Case Report

Amelanotic melanoma: A challenging cytological diagnosis- A case series

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ABSTRACT

Melanoma is an aggressive malignancy, and early diagnosis and treatment can reduce mortality in patients. A new or changing lesion is the most common warning sign of melanoma. In amelanotic tumors, diagnosis may be delayed. Amelanotic melanoma is a form of melanoma in which malignant cells have little or no pigment. Amelanotic melanoma is classically described as skin coloured but a subset of these tumors are red, pink or erythematous. Typical early lesions present as asymmetrical macular lesions. FNAC may show varied cytomorphology ranging from epithelioid to spindled to plasmacytoid pleomorphic cells with marked anisonucleosis and eosinophilic to basophilic cytoplasm with intranuclear pseudoinclusions and cytoplasmic vacoulation admixed with bi- and multinucleate giant cells. We present a case series of varied presentation of amelanotic melanoma with its cytomorphological features.

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1. Introduction

Amelanotic melanoma is frequently underdiagnosed as it resembles clinically many non-melanocytic neoplasms or inflammatory lesions, which may lead to delay in diagnosis and treatment. Many previous studies have shown a poor prognosis as the diagnosis is delayed. Amelanotic melanomas comprise 2–8% of melanomas.¹ This group of tumors produces little or no pigment.

In a study conducted by Cheung et al, majority of the patients were males and age range of males and females ranged from 37–94 years and 38–97 years respectively. The majority of amelanotic melanomas are found on the trunk, head and neck and lower limb of males while in females, lesions are commonly found on the lower limb, upper limb and head and neck region.²

The clinical diagnosis of Amelanotic melanoma is challenging as features such as asymmetry, irregular borders and colour variegation which are frequently seen in melanomas are rarely present in Amelanotic melanomas. It may result in delay in the diagnosis as clinical differentials of the condition ranges from inflammatory to malignant lesions.³

2. Case Summary

2.1. Case 1

A 69-year-old female presented to the dermatology clinic with a nodular swelling in the anterior chest wall for the last 5 months. The swelling was firm, non-tender, skin coloured and partially mobile of size 6x4 cms. FNAC revealed malignant cells with highly varied morphology ranging from epithelioid to spindled pleomorphic cells with marked anisonucleosis, increased nucleocytoplasmic ratio with coarse chromatin and eosinophilic cytoplasm (Figure 1). Histopathological biopsy and immunohistochemistry showed sheets, nests and in lobules of atypical cells which were polygonal having moderate pleomorphism with abundant eosinophilic cytoplasm and frequent mitosis along with HMB-45 positivity, consistent with features of amelanotic melanoma.

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2.2. **Case 2**

A 58-year-old male presented to the surgical clinics with slightly raised erythematous plaque with asymmetrical borders on left forearm of size 2.3x1.0 cms for the past 3 months. There was no history of previous pruritis or pain. FNAC revealed discohesive, pleomorphic, polygonal to plasmacytoid cells with multinucleate giant cells with coarse nuclear chromatin and basophilic cytoplasm with vacuolations. No intracytoplasmic pigment deposition was seen. Histopathological biopsy showed sheets, cords and singly scattered markedly pleomorphic, polygonal cells with eccentrically placed nuclei with conspicuous nucleoli along with eosinophilic cytoplasm. Focal intranuclear inclusions and frequent mitosis was also seen (Figure 2). Immunohistochemistry showed strong cytoplasmic positivity for S-100 (Figure 3) and HMB-45 (Figure 4), which confirmed the diagnosis of amelanotic melanoma.

2.3. **Case 3**

A 60-year-old male presented to the surgical clinics with a non-pigmented lesion on the right cheek for the past 4 months. The lesion was firm, elevated, pinkish to red in colour with irregular margins. FNAC revealed large plasmacytoid cells having prominent nucleoli and intranuclear pseudonclusions and abundant eosinophilic cytoplasm. Binucleated and multinucleated giant cells were also seen. Wide excision biopsy was performed which showed sheets and nests of atypical cells which were polygonal having moderate pleomorphism with abundant amount of eosinophilic cytoplasm and frequent mitosis. Immunohistochemical expression of HMB-45 showed strong cytoplasmic positivity. A final impression of amelanotic melanoma was given. Our patient is doing well after 12 months of surgical follow up.

