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High incidence of venous thromboembolism but not of coronary artery disease in granulomatosis with polyangiitis in first years after diagnosis

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Abstract. *Objectives:* Granulomatosis with polyangiitis (GPA), previously known as Wegener's granulomatosis, is one of antineutrophil cytoplasmic autoantibody (ANCA) – associated vasculitis. In patients with GPA an increased incidence of venous thromboembolism (VTE), mainly during active disease, has been described. The aim of the present study was to assess the incidence of VTE and its relation with classic risk factors for atherosclerosis, presence of coronary artery disease (CAD), echocardiographic parameters and laboratory findings in GPA patients. *Methods:* The group of consecutive patients with GPA were followed in the study. In all patients echocardiography and laboratory tests were performed. *Results:* Ninety six patients with GPA were followed for mean 3 years. In 16 patients (16.6%) VTEs occurred in association with GPA, of which 56% occurred 6 months before or one year after diagnosis of GPA. Classic risk factors for atherosclerosis were present in 77 patients (80.2%) at some moment during follow-up. In patients with VTE there were larger right ventricle diameter (p=0.041) and higher right ventricle systolic pressure (p=0.022) observed. VTEs occurred significantly less frequently in patients treated with cyclophosphamide (p=0.049). In this study group VTE occurred more frequently than CAD: 16 (16.7%) vs. 4 (4.2%); p=0,0049. Patients with VTE were younger than those with CAD (p=0.053) and had higher levels of ANCA-PR 3 (p=0.016). *Conclusions:* Patients with granulomatosis with polyangiitis in first years after diagnosis have higher risk of venous thromboembolism than coronary artery disease. This finding is probably related to hypercoagulability induced by the disease and its therapy. *(Sarcoidosis Vasc Diffuse Lung Dis 2019; 36 (3): 202-208)*

Key words: vasculitis, granulomatosis with polyangiitis, venous thromboembolism, coronary artery disease

Introduction

Granulomatosis with polyangiitis (Wegener's; GPA) is an antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV), which also includes microscopic polyangiitis and eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome). GPA is characterized by granulomatous inflammation and necrotizing vasculitis mainly affecting small- and medium-sized blood vessels and the presence of ANCA directed to specific antigens, particularly proteinase 3 (PR3-ANCA) and myeloperoxidase (MPO-ANCA). The inflammatory processes in GPA have a predilection for the kidneys and respiratory tract, but any organs, including cardiovascular system, can be affected (1).

An increased incidence of various cardiovascular events has been described among GPA patients (2-

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4). In a retrospective analysis from the Danish National Hospital Register, patients with GPA showed an increased rate of cardiovascular events within the first 5 years after a diagnosis of GPA compared to the general population (3). Also in study by Aviña-Zubieta JA et al. patients with GPA have a significantly increased risk of myocardial infarction and a non-statistically significant trend toward an increased risk of ischemic stroke (4).

In recent years, the relationship between inflammation and thrombosis has been investigated and it turned out that immune and coagulation systems are functionally connected. Plasminogen has been described as an autoantigen in PR-ANCA patients. Its interaction with autoantibodies directed towards complementary PR3 is responsible for impairing fibrinolysis by blocking conversion from plasminogen to plasmin (5, 6). A procoagulant state caused by increase in endogenous thrombin and Factor VIII concentration was also reported in AVV patient in stable remission (7). Merkel PA et al. reported a high occurrence of pulmonary embolism (PE) and deep venous thrombosis (DVT) among GPA patients included in a randomized therapeutic trial (8). Of the observed venous thromboembolic events (VTEs), 81% occurred in patients with active or recently active vasculitis. A high incidence rate of VTEs was also calculated for patients with various ANCA-associated vasculitides in subsequent retrospective cohort studies (9-11).

The aim of the present study was to assess the incidence of coronary artery disease, PE, and DVT in a cohort of 96 patients diagnosed with GPA and followed for a median of 3 years.

