International Journal of Scientific Advances
ISSN: 2708-7972
Volume: 5 | Issue: 6 | Nov – Dec 2024 Available Online: www.ijscia.com
DOI: 10.51542/ijscia.v5i6.72

Immunohistochemistry Assay for Malignant Melanoma

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ABSTRACT

Malignant melanoma has been a concern due to its high morbidity and mortality rate throughout the years due to the fast metastatic rate of the cancer cell itself. However, its diagnosis was found hard due to similar findings with other skin cancers in both morphological and clinical characteristics. Until now, skin biopsy evaluation with immunohistological staining still has been the gold standard for the definitive diagnosis of malignant melanoma. With immunohistochemistry examination, it was found to help identify malignant melanoma from other cutaneous tumors that have similar findings. Malignant melanoma itself has a complex pathogenesis that involves specific biomarkers that are shown in certain immunohistological staining. This review aims to provide a comprehensive overview of the immunohistochemistry examination in malignant melanoma diagnosis that includes specific antibodies such as; S100, HMB45, Melan-A, SOX-10, Ki-67, MITF, tyrosinase, gp100, Neuropilin-2, CD-99, p16, p53, PHH3, and MPM-2. S100, HMB-45, and gp100 were found most helpful in diagnosing malignant melanoma itself due to the specific capabilities it displays in detecting the cancer cell. Melan-A and MITF were found specifically in many amelanotic melanoma cases as their vital role in melanogenesis made their expression to be high in nonpigmented cases. Ki-67 and SOX-10 itself were found helpful due to being the marker of the proliferative index in the cancer cell. p16 and p53 were found helpful in differentiating melanoma from non-melanoma cancer as their properties were specific in many non-melanoma cases. Antibodies such as gp100, PHH3, and MPM-2 were found suitable for therapeutic options due to their specific characteristics. Other antibodies like tyrosinase, CD-99, and Neuropilin-2 while still helpful for the diagnosis of malignant melanoma, it is sadly found to be unspecific in differentiating melanoma from other cutaneous tumors that have similar findings.

Keywords: skin cancer; malignant melanoma; S100; HMB-45; Ki-67; gp100; Melan-A; SOX-10; PHH3; MPM2.

INTRODUCTION

Malignant melanoma itself is a primary cutaneous cancer that is derived from melanocyte cells [1]. Melanocytes are the cell that primarily works on the production of pigments in the skin that are called melanin in the epidermis (basal layer). As its origins are from the neural crest, melanocytes themselves have been expressed in many signalling pathways due to their molecules and functions as a migration and metastasis promotion factor after their matrix transforms into malignant cells [2]. Skin cancer, especially malignant melanoma has been quite the highlight with its fast metastatic rate and high mortality rate with a death rate of 80% [3]. As of 2024, Melanoma has been estimated to be around 100,640 new cases with 8,290 people expected to die of it [4]. While still being the third most common skin cancer, malignant melanoma remains the most aggressive with its metastatic properties. The malignant cells will spread widely throughout the organs starting from the regional lymph nodes [5].

Malignant melanoma cells could occur in many different areas of the body such as the uvula or vulva, however, cutaneous melanoma is known to be the cause of 90% of diagnoses [6]. As melanoma occurs in many sun-exposed areas of the body, there has been quite a significant difference in data reported from worldwide incidence with the higher incidence in fair-skinned races such as Europeans and Australians. This shows that people with fair skin tend to get melanoma due to its genes and activities related to UV radiation exposure compared to darker skin [7]. But this doesn't mean that tropical countries with intense UV radiation exposure are protected from melanoma, it needs to be known that many melanoma cases in Central Asia are still underreported due to similar findings with other cutaneous tumors with the patients coming in already late due to the malignancy that already spreads to its vital organs [8].

These similar findings were often not detected by the haematoxylin and eosin (H&E) stain, as of now the diagnosis of melanoma is still done with skin biopsy evaluation that is then stained with haematoxylin and eosin (H&E) to detect the morphological changes [9].

But with malignant melanoma cells, various morphological features can happen thus making a definite diagnosis to be challenging. However, with the rise of specific antibody markers in immunohistochemistry assay, diagnosis of malignant melanoma was found to be easier to differentiate similar lesions from other cutaneous tumors or unclear neoplasm differentiation [10]. The specific antibodies then target the pathomechanism of malignant melanoma cells itself. Most melanomas arise near the melanocytic nevus with the DNA mutation of the BRAF gene or the NRAS GTPase that is caused by UVA and UVB radiation [11].

