Non-Atherosclerotic Causes of Acute Coronary Syndrome and Management of The Patients

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ABSTRACT

Acute coronary syndromes (ACS) are one of the leading causes of death and morbidity in industrialized countries. Typical presentation includes acute chest pain, cardiac troponin elevation and possibly associated electrocardiogram abnormalities. In great majority of the cases, myocardial infarction (MI) is due to atherosclerosis, usually with plaque rupture and consequent vessel occlusion. However, a minority of patients may suffer an MI for a range of other rare reasons such as coronary vasospasm, coronary thrombosis in situ or embolization from a distal source, hypercoagulable states, spontaneous coronary dissection, some coronary anomalies including coronary bridges and inflammatory states.

Key words: *Acute coronary syndrome, non-atherosclerosis, myocardial bridge*

Psöriyazis ve Kardiyovasküler Hastalıklar Arasındaki İlişki

ÖZET

Psöriyazis ve kardiyovasküler hastalık arasındaki ilişki son yıllardaki epidemiyolojik veriler ile desteklenmiştir. Psöriyazis hastalarında kardiyovasküler hastalıklarının birlikte görülme sıklığının artmasından dolayı dermatoloji uzmanları bu hastalığını bir sistemik hastalık olarak düşünmeli ve dikkatli olmalıdır. Bundan dolayı çalışmalar psöriyazis hastalığında kardiyovasküler hastalık gelişme riskini araştırmaya, özel stratejilerin ve kılavuzların geliştirelebilmesine yoğunlaşmıştır.

Anahtar kelimeler: *Kardiyovasküler hastalık, metabolik sendrom, inflamasyon, psöriyazis*

INTRODUCTION

Coronary Artery Spasm (CAS) is a temporary increase in coronary vascular tone of an epicardial artery, resulting a marked and transient reduction in luminal diameter. Sometimes believed to be secondary to endothelial dysfunction, this coronary vasospastic state is usually focal at a single location, and can ocur in either a normal or diseased vessel (1, 2). Cocaine abuse, often involved in acute myocardial infarction (AMI) with normal coronary arteries (3), determines CAS as a result of alfa adrenergic activation (4). Moreover, ethanol intoxication may produce CAS causing MI (5). Withdrawal of calcium channel blockers has been shown to trigger CAS and subsequent MI (6, 7). In some cases, early atherosclerosis, undetected at angiography, may be present and favour CAS (8). An angiotensin II type-1 receptor gene polymorphism has been shown to be associated with increased tendency to vasospasm in angiographically normal coronary arteries (9). Smoking is highly prevalent in patients with AMI and normal coronary arteries at angiography (10, 11), and can actually determine vasospasm by inducing the release of thromboxane A2, decreasing the production of prostacyclin, stimulating the adrenergic system and increasing the generation of vasopressin (12). The coronary endothelium may have a crucial

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role in determining coronary vasospasm (13). Impaired endothelium-dependent vasodilation is the functional hallmark of endothelial dysfunction, and young heavy smokers with normal coronary angiograms indeed have an abnormal coronary vasoconstriction to acetylcholine (14). The main vasodilating substance produced by the endothelium is nitric oxide (NO), and a deficient NO activity in arteries has been shown to contribute to CAS (15). Endothelial dysfunction of angiographically normal coronary arteries can predispose to vasospasm and subsequent thrombosis, resulting in an AMI (16).

Acute management includes use of nitrates and calcium channel blockers. Long-term supplements of magnesium and statins are protective. Refractory cases may need percutaneous stent implantation or surgical intervention (17).

Thrombosis and hypercoagulability

In situ formation of a coronary thrombus may cause the occlusion responsible for an AMI; the subsequent spontaneous lysis of the thrombus may explain the finding of a subsequent normal angiogram. Blood disorders causing hypercoagulability (18), oral contraceptives or oestrogen replacement therapy (19), endothelial dysfunction (20), smoking (21), as well as excess of lipoprotein(a) [Lp(a)] and type-1 plasminogen activator inhibitor (PAI-1) (22), may all lead to coronary thrombosis. An enhanced factor VII coagulation activity has been associated with an increased risk of coronary thrombosis (18). Factor V Leiden is the commonest risk factor for venous thrombosis, occurring in 5–9% of the population and in more than 50% of patients with hypercoagulable states (18).

