# Type 2 Diabetes Mellitus with Plantar Malignant Melanoma: Report of Two Cases and Literature Review

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**Case Report**

**Keywords:** Type 2 diabetes, diabetic foot ulcer, malignant melanoma, case report.

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# Abstract

**Background:** Malignant melanoma is a highly malignant tumour that originates from melanocytes. Its prognosis is poor and motality rate is high. Malignant melanoma usually occurs in the skin, also known as cutaneous melanoma,but rarely in the foot.

**Case report:** Here we report two cases of type 2 diabetes diagnosed as malignant melanoma of the foot and provides a review of literature. The first patient was a 70-year-old woman with a 7 year history of diabetes, who had a ulcer in the right heel for half a year. The second case, which occurred in a 66-year-old woman whose third toe of the right foot had been red, swollen and blackened for 2 months. Both of them had been treated as diabetic foot at first , and then been diagnosed of malignant melanoma by a pathological biopsy of the lesions.

**Conclusion:** From two rare cases of plantar malignant melanoma,we suggest that clinicians should be alert to the occurrence of acral malignant melanoma in diabetic foot patients. When diabetic foot ulcers occur repeatedly and continue not to heal, and the pathological features of the lesions are similar to malignant melanoma, a pathological biopsy of the lesions should be performed promptly to obtain a clear diagnosis, avoid a missed diagnosis and improve the survival rate.


# Introduction

Diabetic foot is one of the most serious chronic complications of diabetes. In severe cases, foot ulcers and gangrene, two of the main causes [1] of diabetic nontraumatic amputation, can occur. High-risk factors for diabetic foot ulcers include poor blood glucose control, peripheral neuropathy, peripheral vascular disease and infection [2]. Malignant melanoma is a rare, extremely malignant tumour that accounts for 5% of all skin malignancies but more than 80% of all skin cancer–related deaths [3]. Some of these tumours can present as colourless ulcers. Such atypical malignant melanoma occurs at the acral of patients with diabetes and is easily confused with diabetic foot ulcers, which poses a challenge for the clinical diagnosis and treatment. Thus, we reviewed the related literature and clinical features of two elderly women with malignant melanoma of the foot as described below.

# Case Presentation

Case 1

Case 1 was a 70-year-old woman with a 7 year history of diabetes. Her right heel had been broken for half a year. Six months before presentation, the patient noticed a broken right heel with the size of a mung bean. Although no fluid was observed, the heel break expanded with fluid. No significant improvement was noted after self-administered medication. After presenting to the local hospital, the patient was diagnosed with type 2 diabetic foot. After blood sugar was controlled, the wound dressing was changed and another treatment was administered, the patient still had no improvement, and she experienced an approximately 10 kg weight loss. The patient was admitted to our department for further treatment. Medical history was positive for hypertension and cerebral infarction. Physical examination revealed a broken mouth of the right full heel (1.2 × 0.9 cm) that was wet with no odour, with thickening of the skin cuticle around the wound (see Figure 1A). The dorsal foot artery was pulsating. Lower extremity vascular colour Doppler showed the formation of multiple plaques in the lower extremity artery. Because of the patients history of diabetes, we considered the formation of arterial plaques in both lower extremities to be diabetic peripheral vascular lesions. The goals of the treatment were to control blood glucose level, control blood pressure, change foot dressing, maintain stable plaque, improve circulation, maintain water and electrolyte balance and provide other symptomatic supportive treatment. However, the patients foot ulcers healed slowly and grew like cauliflower . Pathological biopsy (see Figure 2) of the right foot showed malignant melanoma. Immunohistochemistry (see Figure 3) indicated CK5/6, Melan-A(+), HMB45(+), Ki67(10%+) and P63(−).

