American Journal of Medical Case Reports, 2017, Vol. 5, No. 6, 151-155
Available online at http://pubs.sciepub.com/ajmcr/5/6/5

DOI:10.12691/ajmcr-5-6-5

Severe Pneumonitis in Patient with Kidney Cancer Using Nivolumab after Influenza Vaccine - A Case Report

Nicoli Taiana Henn[1,*], Julia Pastorello[1], Marina Ractz Bueno[2]

[1]Medical oncologist at the Hospital City of Passo Fundo- RS- BR. Street Tiradentes
[2]Medical resident in Oncology at the Hospital City of Passo Fundo
*Corresponding author: nicolihenn@yahoo.com.br

Abstract Immunotherapies are new drugs that are revolutionizing the treatment of many malignancies, among them, the kidney cancer. Because of their mechanism of action they can trigger an important inflammatory responses and immune-mediated adverse events. The safety of influenza vaccination during the use of checkpoint inhibitors is not defined. We report the case of a patient with kidney cancer who evolved unfavorably a few days after receiving the influenza immunization without the consent of the oncology specialists.

Keywords: *kidney cancer, influenza immunization, Nivolumab*

Cite This Article: Nicoli Taiana Henn, Julia Pastorello, and Marina Ractz Bueno, "Severe Pneumonitis in Patient with Kidney Cancer Using Nivolumab after Influenza Vaccine - A Case Report." *American Journal of Medical Case Reports*, vol. 5, no. 6 (2017): 151-155. doi: 10.12691/ajmcr-5-6-5.

1. Introduction

Patients with malignant neoplasms, especially receiving chemotherapy, are considered immunocompromised patients, and they are at greater risk of contracting influenza [1], at the same time they may have more complications and higher mortality rates with this infection than the general population [2].

Influenza mortality in cancer patients reaches 9% [3]. Because of that, studies have been done to assess whether the patients receiving chemotherapy would be able to create an immune response to the vaccine and whether it would be safe in this context.

Although the influenza vaccine is composed of inactivated virus strains, there is some reluctance by oncologists in accepting and indicating the immunization to their patients while on chemotherapy.

The vaccination induces the formation of T and B memory cells that allow the immune system to respond if exposed to the pathogen, but this may take up to two weeks in patients with normal immune systems [4]. Patients undergoing cancer treatment usually have suboptimal responses to vaccinations, but the influenza vaccine has been shown to be safe and minimally invasive for these patients [5].

Although the optimal time to be administered to patients with solid tumors is not defined, it is suggested to be done midway through the cycle, about two weeks after chemotherapy or before the next cycle [6]. More than 30 studies have shown mild adverse effects of the vaccine, indicating that influenza vaccination is generally well tolerated in cancer patients [7].

Influenza vaccine may also be recommended for patients using target therapy for solid tumors [6]. The VACANCE study demonstrated that the association of biological and cytotoxic agents did not affect immunogenicity whereas those using isolated target therapies had better responses than other groups [8].

With the advent of the of immunotherapy era, the assertiveness of indicating the vaccine is not the same. Because these trials are relatively recent and most oncologists are learning to deal with the toxicities of checkpoint inhibitors, the relationship of vaccination and safety are uncertain.

We report the case of a patient using immunotherapy who evolved unfavorably after administration of the influenza vaccine.

2. Case Report

A 64-year-old male patient, with chronic obstructive pulmonary disease (COPD), had been diagnosed with renal cancer in 2014 with mediastinal lymph nodes and lung metastases, with pulmonary nodules up to 1 centimeter. The patient underwent right nephrectomy in November 2014. The histology demonstrated to be a grade 3 clear cell carcinoma. The patient remained in follow-up until September 2015 when he had disease progression with increased mediastinal lymph nodes and started Sunitinib, and then continued its use until July 2016. In August 2016, due to disease progression, characterized as lung carcinomatous lymphangitis, he needed intermittent oxigen use because of grade 2 dyspnea. He then started using Nivolumab on July 25th 2016 at the dose of 3mg/kg body weight every 2 weeks and continued without medication-related toxicity.

