

Rheumatic manifestations as initial presentation of malignancy: A case series from a tertiary care center in India

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Abstract

Objective: Malignant neoplasms can be associated with a wide variety of rheumatological manifestations that may be caused by direct tumor invasion into bones and joints, as a paraneoplastic syndrome, and through altered immune surveillance. To identify the relationship between rheumatic manifestations in various malignancies.

Methods: Twenty patients with various malignancies presenting with rheumatic conditions in our tertiary medical care were studied retrospectively from case records at the Kalinga Institute of Medical Sciences from 2013 to 2018.

Results: In the present study, total of 20 patients including 12 males and 8 females with mean age at diagnosis of was 46.3±22.2 years with various malignancy associated rheumatic diseases were included. In total 20% of patients with were current smokers. Seven (35%) had hematological malignancies whereas 13 (65%) had solid malignancies. Most common presenting feature was arthritis (40%), followed by weight loss (20%), skin rash (10%), fever (15%) and muscle weakness (10%) at the time of diagnosis. All of them developed malignancy within 24 months of diagnosis. Among the autoantibodies, only 6 patients (30%) were positive for both ANA (n= 4, 20%) and RF (n=2, 10%), other antibodies were negative. The patients in the hematological malignancies had significantly higher serum levels of LDH, Mean±SD U/L compared to solid malignancy group (716.8±169.6 vs. 249.9±161.6, p<0.001).

Conclusion: In our cohort, all the patients developed malignancies within 2 years of diagnosis of rheumatic condition. Higher serum LDH levels helpful to differentiates between hematological and solid malignancies. Hence early detection of malignancy is of major importance in these patients.

Keywords: Malignancy, paraneoplastic arthritis, rheumatic disease

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Introduction

There is a complex relationship between malignancies and rheumatic diseases. Many studies have indicated connections between malignancy and rheumatic manifestations. Malignant neoplasms can be associated with a wide variety of rheumatological manifestations that may be caused by direct tumor invasion into the bones and joints, as a paraneoplastic syndrome through altered immune surveillance and as a side effect of cytokine therapy (1). In case of paraneoplastic rheumatic syndromes, symptoms can coincide, precede, or follow the diagnosis of cancer or herald its recurrence, often within 2 years of diagnosis of the associated malignancy (2). With rheumatic manifestations, the common cancer associations are the lungs, breast, ovaries, and lymph nodes, usually seen in the elderly population. Malignancies are associated with a wide similarity of paraneoplastic rheumatic manifestations, which may arise in the joints, fasciae, muscles, vessels, or bones (3). Thus, most malignancy-associated rheumatic syndromes are sometimes difficult to distinguish from primary rheumatic conditions. Therefore, the occurrence of cancer may constitute a major diagnostic and therapeutic challenge. Early detection and institution of therapy may be of utmost clinical importance. The aim of the present study was to identify the relationship between rheumatic manifestations and malignancy.

Methods

Twenty patients with various malignancies presenting with rheumatic conditions in our tertiary medical center were studied retrospectively from the case records at the Kalinga Institute of Medical Sciences from 2013 to 2018. They were divided into two subgroups as those with hematological and the other with sol-

id malignancies. The diagnosis of malignancy was confirmed by histopathology in solid tumors and bone marrow study in hematological malignancies. The patients' demographics, disease duration, final diagnosis of rheumatic conditions and malignancies, reports of blood tests, including erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and serum lactate dehydrogenase (LDH), and serological tests, such as antinuclear antibody (ANA), rheumatoid factor (RF), anti-cyclic citrullinated peptide (CCP), and anti-neutrophil cytoplasmic antibody (ANCA), were recorded in a pro forma. The study was approved by the local institutional ethics committee.

Statistical analysis

Summary statistics for all the categorical clinical parameters were presented as frequency and percentage, whereas continuous parameters were presented as mean±SD. The Fisher's exact was used for comparison of qualitative characteristics between hematological malignancies and solid malignancies, whereas the Mann-Whitney U test was used for comparison of quantitative parameters. A p value of <0.05 was considered as statistically significant. All statistical analysis was performed by using standard statistical significant Stata version 15.1.

Results

Table 1 shows the summary of the demographic parameters of all the patients. A total of 20 (12 male and 8 female) patients with malignancies presenting as rheumatic diseases were analyzed. The mean age of the patients was 46.3±22.2 years at diagnosis. Of all patients, 20% were current smokers.

