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Nodular Melanoma: A Review of Pathogenesis, Presentation, Diagnosis, and Treatment

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Abstract

Nodular melanoma is the second most common subtype of melanoma. Unlike other subtypes, nodular melanoma is characterized by early vertical growth rather than the typical initial radial growth of most melanomas. As a result, nodular melanoma presents clinically in a more aggressive phenotype. Given its more aggressive nature and intrinsic ability to mimic benign lesions, a modified acronym has been developed to allow clinicians to better evaluate, diagnose and treat nodular melanoma in earlier stages. Surgical excision with wide margins is the gold standard of nodular melanoma therapy; however, an emphasis in early detection, diagnosis, staging, and treatment needs to be emphasized among clinicians due to its dismal prognosis in later stages, as compared to other subtypes. A better understanding of the molecular pathophysiology that allows nodular melanoma to act aggressively very early in diagnosis is necessary for the development of therapeutics that may effectively target lesions in more advanced stages.

Introduction

Melanoma tumors are malignant neoplasms of melanocytes, highly differentiated cells that are neural crest in origin and found in the epidermis and hair follicles.[1,2] As they are derived from the neural crest lineage, melanomas have been found in areas where these cells migrate, such as the brain.[3] However, they are more commonly located on the skin and are the most lethal and aggressive form of cutaneous malignancy.[4] Nodular melanoma (NM), the second-most common subtype of melanoma, provides physicians with a diagnostic challenge as they may appear similar to other benign lesions such as seborrheic keratoses, melanocytic nevi, and vascular lesions such as pyogenic granulomas.

Epidemiology, Risk Factors, and Prognosis

According to the American Cancer Society, it is estimated that 106,110 melanoma diagnoses will be made in 2021 with a predilection for the male sex; they estimate that 62,260 of cases will be attributed to males and 43,850 to females.[4] Currently, the average age of melanoma diagnosis is 65 with a majority of diagnoses made between the ages of 55 to 81.[4] Risk factors include the presence of multiple atypical or dysplastic nevi, skin type, a personal history of melanoma, and although rare, inherited genetic mutations such as those encountered in familial atypical multiple mole-melanoma (FAMMM) and FAMMM-pancreatic cancer. Thus, patients with a pronounced familial history of invasive melanoma with or without pancreatic cancer should consider genetic counseling. Environmental

factors that influence the development of melanoma include UV-based artificial tanning and excessive sun exposure.[5,6] There are four major subtypes as categorized by their morphologic features, these include the superficial spreading (SSM), nodular (NM), lentigo maligna (LM), and acral lentiginous (ALM) subtypes of melanoma. In 2018 the World Health Organization (WHO) revised its melanoma classification system to include epidemiologic, genomic, clinical, and histologic characteristics. According to this system, melanomas are categorized into those resulting from cumulative solar damage (CSD), those not consistently associated with CSD (no CSD), and nodular melanoma, which may occur in either the CSD or no CSD category. CSD melanoma tumors have distinct genetic alterations depending on whether there is minimal or marked solar elastosis.; therefore, CSD melanoma tumors may be further subdivided into low and high CSD according to the associated degree of solar elastosis.[7]

NM is the second-most common subtype of melanoma, accounting for 10-15% of primary cutaneous melanomas.[8] However, NM accounts for over 40% of all melanoma-related deaths.[9] Survival rates are variable and the later this malignancy is detected, the more dismal the prognosis. If melanoma is detected and treated prior to lymph node metastasis, the 5-year survival rate is approximately 99%. However, if it spreads to nearby lymph nodes or to distant lymph nodes, this rate declines to 66% and 27%, respectively.[4,10] Sentinel node status is an important prognostic factor for melanoma patients with clinically node negative, localized melanoma in respect to disease progression and disease specific survival (DSS).[11,12] In respect to the NM histologic subtype, a recent multivariate analysis found that distant relapse was independently predicted by positive SLNB (p = 0.015, odds ratio: 2.1, 95% CI 1.2-3.6) and tumor thickness (p = 0.0077, odds ratio: 2.4, 95% CI 1.2-4.3). They also found that tumor thickness (p = 0.020, odds ratio: 2.1, 95% CI 1.1-4.1) and the male sex (p = 0.013, odds ratio: 3.1, 95% CI 1.2-3.9) were independently predictive of melanoma-specific death in NM patients.[13]

