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CASE REPORT

Low-dose Osimertinib in an elderly with EGFR-mutant Metastatic Lung Adenocarcinoma: A case report and literature review

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ABSTRACT

Introduction: Lung cancer is the leading cause of cancer-related mortality worldwide with peak mortality rate occurring in patients aged 80 years and above. While NSCLC are often diagnosed at advanced stage when treatment options are few, access to treatment in elderly are even more limited due to treatment tolerability and potential toxicity. At present, Osimertinib is the first line treatment option for patients with metastatic NSCLC with EGFR mutations. Some adverse reactions are diarrhea, nausea, headaches, stomatitis, and rashes that lead to interruption or even stopping of the medication.
Case Presentation: Here we present a case about an 89-year-old female with smoking history of 20 pack-years who initially presented at the emergency room with progressive shortness of breath. Chest radiograph showed right pleural effusion for which pigtail was inserted. Bronchoscopy revealed a completely obstructing mass at the right upper lobe. Her biopsy showed EGFR-mutated non-small cell lung adenocarcinoma. Patient underwent radiotherapy and was started on osimertinib 80mg daily. However, patient developed severe diarrhea for which her subsequent dosing was reduced to 40mg once daily. Repeat PET CT scan after 10 months showed significant reduction of the primary mass.
Conclusion: In patients with metastatic EGFR-mutated lung adenocarcinoma, Osimertinib proves to be an effective option and is associated with improved overall survival even on a low-dose. This dose reduction strategy may be an option especially for elderly patients with tolerability issues. Nonetheless, treatment choices should prioritize patients' functional status and comorbidities over age, underscoring the importance of personalized approaches despite chemotherapy's inherent risks.

Introduction

Lung cancer is the second most diagnosed cancer in both men and women; however, it is the most common cause of cancer death, leading to more deaths in 2020 than breast, colorectal, and prostate cancers combined. Although most lung cancers are caused by cigarette smoking (80%) [1], the burden among people without a smoking history is still significant, ranking among the top 10 causes of cancer death when categorized separately[2].

As of January 1, 2022, there were 654,620 patients in the United States with a known history of lung cancer [3], majority of which have metastatic disease [4]. Around 80% were 65 years of age or older, which is congruent with the advanced median age of diagnosis at 71 years [5]. More than half (55%) of lung cancer survivors were diagnosed within the past 5 years because of the low survival [3].

Consistent with global data, lung cancer is also considered the second leading cause of mortality and the leading cause of cancer-attributable mortality in the Philippines [6].

Elderly individuals diagnosed with advanced-stage lung cancer confront a substantially higher mortality risk, 28% greater than their younger counterparts, primarily due to the undertreatment of patients who might have otherwise responded well. This elevated risk stems from older patients receiving less cancer treatment, despite their comparable performance status and health conditions to younger patients [27].

Osimertinib, a mono-aniline-pyrimidine compound, selectively binds to the EGFR kinase domain irreversibly. It achieves this by targeting the cysteine-797 residue within the ATP binding site, forming a covalent bond [7]. Preclinical information from various sources and phase 1 clinical findings from the AURA trial indicate that osimertinib might also serve as a viable initial treatment option for individuals with advanced NSCLC who harbor EGFR mutations [7,26]. The frequently observed adverse events of any grade included diarrhea (47%), rash (40%), nausea (22%), and decreased appetite (21%). Notably, diarrhea and rash tended to occur more often and with greater severity at doses of 160 and 240 mg, likely due to the inhibition of wild-type EGFR[31].

In elderly (age >65), when evaluating EGFR tyrosine kinase inhibitors, first-generation agents such as erlotinib and gefitinib are generally administered at full doses. In contrast, afatinib, a second-generation TKI, often requires dosage adjustments in older patients due to tolerability concerns. Osimertinib, a third-generation TKI at a daily dose of 80 mg, is considered the most appropriate treatment for older individuals with EGFR mutations (like exon 19 deletion or L858R mutation) and is also an effective second-line therapy for those who develop the T790M resistance mutation [32].

