SJIF Impact Factor: 5.464

WORLD JOURNAL OF ADVANCE HEALTHCARE RESEARCH

ISSN: 2457-0400
Volume: 7.
Issue: 11.
Page N. 27-32
Year: 2023

Original Article www.wjahr.com

PREVALENCE OF PARANEOPLASTIC RHEUMATIC SYNDROMES AND ASSOCIATION WITH ANTINUCLEAR ANTIBODIES

Amira Alhusein[1*], Abd Alrazak Hassan[2] and Nader Abdullah[3]

[1]Rheumatology Department, Tishreen University Hospital Lattakia, Syria.
[2]Rheumatology Department, Tishreen University Hospital Lattakia, Syria.
[3]Oncology Department, Tishreen University Hospital Lattakia, Syria.

Received date: 31 August 2023 **Revised date:** 20 September 2023 **Accepted date:** 09 October 2023

***Corresponding Author: Amira Alhusein**

Rheumatology Department, Tishreen University Hospital Lattakia, Syria.

ABSTRACT

Paraneoplastic rheumatic syndromes are rare syndromes, but interest in them is increasing due to the proven relationship between immune disorders and malignancies and their enormous clinical impact on diagnosis and outcome of malignancies,. This places great responsibility on rheumatologists in diagnosing malignancies and referring the patient for effective treatment The aims of this study are to assess the prevalence of paraneoplastic rheumatic syndromes in patients with newly diagnosed solid tumours and to describe their autoimmune profile, comparing it to the control. Screening questionnaires distribut for (170) patients, and during a three-step study, 12 patients confirmed to have both paraneoplastic syndrome and oncology diagnoses. The prevalence of paraneoplastic rheumatic syndromes is 7.1% The group of patients with paraneoplastic arthritis and the group of patients with cancer associated myositis are found to prevail among other clinical presentations of paraneoplastic rheumatic syndromes.

KEYWORDS: paraneoplastic rheumatic syndromes, antinuclear antibodies, rheumatic factor, cancer associated myositis, paraneoplastic arthritis.

1. INTRODUCTION

A number of studies have indicated a link between rheumatic diseases, autoimmunity and cancers.[1,2] Rheumatic patients, particularly rheumatoid arthritis patients, appear to be at a higher risk for lymphoma and lung cancer,[3] and oncology patients are likely to develop paraneoplastic rheumatic syndromes.[4] These are considered to be remote, non-metastatic effects of a tumour. Therefore, the clinical manifestation of paraneoplastic syndromes occurs distant from the underlying malignancy and can involve joints, fasciae, muscles, vessels, and bones. To classify a rheumatic disease as truly paraneoplastic, a causal relationship between the malignant disease and the musculoskeletal pathology has to be demonstrated. A syndrome is generally considered paraneoplastic when its musculoskeletal manifestations appear either simultaneously or no longer than 1 year, in some studies up to 2 years, before the detection of the malignancy. The best evidence for causation is established in retrospect, when it is possible to completely eliminate a tumor and the rheumatic symptoms undergo full remission.[5] It is assumed that 15 % of hospitalised patients with malignancy develop paraneoplastic syndromes of different clinical presentations, mainly neurologic, endocrine related, haematologic, rheumatologic and dermatologic. The proportion of each is not known. It is generally accepted that, within the rheumatic paraneoplastic syndromes, the most frequently diagnosed ones include hypertrophic osteoarthropathy, polyarthritis, cancer associated myositis, and paraneoplastic vasculitis, while others are rare. The presence of the antibodies characteristic to the rheumatic condition like rheumatoid factor (RF) and antinuclear antibodies (ANA) is frequent and makes the diagnostic process of the occult malignancy complicated, which sometimes results in delayed diagnosis.[6] In these years, an increasing attention has been focussed in the relationship between tumours and autoimmunity. Different authors have demonstrated that ANAs are presented, not only in autoimmune diseases, also in serum of patients with different types of cancers, and suggested that ANAs could be involved in the pathogenesis of cancer as well as other premalignant disease.[7]

