

## CASE PRESENTATION

# Fracture femur as the first sign of lung adenocarcinoma, a case report

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### ABSTRACT

Lung adenocarcinoma is a leading cause of cancer-related mortality worldwide. Despite being predominantly linked to smoking, it also presents in non-smokers, necessitating diverse diagnostic and treatment strategies. Skeletal metastasis is a common complication, with the femur being a notable site. Here, we reported a 68-year-old non-smoking male presented with a fractured femur, which tended to be pathological due to metastasised lung adenocarcinoma. On presentation, the patient's main complaints were deteriorated pain in the right hip with minimal, if any, chest symptoms. X-ray of the hip showed a cortical defect in the neck of the right femur.

CT scan of the body showed skeletal destruction in the right hip joint with a pathological fracture in the right femur; in addition, we found a mass in the lower lobe of the right lung associated with hilar lymph node enlargement. A decision was made to replace the right head femur with an Austin Moore prosthesis. The histopathological examination of the excised head of the right femur revealed adenocarcinoma. Markers showed that the tumour originated from the lung with a positive EGFR mutation. Accordingly, the patient was treated with Afatinib, which led to the regression of the tumour and improvement of the quality of life. The case highlighted the importance of the molecular diagnosis of tumours in selecting the best treatment.

**Key words:** Lung adenocarcinoma, EGFR mutation, skeletal metastasis, targeted therapy, afatinib, non-smokers.

### INTRODUCTION

Lung cancer is the most prevalent cause of cancer-related deaths globally, accounting for the highest mortality rates among both men and women, with about 2.5 million new cases and 1.8 million mortalities each year.<sup>[1]</sup> In Sweden, the number of new cases of lung cancer in 2014–2018 was approximately 4,200 per year, of which nearly 52% were women with a median age at onset of 69 years.<sup>[2]</sup>

Lung cancer is a serious diagnosis that kills almost three times as many men as prostate cancer and almost three times as many women as breast cancer.<sup>[3]</sup> The condition is often discovered in late stages, but even in

earlier stages, patients have worse outcomes compared to other types of cancers. Even without spreading to other organs, during stage I, the survival rate of lung cancer is under 70%. In comparison, for example, breast cancer has a 95% survival rate in its early stages.<sup>[4]</sup> The expected relative 5-year survival after diagnosis is about 20% in Sweden; 17% in men; 24% in women.<sup>[5]</sup>

Smoking is the leading cause of lung cancer and is responsible for almost 85% of all cases. Other etiological factors like occupational exposure and heredity (hereditary TP53 mutations in adenocarcinoma of the lung) comprise the other 15% of cases.<sup>[6]</sup> Even in non-smokers, lung cancer is not rare, and it is

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considered a separate diagnosis; lung cancer in people who never smoked would still have constituted the 7<sup>th</sup> leading cause of cancer death in the world.<sup>[7]</sup>

Lung cancer can broadly be classified into two main groups:

- Small cell lung cancer (SCLC). The SCLC is one of the most aggressive and rapidly growing lung cancers, comprising 20% of all lung cancers.<sup>[8]</sup>
- Non-small cell lung cancer (NSCLC): It is the most common type of lung cancer and accounts for about 80% of all lung cancers. NSCLC can be divided into three main types: adenocarcinoma, squamous cell carcinoma, and large cell carcinoma.

Metastasis in adenocarcinoma of the lung occurs mainly in CNS, approximately 70% of cases. Leptomeningeal carcinomatosis mainly occurs in relapses of adenocarcinoma with EGFR mutation. Other metastases also occur in the liver and adrenal glands. Skeletal metastasis occurs in approximately 25% of patients, with the most common locations being vertebrae (70%), pelvis (40%) and femur (25%).<sup>[9]</sup> The majority are osteolytic, but osteoblastic metastases occur. In rare cases, monoarticular arthritis with metastasis to the juxtaarticular bone, for example, knee and hip joints, is seen.

EGFR Activating EGFR mutations are detected in 10–15% of all patients with adenocarcinoma. Patients with activating mutations in EGFR should be offered treatment with an EGFR-TKI. There are currently five preparations with this indication – gefitinib, erlotinib, afatinib, dacomitinib, and osimertinib. Gefitinib, erlotinib, and afatinib have been associated in randomised trials with longer progression-free survival (PFS) compared to conventional chemotherapy in previously untreated patients.<sup>[10, 11]</sup>

In the following case, we are presenting a known smoker man with adenocarcinoma of the lung who has skeletal metastasis presented as a fractured head of the right femur. He has an EGFR-positive mutation and responded to the treatment with afatinib.

