Pigmented skin lesions with atypical histopathology indicating a diagnosis of multiple metastases of melanoma: A case report

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Abstract. The present study reports on the case of a middle-aged female patient who presented with a rapidly progressing pigmented skin lesion on the periphery, combined with multiple intracranial, pulmonary, hepatic and skeletal malignancies. The case was not clear in terms of histopathological manifestations and other aspects, which made the diagnosis of melanoma difficult. The present case details the challenges in the diagnostic process, as well as the importance of multidisciplinary comprehensive diagnosis and treatment, aiming to provide a reference for clinicians when dealing with similar complex pigmented skin lesions.

Introduction

Melanoma is a highly malignant and aggressive skin tumor. According to statistics, the global incidence of malignant melanoma has increased from 2.01 per 100,000 in 1990 to 3.75 per 100,000 in 2019 (1), and early and accurate diagnosis is crucial for improving patient prognosis. However, in the clinic, the pathological features of some pigmented skin lesions are not clearly differentiated from melanoma, thus posing a diagnostic challenge. The most common sites of metastasis for cutaneous malignant melanoma are the brain, lungs, liver and lymph nodes, and ~90% of patients diagnosed with metastatic melanoma with three or more metastases die within 1 year (2). Although melanoma metastases can be found almost anywhere in the body, it is uncommon for multiple systemic metastases to be detected (3). The present study reports on a case with unknown diagnosis, but with highly suspected multiple intracranial, lung, liver, bone and lymph node metastases of melanoma.

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Case report

Patient presentation and background information. The patient was a 45-year-old woman who presented with low back pain in June 2024 without any obvious cause, and the pain was not relieved after independently applying a traditional Chinese medicine ointment. In mid-July 2024, the pain worsened, accompanied by coughing and sputum expectoration. The patient was admitted to The First Affiliated Hospital of Hebei University of Chinese Medicine at the beginning of August 2024, due to the presence of low back pain for >2 months and coughing for ~1 month. The patient complained of pigmented skin lesions around their body at birth, with large patches of hyperpigmentation on the back and buttocks. There was no evidence of related diseases in the family and the patient denied that there was a family history of hereditary disease. At the time of admission, the symptoms were mainly an intermittent dry cough with little sputum, fatigue and poor appetite. Written informed consent was obtained from the patient for the present case report, which was also approved by the Ethics Committee of The First Affiliated Hospital of Hebei University of Chinese Medicine (approval no. HBZY2025-KY-004-01; Shijiazhuang, China).

Clinical examination. The oncologist and the consulting dermatologist performed a detailed physical examination of the lesions; the peripheral skin of the patient was seen to have large areas of hyperpigmentation, some of which were markedly elevated to form prominent masses, and notable thickening of the skin lesions on the back and hips was observed, with a thickening of >5 mm (Figs. 1 and 2). No abnormal enlargement of superficial lymph nodes throughout the body was palpable. Upon observation, these skin lesions showed a trend of expansion in scope and thickening of the affected areas within a few days, with the skin on the back and hips being the most prominent. Such rapid skin changes were considered to have a certain malignant tendency.

Laboratory tests. The patient underwent blood tests, including routine blood, liver function, renal function and tumor marker tests. Among them, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, lactate dehydrogenase (LDH), γ-glutamyl transferase (GGT) and neuron-specific enolase (NSE) were all elevated compared

with the normal levels, the Risk of Ovarian Malignancy Algorithm (4) was slightly decreased compared with the normal levels, and the levels of tumor markers, such as carcinoembryonic antigen, α-fetoprotein, cancer antigen (CA)19-9, CA72-4, CA125, CA15-3, squamous cell carcinoma-associated antigen and cytokeratin 19 fragment antigen 21-1, were within the normal range (Table I). Notably, all other indexes did not suggest abnormalities.

Imaging. In the course of diagnosis and treatment, the patient underwent systematic CT examination of the important organs of the body, and the specific results were as follows: CT of the skull and brain showed multiple metastatic tumors in the skull, and multiple soft tissue nodular shadows in the soft tissues of the scalp (Fig. 3). Enhanced CT of the chest and abdomen showed multiple solid nodular shadows in both lungs (the larger one was located in the lower lobe of the left lung, with a long diameter of ~3.6 cm), indicating a pulmonary metastatic lesion (Fig. 4). Multiple slightly low-density shadows were observed in the liver (the larger one with a long diameter of ~3.5 cm), indicating a hepatic metastatic lesion.; and increased soft-tissue shadows were detected in the subcutaneous soft tissues of the back (Fig. 5). Chest CT and frontal and lateral X-ray imaging of the spine revealed right-sided comminuted fracture of thoracic 12 vertebra; formation of a large Schmorl's node in the laryngeal region of lumbar 1 vertebra, accompanied by detachment and displacement of bone fragments; and multiple hypodense foci in the body of lumbar vertebrae (Fig. 6). Lymph node ultrasound showed multiple abnormal lymph nodes in both sides of the supraclavicular fossa, and in conjunction with the medical history, lymph node metastasis was suspected (Fig. 7). Imaging suggested that the patient may have multiple metastases to the cranium, lungs, liver, bone and lymph nodes, but the source was not yet clear. Notably, the patient refused to undergo dermoscopy.