To evaluate the effectiveness of low-dose Osimertinib in EGFR-mutant lung adenocarcinoma and underscore the significance of multidisciplinary care for elderly lung cancer patients, we present a case involving malignant pleural effusion stemming from stage IV EGFR-mutant lung adenocarcinoma, which manifested as breathing difficulties.

Case Presentation

Clinical Features

We present a case involving an 89-year-old Filipino female diagnosed with stage IV NSCLC with EGFR amplification with exon 21 (L858r mutation) in April 2023. Initially, she presented with breathing difficulties, a dry cough, occasional oxygen desaturation, and right scapula pain during inspiration. The patient is confined to bed for more than 50% of waking hours, can communicate, and can eat orally without issues (ECOG PS 3).

She has been managing hypertension effectively with medication for a decade and has a history of atherosclerotic cardiovascular disease, not known

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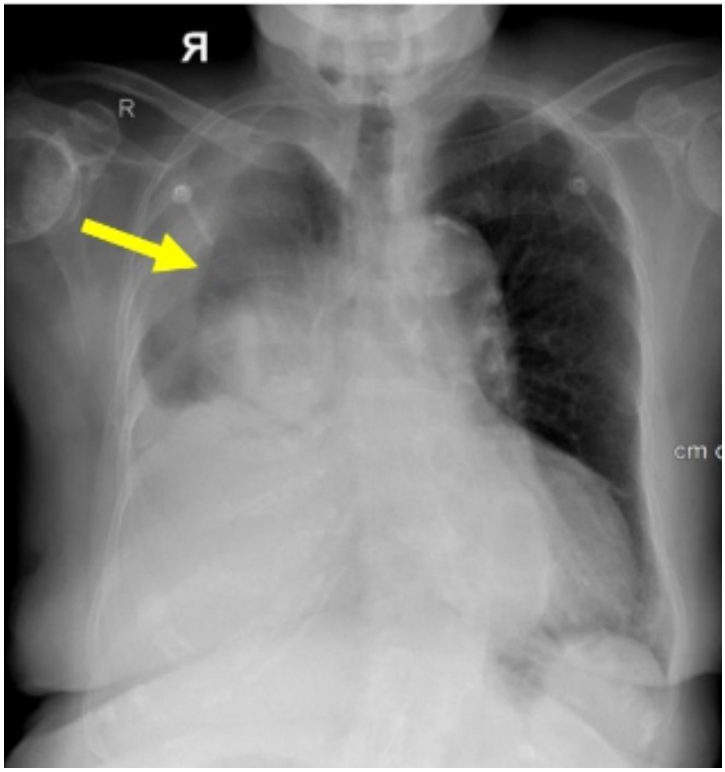

Figure 1. The chest radiograph shows homogeneous opacification of the lower half of the right hemithorax, obliterating the right costophrenic angle and hemidiaphragm. There is a suspicious convex opacity in the right hilar area (pointed) and the left lung shows no active parenchymal opacities.

