Case 1

A 45-Year-Old Man with Substantial Chest Pain

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History of Current Presentation

The subject is a 45-year-old African-American male who presents with a chief complaint of "substantial chest pain" that radiated through his right arm and back. The pain awoke him from his sleep at approximately 3:30 am and was described as constant and as "8 out of 10." He also complained of nausea and shortness of breath. Over the past 2–3 months he stated that he had experienced similar symptoms that radiated through both arms. One month prior to admission, he visited his primary care internist, during which time his electrocardiogram (EKG) and x-rays were normal. A stress test was scheduled but the appointment was missed. On the morning of presentation, the patient took 1 aspirin (325 mg) within 30 minutes of awakening. The subject presents to the emergency department 1 hour [0430 h (4:30 am)] after onset of acute chest pain.

He had a past medical history of hypertension and takes both antihypertensive medication and aspirin daily. He is a smoker (20 years), and occasional drinker, and his father had a fatal myocardial infarction (MI) at the age of 72. At physical examination, temperature, pulse, and respiration were normal, blood pressure 200/40, O_2 saturation (pulse oximetry) 92% on room air and 99% after receiving 100% oxygen. He was alert, awake, and oriented in moderate discomfort. His lungs were clear to auscultation bilaterally with no rales or wheezes. Heart rate and rhythm were regular without murmurs. Chest x-ray showed borderline cardiomegaly, without infiltrates.

At presentation, routine chemistries, CBC, and cardiac biomarkers were within normal limits. The EKG at presentation shows poor R-wave progression anteriorly, with an ST depression in lead III. Consultation with the attending cardiologist following a similar EKG repeated at 1 hour after presentation ruled out MI. The patient was managed medically with nitroglycerin sublingually ($\times 3$ doses), which improved his discomfort to the point where he was pain-free. His blood pressure improved (decreased) following medication. He was also given multiple doses of morphine sulfate for his right arm pain.

Given the history and current presentation, the patient was admitted to the cardiac short-stay unit, and monitored. He was given nitrogycerine and low-molecular-weight

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heparin (LMWH, enoxaparin). Repeat cardiac biomarkers were ordered for 4 and 8 hours after presentation. Four hours following presentation, the EKG showed inverted T waves, now with new Q waves in the anterior leads. Repeat measurements of biomarkers at 0845 h (8:45 am) showed elevated values for total CK, CKMB, and condiac troponin T(cTnT).

Day Reference Intervals	Time, h	Total CK U/L 60–300	CKMB, μg/L ≤7.0	cTnT, μg/L <0.01	EKG
1	0430	40	1.5	<0.01	ST depression
	0845	405	88	3.2	Q wave
	0930	—	—	—	Stent placement
	1445	4850	950	31.5	—
2	0600	3225	505	24.2	—
	1800	1258	245	18.1	—

The diagnosis of an evolving acute MI was made and the patient was immediately taken to the cardiac catheterization lab and a glycoprotein IIB IIIA inhibitor [ReoPro (abciximab)] was started. In the catherization lab (0930 h), the patient's 100% occluded left anterior descending (LAD) coronary artery was opened by angioplasty and a stent was placed, with successful reperfusion. His chest pain was relieved following the procedure, without recurrence. There were no signs of any congestive heart failure issues. His echocardiographic (echo) study showed an ejection fraction of 48%.

In the hospital, the patient tolerated progressive ambulation without difficulty. He was discharged on day 4, on multiple medications, and scheduled for cardiac rehabilitation, medication assessment, and outpatient follow-up. Presently use of biomarkers such as cardiac troponin, BNP (B-type natriurtic peptide), or hsCRP are not routinely used for follow-up in post-MI patients for risk assessment, unless clinically indicated.

Definition of the Disease

Acute myocardial infarction (AMI) is defined as an imbalance between myocardial oxygen supply and demand resulting in injury and eventual death of myocytes. It is now thought that the migration of stem cells has the potential to replace at least some damaged myocytes. When the blood supply to the heart is interrupted, "gross necrosis" of the myocardium results. Necrosis is most often associated with a thrombotic occlusion superimposed on coronary atherosclerosis. The process of plaque rupture and thrombosis is one of the ways in which coronary atherosclerosis progresses and that we currently recognize only the more severe of these events. Total loss of coronary blood flow in a major coronary artery results in a clinical syndrome known as *ST-segment elevation AMI* (STEMI). Partial loss of coronary perfusion can also lead to necrosis as well, is generally less severe, and is known as *non-ST-elevation myocardial infarction* (NSTEMI). Other events of still lesser severity may be missed entirely and can range from stable to unstable angina.

