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Rechallenge with Immunotherapy in Small Cell Lung Cancer – A Case Report

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Abstract

Background: Immune checkpoint inhibitors have emerged as a valuable therapeutic option in many types of advanced cancer, including small cell lung cancer. However, more research and data are still needed to understand how to better combine and sequence immunotherapy with classical chemotherapy agents in order to improve survival. Moreover, identifying and managing immune-related adverse events is still challenging.

Case presentation: We report a case of a recurrent small cell lung cancer. The patient was referred for inclusion in a clinical trial after progression of the disease despite two lines of therapy. After discontinuing both the nivolumab and ipilimumab treatment because of grade 3 hepatitis and grade 2 pneumonitis, and also after progression to a fourth line treatment with chemotherapy, the patient was rechallenged with compassionate use nivolumab monotherapy. This therapy was discontinued due to SOX1-positive dysarthria-clumsy-hand syndrome, which improved with corticosteroid therapy. After almost one year, the tumor remained stable reinforcing the idea that the cause of the complication was an immune-related encephalitis due to anti-PD1. Despite the severe toxicity, the patient achieved a long-term survival of almost four years.

Conclusion: The remarkable long-term survival obtained with immunotherapy rechallenge in this small cell lung cancer patient is promising for its future use in this setting characterized by a poor prognosis. However, immunotherapy rechallenge is not without risks. In fact, this is also the first case report on SOX1-positive autoimmune encephalitis due to anti-PD1. It also highlights the need of a careful diagnosis and therapy monitoring to prevent and mitigate potential irAEs.

Keywords: Immunotherapy; Nivolumab; Rechallenge; Small Cell Lung Cancer (SCLC); Anti-SOX1; Autoimmune encephalitis

Abbreviations: SCLC: Small Cell Lung Cancer; Icis: Immune Checkpoint Inhibitors; Irae: Immune-Related Adverse Events; OS: Overall Survival; CT: Computed Tomography; CAV: Cyclophosphamide-Doxorrubicin-Vincristine; CPT11: Irinotecan; PM1183: Lurbinectedin; MRI: Magnetic Resonance Imagining; TMB: Tumor Mutational Burden; ORR: Objective Response Rate; PFS: Progression Free Survival

Introduction

Lung cancer was the most frequent cancer worldwide with 2.093.876 new cases in 2018 [1]. SCLC accounts for around 15-20% of all lung cancer diagnoses [2]. Although incidence has been decreasing, overall survival (OS) is still low with under 27% of patients with extensive-stage disease being alive at one year [3]. While there is good initial response to platinum-containing chemotherapy doublets, the disease recurs in most of the patients [2]. Therapeutic options in third line and beyond are scarce. In this context, immunotherapy strategies have been studied in this setting in phase I/II randomized controlled trials with promising results [4,5]. These results have led to the recent approval of nivolumab monotherapy in SCLC patients who have progressed to platinum-based chemotherapy and, at least, another line of therapy [4,5]. Furthermore, a recent phase III randomized study demonstrated the superiority of the addition of atezolizumab to platinum-based standard first-line chemotherapy versus chemotherapy alone [6].

The aim of the following case report is to show the remarkable and outstanding long OS of a SCLC patient retreated with nivolumab. The report also intends to shed light on the current role of immunotherapy rechallenge after immune-related toxicities. As far as we know this is the first case of immunotherapy retreatment in SCLC and also the first case of SOX1-positive autoimmune encephalitis.

Case Presentation

In October of 2014, a 55-year-old smoker female was diagnosed of limited-stage SCLC associated with superior vena cava syndrome. According to the multidisciplinary board decision, she underwent four cycles of concurrent chemoradiotherapy with cisplatin and etoposide achieving partial response. Prophylactic cranial irradiation was performed after finishing the thoracic treatment.