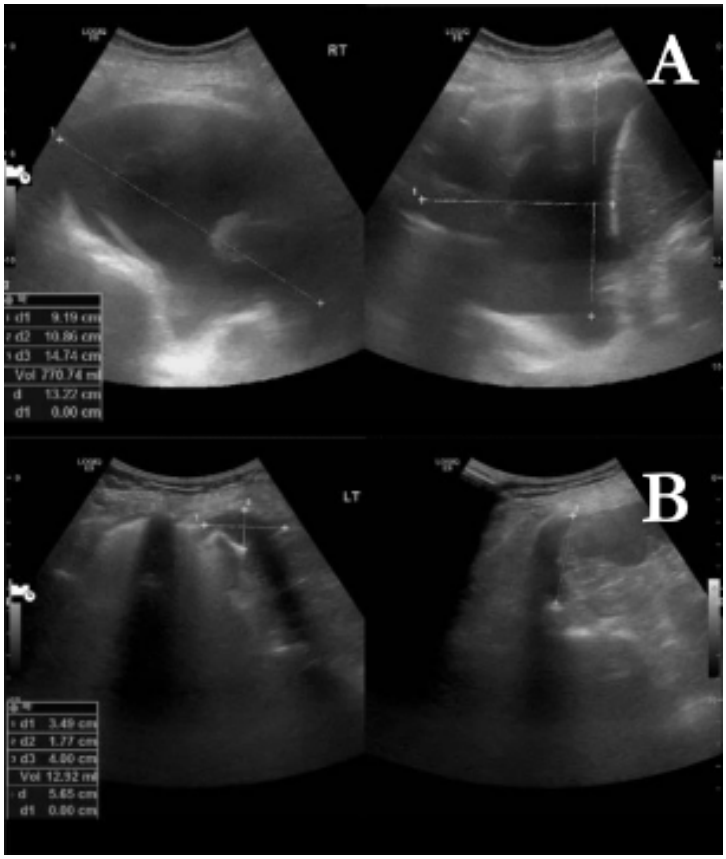

Figure 2. Chest ultrasound shows free fluid on the right (A) amounting to 771 mL and 13 mL on the left (B). Atelectatic segments are seen in the right hemithorax

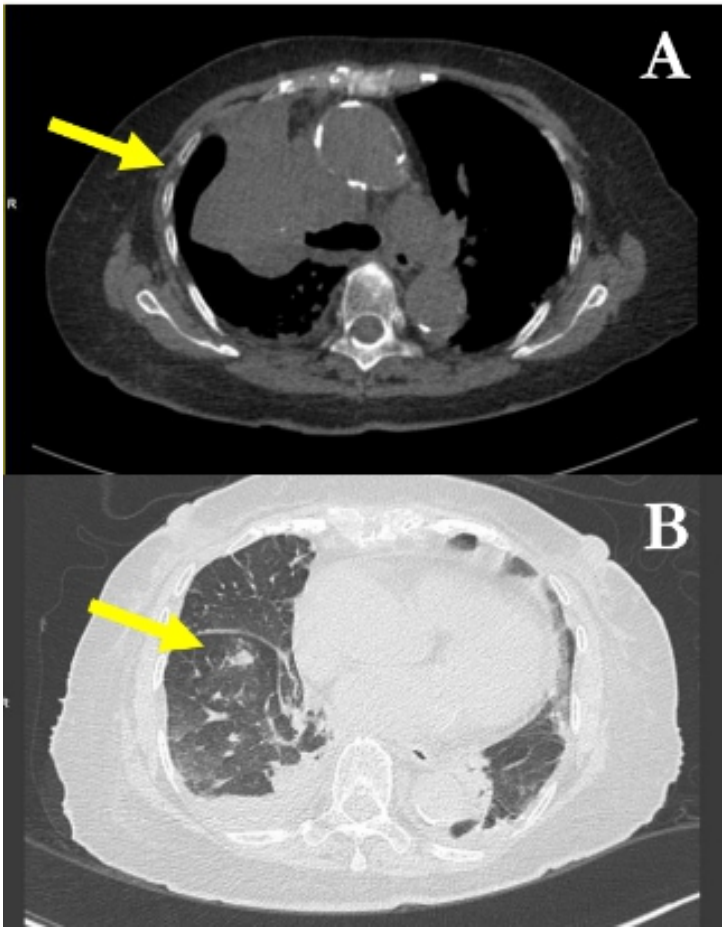

Figure 3. Plain chest CT scan shows complete atelectasis of the right upper lobe (pointed by the yellow arrow in Figure A). Few ground-glass opacities are seen scattered in the visualized right lung parenchyma. Few non-calcified nodules are appreciated in the right lung with the largest located in the anteromedial segment of the lower lobe, measuring 0.8 cm (pointed by yellow arrow in Figure B).

to have CKD. Additionally, she is a known diabetic with well-controlled blood sugar levels. The patient also has a history of degenerative osteoarthritis in both hip joints, managed with pain relief medication. Although she was a smoker with a 20-pack-year history, she quit more than five decades ago. The patient displayed no additional risk factors for lung cancer, such as exposure to asbestos, radiation, or other potential hazards.

