Characteristics of Giant Nodular Melanomas in Special Locations: a Case Series and Review of the Literature

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ABSTRACT

Introduction: Nodular melanoma (NM) is a rare subtype of melanoma, responsible for more than 40% of melanoma deaths, characterized by rapid growth and high metastatic potential. Only a few case studies concerning the dermoscopic presentations of giant nodular melanoma have been reported so far.

Objectives: The aim of the study was to assess dermoscopic features of giant nodular melanomas in special locations, along with their clinical and histopathologic aspects.

Methods: Among 120 patients with histopathologically confirmed melanoma treated by the Skin Cancer and Melanoma Team between September 2020 and February 2021, we identified six patients with giant nodular melanoma in special locations. We retrospectively assessed the archived dermoscopic images to determine the dermoscopic features of these tumors.
**Results:** The group consisted of six cases of giant melanoma in special locations, including the scalp (4/6) and the heel (2/6). The giant tumors were large in size (at least 5 cm in diameter). The most common dermoscopic structures in polarized light included asymmetric distribution of dermoscopic structures, the presence of structureless, multicolored zones (showing three or more colors), and the presence of white perpendicular lines or small, pink globules.

**Conclusions:** It seems that there are no significant differences in dermoscopy between small and giant melanomas; however, further studies should be conducted on a larger scale.

**Keywords:** Acral; Dermoscopy; Giant melanoma; Scalp; Special location

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**Key Summary Points**

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| Nodular melanoma (NM) in special locations is usually characterized by an aggressive course and poor prognosis. |
| To date, few dermoscopic descriptions of giant melanomas have been published. |
| Presented cases of giant melanomas clinically manifested as exophytic, necrotic tumors at least 5 cm in diameter. |
| The most common dermoscopic structures in polarized light, typical of NM, included asymmetric distribution of dermoscopic structures, structureless, multicolored zones (showing three or more colors), white perpendicular lines or small, pink globules, and multiple irregular vessels. |
| Clinicians should perform a total skin examination, with particular emphasis on the specific areas, to avoid a fatal diagnostic error. |

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**INTRODUCTION**

Nodular melanoma (NM) is a rare subtype of melanoma, accounting for about 14% of all cases but at the same time responsible for more than 40% of melanoma deaths. It is characterized by rapid growth and high metastatic potential [1]. Therefore, it is often diagnosed at very advanced stages. In most cases, NM does not exhibit the standard dermoscopic criteria [1].

In the literature, only a few papers reported on the dermoscopic features of NM [1–5]. To our knowledge, probably only one dermoscopic report on primary giant nodular melanoma has been published so far, but it did not address specific locations [2].

**MATERIAL AND METHODS**

We present a clinical, dermoscopic, and histopathologic description of six patients with giant nodular melanoma in special locations selected from 120 patients with histopathologically confirmed melanoma treated by the Skin Cancer and Melanoma Team between September 2020 and February 2021. We also report on clinical and epidemiological data of selected patients with histopathologically proven giant nodular melanoma. The authors have received approval from the local ethics committee of the National Research Institute of Oncology (reference number KB/430-29/19). The study was conducted in accordance with the Helsinki Declaration of 1964 and its later amendments. All subjects provided informed consent to participate in the study as well as for publication.

**RESULTS**

**Case 1**

A 77-year-old male was admitted with giant oozing, necrotic tumor located on the scalp,
sized 10 × 9 cm (Fig. 1a). The patient had ignored the growing tumor for a period of 4 years. He was afraid of surgical excision. Dermoscopy in polarized light showed asymmetry in dermoscopic structure distribution, polychromatic (gray, brown, and red) and structureless zones with multiple white perpendicular lines. Moreover, focally distributed white, shiny clods were observed. Several sticky fibers adherent to the tumor surface were also found (Fig. 1b). Histological analysis of a biopsy sample (collected before the tumor reached nodular shape) revealed dermal, BRAF-mutant melanoma with isolated neoplastic infiltration under the epidermis (Fig. 2a). The infiltration lacked an epidermal component, and there was no evidence of regression. Epithelioid polygonal cells presented mitotic activity 15/1 mm², Ki-67 80%, and tumor-infiltrating lymphocytes (TILs) were non-brisk. The neoplastic mass showed focal necrosis. The patient had been treated for colon carcinoma in the past, and immunohistochemistry (IHC) stains were obtained. IHC results were clear, positive, and strong for Melan-A (Fig. 2b), protein S-100, human melanoma black 45 (HMB-45), and negative for caudal type homeobox 2 (CDX2) and other stains used in differential diagnosis, such as prostate-specific antigen (PSA), thyroid transcription factor 1 (TTF-1), and cytokeratins (CK) CK7, CK20, CK AE1/AE3). Dehydrogenase lactate (LDH) was two times the upper limit of normal. Computed tomography (CT) of the chest, abdomen, and pelvis showed multifocal metastases in the lungs. The stage was T4N0M1b (IV) according to the American Joint Committee on Cancer (AJCC) tumor, node, metastasis (AJCC/TNM) 8th edition classification.

