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Research Article

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Clinical Evaluation of 80 Patients with Solar Keratosis Vs 43 Patients with Squamous Cell Carcinoma of Lower Lips: Basal Cell Carcinoma is a Commonly Associated Disease with no Causal Relation

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Abstract

Background

Solar keratosis, also known as actinic keratosis or senile keratosis, is a skin condition that results from repeated sun exposure and damage, particularly in middle-aged and elderly individuals. It is characterized by rough, scaly, and warty lesions that may be pigmented, erythematous, or both, and can occur as macules, patches, or plaques. Solar keratosis lesions are most commonly found on the face and scalp and can be associated with basal cell carcinoma but not squamous cell carcinoma or solar keratosis of the lower lip. It is more prevalent in fair-skinned individuals who live in areas with high UV radiation, particularly those over 40 years of age.

Objective

The aim of this study was to document all instances of solar keratosis in patients with Fitzpatrick skin types III and IV, using a comprehensive clinical evaluation. Patients with xeroderma pigmentosum were excluded from the study. The study was conducted between 2014-2021 and involved 80 patients with solar keratosis and 43 patients with squamous cell carcinoma of the lower lips. Demographic information, complete medical history, and clinical evaluations were collected, and biopsies were performed on select patients for histopathological confirmation. This was a cross-sectional descriptive study.

Results

The study included 80 patients with solar keratosis, with ages ranging from 50 to 65 years and a mean age of 58 years. Of these patients, 41 (51.3%) were male and 39 (48.7%) were female. The lesions were predominantly located on the face, affecting 58 (72.5%) patients, while 12 (15%) patients had lesions on both the face and scalp, 4 (5%) had lesions on the scalp, forearms, and hands, and 2 (2.5%) had lesions on the eye sclera. Multiple lesions were present in 62 (77.5%) cases, and a butterfly-shaped distribution on the cheeks was observed in 18 (22.5%) patients (8 females and 10 males). The study identified rough, scaly, warty, and pigmented-erythematous rashes in the form of macules, patches, and plaques as the most common characteristics of the solar keratosis lesions. Among the 80 patients with solar keratosis, only 4 (5%) had the condition on their lower lip, and none of them had squamous cell carcinoma. In contrast, basal cell carcinoma was observed in 50 (62.5%) of patients affecting both faces and scalps, but no squamous cell carcinoma was detected. Among the 43 patients with squamous cell carcinoma of the lower lips, 2 (4.65%) had associated solar keratosis of the face. The age range of the patients with squamous cell carcinoma was 20-78 years, with a mean of 50 years, and the majority (83.7%) were males.

Conclusions
Solar keratosis is a common condition affecting the face and scalp of elderly patients of both sexes, and is often found in conjunction with basal cell carcinoma but not squamous cell carcinoma. This association between solar keratosis and basal cell carcinoma is coincidental rather than causal, as both are common conditions that often occur together. Importantly, solar keratosis of the face does not transform into basal cell carcinoma. Conversely, squamous cell carcinoma of the lower lip is predominantly a disease of males and is not associated with either solar keratosis or cancers of the face.

Keywords: Solar keratosis, Basal Cell Carcinoma, Squamous Cell Carcinoma, P53.

Introduction

Actinic keratoses were first described in 1826 by Dubreuilh. They are also called solar keratoses or senile keratoses [1,2]. A few years later, Freudenthal proposed the term ''keratoma senilis'' to describe the lesions, and in 1958 Pinkus renamed the lesions ''actinic keratoses'' [3]. In spite of the fact that they are classically regarded as pre-neoplastic lesions, some authors have suggested that they may actually be in situ neoplasms since they derive from clonal DNA modifications in keratinocytes [2,4]. SK are caused by Keratinocyte proliferation with varying degrees of dysplasia in the epidermis, which is referred to as intraepithelial keratinocyte dysplasias; in addition, the tumors can turn malignant into non-melanoma skin cancer, especially with SCC, and they tend to occur most often in areas that are exposed to the sun [1,5]. In summary, actinic keratoses (AKs) are also known as solar or senile keratoses and were first described in 1826 by Dubreuilh. They are considered pre-neoplastic lesions that may be in situ neoplasms derived from clonal DNA modifications in keratinocytes. The distinction between AKs and thin SCCs is not clear, as AKs are considered embryonic SCCs [2]. The highest rates of AKs are observed in Caucasians over 40 years of age particularly those who live near the equator with Australia having the highest prevalence followed by the United States and Europe[6-8], The prevalence of AKs among Caucasians in Australia is estimated to be between 40% and 60%, and in the United States, it is between 11.5% and 26% [9,10]. An English population-based study discovered that men over 40 years old have a 15% prevalence of actinic keratoses, and women have a 5.9% prevalence. [11] A study in Spain found that 28.6% of patients over the age of 45 had actinic keratoses, according to the study and that there is a lower prevalence of AKs among Asians [11,12]. For example, according to South Korean statistics, the rate ranges from 0.02% in 40-year-olds to 0.09% in 60-year-olds to 0.21% in 70-year-olds [13]. It is interesting to note that despite most people in Iraq having skin types III and IV, solar keratosis is still a common problem [14,15].

In albinos and patients carrying other genodermatoses with defective DNA repairs genes, such as xeroderma pigmentosum, Rothmund-Thompson syndrome, Cockayne's syndrome, and Bloom's syndrome, lesions may appear during their first decade of life, and they may have a greater risk of aggressiveness and risk from their lesions [1,16]. Due to the high level of UV exposure men are exposed to during their lifetimes, it is believed that SK is more common in men [17]. Fair-skinned individuals (types I and II) are more prone to developing actinic keratoses due to their sensitivity to harmful effects of UV radiation on the skin as well as their increased vulnerability to sun damage due to their increased vulnerability to the sun [17,18]. It has been found that solar keratoses are caused by a combination of environmental factors, genetics, and individual factors [9]. The main factor is excessive UV radiation, which acts as a complete carcinogen, causing tumor growth and contributing to cancer [5,7]. As a result of UV radiation, a number of molecular signaling cascades are activated, resulting in modifications in the levels of regulatory cytokines, immunosuppressive effects, as well as impaired differentiation and apoptosis of Cells [5]. As a consequence of these effects, mutations are seen in the P53 protein, which controls the cell cycle and is responsible for DNA damage repair as well as mutations in the telomerase gene, which results in an increase in proinflammatory cytokine production [19]. The relationship between inflammation and the development of Solar keratoses is closely linked. Accordingly, Inflammation, oxidative stress, immunosuppression, inhibited apoptosis, deregulation of the cell cycle, cell proliferation, and remodeling of the tissues are all factors that can affect tissue function and appearance are all mechanisms that lead to the onset of SK [5,7].