Case 2

Case 2 was a 66-year-old woman. The patient had experienced polydipsia and polyuria for 7 months before presentation, and she had repeated lower limb oedema for the previous 3 months. The third toe of her right foot had been red, swollen and blackened for 2 months. The patient displayed red, swollen and black toes after extruding and discharging the pus by herself. Treatment from three local clinics was ineffective, and the patient was transferred to our department. She had a history of hypertension. Physical examination indicated slightly swollen lower limbs, blackening at the end of the third toe of the right foot (see Figure 1B) and normal bilateral foot artery pulsation. Neuromyography showed partial demyelination of the peripheral nerve. Results of the oral glucose tolerance test suggested a delayed insulin spike, which supported the diagnosis of type 2 diabetes. The patient was provided treatment to control blood glucose and blood pressure levels, nourish the nerves and provide anti-infection protection. A positive oblique radiograph of the right foot showed a bone defect of the third distal phalanx with swelling of the surrounding soft tissue. The third toe of the right foot was amputated. A pathological report indicated malignant melanoma (see Figure 4). Immunohistochemistry (see Figure 5) results were S-100(+), Melan-A(+), HMB45(+), Ki67(20%+), CD31(−) and D-20(−). Because of the metastatic characteristics of malignant melanoma, we further performed a colour ultrasound of the systemic superficial lymph nodes and iliac fossa lymph nodes, which demonstrated a right inguinal multiple lymph node enlargement. We considered the diagnosis of toe tumour metastasis and subsequently performed radical resection of the tumour and lymph node dissection.

The clinical features of these two cases of type 2 diabetic malignant melanoma are summarized in Table 1.

## Discussion

Diabetic foot (diabetic foot ulcer) is a serious chronic complication faced by patients with diabetes and is considered a disabling ulcer that poses a great threat to the life and health of these patients. The International Diabetic Foot Working Group, based on the 2019 edition of the International Clinical Guidelines for Diabetic Foot, defines diabetic foot as a patient with an initial diagnosis of diabetes or a history of diabetes who has foot infections, ulcers or tissue damage, usually accompanied by lower-extremity neuropathy and/or peripheral arterial lesions [15]. The main factors leading to poor prognosis of diabetic foot are old age, high glycosylated haemoglobin, long course of diabetes, long course of diabetic foot, malnutrition, combined infection, combined ischaemia and so forth. Additionally, when foot malignant melanoma is misdiagnosed as diabetic foot, the course of the ulcer will also be prolonged.

Melanoma is a malignant tumour caused by an uncontrolled proliferation of melanocytes. The age-standardised incidence rate is approximately 2.8 to 3.1/10 million. The probability of melanoma in a man's life is 1/27 and that in women is 1/42 [16]. Skin melanoma accounts for more than 90% of melanomas [17]. Although the incidence of melanoma is not high, the degree of malignancy is very high and prone to metastasis. According to statistics, skin melanoma accounts for 5% of all skin malignancies but accounts for more than 80% of all skin cancer–related deaths [18]. Therefore, early diagnosis and treatment are of great importance for improving the prognosis of patients with malignant melanoma.

Acral lentiginous melanoma(ALM) is a rare subtype of cutaneous melanoma that occurs mainly in the palm, sole and nail bed. In people with light skin, acral lentiginous melanoma is the rarest subtype, accounting for only approximately 4%–10% of all cutaneous melanomas, whereas in people with deep skin (e.g. Asians and Africans), acral lentiginous melanoma is the most common subtype [19]. On the one hand, because acral lentiginous melanoma does not show typical ABCD signs of malignant melanoma (asymmetry, boundary, colour and diameter) [20], it often shows an ulcer [21]. On the other hand, because early-stage acral lentiginous melanoma is asymptomatic, many patients, especially the elderly, find it difficult to detect changes in the foot skin. Thus, acral lentiginous melanoma is often misdiagnosed, which delays its diagnosis and treatment.

