Acute Myocardial Infarction Due to Antiphospholipid Syndrome – Case Report and Review of the Literature

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Abstract: We present a case of acute myocardial infarction secondary to arterial thromboembolism in a 25-year-old man with systemic lupus erythematosus and antiphospholipid syndrome (APS). To our knowledge, based on the literature review, this patient is the youngest one with the acute coronary syndrome as a complication of APS. Acute myocardial infarction secondary to arterial thromboembolism is a rare presentation of APS. There are different recommended anticoagulation strategies in APS patients according to the presence of thrombosis of arterial or venous origin. Potential difficulties in the treatment may occur based on the clinical scenarios. A large number of APS patients require lifelong oral anticoagulation with vitamin K antagonists. Some non-vitamin K oral anticoagulants are being studied as drugs potentially useful in APS treatment. The recent studies suggest the role of aGAPSS score in assessing the risk of a recurrent thrombotic event as well as acute myocardial infarction in APS patients. (Curr Probl Cardiol 2021;46:100552.)

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Introduction

Antiphospholipid syndrome (APS) also known as Hughes syndrome is an autoimmune disorder associated with an elevated risk of thromboembolic events of arterial and venous origin and frequent gestational complications. On a molecular level, APS is associated with the presence of antiphospholipid antibodies (APL). The antibodies in IgG, IgM and less frequently IgA class are reactive with active polarized cell membrane phospholipids or coagulation proteins (eg phosphatidylserine, phosphatidylcholine, cardiolipin, phosphatidylethanolamine, phosphatidylglycerol, phosphatidylinositol, phosphatidic acid). The most frequently detected antibodies are anticardiolipin antibodies, anti-beta2-glycoprotein-I antibodies and lupus anticoagulant.[1]

The thromboembolic mechanism of APL is not fully understood. The most probable causes are the direct effect of APL antibodies on cell functions, the inhibition of the natural anticoagulant systems or the impairment of fibrinolysis.[2] APL inhibit the activation of protein C and Z, decrease the level of protein S, interfere with the extrinsic coagulation pathway, disrupt fibrinolysis, induce pro-coagulant activity on endothelial cells, monocytes and platelets, and cause the release of membrane-bound microparticles.[2] Complement activation in antiphospholipid syndrome seems to be responsible for pregnancy morbidity.[2,3]

There two types of APS:

- Primary APS - in patients with no evidence of definable associated disease.
- Secondary APS - in patients with rheumatic or autoimmune disease (most often systemic lupus erythematosus (SLE) - 35% of cases).[4]

The frequencies of arterial and venous thrombosis or fetal loss are greater in patients with secondary APS (especially with co-existing SLE) than in primary APS.[5]

The main criteria of APS diagnosis are the presence of at least 1 of the clinical criteria:

1. Vascular thrombosis - episodes of arterial, venous or small vessel thrombosis.
2. Pregnancy morbidity:
   - at least 1 death of a morphologically normal fetus at or beyond 10th week of gestation,

- at least 1 premature birth of a morphologically normal neonate before the 34th week of gestation because of eclampsia, severe preeclampsia or placental insufficiency,
- at least three unexplained consecutive spontaneous miscarriages before the 10th week of gestation, without maternal anatomic, hormonal, chromosomal abnormalities, and one of the laboratory criteria:

3. Presence of lupus anticoagulant on 2 or more occasions at least 12 weeks apart,
4. Presence of anticardiolipin antibodies of IgG and/or IgM class in medium or high titer on 2 or more occasions, at least 12 weeks apart,
5. Presence of anti$-\beta_2$ glycoprotein$-$I antibody of IgG and/or IgM in titer $>$the 99th percentile on 2 or more occasions, at least 12 weeks apart.[6]

Cardiac manifestations of APS are relatively rare. The most common cardiac manifestations include valvulopathies (33% patients with primary APS, 40%-50% patients with secondary APS) and coronary artery disease (15% in primary APS and 30% in secondary APS). Other complications include pulmonary hypertension and intracardiac thrombus.[7]