Patients and methods

In this prospective cohort study, consecutive GPA patients who were hospitalized in the Department of Family Medicine, Internal and Metabolic Diseases at the Medical University of Warsaw in Poland between February 2010 and April 2017 were included. All patients were diagnosed with GPA according to current guidelines (12). Patients were entered into the study at the time point when a new diagnosis of ANCA-associated vasculitis was established and received initial treatment at our centre. Data collection included a full medical history, physical examination, laboratory studies and review of adverse events. Additionally, in all patients an echocardiography was performed. M-mode and two-dimensional standard echocardiography (Mindray M7, Shenzhen Mindray Bio-Medical Electronics Co.) followed by pulsed and continuous-wave Doppler recordings were performed by one experienced cardiologist. Five consecutive measurements were averaged for each parameter. All patients were tested for ANCA by indirect immunofluorescence and enzyme-linked immunosorbent assay (ELISA). Control visits were planned every three months. On each visit physical examination, laboratory studies, review of adverse events and ECG were performed. Additionally, every six months all patients had a scheduled echocardiogram. A patient was considered to have had a VTE if the event was clinically apparent and was confirmed by diagnostic studies (vascular ultrasonography or computed tomographic angiography). All patients with CAD diagnosis had coronarography performed.

All VTEs were counted in patients after diagnosis of GPA, adding a period of 6 months before the diagnosis of GPA was made. We added this period because, due to diagnostic delay, in most cases GPA had been active some time before the diagnosis was made. VTEs occurring in this period were considered GPA associated. VTEs occurring in association with a central venous catheter were excluded. In addition, we compared demographic and clinical characteristics and risk factors in patients who develop a VTE associated with GPA and those who did not develop a VTE. Finally, patients with VTE were compared to patients diagnosed with CAD.

The study protocol was approved by the ethics committee of the Medical University of Warsaw. Written informed consent was obtain from each participant.

Continuous variables are summarized as means and SD or as median and inter-quartile range. Qualitative variables are presented as counts and percentages . Comparisons between groups were made using Student's t-test for numerical, normally distributed data, the Mann-Whitney test for continuous variables not normally distributed and the Pearson's chi2 test or the Fisher's exact test (in case of minimum expected count less than 5) for categorical data. Pearson's or Spearman's correlation coefficients were calculated to investigate the associations between parameters. All hypotheses testing were two-tailed

with a p<0.05 type I error. All analysis were performed with SAS 9.2 software (SAS Institute Inc, Cary, NC, USA).

Results

Patients baseline characteristics is presented in Table 1. The median observation period was 3 years (range: 0.1-5.8 years) and none of the patients were lost to follow-up. Majority of patients (73%) were ANCA - positive at diagnosis. Classic risk factors for atherosclerosis were present in 77 patients (80.2%) at some moment during follow-up. Five or more internal involvement were observed in 22% of GPA patients. Over 84% of patients were treated with glucocorticoids, 16% with azathioprine and 47% with cyclophosphamide. In total VTE occurred in 16 (16.6%) patients; 4 VTEs (4%) occurred before and 12 (12,5%) after inclusion in the study. Among patients with VTE 13 had deep venous thromboses, 2 pulmonary emboli and one both. VTEs which occurred in association with GPA, in 56% occurred six months before or one year after inclusion to the study. Table 2 shows the differences between patients with and without VTEs. There were no difference between patients with and without VTEs in internal organs involvement. There were also no significant differences in age, classic risk factors for atherosclerosis, creatinine, ANCA antibodies and CRP levels. In echocardiography patients with VTE had larger right ventricle diameter (28.9±4.4 vs. 31.6±5.6; p=0.041) and higher right ventricle systolic pressure (32.8±5.4 vs. 36.3±5.9; p=0.022) observed. VTEs occurred significantly less frequently in patients treated with cyclophosphamide (51.9% vs. 25.0%; p=0.049). In this study group VTE occurred more frequently than coronary artery disease: 16 (16.7%) vs. 4 (4.2%); p=0,0049. The CAD events included 2 cases of myocardial infarction, one of unstable angina treated with CABG and one of unstable angina treaded with coronary angioplasty. Table 3 presents a comparison between patients with VTEs and CAD. There were no significant differences in classic risk factors, immunosuppresives use, internal involvement, creatinine and CRP levels. Patients diagnosed with CAD had higher interventicular septal diameter and all of them had left ventricle diastolic dysfunction. Patients with VTE were younger than those with CAD (50.7±16.2 vs. 66.5±10.8; p=0.053), had higher right ventricular systolic pressure (36.3±5.9 vs. 28.7±4.6; p=0.03) and had higher levels of ANCA-PR 3 (16.6 vs. 1.5; p=0.016).

