Case Report

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Malignant melanoma with bone metastases in a child: a case report and review of literature

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Introduction and importance: Melanoma is the fifth most common cancer diagnosed in the US in 2022. While its incidence increased from 1980 to 2017, it rarely happens in children. Its diagnosis and treatment are challenging in pediatric patients due to its rarity and different presentations compared to adults.

Case presentation: An 11.5-year-old boy with a complaint of back pain was admitted to the hospital. Initial examinations were normal; however, due to continued pain and symptoms (e.g., inability to walk, knee pain and ankle ecchymosis, weight loss, vomiting, nausea, and dyspnea), further examinations were performed. Biopsy, nuclear scan, computed tomography (CT) scan, and immunohistochemistry (IHC) confirmed the malignant melanoma diagnosis with bone and lung metastasis. Single-agent treatment with nivolumab was initiated after the diagnosis confirmation with no specific complication. The patient's parents decided to continue the treatment in their city of residence to reduce costs. However, the treatment was not continued, and unfortunately, the patient has passed away.

Clinical discussion: Melanoma is rare in children, making its diagnosis challenging. There are no specific guidelines for treating melanoma in pediatric patients, especially in children under 12, with ongoing debate on the most suitable treatment and follow-up options for these patients. It is important to fully examine resected legions for malignancy.

Conclusion: The study highlights the difficulties in diagnosing and treating malignant melanoma in children, considering its rarity and unusual signs and symptoms compared to adults. Specific guidelines are needed for diagnosing and treating malignant melanoma in pediatric patients.

Keywords: case report, melanoma, neoplasm metastasis, nivolumab

Introduction

Melanoma accounts for 1.7% of all cancers diagnosed worldwide[1]. In 2022, it was the fifth most frequent malignancy diagnosed in the United States[2]. The incidence of melanoma has grown from 10.5 per 100 000 in 1980 to 25.38 per 100 000 in 2017 in the United States[3]. It comprises around 5% of new cancers in men and 4% in women[4]. Melanoma accounts for less than 10% of skin cancer cases[5], and it remains relatively rare in children, with an incidence rate of 5 to 6 per million[6]. Less than 1% of cases of melanoma are in children[7].

Since 2011, new targeted or immunotherapy agents have significantly reduced melanoma mortality rate[8,9]. The annual treatment costs of melanoma are approximately $3.3 billion[10]. The prognosis of melanoma in younger patients is better than in older ones[11].

Melanoma can be metastatic and usually involves lymph nodes at first, and eventually spreads into distant sites such as the lung, liver, brain, bone marrow, and intestine[12]. Melanoma bone metastases are relatively rare, including about 11% to 17% of cases, with some studies suggesting rates as low as 5%[13,14]. Metastatic melanoma used to be a very poor prognosis disease, with a 5-year overall survival rate of less than 5%[15]; however, recent treatments, including immunotherapeutic agents like ipilimumab, a combination of immunotherapy with radiation, have tremendously improved survival rates[16-18].

There are limited options for modern therapeutic methods in children due to its rarity[19]. Ipilimumab and nivolumab are among the few FDA-approved drugs for children over 12 years old[20], while other medications, like Lifileucel, are only approved for adult patients[21]. Off-label drugs could be occasionally used due to the lack of clinical trials and guidelines on the management of melanoma in children, which will further complicate its treatment[22,23].

Herein, we present a case of malignant melanoma in an 11.5-year-old child with metastasis to the spinal bone. This case described an unusual clinical presentation of metastases, diagnosed through paraclinical evaluation, imaging, and examinations.

Case presentation

An 11.5-year-old boy from a migrant family was admitted to the emergency department with a complaint of back pain because of trauma after falling while playing in the yard 3 months ago.

