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A Review On Solar Keratosis: Diagnosis, Treatment & Prevention.

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Abstract

Actinis Keratosis, more commonly known as Solar Keratosis, are cutaneous scaly lesions occurring on the sun exposed parts of the body and are caused due to increased cumulative sun exposure over a long period of time. Generally observed in fair skin people and people who have induced immunosuppression due to receiving certain treatments or therapies, Solar Keratosis are characterized by chromatic cell dysplasia. Although the diagnosis of Keratosis is done clinically, it is possible that other skin lesions can be mistaken for Solar Keratosis and vice versa. The ideal treatment for solar keratosis aims at detection and clearance of both clinical and sub-clinical lesions across the entire cancerous field. The treatment of Solar Keratosis is carried out by two methods: physical method & topical therapy. Physical methods include removal of lesions by methods such as cryotherapy, curettage and photo dynamic therapy, whereas the topical therapy includes usage of NSAIDS and anti tumour drugs. Fundamental to treatment of solar keratosis is usage of high SPF sunscreen, which is also known to reduce UV induced keratinocyte cell mutation and decrease the immunosuppressive effect of sunlight. The objective of present article is to provide a comprehensive review on solar keratosis, discussing its causes, features, diagnosis, available treatment methods and preventive measures for it. This article aims to provide insights to healthcare professionals and general public regarding this condition caused by prolonged sun exposure.

Keywords: -Actinis Keratosis; Solar Keratosis, P53 Gene, UV-Radiation.

Introduction

The role of sun has always been very large in various cultures for religious purposes. Ancient physicians considered Sun as an important factor in treatment of various conditions, which was until 1870, after which the harmful effects of sun started to come into light.[49] Solar Keratosis itself was first discovered by William Dubreuilh in 1896, saying "There is an entire group of lesions of the epidermis which is close to epitheliomia which has a natural tendency to degenerate into epithelial cancer".[16][23] Solar Keratosis are very common skin lesions that occur on sun exposed parts of fair skinned people.[17][19][20] It has also often been observed in players that stay in sun for sports and thus facing increased amount of sun exposure.[11] Solar keratosis can occur in different sizes, shapes and colors depending upon the intensity of the condition. Generally 2-6 mm

in size and are almost never larger than 1 cm, They may occur as flat lesions or can also form horn like shape..[20] They are generally asymptomatic but can sometimes be pruritic or painful. The damaged part of skin has an accumulation of mutated oncogenic cells that develop into Solar Keratosis.[46] Although they're generally limited to epidermis and have less metastatic potential, if left untreated, they can undergo further progression involving other tissues and can metastasize.[30] There are various variants of Solar Keratosis, which are as:

1. Hypertropic Solar Keratosis- which are characterized by formation of a horn-like structure on the affected part of the body.
2. Lichenoid Solar Keratosis- which occur as pinkish papules and generally on the upper part of the body.
3. Proliferative Solar Keratosis- which do not contain well-defined borders.
4. Pigmented Solar Keratosis- which can be of different colour from brown to yellowish-black.
5. Actinic Chelitis- which generally occur on the lips in form of dryness.

Etiology

The parts of body that are generally affected by solar keratosis are the parts that face high amount of sun exposure such as hands, neck, lips, scalp etc.[1][2][4][5][12][21] Solar Keratosis has an approximated prevalence of about 1% to 44% in adult population.[7][14] Due to revolutionization in present era, there have been various disturbances in the environmental conditions. There has been noted depletion in ozone layer, due to increased pollution, which has caused increase in the UV ray exposure on the earth surface. UV radiation is well known for its carcinogenic activity.[38] It has been estimated that there has been increase of about 9% of UV radiation exposure since 1979. UV radiation, which is a major causative factor for solar keratosis, consists of three types of rays[22][26][29][51]

- UV-A (315-400nm)
- UV-B (280-315nm)
- UV-C (100-280nm)

