

ANTIPHOSPHOLIPID SYNDROME A RARE AETIOLOGY OF MYOCARDIAL INFARCTION IN YOUNG ADULTS (REPORTS OF THREE CASES AND LITERATURE REVIEW)

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SYMMARY

We report the observations of 3 young adults (1 woman and 2 men), admitted in our acute care unit for acute myocardial infarction (AMI). A coagulopathy work-up concludes to antiphospholipid syndrome (APLS) in the 3 cases. APLS syndrome was considered primary in 2 cases and secondary to a dermatopolymyosite in one case. All patients presented an intense inflammatory syndrome. Anticardiolipine were present in the 3 cases. Whereas, The B2 microglobulines were detected in only one case. Emergency percutaneous transluminal coronary angioplasty (PTCA) with direct stenting could be performed successfully only in the first case, and the follow-up was uncomplicated. The patient was diagnosed with primary APS. Thereafter, long-term oral anticoagulant appeared to be effective.

In the second case emergency coronarography detected diffuse thrombi in the left coronary artery that could not be recanalised with angioplasty, thus only intensive anticoagulant and antiplatelet therapy were performed, high doses of corticosteroids were also necessary for recovery. Secondary antiphospholipid syndrome to dermatopolymyosite was diagnosed. The last patient was admitted because of peripheral acute ischemia of legs. Standard electrocardiogram showed signs of previous silent anteroseptal wall myocardial infarction confirmed by echocardiography. This latter revealed an apical thrombus and a very low left ventricular ejection fraction. Amputation of the right leg was necessary because of so late consultation. However he died four weeks later.

Keywords : antiphospholipid syndrome, acute myocardial infarction, coronarography

RESUME

Nous rapportons les observations de 3 jeunes adultes (1 femme et 2 hommes), admis dans notre unité des soins intensifs pour infarctus aigu du myocarde (IDM). Un bilan étiologique a conduit à un syndrome des anticorps antiphospholipides (APLS) dans les 3 cas. Le syndrome APLS a été considéré primaire dans 2 cas et secondaire à un dermatopolymyosite dans un cas. Tous les malades ont présenté un syndrome inflammatoire intense. L'anticardiolipine était présent dans les 3 cas. Alors que, Les B2 microglobulines ont été détectées dans un cas. L'angioplastie coronaire percutanée avec stenting direct a été effectuée en urgence dans le premier cas avec succès. Par la suite, l'anticoagulant oral à long terme a paru être nécessaire.

Dans le deuxième cas, une coronarographie en urgence a détecté la présence de thrombi diffus dans l'artère coronaire gauche. Un traitement intensif associant un anticoagulant et un antiagrégant plaquettaire a été prescrit. De hautes doses de corticostéroïdes étaient aussi nécessaires. Le syndrome des APL secondaire à une dermatopolymyosite a été diagnostiqué. Le dernier malade a été admis pour ischémie aiguë périphérique des jambes. L'électrocardiogramme standard a montré les signes d'un IDM antéroseptal passé inaperçu confirmé par l'échocardiographie. Ce dernier a révélé un thrombus apical et une dysfonction systolique ventriculaire gauche sévère. L'amputation de la jambe droite était nécessaire à cause du retard de consultation. Cependant il est décédé quatre semaines plus tard.

Les mot-clés : syndrome des anticorps anti-phospholipides, infarctus du myocarde, coronarographie.

INTRODUCTION

Antiphospholipid syndrome is a thrombotic disorder with a wide spectrum of presentations cutting across all subspecialties of medicine. Clinical features are thrombocytopenia, recurrent fetal loss, and thrombotic events involving the arterial and venous systems, large arteries and veins as well as the microcirculation are involved.

Acute myocardial infarction is rarely associated with this syndrome with a frequency of approximately 4%. The treatment of these patients is a clinical challenge.

We report three cases of antiphospholipid syndrome initiated by acute myocardial infarction in 3 young patients.