Six months later, in April of 2015, a re-evaluation CT scan showed a pelvic lesion, confirmed by percutaneous soft-tissue biopsy to be a tumor recurrence. Four cycles of high dose cyclophosphamide-doxorrubicin-vincristine (CAV) were administered and partial response was achieved. This was followed by pelvic radiotherapy with concomitant weekly paclitaxel (3 cycles) and thus the treatment was completed in September of 2015.

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Two months later, in November of 2015, as retroperitoneal and pelvic progression were detected (Figure 1A), the patient was referred to our hospital for enrolment in the Checkmate-032 clinical trial for recurrent SCLC (NCT019283943). Accordingly, she was assigned to receive four doses of ipilimumab (3 mg/kg) with nivolumab (1 mg/kg) every three weeks followed by nivolumab (3 mg/kg) every two weeks as third line treatment. After three cycles of the combination, in January of 2016, she achieved partial response (Figure 1B). Nevertheless, due to immune-related grade 3 hepatitis and grade 2 pneumonitis (Figure 2A), the study treatment was discontinued, and corticosteroids were started. She remained in partial response until June of 2016. By that time, she had completed almost 10 weeks of full dose corticosteroid therapy (1 mg/kg) followed by gradual reduction with hepatitis and pneumonitis resolution (Figure 2B).

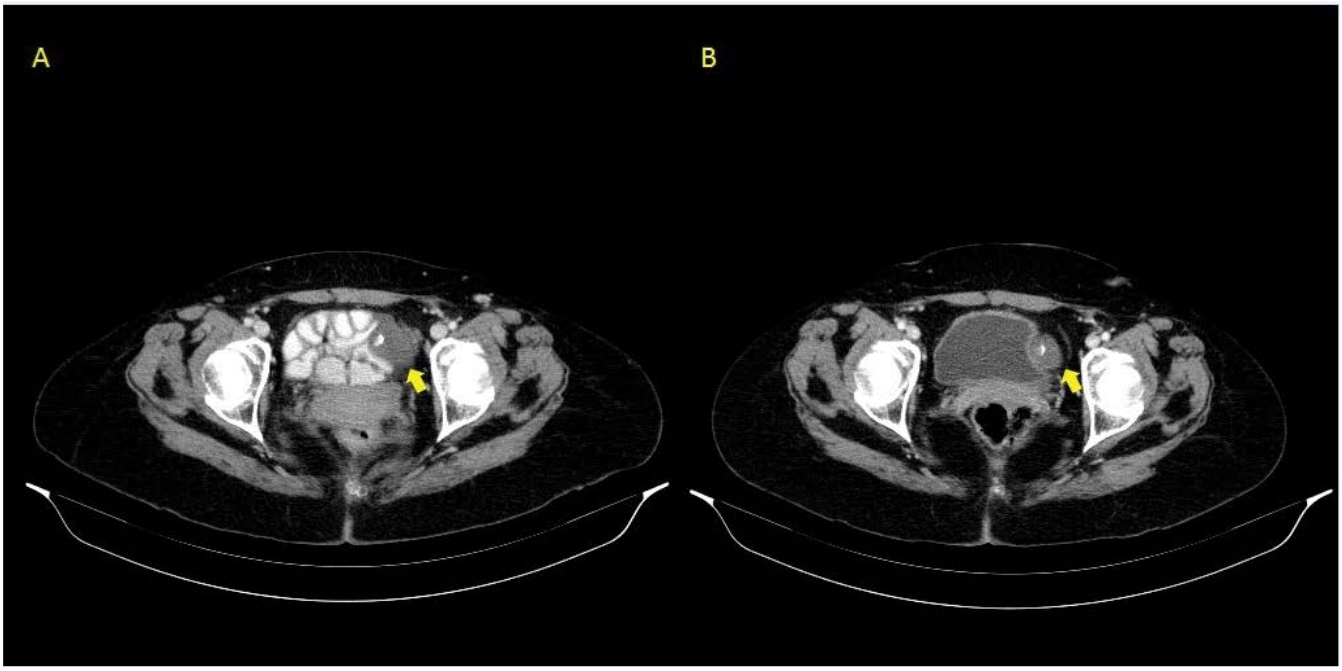

Figure 1: (A) CT scan showing the pelvic parauterine revurrence (arrow), **(B)** CT scan showing the response (arrow) pf the pelvic recurrence to double immune checkpoint blockade with ipilimumab and nivolumab, after 3 cycles.

