Tests for rheumatoid factor after myocardial infarction

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SYNOPSIS An investigation was carried out into the occurrence of positive tests for rheumatoid factor after myocardial infarction. Fifty-five patients, 41 males and 14 females, were studied in 56 separate admissions for acute myocardial infarction. Tests for thyroid antibodies were also performed on all patients.

In 16 patients a positive rheumatoid factor test was obtained in the post-infarction period on at least one occasion. The reaction was usually a weak positive one, and in most cases had disappeared on discharge from hospital. Transient false positive tests for thyroid complement-fixing antibody were obtained in seven male patients.

Positive tests tended to occur in older patients, with a previous history of infarction, and usually with more severe infarcts, as judged from the maximum level of serum glutamic oxaloacetic transaminase obtained in the first 48 hours after infarction, and the occurrence of clinical cardiac failure.

This is probably a relatively non-specific manifestation of tissue damage, the clinical importance of which is unknown.

The changes in plasma proteins after myocardial infarction have been extensively studied. Recently, Finkelstein, Woerner, Smith, Bayles, and Levine (1963) have reported the development of a transient positive 'dextran cell latex test' in the post-infarction period. The dextran cell latex test has, however, been questioned as a specific test for the presence of the rheumatoid factor (Hunder, Vaughan, and Jacox, 1963). Following the chance finding of a positive Rose-Waaler test in a patient with an unequivocal myocardial infarct, and without evidence of rheumatoid arthritis or a collagen disease, it was decided to investigate the occurrence of the rheumatoid factor, as detected by more conventional tests, after myocardial infarction.

It was possible to study 55 patients, in whom a definite diagnosis of acute myocardial infarction had been made, on the basis of unequivocal electrocardiographic evidence of infarction; where the electrocardiographic changes were of a minor nature, or could not be clearly differentiated from previous ischaemic changes, supporting evidence of a raised serum glutamic oxaloacetic transaminase (above 50 units/ml.) was required before a patient was included in the investigation. There were 41 males and 14 females, and the average age of the group was 59

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years. One patient was studied on two separate admissions for acute infarction, making 56 episodes in all.

Tests for thyroid antibodies were performed concurrently on all specimens, in an attempt to evaluate the specificity of any positive results. Positive thyroid antibody tests, occurring with positive rheumatoid factor tests, have been reported in patients with leprosy (Bonomo, Dammacco, Pinto, and Barbieri, 1963).

MATERIALS AND METHODS

Blood was taken on, or soon after admission, and at weekly intervals thereafter, until the patient was discharged, usually four to five weeks after admission. At subsequent out-patient attendances, blood for testing was only taken if positive results had been obtained in hospital.

RHEUMATOID FACTOR This was detected using (1) Ball's modification of the Rose-Waaler sensitized sheep cell test, a titre of 1 in 32 or more being considered positive (Ball, 1952), and (2) the Hyland R-A slide latex test, using a commercial preparation of latex particles coated with human gamma globulin (Cohn fraction II), the serum being diluted to 1 in 20, and the test read as either positive or negative.

THYROID ANTIBODIES The presence of antibodies to thyroglobulin was tested for, using formalinized red cells coated with the antigen (Fulthorpe, Roitt, Doniach, and Couchman, 1961), titres of greater than 1 in 250 being considered significantly positive. Antibodies to thyroid microsomes were tested by a complement-fixation test, using purified antigen and two mean haemolytic doses of complement (Roitt and Doniach, 1958). Titres equal to or greater than 1 in 4 were regarded as positive.

RESULTS

Table I shows that some rheumatoid factor activity occurred in the post-infarction period in 28.5% of the cases studied. More activity against rabbit gamma globulin (Rose Waaler) occurred than did activity against human gamma globulin (R.A. latex). In nine cases, the sensitized sheep cell test only was positive, in five cases, the latex test only was positive, and in two cases both were positive. In one patient in whom the latex test alone was positive, lesser degrees of sensitized sheep cell activity were recorded on one occasion, although in the patients in whom both types of activity occurred, the tendency was to do so at different times. All patients recording positive rheumatoid factor tests had no evidence of rheumatoid or other collagen disease, and in all cases except two, the reaction was a weak positive one (titre 1/32 or 1/64). In three women with a positive test, and two with a negative test, there was evidence of symptomatic osteoarthritis.

Weak positive thyroid complement-fixation tests (titres less than 1/32) developed in seven males with no evidence of thyroid disease. No patient without evidence of thyroid disease developed significant thyroglobulin antibodies. One woman with clinical myxoedema, and another with a family history of goitres, had positive tanned red cell and complement-fixation tests, but these have not been included in the figures. Even when the tanned red cell test has been positive at lower dilutions than that regarded as significantly positive, the titre has remained virtually unchanged throughout the hospital stay, in contrast to the other tests where antibody activity developed and subsided during the course of the illness.

Rheumatoid factor activity alone occurred in 12 patients, thyroid complement-fixing antibody alone in four, and both types of activity in three patients, although at different times in their illness.

TABLE I

INCIDENCE OF POSITIVE RHEUMATOID FACTOR TESTS AND THYROID ANTIBODIES AFTER MYOCARDIAL INFARCTION IN 56 CASES

Test	No. of Patients with Positive Test			Percent Positive	Average Age (yr.)
	Male	Female	Total		
Sensitized sheep cell test	8	3	11	19.6	63
Hyland R-A slide latex test	4	3	7	12.5	66
Rheumatoid factor activity	11	5	16	28.5	64
Thyroglobulin antibody (T.R.C. test)	None	None ¹	nil	—	—
Thyroid microsome complement-fixation test	7	None ¹	7	12.5	56

¹This excludes two patients with thyroid abnormality.

