

Chapter 2

Melanoma—Diagnosis, Subtypes and AJCC Stages

Abstract Unlike several other types of cancer, melanoma can be easily detected in its earliest stages; sometimes they are also detected by the patients themselves as abnormal pigmented spots on the skin. Clinical features of melanoma that helps in the diagnosis, subtypes of melanoma and different types of approaches used to classify the progression of melanoma are discussed in this chapter. The characteristic features of melanoma such as Asymmetric shape, irregular Border, variegated Color, large Diameter and Evolving nature of the lesions (described by the acronym ABCDE) are explained in the beginning of the chapter. Various methods that help in the diagnosis of melanoma are then described in the chapter with emphasis on significance of dermoscopy, histopathology and molecular biomarkers such as S100 in the diagnosis of melanoma. In addition, other newly introduced diagnostic aids like total body photography and in vivo reflectance confocal laser microscopy are also discussed in the chapter. Next, different variants of melanoma such as superficially spreading melanoma, lentigo maligna, acral lentiginous melanoma, nodular melanoma, desmoplastic melanoma, nevoid melanoma and verrucous melanoma are discussed with details on clinical, dermoscopic and histological features, overall incidence, correlation with patient characteristics such as age, gender and location of lesion and comparison with overall melanoma prognosis. Finally, various classification methods developed to determine the stage of melanoma progression are discussed; classifications using Clark's Level of invasion, Breslow thickness, Tumor, Node and Metastasis (TNM) as well as the system developed by AJCC are discussed in detail towards the end of the chapter.

Keywords Melanoma • Diagnosis • Dermoscopy • Histopathology • S-100 • Serum LDH • Subtypes • Clark's level • Breslow thickness • TNM classification and AJCC

2.1 Introduction

Among all types of cancers, the uniqueness of melanoma is that it can be easily detected in its earliest stages as abnormal pigmented spots on the skin surface [1, 2]. In fact, patients can themselves identify abnormally appearing moles and self-detect melanomas and thereby help in the early diagnosis of the disease [3, 4]. However, naevi and other benign pigmented lesions that are seen on the body could be potential precursors of a deadly disease or lesions which merely mimic melanoma. It is therefore a challenge for the healthcare providers to differentiate the lesions which needs further testing through skin biopsy from the lesions which do not need further investigation.

2.2 Signs and Symptoms of Melanoma

The most prominent clinical symptom of melanoma is the development of a new spot on the skin that is different from other spots on the skin and that is changing in size, shape or color [5, 6]. As shown in the Fig. 2.1, the characteristic features of melanoma lesions could be easily remembered by the **ABCDE** rule which is summarized as follows:

A: **Asymmetric** shape of the spot/mole; one half of the mole does not match the other.

B: **Border** of the spot is irregular, ragged, notched or blurred.

C: **Color** of the spot is variegated and includes shades of brown/black or sometimes could include patches of pink, red, white or blue.

D: **Diameter** of the spot is >6 mm.

E: **Evolving** nature of the spot in terms of size, shape or color.

Other signs that would warrant a closer examination include spreading of pigment from the border of a spot into surrounding skin; redness or a new swelling beyond the border; change in sensation of the spot with increased itchiness, tenderness or pain; as well as oozing or bleeding from the spot/mole.

2.3 Diagnosis

Clinical diagnosis of melanoma is usually complex and is based on a complete patient history and a total-body skin examination [8]. In some cases, even the experienced dermatologists find it difficult in diagnosing melanoma as seen by the reported sensitivity (only 60 %) of their clinical diagnosis [9]. In the recent past several diagnostic tools such as dermoscopy, total-body photography, in vivo



Fig. 2.1 Typical ABCDE characteristics of melanoma. Original image can be found in the article, ‘Melanoma review: epidemiology, risk factors, diagnosis and staging’ by Arrangoiz et al. [7]. Image downloaded and reused under the under Creative Commons Attribution (CC BY) license (<http://creativecommons.org/licenses/by/4.0/>) wherein authors of the above article retain ownership of the copyright for their publications, but grant SciencePG a non-exclusive license to publish the work in paper form and allow anyone to reuse, distribute and reproduce the content as long as the original work is properly cited

reflectance confocal laser microscopy, histopathology and analysis of molecular biomarkers have been introduced to aid the dermatologist in deciding if a skin biopsy is required or not [2].

