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Educational Case: Myocardial Infarction: Histopathology and Timing of Changes

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The following fictional case is intended as a learning tool within the Pathology Competencies for Medical Education (PCME), a set of national standards for teaching pathology. These are divided into three basic competencies: Disease Mechanisms and Processes, Organ System Pathology, and Diagnostic Medicine and Therapeutic Pathology. For additional information, and a full list of learning objectives for all three competencies, see http://journals.sagepub.com/doi/10.1177/2374289517715040.[1]

Keywords
pathology competencies, organ system pathology, cardiovascular-heart, atherosclerosis in heart disease, histopathology, timing of changes

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Primary Objective

Objective: CH2.5: Histopathology of Myocardial Infarction. Describe the histologic features of acute myocardial infarction and explain pathophysiology underlying the histologic changes from initial infarction through fibrosis and relate to the laboratory diagnosis of myocardial infarction.

Competency 2: Organ System Pathology; Topic CH: Cardiovascular-Heart; Learning Goal 2: Atherosclerosis in Heart Disease

Secondary Objective

Objective: CH2.4: Timing of Changes in Myocardial Infarction. Compare and contrast the gross and microscopic features of acute myocardial infarction and remote myocardial infarction, and at what point gross or microscopic pathology appears.

Competency 2: Organ System Pathology; Topic CH: Cardiovascular-Heart; Learning Goal 2: Atherosclerosis in Heart Disease

Patient Presentation

A 59-year-old man with a significant previous history of hypertension and right carotid endarterectomy presented to the emergency department (ED) with chest pain radiating to the left arm accompanied by diaphoresis and dyspnea.

Diagnostic Findings, Part 1

His electrocardiogram (ECG) was performed that showed elevation in leads 1, augmented Vector Left (aVL) and V1-V6 (Figure 1), consistent with the diagnosis of extensive anterolateral myocardial infarction (MI). His troponin I levels were found to be elevated, 20 ng/mL (normal reference: cardiac troponin I <0.03 ng/mL, cardiac troponin T <0.1 ng/mL, creatine kinase MB isoenzyme <10 ng/mL, myoglobin <170 ng/mL).

In the ED, his blood pressure dropped and he was placed on vasopressors. After appropriate initial management, he was sent to the cardiac catheterization lab. He was found to have 90% occlusion of the left anterior descending (LAD) coronary

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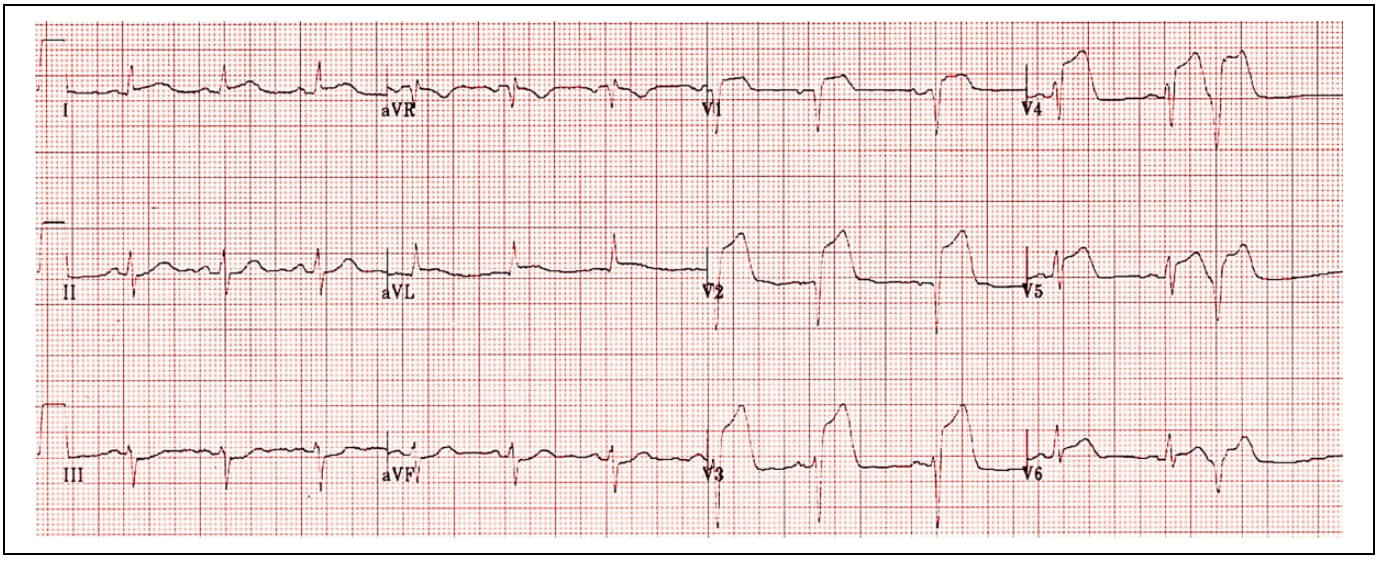