There is compelling evidence that anti-inflammatory therapy has proven to be effective in treating actinic keratoses Inflammatory processes are mediated through the arachidonic acid pathway, the production of proinflammatory cytokines, and the activation of mast cells and inhibitory factors of macrophage migration, which are all components of the inflammatory process; It has been shown that these mediators can lead to lipid peroxidation, an increase in T lymphocytes and Langerhans cells intralesionally, an increase in P53 and Bcl-2, and a decrease in Fas (cd95) and Fas-ligand, both of which are necessary for initiating apoptosis in UV-mutated cells [5,21]. It appears that inflammation and the development of actinic keratoses are closely related in lesions that have progressed to SCC; in some cases, actinic keratoses undergo an inflammatory phase before becoming invasive [20]. In the most common form of the condition, SK appears as erythematous macules, papules, or plaques, usually with poorly defined borders, and they may be covered by dry scales that adhere to them. Occasionally, these conditions can be better diagnosed by palpation than by visual inspection, and the degree of hyperkeratosis that they present can vary [1,22]. Solar keratoses (SK) are skin lesions that can appear as either single or multiple lesions with varying colors ranging from pink erythematous to brownish in pigmented actinic keratosis [23]. They are typically asymptomatic, but some patients may experience discomfort such as burning, pain, bleeding, and pruritus. SK is commonly observed in areas of the skin that are chronically exposed to photo-exposed, including the face, scalp in the bald area,

neck region, shoulders, forearms, and backs of the hands [1, 9, 22]. There are various clinical.

manifestations of SK, including hyperkeratotic, atrophic, pigmented, lichenoid, and cutaneous horns, as well as actinic cheilitis [24]. In cases of severe photodamage, SK may be multiple and poorly delineated, and in such cases, the lesions cannot be counted. As a consequence of the prolonged exposure to carcinogenic agents, especially UV radiation, field cancerization occurs, which is characterized by pre-neoplastic changes of the epithelium; the field cancerization is comprised of lesions of various phases, ranging from subclinical actinic keratoses to stage 4 skin cancers [25,26]. Histopathologically, SKs are characterized by the presence of abnormal and pleomorphic keratinocytes in the basal layer of the epidermis, as well as defective maturation of keratinocytes in the superficial layers of the epidermis, leading to a variety of clinical manifestations and abnormal epidermal architecture. This results in an increase in the number of mitoses and a loss of polarity of the keratinocytes [27]. There are three different ways in which actinic keratoses can develop, the most relevant of which is the transition to SCC. A significant portion, however, remains stable during the evolution of the disease and may also involute spontaneously, but recurrences are common as the disease evolves [5,28]. The risk of malignant transformation in SKs ranges from 0.1% to 16%, Therefore, when evaluating the risk of malignant transformation of SK in patients presenting with multiple lesions, the risk will be higher than that described for patients who present with one lesion [29, 30]. The risk of developing BCC, SCC, and melanoma in patients with solar Keratosis is higher than the risk in the general population [30,31]. In accordance with the proposed mechanism for explaining spontaneous remission of actinic keratoses, a sufficient immune response could lead to the destruction of the lesions, and at the same time, a reduction in UV radiation exposure may also play a role [29]. The treatment for SK consists of either surgical destruction of the lesions, such as excision, curettage, cryosurgery, and a variety of cosmetic resurfacing procedures can be performed, including medium and deep chemical peels, dermabrasion, and laser ablative resurfacing [32-34]. Topical treatments for solar keratosis include various options such as 5-fluorouracil (5-FU) cream at concentrations of 5%, Imiquimod cream at 3.75%, diclofenac gel, PDT with topical delta-aminolevulinic acid, Ingenol mebutate gel (Picato), Zinc Sulphate 25% cream, and Podophyllin Solution 25%. These therapies are designed to target the affected area and help eliminate the abnormal cells [35-40]. Interestingly, while both basal cell carcinoma (BCC) and solar keratosis are known to be associated with sun exposure, the occurrence of combined or collision tumors is rarely reported in literature and often seen in individuals with syndromes like Xeroderma pigmentosa [41,42]. Several theories exist regarding the pathogenesis of collision lesions. One theory suggests that a single cell type (pluripotent cell) can differentiate in more than one direction, leading to a composite or intermingled lesion when it causes a biphasic or biphenotypic collision [43]. As another explanation, there is the possibility of two separate but adjacent neoplasms occurring at the same time because of exposure to certain carcinogenic stimuli, or paracrine factors released from one neoplasm affecting vulnerable cells adjacent to it as a result. [44]

Patients and Methods

Two groups of patients were included, the first group consisted of eighty patients complaining of solar keratosis gathered during the period from 2014-2021 years in this descriptive, cross-sectional clinical and histopathological study. The Declaration of Helsinki was followed during the study. A formal informed consent form was obtained from all patients after a discussion about the nature of the study had taken place with them. The close-up photo was taken at the same place with a fixed distance and illumination. In addition, all included patients accepted the idea to share their photos in this present work. Excluding patients with xeroderma pigmentosum in this study. A thorough full history to establish the right clinical diagnosis with a well-established examination was done. Name, age, gender, residence, occupation especially with outdoor activities, history of smoking, alcohol intake, and past medical and drug history were taken from all patients. The type of lesions, duration of the disease, site, size, morphology, color, number of lesions, and lymph node examination were also evaluated. All patients included were Fitzpatrick skin type III and IV and any signs of sun damage were recorded [45]. Histopathological evaluation was carried out in selected cases.

The second group included forty-three patients with squamous cell carcinoma of lower lips that were screened for solar keratosis of the face as a comparative study with solar keratosis during the same period time. Symptoms related to the lesions such as pain, itching, and tenderness were evaluated. All demographic features were recorded. Shave or incisional biopsies were done for histopathological assessment and were carried out in all cases as a confirmatory test.

Results

The first group comprised 80 patients with varying subtypes of solar keratosis, aged between 50-65 years with an average age of 58 years. Among them, 41 (51.3%) were male and 39 (48.7%) were female. Most of the lesions were found on the face (58 patients, 72.5%), while 12 patients (15%) had lesions on both the face and scalp, 4 patients (5%) had lesions on the scalp, forearms, and hands, and 2 patients (2.5%) had lesions on the eye sclera. The majority of cases (62 patients, 77.5%) had multiple lesions, and 18 patients (22.5%) had butterfly-shaped lesions on their cheeks (8 females and 10 males). The lesions were characterized as rough, scaly, warty, pigmented-erythematous rashes, which could be macules, patches, or plaques. Only 4 patients (5%) had solar keratosis on their lower lip, and no patients had squamous cell carcinoma of the lips. However, 50 patients (62.5%) had basal cell carcinoma affecting both their face and scalp, while no cases of squamous cell carcinoma were observed. The second group consisted of 43 patients with squamous cell carcinoma of the lower lip, aged between 20-78 years with an average age of 50 years. Among them, 36 patients (83.7%) were male and 7 patients (16.2%) were female, and only 2 patients (4.65%) had associated solar keratosis on their face during the same time period.

Table (1): Showing the socio-demographic features in first and second group of patients

Character	Number	Percentage (%)
Patients with solar Keratosis	(n=80)	
Age in years:		
-Range	50-65 years	
-Mean	58 years	
Sex:		
-Males	41	(51.3)
-Females	39	(48.7)
Patients with squamous cell carcinoma of lower lips (n=43)		
Ages		
-Range	20-78 years	
-Mean	50 years	
Sex:		
-Males	36	(83.7)
-Females	7	(16.3)

Table (2): Showing the clinical features of the first and second group of patients

Character	Number	Percentage (%)
Solar Keratosis	(n=80)	
Lesion location:		
-Face	58	(72.5)
-Face and scalp	12	(15)
-Scalp with forearms and hands	4	(5)
-Eye sclera	2	(2.5)
-Lower lips	4	(5)
Associated Carcinoma:		
-Basal cell carcinoma	50	(62.5)
-Squamous cell carcinoma	0	(0)
The number of lesions:		
-Multiple lesions	62	(77.5)
-Butterfly on cheeks	18	(22.5)
Patients with squamous cell carcinoma of lower lips (n=43)		
Association with solar keratosis of face:		
-Yes	2	(4.65%)
-No	41	(95.4%)

