

Cardiac toxicity of EGFR – 3rd generation TKI in patients with metastatic non-small cell lung cancer. Case report and literature data update

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Abstract

Purpose: The incidence of bronchopulmonary cancer has increased significantly in recent decades, especially in developed countries, and today it is the leading cause of death in men and the 3rd in women. The toxicities of tyrosine kinase inhibitor therapy are varied, with cardiac toxicities at the top of the pyramid. Because of the occurrence of these toxicities, depending on their intensity, the dose must be reduced or even treatment stopped.

Patient and method: We present the case of a 72-year-old patient, diagnosed in 2019 with non-small bronchopulmonary neoplasm with histology of adenocarcinoma with EGFR mutation, stage IV.

Results: In the oncology committee, it is decided to start targeted therapy with tyrosine kinase inhibitors of the first generation, Erlotinib, with a partial response to the treatment

in the imaging evaluations, continued treatment until November 2020 when the T790M resistance mutation is detected. According to the new NCCN guidelines, therapy with the third-generation EGFR-TKI, Osimertinib, is initiated. In September 2021, the patient developed a non-ischemic acute antero-septal myocardial infarction that was complicated by LV apical aneurysm and severe LV systolic dysfunction, associated with therapy with tyrosine kinase inhibitors. Osimertinib treatment is stopped and third-line treatment with Vinorelbine is initiated.

Conclusions: Investigation and permanent monitoring of patients, in treatment with 3rd generation tyrosine kinase inhibitors, who may develop cardiac toxicities, but also a good management of these toxicities, lead to both increased survival and improved status of performance.

Key words: non-small lung cancer, EGFR – TKI, cardiotoxicity

Introduction

With approximately 1.76 million deaths each year, bronchopulmonary cancer is the most common malignant tumor worldwide [1]. It is currently the 1st leading cause of cancer death in men and the 3rd leading cause of death in women, after breast and cervical cancer.

From the histopathological point of view, bronchopulmonary cancer is divided into two classes, namely small cell carcinoma (~20%) and non-small cell carcinoma. In turn, non-small cell carcinoma is subdivided into squamous cell carcinoma (~35%), adenocarcinoma (27-30%) and large cell carcinoma (10-15%) [2].

The origin of small cell carcinoma cells is from neuroendocrine cells (APUD cells), which often secrete polypeptide hormones. It has been observed that this type of cancer often develops centrally and metastasizes early [2].

Squamous cell carcinoma occasionally causes cavities with central necrosis. It spreads locally and metastasizes relatively late. Adenocarcinoma has an increased incidence, and it is possible that in the near future it will become the main subtype of bronchopulmonary cancer. It causes peripheral lesions on chest x-ray / CT and metastasizes relatively early. Large cell carcinoma is usually poorly differentiated and metastasizes relatively early [2].

Treatment strategies for patients with non-small lung cancer with genetic mutations have evolved relatively rapidly in recent years. Activating mutations in the EGFR kinase domain represent the most well-known example of oncological factors that can be the therapeutic target for various tyrosine kinase inhibitors [3].

Osimertinib is a third-generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) that has been shown to be highly effective in patients with non-small cell lung cancer with genetic mutations, including the T790M resistance mutation [4]. Although Osimertinib exhibits milder toxicities than other EGFR-TKIs such as Efetinib, Gefitinib, and Erlotinib, Osimertinib-induced cardiotoxicities are life-threatening in cancer survivors [5].

Next, we present the case of a patient with non-small cell bronchopulmonary cancer with genetic mutations, with acute antero-septal non-ischemic myocardial infarction associated with EGFR-TKI of the 3rd generation

Case report

A 72-year-old female patient from the urban environment, non-smoker and denies the consumption of alcoholic beverages, known to have total thyroidectomy, HBP, adherent to treatment, presents herself in March 2019 to the "Marius Nasta" Institute of Pneumoftisiology for dry cough, moderate dyspnea on exertion and fatigue started ~1 month ago, progressively aggravated. The patient also claims that, unintentionally, she lost ~10 kg in the last 2 months.