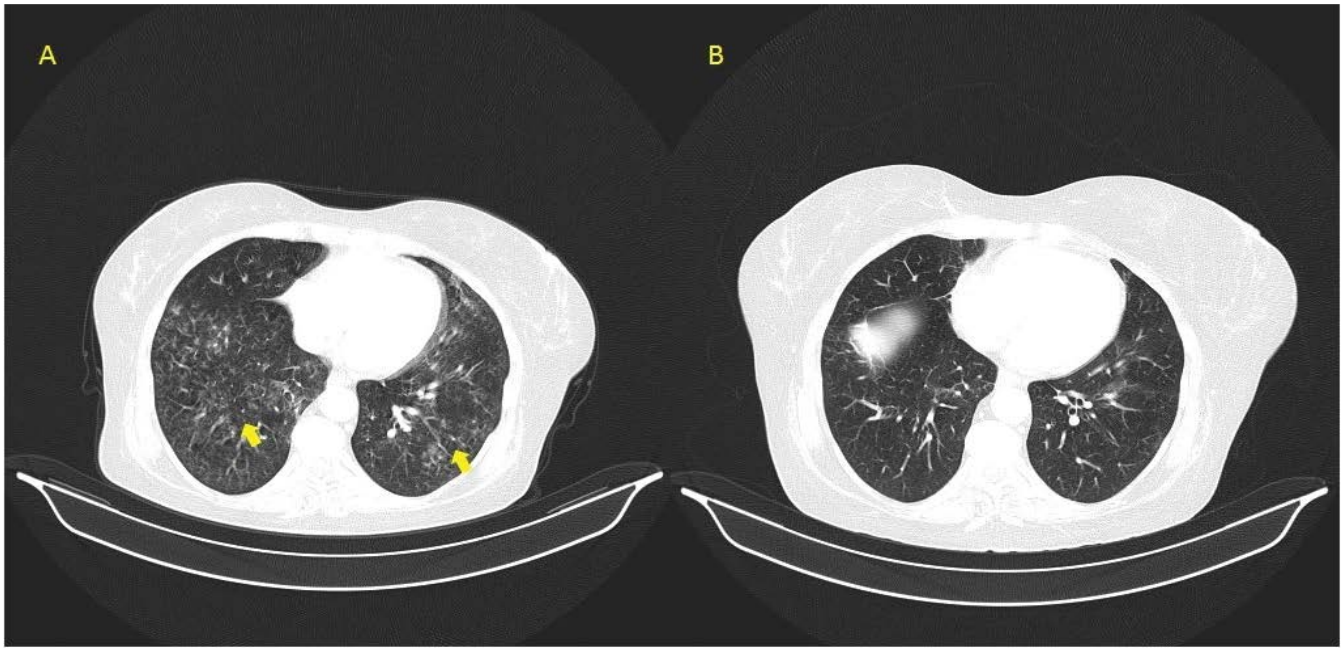

Figure 2: (A) CT scan showing bilateral interstitial infiltrates compatible with pneumonitis, **(B)** CT scan showing resolution of the bilateral infiltrates two months after corticosteroid treatment.

However, pulmonary and pelvic progression were detected on a new reassessment CT scan and the patient entered a clinical trial with irinotecan (CPT11) 75 mg/m^2 on days 1 and 8 plus lurbinectedin (PM1183) 1 mg/m^2 (PM1183 escalation group) on day 1 every three weeks as fourth line treatment. She received 13 cycles with stable disease as best response until ganglionar progression was evidenced in March 2017.

