

A Metastatic Melanoma Patient with Spontaneous Melanoma-Associated Vitiligo Survived for up to 7 Years and 5 Months: A Case Report

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1. Abstract

1.1. Background: Malignant melanoma is a highly malignant tumor caused by abnormal proliferation of melanoma cells in the skin and mucous membranes, with a poor prognosis after metastasis. Skin melanocytes are gradually destroyed in vitiligo patients. There is a certain correlation between these two diseases: In these two conditions, cytotoxic T lymphocytes that target autoantigens shared by normal melanocytes and melanoma cells have been found. Spontaneous melanoma-associated vitiligo was relatively rare before melanoma was diagnosed, and its pathogenesis and prognosis were rarely studied. The cases we reported is extremely rare for a patient to have a metastasis of melanoma that lasts much longer than the moderate survival time of a patient with malignant melanoma.

1.2. Case Presentation: A 63-year-old female patient who was treated in our hospital survived for up to seven years and five months after being diagnosed with malignant melanoma. The primary symptom of the patient was skin darkening on the back of the right index finger. Within seven years, malignant melanoma metastases appeared sequentially in the right axillary region and in the small intestine region. The patient underwent right axillary tumor resection, right index finger distal segment amputation and small bowel tumor resection. The pathological results were all malignant melanoma. Patients were not receiving systemic immunotherapy, but the spontaneous melanoma-associated vitiligo made the patient live longer than the other malignant melanoma patients.

1.3. Conclusion: Spontaneous melanoma-associated vitiligo prolongs survival in patients with malignant melanoma. The emer-

gence of spontaneous melanoma-associated vitiligo should be alerted and its pathogenesis should be studied.

2. Introduction

Malignant melanoma (MM) is a kind of neural crest malignant tumor with strong aggressiveness and poor prognosis [1]. Hematogenous or lymphatic metastasis is prone to occur in the early stage of MM. Metastatic MM accounts for 1% to 3% of gastrointestinal malignancies [2] and the five-year survival rate for patients with metastatic MM is only 5% [3]. Due to the lack of specific signs and symptoms, the pre-mortem diagnosis rate of patients with metastatic MM is only between 1.9% and 4.4% [4]. Vitiligo is an acquired depigmentation disease in which the skin melanocytes are gradually destroyed. The pathogenesis of vitiligo and malignant melanoma is still unclear, however, there is a certain correlation between these two seemingly different diseases: Cytotoxic T lymphocytes (CTLs) against autoantigens shared by normal melanocytes and melanoma cells were found in both cases, suggesting the collapse of immune tolerance [5,6]. In addition, melanoma patients also develop lesions that are very similar to classical vitiligo: melanoma-associated vitiligo (MAV). MAV is different from classical vitiligo, and people have different definitions of it, which are roughly divided into the following two views. One idea has been mentioned in the literature by Hansje-Eva Teulings et al. that melanoma patients may experience skin depigmentation spontaneously or after treatment, called MAV [7]. However, Francisco et al. defined MAV as a loss of pigment that occurs within 1 year before the detection of primary melanoma or 3 years before the discovery of MM with an unknown primary tumor [8]. In this

paper, in order to distinguish the vitiligo-like leukoplakia that appears before and after treatment, MAV is divided into spontaneous melanoma-associated vitiligo (SMAV), which is what Teulings et al. call this condition, and reactive melanoma-associated vitiligo (RMAV), which is vitiligo-like leukoplakia that appears after treatment. In recent years, it has been found that about 2% to 16% of MM patients will gradually develop MAV [7]. Current research also shows that most MAV occurs during or after immunotherapy. MAV is a sign of anti-tumor of the autoimmune system and a good signal for immunotherapy [9,10]. It is worth mentioning that it is relatively rare for SMAV to appear before the definite diagnosis of MM, and there is no single research and report on SMAV in the literature. In our case report, this female patient had a vitiligo-like discoloration spot before the melanoma was diagnosed, and it has appeared for at least one year. She developed axillary lymph node metastasis 1 year after the initial diagnosis of malignant melanoma, and the overall survival time after diagnosis was 7 years and 5 months. Her survival time far exceeded the median survival time of MM patients [11,12]. This phenomenon requires close attention of surgeons. Whether the emergence of SMAV can improve the prognosis of MM patients is worthy of our consideration. We recommend that the first physician perform a careful systemic skin examination of patients with vitiligo-like depigmentation, considering the possibility of malignant melanoma. In addition, in-depth research on the pathogenesis and immune process of MAV may open up new advances in the treatment of malignant treatment of melanoma.