Screening for deficiencies of protein C, protein S and antithrombin, as well as levels of fibrinogen revealed no significant differences between patients with AMI and normal coronary arteries versus matched control groups (23, 24). By contrast, in another study, 36% of patients with AMI and angiographically normal coronary arteries had at least one inherited factor for thrombophilia compared with 3,6% of healthy controls (25). In the literature there are occasional cases of AMI and normal coronary angiograms in patients with protein C deficiency (26, 27), as well as in subjects homozygous for factor V Leiden mutation (28, 29). Hypercoagulability superimposed to a localizing factor such as endothelial dysfunction may however determine local thrombosis and the occlusion of an artery. A large multicentre study found a 12% prevalence rate of factor V Leiden in 107 patients with AMI and normal coronary arteries at angiography (30). A higher prevalence (19,5%) has been found in 41 patients under the age of 50 years with normal or near-normal epicardial coronary arteries referring to <50% diameter stenosis (31). On the other hand, a recent study evaluating the prevalence of thrombophilic disorders in AMI cases under the age of 36, found that the G20210A mutation in the prothrombin gene was the only genetic prothrombotic risk factor associated with the occurrence of AMI at such a young population (32). More recently, in another study in patients with AMI and normal coronary angiograms, the prevalence of congenital disorders of coagulation, including resistance to activated protein C, factor XII variants and protein C deficiency, was 15% (33). Besides inherited thrombophilia, a condition of hyperhomocysteinaemia seems to increase the concentrations of factor VII and thrombin which induce a prothrombotic state (34). In an other study, hyperhomocysteinaemia was found to be an independent risk factor for early MI in Japanese male at a young age under 45 years, and is associated with a hypercoagulable state mediated by the extrinsic coagulation cascade (35). However, overall, there is no clear evidence from the literature that acquired thrombophilias, such as hyperhomocysteinaemia and the anti-phospholipid antibody syndrome, may cause the development of AMI with normal coronary arteries. One early report described decreased platelet survival which is an indirect marker of enhanced platelet activity or increased platelet consumption, in patients with MI and normal coronary arteriograms (36). Oestrogens have been also implicated in the thrombophilia possibly occurring with AMI and normal coronary arteries. Oestrogens exert multiple effects on haemostasis, affecting platelet function and decreasing levels of physiological anticoagulants such as antithrombin, protein C and protein S (19, 37). Platelets from healthy women bind significantly more fibrinogen than platelets from men. This finding is likely oestrogen dependent, as fibrinogen binding varies with the phase of the menstrual cycle and is enhanced in women taking oral contraceptives (38). Human megakaryocytes and platelets express the oestrogen receptor, indicating a possible direct hormonal effect on this cell series (39). These data support the hypothesis that oestrogens have an activating effect on platelets. Their adverse effect on platelet function may be responsible for the significantly greater prevalence (34%) of preg-

nancy or exogenous oestrogen therapy in women with AMI and normal coronary angiograms compared with healthy control women (14%) found in one study (40). In another series of patients, two of three women with AMI and normal coronary arteries were on oral contraceptives (41). A dysfunctional endothelium has reduced resistance to thrombosis (20), owing, at least in part, to decreased NO availability. NO not only determines vasodilatation, but also has anti-platelet effects, since it inhibits P-selectin expression and the calcium dependent conformational change in the glycoprotein IIb/IIIa receptor, which is the ligand for fibrinogen mediating platelet aggregation (20, 42).

Chronic cigarette smoking may also be linked to AMI and normal coronary arteries by determining activation of haemostasis, through a deficiency of the fibrinolytic system leading to insufficient clot lysis, thus favouring subsequent thrombosis. In fact, cigarette smoking is associated with reduced plasma levels of tissue plasminogen activator (tPA) (43). Reduced activity and enhanced inhibition of plasma tPA were interestingly found in a series of 18 patients with AMI and angiographically normal coronary arteries, and patients in this series had a higher prevalence of cigarette smoking (44). This study also confirmed previous evidence that identified increased plasma tPA inhibitory activity in young survivors of AMI (45), especially in those with one-vessel or insignificant obstructive coronary artery disease (CAD) (46). Furthermore, long-term cigarette smoking impairs platelet-derived NO release (47). Since NO inhibits platelet adhesion and aggregation, the increased platelet aggregation resulting from the inhibition of NO bioavailability may lead to coronary thrombosis in angiographically normal arteries. It is worth noting that smoking is also associated with a dose-dependent impairment of endothelial vasodilatory function (48), and a reduced endothelium-derived NO bioavailability (49). Increased levels of Lp(a) have been found in patients with AMI and angiographically normal coronary arteries (50). Lp(a) levels are related to impairment of endothelium-dependent vasodilatation (51). Moreover, Lp(a) impairs fibrinolysis and stimulates the synthesis of PAI-1 (52). PAI-1 is the most important circulating inhibitor of fibrinolysis. It plays a regulatory role in the fibrinolytic process by limiting plasmin production. Elevated PAI-1 plasma levels potentially lead to thrombosis by depressing the action of t-PA. In particular, elevated PAI-1 plasma levels are associated with an increased incidence of unstable angina and AMI (53, 54). Moreover, PAI-1 contributes to the coronary wall thickening detected by intravascular ultrasound (IVUS) in patients with angiographically normal coronary arteries (55). Therefore, all these mentioned conditions isolated or in combination, may favour coronary thrombosis and AMI even if coronary arteries appear morphologically normal at angiography.