Histopathological examination. The patient underwent a biopsy of an abdominal skin mass at The Fourth Hospital of Hebei Medical University in July 2024, and the pathology showed a mixed nevus with cut margins (no tumor cells were found around the surgical incision). In August 2024, a subcutaneous soft-tissue nodule was taken from the left hip and sent to the hospital for another pathological examination, and the results showed that spindle-shaped tumor cells resembling fibroblasts could be seen within the collagen bundles of the tissue, and the spindle tumor cells were arranged in bundles, with atypical cellular properties. The histological pattern and immunohistochemical expression were not specific (Data S1). Combined with the clinical and medical history, a differential diagnosis of neurofibroma and fibroproliferative melanoma was suggested (Fig. 8). The immunohistochemical findings were as follows: Pan-cytokeratin (-), Vimentin (+), Ki-67 (1%), S-100 (+), Melan-A (-), HMB45 (-), P53 (no mutation suggested) and SMA (-). The pathology results were inconclusive; the pathologist considered the sample to be consistent with some features of melanoma, but the evidence was insufficient. Multiple out-of-hospital consultations or genetic testing were recommended for further analysis.

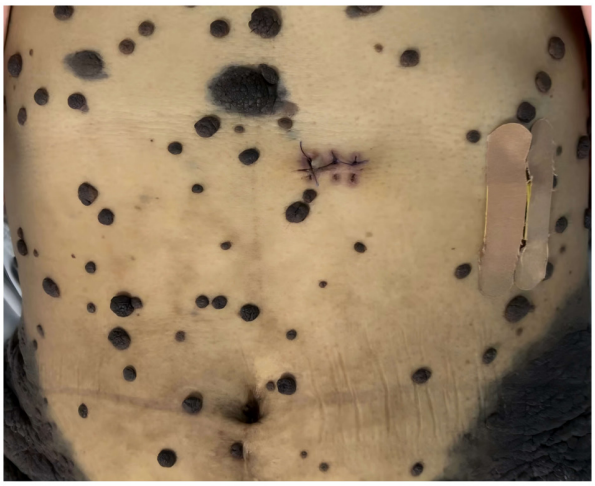

Figure 1. Pigmented lesions on the abdomen of the patient.

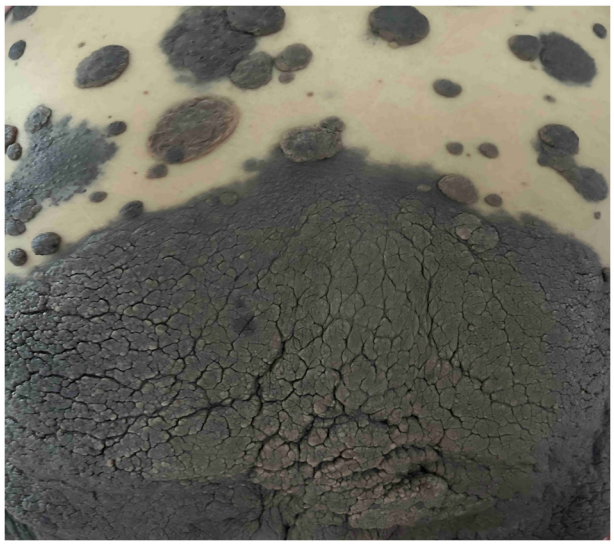

Figure 2. Pigmented lesions on the back of the patient.

Diagnostic considerations. The National Comprehensive Cancer Network (NCCN) guidelines state that cutaneous melanomas tend to develop from nevi, with melanomas originating from giant congenital nevi and melanomas from neurocutaneous melanocytosis (NCM) being rare histological types (3).

Giant congenital melanocytic nevus, a specific type of giant congenital nevus, is closely related to genetic factors or gene mutations (5,6). The size of giant congenital nevus is usually >20 cm in diameter, the border is usually irregular, the shape may be round, oval or irregular, the surface may be rough and uneven with hair growth, the color may be black, brown or tan, and the color is often uneven (2). Giant congenital nevi may be distributed in any part of the body, and are commonly found on the head and neck, trunk area and limbs (1). Dermoscopy and pathological examination are important auxiliary examinations, of which pathological examination is the gold standard for the diagnosis of giant congenital melanocytic nevus, which can accurately determine the nature of the lesion and whether there is a tendency toward

Table I. Laboratory test results.

