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A Case of CR Efficacy of Toripalimab for Stage IV Cutaneous Squamous Cell Carcinoma

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1. Abstract

Squamous cell carcinoma is a relatively common malignant tumor of the skin. There are individual differences among different tumor patients and possible differences in the combination of drugs in treatment. Therefore, it is very difficult to study the specific mechanism of the action of Toripalimab. The mechanisms of drug-drug or drug-organism interactions and the selection of highly effective combination regimens to improve the efficacy of antitumor immunotherapy and reduce the complication rate of Toripalimab need to be further explored. This article mainly reports one case of achieving complete remission after Toripalimab monotherapy for skin squamous cell carcinoma. However, it is a small and limited number of cases, the safety and efficacy of immune drugs in the treatment of skin squamous cell carcinoma still need to be further studied and explored in a large sample.

2. Case Presentation

A 73-year-old man was hospitalized due to a skin ulcer in the right forearm on 10th January, 2020 (Figure 1A). Pathological biopsy of the skin ulcer showed that it was a squamous cell carcinoma. Magnetic resonance (MR) scan showed a shuttle-shaped mass in the skin of the radial side of the right forearm, involving the subcutaneous fat layer, with a maximum cross-section of 2.7cm×0.9cm and a length of 4.0cm (Figure 1B-1E). PET-CT showed that the anterolateral skin of the middle and lower 1/3 segments of the right forearm was thickened and metabolism of the thicken skin was increased. Enlarged lymph nodes with increased metabolism were found in the right supraspinatus, right axilla and Ib and II-IV regions of the left neck (Figure 1G and 1H). These abnormal changes are considered to be skin malignancies with multiple lymph node metastases. The patient underwent surgical resection of the right forearm skin tumor and right axillary and right elbow supra-sliding lymph nodes on 24th March, 2020. Pathological examination of the surgical specimen showed that the lesion was a highly to moderately differentiated squamous cell carcinoma. The maximum diameter of the tumor was 4cm, the depth of invasion was 0.4cm. Subcutaneous fibrous adipose tissue and perineural invasion were seen. The tumor margin was clean. Totally 1 right elbow supratrochlear lymph node and 11 right axillary lymph nodes were resected and the right elbow supratrochlear lymph node and one of the right axillary lymph nodes were invaded and extracapsular extension was observed. The patient was diagnosed as right forearm skin squamous cell carcinoma, pT3N3M0 stage IV, according to the 8th AJCC cancer staging manual. Postoperatively, the patient was treated with rehydration, analgesia, volume expansion, prophylactic anti-infection, deep vein thrombosis prophylaxis and low molecular heparin. However, the patients did not receive other anti-tumor treatment after surgery. MR scan on June 29th, 2020 showed a right elbow subcutaneous mass, with the size of 4.6cm*2.3cm*3.6cm. The mass was considered to be a metastasis of the skin squamous cell carcinoma. The patient received a surgery again to remove the tumor. the postoperative pathological results suggested that the right upper arm anterolateral specimen was the differentiated skin squamous cell carcinoma, the epidermis, dermis and the following fibrofatty tissues, nerve invasion was seen, and no definite vascular tumor embolus was seen. (Soft

tissue lesion on the medial side of the right elbow joint) The skin was infiltrated by moderately differentiated squamous cell carcinoma. In August, a ulceration was developed on the patient's right elbow scar. Squamous carcinoma cells were found in the ulceration secretion. Ultrasound scan on September 9th showed that enlarged lymph nodes in the II, IV and V areas of the left side of the neck. The largest one in the II area was about 3.0x1.3 cm (Figure 1F), the largest one in the IV area was about 0.9x0.7 cm. The enlarged lymph nodes were considered as tumor metastasis. The patients received a course of immunotherapy (intravenous Toripalimab 240mg) on 2020-09-12. Ultrasound scan was performed again 4 weeks after Toripalimab therapy and result showed that the left cervical lymph nodes shrank. The largest one was about 0.7x0.5cm. However, MR scan on October 9th showed multiple massed above the right elbow. PET-CT scan showed that the metabolism of the mass on the right upper arm was increased. The mass was considered as tumor recurrence. On October 19th, the patient underwent the third surgery and the right shoulder was dissected to remove the tumor. the postoperative pathological results suggested that: (right upper limb dissection limb (including axillary lymph nodes) right upper limb skin medium-low differentiated squamous cell carcinoma, the largest diameter of the tumor 15cm; involvement of transverse muscle bone tissue, visible nerve invasion, no clear vascular tumor plugs; vascular cut edge, nerve cut edge, skin cut edge No carcinoma was seen in the vascular margin, nerve margin, skin margin and transverse muscle margin. No metastatic cancer was seen in the axillary fat tissue lymph nodes (0/5). After the surgery, the patient received the second cycle of Toripalimab immunotherapy on 2020-11-20. Ultrasound scan on December 11th showed that no enlarged lymph node in the left neck was seen. The patient continued to receive Toripalimab immunotherapy every 3 weeks (intravenous Toripalimab 240mg). The neck ultrasound scan was repeated every month and no enlarged lymph node was seen. The patient was still receiving Toripalimab therapy every 3 weeks when the current report was written. During the treatment of Toripalimab, no adverse effects was reported and patient's the quality of life was good (Figure 1H-1M).

