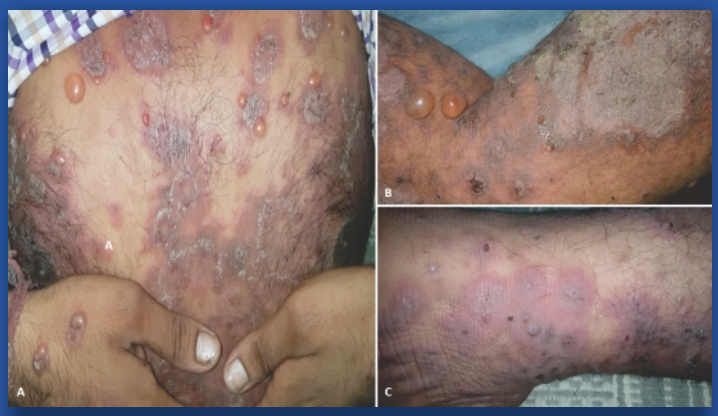
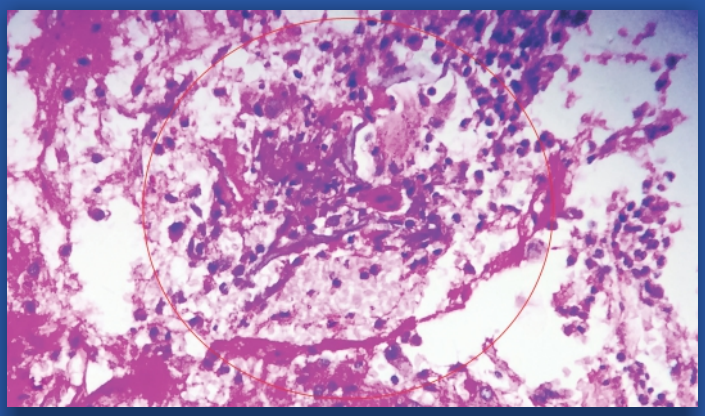
IJCD

JDA **Indian Journal of Clinical Dermatology**

Volume 1 | Issue 1 | August 2018

₹ 800 - Jaipur
Four Monthly





HIGHLIGHTS

Role of dietary intervention in psoriasis: A review

Spectrum of cutaneous manifestations in patients with internal malignancies: A clinico-epidemiological study

Association of the cutaneous markers with coronary artery disease: A case control study

Invasive aspergillosis presenting as scalp osteomyelitis: A rare case report

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INDIAN JOURNAL OF CLINICAL DERMATOLOGY
A Publication of Jaipur Dermatology Association

Volume 01 | Issue 01 | August 2018

Printed and Published by Dr. Dinesh Mathur on behalf of Jaipur Dermatology Association and
Printed at Popular Printers, Fateh Tiba Marg, Moti Doongri Road, Jaipur (Raj.)
Published From : Indian Journal of Clinical Dermatology, D-712, Park Avenue Road, Malviya Nagar, Jaipur (Raj.)
Editor : Dr. Dinesh Mathur

*Available online at : **www.e-ijcd.in**

ISSN (Online): 2582-7612
ISSN (Print): 2581-7604

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INDIAN JOURNAL OF CLINICAL DERMATOLOGY
A Publication of Jaipur Dermatology Association

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FROM THE DESK OF EDITOR

Dear friends

We present to you the first issue of **INDIAN JOURNAL OF CLINICAL DERMATOLOGY**, an another feather in cap of Indian dermatology. We present this journal with the motto that "knowledge can only be spread by sharing." In India, there are many quality journals being published in the field of dermatology, but also are increasing the number of research work in this field. All these researches need to be published and shared. Thus we took the task to start this journal and provide more space for these research works.

You might have gone through the contents of this issue by now and I hope you found it interesting. Our editorial team has left no stone unturned to include a variety of articles covering different aspects of clinical dermatology. Every effort has been made to publish only quality articles with some interesting and new information. I thank all the authors who have entrusted us with their priceless articles. All the articles have been peer reviewed and I request you to kindly go through them.

On our website, i.e., www.e-ijcd.in, a page for suggestions has been added so that we can have your valuable reviews about the articles and also what other topics should be included in the next issue. I request you to send us articles for the coming issues. We have taken this task of publishing a quality journal and with your support we are sure to achieve it.

Once again I thank my team and the authors for their efforts to bring out this issue and hope the readers will enjoy it.

Dr. Dinesh Mathur
Editor

REVIEW
Year: 2018 I Volume: 1 I Issue: 1 I Page: 01-05

ROLE OF DIETARY INTERVENTION IN PSORIASIS: A REVIEW

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Abstract

Psoriasis is a chronic inflammatory disease marked by remissions and exacerbations. The exact etiology is not clear but a mix of genetic and environmental factors is proposed as the cause. The disease is associated with obesity and metabolic syndrome. In these contexts, diet assumes an important role in psoriasis patients. This review aims to discuss the various dietary interventions proposed for the management of psoriasis, the evidence regarding the same and controversies surrounding them. Hypocaloric diet has shown to improve severity of psoriasis of skin and joints. Antibodies to gluten may be seen in otherwise asymptomatic patients of psoriasis and these may benefit from a gluten free diet. Omega-3 fatty acids have shown a strong evidence to be beneficial in several trials. However, the dose and route of administration is yet to be standardized. Amongst the vitamins, vitamin D shows the maximum evidence of benefit, while the role of folate and vitamin B12 needs to be explored further. Same is the case for zinc and selenium. There is evidence of exacerbation of psoriasis with foods such as red meat, eggs and dairy products and those rich in taurine, but the evidence is too scant to advise reduction in intake of these items. Alcohol has been strongly implicated in the initiation and exacerbation of psoriasis. Dermatologists must be aware of these interventions to help their patients make the best choice for dietary modification.

Key Words - Psoriasis, Diet

Introduction

Psoriasis is a common, chronic, inflammatory and proliferative condition characterized by sharply demarcated, red, scaly plaques over the skin, predominantly over the extensor surfaces and scalp. The disease is variable in duration with periodicity of flares and extent.[1] A complex interaction of epidermal keratinocytes, lymphocytes, neutrophils, macrophages and dendritic cells lead to the activation of Th1 immune response, producing numerous signaling molecules and resulting in the clinical disease.[2] It is considered to be a systemic inflammatory disease and has been associated with obesity, cardiovascular diseases and type 2 diabetes mellitus.[3]

The role of nutrition and diet in management of psoriasis has been studied since long. Their role has now been established in the etiopathogenesis of psoriasis by several authors.[4,5] The association of metabolic syndrome with psoriasis has added further interest in this field. Advice regarding dietary intervention is very frequently sought by patients in clinical practice. Thus the treating dermatologist must be abreast with the recent evidence of dietary interventions to advise patients accordingly.

This review aims to highlight the beneficial as well as adverse effects of various dietary interventions in the management of psoriasis. The strength of evidence and controversies regarding these interventions shall be discussed.

Hypocaloric Diet

Several studies have linked increased Body Mass Index (BMI) to the higher incidence and severity of psoriasis. Wolk K et al found that obese patients are twice as likely to get psoriasis as compared to healthy subjects. They stated that with the increase in BMI by one unit, the risk of onset of psoriasis increased by 9% and the Psoriasis Area Severity Index (PASI) increased by 7%.[6] Another study from Taiwan found that increased BMI is associated with increased severity, this association is stronger in men.[7] The observation that psoriasis responds to low energy diet was made when the incidence of psoriasis was found to have decreased during the second world war.[8] This view was reinforced by observations of Simons that 8 of the 13 Dutch prisoners on near starvation diets in the Japanese concentration camps showed resolution of the lesions of psoriasis.[9]

Most prospective trials evaluating low diet therapy with the usual treatments have shown significant reduction in severity of psoriasis as measured by PASI score[10-13,] dermatology quality of life (DLQI)[10,13] or, in case of psoriatic arthritis, the visual analog scale.[14] Jensen et al in a randomized controlled trial found that the group of 30 patients on a low energy diet showed a significantly greater reduction in weight than the control group on normal diet. The test group also showed a greater reduction in PASI and DLQI.[10] Gisondi P et al showed that patients of moderate to severe psoriasis with BMI of more than 30, who were given low energy diet and cyclosporine achieved greater reduction in PASI by 75% (PASI 75) than the group on cyclosporine alone.[11] Rucevic I et al showed that decrease in serum lipids achieved by hypocaloric diet correlated with improvement in psoriasis.[12] Hypocaloric diet also significantly improves psoriasis when given with topical steroids.[13] However, Kimball et al found that low calorie diet did not alter the PASI score when given with narrow band ultraviolet therapy (NB-UVB) than when compared to NB-UVB therapy alone.[15] Another prospective,

investigator-blinded, randomized controlled trial showed that psoriasis patients stabilized on methotrexate and on low calorie diet took longer time for the rebound of their disease.[16]

The improvement in psoriasis with hypocaloric diet has been explained by Li et al on the gene-environment interaction with BMI interacting with IL12B and IL23R genes.[17] Also, low calorie intake has been shown to lower the intake of pro inflammatory mediators circulating in the body.[18] Dietary weight loss should be recommended to patients of psoriasis who are overweight or obese, as the level of evidence is IB, indicating evidence from a randomized controlled trial. [19]

Vegetarian Diet

Epidemiological studies done by Kavli et al showed that the intake of fresh fruits and vegetables was associated with a lower risk of psoriasis.[20] Naldi et al, in a multicentre epidemiological study from Italy showed that psoriasis was inversely related to the intake of vegetables like carrots, tomatoes and fresh fruits.[21] Addition of omega-3 fatty acid rich diet to vegetarian diet interspersed with periods of hypocaloric diet was found to be beneficial in one study.[22] Also, vegetarian diet was found helpful in maintaining the remission induced by hypocaloric diet.[23] The benefits of such a diet has been attributed to the reduced formation of arachidonic acid and its proinflammatory metabolites.[24] This is in addition to the beneficial effects offered by various antioxidants and vitamins.

Gluten Free Diet

A correlation between psoriasis and celiac disease has been established and has been attributed to the common Th1 cytokine profile seen in both the diseases.[5,25] This Th1 cytokine profile is produced due to the release of IL1 and IL8 from the rapidly proliferating keratinocytes. [26]

A study found the prevalence of anti gliadin and anti transglutaminase antibodies to be 18% and 10% respectively in a group of 123 patients of psoriasis. The antibody levels decreased after adopting a gluten free diet, accompanied by complete resolution of skin lesions.[27] Further, it was shown that a gluten free diet produced a highly significant improvement in PASI scores of patients. The disease worsened on stopping this diet.[28] The levels of tissue transglutaminase is found to be increased in psoriatic skin and this level decreases after a gluten free diet is instituted.[29] However, the positive association between the two diseases has been disputed by some authors. [30,31]

Gluten free diet may, thus, be beneficial in psoriasis patients with antibodies specific for celiac disease, but more studies are needed to arrive at a conclusion.[32] Duarte et al recommend antibody screening for patients of moderate to severe psoriasis or those with palmoplantar pustulosis, as a large number of patients with gluten intolerance may be clinically asymptomatic.[23]

OMEGA-3 Fatty Acids

Epidemiological studies show that Eskimos of Greenland have a very low incidence of inflammatory and autoimmune diseases and this was attributed to the high intake of omega-3 fatty acids in them, due to fish being such an important part of their diet.[9] Oils of cold water fish has been found to be rich in eicosapentaenoic acid (EPA) and docosahexaenoic acid(DHA). Omega-3 fatty acid intake leads to decreased production of arachidonic acid derived proinflammatory mediators by competition and production of metabolites that are less inflammatory in nature than the metabolite of arachidonic acid.[33] Their effects may also be due to alteration of intracellular signaling pathways, antioxidant action and regulation of transcription factor activity.[9,34]

Several trials evaluating the role of omega 3 fatty acids have been conducted. Double blinded randomized controlled trials by Mayser et al and Grimminger et al demonstrated the superiority of omega 3 fatty acids over omega-6 fatty acids in decreasing the severity of the disease in chronic plaque and guttate psoriasis respectively.[35,36] Several open studies have also shown clear benefit of fish oils in reducing erythema, scaling, induration, area involved and PASI scores in psoriasis patients, with variable dosages and for variable periods.[37,38]

Fish oils have also shown to improve responsiveness to other therapies.[39] A placebo controlled, double blinded study showed that ultraviolet B therapy showed statistically significant improvement in psoriasis when given with fish oils than when given with placebo.[40] Similar results have been obtained with fish oils in combination with emollients, topical tacalcitol and oral etretinate. [41-43]

However, some trials have shown that omega-3 fatty acids offer no added benefit in psoriasis.[44] This includes two randomized, double blinded, placebo controlled studies, making the argument in favour of omega 3 fatty acids slightly weak. Thus, fish oils are recommended for patients of psoriasis.[9] The intake of omega 3 fatty acids needed to achieve a critical level in the epidermal phospholipids, that may inhibit arachidonic acid derived eicosanoids is probably high.[9] More studies are warranted to arrive at an appropriate dosage recommendation for the same.

Vitamins

Vitamin A: This vitamin has been proven to play important role in epidermal keratinisation by inhibiting the hyper proliferative keratinocytes and inducing terminal differentiation in them. Levels in serum have been found to be decreased in patients of psoriasis of various morphological types and in inactive disease as well.[45,46] Safevi et al, however, found that there was no difference in serum vitamin A levels in patients of psoriasis and those without the disease.[47] Endogenous retinoids have been shown to have increased in the plaques of psoriasis.[48] The effect is largely attributed to the antioxidant activity of carotenoids.[49] The antipsoriatic activity of Vitamin A is only modest, as higher doses needed for clearing may lead to systemic toxicity. This prevented any serious trials evaluating vitamin A supplementation in psoriasis.[50] However, derivatives of vitamin A called retinoids, have been firmly established as important armamentarium in the management of psoriasis.

Vitamin B9 (Folic acid): Patients with psoriasis have folic acid deficiency.[51] This is attributed to decreased intestinal absorption due to inflammation, increased utilization by keratinocytes and elevated levels of homocysteine, an independent risk factor for cardiovascular disease.[25] Malerba et al found a direct correlation between psoriasis severity, measured by PASI, and homocysteine levels and an inverse correlation with folate levels in blood. [51] A case control study showed that obese psoriatic patients have decreased folate and high homocysteine levels.[52] A comparative trial showed that calcium folinate supplementation produced fewer side effects in patients of psoriasis with >6% body surface involvement than another group treated with only

traditional methods, though both groups improved well.[53]

Caution is advised with folate supplementation as daily safety levels are low (1mg/day) and daily supplementation may lead to overexposure, particularly in countries with mandatory fortification of flour.[23] Further evidence is warranted before folate is recommended as supplementation for patients of psoriasis with heart disease.[23]

Vitamin B12: Psoriasis patients have been demonstrated to have low vitamin B12 levels in studies.[54] Ruedemann et al evaluated the efficacy of supplemental vitamin B12 in 34 patients of plaque psoriasis.[41] They gave 1000g/cm3 of intramuscular vitamin B12 followed by maintenance doses and reported complete clearance of lesions in 32% patients and PASI 75 was achieved in 29% cases. However, a later double blinded, placebo controlled trial failed to show any statistically significant benefit of intramuscular vitamin B12 injections over placebo to psoriasis patients. Topical vitamin B12 cream was assessed and compared to calcipotriol cream and response assessed by change in PASI score. The vitamin cream showed a slow response and PASI scores were not changed appreciably.[55] More research is needed for the possible use of vitamin B12 in early psoriasis.[25]

Vitamin D: This vitamin has anti proliferative effect on keratinocytes and produces their differentiation. It also has immunomodulatory activity in psoriasis by directly acting on T cells and antigen presenting cells. Studies show that patients of psoriasis have low serum levels of vitamin D and severity of psoriasis is inversely related to serum levels of vitamin D.[56,57] Several open trials of vitamin D supplementation in psoriasis have been conducted, mostly showing beneficial response. The largest of these was conducted by Perez et al on 85 patients. 88% patients had some benefit with calcitriol supplementation with a fourth of all patients showing complete clearance of lesions and another third showed moderate improvement.[58] Psoriatic arthritis has also been shown to respond to vitamin D.[59] However, the only prospective randomized placebo controlled trial found no statistically significant benefit with vitamin D.[60]

More studies are needed for defining the role of oral vitamin D in psoriasis. Still, owing to the public health problem of vitamin D, its supplementation may be recommended in patients not on topical vitamin D analogues.[23]

Antioxidants

Selenium: Selenium is an antioxidant, has immunomodulatory activity and inhibits DNA synthesis, thus posing as a potential treatment for psoriasis. Research has shown that selenium is deficient in psoriasis patients and deficiency of this essential micronutrient correlates with the disease severity.[61] Harvima et al proposed that selenium alone cannot improve psoriasis. They combined selenium with coenzyme Q10 and vitamin E and reported clinical improvement in patients of psoriatic arthritis and erythroderma.[62] The results were replicated by Kharaeva et al in a larger trial.[63] However, selenium supplementation was not found to be superior when given with narrow band UVB light or with topical treatment.[64,65]

Zinc: Combined with copper, zinc is a powerful antioxidant and is important for maintenance of normal immune responses. Mice fed on zinc deficient diet develop a psoriasis like condition.[9] Plaques of psoriasis are associated with deficiency of zinc.[66] However, supplementation with zinc has failed to show any improvement in psoriasis lesions in clinical trials.[66] The role of zinc in psoriasis as an antioxidant needs to be further assessed as it is a very safe nutrient when used as a daily supplement.