2.3.1 Dermoscopy

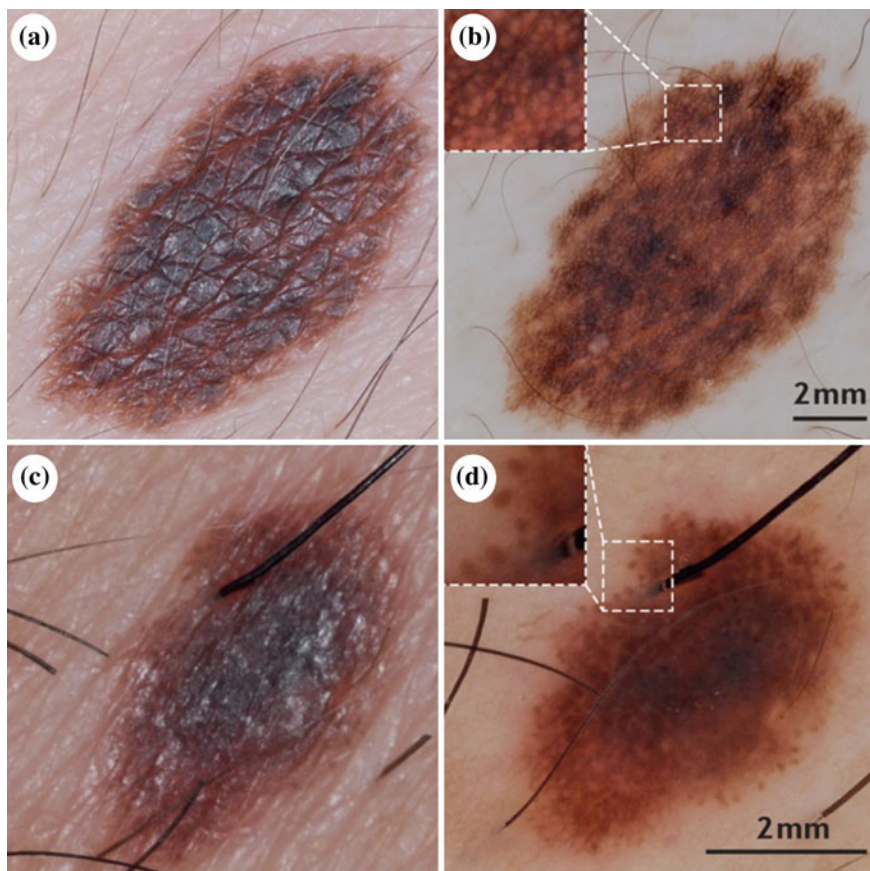
As shown in Fig. 2.2 dermoscopy involves non-invasive imaging of the suspected lesions using a handheld device that permits the visualization of colors, structures and patterns in skin lesions that are not clearly seen with the naked eye [10].

Figure 2.3 illustrates the possibility of making minute visualizations with dermoscope and identifying melanoma-specific characteristics in a skin lesion.

Kitler et al., performed meta-analysis of 27 studies published between 1987 and 2000 and showed that dermoscopy achieved an increase in diagnostic accuracy (sensitivity 89 % and specificity 79 %) over the clinical diagnosis alone in questionable lesions [9]. Although it is criticized by some authors for its limitations like requirement of extensive training and expertise as well as no clear improvements in patient outcomes, dermoscopy has been found to improve diagnostic accuracy for primary cutaneous melanoma and to avoid unnecessary biopsies of benign tumors [11–13]. Additionally, it would be possible to take sequential digital dermoscopic images of indeterminate skin lesions and monitor the ‘suspicious’ moles over a period of time and thereby enabling the detection of melanomas that lack the characteristic features at baseline [14, 15].



Fig. 2.2 Evaluation of skin lesions using dermoscopic device. Original image can be found in the article, ‘Melanoma review: epidemiology, risk factors, diagnosis and staging’ by Arrangoiz et al. [7]. Image downloaded and reused under the under Creative Commons Attribution (CC BY) license (<http://creativecommons.org/licenses/by/4.0/>) wherein authors of the above article retain ownership of the copyright for their publications, but grant SciencePG a non-exclusive license to publish the work in paper form and allow anyone to reuse, distribute and reproduce the content as long as the original work is properly cited



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Fig. 2.3 Dermoscopic evaluation of a skin lesion. **a** Clinical image of a 13×7 mm skin lesion with irregular borders and colour variegation. **b** Dermoscopy shows a bland network-like appearance throughout the lesion, which is diagnostic of a banal melanocytic naevus. The inset highlights a regular network pattern consisting of intersecting pigmented lines and hypopigmented holes. **c** Clinical image of a 5×3 mm symmetrical skin lesion with a dark centre. **d** Dermoscopy reveals pseudopods present focally at the periphery, which is a melanoma-specific dermoscopic criterion. The inset highlights the pseudopods, which are bulbous projections from the tumour body. Histopathological examination confirmed melanoma in situ arising within a compound melanocytic naevus. Reprinted by permission from Macmillan Publishers Ltd: Nature Reviews Disease Primers, [2] © 2015

2.3.2 Total-Body Photography

Digital total-body photography is employed in patients with high numbers of naevi. Photographs of naevi could be used by healthcare providers to compare and identify

new as well as changing lesions. Several studies between 1997 and 2010 have shown that the use of total-body photography has led to improvement in sensitivity and specificity of skin examinations. However, there are no reports from randomized clinical trials supporting the benefits of this technique [16–19]. Total-body photography can be used to complement dermoscopy and digital dermoscopic imaging techniques; and studies have shown that the combination of total-body photography and digital dermoscopy techniques could identify high risk primary melanoma patients [20, 21].

2.3.3 In Vivo Reflectance Confocal Laser Microscopy

Reflectance confocal microscopy is a recently introduced non-invasive technique for ‘in vivo’ visualization of the skin. The procedure involves focusing a near-infrared light from a diode laser on to a microscopic skin target and the light reflected due to differences in refraction indexes of cellular structures is captured and recomposed into a 2-D gray scale image by computer software [22]. As with conventional confocal microscope, images from different levels within the skin can be obtained by adjusting the z-axis. This technique has been used as a second-level diagnostic test in combination with dermoscopy and found to improve the accuracy in the diagnosis of melanoma [23, 24]. However, it is not still widely used in clinical practice and further research demonstrating its benefits and limitations is needed.

Other automated diagnostic systems like computer-aided multispectral digital analysis (MelaFind; USA) and electrical impedance spectroscopy (Nevisense system; Sweden) are being developed to improve the sensitivity and specificity of melanoma diagnosis [25, 26]. Though these systems sound appealing to the patients and health care providers, more data might be needed before including these techniques in clinical practice.

