

# Isolated knee monoarthritis heralding resectable non-small-cell lung cancer. A paraneoplastic syndrome not previously described

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**Objective:** To describe isolated knee monoarthritis as a paraneoplastic syndrome heralding non-small cell lung cancer (NSCLC), and to discuss its clinical characteristics.

**Methods:** Clinical records of all consecutive, new outpatients with isolated knee monoarthritis observed from January 2000 to December 2005 were reviewed. A systematic review of Medline and Cochrane Library databases was performed to identify English-language articles related to rheumatological paraneoplastic syndromes associated with NSCLC.

**Results:** Over 6 years, 6654 new outpatients with different rheumatic disorders were observed. Of these, 296 (4.4%) presented with isolated monoarthritis of the knee. In five out of 296 patients (1.7%) this feature represented the initial manifestation of NSCLC. All five patients were middle-aged men, with a long history of heavy cigarette smoking, who had a non-erosive, isolated knee monoarthritis, with mild articular fluid collection of non-inflammatory type. NSCLC was resectable in all patients, and knee monoarthritis remitted with no relapse confirming its paraneoplastic nature. All five patients are in good condition after a median follow up of 41 months. The literature review revealed that paraneoplastic knee monoarthritis has not previously been reported.

**Conclusion:** Knee monoarthritis may in some cases represent a paraneoplastic syndrome heralding NSCLC at an early stage.

Small-cell lung cancer (SCLC) is associated with various types of paraneoplastic syndromes in approximately 10–20% of cases.<sup>1,2</sup> Paraneoplastic syndromes associated with non-small-cell lung cancer (NSCLC) are less frequent and variable, but of particular interest. Given its resistance to chemotherapy, the prognosis of NSCLC is strictly dependent on the possibility of surgical removal, its early detection is thus of great importance.<sup>3</sup>

Hypertrophic osteoarthropathy (HOA), observed in approximately 5% of patients, is the most frequent paraneoplastic syndrome associated with NSCLC.<sup>1,2</sup>

To the best of our knowledge, isolated knee monoarthritis not associated with HOA, as the presenting feature of NSCLC, has not previously been reported.

A review of the clinical records of all outpatients presenting with isolated knee monoarthritis observed over a 6-year period revealed that this manifestation heralded NSCLC in five patients.

The aim of this study was to describe the clinical characteristics of these patients, and to discuss the differential diagnosis.

## PATIENTS AND METHODS

### Setting

The Rheumatology Unit of Prato, Tuscany, Italy, is a secondary referral centre that serves approximately 300 000 people living in the province of Prato and the surrounding industrial areas. Approximately 75% of patients are sent by their general practitioners, and the remainder are self referred.

Since January 2000, the demographic and clinical data of all new outpatients presenting with rheumatic manifestations were recorded in a computed individual chart.

Isolated knee monoarthritis was defined by the presence of a tender and swollen joint not associated with other rheumatic features at onset. Patients with this manifestation had a standardized diagnostic approach, including history, complete physical examination, arthrocentesis with synovial fluid analysis, laboratory examinations, including blood cell count with differential count, kidney and liver function tests, erythrocyte sedimentation rate, C-reactive protein, calcemia, uric acid level, rheumatoid factor, Lyme serology, antinuclear antibodies, HLA-B27 typing, radiological examination of the affected joint, and pelvis X-rays to investigate sacroiliitis.

Articular inflammation signs such as joint swelling size, warmth, redness, and tenderness, were currently graded with a semiquantitative scale from 1 to 3 (1, mild; 2, moderate; 3, severe). The sum provided the final arthritis grading: mild, 1–4; moderate, 5–8, and severe, 9–12.

Patients were followed up by the same rheumatologist, and visits were scheduled every 4 months or less if needed.

### Data extraction

The clinical records of all new, consecutive outpatients presenting with isolated knee monoarthritis from January 2000 to December 2005 were reviewed. The following data were extracted and imputed in an SPSS statistical package (SPSS Inc., Chicago, Illinois, USA): date of first visit, family history, presence of digital clubbing, HOA, pulmonary symptoms, cutaneous manifestations, symptoms and signs of neuropathy or myopathy, laboratory examinations, HLA B27 typing, synovial fluid analysis results, knee and pelvis radiographic findings, further examination useful for the final diagnosis, treatment, and follow-up duration. The follow-up was extended to December 2006.