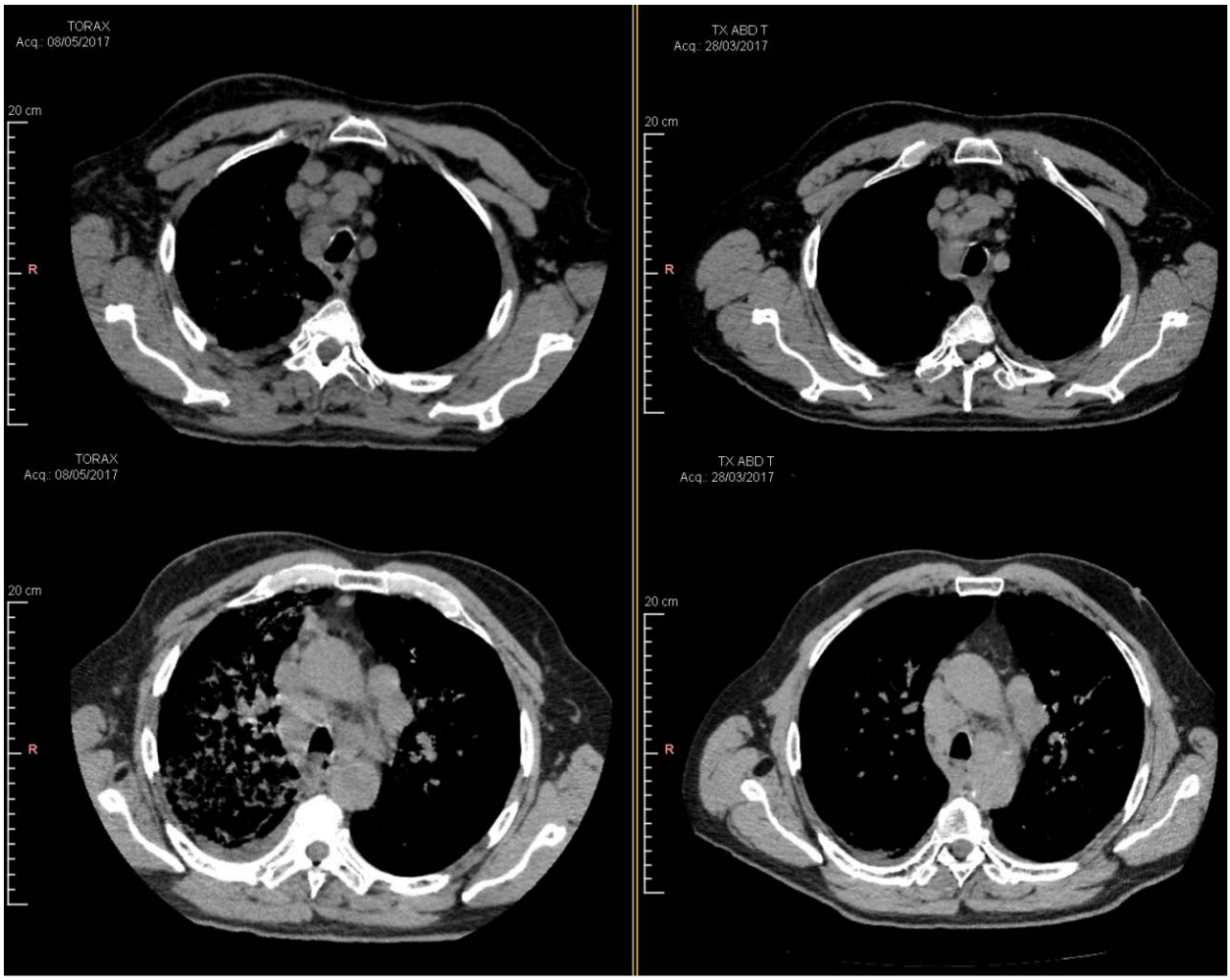

Figure 1. CT scan – Mediastinal window. Demonstrates of lymph node disease

He was with reasonable clinical status, with progressive improvement and reduction of the oxygen need. He then began with grade 2 hemoptysis in February 2017, although tomography (TC) demonstrated a stable disease by RECIST 1.1. He was referred to radiotherapy for the mediastinum metastasis treatment to control hemoptysis, which started on March 17 and received the total dose of 30 Gy in 10 fractions.

