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Case Report

Metastatic malignant melanoma arising in a small congenital melanocytic nevus: A case report

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Abstract Congenital Melanocytic Nevi are benign melanocytic proliferations that are present at birth or present shortly afterwards. While giant melanocytic nevi are often associated with a risk of malignancy, the chances of malignant transformation in a small congenital melanocytic nevus are considered to be very low. In under-developed countries like Pakistan, despite melanocytic nevi being very common in the local population, they are not paid any clinical attention or kept under follow-up. However, this case of a young patient with a rapidly metastatic malignant melanoma that involved her spine, liver, lungs and lymph nodes is a very alarming scenario, that urges all dermatologists to be vigilant regarding their examination of congenital melanocytic nevi. It also indicates a gap in the literature pertaining to the prevalence and incidence of malignant melanoma in the local population. We present the case of a 25-year old female patient who had a small congenital melanocytic nevus on the mons pubis, present at birth, and growing proportionately with her age until it reached just over 1cm in size at adulthood. Prior to presentation, the patient had a sudden increase in size of the nevus, change in surface and pigment density, and pain and swelling in the adjacent left inguinal lymph nodes. The patient was also pregnant at the time. Histopathology and Immunohistochemistry confirmed the diagnosis of a cutaneous malignant melanoma. The disease advanced rapidly, and despite local excision with tumor free margins, was found to have systemic metastasis in all major organs within a few weeks of diagnosis, lending the patient a very poor prognosis at a very young age. Congenital Melanocytic Nevi (CMN) are defined as melanocytic nevi that are present at the time of birth or appear shortly thereafter. They may be noted at birth in around 1% of neonates. While large or giant congenital melanocytic nevi are often assumed to carry some risk of malignant transformation, small ones are usually considered inconsequential and are rarely monitored. However, they occur with the largest frequency in the general population and even a small risk of malignancy is significant enough to merit surveillance in these patients. Melanoma is reported infrequently in people of colored skin, particularly in developing countries. But we urge all dermatologists to keep a low threshold of suspicion and follow up any changes such as rapid growth, change in color or ulceration with a prompt histological examination to aid early diagnosis.

Key words
Malignant Melanoma; Congenital Melanocytic Nevus.

Introduction

Congenital Melanocytic Nevi (CMN) are benign proliferations of melanocytes, derived from the neural crest, which are either present at birth or appear within the first two years of life. The ones of later onset are often called "tardive" CMN.[1] They occur most commonly on the trunk and the lower limbs, followed by the head and neck region. While smaller lesions are very common in their occurrence, they are often considered inconsequential. Large nevi, however, occur rarely, are cosmetically

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disfiguring and carry an increased risk of malignancy.[2] Suspicious clinical characteristics such as rapid growth, change in color or ulceration should prompt a physician to exclude a melanoma with a histological examination.[4] Recent studies show that while small CMN carry little risk of malignant transformation, they are common enough in the general population to present with a large number of cases of malignant melanoma.[1] Hence, they do warrant careful clinical evaluation and follow up by the dermatologist.

Case report

A 25-year-old married female patient from Mianwali District in Punjab, Pakistan presented to us in our tertiary care outpatient department. The patient had three children previously, all via normal vaginal deliveries and was now in her first trimester of pregnancy. She gave history of having a flat black mark on the mons pubis since birth. This mark was very well defined, with regular margins, circular in shape and homogenously pigmented. During childhood, it had been barely noticeable. The lesion grew in size until it reached a size of just over 1 cm in its maximum diameter in her teenage years, and stayed the same thereafter. It was completely asymptomatic, and similar in appearance to other smaller lesions on her body, most of which were only 2-3 mm each in size. Seven months prior to presentation, the patient noticed her nevus growing gradually in size and varying in color at the margins. A few weeks later, the patient developed a small skin colored papular growth over it, with a 'fleshy' look. The lesion exuded yellowish blood tinge discharge on excoriation. The patient had it excised at a local healthcare unit without any histological examination or a dermatologist referral. Two months prior to presentation, just when the patient became of her fourth pregnancy, the black lesion grew rapidly in size, reaching a size of 3.5X3cm. The surface became raised, rough and pebbly. The margins were now irregular, the color uneven and lesion painful to touch. The patient felt this lesion invading below the surface skin and gaining some depth. Adjacent to the lesion, the patient noticed lumps in the left side of her groin, the largest around the size of a small lemon. The lumps were also painful. Other than the symptoms of local pain and lymphadenopathy, there were no systemic features. There was no fever, loss of appetite or weight. There was no other positive finding on a systemic inquiry.

