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AMetastaticMelanomaPatientwithSpontaneousMelanoma-AssociatedVitiligoSurvived for up to 7 Years and 5 Months:ACase Report

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1. Abstract

Background: Malignantmelanomaisahighlymalignanttu- mor caused by abnormal proliferation of melanoma cells in the skinandmucousmembranes,withapoorprognosisaftermetasta- sis. Skin melanocytes are gradually destroyed in vitiligo patients. Thereisacertaincorrelationbetweenthesetwodiseases:Inthese 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 prognosiswererarelystudied.Thecaseswereportedisextremely rareforapatienttohaveametastasisofmelanomathatlastsmuch longerthanthemoderatesurvivaltimeofapatientwithmalignant melanoma.

Case Presentation: A 63-year-old female patient who was treated in our hospital survived for up to seven years and five monthsafterbeingdiagnosedwithmalignantmelanoma.Thepri- mary 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 smallboweltumorresection.Thepathologicalresultswereallma- lignantmelanoma.Patientswerenotreceivingsystemicimmuno- therapy, but the spontaneous melanoma-associated vitiligo made thepatientlivelongerthantheothermalignantmelanomapatients.

Conclusion: Spontaneous melanoma-associated vitiligo pro- longssurvivalinpatients withmalignant melanoma. Theemergence 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 gastrointestinalmalignancies[2]andthefive-yearsurvivalrateforpatients 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 melano- cytes 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: Cy- totoxic T lymphocytes (CTLs) against autoantigens shared by normal melanocytes and melanoma cells were found in both cases,suggestingthecollapseofimmunetolerance[5,6].Inaddition, melanoma patients also develop lesions that are very similar to classicalvitiligo:melanoma-associatedvitiligo（MAV.MAVisdif- ferentfromclassicalvitiligo,andpeoplehavedifferentdefinitions ofit,whichareroughlydividedintothefollowingtwoviews.One idea has been mentioned in the literature by Hansje-EvaTeulings etal.thatmelanomapatientsmayexperienceskindepigmentation spontaneouslyoraftertreatment,calledMAV[7].However,Franciscoetal.definedMAVasalossofpigmentthatoccurswithin1 year before the detection of primary melanoma or 3 years before thediscoveryofMMwithanunknownprimarytumor[8].Inthis paper, in order to distinguish the vitiligo-like leukoplakia that appearsbeforeandaftertreatment,MAVisdividedintospontaneous melanoma-associatedvitiligo(SMAV),whichiswhatTeulingset al. call this condition, and reactive melanoma-associated vitili- go (RMAV), which is vitiligo-like leukoplakia that appears after treatment.Inrecentyears,ithasbeenfoundthatabout2%to16% ofMMpatientswillgraduallydevelopMAV[7].Currentresearch alsoshowsthatmostMAVoccursduringorafterimmunotherapy. MAVisasignofanti-tumoroftheautoimmunesystemandagood signal for immunotherapy [9,10]. It is worth mentioning that it is relativelyrareforSMAVtoappearbeforethedefinitediagnosisof MM, and there is no single research and report on SMAV in the literature.Inourcasereport,thisfemalepatienthadavitiligo-like discolorationspotbeforethemelanomawasdiagnosed,andithas appearedforatleastoneyear.Shedevelopedaxillarylymphnode metastasis 1 year after the initial diagnosis of malignant melanoma,andtheoverallsurvivaltimeafterdiagnosiswas7yearsand5 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 recommendthatthefirstphysicianperformacarefulsystemicskin examinationofpatientswithvitiligo-likedepigmentation,considerингthepossibilityofmalignantmelanoma.Inaddition,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 Repot

