

## SARCOIDOSIS AS A RISK FACTOR FOR VENOUS THROMBOEMBOLISM

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**ABSTRACT.** Sarcoidosis as a chronic condition of immune dysregulation might be associated with increased risk of venous thromboembolism (VTE). In this study we report three cases of sarcoidosis and pulmonary embolism (PE) occurring together, that share common clinical, serological and pathological findings, confirming the diagnosis of active pulmonary sarcoidosis and no others co-existing prothrombotic factors. We hypothesized that the hypercoagulability and increased risk for VTE in sarcoidosis may be attributable to active local and generalized inflammatory process. The possible relation of clinical picture of sarcoidosis that favors thrombus formation and the bidirectional inflammation and coagulation process are discussed. Further investigation of PE in patients with sarcoidosis are required as the co-incidence of both diseases seems to be more frequent than expected. (*Sarcoidosis Vasc Diffuse Lung Dis* 2017; 34: 170-178)

**KEY WORDS:** sarcoidosis, pulmonary embolism, inflammation

### BACKGROUND

Deep venous thrombosis (DVT) and pulmonary embolism (PE), collectively known as venous thromboembolism (VTE) affect more than one per 1000 persons a year in western populations with higher risk among the elderly and patients with recent surgery, immobilization, fractures, pregnancy and cancer (1). In most cases VTE occurs when 2 or more risk factors are present at the same time (2, 3).

Sarcoidosis is a systemic disease of unknown etiology with systemic inflammation leading to formation of granulomas. Macrophages and activated leucocytes, immunological hallmarks of sarcoidosis, are known to increase activation of thrombin and fibrin formation (4, 5). Little is known about the incidence and origin of hypercoagulability and hypofibrinolysis in sarcoidosis. They are present as the result of acquired and/or congenital risk factors in different medical conditions. PE as a multifactorial disease rarely caused by a single risk factor might not be uncommon in advanced sarcoidosis (3). No data are available about the incidence of VTE in recently diagnosed sarcoidosis. We present the coincidence of sarcoidosis and PE in three patients who share some similarities in the clinical course of both diseases in order to search for some profibrotic phenotype of sarcoidosis.

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## CASE 1

A 42-year-old white male with a history of deep venous thrombosis of left lower extremity (confirmed with greyscale ultrasound and spectral Doppler) that occurred after a long car journey 2 years before presentation was admitted to emergency room of cardiology department in May 2013 due to significant and increasing exertional dyspnea (symptoms becoming acutely worse over the course of a few days), chest pain, signs and symptoms of respiratory infection and skin lesion on the left ankle. The patient was non-smoker. Physical examination showed fatigue, normal temperature, respiratory rate of 16/min, heart rate 100/min, oxygen saturation of 96% on room air and normal blood pressure. Lung, cardiac, abdominal examination were normal, no enlarged lymph nodes were found on palpation. No marked swelling, oedema and Homan's sign were found on lower extremities, a skin lesion on right ankle was consistent with erythema nodosum. Abnormal laboratory findings included: monocytosis in white blood count (WBC), elevated: erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), D-dimer, serum angiotensin converting enzyme activity (ACE) and Fibrinogene. NTproBNP : 2576 pg/ml (normal <125 pg/ml); Troponine T: 76,11 ng/l (normal <14) were markedly increased. No other important abnormalities in blood morphology or biochemistry were found (table 1). Transthoracic echocardiograph showed normal left-ventricular (LV) function (LV ejection fraction was greater than 55%), dilated right ventricle (RV A 26 cm<sup>2</sup>) and severe pulmonary hypertension (right ventricular systolic pressure RSVP 70 mmHg); apical hypokinesis of right ventricle; dilatation of pulmonary truncus (30 mm), severely diminished acceleration time (AcT): 55 ms; flat inferior vena cava with diameter of 20 mm and low respiratory variability. A Doppler ultrasound of lower extremities showed thrombosis involving left posterior tibial and peroneal veins. On computed tomography (CT) angiogram bilateral pulmonary thrombus were seen in multiple pulmonary peripheral and central arteries (right inferior lobe artery, subsegmental and segmental right inferior lobe arteries, apical left and lingual arteries, left lower lobe artery, segmental and subsegmental branches of left pulmonary artery (to the posterior and lateral segments of inferior left lobe). Thorax CT scans showed mediastinal lymphadenopathy and pa-