Exposure of UV-A & UV-B rays has been majorly faced by humans. Since UV-C rays cannot surpass ozone layer and reach earth surface, it's exposure is not faced by humans yet.[51] Out of the three types of UV rays, UV-B rays are the major causative factor for Solar Keratosis.[2]The outer most layer of epidermal layer consists of Keratinocyte cells, which are responsible for protection from microbial attack & also prevent UV exposure on the skin. UV-B rays, present in sunlight, are known to cause harm to keratinocyte cells, which is the reason for causing of Solar Keratosis. UV-A radiation is generally less harmful than UV-B but it often directly absorbed by some DNA and proteins.[26] Exposure to UV radiation leads to initiation of a series of molecular, cellular and genetic events that can cause progression of Solar Keratosis to malignancy.[37] Apart from having harmful effects, UV radiations are also important for Vitamin D synthesis in skin.[46] Also in current era, using tanning beds is also a trend among youngsters for getting artificially tanned skin. These tanning beds utilize UV rays to induce tanning, which can also be a factor for causing Solar Keratosis, or Actinis Keratosis in this case.[13] The frequency of Solar Keratosis is determined by age, immunosuppression time, gender, along with other factors such as genes for hair, eye & skin colour.[38]

Pathogenesis

The keratinocyte cells of epidermal layer consists of p53 genes. This p53 gene is responsible for production of tumor suppression protein, which undergo UV-B radiation mutation upon getting in contact with solar light.[10][13] Thus, the keratinocyte cells start propagating and accumulate more genetically damaged cells as they are resistant to apoptotic damage.[2][29] Another major factor responsible for Solar Keratosis is immunosuppression, which can occur in case of induced immunosuppression in case of organ transplant patients.[2] Generally the diagnosis of SK is done clinically, but it is possible to mistake SK for other skin lesions and other skin lesions for SK. The Solar keratosis, after exposure to UV radiations occur in three stages:[28]

i. Initiation- This phase is related to induction of permanent mutation in the target cells, i.e. Keratinocyte cells.

ii. Promotion- It is an intermediate stage, where mutated cells develop into cancerous cells, upon introduction to promoters. (Promoters are physical or chemical agents that are not carcinogenic themselves but have pro-inflammatory effect)

iii. Malignant conversion- This is the stage where the mutated carcinogenic cells undergo malignant transformation into squamous cell carcinoma.

The pathological studies of Solar Keratosis suggest that it is a beginning phase and can lead to Squamous Cell Carcinoma.

Diagnosis

It is very important to carry out early diagnosis of solar keratosis, as it is chronic progressive disease & can be risk to metastasis and is also considered as a major causative factor for squamous cell sarcoma.[33] Diagnosis of Solar Keratosis is generally done clinically depending upon the their appearance. Based on their intensity, Solar Keratosis are divided into three types of lesions:[1]

i. First Degree lesions [Visible & slightly palpable]
ii. Second Degree lesions [Visible & palpable]
iii. Third Degree lesions [Frankly visible and Hyperkeratotic]

Due to their characteristic rough surface, Solar Keratosis are better examined by palpation than done by visual diagnosis.[31] The diagnosis of Solar Keratosis is generally done clinically, but this condition can be mistaken for other skin conditions such as squamous cell sarcoma, Bowen's disease, Basal cell carcinoma, etc. In such cases other methods like biopsy, dermascopy etc are considered for differentiation of the Solar Keratosis from other conditions.[1]] .

Depending on their appearance, dermascopy divides Solar Keratosis into two types:

a. Pigmented
b. Non-pigmented

Pigmented lesions on the facial area can be characterized by pseudo-network, that could be devoid of rete ridges, along with a composite pattern known as "Strawberry pattern" characterized by reddish background with white halo around hair follicles.[32]

A characteristic feature of non-pigmented Solar Keratosis is presence of a number of slate gray to brown dots, having more uniform size and more uniform distribution. A vascular pattern of linear wavy vessels or small coiled vessels is also a characteristic of non-pigmented Solar Keratosis.[31] Dermascopic analysis can be helpful in differentiating non-pigmented solar keratosis from non-pigmented neoplasms by study of the vascular patterns, with a noted diagnostic efficiency of about 98%.[1][25][31]