Given the initial response obtained with immune checkpoint inhibitors (ICIs) and the reported efficacy outcomes of the Checkmate-032 trial-3, nivolumab monotherapy (3 mg/kg every two weeks) for compassionate use was started as fifth line treatment in May 2017. She achieved stable disease as best response to the treatment without any recurrence of the immune-related hepatitis or pneumonitis since the beginning of the immunotherapy rechallenge. However, after the 8th cycle of nivolumab, she began to experience sleepiness, gait instability and dysarthria-clumsy hand syndrome, more evident on her right hand. The cranial CT scan showed no abnormal findings. After neurological evaluation, a cerebellar syndrome was suspected to be either of paraneoplastic origin or due to leptomeningeal dissemination, and therefore a brain MRI was performed. The MRI scan showed no brain metastasis but revealed multiple focal hyperintense lesions in the subcortical white matter (Figure 3), suggesting either an immune-related syndrome or a paraneoplastic syndrome. Spinal puncture showed negative cytology and no evidence of infection. High dose intravenous methylprednisolone was administered for 5 days (1 g/24 h) and nivolumab was discontinued. In the face of the suspicion of a paraneoplastic syndrome, a panel of neuro-oncology antibodies (anti-SOX1; anti-NMDA; anti-AMPA; anti-GABAA/B; anti-mGluR1/R5; anti-DDPX; anti-IgLON5; anti-Neurexine; anti-LGl1 and anti-CASPR2) in the cerebrospinal fluid was requested and showed a positive result for anti-SOX1 antibodies. High dose corticosteroids treatment was followed by prolonged and progressive reduction of corticosteroids dose, but without complete resolution of neurological symptoms. Nine months later no changes were detected on the follow-up brain MRIs and the patient remained with systemic stable disease, leading us to think that this was in fact an autoimmune encephalitis in relation to anti-PD1 rather than to a paraneoplastic syndrome. So far, the patient had almost reached four years of survival since the diagnosis of the first recurrence, which overcomes previous reported median survival of around 12 months for extensive-stage SCLC6 (Figure 4).

Discussion

The treatment options for extensive SCLC are scarce and optimal treatment sequence still requires further studies. "Rechallenge" refers to retreating patients with an earlier line of therapy which already showed positive results. This strategy, in fact, is not new, as it has previously been used with chemotherapy in platinum-sensitive SCLC patients who can be retreated in second line with platinum doublet rechallenge. However, little is known about rechallenge with immunotherapy in SCLC. After the recently proved benefit of the addition of immunotherapy to chemotherapy frontline, as well as the approval of nivolumab monotherapy in third line setting and beyond, there is a stronger base for considering the immunotherapy rechallenge [4-7]. In this sense, the long-term response obtained in our patient with immunotherapy rechallenge is encouraging and deserves further investigation.

In the phase I/II Checkmate-032 trial, a heavily pre-treated and biomarker unselected SCLC population received nivolumab alone or in combination with ipilimumab. The nivolumab monotherapy group showed an objective response rate (ORR) of 11.9% with durable responses (at least 12 months) in 61.5% of these patients [5]. Although no differences were seen depending on the PD-L1 status, an exploratory analysis showed improved outcomes in patients with high tumor mutational burden (TMB) reaching a 21.3% ORR versus a 4.8%