renchymal infiltration with distribution of disseminated opacities typical for sarcoidosis. A diagnosis of DVT and PE coexisting with pulmonary sarcoidosis was made based on clinical and radiological diagnostic criteria of both diseases. Patient was started on rivaroxabane. When his general condition improved he was referred to the pulmonary department for histopathological confirmation of sarcoidosis. A flexible bronchoscopy was performed 2 months after the acute PE event and transbronchial lung biopsy (TBLB) revealed non-caseating granulomas consistent with sarcoidosis. Tissue cultures and specific staining for mycobacterial and fungal pathogens were negative. At this time patient became asymptomatic with good exercise tolerance, pulmonary function tests were normal, including the 6 minute walking test. There was no eye or other organ involvement. Control CT scans showed spontaneous partial regression of disseminated changes and mediastinal lymphadenopathy. Important regression of thrombotic material in pulmonary arteries with only residual mural thrombosis was observed: in middle lobe pulmonary artery, right lower lobe pulmonary artery, in proximal parts of segmental branches (to segments 8, 9, 10); in left pulmonary artery, in lower lobe pulmonary artery and in basal segmental branches. No radiological signs of pulmonary hypertension were seen. At echosonography right heart size became normal, AcT was 100 ms, tricuspid valve pulmonary gradient (TVPG) was 27 mmHg and pulmonary pressure was within normal limits. Laboratory findings at 2 months after initiation of therapy and during the patient's follow up were irrelevant. Serum ACE, non-specific inflammatory biomarkers, D-dimer and fibrinogene plasma levels, biochemical markers of heart injury have normalized. After eight months of anticoagulation patient remained in a good general condition with no respiratory or cardiac symptoms and good exercise tolerance. Control CT scans showed progression of disseminated changes in lung parenchyma (consistent with sarcoidosis stage II according to Scadding classification) with no changes in lymph nodes diameter and no changes in the areas of thrombosis. No abnormalities in cardiac echosonography were observed. PFT and 6MWT remained within normal limits. No signs and symptoms of extrathoracic sarcoidosis were observed. No immunosuppressive therapy was needed, patient was maintained on Rivaroxaban. During patient's follow-up the procoagulant

**Table 1.** Clinical and Laboratory findings in sarcoidosis patients with acute episode of pulmonary embolism

	Case 1	Case 2	Case 3
Age at PE diagnosis	42	48	39
Time interval between sarcoidosis and PE diagnosis (years)	Simultaneous diagnosis	2	0,2
BMI (kg/m <sup>2</sup> )	28,3	29,1	30,4
WBC (x10 <sup>9</sup> /L, N: 4,23-9,07)	9,1	4,6	8,51
Monocytes % (N: 5,3-10)	11	12,7	15
RBC (x10 <sup>12</sup> /L, N: 4,63-6,08)	4,86	5,26	4,67
Hb (g/dL, N: 13,7-17,5)	16,3	14,8	13,7
Ht (% , N: 40-51)	45	44,6	40,5
Platelets (x10 <sup>9</sup> /L, N:130-400)	316	253	284
Glucose (mg/dL, N: 74-99)	85	90	100
Total protein (g/dL, N: )	7,3	8,2	7,8
Albumin (% ,N: 53-66)	62,9	53	50,13
Alpha 1-globulin (% ,N: 2-5,5)	3,5	2,8	5,38
Alpha-2 globulin (% N: 6-12)	8	7,3	10,22
Beta -globulin (% ,N: 8-15)	6,3	14	15,95
Gamma-globulin (% , N: 11-21)	13,8	26	24
D-dimer (mmcg/L, N:68-494);	6430,0	700	3578,0
Fibrinogen (g/L, N: 1,8-3,5)	5,74	4,6	6,05
CRP (mg/L ,N<5)	33	8,2	24
ESR (mm/h, N: <10)	12	15	60
ACE (IU/L , N:8-52)	88	76	113,4
ASPAT (U/L, N: 17-59)	37	40	52
ALAT (U/L, N: 21-72)	51	58	71
GGTP (U/L, N: 15-73)	59	70	61
ALP (U/L, N:38-126)	79	96	100
Creatinine mg/dL, N:66-1,25)	0,9	0,99	1,1
LDH (U/L, N: 313-618)	506	500,0	585
Calcium (mmol/L, N:2,1-2,55)	2,3	2,3	2,3
Phosphor (mmol/L, N: 0,81-1,45)	1,0	0,95	1,2

