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Sustained Viral Response to Ipilimumab Treatment in a Patient with HCV Chronic Infection and Metastatic Melanoma: A Case Report

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Abstract: The treatment of metastic melanoma has rapidly evolved in the last 5 years, giving clinicians and patients the hope for long lasting responses. In the field of modern immunotherapy, we are reaching the point of an expressive percentage of patients achieving long term survival with anti-CTLA4 and anti-PD1 checkpoint inhibitors. Of note, there is a considerable amount of patients excluded from the checkpoint blockade trials because of comorbidities like chronic viral infections. A precaution to avoid autoimmune induced hepatitis rendered HBV (hepatitis B virus) and HCV (hepatitis C virus) infected patients usually ineligible, but real life data in those patients, who are getting treatment despite of that, is pointing toward the feasibility and safety of immunotherapy in this context. To ilustrate that, we report the case of a metastatic non-BRAF mutated melanoma patient with HCV chronic infection and a surprising benefit derived from ipilimumab and pembrolizumab for his latter condition.

Key words: Melanoma, immunotherapy, checkpoint inhibitors, ipilimumab, pembrolizumab, HCV.

1. Introduction

In the last 5 years in the field of melanoma, the oncologist has left behind drugs like interferon, interleukin-2 and cytotoxic chemotherapy and has replaced it with target therapy and immune check-point inhibitors, such as the anti-CTLA4 ipilimumab and anti-PD1 pembrolizumab and nivolumab, especially in the setting of metastatic melanoma and, more recently, non-small cell lung cancer and kidney cancer. While being able to prolong the lifespan of those patients, we have become aware of a myriad of different immune mediated side-effects, such as rash, colitis, endocrinopathies and pneumonitis, among others resulting from the unhindered action of the activated lymphocyte. Post-market reports after years of experience with the use of those drugs are now showing occasional benefits of the activated immune system that goes beyond the scope of oncology, one of these is the unexpected treatment of viral diseases such as the hepatitis C virus, which is exemplified in the following case.

2. Case Presentation

This is a 63 years old caucasian male patient with no known comorbidities who was diagnosed with a non-BRAF mutated metastatic melanoma in September, 2015. His initial complaints were of a painless, slow growing lesion on his back and dizziness that started a week later and prompted his evaluation on our service. On the physical examination, he appeared well. Multiple moles with the same pattern could be noted on his skin. Vital signs were within the normal range. A soft palpable mass measuring approximately 5 cm on the largest diameter was noted on the right flank and, on the neurological exam a cerebellar gait and nystagmus were detected. Initially, a brain MRI

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(magnetic resonance imaging) was obtained and showed a 2 cm nodule with perilesional edema on the right cerebellum (Fig. 1), so further investigation with a PET-CT demonstrated multiple lesions with high FDG (fluorodeoxyglucose) uptake which is consistent with metastases. Sites of disease included the right cerebellar nodule, multiple lesions in both lungs, the largest of which measures 3.2 cm in length, a subcutaneous mass in the right flank of 6 cm and two satellite lesions (Figs. 2 and 3). Due to the neurologic symptoms, he underwent a resection of the cerebellar nodule and also a resection of the larger subcutaneous lesion on September 08, 2015. Pathology reports of both specimens were consistent with metastatic melanoma, BRAF wild type, NRAS mutated and c-KIT wild type. Routine workup revealed a mildly elevated LDH (lactate dehydrogenase) of 640 U/l and abnormal LFTs (liver function tests) as shown in Table 1. Serological investigation was pursued and the patient was tested positive for HCV (hepatitis C virus) antibodies. Reviewing lab works from a year before, he already had an unnoticed positive serology for total anti-HCV. Viral load detection by PCR (polymerase chain reaction) in the serum detected 57.238 UI/ml. Ultrasound Elastography of the liver was compatible with stage (F0), incipient hepatopathy. He then received adjuvant radiotherapy to the cerebellar surgical bed to improve the local control. Based on the availability in the patient's country of residence (Brazil) by that time for the treatment of stage IV, non-mutated BRAF melanoma, an option for first line anti-CTLA4 immunotherapy was done. Ipilimumab was started on