Characteristic	Result	Normal value
ALT, U/l	230.9	7-40
AST, U/l	226.9	13-35
ALP, U/l	295	35-100
LDH, U/l	4,450	120-150
GGT, U/l	183	7-45
NSE, ng/ml	>300	<16.3
ROMAI, %	6.61	<11.4
CEA, ng/ml	0.70	<3.4
AFP, IU/ml	2.28	≤5.8
CA19-9, U/ml	3.38	<27
CA72-4, U/ml	0.96	≤6.9
CA12-5, U/ml	26.30	≤35
CA15-3, U/ml	7.72	0-25
SCC, ng/ml	0.97	0-2.7
CYFRA21-1, ng/ml	1.47	<3.3

ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; LDH, lactate dehydrogenase; GGT, γ-glutamyl transferase; NSE, neuron-specific enolase; ROMA, Risk of Ovarian Malignancy Algorithm; CEA, carcinoembryonic antigen; AFP, α-fetoprotein; CA, cancer antigen; SCC, squamous cell carcinoma-associated antigen; CYFRA21-1. Cytokeratin 19 fragment antigen 21-1.

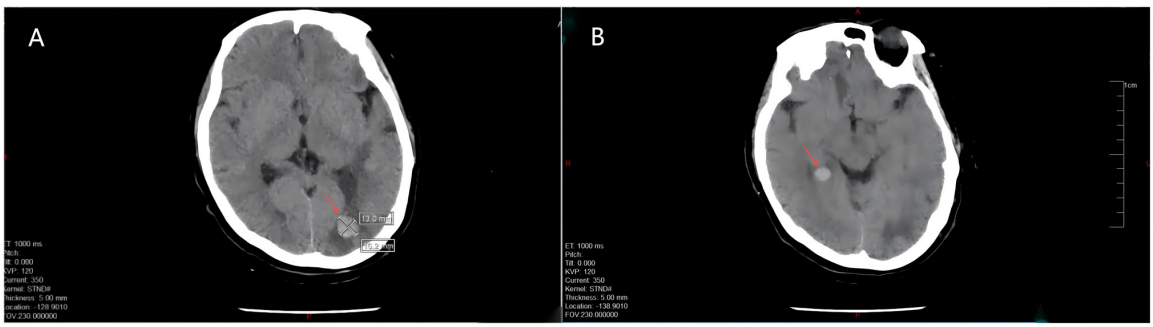

Figure 3. Multiple metastatic intracranial tumors shown on cranial CT (arrows indicate the brain metastasis focus). (A) Level of the body of the lateral ventricle. (B) Level of the midbrain.

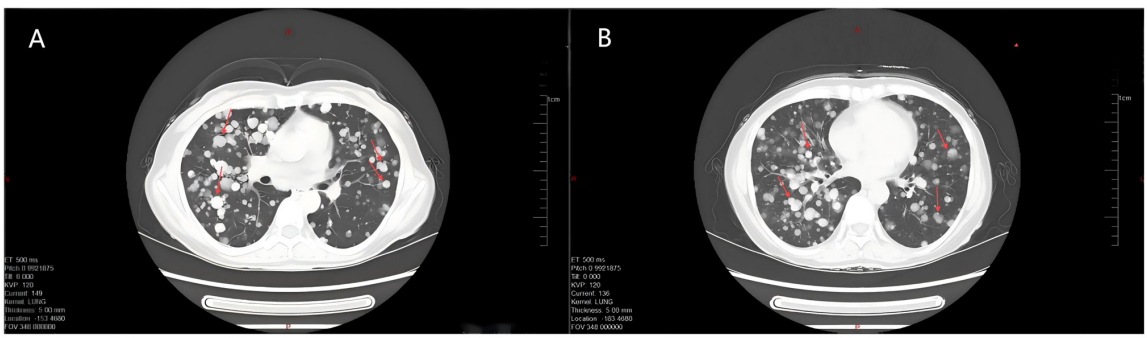

Figure 4. Multiple metastases shown on chest CT (arrows indicate the lung metastasis focus). (A) Level below the carina of trachea 1. (B) Level below the carina of trachea 2.

malignant changes (7). Giant congenital melanocytic nevus is large in size and the nevus cells are often distributed in deeper tissues, sometimes even extending to the borders of muscles or other internal organs (5). Due to the wide distribution and deep location of the nevus cells, it is difficult to detect signs of malignant changes in the early stages through conventional examinations, thus making early diagnosis difficult (5). In the present case, the patient complained of multiple giant nevus