Foods That Worsen Psoriasis

High Glycemic Foods: High glycemic foods increase insulin levels and lead to increase of pro inflammatory cytokines in blood, theoretically leading to worsening of psoriasis. A positive correlation was proposed by Boencke et al between PASI score and insulin levels.[67] Intake of foods with a low glycemic index may become part of management of psoriasis patients' general management, as they improve the disease and decrease cardiovascular disease risk as well.[68]

Alcohol: Extensive evidence links the amount of alcohol and the type of beverage to both the onset and exacerbation of psoriasis.[69] Further, alcoholic patients exhibit decreased response to treatment.[70] The distribution of lesions on the acral parts is akin to that seen in immunocompromised individuals, suggesting that alcohol leads to immunosuppression. Other reasons explaining psoriasis in alcoholics is the hyper proliferation of skin due to alcohol induced production of cytokines and cell cycle activators like cyclin D1 and keratinocyte growth factor.[70]

Red meat, eggs and dairy products: Psoriasis severity has been correlated with consumption of a diet high in red meat.[71] This may be due to the high content of arachidonic acid present in red meat.[72] Eggs and dairy products also contain high amounts of arachidonic acid and may also irritate the intestinal mucosa perpetuating psoriasis outbreaks.[9] However, clinical evidence for the same is not available.

Taurine rich diet: High amounts of taurine in diet, an amino acid, was linked to exacerbation of psoriasis and associated pruritus and taurine's role in pathogenesis of psoriasis was proposed.[25] A low taurine diet caused complete healing in a trial in 9 of the 15 patients, the others showed partial remission. However, excess taurine did not produce exacerbation in patients in another trial.[25,73]

Conclusion

Psoriasis is a chronic and disabling systemic disease. Its management requires a host of factors apart from conventional therapy. Lifestyle modifications and dietary changes should form an important aspect of these interventions. Despite a long period of research in this field, not much headway has been achieved due to various factors like; differences in individual and cultural habits preventing standardizations, use of parallel medications and lack of control over triggers and spontaneous remissions. Dermatologists need to be aware of the various dietary interventions and the evidence regarding the efficacy and safety of these.

How to cite this article:

Amin SS, Adil M, Alam M. Role of dietary intervention in psoriasis: A review. JDA Indian Journal of Clinical Dermatology 2018;1: 01-05.

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ORIGINAL ARTICLE
Year: 2018 I Volume: 1 I Issue: 1 I Page: 06-11

ASSOCIATION OF THE CUTANEOUS MARKERS WITH CORONARY ARTERY DISEASE: A CASE CONTROL STUDY

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Abstract

Objectives: To determine the strength of the association of the cutaneous markers described in coronary artery disease (CAD).

Methods: A hospital-based, case-control study was conducted in Christian Medical College, Vellore for the period of 14 months from September 2012 to October 2013. Two hundred patients were recruited from the cardiology in-patients who underwent coronary angiogram.Cases were 153 patients with CAD and controls, 47 without CAD on the basis of coronary angiogram.Patients were examined for the presence of androgenetic alopecia (AGA), acanthosis nigricans (AN), diagonal earlobe crease (DELC), preauricular crease (PAC), corneal arcus (CA), thoracic hairs, acrochordons, premature canities (PC), xanthelasma and xanthomas. A record of the history of onset, morphology, grading and distribution of the lesions was made.

Results: DELC (diagnostic odds ratio - 811.62, sensitivity- 98.69, specificity- 91.49), PAC (diagnostic odds ratio- 97.63, sensitivity- 67.97%, specificity-97.87%), AGA (diagnostic odds ratio - 21.76, sensitivity- 95.42%, specificity- 51.06%), PC (diagnostic odds ratio- 4.45, sensitivity- 47.71%, specificity- 82.98%), AN (diagnostic odds ratio- 4.01, sensitivity- 41.18%, specificity- 85.11%), thoracic hairs (diagnostic odds ratio – 130.76, sensitivity- 92.02%, specificity- 91.89%), corneal arcus (diagnostic odds ratio - 24.61, sensitivity- 86.93%, specificity- 78.72%) and ear canal hairs (diagnostic odds ratio-22.21, sensitivity- 49.67%, specificity- 95.74%) were found to be associated with CAD. But xanthelasma palpebrarum (diagnostic odds ratio - 0.50) and acrochordons (diagnostic odds ratio- 1.13) were not associated with CAD. Multiple logistic regression analysis showed DELC and thoracic hairs were strongly associated with CAD.

Conclusion: The study suggests that diagonal ear lobe crease, preauricular crease, androgenetic alopecia, premature canities, acanthosis nigricans, thoracic hairs, corneal arcus and ear canal hairs are associated with coronary artery disease while xanthelasma palpebrarum and acrochordons are not.

Key Words- Cutaneous manifestations, Coronary artery disease, Thoracic hairs

Introduction

Recognizing dermatological markers suggesting atherosclerosis at an early age may prove to be supportive in early diagnosis and secondary prevention of coronary artery disease.[1] The heart and the skin have much in common due to common changes during aging and degenerative processes.[2,3,4] A meticulous search for the cutaneous markers such as diagonal ear lobe crease, androgenetic alopecia, premature canities, preauricular crease, acanthosis nigricans, acrochordons, xanthomas, xanthelasma palpebrarum, corneal arcus and thoracic hairs which may be associated with coronary artery disease may prove to be worthwhile in recognizing asymptomatic coronary artery disease in a high risk individual.

Bilateral diagonal earlobe crease (DELC) has been designated as Frank's sign,[5] which develops in relation to CAD, as the heart and the ear lobe are supplied by "end arteries" without the chance for collateral circulation.[6,7,8] Preauricular crease (PAC) is a well formed crease in front of the auricle of the ear. This is easily identifiable during clinical examination.[9] Androgenetic alopecia (AGA) is a genetically determined baldness which is linked to CAD by mechanisms such as increased peripheral sensitivity to androgens,[10] hyperinsulinaemia[11] and chronic inflammation.[12] Premature canities is graying of scalp hairs before the age of 30 in Africans and Asians and may be a surrogate marker of premature atherosclerotic changes.[13,14] Acanthosis nigricans (AN) is characterized by hyperpigmented, velvety thickening of the skin in the axillae, groin and back of the neck.[15] AN has been shown to be associated with insulin resistance and premature atherosclerosis.[15, 16] Thoracic hairs (chest hairs) are androgen dependent hairs which grow on the anterior part of chest of males.[17,18] At present scientific literature is lacking to support its existence as a marker of CAD. Corneal arcus is an easily visualized lipid-rich deposit at the corneoscleral limbus that shares similarities with the lipid deposition of CAD.[19] Acrochordons are asymptomatic pedunculated skin lesions. Acrochordons were found to be associated with atherogenic lipid profile in a few earlier studies.[20,21] Xanthomas are caused by faulty lipid metabolism. Xanthelasma palpebrarum is a type of specific form of xanthoma which presents as soft, velvety, yellow, flat, polygonal plaques around the eyelids.[22,23,24] They are associated with hyperlipidemia, and as hyperlipidemia is characterized by elevated concentrations of circulating

atherogenic lipids, this leads to the process of accelerated atherosclerosis.[25] It was shown in one Indian study that 60.6 % of the patients with xanthelasma palpebrarum had dyslipidemia and 12 % patients had family history of xanthelasma palpebrarum.[26]

Astute assessment of various dermatological markers linked to coronary artery disease would assist physicians to suspect disease in the early phase, and thus make it simpler to judge who requires further detailed investigation. There are multiple studies in the literature showing the significance of Frank's sign,[6,27,28,29,30] androgenetic alopecia,[30-33] premature canities,[13,14,34,35] preauricular crease,[9] xanthomas,[22,23,24] xanthelasma palpebrarum,[24,36] corneal arcus[37,38] and thoracic hairs[18] as cutaneous markers of CAD. But there is no study in the past in which all these above mentioned markers were evaluated simultaneously to establish their diagnostic value. We thus decided to assess these cutaneous markers of coronary artery disease prior to coronary angiogram to establish their role in predicting coronary artery disease. We also assessed the correlation between the severity of coronary artery disease and grades of androgenetic alopecia, pattern of thoracic hairs and grades of diagonal earlobe crease (Frank's sign).

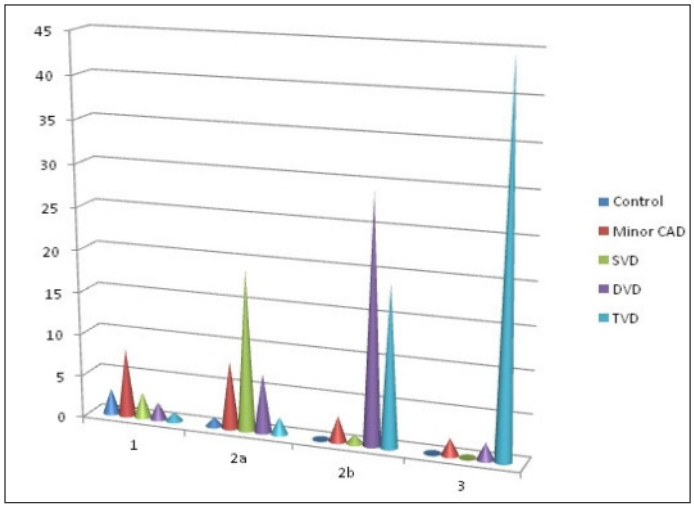

Figure 1: Distribution of various grades of diagonal ear lobe crease among various groups of cases and controls.

Aims and Objective

This study was conducted to assess the association of the cutaneous markers with coronary artery disease. The primary objective was to determine the strength of the association of the cutaneous markers described in coronary artery disease. Other objectives were to assess; 1) the correlation of clinical grading of androgenetic alopecia and severity of coronary artery disease, 2) the correlation of clinical grading of diagonal ear lobe crease and the severity of coronary artery disease and 3) the correlation of pattern of distribution of thoracic hairs with severity of coronary artery disease.

Methods

A hospital-based, case-control study was conducted in our institution. Two hundred patients were recruited by random sampling from the cardiology in-patients who were admitted for coronary angiogram with the probable diagnosis of CAD. Cases were the patients with CAD and control those without CAD on the basis of coronary angiogram. Patients were examined for the presence of androgenetic alopecia (AGA), acanthosis nigricans (AN), diagonal earlobe crease (DELC), preauricular crease, corneal arcus, thoracic hairs, acrochordons, premature graying, xanthelasma and xanthomas. A record of the history of onset, morphology, grading, number and distribution of the lesions was made.

Results

There were 153 cases with CAD and 47 controls without CAD recruited during the study period. The baseline characteristics such as mean age, gender and mean body mass index (BMI) were similar in both the groups.

DELC (prevalence - cases 98.69% and controls 8.51%; diagnostic odds ratio - 811.62, p<0.001, sensitivity- 98.69, specificity- 91.49), preauricular crease (prevalence - cases 67.97 % and controls 2.13 %; diagnostic odds ratio- 97.63, p<0.001, sensitivity- 67.97%, specificity-97.87%) (Fig. 1), AGA (prevalence - cases 95.42 % and controls 48.94 %; diagnostic odds ratio - 21.76, p<0.001, sensitivity- 95.42%, specificity- 51.06%) (Fig. 2), premature canities (prevalence - cases 47.71 % and controls 17.02 %; diagnostic odds ratio- 4.48, p<0.001, sensitivity- 47.71%, specificity- 82.98%), AN (prevalence - cases 41.17 % and controls 14.89 %; diagnostic odds- 4.00, p<0.001, sensitivity- 41.18%, specificity- 85.11%), thoracic hairs (prevalence - cases 98 % and controls 27.66 %; diagnostic odds ratio – 130.76, p<0.001, sensitivity- 92.02%, specificity- 91.89%), corneal arcus (prevalence - cases 86.93 % and controls 21.27 %; diagnostic odds ratio - 24.61, p<0.001, sensitivity- 86.93%, specificity- 78.72%) and ear canal hairs (prevalence - cases 49.67 % and controls 4.25 %; diagnostic odds ratio-22.21, p<0.001, sensitivity- 49.67%, specificity- 95.74%) were found to be associated with CAD. But xanthelasma palpebrarum (prevalence - cases 3.27 % and controls 6.38 %; diagnostic odds ratio - 0.50, p>0.05) and acrochordons (prevalence - cases 68.63 % and controls 65.96 %; diagnostic odds ratio- 1.24, p>0.05) were not associated with CAD. Androgenetic alopecia of severe forms (grades 3v and above) according to the Norwood-Hamilton classification was associated with CAD with odds ratio of 33.33 as compared to androgenetic alopecia 3a and below in which the odds ratio was 7.84. Multiple logistic regression analysis showed DELC and thoracic hairs were strongly associated with CAD.

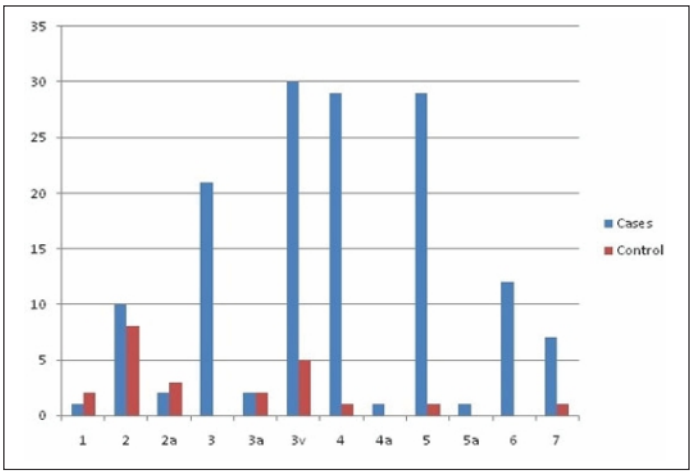

Figure 2: The overall prevalence of various grades of androgenetic alopecia according to Norwood-Hamilton classification and its distribution among cases and controls.

Table 1 shows that diagonal ear lobe crease, preauricular crease, androgenetic alopecia, premature canities, acanthosis nigricans, thoracic hairs, corneal arcus and ear canal hairs are associated with coronary artery disease by univariate analysis.