By 2020, more than 10 cases of diabetes with plantar melanoma have been reported in English literature(see Table 2). Most of these cases were elderly patients and mostly White. The average age of onset was 73 years (range, 48–87 years), the

median patient age was 77 years and the gender ratio difference was small. Most tumours occur on the plantar, followed by the toe. Of these cases, the clinical manifestations of malignant melanoma vary and include ulcers, warts, haematoma, nevus, granuloma and so on. Thus, the tumour is also known as the ‘great makeup artist’. Interestingly, most patients had a history of diabetes for more than 10 to 20 years.

The two patients in this report were elderly, with an onset age similar to that in previous cases. One case occurred at the plantar and one at the toe, with the same site as that in previous cases. The first patient had a long history of diabetes, whereas the second patient had a short history of diabetes, which differed from other cases. The two patients reported in this paper were yellow people. The infection of the foot ulcers was mild in these two cases, and there were no symptoms of diabetic foot ulcers such as pain, redness or bleeding. It is easy to diagnose diabetic peripheral neuropathy as it results in sensory loss and ischaemic ulcer caused by diabetic peripheral vascular disease. In these two cases, the course of the ulcers was prolonged, and they did not heal after conventional wound dressing change. Moreover, in one case, local bone destruction was observed in the toe. In both cases, pathological biopsies of foot ulcers confirmed malignant melanoma of the foot.

Additionally, studies have shown that chronic hyperinsulinemia increases the risk of cancer. Insulin resistance and hyperinsulinemia are characteristic manifestations of type 2 diabetes. Exogenous insulin is required to replace hyperglycaemia with compensatory hyperinsulinemia in patients with type 2 diabetes until β-cell failure. The dose usually exceeds normal insulin levels, which is also associated with an increased risk of cancer [22]. Both patients in this study had a history of exogenous insulin use, and further study is needed to determine whether this is related to tumorigenesis.

The diagnosis of melanoma should rely on biopsy and immunohistochemistry: the application of markers such as the expression of S-100 protein and HMB-45, MART-1/Melan-A and Ki67 also has great value in the melanoma diagnosis. There is currently no consensus on when the pathological biopsy should be performed for intractable foot lesions. However, we recommend the following:(1) For patients with a diagnosis of diabetic foot, who have achieved blood glucose control and in whom factors causing refractory foot disease have been excluded, early pathological biopsy should be considered when the wound still does not heal or even becomes aggravated. (2) When diabetic foot lesions occur without obvious risk factors of diabetic foot disease, such as poor blood glucose control, peripheral vascular neuropathy, trauma history and so on, the clinician should be notified, and a biopsy should preferably be performed to exclude other causes of the disease. (3) When atypical lesions, such as pigmentation and granulation tissue, are present, biopsy should be performed as early as possible for a definite diagnosis, regardless of the presence of risk factors for intractable lesions.

## Abbreviations

ALM
Acral lentiginous melanoma.

## Declarations

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Ethics approval and consent to participate

The study was approved by the Ethics Committee of Xiangya Hospital of Central South University (Changsha, China) and was conducted in accordance with the Declaration of Helsinki. All procedures were performed in accordance with ethical standards. All study participants were told that the data obtained from them would be used only for the purpose of the study. Data is confidential and no name is recorded. Written informed consent was obtained from the patient for publication of this Case Report and any accompanying images.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

HBL conceived of the study and drafted the manuscript. TM participated in the histopathological evaluation and supplied the literature review, LJY, LML,LL and ZM participated in its acquisition of data and analysis. WM participated in its design and coordination and helped to draft the manuscript. All authors read and approved the final manuscript.

