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Case Report

Dramatic Improvement in Dyspnea in A Non-Small Cell Lung Cancer Patient, Following Administration of Anti-IL-6R

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2. Key words

Tocilizumab; Lung Cancer patient

1. Abstract

1.1. Background: Currently in most Lung Cancer cases in which there is tumor progression, the molecular approach is to search for new mutations, usually utilizing circulating free DNA. There are however cases where a trauma, such as an operation, is followed by rapid tumor progression and the key for treatment in these cases, might be the search for abnormal Cytokine levels.

1.2. Methods: A 47 year old Lung Cancer patient presented with severe dyspnea and rapid growth of lung metastases. Three weeks following a major bleeding episode, there was a reduction of Hemoglobin to 3.8. Previously he was treated for nearly 3 years with 3 different treatments. CT demonstrated multiple lung metastases. Since this was such a rapid growth of multiple findings, we postulated that it may result from a general effect and not from a new genetic aberration. We found elevated levels of several Tumor Markers and increased IL-6 levels as well- therefore we treated with Tocilizumab – an Anti IL-6 Receptor antibody.

1.3. Results: Within 2, days he had a significant improvement in his dyspnea but needed a second injection a month later- to which he again responded dramatically. Evaluation of several Tumor Markers and Cytokines levels, revealed a great increase in their levels and he had progressive liver failure due to increase in liver metastases, which have been dormant following radiation for more than 6 months.

1.4. Conclusions: Anti IL-6R antibodies are now widely used for treatment of severe Sars- Cov-2 patients. Such a treatment maybe useful for patients with increased dyspnea or other manifestations of rapid deterioration, following a trauma in which IL-6 levels are high.

3. Introduction

One promising treatment option for the treatment of Covid-19 advanced cases [1,2], is the use of an Anti IL-6 Receptor [3,4] for advanced dyspneic patients, which have overexpression of cytokines [3] at an advanced stage of their disease.

However, to the best of our knowledge, such an approach has been not been described in dyspneic Cancer patients. Here, we describe a complex case of a Lung Cancer patient with severe dyspnea, who had rapid Lung Cancer tumor growth and dyspnea with high levels of IL-6, following a bleeding episode which responded dramatically to Tocilizumab – Anti IL-6 Receptor [5]. Unfortunately, an increase in IL-6, TNFα and other cytokines and Tumor Markers levels was followed by rapid growth and ultimately death from increased liver metastases.

4. Case history

A non-smoker 44 year old male was diagnosed in 2009 as suffering from stage 2 Lung Cancer. He underwent operation and later adjuvant therapy of 4 cycles with a combination of DDP and Vinorelbine. 4 month after finishing this therapy, tumor recurrence at 3 sites including a liver one, were diagnosed.

He responded to a combination therapy based on Pemetrexed Irinotecan and Bevacizumab for over a year. Tumor recurred solely in an abdominal lymph node and was resected. 4 month later, although he continued with the same chemotherapy, multiple liver metastases were discovered as the only active cancer site. He was treated with a single intrarterial SIRTEX (RadioactiveYtrium labled silica beads) injection. PET/CT following this procedure, did not reveal any increased uptake in the liver metastases. He was than treated with a combination based on Docetaxel with an transient response but multiple new small lung nodules and retroperitoneal enlarged nodes, appeared. It is also noteworthy that the patient had a few genomic analyses performed during the disease, which revealed that he was a carrier of the Kif5b-Ret translocation. We then applied Sunitinib which has some Ret inhibitory activity and was available at the time. We combined this treatment with radiation

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to the enlarged retroperitoneal lymph node. He stopped Sunitinib due to fatigue after less than a month.

However, about 2 weeks later he had a major bleeding episode from gastric ulcer with Hemoglobin decrease up to 3.6. The patient was then admitted to an intensive care unit and treated with multiple blood units.

His Hemoglobin normalized thereafter, however he developed severe dyspnea. We performed a CT which revealed rapid increase in the size of multiple lung metastases with new accumulation of pleural fluid compared to the CT performed 3 weeks earlier (Figure 1). These findings suggested the growth may be a result of the influence of a general increase in inflammatory cytokine levels and not a just a clonal mutation, We evaluated levels of several cytokines including IL-6, TNF, sIL-2R, which were significantly elevated compared to normal levels (Figure 2). At this stage the patient suffered from severe dyspnea even with oxygen. While NSAID and steroid therapies have been shown in the past to reduce IL-6 levels, their use was not possible in this patient with a large gastric ulcer. He was then administered with a single dose of Tocilizumab - an Anti-IL-6 Receptor monoclonal antibody (Roche) 4 mg /kg - a dose which is usually used once every month [5]. Within 2 days, he did not need the oxygen and his general condition was greatly improved. However, he developed within 2 weeks hyperbilirubinemia. Abdominal Ultrasound revealed small cirrhotic liver without the ability to identify specific lesions. Though, since his Bilirubin continued to rise, a new CT was performed which did reveal multiple small liver metastases. At around this time he developed again dyspnea and we repeated the injection of Tocilizumab and again, within 2 days he was breathing much better. However, his liver functions continued to deteriorate while his bilirubin continued to rise rapidly. He developed another severe episode of gastric bleeding about 2 month from the initial Tocilizumab treatment, which we were not able to overcome and ultimately succumbed to his disease, more than 3 years after the initial diagnosis of metastatic disease. As can be seen in Fig. 2 the levels of his cytokines IL-6, TNF, sIL-2R and various Tumor Markers – CEA, CA 19-9, CA 15-3, CA-125, VEGF, TPS (Figure 3), also increased rapidly during this time, similar to other studies [6].

