

Paraneoplastic Syndrome of Arthropathies as Presenting Sign for Non-small Cell Lung Cancer

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Abstract

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Running head : Paraneoplastic Syndrome of Arthritis in NSCLC

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Abstract

Paraneoplastic syndrome is often not an obvious or common clinical presentation, but this report demonstrates that migratory arthropathies, may be the first presenting sign for non-small cell lung cancer (NSCLC). This study showcases an example of paraneoplastic syndrome, so other healthcare providers can be aware of early NSCLC manifestations.

(49 words)

Paraneoplastic Syndrome of Arthropathies as Presenting Sign for NSCLC

Introduction

Lung and bronchus cancer is the third leading cancer in the United States (US) and was the leading cause of cancer death in 2019.¹ Deaths from lung and bronchus cancer also accounted for 23% of all deaths related to cancer.² Lung cancer is split up into four major types of lung cancer that account for 88% of primary lung cancer; adenocarcinoma, squamous cell, small cell, and large cell, listed in descending order.³ These non-small cell lung cancers (NSCLC) makes up the majority of all lung cancers, however presentations of these cancers range from a peripheral nodule, central mass, to widely disseminated disease.³ The presentation of lung cancer can sometimes be easily seen when incidentally found on imaging, other times it is more subtle, like when presenting as a Paraneoplastic syndrome. These syndromes can present as hypercalcemia (squamous cell), SIADH (small cell), gynecomastia (large cell), or even connective tissue syndromes such as clubbing and hypertrophic osteoarthropathy (HOA) which are both most often associated with NSCLC.²⁰

In this article, we describe a patient who experienced joint pain in her hands and pain in one knee, which later progressed to her other leg. She was ultimately found to have NSCLC of squamous origin. A thorough literature review on NIH Database has shown multiple case studies that show the correlation between NSCLC and HOA involving large joints. However, there are limited reports of singular joint involvement with later progression to other joints. One case report showed a patient with NSCLC who had 2 weeks of acute joint pain in all four extremities, including his hands, fingers, knees, and ankles and was found to have adenocarcinoma.⁴ Another retrospective study by Cantini and associates did a study from the years 2000 to 2005 which included patients with isolated knee monoarthritis as the initial presenting sign.⁵ The study eventually found that five out of 296 patients with isolated knee monoarthritis were found to have NSCLC.⁵ This conclusion was again demonstrated in 2020 by a case report involving monoarthritis in the knee, a presenting sign of HOA associated with NSCLC. However, the patient evaluated in this article shows that this monoarthritis could spread to other joints, which emphasizes the importance of watching for spreading arthropathies as a presenting symptom of NSCLC and how surgery could be the definitive treatment.

Case Presentation

This patient was a 56-year-old female who presented to a local urgent care due to persistent cough that she had had for about a week. The cough was dry in nature (no hemoptysis) and her only other complaints at the time were severe joint pain, requiring NSAID use, and swelling of her fingers. While she was there, she was tested for COVID, which was negative, and had a CXR which was read after the patient left the urgent care. Of note, this patient had minimal past medical history but did have a 55-pack year smoking history with cessation of tobacco products 2 years prior. Patient does vape daily. After the urgent care visit, she was sent home with azithromycin for suspected community acquired pneumonia but was later called for a suspicious lesion found on the CXR located near the right lateral pleural space. This lesion was not seen on CXR that she had 5 years prior, for an unrelated issue.

She was then referred to a pulmonologist for evaluation of the persistent cough and CXR finding. The pulmonologist did a thorough work up for the right lower lobe lung mass, which included a CT of the abdomen/pelvis, pulmonary function tests, and a PET scan of her body, with plans to biopsy the mass (Figure 1). A CT guided biopsy of the mass was diagnostic for invasive poorly differentiated squamous cell carcinoma. PET CT scan and MRI of the spine revealed the mass to be without metastases. However, the imaging did reveal right posterolateral chest wall involvement.

At this time, she was sent to thoracic surgery for pre-operative evaluation. Upon presentation to our clinic, patient states she was taking ibuprofen for left knee pain that started about a year ago and a few months after the onset the pain migrated to other sites, including her right knee, right ankle, and left foot. She had also noticed progressive swelling in her phalanges and metacarpal bones bilaterally at the time she developed the nonproductive cough.