He evolved with cessation of hemoptysis, but maintained a grade 2 dyspnea and some oxygen need and continue the use of Nivolumab. The patient was inadvertently given influenza vaccination in a primary care clinic 27 days after the last radiation dose. Five days later he came to the ambulatory with worsening of dyspnea and the anti PD1 drug was interrupted, being left only symptomatic drugs and treatment for a possible respiratory infection, without associated corticosteroid therapy. Seven days later he was hospitalized because he was completely oxygen dependent, with resumption of hemoptysis, ventilatory dependent pain and status performance 4. He did not have fever or hypothermia at any given time, and the blood count was normal. CT on May 8 demonstrated small pleural effusion on the right side, as well as bilateral diffuse septal thickening associated with large areas of asymmetrical ground glass opacities, much more extensive than the March 28 CT scan, although the pulmonary nodules and the mediastinal lymphadenopathies were stable. Hemocultures collected were negative. Corticosteroids were started, but the patient did not respond well and died 5 days later.

3. Discussion

PD-1 / PD-L1 target immunotherapy has been shown since 2015 to be effective in treating some low responsive tumors. Since then, several other tumors have been proven to derive benefit from this therapy in different treatment lines.

Immunological checkpoints are molecules used to control the intensity and duration of the immune response, in order to reduce damage to the body's healthy tissue, since an exacerbated response can cause excessive inflammation and immune disorders. Checkpoints Inhibitors, when interacting with these molecules, release and unlock the immune system, allowing a more effective attack on the tumor, reducing its growth [9].

Renal cancer was one of the neoplasms for which this new therapeutic modality showed efficacy. The CheckMate 025 study was a phase III trial that assessed patients with clear cell renal cell carcinoma previously treated with one or more lines but excluding mTOR inhibitors, in which patients were randomized to receive nivolumab or everolimus. The primary outcome was overall survival and it was achieved, reducing the chance of these patients to die by 27 % [10]. Based on this work, we indicated the use of Nivolumab in our patient at that time.

