Factors contributing to the hypercoagulable state. Clinical case of intracardiac thrombosis and massive pulmonary embolism

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ABSTRACT
Thrombophilia, or hypercoagulable state, can cause various thrombotic events. It occurs due to inherited and/or acquired factors. Inherited risk factors, such as factor V Leiden, antithrombin, prothrombin, protein S and C mutations, have been associated with increased presence of venous thrombosis and some suggest an increased arterial thrombosis incidence as well. Acquired risk factors are found more often than inherited. The most prominent acquired risk factors include atrial fibrillation, malignancy, sepsis, obesity, diabetes mellitus, antiphospholipid syndrome and COVID-19 infection. All of these risk factors alone can cause thrombotic events, but most of the time thrombosis occurs due to multifactorial interaction of various established risk factors and patients' overall well-being. With this article we present a case report of intracardial thrombosis in a patient with atrial fibrillation and a brief literature review of the causes of hypercoagulability.

Keywords: *Thrombophilia, thrombosis, tomography.*

INTRO

Thrombophilia, or hypercoagulable state, refers to a blood disorder, which can increase clotting and thrombus formation. This was known since 1856, when Virchow introduced his triad of mechanisms for thrombosis, which remained relevant to modern times [1]. Nowadays, thrombophilia can be classified to inherited or acquired. Specific genetic mutations have been identified, which can greatly affect the blood coagulation and coagulation factor function. There are also various acquired diseases that can increase the risk of either venous or arterial thrombus formation [2]. Thrombophilia can predispose various thrombotic events, however thrombosis or thromboembolisms are often multifactorial [3]. This report analyses the most common inherited thrombophilias and focuses on the various diseases that can have a risk for hypercoagulability.

INHERITED RISK FACTORS FOR HYPERCOAGULABILITY

Inherited thrombophilia is a genetically determined tendency of venous and/or arterial thrombus formation. In current times inherited thrombophilia can be classified according gene altering mutations, which consists of – loss of function and gain of function [4]. The former involves coagulation inhibitor decrease and it includes antithrombin (AT), protein C (PC) and protein S (PS), while the latter incorporates coagulation factor increase – the most prominent being factor V Leiden (FVL) and prothrombin G20210A (PT) mutation [4, 5]. FVL and PT are accountable for 50–70% of inherited thrombophilia that has been diagnosed [2]. However, AT, PC and PS can contribute to severely greater thrombosis, even if they are less frequent [2,4]. Blood group ABO may also plays a role in thrombophilia. It has been reported that people with ABO blood group tend to have an increased risk of venous thromboembolism [2,6,7].

FACTOR V LEIDEN

FVL may depict up to 50% of diagnosed hereditary thrombophilias [4]. Although being the more prevalent, it tends to pose a weaker risk for thrombus formation [2]. Heterozygote carriers of this trait tend to have a 5-fold higher risk

for VTE disease. For homozygotes this risk can reach up to 50-fold higher [8]. Furthermore, women with FVL can have an up to 3-fold greater risk for miscarriage and various gynecological complications during pregnancy, however the rate of successful delivery is still high [9]. A study in Argentina concluded that FVL might have a significant effect on fetal growth retardation, while PT mutations were found insignificant compared to control study [10]. PT is the second most common inherited thrombophilia. Carriers of G20210A mutation have an increased plasma prothrombin of 30% for heterozygous and 70% for homozygous [8]. In general population the prevalence for PT mutation is up to 4% with Caucasians being the most affected race [4]. Comparing PT and FVL mutations for people of 30 years and younger, PT tends to have a higher risk of developing VTE than FVL – 0.44% and 0.25% respectively [11]. Both FVL and PT increase the risk for thrombotic events in women who use oral contraceptives. Women with FVL and PT mutations, who use oral contraceptives are, respectively, at 35 to 99 times and 16 times greater risk than non-carriers who don't use OCs [12]. A prospective study of 354 elderly patients found that FVL and PT were not associated with VTE recurrence [13]. A recent meta-analysis concluded that both FVL and PT, regardless of zygosity, were found in significantly more arterial ischemic stroke cases than control studies [14].