S100

S100 is a protein encoded in calcium binding which works in many signaling pathways as it presents mainly in vertebrates [12]. It is a multiprotein family that is involved in the regulation of many cellular processes as it is expressed in a diverse range of tissues, with the family members including S100A1-S100A18, S100B, S100P, S100G, and S100Z [13]. The member S100B is expressed mainly in cutaneous melanoma, with its serum levels showing high secretion in many cases of the cancer itself and able to recognize the staging of melanoma patients. Especially in most malignant cases, with early detection of regional lymph node metastasis and even recognition of distant metastases [14]. The accuracy and sensitivity of the marker present 98% with high expression in many malignant melanoma cases from primary melanoma even though many newer markers have already emerged [15].

S100 is known to be able to differentiate malignant melanoma cells from similar lesions of other tumors and detect ambiguous tumors that have a differential diagnosis of melanoma due to its cytoplasmic expression [16]. It was found to be able to distinguish poorly differentiated amelanotic malignant melanoma from other common pigmented basal cell tumors [17]. The marker itself is able to differentiate pigmented nevi (blue nevi) from amelanotic melanomas due to low or absent levels of S100 found in blue nevi [18].

HMB-45

HMB-45 (Human Melanoma Black-45) is a specific monoclonal antibody that targets the protein gp100 in the fibrillar matrix of stage II pro-melanosome thus making its expression in both immature and activated melanocytes [19]. Due to its expression, HMB-45 is commonly used to evaluate the maturation in primary melanocytic lesions or benign nevi that is specifically located in the dermo-epidermal junction [20]. This characteristic also helps the marker in detecting malignant melanocytic cells from sentinel lymph node biopsies [21]. However, due to the low sensitivity, HMB-45 is not expressed in 10-15% of cases of malignant melanoma. Thus, making the marker commonly used with other markers such as S100 and Melan-A for melanocytic lesions diagnosis [22]. But with its high specificity, HMB-45 alone could be used to diagnose melanoma in the metastatic stage due to its deep staining of the dermal layer [23].

The marker itself is known to be able to differentiate melanoma with epithelioid origins from other cutaneous tumors, with positive staining of HMB-45 in melanoma [24]. HMB-45 is also helpful in diagnosing melanoma from obscure tumors due to its non-reactivity to most non-melanoma cancers [25]. The marker is found to be able to distinguish between melanoma in situ and extramammary Paget disease due to its positive reaction in melanoma [26]. HMB-45 itself was found to be able to differentiate spitz melanoma from intradermal or dermal nevi due to its deep staining in the dermis and dermo-epidermal junction [27].

MELAN-A

Melan-A (MART-1) is a protein located in the melanocytes that is activated due to immune reactions of cytotoxic T cells against melanoma antigen (MA), which is expressed by normal melanocytes because of tumor infiltration [28]. It is also associated with melanocyte-specific cytoplasmic protein that is involved in stage II melanosome formation, thus making its role in the expression and stability of melanosomes [29]. Due to its properties, Melan-A could be used to detect melanocytic lineage of melanoma making it useful in the diagnosis of metastatic melanoma [30]. With high accuracy and sensitivity of 90% in most malignant melanoma cases, the marker is suitable for diagnosing melanoma from melanocytic lesions [31]. It should be known that while it is specific for melanocytic lesions, the marker could also be positively expressed in keratinocytes and non-melanocytic lesions [32].

Melan-A as a marker is known to be able to distinguish melanoma from other tumors with melanocytic lesions and determine the staging of melanoma, especially in the malignant stage [33]. Due to its properties, Melan-A is commonly used for differentiating malignant melanoma from other tumors with resembling morphological findings [34]. It was found that Melan-A is expressed positively in amelanotic melanoma due to its expression in non-pigmented cells [35]. The marker itself was found if conjoined with S100 to be able to detect lymph node metastasis in melanoma with a high positivity rate [36].

SOX-10

The SOX-10 is a gene that is encoded in the formation of tissues during the embryonic phase and the maintenance of certain cells post-birth [37]. To be able to function, the SOX gene family binds itself to the HMG box in the DNA thus making it a transcription factor and being able to control the activity of specific genes [38]. While in the embryonic phase, SOX-10 is activated in neural crest cells and then migrates to specific regions in the embryo, making the gene able to produce many different types of cells such as melanocytes [39]. Mutation in the SOX-10 gene itself could cause pigment abnormalities making its expression detected in most cases of malignant melanoma [40].