After appropriate clearances patient underwent a flexible bronchoscopy, right posterolateral thoracotomy with a right lower lobectomy with en bloc chest wall resection of posterior ribs 7-8, and a mediastinal lymph node dissection. Patient was discharged on post op day 4 without complications and was seen again in the clinic for a 1 week follow. The final pathology demonstrated an 11 cm, T4 N0 M0 Stage IIIB squamous cell carcinoma. During the visit she noted that her joint pain and swelling had significantly improved. She then continued on to her post operative adjuvant chemotherapy and her follow up surveillance appointments, according to the NCCN guidelines; 6 month follow up PET-CT showed no evidence of active neoplastic disease (Figure 2).

Discussion

HOA is a syndrome with stages in the disease process, most often starting with clubbing of fingers and progressing to other symptoms such as joint pain, periostosis, etc.⁶ These symptoms can differ in severity from patient to patient, making the diagnosis of HOA challenging.⁶ There are several proposed theories on the pathogenesis of HOA; the exact physiology still remains unclear. One popular theory includes release of platelet derived growth factors (PDGF), prostaglandin E, and vascular endothelial growth factor (VEGF) by megakaryocytes that have bypassed the pulmonary capillary network.⁷ These growth factors lead to fibroblast proliferation, distal clubbing, vascular hyperplasia, and new bone formation. Patients with HOA have been shown to have significantly higher levels of PDGF and VEGF.⁷ Although the diagnosis is a clinical one, bone scintigraphy is a useful adjunctive for detection. Characteristic findings on scintigraphy include bilateral increased uptake in long bones, with periostitis being the hallmark of hypertrophic pulmonary osteoarthropathy.⁸

Various treatments of HOA have been studied, however, treatment with surgical resection of the primary tumor results in rapid long-term remission of symptoms.⁹ This was evident in our case with almost complete resolution of our patient's joint pain and swelling during her 1 week follow up. Other treatments that have shown to provide relief in HPO include bisphosphonates¹⁰ and octreotide¹¹. One case was also treated with an EGFR inhibitor, gefitinib.¹² It is important to understand that conventional analgesics, including NSAIDs have limited efficacy on HOA. Utilizing these alternative medications for refractory cases of HOA can help symptomatic relief in many patients.

HOA can also be a sign of a multitude of different organ systems being affected which makes this a syndrome that all physicians should be aware of. According to the study by Martinez-Lavin, the majority of cases will only show manifestations of clubbing in the fingers.⁶ However, although the patient in this report did have clubbing in her fingers during examination, her main complaint, and first to manifest, was the migratory arthritis. This presentation of arthritic pain in her left knee is unusual to appear prior to clubbing of her fingers and the length of time from onset of arthritis to respiratory symptoms are unusual. This patient presentation stresses the importance of always having lung cancer on the differential diagnosis in the setting of any symptom associated with HOA. It also shows monoarthritis that spread to other joints is a potential symptom heralding adenocarcinoma of the lung.

References

1. Cancer of the Lung and Bronchus - Cancer Stat Facts. SEER. Accessed August 25, 2022. <https://seer.cancer.gov/statfacts/html/lungb.html>
2. CDCBreastCancer. An Update on Cancer Deaths in the United States. Centers for Disease Control and Prevention. Published February 28, 2022. Accessed August 25, 2022. <https://www.cdc.gov/cancer/dpcp/research/update-on-cancer-deaths/index.htm>
3. Jameson JL, Fauci AS, Kasper DL, Hauser SL, Longo DL, Loscalzo J. Lung Cancer. In: *Harrison's Manual of Medicine*. 20th ed. McGraw-Hill Education; 2020. Accessed August 25, 2022. accessmedicine.mhmedical.com/content.aspx?aid=1167064169
4. Poddar K, Pathikonda L, Villamil M. Sudden onset polyarthritis as a paraneoplastic syndrome from non-small cell lung cancer. *Journal of Community Hospital Internal Medicine Perspectives*. 2020;10(2):174-178. doi:10.1080/20009666.2020.1749503