Targeted therapy with BRAF and MEK inhibitors was planned, but the patient refused the treatment and further follow-up.

Case 2

A 23-year-old male was admitted to our department with histologically confirmed melanoma presenting as a large (5 × 4 cm), firm, black, necrotic tumor involving the skin of the parietal region (Fig. 1c). He had a 10-month history of the disease before undergoing the diagnostic procedures in our department. The diagnosis was delayed owing to coronavirus disease 2019 (COVID-19) pandemic restrictions. Dermoscopy in polarized light revealed asymmetry in dermoscopic structure distribution, structureless, multicolored (gray, black, and brown) zones with white perpendicular lines. The surface of the tumor showed the presence of a whitish scale (Fig. 1d). Total surgical excision was carried out, with a partial-thickness graft taken from the skin of the thigh. The tumor has been resected along with two satellite foci located 3 mm from the closest surgical margin. The histopathologic report indicated NM, epithelioid subtype, and Breslow thickness 12 mm with the presence of ulceration and microsatellites (Fig. 2c). Moreover, clusters of melanoma cells were found in the lumen of small blood vessels in the tumor front (Fig. 2d). Melanoma cells infiltrated dermal nerve fibers. Mitotic activity was 18/1 mm², Ki-67 was 25%, and TILs were absent. Sentinel lymph node biopsy (SLNB) showed a metastatic melanoma lesion 5 mm in diameter, without extranodal extension. BRAF V600 mutation was confirmed. LDH level was elevated: 332 U/L (normal range up to 220 U/L). Positron emission tomography (PET) scan performed before the start of adjuvant therapy revealed metastases to the cervical lymph nodes and the humeral head. Additionally, magnetic resonance imaging (MRI) of the central nervous system (CNS) showed a single asymptomatic lesion. The final staging was T4bN1M1d (IV).

Therapy with BRAF and MEK inhibitors was started with dabrafenib and trametinib in standard doses. Stereotactic radiotherapy of the bone metastases with a total dose of 16 Gy was performed. Additionally, the patient received stereotactic radiosurgery with a total dose of 24 Gy for brain metastases. After 3 months, the complete metabolic remission in the lymph nodes and bones on PET–CT and partial remission in the CNS on MRI were confirmed. The patient had continued the therapy for 6 months until CNS progression. The therapy was stopped and whole brain radiotherapy (WBRT) with a total dose of 20 Gy was administered. Owing to
the poor performance status of the patient, further systemic therapy was not considered. The patient died 2 months later.

Case 3

A 50-year-old man presented with giant tumor behind his right ear, rapidly growing for the past 4 months. The patient delayed his medical
visit for fear of surgery. Clinical examination revealed a large, bleeding tumor in the right temporal–occipital region, sized 6.5 cm in diameter (Fig. 1e).

Dermoscopy in polarized light revealed asymmetric multiple (black, bluish, and white) structureless zones with white perpendicular lines, several bluish clods, pink globules, and multiple irregular serpentine vessels (Fig. 1f).

MRI of the head and neck showed a giant tumor (about 11 cm in diameter) in the right temporal–occipital region, involving the skin and soft tissues, and two metastatic cervical lymph nodes below.

Biopsy of the primary tumor proved melanoma composed of atypical epithelioid cells with nuclear inclusions (Fig. 2e), presenting strong immune positivity for SOX10, HMB-45, and Melan-A. Some of the tumor cells contained melanin deposits, which were significant for this tumor type (Fig. 2f). Programmed death ligand 1 (PD-L1) expression was assessed as negative. No mutations were detected in the BRAF V600 gene. A PET scan, in addition to lesional uptake along with two small adjacent cervical lymph nodes, revealed multifocal metastases in the liver. Dehydrogenase lactate was three times above the upper limit of normal. The stage was T4bN2bM1c (IV).

