Early Deaths with Thrombolytic Therapy for Acute Myocardial Infarction in Corticosteroid-Dependent Rheumatoid Arthritis

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Summary: Intravenous thrombolytic therapy has become standard treatment for acute myocardial infarction (AMI). We describe three patients with long-standing seropositive rheumatoid arthritis (RA) on chronic corticosteroid therapy who experienced very early (1–6 h) mortality after the use of intravenous thrombolytic therapy for the treatment of AMI. All three patients likely experienced electromechanical dissociation (EMD). Their charts were evaluated in depth, and the literature was reviewed in regard to possible etiopathologic mechanisms. Within 1–6 h of apparently successful thrombolytic therapy for AMI, these three patients experienced sudden and profound bradycardia and hypotension and could not be resuscitated. The potential occurrence of EMD in all three patients raises the possibility of accelerated myocardial rupture, as EMD is one of the clinical hallmarks of this condition. As suggested by the three clustered cases, this heretofore undescribed association between sudden unexpected cardiac death and thrombolytic therapy for AMI in patients with seropositive, corticosteroid-dependent RA suggests that further study and observation are needed. This deleterious association, if verified, has important implications for the treatment of AMI in patients who have RA and are corticosteroid dependent.

Key words: rheumatoid arthritis, acute myocardial infarction, thrombolytic therapy, accelerated cardiac rupture, early mortality, corticosteroids

Introduction

Although thrombolytic therapy is considered standard treatment for acute transmural myocardial infarction (AMI),^{1–4} rare serious complications, such as intracranial hemorrhage and cardiac rupture, have been attributed to the intervention.⁵ However, it is generally felt that these complications have been outweighed by the overall benefit achieved by patients from thrombolytic therapy. Furthermore, it has been documented by the National Registry of Myocardial Infarction that certain subgroups are at a higher risk for cardiac rupture; multivariate analysis indicates an independent association of cardiac rupture with thrombolytics, prior AMI, advancing age, female gender, and intravenous beta-blocker treatment.⁶

Described herein are three patients with seropositive rheumatoid arthritis (RA), receiving long-term corticosteroid therapy, who experienced sudden death within 1–6 h after treatment with thrombolytic therapy for AMI. We suggest that this subgroup, previously not identified, may be at increased risk for the complication of sudden death that might be linked to this particular intervention.

Case Reports

Case No. 1

A 53-year-old man presented to the emergency department (ED) with diffuse anterior chest pain, diaphoresis, and nausea of 4 h duration. Past medical history was significant for the presence of RA previously treated with penicillamine, gold, antimalarials, and methotrexate; he was currently taking prednisone 5 mg/day although he had taken as much as 20 mg/day over a period of years as the only therapy for his arthritis (Table I). There was no history of hypertension, diabetes mellitus, cardiac signs or symptoms, or hyperlipidemia, and no history of smoking or alcohol abuse. The 12-lead electrocardiogram (ECG) on arrival showed normal sinus rhythm and hyperacute ST-segment elevation in leads I and aVL, as well as an incomplete right bundle-branch block noted on a prior ECG (Table

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TABLE I Rheumatologic characteristics of patients with rheumatoid arthritis

Characteristics	Patient No. 1	Patient No. 2	Patient No. 3
Rheumatoid factor	Positive	Positive	Positive
Duration of RA	> 20 Years	> 20 Years	> 20 Years
Steroid dose at presentation	Prednisone 5 mg q.d.	Prednisone 20 mg q.d.	Prednisone 5 mg q.d.
Current immunosuppressive treatment	None	None	Methotrexate
Rheumatoid nodules	Present	Present	Present
Radiographic changes consistent with RA	Yes	Yes	Yes

Abbreviation: RA = rheumatoid arthritis.

II). Initial creatine kinase (CK) enzyme was within normal limits but with a significantly elevated MB fraction. The patient was admitted to the ED and received intravenous lidocaine, streptokinase, heparin, hydrocortisone, and loprofen, as well as oral aspirin; he was then admitted to the intensive care unit (ICU). After 30 min, the patient developed a recurrence of chest pain associated with bradycardia and hypotension. Repeat ECG revealed diffuse ST-segment elevation in the inferior and anterior leads. Prolonged resuscitation was unsuccessful and the patient expired with persistent electromechanical dissociation (EMD).

