Case Report

False Positive Elevation of Cardiac Troponin I in Seropositive Rheumatoid Arthritis

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ABSTRACT. Cardiac troponin I is a sensitive and specific biochemical marker for the diagnosis of acute myocardial injury. We describe a patient with seropositive rheumatoid arthritis (RA) in whom troponin I, measured with a microparticle enzyme immunoassay, was elevated falsely in the absence of acute myocardial infarction. Apparent elevation of troponin I concentration should be evaluated with care in patients with seropositive RA. (J Rheumatol 2001;28:2750–1)

Key Indexing Terms:
TROPONIN I
RHEUMATOID FACTOR
MYOCARDIAL INFARCTION
RHEUMATOID ARTHRITIS

Troponin I, troponin T, and troponin C regulate the interaction between actin and myosin in striated muscle[1]. Cardiac troponin I is expressed only in the myocardium, and circulating troponin I is a biochemical marker for acute myocardial infarction[2,3]. False positive tests for elevated troponin I, however, have been reported recently in a number of sera with rheumatoid factor (RF) activity[4-6]. We describe a patient with rheumatoid arthritis (RA) and a high serum concentration of RF in whom false high levels of troponin I were detected repeatedly over a period of 2 months using the microparticle enzyme immunoassay. During that time, there was no evidence of an acute myocardial infarction.

CASE REPORT

A 68-year-old man developed symmetrical arthritis involving the shoulders, wrists, metacarpophalangeal (MCP) joints, and proximal interphalangeal (PIP) finger joints in 1995. He had fatigue and morning stiffness lasting more than 2 hours. Examination in 1996 revealed boggy swelling of the wrists and MCP and PIP finger joints. RF was 1530 IU/ml (normal 0–30). Radiographs of his hands revealed generalized osteopenia and loss of cartilage in the radiocarpal articulations and the right and left 2nd and 3rd MCP joints. RA was diagnosed. He was treated with weekly intramuscular injections of aurothioglucose 50 mg and prednisone 7.5 mg/day, and the joint swelling and morning stiffness improved. Six months later he was receiving aurothioglucose every 4 weeks, the prednisone dose had been reduced to 2 mg/day, and there were no findings of active arthritis.

The patient had longstanding obstructive pulmonary disease. He also had coronary artery disease. Angina pectoris developed in 1975. A coronary angiogram in 1985 revealed 65% occlusion of the right coronary artery, 99% occlusion of the left anterior descending artery, and 99% occlusion of the circumflex artery. The following month, bypass grafts were applied to the right coronary artery and the left anterior descending, diagonal, and obtuse marginal arteries. One year later, he developed second degree Mobitz type II atrial ventricular block and a pacemaker was inserted.

In March 1999, he came to the emergency room complaining of pain in the thoracic spine that increased with inspiration and was not relieved by sublingual nitroglycerine. Examination showed tenderness to palpation over the right side of the thorax. RF was 1240 IU/ml. Troponin I was 473 ng/ml (normal 0–0.3), and creatine kinase (CK) in serum from the same tube of blood was 42 U/l (normal 21–232). An additional sample of blood was drawn and the troponin I measurement was repeated and was 408 ng/ml. The electrocardiogram showed no changes of myocardial ischemia. New thoracic spine compression fractures were identified on the chest roentgenogram, and these fractures were thought to have caused the pain.

In May 1999, his back pain increased and he was reevaluated. Troponin I was 1267 ng/ml. A second serum sample was obtained, and repeated assays showed troponin I 1280 ng/ml and CK 33 U/l in the same blood tube. The following day, troponin I was > 500 ng/ml and CK in the same sample was 49 U/l. In a second sample of serum obtained later on the same day, troponin I was > 500 ng/ml. The electrocardiogram was not changed from earlier tracings. A whole body ^{99m}Tc scintiscan in June 1999 showed increased uptake in the mid-thoracic spine consistent with vertebral compression fractures. It was concluded that the patient continued to have pain from his vertebral compression fractures, and the apparent elevation of troponin I was an artifact caused by the presence of RF. The patient died with urinary tract infection and sepsis in July 1999.