### Literature review

A review of the literature published between 1966 and December 2006 using Medline and Cochrane Library databases was performed crossing the following indexing terms: lung cancer, SCLC, NSCLC, rheumatic paraneoplastic syndromes,

**Abbreviations:** HOA, Hypertrophic osteoarthropathy; NSCLC, non-small-cell lung cancer; SCLC, small-cell lung cancer

**Table 1** Final diagnoses in 296 consecutive outpatients presenting with isolated knee monoarthritis observed over a 6-year period

Diagnosis	No.	Percentage
Osteoarthritis and knee degenerative disorders	164	55.4
Psoriatic arthritis	49	16.5
Spondyloarthritis	34	11.5
Chondrocalcinosis	22	7.4
Gout	10	3.4
Septic arthritis	6	2.0
Non-small-cell lung cancer	5	1.7
Villonodular synovitis	4	1.3
Emarthrosis	2	0.7

acute monoarthritis, hypertrophic osteoarthropathy, digital clubbing, carcinoma polyarthritis. Articles were selected if they focused on case reports, clinical series, reviews, and meta-analyses of patients with NSCLC and musculoskeletal manifestations.

## RESULTS

Between January 2000 and December 2005, 296 out of 6654 new outpatients (4.4%) had isolated monoarthritis of the knee. The final diagnoses in this cohort are reported in table 1.

Isolated, non-erosive knee monoarthritis represented the first symptom of occult NSCLC in five out of 296 (1.7%) patients. Before the visit, they had taken non-steroidal anti-inflammatory drugs with an unsatisfactory response. As shown in table 2, all patients were middle-aged men, with a history of heavy cigarette smoking.

As summarized in table 3, synovial fluid was of non-inflammatory type in all, with negative cytology.

The arthritis characteristics, the results of synovial fluid analysis, the absence of marked radiological signs of osteoarthritis or sacroiliitis, and also the history of cigarette smoking raised the suspicion of a possible paraneoplastic syndrome.

In all five patients, chest X-rays were highly suggestive of a malignant lung neoplasm. Chest computed tomography, and histological examination of bronchoscopic biopsies confirmed

the diagnosis of NSCLC. Staging excluded extrapulmonary diffusion,<sup>4</sup> and the cancer was resectable in all cases.

Cancer and knee monoarthritis remitted with no flares in all patients over a median follow-up of 41 months (range 19–72).

## DISCUSSION

A wide variety of paraneoplastic syndromes are usually associated with SCLC.<sup>1</sup> NSCLC is almost exclusively associated with HOA.<sup>2</sup> This condition, observed in less than 1% of SCLC and in approximately 5% of NSCLC,<sup>2</sup> consists of digital clubbing, proliferative periostitis of the distal ends of long bones, and arthritis.<sup>5</sup> Symptoms of HOA may precede those of the underlying neoplasm by as much as 18 months,<sup>5</sup> and the arthritis is more often polyarticular, symmetrical, and painful, involving the knees, ankles, elbows, wrists, and the small joints of hands and feet.<sup>6</sup> Synovial fluid is non-inflammatory, with normal appearance, good viscosity, low leukocyte numbers, and low protein concentration.<sup>6</sup> HOA parallels the course of the underlying lung cancer, and usually subsides in the case of successful resection.<sup>5</sup>

In this paper we described five men with NSCLC in whom the presenting clinical feature was acute, non-erosive, asymmetric arthritis of the knee, not associated with systemic or pulmonary symptoms. The originality of this manifestation should be challenged with the possibility of an initial phase or an incomplete form of HOA. This option seems unlikely for at least two reasons: first, in contrast to our patients, joint involvement in HOA is predominantly polyarticular and symmetrical;<sup>5</sup> second, the chronology of the clinical features of HOA is usually characterized by the onset of digital clubbing as the first manifestation, with periostitis and arthropathy occurring in a later phase.<sup>7</sup> Clubbing was absent in all our patients, although this feature is frequently seen in association with NSCLC.<sup>7</sup>

Metastatic involvement of bone occurs in at least 20% of patients with NSCLC.<sup>2</sup> Any bone can be affected, although the axial skeleton and proximal long bones are prevalently involved. Rarely, knee monoarthritis caused by adjacent bone metastases<sup>8–10</sup> or direct synovial invasion has been described in patients with NSCLC.<sup>11</sup> Synovial fluid analysis with negative cytology and the normality of radiographs and radionuclide scanning allowed the exclusion of this possibility in our patients.