Laboratory findings 2 months after the acute episode of PE

risk factors were investigated. No procoagulant risk factors others than long car journey 2 years before presentation were found at the initial evaluation of the patient. Repeated laboratory testing showed (at initial evaluation and after 6 months of treatment): negative antinuclear antibody (ANA), negative anti-cardiolipin antibodies (ACLA) (IgG, IgA, IgM) and lupus anticoagulant (LAC), normal level of serum beta2 glucoprotein antibody (IgG, IgM). Protein S, Protein C and Antithrombin III serum levels were normal before initiation of anticoagulation and after 8 months of therapy. Factor V Leiden, prothrombin G20210A mutations and gene MTHFR C677T mutations were absent. No underlying systemic inflammatory disease other than sarcoidosis or malignant disease were diagnosed over 8 months of follow-up.

## CASE 2

A 48-year-old male was admitted in October 2014 to the pulmonary department for evaluation of progressive pulmonary sarcoidosis. The diagnosis of sarcoidosis was given two years before presentation, based on clinical and radiological findings with no biopsy confirmation (TBLB was inconclusive) when patient underwent diagnostic resection of left side cervical tumor. Pathologic examination showed congenital benign cervical cyst, special stains for acid fast bacilli and fungi were negatives. The chest radiograph (CXR) followed by CT scans both revealed bilateral hilar and mediastinal lymphadenopathy with disseminated parenchymal changes consistent with sarcoidosis. No abnormalities were found in

PFT and 6 minute walking test. No signs and symptoms for extrathoracic sarcoidosis were observed. He was not taking any medication and his symptoms remained non-specific and unchanged until 2 months before presentation to pulmonary department. In August 2014 he experienced an acute episode of worsening chest pain, haemoptysis, dyspnea, fever and orthopnoe. He was consulted by a physician, the diagnosis of respiratory infection was followed by antibiotic therapy with slow symptoms recovery over few weeks. Control CT scans revealed the progression of parenchymal opacities and left low-sized pleural effusion of uncertain etiology. The patient was referred to pulmonary department to confirm the previous diagnosis of sarcoidosis. He was admitted to the hospital 2 months later in a good general condition with no respiratory distress. He did not smoke. He had family history of psoriasis. The patient was diagnosed with psoriasis 1 year previously and asthma- 2 years previously, symptoms were limited to occasional cough and breathlessness which were partially relieved by combination of long acting beta-2 agonist and corticosteroid inhaler. No allergy was found. On admission he was experiencing only minimal non-specific chest discomfort and cough - symptoms which had remained since August 2014. His physical examination was normal with only minimal local skin lesion typical for psoriasis and a skin scar after the left cervical tumor resection- unchanged over the time. Oxygen saturation was 98%, electrocardiogram, standard morphology and chemistry profile (table 1) were unremarkable, apart from monocytosis in WBC. Plasma D-dimers, fibrinogene, CRP, ESR were above normal limits. Hipergammaglobulinemia was found in proteinogramme. PFT and 6 MWT remained normal. Investigation for extrathoracic sarcoidosis revealed splenomegaly in abdominal ultrasound, with the structure of spleen in CT scans suggesting sarcoid granulomas infiltration. Low size bilateral cervical lymphadenopathy in ultrasound examination were observed. No eye (ophthalmic examination), or cardiac involvement in ecg and echocardiography were seen. TBLB showed well-formed non caseating granulomas and confirmed the initial clinical and radiological diagnosis of sarcoidosis. Because of history of hemoptysis which was not a typical symptom for progression of sarcoidosis and history of pleural effusion of uncertain etiology in CT scans