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# Tables

Table 1
Clinical data of two patients with type 2 diabetic malignant melanoma

| Case | Gender | Age | Duration of diabetes | Duration of foot lesion | The glucose treatment | family history | Complications of diabetes | HbA1c | Wound condition |
|---|---|---|---|---|---|---|---|---|---|
| Case 1 | female | 70 | 7 years | 6 months | Treatment with premixed insulin for more than 5 years,Acarbose | No special | Diabetic peripheral vascular disease, Hypertension | 6.8% | Superficial ulcer, no pus,no pain and bleeding, no combined infection |
| Case 2 | female | 66 | 7 months | 2 months | Pioglitazone metformin | No special | Diabetic peripheral vascular disease, Diabetic Nephropathy, Hypertension | 6.3% | Black toe, dry surface, the pain disappeared slightly, combined with infection, treatment with levofloxacin |

Table 2
Clinical data of diabetes complicated with acral malignant melanoma reported in literature

| Cases reported | Gender | Age | Race | Duration of diabetes | Lesion location |
|---|---|---|---|---|---|
| Matteo L. et al,1997[4] | female | 84 | White people | 50 | toe |
| Claudio GuarneriMD. et al, 2011[5] | male | 86 | White people | 30 | ankle |
| Susan Thomas et al, 2012[6] | male | 81 | black people | - | pelma |
| Yunfang Han. et al,2018[7] | male | 71 | yellow people | 20 | toe |
| A Tulin Mansur. et al,2015[8] | female | 87 | White people | - | toe |
| C. L. Gregson. et al,2004[9] | female | 76 | White people | 15 | pelma |
| Sena YeYil.et al,2007[10] | male | 71 | White people | 17 | pelma |
| Muhammad Shoaib Zaidi. et al,2016[11] | male | 67 | White people | 9 | pelma |
| Wei Gao, MD.et al,2017[12] | female | 78 | yellow people | 8 | pelma |
| Paisal Hussin. et al, 2012[13] | male | 80 | White people | 40 | toe |
| Paisal Hussin. et al, 2012[13] | female | 52 | yellow people | 15 | pelma |
| Peter Novodvorsky. Et al, 2018[14] | male | 48 | White people | - | pelma |