These unique properties make SOX-10 able to detect the staging of malignant cells and distinguish immature cells from mature cells, especially in specialized cases such as melanoma [41]. With the accuracy and sensitivity of the marker reaching 100% SOX-10 is one of the leading tools in diagnosing malignant melanoma cases whether it's primary or metastasis cases [42].

SOX-10 is commonly used to differentiate melanoma from other types of obscure cutaneous tumors and other close mimickers as its deep and widespread staining indicates malignancy or aggressive diseases [43]. Higher expression is found to be associated with higher stages of the disease and regional lymph node involvement or even distant metastases [44]. The gene was found to be able to detect desmoplastic melanoma and spindle cell melanomas with its deep and distinct nuclear stain that is positively expressed [45]. SOX-10 was also found to distinguish malignant melanoma that metastasized in lymph nodes from benign nevi and normal dermis based on the positive staining in the cells [46].

Ki-67

Ki-67 also known as MIB-1 is a DNA-binding protein that is mainly expressed in vertebrates and found in the nucleus of the cells that are undergoing division. As its expression is found during all the cell cycle phases, except for the resting phase G0-1 [47]. The Ki-67 test measures the cells that undergo proliferation, with its high proliferation index over 30% means that many cells are dividing rapidly and most likely to be a cancer cell or already a malignancy and it is spreading. These tests function as a diagnostic and prognostic tool for cancer itself, and maybe in the future could serve as a targeted immunotherapy for cancer patients [48]. Due to its characteristics, Ki-67 is used to help distinguish malignant tumors from benign tumors and as a grading tool for various tumors [49]. And with the prognostic of poor survival rate due to increased Ki-67 proliferation index makes the marker a multifunction tool for most malignant cases [50].

The marker is known to be able to distinguish malignant melanoma from other benign cutaneous tumors and detect its staging making Ki-67 the perfect prognostic tool for malignant melanoma and prediction tool for recurrence risk [51]. The melanoma cells slowed their proliferation when entering the dermal layer and then increased it again with the activity of the tumorigenic vertical growth phase making its expression higher in the epidermal layer of the skin and also higher than the radial growth phase [52]. The marker itself is found to be able to distinguish malignant melanoma from benign nevi due to its high percentage of staining in the cell nuclei [53]. Ki-67 is also found to be expressed highly in minimal deviation melanoma compared to other nevomelanocytic tumors [54].

MITF

MITF (Microphthalmia-associated Transcription Factor) is a gene that provides instructions for the formation of a protein called melanocyte-inducing transcription factor. Making its role as the control of development, survival, and functionality of certain cells. Melanocyte-inducing transcription factor itself aids the control of the development and function of melanocytes, making the protein a vital role in melanocyte production [55]. If a mutation occurs in the protein due to multifactorial causes, it will cause certain major changes such as pigment abnormalities [56]. This makes MITF able to detect melanocytic lineage in malignant melanoma and functions as a plasticity tool due to its ability to present different melanoma phenotypes [57].

The gene itself is also recognized as one of the main driving forces of the progression of melanoma due to its properties [58]. However, there has also been evidence that MITF has a role in suppressing the invasion of melanoma cells and metastasis, making the marker useful for targeted immunotherapy in the future [59]. The marker is known to be able to differentiate melanoma from other benign tumors due to its dual role in both benign and malignant melanocytic cells [60]. MITF itself is also used for grading melanoma due to its high and low levels according to the tumor development stages [61]. It was also found that MITF loss is associated with a poor survival rate making the gene a prognosis tool [62].

TYROSINASE

The TYR gene is a gene that provides instructions on enzyme production called tyrosinase. This enzyme has a role in melanin (pigment) production as it is located in melanocytes. Tyrosinase transforms an amino acid called tyrosine into another combination called dopaquinone. It is then morphed into the melanin by a series of chemical reactions making it responsible for melanin production [63]. Mutations in the TYR gene would eliminate the activity of tyrosinase, making melanin production stop altogether, these would cause a lack of pigmentation making melanocytes proliferate rapidly causing melanoma [64]. Due to its mutation, tyrosinase plays an important role in the development and progression of melanoma. Making the enzyme able to be expressed highly in metastatic melanoma, as its expression could be detected in peripheral circulation and regional lymph nodes [65].