Patients presenting with a first episode of arterial thrombosis who are subsequently found to have an inherited thrombophilic condition should receive standard treatment for the acute thrombotic episode. Family screening is recommended, and oestrogen replacement therapy should be discouraged among women found to be carriers of procoagulant gene variants (56). Although long-term anticoagulation with a vitamin K antagonist (VKA) may probably represent an attractive treatment option, data are unsatisfactory. Most clinicians would consider long-term VKA therapy with a target international normalized ratio of 2 to 3 or aspirin-VKA combination therapy based on extrapolated data (57, 58). Dual antiplatelet therapy with aspirin and a thienopyridine may be a reasonable option for events limited to the coronary bed, although dedicated studies have not been performed in patients with arterial thrombophilia. In addition, it may be reasonable to implement vitamin B12, vitamin B6, and folic acid supplementation among patients with markedly elevated homocysteine concentrations. The importance of recognizing acquired causes of arterial thrombophilia relates directly to the availability of beneficial treatments and management strategies for many of these conditions.

Embolization

Embolization in the coronary system may determine the occlusion of a coronary artery responsible for an AMI. Emboli are usually localized in the branches of the left anterior descending coronary artery (59). Aortic valve morphology related to the preferential flow in the left coronary artery may explain more frequent involvement of the left coronary system (60). The incidence of coronary embolization as a cause of AMI resulted between 10% and 13% in autopsy studies (60, 61). Embolic AMI with patency of the epicardial vessels may derive from native valvular heart disease, paroxysmal and chronic atrial fibrillation, prosthetic valve disease (62), left atrial mixoma (63), infectious and marantic endocarditis (64), mural thrombosis, air embolization induced

during heart surgery (65) and dislodgement of calcium depositions originating from calcific valves manipulated during surgical interventions. Coronary atheromatous (61) or air embolization (66) is less frequent than systemic embolization but is a well described complication of cardiac surgery, cardiac catheterization and electrophysiological procedure due to the mobilization of debris or air during vessels and cardiac chamber repair or cardiac catheter manipulation and should be considered in ACS occurring during or immediately after vascular invasive procedures.

Although a greater incidence of mitral valve prolapse and mitral regurgitation was found in patients with AMI and normal coronary angiograms (67), this finding is thought to be consistent with the high frequency of minor mitral valve prolapse in the general population (68, 69). Coronary embolism account for 5–10% of all paradoxical embolism, a patent foramen ovale or an atrial septal defect has been occasionally described as source of paradoxical embolism (70). A case report of AMI in a child homozygous for the prothrombin G20210A mutation ascribed the occurrence of AMI to the paradoxical embolization through a patent foramen ovale (71). However, another study failed to find a significantly increased prevalence of patent foramen ovale in patients with AMI and angiographically normal coronary arteries (70). Thus, although theoretically possible, coronary embolism apparently explains only a minute percentage of cases of AMI with normal coronary arteries. Patients with coronary embolism require anticoagulant therapy and also specific treatment against underlying disease such as antibiotherapy, closure of the intracardiac shunt etc.

Inflammation

Systematic inflammation is well known to increase cardiovascular morbidity and mortality, and acts as an additive to traditional risk factors to enhance the atherosclerosis process. There is currently abundant evidence linking inflammation with cardiovascular disease (72). Markers of inflammation, such as C-reactive protein (CRP), especially when evaluated with high-sensitivity methods, are predictors of cardiovascular events in normal volunteers (73).

A large study in 4162 patients included within 10 days after the diagnosis of an acute coronary syndrome, and randomized to gatifloxacin or placebo, failed to show any benefit in patients treated long term with antibiotic therapy compared with placebo. The antibody titres of such patients were compared with those of matched patients with AMI and CAD, as well as with those of matched healthy subjects. The prevalence of antibodies was higher in both groups of the patients compared with control group, but there were no significant differences between patients with normal coronary arteries and those with CAD. It has to be noted, however, that patients with normal coronary arteries had significantly more frequent febrile infections prior to AMI. The inflammation triggered by these febrile reactions may be linked to the development of the acute event (74).