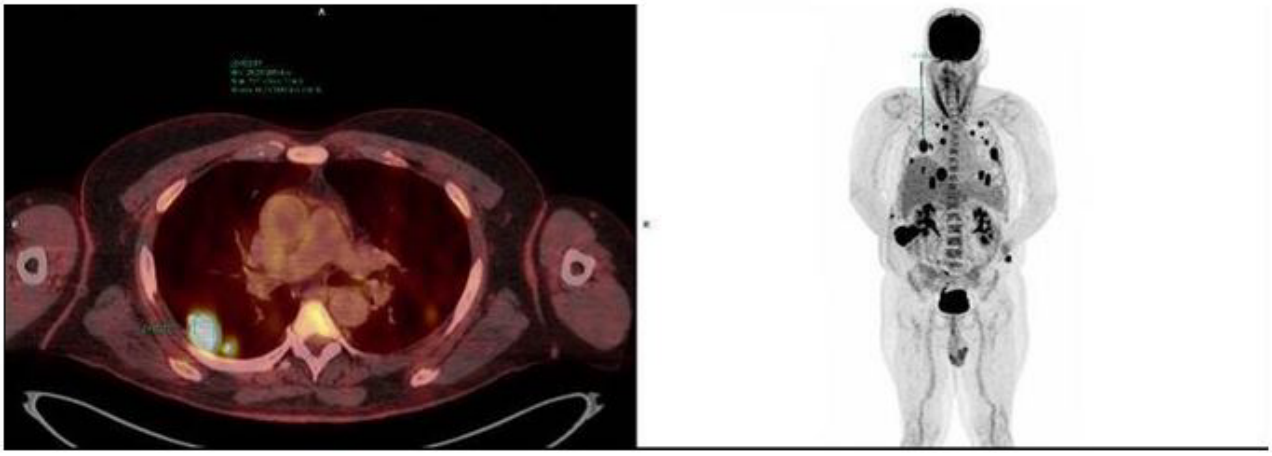

Fig. 1 Initial PET-CT of September 5 of 20015 showing mulyiple lung lesion with avidity for FDG.