On examination, we noticed a large plaque with well-defined margins, irregular surface, and heterogeneous black pigmentation on the mons pubis. This suspicious lesion was accompanied

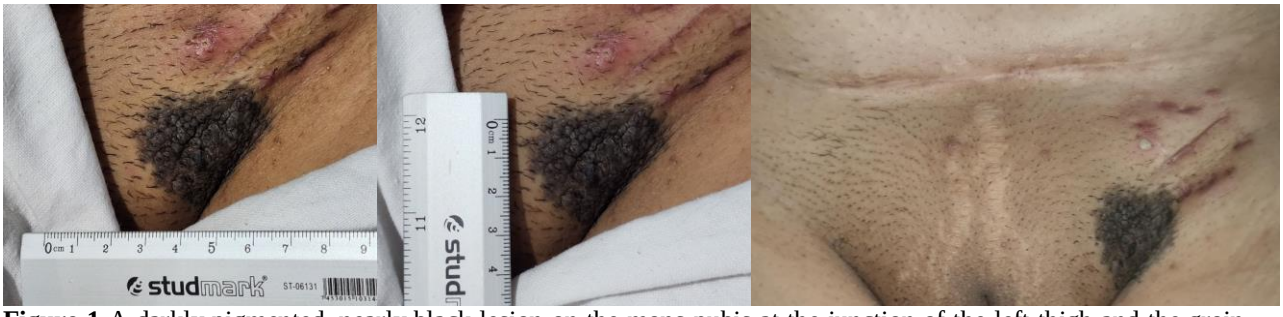

Figure 1 A darkly pigmented, nearly black lesion on the mons pubis at the junction of the left thigh and the groin. The lesion measures 3.5X3 cm in the maximum diameters (rulers placed for measurement reference). The lesion has irregular margins, a pebbly rough surface with heterogeneous pigmentation and a few small hair growing out. Above the lesion are surgical scar marks from excision biopsy of enlarged left inguinal lymph nodes for diagnostic purpose. These photographs were taken pre-operatively.

by tender left superficial inguinal lymphadenopathy, the largest lymph nodes around 3cm in diameter. The patient opted for termination of pregnancy before proceeding with any further investigations. Full body imaging scans were advised to see extent of disease. An MRI of the pelvis showed bilateral internal iliac and inguinal lymph nodes, the largest one measuring 3.3X2.6 cm in the left inguinal region. An excisional lymph node biopsy was performed. Histological examination of the sections showed extensive histiocytic infiltrate, necrosis, and foci of viable tumour composed of atypical epithelioid to spindle cells in sheets. There was abundant melanin pigment and multiple mitotic figures visualized. Immunohistochemistry showed positive staining with HMB45. This confirmed the diagnosis of metastatic cutaneous malignant melanoma.

We referred the patient to the Plastic Surgery and Oncology department for multidisciplinary management. The whole lesion was surgically excised with safe tumor-free margins under frozen section control. Superficial inguinal lymph nodes on the left side were also excised and the wound defect area was covered with a skin flap from ipsilateral thigh. The patient was advised localized radiotherapy. However, follow-up imaging after 6 weeks showed highly aggressive metastatic disease with soft tissue pulmonary nodules, hepatic focal lesions, osseous lytic lesions in the lumbar and thoracic spine, lymph nodes in left inguinal and pelvic sidewall. Disease was classified was as TNM Stage IV Melanoma, with predicted 5-year survival rate of around 20%.