CASES REPORTS

Case report 1:

A 30 years old woman with no vascular risk factors and, a history of spontaneous abortion, was admitted with severe midsternal chest pain, associated with sweating, nausea, and breathlessness. She had never previously experienced chest pain at rest or on exertion. At physical examination, she was pale and sweaty with a tachycardia of 120 beats/min. she's blood pressure was 80/40 mm Hg. There was no peripheral oedema and all peripheral pulses were present. She had a systolic apical murmur and symptoms of left heart failure. A 12 lead electrocardiogram revealed ST-segment elevation in leads V1,V2,V3,V4,V5,V6 , We diagnosed acute anterior myocardial infarction complicated by cardiogenic shock. Two-dimensional echocardiography revealed a markedly reduced left ventricular ejection fraction (30%) and akinesis of the anterior, lateral, inferior wall, and inferior interventricular septum consistent with infarction in the left anterior descending territory. Emergent coronary angiography was performed, the left anterior descending artery presented thrombosis and stenosis at the level of the proximal section (figure1). Left ventriculography revealed that the left ventricle was dilated and markedly hypo kinetic. Therefore, percutaneous transluminal coronary angioplasty (PCTA) with direct stenting was performed, with successful recanalisation (figure 2). Serum creatine kinase peaked at 3500 U/l, haematological tests were normal, other laboratory tests of liver and renal function and lipid profiles were normal. Intravenous heparin infusion was performed for the next 10 days, Clopidogrel, aspirine, pravastatine were also administrated.

Congestive heart failure was controlled by diuretics, nitrate, and low dose of dobutamine.

We performed haematological tests for thrombotic disorders. Blood platelet count was 119 000 /ml and prothrombin time was normal. Levels of protein S, C, ATIII were normal. Anticardiolipin antibodies (Ig M antibodies) and anti-B2-glycoprotein titres were markedly elevated (23.41; 26.74), IgG antibodies were positive in repeated exams. Anti DNA antibody and antinuclear antibody were negative. Antiphospholipid antibodies tests repeated three months later remained positive. These findings satisfy the criteria for diagnosis of antiphospholipid syndrome and this latter was considered primary because she had no typical signs of systemic lupus erythematosus (SLE). The follow-up (24 months) was uncomplicated. Effort tests performed 3 and 6 months after PCTA were negatives.



Figure 1: Left coronary arteriogram on admission shows thrombotic stenosis of left descending coronary artery at the level of the proximal section.



Figure 2: Arteriogram after PTCA shows successful recanalisation

Case report 2 :

A 37 years old male admitted in internal medicine department in February 2005 for chronic fever and unexplained inflammatory syndrome. His only known risk factor for coronary artery disease was smoking. Seven days after admission, the patient presented collapse with a rapid ventricular tachycardia. A 12 lead electrocardiogram after tachycardia reduction revealed ST-segment

elevation in the posterior myocardial wall. Emergency coronarography revealed total distal obstruction of the two laterals, diffuse thrombi in the left descending coronary artery, and septal branches all had diffuse linear defects of contrast, suggesting multiple thrombi (figure 3, figure 4). Physical examination was normal. Echocardiography revealed akinesis of the inferior wall and an ejection fraction of 0.4. Renal function tests and lipid profiles were normal. Laboratory tests of liver function were abnormal (SGPT: 1170, SGOT: 910) and cardiac enzymes peaked with a CK of 6700 UI per l. Heparin, isosorbide dinitrate, platelet glycoprotein IIb/IIIa receptor inhibitors (abciximab) were administered intravenously in addition to oral aspirin and clopidogrel. He had no further chest oppression and his general condition stabilized with this conventional therapy.

The angiography findings of multiple thrombi prompted haematological tests for thrombotic disorders. Blood platelet count was 95000/ml and prothrombin time was normal. Antinuclear antibodies, anti SSA and anti SSB were positive. IgG anticardiolipin antibody was 4.2 (normal<1). Histomorphological study of bony marrow and of hepatic biopsy showed inflammatory status. Thus he was diagnosed with antiphospholipid syndrome secondary to a dermatopolymyosite. Corticotherapy was instaurated. The patient was discharged on high dose of sintrom with an international normalized ratio greater than 3, aspirin and statin. He was admitted once in the following two months because of congestive heart failure and extension of intracoronary thrombosis.



Figure 3: Coronarography findings: diffuse thrombi in the left descending coronary artery, and septal branches all had diffuse linear defects of contrast, suggesting multiple thrombi.



