OLGU SUNUMU CASE REPORT

DOI: 10.5336/ophthal.2016-52701

Giant Conjunctival Melanoma with Breast Cancer and Chronic Lymphocytic Leukemia: A Case Report and Mini-Review of the Literature

Meme Kanseri ve Kronik Lenfositik Lösemi ile Birlikte Olan Dev Konjonktival Melanom: Olgu Sunumu ve Literatürün Mini Derlemesi

Sabit KİMYON,[a]
Alper METE,[a]
Tülay KUŞ,[b]
Yusuf TÜYLÜ,[a]
Kadir Erdoğan ER,[a]
Gökmen AKTAŞ,[b]
Can PAMUKÇU[c]

Departments of
[a]Ophthalmology
[b]Oncology,
Gaziantep University Faculty of Medicine,
[c]Clinic of Ophthalmology,
Private Hatem Hospital,
Gaziantep

Received: 14.07.2016
Received in revised form: 22.11.2016
Accepted: 29.11.2016
Available online: 25.10.2018

Correspondence:
Sabit KİMYON
Gaziantep University Faculty of Medicine, Department of Ophthalmology, Gaziantep, TURKEY/TÜRKİYE
sabitkimyon@gmail.com

ABSTRACT Our aim is to present a case with rapidly progressing conjunctival malign melanoma who was taking treatment for invasive ductal breast cancer and chronic lymphocytic leukemia. 83-year-old male patient with chronic lymphocytic leukemia and breast cancer was presented with a rapidly growing hyperpigmented mass on his upper left eyelid. Slit-lamp examination showed a hyperpigmented mass in the upper tarsal conjunctiva and diffuse hyperpigmentation in the lower tarsal conjunctiva of the left eye. The patient was diagnosed as conjunctival melanoma with rapid progression. We performed exenteration surgery and removed all suspicious tissues. Histopatology report revealed nodular type malign melanoma. Rapidly growing conjunctival melanomas which co-exist with multiple malignancies require more frequent follow-ups and early treatment.

Keywords: Melanoma; breast neoplasms, male; leukemia, lymphocytic, chronic, b-cell; conjunctival neoplasms; conjunctival diseases

ÖZET Amacımız invaziv duktal meme kanseri ve kronik lenfositik lösemi için tedavi gören hızlı ilerleyen konjonktival malign melanomlu hastayı sunmaktır. Kronik lenfositik lösemi ve meme kanseri tanıları olan 83 yaşındaki erkek hasta sol üst göz kapağında hızlı büyüyen hiperpigmente kitle ile başvurdu. Yarıklı lamba muayenesinde sol gözün üst tarsal konjonktivasında hiperpigmente kitle, alt tarsal konjonktivada difüz hiperpigmentasyon tespit edildi. Hastaya hızlı ilerleyen konjonktival melanom tanısı konuldu. Hastanın sol gözüne ekzenterasyon cerrahisi uygulandı ve tüm şüpheli doku eksize edildi. Histopatoloji raporu nodüler tip malign melanom olarak geldi. Hızlı ilerleyen ve birçok tümör ile birlikte olan konjonktival melanomlar daha sıkı takip ve erken tedavi gerektirmektedir.

Anahtar Kelimeler: Melanom; meme neoplazileri, erkek; lösemi, lenfositik, kronik, b-hücreli; konjonktival neoplaziler; konjonktiva hastalıkları

Well-known risk factors for conjunctival malign melanomas (CM) are hyperpigmented nevus, family history, ultraviolet (UV) light exposure, genetic syndromes like familial melanoma syndrome, xeroderma pigmentosum, Hodgkin's lymphoma and hereditery retinoblastoma. However, there is still limited data about risk factors because of its the low incidence.[1-6] Primary acquired melanosis causes 75% of CM, while existing nevus is responsible for 20% and 5% of CM occurs as de novo.[7-9] It account for 0,25% of all melanomas, 2% of extraocular tumours and 5% of ocular region melanomas.[10,11] It mostly develops on bulbar conjunctiva (60-92%) due to the direct UV and it usually has typical pigmentation, however some of them may be amelanotic (15-19%) which can be difficult to differ-

entiate from ocular surface squamous tumours and lymphoma.[7,8] Significant increase in the incidence of conjunctival melanoma was observed in the age group over 60 years and among white men.[12]

