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Case Report

Coronary Artery Aneurysm and Ectasia: Spectrum of Aetio-Pathology, Clinical Presentation and Outcome

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Abstract

The terms coronary artery ectasia and coronary artery aneurysm are used to describe aneurysmal dilation of coronary arteries. Coronary artery aneurysms and ectasia are uncommon and frequently incidental finding in patients advised Coronary Angiography for coronary artery disease evaluation. Aneurysmal dilation of coronary arteries is observed in up to 5% of patients undergoing coronary angiography and are usually describe a localised dilatation of a coronary artery segment more than 1.5-fold compared with adjacent normal segments. Aneurysms and ectasia are associated with a vast group of disorders, and the evaluation and characterization of coronary aneurysms and ectasia represent a great diagnostic task with clinical and therapeutic implications. The underlying etiology is variable and includes degenerative, congenital, inflammatory, infectious, toxic, and traumatic causes. Causative factors include atherosclerosis, Takayasu arteritis, congenital disorders, Kawasaki disease (KD), and percutaneous coronary intervention. Due to their poorly elucidated underlying mechanisms, their variable presentations, and the lack of large scale outcome data on their various treatment modalities, coronary artery aneurysms and coronary ectasia pose a challenge to the managing clinician. Unlike aneurysms, ectasia is more frequently seen in association with atherosclerosis or as a compensatory mechanism in those cases in which a proximal stenosis is noted in the opposite coronary artery; ectasia is also seen in some coronary artery anomalies, such as anomalous origin from the pulmonary artery, or as a result of a high-flow state, as seen in coronary artery fistulas. The natural history of CAAs remains unclear; however, several recent studies have postulated the underlying molecular mechanisms of CAAs, and genome-wide association studies have revealed several genetic predispositions to CAA. Controversies persist regarding the. The diagnostic approach depends on the clinical scenario, and nowadays, noninvasive evaluation with multidetector computed tomography is possible. The purpose of this review is to summarize the present knowledge of CAAs and collate the recent advances regarding the epidemiology, etiology, pathophysiology, diagnosis, and to provide a succinct review of aneurysmal coronary disease, with a special emphasis on the challenges associated with its interventional treatment.

Keywords: coronary artery; ectasia; aneurysm

Case Report

A 58-year-old Asian female with a history of hypertension, and stable coronary artery disease on medical medical management, was referred by his primary care physician to our facility for evaluation and management of dyspnea on mild exertion. Examination showed a woman with a BMI of 35, and an ECG showed a possible old inferior MI, poor R-wave progression and non- specific ST-T wave abnormalities. A left heart catheterisation was done.

This revealed multiple fusiform aneurysms involving the whole Left Anterior Descending artery and smaller aneurysm with severe diffuse disease of left circumflex coronary artery (figure 1,2 and 3) The left ventricular ejection fraction was 40%. A single vessel bypass grafting procedure with the left inferior mammary artery (LIMA) to the LCx was decided. No surgical intervention was performed to the LAD aneurysm due to the anatomy of the aneurysm. There were no complications during the surgery or in the immediate post-operative period. On subsequent follow up, one week, two months and one year after the procedure, the patient showed improvement of the symptoms and continued medical treatment with aspirin, statins, angiotensin receptor blockers and beta-blockers. The subsequent ejection fraction measured by echocardiography four months later improved to 40-45%.