Figure 4: Total distal obstruction of the two laterals

Case report 3:

A 30 year old man was admitted in our intensive care unit because of bilateral acute ischemia of the tow legs. He was regularly treated for Basedow disease. Smoking was the only risk factor of atherosclerosis disease. Physical examination showed skinny patient. The electrocardiogram showed a QS pattern in leads V1, V2, V3, and V4. Echocardiography revealed an apical large thrombus measuring 38 by 18 mm associated with a thinning left ventricular wall suggesting painless myocardial infarction. It also demonstrated a markedly reduced left ventricular ejection fraction (19%) (figure 5). The patient was immediately brought for cardiovascular surgical department where bilateral Embolectomy to Fogarty probe was effectuated. Then amputation of the right leg was done because of so late consultation. Intravenous heparin was administrated with oral aspirine and clopidogrel.

Haematological tests showed normal levels of C, S and ATIII Protein. While FT4, FT3 were high, TSH was low. Anticardiolipin antibodies were also tested and subsequently came back positive for anticardiolipin antibody of the IgM isotype (19.25). The patient was also found to have a false positive VDRL, antinuclear antibodies, antiSSDNA, anti DNA, antiSm, anti SSA, anti SSB were negative. This was consistent with a primary antiphospholipid antibody syndrome. Unfortunately, the patient was died 15 days after his admission because of multiorgans failing.



Figure 5: Echocardiographic four chamber view showing an apical large thrombus measuring 38x18 mm.

DISCUSSION

Antiphospholipid antibodies are the hallmark of the antiphospholipid syndrome which is characterized by thrombosis. It was first described in patients with systemic lupus erythematosus and antiphospholipid antibodies (1). Antiphospholipid antibodies refer to auto antibodies that react to naturally occurring membrane bound phospholipids in human cells such as endothelial cells. These antibodies may be of IgG, IgA or IgM isotypes and consist of the lupus anticoagulant, anticardiolipin antibody, and false positive VDRL.

Antiphospholipid antibodies are associated with autoimmune diseases such as systemic lupus erythematosus. Patients often exhibit positive lupus anticoagulant activity but they infrequently suffer from the typical systemic lupus erythematosus (SLE) that satisfies diagnostic criteria. When they occur in isolation, this is known as primary antiphospholipid syndrome. The main antiphospholipid antibodies implicated in thrombosis and atherosclerosis are the anticardiolipin antibody, the lupus anticoagulant, and Ig G antibodies against plasma phospholipid – binding protein such as B2-glycoprotein I and prothrombin.

Systemic arterial and venous thromboses are prominent and typical features of APS. Vianna et al (2) reported episodes of deep vein thrombosis in 54% of cases and arterial occlusions in 44%. The frequency of myocardial infarction in patients with APS is reportedly 4% and the presence of antiphospholipid antibodies has been associated with myocardial infarction in young patients. There is an increased risk of myocardial infarction in patients with APS (3) caused by coronary thrombosis rather than by premature atherosclerosis. In table 1 we summarise reports of cases of antiphospholipid syndrome with myocardial infarction since the report of Harris (4). The actual mechanism of the thrombosis in APS is as yet unknown, but numerous mechanisms have been proposed. It has been attributed to inhibition of prekallikrein by the lupus anticoagulant or, as recently postulated, to interference with the activation of the protein C and protein S anticoagulant pathways. Recent data show that the binding of certain autoantibodies to endothelial cells and platelets is dependent upon the presence of B2 glycoprotein I (B2GPI). Autoantibodies binding to B2GPI on the surface of endothelial cells induce expression of adhesion molecules and enhance monocyte adhesion to the endothelial cells.

Currently data are supporting an association between these autoantibodies and atherosclerosis as well. Human studies suggest that anti-cardiolipin and anti-beta2-glycoprotein-I antibodies are elevated in patients having coronary artery disease compared with controls. Anti-cardiolipin antibodies are also associated with typical chest pain, significant coronary artery stenosis on angiography and are predictive of myocardial infarction. Laboratory studies and murine models support the pro-atherogenic role of these autoantibodies, as they are involved in uptake of oxidized LDL into macrophages, and immunization of mice with them results in enhanced atherosclerosis. There is some evidence that high anti-beta2-glycoprotein-I antibodies can present a risk factor for atherosclerosis, but more epidemiological data are required in order to confirm whether the pro-atherogenic properties of anti-phospholipid antibodies signifies an independent risk factor for atherosclerosis and its complications. Hamsten et al (5) studied 62 patients who were survivors of acute myocardial infarction under the age of 45, and found that 21% of these patients had anticardiolipin antibodies. In those surviving with positive antibodies, 61% experienced additional cardiovascular events in the subsequent 5 years compared with those without elevated anticardiolipin antibodies. Mattila et al (6) demonstrated an increase in anticardiolipin antibodies in 52% of patients within three months of an acute myocardial infarction.