2. MATERIALS AND METHODS

This prevalence study was carried out during the year 2022-2023 at the Oncology Department and the Rheumatology Department at Tishreen University Hospital. The first-step questionnaire included questions about joint, muscle, cutaneous and mucous lesions that happened to occur recently. 170 solid tumor patients were interrogated and asked about the most common joint, muscular, and extra-articular symptoms. One positive answer for rheumatic complains was an inclusion criterion for the second step. We obtained 35 patients whose interrogation was positive. Then we moved to the third step, where several patients were excluded at this stage because they had previously been diagnosed with rheumatic diseases, whether mechanical, inflammatory, or immunological, and after denying drug causes and metastases as possible causes of skeletal and joint symptoms, we obtained 16 patients. Then we conduct an extensive clinical, laboratory, and radiological examination until paraneoplastic rheumatic syndromes were diagnosed in 12 patients out of 170 solid tumor. The erythrocyte sedimen was recorded from the medical history, and the blood sample was additionally obtained and stored at −20°C before testing for immunology profile including ANA, and RF. ANA were tested by indirect immunofluorescence on hep-2 cells, and RF (the cutoff 20 opt. units was set) were screened for all paraneoplastic rheumatic syndromes' patients with the help of the ELISA. Oncology diagnosis and histology responding to a particular paraneoplastic syndrome was confirmed later after a biopsy was obtained.

Two control groups were designed, comparison between cancer associated myositis (CAM) and idiopathic inflammatory myopathies (IIM) was made in the first group, and a comparison between paraneoplastic arthritis (PA) and rheumatoid arthritis (RA) was made in the second group, in order to identify the characteristics accompanying paraneoplastic rheumatic syndromes and the possibility of benefiting from antinuclear antibodies as a predictive or diagnostic factor in paraneoplastic rheumatic syndromes.

Statistics: The prevalence data were counted as the proportion of patients with rheumatic syndromes in the numerator and divided by the number of patients with confirmed malignancy, and the confidence interval of 95% was assumed. Patient characteristics were summarised by means of descriptive statistics. Differences between the nominal data of the patients and those of the control groups were examined with the help of chi-square statistics and t test for continuous variables. The level of significance was set to 0.05.

RESULTS

Twelve cases of rheumatic syndromes divided by 170 cases of confirmed oncology diagnoses resulted in the prevalence of paraneoplastic syndromes at 7.1%. The demographic data and clinical manifestations are presented in **Table 1**. The group of arthritis (4 cases) and the group of patients with cancer associated myositis (5 cases) were found to prevail among the other clinical presentations of paraneoplastic rheumatic syndromes.

Arthritis was confirmed if swollen joint/joints were present at the time of examination. Oligoarthritis was the main articular manifestation in 3 out of 4 patients. No rheumatoid nodules were observed. Arthritis in most cases occurred in the lower limbs. Myositis was acute with no response on glucorticosteroids in 4 out of 5. The remaining paraneoplastic rheumatic syndromes spread as follows: 1 case for each of Hypertrophic osteoarthropathy, Paraneoplastic vasculitis and Tumour-induced osteomalcia.

Table 1: Demographic and clinical characteristics of 12 patients with paraneoplastic rheumatic syndromes.

Characteristics	Patients with paraneoplastic rheumatic syndromes
Age (range)	54.16
Female (%)	91.6%
Neoplasia in the family(%)	16.6%
Rheumatic conditions in the family(%)	16.6%
Smokers (%)	8.33%
ESR mean value (range)	42.75
Positive RF(%)	16.6%
Positive ANA(%)	25%
Speckled	2
Nucleolar	1
Cancer associated myositis(%)	41.6%
Paraneoplastic arthritis (%)	33.33%
Hypertrophic osteoarthropathy(%)	8.33%
Paraneoplastic Vasculitis(%)	8.33%
Tumour-induced osteomalcia(%)	8.33%

The predominance of the gender is for female (91.6%), and a wide age range is observed among the patients. A rather high proportion of patients had at least one risk factor for malignancy: almost 8.33% are smokers, while genetic predisposition was noted for 16.6% of them with neoplasia observed in the close family.

