Nodular Melanoma in a 53-year-old Male with Glioblastoma Multiforme: A Rare Case Report

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ABSTRACT

Although melanoma only accounts for 1% of skin cancers, it is responsible for most skin cancer deaths. Glioblastoma multiforme, a high-grade astrocytoma, is the most aggressive and devastating primary brain tumor. These two diseases remain to be the biggest therapeutic challenge in both specialties of dermatology and neuro-oncology.

A 53-year-old Filipino male who presented with a 2-year history of generalized dark brown and black patches on the body developed weakness and numbness of the left extremities. Biopsy and immunohistochemical staining of the skin revealed nodular melanoma with adjacent regressing melanoma. Biopsy of the intracranial mass showed glioblastoma multiforme. One month after the partial excision of the intracranial mass, the patient expired due to brain herniation.

Nodular melanoma and glioblastoma multiforme may occur concomitantly in a patient. A review of the literature suggests a shared genetic predisposition. Its existence carries a poor prognosis and requires early detection to start aggressive treatment.

Keywords: melanoma, nodular melanoma, glioma, glioblastoma multiforme, melanoma-astrocytoma syndrome, association, case report

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INTRODUCTION

Although melanoma only accounts for 1% of skin cancers, it is responsible for most skin-cancer deaths.[1] Glioblastoma multiforme, a high-grade astrocytoma, is the most aggressive and devastating primary brain tumor.[2,3]

The coincidence of these two diseases has been reviewed in literature, but reports were limited. Kaufman et al. first proposed a genetic association between melanoma and cerebral astrocytoma after discovering these diseases in eight family members over three generations.[4] A study by Scarbrough et al. explored possible risk factors and hypothesized a shared genetic predisposition that may be responsible for the detected association.[3] A genetic disorder known as Melanoma-Astrocytoma syndrome has been listed as a rare disease by the Office of Rare Disease of the National Institutes of Health.[5] However, less than 20 cases have been reported to date. Thus, the occurrence of melanoma and astrocytoma, such as glioblastoma multiforme, has yet to be elucidated.

CASE PRESENTATION

A 53-year-old Filipino male presenting with generalized dark brown to black patches on his body was referred to the Dermatology Service. Since childhood, he was known to have several melanocytic nevi and lentigines over the face and

trunk. Two years prior to consult, he noted a gradual increase in the size of the lesions on the body, with one of the lesions on the left upper back evolving into an asymmetric nodule with a history of bleeding when scratched. Excision was done on the nodule, but it only recurred after a few months. One year after, he developed left-sided weakness, vomiting, headache, and numbness of the left leg. A brain CT scan revealed an intracranial mass on the right parietotemporal area measuring 1.5 cm with calcifications on both basal ganglia. Past medical history revealed that the patient was diagnosed with a pulmonary mass, probably malignant, one month prior to this admission. No known family history of cancer. But the youngest sibling also had multiple nevi and lentigines over the body. There was no history of sunburns, but the patient admits to having a history of heavy sun exposure due to his occupation as a tricycle driver.

On admission, he was alert and coherent. Motor examination revealed weakness of the left upper and lower extremities by 50%. Other physical examination findings were unremarkable. Examination of the skin revealed multiple, well-defined, dark brown and black macules, papules, patches, annular plaques, and nodules with irregular, asymmetric borders and variegated colors scattered over the face, trunk, and bilateral upper and lower extremities (Figure 1). A solitary, well-defined, friable, round, black nodule on a pale to pinkish background with scar-like depigmentation measuring 2x2 centimeters was also evident on the left upper back (Figure 2).