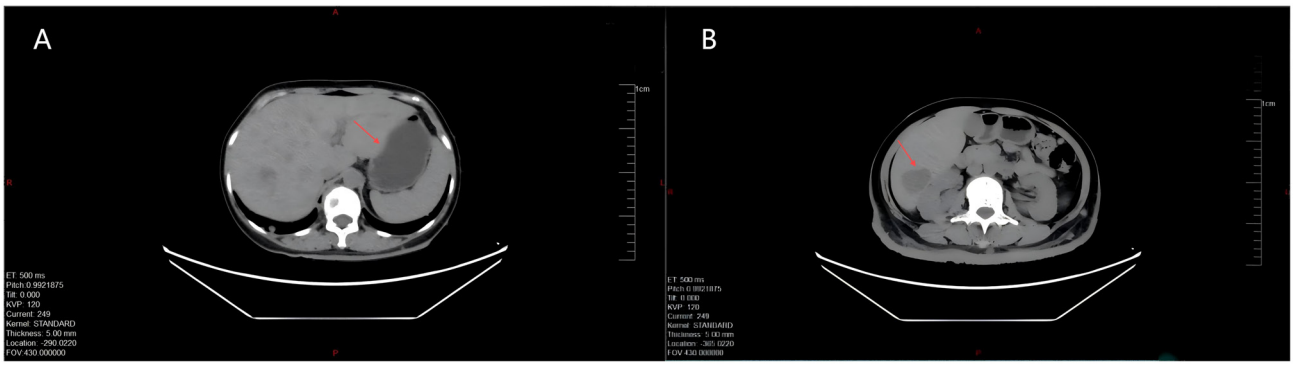

Figure 5. Multiple slightly hypodense shadows shown in the liver on abdominal CT (arrows indicate the liver metastasis focus). (A) Level of the left lobe of the liver. (B) Level above the renal hilum.

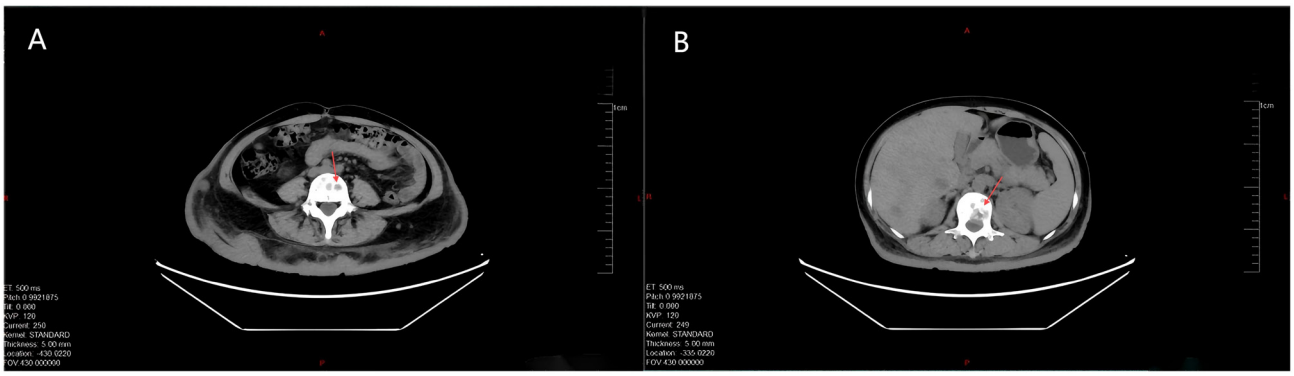

Figure 6. Multiple hypodense foci shown in lumbar vertebral bodies on abdominal CT (arrows indicate the bone metastasis focus). (A) Level of the renal hilum. (B) Level of the porta hepatis-upper margin of the pancreas.