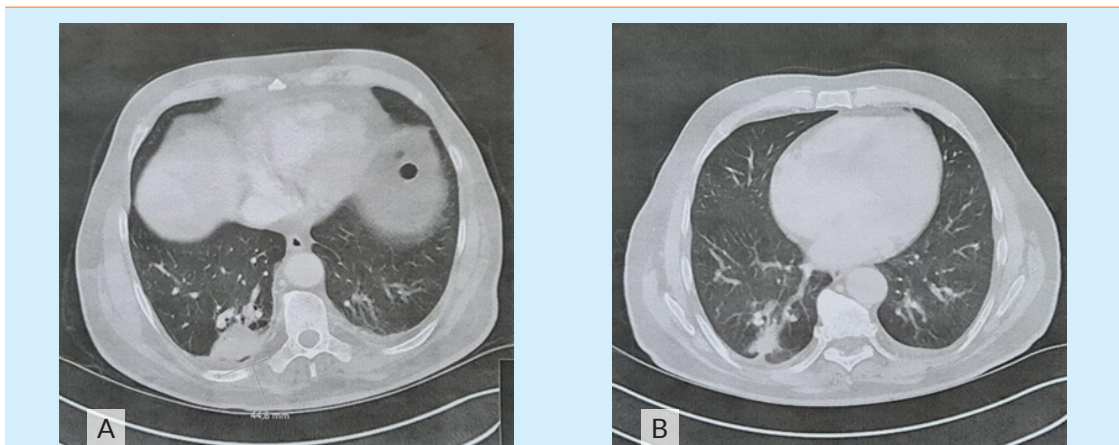
## CASE REPORT

A 68-year-old man presented to the emergency department of a local hospital in Sweden on 20/10/2022, complaining of worsening pain in the right hip, which began in April 2022. He also reported difficulty holding his urine, with no significant respiratory symptoms. The man, originally from Syria, resides in Sweden with his wife and son. He is a non-smoker and previously worked as a principal. Despite being relatively healthy, he has high blood pressure for which he regularly takes medication.

Upon examination, a swelling was noted in the right testicle. Initially, osteoarthritis was suspected, and he underwent investigations at the primary healthcare centre. An X-ray in September revealed a cortical defect in the right neck of the femur. Laboratory tests showed elevated levels of prostatic specific antigen (PSA) and alkaline phosphatase (ALP). Subsequently, a CT scan of the abdomen and thorax was ordered, and he was referred to a urologist for a transrectal ultrasound (TRUS). The urologist suggested that non-urinary problems might explain the patient's complaints without necessitating further investigations of the genito-urinary system.

Upon arrival at the emergency department, the patient complained of exacerbated pain in his hip, which had hindered his sleep for the past two days. He described difficulty lying down and standing up. Initial examination did not reveal redness or significant swelling in the right hip area, but severe tenderness was elicited upon palpation of the hip and pelvis. The neurological assessment indicated no motor or sensory impairment in the upper and lower extremities, with negative Hoffmann and bilateral Babinski tests. There was a slightly increased biceps reflex and no loss of sensation in the buttocks area.

The CT scan report at the time indicated skeletal destruction in the right hip joint with a pathological fracture, along with further destruction in the right pelvic bone and C7 to T2 vertebrae. Suspicion of intraspinal spread



**Figure 1** | Thorax CT scan. A: Before Aftinib treatment showing 45 mm right side tumor on the right lower lobe with lung atelectasis. B: After Aftinib treatment showing tumor regression.

on the right side of T1 was noted. Additionally, a tumour mass was evident in the lower lobe of the right lung, involving local and hilar lymph glands, suggesting a lung tumour with regional and distant metastases.

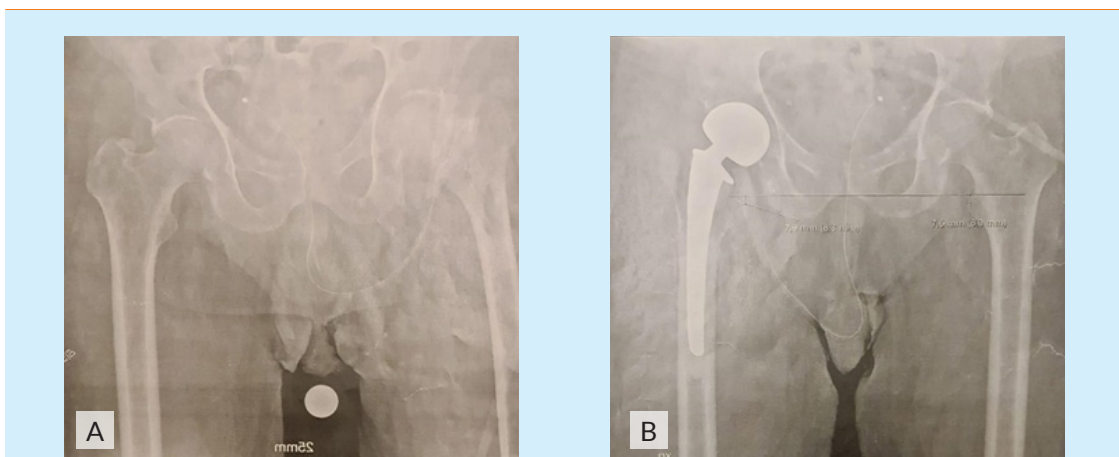
Initially, the patient was managed with opioid analgesia to alleviate hip pain. The following day, an orthopaedic surgeon examined him, ordered an MRI, and recommended a multidisciplinary meeting involving a urologist and a pulmonologist to discuss treatment options.