A recent population-based cross-sectional analysis utilized data from the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) registry to compare 5-year survival of patients with NM and SSM. Two datasets were delineated, one utilizing American Joint Committee on Cancer (AJCC) sixth edition staging guidelines and the other using AJCC seventh edition staging guidelines, accounting for patients diagnosed from 2004 to 2009 and from 2010 to 2015, respectively. Each dataset was further subdivided into two cohorts, that of NM and SSM, wherein 5-year survival was calculated and compared. As compared to the SSM subtype, the most common subtype of melanoma, NM has a significantly worse 5-year survival rate, especially in patients with stage T1b, T2a, and T2b melanoma diagnosed between 2004 and 2009 (Table 1).[14] For patients diagnosed between 2010 and 2015, 5-year survival was also lower in patients with NM as compared to SSM, especially in the T1b stage (Table 2).[14]

Table 1. AJCC Sixth Edition – 5-Year Survival in NM and SSM[14]

	NM (N = 5011)	SSM (N = 22,420)	Z-Score, P
Overall	53.7%	87.3%	-41.35, <.001
T1b	55.7%	85.5%	-12.1928, <.0001
T2a	76.1%	83.3%	-3.8909, <.0001
T2b	56.6%	72.4%	-4.3106, <.001

Table 2. AJCC Seventh Edition – 5-Year Survival in NM and SSM[14]

	NM (N = 2249)	SSM (N = 11,375)	Z-Score, P
Overall	61.5%	89.7%	-2.7078, <.01
T1b	64.4%	91.8%	-4.8815, <.0001

Pathophysiology and Genetics

Melanoma arises when melanocytes undergo malignant transformation of the dermal-epidermal junction. This malignancy may arise from a pre-existing nevus, but they more often arise de novo. Melanoma growth is typically divided into two stages, the first being the radial growth phase and the second being the vertical growth phase. The radial growth phase is characterized by a horizontal array of neoplastic melanocytes in an intraepidermal location, but can also involve the papillary dermis.[15] The vertical growth phase is characterized by invasion of the dermis and formation of a tumor nodule.[16] Histologically, NM, unlike other subtypes of melanoma, does not undergo an initial radial growth phase but rather begins to grow vertically.[17]

Melanoma pathogenesis is also closely associated with the tumor microenvironment (TME) and immune system. The TME refers to the influential network of molecules, cells, and paracrine factors involved in the progression, proliferation, and differentiation of melanoma cells.[18] It is within the TME where immune cells, such as T lymphocytes, also referred to as tumor infiltrating lymphocytes (TILs), B lymphocytes, dendritic cells, myeloid-derived suppressor cells, natural killer (NK) cells, and macrophages are present.[19] These cells in the TME induce apoptosis in neoplastic cells and promote anti-tumor responses through production of cytokines and cytotoxic reactions. For example, NK cells secrete cytokines to recruit antigen presenting cells and phagocytic immune cells, such as macrophages, in the tumor present cancer antigens to T-cells as part of the adaptive immune response. Tumor cells have the potential to develop methods to evade any of these and other anti-tumor responses, e.g. by downregulating tumor-associated antigen production, downregulating MHC molecule expression, and increasing production of programmed death ligand-1 (PD-L1) to inhibit T-cell activation.[20] The TME and immune system have implications in treatment, as therapeutics are developed that target components of

the immune system. The pattern of immune cell infiltration has been shown to have prognostic value for response to immunotherapy and overall survival.[21]