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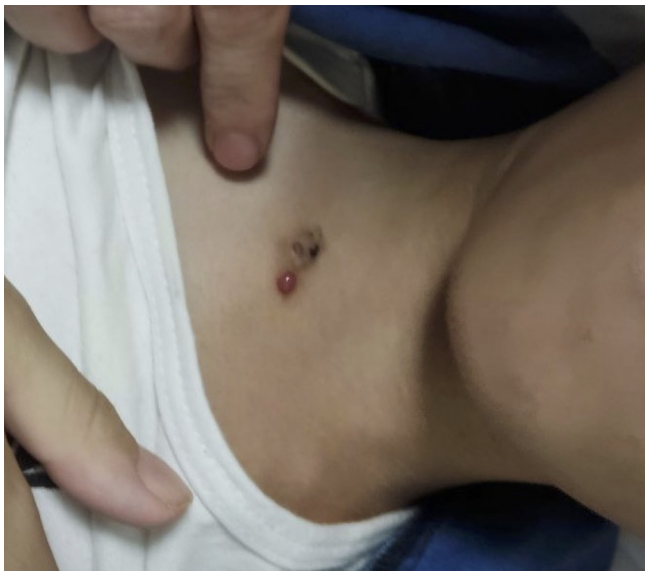

Figure 1. Partial resected hemorrhagic nevus in the patient's neck.

At first, lumbar radiography was normal, and he was discharged. After that, the pain continued and progressively increased, and the new radiograph showed a hairline fracture. The patient was advised to rest. A month later, back pain healed, but he had pain in both his knees. There was no positive sign in the radiography of the knees and pelvis, and his complete blood count (CBC) exam was normal. A month later, he was not able to walk and underwent an emergency operation because of a lumbar vertebrae fracture. He was bedridden for 15 days at the hospital after the operation. There was ecchymosis on both ankles starting about 2 months before, which was not because of trauma. He had weight loss, vomiting, nausea, dyspnea, and increasing anorexia starting from 2 months ago. He had a history of a congenital black nevus on his neck that was hemorrhagic, which had been growing especially for the past 2 years which was partially resected for biopsy last year (Fig. 1). The skin biopsy was sent for pathology examination at the time of resection; however, the patient did not follow up the results. On examination, he was febrile (T:39°C). A hematologic examination revealed anemia. The patient's important signs and symptoms and hemogram and biochemical findings are summarized in Tables 1 and 2, respectively.

A nuclear scan of Tc-99m MDP showed abnormal areas of increased activities in the skull, ribs, thoracolumbar spines (with photopenia in L3 spine), pelvis, and proximal femora, which could be related to traumatism. However, infiltrative and metastatic bone disease was highly probable. Epidural biopsy showed a tumor composed of sheets of polyhedral cells with pleomorphic nuclei, eosinophilic nucleoli, few nuclear pseudoinclusion, and eosinophilic cytoplasm focally were cytoplasmic brown color pigment, which in prussian blue staining were negative for iron, and the diagnosis was malignant melanoma. Skin biopsy had a thickness of 0.8 cm, with the tumor consisting of a layer melanocytic nest composed of spindle and epithelioid cells containing abundant cytoplasm with a small amount of melanin granules. Dermal mitotic figure and moderate nuclear pleomorphism were noted. On the surface of the lesion, ulceration and granulation tissue were seen. The biopsy was compatible with a spitzoid tumor of certain malignant potential or atypical spitz tumor. Immunohistochemistry (IHC) test reported S100 diffused positive, HMB45 positive, ki67 positive in about 20% of cells of epidural biopsy and 15% of cells in skin biopsy, and P16 was not stained in the skin. A computed tomography (CT) scan showed multiple solid nodules measuring up to 8.5 mm throughout both lungs, exhibiting a predominantly peripheral distribution suggestive of pulmonary metastasis. Additionally, multiple lytic lesions involving the vertebral bodies of T4, T8, T9, and T10, as well as the right pedicle and lamina of T4, accompanied by mild focal pleural thickening adjacent to the right side of the T4 vertebral body were seen; indicative of bone metastasis. Focal pleural thickening was observed in the posterolateral aspect of the base of the left hemithorax, with the adjacent rib appearing normal. Abdominopelvic sonography was normal. IHC, cytomorphologic, and imaging findings were compatible with stage IV malignant melanoma with bone and lung metastasis with TNM staging T1NXM1c.