ANTITHROMBIN DEFICIENCY

Antithrombin deficiency may be relevant in about 1% of VTE cases and even less so in arterial thrombosis cases [15]. However, AT is linked with a high risk of thrombosis, with spontaneous VTE occurring in 60% of cases [4]. Without anticoagulation therapy the risk for VTE occurrence is approximately 10.5% per year. Prescribing long-term anticoagulants reduces this incidence significantly, but still about 2.7% of patients will experience recurrent thrombosis [8]. AT mutation in pregnant women can be responsible for first time VTE development up to 31% if there are no other risk factors associated with thrombosis and up to 50% if there are risk factors present [4]. Poor pregnancy outcome of 55.6% was reported in retrospective study of 18 pregnancies of women with AT, however patients treated with anticoagulation were seen to have fewer complications [16]. Although, AT is associated with higher venous thrombosis risk, arterial thrombosis risk seems to be unaffected – meta-analysis of 12 studies found no statistical significance with AT and arterial ischemic stroke cases [9].

PROTEIN S AND C MUTATIONS

Similar to AT deficiency, PC and PS mutations are less frequently found in general population, but both are strong risk factors for thrombosis [17]. PC and PS role in coagulation is associated with one another – activated form of PC is a natural anticoagulant and PS is it co-factor [2]. PC deficiency can be asymptomatic or can lead to extensive thrombosis and disseminated intravascular coagulation [4]. It is reported that people with this mutation have a 2-3 times greater risk of experiencing first episode of VTE than those who have FVL or PT mutations [18]. About 50% of PC mutation carriers experience a thrombotic event as early as 45 years of age [4]. Homozygous PC deficiency can also cause a severe life threatening condition – ischemic necrosis of extremities, which is due to dermal vessel thrombus manifestation [2]. PC and PS are found only about 0.1-0.2% in general population [4,18]. PS, however, is more likely to be detected in Asians [8]. Homozygous or double heterozygous PS deficiency is very rare and symptoms of this mutation is resembling the same PC deficiency mutations [8]. PS defect has been associated with a 10-fold greater risk of VTE [19]. Both PC and PS in the latest meta-analysis were found to be statistically significantly associated with arterial ischemic stroke [5].

BLOOD GROUP ABO

It is well established that people with ABO blood group tend to experience thrombotic events more frequently. The thought behind it is that VTE and other thrombotic developments are associated with ABO because von Willebrand factor, which is about 25% higher in ABO groups, and factor VIII (FVIII) plasma levels [20]. A recent retro-

spective study in China concluded that patients with non-O blood types experienced statistically significantly more VTE episodes than control group [21]. ABO blood groups are linked with 2.6-fold greater risk for occurrence of VTE, with blood group A being the most dominant in this risk [8]. A study in Denmark established that non-O blood type was the most prevalent risk factor for VTE and was significantly associated with VTE manifestations [22]. Moreover, people with non-O blood type accompanied with inherited thrombophilia have a risk of VTE up to 23.2-fold greater than control cases [2].

ACQUIRED RISK FACTORS FOR HYPERCOAGULABILITY

ANTIPHOSPHOLIPID SYNDROME (APS)

One of the acquired risk factors for hypercoagulation is the antiphospholipid syndrome (APS) whereat antibodies are directed against natural constituents of cell membranes, the phospholipids [23]. Antiphospholipid syndrome is a systemic autoimmune disease manifests by arterial or venous thrombosis [24]. Although antiphospholipid antibodies (APLA) occur in 3 to 5% of the population, they are dangerous because of their ability to cause arterial or venous thrombosis, even fetal loss [23]. Common clinical manifestations of APS include stroke, venous thromboembolism, recurrent early miscarriages and late pregnancy losses [25,26]. The presence of APLAs is a significant factor for thrombotic events, but it is noticed that secondary triggers, such as infections, immobility are usually necessary for the progression of the syndrome [27]. APLA is positive when positive tests repeat ≥ 12 weeks apart [28]. According to Sidney criteria, five tests have to be taken: the lupus anticoagulant, anticardiolipin antibodies IgG or IgM and aβ2GP1 IgG or IgM [28]. APLA can also occur secondarily to other diseases like collagen vascular disease or drugs like phenytoin, cocaine [23, 29].

