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Double Trouble: Malignancy and Systemic Rheumatic Diseases: A Single-Center Retrospective Observational Study from South India

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Abstract: ***Background**: A complex bidirectional relationship exists between malignancy and systemic autoimmune rheumatic diseases (SARDs). Chronic inflammation, immunosuppressive therapies, and impaired immune surveillance increase malignancy risk in SARDs, while cancer and its therapies can induce autoimmune manifestations. **Objective**: To identify the common malignancies in rheumatic diseases and paraneoplastic rheumatic manifestations of malignancy. **Methods**: This retrospective observational study was conducted at a tertiary care center in South India from January 2018 to July 2024. Patients with coexisting systemic rheumatic disease and malignancy were identified through hospital records. Data on demographics, disease characteristics, antibody profiles, treatments, and outcomes were collected and analyzed. **Results**: Thirty-four patients (93% female; mean age 52.5 ± 14.1 years) were included. Reproductive cancers were most common (59%), with cervical (26%) and breast (21%) cancers predominating. Hematological malignancies (12%) and colorectal cancers (12%) were also observed. Rheumatoid arthritis (RA) was the most frequent autoimmune diagnosis (41%), followed by systemic lupus erythematosus, dermatomyositis, and systemic sclerosis. Systemic rheumatic disease preceded malignancy in 51.3% of cases (median interval: 6.5 years), developed after malignancy in 31% (median interval: 5 years), or was diagnosed concurrently in 17.3%. Five patients (15%) had paraneoplastic rheumatic manifestations including inflammatory arthritis, dermatomyositis, and complex regional pain syndrome. Notable autoantibodies included RF, anti-CCP, RO52, Scl-70, and anti-TIF-1γ. Two patients died during follow-up. **Conclusion**: Reproductive tract malignancies are the most frequently associated cancers in South Indian patients with systemic rheumatic diseases. Autoantibody profiles and timing of disease onset provide valuable clues in suspecting malignancy in SARDs. Heightened clinical vigilance is essential for early malignancy detection and for recognizing paraneoplastic rheumatic syndromes in such patients.*

Keywords: Systemic autoimmune rheumatic diseases (SARDs), Malignancy, Paraneoplastic syndromes, Autoantibodies

1. Introduction

Systemic autoimmune rheumatic diseases (SARDs) encompass a heterogeneous group of chronic inflammatory conditions, including rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), systemic sclerosis (SSc), dermatomyositis (DM), and others. These diseases are characterized by immune dysregulation, persistent inflammation, and the production of various autoantibodies, which can lead to multiorgan involvement and long-term morbidity. A growing body of evidence suggests a complex, bidirectional relationship between systemic rheumatic diseases and malignancy.

Chronic immune activation, defective apoptotic mechanisms, oxidative stress, and prolonged use of immunosuppressive and cytotoxic therapies are among the key contributors that may predispose patients with SARDs to cancer. Conversely, malignancy itself, as well as its treatments—particularly chemotherapy, radiotherapy, and emerging immune checkpoint inhibitors—can trigger or mimic rheumatic manifestations, sometimes leading to the diagnosis of autoimmune disease. These paraneoplastic syndromes often present a diagnostic challenge and may precede, coincide with, or follow the diagnosis of cancer.

Shared genetic susceptibilities, environmental exposures such as smoking and viral infections, and alterations in immune surveillance mechanisms further compound the interplay between malignancy and autoimmunity. Additionally, certain autoantibodies, such as anti-TIF-1γ in dermatomyositis or anti-Scl-70 in systemic sclerosis, have been linked to specific malignancy profiles, suggesting that serologic markers may offer predictive insight into cancer risk in autoimmune populations. In this context, our study aims to explore the clinical and immunological profiles of patients with coexisting systemic rheumatic diseases and malignancies, to identify the patterns of cancer types observed, and to recognize rheumatic manifestations that may signal underlying or developing malignancy. This is particularly relevant in the South Indian population, where epidemiological patterns may differ from Western cohorts. Early recognition of these associations is vital for optimizing patient outcomes through timely diagnosis, appropriate surveillance, and tailored therapeutic strategies.

2. Methodology

This is a retrospective observational study done from January 2018 to July 2024. Patients diagnosed with systemic rheumatic disease and malignancy attending outpatient and

in-patient departments of Rheumatology at Sri Ramachandra Institute of Higher Education and Research (SRIHER), Chennai, South India were included in the study. Data regarding demography, characteristics of malignancy, systemic rheumatic disease, DMARD therapy, rheumatic manifestation of malignancies, and outcome were collected and analyzed.