5. Cantini F, Niccoli L, Nannini C, et al. Isolated knee monoarthritis heralding resectable non-small-cell lung cancer. A paraneoplastic syndrome not previously described. *Annals of the Rheumatic Diseases* . 2007;66(12):1672-1674. doi:10.1136/ard.2007.075333
6. Martínez-Lavín M. Hypertrophic osteoarthropathy. *Best Pract Res Clin Rheumatol* . 2020;34(3):101507. doi:10.1016/j.berh.2020.101507
7. Davis MC. Hypertrophic Osteoarthropathy as a Clinical Manifestation of Lung Cancer. *Number 5 / October 2011* . 1969;15(5):561-563. doi:10.1188/11.CJON.561-563
8. Ito T, Goto K, Yoh K, et al. Hypertrophic Pulmonary Osteoarthropathy as a Paraneoplastic Manifestation of Lung Cancer. *Journal of Thoracic Oncology* . 2010;5(7):976-980. doi:10.1097/JTO.0b013e3181dc1f3c
9. Albrecht S, Keller A. Postchemotherapeutic Reversibility of Hypertrophic Osteoarthropathy in a Patient with Bronchogenic Adenocarcinoma. *Clinical Nuclear Medicine* . 2003;28(6):463-466. doi:10.1097/01.RLU.0000067504.35952.10
10. King MM, Nelson DA. Hypertrophic Osteoarthropathy Effectively Treated with Zoledronic Acid. *Clinical Lung Cancer* . 2008;9(3):179-182. doi:10.3816/CLC.2008.n.027
11. Angel-Moreno Maroto A, Martínez-Quintana E, Suárez-Castellano L, Pérez-Arellano JL. Painful hypertrophic osteoarthropathy successfully treated with octreotide. The pathogenetic role of vascular endothelial growth factor (VEGF). *Rheumatology* . 2005;44(10):1326-1327. doi:10.1093/rheumatology/keh720
12. Hayashi M, Sekikawa A, Saijo A, Takada W, Yamawaki I, Ohkawa SI. Successful treatment of hypertrophic osteoarthropathy by gefitinib in a case with lung adenocarcinoma. *Anticancer Res* . 2005;25(3c):2435-2438.
13. Murton AJ, Maddocks M, Stephens FB, Marimuthu K, England R, Wilcock A. Consequences of Late-Stage Non-Small-Cell Lung Cancer Cachexia on Muscle Metabolic Processes. *Clinical Lung Cancer* . 2017;18(1):e1-e11. doi:10.1016/j.clc.2016.06.003
14. Lommatzsch M, Julius P, Lück W, Bier A, Virchow JC. Das Marie-Bamberger-Syndrom als Fingerzeig auf ein NSCLC: vier Fälle im Lichte der aktuellen Literatur. *Pneumologie* . 2012;66(02):67-73. doi:10.1055/s-0031-1291476
15. McCormick JP, Trueick R, Connaughton J, McDonnell N. First recurrence of small cell lung cancer presenting as subacute monoarticular arthritis. *BMJ Case Reports CP* . 2021;14(8):e243382. doi:10.1136/bcr-2021-243382
16. Zhang L, Zhao Q, Yuan F, Liu M. Lung cancer in patients with and without rheumatoid arthritis: A propensity score-matched survival analysis cohort study. *Thoracic Cancer* . 2020;11(6):1406-1413. doi:10.1111/1759-7714.13388
17. Ong SK, Li X, Chen T. More Than Knee Pain: A Case of Hypertrophic Osteoarthropathy Secondary to Lung Cancer. *Journal of Emergency Medicine* . 2020;59(5):e179-e181. doi:10.1016/j.jemermed.2020.04.028
18. Mellemkjær L, Linet MS, Gridley G, Frisch M, Møller H, Olsen JH. Rheumatoid arthritis and cancer risk. *European Journal of Cancer* . 1996;32(10):1753-1757. doi:10.1016/0959-8049(96)00210-9
19. Birch E, Jenkins D, Noble S. Treatment of painful hypertrophic osteoarthropathy associated with non-small cell lung cancer with octreotide: a case report and review of the literature. *BMJ Supportive & Palliative Care* . 2011;1(2):189-192. doi:10.1136/bmjspcare-2011-000052
20. Kanaji N, Watanabe N, Kita N, et al. Paraneoplastic syndromes associated with lung cancer. *World J Clin Oncol* . 2014;5(3):197-223. doi:10.5306/wjco.v5.i3.197

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