Valvulopathies are the presence of valve lesions: valve thickening, non-bacterial thrombotic endocarditis (NBTE; Libman-Sacks endocarditis) and moderate to severe valve dysfunction with no history of infective endocarditis or rheumatic fever. Very typical is the involvement of the mitral and more seldom aortic valves with the presence of irregular nodules on the atrial area of the mitral valve and vascular side of the aortic valve.[7]

The various types of APL may play different roles in thrombosis formation, microvascular injury and accelerated atherogenesis. Therefore, APS patients have a higher risk of premature atherosclerosis compared with the general population despite a similar incidence of classical cardiovascular risk factors. About 2.8% of patients with APS may develop myocardial infarction due to atherosclerosis or, especially in young people, coronary embolism.[7,8]

Case Report

We present a case of a 25-year-old man admitted to the hospital with severe chest pain, radiating to the left arm, associated with sweating, nausea and dyspnea. The symptoms started 1 hour before admission, at rest. The patient did not have any history of infection in the preceding months. He had never experienced chest pain nor had a history of exertional dyspnea. The patient had no history of dyslipidemia, smoking or family

history of cardiovascular disease. Only classical cardiovascular risk factors present were overweight (body mass index 29 kg/m^2).

Review of the previous medical history showed, that at the age of 15 years with the patient was diagnosed with systemic lupus erythematosus with renal involvement. In the acute phase of SLE, he temporary required hemodialysis due to acute renal failure and received steroids, cyclofosfamide, azathioprine and hydroxychloroquine. His treatment had been complicated by steroid-induced diabetes. Two years before the current episode, the patient had an episode of unprovoked deep vein thrombosis of the left popliteal, femoral and tibial vein, treated with enoxaparin and initially dabigatran 150 mg twice a day. Due to a double confirmed positive level of anticardiolipin, anti-beta2-glycoprotein-I antibodies and lupus antibodies and the antiphospholipid syndrome was diagnosed. After the diagnosis, the treatment was modified to hydroxychloroquine and warfarin. In spite of education, the patient did not check the international normalized ratio (INR) level regularly (the last measurement 3 months before admission to the hospital) and took a fixed dose of warfarin).

On admission, the patient's blood pressure was 126/70 mmHg and his heart rate was 80 beats per minute. His physical examination did not reveal any abnormal finding. Laboratory results showed cardiac-specific troponin I level of 0.647 μg/L (norm < 0.14 μg/L) and INR 1.42. Electrocardiography on admission revealed prominent ST elevation in leads V_1-V_4. Acute anterior ST-elevation myocardial infarction was diagnosed. Oral aspirin and clopidogrel, in the loading dose, were given immediately and the patient had an urgent coronary angiography.

The study revealed total occlusion of the medial part of the left anterior descending artery (LAD) and critical stenosis of the left marginal artery (Mg1) with the presence of a massive thrombus. Aspiration thrombectomy was performed immediately and everolimus-eluting stents were implanted to left anterior descending artery and Mg1. The final angiogram showed a TIMI-3 flow after successful coronary intervention (Fig 1). Eptifibatide infusion was given during coronary angiography and was continued up to 18 hours.

Echocardiography revealed akinesis in the apical septal, apical anterior mid anterior segments and apex of the left ventricle with hypokinesis of the other segments. The left ventricle ejection fraction was 47%. During further hospitalization, the patient was in good shape, without chest pain, dyspnea or arrhythmias.

On discharge, the patient received double antiplatelet therapy (aspirin 75 mg and clopidogrel 75 mg) with warfarin with a target INR level of 2.5-3 in addition to the standard medical therapy. He was again educated about the rules of antithrombotic therapy. After the discharge, the patient