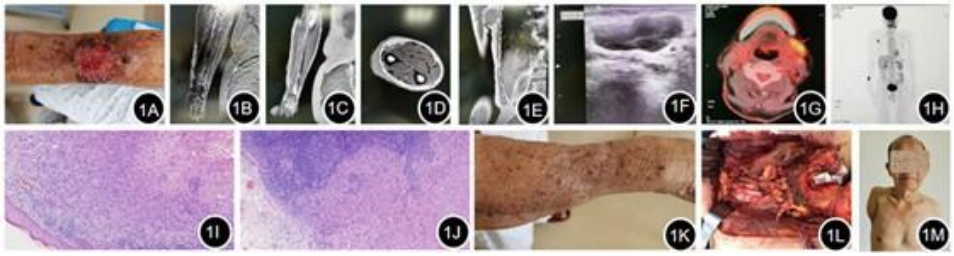

Figure 1: The examination results. (A) Image of the right forearm of the patient with skin squamous cell carcinoma. A skin ulcer was seen. (B) and (E) Image of MR scan of the right forearm. A shuttle-shaped mass shadow was seen in the skin of the radial side of the right forearm. (B) The mass showed high signal in T2WI compression lipid scan; (C) The mass showed slightly high signal in T1WI scan. (D) Cross section image of the right forearm.; (E) Image of the axillary lymph node. (F) Ultrasound scan of the enlarged lymph node in left side of the neck. (G)Image of PET-CT scan of the neck before the first surgery. Lymph nodes in the left neck with increased metabolism were shown. (H) Image of PET-CT scan of the whole body before the first surgery. Masses with increased metabolism in the right forearm, right axilla and left neck were shown.; (I) Pathological image of the surgery specimen of the lesion on the right forearm (10x20). (J) Pathological image of axillary lymph node specimen (10x10). (K) Photo of right forearm appearance 1 month afterthe first surgery. (L) Intraoperative image of right shoulder dissection on 2020-10-19. (M) Frontal photo of patient's appearance more than 4 months after right shoulder dissection.

3. Discussion

Squamous cell carcinoma is a relatively common malignant tumor of the skin [1], most common in middle-aged and elderly people. It is a malignant tumor originating from the epidermis and its appendages keratin-forming cells. The worldwide prevalence is increasing year by year. With the increasing aging of the population in China, the incidence of skin squamous cell carcinoma in China is also increasing gradually, which seriously affects patients' physical health and quality of life [2]. Studies have reported that the number of new patients in the United States is predicted to be about 200,000-400,000 per yeare and the number of related deaths is over 3,000 per year [3]. The etiology and pathogenesis of squamous skin cancer are very complex and remain unclear. Though squamous skin cancer has a low metastatic rate, it can metastasize through lymphatic and blood vessel, Lymphatic metastasis is the most common metastatic way. Patients with advanced tumors have rapid disease progression and often have high recurrence and lethality rates, which are very life-threatening [4-6].

In terms of treatment options, surgery is the preferred option [7, 8], with four surgical modalities, including standard surgical excision, scraping and electrodesiccation and Mohs surgery. Non-surgical treatments include PDT therapy, topical drug therapy, radiotherapy, cryotherapy and laser therapy. However, patients received non-surgical therapy showed relatively poor clinical outcomes. For patients with squamous skin cancer, it is important to evaluate for the presence of metastases in lymph nodes. The detection of metastases and early management are important for the prognosis of patients [9].

Clinically, whenever lymph node metastasis is present, the AJCC tumor stage is no less than stage III. Postoperative adjuvant sys-

