

Successful Combination Therapy of Nivolumab and Radiation for Massive Mucosal Melanoma in Patient with Autoimmune-Myasthenia Gravis, Systemic Lupus Erythematosus and Rheumatoid Arthritis

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Abstract

A 58-year-old woman complicated with autoimmune diseases of myasthenia gravis (MG), rheumatoid arthritis, and systemic lupus erythematosus noticed an irregular black macule on her bilateral major labia, which was diagnosed as malignant melanoma. The melanoma lesion involving the vagina, uterus, and ventral side of rectum was not operable and was treated with nivolumab and concurrent radiotherapy with good control of the MG. This resulted in remarkable tumor shrinkage, possibly due to synergistic effects of both treatments. To our knowledge, few reports have described the effectiveness of combination therapy with nivolumab and radiation for malignant melanoma. The present case showed an enhanced anti-tumor effect with combination therapy.

Keywords

Anti PD-1 Antibody, Radiation, Malignant Melanoma, Myasthenia Gravis

1. Introduction

For over 40 years, there has been no effective treatment for malignant melanoma

that cannot be treated with surgery because of distant metastasis. However, with the development of immune-checkpoint inhibitors, the treatment of advanced-stage malignant melanoma has developed dramatically. Immune-checkpoint inhibitors are drugs that activate immunity against tumors by inhibiting immunosuppressive mechanisms, and their effectiveness has been shown in many large-scale randomized trials [1]. However, many cases have been reported in which symptoms of existing autoimmune diseases are exacerbated in addition to the onset of various immune-related adverse events (irAEs) after the administration of these agents [2]. Therefore, nivolumab treatment in malignant melanoma patients with autoimmune diseases requires physicians practice stringent awareness and promptly manages irAEs.

In the present study, we administered nivolumab to an advanced-stage melanoma patient complicated with autoimmune disorders.

2. Materials and Methods

A 58-year-old woman complicated with autoimmune diseases of myasthenia gravis (MG), rheumatoid arthritis, and systemic lupus erythematosus suffered from malignant melanoma in the anal region and received local resection and subsequent artificial anostomy in 2012. Three years later, she noticed bleeding and pain on her genital region. An irregular black macule on the bilateral major labia to the vagina (**Figure 1(a)**) was observed and diagnosed as recurrence of malignant melanoma, as confirmed by HMB45 and MelanA immune staining (**Figure 1(b)**). Magnetic resonance imaging (MRI) revealed a massive tumor involving the vagina, uterus, and the ventral side of the rectum (**Figure 1(c)**, left panel).

The patient consented to having her case reported after being sufficiently informed.

3. Results and Discussion

A biopsy specimen of the vagina lesion showed the massive proliferation of atypical cells filled with melanin. Because radical tumor resection would be extremely invasive, we decided to perform concurrent therapy of nivolumab and radiotherapy (45 Gy/15 times). Given that the effect of nivolumab might have been weakened by immunosuppressant therapy, the administration of immunosuppressant drugs (azathioprine, tacrolimus, and methotrexate) was paused, and the dose of prednisolone was increased from 5 to 15 mg. Because systemic steroid treatment failed to control the activity of MG, intravenous immunoglobulin (IVIG) was administered after the sixth administration of nivolumab. Since her bulbar palsy improved dramatically after the third administration of IVIG, we continued to administer nivolumab. Abdominal MRI showed the complete disappearance of the massive tumor after the 15th cycle of nivolumab and radiotherapy (**Figure 1(b)**, right panel). In addition, at the ninth cycle of nivolumab, a biopsy specimen showed the dense infiltration of melanophages

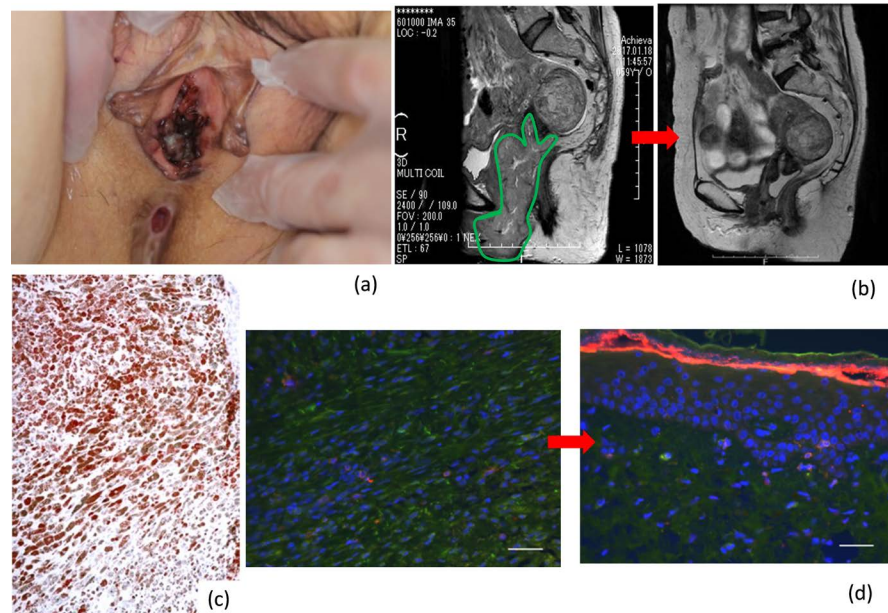


Figure 1. (a) Clinical feature of the genital lesion. An irregular black macule was observed on the bilateral major labia to the vagina; (b) MRI showed the complete disappearance of the massive tumor after the 15th cycle of nivolumab and radiotherapy; (c) Dense infiltration of melanophages positive for CD68 was noted without melanoma cells; (d) Greater infiltration of $CD8^+PD-1^+$ T cells to the lesional skin was noted after treatment than before treatment.

positive for CD68 instead of the complete disappearance of melanoma cells (**Figure 1(c)**). The $CD8^+PD-1^+$ T cells showed greater infiltration to the lesional skin after treatment than before treatment (**Figure 1(d)**, left and right panels indicate before and after treatment, respectively)

The MG status of this patient seemed to have worsened due to the psychological and physiological stress of her advanced-stage malignant melanoma. MG, which is induced by immune-checkpoint inhibitors, is characterized by elevated serum CK levels, accompanied by myositis and myocarditis [3]. The risk of the emergence of lethal myocarditis was deemed low because the anti-striated muscle antibody (anti-titin antibody) was negative. Anti-striated muscle antibody is reported to be a biomarker that enables the use of immune-checkpoint inhibitors even in cancer patients with a history of MG [3] [4]. Although three different immunosuppressant drugs were paused due to concerns of attenuating the anti-tumor immunity, there is no evidence that immunosuppressive drugs or systemic steroids adversely influence the anti-tumor effect. It was reported that there was no marked difference in the overall survival between the patients with and without systemic steroid treatment for adverse events due to ipilimumab [5]. Accordingly, we continued to use oral prednisolone instead of immunosuppressant drugs.

In the present case, an immune-checkpoint inhibitor and radiotherapy were used in combination. Several cases have recently been reported in which combi-

nation therapy with immune-checkpoint inhibitors and radiotherapy malignant melanoma was successful [6]. An abscopal effect is known to manifest as a synergistic effect when using immune-checkpoint inhibitors in combination with radiation therapy [6] [7] [8]. Given that so few reports have described the effectiveness of combination therapy with nivolumab and radiation for malignant melanoma, the accumulation of further cases is needed to provide clinical evidence of the efficacy of such combination therapy.

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