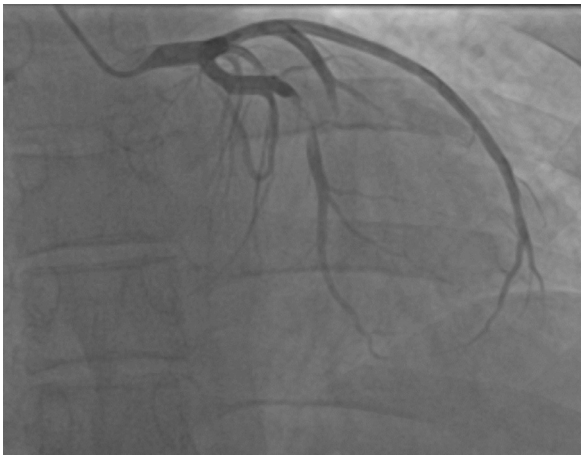


FIG 1. Coronary angiography showing total occlusion of the medial part of the left anterior descending artery and critical stenosis of the left marginal artery with the presence of a massive thrombus.

bought an anticoagulation self-monitoring device to maintain INR in the therapeutic range. Double antiplatelet therapy was continued for 6 months, clopidogrel for one year and warfarin indefinitely. The control echocardiography after 3 months revealed the total resolution of impaired myocardial contractility and an ejection fraction of 55%.

Discussion

APS is connected with a high risk of thromboembolism. Moreover, observational data suggest that patient with the presence of antiphospholipid antibodies without clinical features of APS may also be at increased risk of thrombosis.[7,9] The role of primary prevention of thrombosis in this group of patients is still under discussion. Studies vary in term of the beneficial role of aspirin in comparison with placebo in asymptomatic antiphospholipid antibody-positive individuals.[9,11] The majority of experts recommends against routine use of an antithrombotic medication for primary thrombosis prevention in this group of patients, but the recommendations are mostly based on clinical experience and observational studies. Administration of anticoagulation should be therefore depended on coexisting cardiovascular risk factors, age, sex, concomitant prothrombotic factors, APL antibodies profile and other autoimmune diseases.[12] In high-risk situations for venous thromboses, such as prolonged immobilization or recent surgery prophylaxis with low-molecular-weight heparin is recommended in asymptomatic antiphospholipid antibody-positive individuals.[12]

On the other hand, after the diagnosis of thromboembolism in patients with recognized antiphospholipid syndrome (APS) anticoagulation is recommended with the use of heparin followed by vitamin K antagonists (VKA). Anticoagulation reduces the risk of recurrent venous thromboembolism in APS patients by 80%-90 %.[10] Due to the high rate of recurrent thrombosis indefinite long-term anticoagulation with VKA therapy with a target international normalized ratio (INR) ranging from 2.0 to 3.0 should be maintained as secondary thrombosis prevention. Higher-intensity anticoagulation (INR target range of 3.1-4.0) in comparison to standard-intensity VKA therapy did not decrease the rate of recurrence thrombosis.[13,14]

There is no clear consensus among experts about optimal antithrombotic therapy in patients with APS after the arterial event. It is caused by insufficient data about optimal treatment and lack of large, randomized, prospective study. According to the current statements, it is recommended that patients with APS and an arterial thrombosis should receive either warfarin at an INR >3.0 or low-dose aspirin plus standard-intensity warfarin (INR 2 to 3). Other experts believe that antiplatelet therapy alone or warfarin INR 2.0-3.0 is equivalent.[10]

Okuma et al. published the result of a randomized study comparing single antiplatelet therapy with a combination of antiplatelet therapy and standard-intensity anticoagulation therapy for secondary prevention in 20 patients with ischemic stroke and APS. It has been observed that the incidence of stroke was lower in patients with a combination of antiplatelet and anticoagulant agent despite the similar risk of hemorrhagic complications in the 2 groups.[15] Similar results were reported by Jackson et al. - the researchers using 2 APL antibody databases [New York Presbyterian Hospital and Antiphospholipid Syndrome Alliance for Clinical Trials and International Networking analyzed retrospectively demographic and clinical data of 139 patients with APS and arterial thrombosis treated with antiplatelet and/or anticoagulant therapy.[16] They observed that combined therapy decreases the rate of thrombosis recurrence in patients with APS and arterial thrombosis. Recurrent thrombosis was observed in 37.2% of patients in the antiplatelet group, 23.7% in the anticoagulant group and only 6.9% in the combined therapy group. One of the main shortcomings of this study is the lack of information about bleeding complication.