**Table 2** Demographic and clinical characteristics of the five patients with knee monoarthritis and non small-cell lung cancer

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Sex/age (years)	Male/53	Male/55	Male/56	Male/55	Male/66
Family history of psoriasis or spondyloarthropathy	No	No	No	No	No
Cigarette smoking (> 20/day)	Yes	Yes	Yes	Yes	Yes
Cigarette smoking duration (years)	35	31	34	30	45
Systemic symptoms	No	No	No	No	No
Involved knee	Right	Right	Left	Left	Left
Duration of symptoms (months)	2	1	2	3	3
Knee inflammation*	Mild	Moderate	Mild	Mild	Moderate
Concomitant musculoskeletal features	No	No	No	No	No
HLA B27	No	No	No	No	No
Digital clubbing	Absent	Absent	Absent	Absent	Absent
ESR (mm/h)	25	31	14	28	50
CRP (mg/dl)	0.9	1.0	0.5	0.8	2.1
Articular erosions	No	No	No	No	No
Chest X-rays	Right mass	Left mass	Right mass	Left mass	Left mass
Histology	SCC	SCC	SCC	AC	LCC
International staging	IA	IA	IB	IA	IB
Arthritis flare after cancer resection	No	No	No	No	No
Follow-up duration (months)	72	48	41	22	19

AC, Adenocarcinoma; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; LCC, large cell carcinoma; SCC, squamous cell carcinoma.  
\*Knee inflammation. See methods section in the text.

**Table 3** Paraneoplastic knee monoarthritis: synovial fluid analysis results in five patients

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Volume (ml)	25	20	15	20	30
Viscosity	High	High	High	High	High
Colour	Colourless	Straw	Straw	Colourless	Straw
Clarity	Transparent	Transparent	Transparent	Transparent	Transparent
WBC/mm <sup>3</sup>	200	600	500	800	700
PMN (%)	40	35	45	30	30
Mucin clot	Firm	Firm	Firm	Firm	Firm
Protein (g/dl)	2.0	1.2	1.8	2.1	1.6
Crystals	Absent	Absent	Absent	Absent	Absent
Culture	Negative	Negative	Negative	Negative	Negative
Cytology	Negative	Negative	Negative	Negative	Negative

PMN, Polymorphonucleates; WBCs, white blood cells.

In our 6-year clinical series, isolated knee monoarthritis occurred in 4.4% of 6654 new outpatients. Osteoarthritis and other degenerative disorders of the knee were the most frequent causes, followed by other inflammatory diseases such as psoriatic arthritis and spondyloarthropathies, infectious and crystal-related arthritis, and less frequent conditions including villonodular synovitis and ematrhrosis. The simultaneous occurrence of psoriatic arthritis and lung cancer has recently been described.<sup>12</sup> Moreover, some rheumatic disorders and related therapies are associated with a greater incidence of malignancies.<sup>13</sup> Consequently, the possible coexistence of incidental NSCLC and asymmetric knee arthritis related to an antedating or concomitant cause other than a paraneoplastic one might explain the clinical picture in our patients. This possibility could, however, be ruled out for several reasons: all five patients had a negative family history of psoriasis and spondyloarthropathies, none of them had associated features suggesting spondyloarthropathy, all were HLA-B27 negative, articular symptoms were of short duration, synovial fluid was non-inflammatory, crystals were absent, cultures were negative, and knee radiographs were not indicative of severe osteoarthritis or chondrocalcinosis. Finally, confirming its paraneoplastic nature, after the surgical removal of the lung cancer, no flares of knee arthritis or other rheumatic manifestations occurred in our patients over a prolonged follow-up.

In our 6-year clinical series, paraneoplastic knee monoarthritis was not a remote event, being observed in 1.7% of all patients with isolated asymmetric arthritis of the knee. Notably, this clinical manifestation occurred at an early phase of NSCLC, at stages IA or IB, thus allowing the surgical resection of the tumour.<sup>14</sup> NSCLC is diagnosed at these stages in only 45% of cases, with important positive repercussions on long-term survival.<sup>15</sup> In keeping with this statement, all five patients were disease-free after a median follow-up of 41 months.

Therefore, the most relevant clinical characteristics of paraneoplastic knee monoarthritis associated with NSCLC deserve to be emphasized. In our experience, this paraneoplastic condition should be suspected in all heavy smokers, HLA-B27 negative, who present with mild to moderate isolated knee monoarthritis in the absence of a clear history of psoriasis or spondyloarthropathy, and of radiological features suggestive of severe osteoarthritis or chondrocalcinosis. Arthrocentesis with synovial fluid analysis is mandatory to confirm its non-inflammatory nature, and to exclude other possible causes of joint fluid collection. As in our patients, when the most common causes of knee monoarthritis are ruled out, a chest radiograph is recommended as a first level investigation.

In conclusion, in our clinical series we detected five patients with paraneoplastic knee monoarthritis heralding NSCLC at an early stage. Although not frequent, awareness of the main clinical characteristics of this manifestation may help to facilitate proper diagnosis.

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