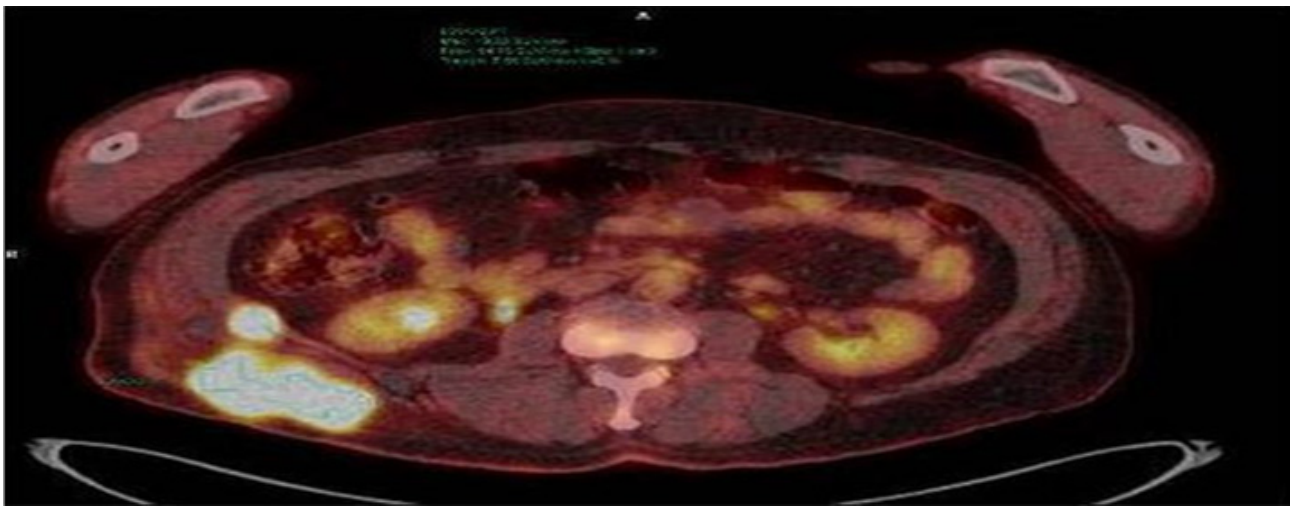

Fig. 2 Same PET-CT showing the large subcutaneous lesion with a maximum SUV of 19 and a satellite smaller one.

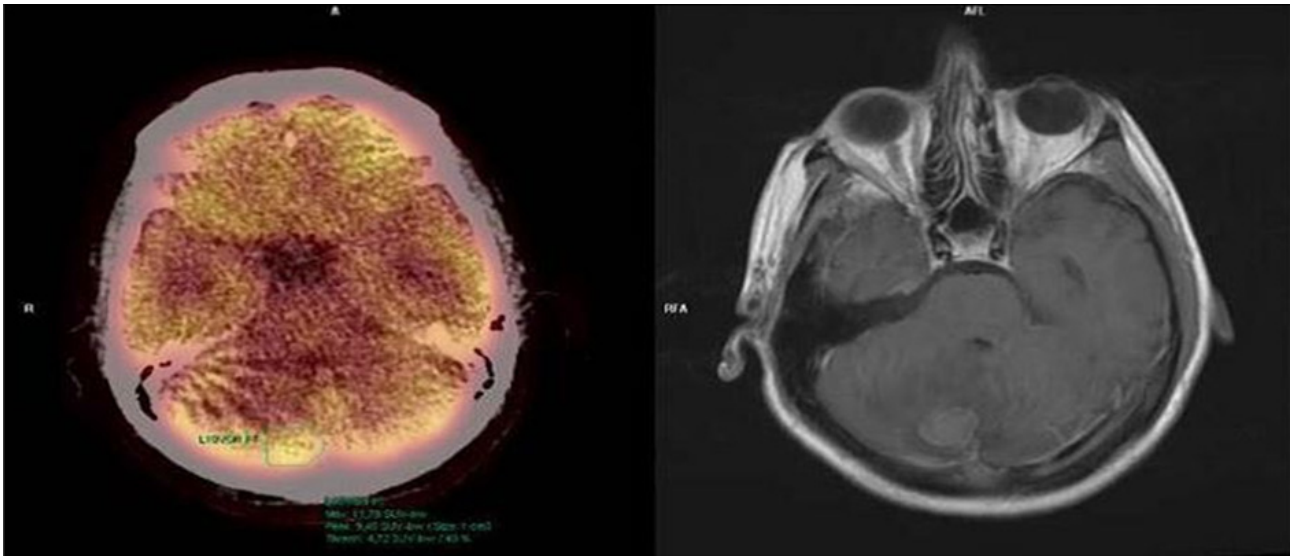

Fig. 3 PET-CT and MRI of the brain, showing a hipermetabolic nodule with sourrounding oedema in the right cerebellar hemisphere.

Table 1 Lab work at diagnosis

Biochemical parameters at the time of diagnosis	
Alanine transaminases (U/L)	131 U/L (1.8 × reference value)
Aspartate transaminases (U/L)	75 U/L (1.2 × reference value)
Albumin (g/L)	4.0 g/L
Bilirrubin (mg/dl)	0.7 mg/dl
LDH (U/L)	640 U/L (1.03 reference value)
WBC (ul)	11×10^3/ul
PLT × 10/L	233×10^3/ul
HCV PCR viral load	57.238 UI/mL
Liber Fibroscan stage	F0