Presenting Symptoms

The clinical history remains of substantial value in establishing a diagnosis. A prodromal history of angina can be found in 40–50% of patients with AMI; approximately one-third have symptoms 1–4 weeks before hospitalization. In the remaining two-thirds, symptoms

predate admission by a week or less, and one-third of these patients will have had symptoms for 24 hours or less.

The pain of AMI is variable in intensity; in most patients it is severe but rarely intolerable. The pain may be prolonged, up to 30 minutes. The discomfort is described as constricting, crushing, oppressing, or compressing; often the patient complains of something sitting on or squeezing the chest. Although usually described as a squeezing, choking, viselike, or heavy pain, it may also be characterized as a stabbing, knifelike, boring, or burning discomfort. The pain is usually retrosternal in location, spreading frequently to both sides of the chest, often favoring the left side and radiating down the left arm. In some instances, the pain of AMI may begin in the epigastrium and simulate a variety of abdominal disorders, which often causes MI to be misdiagnosed as indigestion. In other patients, the discomfort radiates to the shoulders, upper extremities, neck, and jaw. Older individuals, diabetics, and women often present without the typical pain. For example, less than 50% of those over age 80 who present with AMI will have chest discomfort. Sometimes, these patients will present with shortness of breath, fatigue, or even confusion. The pain of AMI may have disappeared by the time physicians first encounter the patient (or the patient reaches the hospital), or it may persist for a few hours.

Diagnostic Criteria

Previously, the diagnosis of AMI established by the World Health Organization in 1986 required at least two of the following criteria: a history of chest pain, evolutionary changes on the ECG, and/or serial elevations of cardiac markers. However, it was rare for a diagnosis of AMI to be made in the absence of biochemical evidence. A 2000 European Society of Cardiology/American College of Cardiology (ESC/ACC) consensus conference has codified the role of biomarkers, specifically cardiac troponin I or T, by advocating that the diagnosis be based on biomarkers of cardiac damage in the appropriate clinical situation.[1–5] The criteria for diagnosis of an acute and established AMI are described in Table 1.1. The guidelines recognize the reality that neither the clinical presentation nor the ECG has adequate sensitivity and specificity for myocardial necrosis. This guideline does not suggest that all elevations of these biomarkers should elicit a diagnosis of AMI;

Table 1.1 Diagnosis of Myocardial Infarction

Acute MI: Either one of the following criteria satisfies the diagnosis for an acute, evolving, or recent MI:

1. Typical rise and gradual fall (cardiac troponin) or more rapid rise and fall (CK-MB) of biochemical markers of myocardial necrosis with at least one of the following:
   a. Ischemic symptoms
   b. Development of pathological Q waves on ECG
   c. ECG changes indicative of ischemia (ST-segment elevation or depression)
   d. Coronary artery intervention (e.g., coronary angioplasty)
2. Pathological findings of an acute MI.

Established MI: Any one of the following criteria satisfies the diagnosis for established MI:

1. Development of new pathologic Q waves on serial ECGs. The patient may or may not remember previous symptoms. Biochemical markers of myocardial necrosis may have normalized, depending on the length of time that has passed since the infarct developed.
2. Pathological findings of a healed or healing MI.

Table 1.2 ESC/ACC Recommendations for Use of Cardiac Biomarkers for Detection of Myocardial Injury and Myocardial Infarction

Increases in biomarkers of cardiac injury are indicative of injury to the myocardium, but not an ischemic mechanism of injury.
Cardiac troponins (I or T) are preferred markers for diagnosis of myocardial injury.
Increases in cardiac marker proteins reflect irreversible injury.
Improved quality control of troponin assays is essential.
Myocardial infarction is present when there is cardiac damage, as detected by marker proteins (an increase above the 99th percentile of the normal range) in a clinical setting consistent with myocardial ischemia.
For patients with an ischemic mechanism of injury, prognosis is related to the extent of troponin increases.
If an ischemic mechanism is unlikely, other etiologies for cardiac injury should be pursued.
Samples must be obtained at least 6–9 hours after the symptoms begin.
After PCI and CABG, the significance of marker elevations and patient care should be individualized.

only those associated with the appropriate clinical and/or ECG findings.[6,7] When elevations that are not caused by an acute ischemia event, the clinician is obligated to search for another etiology for the elevation. The criteria suggested for use with these biomarkers by the Biochemistry Panel of the ESC/ACC Committee is listed in Table 1.2.