The treatment with nivolumab (3 mg/kg) every 2 weeks was started for the patient after the disease was diagnosed: one dose of nivolumab was administered. Considering his weight (25 kg), he received nivolumab once at 75 mg in 1000 cc normal saline per hour intravenous (IV) infusion. There was no specific complication. He received oxycodone tablets daily at a dose of 5 mg

Table 1

Important signs and symptoms

11.5-year-old boy	Weight loss
Back Trauma	Vomiting
Back pain	Nausea
Pain in the knees	Dyspnea
Hairline fracture	Anorexia
Unable to walk	Congenital hemorrhagic black nevus
Vertebrae fracture	Fever
Bruise on ankles	Anemia

Table 2

Hemogram and biochemical findings

Variable (unit)	Result	Normal range
White blood cells (10^3/μL)	10.21	3.5–11
Red blood cells (10^6/μL)	3.78	3.3–5.8
Hemoglobin (g/dL)	10.8	14–18
Hematocrit (%)	30.8	34–50
Mean corpuscular volume (MCV) (fL)	81.5	78–96
Mean corpuscular hemoglobin (MCH) (pg)	28.6	26–35
Mean corpuscular hemoglobin concentration (MCHC) (g/dL)	35.1	31–36
Platelets (10^3/μL)	388	135–410
Erythrocyte sedimentation rate (ESR)/1 h (mm/1 h)	98	1.0–20.0
Differential count	*	*
Neutrophils (%)	71.5	40–60
Lymphocytes (%)	18.5	20–40
Biochemistry	*	*
Lactate dehydrogenase (LDH) (U/L)	1673	<746 (child male 7–12 year)

by mouth (PO) because of his pain, as he didn't respond to acetaminophen. After the first treatment session, the patient and his parents seemed relieved and willing to continue the treatment. However, the patient's parents decided to continue the treatment in their city of residence to reduce costs, and the patient was discharged with parental consent. Despite our follow-up efforts, it was found that the treatment was not continued for the patient, and regrettably, the patient passed away after being discharged from our hospital.

Discussion

Melanomas, although not the most common skin cancer, are the deadliest[24]. It is a more dangerous type of skin cancer than other more common skin cancers like basal cell carcinoma (BCC) and squamous cell carcinoma (SCC)[25]. Melanoma is rare, and it rarely becomes metastatic[6]. In children, melanoma and its metastases are even more uncommon[26]. It is not expected in pediatric patients. Therefore, it may delay the diagnosis process[6]. The differential diagnosis is challenging[27]; the diagnosis of melanoma in pediatrics is not always similar to that of adults; in a study, 60% of patients aged 0–10 and 40% aged 11–19 did not present the conventional ABCDE criteria[28].

In this case, because of the challenging features of melanoma, lack of facilities, and the rarity of the disease and its metastases, especially in children, malignant melanoma and its metastases were out of mind. Considering the positive history of growing hemorrhagic congenital black melanoma in the neck and the abnormal results in his paraclinical examinations and tests, like anemia, melanoma was suspected. Therefore, more diagnostic tests, such as serial CBC exams, epidural biopsy, nuclear Tc-99m scan, IHC test, skin biopsy, abdominopelvic sonography, and CT scan, were done. The result was compatible with bone metastases of malignant melanoma in different sites of body bones like ribs, skull, and vertebrae. It is also worth noting that even though this disease is rare in children, resected legions with abnormal characteristics (like congenital black nevus in this patient) should go under full pathological examinations in case of malignant melanomas.