Table 1. Patients characteristics at baseline

	N=96
Age, years	50,6±14,6
Sex, female, n (%)	62 (64,6%)
Hypertension, n (%)	64 (66,7%)
Hypercholesterolemia, n (%)	66 (68,7%)
Diabetes, n (%)	24 (25,0%)
Hypertension or Hypercholesterolemia or Diabetes, n (%)	77 (80,2%)
Coronary artery disease, n (%)	1 (1%)
Venous thromboembolism, n (%)	4 (4%)
Echocardiography	
Aorta diameter, mm	31,8±3,5
Left atrium diameter, mm	36,4±4,7
Interventricular septal diameter, mm	10,7±1,9
Posterior wall thickness, mm	10,4±1,3
Left ventricular diastolic diameter, mm	45,2±5,5
Left ventricular systolic diameter, mm	24,4±4,8
Right ventricular diameter, mm	29,4±4,7
Pulmonary artery diameter, mm	19,7±1,8
Vena cava inferior diameter, mm	17,1±2,4
Pulmonary acceleration time, ms	129±18
Right ventricular systolic pressure, mmHg	33,4±5,6
Left ventricular ejection fraction, %	62,9±6,7
Left ventricular diastolic dysfunction, n (%)	23 (30,7%)
TAPSE, mm	21,6±2,5
Internal involvement	
Eyes, n (%)	30 (31,2%)
Ears, n (%)	17 (17,7%)
Genitourinary, n (%)	1 (1,0%)
Musculoskeletal, (%)	40 (41,7%)
Upper respiratory tract, n (%)	81 (84,4%)
Lower respiratory tract, n (%)	69 (71,9%)
Kidney, n (%)	50 (52,1%)
Central nervous system, n (%)	11 (11,5%)
Peripheral nervous system, (%)	20 (20,8%)
Skin, n (%)	9 (9,4%)
Creatinine, mg/dl	1,6 (1,3-3,8)
Hs-CRP, mg/dl	1,5 (0,4-10)
Troponin I, ug/l	0,010
Five or more internal involvement, n (%)	21 (21,9%)
ANCA-positive, n (%)	70 (72,9%)
Anti-MPO-positive, n(%)	7 (7,3%)
Anti-PR3-positive, n (%)	63 (65,6%)

Discussion

In this prospective study, we investigated the incidence of venous thromboembolism and coronary

Table 2. Comparison between GPA patients with and without episodes of venous thromboembolism