Palliative antihemorrhagic irradiation of the primary tumor with a total dose of 20 Gy was performed. After radiotherapy, combined immunotherapy was started: nivolumab [1 mg per kg body weight (BW)] plus ipilimumab (3 mg per kg BW) every 3 weeks for four doses, followed by nivolumab (480 mg) continued until now. Up to February 2022, the patient received 11 cycles without any significant adverse events. Two months after the first administration of combined therapy, all melanoma lesions had partially regressed.

Case 4

An 82-year-old patient presented with a scalp lesion measuring 8 × 8.5 cm (Fig. 1g), which had developed within a preexisting pigmented lesion and grew over the past 2 years with the formation of an ulcerated tumor showing signs of necrosis. The patient neglected the disease. A biopsy specimen from the lesion confirmed desmoplastic melanoma; Breslow thickness could not be determined. Contrast-enhanced CT and PET–CT of the head did not confirm the presence of metastases, and LDH levels were normal (pTx, Nx, Mx). The patient is being prepared for surgical excision of the entire lesion with a concurrent SLNB procedure. Currently, there is no possibility of neoadjuvant treatment according to Polish drug programs in oncology. Dermoscopically, we found multiple irregular linear serpentine branched vessels located on a whitish and yellowish structureless zones, covered by multiple yellow and brown scale in a patchy distribution. A positive sticky fiber sign was present (Fig. 1h).

Case 5

A 67-year-old man presented with a rapidly growing (within a period of 6 months), bleeding melanoma tumor measuring 5 cm, covered with necrotic tissue, in the right heel region (Fig. 1i). The patient was afraid of surgical excision. Dermoscopic assessment in polarized light showed asymmetry in dermoscopic structure distribution and multiple (red, black, and white) structureless zones. Moreover, several structureless pink zones, as well as small pink globules, were also reported. In addition, excess discharge from necrotizing tumor made examination under polarized light very difficult (Fig. 1j). Owing to the difficult location and the high risk of microsatellites, the post-resection defect was covered with a graft taken from the skin of the thigh. This was followed by SLNB in the groin region with the resection of two lymph nodes, which contained no melanoma cells. The primary tumor was proved as NM, epithelioid subtype, Breslow thickness 10 mm (Fig. 2h). The reported mitotic activity was extremely high, 48/1 mm² (Fig. 2g), with the presence of microsatellites, radial growth pattern without TILs, angio- or neuro-invasions. In this difficult location, a deep excision was performed with a clear margin of 1 mm. LDH was within the normal limits. Disease stage was assessed as pT4bN1cM0 (IIIC). No mutations
were detected in the BRAF V600 gene. In April 2021, the patient started immunotherapy with pembrolizumab 200 mg every 3 weeks. After three cycles of anti-PD-1 inhibitor treatment, transaminase and bilirubin levels were significantly increased (grade 3 toxicity). A CT scan ruled out evidence of melanoma progression. Pembrolizumab was discontinued, and corticosteroids were started (intravenous methylprednisolone 2 mg/kg). Three days later, liver enzymes continued to worsen, and mycophenolate mofetil was prescribed (1000 mg twice daily). Bilirubin level normalized 4 weeks and transaminases 2 months from the start of immnosuppression. Pembrolizumab was never restarted. The patient was lost to follow-up owing to an acute COVID-19 infection in October 2021.

**Case 6**

A 79-year-old man presented with a 5 × 4.3 cm tumor located on the fourth toe of the left foot. Clinical examination revealed a bleeding erythematous nodule with brown and gray pigmentation on the periphery (Fig. 1k). Dermoscopy in polarized light showed asymmetry of colors and structures. Structureless white–brown areas, white lines, and ulceration were recognized in the center of the lesion, and a residual irregular, brown–gray pigmentation was found on the periphery. Moreover, white, shiny lines and some polymorphous vessels were seen (Fig. 1). Biopsy of the primary tumor showed melanoma with extensive necrosis. CT of the head, chest, abdomen, and pelvis showed no metastases, LDH and S-100 were within the normal limits. Total surgical excision was carried out with amputation of the fourth and fifth toes, and the fifth metatarsal, followed by SLNB. The histopathologic report confirmed melanoma proliferating in the dermis and hypodermis with clear cell sarcoma-like features and partial ulceration. Mitotic activity was high, 25/1 mm², with angio-invasion and Breslow thickness of 12 mm. SLNB in the left inguinal area was positive for subcapsular metastasis. The stage of the disease was assessed as pT4bN1aM0 (IIIC). No mutations were detected in the BRAF V600 gene, and immunotherapy with pembrolizumab was started (200 mg) every 3 weeks.