Computer tomograph with intravenous contrast is performed, which reveals a tumor in the left upper lobe, multiple tumors diffusely disseminated in both lung fields, pleural effusion in the left hemithorax and pericarditis.

Under general anesthesia, thoracoscopy is performed with multicentric biopsy of the parietal pleura, the histology result being non-small bronchopulmonary cancer – ADK with EGFR genetic mutation in exon 19 (Fig.3).

In the oncology committee, it is decided and therapy with tyrosine kinase inhibitors of the first generation is initiated – Erlotinib 150 mg, 1tb / day, continued treatment for one year and six months. Response to treatment is limited, according to imaging investigations (Fig. 1). One and a half years after starting the treatment, venous blood is taken in a Streck tube from which the resistance mutation T790M is detected. Treatment with EGFR-TKI generation I is interrupted and therapy with tyrosine kinase inhibitors of generation III is initiated - Osimertinib 80 mg, 1 tb / day, with a favorable response, documented by imaging (Fig. 2). One year after the initiation of therapy, the patient presented to the hospital for significant worsening of dyspnea and unsystematized chest pain. 2 weeks before presenting to the hospital, she is investigated by ultrasound of the heart, which reveals severe systolic dysfunction of the left ventricle through extensive contractility disorders with apical aneurysm of the left ventricle, ejection fraction = 25%, mitral regurgitation, pericardial fluid in a small amount and left pleural fluid in small quantity. From a biological paraclinical point of view, high values of total CK are correlated with high-sensitivity troponin that shows normal values, which is why an acute coronary syndrome is excluded. It is concluded that the cardiac pathology that occurred is associated with cardiotoxic EGFR-TKI treatment and it is recommended to stop it urgently.

After stopping the third-generation EGFR-TKI - Osimertinib, the patient is started on third-line treatment with Vinorelbine 20 mg, 1 tb / day.