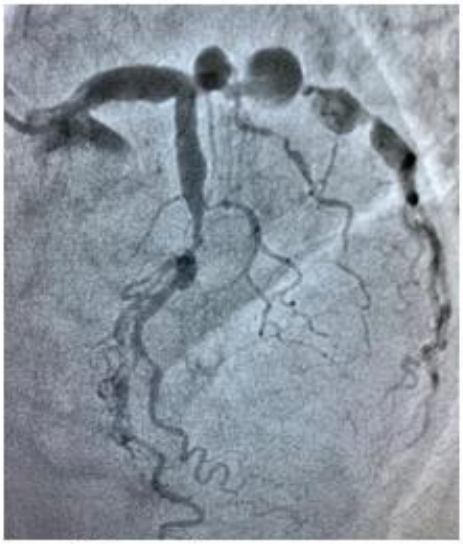

Figure-1

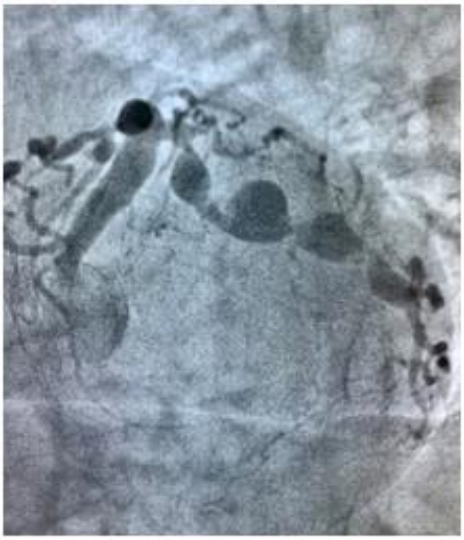

Figure-2

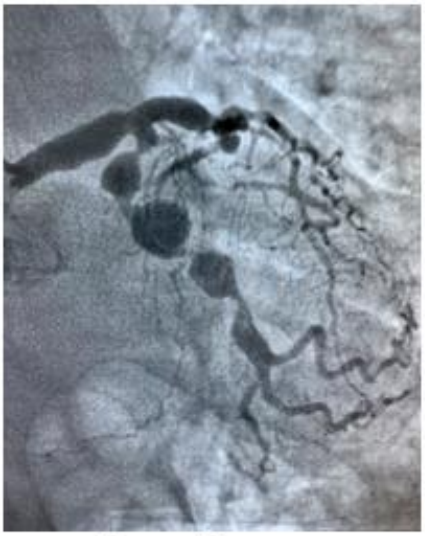

Figure-3

Epidemiology

The estimated incidence of CAAs and ectasia vary from 0.02 to 5.9% [1, 2], with the lower incidence of giant CAAs and higher incidence of congenital aneurysmal fistula [3]. Nowadays, due to increased use of computed tomography and magnetic resonance coronary angiography the possibility of finding of such coronary abnormalities enhances. Variation in the incidence of CAAs in studies is associated with different interpretation of coronary angiography by operators or considering both aneurysm and ectasia [4]. Kawasaki disease known as the common cause of CAA in children is less common among African ethnicity [5]. The incidence of CAAs among Asian ethnicity is lower than north American and European whether genetic predisposition and environmental factors may have influence on the incidence of CAAs [6]. CAA is more common among male gender [7],[2]. CAAs may be found in any age. In elderly patients, occurrence of CAAs were associated with underlying atherosclerotic coronary artery disease proven by angiography, but in younger patients, congenital coronary abnormalities or inflammatory process such as Kawasaki were more common. Right coronary artery is the much common site of CAAs compared with left circumflex artery or left anterior descending artery. Occurrence of CAAs in three coronary arteries or left main coronary artery is a rare incident [8]. Atherosclerotic process or inflammatory vasculitis may involve various parts of coronary arteries, while congenital or iatrogenic aneurysm due to dissection or trauma may be seen in a focal part of coronary artery.

Aetiology

Proposed aetiologies of CAAs and ectasia are atherosclerotic process, vasculitis (Kawasaki, polyarteritis nodosa, Takayasu arteritis, Behcet's disease), connective tissue disorders (systemic lupus erythematosus, rheumatoid arthritis, ankylosing spondylitis, progressive systemic sclerosis), genetic predisposition, hereditary collagen defects (Marfan syndrome, Ehlers-Danlos disease), infection (bacterial, mycobacterial, fungal, syphlistic, lyme, septic emboli, mycotic aneurysm, HIV infection), reaction to drugs (cocaine, protease inhibitor, amphetamine), percutaneous coronary intervention (balloon angioplasty, stenting, atherectomy)