Figure 1. ECG showing ST elevation in leads I, aVL and V1-V6, consistent with acute anterolateral MI. ECG indicates electrocardiogram; MI, myocardial infarction.

artery, and a drug-eluting stent was placed in the LAD. The patient eventually stabilized and was weaned off of vasopressors, and he was transferred to the general cardiology service. His ECG results were stable, and troponins were trending down. The patient was discharged.

Questions/Discussion, Part 1

What Is the Differential Diagnosis in a Patient Presenting With Chest Pain?

The differential diagnosis of a patient presenting with chest pain includes MI, acute gastritis, pulmonary embolism, anxiety, aortic dissection, and musculoskeletal chest pain. Based on the clinical features, a number of differentials can be enlisted in this case:

Acute gastritis. The chest pain in MI may mimic heartburn. However, the typical ECG changes of MI together with elevated cardiac enzymes, in this case makes MI more likely.

Pulmonary embolism. The patient has chest pain associated with tachypnea and dyspnea which are symptoms seen in pulmonary embolism. However, a lack of risk factors and the gradual onset of his pain makes this diagnosis unlikely. The ECG changes together with elevated cardiac enzymes also favor MI.

Musculoskeletal chest pain. It may present with severe chest pain but is associated with point tenderness and does not radiate. Also, it is not associated with ECG changes and elevated cardiac enzymes.

Aortic dissection. The presenting complaint of aortic dissection is also chest pain; however, it starts abruptly with maximal intensity at onset, tearing in character, radiates to the back (interscapular area), and does not show the classic ECG findings of an MI.

Anxiety. Patients with anxiety (panic attack) present with chest pain, sweating, and palpitations. However, the classic ECG findings are absent.

What Is the Workup in a Patient With Chest Pain?

The first and foremost step to evaluate the exact cause of chest pain and the artery involved is to do an ECG. Table 1 describes the findings of ECG in MI in detail.[2]

Cardiac markers (creatine kinase [CK-MB], troponin I, troponin T, and myoglobin) are also done to diagnose MI. Since cardiac troponin has high sensitivity and high specificity for myocardial injury, it is the gold standard marker to diagnose MI. The time when the different markers begin to peak and normalize is shown in Figure 2.

What Is the Definitive Diagnosis in This Patient?

The patient had chest pain radiating to the left arm, accompanied by diaphoresis, dyspnea, and tachycardia, raising a strong suspicion for MI. The ECG changes together with elevated cardiac enzymes confirm the diagnosis.

Two weeks later, he returned with the complaint of mild chest pain radiating to the left arm, associated with diaphoresis, nausea, and shortness of breath and was hypoxic.