OBESITY

Sedentary lifestyle and protracted immobilization are associated with obesity, which is an additional prothrombotic risk factor [30]. The mechanism of the obesity related hypercoagulability includes a pro-thrombotic state secondary to chronic inflammation and decreased clot breakdown via inhibition of the fibrinolytic pathway [31]. The proinflammatory and lesser fibrinolytic response indicates that obesity might be exacerbated by dysregulated expression and secretion of adipokines and microRNAs, which later increase the risk of thrombosis [31]. Obese individuals have shown increased circulating levels of von Willebrand factor (VWF), tissue factor, factor VII and VIII, and fibrinogen, causing a mild to moderate hypercoagulable state [32]. A case-control study with patients aged 18-65 years attending outpatient venous thromboembolism (VTE) clinics, evaluated that prolonged work and computer related immobility increased risk of VTE in adults who were seated for at least 10 hours/day, including at least 2 consecutive hours without getting up [30].

SEPSIS

Sepsis is a rather commonly acquired hypercoagulable state in patients with severe infection. While this condition persists, coagulation system is greatly influenced and can result in disseminated intravascular coagulation (DIC), which in turn can lead to bleeding and/or multiple organ failure [33]. Approximately 50-70% of patients with sepsis are showing signs of significant coagulation effects, but only a third will adhere to the criteria for DIC [34]. Hypercoagulability in sepsis is likely to have numerous pathogenetic mechanisms involved and that is the most likely reason why single substance therapies have not contributed to better outcomes [34]. During sepsis pro-inflammatory cytokines and chemokines are interacting with the natural coagulation process, resulting in impairment of fibrinolysis and tissue-factor activation. This interaction in turn enhances thrombin generation and fibrinogen to fibrin conversion. Platelets interact with vessel endothelium and thrombin resulting in activated platelets circulating and binding with conversed fibrin, which can result in microvascular clot formation [35]. Moreover, it been

known that platelet-activating factor is excreted during inflammation, which accelerates the process even further [34]. Furthermore, activated platelets express protein P-selectin, which affects monocytes increasing tissue factor secretion and pro-inflammatory cytokines and chemokines [35]. Treatment of this condition has been focused on reinforcing natural anticoagulation pathways with antithrombin concentrate and recombinant human activated protein C. However, even though these methods have promising results in restoring normal coagulation states, they haven't shown to improve clinical outcomes of patients [36].

COVID-19

The hypercoagulable state is also observed in the presence of Covid-19 [37-40]. One of the mechanisms is based on increased VWF expression in Covid-19 patients [37,40]. In the case of damaged endothelium, platelets may adhere more easily to VWF on dysfunctional or damaged endothelium [37]. When VWF adheres to the endothelium, platelets are easily activated by proteins like collagen, that may induce immunothrombosis through the immunothyrosine (ITAM) receptor GPVI [37]. Excretion of adenosine diphosphate (ADP) and synthesis of thromboxane A2 (TxA2) supports platelet activity through thromboxane receptor (TR) and purinergic receptors (P2Y) [37]. There is also a hypothesis, that the renin-angiotensin system (RAS) may be involved in the pathophysiology of COVID-19 [42]. When angiotensin II/angiotensin I is activated, aldosterone is being released, which upregulates protein-C receptors in human vascular endothelium [42]. These receptors are affiliated with prothrombotic state [43]. Also, it was noted that D-dimer, fibrinogen degradation products (FDP) and fibrinogen (FIB) values were undoubtedly elevated, meanwhile antithrombin (AT) was decreased [41]. Furthermore, anticipating of D-dimer and FDP can be used to monitor Covid-19 progression [41].