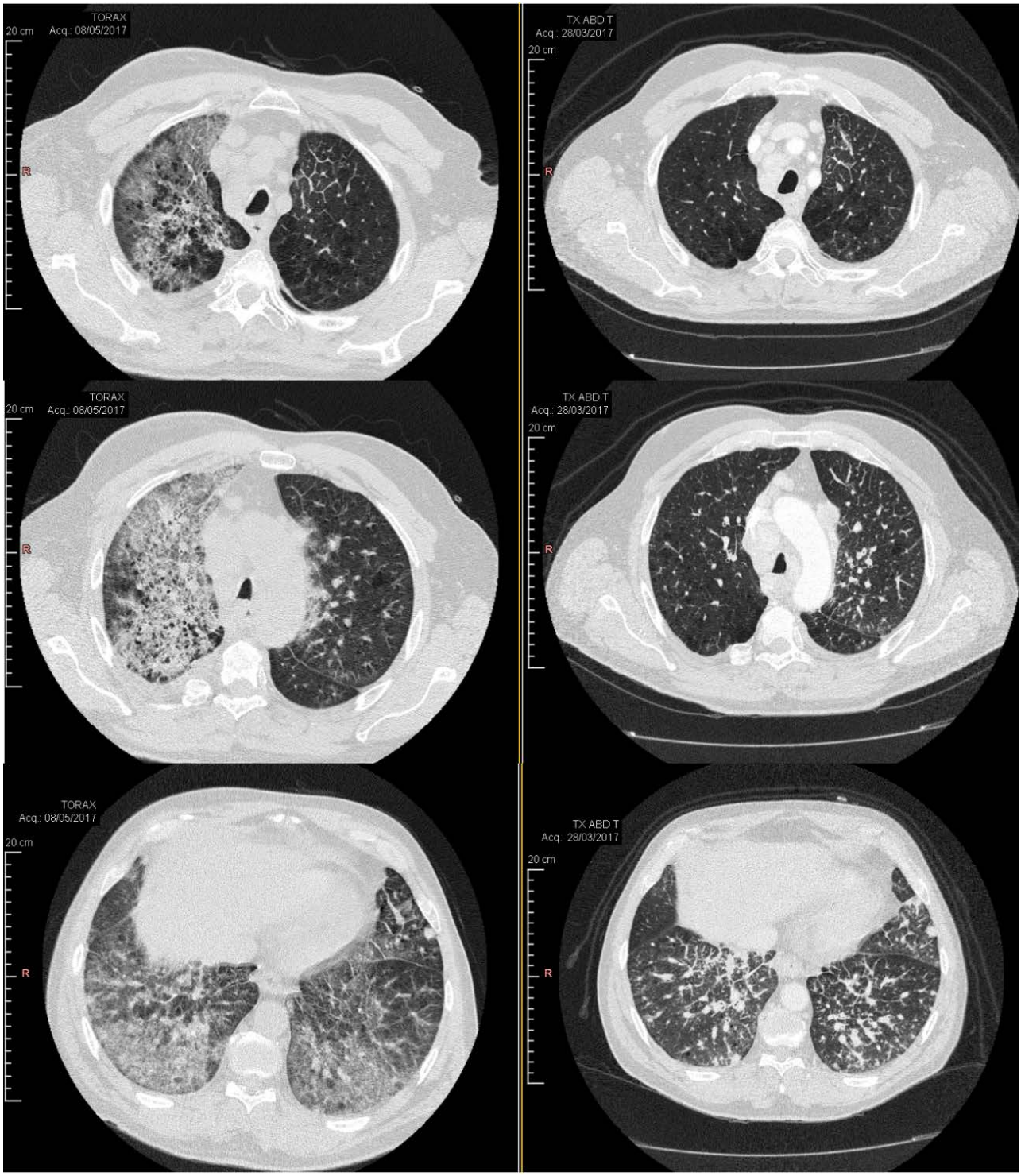

Figure 2. CT scan – Lung window. On the left (May 8) demonstrates large areas of ground glass opacities, much more extensive than the right image (March 28)

The common reported side effects with the use of immunotherapies are from the gastrointestinal tract, the skin and the endocrine system [11]. Hepatic and pulmonary toxicities, among others, can be life-threatening.

Phase II/III meta-analysis using immunotherapies including nivolumab with non-checkpoint inhibitors controls group found a 4.14 relative risk of developing pneumonitis, being considered one of the five key immune-related adverse events [12].

Another meta-analysis with lung cancer and melanoma studies have also reported an increased risk of pneumonitis of all grades with PD-1 / PD-L1 inhibitors, in addition to an increased risk of high-grade pneumonitis compared with chemotherapy (relative risk of 3.21) [13].

In a prospective study with 23 patients receiving anti-PD-1 therapy (Nivolumab in the majority) for non-small cell lung cancer, renal cancer and melanoma, patients received the trivalent influenza vaccine and were followed up. They all had an immunological response to the vaccine without adverse events within the first 30 days, but they had a high incidence of immuno-related adverse events (52.2%) at follow-up, whereas for pneumonitis the rate was 4.3% [14].

