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A Case of Good Clinical Outcome after Panitumumab-Related Interstitial Lung Disease

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Abstract

Background: In Metastatic Colorectal Cancer (mCRC) patients, mutational analysis of KRAS and NRAS genes is mandatory for therapeutic programming as in wild type patients anti-EGFR monoclonal antibodies (panitumumab/cetuximab) demonstrated clinical efficacy.

Case report: We report here-by a case of a 63-years-old woman, no smoker, with mCRC that involved lung, liver and abdominal lymphadenopathies. Molecular analysis revealed NRAS, KRAS and BRAF wild-type adenocarcinoma. From June 2018 to September 2019 patient received chemotherapy in combination with panitumumab followed by maintenance therapy with panitumumab. She reported grade 3 cutaneous toxicity achieving RECIST response. On October 2019, CT scan reassessment evidenced Interstitial Lung Disease (ILD) without acute respiratory symptoms. The treatment with panitumumab was finally suspended; she so started corticosteroid therapy and three months later the CT scan evidenced the resolution of ILD and revealed Stable Disease (SD), so that patient continued with further cancer treatments.

Discussion: Skin toxicity is the most common adverse event among mCRC patients treated with the anti-EGFR antibody. Data from the clinical trials of cetuximab and panitumumab suggest a positive correlation between the presence and severity of rash and survival. A rare adverse event panitumumab-related is the Interstitial Lung Disease (ILD) that can be fatal if not recognized promptly. No data are reported about panitumumab-induced ILD in western population and its association with clinical outcome. The aetiology of EGFR-related pulmonary toxicity can be related to the alveolar repair mechanisms or the reduction of surfactant protein A.

Conclusion: ILD is an extremely rare Adverse Event (AE), requiring close attention considering the possibility of severe complications and mortality. There may be a positive association between this adverse event and disease response, but this correlation should be investigated as hereby depicted.

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Background

Metastatic Colorectal Cancer (mCRC) is a leading cause of death both in Europe and worldwide [1,2]; however, today the median Overall Survival (OS) for patients with mCRC being treated both in phase III trials and in large observational series or registries is ~30 months, more than double that of 20 years ago.

Main factors having contributed significantly in improving patients' outcomes as the biomarker-based patient selection and the introduction of anti-Epidermal Growth Factor Receptor (EGFR) and anti-Vascular Endothelial Growth Factor (VEGF) Monoclonal Antibodies (MoAbs) [3]. Panitumumab is a fully human monoclonal antibody that targets the EGFR. The PRIME trial has demonstrated its clinical efficacy in patients with KRAS wild-type mCRC [4] and dermatologic events are considered the most relevant elements of its toxicity profile [5]. We present a case of a Caucasian woman, no smoker and without pulmonary fibrosis, with a diagnosis of mCRC treated with panitumumab, who developed severe cutaneous toxicity and Interstitial Lung Disease (ILD), positively related to the clinical outcome.

Case report

We report the case of a 63-years-old woman with rectum adenocarcinoma and metastases in left upper pulmonary lobe, liver and abdominal lymphadenopathies. Molecular analysis revealed NRAS, KRAS and BRAF wild-type adenocarcinoma. Her past medical history was previous right apical pulmonary adenocarcinoma, radically operated 3 years before diagnosis of mCRC (pT1b pN0 G2. St IA sec AJCC 2010), and non-symptomatic pulmonary emphysema in no smoker patient. Because of her Karnofsky performance status 90% she started the first-line treatment with oxaliplatin, 5-fluorouracil and leucovorin (Folfox) in combination with panitumumab based on the PRIME study. After two cycles of chemotherapy, patient presented Grade 3 (G3) skin toxicity with papular eruption, erythema and pruritus on the face and upper torso, treated with clindamycin 2% and hydrocortisone 1% in a lotion applied topically and minocycline 100mg per os bis in die for 2 weeks. After resolution of skin toxicity, panitumumab was resumed at a reduced dose (3 mg/mq) in combination with chemotherapy for other three cycles.

