

Case report

Nivolumab Treatment in a Mucosal Melanoma Patient with Pre-Existing Systemic Lupus Erythematosus: A Case Report with Literature Review

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SUMMARY

Introduction. Systemic lupus erythematosus (SLE) represents a multisystemic disease characterized by antibody production, complement activation, and immune complexes deposition. Certain types of malignancies occur more often, and conversely, some of them occur less often in SLE patients. Mucosal melanoma of the anorectal region represents a rare form of melanoma occurring in 1.5% of all melanoma patients, predominantly female. The introduction of novel agents dramatically changed the outcome in melanoma patients and introduced different adverse events, diverse contraindications, and drug interactions.

Immune checkpoint inhibitors have a role in the maintenance of immunologic homeostasis. Patients with underlying autoimmune diseases were often excluded from clinical trials, for fear of possible autoimmune disease exacerbation or high-grade immune-related adverse events. Due to that, data regarding this subgroup of patients is limited, with no clear recommendations. Given the fact that prevalence among the general population is high (5 - 10%), autoimmune diseases represent common comorbidity in cancer patients. Having that in mind, it is of utmost importance to personalize the approach and individualize the SLE treatment and enable the use of PD-1 antibody in the safest and most useful way while keeping the SLE in control.

Case report. Herein we present a 79-year-old with primary mucosal melanoma of the anorectal region, with lung metastasis and preexisting SLE in remission. Hydroxychloroquine was the only treatment for SLE. Nivolumab treatment was initiated in the standard dosing schedule. After the first and second follow-up, no further progression of melanoma was detected, with no SLE exacerbation and immune-related adverse events.

Conclusion. PD-1 treatment in a patient with an underlying autoimmune disease represents a viable choice with a necessity for a multidisciplinary approach and close monitoring.

Keywords: mucosal melanoma, systemic lupus erythematosus, immune checkpoint inhibitors, nivolumab

INTRODUCTION

Systemic lupus erythematosus (SLE) represents a multisystemic disease characterized by antibody production, complement activation, and immune complexes deposition. SLE predominantly affects young and middle-aged women (1).

The association of SLE and different malignancies was vastly researched, with inconsistent results. There are several subtypes of malignancies, in which higher incidence among patients with SLE was observed, such as thyroid cancer, haematological malignancies, and cervical cancer. Contradictory, certain malignancies occur less in SLE patients compared to the general population, with melanoma being one of them (2).

Melanoma represents a type of cancer that originates from melanocytes, with an increase in incidence observed in the past 30 years. As for the melanoma subtypes, the cutaneous form occurs most commonly, followed by ocular and mucosal ones (3). Mucosal melanoma of the anorectal region represents a rare form of melanoma occurring in 1.5% of all melanoma patients, predominantly female.

The introduction of novel agents dramatically changed the outcome in melanoma patients, especially in the cutaneous form (4,5). On the other hand, those agents introduced different adverse events, compared to conventional chemotherapeutic agents, but also diverse contraindications and drug interactions. Herein we report a case of mucosal melanoma patient treated with Nivolumab, with underlying SLE.

CASE PRESENTATION

A 79-year-old woman was admitted to the gastroenterology department for examination due to the presence of blood in the stool. She had been diagnosed with SLE 40 years before, with only skin manifestation in the form of rash and photosensitivity. SLE was well controlled at the time of hospital admission, with hydroxy-chloroquine (HCQ) as the only treatment.

A colonoscopy was performed which showed a prominent tumorous lesion in the lower rectum, and a biopsy sample was taken. Magnetic resonance imaging (MRI) of the pelvis showed wall thickening with low signal intensity. Computed tomography (CT) of the thorax and abdomen excluded disease dissemination. There were no abnormalities in blood test, and normal levels of carbohydrate antigen 19-9 (CA19-9) and carcinoembryonic antigen (CEA) were observed as well.