Due to its unique characteristics, tyrosinase would increase during tumorigenesis, making their staining more common and homologous [66]. It is common knowledge that tyrosinase as an enzyme is a specific marker for melanoma due to its ability as a detection, grading, and prognostic tool for melanoma. The enzyme was found to be able to detect metastatic melanoma and desmoplastic melanoma making it a reliable tool due to its high sensitivity [67]. Tyrosinase was also found to be able to function as a therapeutic option as its activity could be targeted from gene transcription or signaling pathways and there were also natural tyrosinase enzyme inhibitors that could be obtained from some medicinal plants and molecules [68].

gp100

gp100 also called glycoprotein 100 is a specific antigen that serves as a differentiation marker. The protein is expressed in cells that differentiate and cells that undergo malignant transformation [69]. It is also a structural component of the stage I and II melanosome matrix making the protein a vital role in melanogenesis [70]. Due to its unique properties, gp100 could be used for the detection and grading of melanoma as it was found to be expressed highly in tumors of melanocytic differentiation such as melanoma [71].

gp100 was also found to be able to function as a therapeutic option such as targeted immunotherapy, antibodies, and vaccines. As of now, there is even a commercially available cancer vaccine that is developed from fragments of gp100 [72]. While antibodies, it was found to play a role in the diagnosis of metastatic melanoma or tumors of melanocyte lineage. As an immunotherapy, gp100 was found to be able to function as a useful target due to its acceptable cytotoxicity towards normal tissue [73].

The protein is known to detect metastatic melanoma in regional lymph nodes, making it the perfect tool for the diagnosis and prognosis of malignant melanoma [74]. gp100 was found to be able to distinguish advanced melanoma due to its high expression and progression rate [75]. The protein itself was also found to be able to differentiate melanoma from non-melanoma skin cancer due to its deep and positive staining [76]. There has also been a study that found gp100 as targeted immunotherapy for chemoresistant patients as its unique properties made the protein the perfect target [77].

PHH3 and MPM2

PHH3 is a protein located in the core of histone, which is a part of chromatin. The protein is present during the active phase of the cell cycle making its role in the condensation and decondensation of the chromatin. Due to this, the protein is important for gene expression and cell division [78]. As a marker, PHH3 could indicate whether the cells are undergoing mitotic division or not and the proliferation probability of those cells. Making it the perfect immunohistochemistry marker to determine the mitotic index (MI) and tumor grading, especially in melanoma [79]. The immunohistological staining showed positively stained figures in the malignant cells and confirmation of morphological changes of chromatin condensation [80].

PHH3 as a marker could detect malignant melanoma and its metastasis even at the micrometastase level of regional lymph nodes due to its MI determination [81]. The marker could also be used to determine the staging of melanoma and as a prognostic tool due to its unique properties, as most cases of poor survival rate are associated with high expression of PHH3 [82]. It was also found in research that showed the positive staining of PHH3 in malignant melanoma making the marker able to differentiate melanoma from benign nevi [83].

Due to its ability to count the MI, the marker was proven to be a more reliable marker than most as it is associated with a higher grade of nodular melanoma [84].

MPM2 is a phospho-epitope called mitotic protein monoclonal 2 that is formed during mitotic entry, due to this the phospho-epitope is believed to be able to control the mitotic process [85]. MPM2 as a marker could detect the mitotic index (MI) of the cell making it the perfect tool for diagnosis and grading of malignant tumors such as melanoma. Due to its MI detection, the marker could also be used as a prognostic tool for most malignant melanoma patients as it could predict how widespread the metastasis of the melanoma cells [86]. Not only that, MPM2 could also determine the proliferation index of melanoma cells making it a reliable marker due to its specificity and sensitivity [87].

The marker with its unique characteristics could be used in many ways for malignant melanoma, as it could be used for the definitive diagnosis of melanoma and its staging. MPM2 could also be an epidemiology tool for assessing the genetic etiology of malignant melanoma [88]. MPM2 was found to be able to distinguish multiple melanomas from normal melanoma from its clinicopathological characteristics [89]. It was also found in another research that MPM2 could determine that many of the variants of superficial spreading melanoma are composed of large melanocytic nests [90].

NEUROPILIN-2

Neuropilin-2 is a protein that plays the role of a receptor in many physiological processes such as angiogenesis, neuronal guidance, and immune responses [91]. Although neuropilin-2 as a receptor is mainly used for neuronal guidance due to its role in axonal development. The protein was also found in the endothelial cells due to its function in angiogenesis and immune responses [92]. In angiogenesis, neuropilin-2 works as a coreceptor for vascular endothelial growth factor (VEGF-2). Its expression is related to tumor growth and vascularization, making the protein useful in detecting malignant cells in circulation [93]. In immune response, the protein promotes inflammatory response as it suppresses the proinflammatory mediators making the protein useful in detecting the tumor progression [94].