Table 2 shows the details of the clinical characteristics (rheumatological and non-rheumatological) of the patients. Seven (35%) had hematological malignancies, whereas 13 (65%) had

solid malignancies. The clinical manifestations of the patients were both rheumatological (arthritis (40%), skin rash (10%), and muscle weakness (10%)) and non-rheumatological (weight loss (20%) and fever (15%)) at the time of paraneoplastic rheumatic disease diagnosis. All of the patients developed malignancy within 24 months of diagnosis of the rheumatic condition.

Among the solid malignancies (n=13, 65%), the majority were the lung (n=2), carcinoma breast (n=2), and hepatocellular carcinoma (n=2) including one case each of carcinoma stomach, pancreas, oral cavity, left atrial myxoma, and Ewing's sarcoma. Among hematological malignancies, which accounted for 7 (35%) cases, there were 2 cases of chronic myeloid leukemia (CML), 2 cases of acute lymphoblastic leukemia (ALL) including one case each of acute myeloid leukemia (AML), non-Hodgkin's lymphoma (NHL), and myeloma. Table 3 shows the relationship of various characteristics with hematological and solid malignancies among rheumatic disease. Among the autoantibodies, only 6 (30%) patients were positive for both ANA (n=4, 20%) and RF (n=2, 10%), but all tested negative for extractable nuclear antigen. Higher serological positivity was found in solid malignancies compared with hematological malignancies (83.3% vs. 16.7%). None were positive for anti-CCP antibodies and ANCA. The patients in the hematological malignancies had significantly higher serum levels of LDH (mean±SD, U/L) than those in the solid malignancy group (716.8±169.6 vs. 249.9±161.6, p<0.001).

Discussion

Since the first case of rheumatic disease with malignancy was reported in 1916, the number of reported cases is increasing annually. In the present study, all age group of patients with rheumatic manifestation developed malignan-

cy within 2 years of rheumatism diagnosis similar to previous studies (2).

Based on our results, the majority of our patients had solid malignancies (65%), though hematological malignancies can present with rheumatic diseases. In the study by Morel et al. (4), 77% had solid tumors similar to our findings. In a study of pediatric subjects by Gonçalves et al. (5), most patients with paraneoplastic rheumatic manifestations had leukemia rather than solid tumors.

Two patients with solid malignancies had paraneoplastic dermatomyositis, one with hepatocellular carcinoma and the other with pancreatic adenocarcinoma. Both patients presented with typical Gottron's rash and proximal muscle weakness. In addition, there were heliotrope rash and dyspepsia in a patient with pancreatic cancer. There was an 8-month to 1-year delay before the diagnosis of malignancy. In a large series by Fardet et al. (6), in dermatomyositis, the common malignancies described were ovarian, lung, breast, head and neck, and NHL. In the majority of cases (62%), the cancers were diagnosed simultaneously with diabetes mellitus (same time or within 3 months).

One patient developed palmar fasciitis with polyarthritis (PFPA) as a manifestation of the recurrence of carcinoma breast. She had polyarthritis of the hand and feet joints associated with contracture of the hands. Ovarian carcinoma is the most common etiology for PFPA (7). Other malignancies where PFPA is described include gastric, pancreatic, lung, prostate in males and uterus and breast in females. They may either precede or occur along with the underlying malignancy; the underlying mechanisms are presumed to involve the activation of transforming growth factor beta or connective tissue growth factors resulting in increased fibrotic activities primarily involving the hands (8).

One patient with CML had secondary hyperuricemia presenting as acute gout involving the 1st metatarsophalangeal joint of the right great toe even in the absence of renal dysfunction. In the study by Jones et al. (9), three children with T cell ALL had acute renal failure secondary to hyperuricemia. Hyperuricemia in ALL is usually due to high leukemic cell burden. Another case of CML presented with bilateral knee arthritis similar to osteoarthritis.

One patient with squamous cell lung cancer presented with hypertrophic osteoarthropathy (HOA), i.e., clubbing of the fingers and toes associated with bony pain of the extremities.