Conjunctival melanomas are usually diagnosed by well obtained history, careful physical examination and slit-lamp microscopy. History and physical examination should include age, symptoms, sun exposure, development and growth rate of the lesion, cancer history, inspection of eyelids and neighbouring tissues, ocular surface examination, lymph node palpation. Pigmentation on the tarsal conjunctiva should increase the suspicion of CM.[13]

In this paper, we present a case with rapidly progressing conjunctival malign melanoma who was taking treatment for invasive ductal breast cancer and chronic lymphocytic leukemia (CLL). Increased incidence of malign melanoma and breast cancer in CLL patients is well established in the literature, however, to best of our knowledge, this is the first case with co-incidental CM, CLL and breast cancer. There is limited information regarding the treatment of these cases in the literature. These secondary cancers are thought to occur because of the immune supression in CLL patients. We aimed to draw attention to the agressive course and the need of immediate treatment for these cases.

CASE REPORT

A 83-year-old caucasian male admitted to hospital with 2x2 cm sized mass on the nipple of left breast. Breast ultrasononography showed 2x3 cm mass on the areola of the left breast with left and right axillary lypmh node metastasis. Laboratory tests revealed hemoglobin level of 11,9 g/dl, white blood cell count of 14 500 cells/µl (neutrophils, 38% [normal range: [NR]:34-71]; lymphocytes, 62% [NR:19.3-51.7]; monocytes, 2.1% [NR:4.4-12.5]), platelet count of 356 103 cells/µl (NR: 182-369), lactate dehydrogenase (LDH) level of 250 units/l (NR: 125-247), erythrocyte sedimentation rate (ESR) of 45 mm/h NR: 1-20). Excisional biopsy was performed for breast mass and pathologic evaluation was reported as invasive ductal carcinoma, estrogen 95% positive, progesterone 70% positive and HER 3 +++ positive. Fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography (18F-FDG PET/CT) was performed for the staging of breast cancer. 18F-FDG PET/CT revelaed the involvement of mediastinal lymph nodes and bilateral axillary lymph nodes, and hypermetabolic mass in the left breast. Owing to higher lymphocyte rate in complete blood count and common lymph nodes involvement in 18F-FDG PET/CT scan, a flow cytometry analysis from peripheric blood sample was performed. CD5 was 93% and patient was diagnosed with CLL. CLL was staged as II according to Ann Arbor staging system. Chemotherapy for CLL was not administered thanks to absence of B symptoms, anemia, hemolytic anemia, thrombocytopenia. Chemotherapy was administered for breast cancer as transtuzumab 6 mg/m^2, carboplatine (AUC6), and docetaxel 75 mg/m^2 intravenously (IV) per three weeks for three cycles, then oral tamoxifen 10 mg per day was started. Patient did not want to be operated for breast cancer and he was followed only with hormonotherapy. While the patient was taking hormonotherapy, he admitted to ophthalmology department of Gaziantep University with a rapidly growing, painless mass on the upper left eyelid. Best corrected visual acuities (BCVAs) were 5/10 and 2/10 in the right and left eyes, respectively. Slit-lamp examination showed nuclear sclerosis in the right eye, hyperpigmented mass in the upper tarsal conjunctiva and diffuse hyperpigmantation in the lower tarsal conjunctiva of the left eye (Figure 1A). Fundus examination, fundus fluorescein angiography and optical coherence tomography were normal in both eyes. We sent the patient for orbital magnetic resonance imaging (MRI). When the patient has returned with his MRI results two weeks later, the mass had grown and covered the whole interpalpebral fissure (Figure 1B). Orbital MRI revealed a 17x9 mm mass on the anterior of left globe which extends to lateral rectus muscle (Figure 1C). We performed exenteration surgery and removed all suspicious tissues.Histopatology report revealed nodular type malign melanoma (Figure 1E-F). Patient was referred to oncology department for further treatment. An in-