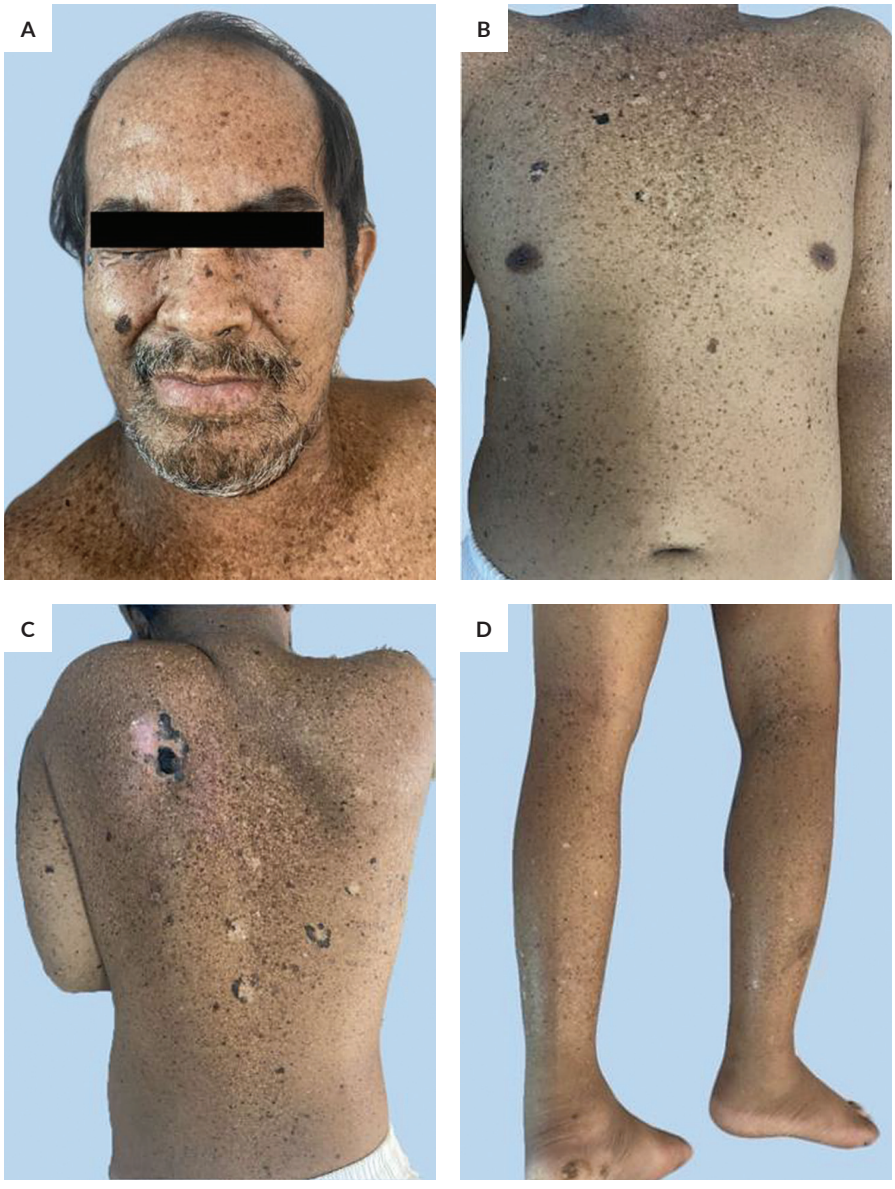

Figure 1. A 53-year-old male presenting with dark brown and black patches and nodules on the face, body, and extremities.

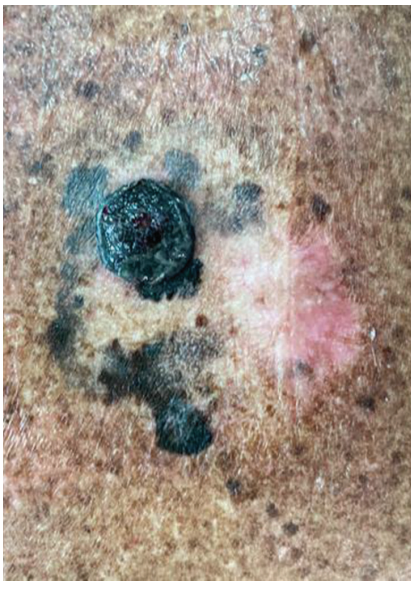

Figure 2. Nodule on the left upper back.