Table 2 HCV copy counts and liver enzymes during treatment

Month/day/year	09/23/2015	11/09/2015	02/03/2016	06/13/2016	10/04/2016
Days after first ipilimumab infusion	Prior to therapy	40 days	154 days	257 days	386 days
Days after first pembrolizumab infusion	Prior to therapy	Prior to therapy	30 days	131 days	242 days
HCV results	Detected*	Not detected	Not detected	Not detected	Not detected
HCV PCR viral load (UI/mL)	57.238 UI/mL*	< 15 UI/mL	< 15 UI/mL	< 15 UI/mL	< 15 UI/mL
Result Log	4.76*	< 1.17	< 1.17	< 1.17	< 1.17
AST	131*	42	31	49	81*
ALT	75*	36	21	47	127*

*denotes out of range values.

on September 30 of 2015, 3 mg per kg every 3 weeks, with a planning for cautious monitoring of the liver function. After 40 days of ipilimumab treatment, a new viral load test was obtained, showing an undetectable viraemia, which persisted after the four doses of ipilimumab and thereafter. This corresponds to a SVR (sustained viral response), as shown in Table 2. Liver enzymes even dropped to normal ranges.

The patient finished the 4th dose of Ipilimumab on December 18 of 2015, with good tolerance, except for the development of knee arthritis. On the following restaging PET-CT on January 01 of 2016, he had

disease progression on the lungs, lymph nodes and subcutaneous lesions. Brain MRI showed no evidence of disease. Pembrolizumab at the dosage of 2 mg per kg every 3 weeks was started on February 2 of the same year, and the patient experienced only a mild rash and fatigue. Despite an initial partial response on the lungs, on the next PET-CT of August 08 of the same year, he had a mixed response showing stability of the lung nodules, decreased FDG uptake on the lymph nodes but growth of the subcutaneous lesions. Since clinically he had no signs of progressions and the brain MRI was still clear, an option to maintain the anti-PD1 was pursued. The patient is still feeling well, waiting for the next restaging PET-CT. Notably, he still has a SVR.

3. Discussion

Melanoma is a rare disease in South America due to the average melanodermic skin feature of our population, especially in the northern and northeast regions of Brazil. According to the INCA (instituto nacional do câncer) database from 2016, the estimated incidence of melanoma for the year will be as low as 5,670 new cases [1] for an entire continental country of 206.6 million people [2] (data from the Instituto Brasileiro de Geografia e Estatística-IBGE). Unlike what occurs in Australia and on the Netherlands, melanoma doesn't represent a public health care problem per se to Brazil, although it does affect more the faired skin people from the southeast and south regions. Most of them have European ancestry, and lack the natural protection against U.V. rays conferred by a darker skin, accounting for 74% of the new cases and with an estimated incidence to be as high as 8,02 new cases per 100 thousand persons.

HCV, on the other side, has a wide prevalence amongst Brazilians, estimated to be 1, 38% for the entire population between the ages of 10 to 69 year according to a nationwide cross-sectional survey of 2010 [3]. More than 10,000 new cases are notified each year [3], following the prevalent trend of intravenous drug usage and unprotected sex, among other risk behaviors between people with poor social support and low income. Fortunately, treatment for this disease has had quite an evolution in the last few years with the newer direct antiviral drugs, such as sofosbuvir, simeprevir and daclatasvir, showing a SVR up to 100 % of cases [4], with less toxicity and shorter treatment time when compared with alfa-peg-interpheron and ribavirin. Since 2015 patients from our public health system have free access to this new treatment modality, but little or no efforts has been made in the preventive setting since 1988, when a federal law was edited prohibiting payments for blood donations [4].