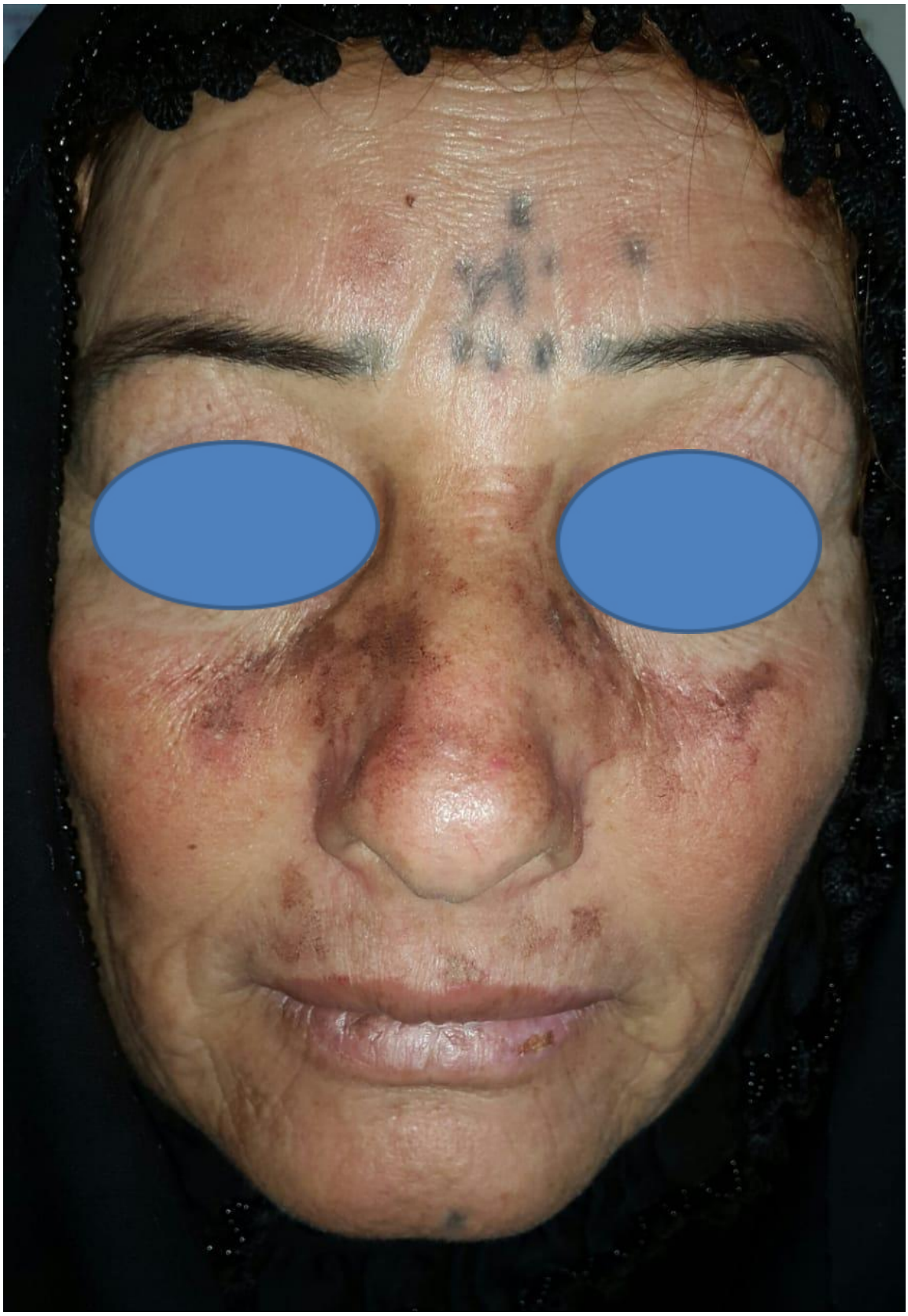

Figure-1- 50-year-old female with butter fly like solar keratosis.

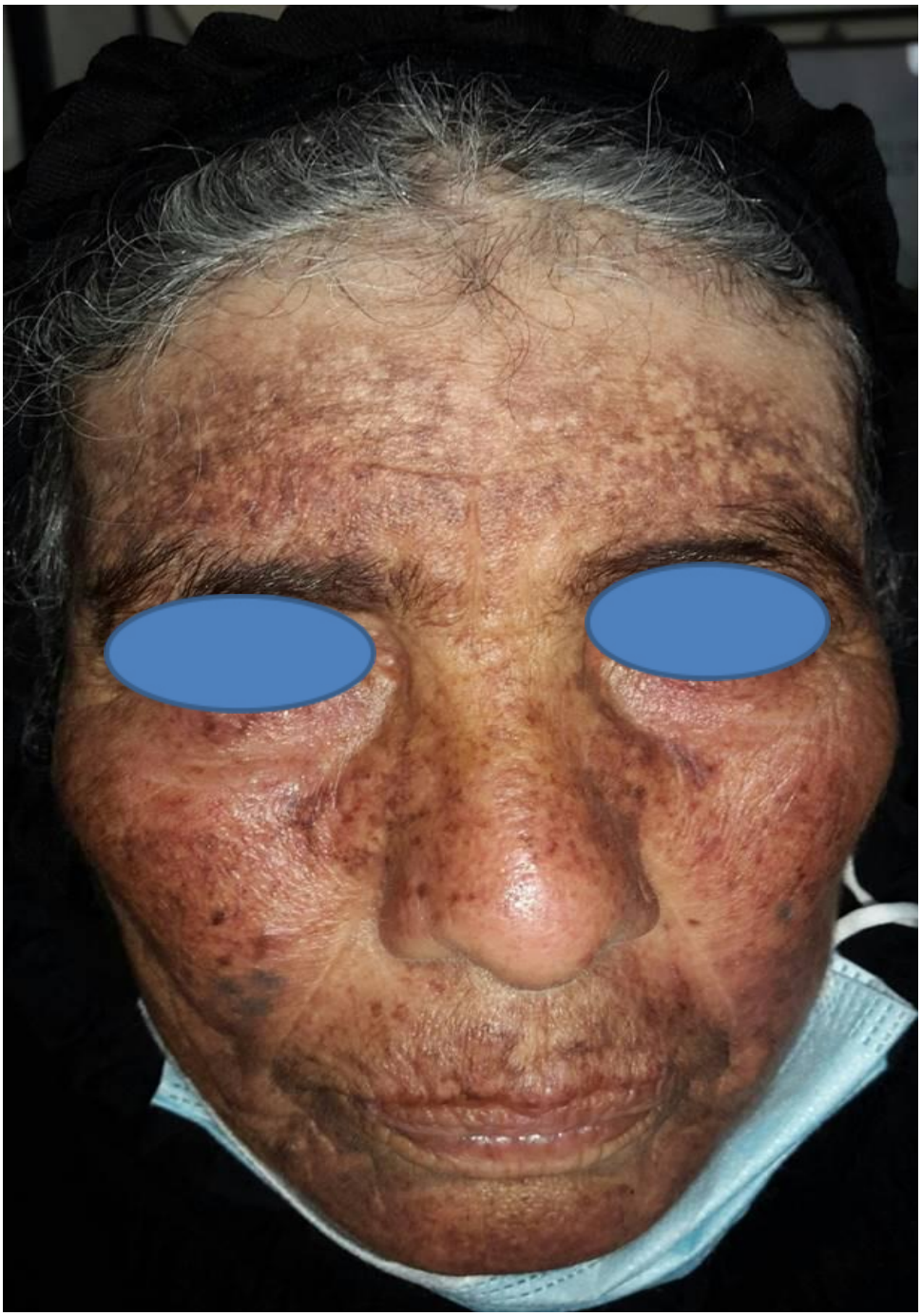

Figure-2- 47-year-old farmer female sowing numerous facial solar keratosis.