Table 1. Demographic characteristics among patients with malignant neoplasm with rheumatological manifestations

Parameter	Description
Age (years); mean±SD	46.3±22.2
Delay in diagnosis of malignancy (months); median (min-max)	5.5 (2-24)
Survival (months); median (min-max)	29 (3-60)
Gender, n (%)	
Female	8 (40)
Male	12 (60)
Smoking, n (%)	
No	16 (80)
Yes	4 (20)

Table 2. Clinical characteristics (rheumatological and non-rheumatological) of the patients

Patient	Age	Sex	Non-rheumatological manifestations	Rheumatological manifestations	Rheumatological test	Rheumatologic diagnosis	Malignancy	Delay in diagnosis (months)	Survival duration (months)
1	14	M	Weight loss	Polyarthralgia	Negative	Lt shoulder arthritis	Hepatoblastoma	6	Lost to follow-up
2	69	M	-	Muscle weakness, Gottron's rash	ANA+	Dermatomyositis	Hepatocellular carcinoma	12	8
3	54	F	Dyspepsia	Muscle weakness, heliotrope rash, Gottron's rash	Negative	Dermatomyositis	Pancreatic adenocarcinoma	8	3
4	4	M	Fever, weight loss	Polyarthralgia	Negative	Systemic onset juvenile idiopathic arthritis	Acute lymphoblastic leukemia	2	60
5	12	F	Fever	Polyarthritits	ANA+	Polyarticular juvenile idiopathic arthritis	Acute lymphoblastic leukemia	3	45
6	55	M	-	Arthritis (Rt 1st MTP joint)	Negative	Acute gout	Chronic myeloid leukemia	5	28
7	65	M	-	Hip arthritis	Negative	OA hip joints	Non-Hodgkin's lymphoma	18	30
8	72	F	Weight loss	Low backache	Negative	Low backache	Multiple myeloma	5	10
9	65	M	Cough, weight loss	Bony pain of the extremities	Negative	Hypertrophic osteoarthropathy	Lung cancer	24	20
10	55	F	Fatigue	Polyarthralgia	ANA+	Undifferentiated connective tissue disease	Oral cancer	4	50
11	47	F	-	Polyarthritits	ANA+	Undifferentiated connective tissue disease	Carcinoma breast	6	30
12	66	F	-	Polyarthritits with contracture of the hands	Negative	Palmar fasciitis with polyarthritits	Carcinoma breast	7	12
13	40	M	-	Arthritis	Negative	OA knees	Chronic myeloid leukemia	9	Lost to follow-up
14	76	M	Lower urinary tract symptoms (LUTS)	Arthritis of the left elbow	Negative	Left elbow monoarthritis	Carcinoma prostate	3	Lost to follow-up
15	14	M	-	Low backache	Negative	Enthesitis-related arthritis	Ewing's sarcoma	2	Lost to follow-up
16	34	F	Fever, weight loss, obstructive uropathy	Low backache	Negative	Retropertitoneal fibrosis	Carcinoma stomach	8	Lost to follow-up
17	25	M	-	Low backache	Negative	Spondyloarthritis	Acute myeloid leukemia	3	Lost to follow-up
18	62	F	Fever	Polyarthritits	RF+	Rheumatoid arthritis	Left atrial myxoma	2	55
19	52	M	-	Gangrene of the fingers and toes	Negative	Systemic vasculitis	Lung cancer	4	Lost to follow-up
20	46	M	-	Polyarthritits	RF+	Rheumatoid arthritis	Hepatocellular carcinoma	6	Lost to follow-up

As commonly seen in aggressive lung cancers, HOA is characterized by digital clubbing, periosteal bone proliferation, and an arthropathy ranging from arthralgia to polyarthritis. The pathogenesis is unclear; however, vascular endothelial growth factor may play a role in the development of HOA (10).

Another patient with adenocarcinoma of the lung presented with gangrene of the fingers and toes. Vasculitis was confirmed by skin biopsy. Detailed vasculitis work-up for autoimmune etiology was negative. In the study by Solans-Laque et al. (11), among 15 patients with solid tumors, cutaneous leukocytoclastic vasculitis was the most common, followed by giant cell arteritis, Henoch-Schonlein purpura, and polyarteritis nodosa. Among the malignancies, carcinoma of the urinary tract was the most common, followed by lung cancer and gastrointestinal cancer.

Only few cases of malignancy-associated sacroiliitis have been reported in the literature. One of our patients with AML had features of spondyloarthritis at onset. He presented with inflammatory low backache. The presence of

sternal tenderness, leukopenia, and thrombocytopenia along with poor response to non-steroidal anti-inflammatory drugs (NSAIDs) were clues to diagnosis. Hoshino et al. (12) and Mondal et al. (13) have reported one case each of AML who presented initially as sacroiliitis. Xu et al. (14) have reported a case of ALL in an adolescent male who presented with sacroiliitis mimicking spondyloarthritis. The patient had atypical features, such as splenomegaly, anemia, neutropenia, monocytosis, and thrombocytopenia with poor treatment response to NSAIDs. To our knowledge, this is the third ever case of AML presenting as sacroiliitis. Other hematological malignancies in our study were multiple myeloma presenting with low backache and NHL presenting as hip arthritis.