Cutaneous marker	Sensitivity	Specificity	Diagnostic odds ratio	Positive likelihood ratio	Negative likelihood ratio	Sig.
Diagonal ear lobe crease	98.69	91.49	811.620	11.59	69.83	0.000
Premature canities	47.71	82.98	4.48	2.80	1.58	0.000
Acanthosis nigricans	41.18	85.11	4.000	2.76	1.44	0.002
Xanthelasma	NA	NA	0.495	NA	NA	0.349
Thoracic hairs	92.02	91.89	130.769	11.34	11.51	0.000
Corneal arcus	86.93	78.72	24.605	4.09	6.02	0.000
Acrochordons	NA	NA	1.240	NA	NA	0.539
Ear canal hairs	49.67	95.74	22.210	11.67	1.91	0.000

Table 1: Cutaneous Markers Of Coronary Artery Disease.

Discussion

The patients recruited into the study were from different states in India however predominantly hailing from Tamil Nadu and West Bengal and few from the neighboring country of Bangladesh. There was no significant difference in the baseline characteristics of cases and controls. The mean age of the cases was around 59 years and of the controls was 54 years and their mean BMI was also similar. The commonest presenting symptom among cases was chest pain (58.82%) followed by dyspnoea on exertion (13%) and the least common symptom was post meal angina (0.65%). Similarly the commonest presenting symptom among controls was also chest pain (31.9%) followed by dyspnoea on exertion (21.27%).

Diagonal ear lobe crease (DELC) is a well acknowledged cutaneous marker for CAD in the literature.[6, 27,28,29,30] There are multiple theories supporting the relationship between DELC and CAD. Majority of them postulate that microvascular disease affects both ear lobes and coronary vasculature simultaneously. Our study showed that prevalence of DELC among cases (98.69%) was almost 11 times more than in controls (8.51%) (Fig. 3). This was high in contrast to the prevalence shown by earlier studies like Christiansen et al[28] (46.8%), Frank[5] (47 %) and Kaukola et al[6] (69%) in their respective studies. The reason for the higher prevalence of DELC in our study could be attributed to the fact that we included even the early grades of diagonal ear lobe crease. So we were able to compare the prevalence of DELC among cases and controls as well as correlate the association of the different grades of DELC with the severity of coronary heart disease. Studies conducted in the past confirmed the association between DELC and CAD but the methodology was not similar.[6, 27,28,29] We also did univariate and multiple logistic regression analysis, which showed its individual diagnostic value. Multiple logistic regression analysis of various cutaneous markers in our study showed DELC as a strong marker of coronary artery disease. The results of this study add to the knowledge available in understanding the association between DELC and CAD status. Such information will be a valuable background data to support future studies for screening vulnerable populations with CAD risk.

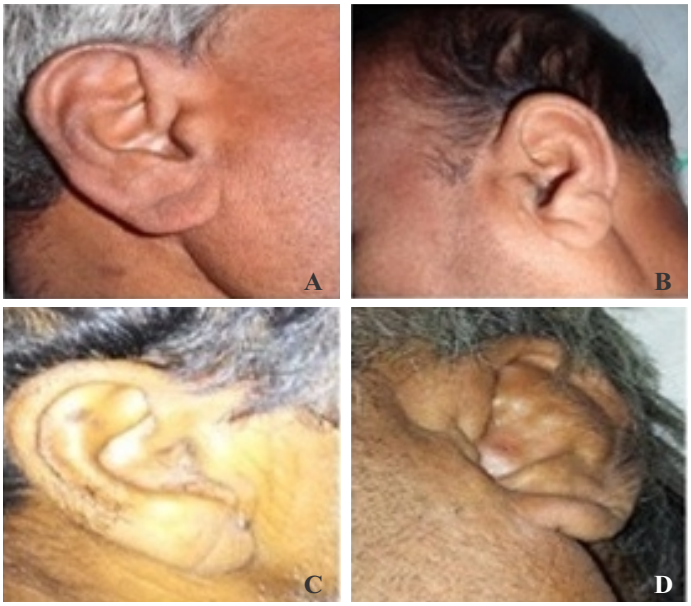

Figure 3: Grades Of Diagonal Ear Lobe Crease; A - Grade 1, B - Grade 2a, C - Grade 2b, D - Grade 3

Preauricular crease (PAC) is a well formed crease in front of auricle of the ear (Fig. 4). There is scarcity of evidence in literature to support preauricular crease as a cutaneous marker of CAD. Our study showed high prevalence of preauricular crease (PAC) among cases (67.97 %) as compared to controls (2.13 %). So it revealed a strong association between preauricular crease and CAD with a diagnostic odds ratio of 97.63($p<0.001$). The odds ratio of PAC was high in our study as compared to Miot et al[9] (OR-5.5, $p<0.05$). This study was conducted similar to our methodology but the controls selected were not completely free of CAD as patients with <50% stenosis of all coronary arteries were considered as controls.[9] The sensitivity and specificity of PAC in our study was 67.97 % and 97.87 % respectively. The sensitivity of PAC in our study was high in contrast to the study done by Miot et al,[9] which showed sensitivity of 59.3%. The positive and negative likelihood ratios were 31.91 and 3.055 respectively. So it can be said to be a marker of CAD with a good diagnostic value.

Our study showed that the prevalence of AGA among cases (95.42%) was almost doubles that of controls (48.94%) (Fig. 5). The prevalence of androgenetic alopecia among the controls was found to be similar to that in general population (40%) as given in literature.[39] In our study androgenetic alopecia was found to be associated with CAD (diagnostic odds ratio - 21.76, $p<0.001$).The higher prevalence of AGA among cases and a more robust diagnostic odds ratio in our study as compared to the study done by Miot et al.[9] It was further demonstrated in our study that the prevalence of AGA was highest in cases with triple vessel disease (97.01%) and lowest in minor CAD (17 %). Our

study was different from earlier studies because we compared the grades of AGA according to Norwood Hamilton classification with the sub types of coronary artery disease based on coronary angiogram. The study showed that androgenetic alopecia of severe forms (3v and above) according to the Norwood-Hamilton classification was associated with coronary artery disease with odds ratio of 33.33 as compared to androgenetic alopecia 3a and below in which the odds ratio was 7.84. Thus the relationship between CAD and baldness is probably dependent on the severity of AGA.

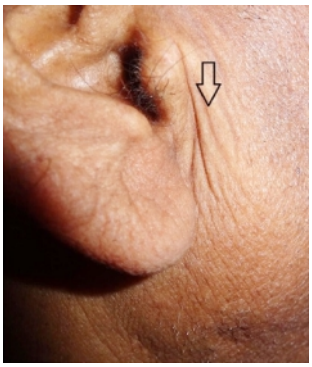

Figure 4: Preauricular crease

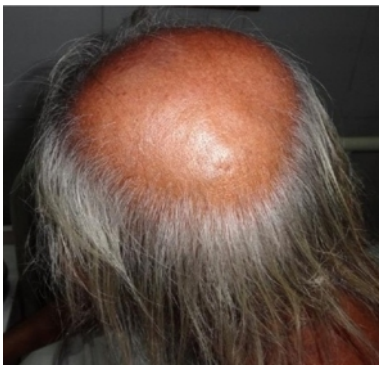

Figure 5: Vertex Alopecia

There are few studies in literature which have shown the association of premature canities and CAD.[14, 15, 40] In our study prevalence of premature canities among cases and controls was 47.71% and 17.02% respectively. This was low when compared to the study by Eisenstein et al, [40] which showed 100% prevalence of premature canities in patients with proven CAD and 55% in controls. This discrepancy may be attributed to racial difference. Premature canities was confirmed in our study as a significant dermatological marker of CAD with diagnostic odds ratio of 4.48 ($p<0.001$).

Acanthosis nigricans has been proved to be associated with hyperinsulinemia,[41] which in turn leads to an increased risk for CAD. The relationship between acanthosis nigricans and coronary artery disease was also compared among cases and controls in our study. We showed that the prevalence of AN was almost 3 times more among cases (41.18%) than that of the controls (14.89%). Acanthosis nigricans was found to have an association with CAD with a significant diagnostic odds ratio of 4.00($p<0.001$).

Xanthelasma palpebrarum is a type of specific form of xanthoma which presents as soft, velvety, yellow, flat, polygonal plaque around the eyelids.[25] It is known to be associated with hyperlipidemia which is characterized by elevated concentration of circulating atherogenic lipids, this leads to the process of accelerated atherosclerosis.[22, 42, 43] In our study it was observed in 27 % of cases and 6.38 % of controls. However our study did not show an association of the same with coronary artery disease (Diagnostic odds Ratio = 0.50, $p>0.05$). This is in contrast to the only study available in the literature which showed the association of xanthelasma palpebrarum and CAD.[36]

Thoracic hairs are commonly called as chest hairs, which are easily identifiable on clinical examination.[17] There is scarcity of literature supporting the association between thoracic hairs and coronary artery disease. Our study showed that 98 % of cases (see table) had thoracic hairs as compared to 27.66 % in controls (Fig. 6). This was high in contrast to the study by Miric et al, which showed that the prevalence of thoracic hairs was 40 % more in cases as compared to controls.18 However the methodology used to define thoracic hairiness was not given and the types of thoracic hairs were not elucidated. In contrast to our study comparison was done to general patients of the same hospital. As the control group was not evaluated by an angiogram, it cannot be elucidated whether their coronary artery was normal at the time of comparison or not. So the result of the above mentioned study may not be comparable. Our study showed a strong association between thoracic hairs and CAD (diagnostic odds ratio = 64.08, $p<0.001$). This potential relationship should be checked in further studies, including well-designed prospective studies.

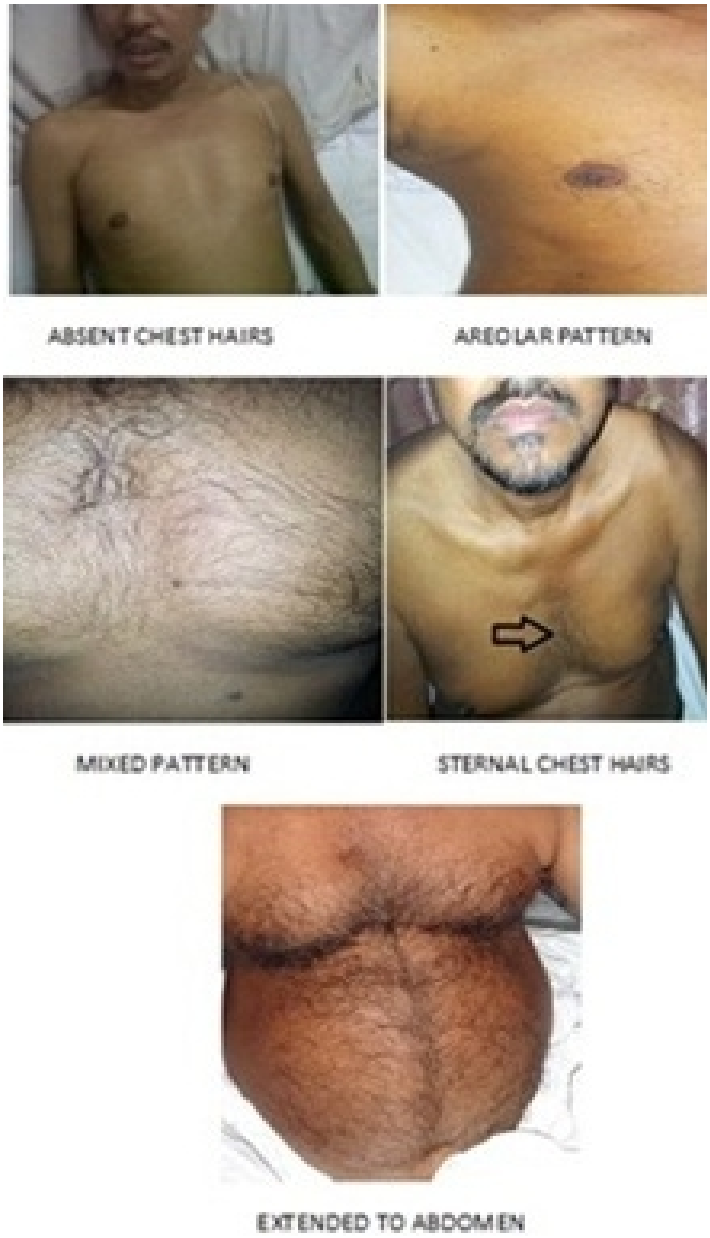

Figure 6: Patterns Of Thoracic Hairs

Corneal arcus is an easily visualized lipid-rich deposit which clinically presents as a grayish white opacity at the periphery of the cornea.[37] Our study showed a high prevalence (86.93%) of corneal arcus among cases as compared to other studies (Fig.

7).[44, 45] The study by Shanoff et al reported a prevalence of 44 % among cases, however none of the controls had corneal arcus.[45] In contrast to this, our study showed a prevalence of 21.27 % among controls. In our study corneal arcus was found to be associated with CAD with diagnostic odds ratio of 24.61 ($p<0.001$). Corneal arcus was found to have a sensitivity and specificity of 86.93 % and 78.72 % respectively. Thus the findings of our study are in accordance with the data given in literature. Our study emphasizes the usefulness of corneal arcus as a clinical marker for coronary artery disease. We suggest that physicians should examine patients for corneal arcus and if present may be a marker of underlying CAD.

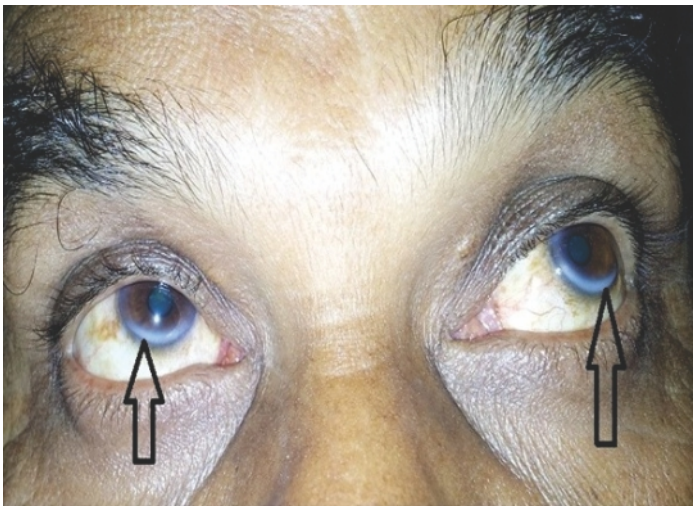

Figure 7: Corneal Arcus

Acrochordons were earlier shown to have a significant relationship with obesity[46] and metabolic syndrome[47] which probably represents a cutaneous sign for impaired carbohydrate or lipid metabolism, liver enzyme abnormalities, and hypertension.[48] Our study showed almost equal prevalence of acrochordons among cases (68.63%) and controls (65.96%) with odds ratio of 1.24 ($p>0.05$). So it is not associated with coronary artery disease. To the best of our knowledge there is no study in literature also to support this association.

Ear canal hairs were found in our study subjects during the clinical examination as an additional observation. Our study showed that ear canal hairs were seen in 49.67 % of cases and 4.25 % of controls. The diagnostic odds ratio was found to be 22.21 $p<0.001$). Thus our study suggests that ear canal hairs should be considered as a marker of CAD. Verma et al[49] and Wagner et al[50] also found a similar association, but comparable data is not available.

Conclusion:

The study suggests that diagonal ear lobe crease, preauricular crease, androgenetic alopecia, premature canities, acanthosis nigricans, thoracic hairs, corneal arcus and ear canal hairs are associated with coronary artery disease while xanthelasma palpebrarum and acrochordons are not. Both presence and severity of diagonal earlobe crease were related to occurrence of coronary artery disease. The grades of AGA with involvement of vertex are more important than just the mere presence of androgenetic alopecia in predicting the risk of CAD. Multiple logistic regression analysis showed DELC and thoracic hairs are strongly associated with CAD. A thorough search for the cutaneous markers of CAD may prove to be a worthwhile exercise in identifying individuals with high risk of CAD.