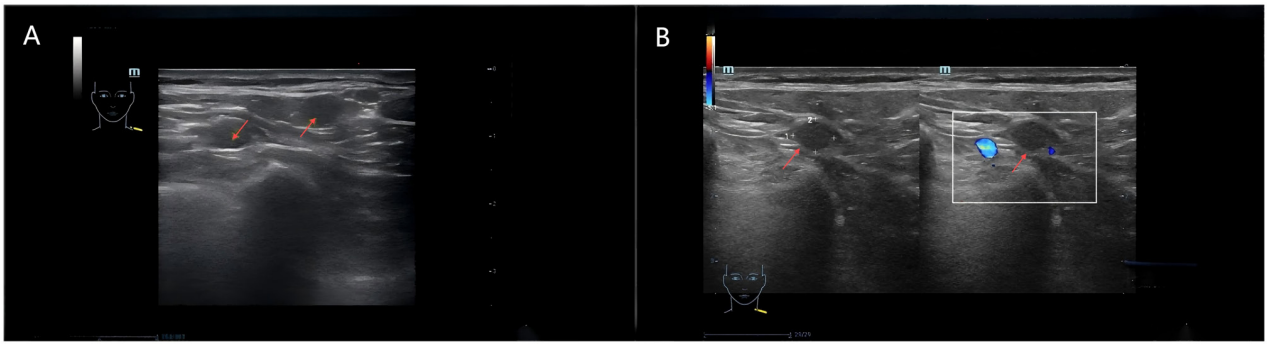

Figure 7. Lymph node ultrasound showed multiple abnormal lymph nodes in both sides of the supraclavicular fossa (arrows indicate the abnormal lymph node). (A) Two-dimensional ultrasonic image. (B) Image combining two-dimensional ultrasound and color Doppler ultrasound.

lesions on the skin at birth, which did not receive sufficient attention and diagnosis at the early stage. Furthermore, the area of the skin lesions was extensive, and upon examination, the pathological features were atypical, which complicated the condition and indicated a potentially severe prognosis.

NCM is a relatively rare congenital disorder. Some cases of NCM are associated with genetic factors, and there may be mutations in genes such as GNAQ, BRAF and NRAS or chromosomal abnormalities, which lead to abnormal distribution of melanocytes in the nerves and skin (8-10). In addition, abnormal embryonic development is a common cause, with abnormal differentiation and migration of neural crest cells being the main cause of NCM (11). Neural crest cells are pluripotent stem cells that can differentiate into various cell types, such as melanocytes and neural cells (11). NCM can be triggered by errors in the migration and differentiation of neural crest cells into the skin and the nervous system, resulting in the accumulation of excessive melanocytes in the skin and the central nervous system; this is similar to the patient described in the present case, who had multiple large nevi of different sizes and shapes that appeared at birth or shortly after birth, often on the head, neck and trunk (9,10). The size and shape of the nevi vary, the border is irregular, and the color can be black, brown or tan (11). Neurological

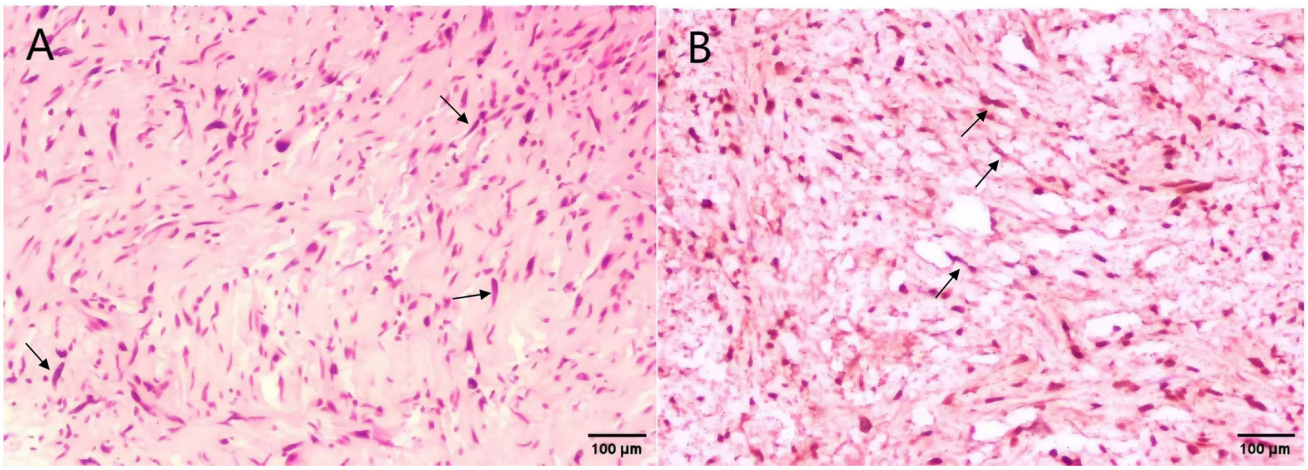

Figure 8. Pathological examination showed that spindle-shaped tumor cells resembling fibroblasts were seen within the collagen bundles of the tissue, and the spindle-shaped tumor cells were arranged in bundles with atypical cellular properties (arrows indicate the spindle-shaped tumor cells) (A) Field of view 1. (B) Field of view 2.