2.3.4 Histopathology

Whenever a suspicious lesion is identified by the dermatologist, further examination of the tissue sections could be advised. Tissue sections could be obtained via shave/tangential biopsy, punch biopsy, incisional and excisional biopsy, fine needle aspiration biopsy, sentinel lymph node biopsy or surgical lymph node biopsy. The choice of type of biopsy needed for further examination depends on extent of tumor growth and degree of invasion of tumor cells into surrounding tissue and lymph nodes. Tissue sections are stained with haematoxylin and eosin (H and E staining) and examined by an experienced dermatopathologist; whose expert opinion is

considered as a gold standard for the diagnosis of melanoma. In addition to the details of diagnosis and clinicopathologic type, the histopathologic report is expected to include the information on tumor thickness in mm (Breslow depth), presence or absence of ulceration, mitotic rate, if any microsatellites are present and the lateral and deep excision margins [10, 27, 28]. In addition, the pathology report could also include information on growth phase (horizontal/vertical), Clark level of invasion (for melanomas ≤ 1 mm thickness), presence/absence of established regression, presence/absence of a dense tumor infiltrating lymphocytes (TIL) infiltrate, lymphatic emboli and vascular or perineural involvement [10, 27, 28]. However, histopathological diagnosis is limited by the absence of objective and reproducible criteria that can be applied to all melanomas. Furthermore, the subset of lesions with contradictory or borderline findings adds to the limitations of histopathology in the diagnosis of melanoma [29, 30].

2.3.5 Molecular Diagnosis

In cases where histologic diagnosis is unclear, analysis of molecular biomarkers (S-100 protein, HMB 45, Melan-A, MIB-1, Ki-67) using immunohistochemical staining could be helpful. Among several markers, expression of S-100 protein (low molecular weight calcium binding protein that is involved in cell division and differentiation) is considered as the most sensitive marker for melanocytic lesions [31, 32]. Interestingly, serum levels of S-100 protein were also found to correlate with progression of metastatic melanoma in patients [33]. While S-100, HMB45 and Melan-A are useful for the confirmation of the melanocytic nature of the tumor, MIB-1 and Ki-67 are indicators of tumor proliferation [31]. Apart from immunohistochemical analysis, analytical genetic and genomic techniques like comparative genomic hybridization (CGH) analysis and fluorescence in situ hybridization (FISH) assay are used to in cases of uncertainty. Chromosomal aberrations such as loss of 6q, 8p, 9p and 10q as well as gain of 1q, 6p, 7, 8q, 17q and 20q were found to be specifically associated with melanoma samples and CGH analysis of the samples effectively differentiated tumors from naevi [34]. On the other hand, an algorithm developed based on the data obtained using FISH assay kit (Vysis Melanoma FISH Probe Kit, Abbott Molecular, USA) has been shown to classify melanoma samples with 86.7 % sensitivity and 95.4 % specificity [35].

Tumor specimens from melanoma patients are further analyzed to obtain crucial information on the mutations that are driving melanomagenesis. The information could be used in selection of appropriate therapeutic agent to treat melanoma. For example BRAF inhibitors like vemurafenib and dabrafenib could be used alone or in combination with MEK inhibitors like trametinib and cobimetinib in melanomas with BRAFV600E and BRAFV600K mutations. NRAS mutations are found in approximately 15 % of samples and MEK inhibitors (binimetinib) are under clinical

Table 2.1 Summary of diagnostic features of melanoma

S.No	Characteristic feature
1	Asymmetric shape of the lesion
2	Irregular border of the lesion
3	Color variegation in the lesion
4	Diameter of the lesion >6 mm
5	Evolving nature of the lesion in terms of color, shape and size
6	Identification of tumor-specific characteristics in dermoscopic evaluation
7	Identification of new or evolving nevi using total body photography
8	Evaluation of H and E stained tissue section by dermatopathologist with details on tumor thickness in mm (Breslow depth), presence or absence of ulceration, mitotic rate, if any microsatellites are present and the lateral and deep excision margins
9	Positive reaction for molecular biomarkers of melanoma such as S-100 protein, HMB-45, and Melan-A
10	High expression of the markers for tumor proliferation such as MIB-1 and Ki-67
11	Detection of chromosomal aberrations such as losses of 6q, 8p, 9p and 10q as well as gains of 1q, 6p,7, 8q, 17q and 20q in the tumor samples
12	Presence of BRAF, NRAS and KIT mutations in the tumor samples

development for the treatment of melanoma patients with NRAS mutations [36, 37]. Similarly, patients with mutations in KIT gene were reported to respond to KIT inhibitor (imatinib) treatment [38, 39].

Additional staging examinations such as sonography of regional lymph nodes and total body CT scans or PET-CT scans are also used in patients with primary melanomas at first diagnosis and in subsequent follow-up examinations to identify the high-risk patients who have greater chances of relapse. Serum LDH and S100 protein levels are also routinely used as markers for relapse [10]. The characteristic features of melanoma that aid in the diagnosis are summarized in Table 2.1.

2.4 Types of Melanoma

Although melanoma is characterized by its typical ‘ABCDE’ features as described above, there are several variations in the presentation of melanoma. One of the biggest challenges to the diagnosis is the identification of melanoma that does not have typical ABCDE features. Different subtypes of melanomas that vary in terms of clinical presentation and histopathological features have been described by practitioners (summarized in Table 2.2). Superficial spreading, lentigo maligna, acral lentiginous and nodular melanoma are the commonly found subtypes of melanoma. Other than these four, there are also some uncommonly seen subtypes like desmoplastic melanoma, verrucous melanoma and nevoid melanoma. The details of clinical presentation and histology are described below.