Limitations

The sample size of this study was small to make a definitive conclusion.

How to cite this article:

Sharma RK, Pulimood S, Peter D, George L. Association of the cutaneous markers with coronary artery disease- a case control study. JDA Indian Journal of Clinical Dermatology 2018;1: 06-11.

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ORIGINAL ARTICLE
Year: 2018 I Volume: 1 I Issue: 1 I Page: 12-15

SPECTRUM OF CUTANEOUS MANIFESTATIONS IN PATIENTS WITH INTERNAL MALIGNANCIES: A CLINICO-EPIDEMIOLOGICAL STUDY

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Abstract

Background: The skin can provide important clues to systemic disease and internal malignancies; recognition of these clues facilitates both early diagnosis and prompt treatment of internal malignancy. This study was undertaken with objectives of knowing the spectrum of cutaneous manifestation in patients suffering from various internal malignancies.

Methods: A total of 1000 patients with internal malignancies were screened in this study. Relevant investigations for diagnosis of internal malignancy and dermatological disorders were carried out.

Result: Skin changes were present in 644 cases (64.4%). Majority of the patients were in the age group of 40-60 years. In seven patients dermatological changes were the presenting sign of internal malignancy. Specific skin lesions were found in 16 cases (1.6%) out of which cutaneous metastases was present in 11 patients (1.1%), lymphoma cutis in 3 (0.3%), carcinoma en cuirasse and inflammatory carcinoma of breast in one patient each. Four hundred and eighty six patients had dermatological conditions under nonspecific category and 222 patients had therapy related cutaneous adversities. Few patients had more than one skin changes. Most common nonspecific skin lesions were paraneoplastic dermatoses (21.8%), fungal infection (9.0%), xerosis (6.6%) and viral infections (6.9%). Radiation dermatitis was the most common therapy related changes seen in 12.8% patients.

Conclusion: A patient of internal malignancy can present with specific or nonspecific skin changes and can be a presenting sign of internal malignancy. Elderly patients with unusual dermatological presentation and unresponsive to conventional therapy must be thoroughly investigated for internal malignancy.

Key words: cutaneous manifestation of malignancies, cutaneous metastasis

Introduction

Skin being the largest and most visible organ of the body, may provide a useful indicator for systemic diseases including malignancies. Internal malignancies may affect the skin both directly and indirectly. Direct involvement implies the presence of tumor cells within the skin which may occur either by local extension or by tumor metastasis through hematogenous and lymphatic routes.[1] Indirect involvement by internal malignancies includes, genodermatoses, paraneoplastic disorders, certain indirect cutaneous markers and adverse effects of either chemotherapy or radiotherapy.[2] These cutaneous markers of malignancy may occur before, at the same time as or after the diagnosis of the tumor.[3,4] The timely diagnosis of these conditions is important as paraneoplastic dermatoses often cause considerable morbidity and in some instances may lead to detection of an otherwise clinically occult tumor at an early and treatable stage. To best of our knowledge, previous reports regarding incidence of cutaneous manifestations of internal malignancies are limited and include mainly case series, reviews and retrospective studies. To know the overall frequency and clinical profile of skin diseases associated with internal malignancies we conducted a study among the patients attending outpatient department of dermatology and regional cancer research and treatment center in Bikaner, North India.

Materials and Methods

One thousand patients of internal malignancies of various duration involving different organs, with or without treatment, were included in present study. Only those cases confirmed to be having internal malignancy were included. A detailed epidemiological data was collected; also history regarding malignancy and dermatological complaints, details about cutaneous changes, systemic examination, relevant investigations and treatment details of internal malignancy were recorded in a printed proforma. Skin biopsies for histopathology, scrapings for fungal infections and Gram staining, culture and sensitivity of purulent material were done whenever required. Diagnosis of malignancies was done by oncologist on the basis of clinical examination and relevant investigations including cytological, histopathological, biochemical, hormonal and radiological examination for respective malignancies. Clinical photographs of skin manifestations were also taken in patients having specific skin lesion.

Results

Out of 1000 patients studied, 477 (47.7%) were males and 523 (52.3%) were females. Majority of the patients were in the age group of 41-50 years (322; 32.2% patients) followed by 259 (25.9%) patients in 51-60 years age group. Only 4 patients were below 10 years (Fig. 1).

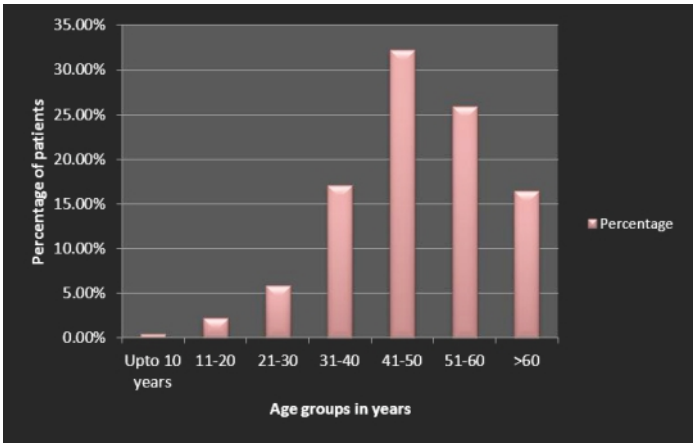

Figure 1: Distribution of cutaneous metastases

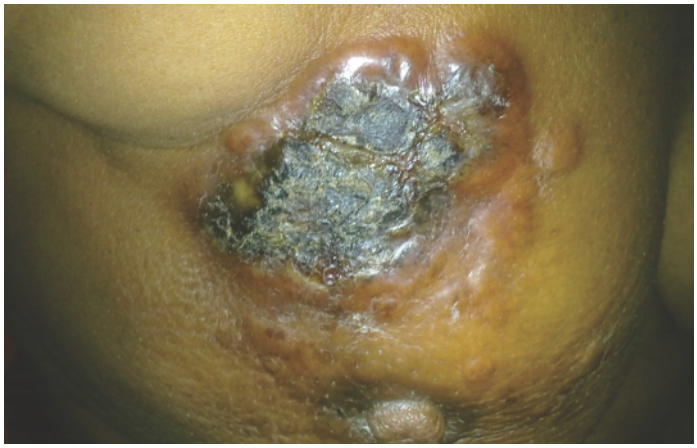

Figure 2: Cutaneous metastases in a breast carcinoma patient

Overall, most common malignancy was carcinoma breast (20.4%) followed by carcinoma cervix (19.6%), lymphoma (12.8%), leukaemia (6.7%), carcinoma oral cavity (6.6%), broncho-pulmonary carcinoma (6.4%) and carcinoma ovary (4.5%). The other malignancies encountered were carcinoma oesophagus, laryngeal carcinoma, gastro-intestinal malignancies, pharyngeal carcinomas, hepato-biliary carcinoma, carcinoma prostate, secondary metastasis with unknown primary, multiple myeloma, carcinoma of testes, urinary bladder, vagina, endometrium, brain and thyroid in decreasing order of frequency.

The malignancies observed in males were lymphomas in 125 (12.5%), broncho-pulmonary carcinomas in 62 (6.2%) and oral cavity malignancies in 56 (5.6%) cases, while in females there was carcinoma breast in 204 (20.4%), carcinoma cervix in 196 (19.6%) and carcinoma ovary in 45 (4.5%) cases.

Skin lesions were found in 644 (64.4%) patients out of 1000 cases studied. Out of 644 patients, in only seven (1.08%) patients cutaneous diseases were diagnosed before diagnosis of internal malignancy.

A total of 51 different types of dermatological manifestations were seen. We observed three categories of cutaneous changes in patients of internal malignancies; 486 patients had nonspecific changes whereas 222 cases were found to have treatment related skin changes and only 16 patients had specific dermatological lesions pertaining to malignancies. Thirty four patients suffered from more than one cutaneous finding.

Cutaneous metastases was the commonest specific lesion in 11(1.1%) patients followed by lymphoma cutis in 03 (0.3%), carcinoma en-cuirasse and inflammatory carcinoma of breast in one patient each (Fig. 2-5).

Out of 11 patients of cutaneous metastases, 8 patients showed contiguous metastases from underlying carcinoma while 3 patients had non-contiguous metastases occurring at a distant site. Most common site of cutaneous metastases was anterior chest wall in 4 cases and most common type of lesion was nodules in 7 cases. There were 3 cases of metastases, manifesting as presenting sign of internal malignancy (Table 1).

Most common non specific cutaneous lesions were paraneoplastic disorders affecting 218 (21.8%) patients followed by infections and infestations in 207 (20.7%) patients (Table 2).

Among them most common skin changes were fungal infections in 90 (9.0%), viral infections in 69 (6.9 %), xerosis in 66 (6.6%) and pruritus in 39 (3.9%) cases. Other non-specific skin lesions included intertrigo, seborrheic dermatitis, lichenoid eruptions, perianal dermatitis, photodermatitis, eczematous eruption around nipple areola complex, pityriasis rosea, aphthous ulcers, icterus, koilonychias, lymphangiactasis, psoriasiform dermatitis and hiderdinitis suppurativa.

Therapy related skin changes were encountered in a total of 222 (22.2%) cases. Radiation dermatitis was the most common in 12.8% patient (Fig. 6), alopecia in 74 (7.4%), flagellate pigmentation was found in 4 cases (Fig. 7).

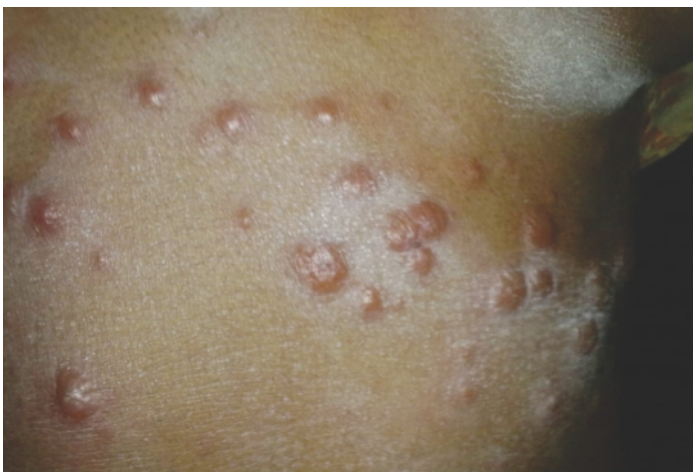

Figure 3a: Lymphoma cutis in a patient with non-Hodgkin's lymphoma

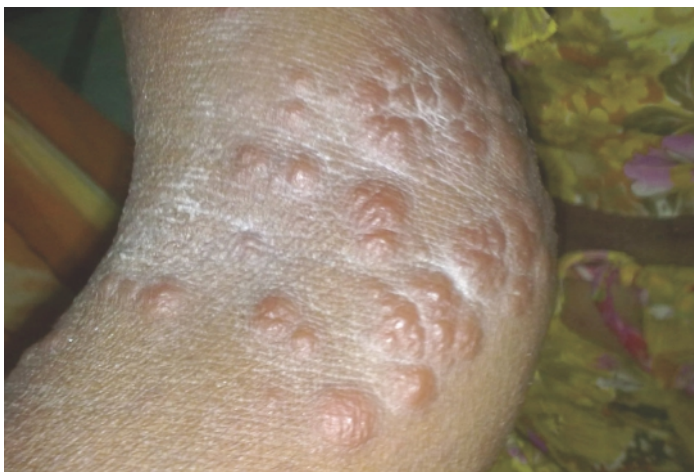

Figure 3b: Lymphoma cutis in a patient with non-Hodgkin's lymphoma

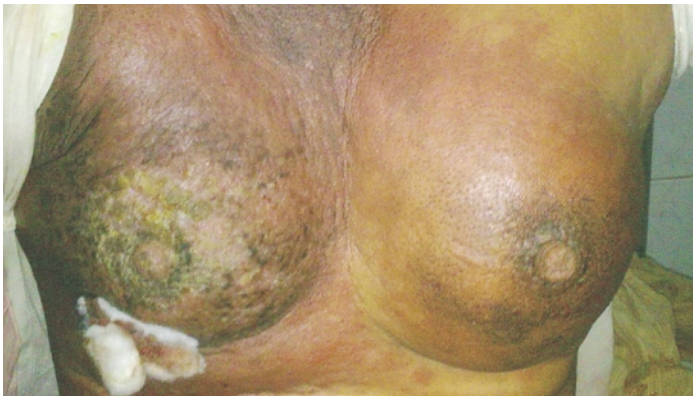

Figure 4: Carcinoma en-cuirrase in a breast carcinoma patient.

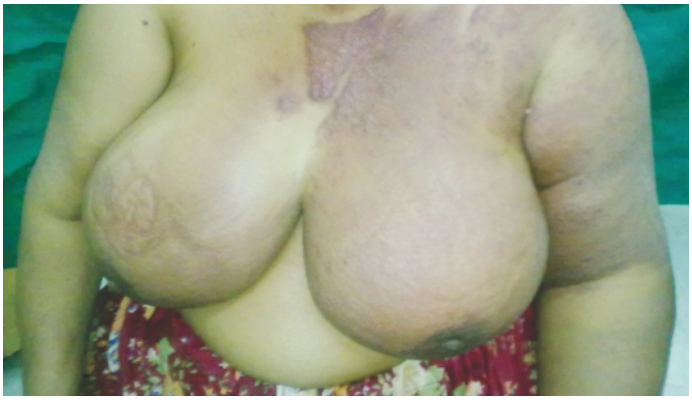

Figure-5: Inflammatory-carcinoma-of-breast

S. No.	Type of the skin lesion	Number of skin lesions	Site of lesions	Time of diagnosis	Associated internal malignancy
(a)	**Contiguous metastases 8 cases**				
01	Non tender, firm to hard nodules	Multiple	Anterior chest wall (inferior quadrant)	Before	Carcinoma breast
02	Fungated ulcerated plaque	Single	Anterior chest wall	Before	Carcinoma breast
03	Erythematous, nontender, firm, papulonodules and fungating ulcers	Multiple	Anterior chest wall	After	Carcinoma breast
04	Ulcerated nodule	Single	Anterior chest wall	After	Carcinoma breast
05	Nontender, skin colored nodule	Single	Axilla	After	Carcinoma breast
06	Hard pigmented plaque	Single	Pubic region	After	Carcinoma cervix
07	Nontender, hard grouped nodules	Multiple	Mental area	After	Carcinoma gingivo-buccal sulcus
08	Hard nodulo-ulcerative plaque	Single	Anterior neck, submandibular area	After	Laryngeal carcinoma
(b)	**Noncontiguous metastases 3 cases**				
01	Nontender, hard skin colored nodules	Multiple	All over body	After	Nasopharyngeal carcinoma, NHL
02	Hard, subcutaleous nodule	Single	Neck	Before	Ca testis
03	Ulcerated plaque	Single	Penis	After	NHL

Table 1: Distribution of cutaneous metastases

Nonspecific skin lesions	Number of patients (n)	Total of patients (%)
Paraneoplastic dermatoses	Papulosquamous disorders (12) • PPK (06) • Ichthyosis (05) • Bazex syndrome (01) Vascular disorders (27) • Erythema multiformae (08) • Vasculitis (06) • Purpura (04) • Necrotizing ulcers (04) • Flushing (02) • Thrombophlebitis (02) • Acral gangrene (01) Nail changes (56) • Hyperpigmentation (34) • Onychodystrophy (12) • Subungular hyperkeratosis (08) • Clubbing (02) Bullous disease (01) • Paraneoplastic pemphigus Miscellaneous (122) • Xerosis (66) • Generalized pruritus (22) • Localized pruritus (17) • Prurigo nodularis (14) • Hyperpigmatation (03)	218 (21.8%)
Infections and infestations	• Pyoderma (23) • Herpes zoster (57) • Herpes simplex (9) • Verruca vulgaris (3) • Tinea (65) • Candida (08) • Paronychia (11) • Pityriasis versicolor (06) • Scabies (15)	197 (19.7%)
Other nonspecific diseases	• Intertrigo (15) • Seborrheic dermatitis(11) • Lichenoid eruptions (11) • Perianal dermatitis (06) • Photodermatitis (06) • Eczematous eruption around nipple areola complex (05) • Pitvriasis rosea (03) • Aphthous ulcers(05) • Icterus (03) • Koilonychia (02) • Lymphangiactasis (01) • Psoriasiform dermatitis (02) • Hideradinitis suppurativa(01)	71 (7.1%)

Table2: Distribution-of-nonspecific-skin-changes

Discussion

Skin is the window to systemic diseases and malignancies, as it is readily visible. Our study revealed a high prevalence (64.4%) of dermatological manifestations in patients suffering from internal malignancies which was greater than the observations of previous studies by Rajagopal et al5 (27.3%), Kilic et al6 (45.14%) and Ayyamperumal et al7 (6.93%). In present study females were more commonly affected than males in contrast to previous studies.[5,6,7,8]

Skin is an infrequent site for metastases and the rates of metastases from internal malignant diseases to the skin varies between 0.7% and 9%.[9,10] In present study incidence of cutaneous metastasis was 1.1% which is consistent with findings of Kilic et al.[6] Cutaneous metastases commonly present as single or multiple nodules, which are always firm and rubbery to stony hard in consistency, often fixed to underlying tissue.[10] In present study, 3 out of 8 cases with contiguous metastases and 1 out of 3 cases of noncontiguous metastases had multiple lesions. Beside the nodules, we also encountered plaques, papules and ulcers. Anterior chest wall was the most common site for metastases as reported in earlier studies conducted by Rajagopal et al,[5] Ayyamperumal et al,[7] Benmously et al,[11] Gul et al[12] and Kanitakis.[13] The common primary malignancies reported with cutaneous metastases are lung cancers in males, and breast cancer in females.[11,14,15] In our study carcinoma breast was found to be the commonest malignancy in females and Non-Hodgkin lymphoma in males.

