

## Mini Symposium on Supportive Care: Original Article

# Post-chemotherapy arthralgia and arthritis in lung cancer

Aref H Amiri, Soleiman Jaferian<sup>1</sup>

### Abstract

**Objective:** Evaluate the characteristics of arthritis, arthralgia and musculoskeletal pain after chemotherapy in patients with lung cancer. **Materials and Methods:** In this study, we evaluate the characteristics of 17 patients with joint symptoms following receiving chemotherapy for lung cancer. Demographic information of patients including sex, age, time of rheumatologic findings after starting of chemotherapy, time of improvement after starting of medication, and relevant laboratory findings for each patient. **Results:** A total of seventeen patients (six women with mean age  $41.2 \pm 5.2$  years and 11 men with mean age  $42.5 \pm 8.2$ ) that received standard chemotherapy for lung cancer according to stage of disease. Joint symptoms usually began about seven months after the first session of chemotherapy. Patients had an average of two tender joints and 1 hr of morning stiffness. Four patients were positive for anti-nuclear antibody, and none of patient was positive for rheumatoid factor. Non-steroidal anti-inflammatory drugs, disease modifying anti-rheumatic drugs (DMARD), corticosteroids, and venlafaxine were prescribed. Four patients did not show an improvement. Follow-up was available for all patients. 11 patients showed favorable responses, characterized by a significant decrease (more than 50%) in morning stiffness, pain, and tender joint counts after a mean of three months' treatment. Two patients had complete resolution of symptoms and did not required further medications for arthritis, arthralgia or musculoskeletal pain. **Conclusion:** Chemotherapy-related arthropathy in lung cancer is not uncommon. Early treatment with NSAID, DMARD, and corticosteroids is effective in the majority of patients.

**Key words:** Arthritis, chemotherapy, lung cancer

## Introduction

Available data on the rheumatologic complaints (including arthralgia and arthritis) following chemotherapy of cancers are based to case reports.<sup>[1-4]</sup> These manifestations may be due to metastasis to musculoskeletal structures, paraneoplastic syndrome or immune reactions that cause both rheumatic and neoplastic disease, as well as adverse reactions to cancer specific chemotherapy.<sup>[3-5]</sup> Several rheumatic manifestations may develop in patients after receiving chemotherapy.<sup>[1,2]</sup> There are reports on development of rheumatoid arthritis (RA), Reiter's syndrome, and

vasculitis in patients after chemotherapy, immunotherapy or radiotherapy, and of exacerbation of RA after chemotherapy.<sup>[6-9]</sup>

Post-chemotherapy rheumatism has been described in patients treated for some kinds of cancers including breast cancer, ovarian cancer, and non-Hodgkin's lymphoma.<sup>[10-15]</sup> This condition is a non-inflammatory, self-limiting, musculoskeletal pain that manifests as stiffness, arthralgia, and arthritis involving both large and small joints within a few months after completion of chemotherapy.<sup>[7-9]</sup> These symptoms can occur without evidence of metastatic disease and without positive laboratory and radiologic findings that are indicative of rheumatic disease.<sup>[16,17]</sup> In this study, we examined the occurrence and prognosis of post chemotherapy arthritis and arthralgia in patients with a lung cancer that refers to Rasoul hospital rheumatology clinic of Tehran over a 2 years period.

## Materials and Methods

Our study comprised of 17 patients with lung cancer who were referred between October 2009 and March 2011 to the rheumatology clinic of Rasoul hospital because of joint symptoms after receiving chemotherapy. The predominant complaint was musculoskeletal pain and

Department of Rheumatology, Imam Khomeini hospital, Mazandaran University of Medical Sciences, Sari, <sup>1</sup>Department of Internal Medicine, Shohada Hospital, Lorestan University of Medical Sciences, Koramabad, Iran

**Correspondence to:** Aref Hosseinian Amiri,

E-mail: aref104@gmail.com

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10.4103/2278-330X.103715

stiffness after periods of inactivity, and myalgia and arthralgia after completion of chemotherapy. We reviewed their charts to obtain information on demographics, underlying tumor, dates of initiation and discontinuation of systemic chemotherapy, chemotherapeutic regimen, and other treatments, such as radiotherapy and/or surgery. None of patients had evidence of metastatic cancer at the time of evaluation. Clinical examination was performed by a rheumatologist.

We documented duration of morning stiffness and the pain intensity was evaluated using a 10cm visual analog scale (VAS) for pain. Joint tenderness and swelling and joints pain on passive and active motion was measured in all joints. Arthritis was verified based on evidence of joint inflammation such as tenderness and swelling; symptoms without these features were recorded as arthralgia. We tested for rheumatoid factor (RF) and anti-nuclear antibody (ANA), anti dsDNA for ANA positive patients and inflammatory markers such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) at the initial visit. Patients had radiographs of their hands and feet and any sites with musculoskeletal findings. The patients were initially managed with NSAID, and in patients with joint inflammation, disease-modifying anti-rheumatic drugs (DMARD) were also prescribed. DMARD used for this patients include HCQ, SSZ, and MTX. Low dose corticosteroids were added if joint symptoms did not improve after two weeks. For patients that didn't response to any of these drugs, venlafaxine was added to the previous regimen. Medication was tapered and eventually discontinued if the joint symptoms disappeared.