**DISCUSSION**

The most common dermoscopic structures seen in polarized light in our case study of NM included asymmetry in dermoscopic structure distribution (5/6) and structureless (6/6), multicolored zones (showing three or more colors) (5/6) (Fig. 1b, d, f, h, j, l), with a presence of white perpendicular lines (4/6) or small, pink globules (1/6). Dermoscopy of small nodular melanoma remains a diagnostic challenge. Corneli et al. distinguished two main dermoscopic patterns of NM, including a combination of structureless blue- and black-colored areas (known as the blue–black rule of Argenziano), as well as lack of pigmentation or the presence of residual pigmentation in amelanotic or hypomelanotic variants of NM, when the diagnosis is based on the vascular patterns [1, 3]. Pigmented NM is characterized dermoscopically by revealing asymmetric pigmentation, blue–black pigmented areas, homogeneous disorganized pattern, and abnormal vascular structures, including polymorphous vessels, milky-red globules/areas, and homogeneous red areas [4]. In a previous International
Dermoscopy Society (IDS) study, Menzies et al. added some important positively correlated features of NM, including not only five to six colors, black color, homogeneous blue pigmentation, atypical vascular pattern (linear irregular or dotted vessels), dark brown color, and milky red-pink areas, but also peripheral black dots/globules, multiple brown dots, irregular black dots/globules, blue–white veil, pseudopods, irregular blotches (black, brown, or gray), irregularly sized and distributed dots/globules, blue–black structures, and central black dots/globules [6].

The late detection of nodular melanoma may be related not only to its aggressive and rapid growth but also to the multiplicity of dermoscopic patterns of this subtype of melanoma, and thus the diversity of morphology of early NM, consisting of lesions that may mimic more common benign or malignant entities [7]. Nodular melanomas with typical clinical morphology include the following dermoscopic types: pigmented nodular melanoma-like, hypo/amelanotic melanoma-like, and nodular melanomas mimicking benign and malignant nonmelanoma lesions, seborrheic keratosis-like, pyogenic granuloma-angioma-angiokeratoma-like, and nonmelanoma skin cancer-like [7].

Unfortunately, in the available literature, there is no clinical classification of NM based on tumor size or diameter. Individual papers define small nodular melanoma as lesions smaller than 6 mm in diameter [8]. The term “giant melanoma,” based on the literature review, has mainly been used for tumors larger than 5 cm in diameter [9–12]. In the case study of Altobrando et al. concerning two giant melanomas, dermoscopy showed a multicolored pattern with a diffuse yellow background and some irregularly distributed red, brown, and gray areas [2]. In the literature, in giant nodular melanomas, the vessels appeared atypical, polymorphic, and mainly dilated over a red and white background [2]. In two of our cases of giant melanoma, we found the following features: the presence of polymorphous vessels in addition to serpentine vessels (3/6) (Fig. 1f, h, l) and small, pink globules (1/6) (Fig. 1j). According to the dermoscopic case series study of NM by Rosendahl et al., the clues to malignancy, such as gray or blue structures and polarizing specific white lines (defined as perpendicularly oriented white lines visible only on polarized dermoscopy), displayed the highest sensitivity for NM (Fig. 1b, d, f, l) [5].

Moreover, the “fiber sign” was described, defined as the presence of gauze filaments trapped into the irregular surface of the tumor, similarly to our observations in acral giant nodular melanoma (Fig. 1f, h, j, l) [2].

NM in special locations, including the scalp, also lacks specific dermoscopic features and only exhibits structureless, blue patterns, in some cases irregular, polymorphous vessels, and black blotches or dots [13, 14].

It should be highlighted that the presented cases of giant nodular melanomas in special locations, including the scalp and acral areas, did not reveal the typical dermoscopic features of melanoma in selected special locations. In NM of the scalp, dermoscopic structures, including structureless patterns with white perpendicular lines, were reported [13]. Acral invasive melanomas dermoscopically demonstrate the presence of specific colors (red, blue, and white), so-called polychromia, atypical vascular patterns, blue–white veil, and ulcers [15].

The diagnosis of nodular-type lesions, especially those located in so-called special locations, remains a great diagnostic challenge. The latest data from the IDS study concerning the differentiation between nodular thin and thick melanomas and other nonmelanoma nodular lesions proved that irregular blue structureless areas and dotted and serpentine vessels were predictors of all NMs compared with nonmelanoma nodular lesions [16]. Moreover, dotted vessels, white shiny streaks, and irregular blue structureless areas were predictors for thinner NMs compared with nonmelanoma nodular tumors [16]. Table 1 shows the dermoscopic diagnostic features of selected skin cancers in specific locations (including the scalp) [17–24].