temic chemotherapy is recommended for metastatic cutaneous squamous carcinoma. Due to the side effects of chemotherapeutic drugs and the poor tolerance of chemotherapeutic drugs for patients in middle-aged and elderly groups, there is an urgent need to explore new therapeutic approaches. Meanwhile, immune checkpoint inhibitors offer a new possibility for treatment options for patients with unresectable, locally progressive, and metastatic skin squamous cell carcinoma [10-12]. However, how different immune checkpoint inhibitors are selected for use and their predictive markers of efficacy remain unclear [13]. PD-1 is known to play a crucial role in suppressing immune responses and improving self-tolerance by regulating T-cell activity, activating apoptosis in antigen-specific T cells and inhibiting apoptosis in regulatory T cells. PD-L1 is a transmembrane protein that is thought to be a co-suppressor of immune responses, which binds to PD-1 to reduce the proliferation of PD-1-positive cells, inhibit their cytokine secretion and induce apoptosis [14]. Studies have shown that immunotherapy monotherapy does reduce the risk of death in patients with recurrent or metastatic squamous cell carcinoma of the head and neck (R/M SCCHN) and has a good safety profile [15]. With the continuous progress and development of diagnostic and treatment techniques, immunotherapy has promising therapeutic effects for patients with recurrent or metastatic advanced disease and has good application prospects and future [16-19].Therefore, when choosing the best treatment plan, a patient's individualized comprehensive diagnosis and treatment plan should be developed based on many factors, such as patient survival, tumor recurrence rate, function of the affected limb, potential toxic side effects of drugs, patient expectations and prognosis of quality of life. In this paper, we reported an effective case of Toripalimab for metastatic cutaneous squamous cell carcinoma. The diagnosis of the patient was confirmed by pathological biopsy combined with image examination. PET-CT scan results suggested that the lymph nodes in the right supra-humeral glide, right axilla and left neck Ib and II-IV areas were considered to be metastasis. The above invaded lymph nodes were removed by right axillary lymph node dissection + right elbow supra-glide lymph node removal. The pathologic examination of the surgery specimen confirmed that the lymph nodes were metastases of the skin squamous cell carcinoma. The patient was diagnosed as stage IV squamous skin cancer. After two surgeries in March and July 2020, the right elbow and axillary metastases recurred again and the left neck metastatic lymph nodes further increased in size. Considering that the tumor progressed again, we gave the Toripalimab therapy to the paitent. After the first cycle of Toripalimab treatment, the lymph nodes in the left neck and the left supra- and subclavian regions were significantly reduced in size, and metabolism compared with 2020-01-20 PET-CT scan. After the third surgery and the second and third cycles of Toripalimab therapy, ultrasound scan did not show any significant enlarged lymph nodes in bilateral neck lymph nodes and lymph nodes in the supra- and infra-clavicular regions, which were evaluated as complete remission (CR). The Toripalimab immunotherapy was continued as planned, and no tumor recurrence was seen up to now.

However, there were some shortages during the treatment of this patient. Before the first surgery of this patient, PET-CT results suggested that the lymph nodes in the right supra-humeral glide, right axillary fossa and left cervical area Ib and II-IV were considered metastases. The postoperative pathologic examination of the right supra-humeral glide and right axillary lymph nodes confirmed that the patient's lymph nodes were metastases. The results were consistent with PET-CT examination, But the left cervical lymph nodes were not. No further puncture or excisional biopsy was performed to clarify the pathological findings of the cervical lymph nodes. After anti-infection treatment, the lymph nodes in the Ib and II-IV areas of the left neck did not shrink and the lymph nodes in the Ib and II-IV areas of the left neck were slightly larger than before. And the right supraumbilical lymph node recurred. After immunotherapy with Treprolipmab, the lymph nodes in the Ib and II-IV areas of the left neck shrank significantly until they disappeared completely.

Toripalimab is a novel recombinant humanized (97%) PD-1 inhibitor, which belongs to human IgG4/Kappa subtype. It has a novel CDR sequence and a unique FG-loop binding site. The present case of a stage IV skin squamous cell carcinoma patient achieved promising results during immunotherapy. Combined with the principle of Toripalimab itself, this paper makes the following conjectures on the possible mechanism of tumor inhibition in squamous cell carcinoma treatment: Toripalimab may potently inhibit tumor by blocking PD-1/PD-L1 pathway and mediating PD-1 receptor endocytosis dual mechanism. Firstly, Toripalimab monoclonal antibody has a high affinity for binding PD-1 1, blocking the PD-1/PD-L1 pathway and improving anti-tumor efficacy. Secondly, the PD-1 pathway inhibits Ca2+ ion influx through intracellularly bound dephosphatase and thereby suppressed T cell function. Even in the absence of the ligand PD-L1, T lymphocytes with high PD-1 receptor expression are in a functionally suppressed state. Reducing cell surface PD-1 receptor expression decreases the concentration of dephosphatase in the proximal membrane region and thereby enhanced the T cell's own activation function. Therefore, Toripalimab induces PD-1 endocytosis effect and reduces PD-1 expression on cell membrane. Regardless of PD-L1 dynamic changes, PD-1 endocytosis makes PD-L1/PD-1 pathway can be blocked, and through endocytosis, release T cells from anti-tumor immunosuppression, and also through blocking PD-1/PD-L1 pathway, finally achieve the purpose of powerful tumor suppression.

4. VI. Summary

The human immune system is a very complex and delicate system. There are individual differences among different tumor patients and possible differences in the combination of drugs in treatment. Therefore, it is very difficult to study the specific mechanism of the

action of Toripalimab. The mechanisms of drug-drug or drug-organism interactions and the selection of highly effective combination regimens to improve the efficacy of antitumor immunotherapy and reduce the complication rate of Toripalimab need to be further explored. This article mainly reports one case of achieving complete remission after Toripalimab monotherapy for skin squamous cell carcinoma. However, it is a small and limited number of cases, the safety and efficacy of immune drugs in the treatment of skin squamous cell carcinoma still need to be further studied and explored in a large sample.

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