

CASE REPORT

Paraneoplastic syndrome of arthropathies as presenting sign for non-small cell lung cancer

Alexander Kyle Lee | Gurpreet Singh | Cleveland W. Lewis Jr

Division of Thoracic Surgery,
Department of Surgery, Garnet Health
Medical Center, Middletown, New
York, USA

Correspondence

Cleveland W. Lewis Jr, Division of
Thoracic Surgery, Department of
Surgery, Garnet Health Medical Center,
Middletown, NY, 707 East Main St.,
Middletown, NY, 10940, USA.
Email: clewis@garnethealth.org

Abstract

The aim of this study is to showcase an example of paraneoplastic syndrome, so other healthcare providers can be aware of early NSCLC manifestations. This is also important so providers do not dismiss review of symptoms that may not seem pertinent.

KEYWORDS

arthritis, migratory arthropathy, non-small cell lung cancer, paraneoplastic syndrome

1 | INTRODUCTION

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.

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 Moreover, deaths from lung and bronchus cancer accounts for 23% of all deaths related to cancer.² Lung cancer is split up into two broad categories: small-cell lung cancers and non-small cell lung cancers (NSCLS). NSCLS make up the majority of lung cancers and are comprised of adenocarcinomas, squamous cell cancers and large cell cancers.³ Presentations of NSCLS range from a peripheral nodule, a central mass, or even to a widely disseminated disease.³ In general, lung cancers are sometimes easily visualized when incidentally found on imaging, but other cases present more subtly. For example, lung cancers may initially present as paraneoplastic syndrome with a wide variety of pathologies:

squamous cell carcinoma presents as hypercalcemia; small cell as SIADH; and large cell as gynecomastia. The most common manifestation of paraneoplastic syndrome in NSCLS is connective tissue clubbing and hypertrophic osteoarthropathy (HOA).⁴

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. 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. The patient was later found to have adenocarcinoma.⁵ Another study by Cantini and associates retrospectively analyzed patients with isolated knee monoarthritis as the initial presenting sign.⁶ The study eventually found that 5 out of 296 patients with isolated knee monoarthritis were found to have NSCLC.⁶ The conclusion that HOA is associated with NSCLS was again demonstrated in a 2020 case report involving monoarthritis in the knee. Interestingly, this particular article showed that monoarthritis could spread to other joints.⁷ The possibility of monoarthritic

This is an open access article under the terms of the [Creative Commons Attribution-NonCommercial-NoDerivs](https://creativecommons.org/licenses/by-nc-nd/4.0/) License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

© 2023 The Authors. *Clinical Case Reports* published by John Wiley & Sons Ltd.

spreading emphasizes the importance of monitoring arthropathies as a presenting symptom of NSCLC and should not be mistaken for typical osteoarthritis.

2 | CASE PRESENTATION

This patient is a 56-year-old female who developed vague left knee pain, about 1 year prior to presentation at our office. She stated she was seen by an orthopedist a few months after the onset of her knee pain, and that her pain was determined to be osteoarthritis of the left knee. A few months after this diagnosis, the pain migrated to other sites, including her right knee, right ankle, and left foot. A few weeks after the pain started in her foot, she presented to a local urgent care due to a developing 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 in her both knees, hands, feet and swelling of her fingers. She described the sensation in her hands and feet as pulsating and throbbing. Though the patient had a minimal past medical history, she did have a 55-pack year smoking history with cessation of tobacco products 2 years prior. The patient also reported vaping daily. While in urgent care, she received a COVID test (negative) and a CXR. 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 a 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.

The patient was then sent to thoracic surgery for pre-operative evaluation. Upon presentation to our clinic, the patient stated she was only taking ibuprofen for the left knee pain that started about a year ago. She also mentioned that since the time of the urgent care visit, she noticed progressive swelling in her phalanges and metacarpal bones bilaterally. She said that this swelling developed concurrently with nonproductive cough.

After appropriate clearances, the patient underwent a flexible bronchoscopy, right posterolateral thoracotomy with a right lower lobectomy with en bloc chest



FIGURE 1 This image is an axial image on CT showing the large 7.3 × 8.3 cm right lower lobe pulmonary mass. This image was done 13 days prior to the patients surgery, as part of the pre-operative work up.

wall resection of posterior ribs 7–8, and a mediastinal lymph node dissection. She was discharged on post-op day 4 without complications and was seen again in the clinic for a 1 week follow up. 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 follow-up surveillance appointments according to the NCCN guidelines. Her 6-month follow-up PET-CT showed no evidence of active neoplastic disease (Figure 2).