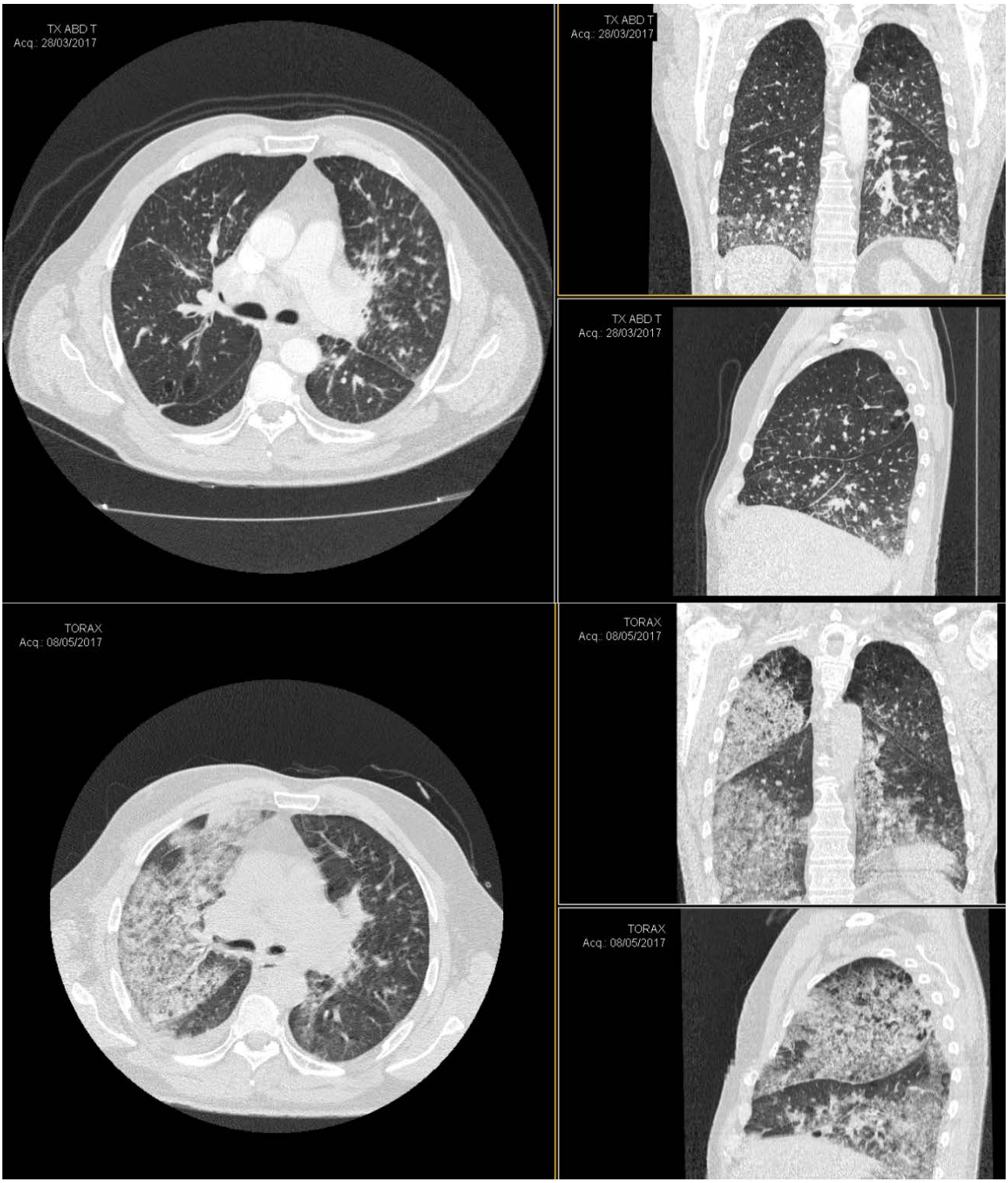

Figure 3. CT scan-Lung Window. Axial, coronal and sagittal views of March 28 (upper photos) and May 8 (lower photos)

Though rare, the influenza vaccine has also been associated with an occurrence of interstitial pneumonia. Among nine cases reported in the literature, the mean interval between symptom onset and vaccination was 3.25 days (1-7) and the mean time between vaccination and diagnosis was 10 days (2-41). The tomography results of the majority showed ground glass opacities [15].