3. Case Report

A 63-year-old female patient who had been treated in our hospital survived for up to 7 years and 5 months after being diagnosed with MM. A year before the diagnosis of MM, the patient began to develop vitiligo-like decolorization, initially on the face, followed by the same vitiligo-like decolorization lesions on her neck. It is worth mentioning that this patient has no family history of skin cancer and no family history of vitiligo. In March 2010, she went to the doctor for the first time because the skin on the back of the right index finger turned black as the first symptom. During the skin examination, the doctor found that, except the abnormality of the right index finger, the patient's face had vitiligo-like discoloration skin lesions. After asking the medical history, he learned that the facial lesions had been more than one year, and it was earlier than the right index finger lesions. Doctors believed that the patient's diagnosis was melanoma with a right-handed index finger and recommended that she should undergo right-handed index finger amputation, but the patient refused surgery. In May 2011, the patient found a mass on the right armpit, about 2*3 cm in size, which had not been diagnosed and treated. After 6 months, the tumor had progressively increased to 6*3cm. The patient went to our hospital again and underwent a right axillary tumor resection in November 2011. The postoperative pathological result was

MM. Immunohistochemical results: Vimentin (+), CK(-), CD34(-), HMB45(+), Melan A (+), S-100(+), LCA(-). The patient's axillary melanoma was considered as axillary lymph node metastasis of the primary lesion. Therefore, after be tracked the primary tumor by the doctor, the patient underwent a right-handed index of the middle and distal finger amputation in December 2011. Combined with the results of postoperative pathological diagnosis, the patient was definitely diagnosed as stage IV MM of the right hand index finger. The doctor recommended that she should receive standardized immunotherapy after the operation, but she was flatly rejected, and the patient has not been reviewed regularly since then. Until December 2,2017, the patient was treated again with intermittent epigastric pain for 1 month and aggravation with 7 days of cessation of exhaust and defecation. Examination reveals a full abdominal bulge, hyperinvertine sounds, mild tenderness in the left upper quadrant, and no mass touched. Abdominal Computer Tomography (CT) showed dilation of the small intestine in the abdominal cavity, multiple air-liquid levels (Figure 1A), and local space-occupying lesions in the pelvic intestine (Figure 1B). On initial admission, the patient's initial clinical diagnosis was incomplete intestinal obstruction. Gynecological ultrasound examination suggests that there may be large pelvic intestinal space-occupying lesions (Figure 2). The patient had undergone a small bowel tumour resection. The postoperative histopathological results showed small intestine MM (Figure 3). Under the light microscope, it could be seen that the submitted tumor cells were diffusely distributed, with organ-like structures in individual areas. The tumor cells were medium in size and rich in cytoplasm. Some nuclei were slightly eosinophilic, and some were more translucent. The nucleus was round or oval, and the size was relatively smaller, split elephants were more common (Figure 3A-B). The immunohistochemical results displayed HMB45 (+), S-100 (+), MelanA (+), Vimentin (+) and CK (-) (Figure 3C). Owing to personal reasons, the patient and his family refused to undergo follow-up immunotherapy. We considered that the patient's small bowel melanoma was still a small bowel metastasis of the primary focus, and combined with the pathological results, the patient was diagnosed as small bowel malignant melanoma stage IV. Two years later, a progressively enlarging 4x4 cm tumour appeared in her abdomen (Figure 4A-C). After admission, this patient underwent a physical examination. She was clear-headed, poor in spirit, and generally in poor condition. The patient's superficial lymph nodes were not palpable and enlarged. We could see three old surgical scars about 5cm in size on her abdomen. Percussion of the abdomen revealed a drum sound throughout the abdomen. In addition, in the middle of her lower abdomen, we found a mass of approximately 4x4 cm, with hard texture, poor mobility and no tenderness. This patient has a distended abdomen with positive mobile turbid sounds. Finally, we also found that her right hand index finger was surgically removed, and large areas of white spots on both sides of