Multiple mutations have been associated with the development of malignant melanoma. The mitogen-activated protein kinase (MAPK) pathway is involved in the regulation of cellular growth, proliferation, and apoptosis. Derangements in this pathway, such as its unintended activation, is involved in the pathogenesis of multiple cancer types including melanoma.[22] Proto-oncogene B-raf (BRAF) gene mutations, typically missense mutations at valine 600, are the most common genetic abnormalities resulting in aberrant MAPK signaling.[23,24] The phosphoinositol-3-kinase PI3K/AKT pathway, which plays a role in cellular homeostasis, is also implicated in melanoma pathogenesis.[25] Activating mutations in the neuroblastoma RAS viral oncogene (NRAS) gene are also involved in melanoma pathogenesis via the aberrant activation of either MAPK or PI3K/AKT signaling. Activating mutations in the N-Ras gene result in a prolonged activation of the N-Ras protein, and thus uncontrolled cellular division.[24,26] BRAF and NRAS mutations have been found to be more frequent in patients with NM, allowing for therapeutic potential.[27] Mutational burden also portends poor prognosis in NM patients, as BRAF-V600E expression has been associated with reduced survival and aggressive tumor features.[28]

Neurofibromatosis type 1 (NF1) gene, a tumor suppressor, has also been found to be mutated in melanomas and is the third most common gene mutation, behind BRAF and NRAS mutations.[29,30] Loss of function mutations in NF1 cause upregulation of NRAS, causing increased activation of MAPK and PI3K/AKT pathways.[29,31]

The p16 kinase inhibitor gene (CDKN2A) has been posited to be responsible for causing both familial, such as FAMMM, and sporadic melanoma.[32] Mutations in CDKN2A gene have been described in both sporadic and familial cases of melanoma in about 80% of cases.[33] Patients with FAMMM are more likely to develop SSM and NM.[34]

Clinical Presentation, Evaluation, and Diagnosis

The acronym ABCDE is commonly used to describe the typical melanoma lesion, wherein A stands for asymmetry, B for irregular border, C for color variation within the lesion itself in addition to color variation as compared to the patient's other nevi, D for a diameter greater than 6 mm, and E for an evolving lesion.[35] NM can present as rapidly enlarging papules or nodules and can lack some of the other characteristic features associated with other subtypes of melanoma, making the ABCDE's mnemonic less useful in their diagnosis. Rather, a modified Elevated, Firm, Growing (EFG) rule can be applied in the detection of NM, given that NM is elevated, firm on palpation, and rapidly growing.

NM are usually symmetric, uniform in color, have regular borders, and small diameters.[36,37] Given their lack of characteristic features, NM may go undetected, leading to devastating consequences as their greater thickness portends a poorer prognosis.[38] NM may also be amelanotic or hypomelanotic, further adding difficulty during diagnosis.

Also, in contrast to other subtypes, NM is more likely to arise in the absence of a pre-existing nevus.[39] Thus, patient education should emphasize the detection of new-onset lesions in addition to evolving ones. Diagnosis begins with a complete skin examination. Physicians may implement dermoscopy during diagnosis, as nodular melanoma lesions can show blue-white veil and atypical vessels.[40,41] Pigmented NM, in contrast to nodular non-melanoma lesions, can exhibit multiple brown dots, peripheral black dots/globules, irregular black dots/globules, homogeneous blue pigmentation, black color, and the presence of multiple colors.[41] Other dermoscopic features suggestive of NM include the presence of polarizing-specific white lines and gray or blue-colored structures.[42]

However, if a dermatologist finds a suspicious pigmented lesion, the patient should undergo an excisional biopsy. Once the diagnosis is confirmed histopathologically, other characteristics of the tumor can be assessed, such as the mitotic rate (#/mm^2), Breslow thickness, ulceration status, deep and peripheral marginal status, presence of desmoplasia, presence or absence of microsatellites, and Clark level if the mitotic rate cannot be determined in nonulcerated lesions ≤1.0 mm.[43]