2.4.1 Superficial Spreading Melanoma

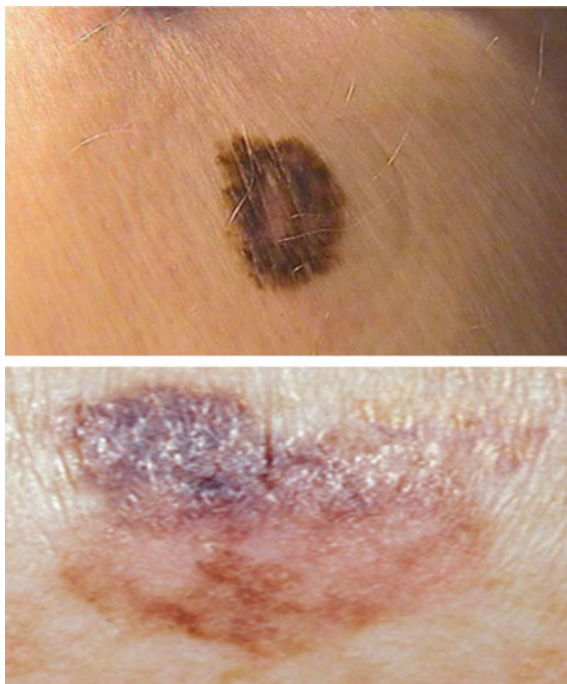
Superficial spreading melanoma (SSM) or pagetoid melanoma is one of the most common types of melanoma [5]. Majority of the epidemiological studies report it as the most common type of melanoma constituting more than 60 % of all melanoma cases; however some studies found it to constitute less than 30 % [1, 5, 40–42]. Usually SSMs reportedly occur in younger patients (median age: 5th decade) as compared to other types of melanomas like nodular or lentigo maligna melanoma [43]. Incidentally, SSMs were shown to have highest frequency of BRAFV600E mutation among different melanoma subtypes by several studies on the mutation frequencies in different histological subtypes of melanoma [44–48].

The characteristic feature of the SSM histology is the presence of large epithelioid melanocytes singly or in nests mostly along the dermal-epidermal junction and sometimes in the stratum granulosum or stratum corneum. In some cases, the tumor cells can also invade the papillary dermis with an inflammatory infiltrate [5, 10]. The tumor cells of SSM are mostly large with ample cytoplasm and the arrangement of cells is in the form of an intraepidermal buckshot (pagetoid) pattern giving it the name pagetoid melanoma [42]. Typically, SSM appears as a macule that slowly evolves into a plaque with an intraepidermal horizontal or radial growth phase. SSMs are usually flat in the beginning but slowly grow into an irregular lesion with variegated pigmentation and enlarge in a radial manner. Dermal invasion of the tumor is clinically manifested by the presence of an elevated area. Other features of SSM include average lesion diameter of 2 cm, circumscription, variable epidermal thickening and prominent intracytoplasmic melanisation [43]. Images of superficially spreading melanoma can be found in Fig. 2.4.

2.4.2 Lentigo Maligna Melanoma

Lentigo maligna (LM) is the term used to describe melanoma in situ of sun-damaged skin. It represents 4–10 % of all melanoma cases and occurs mostly on the face (and other sun exposed areas) in elderly patients [5, 49, 50]. Commonly, LM develops as a slow growing asymmetric macule with brown to black color and irregular indented borders; tumors are flat, larger than 3 cm in diameter and are accompanied by dermal and epidermal changes from sun exposure (Fig. 2.5). Upon dermoscopic evaluation, LM presents a number of unique features like asymmetric perifollicular openings and rhomboidal structures [1]. Other features such as interfollicular peppering or ‘annular granular structures’ that are commonly seen in solar lentigines, lichenoid or solar keratoses are seen in LM lesions. Obliteration of follicular openings or milky pink erythema could be used as an indicator of invasive melanoma [1]. Histopathologic features of LM include proliferation of atypical melanocytes arranged as solitary units and in the form of spindle-shaped nests along the junction between dermis and epidermis, scattered above it and focally within epithelial

Fig. 2.4 Superficially spreading melanoma. Original image can be found in the article, ‘Melanoma review: epidemiology, risk factors, diagnosis and staging’ by Arrangoiz et al. [7]. Image downloaded and reused under the under Creative Commons Attribution (CC BY) license (<http://creativecommons.org/licenses/by/4.0/>) wherein authors of the above article retain ownership of the copyright for their publications, but grant SciencePG a non-exclusive license to publish the work in paper form and allow anyone to reuse, distribute and reproduce the content as long as the original work is properly cited



structures of adnexa. The epidermis is usually atrophic with loss of rete ridges whereas the dermis contains features of solar elastosis with chronic inflammatory infiltrates and accumulation of melanophages in the upper dermis [5, 10, 43, 49]. Occasionally, multinucleate or giant melanocytes are also seen. As the tumor grows, the epidermal component shows confluent lentiginous growth, nesting and pagetoid epidermal invasion as seen in superficial spreading melanoma [43].