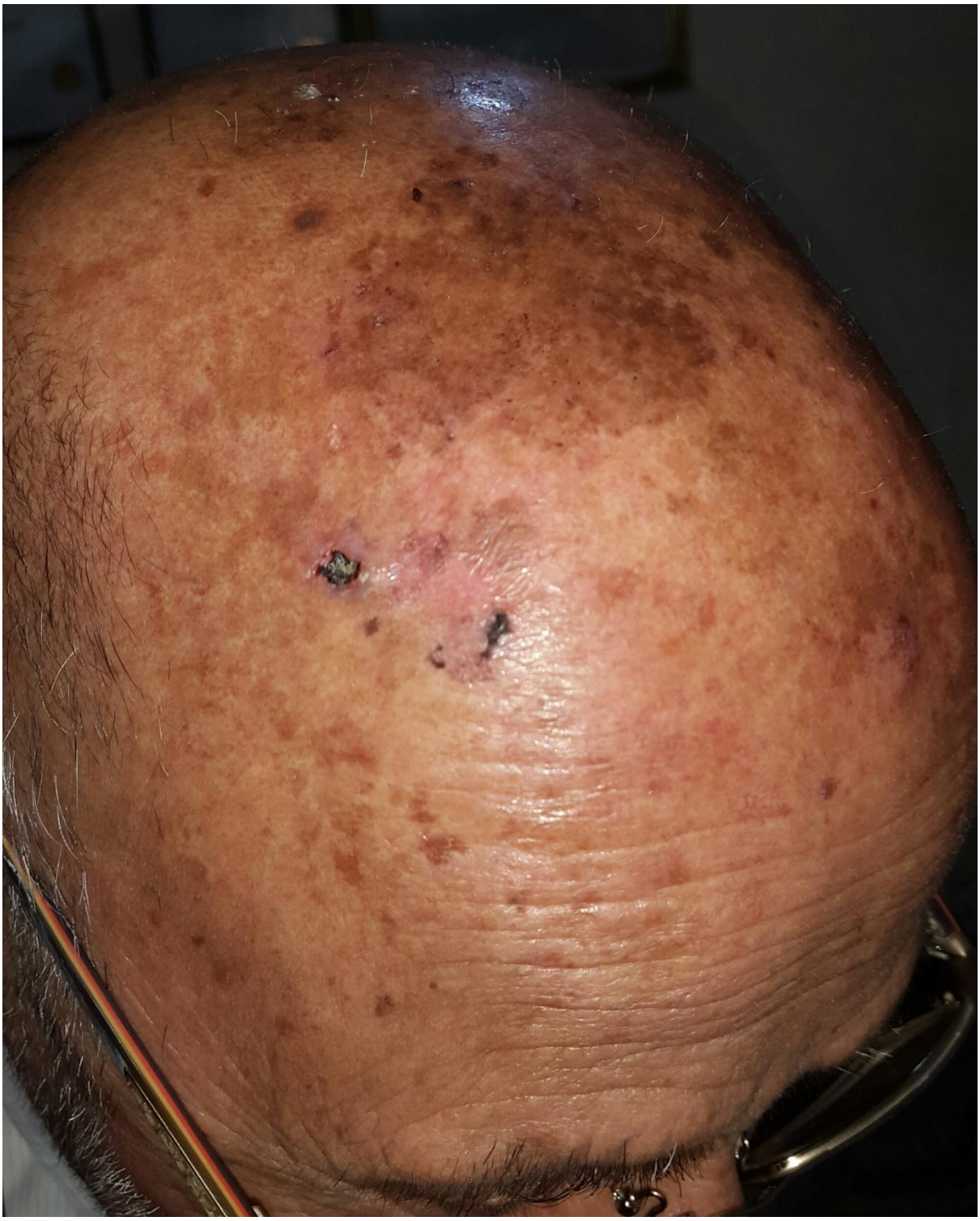

Figure-3- 67-year-old male with multiple solar keratosis and basal cell carcinoma of scalp.

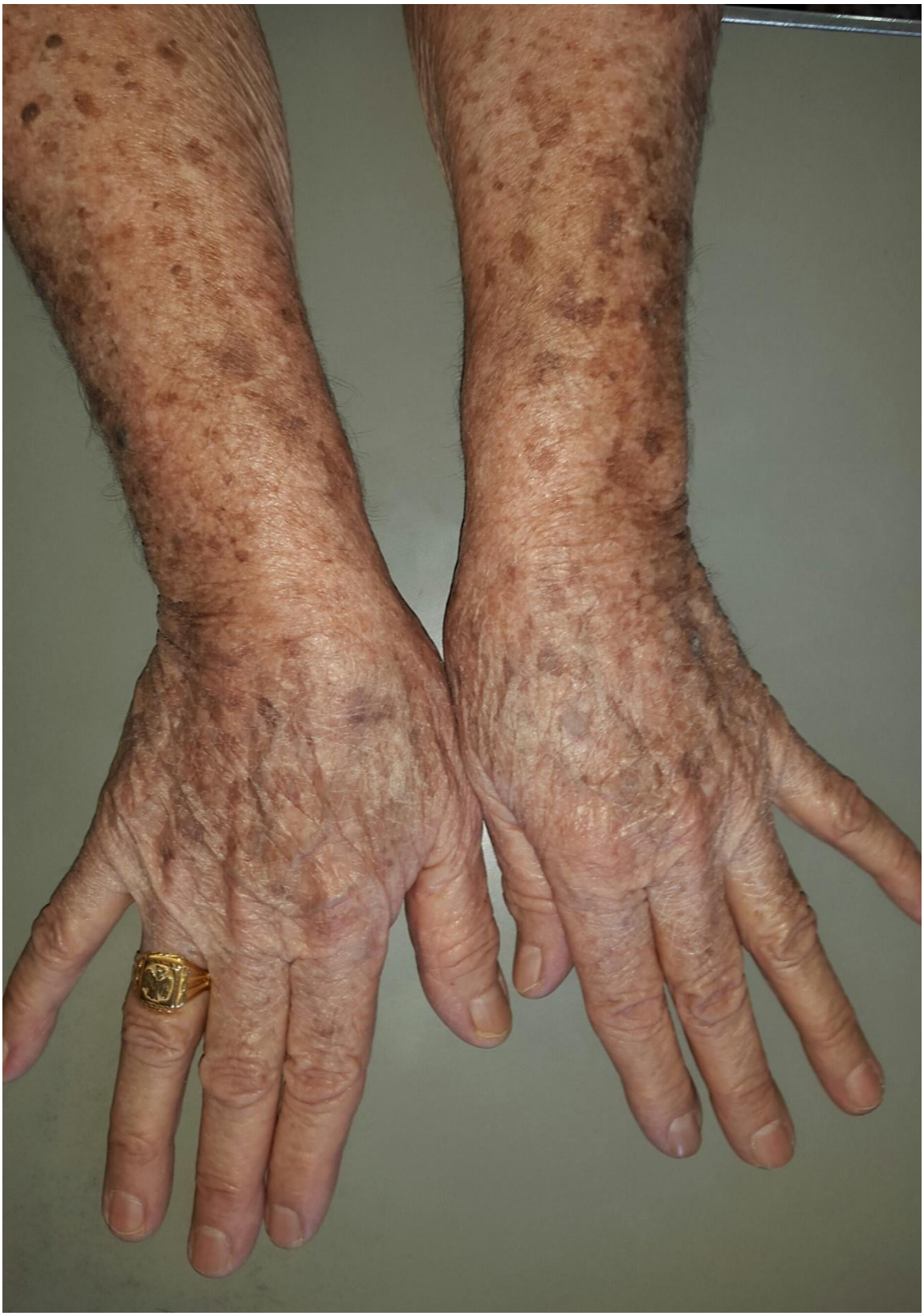

Figure-4- 58-year-old patient with solar keratosis of hands and forearms.

