CASE REPORT

Recurrent Myocardial Infarction in a Young Man
Due to Coronary Arterial Spasm
Demonstrated at Autopsy

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SUMMARY A case is presented, believed to be the first reported, describing recurrent myocardial infarction in an athletic 25-year-old man due to coronary arterial spasm, which was demonstrated at autopsy. A previous angiogram performed during life, after the first myocardial infarction, showed normal coronary arteries. The findings in this case are discussed with a review of the current knowledge pertaining to coronary arterial spasm.

THERE IS CONSIDERABLE controversy whether coronary thrombosis is a primary1-9 or a secondary3-5 event in the development of myocardial infarction. When no thrombus is found in the presence of myocardial infarction, the coronary arteries are usually diseased and severely stenosed.6-7 However, myocardial infarction with normal or minimally diseased coronary arteries is not uncommon, particularly in young people.8-11 Several mechanisms have been proposed to explain this paradox, including coronary artery embolism followed by resolution12 or recanalization,19 in situ coronary thrombosis with subsequent lysis,14 functional or anatomic disturbance of the coronary microcirculation,15,16 and myocardial hypoxia due to abnormal blood oxygen release17,18 or partial block of the cellular respiratory enzyme system.19 More recently, coronary arterial spasm, which is known to occur with or without underlying coronary arterial disease,20,21 has been implicated as a cause of myocardial ischemia and infarction.22,23

Case Report

The patient was a 25-year-old married man who was a fire fighter, nonsmoker, extremely physically active and practiced weight lifting. He was first admitted to the hospital 15 months before his death because of severe chest pain. He had had an episode of chest pain 5 weeks before admission. Three days before admission to hospital he developed diffuse, aching, upper chest pain radiating to the left arm that persisted for many hours and was described as the worst pain he had ever experienced. On examination, he was in no distress, normotensive, and had no abnormal physical signs. His ECG was abnormal and suggestive of inferior wall infarction. On the fourth day of hospitalization, repeat ECG showed classic findings of an inferior wall infarction, with Q waves, ST-segment elevation and T-wave inversion in leads II, III and aVF (fig. 1). Aspartate aminotransferase (SGOT) was elevated at 49 U/l; the chest x-ray was normal. During his 10-day hospitalization, there were no significant events except for a few ventricular extrasystoles. Subsequent investigations, including serum cholesterol and triglycerides, glucose tolerance and platelet survival tests, were all normal. Virus studies, including convalescent virus sera, were not helpful. A maximal treadmill test was performed 10 weeks after his infarction, when the patient was able to perform for 12 minutes on the treadmill according to the Bruce protocol without chest pain, arrhythmia or ECG changes. His blood pressure response was appropriate. Twelve weeks after infarction (1 year before death), the patient underwent elective cardiac catheterization. The left ventricular pressure was 117/14 mm Hg and the end-diastolic pressure rose to 22 mm Hg after the angiogram. There was no significant gradient across the aortic valve. The left ventricular angiogram showed an area of inferior and apical hypokinesis. The coronary arteries were studied after sublingual nitroglycerin, and were completely normal in every respect (figs. 2A and B). On subsequent follow-up, the patient twice had had fleeting bouts of chest pain that were not typical of angina pectoris. He also had ventricular ectopic complexes on several occasions, and was given propranolol 20 mg three times daily. He returned to normal activities, including fire fighting, but was advised against weight lifting. Twenty-four hours before his final illness, the patient had chest pain, but thought he had a cold and did not seek medical advice. He was attending a night class when he became severely breathless and distressed. He collapsed suddenly and by the time he had reached the

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emergency department of a nearby hospital, the pupils had dilated and resuscitative measures were unsuccessful. He was pronounced dead less than 1 hour after the terminal event.

Autopsy Findings

Autopsy examination was carried out 16 hours after death. The heart was normal in size, with a smooth pericardial surface, and weighed 274 g. Postmortem coronary angiography was carried out by inserting catheters into the coronary ostia. Each coronary artery was injected in turn by contrast medium composed of 50% mixture of water and colloidal suspension of Barium sulphate (60% W/W). The perfused contrast medium was delivered from a reservoir at constant pressure of 120 mm Hg for 2 minutes. At the end of the injection the catheter was clamped and the heart radiographed in the anteroposterior position. Kodak XM-2 x-ray films were exposed for 15 seconds at KVP 60–70. The angiograms showed long, cylindrical narrowing of the middle third segment of the left anterior descending artery (fig. 3A) and prominent segmental irregularities of the middle third of the right coronary artery due to multiple stenotic (constriction) lesions, with estimated 60% stenosis (fig. 3B).