History of duration, resolution, and change in severity of their joint symptoms, particularly in relation to the administration of medications were carefully recorded.

## Results

Patients studied were 17 patients with lung cancer. This included six women with mean age of  $41.2 \pm 5.2$  years (range: 34-57 years), and 11 men with the mean age of  $42.5 \pm 8.2$  years (range: 34-57 years). The follow-up duration was  $12 \pm 6$  months (range: 6-18 month).

All patients received classic chemotherapy for lung cancer according to stage and grade of disease. Supportive care included anti-emetic medication (all patients received 5-HT3 antagonist and metoclopramide IV on each day of their chemotherapy and 15 patients were given IV steroids). Of these, a total of seven patients also received additional radiation therapy.

None of patients had joint symptoms prior to administration of chemotherapy. Joint symptoms usually began  $4 \pm 3$

months (range: 1-7 months) after the first session of chemotherapy [Table 1]. In three patients, symptoms began within four months after the last session of chemotherapy; in four patients, after five month of chemotherapy; and in one patient, within three months after the first session of chemotherapy. They complained of 1 hour of morning stiffness (range: 15-120 min) and had, on average, two tender joints (range: 0-3).

The commonly-involved joints were toes, shoulders, fingers, ankles and knees [Table 1]. None of patients showed a symmetrical distribution. Ten patients complained of joint pain without evidence of joint inflammation such as tenderness and swelling; these patients had arthralgia without arthritis. Seven patients had arthritis including joint tenderness and swelling. None of cases had symmetric polyarthritis, and 3 cases presented with pauciarticular arthritis.

All of patients had abnormal inflammatory markers. Mean ESR was  $35.6 \pm 11.2$  mm/h (range: 0-52), and mean CRP was  $0.68 \pm 0.6$  mg/dl (range: 0.02-1.18). Four patients were positive for ANA and none of them for RF. None of ANA positive patients were positive for anti dsDNA antibody, nor did they have other signs or symptoms of lupus erythematosus.

In two patients, symptoms were completely resolved eleven other patients had partial resolution of symptoms after receiving medications. Four patients did not show any improvement in spite of all medications. Of the two patients who had complete resolution, initially there was partial resolution of symptoms with NSAID and DMARD. They improved to complete resolution of symptoms after receiving additional low dose oral corticosteroids and remained so even after stopping the corticosteroids. None of patients fulfill the American College of Rheumatology (ACR) criteria for classification of RA and systemic lupus erythematosus. The 11 patients with partial resolution, significant decrease (more than 50%) in duration of morning stiffness, VAS for pain, and tender and swollen joint counts at a mean period of 6 months (range: 3-8 months) after additional treatment with low dose oral corticosteroids.

## Discussion

Musculoskeletal manifestations including arthralgia and arthritis can develop in a patient after chemotherapy. Musculoskeletal symptoms after an administration of chemotherapy were first reported as post-chemotherapy rheumatism by Loprinzi.<sup>[10]</sup> They described 8 patients who developed joint symptoms 1-2 months after receiving adjuvant chemotherapy for breast cancer with a regimen of cyclophosphamide, methotrexate, and 5-FU. Treatment

**Table 1: Characteristics of patients with chemotherapy-related arthropathy**

Age	Symptoms onset (month After chemotherapy)	Positive serology	Medication	Time to improvement	Other treatment	Arthralgia	Tender joint	Swollen joint	Morning stiffness (min)
43	6	-	NSAID	5	OP	Ankle-toe	2	0	120
35	6	ANA	NSAID + DMARD	6	OP + RTx	Ankle-toes-fingers	1	0	60
51	7	-	NSAID + DMARD	5	OP + RTx	knee	0	0	20
40	4	-	NSAID + DMARD	4	OP	knee	1	0	10
63	5	-	NSAID + DMARD + STEROID	4	OP	Shoulder-knee	1	1	15
41	5	-	NSAID + DMARD	4	OP + RTx	Neck-back	0	0	60
59	7	-	NSAID	-	OP	Ankle-knee	1	0	10
54	6	-	NSAID + DMARD + VENLAFAXINE	3	OP + RTx	Back-Ankle	1	1	50
55	6	ANA	NSAID + DMARD + VENLAFAXINE	5	OP	toes-fingers	3	2	120
59	7	-	NSAID	7	OP	Shoulder-Back	0	0	10
50	6	-	NSAID + DMARD + STEROID	6	OP	toes-fingers	3	1	60
48	6	ANA	NSAID + DMARD	3	OP + RTx	fingers	2	1	50
71	5	-	NSAID	7	OP	Shoulder-knee	1	0	10
55	3	-	NSAID	5	OP + RTx	Ankle-toe	2	0	60
54	7	-	NSAID + DMARD + STEROID	5	OP	Neck-back	0	0	5
48	4	ANA	NSAID + DMARD	6	OP + RTx	Ankle-knee	0	0	15
51	5		NSAID	6	OP	Shoulder-Back	0	0	10