performed in August 2014, elevation of plasma D-dimers in onetime laboratory examination the control chest CT angiogram was performed. Images were compared to CT scans from August 2014. The retrospective analysis of CT scans from August 2014 confirmed the presence of pleural fluid on left side which disappeared over two months' time in onetime pictures and showed the peripheral parenchymal opacities typical for pulmonary infarction in segment 10 of lower left lobe, that were misinterpreted as progression of sarcoidosis. The clot in segmental artery was difficult to visualize because the radiological examination was not performed in vascular protocole. The diagnosis of pulmonary thromboembolism was given, based on retrospective analysis of chest CT scans from August 2014. A very good clinical outcome over 2 months (no thrombotic changes, complete resolution of pleural effusion in control chest CT angiogram from October 2014) without anticoagulation was observed. The progression of parenchymal sarcoidosis was reconfirmed. His chest symptoms (in August 2014) misinterpreted as respiratory infection were almost certainly due to undiagnosed pulmonary embolism. A venous Doppler ultrasound revealed normal and patent vessels of lower extremities. Despite the spontaneous resolution of pulmonary thrombus and good general condition the patient was anticoagulated with rivaroxaban to reduce the risk of recurrent thrombosis. During the follow-up the patient underwent the procoagulant risk factors evaluation. He was not taking any medication, was not obese, had no injury, immobilization, surgical intervention previous to thrombotic event. No underlying malignant disease was found during clinical, radiological and laboratory investigations. Laboratory studies showed normal levels of Antithrombin III, Protein S, Protein C, absence of genetical mutations of Factor V Leiden, gene MTHFR C677T and prothrombin G20210A. ESR and CRP became normal, Rheumatoid factor (RF), ACLA (IgG, IgA, IgM) were negative, serum beta2 glycoprotein antibody (IgG, IgM) were within normal limits. On the other hand LAC was found and reconfirmed after 12 weeks to be positive by coagulometric assays. ANA was greater than 1:640. ACLA antibodies on repeated profile testing were negatives. Repeated testing showed persistent elevation of ANA and LAC six months later. Clinical and radiological joint examination revealed no changes,

no neurological symptoms or renal dysfunction were observed. No clinical symptoms or biochemical manifestation were consistent with systemic lupus erythematosus (SLE) and patient didn't fulfill the diagnostic criteria. The serological abnormalities of elevated ANA and LAC might have been attributable to sarcoidosis. The patient was maintained on anticoagulation during 6 months. There was no indication for immunosuppressive therapy for sarcoidosis as the patient was asymptomatic and his PFT remained stable over time of follow-up.