Risk of infections is generally increased in internal malignancies due to an immunocompromised status which is caused either by chemotherapy or disease process itself.[16] Most frequent non-specific skin lesions encountered in our study were fungal infections in 90 (9.0%) patients which is similar to study conducted by Kilic et al.[6] Herpes zoster was present in 5.7% cases and found to be disseminated, nondermatomal and ulcerated in most of the cases. It has been reported to be most often seen in hematological malignancies like chronic lymphocytic leukemia and lymphomas,[5,6,17] while present study revealed carcinoma breast to be the most common malignancy

associated with herpes zoster.

Xerosis and nonspecific pruritus were found in 6.6% and 3.9% out of 1000 cases in our study. Among the malignant diseases, it was most often observed in leukemia and lymphomas. Goldman and Koh found pruritus in 35% of patients suffering from Hodgkin's disease.[18] In our study xerosis was most commonly associated with carcinoma breast (1.8%) and carcinoma cervix (1.6%) while pruritus was associated with carcinoma cervix (0.7%) and carcinoma breast (0.6%). Lymphoma was the third most common malignancy with four cases. This difference may be due to more prevalence of the carcinoma of breast and cervix cases in our study. Up to 50% of the patients with pruritus without any obvious dermatological cause also have an underlying systemic disease process including malignancies.[19] Persistent pruritus not otherwise explained by an obvious dermatologic condition should prompt an investigation for underlying systemic cause.

Palmoplantar keratoderma (PPK) both acquired and familial forms are also related with malignancies.[20,21] We found acquired palmoplantar keratoderma in 6 patients, most commonly associated with hematological malignancy (0.4%) which was similar to study by Kilic et al.[6] In one case palmoplantar keratoderma was presenting sign of carcinoma brain (astrocytoma). Kilic et al[6] also reported diffuse hyperpigmentation in 0.28% patients with gastrointestinal carcinomas. In our study it was seen in hepato-cellular carcinoma, carcinoma lung and multiple myeloma with a prevalence of 0.3%.

In our study we encountered 27 (2.7%) cases of vascular disorders. These included erythema multiformae (0.8%), vasculitis (0.6%), purpura (0.4%), necrotizing ulcers (0.4%), flushing (0.2%), thrombophlebitis (0.2%) and acral gangrene (0.1%). In one case of vasculitis, Raynaud's phenomenon was also positive and it was associated with non-Hodgkin's Lymphoma (NHL). Cutaneous vasculitis is more likely to be associated with hematologic cancers.[22] Flushing is most commonly associated with carcinoid syndrome of gastrointestinal and bronchial origin[23] but in our study one case was associated with carcinoma of testis and other was the case of acute lymphocytic leukemia (ALL).

Radiation dermatitis was the most common treatment related change in 12.8% patients followed by alopecia in 7.4% patients. Drug induced urticaria were found in 16 (1.6%) patients which was higher than the findings of Kilic et al[6] study (0.42%) and Rajagopal et al[5] study (0.66%). The antigens originating from various foci from the tumor may be urticariogenic. Flagellate pigmentation was found in 4 (0.4%) patients due to bleomycin which was almost similar with Rajagopal et al study (0.3%).

In addition, our study showed some cutaneous manifestations which had very low incidence such as scabies, intertrigo, seborrheic dermatitis, lichenoid eruptions, perianal dermatitis, photodermatitis, eczematous eruption around nipple areola complex, pityriasis rosea, aphthous ulcers, icterus, koilonychia, paraneoplastic pemphigus, Bazex' syndrome, lymphangeictasis and psoriasiform dermatitis.

Conclusion

We conclude that skin is an indicator of milieu interior. Skin manifestations might occur before, simultaneously or after the diagnosis of internal malignant disease. A patient presenting with dermatological manifestation with unusual presentation, long duration and resistant to treatment should be thoroughly investigated for internal malignancies.

Limitations

In the study all types of malignancies could not be covered so some cutaneous findings could have been missed and also genodermatoses were not covered.

How to cite this article:

Naushin Aara, Mehta RD, Bumb RA, Ghiya BC, Soni P, Kumar HS. Spectrum of cutaneous manifestations in patients with internal malignancies: a clinico-epidemiological study. JDA Indian Journal of Clinical Dermatology 2018;1:12-15.

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ORIGINAL ARTICLE
Year: 2018 I Volume: 1 I Issue: 1 I Page: 16-18

FEMALE FACIAL MELANOSIS IN INDIA : ROLE OF CONTACT SENSITIVITY

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Abstract

Background: The wish to get lighter skin in Asian women, in particular, is very high as it is believed to be an indication of superiority and higher socioeconomic status. Paradoxically there is sudden increase in the number of female patients seeking consultation for facial melanosis. We hereby report a series of such patients with an attempt to delineate the probable role of contact sensitivity .

Aim: To delineate the probable role of contact sensitivity in facial melanosis

Methods: Thirty three female patients, aged between 18 - 57yrs, with predominantly diffuse pigmentation of the face and neck(Fig. 1 a,b) were included in the study, carried out from May 2015 to September 2016.

Results: 21 out of 33 patch-tested patients showed positive reactions to various allergens

Limitations: The sample size is small to make a definite conclusion.

Conclusion: Whereas cosmetics are intended to improve the appearance of the skin or enhance the attractiveness of the users, paradoxically skin lightening creams have led to an epidemic of diffuse hyperpigmentation. Therefore, stringent regulations are needed, since such preparations should not be made available over the counter; moreover, mandatory labeling of the constituents should be required.

Key words: Cosmetics, Pigmented cosmetic dermatitis, Isoeugenol, Females Facial Melanosis, YlangYlang oil, Canangaodorata oil.

Introduction

The wish to get lighter skin in Asian women, in particular, is very high as it is believed to be an indication of superiority and higher socioeconomic status. Recently the spread of visual media even to the smaller towns of India as well as on the counter availability of large number of fairness creams have resulted in their increasing usage with very little information regarding the safety profile and side effects. Paradoxically there is sudden increase in the number of female patients seeking consultation for facial melanosis. We hereby report a series of such patients with an attempt to delineate the probable role of contact sensitivity .

Materials and Methods

Thirty three female patients, aged between 18 - 57yrs, with predominantly diffuse pigmentation of the face and neck(Fig. 1 a,b) were included in the study, carried out from May 2015 to September 2016. In some patients the volar aspect of the forearms (Fig.1c) or upper back of the trunk were also involved (Table 1).Case series is small, reason being only patients who agreed for patch testing were included. A small number of patients (*n* =7) had previously also suffered from mild dermatitis. The duration of hyperpigmentation varied from 6 month to 3 years.

All patients were patch tested with the Indian baseline series, the fragrance series (Chemotechnique Diagnostics, Vellinge, Sweden) and some also with their own products used.

The closed patches were applied on the back and occluded for 2 days, and the readings were taken on D 2 and 4 according to the ICDRG guidelines. In 6 patients, biopsy specimens were obtained from a pigmented area for histopathological examination. Photo Patch test could not be done because of non availability of Photo Patch test facility.

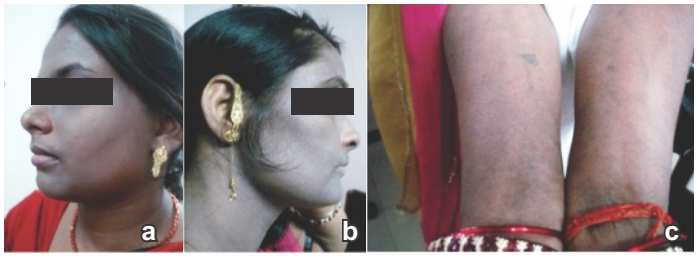

Fig No1 (a, b, c). Patient with predominantly diffuse pigmentation of the face and neck

Results

21 out of 33 patch-tested patients showed positive reactions to various allergens, the results of which are given in Tables 1 and 2. Most patients presented with contact sensitivity to isoeugenol (n=14) followed by Hydroquinone and Fragrance mix 1 (n=5), and *Canangaodorata* or YlangYlangOil (n=4). Among the

Table 1: The sites affected and positive patch-test results

Case No.	Age (years)	Affected Sites	Patch-test results
1.	35	Face, neck	Isoeugenol
2.	42	Face, neck, forearms	PPDA, Nickel, Isoeugenol, Frag Mix II
3.	28	Face, neck upper back	PPDA, Isoeugenol, Frag Mix II, Amyl cinnamic alcohol
4.	22	Face	Benzyl salicylate, HQ
5.	43	Face neck & foearm	FMI, isoeugenol, POM
6.	38	Face	Nickel, POM, Benzyl salicylate
7	36	Face,neck	Potassium dichromate, cobalt, isoeugenol
8	27	Face, neck forearms	FMI, isoeugenol, HICC, citral
9.	24	Face & neck	FMI, isoeugenol, HQ
10.	57	Face & neck	Nickel, POM, isoeugenol
11.	22	Face	PPDA, isoeugenol, coumarin, sandalwood
12.	39	Face	Potassium dichromate, FMI, colophonium,POM
13.	26	Face, neck & foearms	Farnesol, isoeugenol, POM, HQ
14.	35	Face & neck	Isoeugenol, *evernia prunastri* (oakmos absolute), *Canangaodorata* (YYO)
15.	18	Face & neck	Cobalt, colophonium, Nickel, FMI
16.	46	Face, neck forearms & upperback	YYO,cinnamic aldehyde,cinnamic alcohol, isoeugenol, HQ
17	33	Face & neck	Myroxeilon pereirae (Balsam Peru), YYO
18.	28	Face & neck	Isoeugenol, Santalum Album (sandalwood) oil
19.	22	Face & neck	Nickel, geraniol, HQ
20.	48	Face, neck & forearms	Isoeugenol, POM
21.	53	Face & neck	PPDA, colophonium, YYO

PPDA: Para-phenylenediamine; HICC: hydroxyisohexylcyclohexene carboxaldehyde; HQ: Hydroquinone; YYO: YlangYlang oil; POM: Patient own material; FMI: Fragrance Mix1; FM II: Fragrance Mix 2

Table 2: Number (Nr.) of positive patch-test reactions to the different series and the patients' own cosmetics

Indian Standard Series	Nr.	Fragrance Series	Nr.	Own cosmetics (POM)	Nr.
Nickel	5	Isoeugenol	14	Herbal Fairness cream	5
Potassiumdichromate	2	YlangYlang Oil	4	Fairness cream	1
Colophonium	3	Fragrance Mix II	2	Sunscreen gel	1
FragranceMix 1	5	Sandalwood oil	2		
PPDA	4	Benzyl Salicylate	2		
Balsam Peru	1	Cinnamal	1		
Cobalt	2	Cinnamic Alcohol	1		
HQ	5	Farnesol Geraniol Everniaprunastri	1 1		

fifteen patients tested with their personal products seven had a positive reaction,of which three were considered irritant. The biopsy specimens showed mild hyperkeratosis, occasional basal layer liquefaction degeneration along with accumulation of melanin pigment, and a mononuclear cell infiltrate in the upper dermis. However a band like infiltrate with lymphocytes and histiocytes, hypergranulosis, saw toothed appearance and acanthosis of epidermis, or Hyaline bodies were absent. (Figure 2)

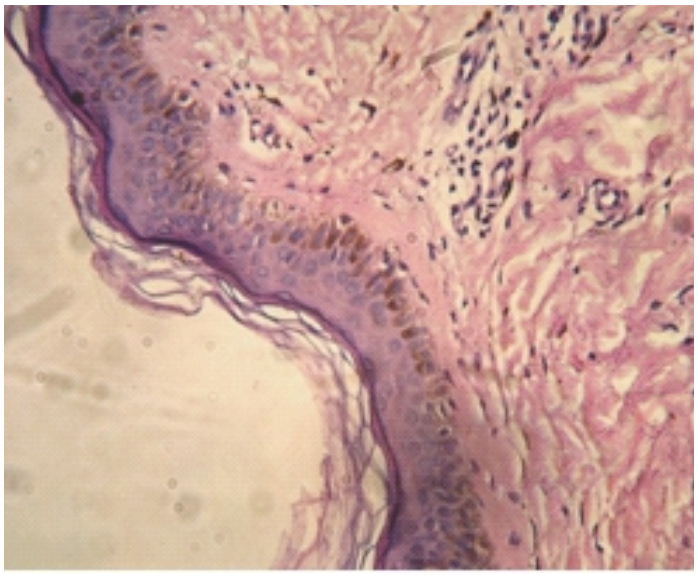

Fig-2 Histopathology showing liquefaction degeneration and accumulation of melanin pigment in the basal layer, and a sparse mononuclear infiltrate of the upper dermis (H&E staining) (40x).

Table 3: Number of patients with positive patch tests and of results of clinical follow-up after withdrawal of the allergens identified

Positive reactions	21
With follow up after 02yrs	15
With perceptible improvement after avoidance of allergens	9
Very little improvement	2
No improvement	4

Discussion

Widespread or localized hyperpigmentation may be associated with a large number of conditions (1). In our study, patients were having diffuse hyperpigmentation of the face and neck with history of application of various cosmetic creams, aromatic oils, or fragrances. In some patients mild dermatitis preceded the onset of hyperpigmentation.

The majority of our patients (21/33) showed positive patch-test reactions to various components of cosmetics, particularly the fragrance ingredients isoeugenol followed by Canangaodorata or YlangYlang Oil, and Fragrance Mix1, components which have been implicated to cause Pigmented Cosmetic Dermatitis (2). Five patients reacted to a popular brand of herbal fairness cream, found to contain geraniol, citronellol, Santalum Album or sandalwood oil, and eugenol, also known to produce hyperpigmentation (3, 4). The positive reactions to nickel and potassium dichromate in 5 and 2 patients respectively, were not considered relevant to the present condition.

