



## Case report

## EGFR or PD-L1 decision for first line therapy in a case series of EGFR positive and PD-L1 &gt;50%



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## ARTICLE INFO

## Article history:

Received 19 May 2017

Received in revised form

28 May 2017

Accepted 29 May 2017

## Keywords:

Adenocarcinoma

NSCLC

Epidermal growth factor

Anaplastic lymphoma kinase

Programmed death-ligand 1

## ABSTRACT

Targeted therapies are on the market for the past five years and recently pembrolizumab was approved as first line treatment for patients with PD-L1 >50%. We present three cases of patients which had epidermal growth factor receptor positive expression and programmed death-ligand 1 (PD-L1), PD-L1 >50% overexpression.

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## 1. Introduction

In the past five years targeted therapy is being used with tyrosine kinase inhibitors for epidermal growth factor receptor positive (EGFR) patients and anaplastic lymphoma kinase (ALK) positive patients in non-small cell lung cancer (NSCLC) adenocarcinoma [1–3]. There are three agents that are being used as first treatment for EGFR positive patients; erlotinib, gefitinib and afatinib. These agents presented excellent results for overall survival and minor adverse effects [1]. In the case of a patient receiving afatinib, the dosage can be altered based on the adverse effects. The same with erlotinib. In the case where a patient was receiving gefitinib and disease relapse is observed then re-biopsy can be performed in the site of disease relapse which it can be a lymph node, initial tumor or

new emerged metastasis [4]. In the case where re-biopsy is not feasible due to performance status then liquid biopsy can be performed in order to identify the existence mutation T790M [5]. In pembrolizumab's SPC, as 1st line treatment, pembrolizumab is indicated in EGFR and ALK wild type patients pembrolizumab as monotherapy is indicated for the first-line treatment of metastatic non-small cell lung carcinoma (NSCLC) in adults whose tumors express PD-L1 with a  $\geq 50\%$  tumor proportion score (TPS) with no EGFR or ALK positive tumor mutations [6,7]. Both tyrosine kinase inhibitors and immunotherapy have a good safety profile versus non-specific chemotherapy. Tyrosine kinase inhibitors cost less than immune therapy at least for now.

## 2. Case 1

A 56-year-old woman was diagnosed with adenocarcinoma, stage IV, on 18/1/2016 with medical thoracoscopy. The CT on the chest showed nodules on the left lung and lymphadenopathy (Fig. 1). The bone scan revealed metastasis on the spinal column,

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Fig. 1. Ct of the thorax after medical thoracoscopy.



Fig. 3. Ct thorax during biopsy.

### 3. Case 2

A 76-year-old man was diagnosed with biopsy (under CT guidance) with adenocarcinoma 15/1/17. He was a smoker with 120 p/y. The patient underwent a PET-scan which revealed both a mass in the right lung and nodules in the left lung (N3 disease) (Fig. 2). Also, a mutation of EGFR was found on the 21st exonum. In addition, the percentage of PD-L1 was 80%. The patient initiated afatinib 40mg, however; after 6 months he presented disease relapse with malignant pleural effusion. He had a negative liquid biopsy for T790M and pembrolizumab was initiated. The patient refused an interventional method of re-biopsy (see Fig. 4).

pelvis, ribs, femur and sternum (Fig. 2). Also, a mutation of EGFR was found on the 19th exonum. She was initiated targeted treatment with afatinib 40mg. Due to the skin rash grade 4 the dosage was reduced firstly to 30mg and unfortunately to 20mg within 2 months of treatment. During the next 4 months she continued the targeted treatment with partial response according to targeted RECIST criteria [8]. On 11/5/2017 zoledronic acid was for pain management. Upon diagnosis PD-L1 expression was 60% with Dako pharmDx kit. Upon disease relapse (primary site) treatment was switched to carboplatin and pemetrexed due to negative liquid biopsy for T790M. Also, therapy included zoledronic acid. We chose to administer carboplatin pemetrexed due to the fact that this patient was diagnosed several years before with ulcerative colitis, and we considered this disease a contraindication for immunotherapy. This patient had undergone pleurodesis and re-biopsy was not possible from the pleura (see Fig. 3).



Fig. 2. Bone scan.

