International Journal of Research and Review
Vol. 10; Issue: 2; February 2023
Website: www.ijrrjournal.com
Case Report *E-ISSN: 2349-9788; P-ISSN: 2454-2237*

Case Report: Nevus-Melanoma Misdiagnosis in Seborrheic Keratosis of the Eyelid

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DOI: https://doi.org/10.52403/ijrr.20230201

ABSTRACT

Seborrheic keratosis is a benign tumor originating from keratinocytes. In this case, a 51-year-old woman with a lump on the left upper eyelid that was growing rapidly, accompanied by itchiness since 1 month. The lumps appeared to be blackish brown, with uneven edges that clinically similar to nevus and malignant melanoma lesions. To rule out the possibility of a nevus, malignant melanoma and other malignancies, excisional biopsy was performed as a diagnostic and treatment management. The similar clinical appearance between benign and malignant lesions is a consideration in performing an excisional biopsy. Histopathological examination in this case, confirmed the diagnosis of seborrheic keratosis as a gold standard that will determine further management.

Keywords: Seborrheic keratosis, nevus, malignant melanoma, misdiagnosis

INTRODUCTION

The eyelids have an important role in protecting the eyeball, preventing tear evaporation, keeping the eye moist and as aesthetics. The skin on the eyelids lacks subcutaneous fat which is the thinnest layer of the body.[1]

A wide variety of eyelid lesions are encountered because of the unique anatomy such as the presence of all layers of the skin, muscles, glands and mucous membranes. Lesions of the eyelids can be divided into congenital, inflammatory, traumatic, or neoplastic (benign and malignant). Neoplastic lesions are classified according to their anatomical origin. Clinical diagnosis will tentatively be established based on the typical appearance of the lesion, but histopathological examination of tissue specimens is still performed because benign lesions have the potential to become malignant.[2]

Seborrheic keratosis is the most common benign tumor. Although surgery is often performed for cosmetic and inflammatory reasons, the clinical appearance of seborrheic keratosis closely resembles that of other skin malignancies or epithelial tumors. Therefore, histopathological examination is necessary to exclude the possibility of malignancy. According to Yasser's study, pre-excision clinical diagnosis (PECD) lesions on the eyelids such as skin tags or warts, epidermal cysts, and nevus will change after histopathological examination to become seborrheic keratosis.[2]

According to the Yu-Yun Huang retrospective study at the Taipei Veterans General Hospital, 4,294 (95%) of the total 4521 patients who underwent histological examination showed benign tumors with the following distribution, intradermal nevus (21.1%), seborrheic keratosis (12.6%), xanthelasma (11.2%), and epidermal cyst (8.2%).[1] The difficulty in clinically

diagnosing between seborrheic keratosis and nevus was revealed through Jennifer DeFazio's study. Seborrheic keratosis may develop over a mature nevus. The keratosis may enlarge and eventually cover the underlying nevus. A malignancy such as nevus melanoma is often misdiagnosed because seborrheic keratosis accumulates on it. This occurs because melanocytes in seborrheic keratosis mutate into melanoma which histologically has a hyperkeratotic epidermal appearance, pseudo-horn cysts and appears warty clinically so that it is misdiagnosed as seborrheic keratosis.[3]

CASE ILLUSTRATION

A 51-year-old woman came to the eye clinic at Mangusada Hospital with complaints of a lump appearing on the upper left eye. Over the past 1 month it was said to have grown in size quickly and was disturbing her comfort. The lump was felt without pain, without itching, didn't bleed easily, and there was no discharge in the area around the lump or in the eye. The patient had no history of other diseases, and there was no family history of having the same complaints as the patient.

Figure 1: (a), (b) Clinical photograph preoperative eye conditions

On examination, there was a lump on the upper eyelid of the right eye measuring 7 mm x 3 mm x 5 mm, blackish brown with uneven edges. Other ophthalmologic examinations of the eyes were found to be within normal limits, visual acuity 6/6 in both eyes, intraocular pressure within normal limits.