Diagnostic Findings, Part 2

Pulse: 112 bpm, irregularly irregular
Blood pressure: 100/60 mm Hg
Respiratory rate: 22 per minute
Temperature: 98 °F

On this second visit, his ECG showed Q waves, consistent with old infarct, while his troponin I was elevated, 5 ng/mL. The patient progressed to ventricular fibrillation the same day.

Table 1. Arteries involved in MI with respective ECG findings.

Artery	Area of supply	EKG findings
LAD (branch of the left coronary artery)	Most of the apex, the anterior wall of the left ventricle and the anterior two-thirds of the ventricular septum	ST elevation in V1-V6
RCA	Free wall of the right ventricle, the posterolateral wall of the left ventricle, and the posterior third of the ventricular septum	ST elevation in II, III, aVF
LCX	Lateral wall of the left ventricle	ST elevation in I, aVL, or depression in V1-V6

Abbreviations: LAD, left anterior descending artery; RCA, right coronary artery; LCX, left circumflex artery.

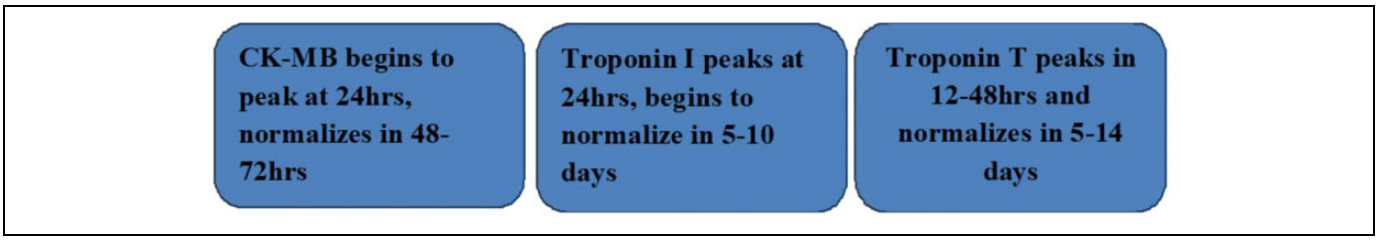


Figure 2. Timing of changes of cardiac markers.

Chest compression and resuscitation efforts were performed, but his condition deteriorated and he was found to be unresponsive and pulseless. The patient was intubated and required multiple vasopressors. Despite these interventions, the patient expired 13 to 15 hours after the presentation to ED. At the request of the patient's family, an autopsy was performed.

Questions/Discussion, Part 2

What Is an MI?

Myocardial infarction, commonly called a heart attack, is the death of cardiac muscles as a result of prolonged severe ischemia.[2] Ischemia is defined as restricted blood supply to cells and tissues that cause shortage of oxygen, vital to cell metabolism.

What Is the Classic Clinical Presentation of an MI?

Patients with MI present with chest pain that typically radiates to the left arm, jaw, back or shoulder, dyspnea, diaphoresis, lightheadedness, and tachycardia. Additionally, inferior wall MI can present with bradycardia because of vagal stimulation.[2]

What Is the Pathogenesis of MI?

An inability of coronary blood flow to meet the myocardial demand is the major cause of MI. Most commonly, there is a narrowing of the coronary arteries due to atherosclerotic plaques with varying degrees of superimposed changes, for example, thrombosis and vasospasm. Certain conditions, such as hypertrophy, tachycardia also lead to MI, in which demand outweighs supply. The sequence of events underlying MI is detailed below.[2]

Most MIs are caused by coronary artery occlusion. The pathogenesis is shown in the Figure 3.[2]

However, in approximately 10% of cases of transmural MI, coronary atherosclerosis is absent. In these cases, other mechanisms are responsible for the reduced myocardial perfusion including[2]

- vasospasm, which might be associated with platelet aggregation or resulting from drug ingestion (eg, cocaine or ephedrine);
- atrial fibrillation resulting in emboli formation, infective endocarditis vegetations, and prosthetic material inside the heart; and
- an embolus from the right side of the heart or the peripheral veins, traversing a patent foramen ovale into the coronary arteries.