with NSAID was ineffective, but symptoms abated in most patients within a year.<sup>[10]</sup> Study of Rader, Smith and some other studies have reported similar cases for patients with ovarian cancer, breast cancer, and with lymphoma.<sup>[11-15]</sup> Another study performed by MI-JEONG KIM and co-workers that describe 25 patients with different kinds of cancers and arthralgia or arthritis after chemotherapy.<sup>[18]</sup> In some studies about 30% of the patients developed joint symptoms after receiving chemotherapy for cancers;<sup>[1-5]</sup>

Our study includes 17 patients who developed arthritis or arthralgia within a relatively short period (about seven months) after chemotherapy for lung cancer.

Among these, none of patients had any symptoms prior to administration of chemotherapy. Joint symptoms were well-controlled by NSAID and DMARD with/without corticosteroids in most patients.

There are some differences between other studies with patients who had post-chemotherapy rheumatism and our patients. Our study was limited to patients with chemotherapy for lung cancer. Other studies included

a more heterogeneous group receiving various chemotherapeutic agents such as 5-FU, cyclophosphamide, cisplatin, doxorubicin, mitomycin-C and paclitaxel.

These findings suggest that musculoskeletal symptoms may develop independent of type of cancer or chemotherapeutic regimen.

In most studies, arthralgia, or arthritis developed in a short period after finishing chemotherapy. We suggest that chemotherapy can induce joint symptoms and this should be kept in mind for cancer patients developing joint related features. Some of our patients showed definite evidence of joint inflammation, such as tenderness and swelling. Others have reported clinical manifestations similar to RA such as morning stiffness, polyarthritis that frequently involves fingers and toes, and symmetric distribution,<sup>[18]</sup> This was not the case in our study. None of patient was positive for RF, and of course none of patients completed the ACR criteria for RA. Inflammation markers were abnormal in most of our patients.

The main difference between our results and those of

Loprinzi is the response to treatment. In the study of Loprinzi, no patient with post-chemotherapy rheumatism responded to NSAID and responses to corticosteroid therapy were variable. Also most symptoms resolved spontaneously within 1 year.<sup>[10]</sup> In our study, only four patients failed to show a response to medication. The response was as early as two month in some patients and the response time ranged up to eight months. Two patients were completely free of joint symptoms whereas 11 patients still reported mild arthralgia despite receiving medication.

Only four patients showed no improvement with medication. Like the study of MI-JEONG KIM, it seems likely that complete resolution of pain in most of our patients was a result of initial administration of DMARD.

We used a variety of DMARDs including hydroxychloroquine, sulfasalazine, and methotrexate for controlling of arthritis and arthralgias. For patients who showed an unsatisfactory initial response, the addition of corticosteroids resulted in improved joint symptoms. An important matter for the management of chemotherapy-related arthropathy is early detection and early administration of NSAID and DMARD with/without corticosteroids.

The pathophysiologic mechanisms of chemotherapy-related arthropathy remain uncertain. It seems that combination chemotherapy may disturb the immune system, resulting in the production of auto antibodies and musculoskeletal manifestations.<sup>[16]</sup> This idea is supported by a report that gonadal ablation by chemotherapy can result in thymic hyperplasia and altered thymic function that leads to autoimmunity.<sup>[17]</sup> Development of rheumatic symptoms in patients treated with tamoxifen has been described in some studies.<sup>[19]</sup> Several observations suggest that tamoxifen may induce or exacerbate arthritis through its anti-estrogen effect.<sup>[15]</sup>

In the study of creamer, it is suggested that chemotherapy and tamoxifen may induce gonadal atrophy, and this result in T cell activation and autoimmune manifestations.<sup>[19]</sup>

Chemotherapy-related arthralgia and arthritis is not a rare event, and the physician's awareness of this syndrome is important as it may limit the need for an extensive investigation to exclude recurrent cancer or other rheumatologic disease. Besides our study in lung cancer, other studies for post chemotherapy rheumatism involved patients with breast cancer and lymphoproliferative disorders.

## Conclusion

Our study indicates that post-chemotherapy arthritis and arthralgia is not uncommon after lung cancer chemotherapy. Post-chemotherapy musculoskeletal pain can adversely affect

quality of life but frequently are not life-threatening.

Characterization of features such as pattern, severity, and treatment is required for post-chemotherapy arthritis and arthralgia will help in making it a well recognized entity. This will streamline its distinction from metastatic disease, hasten correct diagnosis without unnecessary investigations, permit early institution of appropriate therapy and ultimately decreasing patient anxiety as well as improve their quality of life

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**How to cite this article:** Amiri AH, Jaferian S. Post-chemotherapy arthralgia and arthritis in lung cancer. *South Asian J Cancer* 2012;1:72-5.  
**Source of Support:** Nil. **Conflict of Interest:** None declared.