A re-staging total body contrast enhancement Computed Tomography (CT) scan evidenced a Partial Response (PR) based RECIST criteria so she continued maintenance therapy with panitumumab from June 2018 to September 2019 experiencing G2 cutaneous toxicity but, thanks to specific symptomatic treatments, she showed a good compliance and persisting PR at quarterly CT evaluation.

On October 2019, the restaging CT showed surprisingly bilateral pulmonary ground-glass areas, larger in the lower lobes, associated with diffuse thickening of interlobular septa (Figure 1). The patient was eupnoeic at rest and reported mild dyspnea from exertion, no fever or cough; at physical examination, murmur vesicular was normally transmitted and rare rhonchi in forced expiration were evidenced. Spirometry was in the range. In consideration of the most probably drug-related ILD, the treatment with panitumumab was finally suspended, she started so a therapy with budesonide 0.5 mg and salbutamol 1.25 mg bis in die for aerosol, azithromycin 500 mg once per day for six days and methylprednisolone 4 mg bis in die for a week followed by tapering of 2 mg per week until suspended. On December 2019, CT scan evidenced the resolution of ILD and revealed a Stable Disease (SD) (Figure 2). In view of the previous answer and the pause >one year, we decided to resume CHT with Folfox; despite the presence of the primitive tumor at rectum level, in order to do not undertreat the patient, we added anti-VEGF MoAb Avastin; as result of this combined approach, she obtained an excellent local response (Figure 3-4) without occurencing any leeches.

Discussion

The EGFR, a member of the ErbB family of receptor tyrosine kinases 1,2,3 is a transmembrane glycoprotein composed of an extracellular ligand-binding domain, a transmembrane lipophilic segment, and an intracellular protein kinase domain [6-9] overexpressed in a variety of solid tumors; its overexpression in CRC may be associated with an advanced disease stage [10-14]. Anti-EGFR MoAbs compete with endogenous ligands, including EGF and TGF-α, to block ligand-dependant activation of EGFR, and induce receptor internalization and consequent downregulation [15]. The most common adverse event among mCRC patients treated with the anti-EGFR MoAbs is skin toxicity characterized by erythema, dry skin, papulopustular eruption followed by crusting affecting sun-exposed areas of the body such as the face, neck, shoulders, upper body, and scalp [16,17,19]; this Adverse Event (AE) can impact the patient's quality of life and compliance to the treatment, so it's very important its correct management. The severity of the rash is dose-dependent and data from clinical trials suggest a positive correlation between the presence and severity of skin toxicity and response to the anti-EGFR treatment [20-23].

Less common side effects include ocular toxicity, diarrhoea, infusion reactions and hypomagnesemia [24-25]. Interstitial lung disease and interstitial pneumonitis are rare: a Japanese post-marketing all-case surveillance study from 2010 to 2015, reported panitumumab-induced ILD incidence of 1.3% and mortality rates of 51.3% [26] but no such data are available in the western population, necessary to understand ethnicity-related risk factors. The aetiology of EGFR associated pulmonary toxicity is not fully understood. However, it can be resulted from impairing the cell and tissue repair sequence as EGFR is expressed on type II pneumocytes, which are involved in alveolar wall repair. Thus, agents targeting the EGFR may impair alveolar repair mechanisms [27,28]. In addition, preclinical in vivo models suggest that the mechanism maybe related to reduced surfactant protein A expression in lung tissues with EGFR inhibition [29].

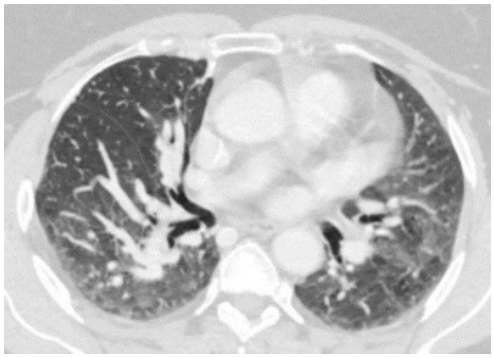

Figure 1: Panitumumab-induced ILD: CT scan shown chest bilateral pulmonary ground-glass areas, larger in the lower lobes, associated with diffuse thickening of interlobular septa.