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**Fig. 1:** FNAC revealed malignant cells with highly varied morphology ranging from plasmacytoid to spindled pleomorphic cells with marked anisonucleosis, increased nucleocytoplasmic ratio with coarse chromatin and eosinophilic cytoplasm. Papanicolaou stain x 40X.

**Fig. 2:** Histopathological biopsy showed sheets, cords and singly scattered markedly pleomorphic, polygonal cells with eccentrically placed nuclei with conspicuous nucleoli along with eosinophilic cytoplasm. Focal intranuclear inclusions and frequent mitosis was also seen. Haematoxylin and Eosin x40X.

**Fig. 3:** Immunohistochemistry showed strong cytoplasmic positivity for S-100. IHC S-100 x40X.

**Fig. 4:** Immunohistochemistry showed strong cytoplasmic positivity for HMB-45. IHC HMB-45 x40X.
3. Discussion

Amelanotic melanoma is often difficult to diagnose clinically because of lack of pigmentation and can mimic other inflammatory lesions and malignant tumors. Clinically, it may mimic superficial basal cell carcinoma, keratoacanthoma, Merkel cell carcinoma, hemangioma, pyogenic granuloma, actinic keratosis, Bowen’s disease and also dermatitis. Dermoscopy may help in the diagnosis of hypopigmented melanoma but not as much in true amelanotic melanoma. In our study we observed pinkish to red colour lesions with a single case having nodularity. Jaime et al and McClain et al have also encountered pink, asymmetric lesions with ill defined borders and elevated margins in their study.

Amelanotic melanoma is commonly used as a clinical description for any melanoma lacking pigment. However, it is seen that there are melanomas that do not produce any discernable eumelanin (i.e. pure Amelanotic melanomas) while there are also melanomas that produce low levels of eumelanin (i.e. hypomelanotic melanomas). But clinically these lesions may appear to have no pigment. Dermoscopy reveals no pigment in pure amelanotic melanoma while hypomelanotic melanomas reveal subtle pigment, which is seen only focally. Hence, pure amelanotic melanomas do not have melanin pigment (i.e. brown, black or blue) clinically as well as on dermoscopic examination.

Melanomas have four subtypes, i.e. superficial spreading, nodular, acro lentiginous and lentigo maligna. All these subtypes can present as an amelanotic variant. Among these histological variants; desmoplastic melanoma is the most common variant seen in amelanotic melanoma, followed by nodular melanoma and acro lentiginous melanoma. A small proportion of cases of lentigo maligna melanoma and superficial spreading melanoma are amelanotic. Amelanotic melanomas consists of greater proportions of these histological subtypes as compared to pure melanomas. Traditionally, amelanotic melanoma have been described as erythematous, asymmetric macules with border irregularity and with a light brown or grey colour at the periphery.

Amelanotic melanoma may show variable cytological morphology. The cells may show epithelioid to spindle shaped cells. Bizzare forms may also be seen. The cytoplasm may be eosinophilic to basophilic or clear with vacuolations. Intranuclear inclusions, prominent nucleoli along with mitosis, foamy histiocytes and stromal fragments are also seen. In our study we observed highly cellular smears having plasmacytoid, pleomorphic, discohesive cells with increased N:C ratio with prominent nucleoli, nuclear pseudo inclusions with cytoplasmic vacuoles and bi- and multinucleated forms with eosinophilic cytoplasm.

Histopathological findings of our study correlated well with the other studies. Microscopic examination showed sheets, cords and singly scattered markedly pleomorphic, polygonal with eccentrically placed nuclei with conspicuous nucleoli along with eosinophilic cytoplasm. Focal intranuclear inclusions and frequent mitosis was also seen. Melanin pigment was absent in the tumor cells. Immunohistochemistry showed strong cytoplasmic positivity for S-100 and HMB-45, which confirmed the diagnosis of amelanotic melanoma.