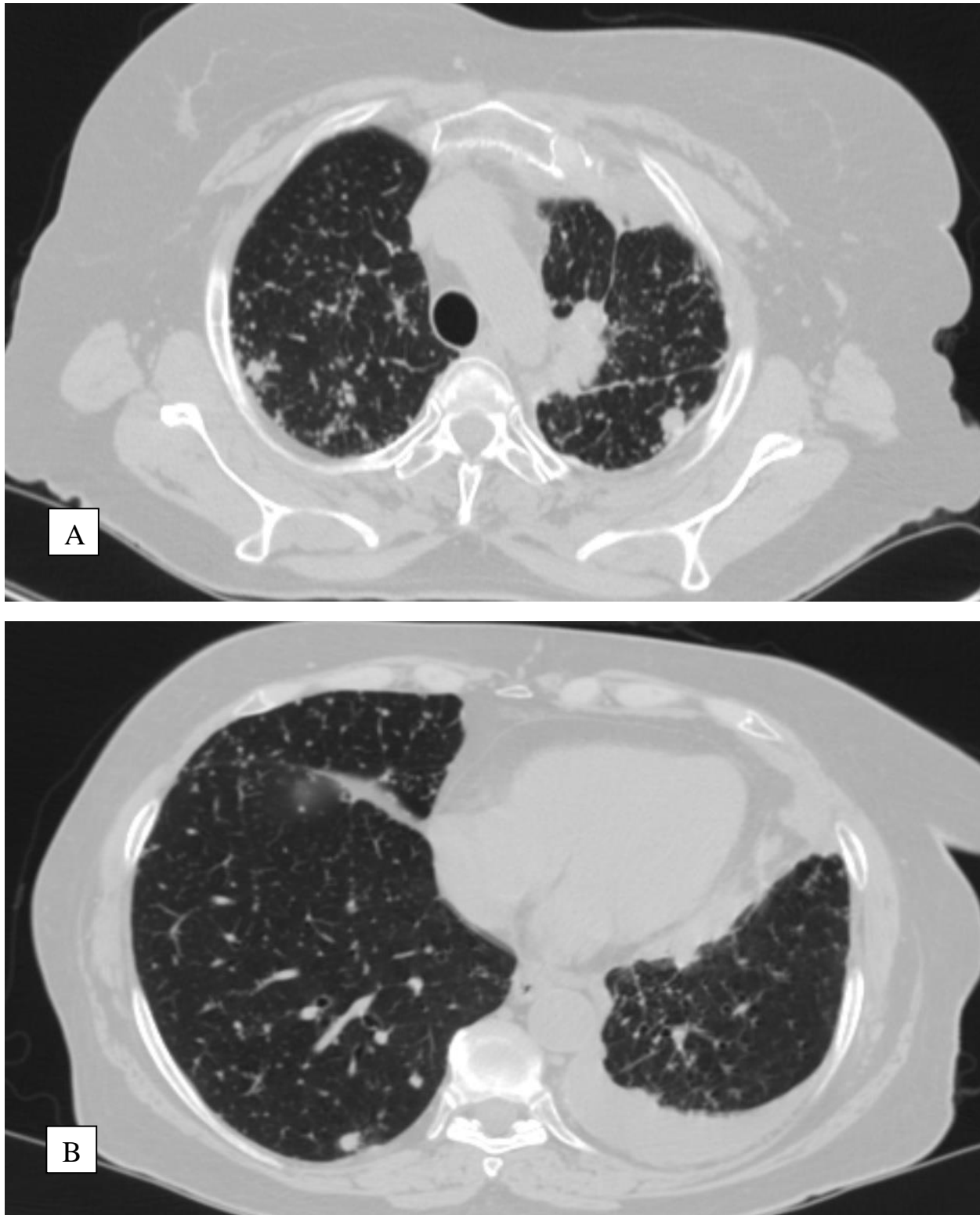


Figure 1: Chest CT with IVC – iodophilic tumor in LUL, multiple diffusely disseminated nodular lesions 1 year after EGFR-TKI gen. 1 – Erlotinib – limited response (A) – moderate left hemithoracic pleural effusion, pericarditis (B)