Mildly elevated PSA (4.8 µg/L) and ALP, CT findings of lymph nodes in the abdomen and pelvis, and the right testicular swelling suggested a genitourinary cause. However, the urologist decided that the inconsistent

PSA levels with benign-looking palpatory findings of the prostate and the cyst of the right testicle were enough to make prostatic cancer of a low suspicion and advised against further investigations in this regard.

A subsequent MRI proved lung cancer with metastases to the skeleton, specifically in the C7, T1, and T2 areas, fortunately, without a compression on the spinal cord.

In response to the patient's condition, the physiotherapist administered tunnelled epidural analgesia in the L2-L3 areas and initiated ropivacaine at a rate of 2mg/ml at 8ml/h. A urethral catheter was also inserted to assist the patient, who was unable to stand or walk without support, and to minimise the risk of further skeletal complications.



**Figure 2** | A: Hip X-ray shows the destruction of the femur head. B: After surgery. Partial hip replacement with Austin Moore.

The orthopaedic surgeon decided to remove the head of the right femur, sending it for histopathological examination and inserting an Austin Moore prosthesis. The surgery was successfully performed on 1/11/2022. The early post-operative days were uneventful, and the patient was discharged home ten days later. A few days before the surgery, the patient was seen by the oncologist, who examined the patient, reviewed his investigations, and advised post-operative palliative radiotherapy targeting C6 to T2, the right pelvic bone, and the right femur proximally, with a total dose of 25 Gy (5 Gy x 5).

The final Pathology report on 16/12/2022 indicated that the tumour is stage IVB lung adenocarcinoma, graded as T3 N2 M1c. The immunohistochemical examination revealed strong and diffuse positivity for CK7, CKMNF, and TTF1 in the tumour cells, while NKX3.1, p40, and PAX8 were negative, suggesting adenocarcinoma of the lung. A liquid biopsy of the head femur was not conducted due to detecting an EGFR exon 19 deletion mutation.

Based on the pathology reports, the pulmonologist initiated treatment with Afatinib 40 mg x 1, which started on 4/1/2023, and followed radiologically and laboratory tests for treatment evaluation.

During the follow-up appointment on 9/3/2023, the pulmonologist observed significant improvement in the patient's post-operative hip pain and leg swelling, allowing the patient to stand without support. Opioid use has been stopped, and the patient is now consistently taking Paracetamol. The treatment side effects, like dryness of the skin and mucous membranes of the nose and lips, as well as diarrhoea, were reported and treated symptomatically with skin emollient, nasal oil and loperamide, respectively. Due to effective moisturising, there were no signs of mouth blisters or infection. The urinary catheter, which was initially used for immobilisation management and later due to post-operative urine retention, was no longer required. The patient appeared to tolerate the treatment well and did not exhibit any pulmonary symptoms. It

was decided to continue with the current dose of Afatinib at this stage.

The thorax and abdomen CT scan was done in February 2023 and showed partial regression of the 45 mm primary tumour and known metastases, with no new metastases observed (figure 1). Subsequent radiological follow-up on 21/7/2023 revealed that the known tumour in the dorsal right lower lobe measured 14 mm compared to 17 mm in the previous examination. Otherwise, there were no changes in status. The next CT evaluation is scheduled for October 2023.

## DISCUSSION

Adenocarcinoma of the lung is a particularly aggressive form of cancer that requires specialised attention from primary healthcare providers. Detecting this condition early is crucial as it significantly increases the chances of patient survival. While smoking is the primary cause of lung cancer, it is important to note that this condition can also develop in non-smokers.