Case No. 2

A 74-year-old woman presented to the ED with intermittent left shoulder pain of 1 week duration and persistent pain for

approximately 3 h. She gave a history of longstanding RA treated in the past with gold, antimalarials, and penicillamine; current therapy consisted of prednisone, a drug she had taken for many years (Table I), and lovastatin for hypercholesterolemia. The patient was a prior smoker (quit 25 years previously), and there was no previous history of angina pectoris, myocardial infarction, hypertension, or diabetes mellitus. The initial ECG revealed normal sinus rhythm (NSR) and nonspecific ST-T abnormalities, and the CK enzyme level was normal. The patient was given intramuscular ketorolac and betamethasone and was discharged from the ED pain free. The patient returned to the ED 3 h later with recurrent left shoulder pain and new onset midsternal chest pain radiating to the neck and left arm. The ECG revealed hyperacute ST-segment elevation in the inferolateral leads (Table II). In the ED, the patient received intravenous r-tissue plasminogen activator

TABLE II Cardiac characteristics of patients with acute myocardial infarction

Characteristics	Patient No. 1	Patient No. 2	Patient No. 3
Date of presentation	8/29/95	1/29/96	4/21/96
Age (years)	53	74	68
Sex	Male	Female	Female
Previous myocardial infarction/angina	None	None	None
Type of myocardial infarction	High lateral	Inferolateral	Anterior
ECG on presentation	ST-segment elevation in I, aVL	ST-segment elevation in II, III aVF, V ₄ , V ₅ , V ₆	ST-segment elevation in aVL, V ₁ , V ₄
Admission enzyme levels			
Total CK (nl 57–374 IU/L)	171	< 20	83
CK-MB (nl 0–5 ng/ml)	21.6	Not done	Not done
MB index (nl 0–3.2%)	6.4 %	Not done	Not done
Onset of symptoms prior to thrombolytics	6 h, 30 min	6 h, 40 min	2 h
Thrombolytic agent (dose/duration)	Streptokinase 1.5 million units in 1 h	rTPA 90 mg/90 min	rTPA 83 mg/90 min
Steroid bolus	Hydrocortisone 100 mg IV	Betamethasone 12 mg IM	Methylprednisolone 40 mg IV
Adjuvant treatment	Nitroglycerin IV Heparin IV Lidocaine IV Aspirin P.O. Metoprolol IV	Nitropaste 2% Heparin IV Lidocaine IV Aspirin P.O.	Nitropaste 2% Heparin IV Lidocaine IV Aspirin P.O. Atenolol 50 mg P.O.
Initiation of thrombolytics prior to death	4 h	2 h	6 h

Abbreviations: ECG = electrocardiogram, CK = creatine kinase, TPA = tissue plasminogen activator, IV = intravenous, IM = intramuscular, P.O. = orally.

(rTPA), heparin, lidocaine, nitroglycerin, and oral aspirin. She was admitted to the ICU, and soon after the rTPA infusion she was pain free. Subsequently, she developed a sudden onset of severe bradycardia and hypotension. In spite of prolonged resuscitative efforts, she expired with EMD.

Case No. 3

A 62-year-old woman presented to the ED with a 2-h history of severe anterior chest pain. The patient had long-standing RA previously treated with gold, antimalarials, and penicillamine; her current management consisted of prednisone and methotrexate (Table I). There was no prior history of hypertension, diabetes mellitus, angina pectoris, or cerebrovascular disease. Initial ECG showed ST-segment elevations compatible with anterior wall AMI (Table II). She received intravenous rTPA, heparin, lidocaine, and methylprednisolone along with oral aspirin. A beta blocker and nitropaste were administered in the ED. She became asymptomatic 2 h after treatment was initiated and was admitted to the ICU. Six h after the administration of rTPA, sudden, severe bradycardia was observed and the patient could not be resuscitated. She expired with persistent EMD.

Discussion

All three patients with RA described above had their transmural AMI treated with intravenous thrombolytic therapy. What they had in common was long standing, seropositive, erosive RA that had been treated with systemic corticosteroids for many years. In addition to "stress" doses of parenteral corticosteroids used at the time of the acute event, these patients received beta blockers, heparin, and lidocaine. All three patients experienced abrupt and unexpected early mortality, with their demise characterized by profound sinus bradycardia and hypotension, unresponsive to atropine and vasopressors. Vigorous resuscitation was unsuccessful in all three patients, and the terminal event was felt to be electromechanical dissociation (EMD) in all. One of three patients had recurrence of chest pain and two had profound bradycardia prior to the clinical picture of EMD. Postmortem examinations were not granted by the families. Findings from these three cases raise the hypothesis that patients with seropositive RA taking long-term systemic corticosteroids are at risk for accelerated cardiac rupture in the setting of transmural AMI treated with thrombolytics.