Discussion

Congenital Melanocytic Nevi are neuroectodermal hamartomas that are present at birth or manifest shortly thereafter. The ones that appear within the first few years of life are called “nevus tardive”. They often have terminal hair growth in the lesion due to their hamartomatous origin.[3] CMN can have great morphological variability, with a color ranging from tan to black. They usually have irregular margins and increase proportionately in size as a child grows. The initial lesions can be homogenously pigmented macules or thin plaques that later progress to a lighter, darker or patchy appearance. These plaques may have a raised, verrucous, cerebriform or pebbly surface.[4]

Several different mechanisms have been proposed in the pathogenesis of a congenital melanocytic nevus. These include defects in neural crest development, cutaneous mosaicism and gene mutations leading to dysregulated proliferation of melanocytes. Genes that are implicated are MITF and KIT, involved in the maturation and migration of neural crest cells. The RAS/RAF/MAPK signaling pathway is also involved, including the NRAS, BRAF, and GNAQ genes.[10] There is a greater tendency towards BRAF mutations in smaller lesions, and NRAS mutations in large or giant nevi.[3]

Congenital Melanocytic Nevi are usually classified on the basis of their size as either small (less than 1.5cm), medium (1.5 to 19.9cm), and large (20 cm or more). This size refers to the maximum diameter of the lesion achieved in adulthood.[2] The definition of a giant congenial nevus carries some ambiguity, with some others considering it to be larger than 20cm and other measuring it in terms of percentage of body surface area. Our patient had a small melanocytic nevus, measuring just over 1cm, before transformation to a melanoma.

Previously, melanocytic nevi were also classified based on the location and pattern of appearance on the body, including patchy indented, round/ oval, teardrop/ triangular,

cannonball, diffuse patchy, blashko-linear, flag-like, and extensive garment-like patterns.[6] More recently, other classifications such as the 6B rule by *Martins da Silva et al.*, a classification based on the migration of precursor melanocytes by *Kinsler et al.*, and a classification based on the sequence of events during embryonic development have also been proposed.[3]

The histological appearance of Congenital Melanocytic Nevi can resemble that of acquired congenital nevi, the main differences being their greater size, increased cellularity and deeper penetration into the dermis and subcutis. CMN may also have segments of immature neural supportive tissues.[7] Other typical features may include melanocytes present in the reticular dermis as single cells or cords of cells in an 'indian file' pattern; a perivascular, perifollicular and periadnexal distribution of nevomelanocytes, and melanocytic infiltration of the arrector pili muscles. These findings are not diagnostic of a CMN, but can be a useful pointer to the nevus being congenital in origin if it had not been documented at birth. In a giant CMN, there may be any of a variety of histological patterns such as compound nevus, blue rubber nevus, neural, spindle or epithelioid cell nevus.[9]

The chances of developing a melanoma in a melanocytic nevus increase proportionately with the size of the nevus. The exact risk of developing a melanoma in a small or medium sized CMN is unknown.[5] Several studies have shown a risk of less than 1-4.9%. The lifetime risk of developing a melanoma in a giant Congenital Melanocytic Nevus can be between 5 and 15%.[8] Risk of melanoma is also higher in case of a lesion on the patient's spine or the presence of multiple satellite nevi.[3] The literature available on the malignant transformation of CMN shows inconsistent data and great regional variability. This leads to ambiguity regarding the monitoring and management of these lesions.

A melanoma arising in a CMN can be a diagnostic challenge for a dermatologist, especially in the pediatric age group where most of these tumors arise. The nodular, pebbly or hairy surface of these lesions can conceal the early signs of a tumor.[11] Physicians usually keep an eye out for any rapid change or ulceration as a marker of transformation, and lean on dermoscopic and histological examination for early diagnosis in case of any suspicious lesions. Despite this, melanoma arising in a melanocytic nevus is rarely ever reported in our part of the world, with patients of 'brown' skin being underrepresented in literature.

Conclusion

Congenital Melanocytic Nevi (CMN) are defined as melanocytic nevi that are present at the time of birth or appear shortly thereafter. They may be noted at birth in around 1% of neonates. While large or giant congenital melanocytic nevi are often assumed to carry some risk of malignant transformation, small ones are usually considered inconsequential and are rarely monitored. However, they occur with the largest frequency in the general population and even a small risk of malignancy is significant enough to merit surveillance in these patients. Melanoma is reported infrequently in people of colored skin, particularly in developing countries. But we urge all dermatologists to keep a low threshold of suspicion and follow up any changes such as rapid growth, change in color or ulceration with a prompt histological examination to aid early diagnosis.

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