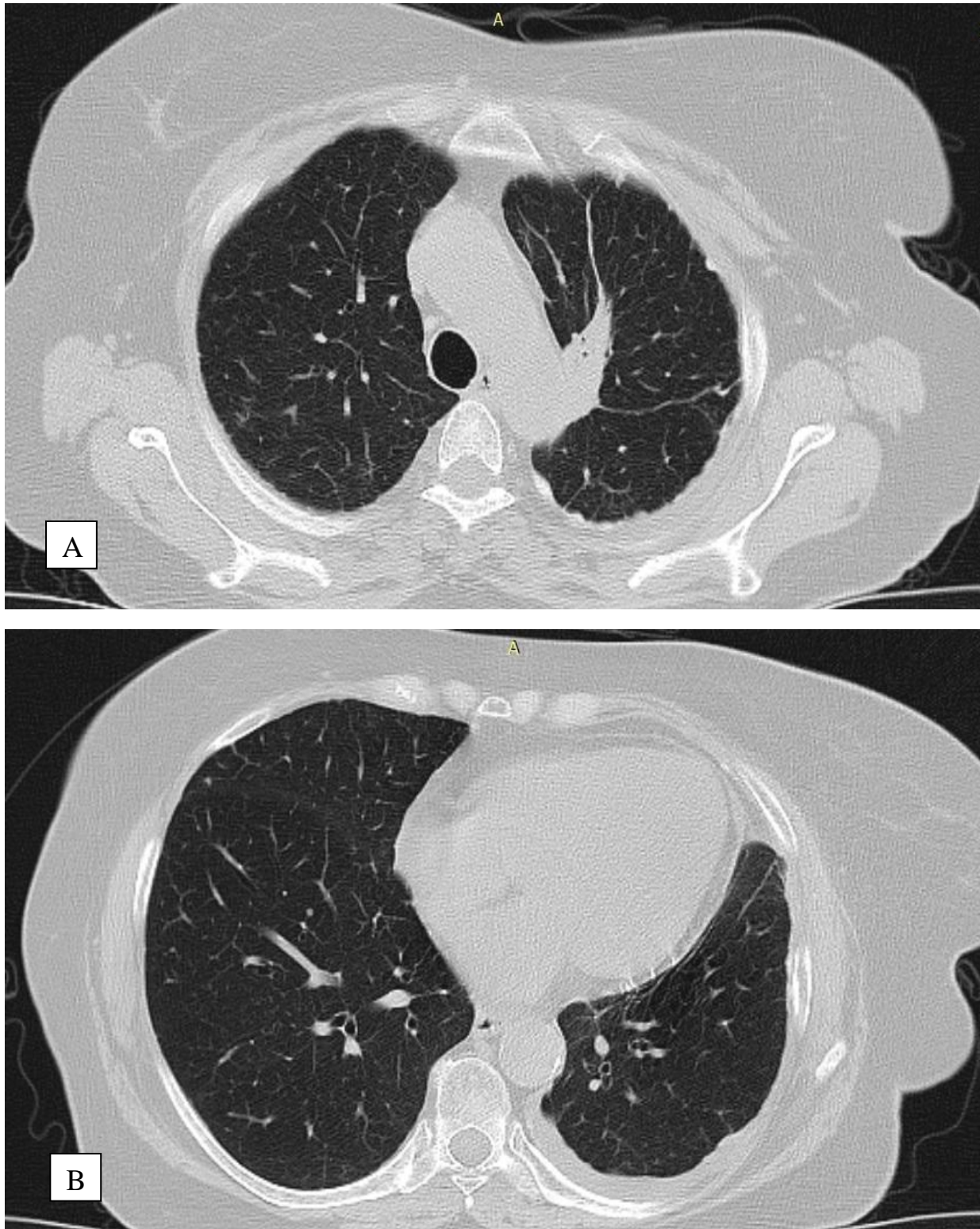


Figure 2: Chest CT with IVC – iodophilic tumor in LUL, multiple diffusely disseminated nodular lesions 1 year after EGFR-TKI gen. 3 – Osimertinib – favorable response (A), left hemithoracic pleural effusion in small amount, pericarditis (B)