DIABETES MELLITUS

Vascular complications are frequently provoked by endothelial dysfunction, hypercoagulability and inflammation among patients with diabetes mellitus [44]. Hypercoagulable state is a consequence of these vascular abnormalities [44-46]. Hyperglycemia leads to a development in oxidative stress, which may cause increased markers of inflammation, endothelial dysfunction, decreased adiponectin [44,46]. Also, it was noted, that VWF, IL-6, TNF-α, D-dimer and plasminogen activator inhibitor-1 (PAI-1) are higher in diabetic patients [44,47].

MALIGNANCY

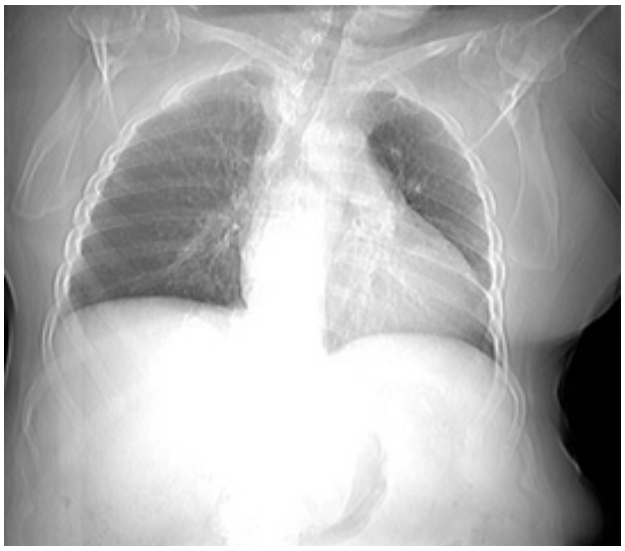
Hypercoagulable state can also be induced by tumor cells [48-50]. One of the mechanisms is that tumor cells produce fibrinolytic substances and inflammatory cytokines such as TNF-alpha, IL-1 and IL-6 and they develop blood thickening [48,49]. Malignancy can also cause hypercoagulability because of inflammation, anomalous protein metabolism and stasis [48]. It was noticed, that tissue factor (TF) and cancer pro-coagulant (CP) are being released which can cause plaque destabilization and hewing of factors X to Xa, which results in the formation of thrombin [49]. Also it should be considered, that stroke can be associated with cancer because of hypercoagulable state and it was noted, that D-Dimer levels and fibrin degradation products are higher [50].

ATRIAL FIBRILLATION

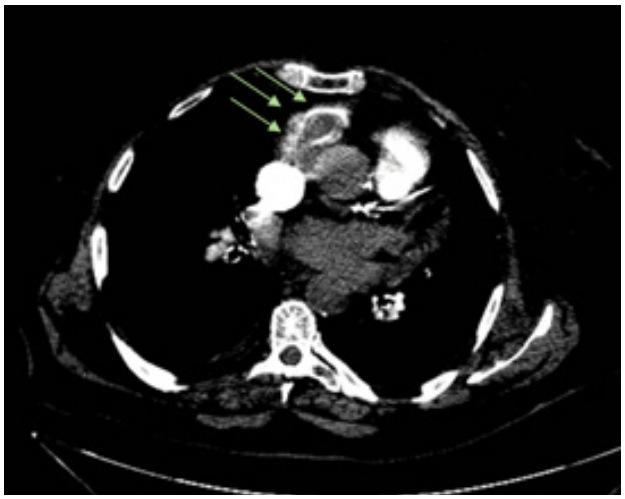
Atrial fibrillation (AF) is one of the most common continuous cardiac arrhythmias which is associated with hypercoagulable state [51-53]. It was noticed in the meta-analysis, that high levels of circulating hemostatic markers such as PF-4, BTG, P-selectin, D-dimer, fibrinogen, TAT, F1+2, AT-III, and VWF were associated with AF [51]. In this meta-analysis were described significantly higher coagulation activation markers, including plasma D-dimer, fibrinogen, thrombin-antithrombin (TAT), prothrombin fragment 1+2 (F1+2), and antithrombin- III (AT- III) in patients with AF than in control group [1]. Also, the endothelial dysfunction marker VWF was higher in AF patients [51]. In another article it was noted, that prothrombotic state in atrial fibrillation is mostly driven by inflammation and

the release of various growth factors [52]. During the inflammation, IL-6 boosts platelet production and sensitivity to thrombin, triggers transcription of fibrinogen, and is linked to endothelial activation and damage [52]. Meanwhile, vascular endothelial growth factor is heightened in persistent and permanent atrial fibrillation, with an interrelated increase in TF [52]. Another study highlighted D-dimer because its values may be associated with the appearance of atrial thrombosis, might predict primary negative outcomes and death in patients with AF, and also might be a practical guideline for assessing the degree of hypercoagulability of AF patients after cardioversion [53].