### CASE 3

A 39-year-old male with previously confirmed pulmonary sarcoidosis, hypertension, obesity and glucose intolerance, with no smoking history and no relevant family history was admitted to the Pulmonary department in March 2007 for fatigue and exertional dyspnea, fever for 8 weeks and continuous weight loss of 20 kg in 12 week. He was diagnosed with pulmonary sarcoidosis 2 months before presentation. In that time he was seen in his district hospital emergency room for progressive dyspnea, fatigue, fever, weight loss, swelling of both lower extremities and intense disseminated joint pain with no marked skin lesions or other important abnormalities in cardiac or respiratory physical examination. The diagnosis of sarcoidosis was based on clinical and radiological examination (thorax CT scans revealing hilar and mediastinal lymphadenopathy) and confirmed by biopsy of mediastinal lymph nodes (mediastinoscopy). Due to persistent respiratory and general symptoms he was reconsulted by a physician who decided to perform the second CT scan. The high resolution CT (HRCT) showed progression of mediastinal lymphadenopathy and disseminated changes in lung parenchyma - images consistent with progression of pulmonary sarcoidosis. The presence of non-caseating epithelioid cell granuloma containing giant cells was re-confirmed in TBLB. The patient was referred to our pulmonary department. On admission he was in good general condition. He complained of fatigue, dyspnea and swelling of both ankles. At physical examination there were no signs of peripheral lymph nodes enlargement, cutaneous nodules, erythema or uveitis, Homan's signs were negatives in both legs. Lung and cardiac examination

were normal. The CXR showed lymphadenopathy and bilateral opacities typical for sarcoidosis stage II according to Scadding classification. No signs or symptoms for extrapulmonary sarcoidosis were observed, no abnormalities in ecg, echosonography, abdominal ultrasonography were detected. Repeated testing showed persistent plasma D-dimer elevation (3578,0 mcg/l, normal range 68-494). Plasma ACE activity (113,4 IU/l; normal range 8-52), CRP and ESR were increased. Monocytosis in WBC and unspecific hipergamma globulinemia at proteinogram were observed. No other important abnormalities were found at standard morphology and chemistry (table 1). Blood gas analyses and respiratory function tests were normal. Because of respiratory symptoms and laboratory findings the patient was investigated for PE. He refused the third chest CT to be performed in 2 months' time. Scintigrams of pulmonary perfusion (vascularization) and ventilation were performed after application of intravenous radioactive isotopes labeled with technetium 99 m. A high-probability test result, with bilateral multiple segmental defects on perfusion scintigraphy in combination with a normal ventilation scintigraphy, was diagnostic for PE. The patient was treated with subcutaneous low molecular weight heparin and then was maintained on warfin. Ultrasound studies of the lower extremities showed no signs of thrombosis. The procoagulant risk factors other than his obesity were investigated. No underlying malignant disease or other known extrinsic risk factors for VTE were discovered. Levels of Antithrombin III, Protein S, Protein C were within normal limits, Factor V Leiden, gene MTHFR C677T and prothrombin G20210A mutations were absent. The repeated testing for ACLA (IgG, IgM), ANA, ANCA, LAC, RF, beta2 glicoprotein antibody (IgG, IgM) was negative and remained persistently negative during patients follow up. His perfusion scintigraphy became normal after 2 months of anticoagulation and patient recovered after therapy from all respiratory symptoms. Plasma D-dimer and others unspecific biomarkers of inflammation became normal. During 7 years of follow-up for his pulmonary sarcoidosis no immunosuppression therapy was needed as the spontaneous partial regression of radiological changes was observed and patient remained asymptomatic.

## DISCUSSION

Recent data from the U.K. suggest that sarcoidosis is a risk factor for PE (6). The risk of PE was significantly higher in sarcoidosis patients (rate ratio 2.0, 95% CIs 1.1 to 3.4, for the under 65 year old) comparing to reference cohort but the authors admit that little was known about the patients other than their International Classification of Diseases (ICD) codes (e.g. sarcoidosis, PE). No data was collected on diagnostic criteria of PE, sarcoidosis and potential confounding factors (eg corticosteroid CS therapy, smoking status, other risk factors for venous thrombosis) in this study. The authors could not examine the effect of age, gender, race on the association between sarcoidosis and PE. Swigris et al using death certificate data from 1988 to 2007 detected an association between sarcoidosis and PE (2.5% of PE among US decedents with sarcoidosis) regardless of gender, race or age (7). Authors admit the data set they used didn't allow them to determine the level of sarcoidosis activity at the time the PE occurred and they could not conclude what is driving the risk of PE in sarcoidosis. A retrospective chart review on treatment outcomes in sarcoidosis revealed a disproportionately high number of PE (6.2%) in sarcoidosis Netherlands cohort.