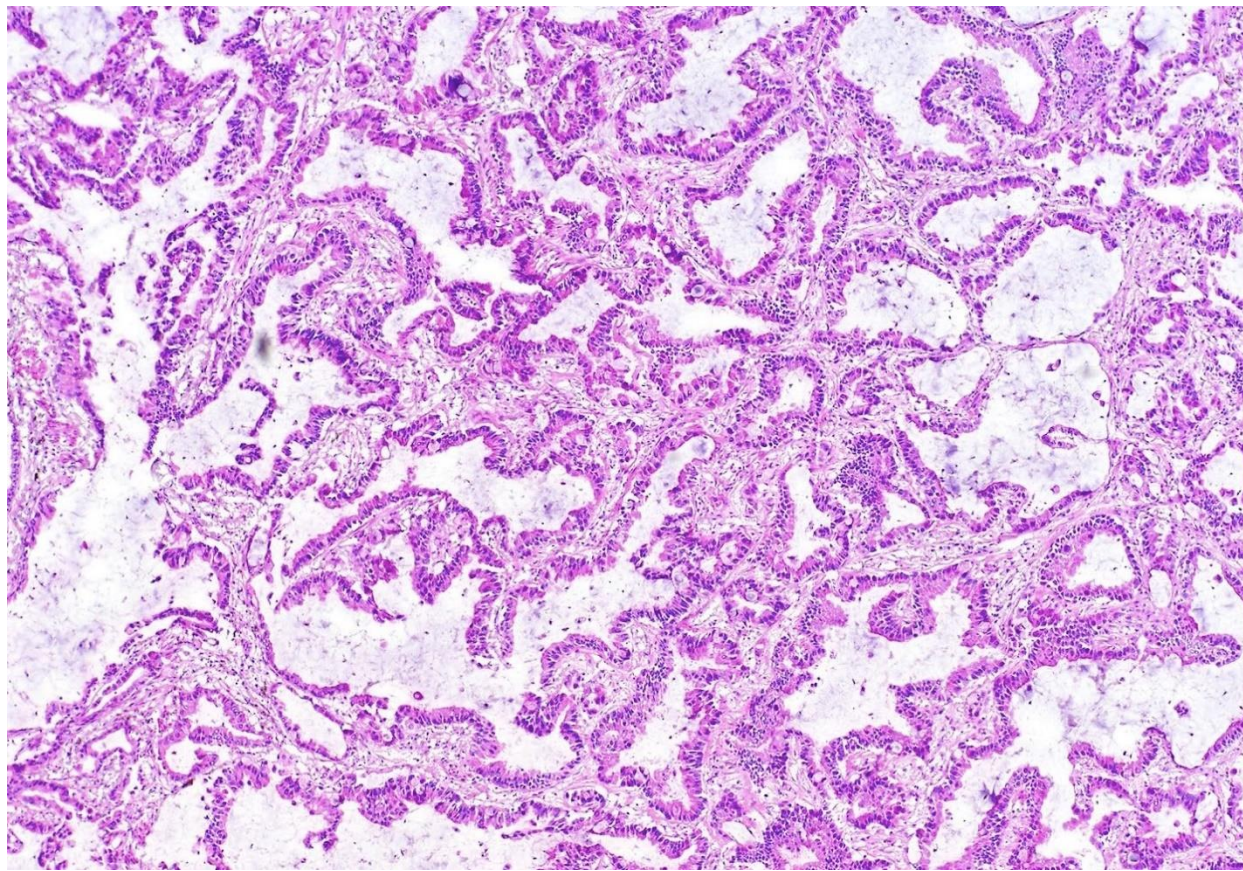


Figure 3: Fragment of parietal pleura – Acinar and papillary adenocarcinoma

Discussions

During the period between 2016 and 2018, 8450 adverse effects were reported, of which 3.7% were cardiotoxicities induced by EGFR-TKIs (osimertinib, erlotinib, afatinib and gefetinib) [7]. Reported cardiotoxicities include heart failure, atrial fibrillation, QT prolongation, myocardial infarction, and pericarditis. From the total of cardiotoxicities mentioned above, the frequency of reports following therapy with 3rd generation TKIs – Osimertinib, was higher than the frequency of reports following therapy with 1st and 2nd generation TKIs, namely 6.1% vs. 2.1%. [7]. Osimertinib also reported an increased incidence of heart failure compared to other TKI-induced cardiotoxicities. However, the mechanism underlying the induction of cardiotoxicity could not be clearly specified.

In a previously conducted study, the reported cardiac toxicities associated with 3rd generation TKI – Osimertinib were: heart failure – 1.6%, atrial fibrillation – 1.2%, QT interval prolongation – 1.3% and pericarditis – 0.7% [7].

Therefore, awareness of TKI-induced adverse effects, which may put the patient's life at risk, is very important.

Conclusions

Ongoing investigation and monitoring of all patients on third-generation EGFR-TKIs remains a mainstay of resistance. Also, the early identification of all toxicities, in general, and cardiac, in particular, but also the early initiation of their treatment, lead to increased survival and improved performance status.

A complete understanding of the mechanism of induction of cardiotoxicity is needed, but also the identification of the kinases responsible for these adverse effects.

Ethical approval

Ethical approval was obtained from the Ethics Committee of the "St. Ap. Andrei", Galati.

Disclosure

The authors declare that they have no competing interests

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