Pathophysiology

The exact pathophysiology of CAAs and ectasia is not fully understood yet. However due to underlying process of arterial wall weakening some mechanism have been addressed. Atherosclerotic coronary artery disease is the common cause of CAAs (50%) with the prevalence about 2.83% of patients undergoing coronary angiography [2],[1]. Conventional risk factors of atherosclerotic coronary artery are similar to CAAs. In histopathologic species of atherosclerotic CAAs, hyalinization and lipid deposition and disruption of intimal layer, medial layer and muscular elastic components along with focal area of calcification leading to reduced elasticity of vessel walls and further dilation and aneurysmal formation were evident. In addition, arterial wall weakening may be seen in the presence of atherosclerotic stenotic lesions with chronic pressure effect on median layer. The role of genetic polymorphism in genome- wide- association-study (GWAS) has been supported by explaining the presence of gene variation on the chromosome 9p21.3 and evidence of coronary artery disease and vascular remodeling and occurrence of aneurysm in other arteries including aorta aneurysm and intracranial aneurysm [9]. Another rare aetiology of CAAs is interventional procedures of coronary artery such as balloon angioplasty, stent implantation with incidence of 1.25%-3.9% in follow-up angiography in which has fatal outcome [10]. Two proposed mechanisms are coronary dissection due to use of oversized, high pressure balloons during PCI and last stent malposition. In addition, implantation of drug eluting stent (DESs) containing various cytotoxic antirestenothic agents may lead to suppression of smooth muscle and endothelial proliferation and reduced neointimal healing and re- endothelialization, increased fibrin deposition and macrophage infiltration. Moreover, focal hypersensitivity reaction to DESs may lead to weakening of three layers of arterial wall and aneurysmal formation [11],[7]. In children, kawasaki disease commonly considered as the cause of CAAs which is an acute coronary artery vasculitis due to infiltration of mononuclear cells, lymphocytes, and macrophages during Inflammatory process and cytokines release leading to breakdown of elastin layer and aneurysmal formation. The role of genomic variants in increased expression of matrix metalloproteinase activity and weakening vessel wall has been suggested in some studies [12]. CAAs have been reported in other

types of vasculitis including Takayasu arteritis (TA), systemic lupus erythematosus, polyarteritis nodosa, and rheumatoid arthritis [13,14]. In patients with Marfan syndrome, presence of CAAs has been shown to be associated with cystic media necrosis via fibrillin 1 (FBN1) gene mutation and over production of TGF-b [15]. Infections such as bacterial, mycobacterial, fungal, syphilitis, lyme, septic emboli, mycotic aneurysm, HIV may cause CAAs with the mechanisms of direct invasion to arterial wall or induction of inflammatory response [16-20]. Use of drugs such as cocaine, amphetamine, protease inhibitors have been shown to be associated with CAAs. Presence of hypertension crisis and vasoconstriction by use of cocaine may lead to endothelial injury and aneurysmal formation [21,22]. In fibromascular dysplasia involvement of intimal, medial, adventitial, and periarterial layers in CAAs were evident [23]. The aetiology of congenital CAAs is not clear.

Clinical Presentation

CAA and CAE are usually silent disorders incidentally detected by coronary angiography or computed tomography (CT) angiography. The development of complications and/or the presence of obstructive coronary artery disease leads in a wide range of clinical manifestations spanning from chest pain to sudden cardiac death. It is not a benign disease as patients with CAA and CAE often reveal ischemic changes on electrocardiograms, reduced left ventricular wall motion echocardiography and myocardial injury (rise in troponin) in the absence of significant epicardial coronary artery stenotic regions. [1] Diminished coronary flow, or stagnancy of blood flow, may cause exercise-induced angina regardless of the severity of coexisting stenotic lesions. The formation of intracoronary thrombus and distal dissipation of emboli may be the cause of acute coronary syndrome, which is exacerbated by stationary flow in the ectatic coronary segment. Both CAA and CAE are frequently seen in association with atherosclerotic disease secondary to smoking, hyperlipidemia, obstructive sleep apnea and uncontrolled hypertension, which comprises nearly half of the reported cases. [2,3] The rest of the cases have been described secondary to a sequela of connective tissue or vasculitic coronary disorders. No reported data confirmed a relationship between the diameter of an ectasic artery and the symptoms nor the prognosis. However, the significant dilatation coupled with the potentially long asymptomatic period may result in a delayed diagnosis or, in the worst-case event, sudden cardiac death. [4]

Investigation

Various imaging techniques are used for depiction of coronary artery anatomy, including transthoracic and transesophageal echocardiography, electrocardiographically gated CT angiography, MR imaging and/or MR angiography, coronary angiography and intravascular ultrasound. Assessment of a coronary artery aneurysm should include evaluation of its shape, structure, and morphology (fusiform or saccular), its diameter, wall calcification, luminal thrombosis, and any significant stenosis. Should be determined the origin and termination of the CAA, eventually its number: singular or multiple. Finally, the search should exclude potential complications, including myocardial perfusion abnormalities, fistula formation, appreciable extrinsic mass compression, or evidence of active rupture, including hemopericardium [1].