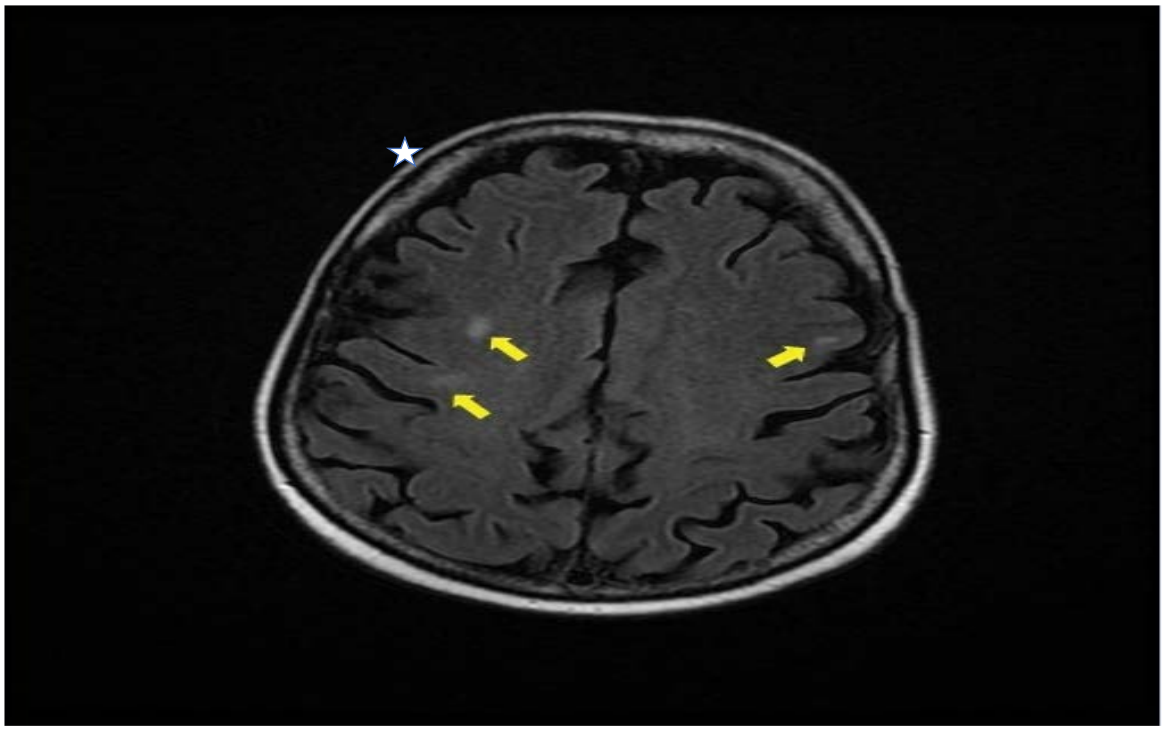

Figure 3: Brain MRI showing no brain metastasis but revealing multiple focal hyperintense lesions in the subcortical white matter (arrows).