	Patients without VTE, N=80	Patients with VTE, N=16	p
Age, years	52,6±14,4	52,7±16,2	0,978
Disease duration since diagnosis, years	2 [0,1-4,60]	2 [0,2-5,8]	0,996
Sex, female, n (%)	52 (65,0%)	10 (62,5%)	0,849
Hypertension, n (%)	55 (68,7%)	9 (56,2%)	0,339
Hypercholesterolemia, n (%)	56 (70%)	10 (62,5%)	0,555
Diabetes, n (%)	20 (25,0%)	4 (25,0%)	1,00
Hypertension or Hypercholesterolemia or Diabetes, n (%)	67 (83,7%)	10 (62,5%)	0,081
Coronary artery disease, n (%)	4 (5%)	0 (0%)	1,000
Echocardiography			
Aorta diameter, mm	31,7±3,3	32,2±4,3	0,603
Left atrium diameter, mm	36,2±4,7	37,1±4,8	0,499
Interventricular septal diameter, mm	10,7±1,3	10,6±1,4	0,852
Posterior wall thickness, mm	10,4±1,3	10,4±1,1	0,972
Left ventricular diastolic diameter, mm	45,0±5,5	46,0±5,2	0,513
Left ventricular systolic diameter, mm	24,2±4,9	25,2±4,4	0,416
Right ventricular diameter, mm	28,9±4,4	31,6±5,6	0,041
Pulmonary artery diameter, mm	19,6±1,9	19,9±1,6	0,655
Vena cava inferior diameter, mm	17,0±2,4	17,4±2,8	0,544
Pulmonary acceleration time, ms	129±16	131±24	0,748
Right ventricular systolic pressure, mmHg	32,8±5,4	36,3±5,9	0,022
Left ventricular ejection fraction, %	62,6±7,0	64,2±5,2	0,378
Left ventricular diastolic dysfunction, n (%)	21 (33,9%)	2 (15,4%)	0,321
TAPSE, mm	21,3±2,4	22,4±2,8	0,236
Glucocorticoids, n (%)	69 (86,2%)	12 (75%)	1,00
Azathioprine, n (%)	12 (15,2%)	4 (25%)	0,462
Cyclophosphamide, n (%)	41 (51,9%)	4 (25,0%)	0,049
Creatinine, mg/dl	0,9	1,0	0,219
Hs-CRP, mg/dl	0,40	0,50	0,794
Troponin I, ug/l	0,010	0,008	0,811
MPO-positive, n(%)	6 (7,5%)	1 (6,2%)	1,00
PR3-positive, n (%)	51 (63,7%)	12 (75,0%)	0,3871

artery disease (CAD) in a large homogenous cohort of GPA patients and the possible influence of disease duration and classic risk factors for CAD on the occurrence of VTEs and CAD episodes. We found an increased incidence of VTE in comparison to CAD in first years after the diagnosis of GPA. Interestingly, although most of GPA patients (80%) had CAD risk factors (hypertension, hypercholesterolemia or diabetes), they presented more frequently with VTE than with CAD episodes. However, some risk factors for atherosclerosis (cigarette smoking, obesity, hypercholesterolemia, hypertension and diabetes mellitus) are shared with venous thromboembolism. Our data are in line with the findings by Merkel et al. from Wegeners's granulomatosis Etanercept Trial (WGET). In the WGET trial 180 patients with GPA were followed for more than 2 years. In the end of the observation period, 29 of 180 GPA patients (16%) have had a VTE diagnosed. They found that an increased incidence of VTEs, mainly (83%) occurred 2 months prior to or following a diagnosis of active disease (8). The pathogenic background for the high VTE risk in GPA is poorly understood. The development of VTEs was not related to traditional clinical risk factors for venous thromboembolism in 2 studies of patients with ANCA-associated vasculitis (9, 10), while Allenbach et al. identified higher age, male sex, previous VTE and strokes as risk factors for VTEs in a retrospective analysis involving 1130 patients with systemic necrotizing vasculitides (11). Novikov et al. reported than majority of their patients with VTE were young, had no known risk factors for thrombo-

Table 3. Comparison between patients with venous thromboembolism and patients with coronary artery disease