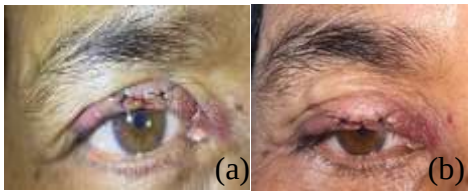

Figure 2: (a), (b) Clinical photograph one day after surgery

Excisional biopsy was performed with a distance of 3 mm from the tumor boundary from the superior, medial, and lateral sides. There was no deep attachment to the surrounding tissue with the base of the tumor in the orbicularis oculi muscle. The excision wound was closed by direct closure with 3 interrupted sutures using Prolene 6.0 thread, given an antibiotic ointment and covered with sterile gauze. The sutures were opened on the 14th day, no lagophthalmos, entropion, or ectropion were found.

Figure 3: (a), (b), (c) Clinical photograph 14 days postoperatively

Histopathological examination in 4 cassettes, the tumor consists of the epidermis, dermis, and subcutis. The epidermis undergoes proliferation of squamous cells with cysts filled with keratin lamellar material between them (Horn Cysts). On the other side, squamous eddies and a little distribution of melanin pigment

can be seen. The results of histopathological examination of the superior lid are suitable for seborrheic keratosis.

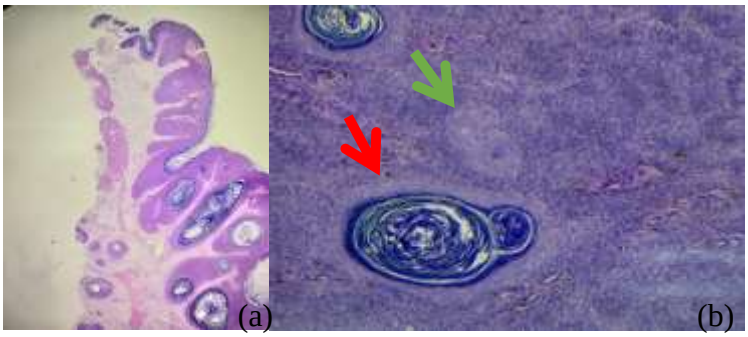

Figure 4: (a) scanning view (40x), (b) high power view 120x, Hyperkeratosis layer accompanied by a keratin filled cyst/ horn cyst (red arrow), squamous eddies (green arrow)

DISCUSSION

In the case of a 51-year-old woman who came to the eye clinic at Mangusada Hospital with complaints of a lump appearing on the upper left eye. Over the last 1 month it was said to have grown in size quickly accompanied by itching so that it interferes with her comfort. On examination, a lump with a size of 7 mm x 3 mm x 5 mm was found, brown-black in color, risen from the surface of the skin, well-defined, with an uneven surface. Other ophthalmologic examinations of the eyes were found to be within normal limits, visual acuity 6/6 in both eyes, intraocular pressure within normal limits. These clinical features were consistent with pigmented skin lesions of seborrheic keratosis, melanocytic nevus, malignant melanoma, pigmented basal cell carcinoma or squamous cell carcinoma. A change in the pattern of rapid growth lesion gave suspicion towards malignancy therefore it was necessary to perform tumor excision followed by histopathological examination.

Seborrheic keratosis is a benign skin lesion originating from keratinocytes, often found in old age, especially in the neck and back areas, and often found in the face and periocular areas. These tumors are found in areas of hairy skin, and are not found on the palms, soles of the feet or mucous membranes. The lesions are solitary but may also be multiple and may be inherited in an autosomal dominant manner.[4,5] Previous epidemiology studies of seborrheic keratosis found more than 80 million Americans with a mean age of more than 50 years. White race has a higher risk than dark skin color race. Men and women have the same risk of developing seborrheic keratosis.[6,7]

Clinically, seborrheic keratosis first appears as slightly raised, brown or pale hyperpigmented plaques. The growth of the lesions is slow, but over time the seborrheic keratosis becomes increasingly elevated, the surface becomes rough/verrucous with irregular protrusions that look like they are sticking to the surface of the skin.[5,8] Genetic, idiopathic, and sun exposure factors have an effect on the emergence of seborrheic keratosis.[9,10] According to a study by Brash et al, ultraviolet radiation caused specific mutations in the pyrimidine dimer tumor suppressor gene p53 of keratinocytes. Keratinocytes with this DNA damage will undergo apoptosis and clinically will appear as keratosis.[11] Another theory is that seborrheic keratosis occurs due to mutations in epidermal keratinocytes. The most common gene mutations in seborrheic keratosis are FGFR3 (fibroblast growth factor receptor 3) in 71% of sporadic seborrheic keratosis and the catalytic p110 subunit of phosphatidylinositol 3 kinase (PI3K) is found in 50% of sporadic seborrheic keratosis.[5,12] In the study of