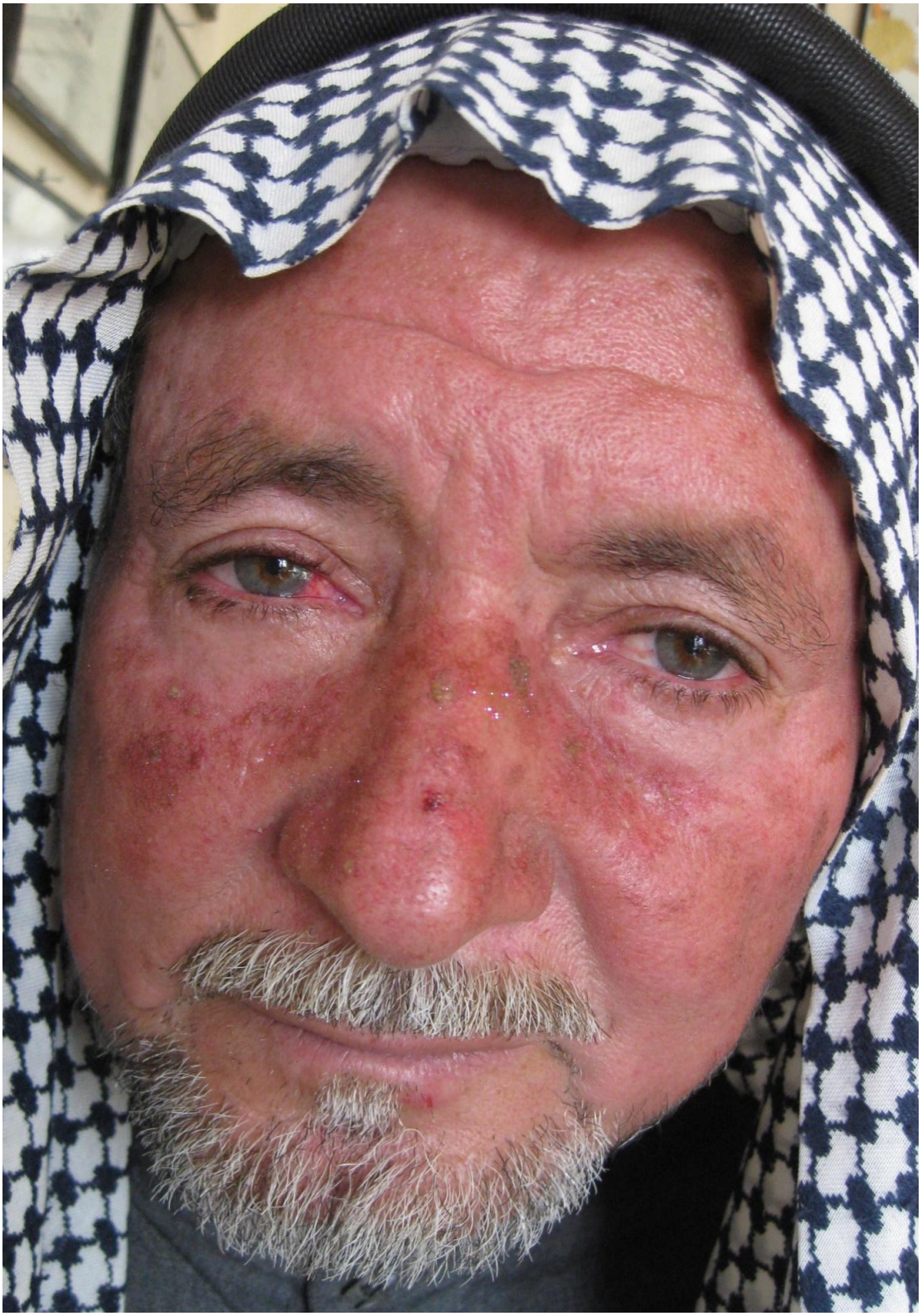

Figure-5- 60-year-old male with butter fly solar keratosis with solar keratosis of eye sclera and basal cell carcinoma.

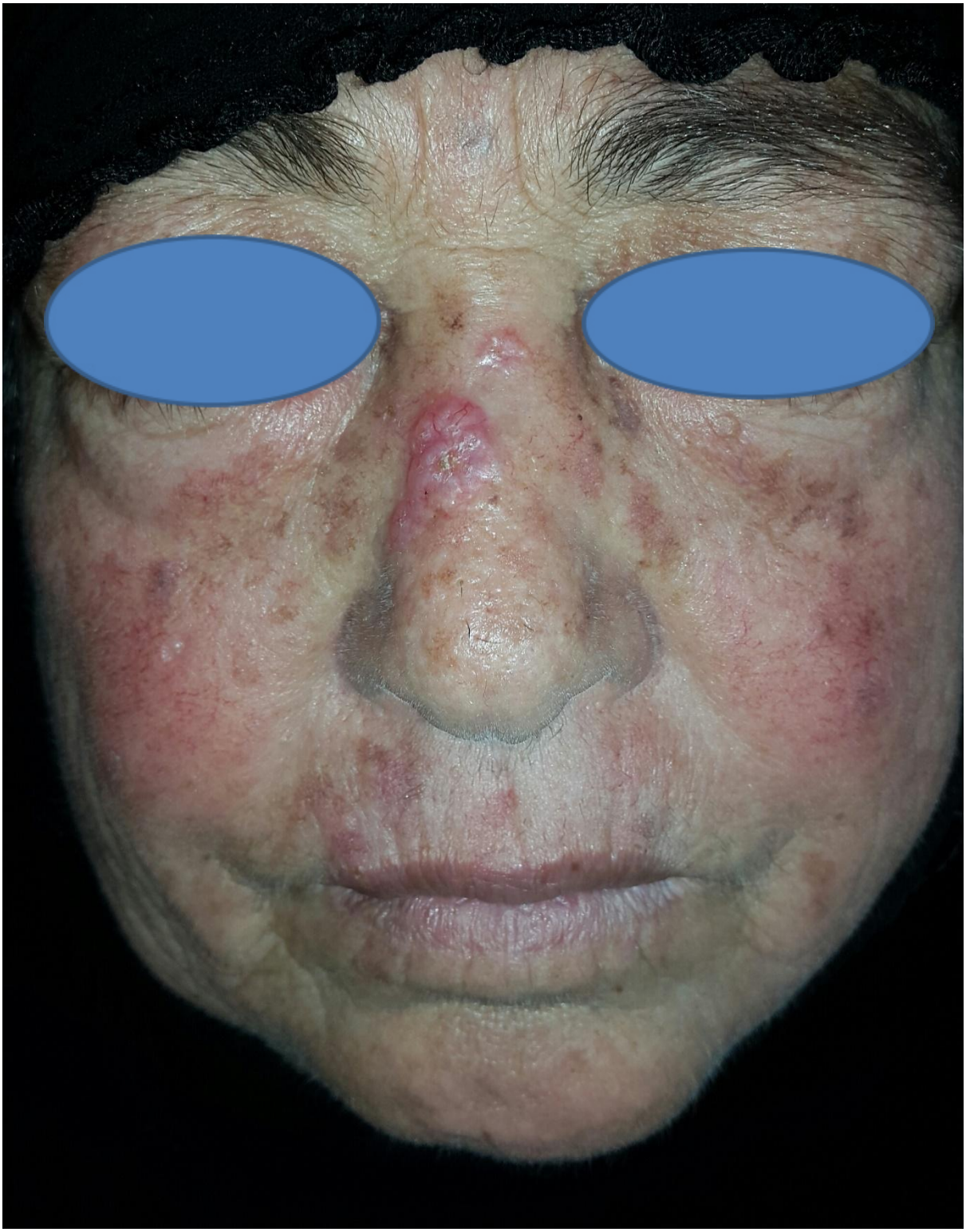

Figure-6-50-year-old female with multiple solar keratosis and basal cell carcinoma.