Without a postmortem examination, we cannot prove that cardiac rupture was the cause for these early deaths; however, the common thread in all three deaths appeared to be EMD. Supporting our suggestion that cardiac rupture had occurred is the recent study by Figueras *et al.* which showed that EMD was highly predictive of cardiac rupture in AMI.⁷ Other possible causes of these catastrophic events include extension of the AMI with cardiogenic shock, aortic dissection with shock, pericardial tamponade secondary to hemorrhagic acute pericarditis, acute coronary dissection with subsequent myocar-

dial hemorrhage and tamponade, and profound bradyarrhythmias induced either by AMI with failure of thrombolysis, by cardiac medications, and/or the presence of cardiac rheumatoid nodules.

With regard to thrombolytic therapy, several studies have shown an increased mortality in thrombolysis-treated patients during the first 24 h of treatment, and cardiac rupture was responsible for many of these early deaths.^{1, 8, 9} In addition to the recent review⁶ demonstrating that cardiac rupture caused a 12.1% in-hospital mortality with thrombolytics compared with 6.1% without treatment, similar findings were observed by Oliva *et al.*, with cardiac rupture being noted in 20% of fatal AMIs.¹⁰ The postulated mechanism for the increased risk of rupture is the observation that thrombolytic agents stimulate plasmin production, causing a breakdown of collagen as well as an inhibition of its synthesis.¹¹ In the patients described in our study, the unusually early clinical picture compatible with myocardial rupture suggests an accelerated process, perhaps superimposed upon chronic structural damage.

It is entirely possible that underlying cardiac involvement emanating from the rheumatoid process itself, long recognized in patients with RA,^{12, 13} played a contributing role toward the risk of early cardiac death in our cases. Autopsy studies in RA cases have revealed a 20% prevalence of myocardial inflammation and myocardial fibrosis,¹⁴ and in another study, 26% of RA patients were found to have left ventricular abnormalities on echocardiography, probably secondary to myocardial fibrosis.¹⁵ Rheumatoid cardiac nodules have been described in multiple cardiac sites, with some nodules producing heart block.¹⁶ Furthermore, a recent report¹⁷ demonstrated that patients who developed myocardial rupture after AMI had significantly higher levels of C-reactive protein. This suggests a heightened generalized or systemic inflammatory response, possibly making the myocardium of patients with RA more vulnerable to early cardiac rupture.

Long-standing glucocorticoid treatment may have played a part in permitting cardiac rupture to occur in our patients. The effects of chronic glucocorticoid administration on the myocardium is thought to be similar to well-documented effects on skeletal muscle producing the clinical picture of steroid myopathy.¹⁸ Methylprednisolone has been demonstrated to decrease overall scar collagen in experimental myocardial infarction in rats.¹⁹ Roberts *et al.* have shown that methylprednisolone administration in humans does increase infarct size and the frequency of malignant arrhythmias;²⁰ two patients in this study demonstrated ventricular septal rupture. Additional recent studies have shown that corticosteroid treatment may lead to late rupture of true left ventricular aneurysms.^{21, 22}

Our literature review has been unable to disclose previous reports pointing to or emphasizing the association of early mortality with thrombolytic therapy for AMI in seropositive patients with RA treated with systemic corticosteroids. It is not known whether these cases truly represent an increase over the expected incidence of cardiac rupture following thrombolytic therapy in AMI. This apparent "cluster" of cases is only intended to generate a hypothesis that needs to be tested. Fur-

thermore, based on such limited data, it would be impossible to sort out the individual contributory roles of the thrombolytic agent, underlying RA heart disease (inflammation, fibrosis, nodules), or chronic corticosteroid use. We are not certain as to the cause of death in our patients, and clearly a weakness of our report is the lack of confirmatory pathologic data. However, the presence of evidence for EMD during the terminal stages of our patients' illness is highly suggestive of myocardial rupture. We feel that further observation and study are necessary to assess the safety of thrombolytic agents for the treatment of AMI in patients with RA receiving chronic glucocorticoid therapy. Until additional studies are conducted, it is not prudent to withhold potential lifesaving thrombolytic therapy in patients with AMI and underlying RA who are not on chronic corticosteroid therapy. However, for the group of corticosteroid-dependent seropositive patients with RA, primary PTCA should be given strong consideration as the first line of therapy for AMI.

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