Cardiac Manifestations in a Young Man with Takayasu Arteritis Associated with Antiphospholipid Syndrome

Renáta Laczik MD PhD[1], Zoltán Galajda MD PhD[2], Henriett Dér MD PhD[1], Judit Végh MD PhD[1], György Kerekes MD PhD[1], Zoltán Szekanecz MD PhD DSc[3], Pál Soltész MD PhD DSc[1] and Edit Szomják MD[1]

[1]Angiology and Intensive Care Unit, Third Department of Medicine, Institute of Internal Medicine, [2]Institute of Cardiology, and [3]Department of Rheumatology, Institute of Medicine, University of Debrecen Medical and Health Science Center, Debrecen, Hungary

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Takayasu arteritis is a chronic systemic vasculitic syndrome that involves the wall of the aorta and the large elastic arteries. TA occurs mainly in young female adults under the age of 40 [1,2]. The pathology of TA features chronic giant cell vasculitis of the aorta and its main branches including the carotid, subclavian, brachiocephalic, vertebral arteries, and rarely, the coronary, renal and pulmonary arteries [1]. Long-term complications, such as thrombus formation within the affected arterial segments, consequent arterial occlusions or aneurysm ruptures, determine the clinical picture and the prognosis [1]. Early TA is characterized by non-specific symptoms such as fever, weight loss, fatigue, night sweats, palpitations, muscle and joint pain, and elevated levels of laboratory markers of systemic inflammation. Clinical symptoms and increased erythrocyte sedimentation rate or C-reactive protein are not always concordant with disease activity [1]. In late stages, when vessel occlusions or aneurysms occur, the subsequent critical ischemia or arterial bleeding could be life threatening. At this stage, the common symptoms include dizziness, syncope, angina pectoris and vision loss. Imaging techniques – including ultrasonography, magnetic resonance imaging or MR angiography, computed tomography-angiography and, recently, FDG-positron emission tomography, as well as the gold standard angiography – are essential tools for the accurate evaluation of vascular lesions and for the diagnosis [1,2]. The final diagnosis is based on the 1990 classification criteria of the American College of Rheumatology [2].

We present a case of a young male with severe generalized Takayasu arteritis associated with antiphospolipid syndrome characterized by symptoms of myocardial ischemia.

PATIENT DESCRIPTION

A 24 year old Romanian man presented with hypertension of more than 10 years duration and recurrent episodes of myocardial infarction. The first episode of MI with ST segment elevation occurred at the age of 18 in Romania; however, revascularization was not performed since he was admitted too late. After being symptom free for 2 years despite continuous antiplatelet, antihypertensive and vasculoprotective treatment, he experienced recurrent ischemic chest pain and a second attack of anterior wall STEMI at the age of 23. At that time coronarography revealed proximal occlusion of the right coronary artery and dual proximal significant stenoses of the left anterior descending artery. Balloon angioplasty was performed with stent implantation. At the same time, he was referred to aortic angiography because of suspected renovascular hypertension. Stenosis of the proximal segment of the right common iliac artery and bilateral proximal stenoses of the renal arteries were observed. Percutaneous transluminal angioplasty was performed in the renal arteries and an incomplete dilation of the vessels was obtained without additional stent implantation. After these procedures the patient was again symptom free for some time and continuously received antihypertensive, dual antiplatelet and beta-blocker therapy.

At age 24 he was admitted to the Department of Cardiology at the University of Debrecen with angina pectoris. He was referred to urgent percutaneous transluminal coronary angioplasty when a third STEMI was diagnosed. Coronarography showed occlusion of the left internal mammary artery and in-stent restenosis of the LAD which was redilated using a balloon catheter. In addition, stenosis of the left subclavian artery stenosis was also discovered. As TA was then suspected, the patient was transmitted to the Third Department of Medicine of our university for further tests.