Rheumatic conditions among close relatives are remembered by 16.6% of the patients. Autoimmune features were not rare, and RF positivity was shown to be present in 16.6% of the patients, ANA positivity in 25% of the patients. The speckled pattern was observed in most ANA-positive patients.

Types of tumors associated with paraneoplastic rheumatic syndromes **Table 2.** The most frequent were tumours of the breast.

Table 2: Types of tumors associated with paraneoplastic rheumatic syndromes.

Syndrome	Tumor (number of caseses)
Cancer associated myositis	Breast cancer(2), colon cancer(1), uterine cancer(1), thymus cancer (1)
Paraneoplastic arthritis	Breast cancer(1), gallbladder cancer(1), lung cancer (1), ovarian cancer (1)
Hypertrophic osteoarthropathy	Lung cancer(1)
Paraneoplastic Vasculitis	Stomach cancer (1)
Tumour-induced osteomalcia	Stomach cancer (1)

For further comparative analysis, two major paraneoplastic groups were considered as cases, and the rheumatoid arthritis group, idiopathic inflammatory myopathies as controls **Table 3.** In total, 9 patients with paraneoplasias, including 5 patients with cancer associated myositis and 4 with paraneoplastic arthritis, were compared to 9 patients including 5 patients with idiopathic inflammatory myopathies and 4 patients with rheumatoid arhtitis.

In the first setting of patients, ANAs were found similarly frequent in the cancer associated myositis (CAM) and control group, while RF was found less often among the (CAM) group ($p<0.05$). Differences were observed for patients with (CAM) being older ($p<0.05$) and mean value of ESR was higher ($p<0.05$). The response to steroids was complete for (4 patients IIM out of 5 patients) while there was no response at all for (4 patients CAM out of 5 patients) ($p<0.05$).(see **figure 1, 2**)

In the second setting of patients, ANAs were found similarly frequent in the Paraneoplastic arthritis (PA) and control group, while RF was found less often among the (PA) group ($p<0.05$). Differences were observed for patients with (PA) being older ($p<0.005$) and mean value of ESR were higher ($p<0.05$). (see **figure 1, 2**)

DISCUSSION

To our knowledge, this is one of the few studies designed to investigate the prevalence and clinical rheumatic manifestations among the malignancy patients consecutively admitted to the Oncology Institute. Several studies investigated the occurrence of rheumatic symptoms among patients with malignancies of certain localisation like pulmonary,[5] haematopoetic[6] and ovarian,[7] while the occurrence of rheumatic paraneoplastic syndromes in daily oncology practice was not investigated yet, except for two study, one by Solans-Laque et al. in 2004,[8] and one by Rugienė, Rita, et al. in 2011.[6] In our study, the prevalence of paraneoplastic rheumatic syndromes among the patients with malignancies was found to be in up to 7.1% of patients. Though the overall prevalence of paraneoplastic syndromes is quoted to be from 7% to 15%, the proportions of clinical manifestations within this condition have not been established yet.[9] The overview of the literature fosters the thinking that neurological paraneoplastic conditions are described more thoroughly if compared to rheumatic, haematologic and endocrinologic conditions since the diagnostic criteria and even laboratory markers for some of them are established and proved to be helpful in daily clinical practice.[10,11] The lack of diagnostic criteria for rheumatic paraneoplasias leads to misclassification of some of them, also the studies focusing on rheumatic conditions in malignancies are mostly based on case or case series reports, while epidemiological studies are few.[12] In the study from Solans-Laque et al,[6] 20 out of 274 malignancy patients reported paraneoplastic rheumatic syndrome or symptom comprising around 7.3%, In the study from Rugienė, Rita, et al. in 2011[6] 94 out of 3770 malignancy patients reported paraneoplastic rheumatic syndrome or symptom comprising around 2.65%, If compared with our study, the prevalence data in our study seem to be rather close.