Thus, the interaction of these atherosclerotic and prothrombotic risk factors substantially increased the risk of myocardial infarction in the young patients. Subjects at risk of developing early coronary artery disease often have clustering of multiple risk factors (case 2 and 3).

Primary angioplasty may be considered the treatment of choice in case of myocardial infarction. Anticoagulant therapy started immediately after the PTCA may contribute to long term coronary patency and to prevent acute stent occlusion. Therefore, long-term oral anticoagulant appeared to be effective. When thrombi are diffuse like in the second case, PTCA could not be done in emergency, intravenously platelet glycoprotein IIb/IIIa receptor inhibitor may be effective. Fibrinolysis may be effective as initial treatment for acute thrombotic disorder including acute myocardial infarction Harpaz et al and Ho et al (7, 8).

When patients presented catastrophic antiphospholipid syndrome with diffuse

thromboembolism (last observation), treatment with methylprednisone under a broad spectrum of anti-infective therapy may be effective, more aggressive therapy modalities may be necessary to save life such as plasmapheresis, immunoglobulin and cyclophosphamide.

For chronic management, the Committee consensus recommends in patients suffering from APLS, aggressive treatment of all risk factors for atherosclerosis(ypertension, ypercholesterolaemia, smoking) and liberal use of folic acid, B vitamins and cholesterol-lowering drugs (preferably statins). Hydroxychloroquine for cardiac protection in APS patients may be considered. The Committee also recommends warfarin anticoagulation for those who have history of thrombosis in the absence of atherosclerosis, but recognizes that developing data may support the use of antiplatelet agents instead. In presence of intracardiac thrombi, the Committee recommends intensive warfarin anticoagulation (9). But in a recent study, high-intensity warfarin therapy (INR 3 to 4) was not superior to moderate-intensity warfarin for thromboprophylaxis in patients with APS and previous thrombosis (10).

CONCLUSION

Acute myocardial infarction is unusual in young adults; antiphospholipid syndrome may be one of the aetiologies. Thus, immunological tests should be performed (lupus anticoagulant, anticardiolipin antibodies,...) especially when there is a history of recurrent fetal loss or in presence of symptoms of an associated connective tissue disorder. In such a case, PTCA followed by antithrombotic therapy is effective when angiographic data are favourable. Long term anticoagulant and antiplatelet therapies are recommended. Given the high mortality of catastrophic antiphospholipid syndrome in some cases, this report emphasizes the need for rapid diagnosis and effective multimodal treatment in an intensive care unit setting for these patients.

Table I: Case reports of antiphospholipid syndrome with acute myocardial infarction

Case	Reference	Age	Sex	Lesion	Treatment	Other thrombosis
1	Harpaz <i>et al</i> (7)	40	M	Anterior	t-PA (iv)	Pulmonary embolism amaurosis fugax
2	Kattwinkel <i>et al</i> (11)	29	F	Diffuse	Conservative	Not described (recurrent fetal loss)
3	Thorp <i>et al</i> (12)	29	F	Inferior	Conservative	DVT
4	Miller <i>et al</i> (13)	8	F	Lateral	Resuscitation death	Not described
5	Hoet <i>al</i> (8)	62	M	Anterior	t-PA (iv)	DVT
6	Sakakibara <i>et al</i> (14)	32	F	Inferior	Conservative CABG	Cerebral infarction
7	Chambers <i>et al</i> (15)	56	F	Inferior	Streptokinase (iv) PTCA CABG	Not described
8	Kovacs <i>et al</i> (16)	56	F	Diffuse	t-PA (iv)	DVT
9	Derksen <i>et al</i> (17)	32	F	Anterior	Conservative	DVT
10	Susumu <i>et al</i> (18)	20	M	Inferior	PTCA t-PA (iv)	Not described
11	Stoupakis <i>Et al</i> (19)	32	M	Anterior	PTCA	Not described
12	Ibrahim <i>et al</i> (20)	44	F	Inferior	Surgery (mass excision)	Cerebral infarction

t-PA :tissue plasminogen activator
 CABG:coronary artery bypass grafting
 PTCA:percutaneous tansluminal coronary angioplasty
 DVT:deep vein thrombosis.

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