The true incidence of co-incident sarcoidosis and VTE is unknown.

The co-existence of sarcoidosis and VTE might be discussed from different points of view:

1. The clinical picture of sarcoidosis that favors thrombus formation, ex chronic disabling sarcoidosis associated with steroid treatment and its complications (immobilization because of pulmonary fibrosis, pulmonary hypertension, osteoporosis with fractures and immobilization, obesity etc), presence of vascular granuloma, extrinsic compression of pulmonary arteries by mediastinal/hilar lymphadenopathy,
2. The bidirectional inflammation and coagulation process,
3. Co-existence of sarcoidosis and others acquired or genetically transmitted diseases that are known to be at high risk of DVT (eg antiphospholipid syndrome).

We have conducted a retrospective analysis of clinical outcome and comorbidities among 798 sarcoidosis patients that have been hospitalized in the

pulmonary department of our Institution between 2004 and 2014. We have found 8 symptomatic cases of sarcoidosis co-existing with PE with a fatal outcome in one case (data not published). From the follow-up we have excluded patients who developed PE during steroid therapy in a settle of chronic progressive sarcoidosis, because those are known risk factors for VTE and one patient in whom PE was associated with gene V Leiden mutation.

We have recently followed three cases as presented above, of sarcoidosis occurring together with PE. We have found some similarities in clinical outcome of both diseases. All patients were males at the middle age of 43 years. All patients were non-smokers. None of our patient at PE diagnosis had severe disabling sarcoidosis with respiratory, cardiac, joint, muscle or neurologic system involvement that could led to immobility and in this way contribute to VTE. Swigris in his study found that sarcoidosis decedents with PE were less likely than those without PE to have certain other conditions that might have predisposed to PE, including myocardial infarction or ischemia, congestive heart failure, cardiomyopathy, cardiac dysrhythmia, sudden cardiac death, pneumonia or stroke contribute to death (7). None of the medical conditions mentioned above were not found in our sarcoid patients with PE. None of our patients suffered of pulmonary hypertension (PH) prior to PE diagnosis and no one was on immunosuppressive treatment-two conditions known to contribute to VTE complications (8). Extrinsic arterial compression at mediastinal or hilar level was not seen in pulmonary angiography and there was no evidence of pulmonary vascular compression on the CT scans despite chest adenopathy in any of our patients (9). As the histopathological diagnosis was based on fine needle biopsy it was impossible to determine about the presence of vascular granulomata as a risk factor for local thrombosis (10, 11). PE was discovered in a settle of recently diagnosed active sarcoidosis in all cases (12, 13). Respiratory and chest complaints at presentation are difficult to interpret as both medical conditions can have similar symptomatology.

A number of markers of disease activity among subjects with sarcoidosis have been reported (14-19). We have observed several common laboratory findings (monocytosis, elevated ACE, CRP, ESR) in our set of patients that correspond to active sarcoidosis. A definitive role for humoral immunity in