Histopathological study by Garg et al have shown that the tumor cells were markedly pleomorphic, round to polygonal or spindle-shaped having eccentric nuclei and prominent nucleoli along with moderate amount of cytoplasm. Focal intranuclear inclusions, eosinophilic macro nucleoli, nuclear grooving, intracellular/extracellular hyaline globules and few multinucleated giant cells were also seen. Numerous atypical and bizarre mitotic figures were frequent along with lymphocytic infiltrate and necrosis. On immunohistochemistry tumor cells were strongly positive for HMB45, vimentin and S-100.

In another study by Khairwa et al, microscopic findings showed an infiltrating tumour in the surrounding tissue, arranged in sheets, nests and lobules with atypical cells showing moderate pleomorphism with abundant eosinophilic cytoplasm and frequent mitosis. On immunohistochemistry, the tumour cells showed positivity for HMB45 and S-100. Boggie et al have stated that the vaginal lesions were composed of sheets of discohesive epithelioid cells with prominent red nucleoli. The malignant cells were strongly positive for HMB-45, S-100 and Melan A.

Histology along with immunohistochemistry remains the gold standard for diagnosing amelanotic melanoma. Microscopy showing cords and nests of atypical pigmented melanocytes in the dermis usually leads to the diagnosis of melanoma. But histopathologic and cytological features may be varied in amelanotic melanoma and immunohistochemistry is the mainstay in the diagnosis of amelanotic melanoma. S100, MelanA, HMB-45, tyrosinase, MITF and Ki-67 can be used for the confirmation of diagnosis. Among these markers, S100 protein staining is the most sensitive marker while HMB-45, Melan-A, MITF, and tyrosinase are relatively specific.

The Breslow thickness or Clark’s level of amelanotic melanomas is higher when compared to pure melanoma. Amelanotic melanomas are usually come to attention at advanced stages with greater tumor thickness which leads to poor prognosis.

Moreau et al observed that amelanotic melanomas are usually ulcerated and become non localized with time showing its aggressive behaviour. A study conducted by Gualandri et al found no delay in the diagnosis for amelanotic melanoma and nodular amelanotic melanomas having more Breslow thickness which are diagnosed late because of rapid growth rate. Shen et al have shown...
relationship between amelanotic melanoma with rapid growth rate and mitotic rate and rapid growth rate was associated independently with high mitotic rate.15 Hence, amelanotic melanomas have higher growth rate and mitotic rate as compared to other melanomas. 15,16

Clinical management of the tumor includes surgical excision with a large margin of normal-appearing skin. Underdiagnosis or inadequate excision may result in local recurrence and mortality greater than with an adequately excised primary lesion.16,17 A combination of surgery plus adjuvant therapy is most commonly used treatment modality. Recently immunotherapy is being widely used in melanoma.17,18 Patients of amelanotic melanoma have a poor prognosis with 5-year survival rate of less than 20%,1,19 It is seen that the overall survival rate and progression-free survival rate of patients with pigmented melanoma are higher than in patients with amelanotic melanoma.20 Cascardi et al have also reported poor prognosis with a 5-years survival rate of 30-35% and a median survival of 36 months.21 Paulo et al observed no particular type of treatment can improve the survival rate of patients with amelanotic melanoma (p >0.05).22

4. Conclusions

An asymmetric lesion presenting as red plaque or nodule with ill defined borders and elevated margins with cytomorphology showing plasmacytoid, markedly pleomorphic cells having coarse chromatin, prominent nucleoli, nuclear pseudoinclusions and multinucleate giant cells with absence of melanin pigment should be suspected as a case of amelanotic melanoma. Biopsy and suitable immunohistochemical marker study should be performed for a definitive diagnosis, so as to initiate prompt and early adjuvant therapy for a better prognosis.

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6. Conflict of Interest

The authors declare they have no conflict of interest.