2.4.3 *Acral Lentiginous Melanoma*

Acral lentiginous melanoma (ALM), which accounts for 2–3 % of all melanoma cases, is one of the most common types of melanoma in dark-skinned people [50, 51]. A study published in 2009 reported that ALM accounted for 36 % of all cutaneous malignant melanomas in people from African descent, 18 % in Asians or Pacific Islanders, 9 % in Hispanic Whites and only 1 % in Non-Hispanic Whites [50]. Compared to other subtypes ALM generally occurs later in life and studies have reported the mean age at diagnosis as 63 years [52, 53]. Typically it occurs on the palms of the hands, soles of the feet, wrists, heels and under the nail beds [52]. Dermoscopic examination of the lesions reveals the highly specific parallel ridge pattern with small, round eccrine openings that is distinct from other patterns associated with benignity, like the furrow, fibrillar or lattice patterns [54]. In some

Fig. 2.5 Lentigo maligna. Original image can be found in the article, 'Melanoma review: epidemiology, risk factors, diagnosis and staging' by Arrangoiz et al. [7]. Image downloaded and reused under the under Creative Commons Attribution (CC BY) license (<http://creativecommons.org/licenses/by/4.0/>) wherein authors of the above article retain ownership of the copyright for their publications, but grant SciencePG a non-exclusive license to publish the work in paper form and allow anyone to reuse, distribute and reproduce the content as long as the original work is properly cited



cases symmetric arrangement of globules on either side of the furrows could be seen in acral naevi. Application of liquid ink would preferentially stain over the ridges and thereby help to distinguish the doubtful dermatoglyphic furrows [55]. ALM is characterized histologically by the presence of single atypical melanocytes scattered along the dermal-epidermal junction. Lymphocytic infiltrate partly obscuring the dermoepidermal junction could be used as a diagnostic marker in the identification of ALM. In the early intraepidermal phase of ALM, irregular, poorly circumscribed pigmentation is seen and in later stages a nodular region that reflects the invasive growth pattern of tumor is seen [5, 10]. The production of melanin granules which fills the dendritic extensions is increased in the cells. Advanced forms of ALM could

Fig. 2.6 Acral lentiginous melanoma. Original image can be found in the article, ‘Melanoma review: epidemiology, risk factors, diagnosis and staging’ by Arrangoiz et al. [7]. Image downloaded and reused under the under Creative Commons Attribution (CC BY) license (<http://creativecommons.org/licenses/by/4.0/>) wherein authors of the above article retain ownership of the copyright for their publications, but grant SciencePG a non-exclusive license to publish the work in paper form and allow anyone to reuse, distribute and reproduce the content as long as the original work is properly cited



also show confluent lentiginous and nested growth, pagetoid epidermal invasion and ulcerations [43]. Images of acral lentiginous melanoma can be seen in the Fig. 2.6.

Due to unconventional sites (under the nails) of development, ALMs are usually diagnosed at later stages as compared to lentigo maligna or superficial spreading melanoma [52]. Possibly due to late diagnosis, ALMs have worse survival rates as compared to other melanoma subtypes. Overall and melanoma-specific 5-year and 10-year survival rates in ALM patients have been reported to be 80.3 % (95 % CI, 77.6–83.0) and 67.5 % (95 % CI, 63.4–71.6) respectively, which were significantly lower than the overall and disease-specific 5- and 10-year survival rates for all melanomas [91.3 % (95 % CI, 91.1–91.5, $p < 0.001$) and 87.5 % (95 % CI, 87.1–87.9, $p < 0.001$) respectively] [50].

2.4.4 Nodular Melanoma

Nodular melanoma (NM), commonly seen on sun-damaged regions of head and neck of elderly patients, accounts for 15–30 % of all melanoma and is the second

most common subtype after superficial spreading melanoma [1, 40, 41, 56]. It constitutes nearly half of the thick melanoma tumors (>2 mm) and is the most rapidly growing subtype of all melanomas with a median growth rate of 0.49 mm depth per month [1, 40, 57]. Most of the times, it is not diagnosed until it is at an advanced stage leading to a relatively poor prognosis [58]. Clinically NM manifests as firm, symmetrical and evenly pigmented papules (less color variegation) or nodules that ulcerate eventually and bleed thereby draw the patient's attention to the site (Fig. 2.7). NMs usually do not show the color change that is commonly seen with radial growth phase melanomas [1]. Due to their predominant (over 50 %) hypomelanotic nature, NMs are commonly mistaken for nonmelanoma skin cancer [59]. The typical ABCD (asymmetry, border irregularity, color variation and diameter >6 mm) characteristics of melanoma cannot be applied for the diagnosis of NM. Instead, EFG mnemonic could be used to describe the elevation, firm consistency and rapid growth of the MN lesions.

Dermoscopic features of NM include an atypical vascular pattern along with blue-grey veil and multiple colors. Other common features like branched streaks, pseudopods, atypical or inverse network seen in radial growth phase melanomas or thin melanomas are not seen in NM. Traces of pigment are often seen dermoscopically, at the margins of the tumors [1]. Further detailed descriptions of dermoscopic features of NM can be found in the recent report by Menzies et al [58]. Histologically NM is characterized by lack of significant intraepidermal tumor cells beyond the edge of the dermal component [43].

2.4.5 *Desmoplastic Melanoma*

Desmoplastic melanoma is a rare, fibrosing subtype of melanoma that accounts for 1–4 % of all melanoma cases [1, 5, 60–62]. It is reported to be seen typically in elderly (mean age at diagnosis, 66 years) and sun damaged patients, frequently located on the head and neck, extremities and trunk. Men are reportedly two times more susceptible to DM as compared to women [60–62]. Usually, DMs present as nonpigmented, skin colored and scar-like indurated dermal papules, plaques or nodules (Fig. 2.8). Due to lack of prominent clinical features, the tumors are detected late and most reach significant depth (reticular dermis or even deeper) at the time of diagnosis. DMs are sometimes associated with neurotropism with a tendency of perineural invasion; in these cases the term 'desmoplastic neurotrophic melanoma' is used to describe the tumors.