the pathogenesis of sarcoidosis is not established but the B cell activation expressed by nonspecific hypergammaglobulinemia that is observed in active disease may reflect the more generalized inflammatory process (20). In 2 out of 3 presented cases non-specific hypergammaglobulinemia was observed. Granulomatous inflammation in sarcoidosis develops under the regulatory influence of cytokines produced by local mononuclear phagocytes (5, 21). One of the hallmark of sarcoidosis is the compartmentalization of blood monocytes. Epithelioid cells and Giants cells develop and aggregate into compact structures under the influence of the inflammatory milieu. Mononuclear cell infiltrates may be found surrounding discrete granulomata and at tissue sites that do not contain well-formed granulomata (5, 21, 22). Laboratory studies have shown that peripheral blood monocytes, when incubated with highly purified (>90%) human CRP for 6 hours, exhibit a significant increase in procoagulant activity due to an increase in the expression of tissue factor, an initiator of the extrinsic pathway of coagulation (23). This finding could partially explain the high procoagulant ability of granulomatous inflammation in sarcoidosis. The cell-associated procoagulant activity of macrophages lavaged from patients with sarcoidosis has been examined (24). The enhanced BAL fluid tissue factor and plasma Factor VII activities were observed in sarcoid patients as compared to normal control subjects and the tissue factor activity correlated with disease activity as judged by radiographic stage. Only patients with stage II or stage III disease had consistently elevated procoagulant activity. Additionally the enhanced procoagulant activity corresponded to the side most involved radiographically. The asymmetry of arterial thrombotic process in the lungs or other sites of granulomatous inflammation may depend on the heterogeneity of inflammation that has been proved to correspond to the local variability of tissue factor activity (23, 24).

The high BAL concentration of D-dimers was demonstrated in active pulmonary sarcoidosis (25, 26). Locally derived IL-6 and IL-8 were increased in sarcoidosis and correlated with activity of this granulomatous lung disease (18). It may reflect the local abnormalities of procoagulation and fibrinolysis and explain local thrombus formation (pulmonary vessels involvement). Active pulmonary sarcoidosis with progression of parenchymal granulomatous process

might be associated with local tissue thrombophilia. Those findings are consistent with our observations as in all presented cases active pulmonary sarcoidosis with parenchymal infiltrations (stage II) was diagnosed. In 2 cases no peripheral DVT was found. There are few reported cases of thrombus formation in a variety of organs in sarcoidosis but the common feature of them was that venous thrombosis were in close anatomic relation with active sarcoidosis: mural thrombus in myocardial sarcoidosis (27), vein thrombosis in neurosarcoidosis (28-30), thoracic vein thrombosis in mediastinal disease (31, 32), portal vein hypertension in hepatic sarcoidosis (11). PE in pulmonary sarcoidosis might result from local hypercoagulability being the consequence of active granulomatous inflammation.

In all presented cases we observed high D-dimer plasma concentration which contributed to correct PE diagnosis at initial evaluation. D-dimer, a product of cross-linked fibrin, indicates on-going coagulation cascade activation and inflammation. The clinical role of D-dimer in different inflammatory conditions have been studied. Elevated plasma D-dimers have been associated with: occurrence of myocardial infarction in peripheral arterial disease (33), higher risk for multisystem organ failure (MSOF) and death in critically ill patients (34). It has been shown that D-dimers plasma levels correlate with activation of the proinflammatory cytokine cascade (IL-6, IL-8, TNF  $\alpha$ ). In the same study the authors have observed an absence of a relationship between D-dimers and anti-inflammatory cytokine (IL-10). They concluded that plasma elevation of D-dimers in critically ill patients may reflect the imbalance between proinflammatory and anti-inflammatory cytokines (34). Some sarcoid patients without DVT have elevated D-dimer level in peripheral circulation (25, 35). The correlations were observed between high plasma or BAL D-dimers levels and symptomatic sarcoidosis, sarcoidosis activity, pulmonary infiltrations, need for systemic therapy, worsening lung function (25, 26, 35). The plasma D-dimer concentration does not correlate with BAL D-dimer levels in sarcoidosis (25). In our group of patients the high plasma D-dimers reflected the hypercoagulation and prothrombotic status rather than was a marker of unfavorable prognosis of sarcoidosis. In our patients plasma D-dimers level went back to normal values with the antithrombotic therapy and the clinical outcome of sarcoidosis was

