Case Study

Anginal Pain And Normal Coronary Arteries

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CASE HISTORY

A 51 year old female non-smoker, applying for $350,000 of term insurance, provided a history of chest tightness beginning 15 months prior to her application. The discomfort was located retrosternally, occasionally extending to the left shoulder, and was usually associated with exertion or excitement. The lady reported having taken sublingual nitroglycerine for a period of several months with little relief. At the time of application she was taking nifedipine, 60 mg/day and was on no other medication. A paramedic examination recorded a height and weight of 5'6" and 153 pounds. Her blood pressure was initially 148/90, falling to 132/78 at the conclusion of the exam. Routine blood chemistry screening and urinalysis were entirely normal. A resting EKG revealed low to flat T waves in I, AVL and V6 but was otherwise normal.

Additional Information

An attending physician's statement confirmed the history given at the time of application and included the results of a graded exercise test with myocardial perfusion scintigraphy conducted eleven months prior to the application. Clinically, chest discomfort occurred at the 9 met level but was said to be "less typical than her recent history". Concurrently, the electrocardiographic portion of the study revealed 2-2½ mm of downsloping ST segment depression in leads II, III, AVF and V5-6, persisting through 4½ minutes of recovery. SPECT images indicated a moderate size reversible defect in the inferoapical region.

In anticipation of probable revascularization, the lady underwent cardiac catheterization and coronary cineangiography with ergonovine challenge. The study revealed a normally functioning left ventricle and coronary arteries which were totally free of both atherosclerototic obstructive disease and spasm. It was concluded that the chest pain was non-cardiac and that the stress results represented a "false positive" response. Nevertheless, sublingual nitroglycerine was prescribed as needed for chest pain. The applicant continued to experience periodic retrosternal tightness both at rest and with exertion, and this did not seem to abate with nitroglycerine. She was then placed on nifedipine about six months prior to application. Shortly thereafter the chest discomfort became much less frequent and rather fleeting. She had abandoned use of the nitroglycerine. She was last seen by her attending physician two months prior to application. At that time she was reassured and advised to return in six months for a routine follow up.

The Incongruity of Angina and Coronary Patency

The scenario of angina-like chest pain, positive stress testing and normal coronary angiography is quite familiar in both clinical medicine and insurance risk classification. Such contradictory findings have often prompted cardiologists to conclude that the stress test results are "falsely positive." However, other possibilities exist.

The differential diagnosis includes coronary spasm and various gastrointestinal disorders such as peptic ulcer disease, gastroesophageal reflux disease, gall bladder disease, pancreatitis and splenic flexure syndrome, as well as other causes of ST segment depression (myocardial hypertrophy, electrolyte abnormalities, pharmacologic effects, etc.). All these possibilities must be viewed with some degree of skepticism in the presence of two separate surrogate tests for myocardial ischemia which are both positive and concordant, as in the case at hand. Under such circumstances other cardiac causes should be given consideration.

Over the past two decades the literature has cited
case histories such as the one presented here, often with little attempt to reconcile the seemingly contradictory observations. Originally, there existed an apparent contentment to accept this clinical picture as an evasive perplexity. However, more recently, greater effort has been extended in attempts to elicit the pathogenesis of this phenomenon. This has resulted in a number of theoretical etiologies.

The Concept of Syndrome X

The clinical picture exhibited by the case presented here was first described by Likoff et al in 1967 and later given the name of “Syndrome X” by Kemp in 1973. Using the broad definition of Syndrome X, the generally accepted diagnostic criteria are (1) typical angina pectoris and (2) angiographically normal coronary arteries. Most authors require, as a third criterion, an abnormal rest/stress study providing objective evidence of myocardial ischemia, impaired myocardial perfusion and/or myocardial wall motion abnormalities.

Beyond this basic definition, there is less agreement on certain exclusionary criteria. The majority opinion requires that coronary epicardial arterial spasm and left ventricular hypertrophy be ruled out. Additionally, it is commonly held that systemic hypertension and valvular heart disease also should be excluded.

Incidence

Because of this lack of a single definition of Syndrome X, it is difficult to ascertain its true incidence. However, various studies have found that between ten and thirty percent of patients undergoing coronary angiography for chest pain have normal coronary arteries.¹⁻³

Clinical Presentation

The typical patient is a middle aged female.⁵ Clinically, the patient experiences chest pain which is typical of angina in most respects. However, the pain commonly occurs at rest as well as with exertion, is frequently prolonged (duration up to 30 minutes or more), and is usually poorly responsive to sublingual nitroglycerine.²⁵ Electrocardiographic ST depression, if present, is indistinguishable from that encountered with significant epicardial coronary artery disease, whether induced by stress testing or detected during continuous ambulatory electrocardiography.⁴ ST segment elevation, as observed with Prinzmetal’s variant angina, does not occur.⁷

Other surrogate markers of myocardial ischemia (myocardial perfusion scintigraphy, wall motion studies and measures of systolic and diastolic left ventricular function) are less likely to be abnormal than electrocardiographic stress testing.⁵⁻⁷⁻¹⁰