Other than coronary artery vasculitis and aneurysm formation, AMI with normal coronary arteries in systemic lupus erythematosus (SLE), Wegener's granulomatosis, and rheumatoid arthritis have been published as case reports (75, 76) [24, 25]. Several explanations have been suggested for impaired myocardial perfusion such as thrombosis followed by spontaneous thrombolysis, CAS and endothelial dysfunction (75). Some other cases of AMI and normal coronary arteries in patients with SLE without evident vasculitis (77) or with SLE and the antiphospholipid antibody syndrome (78) are reported in the literature. Such cases may support the concept of a role for inflammation in the occurrence of AMI with angiographically normal coronary arteries. The overall risk of future AMI remains high in these patients, but acute myocardial ischemia may respond to a trial of immunosuppressive drugs (76).

Kawasaki disease (KD) is a vasculitis of infancy and early childhood. The etiology of KD is unknown, although an inflammatory response precipitated by an infectious agent is suggested by some epidemiologic data. The most important complication of KD is coronary vasculitis, leading to coronary aneurysm formation in 20 to 25 percent of untreated patients during the acute stage of the disease. Nearly half of acute aneurysms regress, but approximately 20 percent lead to the development of coronary stenosis in the long term. Patients can present with MI or sudden cardiac death. Thus, young patients with MI should be asked about a possible childhood history of KD. Standard treatment with high-dose acetylsalicylic acid and intravenous immune globulin has been shown to decrease the rate of coronary artery aneurysm development. Anti-coagulation has an important place in the management of KD, although guidance based on evidence is lacking (79).

Spontaneous dissection of coronary arteries

Spontaneous coronary artery dissection (SCAD) is an infrequent cause of ACS (79, 81) mainly affecting young healthy women (82, 83). SCAD mostly occurs in the peripartum and, especially in the early postpartum period. The most cases have indeed been described from the ninth week of pregnancy until the third month after delivery (84, 85). SCAD may affect both the left and the right coronary artery, while the left coronary system is more frequently involved, particularly in women, the right coronary artery appears more often affected in men (86). It was first described in a young Caucasian woman who had a sudden death after developing chest pain (87) . Since then only 116 cases have been reported in the literature. The incidence has been reported to range from 0,1 – 1.1% (86, 88). Sudden death is the most common presentation reported in 60 – 80% of the cases (82). The pathogenesis of SCAD is unknown. SCAD may be the consequence of an intramural haemorrhage affecting the media of the arterial wall, and forming a false lumen. The expansion of such intramural haemorrhage leads to coronary dissection with compression of the real lumen, potentially causing AMI or sudden death. The body undergoes different hormonal and hemodynamic changes during pregnancy and it may take upto six months after delivery for the body to achieve the pre-pregnancy status. Several theories have been postulated with regards to pregnancy related SCAD. It is suggested that the morphological changes in arterial wall associated with hemodynamic changes may be a contributory factor. Excess progesterone during pregnancy induces the loss of normal ondulation of elastic fibres and degeneration of medial wall collagen and all this may result in weakening of the arterial wall leading to arterial dissection. A two-step process leading to SCAD was suggested as an initial intimal rupture followed by delayed bleeding in tunica media likely caused by the clotting changes that occur in pregnancy (89, 90) . Bleeding from vasa vasorum into tunica media has also been proposed as a possible cause of arterial dissection (88, 91). An association with vasculitis and peri-adventitial infiltrates composed of eosinophilic lymphocytes or histiocytes was postulated as well (92). Peri-adventitial inflammation were thought to be a consequence of SCAD and not the actual cause (93).

Cocaine abuse and the strenuous physical exercise have been suggested as possible causes in the literature (94, 95). Other factors such as use of oral contraceptives, immunosuppressant drugs, drug reactions, blunt trauma to chest (96) type IV Ehlers Danlos syndrome (97) Marfan's syndrome (98) and α1-antitrypsin deficiency (99) have also been described as possible mechanisms leading to arterial dissection (100, 101). Cystic medial necrosis of the coronary arteries is another possible mechanism of SCAD, as it determines focal fragmentation of elastic fibres and the loss of smooth muscle cells in the media after the deposition of acid mucopolysaccharides (102).