# Figures

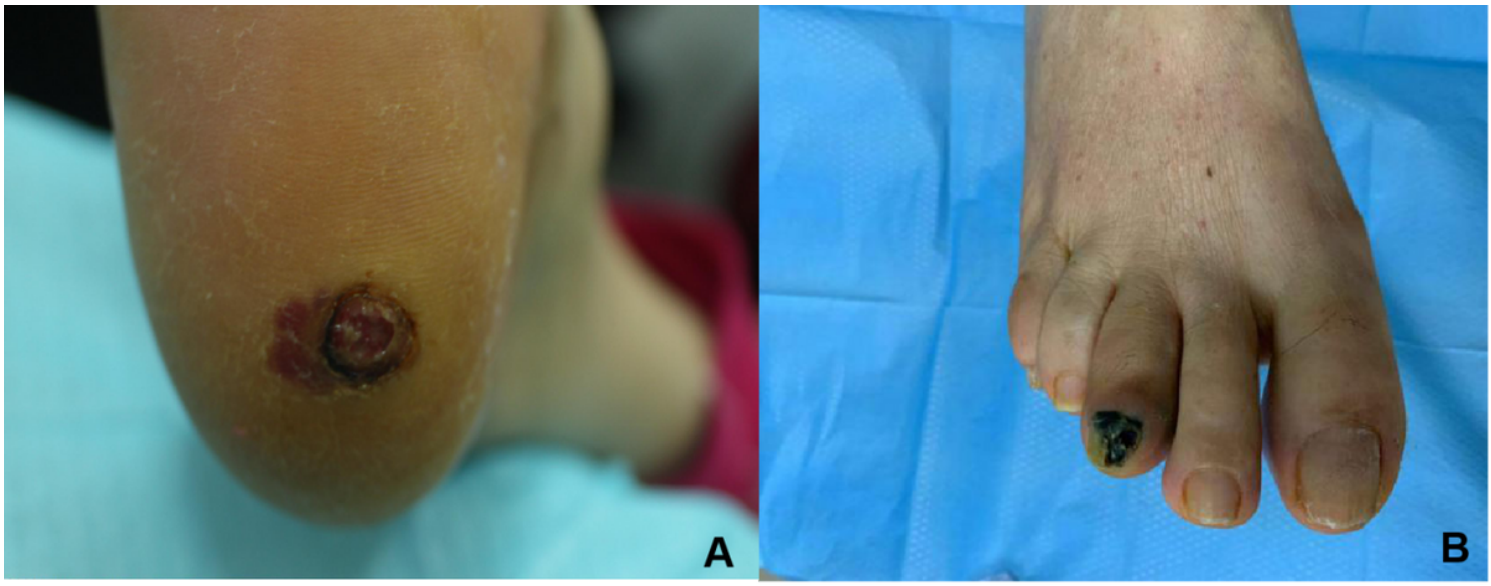


**Figure 1**

Patients' foot wound: Case 1, female, 70 years old, with right foot ulcer(Figure1A), and Case 2, female,66 years old, with blackening at the end of the third toe of the right foot.

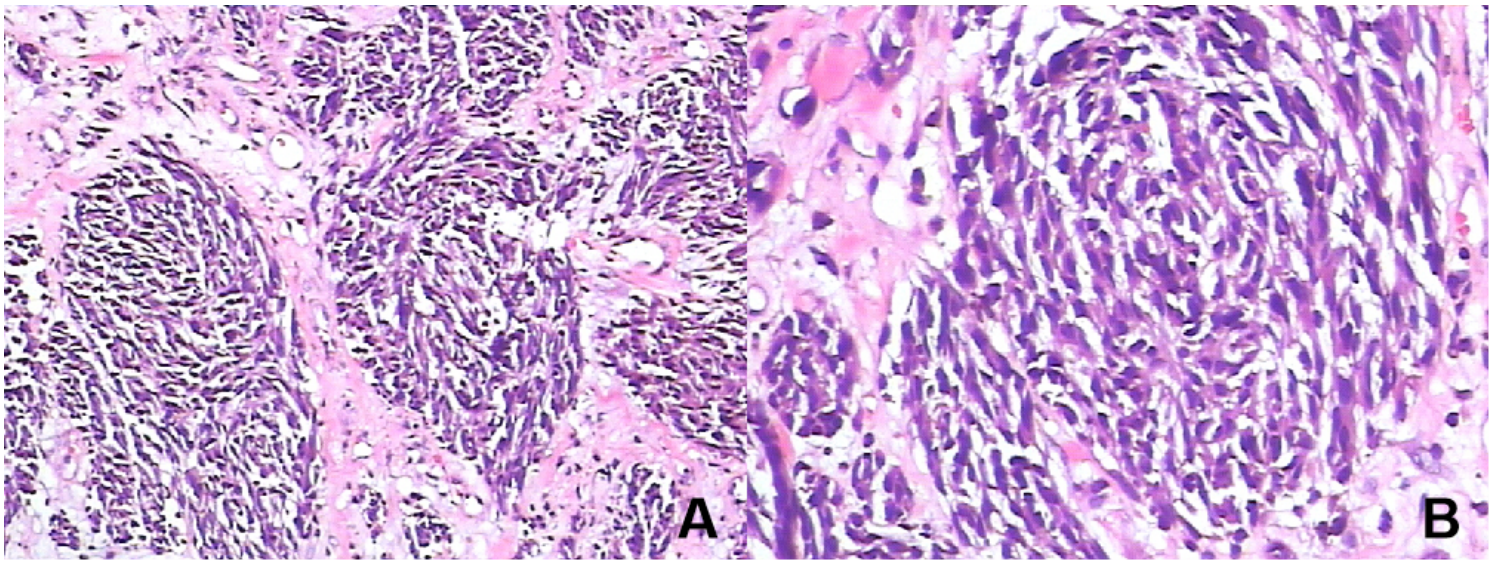


**Figure 2**

Histopathological characteristics of malignant melanoma in case 1 (Figure 2A×40, Figure 2B×100).