Diagnostic Approaches

Initial Chest radiograph showed pleural effusion on the right and a note of a convex opacity in the right hilar area which may be a mass lesion or may be due to consolidation (Figure 1).

Chest ultrasound showed right pleural effusion with passive atelectasis and trace pleural effusion on the left (Figure 2). Initial 2D echocardiography showed normal left ventricular dimensions with segmental wall motion abnormality and an ejection fraction of 50%.

Ultrasound-guided pigtail insertion of the right pleura was done, draining 750 mL which was noted to be tea colored. Based on Light's criteria, the pleural fluid was exudative. Pleural fluid also tested negative for TB GeneXpert and did not show the presence of microorganisms in Gram staining.

A plain CT scan of the chest was done which showed complete atelectasis of the right upper lobe, and minimal pleural effusion, bilateral. (Figure 3).

The patient underwent flexible bronchoscopy which showed a completely obstructing mass at the right endobronchial area, upper lobe (Figure 4). A biopsy followed by thallium laser ablation of the right endobronchial mass was done.

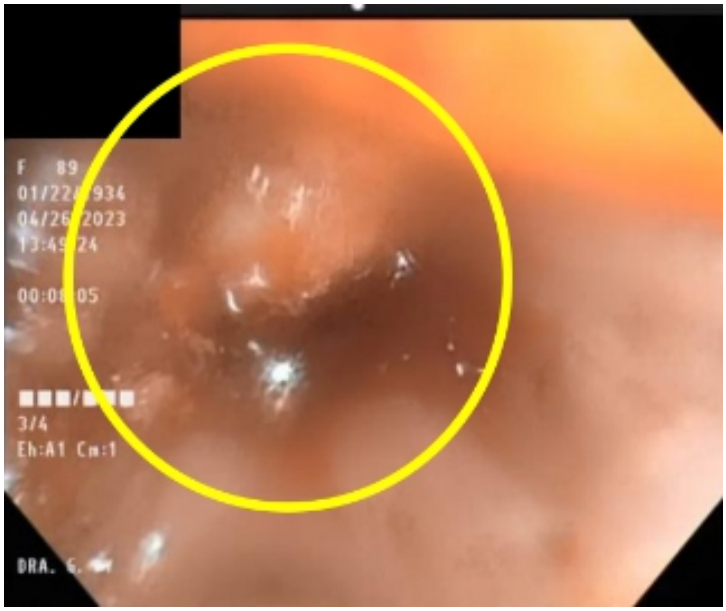

Figure 4. Bronchoscopy showed a mass (encircled) completely obstructing the right endobronchial area on the upper lobe. Specimen taken with biopsy forceps for histopathology, followed by thallium ablation. Bronchial washing was also obtained and sent for cytologic analysis.

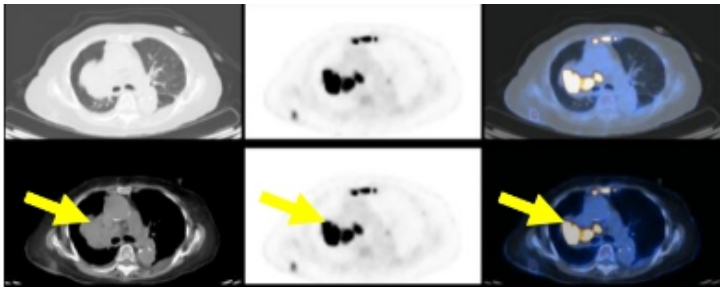

Figure 5. The right upper lobe bronchus is obstructed with resultant atelectasis of the right upper lung. Furthermore, the inferior border of the atelectasis appears lobulated with multiple foci of increased FDG activity (pointed by yellow arrow).