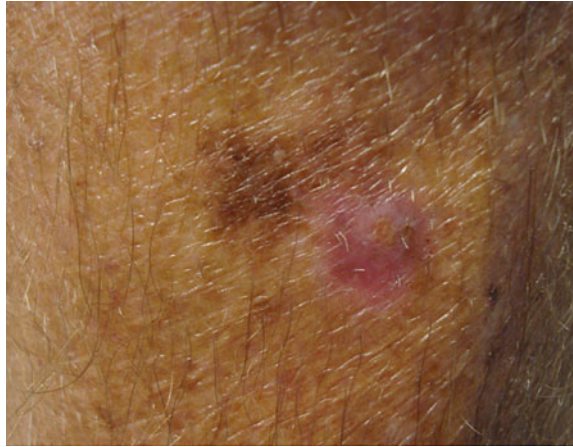
Dermoscopic evaluation reportedly demonstrated that though majority of DMs lacked melanocytic pigmented structures, all cases of DM had at least one melanoma-specific structure, like atypical vascular structures, peppering, blue-white veil, atypical globules, crystalline structures, and atypical network. In some cases

Fig. 2.7 Nodular melanoma. Original image can be found in the article, ‘Melanoma review: epidemiology, risk factors, diagnosis and staging’ by Arrangoiz et al. [7]. Image downloaded and reused under the under Creative Commons Attribution (CC BY) license (<http://creativecommons.org/licenses/by/4.0/>) wherein authors of the above article retain ownership of the copyright for their publications, but grant SciencePG a non-exclusive license to publish the work in paper form and allow anyone to reuse, distribute and reproduce the content as long as the original work is properly cited



dermoscopic features overlap with features of LM such as annular granular pattern and polygonal lines [62]. Histologically, desmoplastic melanoma is characterized by atypical, spindle shaped melanoma cells that are intimately admixed with ropy

Fig. 2.8 Desmoplastic melanoma. Image courtesy and copyrights owned by Prof Scott Menzies, Director, Sydney Melanoma Diagnostic Centre, The University of Sydney, Australia; image originally published in the article, 'Evolving concepts in melanoma classification and their relevance to multidisciplinary melanoma patient care' by Scolyer et al. [43]



and dense collagen fibrils. DMs are subdivided into pure DM (pDM), comprising of entirely or almost entirely desmoplastic components, and combined DM (cDM) comprising of a desmoplastic component admixed with a nondesmoplastic component [60]. The type of DM was found to be associated with disease recurrence and patient survival. Positive sentinel node biopsy was more frequently found in cDMs as compared to pDMs and cDM patients reportedly had worse prognosis as compared to pDM patients [63].

2.4.6 *Nevoid Melanoma*

Nevoid melanoma is a rare form of nodular melanoma that resembles the histological features of a common benign melanocytic nevus when the melanoma cells are small or Spitz's nevi when the cells are large [64, 65]. There are no reports on age or gender specific associations with nevoid melanomas. Due to its confusing histological features like symmetrical silhouette, sharp lateral circumscription and evidence of incomplete maturation with descent in the dermis, detection of nevoid melanoma is difficult in routine histological examination. Histopathological features that help in the diagnosis of nevoid melanoma include presence of dermal mitotic figures, partial intraepidermal component with little or no pagetoid spread, presence of nevus-like cells in the dermis with a sheet-like growth pattern, clear nucleoli at the base of the lesion and absence of complete maturation. Diagnosis of nevoid melanoma can be confirmed using molecular techniques like immunohistochemical analysis of HMB45, MART-1 or MiTF expression, comparative genomic hybridization and FISH analysis [64, 65].

2.4.7 Verrucous Melanoma

In very rare cases, melanoma is presented as warty and papillomatous lesions, termed as verrucous melanoma (VM). The lesions tend to be large, mimic either a verruca, seborrhoeic keratosis or a compound or congenital naevus and mostly develop on the extremities of women. VM could develop on any conventional clinical type of melanoma like LM or SSM, or could be totally *de novo*. The *de novo* VM is generally an exophytic tumor diagnosed in *in situ* or at microinvasion stages, with a less aggressive phenotype and more favorable prognosis. VMs are presented as small, slightly elevated lesion, devoid of nodules and without areas of regression. Possibly because of its rare manifestation, details of dermoscopic evaluation of VM have not been described. Histologically, VMs have proliferating neoplastic cells to a greater extent at the dermo-epidermal interface as compared to upper layers of the epidermis and have very low mononuclear inflammatory-cell infiltration [66–68] (Table 2.2).

2.5 Melanoma Stages

Melanoma is classified into different stages to indicate extent of tumor growth, invasion tumor into surrounding tissues and spread of tumor to neighboring/distant site. Three types of schemes have been developed to classify melanoma based on histological examination, vertical thickness or the current TNM (tumor, node and metastasis) based AJCC system.

2.5.1 Clark Classification

The oldest system of melanoma staging was developed by Dr. Wallace Clark in 1966 [69]. It is based on histological examination of the tumor specimen and indicates the extent of downward invasion of tumor into skin. The system classifies melanoma into five ‘Clark’s levels’ [10].

- Level I also known as *in situ* melanoma, involves only epidermis and there is no invasion
- Level II invasion of tumor cells into papillary dermis is seen; but there is no invasion into papillary-reticular dermal interface
- Level III tumor cells invade and expand in papillary dermis up to the papillary-reticular dermal interface; but there is no invasion into reticular dermis
- Level IV invasion of tumor cells into reticular dermis is seen; but there is no invasion of subcutaneous tissue
- Level V invasion of tumor cells into subcutaneous tissue is seen.