In many cases, the radiologic findings of a CAA do not point to a specific underlying disease. However, some conditions have typical features that may be suggestive of a specific cause. For example, an ACAA is suggested by the presence of calcified atherosclerotic plaque in other vessels, including the aorta. Kawasaki disease is characterized by multiple CAAs marginated with rims of calcification in a child or young adult. A mycotic CAA may be found in the setting of an immunocompromised patient and/or a patient with bacteremia. Patients with a history of cocaine abuse are at considerable risk for the development of CAAs. In more unusual cases, a CAA is the consequence of a primary inflammatory vasculitis or a noninflammatory inherited vasculopathy and/or connective tissue disease. [2]

Coronary Angiography

Coronary angiography provides important information about the size, shape, location, and frequency of aneurysms, as well as the degree of coronary artery atherosclerosis. As well as evaluating any coronary artery stenoses, coronary angiography is also able to detect thrombotic occlusions and determine the extent of collateral artery formation. Prior to referring a patient for invasive angiography, it is important to consider the benefits and risks of the procedure, particularly in younger patients with KD. While coronary angiography may not provide further information in patients with mild ectasia or small fusiform aneurysms, it can play a larger role in more complex coronary lesions. Also, conventional angiography is limited to a "luminogram" and does not reflect information about the vessel wall, and this could lead to the underestimation of the actual size of aneurysm or even overlook a CAA that may be occluded by a large thrombus or a plaque. [3]

Intravascular Ultrasound

Intravascular ultrasound could be associated to the invasive angiographic evaluation of CAAs, and treatment of CAAs oculd be initiated during the same procedure [4]. Unlike angiography, IVUS provides detailed, high-quality transmural images of coronary arteries in vivo including both the lumen and the arterial wall. This is also important in terms of prognosis [5]. This is important for the differentiation between the different types of aneurysms, which vary in prognosis [3]. The study in 77 patients of Maehara et al., that used intravascular ultrasound to assess coronary artery aneuryms diagnosed by angiography, discovered that only a part of angiographically confirmed CAAs were true or pseudoaneurysms. IVUS revealed that more than 60% of the remainder of these aneurysms had the morphology of complex plaques or were normal segments adjacent to stenotic regions [6]. Moreover, IVUS is also useful for clarifying the relationship of a coronary aneurysm with a previously implanted stent, and this is important given the recent association of CAAs with percutaneous coronary interventions. IVUS can also be used during the treatment of CAAs; it proves to be an invaluable tool in guiding the adequate coverage of aneurysms. [3]

Echocardiography

The non-invasive nature of echocardiography, as well as its high sensitivity and specificity for the detection of abnormalities in the proximal LMCA and RCA, makes it an ideal imaging modality for the assessment of the cardiac sequel of KD in children. Echocardiography allows for the quantitative assessment of the internal vessel diameters, providing information on the location of the aneurysms and the presence or absence of intraluminal thrombi [3].

CT Angiography

Coronary CT angiography (CTA) has evolved into a widely used imaging tool in mainstream practice. Consequently, entities such as coronary artery aneurysms that were thought to be uncommon are now seen not infrequently in clinical practice in our experience [7]. CT data acquisitions can be reconstructed to provide information regarding the nature of the dilatation in the coronary vessel, such as the maximum diameter, shape, morphology, and presence of any concomitant stenosis, plaque composition, and its location in relation to the surrounding vasculature [3]. While coronary angiography allows for both diagnosis and treatment of CAAs, CTA could be used for the follow-up of patients with suspected or treated CAAs [3]

Coronary MR Angiography (MRA)

MRA could be a useful alternative in young patients or in those for whom the use of other non- invasive modalities may be contraindicated both as a diagnostic tool and as a follow-up method. Current literature supports the ability of MRA to investigate large proximal segments of the coronary vasculature; however, the resolution of MRA is reduced when it comes to imaging the smaller distal segments [3].