	Patients with VTE, N=16	Patients with CAD, N=4	P
Age, years	50,7±16,2	66,5±10,8	0,053
Disease duration since diagnosis, years	2 [0,1 – 5,8]	2 [1 – 3,5]	0,8844
Sex, female, n (%)	10 (62,5%)	2 (50%)	1,00
Hypertension, n (%)	9 (56,2%)	4 (100%)	0,249
Hypercholesterolemia, n (%)	10 (62,5%)	4 (100%)	0,267
Diabetes, n (%)	4 (25,0%)	0 (0%)	0,538
Hypertension or Hypercholesterolemia or Diabetes, n (%)	10 (62,5%)	4 (100%)	0,267
Echocardiography			
Aorta diameter, mm	32,2±4,3	33,7±2,1	0,497
Left atrium diameter, mm	37,1±4,8	40,2±2,9	0,237
Interventricular septal diameter, mm	10,6±1,4	12,2±1,5	0,050
Posterior wall thickness, mm	10,4±1,1	11,7±1,0	0,051
Left ventricular diastolic diameter, mm	46,0±5,2	49,5±9,6	0,321
Left ventricular systolic diameter, mm	25,2±4,4	31,5±9,6	0,285
Right ventricular diameter, mm	31,6±5,6	32,0±3,3	0,884
Pulmonary artery diameter, mm	19,9±1,6	20,7±1,7	0,343
Vena cava inferior diameter, mm	17,4±2,8	20,2±2,9	0,095
Pulmonary acceleration time, ms	131±24	119±15,9	0,366
Right ventricular systolic pressure, mmHg	36,3±5,9	28,7±4,6	0,030
Tricuspid valve regurgitation velocity, m/s	2,8±0,4	2,4±0,1	0,017
Left ventricular ejection fraction, %	64,2±5,2	52,5±13,2	0,173
Left ventricular diastolic dysfunction, n (%)	2 (15,4)	4 (100)	0,0063
Glucocorticoids, n (%)	12 (75%)	3 (75%)	1,00
Azathioprine, n (%)	4 (25%)	2 (50%)	0,538
Cyclophosphamide, n (%)	4 (25%)	1 (25%)	1,00
Internal involvement			
Eyes, n (%)	6 (37,5%)	1 (25%)	1,00
Ears, n (%)	5 (31,2%)	1 (25%)	1,00
Genitourinary, n (%)	1 (6,2%)	0	1,00
Musculoskeletal, (%)	7(43,7%)	1 (25%)	0,619
Upper respiratory tract, n (%)	15 (93,7%)	4 (100%)	1,00
Lower respiratory tract, n (%)	14 (87,5%)	4 (100%)	1,00
Kidney, n (%)	10 (62,5%)	3 (75%)	1,00
Central nervous system, n (%)	3 (18,7%)	1 (25%)	1,00
Peripheral nervous system, (%)	5 (31,2%)	0 (0%)	0,530
Skin, n (%)	1 (6,2%)	0 (0%)	1,0
Five or more internal involvement, n (%)	6 (27,5%)	2 (50%)	1,00
Creatinine, mg/dl	1,0 [0,85-1,2]	1,1 [0,90-1,40]	0,924
Hs-CRP, mg/dl	0,50 [0,05-235]	2,25 [0,90-3,25]	0,298
Troponin I, ug/l	0,008 [0,006-0,060]	0,030 [0,006-0,020]	0,449
PR 3, U	16,6 [4,85-83,5]	1,5 [0,9-1,5]	0,016
MPO, U	1,7 [1,3-2,4]	2,3 [1,7-2,50]	0,448
MPO positive, n (%)	1 (6,2)	1 (25)	0,368
PR3 positive, n (%)	12 (75,0)	1 (25)	0,101

embolic events and developed VTE during first year after diagnosis (13). In our study higher incidence of VTE was not related to age, sex, CRP or ANCA antibodies levels. In a retrospective study by Stassen et al. in 198 patients with AAV increased risk of developing VTEs was observed. More than half of VTEs (52%) occurred during active disease, defined as 3 months before and after diagnosis or relapse of AVV. Also in this cohort there were no significant differences in classic risk factors between patients with and without AAV-associated VTE . In their study VTEs occurred less frequently in patients with PR3-ANCA (10). Weidner et al. retrospectively reviewed patients who were treated for AAV at a single centre during a 16-year period. This patient population with kidney involvement, included patients with microscopic polyangiitis and renal-limited vasculitis. Thirteen of 105 patients had VTEs during the observation and 12 of the 13 events occurred during periods of active vasculitis (9).