Roberto Betti et al., seborrheic keratosis consisted of three cell types, namely basaloid keratinocytes, pale eosinophilic spinous cells, and melanocytes. Keratinocytes in seborrheic keratosis are formed from basal cells of the epidermis or follicular epithelium, in which the follicular germ consists of pluripotential stem cells that allow the formation of tumors with differentiated stem cells.[13]

Melanocytic nevus is a benign tumor that originates from melanocytes. Melanocytic nevus can be congenital or acquired, starting to appear at the age of 5-15 years as small relatively dormant macules, but mostly appearing during adolescence to early adulthood.[14] Clinically, a nevus may be pigmented (melanotic) or non-pigmented (amelanotic) with a smooth or verrucous surface and no loss of cilia. Nevus can be darker in color and has a large, slightly raised surface accompanied by a lot of cilia growth and has a risk of developing into malignancy. In this case the size of the lesion was more than 6 mm with rapid growth progression including the warning sign of a melanocytic lesion. Melanocytic lesion warning signs consist of indeterminate lesion boundaries, variable color, asymmetric lesions, lesion diameter of more than 6 mm with changes in size and color, pain, itchy, ulcers, easily bleed, and crust.[15] Congenital melanocytic nevus with extensive lesions can increase the risk of developing melanoma with a percentage of 0 to 50%. Several theories suggest that the cause of melanoma in melanocytic nevus is an increased percentage of NRAS gene mutations (70%) and a low percentage of BRAF gene mutations (15%) and an increase in the number of melanocytes accompanied by malignant degeneration.[16]

The difference between melanocytic and nonmelanocytic lesions is very important as an early stage because detection of malignant melanoma at an early stage affects patient survival.[15] Malignant melanoma is a malignant growth originating from melanocytes, which can be de novo or can originate from a preexisting nevus. Clinical features vary from brownish macules with irregular edges to nodule-shaped or raised lesions with variations in brown, black, gray, pink, blue or white. Malignant melanoma also presents as an amelanotic lesion which makes it difficult to identify, especially in pale-skinned individuals.[1,9]

The similar clinical features of seborrheic keratosis, melanocytic nevus and melanoma is a challenge for clinicians to differentiate between malignant and benign lesions through history and physical examination. Predilection for benign tumors is mostly found on the upper eyelid, while malignant tumors are more commonly found on the lower eyelid.[1] Christina Leung's study regarding prediction of malignancy morphology of the eyelids which can help differentiate malignant and benign lesions, at the initial examination of the history can use LUI and ABCDE criteria. The LUI criteria consist of Loss of eyelashes, Ulceration, Infiltration of tissue. The ABCDE criteria consist of Asymmetry, Irregular Borders, Multiple Colors, Diameter > 6 mm, Horizontal Enlargment.[17] Lesions with an asymmetrical shape, indistinct boundaries, graded colors, and a diameter of more than 6 mm led to the diagnosis of melanoma, even the size of the lesion can exceed 1 cm with a depth from the dermis to the subcutis. The term "ugly duckling" is used to predict the diagnosis of melanoma by comparing suspected lesions with other lesions which mean that melanoma sufferers will complain of lesions with changes in color, size, and the growth of new lesions compared to other lesions on the body.[18] The incidence of melanoma in the USA is estimated at 1 in 62 people. The American Cancer Society estimates 111,900 new cases of melanoma in 2006.[18]

Benign and malignant lesions have a similar clinical picture, therefore histopathological examination is important as a follow-up examination after excision. Seborrheic keratosis is a benign intraepidermal neoplasm that develops from epidermal keratinocytes.[5,9] The presentation features of

seborrheic keratosis preparations are well-defined coin-like pigmented lesions in which keratin and epidermal basal cells are present. There is a picture of massive keratin (hyperkeratosis) and cysts filled with keratin (horn cysts) and keratin invagination into the main locus (invagination cysts), if there is squamous inflammation it will differentiate to form whirling foci resembling a vortex (eddy squamous) which is a typical appearance of seborrheic keratosis.[5,12] This theory is in accordance with the histopathological findings in case reports.