Histopathology showed positive immunostaining for S-100, HMB-45, and Melan-A, therefore indicating melanoma. No suspicious lesions were seen on the skin during the whole body dermoscopy examination, therefore the diagnosis of primary mucosal melanoma of the rectum was made. Surgical wide local excision was performed as a primary therapeutic approach. Pathology staging report showed invasion of muscularis propria, therefore, stage I (pT2, N0, M0) was ascertained. The patient recovered without complications and was discharged from hospital. No adjuvant treatment was introduced, with a 3-month follow-up as an approach.

Three months after surgery reevaluation was made using the whole-body CT which showed a metastatic deposit in the medial segment of the left lung. The melanoma specimen was tested for BRAF and RAS, and no mutations were detected. Given the fact that SLE was in remission, with HCQ as the only treatment, we decided to initiate Nivolumab treatment (480 mg every 4 weeks). After 4 and 8 cycles of treatment, CT scans were performed, showing no change in the number and diameter of lung deposits. Administration of Nivolumab was continued, without any irAEs or SLE exacerbation. Nivolumab was continued with strict follow-up by both the oncologist and rheumatologist and no progression was observed at 12 months from Nivolumab initiation.

DISCUSSION

ICIs have a role in the maintenance of immunologic homeostasis. Patients with underlying autoimmune diseases were often excluded from clinical trials, for fear of possible AD exacerbation or high-grade irAEs (6, 7). Consequently, data regard-

ing this subgroup of patients is limited, with no clear recommendations.

The introduction of ICIs drastically changed outcomes in melanoma patients, therefore making them a crucial part of treatment. Given the fact that prevalence among the general population is high (5 - 10%), AD represents common comorbidity in cancer patients (8). Having that in mind, it is of utmost importance to personalize the approach and individualize the SLE treatment and enable the use of PD-1 antibody in the safest and most useful way while keeping the SLE under control. Also, irAEs of ICIs may resemble certain AD, which could be a clinical challenge, in terms of differentiation of irAEs and disease exacerbation. The pathophysiology of those adverse events remains uncertain, but there are indications that CTLA-4 and/or PD-1 inhibition leads to T cell activation resulting in the production of different proinflammatory cytokines causing off-target inflammation and autoimmunity [9, 10].

Patients with AD should be stratified into two subgroups, based on the disease activity and requirement for immunosuppression. The first group represents patients with low activity of the disease, requiring no treatment or a low dose of immunosuppression. Several retrospective studies which included melanoma and NSCLC patients with low activity of AD at the beginning of PD-1 administration, as was the case with our patient, reported no safety signals regarding the response to treatment, with only a few AD exacerbations that were manageable (11 - 13). As for the SLE patients treated with PD-1 data is limited, but based on the data, available risk of de novo irAEs and SLE flare-up seems acceptable (14). Treatment with hydroxychloroquine (HCQ) and low-dose corticosteroids (prednisolone < 7.5 mg, or equivalent) represents a possible choice in this subgroup of patients. Corticosteroids should be minimized, up to the complete exclusion in the maintenance setting, if possible (15). As for the HCQ and PD-1 agent interaction, contradictory reports are showing both positive and negative effects of HCQ on the PD1 treatment.

The second group represents patients with higher activity of the disease or disease flare-up, in which AD control is not possible with HCQ and low-dose corticosteroids. There are indications that non-

selective immunosuppressants (NSI) should be stopped, such as high doses of corticosteroids, methotrexate, azaran, mikofenolat mofetil, etc. It is reported that corticosteroids have a negative, dose-dependent effect on the efficacy of ICIs, therefore, the doses higher than 10 mg of prednisolone, or the equivalent should be avoided (16, 17). A possible mechanism which leads to poorer response to PD-1 treatment among patients treated with NSI is a modulation of peripheral blood immune cells. This reduces proliferative bursts of CD8+ T cells, which are needed in cancer response to ICIs (18 - 20).