References

1. Muinonen-Martin AJ, Shea SJO, Newton-Bishop J. Amelanotic melanoma. BMJ. 2018;3:60–7.
2. Cheung WL, Patel RR, Leonard A, Firoz B, Meehan SA. Amelanotic melanoma: a detailed morphologic analysis with clinicopathologic correlation of 75 cases. J Cutan Pathol. 2012;39(1):33–9.
3. Gong HZ, Zheng HY, Li J. Amelanotic melanoma. Melanoma Res. 2019;29(3):221–30.
4. Zhu YH, Zhang GX, Tang L, Li XJ, Zhu WY, Zhang RZ, et al. Tumors of the Skin in Atlas of Skin Disorders. In: 2nd Edn. Springer. 2018. p. 457–94.
5. Russo T, Piccolo V, Lallas A, Jacomel J, Moscarella E, Alfaro R, et al. Dermoscopy of Malignant Skin Tumours: What’s New? Dermatol. 2017;233(1):64–73.
6. James N, Braun RP, Thomas L, Marghoob AA. Clinical and dermoscopic characteristics of amelanotic melanomas that are not of the nodular subtype. J Eur Acad Dermatol Venereol. 2012;26(5):591–6.
7. McClain SE, Mayo KB, Shada AL, Smolkin ME, Patterson JW, Slingsluff CL, et al. Amelanotic melanomas presenting as red skin lesions: a diagnostic challenge with potentially lethal consequences. Int J Dermatol. 2012;51(4):420–6.
8. Koch SE, Lange JR. Amelanotic melanoma: The great masquerader. J Am Acad Dermatol. 2000;42(5):731–4.
9. Gualandri L, Bettì R, Croatti C. Clinical features of 36 cases of amelanotic melanomas and considerations about the relationship between histologic subtypes and diagnostic delay. J Eur Acad Dermatol Venereol. 2009;23(3):283–7.
10. Siddaraju N, Yaranal PJ, Mishra MM, Soundararaghavan J. Fine Needle Aspiration Cytology in Recurrent Amelanotic Melanoma. Acta Cytol. 2007;51(5):829–32.
11. Khairwa A. Amelanotic melanoma recurrence diagnosed by fine-needle aspiration cytology: A case report. Diagn Cytopathol. 2020;48(12):1–3.
12. Garg R, Gupta N. Immunohistochemistry: sole tool in diagnosing a rare case of primary vaginal amelanotic melanoma. Obstet Gynecol Sci. 2018;61(6):698–701.
13. Boggio F, Lopez G, Gobbo AD, Scarfone G, Marchini M, Cribiù F, Ancillotto A, et al. Amelanotic primary vaginal melanoma: A case report with cyto-histological correlations. Diagn Cytopathol. 2019;47(3):230–3.
14. Moreau JF, Weisfeld JL, Ferris LR. Characteristics and survival of patients with invasive amelanotic melanoma in the USA. Melanoma Res. 2013;23(5):408–13.
15. Shen S, Wolfe R, McLean CA, Haskett M, Kelly JW. Characteristics and Associations of High-Mitotic-Rate Melanoma. JAMA Dermatol. 2014;150(10):1048–55.
16. Guo W, Yin G, Liu H, Duan H, Huang Z, Chen X, et al. Matched analysis of the prognosis of amelanotic and pigmented melanoma in head and neck. Acta Oto-Laryngol. 2020;191:1–4.
17. Strashilov S, Kirov Y, Yordanov A, Simeonova Y, Strashilova MM. Amelanotic melanoma of the oronasal region: report of two new cases and literature review. Australas Med J 2019;12:1101–5.
18. Zhang J, Yang H, Lin J, Zhang F, Shi J, Chen R, et al. Primary acralamelanotic melanoma: A rare case report. Mol Clin Oncol. 2020;12(5):1–7.
19. Baniyaseen KA, Saeed M, Albonni AO, AbdShakour BM, Dairi M, Napoli A. Multifocal amelanotic melanoma of the head and neck: The First Case Report from Saudi Arabia. Middle East J Dig Dis. 2019;11(3):166–7.
20. Saeed DM, Braniecki M, Groth JV. A rare case of acral amelanotic melanoma, nodular type. Int Wound J. 2019;16(6):1445–9.
21. Cascardi E, Limongelli L, Tempesta A, Capodiferro S, Mastropasqua M, Napoli A. Multifocal amelanotic melanoma of the head and neck: A challenging case. Oral Sur Oral Med Oral Pathol Oral Radiol. 2019;128(1):74–7.
22. Baniyaseen KA, Saeed M, Albonni AO, AbdShakour BM, Dairi M, Napoli A. Multifocal amelanotic melanoma of the oronasal region: report of two new cases and literature review. Oral Maxillofac. 2015;19(4):333–9.

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