Ischemia caused by disorders of small intramural coronary vessels (eg, vasculitis), hematologic abnormalities (eg, sickle cell disease), amyloid deposition in the walls of the vessels, and arterial dissection

- hypertrophy (eg, aortic stenosis), hypotension (eg, shock), or inadequate myocardial protection during cardiac surgery.

There is a characteristic myocardial response associated with MI. The occlusion of a coronary artery reduces blood flow to an area of the myocardium, causing ischemia, dysfunction of the myocardium, and eventually myocyte death due to prolonged vascular compromise. The duration and severity of blood flow reduction are the 2 factors that determine the outcome. Inadequate production of high-energy phosphates (eg, ATP and creatinine phosphate) and accumulation of potentially noxious metabolites (eg, lactic acid) are a result of the cessation of aerobic metabolism. The contractility of the myocardium stops soon after the ischemic insult begins

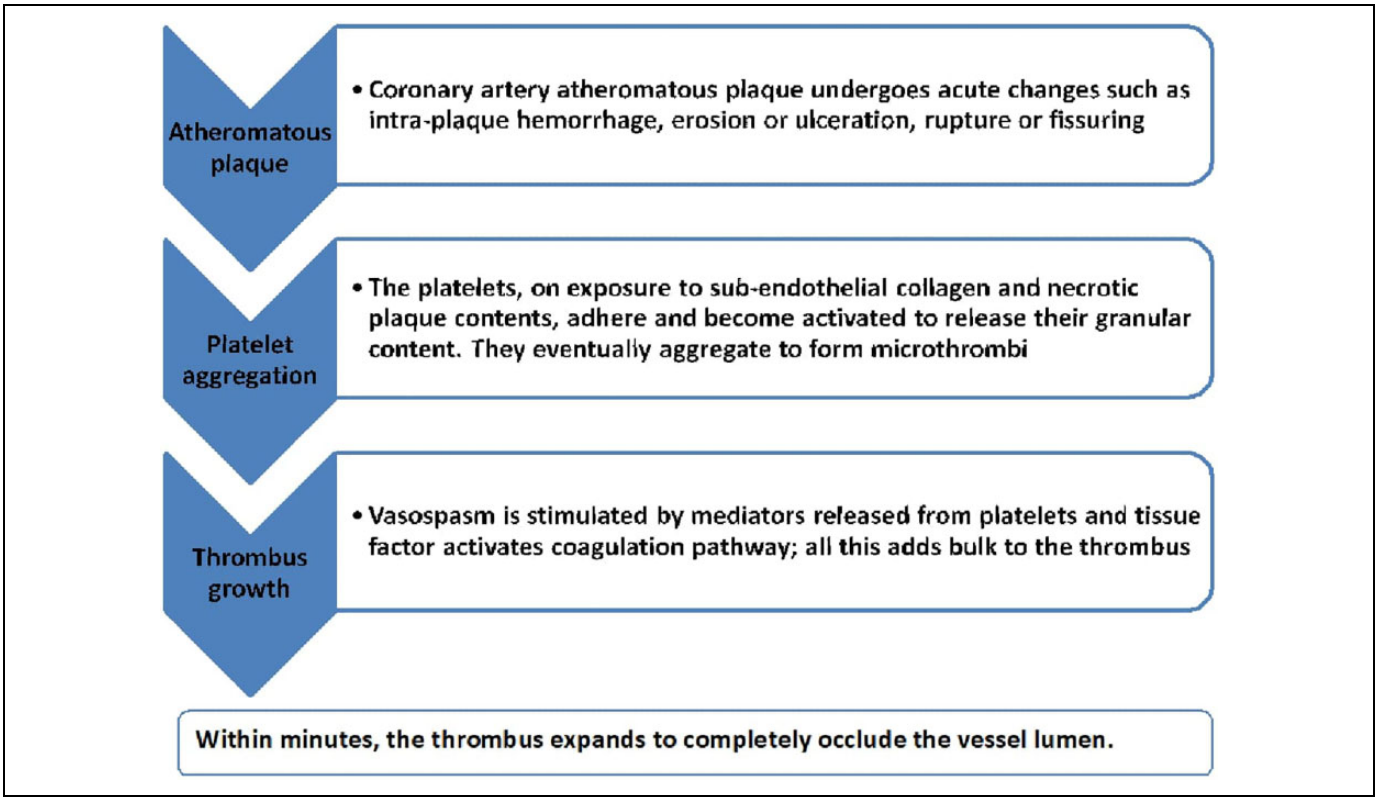


Figure 3. Pathogenesis of the vessel occlusion.

because the myocardial function is largely dependent on oxygen and nutrients. Ultimately, heart failure pursues even before myocyte necrosis.

Within a few seconds of the onset, changes in the ultrastructure develop (including relaxation of myofibrils, depletion of glycogen, cell, and mitochondrial swelling). However, the early manifestations of ischemic injury are potentially reversible.[2]

How Is Pathophysiology Related to Laboratory Diagnosis?

The disruption of sarcolemmal membranes of necrotic myocytes allows leakage of intracellular macromolecules into the interstitial tissue and finally into microvasculature and lymphatics. This forms the basis of elevated cardiac enzymes in MI.[2]

The cardiac enzymes include creatine kinase (CK-MB), troponin I, and troponin T. The CK-MB peaks at 24 hours and normalizes in 48 to 72 hours. Troponin I peaks in 24 hours and begins to normalize in 5 to 10 days, whereas troponin T peaks in 12 to 48 hours and normal in 5 to 14 days. These cardiac enzymes are used for diagnosis and following up the patient.