Selective immunosuppressants that could be taken into consideration are Belimumab and Rituximab. Belimumab represents an anti-B lymphocyte stimulator, which could be introduced in patients with inadequate disease control with first-line treatment (HCQ and prednisolone < 7.5 mg). Also, among the SLE patients with the extrarenal disease treated with NSI upon the introduction of ICI, Belimumab could be a drug of choice to replace NSI, in concomitant treatment with ICIs (21 - 24).

Rituximab (RTX) represents a chimeric anti-CD-20 antibody, which is due to negative randomized controlled trials only used off-label in SLE patients with severe renal and extrarenal (neuro-psychiatric and haematological) disease. RTX is introduced upon the failure of first-line therapies (MMF, CYC) (15). In patients with renal SLE, which are candidates for ICI introduction, RTX could be a therapeutic possibility. Furthermore, there are suggestions that drug resistance in melanoma is through tumor-associated B cells. Also, CD-20 is abnormally expressed in certain melanoma cells (25, 26). Depletion of B cells showed no effect on the response to PD-1 inhibition or survival. Also, the use of RTX in irAEs treatment of ICIs is widely reported, therefore supporting the potential use of RTX in this subpopulation of patients furthermore (27 - 31).

CONCLUSION

In conclusion, PD-1 treatment in a patient with an underlying autoimmune disease represent a viable choice with a necessity for a multidisciplinary approach and close monitoring.

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Primena nivolumaba kod bolesnice sa mukozalnim melanomom i sistemskim lupusom: prikaz slučaja sa pregledom literature

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SAŽETAK

Uvod. Sistemski lupus predstavlja multisistemsku bolest koju karakterišu stvaranje antitela, aktivacija komplemenata i nagomilavanje imunskih kompleksa. Različite vrste maligniteta mogu se češće odnosno ređe javiti kod bolesnika sa sistemskim lupusom. Mukozalni melanom anorektalne regije je retka forma melanoma. Javlja se prvenstveno kod žena i čini oko 1,5% bolesnika sa melanomom. Uvođenje inovativne terapije drastično je izmenilo terapijski ishod kod bolesnika sa melanomom, ali je dovelo i do pojave novih neželjenih efekata, kontraindikacija i interakcija sa drugim lekovima.

Inhibitori kontrolnih tačaka imaju ulogu u održavanju imunološke homeostaze. Pacijenti sa autoimunim bolestima često su isključivani iz kliničkih studija zbog bojazni od egzacerbacije autoimune bolesti i pojave neželjenih efekata visokog stepena. Usled toga, za ovu podgrupu bolesnika ne postoje jasne preporuke. Prevalencija autoimunih bolesti u populaciji je visoka (od 5% do 10%), te one predstavljaju čest komorbiditet kod onkoloških bolesnika. S obzirom na gorenavedeno, neophodan je personalizovani pristup koji bi omogućio tretman inhibitorima kontrolnih tačaka na najsigurniji način, uz adekvatnu kontrolu sistemskog lupusa.

Prikaz slučaja. Predstavljen je slučaj sedamdesetdevetogodišnje žene sa metastatskim primarnim mukozalnim melanomom anorektalne regije i ranije postavljenom dijagnozom sistemskog lupusa. U trenutku postavljanja dijagnoze melanoma, sistemski lupus bio je u remisiji, sa hidroksihlorokinom kao jedinom terapijom. Započeta je terapija nivolumabom u standardnim dozama, bez izmene konkomitantne terapije sistemskog lupusa. Nakon prvih triju kontrola i ukupno 12 ciklusa imunoterapije, nije detektovana ni dalja progresija onkološkog oboljenja, ni egzacerbacija sistemskog lupusa, ni pojava imunoloških neželjenih efekata nivolumaba.

Zaključak. Primena antitumorske PD-1 terapije kod bolesnika sa autoimunim komorbiditetima predstavlja mogući terapijski pristup, koji zahteva redovno praćenje od strane multidisciplinarnog tima.

Ključne reči: mukozalni melanom, sistemski lupus, inhibitori kontrolnih tačaka, nivolumab