CT topogram. Enlarged heart.



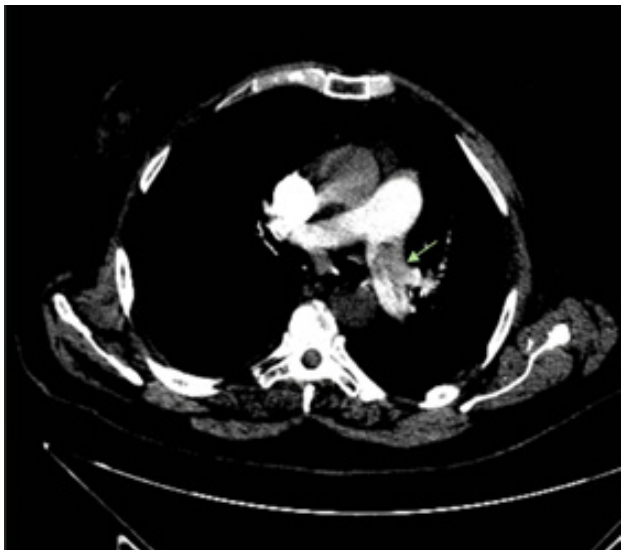
CTA. Axial plane. No. 3. Thrombus in right atrial appendage. (Green arrows).



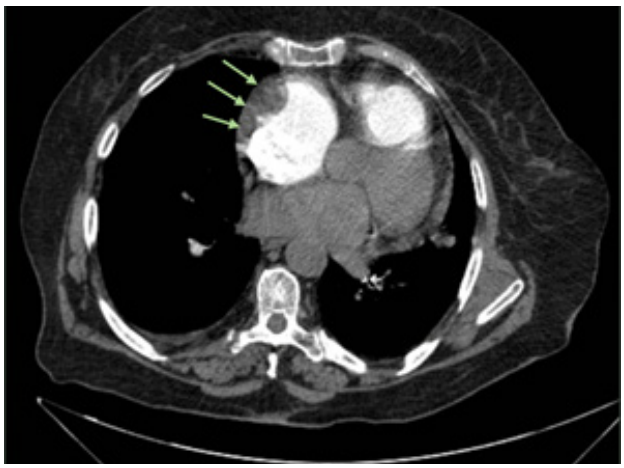
CLINICAL CASE

76 years old female patient came to admission complaining about a month-long shortness of breath at rest. Patient with anamnesis of heart failure, chronic atrial fibrillation, claimed to consuming Warfarin, Spironolactone, Torazemide, Bisoprolol, Zofenopril.
Blood pressure: 143 mm [Hg] / 82 mm [Hg], pulse: 100 rpm.
SPO2: 94%. The patient conscious, focused. Hemodynamics stable, cardiac arrhythmia. Breathing in the lungs is vesicular, without corpuscles. Abdomen soft, painless. No peripheral edema.
ECG – tachycardia and atrial fibrillation.