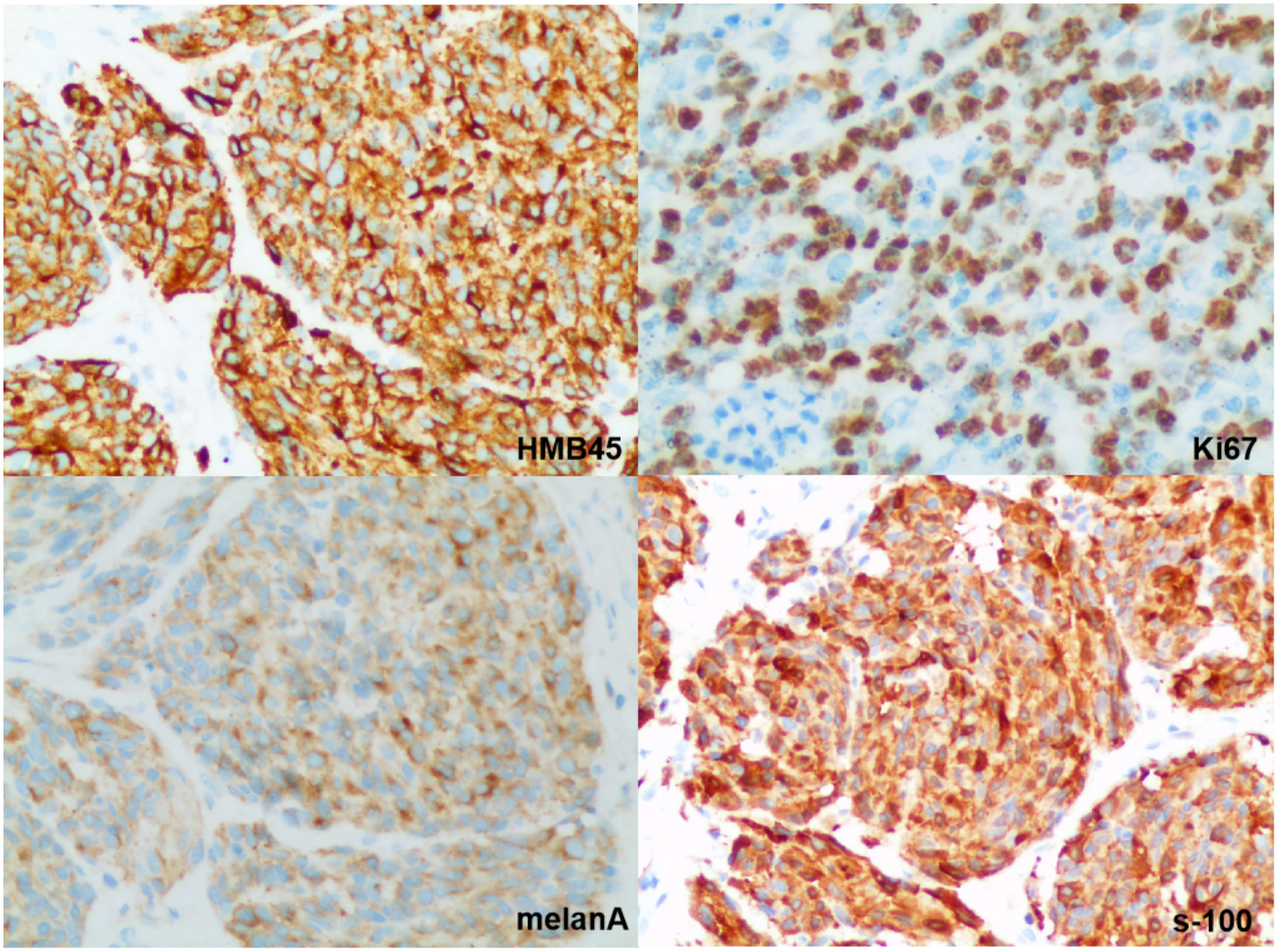


**Figure 3**

The immunohistochemical features of malignant melanoma in case 1 : The results of immunohistochemical staining demonstrated the tumor cells were positive for HMB45, Ki67, melanA and S-100 protein.