her face and neck. We consider that the patient has advanced malignant melanoma with extensive metastasis to the abdominal cavity. Combined with the patient's medical history and general status, the opportunity to re-operate had been lost. Patients were discharged after 1 cycle of cindilizumab 200 mg immunotherapy. The patient died 1 month after discharge.

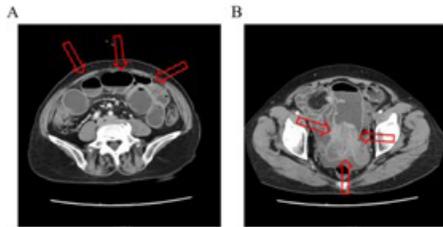


Figure 1: The abdominal CT. A: The red arrows point to the dilation of the small intestine in the abdominal cavity, and the gas-liquid plane is visible inside; B: The red arrows point to the local soft tissue density shadow in the pelvic intestine, and the enhanced scan shows uneven enhancement and pelvic fluid accumulation.



Figure 2: Gynecological ultrasound. The red arrow points to a non-uniform meso-echoic mass of 90.3 mm x 63.7 mm x 76.8 mm in the pelvic cavity, with unclear borders and unregular morphology. CDFI examination revealed that the color blood flow signals were scattered inside the pelvic cavity.

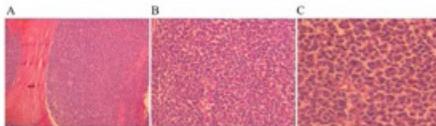


Figure 3: Pathological results. A: Tumor cells are diffusely distributed in sheets, separated by slender fibrous tissue, showing an organ-like structure; B and C: Tumor cells are medium in size, rich in cytoplasm, some nuclei are slightly eosinophilic, some are more translucent, and have round nuclei or oval, relatively small in size, split phenomenon is more common. The pathological diagnosis was malignant melanoma of the small intestine, and no tumor component was seen at the cut edge. Immunohistochemistry HMB45(+), S-100(+), MelanA(+), Vimentin(+), CK(-).

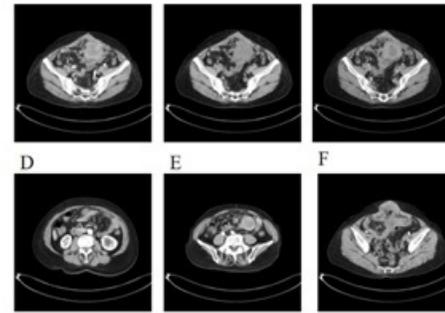


Figure 4: The abdominal CT. A, B, C: the images of the tumor arterial phase, venous phase, and delayed phase in sequence; D, E: multiple enlarged nodules around the small intestine and abdominal cavity, the larger one is about 4.0 cm, the enhanced scan is unevenly enhanced; F: Part of the intestinal wall above the anastomosis is thickened, the lower abdominal wall is strengthened and abnormally strengthened, and soft tissue herniation can be seen locally.