What Are the Morphological Features of MI?

The morphologic findings in MI vary with the time since infarction, as shown in Table 2.[2] How long the patient survives following an MI determines the gross and microscopic features seen thereafter. Coagulative necrosis is the cell death that occurs due to ischemia, leading to denaturation of structural proteins. It is the first change that occurs in a cell after an MI. After the necrosis, neutrophilic influx is seen in around 12 to 24 hours. This is followed by loss of nuclei on days 1 to 3, phagocytosis by macrophages on days 3 to 7, and granulation tissue formation at the margins. Fibrosis, or scarring, begins in around 2 weeks, and eventually, complete scar formation occurs in 2 months. Changes on gross examination are not apparent before 12 hours. It can be difficult to histologically recognize MI early as myocardium takes 6 to 12 hours to undergo secondary changes of necrosis.[3]

The postmortem autopsy of the patient described above revealed an extensive MI, involving the right and left ventricles, papillary muscles, and interventricular septum. Gross examination shows 2 lesions, dark, mottled area corresponds with an MI 12 to 24 hours old, and the yellow, softened lesion with red-tan borders is grossly consistent with a 10 to 14 days old MI (Figure 4A and B, respectively). The microscopic examination shows coagulative necrosis of myocytes and neutrophilic infiltration (Figure 5) corresponding with 12 to 24 hours of infarction. Figure 6 shows granulation tissue at the margins with extensive collagen deposition, corresponding with an approximate age of infarction of 10 to 14 days prior to death.

What Pathophysiologic Mechanisms Underlie the Histologic Changes?[2]

The waviness of fibers seen at 30 minutes to 4 hours following infarction results from the forceful pull of the viable fibers on

Table 2. Timing of Gross and Microscopic Changes After Myocardial Infarction.