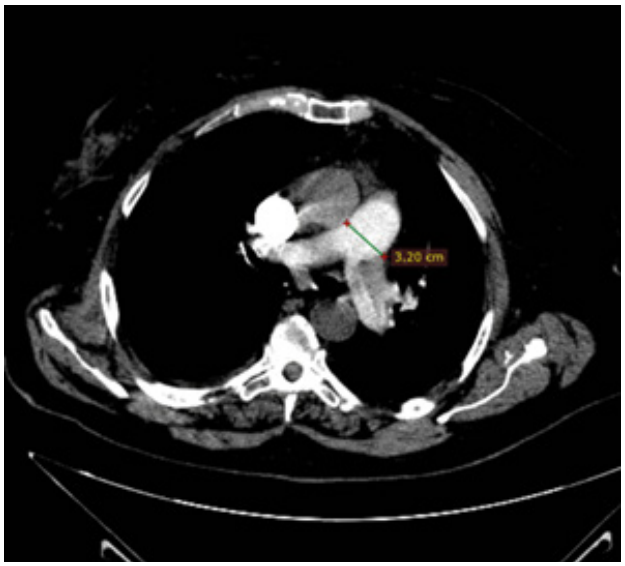
CTA. Axial plane. No. 2. Massive thrombus is seen in the left main pulmonary artery (green arrow).



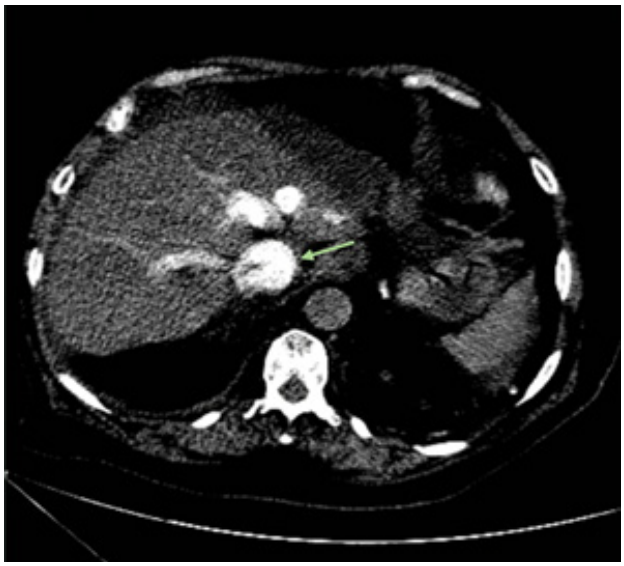
CTA. Axial plane. No. 4. Thrombus in right atrial lateral side, enlarged atrial space. (Green arrows).



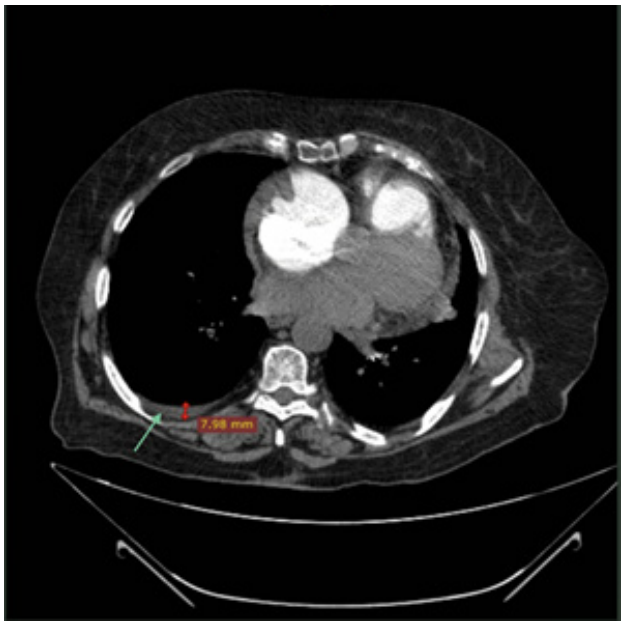
CTA. Axial plane. No. 5. Enlarged diameter of pulmonary trunk indicating pulmonary hypertension.