The coronary arteries were then carefully opened along the length of the vessels, and subsequently sectioned at 3-mm intervals for histologic examination. The right coronary artery showed puckering of the intimal layer represented by a series of circular ridges across the vascular lumen (fig. 4), corresponding to the angiographically demonstrated stenotic lesions. The middle third of the left anterior descending artery was cylindrically narrowed compared with the proximal and distal segments of the vessel. The intimal surface of all main coronary arteries was otherwise smooth, with no significant atheromatous lesions and no evidence of vascular thrombosis. Microscopic examination of the arteries showed only mild intimal fibrosis with minimal atheromatous changes.

The size of all the cardiac chambers was within normal limits, and the heart valves were anatomically normal. The ventricular myocardium was sectioned into 1-cm thick slices, starting at the apex and proceeding proximally to within 3 cm from the atrioventricular groove. Blocks 2 cm wide, passing from the epicardial to the endocardial surface, were taken from the anterior, lateral and posterior left ventricular walls, the anterior and posterior right ventricular walls, and the ventricular septum. These blocks were taken at two levels corresponding to the proximal and middle thirds of the ventricles and, in addition, two blocks were taken from the apical region, giving 14 blocks. One section stained with hematoxylin and eosin was examined from each block, with selective use of Trichrome, elastic Van Gieson and Martius scarlet blue stains. The ventricular sections showed two laminar infarcts: an old posteroinferior infarct extending into the adjacent portion of the ventricular septum (fig. 5A), and a more recent anterolateral infarct involving mainly the middle layer of the ventricular myocardium, and to a lesser extent the subepicardial layer of the anterior wall (fig. 5B). The subendocardial layer of the myocardium was essentially normal throughout. Microscopically, the healed posteroseptal infarct was represented by mature collagenous fibrosis, including some elastic fibers (fig. 6A). The morphologic appearance of the infarct was consistent with the clinical history of inferior wall infarction 15 months previously. The anteroseptal infarct, in contrast, was estimated to be approximately 7 days old. The necrotic fibers showed active phagocytosis leaving behind empty sarcolemmal sheaths (fig. 6B), and in between there were markedly congested capillary vessels. At the edge of the infarct, some viable myocardial fibers showed evidence of regeneration with abundant bluish cytoplasm and atypical hyperchromatic nuclei.

The rest of the ventricular myocardium showed microscopic foci of fiber necrosis and myofibrillar lesions that were particularly marked in the ventricular septum. A few capillary vessels adjacent to the area of infarction contained platelet aggregates (fig. 7A), while no such aggregates were seen in the epicardial coronary vessels. Several intramyocardial
arterioles, particularly in the subendocardial zone of myocardium, showed marked intimal fibrous hyperplasia with corresponding narrowing of the vascular lumina (fig. 7B).

The lungs were acutely congested and edematous. They weighed 812 and 715 g and showed no evidence of pneumonic infiltration. The rest of the examination was noncontributory.

Discussion

Coronary arterial spasm is primarily a clinical term. However, the coronary arterial changes demonstrated by postmortem angiography in the present

Figure 2. A) Normal left coronary angiogram in the left anterior oblique view 12 weeks after the first (inferior) myocardial infarction. The arrows point to the segment of the left anterior descending artery that showed pathologic changes at autopsy (compare with fig. 3A). B) Normal right coronary angiogram, in the right anterior oblique view 12 weeks after the first (inferior) myocardial infarction. The arrows point to the segment of the vessel that showed pathologic changes at autopsy (compare with fig. 3B).

Figure 3. A) Postmortem left coronary angiogram in the anteroposterior view, showing long segmental narrowing (arrowed) involving the anterior descending artery between the first and second diagonal branches, which has the appearance of spasm (compare with figure 2A). B) Postmortem right coronary angiogram in the anteroposterior view, showing segmental irregularities (arrowed) of the middle third due to multiple stenotic (constriction) lesions (compare with figures 2B and 4).
case are striking and have all the appearances of spasm. We have no satisfactory explanation for the persistence of coronary arterial spasm for 16 hours after death, although it may be analogous to "cadaveric spasm," which involves the skeletal muscles and is frequently seen in forensic pathology. The lack of other obvious causes for the recurrent myocardial infarction in this young man further supports the coronary spasm hypothesis. This case is probably not unique, as coronary arterial spasm was implicated in two cases of recurrent myocardial infarction in young people with otherwise normal coronary arteries.24, 25 Since Prinzmetal published his classic description of variant angina,26, 27 much information has accumulated in the medical literature covering this syndrome and its relationship to coronary arterial spasm. The frequency of coronary arterial spasm is probably greater than generally appreciated,21, 23 with an estimated incidence of 3% in one angiographic study.28 An underlying coronary atherosclerotic lesion is a common, if not a prerequisite, association.20, 21, 29 The spasm may occur either spontaneously or on pharmacologic provocation,29, 30 and may completely or incompletely occlude the lumen of the coronary artery.20, 29, 30 The spasm is usually accompanied by hemodynamic changes21, 31 and electrocardiographic changes with ST-segment elevation or depression,29, 32 reflecting the severity of the myocardial hypoxia, as confirmed by the myocardial perfusion studies using thallium-201 scintigraphy.29, 33 The electrocardiographic changes during the anginal attack, though reversible, may be associated with Q waves to mimic myocardial infarction,33 and are frequently accompanied by ventricular dysrhythmias.21, 26, 34 During the vasospastic anginal attack, chest pain is usually present,21, 23, 27 but can be conspicuously absent despite the considerable myocardial hypoxia during the attack,35, 36 or after the onset of myocardial infarction.26 The vasospasm and the anginal attacks can be abolished by the administration of nitroglycerin.21, 23, 24 The persistence of coronary arterial spasm results in acute myocardial infarction, with subsequent thrombosis forming at the site of the arterial stenosis.22, 23 In one series, Oliva et al. estimated that coronary spasm may occur in as many as 40% of cases of acute myocardial infarction associated with coronary arterial disease.22