According to Osmundsun (5) pigmented contact dermatitis

(PCD) is an idiosyncratic reaction. Although the exact mechanism by which the allergic reaction induces epidermal and dermal hyperpigmentation is still not known. It has been hypothesized that allergens responsible for PCD may have special affinity for melanin, inciting an inflammatory reaction around the melanocytes and around the cells incorporating melanin granules (6). Nakayama et al. (7) hypothesized that the concentration of allergens in commercial preparations were too low to produce spongiotic dermatitis but may give rise to a cytolytic type IV allergy at the basal layer of the epidermis, resulting in PCD. Similar histopathological features were observed in our cases as well.

In a recent Thai study(8) patients having hyperpigmentation due to Ashy dermatosis(AD), Lichen planuspigmentosus(LPP) and suspected pigmented contact dermatitis (PCD) were patch tested and almost half of them (21 of 43 ; 48.83 %) showed relevantly positive reactions. The positive reactions were seen in 40% cases of Ashy dermatosis, 36.36 % cases of LPP and 80% cases of PCD. Our study has almost similar results and follow up of our cases over 2 years with avoidance of putative allergens resulted in improvement of pigmentation in significant number of patients.It is suggested that patch testing in patients with hyperpigmentation will go a long way in proper management of these cases.

Conclusion

Whereas cosmetics are intended to improve the appearance of the skin or enhance the attractiveness of the users, paradoxically skin lightening creams have led to an epidemic of diffuse hyperpigmentation. Therefore, stringent regulations are needed, since such preparations should not be made available over the counter; moreover, mandatory labeling of the constituents should be required.

Patch testing, also with the personal products used, is a useful tool in identifying the etiology of female Facial Melanosis, since, at least in significant number of cases, elimination of the allergens identified resulted in clinical improvement.

Limitations

The sample size is small to make a definite conclusion.

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How to cite this article:

Srivastava P.K, Bajaj A.K. Female Facial Melanosis in India : Role of contact sensitivity. JDA Indian Journal of Clinical Dermatology 2018;1:16-18.

LETTER TO EDITOR
Year: 2018 I Volume: 1 I Issue: 1 I Page: 19-22

A DOUBLE BLIND PLACEBO CONTROLLED TRIAL TO COMPARE THE EFFECT OF ORAL ISOTRETINOIN AND TRETINOIN (0.05%) CREAM COMBINATION WITH TRETINOIN (0.05%) CREAM ALONE FOR TREATMENT OF CUTANEOUS WARTS

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Sir,

Warts or verrucae are benign proliferations of the skin and mucosa caused by infection with human papilloma viruses (HPVs). Various treatment modalities are available which are classified into destructive, virucidal, antimitotic and immunotherapy. Treatment is exhaustive both for clinician and patient due to high recurrence rate and unwanted adverse effects associated with treatment. Problem is further increased when there is large number of warts, i.e. 15-20 or more. Use of destructive methods is difficult in such cases as multiple sittings are required along with risk of scarring and post inflammatory hypo or hyper pigmentation. Therefore, destructive methods are unsuitable for cosmetically important sites such as face where these side effects are undesirable. Thus, there is always a need for effective medical treatment of warts to overcome these disadvantages.

The two major goals of management of warts are to prevent recurrences by control of viral replication and minimal cosmetic disfigurement. Immunotherapy and antimitotic therapy for treatment of warts are two potential areas where we can achieve these goals. Retinoids are antimitotic as well as immunomodulator drugs. Retinoids have been found to be effective for treatment of warts in some previous case reports and studies [1-11]. In these studies isotretinoin or etretinate has been used in patients with refractory genital warts or in patients with recalcitrant extensive warts. Isotretinoin being cheaper should be preferred over etretinate in developing countries like India. Topical tretinoin (0.05%), a first generation retinoid, has been successfully used for treatment of warts especially plane warts. [12,13] We conducted a double blind placebo controlled trial to compare the effect of oral isotretinoin and tretinoin cream (0.05%) combination with tretinoin cream (0.05%) alone to treat non genital cutaneous warts in immunocompetent persons as well as to study its effect with respect to site, morphology and number of warts.

A prospective, open label study was conducted and a total of 80 patients were enrolled in the study. Inclusion criteria were patients who were willing to give a written informed consent, patient with six or more cutaneous warts, married female who had underwent sterilisation (tubectomy or vasectomy in partner), women of childbearing potential, if sexually active, were included if they were using two forms of contraception. Exclusion criteria were pregnancy and lactation, age less than 12 years of age, liver dysfunction, hyperlipidemia, any associated systemic disease and patients with genital warts. Qualitative and quantitative data was analyzed with Medcalc (version 11.6.0.0) software. Quantitative data was summarized with mean and standard deviation. Mean observations at week 0 and week 12 were compared with Paired t-test. Qualitative data was analyzed with CHI-SQUARE TEST. P value <0.05 was considered to be of statistical significance.

All patients underwent thorough history taking, clinical examination including relevant laboratory investigation e.g. Liver function test and total lipid profile to monitor side effects of retinoids. Patients were randomized into two groups by computer generated random number table. Both groups were given topical tretinoin 0.05% cream to be applied as single night time application. Patients who were randomized into retinoid group were given isotretinoin capsule 20 mg /day after meal for 12 weeks (group 1). Patients who were randomized into placebo group were given placebo capsule of same colour and size containing sugar powder for 12 weeks (group 2).

Patients were followed up after 2, 4, 6, 8, 10, 12 weeks. Treatment was given for three month duration. They were further followed for next four weeks to note any recurrence. Patients were investigated monthly to identify any side effect. During the whole study period, clinical responses as well as adverse effects were recorded.

Clinical response was determined and noted at each visit by reduction in the number of lesions; No response = 0; Poor response = + 1 (<30% reduction in the number of lesions); Fair response = +2 (30-60% reduction in the number of lesions); Good response = +3 (60-90 % reduction in the number of lesions); Complete clearance, excellent response = +4.

A total of 80 patients (59 males, 21 females) with age ranging from 13 to 54 years (mean 24.84) were included in the study. Demographic data of both groups were comparable in all variables including age, sex, occupation of patients and site, type,

	Group 1	Group 2	Total
Males	31	28	59(73.75%)
Females	9	12	21(26.25%)
Common warts	15	17	32(40%)
Plane warts	13	14	27(33.75%)
Face	25	25	50(62.5%)
Hand	17	13	30(37.5%)
Forearm	13	8	21(26.25%)
Students	20	18	38(47.5%)
Housewives	6	5	11(13.75%)

Table 1: Demographic data of both groups

duration of warts. Table 1 shows demographic data of both groups.

Common wart (verruca vulgaris) was the commonest type of wart (40%) followed by plane wart (33.75%). Face (62.5%) was the most common site of involvement followed by hands (37.5%) and forearm (26.25%). Most of the patients were students (47.5%) followed by housewives (13.75%) and were in 15-24 year age group. Mean duration of wart was 12.63 months in group 1 and 13.83 months in group 2. Mean numbers of warts were 37.04 in group 1 and 36.08 in group 2. Past history was present in two and family history was present in seven out of 80 patients. Fifteen patients were lost to follow up, five from group 1 and ten from group 2.

Table 2 shows treatment response in group 1. There was no case of filiform wart in this group. Patients with periungual warts showed mean response score +0.5 at the end of 12 weeks indicating poor response, while patients with common, plantar and palmar warts showed fair response with mean score 1.2, 1.71 and 2 respectively at the end of 12 weeks. Three out of

Type of wart	Number of patients	Response-According to reduction in number of lesions (mean response score)					
		2 weeks	4 weeks	6 weeks	8 weeks	10 weeks	12 weeks
Common	15(37.5%)	+0.18	+0.31	+0.5	+0.59	+1.10	+1.22
Plane	13(32.5%)	+0.66	+1.27	+1.72	+2.33	+2.77	+3.05
Filiform	0	0	0	0	0	0	0
Periungual	2(5%)	0	0	0	0	+0.5	+0.5
Palmer	3(7.5%)	0	0	+0.33	+0.33	+2	+2
Plantar	7(17.5%)	0	+0.14	+0.85	+0.85	+1.71	+1.71

Table 2: Treatment response in group 1

fifteen patients of common warts and two out of ten patients of palmoplantar warts showed complete clearance. Patients of plane wart showed mean response score +0.66 at two weeks which increased to +3.05 at the end of twelve weeks, indicating excellent response. Six out of thirteen patients showed complete clearance.

Type of wart	Number of patients	Response-According to reduction in number of lesions (mean response score)					
		2 weeks	4 weeks	6 weeks	8 weeks	10 weeks	12 weeks
Common	17(42.5%)	+0.04	+0.04	+0.12	+0.17	+0.22	+0.33
Plane	14(35%)	+0.1	+0.1	+0.35	+0.63	+0.88	+1.2
Filiform	2(5%)	0	0	0	0	0	0
Periungual	2(5%)	0	0	0	0	0	0
Palmer	5(12.5%)	0	0	0	0	0	0
Plantar	0	0	0	0	0	0	0

Table 3: Treatment response in group 2

Table 3 shows treatment response in group 2. There was no response in patients with filiform, periungual and palmar type of warts during whole period of 12 weeks in group 2. There was no case of plantar wart in this group. Patients of common wart showed mean response score +0.04 at two weeks which increased to +0.33 at the end of twelve weeks, indicates poor response, whereas patients of plane wart showed mean response score +0.1 at two weeks which increased to +1.2 at the end of twelve weeks which indicates fair response. None of the patient showed complete clearance in this group.

Table 4 shows comparative results at the end of 12 weeks between group 1 and group 2. For common wart 'p' value is 0.005 which is significant while in case of plane wart 'p' value is 0.0000 which is highly significant. It showed that there was significant difference in response in group 1 and 2 in patients of common and plane wart.

Table 5 shows adverse effect profile in group 1 and 2. Cheilitis was the most common adverse effect in group 1 seen in 36 (90%)

Type of wart	Mean response score at the end of 12 weeks		'P' value
	Group 1	Group 2	
Common	+1.22	+0.33	0.005
Plane	+3.05	+1.2	0.0000
Filiform	0	0	NA
Periungual	+0.5	0	NA
Palmer	+2	0	NA
Plantar	+1.71	0	NA

Table 4: Comparative mean response score at the end of 12 weeks

of patients. Other adverse effects such as dryness, redness and itching were seen in few patients.

Recurrence was defined as reappearance of wart, which cleared earlier or appearance of new lesions after successful treatment. Recurrence occurred in two patients in group 1 after successful treatment (i.e. having score +4). Both of these patients had plane warts in high number (>90).

Side effect	Group 1	Group 2
Chelitis	36	0
Dryness	4	1
Redness	4	1
Itching	3	1

Table 5: Adverse effects

The management of warts still remains a challenge. There are multiple modalities of treatment with variable efficacy and side effects. Topical tretinoin is a first generation retinoid, which has been reported to be useful for the treatment of warts. [12,13] The available evidence suggests that topical tretinoin has multiple effects such as antiviral, antiproliferative and peeling effect. Many authors have reported use of systemic retinoids in the treatment of wart which is summarized in table 6.

There are multiple proposed mechanisms of action of retinoids in warts. First is immunomodulatory activity as retinoid may increase or prolong expression of HPV antigens to T or B cell allowing clearance of the warts by immune mechanisms. The hallmark of HPV infection is epithelial hyperplasia and retinoids have an endogenous antiproliferative effect. It has been proposed that the retinoids by altering keratinisation are able to inhibit replication and assembly of the virus, which requires keratinocytes in an advanced rate of differentiation. Warts display abnormal keratin expression. [14,16] Retinoids regulate epithelial cell differentiation and keratin expression. [17] An inverse relation was observed between concentration of retinoids and HPV-DNA within infected epithelial cells, suggesting a downregulation of viral replication by the retinoids. [18] Lastly, their potent apoptotic activity may also play a part. [19]

In our study patients of common wart showed mean response score of +1.22 and +0.33 in group 1 and 2 respectively at the end of 12 weeks. In group 1, three out of fifteen patients showed excellent response i.e. complete clearance. Majority of patients showed no or poor response, thus oral isotretinoin cannot be considered as an effective treatment option for treatment of common wart. Poor response (i.e. +0.33) in 17 patients of group 2 signifies that topical tretinoin 0.05% cream alone is also ineffective in common warts.

In patients of plane wart mean response score at the end of 12 weeks were +3.05 and +1.2 in group 1 and 2 respectively. Also in group 2, out of 14 patients only one patient showed +3 score (i.e. good response) and four patients showed +2 score (i.e. fair response) at the end of 12 week treatment. Rest of the patients showed either poor or no response. No patient showed complete clearance. These findings are in contrast with study of EP Kubeyinje, [12] who observed clearance of plane wart in 84.6% children after 12 week application of tretinoin 0.05% cream. In

S.No.	*Authors(Reference)*	*Number of patients*	*Type of warts*	*Retinoid used*	*Dose*	*Duration*	*Success rate*
1.	Gelmetti et al[1]	20	Extensive	Etretinate	1mg/kg	3 months	16(80%)
2.	Olguin Garcia et al[2]	12	Recalcitrant facial flat wart	Isotretinoin	0.5mg/kg	3 months	100%
3.	Alexandra Monastirl et al [3]	1	Recalcitrant wart in low grade lymphoma pt.	Isotretinoin	1mg/kg	10 weeks	100%
4.	Clara DE Simone et al[4]	1	Giant common wart in HIV pt.	Acitretin	25mg/day	2 months	Dramatic improvement
5.	*Yun-Lim Choi* , MD et al [5]	1	Refractory warts	Acitretin	1mg/kg	2 months	100%
6.	D. S. Krupashankar et al[6]	1	Warts	Acitretin	0.5mg/kg	3 months	100%
7.	S Georgala et al [7]	28	Refractory genital warts	Isotretinoin	0.5mg/kg	12 weeks	9(32.1%)

Table 6: Summary of previous studies using systemic retinoid for treatment of warts

our study we found that that topical tretinoin 0.05% cream alone is not an effective treatment option for treatment of plane wart. In group 1 mean score was +3.05 indicating excellent response. Six out of thirteen patients showed complete clearence. As majority of patients showed good to excellent response, the combination of oral isotretinoin and topical tretinoin 0.05% can be considered as an effective treatment option for treatment of plane wart. Our findings are similar to Olguin Garcia et al [2] study which showed 100% response of oral isotretinoin 0.5mg/kg for treatment of recalcitrant facial flat warts. We have used lower dose of isotretinoin which have the advantage of cost effectiveness as well as less incidence of side effects. In our previous study the use of low dose isotretinoin in acne had similar advantage.20

Numbers of patients with filiform, periungual, palmoplantar warts were less in both groups. In group 2 there was no response in all patients while in group 1 the response was poor. Two out of ten patients of palmoplantar warts showed excellent response with complete clearance in group 1, indicating variable effect of oral isotretinoin in this group.

No major side effect was observed except for chelitis in group 1. Isotretinoin is a well tolerated drug in low dose. No systemic side effects were found and laboratory investigations remained within normal limit.

Topical tretinoin 0.05% cream was found to ineffective for common, filiform, periungual and palmer type of warts. Oral isotretinoin along with topical tretinoin was found to be effective in treatment of plane warts. We strongly recommend use of this combination and it is worth trying before any destructive measure of treatment. For common and palmoplantar warts oral isotretinoin alone is not an effective treatment option but can be used as adjunctive to some effective treatment modality.

How to cite this article:
Gupta R, Agarwal US, Meena RS. A double blind placebo controlled trial to compare the effect of oral isotretinoin and tretinoin (0.05%) cream combination with tretinoin (0.05%) cream alone for treatment of cutaneous warts. JDA Indian Journal of Clinical Dermatology 2018;1:19-22.