Pathogenesis

The medical community is generally in agreement that Syndrome X is not a single entity. The term is probably best used to describe a clinical presentation common to a heterogeneous group of functional and organic disorders.¹¹ More than a few authorities disparage the use of the term as misleading.¹²,¹³ The term can also be confusing, since “Syndrome X” has also been applied to another syndrome combining the features of diabetes mellitus, insulin resistance, hyperinsulinemia, dyslipidemia, systemic hypertension and obesity.¹⁴ Because of these concerns it has been suggested that the syndrome should merely be referred to as “angina pectoris with angiographically normal coronary arteries”. If this becomes the accepted terminology, then it might also be appropriate to designate two subsets: Type A (with objective evidence of ischemia) and Type B (without objective evidence of ischemia).

Several possible causes of Syndrome X have been postulated. A brief review of these pathogenic mechanisms is appropriate.

Non-cardiac Postulates

These conditions should properly be labeled with their legitimate diagnoses rather than being included within the designation of Syndrome X. However, they are mentioned briefly, because of their inclusion by some authors within the list of possible causes of this syndrome.

- Esophageal reflux and motility disorders
- Psychosomatic disorders (neurocirculatory asthenia, hyperventilation syndrome, Da Costas syndrome)
- Increased adrenergic tone (hyperkinetic heart syndrome)
- Abnormal pain perception

Cardiac Postulates

- Early atheromatous coronary heart disease (or angiographic misinterpretation)
“Microvascular Angina.” This term, used incorrectly by some as a synonym for Syndrome X, was first introduced by Cannon and Epstein in 1988 to describe angina, normal coronary angiography and metabolic evidence of ischemia (i.e. lactate production). They theorized that the mechanism was at least partially due to an abnormality of dilatation of the prearteriolar coronary vessels. Chauchan sees this abnormality as an impairment of smooth muscle relaxation causing limitation of coronary vasodilator reserve, which translates into a diminished coronary flow reserve (the difference between baseline flow and flow with maximal vasodilatation). This abnormal vasodilator reserve may be attributable to coronary endothelial dysfunction in which there occurs deficient release of endothelial-derived relaxing factor. This phenomenon is known to exist in atherosclerotic epicardial coronary heart disease (accounting for so-called “mixed angina”), but evidence exists that it also may be operative in pure microvascular angina, accounting for impaired endothelium-dependent vasodilatation of the prearteriolar coronary vessels. Additionally, the loss or attenuation of vasodilatation may form the basis for increased coronary arteriolar reactivity to vasoconstrictor stimuli.

Quantitation of coronary flow reserve involves great cardiac vein flow measurement or Doppler-derived indices of coronary arterial blood flow. These procedures are cumbersome, time-consuming and subject to distortion by confounding hemodynamic variables. However, reliable studies have yielded insightful information bearing on the pathogenesis of microvascular angina. Chauchan et al reported significantly lower coronary flow reserves among 53 patients meeting the criteria for Syndrome X (2.72±1.39) compared to 26 controls (5.22±1.26, p<0.01). Opherk et al made similar observations. On the other hand, Rosen et al found no significant difference in comparing 29 Syndrome X patients against 20 controls.

Microvascular coronary disease differs from atherosclerotic epicardial coronary heart disease in certain important aspects. First, it is functional (not structural) as evidenced by normal myocardial biopsies. Secondly, it is diffuse as opposed to the regional involvement of atherosclerotic coronary heart disease. There are also major differences with respect to management and prognosis, as discussed below.

“Myocardial Migraine.” This intriguing postulate relates to the effect of adenosine on receptors within the myocardium and coronary microvasculature. Adenosine is released from myocytes into the myocardial interstitial space and is a potent vasodilator of the coronary microvasculature, particularly in the subendocardium. It is also recognized as a nociceptive agent (neurohumoral mediator of painful stimuli). Based on this information and the knowledge that aminophylline blocks cardiac adenosine receptors, Michel et al developed and tested the hypothesis that adenosine (through excessive accumulation or increased sensitivity of its receptors), not myocardial ischemia, is responsible for both the chest pain and the ST segment changes encountered in at least some patients meeting the criteria for the diagnosis of Syndrome X.

These authors studied a 53 year old female who presented with disabling angina-like pain, a positive treadmill exercise test and normal coronary angiography. This lady received an intravenous infusion of adenosine in a dose of 140µg/min for 5 minutes with and without pretreatment with intravenous aminophylline (125 mg). Both the characteristic chest pain and the ST segment depression were reproduced within 30 seconds of the adenosine challenge without aminophylline pretreatment. When the challenge was repeated after aminophylline pretreatment, neither the pain nor the ST segment changes developed. Moreover, the patient was then treated with oral aminophylline (200 mg bid) and had remained asymptomatic during the succeeding year. The authors point to the non-ischemic nature of adenosine-induced chest pain with ST segment changes and make the interesting observation that this postulated variant of Syndrome X (involving vasodilatory pain) might be viewed as a form of “myocardial migraine.” They acknowledge the absence of any explanation for the ST segment changes. This same response to aminophylline has also been reported by others.