The other kind of approach to the antithrombotic treatment in these patients is a point-score evaluation, similar for example to the CHA_2DS_2-VASc score used for atrial fibrillation. One of the scores that gain value in the recent year is the adjusted Global AntiphosPholipid Syndrome Score (aGAPSS) in predicting the incidence of recurrent thrombosis in patients with APS grows in importance (Table 1).[17] The aGAPSS is a

risk score for predicting clinical manifestations of APS, which incorporates independent cardiovascular disease risk factors and autoimmune antibody profile. Radin et al. observed that APS patients with recurrent thrombosis (arterial or venous) have significantly higher aGAPSS values (7.8 ± 3.3 vs 6.0 ± 3.9, $P < 0.05$) compared with those without recurrence.[18] The authors suggest that aGAPSS score might be a helpful tool in assessing the thrombotic risk and making the decision about antithrombotic treatment in APS patients.

APL antibodies have not only procoagulant but also pro-inflammatory activity on vascular endothelial cells. It has been observed that APS patients have a high risk of AMI due to high risk of thromboembolism as well as accelerated atherosclerosis.[7] The recent studies suggest, that the adjusted Global AntiphosPholipid Syndrome Score result seems to be a valid tool for the risk quantification of acute myocardial infarction in young patients especially ≤ 50 years old. Young APS patients with myocardial infarction have significantly higher aGAPSS values compared to others.[19] This suggests that after further evaluation, the aGAPSS score might be useful in the management of high-risk patients in the prevention of coronary thrombotic events.

Nevertheless, another factor in APS patients with acute myocardial infarction is dual antiplatelet therapy. APS patients with STEMI should undergo percutaneous coronary intervention, usually associated with thrombus aspiration, and in selected cases stent implantation in the culprit lesion.[7,20] In the case of stent implantation dual antiplatelet therapy is recommended for a short period in addition to long term oral anticoagulant therapy.[7,21] The duration of triple antithrombotic therapy must balance the risk of thrombosis in the implanted stent and increased risk of bleeding.

Table 1. Global Antiphospholipid Syndrome Score (GAPSS)*

	Factor	Point value
Cardiovascular risk factors	Hyperlipidemia (total cholesterol of <5.0 mmol/l; <3.0 mmol/l for low-density lipoprotein cholesterol)	3
	Arterial hypertension (high blood pressure -140/90 mm Hg or higher- at least in 2 occasions or use of oral antihypertensive medications)	1
Antiphospholipid antibodies	Anticardiolipin IgG/IgM	5
	Anti-β2-glycoprotein IgG/IgM	4
	Anti-prothrombin/phosphatidylserine complex (aPS/PT) IgG/IgM**	3
	Lupus anticoagulant	4