symptoms may appear gradually in childhood or adolescence, and the severity varies with individual differences, including headache, vomiting, seizures, movement disorders and intellectual disabilities (12). Although the patient did not exhibit typical symptoms of neurological involvement, the NSE level of the patient was >300 ng/ml and cranial CT imaging showed multiple metastatic intracranial tumors, suggesting the existence of neurological lesions. Dermatopathological examination is an important basis for the diagnosis of NCM skin lesions. Pathological biopsy reveals increased melanocytes in the epidermis, with a nested or diffuse distribution, and the cell morphology may show some degree of heterogeneity (10). Neuroimaging may show melanin deposits or space-occupying lesions in the brain parenchyma, commonly in the cerebral hemispheres, cerebellum and brainstem (11). In addition, some patients may have abnormalities in the cerebrospinal fluid, such as elevated protein levels and increased cell counts, with melanoma cells sometimes detected (9,10). Patients are often not diagnosed until they develop significant neurological symptoms or tumor metastasis, and early diagnosis is challenging (9).

The NCCN guidelines summarize the symptoms of early nevus malignancy as the 'ABCDE' rule: Asymmetry, border irregularity, color variation, diameter and elevation (7). The clinical symptoms of the patient in the present study fully conformed to the 'ABCDE' rule. The guidelines state that a shortcoming of this rule is that it does not take into account the speed of development of melanoma, such as the tendency of notable changes in weeks or months. In the present case report, the skin lesions on the back and both hip areas exhibited an obvious trend of enlargement and thickening over a few days, which had a certain malignant tendency.

The current gold standard for diagnosing melanoma is histopathology combined with immunohistochemistry, with adjunctive diagnostic modalities including visualization, dermoscopy, skin confocal technology, skin CT and artificial intelligence-assisted diagnosis. In the present case, the histopathological pattern and immunohistochemical expression of the patient were not specific, and the patient and their family refused further genetic testing and consultation with outside hospitals, which made it difficult to make a definitive diagnosis. The pathological report of the present patient suggested that the diagnosis needed to distinguish between neurofibroma and pro-fibroproliferative melanoma. The spindle cells in melanoma may be indistinguishable from those of neurofibroma, but features such as marked fibroproliferative growth, poor lateral borders, and diffuse infiltration of subcutaneous tissues and lymphoid aggregates may be useful information for the diagnosis (13). Specific immunohistochemical markers include S-100, SOX-10, HMB45, Melan-A, PNL2, tyrosinase, MITF and Vimentin; however, there is a lack of objective, highly reproducible immunohistochemical markers for all melanoma (14,15).

The NCCN guidelines state that S-100 is the most sensitive marker and is a screening indicator for melanoma. In addition, it is recommended that two to three of the aforementioned markers be used in conjunction with S-100 when differential diagnosis is needed to improve the detection rate of melanoma. Although LDH is not a sensitive indicator for detecting metastasis of melanoma, it is an effective guide to prognosis of melanoma (7). The patient had positive expression of the immunohistochemical markers S-100 and Vimentin; of which, positive expression of S-100 suggested the possible presence of a neurogenic or melanocytic origin. However, Melan-A and HMB45 negativity did not support the typical melanoma manifestations, which made differential diagnosis difficult, and the markers S-100 and Vimentin are not specific in distinguishing between neurofibroma and pro-fibroproliferative melanoma. However, it should be noted that the S-100 protein is usually positive in melanocytes and their tumors, and it is also a marker for neural tissues and tumors of neural origin, and can thus be expressed in tumors with neural differentiation; therefore, S-100 may be positive when NCM develops into melanoma. Vimentin (waveform protein) is a marker for tumors of mesenchymal origin, and melanoma originates from melanocytes of neural crest origin, which are of mesenchymal origin, and thus Vimentin is usually positive in melanoma.

Notably, the LDH levels of the patient in the present case were >10 times higher than the normal range, and LDH has a role in distinguishing neurofibromas from melanomas (7,16).

Studies have shown that serum LDH levels are often associated with disease progression in patients with melanoma, and the serum markers LDH and S-100B independently predict recurrent metastasis and disease prognosis in these patients (16,17). When melanoma metastasizes or is in advanced stages, tumor cells proliferate rapidly and are metabolically active, leading to increased LDH release (17). High levels of LDH are usually indicative of a poor prognosis, shorter survival and faster disease progression in patients with melanoma (7). By contrast, neurofibroma is a benign tumor with slow growth and relatively inactive metabolism, and thus serum LDH levels are generally within the normal range in cases of neurofibroma (16,17). Considering that the present patient was suspected to have melanoma and had a history of congenital giant nevus, the RAS gene of the patient should be tested for mutations. Studies have shown that RAS gene mutations serve an important role in the development of congenital nevi into melanoma (1,7,15). However, the patient and their family refused further pathological consultations and genetic testing, which made it difficult to clearly diagnose the disease, and to accurately determine the molecular typing and genetic status of the disease. In addition, to a certain extent, this affected the accuracy of the diagnosis and optimization of the treatment plan. Subsequently, the skin lesions rapidly expanded and thickened during the hospitalization period. Taking into account the symptoms, signs, and test and examination results of the patient, a preliminary diagnosis of melanoma with multiple metastatic foci that developed from a giant congenital melanocytic nevus or NCM was finally made.