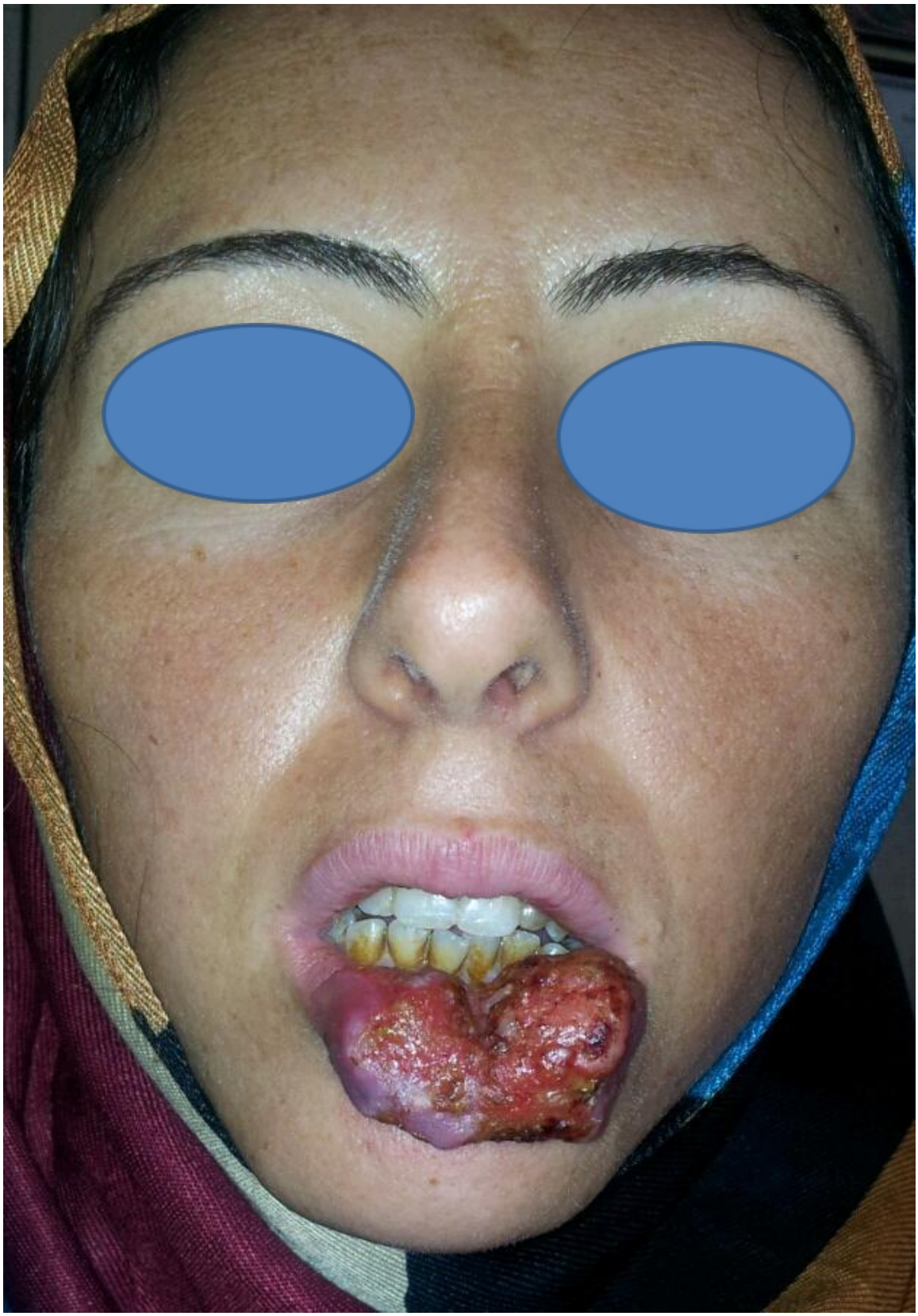

Figure-7- 30-year-old female with squamous cell carcinoma lips but with no solar keratosis of face.

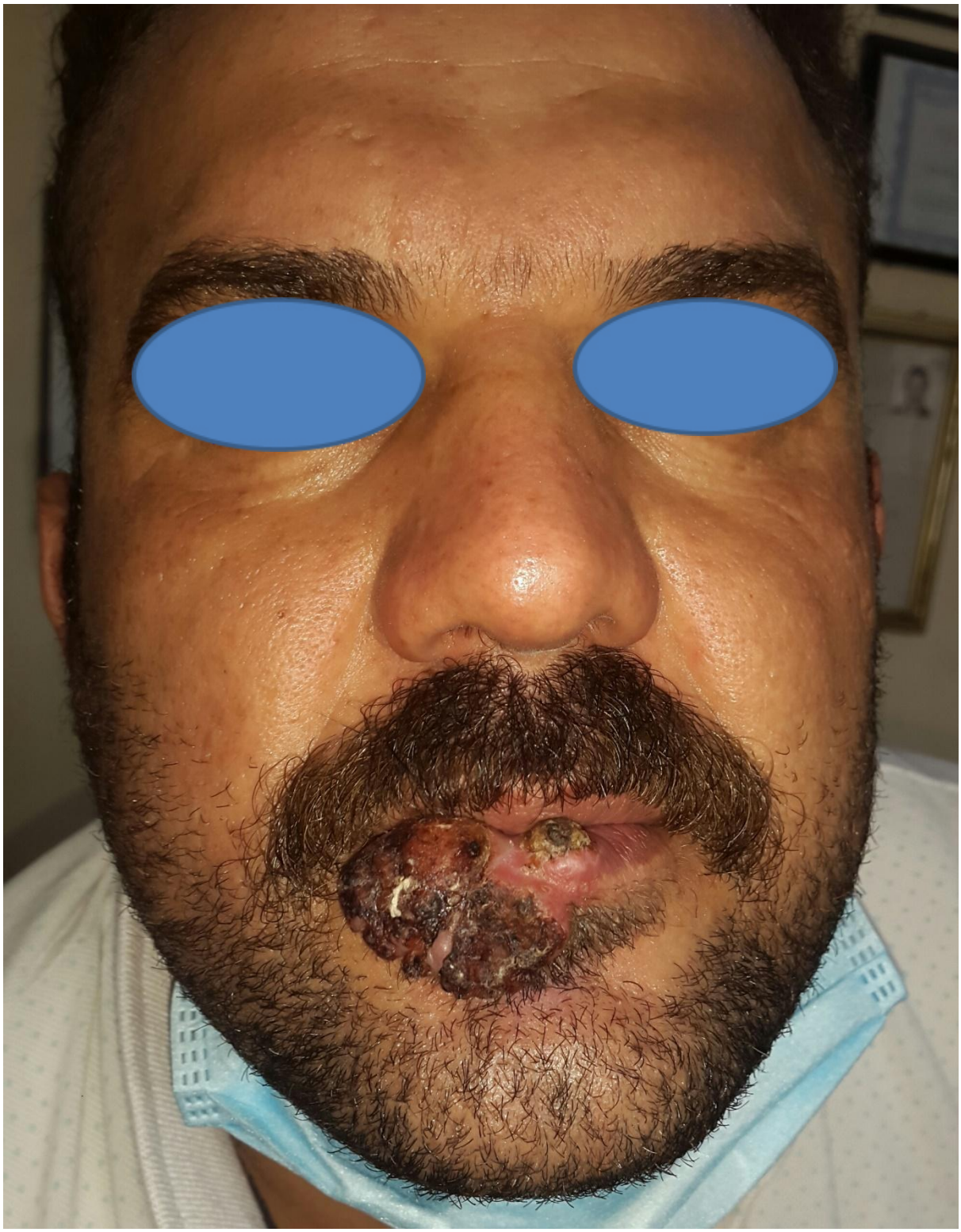

Figure-8- 28-year-old male with squamous cell carcinoma lips but with no solar keratosis of face.