A retrospective study conducted in a Tertiary Reference Centre in Denmark also has confirmed that patients diagnosed with GPA have a significant risk of VTE both early and late during the course of their follow-up and are hospitalized several times for PE and DVT. They have also observed that within the first two years following the diagnosis of vasculitis, the incidence of PE and DVT were increased among the patients but the incidence of stroke was not increased during this time interval (14). Their results and our observations together suggest that manifestation of atherosclerosis (stroke, coronary artery disease) is less common complication than venous thromboembolism in first years after GPA diagnosis.

In Santana et al. study with confocal laser scanning microscopy, a significant association between pulmonary microvascular thrombosis and GPA was found. Their results suggests a possible role of microvascular thrombosis in the pathophysiology of pulmonary GPA and the potential benefits of anticoagulation therapy in pulmonary GPA (15). In our study increased risk for thromboembolism was unrelated to specific organ involvement. It was also independent of number of organs and systems involved.

The treatment with high doses of corticosteroids may also explain the increased incidence of VTE in GPA patients. In our study use of corticosteroids was equal in patients with VTE and without VTE, nevertheless, use of cyclophosphamide was related to lower incidence of VTEs. In 2011 a prognostic tool to define the 5-year cardiovascular risk was created for AAV patients based on data from four European Vasculitis Study Group (EUVAS) trials of GPA and MPA considering a total population of 535 patients. The results indicated that almost 12% of newly diagnosed GPA had presented at least one cardiovascular event, defined as cardiovascular death, myocardial infarction, coronary artery bypass graft/percutaneous coronary intervention or stroke (16). Also in a retrospective study conducted using Danish National Hospital Register on 293 patients with GPA, an increased risk of acute myocardial infarction was observed. Interestingly, this GPA population had an increased risk of cardiovascular events both in early (within 5 years) and in the late phase of the disease (3). In our study the incidence of CAD episodes was much lower and comparable to McGeoch et al. results. In their group of 517 patients with GPA only 3,3% had cardiac involvement and in two patients CAD was diagnosed (17). This differences could be related to short time of observation in our study. Furthermore, different diagnostic methods were used in other studies to evaluate coronary artery disease (ECG, echocardiography, magnetic resonance imaging or coronarography), whereas, in our observation all patients diagnosed with CAD had coronarography performed.

Conclusions

The present study demonstrated that granulomatosis with polyangiitis was associated with a much higher risk of venous thrombosis than coronary artery disease in first years after diagnosis, although classic risk factors for atherosclerosis were common in this study group. The underlying mechanism for this increased risk of VTE is unknown, but is likely to be associated with changes in endothelial function and with induction of hypercoagulability resulting from changes in pro and anticoagulant factors associated with inflammation and its therapy. Furthermore, patients with active GPA are not only at a higher risk for VTEs, but also at risk for bleeding, specifically those with severe lung and renal manifestations. For this reason, acute management of VTEs as well as initiation and duration of anticoagulation therapy is particularly challenging. Our study demonstrates that patients with GPA are rather at increased risk for venous thromboembolism than coronary artery disease, especially during first years after diagnosis. Therefore, we can recommend including active vasculitis among risk factors for venous thromboembolism. This study has also some limitations. It was carried out in one centre and no active screening for coronary artery disease or venous thromboembolism episodes was performed. More research is needed to clarify the cause of the high incidence of VTE in patients with GPA and to develop a strategy of screening to identify patients who require prophylactic anticoagulation.

References

1. Jennette JC, Falk RJ, Bacon PA, Basu N, Cid MC, Ferrario F, et al. 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. Arthritis Rheum 2013; 65: 1-11.