Although our patient did not have any symptoms or electrocardiographic changes on exercise after his first myocardial infarction, he was not exercised to the point of exhaustion. Recently Specchia et al. reported that when patients with variant angina were exercised to a symptomatic end point, coronary arterial spasm with ST-segment elevation was induced.33 The time of day when the exercise test is performed may constitute another variable in eliciting coronary arterial spasm in patients with variant angina.38 The results of surgical treatment of variant angina have been generally disappointing.39, 40 The reason for this probably lies in the mechanism by which coronary arterial spasm occurs, and in the functional rather than the organic nature of the disease. The tone of the coronary arteries is controlled by the autonomic nervous system. Coronary arterial spasm is caused primarily by activation of the sympathetic α-vasoconstrictor receptors, either by the action of catecholamine in susceptible subjects,41, 42 or indirectly through prior stimulation of the parasympathetic nervous system.43 Pain is, however, not considered to be due to the arterial spasm, but the result of the myocardial anoxia.41 The neural mechanism would explain the common occurrence of the anginal pain at rest or even during sleep.44 Cold pressor tests in patients with ischemic heart disease resulted in actual decline in coronary arterial flow despite increased coronary arterial pressure,45 which is thought to be due to adrenergically mediated vasoconstriction. Experiments in dogs showed that abolishing the reflex coronary vasospasm by removal of the cardio sensory pathways or by anaesthesia eliminated pain and markedly reduced the mortality rate after sudden occlusion of the left coronary artery.46, 47
FIGURE 5.  A) Tissue section from the posterior left ventricular wall, showing a healed infarct involving the middle layer of the myocardium. Trichrome; magnification $\times 5$. B) Tissue section from the anterior left ventricular wall, showing a recent infarct involving the middle and outer layers of the myocardium. Trichrome; magnification $\times 5$. 
An alternative mechanism for the induction of coronary arterial spasm is by the direct action of drugs or chemicals on the smooth muscle of the arteries. Injection of ergonovine maleate caused narrowing of the coronary arterial diameter in transplanted human hearts that lacked extrinsic neural control. Acute myocardial infarction was reported after therapeutic administration of ergot compound, which acts directly on the vessel wall. Also, the coronary spasm and anginal symptoms resulting from withdrawal of the chronic industrial exposure to nitroglycerin could be explained by a similar mechanism. However, it is unlikely that this mechanism is applicable to our case.

Platelet aggregation at the site of endothelial vascular injury or an atherosclerotic plaque may further potentiate the coronary vasospasm, which tends to spread along the vessel. This action is thought to be mediated by thromboxane A2 released from platelets. The role of platelets in coronary arterial spasm is of particular interest in the case...
FIGURE 7. A) An intramyocardial capillary vessel including platelet aggregates and some leukocytes. A few red cells are seen at the right end of the vessel. Martius scarlet blue; magnification × 450. B) An intramyocardial arteriole showing prominent intimal fibrous hyperplasia with narrowing of the lumen. Hematoxylin and eosin; magnification × 450.

Presented. Although no platelet aggregates were seen in the main coronary arteries, a few aggregates were found in the intramyocardial capillary vessels. These aggregates may have been due to distal embolization from a small mural platelet thrombus in a proximal main vessel that had broken up and disintegrated. Stress is known to induce intravascular platelet aggregation in the heart. Our patient was in a very stressful occupation that is associated with a higher incidence of ischemic heart disease than in the general population, as revealed in a random study of Los Angeles fire fighters. The intimal fibrosis observed in the intramyocardial arterioles in this case, and possibly a contributory factor to the myocardial ischemia, may also have been due to platelet effect. Experimental platelet embolization in laboratory animals has been shown to cause intimal hyperplasia of the renal arterioles with secondary ischemic manifestations.

We hope that this case report will stimulate further
studies of autopsy hearts, including routine post-mortem angiography by standard techniques, particularly in patients who die of acute myocardial infarction with normal coronary arteries. Such methodical search should help to unravel some of the basic pathophysiologic mechanisms that lead to myocardial infarction.

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