Time	Gross features	Light microscope	Electron microscope
Reversible Injury			
0-30 minutes	None	None	Relaxation of myofibril; loss of glycogen; swelling of mitochondria
Irreversible changes			
30 minutes-4 hours	None	Usually none; wavy fibers at border	Sarcolemma destruction; mitochondria amorphous densities
4-12 hours	Occasional dark mottling seen	Early coagulative necrosis, edema, hemorrhage begin; hypereosinophilia of cytoplasm	
12-24 hours	Dark mottling	Continued coagulative necrosis; pyknotic nuclei; contraction band necrosis at margins; neutrophil influx	
1-3 days	Mottling with the yellow-tan center of the infarct	Coagulative necrosis, with absent nuclei and striations, interstitial neutrophilic infiltrate	
3-7 days	Central yellow-tan softening with hyperemia at the borders	Myofibers begin to disintegrate; dying neutrophil; macrophages phagocytose necrotic cells	
7-10 days	Maximally yellow-tan and soft; depressed red-tan margins	Well-developed phagocytosis of necrotic cells; marginal granulation tissue	
10-14 days	Red-grey depressed infarct borders	Well-formed granulation tissue with neovascularization and collagen deposit	
2-8 weeks	Grey-white scar, progressive from the border toward the center of infarct	Increased collagen deposition and decreased cellularity	
>2 months	Scarring complete	Dense collagenous scar	

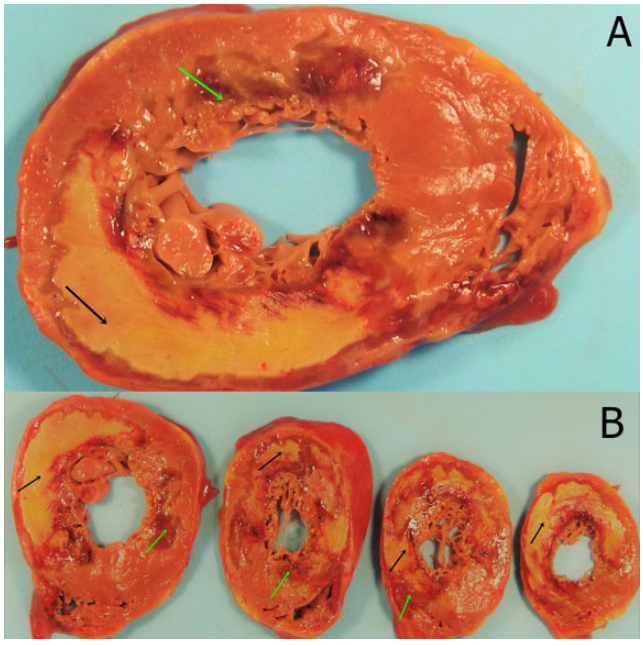
adjacent dead fibers that cannot contract during systole. The margins of infarcts may show an additional ischemic change known as myocyte vacuolization or myocytolysis, which occurs as a consequence of intracellular salt and water retention in the sarcoplasmic reticulum. The necrotic muscle evokes an acute inflammatory response followed by the removal of the dead myocytes by macrophages. Granulation tissue replaces the damaged area leading to a "fibrous scar" formation. Mostly, a well-developed scar is formed in 6 weeks. After an infarct is healed, it becomes impossible to assess its age.

How Is MI Managed?

"Time is myocardium" signifies the importance of immediate treatment; the main goal is to achieve reperfusion, that is, restoration of blood flow to the ischemic myocardial tissue, to rescue the cardiac muscle and limit the infarction size.[2]

As the patient approaches the ED with acute coronary syndrome (a term that encompasses unstable angina as well as MI), management includes[4]:

- immediate ECG and troponins
- oxygen and rhythm monitoring
- analgesics
- antiplatelet; aspirin 300 mg orally
- anticoagulant
- intravenous nitrates



Figures 4. A and B, On gross examination, 2 lesions involving the myocardium and the papillary muscles are seen. Green arrows point to dark mottling, and the black arrows point to a yellow, softened lesion with red-tan borders; these correspond to a myocardial infarction in between 12 to 24 hours and 10 to 14 days, respectively.