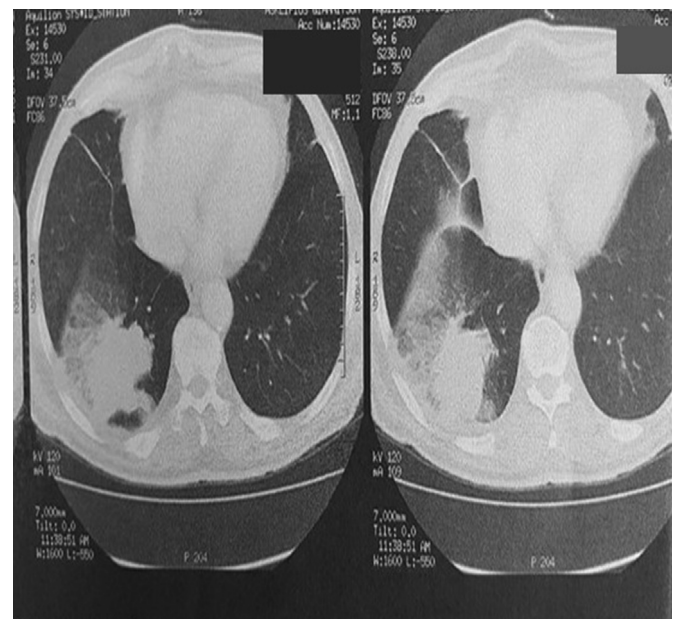


Fig. 4. Ct thorax after biopsy.

### 4. Case 3

A 54-year-old woman was diagnosed with adenocarcinoma of the lungs 8/1/17, stage IV (brain and bone metastasis). The



Fig. 5. Ct thorax upon diagnosis.

diagnostic method was lung biopsy under CT guidance. She also was a non-smoker. The chest CT revealed a mass on the left lung and lymphadenopathy (Figs. 5 and 6). Radiotherapy for brain metastasis was administered. The patient had a mutation of EGFR on the 19th exonium and PD-L1 65% with Dako pharmDx kit. Gefitinib 250mg was initiated. Pembrolizumab was initiated when new brain metastasis where observed almost 3.5 months after tyrosine kinase inhibitor initiation. Liquid biopsy was negative for T790M, we chose liquid biopsy for this patient since we considered brain metastasis a contraindication for any interventional diagnostic approach.

## 5. Discussion

Current recommendations indicate that for adenocarcinoma a thorough investigation has to be made in order to identify EGFR mutations, ALK and PD-L1 genes [9]. As first line treatment, current recommendations are clear regarding the situation where there is EGFR/ALK mutation and when there is PD-L1 overexpression. In

general we have to investigate from the date of diagnosis additional mutations such as Proto-oncogene tyrosine-protein kinase ROS (ROS-1) and proto-oncogene B-Raf (BRAF) [10]. Dabrafenib and trametinib have been recently approved for BRAF in NSCLC [10,11]. The immune status is important in order for immunotherapy to act efficiently [12]. Moreover; cost effectiveness is a serious issue for several health systems in many countries. Since immunotherapy cannot be stopped, but only after disease progression the cost becomes a serious issue [13]. Fortunately Dako pharmDx kit was provided to our hospital by the involving pharmaceutical companies, this is another issue currently under discussion where a lot of cancer cells >100 have to be visible in a tissue slice in order for the specific technique to be performed. Several other techniques are currently on the market, however the FDA accepts only Dako pharmDx kit, while on the other hand EMA accepts all diagnostic techniques for PD-L1 expression. Immunotherapy has different adverse effects from tyrosine kinase inhibitors and non-specific chemotherapy, however; the medical background of a patient is very important. In one of our patients ulcerative colitis was considered an issue for immunotherapy treatment, since we know that this form of therapy induces colitis [14]. There is no way to actually compare these two treatments since their mode of action is based on two different concepts. In the case of tyrosine kinase inhibitors, performance status and disease stage does not play a therapeutic role, on the other hand stage and performance status are very important for the effectiveness of immunotherapy [1,2,15,16]. Another issue that we had to carefully consider was the case where we had disease relapse on the primary site which was the pleura, however; pleurodesis was previously performed to the patient. We considered PET-CT as a method to have a targeted biopsy, however; this radiologic method was not performed since it was not a very important issue for the patient, we had an alternative therapy.

## Conflict of interest

None to declare.

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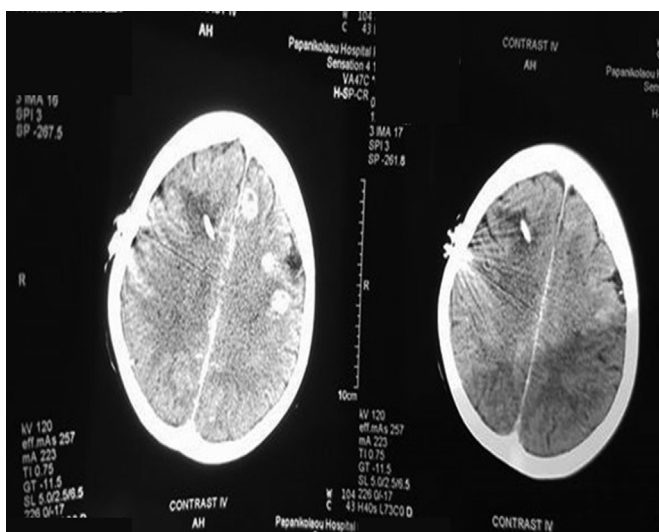


Fig. 6. Brain metastasis upon diagnosis.

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