Table 2.2 Summary of different subtypes of melanoma

Subtype	Incidence rate	Characteristic features
Superficially spreading melanoma (SSM)	Most common type; accounts for nearly 60 % of all melanoma cases	Commonly associated with BRAFV600E mutations appears as a flat macule that slowly evolves into a plaque with variegated pigmentation and enlarge in a radial manner Characterized by the arrangement of tumor cells in the form of an intraepidermal buckshot (pagetoid) pattern giving it the name pagetoid melanoma
Lentigo maligna	Accounts for 4-10 % of melanoma cases; mostly seen in elderly patients	Occurs mostly in sun-exposed areas and is associated with sun-burns Develops as a slow growing asymmetric macule with brown to black color and irregular borders Dermoscopic evaluation shows asymmetric perifollicular openings and rhomboidal structures Histopathologic features include atypical melanocytes arranged as solitary units and in the form of spindle-shaped nests along the junction between dermis and epidermis
Acral lentiginous melanoma	Accounts for 2–3 % of melanoma cases; most commonly seen in ‘dark-skinned’ people and not usually seen in ‘white-skinned’ people	Typically occurs on the palms, soles, wrists, heels and under nail beds Parallel ridge pattern with small, round eccrine openings are seen upon dermoscopic evaluation Histological evaluation reveals the presence of single atypical melanocytes scattered along the dermal-epidermal junction and the lymphocytic infiltrate that obscures the dermoepidermal junction ALMs have comparatively worse survival rates possibly due to late diagnosis
Nodular melanoma	Accounts for 15–30 % of melanoma cases; second most common subtype of melanoma	It is the most rapidly growing subtype and constitutes nearly half of the thick melanoma tumors (>2 mm) Manifests as firm, symmetrical and evenly pigmented papules

(continued)

Table 2.2 (continued)

Subtype	Incidence rate	Characteristic features
		that ulcerate eventually; ABCD characteristics cannot be applied but EFG mnemonic (elevation, firm consistency and rapid growth) is useful in diagnosis Dermoscopy reveals an atypical vascular pattern along with blue-grey veil and multiple colors Histological features include lack of significant intraepidermal tumor cells beyond the edge of the dermal component Due to delay in diagnosis, NMs have relatively poor prognosis
Desmoplastic melanoma	Accounts for 1–4 % of melanoma cases; frequently seen in men	Presents as nonpigmented, skin colored and scar-like indurated dermal papules/plaques/nodules DMs are sometimes associated with perineural invasion and termed as ‘desmoplastic neurotrophic melanoma’ Dermoscopic evaluation shows at least one melanoma specific structure like atypical vascular structures, crystalline structures, peppering, blue-white veil, atypical globules and atypical network Histological features include atypical, spindle shaped melanoma cells that are intimately admixed with ropy and dense collagen fibrils Due to lack of prominent clinical features, tumors cannot be detected early
Nevoid melanoma	Rare form of melanoma	Characteristic histological features include presence of dermal mitotic figures, partial intraepidermal component with little or no pagetoid spread, presence of nevus-like cells in the dermis with a sheet-like growth pattern, clear nucleoli at the base of the lesion and absence of complete maturation IHC analysis of HMB45, MART-1 or MiTF expression could be used to confirm the diagnosis

(continued)

Table 2.2 (continued)

Subtype	Incidence rate	Characteristic features
Verrucous melanoma	Very rare form of melanoma; mostly seen on the extremities of women	Presented as large, warty and papillomatous lesions that mimic either a verruca, seborrhoeic keratosis or a compound or congenital nevus Histological evaluation shows proliferating neoplastic cells to a greater extent at the dermo-epidermal interface as compared to upper layers of the epidermis and low lymphocyte infiltration

2.5.2 Breslow Classification

In 1970, Dr. Alexander Breslow identified the significance of tumor thickness in prognosis of melanoma and developed a staging system based on ‘Breslow thickness’, which is defined as the total vertical depth of the melanoma from the granular layer of the epidermis to the area of deepest penetration into the skin [70].

- Stage I thickness of tumor is ≤ 0.75 mm
- Stage II thickness of tumor is 0.76–1.5 mm
- Stage III thickness of tumor is 1.51–4 mm
- Stage IV thickness of tumor is >4 mm

2.5.3 TNM (Tumor, Node and Metastasis) Classification

In 2001, AJCC (American Joint Committee on Cancer) melanoma staging committee published guidelines to determine criteria that are used in TNM classification and the subsequent stage groupings [71]. The committee regularly performs evidence-based analysis based on the updated melanoma database and makes staging recommendations. Currently used independent prognostic factors for defining the TNM categories and stage groupings were last updated in 2009 [72].