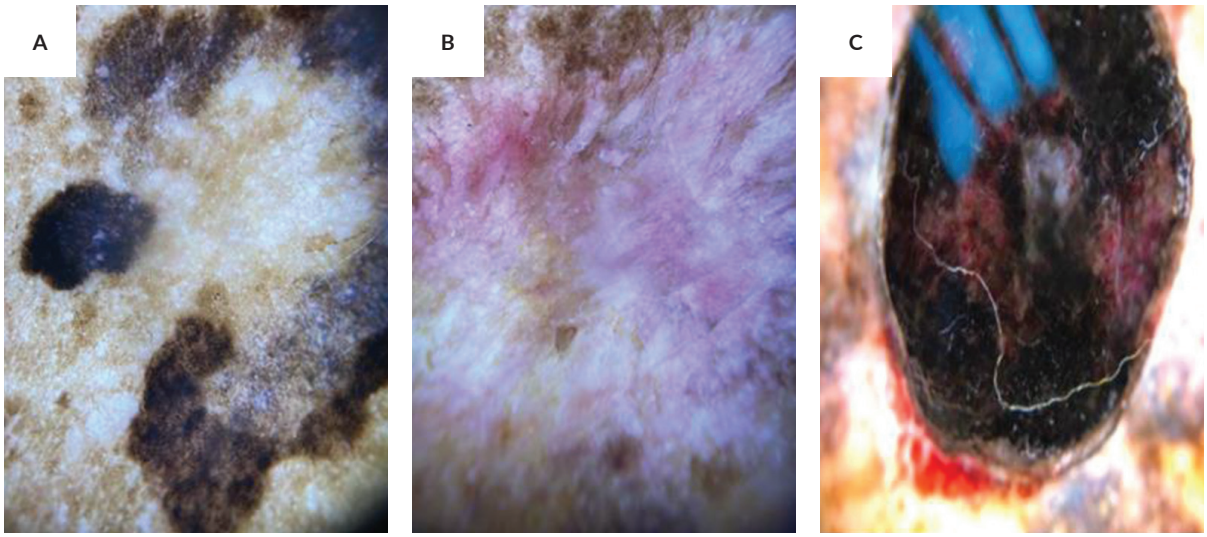

Figure 3. Dermoscopy of the left upper back reveals **(A)** asymmetry, atypical pigment network, variegated colors, and off-centered blotch, **(B)** a scar-like depigmentation and chrysalis, and **(C)** atypical vascular structures with dotted vessels and milky-red areas.

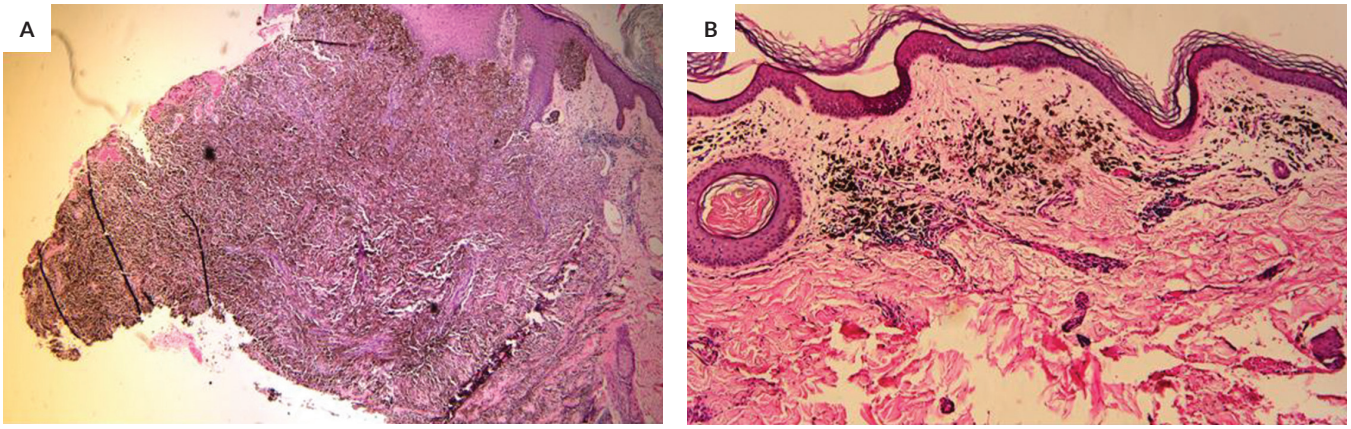

Figure 4. Hematoxylin and eosin (H&E) staining of the nodule on the left upper back shows **(A)** Nodular melanoma with nodular collection of pigmented atypical pleomorphic cells occupying the papillary and reticular dermis. An epidermal acanthosis with nests of atypical melanocytes in the dermo-epidermal junction is observed. **(B)** Regressing melanoma with dermal melanocytic collection of epithelioid and pigmented cells, melanophages, and mild inflammatory infiltrates of lymphocytes in the dermis.

Dermoscopy of the lesions on the trunk and extremities revealed typical pigment network, with black dots and globules. However, dermoscopy of the nodule on the left upper back showed asymmetry, atypical pigment network and variegated colors, atypical and off-centered blotch with regression structures, and atypical vascular structures (Figure 3). Patient was then diagnosed with nodular melanoma with multiple nevi and lentigines.