It is widely recognised that smoking constitutes the primary risk factor for lung cancer. Compared with non-smokers, smokers have as much as a 30-fold increased risk of developing cancer.<sup>[12]</sup> However, it's crucial to acknowledge that non-smokers are not immune to this devastating disease. Worldwide, 15–20 per cent of men and 50 % of women with lung cancer are non-smokers.<sup>[13]</sup> According to the American Cancer Society, as many as 20 per cent of people in the United States who died from lung cancer in 2018 never smoked.<sup>[14]</sup>

In the United States, roughly 19 per cent of women, compared to 9 % of men with lung cancer, were non-smokers.<sup>[15]</sup> It has been suggested earlier that lung cancer in non-smokers tends to occur in younger age groups compared to smokers. However, Several studies have shown that increasing age is a common predisposing factor for lung cancer in non-smokers.<sup>[16,17]</sup> The mean age at diagnosis for smokers and non-smokers patients with lung cancer is in the late 60s and above.<sup>[16]</sup> Our patient is a 68-year-old non-smoker

man who presented to the health care centre complaining of hip pain for more than seven months duration. The non-specific symptoms caused this delay in the presentation, and this is consistent with the literature, which states that 62 % of non-smokers present with stage IV lung cancer compared to 49 % of smokers.<sup>[16]</sup> This relative delay in the presentation on non-smokers might be due to the false belief among the patients and physicians that non-smokers do not get lung cancer.

The first presenting symptom in our patients was right hip pain due to a fractured neck femur, which tends to be due to metastasis from primary lung cancer without significant pulmonary symptoms. Rarely, the initial symptoms of lung cancer presented as fractures caused by skeletal metastases.<sup>[18,19]</sup> The absence of respiratory symptoms in our patient might add to the delay in the presentation.

The pathological diagnosis was adenocarcinoma. Adenocarcinoma is the most common type of lung cancer in smokers and non-smokers alike. However, it is reported in 93 % of lung cancer in non-smokers compared to 65 % in smokers.<sup>[16]</sup>

Exposure to environmental substances or risk factors in a person with a susceptible genetic mutation might play a significant role in the development of lung cancer in non-smokers. These risk factors are radon exposure, second-hand smoke, cancer-causing agents at work like prolonged and repeated exposure to asbestos, heavy metals, diesel exhaust, and air pollution. Our patient, who is originally from Syria, may be subjected to many exposures like air pollution, diesel exhaust, and second-hand smoke. Although the patient did not report a similar condition in his family, the immunohistochemical test suggested being positive for epidermal growth factor receptor (EGFR). Many specific germline mutations have been identified in families with high rates of lung cancer in non-smokers. The most prominent is the germline mutation in the epidermal growth factor receptor (EGFR).<sup>[20]</sup> The EGFR gene mutation is the most common oncogenic driver in NSCLC, reported in 30%–

50% of Asian patients compared to 10-15 % of Caucasians.<sup>[21]</sup> EGFR is linked to lung cancer in non-smokers; it is found in 36 % of non-smokers compared to only 8 % of smokers.<sup>[16]</sup>

Special immunohistochemistry and molecular diagnosis of cancerous tissue is essential for rapid diagnosis, precluding more invasive procedures and guiding therapy. Our patient's special immunohistochemistry and molecular test saved him from another operation to get lung tissue for the diagnosis. In addition, positive EGFR guided the decision to use Afatinib, an EGFR tyrosine kinase therapy. Our patient was treated by surgical excision of the head of the right femur with an Austine Moore prosthesis in addition to radiotherapy for skeletal metastasis and afatinib. On follow-up, the patient improved clinically with a significant reduction in the tumour size and prevention of having new lesions. The patient tolerated the treatment well and developed minor symptoms like dryness of the skin and mucous membranes of the nose and lips, in addition to diarrhoea, which were treated symptomatically. Epidermal growth factor receptor (EGFR) mutation status can be used as a predictive factor for the efficacy of EGFR tyrosine kinase inhibitor as the first-line treatment among patients with metastatic NSCLC [22]. Patients with Ex19del have significantly better outcomes in terms of response and survival rates.<sup>[23]</sup> These results highlight the importance of personalised and targeted therapies in treating adenocarcinoma of the lung.

## CONCLUSION

Lung cancer is a common tumour in both sexes. Although smoking is the major risk factor for its development, non-smokers could also be affected. It is not uncommon to have a patient present with the symptoms of secondary metastasis without significant and noticeable respiratory symptoms. Immunohistochemistry and molecular diagnosis are needed not only for diagnosis but also for guiding therapy of lung cancer.

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**Abbreviations list:** Alkaline phosphatase (ALP), Central nervous system (CNS), Cervical (C), Computerized tomography (CT), Epidermal growth factor receptor (EGFR), Magnetic Resonance Image (MRI), Non-small cell lung cancer (NSCLC), Progression-free survival (PFS), Prostatic specific antigen (PSA), Small cell lung cancer (SCLC), Thoracic (T), Transrectal ultrasound (TRUS).

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