A PET scan was also done showing a malignant neoplastic process of undetermined primary origin. Furthermore, the right upper lobe was atelectatic with hypermetabolic activity and lobulated margins, which may relate to a mass lesion obstructing the right upper lobe bronchus (Figure 5). There were also hypermetabolic findings which may likely represent metastases such as a right lung apex nodule with lytic changes in the adjacent osseous structures. The scan also shows findings that may represent a malignant neoplastic process on the right upper lobe with multiple metastases on the liver, bones, and adrenal glands.

The patient was then referred to Radiation Oncology service and was given 10 fractions of Radiotherapy (3100 cGy to lung mass and 3000 cGy to right hip) for the bronchial obstruction. Histopathology results showed findings of pulmonary adenocarcinoma.

Outcome and Follow-up

Additional immunohistochemical staining was then requested as summarized in Table 1. The patient was then diagnosed with NSCLC Stage IV and started on Osimertinib.

Table 1. Summary of Immunohistochemical Staining Results

Cytokeratin	Positive
TTF-1	Positive
Napsin A	Positive
EGFR L858r	Positive
Ki-67	>30%
PD-L1	80%
Cytokeratin 20	Negative
CDX2	Negative
p40	Negative

During the initial treatment phase, the patient received the standard dosage of Osimertinib (80 mg per tablet), and after 3 months of treatment experienced intolerance due to diarrhea. Consequently, the dosage was halved (40 mg per tablet), which was the dose adjustment set based on expert opinion, which the patient could tolerate up to this date. Currently, it has been eleven (11) months since the patient's diagnosis. During this time, the Pigtail drain was removed, however, there was a recurrence of effusion of approximately <200ml (Figure 6), which is currently under observation. A recent 2D echo with Doppler scan revealed no change from the baseline. Subsequent follow-up PET/CT scan 10 months after starting Osimertinib demonstrated a partial response, evidenced by regression in size and metabolic activity of the primary right upper lobe mass, as well as metabolic resolution of the unenlarged mediastinal lymph nodes, with no new hypermetabolic focus detected elsewhere (Figure 7). Clinically, the patient has shown significant improvement in symptoms and quality of life, transitioning from being mostly bedbound to being able to walk with assistance and being able to do some activities of daily living.

Discussion

Dose reduction for Osimertinib

In previous studies, treatment with first and second-generation EGFR tyrosine kinase inhibitors (TKI) has been shown to improve progression-free survival (PFS) compared with chemotherapy in previously untreated patients with EGFR-mutated advanced non-small-cell lung carcinoma; however, the PFS benefits have not translated to benefits in overall survival (OS) [8-10].