Staging and Adjuvant Treatment

The American Joint Committee on Cancer (AJCC) melanoma staging system is used for staging NM.[44] The primary treatment for NM is surgical excision - the National Comprehensive Cancer Network (NCCN) Guidelines on melanoma outline their recommendations on excisional margins.[45] However, some patients will relapse and develop locally advanced or metastatic disease. Our improved understanding of genetic alterations and the immune system's role in melanoma pathogenesis has allowed for improved systemic, adjuvant therapeutic options that result in better survival outcomes.[46] Immune checkpoint inhibitors (Table 3), such as therapies that target cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) or programmed cell death protein 1 (PD-1), and targeted therapies (Table 4), such as BRAF-targeted and BRAF/MEK combination drugs, serve as therapeutic options for patients with advanced stage melanoma and have replaced interferon alfa (IFN alfa) as adjuvant therapy.

Clinical trials have shown that treatment with either targeted therapy or immunotherapy is efficacious as adjuvant therapy in patients with stage III-IV melanoma. The COMBI-AD phase III clinical trial compared adjuvant

Dabrafenib plus Trametinib to placebo. Patients with stage III melanoma with BRAF V600E or V600K mutations were administered Dabrafenib plus Trametinib (n = 438) or placebo (n = 432) for 12 months. 52% of patients treated with combination therapy were alive without relapse at 5-years (95% Confidence Interval [CI], 48-58), as compared to 36% of patients treated with placebo (95% CI, 32-41). 65% of patients treated with combination therapy were alive without distant metastases at 5-years (95% CI, 61-71) as compared to 54% of patients treated with placebo (95% CI, 49-60).[47] The European Organization for Research and Treatment of Cancer (EORTC) 1325/KEYNOTE-054 phase III, clinical trial compared Pembrolizumab (n = 514) to placebo (n = 505) in patients with resected high-risk stage III melanoma every 3 weeks for up to 18 doses, or until recurrence of disease or unacceptable toxicity. At 3.5 year follow-up, the Pembrolizumab cohort had a distant metastasis-free survival of 65.3% (95% CI, 60.9-69.5) as compared to 49.4% in the placebo group (95% CI, 44.8-53.8). Recurrence free survival was also greater in the Pembrolizumab group at 59.8% (95% CI, 55.3-64.1) as compared to placebo at 41.4% (95% CI, 37.0-45.8).[48]

One phase III clinical trial, CheckMate-239, randomly assigned over 900 patients who were undergoing resection of stage IIIB, IIIC, or IV melanoma to receive adjuvant nivolumab or ipilimumab for up to 1 year or until recurrence of the melanoma.[49] After 12 months of treatment, patients treated with nivolumab experienced longer recurrence-free survival and less frequent grade 3 or 4 adverse events than patients assigned to receive ipilimumab as adjuvant therapy. Based on this study, the FDA granted approval for the use of Nivolumab monotherapy as an adjuvant treatment option for patients with metastatic melanoma or melanoma involving the lymph nodes who have undergone complete resection. Patients are recommended to receive this immunotherapy agent once every two weeks for a maximum of one year.[50]

Although efficacious, systemic adjuvant treatment with targeted therapy or immunotherapy may produce undesirable side effects and may even result in resistance. Patients taking BRAF/MEK inhibitor combination therapy frequently report flu-like symptoms including pyrexia, chills, fatigue, headache, musculoskeletal aches, and gastrointestinal-related symptoms (e.g., nausea, vomiting, diarrhea). Although rare, BRAF/MEK inhibitors may also experience more severe side effects such as deep venous thrombosis and retinal pathologies. Immune checkpoint inhibitors frequently cause cutaneous toxicities (e.g., pruritis and rash), gastrointestinal adverse events (e.g., diarrhea and colitis), and fatigue. Although less common, high-grade toxicities of the endocrine system (e.g., adrenal insufficiency and hypo- or hyperthyroidism) or gastrointestinal system (e.g., pancreatitis, hepatitis) may also occur. Some of the potentially life-threatening, high-grade toxicities that have also been reported in patients taking immune checkpoint inhibitors include nephritis, pneumonitis, and myocarditis. Despite these side effects, immunotherapy is particularly effective against melanoma because this type of cancer is known to be more immunogenic than other types of cancer.[45]