The published data describes different management strategies including conservative treatment, percutaneous coronary intervention (PCI), coronary artery bypass grafting (CABG) and heart transplantation but optimal therapy is yet to be determined (80, 90, 103). The factors that may influence making the decision for the best treatment option include hemodynamic stability of the patient, number of vessels involved, site of dissection and availability of coronary intervention services. It was mentioned that the location and the extent of the dissection guided the treatment strategy (104). While lesions that involved left main stem were treated with CABG, proximal lesions of coronary arteries were treated with PCI, and distal lesions were managed conservatively in that study (104). PCI is the treatment of choice in SCAD with involvement of a single vessel with ongoing ischemia (105). CABG is also the preferred mode of treatment in patients with multivessel dissection, complex lesions or in patients with failed coronary intervention (106, 107). One of the major problems with CABG is that it is difficult to clearly identify the true lumen, which may result in grafting of the false lumen leading to irreversible myocardial damage or death (105) Heart transplantation has been tried with success in cases of severe heart failure following SCAD (108).

Urgent coronary angiography and IVUS are indicated in the acute phase in order to establish the certain diagnosis and determine the best therapeutic approach (90, 105, 109). The conservative management may include use of heparin, beta blockers, calcium channel blockers, nitrates, diuretics, antiplatelet therapy including aspirin, clopidogrel, and glyprotein IIb/IIIa inhibitors (57, 110). It was suggested that patients who have completed an acute event or those with no evidence of ongoing ischemia and no significant stenosis on cardiac catheterisation may do well with conservative treatment in short term but most of these patients have had recurrent angina, subsequent MI or sudden death due to extension of dissection (111).

Coronary Anomalies

The estimated incidence of coronary artery anomaly is 5,6% (112). Anomalies that can produce myocardial ischemia are ostial stenosis or atresia, a coronary artery from the opposite sinus (ACAOS) with an intramural course, coronary artery fistula, origin of the left coronary artery from the pulmonary artery, and myocardial bridging (112). A pre-capillary fistula connecting a major coronary artery with the cardiac chamber or superior vena cava is the most common among these anomalies (112). Potential complications of coronary fistula include heart failure, ischemia, thrombosis, dysrhythmia, endocarditis, and even rupture. An ACAOS is usually asymptomatic or present with atypical chest pain, but some patients die in young age after strenuous exertion (113). Origin of the left coronary artery from the pulmonary artery inevitably causes the development of myocardial ischemia. Any significant compensatory enlargement of coronary arteries discovered in a pediatric age group should be suspected to have a hemodynamically significant coronary anomaly. If possible surgical correction of these anomalies or interventional closure of coronary fistulas must be considered.

Myocardial bridging (MB) is described as an angiographic entity where systolic narrowing of a coronary artery is observed in at least one angiographic projection. These arteries have a normal lumen, however the segment of a major epicardial coronary artery which goes intramurally through the myocardium beneath the muscle bridge gets compressed during systole. The degree of coronary artery compression by the MB depends on the location of the artery, thickness and length of the MB and degree of cardiac contractility. The reported frequency of MB in angiographic studies is variably ranging from 0.5 to 7.5% (114, 115). It is commonly seen in the middle to distal part of the left anterior descending artery. Although it does not cause significant hemodynamic compromise to myocardium, rare incidents of myocardial ischemia have been reported during stress testing (115). A thrombus or atherosclerotic lesion is likely to develop in the proximal segment because of the hemodynamic disturbances (116). The majority of MBs are incidental findings detected on angiography. The clinical presentation of a symptomatic MB is not significantly different from CAD.

The first line of management is medical therapy using negative inotropic and chronotropic agents such as beta-adrenergic blockers and calcium channel blockers to relieve symptoms, and antiplatelet agents to prevent the risk of CAD in future. The utility of nitrates in these patients is not very clear. Preload reduction and coronary artery dilatation relieve symptoms to a certain extent, but the reflex tachycardia secondary to systematic vasodilatation has been shown to increase the milking effect on angiography (116). Refractory cases may require stents, minimally invasive coronary artery bypass grafting, and surgical myotomy.

CONCLUSION

In conclusion, the absence of atherosclerosis in patients with ACS remains an uncommon but problematic finding in patients undergoing coronary artery angiography. Alternative substrates of ACS including coronary vasospasm, coronary thrombosis or embolization, hypercoagulable states, spontaneous coronary dissection, some coronary anomalies such as coronary bridges and inflammatory states should be considered. Complying with the ACS international guidelines, evaluation of the age and gender, electrocardiographic profile, stress tests, and imaging tests like IVUS have to be taken into account by cardiologists when they have to deal with the patients with ACS without visible atherosclerosis.

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