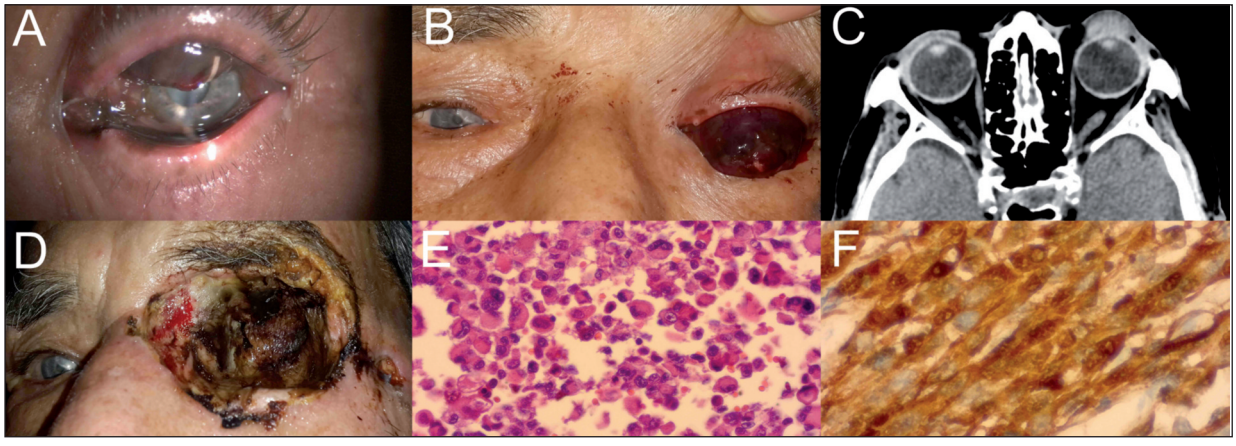

FIGURE 1: A) Mass at the upper tarsal conjunctiva, melanosis at the lower tarsal conjunctiva. **B)** Appearence of the patient two weeks after the first addmission. Mass at the upper tarsal conjunctiva has grown. **C)** MRI shows the mass at the upper left eyelid. **D)** Appearance of the patient after exenteration procedure. **E,F)** Histological view of the excised material which was compatible with nodular malign melanoma.

formed consent was obtained from the patient for reporting his medical data.

DISCUSSION

Conjunctival melanomas arise from melanocytes settled in the basal layer of the epithelium of the conjunctival membrane which is a vulnerable area on account of direct exposure to sun radiation unlike the other mucous membranes.[14] A large retrospective study evaluated the 84836 cases with cutaneous and non-cutaneous malign melanoma during 9 years. Accordingly, the rate of cutaneous, ocular, mucosal, and unknown primaries site melanomas were 91,2%, 5,2%, 1,3%, and 2,2%, respectively. Ocular melanomas were the second most frequent type of the malign melanomas and 85,0% of all were uveal, 4,8% were conjunctival melanomas.[11] Several clinical factors are associated with high mortality, including advanced stage, tumor size, extrabulbar location, caruncular location and invasion of adjacent tissues, nodular or acral lentiginous histology, increased age, male gender, and lower income features.[7,11,15] The most common symptoms are pigmented spot or lump, and irritation on conjunctiva, our case applied with a round, hyperpigmented, giant mass which is different from other presentations in the literature.[7]

Primary treatment modalities are wide local excision in the case of patient which is suitable for resection with adjuvant therapy, including cryotherapy, brachytherapy, and topical mytomicin C.[16-18] Despite the effective treatment options for the conjunctival malign melanoma, high local recurrence rate is still the most important problem for the management of the disease. It is a rare ophthalmologic pathology with high mortality risk which may infiltrate neighbouring tissues and spread systemically via lymphatic and hematogenous pathways, and can show recurrence despite treatment.[13] It may spread extensively in 1% of the patients and this invasion usually occurs via lymphatic pathways.[8] Orbital exenteration as the primary therapy is used for advanced conjunctival melanoma as in our case. Although survival benefit with early exenteration was not shown, owing to course of locally advanced tumor with multiple recurrences, unfortunately exenteration remains as the primary treatment approach in this area and was performed still in about one third of cases.[19,20]

Previous studies showed that patients with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) have increased risk of developing a secondary cancer and an increased frequency of certain cancer types. Possible responsible pathogenesis are administered chemotherapy and radiotherapy, and underlying immune dysfunction.[21-27] Untreated 2,028 patients with CLL/SLL were analysed to determine of the co-incidence the other malignities rates. Accordingly, 16% of all had a history of other cancers at diagnosis and 11.2%

developed other malignancies during the follow-up and treatment period. Rate of breast cancer co-incidance with CLL/SLL was 9% and it was 9% for malign melanoma.[28] Lam et al. showed that melanoma risk after CLL/SLL was significantly increased among patients who received infused fludarabine-containing chemotherapy with or without rituximab (hazard ratio [HR], 1.92; 95% CI, 1.09-3.40, HR, 2.92; 95% CI, 1.42-6.01, respectively).[29] All mentioned studies above were evaluated malign melanoma of skin cancer unlike our patient, ocular melanoma. Also our case did not take immunosuppressive treatment for CLL, he only received tamoxifen for breast cancer. Presented case is the first case in the literature with ocular melanoma which co-existed with CLL and breast cancer.