It has also been reported in patient with previous lung disease (idiopathic pulmonary fibrosis), leading the authors to conclude that although safe in case of chronic lung disease, the vaccine can also cause exacerbation of the same [16].

PD-1 blockade tends to increase the immune response and may trigger an inflammatory syndrome, which is particularly worrying in cases of previous lung disease. In patients receiving this blockade, the influenza vaccine could cause an exacerbated immune system response, greatly affecting the patient with pre-existing pulmonary illness.

In our service, as in most cases, we recommend influenza vaccination for all patients receiving cytotoxic or target therapy, but we evaluated each patient case using new immunotherapeutics. Unfortunately this patient did not ask the assistance team about the possibility of taking

the vaccine and received it at another care facility, thinking that it would have no problem like the previous year when he received the vaccine, while on sunitinib.

We cannot ascertain that the evolution of the patient was due to the administration of the vaccine and possible adverse events, but the temporal evolution is compatible, since the cancer has been stable for months and in a few days the clinical condition declined substantially, besides that, tomographically, the areas with ground glass opacity were much larger than previous studies, however the lymph node enlargement and pulmonary nodules were absolutely the same, not being the expected scenario, therefore raising the hypothesis of acute pulmonary inflammation associated with vaccination, rather than cancer progression.

The outcome of our patient occurred in less than 30 days, unlike in the Rothschild S study [14], but the time is more compatible with an adverse effect of the vaccine.

There are reports of interstitial pneumonia after influenza vaccine and also description of pneumonitis due to immunotherapy. We know that immunotherapy may exacerbate an immunological response of the vaccine and potentiate possible lung damage caused by the vaccine itself, it is perceived that our patient may have been a victim of the combination. The time between vaccine and symptom onset and time to diagnosis is in line with a description in the literature, but if the diagnosis and steroid therapy was given before, the outcome of the patient could have been different.

In conclusion, we certainly need more data to assess the safety or not of the influenza vaccine in patients using inhibitors checkpoints, especially in patients with severe lung disease.

Therefore in patients taking immunotherapy, especially after influenza vaccine, the development of new symptoms such as worsening dyspnea and cough, chest imaging is mandatory. After infection is ruled out, steroids should be started to optimize the outcome of the patient, according to the degree of adverse effect [17].

Statement of Competing Interests

The authors have no conflicts of interest.

References

[1] Barker WH, Mullooly JP: Pneumonia and influenza deaths during epidemics: Implications for prevention. Arch Intern Med. 1982 Jan; 142(1): 85-9.

[2] Whimbey E, Elting LS, Couch RB, Lo W, Williams L, Champlin RE, Bodey GP. Influenza A virus infections among hospitalized adult bone marrow transplant recipients. Bone Marrow Transplant. 1994 Apr;13(4):437-40.

[3] Meerveld-Eggink A, de Weerdt O, van der Velden AM, Los M, van der Velden AW, Stouthard JM, Nijziel MR, Westerman M, Beeker A, van Beek R,Rimmelzwaan GF, Rijkers GT, Biesma DH. Response to influenza virus vaccination during chemotherapy in patients with breast cancer. Ann Oncol. 2011 Sep; 22(9): 2031-5.

[4] Centers for Disease Control and Prevention: Prevention and control of influenza: Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Morb Mortal Wkly Rep. 2006; (55): 1-42.

[5] Pollyea DA, Brown JM, Horning SJ. Utility of influenza vaccination for oncology patients. J Clin Oncol. 2010 May 10; 28(14): 2481-90.

[6] Pedrazzoli P, Baldanti F, Donatelli I, Castrucci MR, Puglisi F, N. Silvestris N and Cinieri S. Vaccination for seasonal influenza in patients with cancer: recommendations of the Italian Society of Medical Oncology (AIOM). Annals of Oncology 2014; 25: 1243-47.