3 | DISCUSSION

Hypertrophic osteoarthropathy is a syndrome with several stages, most often starting with clubbing of fingers and progressing to other symptoms such as joint pain and periostosis.⁸ These symptoms can differ in severity from patient to patient, making the diagnosis of HOA challenging.⁸ There are several proposed theories on the pathogenesis of HOA, though 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.⁹ 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.⁹ Although the diagnosis is a clinical one, bone scintigraphy is a useful adjunctive for detection. Characteristic findings

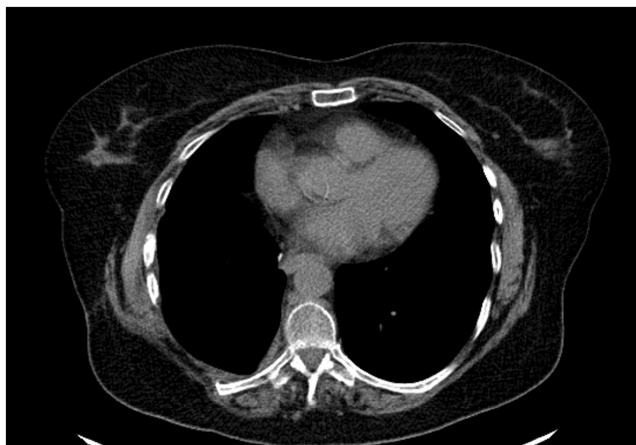


FIGURE 2 This is the CT scan at the 6 month post operative follow-up appointment. This image shows the post-surgical changes of the chest wall and shows the absence of the lung mass seen prior to surgery. In this scan the patient was also found to have no evidence of active neoplastic disease within the right lung.

on scintigraphy include bilateral increased uptake in long bones, with periostitis as the hallmark of hypertrophic pulmonary osteoarthropathy.¹⁰

Various treatments have been shown to provide relief in HPO include bisphosphonates¹¹ and octreotide.¹² One case was also treated with an EGFR inhibitor, gefitinib.¹³ 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. However, treatment with surgical resection of the primary tumor results in rapid long-term remission of symptoms.¹⁴ This was evident in our case with almost complete resolution of our patient's joint pain and swelling during her 1 week follow-up.

Since HOA can involve a multitude of organ systems, physicians should be especially aware of the signs of HOA. Many cases will solely manifest as clubbing in the fingers.⁸ However, as in the case of our patient, migratory arthritis may be the patient's chief complaint. In fact, both the presentation of arthritic pain in our patient's left knee prior to clubbing of her fingers and the length of time from onset of arthritis to respiratory symptoms were unusual. Our case report also shows that spreading monoarthritis may herald adenocarcinoma of the lung.

In summary, this unique patient presentation stresses the importance of consistently having lung cancer on the differential diagnosis in the setting of any symptom resembling HOA.

AUTHOR CONTRIBUTIONS

Alexander Kyle Lee: Conceptualization; data curation; formal analysis; investigation; methodology; writing

– original draft; writing – review and editing. **Gurpreet Singh:** Conceptualization; formal analysis; investigation; writing – review and editing. **Cleveland W. Lewis JR:** Conceptualization; data curation; investigation; project administration; resources; supervision; validation.

FUNDING INFORMATION

The authors have no source of funding to disclose and have no financial or proprietary interest in the subject matter of this article.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

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/dccp/research/update-on-cancer-deaths/index.htm>
3. Jameson JL, Fauci AS, Kasper DL, Hauser SL, Longo DL, Loscalzo J. Lung cancer. *Harrison's Manual of Medicine*. 20th ed. McGraw-Hill Education; 2020 Accessed August 25, 2022. <https://accessmedicine.mhmedical.com/content.aspx?aid=1167064169>
4. 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
5. Poddar K, Pathikonda L, Villamil M. Sudden onset polyarthritis as a paraneoplastic syndrome from non-small cell lung cancer. *J Community Hosp Intern Med Perspect*. 2020;10(2):174-178. doi:10.1080/20009666.2020.1749503
6. Cantini F, Niccoli L, Nannini C, et al. Isolated knee monoarthritis heralding resectable non-small-cell lung cancer. A paraneoplastic syndrome not previously described. *Ann Rheum Dis*. 2007;66(12):1672-1674. doi:10.1136/ard.2007.075333
7. Ong SK, Li X, Chen T. More than knee pain: a case of hypertrophic Osteoarthropathy secondary to lung cancer. *J Emerg Med*. 2020;59(5):e179-e181. doi:10.1016/j.jemermed.2020.04.028
8. Martínez-Lavin M. Hypertrophic osteoarthropathy. *Best Pract Res Clin Rheumatol*. 2020;34(3):101507. doi:10.1016/j.berh.2020.101507
9. Davis MC. Hypertrophic Osteoarthropathy as a clinical manifestation of lung cancer. 1969;15(5):561-563. doi:10.1188/11.CJON.561-563
10. Ito T, Goto K, Yoh K, et al. Hypertrophic pulmonary Osteoarthropathy as a paraneoplastic manifestation of lung

- cancer. *J Thorac Oncol*. 2010;5(7):976-980. doi:10.1097/JTO.0b013e3181dc1f3c
11. King MM, Nelson DA. Hypertrophic Osteoarthropathy effectively treated with Zoledronic acid. *Clin Lung Cancer*. 2008;9(3):179-182. doi:10.3816/CLC.2008.n.027
 12. 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
 13. 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.
 14. Albrecht S, Keller A. Postchemotherapeutic reversibility of hypertrophic Osteoarthropathy in a patient with bronchogenic adenocarcinoma. *Clin Nucl Med*. 2003;28(6):463-466. doi:10.1097/01.RLU.0000067504.35952.10

How to cite this article: Lee AK, Singh G, Lewis CW Jr. Paraneoplastic syndrome of arthropathies as presenting sign for non-small cell lung cancer. *Clin Case Rep*. 2023;11:e7204. doi:10.1002/ccr3.7204