2. Morgan MD, Turnbull J, Selamet U, Kaur-Hayer M, Nightingale P, Ferro CJ, et al. Increased incidence of cardiovascular events in patients with antineutrophil cytoplasmic antibody-associated vasculitides: a matched-pair cohort study. Arthritis Rheum 2009; 60: 3493-500.
3. Faurschou M, Mellemkjaer L, Sorensen IJ, et al. Increased morbidity from ischemic heart disease in patients with Wegener's granulomatosis. Arthritis Rheum 2009; 60: 1187-1192. doi: 10.1002/art.24386.
4. Aviña-Zubieta JA, Mai A, Amiri N, et al. Risk of Myocardial Infarction and Stroke in Patients With Granulomatosis With Polyangiitis (Wegener's): A Population-Based Study. Arthritis Rheumatol 2016; 68(11): 2752-2759. doi: 10.1002/art.39762.
5. Hewins P, Wolberg AS, Yang JJ, Hogan SL, Chin H, Moll S, et al. Antibodies with dual reactivity to plasminogen and complementary PR3 in PR3-ANCA vasculitis. J Am Soc Nephrol 2008; 19: 2421-9.
6. Berden AE, Nolan SL, Morris HL, Bertina RM, Erasmus DD, Hagen EC, et al. Anti-plasminogen antibodies compromise fibrinolysis and associate with renal histology in ANCA-associated vasculitis. J Am Soc Nephrol 2010; 21(12): 2169-79.
7. Hilhorst M, Winckers K, Wilde B, van Oerle R, ten Cate H, Tervaert JW. Patients with antineutrophil cytoplasmic antibodies associated vasculitis in remission are hypercoagulable. J Rheumatol 2013; 40: 2042-6.
8. Merkel PA, Lo GH, Holbrook JT, Tibbs AK, Allen NB, Davis JC Jr, et al. Brief communication: high incidence of venous thrombotic events among patients with Wegener granulomatosis: the Wegener's Clinical Occurrence of Thrombosis (WeCLOT) Study. Ann Intern Med 2005; 142: 620-6.
9. Weidner S, Hafezi-Rachti S, Rupprecht HD. Thromboembolic events as a complication of antineutrophil cytoplasmic antibody-associated vasculitis. Arthritis Rheum 2006; 55: 146-9.
10. Stassen PM, Derks RP, Kallenberg CG, Stegeman CA. Venous thromboembolism in ANCA-associated vasculitis: incidence and risk factors. Rheumatology (Oxford) 2008; 47: 530-4.
11. Allenbach Y, Seror R, Pagnoux C, Teixeira L, Guilpain P, Guillevin L. High frequency of venous thromboembolic events in Churg-Strauss syndrome, Wegener's granulomatosis and microscopic polyangiitis but not polyarteritis nodosa: a systematic retrospective study on 1130 patients. Ann Rheum Dis 2009; 68: 564-7.
12. Jennette JC, Falk RJ, Bacon PA, Basu N, Cid MC, Ferrario F, et al. 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. Arthritis Rheum 2013; 65: 1-11.
13. Novikov P, Makarov E, Moiseev S, Meshkov A, Strizhakov L. Venous thromboembolic events in systemic vasculitis. Ann Rheum Dis 2015 Mar; 74(3): e27. doi: 10.1136/annrheumdis-2014-206849.
14. Faurschou M, Obel N, Baslund B. High risk of pulmonary embolism and deep venous thrombosis but not of stroke in granulomatosis with polyangiitis (Wegener's). Arthritis Care Res (Hoboken) 2014; 66: 1910-4.
15. Santana AN, Ab'Saber AM, Teodoro WR, Capelozzi VL, Barbas CS. Thrombosis in small and medium-sized pulmonary arteries in Wegener's granulomatosis: a confocal laser scanning microscopy study. J Bras Pneumol 2010; 36(6): 724-30.
16. Suppiah R, Judge A, Batra R, Flossmann O, Harper L, Höglund P, et al. A model to predict cardiovascular events in patients with newly diagnosed Wegener's Granulomatosis and microscopic polyangiitis. Arthritis Care Res (Hoboken) 2011; 63(4): 588-96.
17. McGeoch L, Carette S, Cuthbertson D, et al, and The Vasculitis Clinical Research Consortium. Cardiac Involvement in Granulomatosis with Polyangiitis. J Rheumatol 2015 Jul; 42(7): 1209-1212. doi:10.3899/jrheum.141513.