Treatment

The management of coronary aneurysm and ectasia is difficult due to the lack of a guided approach to treat these patients. It is a case-by-case decision depending on the anatomical finding, the clinical setting (incidental finding

or acute setting) and the patient characteristics. Optimal therapeutic approach is not yet clear, but different approaches were used including medical therapy, interventional with stent and coiling and even surgical resection. Due to lack of evidence, treatment is still controversial. In majority of patients, there is coexistence of coronary artery ectasia with obstructive coronary lesions and increased incidence of myocardial infarction. Hence, aspirin is a suggested treatment for all the patients with CAE. A study showed that patients with CAE have higher levels of plasma P-selectin, beta-thromboglobulin and platelet factor 4 suggesting increased platelet activation. Chronic anticoagulation with warfarin is also recommended due to flow disturbances in the ectatic segments. There is a relationship between ACE gene polymorphism and CAE; so ACE inhibitors can be helpful in suppressing CAE progression. Increased levels of MMP-3 is associated with coronary artery aneurysm and statin might play a role in stopping the progression of CAE by inhibiting MMP-3 activity. In isolated CAE, nitroglycerine and nitrate derivatives can induce angina pectoris. So these drugs should be avoided. CAE is a form of atherosclerotic cardiovascular disease; so intense risk factor modification is extremely necessary as primary and secondary prevention.

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Medical therapy:

Risk factor modifications is an important tool regarding the treatments of such conditions. Higher coronary events and major cardiovascular risks were seen in the aneurysm population with some observational studies [2]. ACEI and statins showed benefit in this population [3-4].

Data on antithrombotic therapy were controversial. Some retrospective studies conclude that anticoagulation is unbeneficial and showed a similar rate of thrombotic events in patients with normal coronary morphology and patients with CAA [5-6]. Whereas on the other hand, Doi et al, demonstrated that coronary aneurysm and ectasia is an independent predictor of mortality in patients with acute coronary syndrome and concluded that patients at higher risks may benefits from anticoagulation [7]. For Kawasaki disease, intravenous immunoglobulin therapy promotes CAA regression and decreases the incidence of MACE. [8].

Stem Cells

Stem cell research led to many therapies becoming available to treat or repair injured or diseased tissues in a range of diseases, from cancers to spinal cord injuries. For cardiovascular therapy, the unique capacity of pluripotent stem cells to replicate and provide large numbers of replacement cells in culture for transplantation purposes may give an advantage over the use of adult stem cells. When tissue is injured, inflammatory cells infiltrate the injured area and remodel the extracellular matrix (ECM) to clear damaged or dead cells and degraded proteins. Whether stem cells also aid in repairing or replacing damaged thoracic aortic tissue is unknown. Multipotent stem cells play an important role in tissue repair and regeneration. Multipotent stem cells are known to play an important role in arterial remodeling after injury. The presence of circulating endothelial progenitor cells has been previously reported in a murine model of abdominal aortic aneurysms [1], in patients with abdominal aortic aneurysms [2]. Mechanisms of their retention are in correlation with route and method of cell delivery, a build-up of cell constructs with materials as well as delivered doses and optimal timing. The main role of adult stem cells is assumed to be replacement of damaged and injured tissue. Cells can be grown and manipulated in vitro to obtain various mature and functional cell types. Of these, mesenchymal stem cells (MSC) show multilineage potential, a clinically substantial immunomodulatory ability and secretion of anti- inflammatory molecules which make these cells effective clinical products in autoimmune and degenerative diseases. Yet, their cell potency in vivo is a critical element which warrants a better description. Reliable biomarker identification will advance our understanding of how long the replacement cells will continue to function and their mechanism of action; leading to accelerated novel therapies where cell therapy products show a better homing, integration, quantity, or overall quality upon transplantation. [3]. MSC have also been investigated in a number of ongoing clinical trials for cardiac regeneration because of their low immunogenicity, there were no adverse events reported related to immune responses during allogeneic transplantations. However, their main limitation remains that MSC show large diversity in origin from different tissues; characterization and cell surface markers are controversial and nomenclature is not standardized either [4]. Ethical and regulatory concerns may be related to the invasive nature of bone marrow harvest. Their mechanisms of action are not entirely clarified either (such as a limited direct myogenic differentiation), which overall makes specification, analysis of the product comparability, stability as well as compatibility tests difficult. The attractiveness of using MSC populations alone or in combination with other cell types for regenerative therapies relies not only on their capacity to differentiate into various lineages, but also on their paracrine-mediated repair mechanism via immunomodulatory, angiogenic, and pro-survival effects [5]. The increasing prevalence of cardiovascular disease worldwide and the lack of available causative therapies to reverse the loss of myocardium warrant new strategies. Advances in regenerative stem cell therapy may at least in part address this problem. However, an integrated science is needed to use stem cell based technologies as clinical applications. Standardized, detailed designed potency and characteristic assays, furthermore preclinical safety and efficacy data are key for translation.