DISCUSSION

We describe a patient with longstanding RA and a high level of RF. He had spurious elevation of serum troponin I at a time when electrocardiograms and serial, simultaneous measurements of CK showed no indication of acute myocardial infarction. The extraordinarily high values for troponin I did not show the time-dependent increase and decrease that are expected to follow myocardial infarction. The patient's serum was tested using the unmodified version of the microparticle enzyme immunoassay (Abbott Laboratories, Abbott Park, IL, USA), run in the AxSYM

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Submitted March 8, 2001; revision accepted June 19, 2001.

analyzer (Abbott). The assay depended upon microparticles coated with monoclonal mouse anti-troponin I antibodies. RF is by definition an antibody that reacts with the Fc receptor of IgG. The microparticle enzyme immunoassay was therefore subject to interference from heterophilic antibodies and RF[7].

Troponin I is not detectable in the blood of normal persons. It appears in serum or plasma 4 to 6 hours following acute myocardial infarction, peaks at 24 hours, and falls to very low levels 96 hours after the event[8]. Krahn[4] tested 100 RF positive sera using the microparticle enzyme assay for troponin I, run on the AxSYM analyzer. Values for RF were 104 to 7320 IU/ml. In 15 samples, troponin I was elevated into the range consistent with acute myocardial infarction. False elevations of troponin I were not associated with the highest RF concentrations, and it was postulated that the variance in interference reflected heterogeneity among RF[4]. In another survey, the microparticle enzyme assay detected measurable concentrations of troponin I in 7 serum samples from 12 RF positive individuals[5].

The high occurrence of positive tests for troponin I in patients with RF suggests that myocardial infarction can be misdiagnosed initially in these individuals. The false positive elevation of troponin I can be differentiated from true elevation in several ways. The false test result does not show the typical rise and fall that follow cardiac injury, and there is not a concurrent rise and fall of total CK and the CK MB isoenzyme. The unmodified microparticle enzyme assay for troponin I, run on the AxSYM analyzer, has been associated with false positive results in 3 surveys[4-6]. Interference with this assay can be eliminated by adding polyclonal antisera against RF (RF removal reagent, ICN Biochemicals, Costa Mesa, CA, USA) to specimens before testing. Further, this RF blocking reagent does not block the ability of the test to detect a true elevation of troponin I in the patient with RF who has had an acute myocardial infarction[5]. A positive troponin I test in a patient with RF can also be verified by retesting the serum sample in another system. The Bayer Immuno 1™ system (Bayer Corp., Tarrytown, NY, USA)[4] and the chemiluminescent assay run on the ACS:180 analyzer (Bayer Diagnostics, East Walpole, MA, USA)[5] have been tested against the unmodified microparticle enzyme assay and demonstrated no interference from RF[4,5].

In May 1999, the Diagnostic Division of Abbott Laboratories notified customers that its microparticle enzyme assay had been modified to reduce cross reactivity. The effectiveness of this modification was examined by Onuska and Hill[6], who used both the unmodified assay and the new modified assay to test 19 samples of RF positive serum. The original assay produced 8 values above 0.3 μg/l. Testing in the modified assay showed that one value of 0.2 increased to 0.4, whereas a value of 4.3 was reduced to 0.5. The other 17 samples yielded results of 0[6].

In summary, we described a man with severe RA and a high concentration of RF. He did have coronary artery disease. During a period in which his heart disease was quiescent, he had persistent and apparently false positive elevations of troponin I when his serum was tested in the Abbott unmodified microparticle enzyme assay. We believe the false elevation resulted from RF interference with the assay. This phenomenon could be observed with other immunological assays, of which there are many. At present, false elevation of troponin I should occur only rarely when the modified microparticle assay is used with the AxSYM analyzer. It is still possible that the modified Abbott microparticle enzyme assay could produce a mild false elevation of troponin I in a patient with RF[6].

This case reminds us that laboratory test results that appear inappropriate for the clinical status of the patient should be questioned. If the result is in doubt and the patient has RF, evaluating the clinical status of the patient and repeating the test in another assay system or with RF removal agent should determine if there has been a true elevation of troponin I.

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