On admission, the patient was thin and weak with tachycardia. He had never smoked, never took psychotropic drugs and only rarely consumed alcohol. He complained of palpitations and experi-

TA = Takayasu arteritis

MI = myocardial infarction
STEMI = ST segment elevation

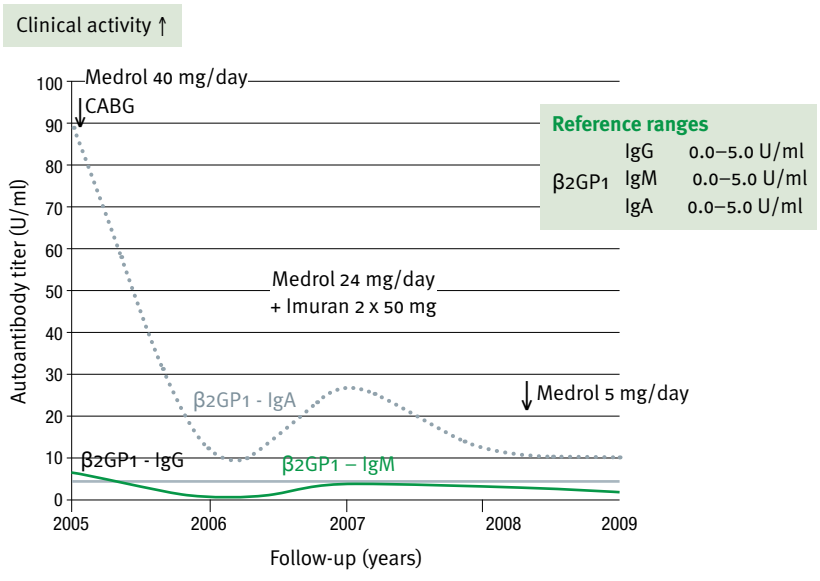
LAD = left anterior descending artery

enced intermittent claudication with a dysbasia index of 3–50 m. He had nycturia four to five times a night and ankle swelling. He had subfebrile periods and had lost 8 kg in weight within a month. His radial pulses were impalpable. Blood pressure above the left and right brachial arteries was 180/85 mmHg and 170/70 mmHg, respectively. Carotid bruits were felt over the carotid arteries. There was a grade 3/6 systolic cardiac murmur in the second right intercostal space. Carotid Doppler ultrasound scanning revealed severe stenosis in the middle segment of the right common carotid artery. Angiography demonstrated a very thin renal artery on the right side, a severe narrowing of abdominal aorta below the level of the renal artery. Ultrasound imaging showed moderate stenosis of the right internal carotid artery, narrowing of the left vertebral and subclavian arteries, and multiple stenoses of the aortic arc. This case was characterized by segmental and mainly proximal stenoses with post-stenotic dilatations. Neurological, respiratory and abdominal examinations were normal. Laboratory tests revealed normal hemoglobin level (15.8 g/dl), leukocytosis (17.9 g/L), and elevated C-reactive protein (9.5 g/L) and erythrocyte sedimentation rate (40 mm/hr). Syphilis and hepatitis serology, immunoglobulin M, rheumatoid factor, anti-neutrophil cytoplasmic antibody, autoantibody (ANA and ENA) screens were all negative except for antiphospholipid antibodies. IgA, IgM, and IgG isotypes of anti-β2-glycoprotein I antibodies and the IgM isotype of anticardiolipin antibodies were positive [Figure A]. Lipid profile (triglyceride, total cholesterol, high density lipoprotein-cholesterol and low density lipoprotein-cholesterol), as well as serum urea, creatinine and glomerular filtration rate were within normal range. High levels of fibrinogen, homocysteine and lipoprotein A were identified as additional cardiovascular risk factors. Based on these observations, the patient met the American College of Rheumatology classification criteria for TA [2], as well as the Miyakis classification criteria for antiphospholipid syndrome [3].

Because of recurrent ischemic pain despite standard therapy, coronary bypass surgery was performed. After surgery, remission of TA could not be achieved even after high dose corticosteroid treatment and anticoagulants. Since the patient continued to suffer recurrent chest pain, we initiated azathioprine as immunosuppressive treatment. Since introducing azathioprine we have been following the patient regularly for 3 years. He remains symptom free and there has been no progression in his condition. The antiphospholipid antibody levels correlated well with the course of TA [Figure].

