Rheumatoid Arthritis and Malignancy*

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In view of the fact that rheumatoid arthritis is considered to be a disturbance of the immune mechanism (Lawrence, 1965), we thought it seemed reasonable to direct a study of possible correlation with malignant diseases, which are also possibly related to immune mechanism disturbances. Calabro (1967), Lansbury (1953), Litman, et al (1966), and MacKenzie and Scherbel (1963) have reported the appearance of malignancy accompanying the development of polyarthritis. Calabro (1967) emphasized the importance of arthritis as a diagnostic warning of occult cancer.

Ragan and Synder (1955) noted that 2 per cent of 374 patients with rheumatoid arthritis, followed for more than five years, developed malignancy. However, he made no comparison to matched controls. Lansbury (1953) collected six cases of collagen disease which occurred in patients suffering from malignancy. MacKenzie and Scherbel (1963) studied the musculoskeletal symptoms of visceral malignancy in 77 patients. Only 18 of these had arthropathy, and the symptoms ranged from mild arthralgia to progressive polyarthritis. No rheumatoid nodules were present, and rheumatoid factor was present in only one patient.

Miller (1967) studied 17 patients with malignant lymphomas associated with a variety of so-called "immune diseases" such as rheumatoid arthritis, systemic lupus erythematosus (SLE), ataxia-telangiectasia, vasculitis, nephrotic syndrome, and dermatomyositis. He concluded that the same individual may be susceptible to both types of disease. In addition, Miller (1967) searched for cases of connective tissue disease in 1893 patients with solid malignant tumors and found 11. Eight were classified as rheumatoid arthritis, one as SLE, and one each as dermatomyositis and vasculitis. Among the 264 patients with lymphoproliferative neoplasms, only one case of rheumatoid arthritis was recognized among the five having diffuse connective tissue disease.

In none of these studies were the patients and the control population matched for age and socioeconomic status, nor was the possible influence of anti-inflammatory drug therapy on the incidence of malignancy taken into account.

The unique availability of private patient records covering a period of over 26 years with examination in all instances being done by either of two rheumatologists, plus long term follow-ups averaging over four years, provided an opportunity for a definitive study of the incidence of malignancy in patients with rheumatoid arthritis. These patients were controlled by carefully matched patients without rheumatoid arthritis, though suffering from a variety of arthritic disorders such as degenerative arthritis and gout.

Materials and Methods

A survey of the private patient files over a 26 year period showed 196 patients with rheumatoid arthritis whose ages were between 50 and 74 (mean age 60.3). These selected charts were carefully reviewed. There were 106 females and 90 males. The observation period ranged from one month to 24 years with a mean of 49.5 months. These patients had either classic or definite rheumatoid arthritis, according to the criteria of the American Rheumatism Association (Ropes, 1958). A rigorous selection resulted in loss of over 50 per cent of the patients orginally thought to have rheumatoid arthritis. For comparison, charts of 125 patients with arthritis of a non-rheumatoid type—degenerative joint disease, primary gout, non-specific tendinitis, and psoriatic arthritis—and of the same age group (mean age 60.5) were reviewed. There were 72 females and 53 males. The observation period ranged from one month to 20 years with a mean of 56.8 months. An older age group was selected for both groups on the premise that the higher incidence of malignancies in this advanced age group would tend to make the results more valid in the relatively small number of patients. Cases of hypertrophic pulmonary osteoarthropathy were excluded from the study. All patients were, or had been, on the private service and in the middle or upper classes. Each patient had a complete history and physical examination performed, and those who were followed longer than one month had periodic complete examinations.

Laboratory studies performed on all patients included hemoglobin, white blood count and differential, erythrocyte sedimentation rate (Wintrobe), urinalysis, serum uric acid and rheumatoid pattern (latex flocculation, sensitized human cell, and sensitized sheep cell tests). Methods used include those previously described by Waller et al (1961), and the Venereal Disease Research Laboratory test (VDRL). If systemic lupus erythematosus was suspected, one or more LE cell tests were performed.† Appropriate X-ray studies were also performed on each patient.

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† Patients with positive LE cell tests were excluded from the study.

Results

A total of eight patients out of 196 with rheumatoid arthritis had systemic malignancies. Table 1 summarizes the main features of these cases. All cases had significant titers of rheumatoid factor. Six of the eight cases were receiving adrenocorticosteroid preparations at the time the malignancy was diagnosed, and all six had taken an equivalent of 5–10 mg of prednisone daily for over one year.

A total of five out of 125 patients with arthritis of a non-rheumatoid type were discovered to have systemic malignancies. Table 2 summarizes the main features of these cases. None had rheumatoid factor or were receiving adrenocorticosteroids.

Discussion

Correspondence with 12 clinicians throughout the nation, specializing in the treatment of connective tissue diseases, revealed that the majority felt that

TABLE 1

Summary of 8 patients with systemic malignancies discovered in a study of 196 patients with rheumatoid arthritis in the 50–74 age group.