The major challenge for the clinical rheumatology practice is to find the clues helpful to differentiate between pure rheumatic symptoms and rheumatic symptoms induced by malignancies. Often, clear distinctions cannot be made just on clinical examination, and wide instrumental investigations are required.[13-15]

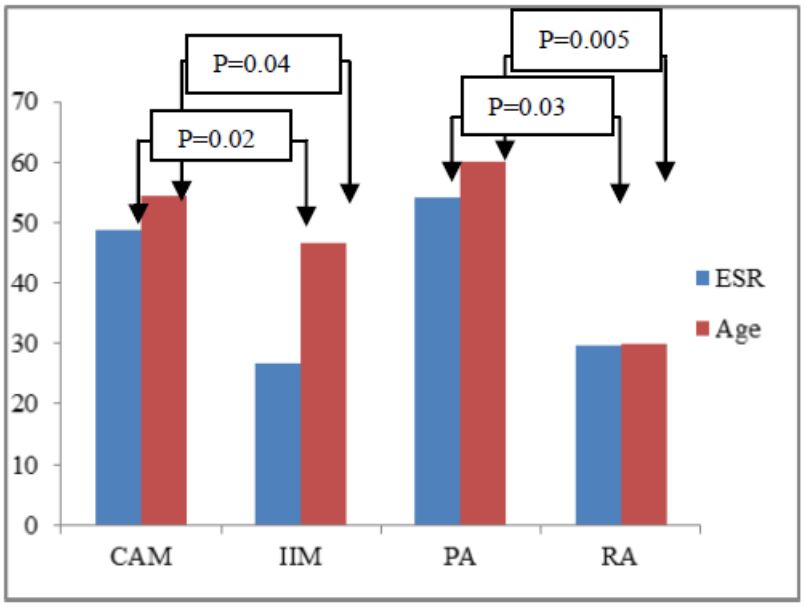

Fig. 1: Comparison of (CAM) and (IIM), (PA) and (RA).

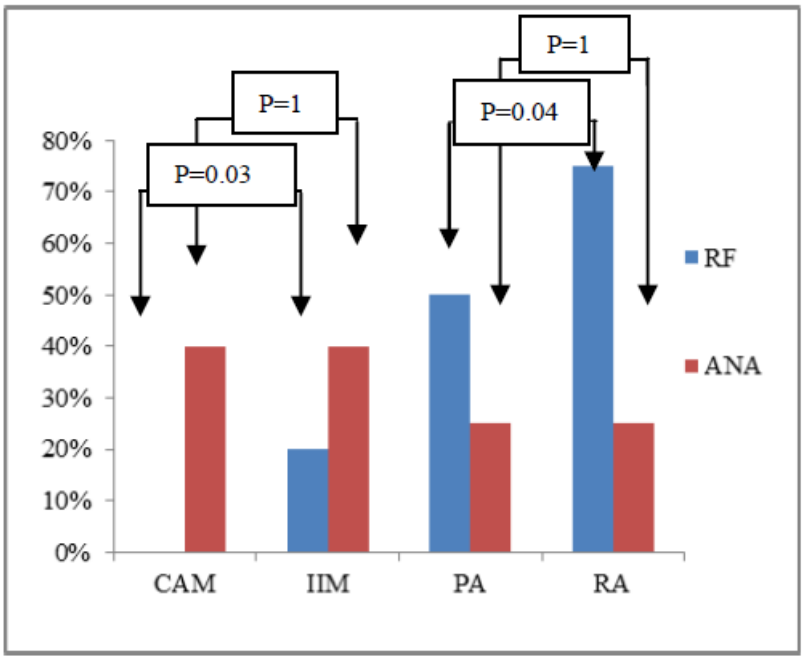

Fig. 2: Comparison of (CAM) and (IIM), (PA) and (RA).

The studies suggest that rheumatic manifestations of hidden cancer include: the rapid onset of an unusual inflammatory arthritis occurring in patients 50 years of age or older, without family history and smokers, test negatively for rheumatoid factor and the absence of rheumatoid nodules are major clinical implications for thorough oncological examinations.[16] In the study from Rugienė, Rita, et al. in 201,[6] the most frequent syndrome were arthritis and Raynaud's syndrome, they were linked to the malignancies of the urogenital system. older age was a definitely helpful demographical feature to distinguish the diseases of different origins. In both paraneoplastic groups, the patients were definitely older.