Melanocytic nevus is considered as a benign proliferation of melanocytes in which melanocytes are present that differ from the normal form. Early in the development of a melanocytic nevus, nevus cells will be found at the bottom of the epidermis and then will develop in the deep layers of the skin down to the dermis and nervous tissue. The naming of a nevus is based on the location of the nevus cells, such as junctional nevus, compound nevus, intradermal nevus, and neurotization.[12] Histopathological appearance shows the presence of nevus cells which some appear to be clustered or a nest-like appearance with cells that appear round, dendritic, and have pigment in the cytoplasm.[14]

Malignant melanoma can coexist with seborrheic keratosis. The development of melanoma can be radial and vertical. Radial development, where the melanoma spreads horizontally in the epidermis. The vertical phase is the next phase where the tumor grows into the dermis as a nodule with the ability to metastasize. Melanoma can metastasize to regional lymph nodes. The histopathological appearance of melanoma shows that melanocyte cells are larger than normal melanocytes or in melanocytic nevus, with nuclei with irregular chromatin. Another histological finding is the presence of atypical lesions.[12] The histological appearance of melanoma looks irregular with abnormal cell maturity, asymmetrical, pagetoid distribution, the cells are pleomorphic which means the nucleus and all of the melanocyte cytoplasm are different from one another. The nucleus is enlarged with clumping chromatin and prominent nucleoli. Some cells have abundant cytoplasm, and some have little cytoplasm. A definite indication of melanoma is the presence of mitosis in the deep dermis along with cellular atypia and pleomorphism.[19,20]

Initial suspicion a malignant lesion prior to histopathological examination is a consideration in excision technique. Based on previous studies, excision techniques for suspected melanoma can be performed within 1-5 mm of the lesion boundary, while for benign lesions 1-2 mm from the tumor boundary.[21,22]

CONCLUSION

Seborrheic keratosis is a benign tumor originating from epidermal keratinocytes. The clinical appearance of seborrheic keratosis can resemble a nevus, melanoma and other malignant lesions, that often leads to misunderstanding in the diagnosis. It is still a challenge for clinicians to diagnose seborrheic keratosis through clinical examination. Excisional biopsy accompanied by histopathological examination is a gold standard to rule out the possibility of malignancy, and as a treatment.

Declaration by Authors

Acknowledgement: The authors thank the patient's family for allowing them to share this case.

Source of Funding: None

Conflict of Interest: The authors declare no conflict of interest.

REFERENCES

1. Huang YY, Liang WY, Tsai CC. et al. Comparison of The Clinical Characteristics and Outcome of Benign and Malignant Eyelid Tumor: An Analysis of 4521 Eyelid Tumors in a Tertiary Medical Center. Hindawi Publishing Corporation Biomed Research International. 2015. http://dx.doi.org/10.1155/2015/453091.
2. Chen, S., Zhou, Y., and Song, W. Cutaneous Horn Masquerading As A Seborrheic Keratosis.