The use of these new criteria has led to the NSTEMI diagnosis. The initial ECG used to have a sensitivity of about 50% for AMI. As the diagnosis of NSTEMI is made with greater and greater sensitivity, the frequency of STEMI among all AMI has decreased. Serial ECG tracings are helpful for STEMI but not for what now makes up almost 70% of AMIs, those with NSTEMI. The classic ECG changes of an STEMI are ST-segment elevation, which often evolves to the development of Q waves without intervention. Most NSTEMIs present with either ST segment depression, with or without T-wave changes; T-wave changes alone; or occasionally in the absence of any ECG findings. Those with ST-segment change have a substantially worse prognosis. There are many other clinical aspects that might suggest AMI as the etiology of a given biomarker elevation. For example, the finding of significant coronary obstructive lesions, especially in a pattern suggestive of recent plaque rupture, is highly suggestive. At times, a positive stress test with or without imaging may be necessary to help make the diagnosis. However, if the clinical situation is not suggestive, other sources for cardiac injury should be sought.

The term *acute coronary syndrome* (ACS) is increasingly used in the literature and encompasses all patients who present with unstable ischemic heart disease. If they have STE, they are called *STEMI*. If they do not have STE but have biochemical criteria for cardiac injury, they are called *NSTEMI*, few of whom develop ECG Q waves. Those who have unstable ischemia and do not manifest cardiac necrosis markers are designated patients with unstable angina (UA). Most of these syndromes occur in response to an acute event in the coronary artery when circulation to a region of the heart is obstructed. If the obstruction is high-grade and persists, then necrosis usually ensues. Since necrosis is known to take some time to develop, it is apparent that opening the blocked coronary artery in a timely fashion can often prevent death of myocardial tissue.

Pathogenesis

The major cause of ACS is atherosclerosis, which contributes to significant narrowing of the artery lumen and a propensity for plaque disruption and thrombus formation.

Myocardial ischemia and subsequent infarction usually begin in the endocardium and spread toward the epicardium. The extent of myocardial injury reflects (1) extent of the occlusion, (2) duration of the imbalance between coronary supply and substrate availability, and (3) the metabolic needs of the tissue. Irreversible cardiac injury consistently occurs in animals when complete occlusion is present for at least 15–20 minutes. Most of the damage occurs within the first 2–3 hours. Restoration of flow within the first 60–90 minutes evokes maximal salvage of tissue, but the benefits of reperfusion up to 4–6 hours are sufficient to be associated with increased survival. The percentage of tissue at risk that undergoes necrosis (infarct size) is highly variable and difficult to predict.

In most cases, the left ventricle is affected by AMI. However, with right coronary and/or circumflex occlusions, the right ventricle can also be involved. Coronary thrombi will undergo spontaneous lysis, even if untreated, in about 50% of cases within 10 days. However, for patients with STEMI, opening the vessel earlier with clot-dissolving agents (thrombolysis) and/or percutaneous intervention (PCI) can often save myocardium and lives. Consequently, percutaneous intervention with stenting is the preferred therapy for STEMI. However, many hospitals cannot or do not offer urgent PCI 24 hours a day, 365 days per year. Thus clot-dissolving medications still play a major role in the treatment of these patients. It is now apparent that urgent invasive revascularization also benefits those with NSTEMI. We now know that many treatments, such as newer anticoagulant, antiplatelet, and antiinflammatory agents in conjunction with coronary revascularization, save lives in this group.

Precipitating Factors

In many patients with AMI, no precipitating factor can be identified. Studies have noted the following patient activities at the onset of AMI: modest, heavy, or usual physical exertion, surgical procedure, rest, and sleep. If and when these activities trigger an infarction, the window of risk is often brief, usually only an hour or two. The severe exertion that preceded an infarction was often performed at times when the patient was fatigued or emotionally stressed.

There are causes of infarction other than acute atherothrombotic coronary occlusion. Prolonged vasospasm can induce infarction, and spontaneous dissections are becoming more commonly appreciated, especially in pregnant females. Other conditions can also cause the death of cardiomyocytes and lead to a biochemical signal of myocyte damage, but should not be confused with myocardial infarction. These include (1) trauma that may precipitate myocardial contusion; (2) toxic reactions to chemotherapy agents, such as Adriamycin, or myocardial depressant substances released with sepsis; (3) heat-induced injury after cardioversion; (4) increases in wall stress with impairment of subendocardial perfusion caused by severe hypo- or hypertension; and/or (5) injury caused by catecholamine release in patients with acute neurological catastrophes. Pulmonary embolism is another common cause of biomarker increase.