In the study from Solans -Laque et al. in 2004,[8] the most frequent syndrome were arthritis and paraneoplastic vasculitis , they were linked to colorectal cancer, lung and breat cancers.

However, ANAs have been detected in patients with different cancer types with or without any autoimmune disease.[7] To date, as many as 140 genes have been identified as driver genes, and mutations in several genes confer growth advantage to tumour cells. Different authors have described that the immunogenicity of tumour cells could induce the production of a variety of autoantibodies like SP2/0 tumour cell nuclei and normal

DNA-immunized Balb/c mice, anti-dsDNA, anti-histone, anti-Sm, anti-ds-DNA, anti-ss-DNA, anti-histone, anti-Sm, anti- SS-A, anti-SS-B, etc… Preclinical data results showed that ANAs have anti-tumour activity and it could be mediated by antibody-dependent cell-mediated cytotoxicity (ADCC).[7] This mechanism includes cytokines, that enhance the immune function secondary to ANA immune complexes, and by eliminating or reducing the inhibitory effect of extracellular chromatin on natural killer (NK) cell activity through the binding of ANAs and extracellular nuclear chromatin released from apoptotic cancer cells.[7] Some cancer patients have been misdiagnosed in clinical situations owing to various serum autoantibodies and manifestations of rheumatism.[7] In the present study we found ANA positivity is among 12 patients (25%), and the speckled pattern is the most frequent, but we did not found differences when comparing ANAs positivity in (CAM) and (IIM), (PA) and (RA) (p=1) . In the study from Rugienė, Rita, et al. in 201,[6] the ANA positivity among 94 patirnts was (22.3%) and the immunology profile does not help in discriminating between arthritis and paraneoplastic arthritis patients(p=0.1) and is of limited use in Raynaud's differential diagnosis. In the study from Solans -Laque et al. in 2004,[8] the ANAs were detected in 76 of 274 patients (27.7%), and (17.1%) of patients positive ANAs developed paraneoplastic syndromes, no relationship was found between the highest ANAs titers and development of paraneoplastic syndromes, but musculoskeletal symptoms and rheumatic paraneoplastic syndromes seem to be more frequent in patients with cancer-associated positive ANAs.

3. CONCLUSION

In conclusion, the paraneoplastic rheumatic syndromes are rare, and the most frequent syndromes in the present study are cancer associated myositis and paraneoplastic arthritis. Both paraneoplastic syndromes are linked to malignancies of the breast. The parneoplastic arthritis patients were older, with negative RF, and high rate ESR. The cancer associated myositis patients were older, with negative RF, high rate of ESR, and with no response on glucorticosteroids. In our study, we did not notice a difference in terms of antinuclear positivity. It is therefore unclear to what extent these antibodies can be considered only an epiphenomenon or whether they reflect an autoimmune response to nuclear antigens perturbed in cellular transformation. The immunology profile does not help in discriminating between paraneoplastic arthritis and rheumatoid arthritis, cancer associated myositis and idiopathic inflammatory myopathies. The comparison of immunological data between the studies or different paraneoplastic syndromes is not helpful as no specific antibody reactivity in paraneoplastic syndromes has been described yet. Probably, both ANAs and paraneoplastic rheumatic syndromes might reflect a breakdown in selftolerance associated with cancer but leads to an antigen-driven immune reaction. Further studies are required to characterize the molecular specificity of ANAs in malignancy and to assess their diagnostic and/or prognostic value.

Table 3: Comparison of cancer associated myositis and idiopathic inflammatory myopathies, paraneoplastic arthritis and rheumatoid arhtitis.