A63-year-oldfemalepatientwhohadbeentreatedinourhospital survivedforupto7yearsand5monthsafterbeingdiagnosedwith MM.A year before the diagnosis of MM, the patient began to developvitiligo-likedecolorization,initiallyontheface,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 abnormalityoftherightindexfinger,thepatient'sfacehadvitiligo-likediscol- oration 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 insize,whichhadnotbeendiagnosedandtreated.After6months, thetumorhadprogressivelyincreasedto6*3cm.Thepatientwent to our hospital again and underwent a right axillary tumor resectioninNovember2011.Thepostoperativepathologicalresultwas MM.Immunohistochemicalresults: Vimentin(+),CK(-),CD34(-), HMB45(+), MelanA(+), 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 wasflatlyrejected,andthepatienthasnotbeenreviewedregularly since then. Until December 2,2017, the patient was treated again withintermittentepigastricpainfor1monthandaggravationwith 7 days of cessation of exhaust and defecation.Examination reveals a full abdominal bulge, hyperinvertine sounds, mild tender- ness in the left upper quadrant, and no mass touched.Abdominal Computer Tomography (CT) showed dilation of the small intes- tineintheabdominalcavity,multipleair-liquidlevels(Figure1A), 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 resultsshowedsmallintestineMM(Figure3).Underthelight microscope, it could be seen that the submitted tumor cells were diffuselydistributed,withorgan-likestructuresinindividualareas. Thetumorcellsweremediuminsizeandrichincytoplasm.Some nucleiwereslightlyeosinophilic,andsomeweremoretranslucent. Thenucleuswasroundoroval,andthesizewasrelativelySmaller,splitelephantsweremorecommon(Figure3A-B).Theimmunohistochemical 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.Weconsideredthatthepatient'ssmallbowelmelanomawasstillasmallbowelmetastasisoftheprimaryfocus,and combinedwiththepathologicalresults,thepatientwasdiagnosed as small bowel malignant melanoma stage IV. Two years later, a progressively enlarging 4x4 cm tumour appeared in her abdomen (Figure4A-C).Afteradmission,thispatientunderwentaphysical examination. She was clear-headed, poor in spirit, and general-ly 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 revealedadrumsoundthroughouttheabdomen.Inaddition,inthe 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,wealsofoundthatherrighthandindexfingerwas surgicallyremoved,andlargeareasofwhitespotsonbothsidesof

herfaceandneck.Weconsiderthatthepatienthasadvancedmalignantmelanomawithextensivemetastasistotheabdominalcavity. Combinedwiththepatient'smedicalhistoryandgeneralstatus,the opportunity to re-operate had been lost. Patients were discharged after1cycleofcindilizumab200mgimmunotherapy.Thepatient died 1 month after discharge.

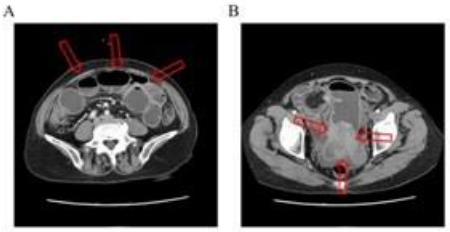

Figure1: TheabdominalCT.A:Theredarrowspointtothedilationofthe smallintestineintheabdominalcavity,andthegas-liquidplaneisvisible inside; B:The red arrows point to the local soft tissue density shadow in the pelvic intestine, and the enhanced scan shows uneven enhancement and pelvic fluid accumulation.

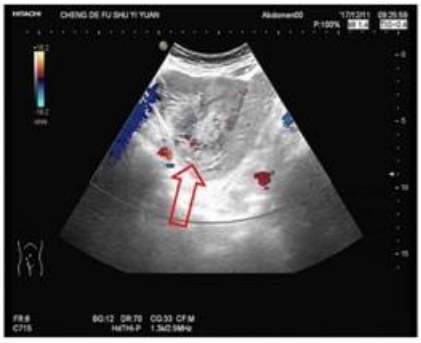

Figure 2: Gynecological ultrasound. The red arrow points to a non-uniform meso-echoic mass of 90.3 mm x 63.7 mm x 76.8 mm in the pelvic cavity, with unclear borders and unregular morphology. CDFI examination revealed that the color blood flow signals were scattered inside the pelvic cavity.

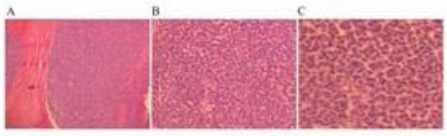

Figure3: Pathologicalresults. A:Tumorcellsarediffuselydistribut- ed in sheets, separated by slender fibrous tissue, showing an organ-like structure; B and C: Tumor cells are medium in size, rich in cytoplasm, somenucleiareslightlyeosinophilic,somearemoretranslucent,andhave rounc nuclei Or oval, relatively small in size, split phenomenon is more common. The pathological diagnosis was malignant melanoma of the smallintestine,andnotumorcomponentwasseenatthecutedge.Immunohistochemistry HMB45(+), S-100(+), MelanA(+)Vimentin(+), CK(-).