Treatment. The lack of further genetic testing to clearly diagnose and identify the molecular typing of the disease and potential therapeutic targets, as well as the preference of the patient and their family for conservative treatment, limited the optimization of the treatment plan to a certain extent. The treatment strategy was actively adjusted and the clinical team communicated with the patient and their family, explaining in detail the positives and negatives of conservative treatment, and the possible risks of disease progression. According to the symptoms of the patient, a personalized symptomatic treatment plan was formulated. Due to obvious lung infection, wheezing and shortness of breath, the patient was given 4.5 g piperacillin sodium and sulbactam sodium by intravenous drip and 30 mg methylprednisolone sodium succinate by intravenous injection for 8 days, and received ceftazidime (2 g) by intravenous drip for 11 days. Due to multiple metastatic tumors in the liver combined with hepatic insufficiency, 20 ml magnesium isoglycyrrhizinate injection and an intravenous drip of 1.2 g glutathione were administered to protect the liver and lower the enzyme levels, such as ALT, AST and GGT, for 13 days. Due to the multiple bone metastases and neuropathy, the patient was administered one tablet of the oral analgesic paracetamol (500 mg) and dihydrocodeine tartrate (10 mg) tablets every 6 h along with other symptomatic treatments, such as oxygen inhalation, cough suppression, laxative administration and nutritional supplementation. After 2 weeks of conservative treatment, the condition of the patient progressed rapidly, and they developed respiratory failure, which could not be improved by mask oxygenation. Approximately 1 week later, the patient entered a shallow comatose state and the family requested an automatic discharge. Through subsequent telephone follow-up, it was confirmed that the patient had succumbed in September 2024.

Discussion

The histopathological recommendation for the diagnosis of cutaneous melanoma is excisional biopsy, although partial biopsies (scraping and puncture) are also frequently used (18). In the present patient, excisional biopsy of the abdominal and hip skin was selected separately because the lesions were very extensive in terms of body surface area, with near circumferential involvement, which created some uncertainty in the accuracy of the diagnosis. In the present case, the patient was suspected to have developed melanoma from a congenital nevus, in which RAS mutation was a potential factor. The RAS gene family includes NRAS, HRAS and KRAS, of which the NRAS mutation is the most common, which leads to continuous activation of the RAS protein and activation of downstream signaling pathways, such as MAPK and PI3K/AKT. This activation promotes cell proliferation, survival, migration and invasion, ultimately promoting melanoma development (1,19). If the RAS gene status can be clarified, it is considered to be of value for the diagnosis and treatment of the case (7,15,19). In diagnosis, it can be used as additional evidence for a melanoma diagnosis, particularly in cases with atypical immunohistochemistry and pathology results; in treatment, targeted therapeutic drugs or combination therapies targeting RAS mutations may provide more effective therapeutic choices for patients (7,15). In addition, RAS mutation status is important in assessing the prognosis of patients, as patients with these mutations may have a poorer prognosis and a higher risk of disease progression (19). Since the present patient and their family refused further genetic testing and opted for conservative treatment, this affected the accuracy of the diagnosis and optimization of the treatment plan to a certain extent, and posed a number of challenges for the medical team regarding diagnosis and treatment.

Surgical resection is the first choice of treatment for early-stage melanoma. Since the present patient had a large peripheral area of involved skin and multiple organ metastases, it was recommended that systemic treatment options, such as immunotherapy and targeted therapy, be considered. Immunotherapy mainly includes immunosuppressants, cellular immunotherapy and tumor vaccines (7,15,20). The more widely used immunosuppressants include PD-1 inhibitors, such as pembrolizumab and nivolumab, PD-L1 inhibitors, such as atezolizumab, and CTLA-4 inhibitors, such as ipilimumab (7,15). Cellular immunotherapy involves extracting immune cells from the body of the patient, culturing, transforming or modifying them *in vitro* to make them more capable of recognizing and attacking tumor cells, and then infusing them back into the body to exert antitumor effects (20). For example, tumor-infiltrating lymphocyte (TIL) therapy has been shown to achieve good results in some patients with advanced melanoma (21). Furthermore, tumor vaccines, such as the MAGE-A3 vaccine, although still in the research and development stage, provide novel potential options for the treatment of melanoma (22).