Discussion

Solar keratosis is a type of skin tumor that is predominantly found on sun-exposed skin surfaces. It is a major problem among fair-skinned Europeans, while in Middle Eastern countries, where skin types III and IV are more common, solar keratosis is less prevalent due to the protective effects of melanin. However, recent studies have shown that people in middle and older age groups in these regions are not immune to this condition. Previous studies on the coexistence of solar keratosis with basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) mainly included patients with skin types I and II. This study is the first in the Middle East to investigate the relationship between solar keratosis, BCC, and SCC among patients with skin types III and IV. In other countries such as Finland, Germany, Greece, Italy, Malta, Poland, Scotland, and Spain, a study of 343 patients with solar keratosis, 409 with SCC, 602 with BCC, 360 with invasive melanoma, 119 with in situ melanoma, and 686 controls found that 58% of patients with solar keratosis and a history of previous SCC had coexisting SCC. BCC coexistence was found in 30% of cases, while coexistence with melanoma in situ and invasive melanoma was detected in 12% and 6%, respectively. These studies suggest that prolonged exposure to UV radiation or sunlight is a significant contributor to the development of premalignant skin lesions. UV exposure can induce variations in the tumor suppressor gene TP53, which is a reliable marker of solar keratosis. Histological, immunohistochemical, and molecular studies of solar keratosis suggest a related pathogenesis to Bowen disease and SCC. BCC has also been observed to be predisposed to UVR, and there is an association between BCC and a wide range of sun-induced skin lesions, including solar keratosis on the face, actinic cheilitis, solar lentigines, facial telangiectasias, and cutis rhomboidalis nuchae when exposed to UVR. It has been proposed that pluripotent epidermal stem cells resulting from chronic exposure to UV light are responsible for the development of antigenically different skin tumors in the same patient. The Iraqi population has relatively low incidence rates of NMSC, melanoma, and other forms of skin cancers due to the presence of skin types III and IV, which

provide melanin photoprotection to the skin[49,50] In a study performed by Sharquie et al. suggested the most common skin tumor in the Iraqi population is BCC followed by SCC, basosquamous, keratoacanthoma, and lastly seborrheic keratosis. [14] In the present study, the prevalence of solar keratosis is quite high among middle-aged and elderly individuals who are between ages 50 and 65 years, and males (51.3%) are prone to developing these lesions almost comparable to women (48.7%) because almost all people have outdoor activity and chronic exposure to the sun. Most of the lesions were occurring on the face (72.5%), which is consistent with what has been reported in the literature [1-5]. One of the most important results concluded from this study is that there was no co-existence association between solar keratosis and SCC in all eighty patients. And similarly, in forty-three patients with SCC of the lower lip as a comparative study, facial SK was reported in just only 4.6% of the patients, while a common association between SK and BCC was reported in 62.5% of BCC in SK cases. BCC and SK are both common disease types, so the association between them is more likely to be coincidental than cause-related or due to other unknown causes. Most recently Sharquie et al. conducted a study in a series of 140 patients with BCC and showed solar keratosis was only detected in 14.3% with BCC while in the present study patients with SCC of lower lips had only 4.65% of cases associated with solar keratosis [51]. Accordingly, patients with primary BCC and SCC are more protective and immune to developing solar keratosis during the course of the disease. But when patients who already have solar keratosis are more liable to have BCC as observed in the present work. This controversial association could not be well explained but we can speculate that patients with primary onset of BCC and SCC are more immune to develop solar keratosis. In addition, several other factors may play a role, including skin color type, ethnicity, and intensity of UV exposure, in the formation of this association and in affecting mutations in pluripotent epidermal stem cells. However, there are still many studies to be conducted to prove this hypothesis.

Conclusion

Solar keratosis is a disease of the face and scalp of elderly patients of almost equal sexes that is commonly associated with basal cell carcinoma but not squamous cell carcinoma and this association is coincidental rather than cause-related as both BCC and SK are common diseases. So Solar keratosis of the face does not change into basal cell carcinoma. But patients with facial solar keratosis were not associated with either solar keratosis or squamous cell carcinoma of the lower lip. While patients with squamous cell carcinoma of the lower lips is a disease of males who are immune to developing either solar keratosis or cancers of the face. Lastly patients with primary onset of BCC or SCC will not develop solar keratosis during the course of the disease.

References

1. Schmitt, J. V., & Miot, H. A. (2012). Actinic keratosis: a clinical and epidemiological revision. Anais brasileiros de dermatologia, 87, 425-434.
2. Heaphy, M. R., & Ackerman, A. B. (2000). The nature of solar keratosis: a critical review in historical perspective. Journal of the American Academy of Dermatology, 43(1), 138-150.
3. Cockerell, C. J. (2000). Histopathology of incipient intraepidermal squamous cell carcinoma ("actinic keratosis"). Journal of the American Academy of Dermatology, 42(1), S11-S17.
4. Lober, B. A., Lober, C. W., & Accola, J. (2000). Actinic keratosis is squamous cell carcinoma. Journal of the American Academy of Dermatology, 43(5), 881.
5. Berman, B., & Cockerell, C. J. (2013). Pathobiology of actinic keratosis: ultraviolet-dependent keratinocyte proliferation. Journal of the American Academy of Dermatology, 68(1), S10-S19.
6. Lucas R, Prüss-Üstün A, World Health Organization. Solar ultraviolet radiation: global burden of disease from solar ultraviolet radiation. Geneva: World Health Organization, Public Health and the Environment; 2006.
7. Reinehr, C. P. H., & Bakos, R. M. (2020). Actinic keratoses:

review of clinical, dermoscopic, and therapeutic aspects. Anais Brasileiros de Dermatologia, 94, 637-657.
8. Flohil, S. C., Van Der Leest, R. J., Dowlatshahi, E. A., Hofman, A., De Vries, E., & Nijsten, T. (2013). Prevalence of actinic keratosis and its risk factors in the general population: the Rotterdam Study. Journal of Investigative Dermatology, 133(8), 1971-1978.
9. Frost, C. A., & Green, A. C. (1994). Epidemiology of solar keratoses. British Journal of Dermatology, 131(4), 455-464.
10. Salasche, S. J. (2000). Epidemiology of actinic keratoses and squamous cell carcinoma. Journal of the American Academy of Dermatology, 42(1), S4-S7.
11. Memon AA, Tomenson JA, Bothwell J, Friedmann PS. Prevalence of solar damage and actinic keratosis in a Merseyside population. Br J Dermatol. 2000; 142:1154-9.
12. Ferrándiz, C., Plazas, M. J., Sabaté, M., Palomino, R., & EPIQA Study Group. (2016). Prevalence of actinic keratosis among dermatology outpatients in Spain. Actas Dermo-Sifiliográficas (English Edition), 107(8), 674-680.
13. Lee, J. H., Kim, Y. H., Do Han, K., Park, Y. M., Lee, J. Y., Park, Y. G., & Lee, Y. B. (2018). Incidence of actinic keratosis and risk of skin cancer in subjects with actinic keratosis: a population-based cohort study. Acta Dermato-Venereologica, 98(3), 382-383.
14. Sharquie, K. E., Al-Rawi, J. R., & Al-Rawi, A. S. (2009). Association between Facial Skin Tumors and Wrinkling. IRAQI JOURNAL OF COMMUNITY MEDICINE, 22(3).
15. Sharquie KE, Kadim KA, Actinic Keratosis in Iraqi patients, a clinical and Histopathological study. Thesis for the fellowship of the Iraqi Board. Iraqi Board for medical specialization in Dermatology and Venereology, 2002: 38-40.
16. Agale, S. V., D'Costa, G. F., Bharambe, B. M., & Bhatia, V. (2012). Childhood actinic keratosis in an albino transforming into squamous cell carcinoma. Indian Dermatology Online Journal, 3(3), 199.
17. Fargnoli, M. C., Altomare, G., Benati, E., Borgia, F., Broganelli, P., Carbone, A., ... & Peris, K. (2017). Prevalence and risk factors of actinic keratosis in patients attending Italian dermatology clinics. European Journal of Dermatology, 27, 599-608.
18. Schaefer, I., Augustin, M., Spehr, C., Reusch, M., & Kornek, T. (2014). Prevalence and risk factors of actinic keratoses in Germany–analysis of multisource data. Journal of the European Academy of Dermatology and Venereology, 28(3), 309-313.
19. Dodds, A., Chia, A., & Shumack, S. (2014). Actinic keratosis: rationale and management. Dermatology and therapy, 4, 11-31.
20. Wang L, Eng W, Cockerell CJ. Effects of ultraviolet irradiation on inflammation in the skin. Adv Dermatol. 2002; 18:247-86.
21. Bowden, G. T. (2004). Prevention of non-melanoma skin cancer by targeting ultraviolet-B-light signalling. Nature Reviews Cancer, 4(1), 23-35.
22. Peris, K., Micantonio, T., Piccolo, D., & Concetta, M. (2007). Dermoscopic features of actinic keratosis. JDDG: Journal der Deutschen Dermatologischen Gesellschaft, 5(11), 970-975.
23. Anwar, J., Wrone, D. A., Kimyai-Asadi, A., & Alam, M. (2004). The development of actinic keratosis into invasive squamous cell carcinoma: evidence and evolving classification schemes. Clinics in dermatology, 22(3), 189-196.
24. Moy RL. Clinical presentation of actinic keratoses and squamous cell carcinoma. J Am Acad Dermatol. 2000;42: 8-10.
25. Cohn BA. From sunlight to actinic keratosis to squamous cell carcinoma. J Am Acad Dermatol. 2000; 42:143-4.
26. Slaughter DP, Southwick HW, Smejkal W. Field cancerization in the oral stratified squamous epithelium; clinical implications of multicentric origin. Cancer. 1953; 6:963-8.
27. Roewert-Huber J, Stockfleth E, Kerl H. Pathology and pathobiology of actinic (solar) keratosis - an update. Br J Dermatol. 2007; 157:18-20.
28. Criscione VD, Weinstock MA, Naylor MF, Luque C, Eide MJ, Bingham SF, et al. Actinic keratoses: natural history and risk of malignant transformation in the Veterans Affairs Topical Tretinoin Chemoprevention Trial. Cancer. 2009; 115:2523-30.
29. Marks R, Foley P, Goodman G, Hage BH, Selwood TS. Spontaneous remission of solar keratoses: the case for conservative management. Br J Dermatol. 1986; 115:649-55.
30. Moon TE, Levine N, Cartmel B, Bangert JL, Rodney S, Dong Q, et al. Effect of retinol in preventing squamous cell skin cancer in moderate-risk subjects: a randomized, double-blind, controlled trial. Southwest Skin Cancer Prevention Study Group. Cancer Epidemiol Biomark Prev. 1997; 6:949-56.
31. Foote JA, Harris RB, Giuliano AR, Roe DJ, Moon TE, Cartmel B, et al. Predictors for cutaneous basal- and squamous cell carcinoma among actinically damaged adults. Int J Cancer. 2001; 95:7-11.
32. Hantash BM, Stewart DB, Cooper ZA, Rehmus WE, Koch RJ, Swetter SM. Facial resurfacing for nonmelanoma skin cancer prophylaxis. Arch Dermatol. Aug 2006; 142(8):976-82.
33. Sherry SD, Miles BA, Finn RA. Long-term efficacy of carbon dioxide laser resurfacing for facial actinic keratosis. J Oral Maxillofac Surg. Jun 2007; 65(6):1135-9.
34. Winton GB, Salasche SJ. Dermabrasion of the scalp as a treatment for actinic damage. J Am Acad Dermatol. Apr 1986; 14(4):661-8.
35. Spencer JM, Hazan C, Hsiung SH, Robins P. Therapeutic decision making in the therapy of actinic keratoses. J Drugs Dermatol. May-Jun 2005; 4(3):296-301.
36. Tutrone WD, Saini R, Caglar S, Weinberg JM, Crespo J. Topical therapy for actinic keratoses, I: 5- Fluorouracil and Imiquimod. Cutis. May 2003; 71(5):365-70.
37. Tutrone WD, Saini R, Caglar S, Weinberg JM, Crespo J. Topical therapy for actinic keratoses, II: Diclofenac, colchicine, and retinoid. Cutis. May 2003; 71(5):373-9.
38. Lebwohl M, Swanson N, Anderson LL, Melgaard A, Xu Z, Berman B. Ingenol mebutate gel for actinic keratosis. N Engl J Med. Mar 15 2012; 366(11):1010-9.
39. Sharquie KE, Al-Mashhadani SA, Noaimi AA, Hasan AA. Topical zinc sulphate (25%) solution: A New Therapy for actinic keratosis. Journal of Cutaneous and Aesthetic Surgery

– 2012; 5:53-56.
40. Sharquie KE, Noaimi AA, Al-Zoubaidi MS (2015); Treatment of actinic keratosis by topical 25% podophyllin solution Int. J. of Adv. Res. 3 (Oct). 1232-1240] (ISSN 2320-5407).
41. Boyd AS, Rapini RP. Cutaneous collision tumors. An analysis of 69 cases and review of the literature. Am J Dermatopathol 1994; 16:253-7.
42. Smith LJ, Husain EA. Colonization of basal cell carcinoma and actinic keratosis by malignant melanoma in situ in a patient with xeroderma pigmentosum variant. Clin Pract. 2012 Apr 16; 2(2): e47. doi: 10.4081/cp.2012.e47.
43. Braun-Falco M. Combined malignant melanoma and basal cell carcinoma tumor of the intermingled type. J Cutan Pathol 2007; 34:731-5.
44. Pecorella I, Memeo L, Ciardi A, Rotterdam H. An unusual case of colonic mixed adenoendocrine carcinoma: collision versus composite tumor. A case report and review of the literature. Ann Diagn Pathol 2007; 11:285-90.
45. Browder JF, Beers B. Photo aging Cosmetic effects of sun damage. Postgraduate medicine. 1993: 93(8): 74-92.
46. Duncan KO, Geisse JK, Jeffell DJ. Epidermal and appendageal tumors. In: Freedberg IM, Eison AZ, Wolff K, Austenk F, Goldsmith LA, Katz SI, editors. Fitzpatrick's Dermatology in General Medicine. 6th ed. Vol. 21. New York: McGraw Hill Book Company; 2008. pp. 1007–15.
47. Traianou A, Ulrich M, Apalla Z, De Vries E, Bakirtzi K, Kalabalikis D, Ferrandiz L, Ruiz-de-Casas A, Moreno-Ramirez D, Sotiriadis D, Ioannides D, Aquilina S, Apap C, Micallef R, Scerri L, Pitkänen S, Saksela O, Altsitsiadis E, Hinrichs B, Magnoni C, Fiorentini C, Majewski S, Ranki A, Proby CM, Stockfleth E, Trakatelli M; EPIDERM Group. Risk factors for actinic keratosis in eight European centers: a case-control study. Br J Dermatol. 2012 Aug; 167 Suppl 2:36-42.
48. Aydin A, Koçer NE, Bekerecioglu M, Sari I. Cutaneous undifferentiated small (Merkel) cell carcinoma, that developed synchronously with multiple actinic keratoses, squamous cell carcinomas, and basal cell carcinoma. J Dermatol. 2003; 30(3):241-4.
49. Al-Waiz, M. Skin cancer in Iraq: an epidemiological study. Iraqi Med. J.1998; 47: 1–4.
50. Sharquie KE, Al-Janabi WK. "Squamous cell carcinoma of lower Lip: topical podophyllin is an alternative therapy for early Cases." American Journal of Dermatology and Venereology 2019; 8(4): 61-65.
51. Sharquie KE, Waqas SA. Pigmented basal cell carcinoma develops De nova without pre-existing solar keratosis in skin type 111 and 1V. Journal of Pakistani Association of Dermatologists.2023

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