Patient	Age	Sex	Malignancy	Length of R A prior to malignancy (years)	Rheumatoid Factor			Long term steroids (>12 mos.)	Comments
					Latex	SHC*	SSC**		
1. A.M	74	F	Carcinoma of stomach	11	+	1 : 80	—	Yes	Metastatic disease
2. H.L.	63	M	Transitional cell carcinoma of urinary bladder	8	+	1 : 2048	1 : 2048	No	Metastatic disease
3. D.S.	68	F	Carcinoma of breast	4	+	1 : 1280	1 : 320	Yes	Metastatic disease
4. E.P.	68	M	Carcinoma of lung	17	+	1 : 640	1 : 160	No	Steroids—discontinued 6 yrs before development of malignancy
5. L.H.	65	F	Carcinoma of breast	10	+	1 : 1280	1 : 160	Yes	Peripheral neuropathy present
6. R.M.	51	M	Acute lymphatic leukemia	4	+	1 : 640	1 : 160	Yes	Pt. had not received phenylbutazone for 3 yrs
7. C.T.	74	M	Lymphosarcoma, reticulum cell type	4	+	1 : 640	1 : 40	Yes	Terminal development of stem cell leukemia Pt. had taken phenylbutazone intermittently including period several wks prior to discovery of lymphoma
8. H.R.	50	M	Carcinoma of lung	4	+	1 : 320	1 : 160	Yes	Metastatic disease

* Sensitized Human Cell
** Sensitized Sheep Cell

TABLE 2

Summary of 5 patients with systemic malignancies discovered in a study of 125 patients with arthritis of a non-rheumatoid type in the 50–74 age group.

Patient	Age	Sex	Malignancy	Type of Arthritis
1. M.B.	66	F	Carcinoma of colon	Degenerative joint disease
2. F.C.	55	M	Adenocarcinoma of kidney	Gout
3. J.G.	52	M	Carcinoma of prostate	Degenerative joint disease
4. E.H.	70	F	Carcinoma of breast	Degenerative joint disease
5. J.K.	71	M	Chronic granulocytic leukemia	Gout (onset 20 years prior to diagnosis of leukemia)

systemic malignancies were quite rare in cases of rheumatoid disease. Ragan and Snyder (1955), however, believed the incidence to be the same as in the general population.

Rheumatoid disease was diagnosed an average of 94 months prior to the onset of systemic malignancy in our eight cases. We did not observe the apparent malignancy-induced polyarthritis such as was described by MacKenzie and Scherbel (1963).

Essentially no difference (4 per cent of each group) was noted in the incidence of malignancies in the rheumatoid and non-rheumatoid groups. However, in the rheumatoid group a case of lymphosarcoma (reticulum cell type) with terminal state of stem-cell leukemia, and a case of acute lymphatic leukemia was noted among the eight cases of malignancy. The patient with lymphosarcoma (C. T.) had taken either phenylbutazone (Butazolidin®) or oxyphenbutazone (Tandearil®) on an intermittent basis for approximately 40 months after the onset of rheumatoid arthritis. The patient reinstituted phenylbutazone several weeks prior to the discovery of lymphosarcoma. He did not have Sjögren's syndrome, an association noted by Talal (1966). The patient with the leukemia (R. M.) had not received phenylbutazone for three years prior to the discovery of the leukemia. A cause-effect relationship between these drugs and leukemia has been suggested by Fraumeni (1967).

Although Miller (1967) reported a statistically significant difference between the incidence of diffuse connective tissue disease in patients with solid tumors (0.58 per cent) and patients with malignant lymphomas (1.86 per cent), a review of his data shows no difference in incidence for the two groups of malignancies when the disease rheumatoid arthritis is considered by itself. Among his 264 patients with lymphoproliferative neoplasms there were five patients with connective tissue diseases, but only one had rheumatoid arthritis while two had dermatomyositis.

Hench (1962) found 22 cases of diffuse connective tissue disease in a study of 1000 cases of lymphoma (2.2 per cent), but the diffuse connective tissue diseases were not further divided into specific diseases. In a pension study in Great Britain, Lea (1964) noted a 6.5 per cent incidence of "rheumatic" disease in cases of lymphoproliferative disease, in contrast to 1.5 per cent in a control population. However, once again the rheumatic diseases were defined as all those conditions presently classified under this heading, with the exception of arthritis following trauma. The diagnoses were derived from hospital records. Lea (1964) concluded that there was a very definite association between the reticuloses and the "rheumatic" diseases. In Miller's study of immune disease and malignant lymphoma (1967), there was no overall pattern to suggest a cause-effect relationship.

It is noted that six of our 13 patients (46.1 per cent) with malignancy had taken adrenocorticosteroids on a long-term basis. However, only 51 of the 308 patients (16.5 per cent) without malignancy had received this therapy. This is a significant difference (P is < 0.007).

This carefully directed study suggests that among patients in the age range of 50 to 74 years, malignancy may be more closely associated with steroid therapy than it is with the disease rheumatoid arthritis.

Summary

A retrospective study of the incidence of rheumatoid arthritis and systemic malignancy was performed using the records of 196 older age patients with classic or definite rheumatoid arthritis. The results were compared to 125 patients in the same age group who had arthritis of a non-rheumatoid type. There was no difference in the incidence of malignancy in the two groups of patients. However, there was a positive correlation between the incidence of malignancy and the use of long term adrenocorticosteroid therapy.

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