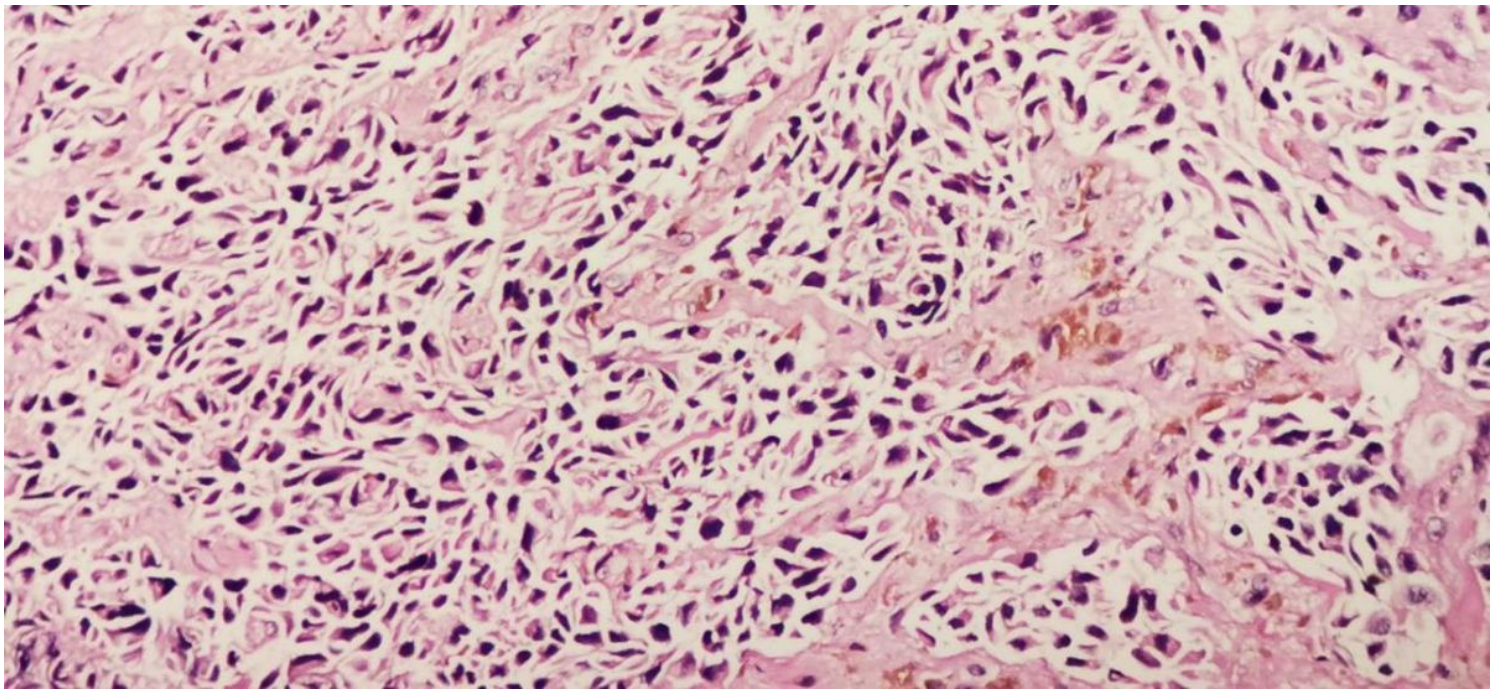

**Figure 4**

Histopathological characteristics of malignant melanoma in case 2 .