[7] Beck CR, McKenzie BC, Hashim AB, Harris RC, University of Nottingham Influenza and the ImmunoCompromised (UNIIC) Study Group and Nguyen-Van-Tam JS. Influenza Vaccination for Immunocompromised Patients: Systematic Review and Meta-analysis by Etiology. J Infect Dis. 2012 Oct; 206(8): 1250-9.

[8] Rousseau B, Loulergue P, Mir O, Krivine A, Kotti S, Viel E, Simon T, de Gramont A, Goldwasser F, Launay O, Tournigand C. Immunogenicity and safety of the influenza A H1N1v 2009 vaccine in cancer patients treated withcytotoxic chemotherapy and/or targeted therapy: the VACANCE study. Ann Oncol. 2012 Feb; 23(2): 450-7.

[9] Dizon DS, Krilov L, Cohen E, Gangadhar T, Ganz PA, Hensing TA, Hunger S, Krishnamurthi SS, Lassman AB, Markham MJ, Mayer E, Neuss M,Pal SK, Richardson LC, Schilsky R, Schwartz GK, Spriggs DR, Villalona-Calero MA, Villani G, Masters G. Clinical Cancer Advances 2016: Annual Report on Progress Against Cancer From the American Society of Clinical Oncology. J Clin Oncol. 2016 Mar 20; 34(9): 987-1011.

[10] Motzer RJ, Escudier B, McDermott DF, George S, Hammers HJ, Srinivas S, Tykodi SS, Sosman JA, Procopio G, Plimack ER, Castellano D, Choueiri TK,Gurney H, Donskov F, Bono P, Wagstaff J, Gauler TC, Ueda T, Tomita Y, Schutz FA, Kollmannsberger C, Larkin J, Ravaud A, Simon JS, Xu LA, Waxman IM, Sharma P; CheckMate 025 Investigators. Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma. N Engl J Med. 2015 Nov 5; 373(19): 1803-13.

[11] González-Rodríguez E, Rodríguez-Abreu D; Spanish Group for Cancer Immuno-Biotherapy (GETICA). Immune Checkpoint Inhibitors: Review and Management of Endocrine Adverse Events. Oncologist. 2016 Jul; 21(7): 804-16.

[12] De Velasco G, Je Y, Bossé D, Awad MM, Ott PA, Moreira RB, Schutz F, Bellmunt J, Sonpavde GP, Hodi FS, Choueiri TK. Comprehensive Meta-analysis of Key Immune-Related Adverse Events from CTLA-4 and PD-1/PD-L1 Inhibitors in Cancer Patients. Cancer Immunol Res. 2017 Apr; 5(4): 312-8.

[13] Nishijima TF, Shachar SS, Nyrop KA, Muss HB. Safety and Tolerability of PD-1/PD-L1 Inhibitors Compared with Chemotherapy in Patients with Advanced Cancer: A Meta-Analysis. Oncologist. 2017 Apr; 22(4): 470-9.

[14] Immune response and adverse events to influenza vaccine in cancer patients undergoing PD-1 blockade. Abstract 112P_PR. European Lung Cancer Conference 2017. To be presented May 6, 2017.

[15] Hibino M, Kondo T. Interstitial Pneumonia Associated with the Influenza Vaccine: A Report of Two Cases. Intern Med. 2017; 56(2): 197-201.

[16] Umeda Y, Morikawa M, Anzai M, Sumida Y, Kadowaki M, Ameshima S, Ishizaki T. Acute exacerbation of idiopathic pulmonary fibrosis after pandemic influenza A (H1N1) vaccination. Intern Med. 2010; 49(21): 2333-6.

[17] Working Group of the Brazilian Society of Clinical Oncology. Brazilian guidelines for the management of immune-related adverse events associated with checkpoint inhibitors. Braz J Oncol. 2017; 13(43): 1-15.