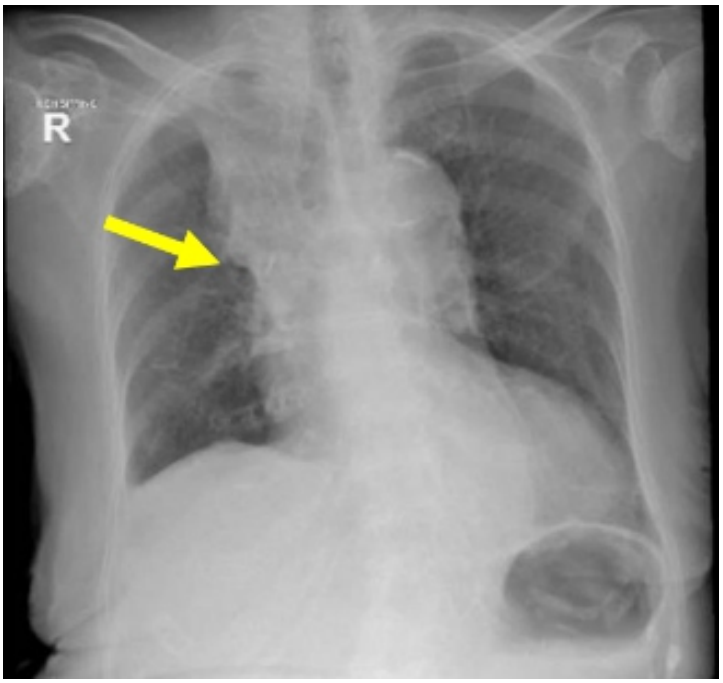

Figure 6. Repeat chest radiograph post-treatment, on follow-up, shows a significant decrease in the right pleural effusion with decreased haziness in the right upper lobe (pointed).

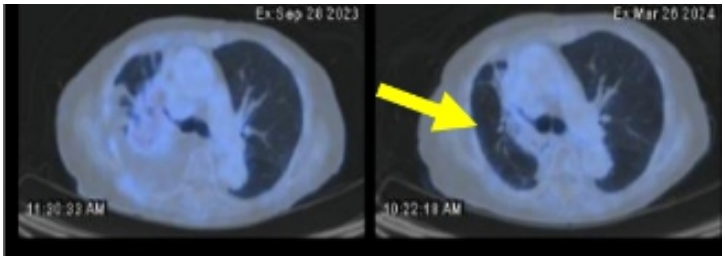

Figure 7. The latest PET-CT scan noted a further decrease in size and FDG uptake of the lobulated soft tissue mass in the right upper lobe now measuring approximately 1.8 x 3.0 cm (previously 3.5 x 3.1 cm) 10 months since starting treatment. (pointed)

In the global phase III FLAURA study, Osimertinib demonstrated significantly longer PFS than comparator EGFR TKIs such as erlotinib or gefitinib, in the first-line treatment of patients with EGFR-mutated advanced non-small-cell lung carcinoma with a median PFS of 18.9 versus 10.2 months [11]. A final OS analysis in FLAURA also demonstrated significantly longer OS with osimertinib than with comparator EGFR TKI [12].

In patients with NSCLC, the two most found EGFR gene mutations are deletions in exon 19 (45% of patients with EGFR mutations) and a point mutation in exon 21 (L858R in 40%) [13]. Based on the NCCN guidelines, for EGFR mutations in NSCLC, the preferred treatment is Osimertinib [14]. with the standard dose at 80mg/tab 1 tab daily [15].

Targeted therapies are recommended for patients with metastatic NSCLC and specific oncogenic drivers, independent of PD-L1 levels. Patients with metastatic NSCLC and PD-L1 expression levels of 1% or more, such as in the case presented, should receive first-line targeted therapy since it yields higher response rates than immune checkpoint inhibitors (ICI) in the first-line setting. Furthermore, targeted therapy is better tolerated, and these patients are less likely to respond to single-agent ICIs [16].

Most patients with EGFR mutations and metastatic NSCLC typically have disease progression after about 9.7 to 13 months of therapy with erlotinib, gefitinib, or afatinib [17-18]. Data show that patients receiving Osimertinib as first-line therapy have PFS of about 19 months [19-20]

Despite its promising effects on PFS and OS, published literature has also reported cases of cardiac dysfunction using Osimertinib. The study by Kunimasa et al. describes the clinical features of patients developing cancer-therapeutics-related cardiac dysfunction while on treatment with Osimertinib. A total of 183 patients with advanced EFGR mutated NSCLC who received Osimertinib either in frontline or subsequent lines were retrospectively queried. Out of fifty-eight (58) patients, a total of eight (4.4 %) patients had a decrease in LVEF which meets the criteria for cancer-therapeutics-related cardiac dysfunction [21].