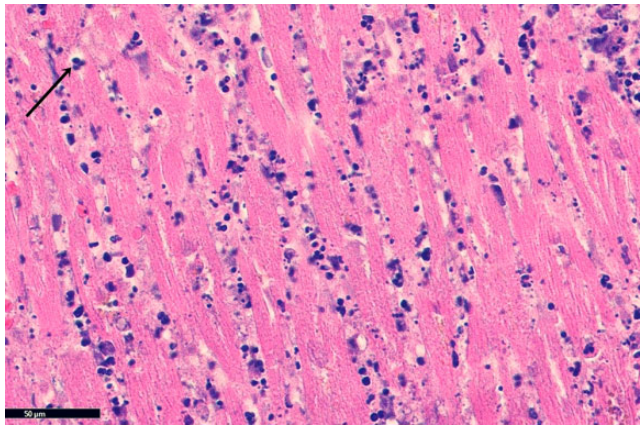


Figure 5. Coagulative necrosis of the myocytes with absent nuclei and an interstitial neutrophilic infiltrate (black arrow).

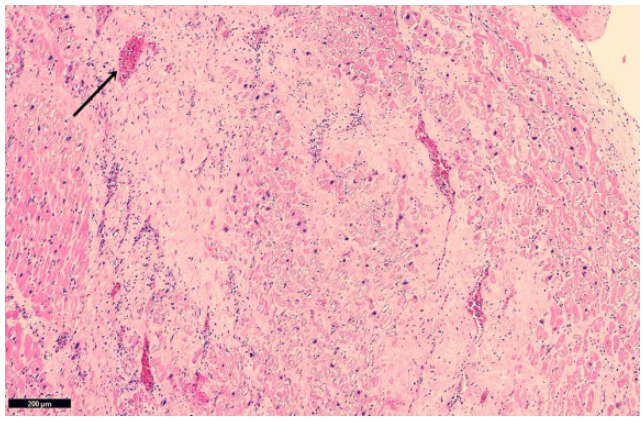


Figure 6. Well-formed granulation tissue with collagen deposition and neovascularization (black arrow).

The management of ST-elevation MI (STEMI) differs from that of Non-ST-elevation MI (NSTEMI). In STEMI, there is complete occlusion by the thrombus, ECG shows ST elevation, and cardiac enzymes are elevated. While in NSTEMI, the occluding thrombus causes either partial occlusion of a major artery or complete occlusion of a minor artery, ECG shows ST depression, and cardiac enzymes are found to be elevated.

If the patient has STEMI, percutaneous coronary intervention (PCI) is preferred to restore the patency of the coronary artery. The standard of care is to perform PCI within 90 minutes after the patient comes to the ED. If PCI is unachievable, thrombolytic therapy should be administered. In case of NSTEMI, PCI does not prove to be helpful.

Teaching Points

- Myocardial infarction is the death of cardiac muscles due to prolonged severe ischemia.
- The primary diagnostic tests are ECG, followed by serum cardiac enzymes, normal reference range being: cardiac troponin I <0.03 ng/mL, cardiac troponin T <0.1 ng/mL, creatine kinase MB isoenzyme <10 ng/mL, myoglobin <170 ng/mL).
- Cardiac troponin has high sensitivity and high specificity for myocardial injury.
- The main pathophysiologic steps include coronary artery occlusion leading to myocardial ischemia due to which myocardial contractility ceases.
- Gross changes appear only after 12 hours showing characteristic dark mottling.
- Histological changes take 6 to 12 hours to develop with the first apparent change being coagulative necrosis.
- After the necrosis, neutrophilic influx is seen in around 12 to 24 hours.
- Loss of nuclei occurs on days 1 to 3, phagocytosis by macrophages on days 3 to 7, and granulation tissue formation at the margins.
- Eventually complete scar takes around 2 months to form.
- The primary goal is to manage MI as early as possible.

Declaration of Conflicting Interests

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