A wedge incision biopsy was performed on the nodule on the upper back, which revealed a primary nodular melanoma adjacent to a regressing melanoma. It has a Breslow thickness of at least 2 millimeters, a mitotic rate of 3 per mm^2, Clark level IV, and presence of tumor regression. Microsatellites, lymphovascular invasion, and tumor-infiltrating lymphocytes were absent (Figure 4). Thus, the pathologic staging is T3bN0M0, with a clinical staging of Stage IIB.

Immunohistochemically, Melan-A/MART1, a melanocytic marker, was strongly positive for collection of pigmentary cells in the dermis (Figure 5A), as well as the spindled and epithelioid granular cells adjacent to it (Figure 5B). HMB45, a marker for melanocytic maturation, was also requested and was strongly positive for the entire mass of pigmentary cells within the dermis including nests in the deep dermis (Figure 5C). It was also intensely positive in the spindled and epithelioid cells at this far end of the specimen (Figure 5D). Finally, Ki-67, a cell proliferation marker, was also positive

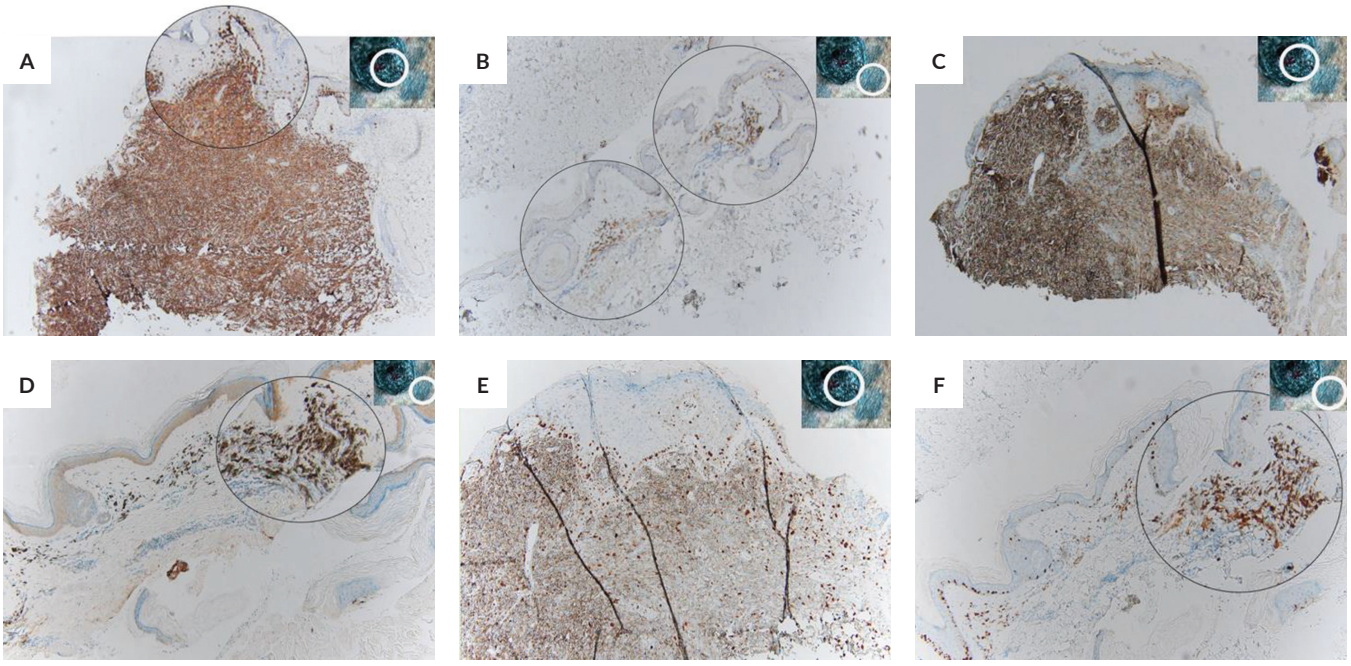

Figure 5. (A) and **(B)** indicate immunohistochemical staining for Melan-A/MART 1. **(C)** and **(D)** show immunohistochemical staining for HMB45. **(E)** and **(F)** indicate immunohistochemical staining for Ki-67.

for multiple cells in the nodular dermal collection (Figure 5E) and the spindled granular and epithelioid cells in the far end of the specimen (Figure 5F).

During his admission, he underwent right parieto-occipital craniotomy and partial excision of the intracranial mass. Biopsy of the mass revealed poorly differentiated pleomorphic cells with atypia, suggestive of glioblastoma multiforme. He was immediately referred to Oncology Department for possible radiotherapy and chemotherapy for the glioblastoma multiforme and nodular melanoma. Unfortunately, patient was not optimized for treatment and continued to deteriorate. One month after the operation, patient expired due to brain herniation.