4. Discussion

MM, a malignant tumor caused by the abnormal proliferation of melanocytes in the skin and mucous membranes, is the least common type of skin cancer, but accounts for 75% of skin cancer deaths. In recent years, its incidence rate has been accelerating, second only to lung cancer [12]. According to the latest U.S. data for 2020, it was estimated that 325,000 new cases of MM would be added last year, and the number of deaths due to MM would be 57,000 [13]. So far, MM is the deadliest skin cancer, and it is easy to metastasize at an early stage. The prognosis of metastatic MM is worse, with a median survival of about 9 months or less [11,12,14]. At present, surgery is still an important treatment for MM. For MM patients who are generally in good condition and have the possibility of radical cure, radical surgery can significantly prolong the overall survival and disease free survival time of MM patients [4, 15, 16]. Palliative surgery can also improve the complications of patients with metastatic MM, even if the general condition is poor and radical surgery cannot be performed for metastatic MM. The prognosis of untreated metastatic MM is extremely poor. Therefore, the early diagnosis of MM is particularly important. Currently, there is a lack of effective screening methods for MM. The case we reported became intriguing to us with vitiligo and MM, and after reviewing the literature we found an interesting link between MM and vitiligo [6,8,10,17] and has been studied by scholars from all over the world. Both MM and vitiligo are melanocyte-related diseases. MM is a highly malignant tumor derived from melanocytes, and the melanocytes of vitiligo patients are destroyed, resulting in skin discoloration [9]. Although the specific pathogenesis of both MM and vitiligo is not well understood, there is a common differentiating antigen between the two [10,20]. Most of the antigens recognized by CTL in melanoma patients are expressed by melanoma cells and normal melanocytes [5,6] and autoantibodies

isolated from vitiligo patients have a destructive effect on melanoma cells both in vivo and in vitro [5]. Another study reported that patients with vitiligo had a slightly lower risk of MM than normal people [17]. This makes it clear that leper is a protective factor in melanoma. In fact, Wen and colleagues used Mendelian randomization to evaluate the causal relationship between vitiligo and MM, and found that vitiligo is indeed a protective factor for MM [17]. Lengaghe et al. also found that experimental animals with vitiligo had significantly later tumor metastasis than experimental animals without vitiligo [21], which is consistent with the above view. With the further development of MM immunotherapy, there is growing evidence that patients can develop leukoplakia similar to classic vitiligo-like during immunotherapy, known as RMAV. This phenomenon is a sign of good immunotherapy, and patients with leukoplakia after or during immunotherapy have a relatively good prognosis. A small number of patients develop SMAV without immunotherapy or even before primary melanoma is detected [8], it because the immune response of anti-tumor cells in MM patients can act on their normal melanocytes, causing their own destruction and leading to the occurrence of SMAV [6]. The case we reported is MM with SMAV, a patient with an overall survival of seven years and five months after diagnosis of MM, and survived for 6 years after the onset of axillary lymph node metastasis, well over 9 months. To our knowledge, there is no statistical description of the median survival of MM in the population with concomitant SMAV. We think it's no accident that the survival time difference is so large, which may have a lot to do with SMAV. Some pathogenesis of SMAV inhibits the occurrence and rapid progression of MM, or the occurrence of SMAV itself is a dominant manifestation of the body's immune system against MM. However, people currently know little about the pathogenesis of SMAV and even MAV. What is the pathogenesis of SMAV? What is the connection between SMAV and classic vitiligo? What's the relationship between SMAV and MM in pathogenesis? These issues also require a lot of clinical trial research and exploration.

Therefore, the main purpose of this study is to remind clinicians of the following two points through this case report. First, the pathogenesis of SMAV may play an important role in inhibiting the occurrence and development of MM. In-depth research on the pathogenesis of SMAV will make a significant contribution to the treatment of MM. Secondly, currently MAV is not considered to be a subtype of vitiligo, and the distinction between the two is of great significance to patients. For patients with initial vitiligo-like discoloration lesions, careful whole-body skin examinations should be performed to be alert to the possibility of suffering from malignant melanoma.

5. Conclusion

SMAV is the protective factor of MM. Its pathogenesis needs to be further studied, or it can provide new ideas for the treatment of MM and bring good news to MM patients. For patients with

symptoms of vitiligo-like decolorization, vitiligo cannot be blindly diagnosed, and the first physician should conduct a careful systemic skin examination of the patient and ask him to follow up regularly to be alert to the possibility of SMAV.

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