Characteristics	Cancer associated myositis	Idiopathic inflammatory myopathies	Paraneoplastic arthritis	Rheumatoid arhtitis
n	5	5	4	4
Age(range)	54.4(34-74)	46.6(30-59)	60(50-75)	30(25-40)
ESR(range)	48.8(7-102)	26.8(3-47)	54.2(15-125)	29.7(7-60)
Positive RF(%)	0%	20%	50%	75%
Positive ANA(%)	40%	40%	25%	25%
Response on glucorticosteroids(%)	Partial(20%) Complete(0%) No response(80%)	Partial(20%) Complete(80%) No response(0%)	-	-

REFERENCES

1. Manger B, Schett G. Paraneoplastic syndromes in rheumatology. Nat Rev Rheumatol, 2014; 10(11): 662-670. doi:10.1038/nrrheum.2014.138
2. Szekanecz Z, Gomez I, Soós B, et al. Eight pillars of oncorheumatology: Crossroads between malignancies and musculoskeletal diseases. Autoimmun Rev, 2020; 19(11): 102658. doi:10.1016/j.autrev.2020.102658.
3. Smitten AL, Simon TA, Hochberg MC, Suissa S (2008) A metaanalysis of the incidence of malignancy in adult patients with rheumatoid arthritis. Arthritis Res Ther, 10: 109.
4. Morel J, Deschamps V, Toussirot E, Pertuiset E, Sordet C, Kieffer P et al (2008) Characteristics and survival of 26 patients with paraneoplastic arthritis. Ann Rheum Dis, 67: 244–247.
5. G. S. Firestein and R. C. Budd, Firestein & Kelley's Textbook of Rheumatology, 11th ed. 2020.
6. Rugienė R, Dadonienė J, Aleknavičius E, et al. Prevalence of paraneoplastic rheumatic syndromes and their antibody profile among patients with solid tumours. Clin Rheumatol, 2011; 30(3): 373-380. doi:10.1007/s10067-010-1676-z.

7. Vlagea A, Falagan S, Gutiérrez-Gutiérrez G, et al. Antinuclear antibodies and cancer: A literature review. Crit Rev Oncol Hematol, 2018; 127: 42-49. doi:10.1016/j.critrevonc.2018.05.002.
8. Solans-Laque R, Perez Bocanegra C, Salud-Salvia, Fonollosa-Plá V, Rodrigo MJ, Armadans L et al (2004) Clinical significance of antinuclear antibodies in malignant diseases: association with rheumatic and connective tissue paraneoplastic syndromes. Lupus, 13: 159–164.
9. The Medscape site [Online]. Available: https://emedicine.medscape.com/article/280744-overview.
10. Beukellaar JW, Smitt PAS (2006) Managing paraneoplastic neurological disorders. Oncologist, 11: 292–305.
11. Graus F, Delattre JY, Antoine JC, Dalmou J, Giometto B, Grisold W et al (2004) Recommended diagnostic criteria for paraneoplastic neurological syndromes. J Neurol Neurosurg Pscychiatry, 5: 1135– 1140.
12. Cho Y, Anderson EW, Guevara SJ, et al. Diagnostic Dilemma of Paraneoplastic Rheumatic Disorders: Case Series and Narrative Review. Cureus, 2021; 13(11): e19993. Published 2021 Nov 29. doi:10.7759/cureus.19993.
13. Manger B, Schett G. Paraneoplastic syndromes in rheumatology. Nat Rev Rheumatol, 2014; 10(11): 662-670. doi:10.1038/nrrheum.2014.138.
14. Cho Y, Anderson EW, Guevara SJ, et al. Diagnostic Dilemma of Paraneoplastic Rheumatic Disorders: Case Series and Narrative Review. Cureus, 2021; 13(11): e19993. Published 2021 Nov 29. doi:10.7759/cureus.19993.
15. Kisacik B, Onat AM, Kasifoglu T, et al. Diagnostic dilemma of paraneoplastic arthritis: case series. Int J Rheum Dis. 2014; 17(6): 640-645. doi:10.1111/1756-185X.12277.
16. Racanelli, V., Prete, M., Minoia, C., Favoino, E., & Perosa, F. (2008). Rheumatic disorders as paraneoplastic syndromes. Autoimmunity reviews, 7(5): 352-358.