DISCUSSION

Melanoma has one of the fastest rising incidence rates of skin cancer.[1,6] Among the different subtypes of melanoma, nodular melanoma is the second most common after superficial spreading melanoma.[7] It usually presents with greater thickness than the other subtypes. Even at its early stages, it has the potential to metastasize to vital organs such as the subcutaneous lymph nodes (59%), lung (36%), brain (20%), liver (20%), bone (17%), and others (12%).[6] Hence, this subtype often carries a poorer prognosis.

Our patient has several risk factors for melanoma. Aside from a history of heavy sun exposure, our patient presented with several typical and atypical nevi all over the body. Studies have shown an increased risk of melanoma associated with nevi.[3] Adults with more than 100 clinically typical-appearing nevi and patients with atypical nevi are at risk for melanoma.[7] However, nevi more often serve as a genetic marker of increased risk rather than a premalignant lesion, as most melanomas arise de novo.[3]

The tumor thickness or Breslow index, level of invasion, presence of ulceration, and number of lymph nodes involved are the most powerful prognostic indicator of nodular melanoma.[7] Our patient presented with a 2-year history of an evolving asymmetric nodule with an irregular border, variegated colors, a diameter of 2x2 centimeters, and recurrence after excision, all characteristics of cutaneous melanoma. On histopathology, a Breslow index of at least 2 mm, mitotic rate of 3 per mm^2 and the presence of ulceration indicate a decreased survival in this patient. Although no biopsy was done, the pulmonary mass of the patient could represent a metastatic lesion of melanoma due to its capacity to metastasize in vital organs. Therefore, a metastatic melanoma on the brain was initially considered on admission. The patient was initially advised surgical excision of the mass with adjuvant radiotherapy and chemotherapy since he was initially diagnosed with stage IV melanoma.

Surprisingly, the biopsy of the intracranial mass revealed a malignant brain tumor, Glioblastoma multiforme, a Grade IV astrocytoma.[2] The prognosis of this disease remains very poor despite optimal therapy, including surgical resection, radiation therapy, and chemotherapy. Despite the emergence of several targeted therapies and novel therapeutic strategies, this condition remains a therapeutic challenge with most patients dying within one year after diagnosis.[8]

Several studies tried to explain the association between melanoma and gliomas in general. A study reported that the incidence rate of gliomas was greater among melanoma cases

than in the general population.[3] Scarbrough et al. reviewed no common environmental risk factors for glioma and melanoma. It is theorized that a common genetic predisposition is the most probable explanation for their association. This genetic basis was explained by common molecular and cell signaling pathway mutations such as p53 and epithelial growth factor receptors.[2,9] A rare condition known as melanoma-astrocytoma syndrome caused by the inactivation of the germline alteration of the CDKN2A tumor suppressor gene on chromosome 9p21 has been proposed.[10] The prevalence and incidence rates of this syndrome are still unknown. Fewer than 20 cases have been reported to date. The diagnosis of this syndrome requires the presence of cutaneous melanoma in histology, the presence of a nervous system tumor (nerve sheath tumor, neurofibroma, medulloblastoma, glioblastoma multiforme, ependymoma, glioma, and meningioma) and a documented mutation in the CDKN2A gene.[5] The patient was diagnosed with cutaneous melanoma and glioblastoma multiforme. However, the syndrome cannot be established due to the patient's demise and unavailability of genetic testing for the CDKN2A gene in the country.

Like any other skin carcinoma, early diagnosis is the key to increasing survival rates. In addition, a family history of melanoma and numerous nevi should prompt the patient's family members, especially his youngest sibling to undergo melanoma screening.

CONCLUSION

This case report presents a rare occurrence of both nodular melanoma and glioblastoma multiforme in a 53-year-old Filipino male. Given the aggressive nature of these diseases, the prognosis in a patient with both conditions remains poor. Their association is also likely not due to a coincidence. Thus, more reported cases with genetic and molecular studies are needed to explore their association. This case also emphasizes that prompt diagnosis is paramount for physicians to start an aggressive treatment for these threatening conditions.

Informed Consent

Verbal informed consent was obtained from the patient. Verbal and written informed consent were obtained from the patient's wife.

Statement of Authorship

All authors contributed in the conceptualization of work, acquisition and analysis of data, drafting and revising of manuscript, and final approval of the version to be published.

Author Disclosure

All authors declared no conflicts of interest.

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