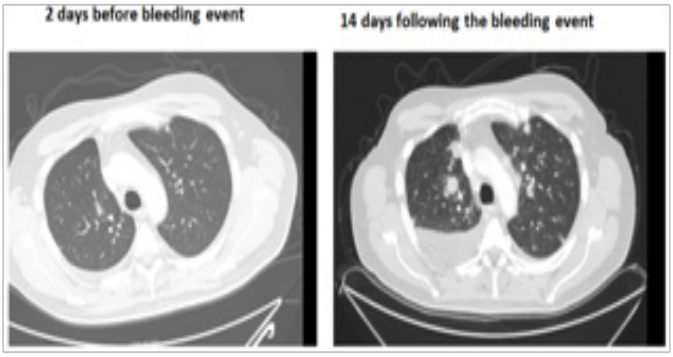

Figure 1: Patients C.Ts

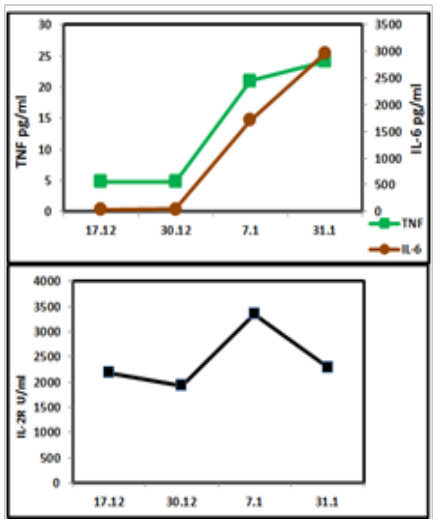

Figure 2: Patient's Cytokine Levels

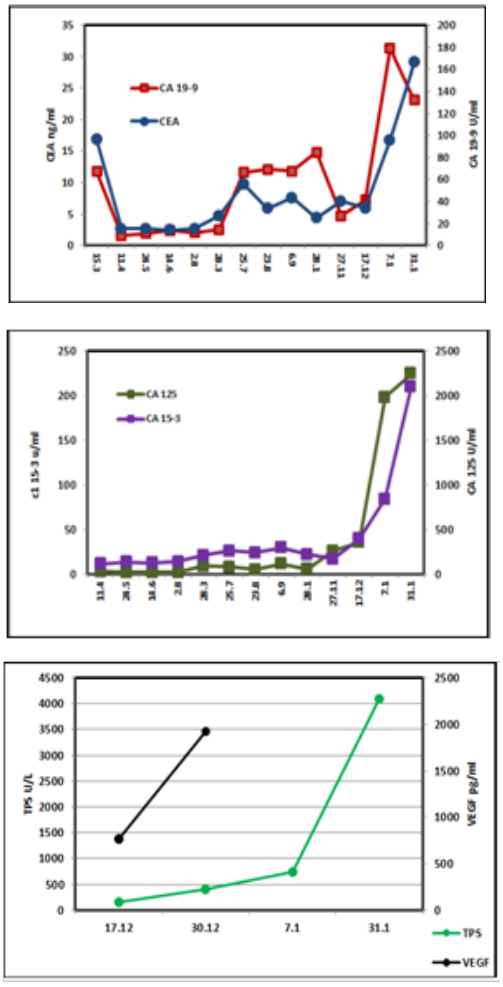

Figure 3: Patient's Tumor Marker Levels

5. Discussion

The patient at this time in his treatment had progressive disease after failure of 3 chemotherapeutic lines. However, the rapid disease progression in the lungs following the traumatic bleeding episode, strongly suggested that release of a hormone like substance with general effect might be responsible - rather than accumulation of

new genetic aberrations. This scenario might be more common than is usually suspected.

Currently, most of the emphasis in treating cancer and resistant cancer, is on the appearance of new mutations such as EGFR 790 resistant mutation.

In many cases, one can detect rapid tumor progression in several metastases and then it seems that perhaps not just a single new mutation is responsible for this tumor progression - but perhaps some systemic effect due to an inflammatory cytokines storm [7, 8].

In this case there was a striking response which occurred twice to the treatment with Tocilizumab. The patient almost immediately weaned from the oxygen treatment. Since it occurred twice, it seems that the Anti IL-6 Receptor antibody, indeed was very effective here in overcoming the dyspnea.

In the liver, during this time there was rapid development of new liver metastases while in the lungs, the lung metastases stabilized. We were worried that the Tocilizumab treatment had in some ways induced the regrowth of liver metastases which have been dormant for about 8 months. However, we decided to administer the second therapeutic dose of antibody, due the redevelopment of dyspnea.

Several possibilities as to the rapid appearance of liver metastases are possible:

They might not be linked to the use of Tocilizumab and just happened as a manifestation of rapid disease progression at times in which we could not administer effective therapies, or as a result of the increase in systemic levels of IL-6, TNF or other cytokines (Figure 2) and perhaps the existence of an IL-6 Receptor which Tocilizumab could not recognize. Another possibility which is rarely mentioned, is that IL-6 had a suppressive effect on the liver metastases, which was relieved by the use of Tocilizumab.

6. Conclusions

A rapid relief in severe dyspnea was noted with the use of an Anti-IL-6 Receptor (Figure 4) in a patient with multiple sites of metastases following rapid tumor growth and high levels of IL-6.

He ultimately succumbed to rapidly progressive disease- an event which may or may not have been related to the use of the Anti-IL-6 Receptor drug.

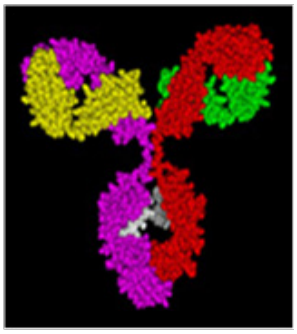

Figure 4: Tocilizumab-a humanized Anti IL-6 Receptor monoclonal antibody.

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