In most cases, maximum activity occurred in the second and third weeks, although a few cases had positive tests within a few days of the infarct. The positive thyroid complement-fixation test tended, on the whole, to appear later than rheumatoid factor activity. Anti-rabbit gamma globulin activity, as shown by some degree of sensitized sheep cell reaction, occurred on the average between two and three times during the in-patient stay, during which time tests were done, on the average, between four and five times. Tests were negative on discharge from hospital in all patients except two, and in these the tests were negative when they were seen one month later in the out-patient department.

Antihuman gamma globulin activity, as shown by a positive slide latex test, occurred less often; once for each patient, except in two patients in whom it occurred on three occasions.

The thyroid complement-fixation test was positive once in the illness of each of five patients and twice in two.

Sixteen other patients, in whom a diagnosis of pulmonary embolus had been made, had blood taken for testing on two or three occasions when in-patients; no positive results were obtained.

An attempt was made to correlate the development of positive tests with some of the clinical

TABLE II

CORRELATION OF RHEUMATOID FACTOR AND THYROID ANTIBODY ACTIVITY WITH CLINICAL FEATURES

	Eventful Course						No Previous Infarct
	Uneventful Recovery	Death	Heart Failure	Miscellaneous Complications	Total	Previous Infarct	
Total no. of patients	35	6	11	4	21	16	40
Rheumatoid factor positive	6 (16%)	2 (33%)	7 (63%)	1 (25%)	10 (48%)	7 (44%)	9 (22%)
Thyroid C.F.T. positive	5 (14%)	None	1 (9%)	1 (25%)	2 (10%)	3 (18%)	4 (10%)

features (Table II). The appearance of rheumatoid factor activity tended to be associated with the development in the post-infarction period of clinical cardiac failure. Patients with evidence of a previous infarct appeared more likely to develop positive tests for rheumatoid factor. Although the number of cases was smaller, there seemed to be no clear trend in the occurrence of positive thyroid complement-fixation tests.

In 49 of the patients, it was possible to take two specimens of blood for estimation of the serum glutamic oxaloacetic transaminase levels within the first 48 hours. Of 17 patients with a maximum transaminase level from 50 to 100 units/ml., three (17%) developed positive rheumatoid factor tests, and two (12%) developed positive thyroid complement-fixation tests. Of the remaining 32 patients, with maximum transaminase levels in the first 48 hours above 100 units/ml., nine (28%) had positive rheumatoid factor tests, and five (16%) positive thyroid complement-fixation tests.

DISCUSSION

Positive tests for specific immunoglobulins occur too infrequently after myocardial infarction to be of much value as diagnostic aids. However, in a recently published Clinical-Pathologic Conference (1963), a case was discussed of a patient with chest pain, heart failure, and an unhelpful electrocardiogram, in whom a sequence of positive and subsequent negative rheumatoid factor tests was obtained during life. At necropsy, death was found to be due to extensive myocardial infarction, and it seems likely that the rheumatoid factor test was more significant than was apparent at the time.

The significance of the development of these positive tests is open to considerable speculation. The occurrence of positive tests for rheumatoid factor in conditions other than rheumatoid arthritis, or the collagen diseases, is well documented. It occurs in patients with liver disease (Dresner and Trombly, 1959; Atwater and Jacox, 1963; Bouchier, Rhodes, and Sherlock, 1964), pulmonary tuberculosis (Singer, Peralta, Lyons, and Plotz, 1961), sarcoidosis (Kunkel, Simon, and Fudenberg, 1958), syphilis (Peltier and Christian, 1959), subacute bacterial endocarditis (Williams and Kunkel, 1962), aged populations (Heimer, Levin, and Rudd, 1963), the relatives of patients with agammaglobulinaemia (Fudenberg and Franklin (1963), and in the relatives of patients with rheumatoid arthritis (Ziff, Schmid, Lewis, and Tanner, 1958).

The figures for false positive rheumatoid factor in these conditions are usually of the order of 10 to 20%, with the exception of liver disease, where the

latex fixation test is positive more often. Except in those groups where the abnormal reaction may have a genetic basis, the common factors in the other groups with false positive tests are tissue damage and hyperglobulinaemia, especially hypergammaglobulinaemia.

Russell and Hutt (1962), studying more than 100 samples of blood sent for grouping, found 14.5% false positive reactions, using the bentonite flocculation test. Most of these reactions occurred in patients who had sustained an injury or operation, or had extensive carcinoma. The E.S.R. and alpha-2-globulins were elevated, but the gamma globulin levels were normal. They mention studying one patient with a myocardial infarct, in whom the test became positive on the fourth day, and subsequently became negative.

Thus it appears that after tissue damage, there is often a tendency for a transient increase in immunoglobulins. The patients under study were for the most part of an age when an increased incidence of false positive tests of this sort is to be expected. The patients with a diagnosis of pulmonary embolus are not strictly comparable as they were, in the main, considerably younger (average age 45 years); moreover, the extent of tissue damage following a pulmonary embolus is more difficult to assess. There is no evidence that this increase in immunoglobulins has any influence on the clinical picture, but the question seems worthy of further investigation.

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