good although the observational time in 2 patients is too short to derive a definite conclusion. In this context only high BAL D-dimer concentration and not plasma level may be regarded as a risk factor or marker of PE in sarcoidosis. Among sarcoidosis patients there may be important differences in the initial inflammatory reaction that affect the procoagulant potential. The intensity of the inflammatory reaction varies among patients, and inflammation often fluctuates over time in a given patient. Failure to downregulate inflammation in sarcoidosis explains the long course of the disease (21). It is tempting to hypothesize that it also may be an important contributor to hypercoagulation in active sarcoidosis. Clinical picture of active sarcoidosis complicated by PE in middle age males in good general condition with no significant comorbidities is consistent with observation of Swigris and might suggest that the inflammatory granulomatous process alone may contribute to PE development, without any other risk factors (7). In 2 out of 3 patients diagnosis of sarcoidosis preceded the diagnosis of PE, in one case the diagnosis of both conditions was simultaneous. In the analysis of bidirectional relation between sarcoidosis and VTE this fact might support the hypothesis that an exaggerated or insufficiently controlled sarcoid inflammatory process leads to local or systemic activation of coagulation.

As the relationship of sarcoidosis and VTE is not clearly understood it might be related to comorbidities. Antiphospholipid antibodies - one of diagnostic criteria for antiphospholipid syndrome (APS) which by definition is characterized with recurrent thromboembolic events (36), were detected in 38% of sarcoidosis patients (37). They were associated with extrathoracic lesions in sarcoidosis, persistence of abnormal findings in CXR and judged by authors to be a useful marker for prolonged disease. The authors didn't search for DVT complications and PE in that group of sarcoid patients, although those patients should be considered at high risk for such events. Authors could not conclude about the presence of concomitant APS in that group of sarcoid patients. On the other hand in the numerous reports concerned with thrombotic events among sarcoidosis patients the level of antiphospholipid antibody was not determined (11, 27-31). It is impossible to conclude from the literature that the increased risk for VTE in sarcoidosis depends on the presence of an-

tiphospholipid antibodies. In any of our sarcoidosis patients with confirmed PE we didn't find the presence of antiphospholipid antibodies by repeat testing, so the VTE in those cases can definitely not be associated to concomitant APS syndrome.

In all our cases the VTE had favorable course with no serious late complications. In all cases we observed the favorable course of pulmonary sarcoidosis with no impact on PFT and exercise ability. No clinically significant organ involvement was seen although in one case splenomegaly and peripheral lymph nodes sarcoidosis were diagnosed. Immunosuppressive therapy was not needed in any of presented cases.

Regarding some similarities in clinical and laboratory findings in our patients it was tempting to hypothesize that there might exist a prothrombotic phenotype of sarcoidosis.

## CONCLUSION

We have described three cases of patients with active pulmonary sarcoidosis accompanied by pulmonary embolism. No predisposing factors for VTE were detected. We hypothesized that the hypercoagulability and increased risk for VTE in sarcoidosis may be attributable to active local and generalized inflammatory process. Further investigation of PE in patients with sarcoidosis are required as the coincidence of both diseases seems to be more frequent than expected. Up to the present time the length of secondary prophylaxis is undetermined. In our opinion in active sarcoidosis complicated by VTE anticoagulation should not be discontinued.

Written informed consent was obtained from the patients for publication of this cases report. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

### Authors' contributions:

Dr Anna Goljan Geremek has made substantial contributions to conception and design, acquisition of data and intellectual content, analysis and interpretation of data, has written the manuscript, has given final approval of the version to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Prof Witold Tomkowski, Dr Marcin Geremek have made substantial contributions to analysis and interpretation of data, have been involved in revising manuscript critically for important intellectual



content, have given final approval of the version to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Dr Elzbieta Puscinska, Dr Michal Bednarek, Dr Adam Nowinski, Prof Grzegorz Malek have made substantial contributions to collection and interpretation of data, have given final approval of the version to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Prof Pawel Sliwinski, has been involved in revising the manuscript critically for important intellectual content, has given final approval of the version to be published and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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