripheral blood monocytes incubated with highly purified (> 90%) human CRP for 6 hours present a significant increase in the tissue factor (TF) expression and acquire a significant pro-coagulant activity [23]. The same phenomenon might be responsible for the increased pro-coagulant ability of granulomatous inflammation in sarcoidosis. In sarcoidosis patients, as compared to normal control subjects, an enhanced activity of BAL fluid TF and plasma Factor VII were found [24]. The radiologic stage of the disease correlated with TF activity. Only patients with stage II or stage III disease had a consistently elevated procoagulant activity that corresponded to the site most involved radiographically [24].

Different cytokines modulate the risk for venous thrombosis [14]. Shorr et al. found that DD plasma levels correlate with activation of the proinflammatory cytokine cascade [interleukin (IL)-6, IL-8, tumor necrosis factor α (TNF-α)] but not with IL-10 [25]. Tumor necrosis factor α (TNF-α) is a key cytokine in the pathogenesis of sarcoidosis and may indicate the activity of the disease [26, 27]. Elevated TNF-α concentration in active sarcoidosis might be responsible for the increased risk of VTE. Locally derived IL-6 and IL-8 were increased in sarcoidosis and correlated with activity of this granulomatous lung disease [19]. Interleukin 10, an anti-inflammatory cytokine, expresses protective potential against venous thrombosis [14, 28]. A down-modulating mechanism resulting in the spontaneous resolution of sarcoid alveolitis is partially controlled by an increased local secretion of IL-10 [29]. The question whether an increased IL-10 concentration is associated with prolonged VTE needs further investigations.

Clinical characteristics

The risk factor for the development of VTE in sarcoidosis might be related to clinical characteristics such as: compression of pulmonary arteries by the enlarged mediastinal lymph nodes. Nevertheless, according to the literature, mediastinal lymphadenopathy was combined with thoracic vein thrombosis than pulmonary artery thrombosis [10-12].

Patients with chronic disabling sarcoidosis on steroid therapy (resulting in immobilization because of pulmonary fibrosis, pulmonary hypertension, osteoporosis with fractures, obesity etc.) should be at the highest risk of VTE [30]. Nevertheless, our own experience indicates that sarcoidosis patients in whom VTE was recognized, recruited from a group with active stage II sarcoidosis, receiving no treatment at the time of this complication, and not disabled otherwise.

In recently recognized three cases of PE in the course of sarcoidosis we have found some similarities. All of them concerned middle-aged, non-smoking males with active sarcoidosis according to international consensus [31]. None of them had severe disabling sarcoidosis with respiratory insufficiency at the time of PE development. None of our patients suffered from pulmonary hypertension prior to PE diagnosis and no-one was on immunosuppressant treatment. No clinically significant organ involvement was seen although in one case splenomegaly and peripheral lymph nodes sarcoidosis were diagnosed. Extrinsic arterial compression at a mediastinal or hilar level was not diagnosed in pulmonary angiography. As the histopathological diagnosis was based on fine needle biopsy, it was impossible to conclude about the presence of vascular granulomata as a risk factor for local thrombosis [13, 32]. In all our cases, the VTE had favorable course with no serious late complications. In all cases we observed favorable course of pulmonary sarcoidosis with no impact on PFT and exercise ability. Regarding some similarities in the clinical picture of sarcoidosis in our set of patients, we hypothesized that there might exist a prothrombotic phenotype of sarcoidosis, probably related rather to the inflammatory process than to clinical characteristics of patients.

Comorbidities

The risk of VTE in sarcoidosis patients may be also due to comorbidities. Nevertheless, Swigris et al. found that sarcoidosis decedents with PE were even less likely than those without PE to have certain other conditions predisposing to PE, including myocardial infarction or ischemia, congestive heart failure, cardiomyopathy, cardiac dysrhythmia, sudden cardiac death, pneumonia or stroke contributing to death [5].

The other VTE risk factors may influence the development of a thrombotic event. The risk of VTE might be associated with congenital or secondary thrombophilia. Antiphospholipid antibodies – one of the diagnostic criteria for antiphospholipid syndrome (APS) – which by definition are characterized by recurrent thromboembolic events [33], were detected in 38% of sarcoidosis patients [34]. No concomitant APS in that group of sarcoidosis patients was diagnosed. The presence of antiphospholipid antibodies was associated with extra-thoracic lesions and persistence of abnormal radiological findings in sarcoidosis, and were judged by the authors to be a useful marker for prolonged disease [34]. The authors did not search for VTE occurrence in that group of sarcoidosis patients, although they should be considered at a high risk of such events. On the other hand, in numerous case reports concerning sarcoidosis complicated by VTE, the level of antiphospholipid antibodies was not examined [6-10, 13]. Thus, so far it has been impossible to conclude based on the literature whether...
the increased risk of VTE in sarcoidosis is combined with the presence of APS. In our group of patients with sarcoidosis complicated by VTE, antiphospholipid antibodies were not found by repeated testing in any of the patients.

Factor V Leiden mutation is the most common inherited form of thrombophilia [35]. Nevertheless, at least 50% of thrombotic episodes in individuals with Factor V Leiden mutation are provoked by additional predisposing factors [36]. To the best of our knowledge, only one case of sarcoidosis with Factor V Leiden mutation, presenting with cerebral venous thrombosis was described in the literature [9]. Authors concluded that since most factor V Leiden gene heterozygous individuals do not develop clinical thrombosis, the venous thrombosis of their patient suggested convergence of an inherited predisposition (heterozygous Factor V Leiden mutation) with an acquired thrombogenic stimulus (sarcoidosis). We have recently described a case of sarcoidosis complicated by PE in a sarcoidosis patient, in whom subsequently congenital Factor V Leiden mutation was found (data not published). We observed the favorable course of pulmonary sarcoidosis (total resolution of chest lymphadenopathy) with no impact on PFT and exercise ability during anticoagulation therapy in our patient with PE. A persistent disappearance of the pulmonary infiltrates in the patient with sarcoidosis during anticoagulant treatment for venous thrombosis has already been observed [37]. It is tempting to speculate about the anti-inflammatory potential of antithrombotic therapy. Unfractionated heparin (UFH) and LMWH proved to have the anti-inflammatory properties [38].

Conclusions

Pulmonary embolism, as a potentially fatal condition, may complicate clinically insignificant sarcoidosis. Pulmonary embolism should be considered in all patients with sarcoidosis and worsening respiratory symptoms in presence of a high plasma DD level although elevated plasma DD should be interpreted in the context of an active inflammatory process. In our opinion, an increased risk of VTE in sarcoidosis patients may depend mostly on a procoagulative phenotype related to the activity of inflammation. Congenital or acquired thrombophilia may also play a role in pathogenesis.

The authors declare no conflict of interest.

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