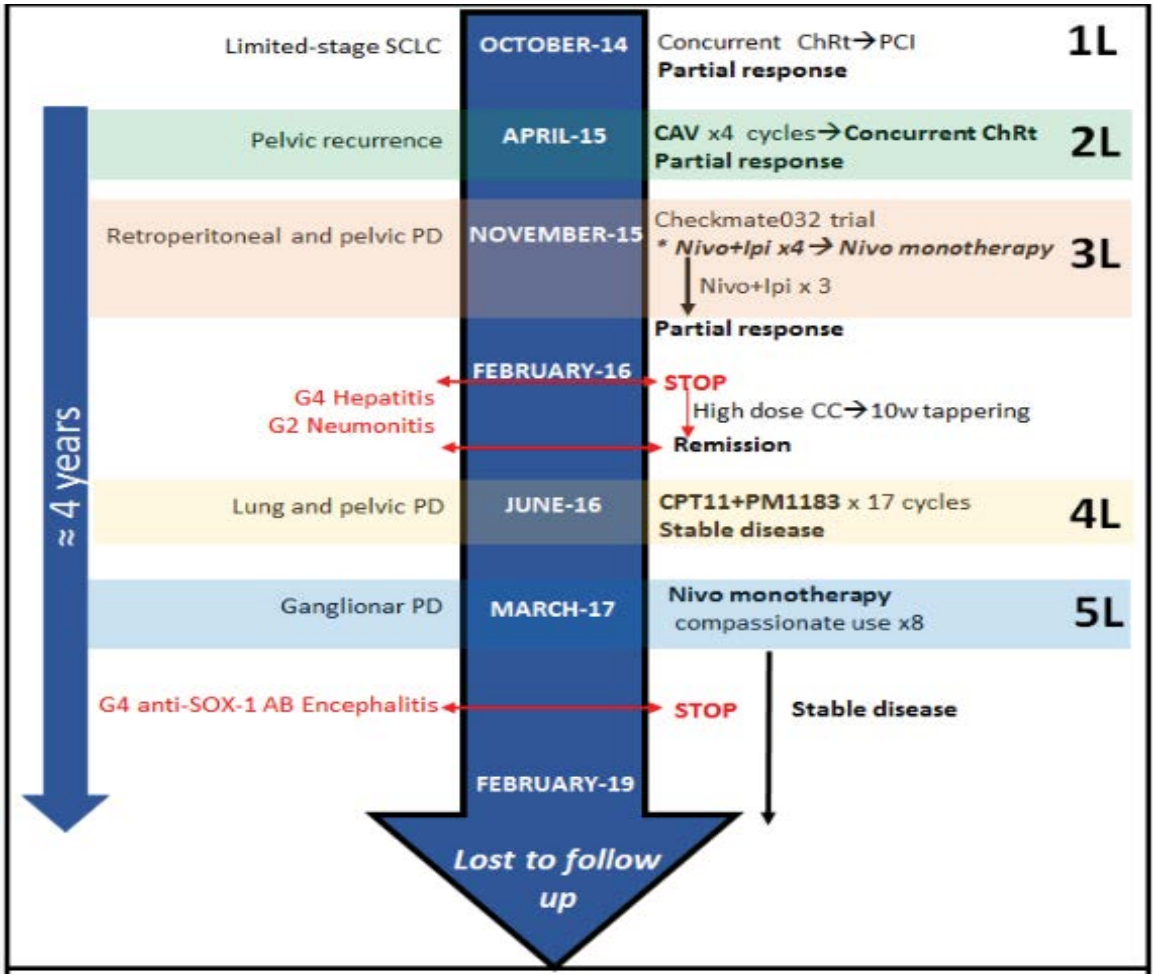

Figure 4: Case report timeline figure. [ChRt: Chemo-radiotherapy; SCLC: Small cell lung cancer; CAV: Cyclo phosphamide, adriamycin, vincristine; PD: Progression; Niivo: Nivolumab; Ipi: Ipilimumab; CC: Corticosteriods; W: Week; G: Grade; CPT11: Irinotecan: PM1181: Lurbinectidin; AB: Antibody].

in those with low TMB [8]. The impact of the TMB was even greater for the combination group (46.2%) in which our patient was included [8]. This data suggests TMB as a potential predictive biomarker of response to immunotherapy in SCLC. Median progression free survival (PFS) and OS were 1.4 and 5.6 months respectively for the nivolumab monotherapy arm [5]. These results have led to the approval of nivolumab in SCLC patients who have progressed to platinum-based chemotherapy and, at least, another line of therapy. Recently pembrolizumab was also approved in the same setting by the FDA according to the results of the Keynote-158 trial [9]. Interestingly in the Keynote 158, OS/PFS and response rate differed depending on the PD-L1 status, with best responses and better survival outcomes seen in PD-L1 positive patients. Morevover, the phase III IMPOWER133 trial (NCT02763579), studied the addition of atezolizumab to standard first-line chemotherapy, carboplatin and etoposide, showing a significant increase in both PFS and OS versus chemotherapy alone, as well as longer ongoing responses [6]. However, in contrast to previous studies [8] the TMB didn´t seem to be a predictive biomarker of response to atezolizumab [9].

In addition, chemotherapy has been shown to increase tumor immunogenicity by enhancing tumor-specific neoantigen presentation and decreasing immunosuppressive cytokines. This would reinforce the strategy of using immunotherapy rechallenge after chemotherapy [10]. In this sense, this case represents, as far as we know, the first example of immunotherapy retreatment in SCLC with positive outcomes, despite the potential toxicity it involves.