In conclusion, local excision, chemotherapy or brachytherapy are the treatment options for early detected conjunctival malign melanomas. We had to perform exenteration in our case because of the rapidly growing lesion and the risk of metastasis. Rapidly growing conjunctival melanomas which co-exists with multiple malignancies require frequent follow-ups and early treatment.

Acknowledgements

We do not have someone to acknowledge.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Sabit Kimyon, Alper Mete, Tülay Kuş;* ***Design:*** *Sabit Kimyon, Alper Mete, Tülay Kuş;* ***Control/Supervision:*** *Sabit Kimyon, Alper Mete, Tülay Kuş;* ***Data Collection and/or Processing:*** *Yusuf Tüylü, Kadir Erdoğan Er, Gökmen Aktaş, Can Pamukçu;* ***Analysis and/or Interpretation:*** *Sabit Kimyon, Alper Mete, Tülay Kuş, Can Pamukçu;* ***Literature Review:*** *Sabit Kimyon, Alper Mete, Tülay Kuş, Yusuf Tüylü, Kadir Erdoğan Er, Gökmen Aktaş;* ***Writing the Article:*** *Sabit Kimyon, Alper Mete, Tülay Kuş, Yusuf Tüylü, Kadir Erdoğan Er, Gökmen Aktaş;* ***Critical Review:*** *Sabit Kimyon, Alper Mete, Tülay Kuş, Yusuf Tüylü, Kadir Erdoğan Er, Gökmen Aktaş, Can Pamukçu;* ***References and Fundings:*** *Sabit Kimyon, Alper Mete, Tülay Kuş, Yusuf Tüylü, Kadir Erdoğan Er, Gökmen Aktaş, Can Pamukçu;* ***Materials:*** *Yusuf Tüylü, Kadir Erdoğan Er, Gökmen Aktaş, Can Pamukçu.*

REFERENCES

1. Gandini S, Sera F, Cattaruzza MS, Pasquini P, Zanetti R, Masini C, et al. Meta-analysis of risk factors for cutaneous melanoma: III. Family history, actinic damage and phenotypic factors. Eur J Cancer 2005;41(14):2040-59.
2. Thomas NE, Edmiston SN, Alexander A, Millikan RC, Groben PA, Hao H, et al. Number of nevi and early-life ambient UV exposure are associated with BRAF-mutant melanoma. Cancer Epidemiol Biomarkers Prev 2007; 16(5):991-7.
3. Balato N, Gaudiello F, Balato A, Monfrecola G. Sun habits in the children of Southern Italy. J Am Acad Dermatol 2007;57(5):883-7.
4. Cooper C, Sorrell J, Gerami P. Update in molecular diagnostics in melanocytic neoplasms. Adv Anat Pathol 2012;19(6):410-6.
5. Paszkowska-Szczur K, Scott RJ, Serrano-Fernandez P, Mirecka A, Gapska P, Górski B, et al. Xeroderma pigmentosum genes and melanoma risk. Int J Cancer 2013;133(5): 1094-100.
6. Braam KI, Overbeek A, Kaspers GJ, Ronckers CM, Schouten-van Meeteren AY, Van Dulmen-Den Broeder E, et al. Malignant melanoma as second malignant neoplasm in long-term childhood cancer survivors: a systematic review. Pediatr Blood Cancer 2012;58(5):665-74.
7. Shields CL. Conjunctival melanoma: risk factors for recurrence, exenteration, metastasis, and death in 150 consecutive patients. Trans Am Ophthalmol Soc 2000;98:471-92.
8. Shields CL, Markowitz JS, Belinsky I, Schwartzstein H, George NS, Lally SE, et al. Conjunctival melanoma: outcomes based on tumor origin in 382 consecutive cases. Ophthalmology 2011;118(2):389-95.e1-2.
9. Shields JA, Shields CL, Mashayekhi A, Marr BP, Benavides R, Thangappan A, et al. Primary acquired melanosis of the conjunctiva: experience with 311 eyes. Trans Am Ophthalmol Soc 2007;105:61.
10. Isager P, Engholm G, Overgaard J, Storm H. Uveal and conjunctival malignant melanoma in Denmark 1943-97: observed and relative survival of patients followed through 2002. Ophthalmic Epidemiol 2006; 13(2):85-96.
11. Chang AE, Karnell LH, Menck HR. The National Cancer Data Base report on cutaneous and noncutaneous melanoma: a summary of 84,836 cases from the past decade. The American College of Surgeons Commission on Cancer and the American Cancer Society. Cancer 1998;83(8):1664-78.
12. Yu GP, Hu DN, McCormick S, Finger PT. Conjunctival melanoma: is it increasing in the United States? Am J Ophthalmol 2003;135(6): 800-6.