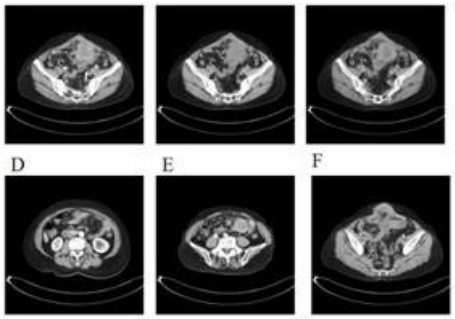

Figure 4: The abdominal CT. A, B, C: the images of the tumor arterial phase, venous phase, and delayed phase in sequence; D, E: multiple enlargednodulesaroundthesmallintestineandabdominalcavity,thelarger oneisabout4.0cm,theenhancedscanisunevenlyenhanced;F:Part of the intestinal wall above the anastomosis is thickened, the lower abdominalwallisstrengthenedandabnormallystrengthened,andsofttissue herniation can be seen locally.

4. Discussion

MM, a malignant tumor caused by the abnormal proliferation of melanocytesintheskinandmucousmembranes,istheleastcom- mon type of skin cancer, but Maccounts for75%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 beaddedlastyear,andthenumberofdeathsduetoMMwouldbe 57,000[13].Sofar,MMisthedeadliestskincancer,anditiseasy tometastasizeatanearlystage.TheprognosisofmetastaticMMis worse,withamediansurvivalofabout9monthsorless[11,12,14]. Atpresent,surgeryisstillanimporttreatmentforMM.ForMM patients who are generally in good condition and have the possibilityofradicalcure,radicalsurgerycansignificantlyprolongthe overall survival and disease free survival time of MM patients[4, 15, 16]. Palliative surgery can also improve the complications of patientswithmetastaticMIM,evenifthegeneralconditionispoor and radical surgery cannot be performed for metastatic MM. The prognosis of untreated metastatic MM is extremely poor. Therefore,theearlydiagnosisofMMisparticularlyimportant.Currently,thereisalackofeffectivescreeningmethodsforMM.Thecase wereportedbecameintriguinguswithvitiligoandMM,andafter reviewingtheliteraturewefoundaninterestinglinkbetweenMM and vitiligo [6,8,10,17] and has been studied by scholars from all overtheworld.BothMMandvitiligoaremelanocyte-relateddiseases.MMisahighlymalignanttumorderivedfrommelanocytes, and the melanocytes of vitiligo patients are destroyed, resultingin 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 melanomacellsandnormalmelanocytes[5,6]andautoantibodies

isolatedfromvitiligopatientshaveadestructiveeffectonmelano- ma cells both in vivo and in vitro [5].Another study reported that patientswithvitiligohadaslightlylowerriskofMMthannormal people[17]. Thismakesitclearthatleperisaprotectivefactor in melanoma. In fact, Wen and colleagues used Mendelian randomizationtoevaluatethecausalrelationshipbetweenvitiligoand MM, and found that vitiligo is indeed a protective factor for MM [17]. Lengaghe et al. also found that experimental animals with vitiligohadsignificantlylatertumormetastasisthanexperimental animals without vitiligo [21], which is consistent with the above view.WiththefurtherdevelopmentofMMimmunotherapy,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 goodprognosis.AsmallnumberofpatientsdevelopSMAVwithoutimmunotherapyorevenbeforeprimarymelanomaisdetected [8],itbecausetheimmuneresponseofanti-tumorcellsinMMpa- tients can act on their normal melanocytes, causing their own destructionandleadingtotheoccurrenceofSMAV[6].Thecasewe 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 over9months.Toourknowledge,thereisnostatisticaldescription ofthemediansurvivalofMMinthepopulationwithconcomitant SMAV.Wethinkit'snoaccidentthatthesurvivaltimedifference issolarge,whichmayhavealottodowithSMAV.SomepathogenesisofSMAVinhibitstheoccurrenceandrapidprogressionof MM,ortheoccurrenceofSMAVitselfisadominantmanifestation of the body's immune system against MM. However, people currentlyknowlittleaboutthepathogenesisofSMAVandevenMAV. What is the pathogenesis of SMAV? What is the connection betweenSMAVandclassicvitiligo?What'stherelationshipbetween SMAVandMMinpathogenesis?Theseissuesalsorequirealotof 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 theoccurrenceanddevelopmentofMM.In-depthresearchonthe pathogenesisofSMAVwillmakeasignificantcontributiontothe treatmentofMM.Secondly,currentlyMAVisnotconsideredtobe asubtypeofvitiligo,andthedistinctionbetweenthetwoisofgreat significance to patients. For patients with initial vitiligo-like discoloration lesions, careful whole-body skin examinations should beperformedtobealerttothepossibilityofsufferingfrommalig- nant 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 treatmentofMMandbringgoodnewstoMMpatients.Forpatientswith symptomsofvitiligo-likedecolorization,vitiligocannotbeblindly 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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