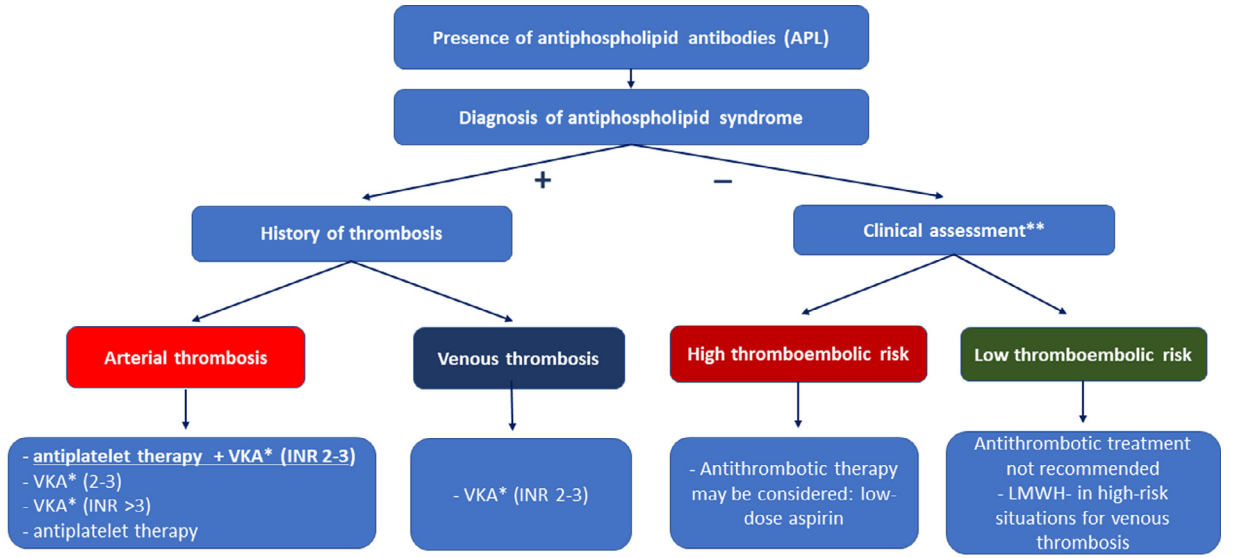
*The cutoff value of GAPSS for the high-risk thrombotic patients is reported as ≥ 10.[17]
**The adjusted global antiphospholipid syndrome score (aGAPSS) do not include aPS/PT antibodies (not routinely tested in most clinical laboratories).

Patients with APS are a group of higher rates of stent thrombosis complications after coronary angioplasty, but it has been observed that long-term oral anticoagulant is effective to prevent this complication.[20]

The potential benefit for long-term management of APS patients may be associated with switching VKA-based regiments to non-vitamin K oral anticoagulants (NOACs) in secondary thrombosis prevention. But the feasibility of this strategy has yet to be established.[10] Available evidence suggests that some DOACs might be less effective than warfarin for thrombosis prevention. In the TRAPS trial (Trial on Rivaroxaban in AntiPhospholipid Syndrome) rivaroxaban, 20 mg once daily (or 15 mg once daily based on renal function) was compared with warfarin for the prevention of thromboembolic events in high-risk patients with antiphospholipid syndrome (triple positive for lupus anticoagulant, anti-cardiolipin, and anti$-\beta$2-glycoprotein I).[22] The trial was terminated prematurely because after mean follow-up 569 days. In rivaroxaban-treated patients, 7 (12% of patients) thromboembolic event (4 ischemic strokes and 3 myocardial infarctions) occurred, while in the warfarin group, there was no thromboembolic event. Furthermore, the risk of major bleeding was higher in the rivaroxaban group: 7% vs 3% of patients. The main aim of the next ongoing trial: Apixaban for Secondary Prevention of Thromboembolism among Patients with AntiphosPholipid Syndrome is to establish the safety and efficacy of apixaban for the prevention of recurrent thrombosis in APS patient.[23] This prospective, open-label, blinded event, pilot study randomize patient with a history of venous thrombosis and APS to anticoagulation with warfarin or apixaban. The result of this study will be available in 2021. Studies on dabigatran or edoxaban vs warfarin in APS patients are yet to be designed.

Conclusion

In summary, we demonstrated a case of very young patients with STEMI due to poorly treated APS. All physicians should be aware of the high risk of acute myocardial infarction in patients with APS despite young age and lack of classical cardiovascular risk factors. The recent studies suggest the role of aGAPSS score in assessing the risk of a recurrent thrombotic event as well as acute myocardial infarction in APS patients. The kind of antithrombotic treatment after arterial thrombosis is still discussed due to lack of large, randomized, prospective studies analyzing not only the risk of recurrent thrombosis but also hemorrhagic complications. Current recommendations are outlined in the Figure 2 and Table 1. Some further therapeutical advantages might come after the completion of DOAC studies.



* apixaban is under evaluation in this indication; rivaroxaban is not recommended; edoxaban and dabigatran have not been evaluated yet
**taking into account the aPL profile, conventional cardiovascular risk factors and the autoimmune antibody profile (e.g. assessment by GAPSS Score)

FIG 2. Proposition of the antithrombotic treatment scheme in patients with APS.

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