We have performed a systematic literature review on MEDLINE, EMBASE and Web of Science platforms in search of published articles dealing with immunotherapy rechallenge in lung cancer and, specifically, in SCLC. We found 2 case reports [11,12] of non-small-cell lung cancer (NSCLC) who were treated with nivolumab monotherapy as third- or fourth line of treatment. Although in both cases there was tumor response, treatment was stopped due to irAE (grade 3 encephalitis and grade 2 pneumonitis) and corticosteroids were initiated with relief of symptoms. Unfortunately, when both patients were retreated with nivolumab, the irAEs recurred.

We also found two retrospective cohort studies describing the experience of two large centers in managing irAEs in patients included in randomized controlled trials with ICIs. The Dana-Farber group [13] characterized a series of 20 patients who developed any grade of pneumonitis. After withholding the treatment and initiating corticosteroids, nivolumab was reinitiated in seven of the patients, none of whom were lung cancer patients. On the other hand, the MD

Anderson group [14] reported all irAEs in 290 patients with solid tumors treated with PD-1 inhibitors in clinical trials and 35 were NSCLC. Of the 15 patients who developed grade 3 or higher irAEs, five were rechallenged and four of them showed favourable response. Also, an association between development of grade ≥3 irAE and improved ORR and time to disease progression was observed.

Recently Santini et al. studied 68 NSCLC patients treated with anti-PD-L1 therapy which had been withheld due to irAEs and divided them into two groups, the retreatment cohort and the discontinuation cohort. Interestingly, immunotherapy rechallenge only seemed to benefit those patients with no prior treatment response [15].

However, the greatest bulk of evidence in relation to immunotherapy rechallenge comes from retrospective cohorts of metastatic melanoma patients treated with either ipilimumab [16,17], nivolumab [18] or both [19,20].

Regarding the diagnosis of autoimmune encephalitis (AIE) this case would be to our knowledge the first reported anti-SOX1-positive case. Encephalitis has been described with combined immunotherapy (nivolumab and ipilimumab) [21,22], with sequential immunotherapy (chemotherapy plus ipilimumab followed by lambrolizumab) [23] and in monotherapy with either nivolumab [24,25] or ipilimumab [26]. Larkin et al. reported a series of 3763 metastatic melanoma patients who were treated with ICIs and found 35 cases (0.93%) of serious neurological irAEs, of which only six patients had AIE [27].

In this clinical setting and in the face of newly developed neurological symptoms imaging assessment should always be considered to exclude disease progression. This is the main concern in differential diagnosis because it requires a new oncological treatment. Furthermore, paraneoplastic syndromes with CNS-involvement should also be considered. Neuro-oncological autoantibodies may help with in the diagnosis, but they lack sensitivity and specificity. Therefore, neurological irAEs are an exclusion diagnosis which cannot be confirmed with a simple therapeutic test. In most of the reported cases, neurological impairment resolved after discontinuation of immunotherapy and corticosteroid treatment [21-27]. Of all the reported cases, there was only one fatal outcome following discontinuation of immunotherapy and it was related to brainstem AIE [22].

Our case involves an anti-SOX1-positive neurological syndrome. This recently discovered onco-neural antibody has been described as a marker of SCLC and has been seen in paraneoplastic neuropathies associated to SCLC [28,29]. Current studies have shown that SOX1 antibodies fail to differentiate paraneoplastic neuropathies from non-paraneoplastic, as they can be present in both [30]. The clinical and radiological evolution that was seen in our patient after the start of corticosteroids, with no evidence of disease progression months after this episode, led us to believe that this is,in fact, a unique case of checkpoint inhibitor-associated AIE with positive anti-SOX1 antibodies. This is of outstanding interest as it can raise the basis for future research on this issue. In addition, the impact of neurological events is remarkable and still deserves to be studied in depth [31].

Conclusion

In conclusion, the long-term survival obtained with immunotherapy rechallenge in this patient with SCLC is promising and encouraging for future prospective studies. In addition, to the best of our knowledge, this is the first case of SOX1-positive AIE due to checkpoint inhibitors, highlighting the need of careful diagnosis and monitoring to prevent and mitigate potential irAEs. In this regard, there is a need for predictive biomarkers to better identify which patients are more likely to develop severe toxicities.

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