A biopsy is considered in case of coiled, hairpin or polymorphous vessels and/or white homogeneous parts, detected by dermascopy. It is also considered in patients where clinical clearance cannot be achieved.[25]

Treatment

The ideal treatment of Solar Keratosis focuses on identification & clearing both clinical and sub-clinical lesions from the affected part of the skin.[3] There has been strong evidence that anti inflammatory treatment can be helpful in treatment of Solar Keratosis. It might not be possible to always achieve complete eradication of lesions, so its important to focus on reducing the maximum possible number of lesions and also to achieve long term disease control.[25] Compliance is an important factor in patient-administered therapy as it requires patient to stick to treatment plan which can be time consuming and cause discomfort to patient. The selection of choice of treatment of Solar Keratosis is done depending on the basis of three factor:

i. Density & Clinical manifestation of lesion.
ii. Tolerability & cost of treatment.
iii. Age & compliance of patient.

The various treatment method utilized for treatment of Solar Keratosis are :

a. Topical treatment
b. Curettage
c. Cryotherapy
d. Photo Dynamic Therapy

Topical treatment

For topical treatment of Solar Keratosis, drugs such as 5-fluoruracil, diclofenac, imiquimod, nicotinamide, etc are used. This treatment method utilizes usage of drugs in form of topically applied dosage forms.

5-Fluorouracil

5-fluorouracil has been a major drug that has been used for the treatment of Solar Keratosis since 1960.[12] It is used in the form of 5% 5-fluorouracil cream alone or in combination therapy.[2] 5-fluorouracil is a thymidylate synthase inhibitor. It binds to thymidylate synthase enzyme, which is responsible for conversion of deoxyuridine nucleotides to thymidine nucleotides. Thymidine nucleotides play an important role production of DNA. When thymidylate synthase enzyme is inhibited, it causes reduction in number of thymidine nucleotides, which leads to reduced DNA synthesis.[27] Thus, it causes selective cell death in affected cells. Commonly used method is use of cream twice everyday for 2 weeks. The cumulative probability of treatment success for 5-fluorouracil was found to be 74.7% in a trial.[24] Usage of fluorouracil cream can cause certain side effects such as local irritation, swelling, pain and erythema.[2]

Diclofenac

Diclofenac is a Non-Steroidal Anti Inflammatory Drug which is known to have effectiveness in treatment of Solar Keratosis. Even though, its specific mechanism behind activity in Solar Keratosis is still not known, it has been estimated that it affects the Cyclooxygenase enzymes(COX-1 & COX-2). Diclofenac is estimated to inhibit these enzymes, which are intermediates for production of prostaglandins. Reduction in levels of prostaglandins can help in reducing the inflammation. It can be helpful in clearance of both clinical and sub-clinical solar keratosis lesions.[41] Use of Diclofenac cream of 2% daily twice has been known to cause reduction in inflammatory response.[4] It can also be used in combination with photodynamic therapy to increase therapeutic potential. The most commonly observed side effects due to use of diclofenac are pruritis, dry skin, erythema, and reactions at site of application.

Nicotinamide

Nicotinamide, more commonly known as niacinamide, is a amide form of vitamin B3.

Nicotinamide is responsible for production of NAD+, which is a key intermediate in production of ATP. It has been hypothesized that increase on NAD+ induced by nicotinamide can reduce Solar Keratosis. Nicotinamide is believed to enhance DNA repair and support the immune response on the affected part of the skin. It is expected to enhance repair of Keratinocytes affected by UV & protect against UV by immunosuppression.[5] Nicotinamide is used in the form of 1% cream, twice, daily. Application of Nicotinamide has been known to cause skin irritation, burning, dryness, peeling & can also cause allergic reactions. These reactions are generally very mild or rare.