Interventional

PCI is a preferable approach for small CAA. Data were scarce but some conclusions could be drawn from several publications. Several PCI techniques were used to treat this entity as covered stent implantation, coiling embolization and stent-assisted coil insertion. Some difficulties to deliver stents were seen with these cases and higher rate of restenosis were noticed with covered stents [1]. Symptomatic patients with acute MI were more studied than the asymptomatic ones. AMI in these cases resulted with a lower success rate, no reflow, distal embolization in the acute setting and higher stent thrombosis and mortality at follow-up [9,10,11,12,13]. Due to this higher risk of thrombosis the primary goal in such cases is to restore blood flow that's why these cases are mostly assisted with thrombectomy whether mechanical or by aspiration and glycoprotein (GP

IIb IIIa) inhibitors [14,15]. For the asymptomatic patients, interventional decision is difficult because of lack of data [16,17] When the aneurysm does not involve a major side branch a covered stent is into consideration. On the other hand, if a big side branch is involved, excessive tortuosity and calcification balloon or stent assisted coil embolization is preferable. No specific covered stents were designed for CAA but they are used off label. Proper sizing and landing zone assessment is an important key to the PCI management in these patients. Thrombosis in aneurysm could underestimate the sizing. Data on Kawasaki patients is also scarce. It seems that in such pediatric population IVUS is interesting because aneurysms may be lined with thrombus [18,19].

Surgical approach

Although it is considered as a first line therapy for giant aneurysm, aneurysm with major side branch involvement and left main, an ideal surgical approach was not profusely studied. CAA therapy may include a surgical resection, ligation, or marsupialization. Surgical success rate is not yet known because of the rarity of these special cases [1].

Conclusion

Majority of coronary aneurysms usually present as asymptomatic, but few might present with angina pectoris, myocardial infarction, fistula formation, cardiac tamponade, compression of surrounding structures, or congestive heart failure or even sudden death. The clinical presentation depends on the size and number of aneurysm, and coexisting atherosclerotic coronary artery disease. Atherosclerotic or inflammatory coronary aneurysms are usually multiple and involve more than one coronary artery while congenital, traumatic, or dissecting aneurysms typically involve a single artery. Angina pectoris and left ventricular dysfunction can occur with coronary artery aneurysms without coronary artery obstruction; although the specific role of the aneurysm, thrombosis and embolization has not been elucidated as the cause of myocardial infarction in patients with stenosis. The diagnosis can be made through multiple imaging technologies including echocardiography, magnetic resonance and computed tomography, but coronary angiography remains the gold standard as it provides information regarding the size, number, position of the aneurysms, and the presence or absence of coronary artery atherosclerosis. Our case describes an elder woman with a history of dyspnea on mild exertion and high risk for CAD. The inducible ischemia could have been caused by the stenosis, the aneurysms or a combination of both. There is no accepted preferred management of coronary aneurysms but surgical correction is the most commonly used therapy. Endovascular techniques and conservative medical therapy with either antiplatelets or anticoagulants are other viable options with variable rates of success. Surgical interventions include aneurysm ligation with distal bypass grafting, isolated coronary artery bypass grafting, aneurysm plication, and saphenous vein patch repair of the aneurysm. These procedures are often performed as part of a multivessel bypass operation. In a fusiform aneurysm proximal and distal ligation with bypass grafting is a feasible option; adequate caliber is required in the vessel. We preferred to perform a single graft to the LCx. After the procedure, medical management with antiplatelets was also indicated. Endovascular therapies (coiling and stenting) with exclusion of the aneurysm were discouraged, since these are described with satisfactory results in saccular aneurysm but not in multiple fusiform morphologies. The improvement of symptoms was sustained in the immediate and subsequent follow up.

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