13. Wong JR, Nanji AA, Galor A, Karp CL. Management of conjunctival malignant melanoma: a review and update. Expert Rev Ophthalmol 2014;9(3):185-204.
14. Jovanovic P, Mihajlovic M, Djordjevic-Jocic J, Vlajkovic S, Cekic S, Stefanovic V. Ocular melanoma: an overview of the current status. Int J Clin Exp Pathol 2013;6(7):1230-44.
15. Tuomaala S, Eskelin S, Tarkkanen A, Kivelä T. Population-based assessment of clinical characteristics predicting outcome of conjunctival melanoma in whites. Invest Ophthalmol Vis Sci 2002;43(11):3399-408.
16. Damato B, Coupland SE. An audit of conjunctival melanoma treatment in Liverpool. Eye (Lond) 2009;23(4):801-9.
17. Anastassiou G, Heiligenhaus A, Bechrakis N, Bader E, Bornfeld N, Steuhl KP. Prognostic value of clinical and histopathological parameters in conjunctival melanomas: a retrospective study. Br J Ophthalmol 2002;86(2):163-7.
18. Kurli M, Finger PT. Topical mitomycin chemotherapy for conjunctival malignant melanoma and primary acquired melanosis with atypia: 12 years' experience. Graefes Arch Clin Exp Ophthalmol 2005;243(11):1108-14.
19. Paridaens AD, McCartney AC, Minassian DC, Hungerford JL. Orbital exenteration in 95 cases of primary conjunctival malignant melanoma. Br J Ophthalmol 1994;78(7):520-8.
20. Missotten GS, Keijser S, De Keizer RJ, De Wolff-Rouendaal D. Conjunctival melanoma in the Netherlands: a nationwide study. Invest Ophthalmol Vis Sci 2005;46(1):75-82.
21. Callea V, Brugiatelli M, Stelitano C, Gentile M, Nobile F, Morabito F. Incidence of second neoplasia in patients with B-cell chronic lymphocytic leukemia treated with chlorambucil maintenance chemotherapy. Leuk Lymphoma 2006;47(11):2314-20.
22. Cheson BD, Vena DA, Barrett J, Freidlin B. Second malignancies as a consequence of nucleoside analog therapy for chronic lymphoid leukemias. J Clin Oncol 1999;17(8):2454-60.
23. Mellemgaard A, Geisler CH, Storm HH. Risk of kidney cancer and other second solid malignancies in patients with chronic lymphocytic leukemia. Eur J Haematol 1994;53(4):218-22.
24. Morrison VA, Rai KR, Peterson BL, Kolitz JE, Elias L, Appelbaum FR, et al. Therapy-related myeloid leukemias are observed in patients with chronic lymphocytic leukemia after treatment with fludarabine and chlorambucil: results of an intergroup study, cancer and leukemia group B 9011. J Clin Oncol 2002;20(18):3878-84.
25. Robak T, Blonski JZ, Gora-Tybor J, Kasznicki M, Konopka L, Ceglarek B, et al. Second malignancies and Richter's syndrome in patients with chronic lymphocytic leukaemia treated with cladribine. Eur J Cancer 2004;40(3):383-9.
26. Travis LB, Curtis RE, Hankey BF, Fraumeni JF Jr. Second cancers in patients with chronic lymphocytic leukemia. J Natl Cancer Inst 1992;84(18):1422-7.
27. Morton LM, Curtis RE, Linet MS, Bluhm EC, Tucker MA, Caporaso N, et al. Second malignancy risks after non-Hodgkin's lymphoma and chronic lymphocytic leukemia: differences by lymphoma subtype. J Clin Oncol 2010;28(33):4935-44.
28. Tsimberidou AM, Wen S, McLaughlin P, O'Brien S, Wierda WG, Lerner S, et al. Other malignancies in chronic lymphocytic leukemia/small lymphocytic lymphoma. J Clin Oncol 2009;27(6):904-10.
29. Lam CJ, Curtis RE, Dores GM, Engels EA, Caporaso NE, Polliack A, et al. Risk Factors for Melanoma Among Survivors of Non-Hodgkin Lymphoma. J Clin Oncol 2015;33(28):3096-104.