In another study by Patel, *et al.,* eleven (11) cases of Osimertinib-induced cardiomyopathy have been described. A review of the 7 patients who underwent follow-up echocardiography after drug cessation showed improvement in ejection fraction after cessation of Osimertinib in 6 patients. This indicates that cardiotoxicity from Osimertinib is likely reversible. Additionally, all reported cases with known dosing levels indicated the development of cardiac dysfunction at a dose of 80 mg of osimertinib [22-25]. In one of the cases presented, the patient was initially started on 40 mg of Osimertinib for 7 months, with no evidence of cardiac dysfunction. Four weeks after her dose was escalated to 80 mg/day, she presented with acute heart failure. Although dose reduction can potentially be considered to prevent initial or recurrent cardiotoxicity, the FLAURA clinical trial results, which guide the clinical use of Osimertinib, were based on therapy at 80 mg/day.

A study conducted by Hori, *et al.*, the median progression-free survival (PFS) was significantly longer in the group that received a reduced dose compared to the group that was given the standard dose of 40 mg/day. The study concluded that early dose reduction of osimertinib is an effective strategy for extending PFS in patients with EGFR-mutated NSCLC [33].

Role of treatment in elderly patients

Despite improvements in treating patients diagnosed with late-stage lung cancer, the overall prognosis remains bleak, with 5-year survival rates ranging from less than 5% to 23% [28]. The choice of treatment for elderly patients diagnosed with stage IV NSCLC should be determined by their functional status and comorbidities, rather than solely by age [29].

In a study by Pham, *et al.*, older patients with advanced-stage lung cancer face a significantly higher risk of mortality compared to younger patients. This increased risk is linked to the reduced administration of cancer treatments to older individuals, despite having similar performance status and comorbidities as their younger counterparts. A possible reason for the reduced prescription of cancer treatments for elderly patients is attributed to treatment nihilism. Clinicians, family members, or the patients themselves may view treatment at an advanced age as futile, particularly when faced with incurable illness and the substantial risk of treatment-related toxicity. A survey of clinicians caring for elderly lung cancer patients revealed that the stage of the disease was a significant determinant in treatment decisions. New evidence indicates that, despite the difficulties of late-stage lung cancer, modified treatment regimens designed specifically for the elderly for elderly patients can offer a more tolerable side-effect profile while still ensuring a survival advantage [27]. Tyrosine kinase inhibitors (TKIs) can be a valuable alternative or complement to chemotherapy. When compared directly with single-agent chemotherapy, TKIs showed comparable survival benefits while offering good tolerability in elderly patients [34].

Ahmed, *et al.,* conducted a study involving patients aged over 80 diagnosed with advanced NSCLC. Among them, only 29% underwent chemotherapy, and those who did experienced a median overall survival of 8 months, contrasting with 2 months for those who did not receive chemotherapy. Despite the evident advantages of chemotherapy, the percentage of patients aged 80 and above receiving this treatment remained unchanged over time [30].

Conclusion

Lung cancer remains the foremost cause of cancer-related deaths. Despite advancements in treating advanced-stage lung cancer, elderly patients often refrain from treatment due to their significantly higher mortality risk compared to younger individuals, as well as the considerable threat of treatment-related complications.

In the presented case, the patient initially experienced breathlessness, and imaging revealed a substantial pleural effusion on the right side, along with a convex opacity in the right hilar area suspected to be malignant. A PET scan confirmed distant metastases to the liver, bones, and adrenal glands. A bronchoscopy identified an endobronchial tumor, followed by a biopsy revealing an EGFR-mutated metastatic lung adenocarcinoma.

For patients with this histological profile, current management typically involves Osimertinib due to its demonstrated improvement in progression-free survival (PFS) and overall survival (OS). For elderly patients or those unable to tolerate the standard dose, dose reduction is a viable approach. This adjustment is expected to yield comparable outcomes while minimizing adverse effects. However, it's crucial to emphasize that treatment decisions should be based on the patient's functional status and comorbidities rather than solely on age, despite the potential risks associated with chemotherapy.

Timeline

See Appendix 1.

Informed Consent

Informed consent was obtained from patient prior to writing of the study. Strict anonymity is observed and maintained in this paper.

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Appendix 2

Case Report Timeline