Statistical Analysis

Statistical Package for Social Sciences (SPSS version 21) was used for data analysis. Categorical data was expressed as frequencies and percentages. Numerical data were expressed as the mean and standard deviation for normally distributed data.

3. Results

The study included 34 patients, mostly females (93%). The mean age ± SD of the patients was 52.5 ± 14.1 years. The most common malignancy type was reproductive cancers, which accounted for 20 patients (59%), followed by hematological malignancies and colorectal cancers **(**both 4 patients, 11.7% each), lung cancers **(**3 patients, 8.8%**),** sarcomas **(**2 patients, 5.8**%**), and urinary bladder cancer **(**1 patient, 3%**).** Among the reproductive cancers, 9 patients had cervical cancer, **7** had breast cancer, **3** had ovarian cancer, and **1** had endometrial cancer. The 4 patients with hematological malignancies included **2** cases of acute leukemia and 2 cases of non-Hodgkin's lymphoma. Four patients (11.8%) presented with metastatic cancer, and one patient (2.9%) experienced cancer recurrence.

The distribution of systemic rheumatic diseases and types of malignancies occurring in our patients is shown in table 1.

Table 1: Systemic rheumatic diseases and associated malignancies.

SYSTEMIC RHEUMATIC DISEASE (n=29)	n (%)	Malignancy
Rheumatoid arthritis	14 (48.4)	CA cervix, ovary, breast, lung, sigmoid colon, rectum, Urinary bladder sarcoma, Non-Hodgkin's lymphoma.
Systemic lupus erythematous	3 (10.5)	CA cervix, ovary, breast.
Dermatomyositis	2 (6.9)	CA cervix, breast.
Sarcoidosis	2 (6.9)	CA sigmoid colon, endometrium.
Systemic sclerosis Diffuse Limited	2 (6.9) 1 1	CA lung
Mixed connective tissue disease	1 (3.4)	CA breast
Sjogren's syndrome	1 (3.4)	CA cervix
Overlap	1 (3.4)	CA cervix
Bechet's disease	1 (3.4)	CA cervix
Juvenile idiopathic arthritis	1 (3.4)	B-cell ALL
Giant cell arteritis	1 (3.4)	Sarcoma

CA – carcinoma.

Of the 34 patients, five exhibited paraneoplastic rheumatic manifestations, as detailed in Table 2.

Table 2: Paraneoplastic rheumatic manifestations and associated malignancies.

Paraneoplastic rheumatic manifestation (n = 5)	n (%)	Malignancy
Inflammatory arthritis	2 (40)	Leukaemia, CA colon
Myositis	1 (20)	CA ovary
Complex regional pain syndrome	1 (20)	CA breast
Macrophage activation syndrome	1 (20)	Lymphoma

CA – carcinoma.

The antibody profiles of our patients are depicted in Table 3.

Table 3: Antibody profile of patients.

Systemic Rheumatic disease	Antibody Profile	Number of Patients (n)
Rheumatoid Arthritis (RA)	High-titre RF and Anti-CCP (10), Anti-CCP only (2), RF only (1), Seronegative (1)	14
Dermatomyositis	TIF-1 gamma	2
Systemic Lupus Erythematosus (SLE)	RO52 (1), Histone and Nucleosome (2)	3
Mixed Connective Tissue Disease (MCTD)	RNP/Sm	1
Overlap Syndrome	Scl-70	1
Sjögren's Syndrome	SSA and SSB	1
Systemic Sclerosis	Diffuse: Scl-70, Limited: Centromere	2

Systemic rheumatic diseases preceded the onset of malignancy in 51.3% of patients, with a median duration of 6.5 years. In 31% of cases, the rheumatic diseases developed after the malignancy, with a median interval of 5 years. In the remaining 17.3% of patients, the rheumatic diseases and malignancies were diagnosed concurrently.

Among the patients with systemic rheumatic diseases preceding the onset of malignancy, the most frequently administered therapy was a combination of DMARDs (methotrexate and hydroxychloroquine), used in 11 patients. This was followed by mycophenolate mofetil and sulfasalazine in 5 patients each, cyclophosphamide in 2 patients, and azathioprine in 1 patient. Biologic therapies were used in 2 patients with rituximab and tocilizumab in 1each.

Chemotherapeutic agents used in patients developing systemic rheumatic diseases after the onset of malignancy included doxorubicin, cyclophosphamide and taxanes.