Imiquimod

Another agent used for treatment of Solar Keratosis is Imiquimod. Imiquimod is an anti-cancer drug, which acts as an immuno modulator, belonging to the category of imidazolequinolinamine. Application of Imiquimod causes increase in levels of IFN-a , IFN-b , IFN-g , and TNF-a. These along with increased levels of IFN-a , Il-6, and Il-8 in drug induced keratinocyte cells, cause activation of local immune system. This leads to localized immune response to the affected cells and cause cell death of the affected cells.[4][5] It is available in the form of 2.5%, 3.75% & 5% cream. The patients receiving this treatment experience puritis, mild/moderate erythema and scabbing upon long tern treatments, hence short term treatments are preferred over long term.[1]

Curettage

Curettage therapy is a surgical procedure in which a sharp edged instrument is used to scrape and remove tissue from surface of the body or within a body cavity. Generally performed under the influence of anesthesia, It is generally an out patient procedure. It removes lesions in such a manner that along with treatment, the sample collected after removing from affected part can also be used for study of histopathological characters of the cells. Curettage can be followed by electrodessication for post treatment metastasis. Electrodessication is a medical procedure that uses high frequency electric currents to cut or remove tissue.[36] Electrodessication leads to longer healing time, uses inexpensive and reliable instruments and can be useful for variety of conditions.[36] Common side effects that can be caused by curettage therapy are pain, bleeding, infection, scarring, changes in pigmentation, delayed healing and nerve damage in some cases. It should be avoided to carry out curettage in case of thick lesions, as thick lesions tend to bleed a lot, which can cause discomfort and can be inconvenient.[43]

Cryotherapy

Cryotherapy is a type of treatment procedure that includes use of extreme cold by the use of agents called cryogens, which are capable of producing such low temperatures. This therapy eradicates damaged cells by freezing them based on their sensitivity to low temperatures.[14] Liquid nitrogen (-40°C) is the more commonly used cryogen for cryotherapy.[14][34] Other than liquid nitrogen, carbon dioxide, nitrous oxide etc can also be used as cryogens. The easiest way to carry out cryotherapy is by using nitrogen sprays or cotton applicators.[41] The dosage and type of cryogen used depends on certain factors such as degree in injury, thickness of epidermis, thickness of lesions, intensity of lesions and certain patient related factors.[34] The time for required for thawing after administration with cryogen is 20-45 seconds. The thawing time or time for thawing is defined as the time required after freezing for the halo to reach to the pen marking around the lesion. This technique requires anesthesia and has a high risk of scarring, but being a surgical method can be helpful in obtaining sample for histopathology examination. Cryotherapy is useful in treatment of number of scattered lesions.[7]

The mechanism of cryo-tissue injury occurs in 4 phases:[34]

1. Rapid heat transfer- this depends on quick transfer of heat from skin to vessel & depends on the temperature difference between two media.
2. Tissue injury- there is an irreversible damage to cell due to intracellular ice formation & is dependant on rate of cooling and the minimum temperature achieved by the cryogen.
3. Vascular stasis- endothelium gets damaged and platelet aggregation occurs. This stage causes ischaemic necrosis of treated cells.
4. Inflammation- inflammation occurs on the treated part due to cell death over next 24 hours.

Even though cryotherapy is widely available and is easy to perform, the only disadvantage of cryotherapy treatment is that it can treat only limited numbers of lesions at a time and thus cannot be utilized in case of large number of lesions.[40] The success rate of cryotherapy depends on the technique of administration and time of exposure. According to a study, 1-5 second exposure shows a success rate of 39%, while more than 20 second exposure has a cure rate of 83%.[44]

Side Effects

Side effects originates by cryotherapy can be of 4 types:

1. Immediate
a. Pain
b. Oedema
c. Headache

2. Delayed
a. Haemorrhage
b. Infection
c. Excessive granulation

3. Prolonged but temporary
a. Hyperpigmentation
b. Hypertropic scars

4. Prolonged and permanent
a. Hypopigmentation
b. Alopecia
c. Atropy

Photodynamic Therapy

A non-surgical method for treatment of Solar Keratosis is photodynamic therapy, which includes use of topical photosensitizer that is then activated by a light source to create a therapeutic effect. Most commonly used drugs in Photodynamic therapy for Solar Keratosis are Aminoevulinic acid (ALA), Methyl Aminoevulinate (MAL) and a nano emulsion based gel formulation of 7% 5-ALA (10% ALA Hydrochloride), all of which are used in form of topical dosage forms.[9][45] These agents get captured by

premalignant tissues and then get activated by exposure to lights with certain wavelength to produce effective therapeutic effect. When the drug is applied to skin, it gets converted to haem precursor, which acts as a precursor. When these precursors get in contact with light source, a cytotoxic reaction occurs which causes death of the treated cells and treats solar keratosis.[42] Photodynamic therapy has been known to successfully treat field carcinoma and basal cell sarcoma. This method is used when lesions are not easy to be treated by surgery and when topical therapy cannot be adhered. Since Photodynamic Therapy cannot penetrate into skin more than 2 mm of depth, in that case curettage is done before considering Photodynamic therapy. Efficiency of Photodynamic therapy can be increased by combining it with topical treatments.Use of Ablative fractional resurfacing has also been proposed that can create microscopic channels, which would be helpful in increasing penetration of photosensitizer drugs such as 5-ALA. Another method for increasing photo sensitizing action is to warn the skin to a bearable range, followed by drug administration. Photodynamic therapy has shown better results and more satisfaction among patients than cryotherapy.[40] It is a comparably safer treatment procedure, but still there can be possibility of certain side effects such as redness, swelling, itchiness and burning sensation. In certain cases, observation of changes in colour or texture of skin is possible, however this is only temporary.

Prevention

To prevent from being affected by Solar Keratosis, one can always consider reducing solar exposure, but reducing solar exposure itself would not be sufficient to stop progression of solar keratosis. Use of sunscreen has been widely and majorly suggested by professionals; along with other methods such as using shades, covering clothes, hats etc, for prevention of Solar Keratosis.[15] The use of sunscreen is helpful in prevention of sunburn (which was the original motive for formulation of sunscreens) and Solar Keratosis, however its effectiveness in prevention of UV induced skin cancer is still a matter of debate.[6] The sunscreen that absorb UV radiations in range on 280-320 nm are known for their protective activity when applied on epidermal layer.[50] In a study, it was observed that daily application of sunscreen was helpful in prevention of Solar Keratosis among patients with younger age and/or no history of skin cancer.[8] Although all the sunscreens show similar action, the specific activity of each sunscreen depends on the physical or the chemical photoprotector or the UV absorbing agent used in preparation of that sunscreen.[50] Also, even though sun-protection activity of sunscreens is widely known, it's effectiveness in prevention of UV induced immunosuppression still remains unknown.[35] The use of protective clothing should be avoided to affirm preventive measure.[46] Several study suggest use of sunscreens for reducing carcinogenic and immunosuppressive effects of sunlight.[48] The protective action of sunscreen is dependant on the SPF value of it and also on the photochemical characteristics of its components and their ability to undergo photobiological interaction. To sum up, effective preventive measures for Solar Keratosis include:[39][47]

- Avoiding sun exposure
- Avoiding artificial source of UV radiations
- Wearing protective clothing
- Repeated application of broad spectrum sunscreens (SPF 15 or higher)

In spite of various innovations in spectrum of products and introduction of newer facilities for solar protection, it is more important to provide knowledge and awareness among patients regarding the conditions and also about the proper methodologies to adopt for protecting oneself from such sun related conditions.

Conclusion

Solar Keratosis is a major skin condition that is faced by people all around the world due to increased sun exposure due to lifestyle. It generally occus on the outermost layer of the skin and is caused due to UV induced mutation of Keratinocyte cells of the epidermal layer. Early diagnosis ios Solar Keratosis is essential due to its potential to develop into various more serious skin conditions that can prove fatal to human life. Various treatment methods are available for curing solar keratosis, however the choice of treatment is done based on the intensity of condition and moreover it depends on patient compliance. However, it is more important to try to prevent causing of the disease. Since, it is a major condition at this present age, it is important to create awareness among people regarding this condition to ensure the condition does not develop into something more serious.

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