Two patients had associated urinary tract symptoms along with rheumatic manifestations. An elderly male had lower urinary tract symptoms and left elbow arthritis due to metastasis as presenting feature of carcinoma prostate. One young female had low backache and obstructive uropathy due to retroperitoneal fibrosis (RPF) as a paraneoplastic man-

ifestation of gastric adenocarcinoma. Other malignancies associated with RPF include lymphomas (both Hodgkin's and NHL), carcinoid tumor, inflammatory myofibroblastic tumor, sarcomas, carcinoma breast, prostate, and colon (15).

There were four children in our study, two had ALL (one had features of systemic onset juvenile idiopathic arthritis (JIA) and the other had polyarticular JIA at onset), one had hepatoblastoma, and one had Ewing's sarcoma. Both the children with ALL had fever along with joint symptoms. The child with hepatoblastoma presented with left shoulder arthritis. Inflammatory low backache similar to enthesitis-related arthritis was the presentation of the child with Ewing's sarcoma. In the study by Brix et al. (16), 18.5% of children with ALL presented with arthritis. The common presenting rheumatic conditions were reactive arthritis, osteomyelitis, and JIA. The objective signs for leukemia were less common in patients with ALL.

Overall, 30% of patients with malignancy tested positive for antibodies in our study, out of which 2 patients (one with oral cancer and the other with breast cancer) presented with undifferentiated connective tissue disease with ANA positivity. Two patients (one with left atrial myxoma and the other with hepatocellular carcinoma) had rheumatoid arthritis (RA)-like presentation with positive RF. All patients were tested negative for ANCA and anti-CCP antibodies. In RA diagnosis, anti-CCP is highly specific; this may demonstrate that using positive results, anti-CCP antibody may be useful to distinguish between paraneoplastic rheumatic syndromes and RA, especially in patients with early-onset RA (17).

Acute phase reactants, such as ESR and CRP, are often elevated in most systemic autoimmune diseases. In our study, the levels of acute phase reactants were elevated even in patients with malignancies with similar levels in both solid and hematological malignancies. Serum LDH levels were significantly higher among hematological malignancies with rheumatic manifestations than among solid malignancies. This is similar to the observation by Kisacik et al. (18).

In summary, across all age group, every patient with rheumatic disease should be comprehensively examined for cancer especially in the first 2 years of diagnosis. The presence of weight loss, skin rash, and fever and muscle weakness are important extra-articular manifestations. In patients with early arthritis, anti-CCP is use-

Table 3. Relationship of various characteristics with hematological and solid malignancies among rheumatic disease

Characteristics	Hematological (n=7, 35%)	Solid (n=13, 65%)	p
Age (years); mean±SD	39±26.4	50.3±19.5	0.362
Delay in diagnosis (months); mean±SD	6.42±5.6	7.10±5.8	0.604
Mean survival (months); mean±SD	34.6±18.9	25.4±20.5	0.416
ESR; mean±SD	59.3±28.9	46.9±10.8	0.284
CRP; mean±SD	16.1±9.1	14.5±7.3	0.781
LDH; mean±SD	716.8±169.6	249.9±161.6	<0.001
Sex; n (%)			
Female	2 (25)	6 (75)	
Male	5 (41.7)	7 (58.3)	0.642
Smoking; n (%)			
No	6 (37.5)	10 (62.5)	
Yes	1 (25.0)	3 (75)	1.000
Autoantibody test; n (%)			
ANA+	1 (25)	3 (75)	
RF+	0 (0)	2 (100)	
Nil	6 (42.9)	8 (57.1)	0.793
Any positive (ANA or RF); n (%)			
Positive	1 (16.7)	5 (83.3)	
Negative	6 (42.9)	8 (57.1)	0.354

ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; LDH: lactate dehydrogenase; ANA: antinuclear antibody; RF: rheumatoid factor

ful to differentiate RA from patients with malignancy with arthritis. Serum LDH level is a valuable marker to differentiate hematological from solid malignancies. Since our study is a small retrospective cohort, larger prospective studies are needed to verify these findings.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of KIIT University.

Informed Consent: Written informed consent was obtained from the patients who participated in this study.

Peer-review: Externally peer-reviewed.

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