As compared to SSM, earlier stages of NM have a worse overall survival and cancer-free survival. One study showed that compared to SSM tumors, NM tumors had an upregulation of over 200 genes involved in immune-related pathways.[51] This finding not only provides a basis for understanding the difference in survival between these two melanoma subtypes, but also suggests that an increased propensity to influence immune responses in the TME may explain why patients with NM have been shown to have a better response than patients with SSM to immunotherapy agents, such as anti-PD-1 drugs.[51]

In recent years, there has been an increase in research examining the melanoma TME to identify clinically significant biomarkers of treatment response. One study developed an algorithm to quantify immune cell infiltration (ICI) in melanomas and found that several ICI and gene clusters were associated with a better rate of response to immunotherapy and longer overall survival.[21] Another study found that NMs overexpress genes related to generating an immune response to tumor antigens, such as MHC-II molecules. An overexpression of MHC-II molecules is associated with better responses to anti-PD-1 agents.[51] Thus, there is evidence to suggest that the histologic subtype of melanoma may also determine how responsive a patient will be to immunotherapy.

Table 3. Immune Checkpoint Inhibitors and FDA-Approved Indications[45]

Drug	Treatment for Metastatic or Unresectable Disease	Adjuvant Therapy
Ipilimumab (anti-CTLA-4)	Unresectable or metastatic melanoma	Cutaneous melanoma with pathologic involvement of regional LN (> 1mm) who have undergone complete resection (including lymphadenectomy)
Nivolumab (anti-PD-1)		Melanoma with LN involvement or metastatic disease who have undergone complete resection
Pembrolizumab (anti-PD-1)		Melanoma with involvement of LN following complete resection
Nivolumab and Ipilimumab (anti-PD-1 and anti-CTLA-4)		No FDA approval in this setting

Table 4. Targeted Therapy and FDA-Approved Indications[45]

Drug	Treatment for Metastatic or Unresectable Disease	Adjuvant Therapy
BRAF Targeted Therapies		
Dabrafenib	Unresectable or metastatic melanoma with BRAF V600E or V600K mutations	No single agent FDA approval in this setting
Vemurafenib	Unresectable or metastatic melanoma with BRAF V600E or V600K mutations	No single agent FDA approval in this setting
BRAF and MEK Therapies		
Dabrafenib and Trametinib	Unresectable or metastatic melanoma with BRAF V600E or V600K mutations	Melanoma with BRAF V600E or V600K mutations and involvement of LN, following complete resection
Vemurafenib and Cobimetinib	Unresectable or metastatic melanoma with BRAF V600E mutation	No FDA approval in this setting
Encorafenib and Binimetinib	Unresectable or metastatic melanoma with BRAF V600E or V600K mutations	No FDA approval in this setting

Conclusion

Although the second-most common form of melanoma, NM provides clinicians with a distinct diagnostic challenge as they may mimic benign cutaneous lesions. Consequently, clinicians should be aware of their variable presentation and err on the side of caution during evaluation. Dermoscopy may be of assistance in diagnosis as certain features have been recently elucidated; however, excisional biopsy should be undertaken in any suspicious lesion as NM has a significantly worse prognosis when compared to other subtypes of melanoma. Excisional biopsy is used for definitive diagnosis, with AJCC and NCCN guidelines delineating staging criteria and definitive treatment options. Further research will delineate NM-specific survival outcomes with new adjuvant therapy regimens.

Conflict of Interest

The authors have no conflicts of interest to declare that are relevant to the content of this article. The authors have no relevant financial or non-financial interests to disclose.

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