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LETTER TO EDITOR
Year: 2018 I Volume: 1 I Issue: 1 I Page: 23-25

PSORIASIS WITH BULLOUS PEMPHIGOID: PLAUSIBLE ASSOCIATION OR CHANCE CO-INCIDENCE?

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Sir,

A 35-year-old male, known case of psoriasis for 25 years, presented with exacerbation of psoriasis since 1 month with body surface area of 20% involvement and PASI of 13.4. The patient had received various topical as well as oral therapies including oral psoralen with ultraviolet A (PUVA) therapy for psoriasis and was off treatment for 6 months. Four days prior to consultation, he started developing multiple, severely itchy, mildly erythematous urticarial plaques with occasional targetoid lesions in a generalized distribution. The lesions were predominantly present on the chest, upper back and acral areas, both on psoriatic plaques as well on unaffected skin. There was no mucosal involvement. In the next 2 days, clear fluid-filled tense vesicles and bullae developed on these lesions (Figure 1A-C).

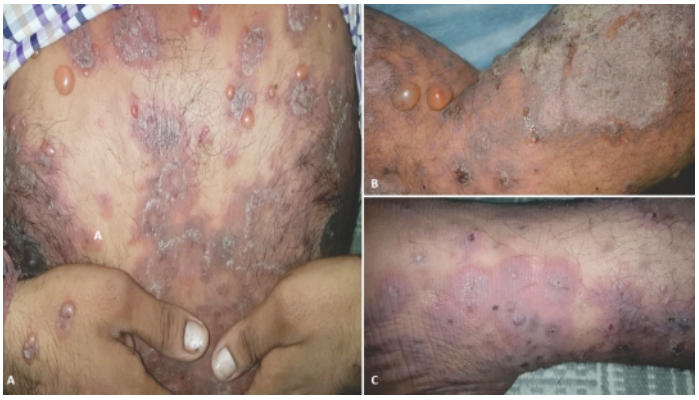

Figure 1(A-C): A&B: Involvement of chest, right lower thigh and right upper leg in form of multiple clear fluid filled tense vesicles and bullae on psoriatic plaques as well on normal skin. **C:** Occasional targetoid lesions with central vesiculation and circumferential oedematous, dusky erythema over right ankle.

Nikolsky sign was negative, while bulla spread sign was positive. A biopsy from the margin of a bulla was taken with clinical differentials of bullous pemphigoid (BP) and linear IgA disease. It revealed a subepidermal cleft with occasional eosinophils and neutrophils admixed with RBCs (Figure 2A). Direct immunofluorescence (DIF) from perilesional skin showed C3 and IgG deposition at dermo-epidermal junction. Indirect immunofluorescence (IIF) was done on salt split study of normal skin which showed linear deposition of IgG along the epidermal roof confirming the diagnosis of BP (Figure 2B). The patient was treated with methotrexate 15 mg/week, prednisolone 40mg/day and dapsone 100mg once daily. There was more than 80% improvement in both psoriasis and bullous pemphigoid lesions in the next 2 weeks following which prednisolone was rapidly tapered and stopped in 2 months while methotrexate and dapsone were continued. Four months later, methotrexate was stopped, however, dapsone was continued. There was no recurrence of bullous lesions after 5 months of follow-up.

Bullous pemphigoid is an autoimmune bullous disease characterized by extremely pruritic, tense, clear as well as hemorrhagic fluid-filled bullae over the erythematous, urticarial, or non-inflammatory base with relative sparing of the mucous membranes. The typical histopathological finding in bullous pemphigoid is a subepidermal bulla with eosinophils. DIF shows linear deposition of C3 and IgG in most cases. IIF done on salt-split study of normal skin is diagnostic which shows linear deposition of IgG at the roof of the blister. Our patient had clinical as well as laboratory tests findings consistent with bullous pemphigoid.

Several autoimmune bullous disorders have been described

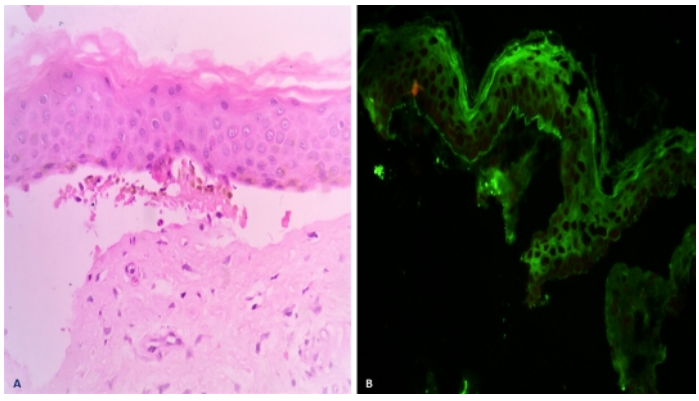

Figure 2(A,B): A: Split at dermo-epidermal junction with occasional eosinophils and neutrophils admixed with RBCs (haematoxylin and eosin, 40X). **B:** Indirect immunofluorescence (IIF) done on salt split showed linear deposition of IgG along the epidermal roof.

in association with psoriasis, of which bullous pemphigoid (BP) is the most common [1]. The inciting factor responsible for the development of BP in patients with psoriasis remains unknown. Though various hypothesis have been proposed, of which immunological damage at the basement membrane zone secondary to primary disease, damage induced by psoriasis treatment (anthralin, tar, ultraviolet B, PUVA), and common immunological mechanisms in both the diseases are the important ones[1,2]. The concept of "epitope spreading" appears quite plausible in this process, whereby tissue damage from a primary inflammatory process leads to release and exposure of a 'sequestered' antigen in exciting a secondary autoimmune response[1]. Our patient was a known case of psoriasis who received various drugs i.e. tar, PUVA in the past. Thus, immunological damage secondary to psoriasis or these therapies could possibly have contributed to the development of bullous pemphigoid in him. Recently, many biologics i.e. etanercept, efalizumab, ustekinumab and secukinumab have been attributed for development of BP in patients of psoriasis[3–5]. We have summarized the recently reported cases of BP developing in psoriasis patients (Table 1)[3-13].

Various drugs, alone or in combination i.e. methotrexate, acitretin, azathioprine, dapsone, mycophenolate mofetil, etanercept,and rituximab have been used successfully to treat BP with psoriasis[1,14–16].

We report this case in view of the rarity of these two common dermatological disorders occurring in the same patient and a good response to a combination therapy of prednisolone, methotrexate and dapsone.

How to cite this article:
Singh S, Dev T, Ali F, Bhari N, Verma KK. Psoriasis with Bullous Pemphigoid: plausible association or chance co-incidence?. JDA Indian Journal of Clinical Dermatology. 2018;1:23-25.

Authors	Age & Sex	Duration of psoriasis	Type of Psoriasis and BP	Associated disorder	Treatment	Response
Wilmer et al.[3]	79y/F	-	CPP; anogenital bullous pemphigoid (BP) became generalized after etanercept	Type 2 diabetes	Dapsone 100 mg/day	No new lesions after 3 weeks of treatment
Lesniewska et al.[6]	35y/M	15 years	CPP[#]	Metabolic syndrome	Methotrexate 12.5-20 mg/week with topical clobetasol propionate	Complete remission after 2 months of methotrexate (20mg/week)
Loget et al.[7]	88y/F	19 years	CPP[#] and relapsing BP	-	Ustekinumab 45 mg s.c. (0,4 then every 12 weekly) with topical clobetasol (30g/day initially, tapered rapidly)	Rapid improvement in both psoriasis and BP lesions
Okahashi et al.[8]	82y/M	40 years	CPP[#]	-	Intravenous prednisolone 30 mg/day and subsequently 70 mg/day followed by IVIg 400 mg/kg per day for 5 days	Rapid suppression of new bulla formation after IVIg administration
Caca-Biljanovska et al.[9]	58y/M	>20 years	CPP[#]	-	Methotrexate 10mg/week with topical corticosteroid	No new blisters after 2 weeks. Remission of psoriasis after 4 weeks
Garrido Colmenero et al.[10]	62y/M	-	Erythrodermic psoriasis	-	Systemic corticosteroid at dose of 1 mg/kg orally	Psoriatic lesions and BP both improved after 1 month
Iskandarli et al.[11]	77y/M	20 years	Pustular psoriasis with CPP. BP lesion developed at base of pustules	-	Methotrexate 10 mg/week and potent topical corticosteroid	Pustular and bullous lesion both resolved at end of 2nd week
Ho et al.[5]	65y/M	7 years	CPP[#]	-	Topical clobetasol dipropionate	Resolution of BP lesions in 2 weeks
Onsun et al.[12]	58y/M	13 years	CPP[#]	Type 2 diabetes and hypothyroidism	Oral prednisolone and cyclosporine	Complete remission within three months
Nakayama et al.[4]	63y/M	4 years	Psoriatic onycho-pachydermo periostitis (POPP) with GPP	-	Oral prednisolone 30 mg once daily	BP and POPP improved within 3 weeks.
Guern et al.[13]	62y/M	20 years	CPP[#]	Hypertension and type 2 diabetes	Topical corticosteroid	Complete regression of the urticarial plaques and bullae within 3 weeks

Table 1: Bullous pemphigoid associated with psoriasis[3-13]

([#]CPP-Classical Plaque Psoriasis)

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LETTER TO EDITOR
Year: 2018 I Volume: 1 I Issue: 1 I Page: 26-27

A RANDOMIZED CONTROLLED STUDY OF THE EFFECT OF INTRALESIONAL INJECTION OF AUTOLOGOUS PLATELET RICH PLASMA (PRP) COMPARED WITH TOPICAL APPLICATION OF 10% MINOXIDIL IN MALE PATTERN BALDNESS

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Sir,

Human skin contains approximately 50 lacs hair follicles out of which one lac of the scalp including those of the eyelashes and eyebrows are the most visible. AGA is the most common form of non-cicatricial alopecia and has a polygenic inheritance. The hormone specifically involved is the dihydrotestosterone (DHT) which leads to change in local metabolism leading to conversion of susceptible terminal hairs into vellus hairs [1]. Minoxidil is a vasodilator which was initially used as an oral drug to treat high blood pressure, however was found to cause hypertrichosis [2]. PRP in medicine was first used in 1987, following an open heart surgery, to avoid excessive transfusion of homologous blood products. But now it has become an exciting non surgical therapeutic option for hair growth and stimulation. The clinical benefit of PRP in hair restoration has been recognized since the early 1990s [3]. Aim of the present study was to compare the effect of Intralesional Autologous PRP and topical 10% Minoxidil in the patients of Male Pattern Baldness.

A randomized double blinded control trial was conducted which included a total of 105 cases. The cases were divided randomly into 3 groups; Group A (injected with PRP), Group B (applied 10% minoxidil) and Group C was the control group. Each group had 35 patients with similar age and sex profile. Six injections of PRP (0.1ml per cm^2) were given in all 35 patients at an interval of 21 days. The patients in group B applied 1ml 10% minoxidil twice daily for 32 weeks, while the patients in group C were told to apply topical rose water for 32 weeks. The patients were evaluated by trichoscan for hair thickness and density. A baseline value was recorded for all patient and then were observed monthly for a period of six months.

PRP was prepared by the use of an automated REMI centrifuge (6×50 ml), just prior to the procedure. Under aseptic precautions, 20 ml of blood was withdrawn from the antecubital vein of the patient lying in the supine position. The blood was immediately transferred to 4 sterile test tubes of 5 ml each containing 0.75 ml anticoagulant, citrate phosphate dextrose A. The test tubes were then subjected to centrifuge at the rate of 1000 rpm for 10 min. Subsequently, the supernatant, which constitutes the platelet rich plasma (PRP), was withdrawn into a new sterile test tube. 0.1ml of 10% calcium chloride was added for each ml of PRP; however this addition was done immediately before injecting in the scalp, so as to avoid crystallization of PRP solution. After applying topical anaesthetic ointment for 45 minutes, PRP was then injected into the scalp intradermally by an insulin syringe. Patients were prescribed tab. amoxicillin + clavulanic acid TDS for 7 days along with analgesics (tab. diclofenac sodium+ paracetamol BD) as and when required and were advised to revisit after 21 days.

Group	N	Mean age	P- Value
A	35	25.80	0.6713
B	35	26.89	
C	35	26.34	
Total	105		

Table 1: Table showing average age of patients (in years)

In the present study conducted, average age of patients in the group A was 25.8 yrs, group B was 26.8 yrs and the group C was 26.3 yrs (Table 1). Thus, there was no significant difference between the mean age of all the three groups and were comparable. The mean hair thickness of group A at baseline and last visit were 22.8 µm and 25.7 µm, group B were 20.9 µm and 23.5 µm and group C were 25 µm and 25.9 µm respectively (Table 2). The mean hair thickness at last visit did not show a significant difference in any of the groups statistically or clinically. The mean hair thickness increased by 2.9 µm in group A, 2.6 µm in group B and 0.3 µm in group C. Though the increase in thickness was more in PRP group, this was not statistically significant. The mean hair density in the group A at baseline and the last visit were 100.9 and 121.8 follicular units per cm^2 respectively, group B was 98.4 and 106.4 follicular units per cm^2

	Mean Baseline Value	Mean Final Value	P- Value
Group A	22.8	25.7	0.145
Group B	20.9	23.5	0.546
Group C	25	25.3	0.564

Table 2: Table Showing Mean Hair Thickness in 1st visit and last visit (in µm)

	Mean Baseline Value	Mean Final Value	P- Value
Group A	100.9	121.8	0.005
Group B	98.4	106.4	0.132
Group C	104.2	104.97	0.875

Table 3: Table showing Hair Density in 1st visit and last visit (in follicular units per cm2)

and group C was 104.2 and 104.9 follicular units per cm^2 respectively (Table 3). Patients of group A showed statistically significant increase in their mean hair density. Although the mean hair density increased in group B and C as well, it was not statistically significant. In present study, 62.9% of the patients had a family history of Androgenetic Alopecia.

The growth factors in the PRP when released promote tissue repair, angiogenesis (capillary formation), collagen production and encourages normalization of the hair follicular unit. PRP contains platelets in amount much greater (around 1,000,000 platelets/ul) than normally in blood [4]. As mentioned, AGA is the most common cause of non cicatricial alopecia and the available treatments are sometimes unable to achieve adequate results. Thus PRP has proved to be an important adjunct in treatment options of AGA [5]. However this requires further studies to gain more evidence before it is used more extensively.

How to cite this article:
Goyal V, Mathur D, Nijhawan M. A Randomized Controlled Study of The Effect of Intralesional Injection of Autologous Platelet Rich Plasma (PRP) Compared With Topical Application of 10% Minoxidil In Male Pattern Baldness. JDA Indian Journal of Clinical Dermatology 2018;1:26-27.

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CASE REPORTS
Year: 2018 I Volume: 1 I Issue: 1 I Page: 28-29

LOC SYNDROME - A CASE TO UN"LOC" OUR MINDS

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Abstract

Laryngo-onycho-cutaneous syndrome (LOCS) or Shabbir's syndrome is an inherited autosomal recessive disorder affecting consanguineous Muslim families of Punjabi origin. In this condition excessive dermal and submucosal granulation tissue formation leads to hoarse/weak cry, respiratory obstruction, pterygium and symblepheron in the eye. It represents a distinctive form of junctional epidermolysis bullosa (JEB) affecting laminin alpha-3 (LAMA3) gene. All the patients reported so far are from Muslim community and of consanguineous parentage. But our patient is born of non-consanguineous parentage, is a non- Muslim (Hindu) and hails from Chattisgarh province in India with a long survival age.