Thus, neuropilin-2 is a reliable tool for prognosis value as it can detect malignant tumors such as melanoma cells in the circulation and lymph nodes. The protein also serves as both a detection and grading tool due to its ability to detect malignant cell progression [95]. It was found that neuropilin-2 promotes extravasation and metastasis of melanoma cells due to its high expression in metastatic melanoma compared to primary melanoma, with the protein capable of distinguishing most melanoma cases from nevi [96]. Neuropilin-2 was also found to inhibit drug resistance and progression of melanoma due to its depletion [97].

The protein was found to be able to differentiate spitzoid melanoma from spitz nevi shown by the positive staining in the spitzoid melanoma [98].

CD-99

CD-99 works as a transmembrane protein that functions in signal transduction and adhesion, making the protein able to be expressed in a variety of cells whether it is a normal or tumor cell [99]. Although the protein has been sought after as the diagnostic marker for Ewing's Sarcoma (EWS) due to its high expression in most cases of EWS tumors [100], this doesn't limit CD- 99 capability as a diagnostic tool for other malignant tumors as the protein itself is mostly involved in the diapedesis of lymphocytes and other immune cells, mainly inflamed endothelium making the protein useful in detecting the migration, invasion, and metastasis of tumor cells including melanoma [101]. CD-99 is also found to be able to function as a targeted immunotherapy due to its invasive properties and immunoreactivity [102].

There have been some cases that reported CD-99 expression in malignant melanoma due to its angiogenesis function making the protein useful in detecting invasive malignant melanoma [103]. CD-99 is also capable as a prognostic tool for malignant melanoma due to its ability to detect metastases in regional lymph nodes with higher expression associated with poor survival rate of the patients [104]. But it should be known that CD-99 has a limited utility in diagnosis due to its usual function to rule out EWS from other malignant tumors [105].

p16 AND p53

p16 also known as CDKN2A is a protein that acts as a tumor suppressor due to its ability to inhibit cyclin-dependent kinase (CDK) making the cell cycle (G1-S phase) decelerate as it is associated with Rb phosphorylation [106]. Making the protein useful in detecting a variety of tumor cells including melanoma as its low count or loss means that it is probably a tumor cell [107]. The p16 gene is encoded in chromosome 9p21, which is associated with familial melanoma, making it a reliable tool for the diagnosis of malignant melanoma itself. The protein itself typically functions to distinguish melanoma from benign melanocytic nevi due to its decreased or absent count in melanoma cells [108].

Loss of p16 expression is also associated with poor prognosis in vertical growth phase melanoma due to its loss of expression in metastatic lesions [109]. The protein was also found to be able to distinguish metastatic nodal melanoma from nodal nevi from its presence in lesional tissues [110]. p16 was also found to be an important tool in assessing prognosis for malignant cutaneous melanoma patients as weak or absent expression of the protein is associated with aggressiveness or metastasis of the melanoma [111].

p53 is a tumor suppressor protein that plays a role in the regulation of cell growth, DNA repair, and cell apoptosis. The protein is activated if the cell is stressed, p53 then will hold the stressed cell in a checkpoint until it is repaired back to normal [112]. If the damage is irreversible, the protein will then trigger apoptosis making the cell dead or necrosis. But if a mutation happens in p53, the damaged cell's protein then would have a longer half-life which then accumulates in the cell itself. This accumulation could be detected in an immunohistochemistry assay with positive staining associated with malignant tumors including melanoma [113].

p53 would be often inactivated in melanoma cells, these would cause increased aggressiveness and resistance to therapy making the protein useful as a diagnosis and prognosis value for most malignant melanoma cases [114]. As it is associated with increased aggressiveness, loss of p53 could also indicate metastasis in the regional lymph nodes of melanoma patients [115]. The protein was also found to be able to distinguish melanoma from benign nevi due to its positive expression that indicates a mutation in the p53 gene [116]. In another research, p53 was stated to be able to function as targeted immunotherapy due to its ability to trigger cell death and suppress tumor cells [117].

CONCLUSION

Immunohistochemistry assay of malignant melanoma offers diagnostic significance due to its capability to detect malignant melanoma from benign nevi and its staging. The examination also plays an important role in prognosis as some specific antibodies could predict its proliferation index and mitotic rate.

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