Based on tumor thickness, melanoma is classified as follows:

- Tis tumor in situ
- T1a thickness ≤ 1.00 mm; mitotic rate $<1/\text{mm}^2$; and no ulceration
- T1b thickness ≤ 1.00 mm; with ulceration or mitotic rate $>1/\text{mm}^2$
- T2a thickness between 1.01 and 2.00 mm and no ulceration

- T2b thickness between 1.01 and 2.00 mm and with ulceration
- T3a thickness between 2.01 and 4.00 mm and no ulceration
- T3b thickness between 2.01 and 4.00 mm and with ulceration
- T4a thickness >4.00 mm and no ulceration
- T4b thickness >4.00 mm and with ulceration

Based on the number of nodes involved and the metastatic burden in the nodes, melanoma is classified as follows:

- N0 no nodal metastasis.
- N1a metastasis seen in 1 lymph node with micrometastasis (diagnosed by sentinel node biopsy).
- N1b metastasis seen in 1 lymph node with macrometastasis (clinically detected nodal metastasis confirmed with pathological examination).
- N2a metastasis seen in 2–3 lymph nodes and diagnosis of micrometastasis.
- N2b metastasis seen in 2–3 lymph nodes and diagnosis of macrometastasis.
- N2c metastasis seen in 2–3 lymph nodes and diagnosis of in transit metastases or satellites without metastatic nodes.
- N3 metastasis seen in ≥ 4 lymph nodes or matted nodes or in transit metastases or satellites with metastatic nodes.

Based on presence or absence of distant metastasis, melanoma is classified as follows:

- M0 absence of distant metastases.
- M1a distant skin, subcutaneous or nodal metastases and normal serum LDH levels.
- M1b metastasis of melanoma to lung and normal serum LDH levels.
- M1c metastasis to all other visceral organs and normal serum LDH levels; or any distant metastasis with elevated serum LDH levels.

2.5.4 Melanoma Staging—AJCC System

AJCC system further combined different levels in the TNM system and categorized melanoma progression into stage 0 and stages I–IV.

Stage 0: In this stage melanoma is in situ and did not spread to the dermis (Tis, N0 and M0)

Stage IA: In this stage thickness of tumor is <1.00 mm and is localized in skin without any metastasis to lymph nodes or distant organs. Tumor is also not ulcerated in this stage.

(T1a, N0 and M0)

Stage IB: This stage includes conditions where tumors are ulcerated, localized and with thickness <1.00 mm as well as where tumors are not ulcerated, localized and with thickness between 1.01 and 2.00 mm.

(T1b/T2a, N0 and M0)

Stage IIA: This stage includes conditions where tumors are ulcerated, localized with thickness between 1.01 and 2.00 mm as well as where tumors are not ulcerated, localized and with thickness between 2.01 and 4.00 mm.

(T2b/T3a, N0 and M0)

Stage IIB: This stage includes conditions where tumors are ulcerated, localized tumors with thickness between 2.01 and 4.00 mm as well as where tumors are not ulcerated, localized and with thickness >4.00 mm.

(T3b/T4a, N0 and M0)

Stage IIC: This stage includes conditions where tumors are ulcerated, localized and with thickness >4.00 mm.

(T4b, N0 and M0)

Stage III: This stage includes conditions where melanoma has spread to lymph nodes near the affected skin area, but did not spread to distant organs. Thickness of the tumor is not a factor in this stage but commonly tumors are thick in stage III melanoma.

Based on the pathological examination of metastasis in lymph nodes, stage III is further categorized into A, B and C.

Stage IIIA: This stage includes conditions where tumors are not ulcerated, thickness is between 1.00 and 4.00 mm and micrometastasis is seen in 1–3 lymph nodes.

Stage IIIB: This stage includes conditions where tumors are ulcerated, thickness is between 1.00 mm and 4.00 mm and micrometastasis in 1–3 lymph nodes as well as where tumors are not ulcerated, thickness is between 1.00 and 4.00 mm and macrometastasis or in transit metastases is seen in 1–3 lymph nodes.

(T1–4b, N1a/N2a and M0; T1–4a, N1b/N2b/N2c and M0)

Stage IIIC: This stage includes conditions where tumors are ulcerated, thickness is between 1.00 and 4.00 mm and macrometastasis or in transit metastases is seen in 1–3 lymph nodes as well as conditions where irrespective of ulceration status or thickness, metastasis is seen in more than 4 nodes.

(T1–4b, N1b/N2b/N2c and M0; Any T, N3 and M0)

Stage IV: In this stage melanoma has spread beyond the original site of development and nearby lymph nodes to other organs such as lungs, liver, brain or other distant areas of the skin. If distant metastasis is found, melanoma is categorized as stage IV regardless of the thickness, ulceration and lymph node status.

(Any T, Any N and M1)

Summary of AJCC staging of melanoma based on clinical and pathological findings is presented in Tables 2.3 and 2.4 respectively.

Table 2.3 AJCC staging of melanoma based on clinical findings [72]

AJCC stage	T	N	M
0	T _{is}	N0	M0
IA	T1a	N0	M0
IB	T1b	N0	M0
	T2a	N0	M0
IIA	T2b	N0	M0
	T3a	N0	M0
IIB	T3b	N0	M0
	T4a	N0	M0
IIC	T4b	N0	M0
III	Any T	N > N0	M0
IV	Any T	Any N	M1

Table 2.4 AJCC staging of melanoma based on pathologic findings [72]

AJCC stage	T	N	M
0	T _{is}	N0	M0
IA	T1a	N0	M0
IB	T1b	N0	M0
	T2a	N0	M0
IIA	T2b	N0	M0
	T3a	N0	M0
IIB	T3b	N0	M0
	T4a	N0	M0
IIC	T4b	N0	M0
IIIA	T(1-4)a	N1a	M0
	T(1-4)a	N2a	M0
IIIB	T(1-4)b	N1a	M0
	T(1-4)b	N2a	M0
	T(1-4)a	N1b	M0
	T(1-4)a	N2b	M0
	T(1-4)a	N2c	M0
	T(1-4)b	N1b	M0
IIIC	T(1-4)b	N2b	M0
	T(1-4)b	N2c	M0
	Any T	N3	M0
IV	Any T	Any N	M1

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