Tracing a small parallel with HCV care, melanoma's treatment has also evolved quickly in the last half decade. Until 2011, if a patient wasn't fit enough to tolerate high dose Interleukin-2 (IL-2), the clinical armamentarium for unresectable/metastatic melanoma was restricted solely to cytotoxic chemotherapy (such as taxanes and alkylating agents) with response rates lower than 20% and no proven gain in survival [5]. Fortunately, after the publication of the watershed phase 3 trial by Drs Hodi and O'day, comparing ipilimumab alone or combined with a gp100 vaccine to the vaccine isolated after failure to previous systemic treatment that showed an overall survival advantage for the 2 experimental arms [6], approval of ipilimumab by the U.S. FDA (food and drug administration) ensued and modern immunotherapy has established a central role in the management of metastatic melanoma. Checkpoint blockade with anti-PD1 alone has been proven better than anti-CTLA4 [7], with less toxicity and better response rates, and when both are combined, one can expect an overall response rates as high as 57% and a long lasting progression free survival of 11, 5 months [8]. Nonetheless it remains an area of concern: all the immune-mediated toxic effects and its management and, equally important, the financial toxicity that arises with such an expensive treatment, especially in developing countries. Also, for those 40% to 60% of patients with a target activating mutation, such as BRAF V600E or K, it is unknown what the best

sequencing of treatment is.

An open question is whether or not it is safe to administer immunotherapy to patients with HCV infection, since most of the melanoma trials excluded specifically this population because ipilimumab itself can cause autoimmune hepatitis. Now with years of accumulated experience outside clinical trials, the body of data in this matter may be pointing toward the feasibility of check-point inhibition in chronic HCV patients, as shown by Ravi et al [9]. In a case series of 9 melanoma patients with HCV or HBV infection, where only two HCV patients had fluctuations of their liver enzymes, one that had pretreatment elevation experienced normalization and also an HCV viral load decrement to undetectable level after the fourth dose of Ipilimumab; none had to stop treatment because of liver toxicity [9]. Yazici [10] in their review article also described two melanoma patients safely treated with ipilimumab who did not experience any HCV flare. Minter [11] reported in 2013 the first patient of the medical literature by that time to have a decrement in his viral load with ipilimumab treatment, but not to the point of a VSR.

From a biological standpoint, the previous concern of HCV reactivation with immune checkpoint blockade, similarly to chemotherapy, may not proceed: hierarchical CD-8 + T lymphocyte exhaustion is a well-described mechanism associated with viral persistence. Due to a high co-expression of the down-regulators PD-1 and CTLA-4 in the HCV-specific CD-8 + T cell in the liver, which is directly responsible for fighting the infection, profound functional impairment of the lymphocyte subsides. Based on that rationale, Nakamoto et al. [12] showed that combined PD-1/CTLA-4 blockade can reverse HCV specific CD8 + T cell dysfunction during acute hepatitis C, which ultimately could lead to a better viral clearance.

In this case report, not only did the patient not have any flare of hepatitis with immunotherapy, he also had a sustained viral response and initial normalization of his liver enzymes. Gathering this case with the current body of literature, one could argue for immunotherapy treatment with judicious monitoring of the LFTs and viraemia in melanoma patients with HCV infection. Further studies and post-market reports are needed to better clarify this statement.

4. Conclusions

In summary, we report an anecdotal case of a patient with non-mutated BRAF metastatic melanoma with HCV chronic infection diagnosed in his initial workup, who obtained a complete and sustained viral clearance with ipilimumab, and is still benefiting from second line immunotherapy 13 months after his diagnosis. Epidemiological data are presented showing the high prevalence of HCV in Brazil, configuring a true public health problem, and what has been done so far to fight it. Small case series are presented showing that no aberrant liver toxicity occurs when infected patients are given ipilimumab, and our patient isn't the first one to show a viral load decrement. We provide a rationale to explain this unexpected collateral treatment of the infection that resides on the fact that one can reverse CD8 + T cell exhaustion against HCV with combined checkpoint blockade of CTLA-4 and PD1. In our case presentation, the first one on the literature to our knowledge at this time, that may be the explanation for our patient having a SVR. We suggest that, despite the exclusion of HCV positive patients from trials of modern immunotherapy due to the concern of autoimmune induced hepatitis and HCV flare, there is evidence on the literature pointing towards the feasibility of this treatment in carefully monitored patients, who may even benefit from the point of view of the infection.

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