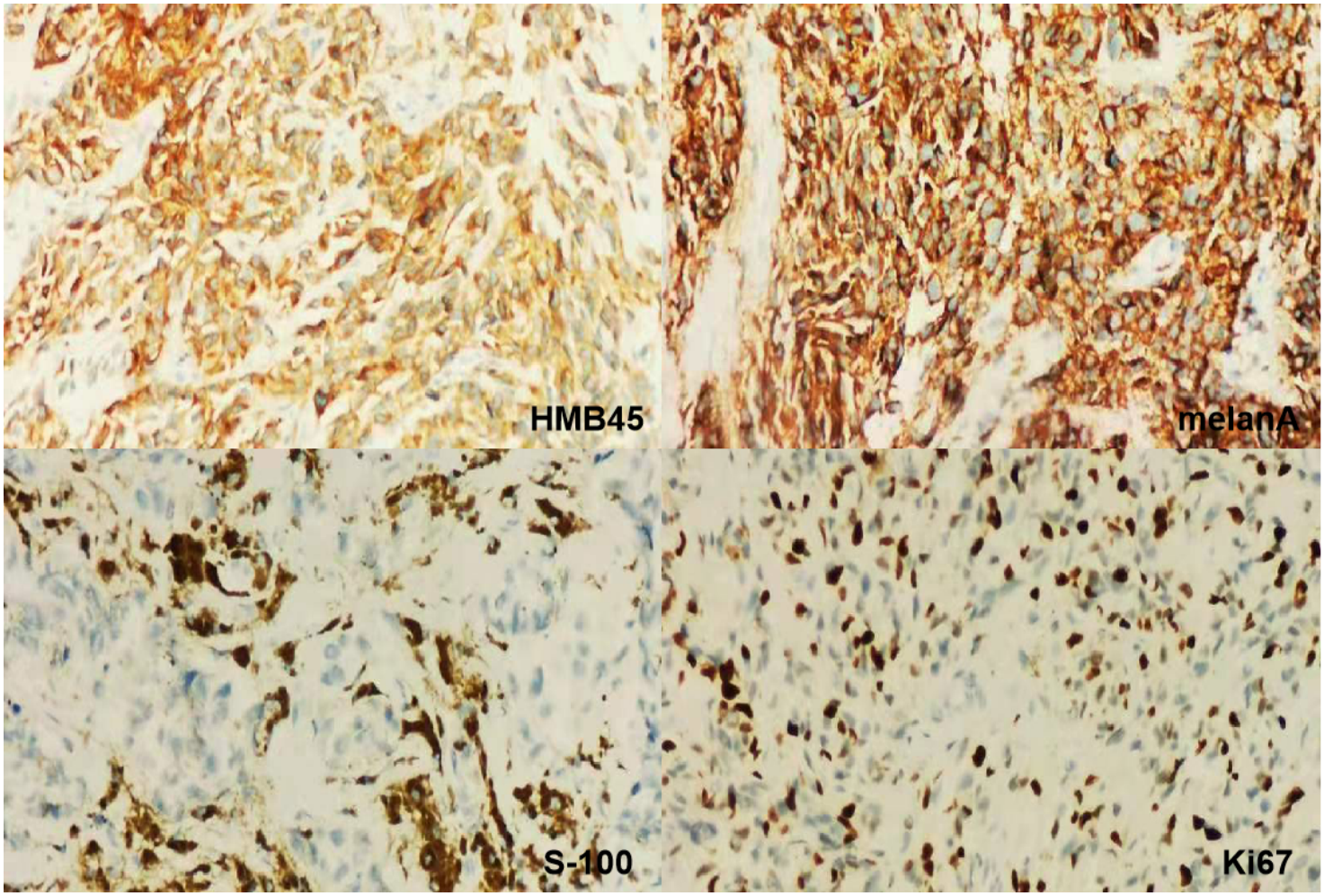

**Figure 5**

The immunohistochemical features of malignant melanoma in case 2 : The results of immunohistochemical staining demonstrated the tumor cells were positive for HMB45,melanA, S-100 protein and Ki67.

## Supplementary Files

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