Elsevier American Journal Of Ophthalmology Case Reports. 2016; 4: 64-66.
3. DeFazio J, Zalaudek I, Busam KJ, et al. Association Between Melanocytic Neoplasms and Seborrheic Keratosis: More Than A Coincidental Collision? Dermatology Practical & Conceptual. 2012; 2(2): 35-41. http://dx.doi.org/10.5826/dpc.0202a09.
4. Tumors of The Conjunctiva and Cornea. Shields, Carol L. and Sheilds, Jerry A. Philadelphia: Wolters Kluwer-Medknow, 2019, Vol. 67, pp. 1930-48.
5. Pe'er, J. Pathology of Eyelid Tumors. Indian J Ophthalmol. 2016; 64: 177-190.
6. Al. Faky YH. Epidemiology of benign eyelid lesions in patients presenting to a teaching hospital. Saudi Journal of Ophthalmology. 2012; 26: 211-216. Doi: 10.1016/j.sjopt.2011.05.005
7. Greco MJ, Bhutta BS. Seborrheic Keratosis. [Internet] 2022. https://www.ncbi.nlm.nih.gov/books/NBK545285.
8. Chi MJ and Baek SH. Clinical Analysis of Benign Eyelid and Conjungtival Tumors. Ophthalmologica.2006; 220 (1): 43-51. Doi: 10.1159/000089274
9. Waqar S, George S, Jean-Baptiste W, et al. Recognizing Histopathological Simulators of Melanoma to Avoid Misdiagnosis. Cureus. 2022; 14(6): e26127. doi:10.7759/cureus.26127
10. Cochran ML, Czyz CN. Eyelid Papilloma [Internet]. StatPearls Publishing LLC; 2022. Available from: https://www.ncbi.nlm.nih.gov/books/NBK470251/
11. Brash, D. E., Rudolph, J. A., Simon, J.A. et al. A Role for Sunlight In Skin Cancer: UV-Induced p53 Mutations In Squamous Cell Carcinoma. Proc. Natl. Acad. Sci. USA. 1991; 88: 10124-128
12. Lazar, Alexander J**.** The Skin. [book auth.] Abul K. Abbas, Vinay Kumar and Jon Aster. Robbins & Cotran Pathologic Basis of Disease. Philadelpia : Elsevier; 2021 Vol X:1142-1144
13. Betti, R., Menni, S., Cerri, A., et al. Seborrheic Keratosis With Compound Nevus, Junctional Nevus and Basal Cell Carcinoma In The Same Lesion. Dermatology. 2001; 203: 265-267
14. Gundalli, S., Kadadavar, S., Singhania, S., et al. et al. Histolpathological Spectrum of Benign Melanocytic Nevi - Our Experience In Tertiary Care Centre. Our Dermatol Online. 2016; 7 (1): 21-25. Doi: 10.7241/ourd.20161.5
15. Thomas, I., Kihiczak, N., Rothenberg, J., et al. Melanoma Within The Seborrheic Keratosis. American Society for Dermatologic Surgery. 2004;30:559-561
16. Sjambali S, Ragmayani S, Wirohadidjojo YW. et al. Nevus Melanositik Kongenital Luas Laporan Kasus dan Telaah Literatur. MDVI, 2018; 45 (3): 136-141
17. Leung C, Johnson D, Pang R, Kratky V. Identifying predictive morphologic features of malignancy in eyelid lesions. Can Fam Physician. 2015 Jan;61(1):e43-9. PMID: 25756148; PMCID: PMC4301785.
18. Paek, Sandra C. et al. Fitzpatrick Dermatology In General Medicine: Cutaneous Melanoma (7th ed.), United States of America: McGraw Hill Companies; 2008: 1134-1157. Doi: 10.1036/0071466908
19. Moscarella, Elvira, et al. Differential Diagnosis and Management on Seborrheic Keratosis in Elderly Patients. Dove Medical Press Limited. 2021; 14: 395-406.
20. Galatoire O, et al. Eyelid and Conjunctival Tumors Photographic Atlas. Laboratories Thea. Available at https://www.laboratoires-thea.com/medias/bat02_brochure_tumeurs_et_paupieres_wcoratltumors0719.pdf
21. Hwang SM, Pan HC, Hwang MK, et al. Malignant Skin Tumor Misdiagnosed as a Benign Skin Lesion. Archives of Craniofacial Surgery. 2016; 17 (2) : 86-89. Doi: 10.7181/acfs.2016.17.2.86
22. Harish V, Bond JS, Scolyer RA, et.al. Margins of excision and prognostic factors for cutaneous eyelid melanomas. Journal of Plastic & Reconstructive Aesthetic Surgery. 2013; 66(8): 1066-73. doi: 10.1016/j.bjps.2013.04.032.

How to cite this article: I G. N. A. Wisnu Kresnan Dana, Ni Nyoman Triharpini, Ida Bagus Caka Gunantara. Case report: nevus-melanoma misdiagnosis in seborrheic keratosis of the eyelid. *International Journal of Research and Review*. 2023; 10(2): 1-6. DOI: *https://doi.org/10.52403/ijrr.20230201*

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