Mortality was observed in 2 patients.

4. Discussion

Our study identified a broad spectrum of malignancies in patients with systemic rheumatic diseases (SARDs), with reproductive cancers—especially cervical, breast, and ovarian cancers—being the most common, followed by hematological malignancies. This differs from previous studies [1-4], which predominantly reported hematological cancers as the most frequent in SARD patients. The higher prevalence of female patients and the distribution of cancer types in our study are consistent with findings from China [5], while a U. S. study [6] noted a higher incidence of cervical dysplasia and cancer in patients with rheumatoid arthritis and systemic lupus erythematosus. However, variations in cancer incidence across different studies, influenced by genetic, environmental, and treatment factors, make it challenging to draw definitive conclusions about the specific cancer risks associated with each rheumatic disease.

Turning to paraneoplastic rheumatic manifestations, research has consistently shown their occurrence in patients with malignancies. Studies from China [7], France [8], and Scandinavia [9] have reported arthritis as a frequent paraneoplastic rheumatic manifestation in both solid and hematologic cancers. In our cohort, two patients developed acute, symmetrical inflammatory polyarthritis simultaneously with cancer. Paraneoplastic inflammatory myopathy, often presenting as an early sign of ovarian cancer, was noted in our case, corroborating findings by Buchbinder et al. [10]. A large Brazilian case series by Chanon and colleagues [11] also described complex regional pain syndrome (CRPS) following cancer therapy; similarly, our patient developed CRPS two years after breast cancer surgery and radiotherapy. Furthermore, an analysis of hemophagocytic lymphohistiocytosis (HLH) cases in the German registry [12] identified lymphoma as the most common trigger, aligning with multiple case reports. Our patient presented with macrophage activation syndrome (MAS) as the initial manifestation of lymphoma.

The majority of our rheumatoid arthritis (RA) patients with malignancy are seropositive for high-titre rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA), which are linked to an increased risk of non-Hodgkin lymphoma (NHL) and lung cancer [13, 14]. In systemic lupus erythematosus (SLE), studies by Buchbinder et al. [22] and Inoue et al. [23] showed that RO52 antibodies are associated with ovarian cancer, similar to our findings. Additionally, antibodies against histones and nucleosomes have been linked to solid tumors like breast and ovarian cancer due to their role in genomic instability and impaired DNA repair [16, 17]. In Sjögren's syndrome (SS), SSA/SSB positivity has been linked to an increased risk of cervical cancer, likely due to immune dysregulation affecting HPV clearance [20, 21], consistent with our SS patient with cervical cancer. Anti-Scl-70 antibodies in systemic sclerosis (SSc) are associated with a higher risk of lung cancer, particularly in those with progressive pulmonary fibrosis, as seen in our SSc patients [24]. Similarly, anti-centromere antibodies increase the risk of lung cancer and other solid tumors in SSc patients [25]. Studies from Australia, the USA, and Japan have found that anti-TIF-1 gamma antibodies in dermatomyositis (DM) are linked to cervical and breast cancer [26–28]. RNP/Sm antibodies are also associated with breast cancer in mixed connective tissue disease (MCTD), as reported by Miyoshi et al. [29] and, Zhou et al. [30].

The interval between the onset of rheumatic diseases and malignancy varies. In **RA**, malignancies often develop after many years, particularly in **RF-positive** patients [1]. **SLE** patients may develop **lymphoma** within **5-10 years** [3, 4]. In **SSc** and **DM**, malignancies typically emerge **10-20 years** after diagnosis, while in **Sjögren's syndrome**, lymphoma can develop years after autoimmune symptoms [5, 6].

Methotrexate (MTX) and **biologic agents** like **TNF inhibitors** are associated with an increased risk of **lymphoma** and other cancers, particularly with long-term use [11, 12]. **Leflunomide** also carries a lower, but significant, cancer risk [13]. Chemotherapy, especially **alkylating agents** and **platinum-based drugs**, can trigger **chemotherapy-induced lupus erythematosus (DILE), arthritis**, and **vasculitis**,

likely due to immune dysregulation caused by the treatment [14, 15].

5. Conclusion

Data from our study shows that reproductive cancers commonly occur in patients with systemic rheumatic diseases. In most cases, systemic rheumatic diseases precede the onset of malignancy. Autoantibody profiles and timing of disease onset provide valuable clues in suspecting malignancy in SARDs. Heightened clinical vigilance is essential for early malignancy detection and for recognizing paraneoplastic rheumatic syndromes in such patients.

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