In the presented cases of giant melanomas, histopathologic examinations showed high mitotic activity (15–48/1 mm²) and the presence of microsatellites (2/6). Histologically, NM presented with a tumorigenic component in the
dermis with or without junctional melanoma nests, sometimes associated with ulceration (3/6). NM tumors reported in our series expressed typical melanocytic immunostain markers (S100, MelanA, HMB-45, SOX 10). Of note, it is important to be aware of melanomas with heterologous differentiation that express keratin, vimentin, antihuman epithelial

Table 1 Differential diagnosis based on diagnostic features of selected nodular skin cancers in specific locations (including the scalp)

| Source (author and reference) | Histopathological diagnosis | Location | Clinical presentation | Dermoscopic features: background | Dermoscopic features: vessels |
|--------------------------------|-----------------------------|----------|-----------------------|---------------------------------|-------------------------------|
| Suppa et al. [17]             | Basal cell carcinoma        | Scalp    | Nodular               | Not given                        | More frequent presence of blue–gray ovoid nests, leaf-like areas, multiple brown–black dots/globules, blue–white veil-like structures and ≥ 1 melanocytic pattern and ≥ 1 vascular pattern (classic or diverse) was significantly less common than in BCCs of other sites; no dermoscopic difference according to BCCs’ location, including scalp and trunk |
| Fagotti et al. [18]           |                             |          |                       |                                 |                               |
| Lin et al. [19]               | Squamous cell carcinoma     | Head and neck | Nodular               | Pink with hemorrhages and keratinization | Glomerular, hairpin or linear irregular vessels; polymorphic vascular pattern |
| Ciudad et al. [20]            | Merkel cell carcinoma      | Scalp    | Regressing amelanotic tumor | Homogeneous pinkish              | Irregular linear vessels, long and curved (horseshoe-like structures) |
| Moscarella et al. [21]        | Fibroxanthoma               | Scalp    | Amelanotic tumor      | Red, white structureless areas   | Polymorphic vascular pattern  |
| Di Brizzi et al. [22]         | Pleomorphic dermal sarcoma  | Scalp    | Amelanotic tumor      | Red, white structureless areas   | Linear and irregular          |
| Minagawa et al. [23]          | Cutaneous angiosarcoma      | Scalp    | Purple nodule         | Purple to black homogeneous areas, whitish veil, red to brown hemorrhages; various color gradations | Polymorphous atypical vessel-like appearances: dotted, irregular linear, glomerular vessel-like features |
| Oiso et al. [24]              |                             |          | Macular               |                                 |                               |
membrane antigen (EMA), or smooth muscle actin (SMA). Tumors that have no, very limited, or heterologous expression of melanocytic markers remain a diagnostic challenge. These tumors must also be distinguished histopathologically from sarcomas, squamous cell carcinomas, appendageal tumors, and cutaneous lymphomas [25].

Owing to histopathologic and clinical features, true NM may create difficult diagnostic pitfalls, particularly in the setting of metastatic malignancy. According to the World Health Organization (WHO), the skin is the most common site of melanoma metastases in the form of epidermotropic tumors arising from local, regional, or distant lymphatic or hematogenous spread [26, 27]. Differential diagnosis between metastatic melanoma and primary NM is not an easy task; in such cases, close cooperation of a dermatologist, dermatopathologist, and oncological surgeon helps us to make proper tumor assessments.

The presented cases and dermoscopic descriptions of giant nodular melanoma should make clinicians aware of the aggressive biology of this subtype, often with its occult course and late detection that, unfortunately, drastically reduces the patient’s chances of full cure and complete remission.

Limitations of the Study

The main limitation of this observation is its retrospective nature and the lack of a control group, including small nodular melanomas. Therefore, further studies are still needed.

CONCLUSION

All patients had giant, exophytic, necrotic tumors at least 5 cm in diameter at clinical presentation. The most common dermoscopic structures in polarized light, typical of NM, were asymmetric distribution of dermoscopic structures, structureless, multicolored zones (showing three or more colors), white perpendicular lines or small, pink globules, as well as multiple irregular vessels. It seems that there are no significant dermoscopic differences between small and giant melanomas; however, further studies on a larger scale should be conducted.

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Compliance with Ethics Guidelines. The authors have received approval from the local ethics committee of the National Research Institute of Oncology (reference number KB/430-29/19). The study was conducted in accordance with the Helsinki Declaration of 1964, and its later amendments. All subjects provided informed consent to participate in the study as well as for publication.

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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