Anatomy of an MI

On gross pathological examination, AMI can be divided into subendocardial (nontransmural) infarctions and transmural infarctions. The pathological changes correlate poorly with clinical, ECG, and biochemical markers of necrosis. In experimental infarction,

the earliest ultrastructural changes in cardiac muscle following occlusion of a coronary artery noted within 20 minutes by electron microscopy, consist of a reduction in the size and number of glycogen granules, intracellular edema, and swelling and distortion of the transverse tubular system, the sarcoplasmic reticulum, and the mitochondria. These early changes are partially reversible. Changes after 60 minutes of occlusion include myocardial cell swelling and mitochondrial abnormalities. After 20 minutes to 2 hours of ischemia, changes in some cells become irreversible, with a progression of these alterations, including enlarged mitochondria with few cristae and clumping, and thinning and disorientation of myofibrils. Cells irreversibly damaged by ischemia are usually swollen, with an enlarged sarcoplasmic reticulum. Defects in the plasma membrane may appear.

In some infarcts a pattern of wavy myocardial fibers may be seen by light microscopy 1–3 hours after onset, especially at the periphery. After 8 hours, edema of the interstitium becomes evident, as do increased fatty deposits in the muscle fibers. By 24 hours there is clumping of the cytoplasm and loss of cross-striations, with appearance of irregular cross-bands in the involved myocardial fibers. During the first 3 days, the interstitial tissue becomes edematous. On about day 4 after infarction, removal of necrotic fibers by macrophages begins, again commencing at the periphery. By day 8, the necrotic muscle fibers have become dissolved; by about 10 days the number of polymorphonuclear leukocytes is reduced, and granulation tissue first appears at the periphery. Removal of necrotic muscle cells continues until weeks 4–6 following infarction. By the sixth week, the infarcted area has usually been converted into a firm connective tissue scar with interspersed intact muscle fibers. Gross alterations of the myocardium are difficult to identify until at least 6–12 hours following the onset of necrosis. By 18–36 hours after onset of the infarct, the myocardium is tan or reddish purple (because of trapped erythrocytes). These changes persist for approximately 48 hours; the infarct then turns gray and fine yellow lines. Eight to 10 days following infarction, the thickness of the cardiac wall in the area of the infarct is reduced as necrotic muscle is removed by mononuclear cells. Over the next 2–3 months, the infarcted area gradually acquires a gelatinous, gray appearance, eventually converting into a shrunken, thin, firm scar that whitens and firms progressively with time.

Prognosis

The prognosis of patients with ischemia but without necrosis is far better, and there are no differences thus far described that distinguish medical from invasive therapies. A major determinant of mortality and morbidity is the amount of myocardial damage. With STEMI, most of it is acute whereas with NSTEMI, it may evolve because of repetitive events over many months. Thus interrupting the process improves survival.

STE and NSTE infarctions have distinctly different short-term prognoses. STEMI is associated with a higher early and in-hospital mortality. It is said that mortality associated by STEMI can occur up to 6 months postevent, but the vast majority (at least two-thirds) occurs during the first 30 or 40 days. It is this process that coronary recanalization seems to benefit. NSTEMI is associated with a lower acute mortality and complication rates but a longer period of vulnerability to reinfarction and death. As a result, 1–2-year survival rates are similar to those for transmural infarction. This is why intervention has been so effective in this group.

In today's environment of preventive and evidence-based medicine, the use of cTnI or cTnT measured once at presentation and again at 12–24 hours in patients with ischemia

will allow clinicians to use markers as both exclusionary and prognostic indicators.[8–12] The results will assist in determining who is more at risk for AMI and death, and thereby determine who may benefit from early medical or surgical intervention. An evaluation of the majority of risk stratification studies shows that approximately 30% of all UA and NSTEMI patients present with an increased cardiac troponin level. Of these, approximately 30% (or 9–10% overall) have an adverse short-term (30–40 days) and long-term (1–2 years) prognosis. Identifying patients at greater risk for cardiac events allows them to be treated more aggressively, with proven beneficial outcomes. Clinical performance of cardiac troponin assays have been shown to be strongly dependent on the analytical sensitivity and precision of measured concentrations around the 99th percentile reference limit.[13–16] Several studies have now documented that assays with lower limits of detection are able to identify more ACS patients with poor prognosis who may be candidates for early invasive procedures. There are now data that such patients benefit from the use of low-molecular-weight heparin, IIB/IIIA platelet antagonists, and an early invasive strategy. General population screening of hospitalized patients with cTnI or cTnT is not recommended.

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