In pediatrics, melanoma and bone metastases are exceptional; a few case reports have been published about them. Franklin *et al* presented an 18-year-old male with the primary site in his left neck with weaknesses, vomiting, shortness of breath, and anemia[29]. Spiller *et al* reported a 3-year-old male with an unknown primary site. Clinical features were intermittent limping, back pain, episodes of brown urine, preorbital edema with pancytopenia, and giant nevus extending from scalp to back and chest; he was undertreated with chemotherapy and at last died[30]. Larrosa *et al* reported a 1-year-old female with the primary site in the right malleolus. The patient received adjuvant therapy, which was tolerated. Ten years later, the patient is still in remission[31]. There are some case series about metastatic melanoma in children. Anemia was the most common clinical feature. A significant amount of cases died because of disseminated diseases caused by metastases despite chemotherapy[32].

Malignant melanoma is responsible for 18 deaths per year in patients under 20 years old based on a study from 1968 to 2004 in the United States[33]. The distribution of the disease in children 1–19 is measured to be 3.8% in 1–4 years old, 5.7% in 5–9 years old, 17.3% in 10–14 years old, and 73.2% in 15–19 years old in a study of 3158 patients[34,35].

Malignant melanoma is not considered to be very sensitive to radiotherapy. Still, it is a treatment method in some exceptional cases, like in the dissection of lymph nodes, head and neck post-operative, and complementary treatment[36]. Chemotherapy and targeted treatment can be choices for malignant melanoma and metastatic melanoma that cannot be surgically removed[37]. Literature indicates that small molecule mitochondrial uncoupling agents like SR4 and niclosamide for malignant melanoma treatment may be usable as first-line drugs[38]. Melatonin can also be one of the drugs that improve its prognosis[39].

There are no particular guidelines for pediatric melanoma[6,31]. Wide local excision with an acceptable margin is the first-line treatment[40]; while the biopsy of the sentinel lymph node is still a matter of debate[41], serial ultrasound is suggested to replace biopsy for follow-up, especially in children[7]. Interferon alfa is better tolerated in children than adults, with fewer side effects; however, the benefits are still controversial[6].

In the case of this patient, nivolumab was used for his treatment, which is an FDA-approved drug for metastatic melanoma or when it cannot be surgically removed. Many studies have shown the effectiveness of nivolumab in melanoma treatment[42-44]. However, a few case reports have reported the adverse side effects of nivolumab treatment in pediatric patients. One case presents a 15-year-old girl with metastatic melanoma to the breast who had undergone nivolumab plus ipilimumab treatment and developed Drug-induced hypersensitivity syndrome after 2 weeks of her second cycle[45]. Another case reports a 12-year-old boy with stage IIIC spitzoid melanoma diagnosed with lichen planus pemphigoides following nivolumab treatment[46]. Other side effects like capillary leak syndrome and hypothyroidism have also been reported in a 17-year-old girl diagnosed with malignant melanoma[47]. More research is needed to determine the safety and efficacy of nivolumab in malignant melanoma treatment, especially in patients under 12 years old.

Conclusion

Our study sheds light on the existing literature on melanoma, especially in pediatric patients, highlighting its challengeable diagnosis in pediatrics due to its rarity, the necessity of examining abnormal lesions, and the lack of profound treatment. Future studies focusing on diagnosing and treating melanoma in pediatric patients would further address this issue.

Patient perspective

The patient and his parents were anxious and distressed at the beginning of the treatment, mainly because of the ongoing pain the patient had and the delay in the diagnosis of the disease. In the course of the treatment and by managing the pain, the patient and his family gained trust and hope to continue the treatment.

Ethical approval

Not applicable.

Consent

Written informed consent was obtained from the patient's parents/legal guardian for publication and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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Author's contribution

N.A., and Gh.M. contributed to supervision, investigation, and resources. N.A., M.J., and A.P. contributed to conceptualization, design, writing – review & editing. A.P. and P.Kh. contributed to the investigation, writing – original draft, writing – review & editing. All authors have read and approved the final version of the manuscript.

Conflict of interest

The authors declare no conflict of interest.

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Raw data files can be accessed by request.

Assistance with the study

None.

Presentation

None.

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