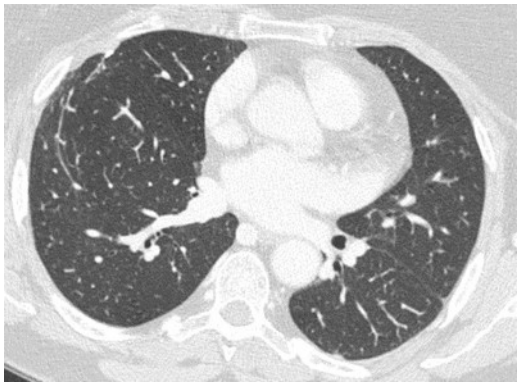

Figure 2: Resolution of Panitumumab-induced ILD: CT scan shown normal representation of pulmonary parenchyma.

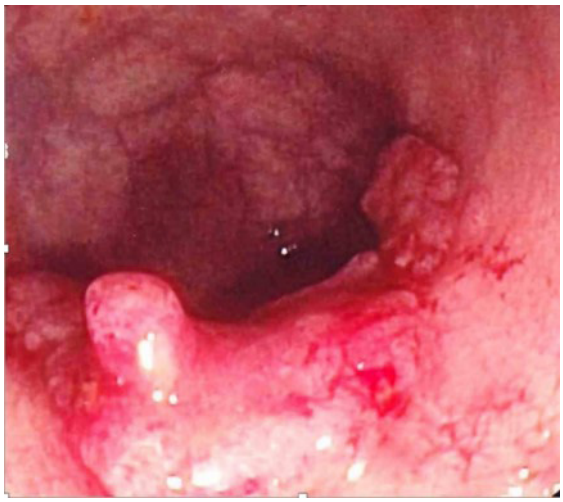

Figure 3: Endoscopy at start Avastin-treatment shows voluminous neoformation of the middle rectum about 8-10 centimeters from the anal rhyme.

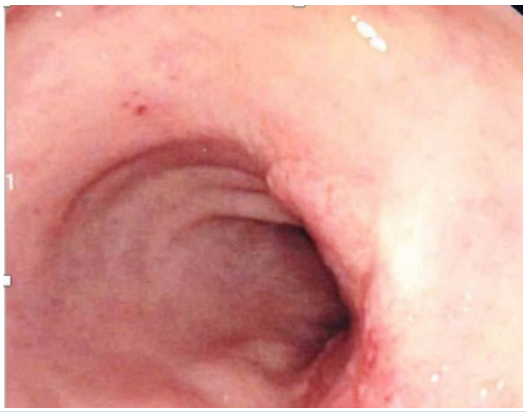

Figure 4: Endoscopy after 9 months of Avastin- treatment, shows locoregional respon.

Conclusion

Patient object of this case, reported a very common AE panitumumab-related such as skin toxicity with RECIST response for a long time, but after several administrations she developed pulmonary toxicity. Although this type of toxicity may be caused by chemotherapy, in this situation it occurred after chemotherapy's interruption. ILD is an extremely rare panitunumab AE, but it required close attention considering the possibility of severe complications and mortality. Death due to ILD can be prevented by promptly monitoring pre-existing lung conditions, recognizing new-onset respiratory symptoms, discontinuing treatment, performing radiographic assessment, and starting corticosteroid therapy in order to preserve the clinical conditions and continue with other treatments. As well as in our patient who has maintained a partial response to panitunumab therapy for a long time, there may be a correlation between a serious adverse event as ILD and the clinical response; up to date current state of art, however, this correlation is not well-known and should be furtherly investigated.

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