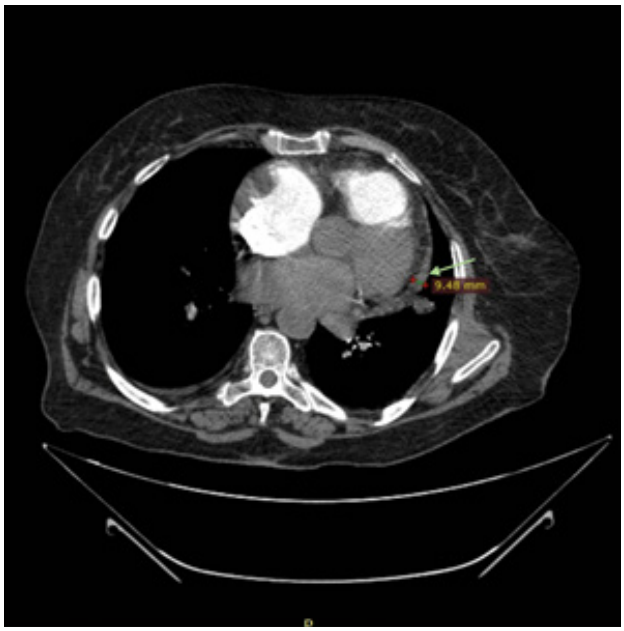
CTA. Axial plane. No. 5. Contrast regurgitation to inferior v. cava and hepatic veins indicating right heart chambers overuse. (Green arrow).



CTA. Axial plane. No. 6. Thin free fluid layer in right pleural space. (Green arrow).



CTA. Axial plane. No. 7. Thin fluid layer in pericardial space. (Green arrow).



Laboratory examination results

Test	Result	Normal range
Prothrombin Time (%)	47	70 - 130
International Normalized Ratio	1.45	0.9 – 1.2
Activated partial thromboplastin time (APTT) (s)	31.7	26.3 – 40.3
D-dimer (mg/l)	>4.00	0 – 0.5
Troponin I (ng/l)	15	0 – 10
MCHC (g/l)	334	320 – 360
PLT (µU/ml)	192	150 – 400
MPV (fl)	10	6 – 11
PDW (%)	13.7	11 – 18
PCT (l/l)	0.0019	0.0015 – 0.004
WBC (µU/ml)	9.3	4 – 10
LYM# (µU/ml)	1.35	1 – 4
RBC (µU/ml)	5.03	4.1 – 5.1
HGB (g/l)	152	120 – 150
HCT (l/l)	0.455	0.35 – 0.47
MCV (fl)	90.4	82 – 98
MCH (pg)	30.2	27 – 31
LYM% (%)	14.7	22 – 43
NEU % (%)	76.3	42 – 68
EOS% (%)	0.8	1 – 4.9
BAS% (%)	0.5	0.1 – 0.9
MON% (%)	7.7	4 – 12
LIC% (%)	0.6	0 – 3
MON# (µU/ml)	0.71	0.2 – 1
NEU# (µU/ml)	7.05	2 – 7.5
EOS# (µU/ml)	0.07	0.04 – 0.48
BAS# (µU/ml)	0.04	0.01 – 0.24
LIC# (µU/ml)	0.05	0 – 0.35
RDW- CV (%)	14	11 – 17
RDW-SD (%)	47	37 – 49
P-LCR	28.1	18 – 50
P-LCC	54	44 – 140
Hemolysis	+	
Potassium (mmol/l)	4.1	3.5 – 5.2
Sodium (mmol/l)	138	135 – 145
Blood glucose (mmol/l)	6.28	3.9 – 6.4
Urea (mmol/l)	6.5	3.5 – 7.2
Creatinine (µmol/l)	77.3	45 – 84
CRP (mg/l)	8.3	0 – 5

- X- ray was not informative, dilatation of heart was seen.
- Computer tomography angiography was performed with indication: pulmonary embolism.

After the diagnosis of massive pulmonary embolism and intracardial thrombosis patient was hospitalized to intensive care department of cardiology for further treatment.

CONCLUSION

This case report is a reminder for health care workers that hypercoagulable state can be caused by many acquired and hereditary factors. By having this in mind, doctors can notice risk factors and diagnose hypercoagulability sooner which can prevent life threatening outcomes.
In our case main factors for hypercoagulable state were atrial fibrillation and heart failure, however case it self-showed, that patient tolerated massive thrombosis with minor symptoms.
Considering imaging examinations CTA is still one of the most accurate test for hypercoagulable complications diagnosis.

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