Ig = immunoglobulin

Level of antiphospholipid antibodies in association with the clinical activity of TA



COMMENT

We present a severe case of TA associated with antiphospholipid syndrome in a young man. This TA case could be classified as generalized type V in the angiographic classification, which includes stenosis of the aortic arch and main branches with abdominal aortic narrowing and massive coronary involvement [1]. Multiple coronary stenoses may primarily be due to TA, but also to APS. To date there has been only one case report on the association of TA with clinical APS [4]. In our patient, clinical APS remained isolated and systemic connective tissue disease, such as lupus, did not develop. Anticoagulation and immunosuppressive treatment may be introduced into the treatment of both TA and APS. Apart from traditional immunosuppressive drugs, tumor necrosis factor-alpha inhibitors, mainly infliximab, have been tried in selected cases of TA [5]. Infliximab may confer a clinical benefit in refractory cases of TA, but more clinical evidence is needed. Since corticosteroid monotherapy was ineffective in our patient, azathioprine in addition to methylprednisolone was introduced and led to remission for more than 3 years of follow-up [Figure]. The fact that immunosuppressive therapy had parallel effects on both the clinical course of TA and levels of aPA suggests the possible involvement of aPA in the pathogenesis of TA. Early recognition and appropriate treatment of cardiac manifestations in TA are essential for improving the survival and quality of life in these young patients.

APS = antiphospholipid syndrome
aPA = antiphospholipid antibodies

Corresponding author:
Dr. Z. Szekanecz
University of Debrecen Medical and Health Sciences Center, Dept. of Rheumatology, Nagyerdei str 98, Debrecen, H-4032, Hungary
Phone/fax: +36-52-255-091
email: szekanecz.zoltan@med.unideb.hu

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Capsule

An ultraviolet radiation-independent pathway to melanoma carcinogenesis in the red hair/fair skin background

People with pale skin, red hair, freckles and an inability to tan – the 'red hair/fair skin' phenotype – are at highest risk of developing melanoma, compared to all other pigmentation types. Genetically, this phenotype is frequently the product of inactivating polymorphisms in the melanocortin 1 receptor (*MC1R*) gene. *MC1R* encodes a cyclic AMP-stimulating G protein-coupled receptor that controls pigment production. Minimal receptor activity, as in red hair/fair skin polymorphisms, produces the red/yellow pheomelanin pigment, whereas increasing *MC1R* activity stimulates the production of black/brown eumelanin. Pheomelanin has weak shielding capacity against ultraviolet radiation relative to eumelanin, and has been shown to amplify ultraviolet A-induced reactive oxygen species. Several observations, however, complicate the assumption that melanoma risk is completely ultraviolet radiation dependent. For example, unlike non-melanoma skin cancers, melanoma is not restricted to sun-exposed skin and ultraviolet radiation signature mutations are infrequently oncogenic drivers. Although linkage of melanoma risk to ultraviolet radiation exposure is beyond doubt, ultraviolet radiation-independent events are likely to play a significant role. Mitra and co-workers introduced a conditional, melanocyte-targeted allele of the most common melanoma oncoprotein, $BRAF^{V600E}$, into mice carrying an inactivating mutation in the *MC1R* gene (these mice have a phenotype analogous to red hair/fair skin humans). The authors observed a high incidence of invasive melanomas without providing additional gene aberrations or ultraviolet radiation exposure. To investigate the mechanism of ultraviolet radiation-independent carcinogenesis, they introduced an albino allele, which ablates all pigment production on the $Mc1r^{e/e}$ background. Selective absence of pheomelanin synthesis was protective against melanoma development. In addition, normal $Mc1r^{e/e}$ mouse skin was found to have significantly greater oxidative DNA and lipid damage than albino-$Mc1r^{e/e}$ mouse skin. These data suggest that the pheomelanin pigment pathway produces ultraviolet radiation-independent carcinogenic contributions to melanomagenesis by a mechanism of oxidative damage. Although protection from ultraviolet radiation remains important, additional strategies may be required for optimal melanoma prevention.

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Eitan Israeli

Capsule

Clonal allelic predetermination of immunoglobulin-κ rearrangement

Although most genes are expressed biallelically, a number of key genomic sites – including immune and olfactory receptor regions – are controlled monoallelically in a stochastic manner, with some cells expressing the maternal allele and others the paternal allele in the target tissue. Very little is known about how this phenomenon is regulated and programmed during development. Using mouse immunoglobulin-κ (*Igκ*) as a model system, Farago and team demonstrate that although individual hematopoietic stem cells are characterized by allelic plasticity, early lymphoid lineage cells become committed to the choice of a single allele, and this decision is then stably maintained in a clonal manner that predetermines monoallelic rearrangement in B cells. This is accompanied at the molecular level by underlying allelic changes in asynchronous replication timing patterns at the κ locus. These experiments may serve to define a new concept of stem cell plasticity.

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Eitan Israeli