Commonly used drugs for targeted therapy include BRAF inhibitors and MEK inhibitors (7,15). For patients

with distant metastases or localized metastases that cannot be radically resected, BRAF V600 gene testing is important for guiding subsequent treatment (1,7,15). For patients with wild-type BRAF, immunotherapy with PD-1 inhibitors alone or in combination with a CTLA-4 antibody should be considered (7,15). For patients with concomitant BRAF V600 mutations, BRAF inhibitors such as vemurafenib and dabrafenib may be selected as first-line treatment options for patients with melanoma (7,15). MEK inhibitors, such as trametinib, are often used in combination with BRAF inhibitors to improve efficacy and delay resistance (7,15).

Notably, the lack of genetic test results in the present case report made it difficult to identify potential therapeutic targets and optimize the treatment plan. The only option was for a multidisciplinary team to develop a personalized symptomatic treatment plan, and to closely monitor the condition of the patient during the course of conservative treatment. However, conservative treatment could not stop the progression of the disease, and the patient eventually developed severe respiratory failure and entered a shallow coma.

Notably, progress is being made in clinical trials for advanced melanoma. In terms of immunotherapy, new immune checkpoint targets are being explored, such as TIM-3 and LAG-3 inhibitors, for which clinical trials are ongoing (23). Several studies have shown that inhibitors of these new targets may further improve therapeutic efficacy when used in combination with established immunotherapeutic agents (24,25). In the field of targeted therapies, the development of targeted drugs against mutations other than BRAF is also advancing. For example, clinical trials of drugs targeting NRAS mutations have made some breakthroughs (19). As for cell therapy, in addition to TIL therapy, chimeric antigen receptor (CAR)-T cell therapy and CAR-natural killer therapy also have some potential in advanced melanoma (26,27). In addition, clinical trials of combination therapies are increasing; for example, immunotherapy and radiotherapy, targeted therapy and chemotherapy, and the combination of anti-angiogenic drugs and immunotherapy, in order to identify more optimal therapeutic combinations and regimens (7,15,24).

There are some new research advances worth noting: Cui *et al* (28) conducted a trial evaluating the safety and efficacy of OrienX010, a modified herpes simplex virus 1 oncolytic virus, for the treatment of patients with unresectable stage IIIC-IV melanoma in China. The results showed an objective remission rate of 19.2%, a disease control rate of 53.8%, a median duration of remission of 6.0 months, a median progression-free survival time of 2.9 months and an overall survival time of 19.2 months. Preliminary evidence indicates that OrienX010 oncolytic viral therapy has a tolerable safety profile and antitumor effects in both the injected metastases and other non-injected metastatic sites in patients. Overall, clinical trials in advanced melanoma continue to bring new promise and breakthroughs, offering more treatment options and better prognosis for such patients.

In conclusion, the present case provides valuable experience and considerations. Firstly, patients with congenital skin lesions, particularly when the lesions are extensive and rapidly developing, should be alerted to the possibility of malignant transformation to melanoma. These patients should be examined comprehensively as early as possible to achieve a timely diagnosis and treatment, and to improve their prognosis. Secondly, accurate pathological and genetic test results are crucial to the diagnosis and treatment of the disease. In the future, the communication with patients and their families should be strengthened, and they should be fully informed of the importance of genetic testing, so as to obtain more comprehensive information about the disease, and to ensure accurate diagnosis and treatment. In addition, the active search for immunohistochemical markers of melanoma with high specificity is an urgent clinical issue. The choices of patients and their families are often influenced by a variety of factors, such as cultural background, economic status and psychological factors; therefore, healthcare professionals should provide comprehensive information and support, so that even in cases where patients refuse certain key tests and therapeutic treatments, the professionals can still work closely with multidisciplinary diagnostic and therapeutic teams to optimize treatment strategies. The aim of this case report is to encourage more medical personnel and patients to pay attention to early and accurate diagnoses, so as to avoid any delay, and to improve the prevention and treatment of such complex diseases.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

YH, HF and ZD designed the study. HF and DL advised on patient treatment. YH, ZD, YG and ZL acquired the data. HF, DL, YH and ZD analyzed and interpreted data for the work. YH, HF, ZD, DL, YG and ZL confirm the authenticity of all the raw data. All authors agree to be accountable for all aspects of the work. All authors read and approved the final version of the manuscript, and agreed on the journal to which the article has been submitted.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of The First Affiliated Hospital of Hebei University of Chinese Medicine and was conducted in accordance with the 1964 Helsinki Declaration and its subsequent amendments or comparable ethical standards.

Patient consent for publication

The patient provided written informed consent for the publication of their data before they succumbed to the disease.

Competing interests

The authors declare that they have no competing interests.

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