Treatment

The management of patients diagnosed as having Syndrome X should attempt to identify subsets within the heterogeneity of the broad syndrome. Non-cardiac causes call for specific interventions (psychotherapy, psychoactive drugs, anti-reflux measures, etc.). True microvascular angina may respond to nitrates and calcium channel entry blockers. Romeo et al found nitrates and beta-blocking agents to be largely ineffective but observed that most Syndrome X patients improved with calcium antagonists. Lessening of exercise-induced angina and ST segment depression by angiotensin-converting enzyme inhibitors has been reported by Kaski et al. This choice of therapy is particularly prudent if microvascular angina occurs in the...
setting of hypertensive left ventricular hypertrophy.25,26 Based on the observations of Michel et al,21 amino-
phylline or theophylline may be effective when symp-
toms are not felt to be ischemic. In many cases the
complexities of diagnostic investigation will be pro-
hibitive in defining subsets of Syndrome X. Recognizing this limitation, it is appropriate in some
cases to conduct therapeutic trials using the pharma-
cologic agents mentioned.

Prognosis and Risk Classification

Syndrome X usually has a very favorable long-
term outlook with respect to both the incidence of
myocardial infarction and life expectancy.6 The prog-
nosis is considerably better than that of epicardial
coronary heart disease.16 However, a small percentage
of Syndrome X patients exhibit progressive deteriora-
tion of left ventricular function over a 4-5 year peri-
d.24,27 This course appears to be more likely in the set-
ing of left bundle branch block.23,27 It has been theo-
rized that this deterioration of left ventricular function
may be the result of small, patchy areas of infarction,16
although there is no confirmation of this.

Classification of the risk of mortality should
attempt to define special features of the case at hand.
As a first step, non-cardiac cases should be separated
from those related to a cardiac cause and then consid-
ered in terms of the risk of the specific disorder, if iden-
tifiable.

If a given case is likely cardiac in nature, it should
be determined whether or not the case fits into the low
risk category: features confined to chest pain, an elec-
trocardiographically positive stress test and angiogra-
phically normal coronary arteries. This category
excludes pain-related vascular instability or arrhyth-
mia, abnormalities of myocardial perfusion scintigra-
phy or left ventricular wall motion, systemic hyper-
tension, left ventricular hypertrophy, left bundle
branch block and significant impairment of left ven-
tricular function. If the risk falls into this category,
then the expectation of extra mortality should be mild
to modest. And if symptoms are eliminated with med-
ication, standard mortality should usually be expect-
ed. The occurrence of exercise-induced myocardial
perfusion defects or wall motion abnormalities would
justifiably predict significant extra mortality, perhaps
one fourth to one half that associated with the average
case of atherosclerotic coronary heart disease, depend-
ing on the extent to which symptoms are controlled.

The coexistence of microvascular angina and sys-
temic hypertension and/or left ventricular hypertro-
phy should be viewed with caution—usually warrant-
ing a modest augmentation of the sum of the separate
ratings. Some of these cases may pose unacceptable
mortality. Microvascular angina accompanied by left
bundle branch block or significant impairment of left
ventricular function is an ominous situation, often pre-
dictive of unacceptable mortality.

Insofar as concerns disability income and medical
expense insurance, it should be recognized that con-
siderable morbidity may be associated with Syndrome
X, even when life expectancy is unaffected. The extent
of this morbidity is predictable from the recent history
of symptoms, medication requirements, office visits,
hospitalizations, diagnostic tests and therapeutic tri-
als. In cases involving minimal symptoms, no incapaci-
ty and infrequent need of medical attention, morbidi-
ty expectations are of little consequence. On the other
hand, symptoms interfering with daily activities, a
recent history of major medical expense or the likeli-
hood of impending diagnostic studies should signal
an unacceptable expectation of future morbidity.

CONCLUSION

The coexistence of typical angina-like symptoms
and angiographically normal coronary arteries is a
common contradictory scenario. This circumstance is
even more perplexing when accompanied by objective
evidence of myocardial ischemia. Perhaps as an
expression of bewilderment, this clinical picture has
come to be known as “Syndrome X.” It should be
understood that Syndrome X is not a disease entity
but, rather, a clinical presentation. The syndrome most
likely occurs as the result of several heterogeneous dis-
orders—some of which are cardiac and others non-car-
diac.

Various theories on the pathogenesis of Syndrome
X have been offered. Some of these theories suggest a
non-ischemic cardiac cause. Others are based on evi-
dence supporting the existence of a functional impair-
ment of the coronary microvascular tone. These theo-
ries probably point to various subsets of Syndrome X,
each with its individual pathologic or biochemical
mechanism, treatment indication, and prognosis.

Most cases of Syndrome X have a favorable long-
term outlook for survival, but morbidity can be con-
siderable. A small percentage of cases exhibit progres-
se left ventricular dysfunction and substantial extra
mortality. Risk classification should seek to individu-
alize within the wide spectrum of conditions grouped
together under the heading of Syndrome X.

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References