Key words: Junctional Epidermolysis Bullosa (JEB), Shabbir's syndrome, Laryngo- onycho- cutaneous syndrome (LOC)

Introduction

Laryngo- onycho- cutaneous syndrome (LOC) or Shabbir's syndrome, is an inherited autosomal recessive disorder that affects mainly the offspring of consanguineous Muslim families originating in the Punjabi region of Indian subcontinent.[1] The disease presents with hoarseness of voice, blisters, erosions, ulcerations, dystrophic nail changes, eye changes and deformed teeth. In this condition excessive dermal and submucosal granulation tissue formation leads to hoarse/weak cry, pterygium and symblepheron in the eye and respiratory obstruction which may lead to premature death.

Case Report

A female aged 36yrs from Chhattisgarh, born of non-consanguineous marriage, developed multiple, painful fluid filled lesions over elbows, knees, trunk, back, scalp and extremities since age of 2 months. They used to occur on and off up to the age of 12yrs and used to heal in 2-4 weeks forming scars. Nail changes and dental abnormalities were seen since the age of 15yrs. (Figure 1-7)

She has history of feeble cry and hoarse voice since childhood and recurrent episodes of difficulty in breathing and consulted an ENT surgeon. She was found to have vocal cord thickening and nodules. As it became increasingly difficult for her even to breathe, emergency tracheostomy was done 2 years back at the age of 34 yrs. Since 2 years she started developing redness of eyes with watering, swelling and obstruction of vision.

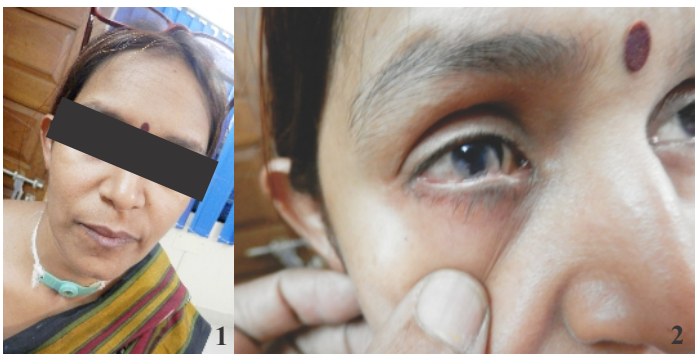

Figure 1 & 2: 1: A permanent tracheostomy. **2:** Pterygium encroaching on to the cornea (rt) and granulation

Routine investigations were all normal. Biopsy showed unremarkable epidermis with patchy dermal lymphocytic infiltration. Immunohistochemistry for G71 and GB3 was requested but it was not done as they were not available.

On the basis of these distinctive clinical features final diagnosis of laryngo-onycho-cutaneous syndrome was made.

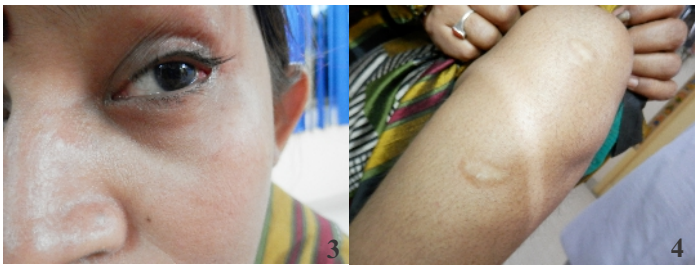

Figure 3 & 4: 3: Symblepharon (adhesion of the palpebral conjunctiva of the eyelid to the bulbar conjunctiva). **4:** Old healed and atrophic scars over lower legs

Discussion

LOC Syndrome (laryngo-onycho cutaneous syndrome) or LOGIC syndrome[2] was first reported by Shabbir[1] in 1986, in Muslim families of Punjab origin; subsequently there were reports of similar cases from UK, Australia and all of these families originally belonged to Punjab Province of Pakistan or India[2,3,4]. The mystery of this syndrome was unravelled in 2003

when McLean et al[5], observed mutations in a candidate gene, laminin alpha-3 (LAMA3) located on chromosome 18q11.2, in which loss of expression mutation also cause Junctional Epidermolysis Bullosa (JEB). In LOC syndrome the causative mutation was frameshift mutation (N-terminal deletion) of laminin 3a isoform. Based on this, it has now been finally established as a subtype of JEB[6,7].

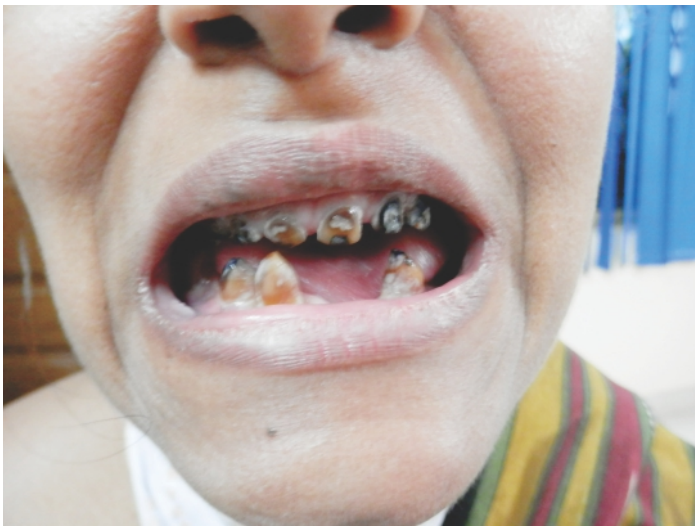

Figure 5: Loss of teeth, discolored and distorted teeth with caries

In contrast to the other JEB subtypes, patients with LOC syndrome have minimal blistering and extensive granulation tissue formation[7,8] which leads to chronic non healing ulcers, dystrophic nail changes, vocal cord thickening and thickening of conjuctival tissue, clinically manifesting as hoarse voice or weak cry at infancy, respiratory obstruction, failure of tooth enamel formation and marked dental malformations.

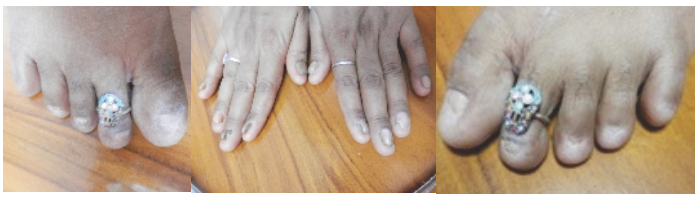

Figure 6: (a, b & c) - Twenty nail dystrophy

Although eye involvement in LOC syndrome was not mentioned in the original description, ocular granulation tissue resembling pterygium was reported in all subsequent patients[2,3,4,8] and is a prominent feature in our patient also. Our patient also had symblepheron, granulation tissue at the lateral border of left eye and her visual acuity was diminished. Nail dystrophies have been reported in all patients but twenty nail dystrophy as seen in our patient is unusual.

All the patients reported so far are from muslim community and of consanguineous parentage. But our patient is born of non-consanguineous parentage, is a non- Muslim (Hindu) and hails from Chattisgarh province in India.

Most of the patients die due to respiratory obstruction and infections and do not survive beyond second decade. Our patient is now 36 years old and she is the longest surviving individual affected with this syndrome so far.

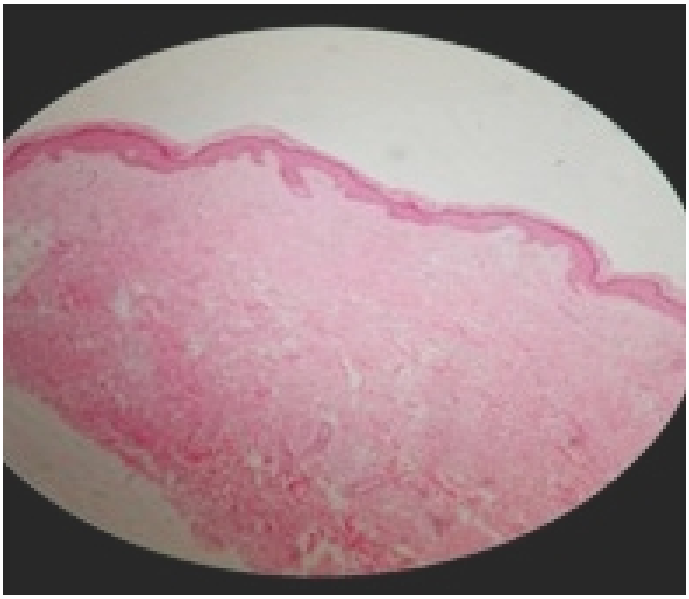

Figure 7: Histopathology of skin (haematoxylin and eosin, 10X)

How to cite this article:
Komeravelli H, Anchala P. LOC Syndrome - A case to UN"LOC" our minds. JDA Indian Journal of Clinical Dermatology 2018;1:28-29.

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CASE REPORTS
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A CASE OF PHAKOMATOSIS PIGMENTOVASCULARIS TYPE IIB WITH SEIZURES

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Abstract

Phakomatosis pigmentovascularis (PPV) is a genetic disorder characterized by association of capillary malformation with pigmentary nevi. We hereby report a rare presentation of PPV with Sturge-weber syndrome (SWS), Klippel-trenaunay syndrome (KTS) and Nevus of Ota (PPV typeIIb) in a 7 - year old female child.

Key words: Phakomatosis pigmentovascularis, Sturge weber syndrome, Klippel trenaunay syndrome, nevus of Ota, mongolian spots

Introduction

Phakomatosis pigmentovascularis (PPV) is a rare genetic disorder characterized by association of capillary malformation with pigmentary nevus. Five types of PPV are described with further subtype 'a' for cutaneous involvement only and subtype 'b' for cutaneous as well as systemic involvement.[1,2] Sturge-Weber syndrome (SWS) is a neurological disorder characterized by facial capillary malformation with ipsilateral ocular and brain anomalies.[3] Klippel-trenaunay syndrome (KTS) is defined as limb capillary venous malformation (CVM) associated with progressive overgrowth of the affected extremity and anomalies of venous system.[4] Nevus of Ota are bluish, patchy, dermal melanocytosis that affects the sclera and the skin around the eye.

Case Report

A 7-year old girl child came to outpatient department with complaints of asymmetry of left half of body and red patch on left side of face since birth along with history of seizures. She was full term vaginal delivery in hospital with birth weight of two kilograms. Her developmental milestones were normal. Her body weight was 15.7 kgs. and height was 108 cms. Examination revealed non-blanchable erythematous patch of port wine stain on left side of face in the distribution of all V1, V2 and V3 branches of trigeminal nerve (Fig.1). Multiple aberrant mongolian spots were present on trunk and back (Fig.2).

The patient had hypertrophy of left side of body with enlargement of left half of face, left lower limbs and left half of genitalia (Fig. 1,3,4,5). There was engorgement of veins on left lower abdomen crossing the mid-line. Higher mental functions including speech were normal. She had limping gait and motor examination was normal. The eye examination revealed bluish discoloration of sclera on both side consistent with Nevus of Ota. (Fig.5).

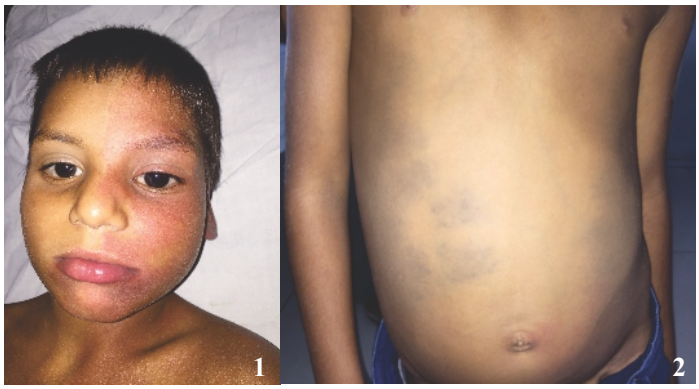


Figure 1 & 2: 1: Shows port wine stain and Hypertrophy of left half of face. **2:** Shows aberrant multiple mongolian spots.

Magnetic resonance imaging (MRI) of the brain showed cerebral hemiatrophy on left side with loss of white matter more significant in temporo-parieto-occipital region with mild peritrigonal FLAIR hyperintensity (Fig.6). Color doppler studies of lower limbs showed chronic thrombosis of left deep venous system with formation of superficial collaterals in left

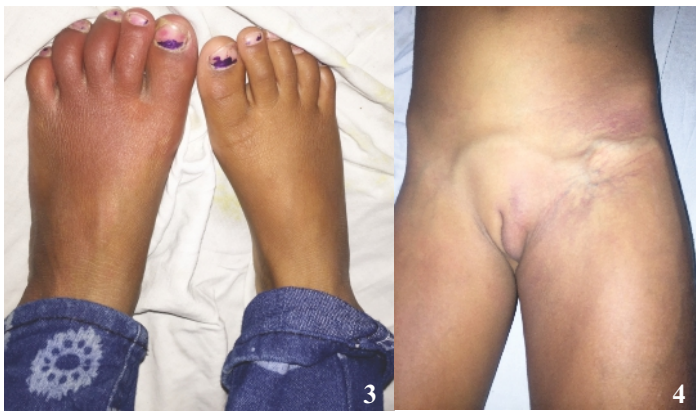
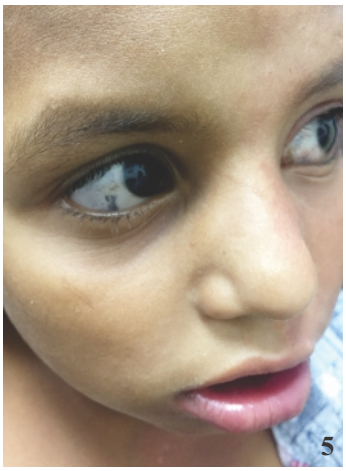


Figure 3 & 4: 3: Shows gross enlargement of left foot. **4:** Shows hypertrophy of left half of external genitalia & engorgement of veins.

inguinal region and upper part of left thigh. Right lower limb venous system was normal. Ultrasonography of abdomen was normal. Complete blood count, bleeding & clotting profile, liver function tests, renal function test were normal.



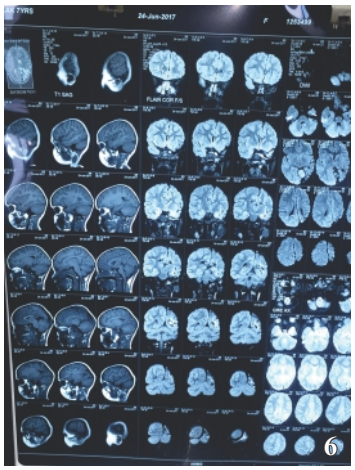


Figure 5 & 6: 5: Shows nevus of ota in both eyes. **6:** MRI Brain shows cerebral hemiatrophy on left side with loss of white matter more significantly in temporo-parieto-occipital region with mild peritrigonal FLAIR hyperintensity.

Discussion

Ota et al[1] in 1947 coined the term "Phakomatosis pigmentovascularis" and reported associations between cutaneous venous malformations and pigmented nevi. Further studies proposed that the vascular and pigmentary anomalies arises as a result of a genetic concept called twin spotting.[2,3] PPV was further delineated in five types with subtype 'a' for cutaneous involvement only and subtype 'b' for cutaneous as well as systemic involvement. Also, among five types of PPV, type II (Phakomatosis cesioflammea) was the most common with 75% reported cases.[4,5,6] However Goyal T et al[5] reported first case of Phakomatosis cesioflammea (typeIIb) from India in a 4-year old girl child. The largest series of PPV was published by Cordisco et al[7], who presented 25 patients in Argentina. In that, type IIb was the most common type. In another study it was reported that the most common association with extra cutaneous presentations was with the Sturge-Weber syndrome (SWS) and with the Klippel-trenaunay syndrome (KTS), individually or combined.[8] Okunola et al.[9] reported two cases of Phakomatosis pigmentovascularis type IIb in association with external hydrocephalus. Pradhan S et al[10] reported a case of Phakomatosis pigmentovascularis Type IIb with Sturge–Weber syndrome and cone shaped tongue. Jahangir et al.[11] reported a case of Phakomatosis pigmentovascularis with lower limb vascular abnormalities in a young Kashmiri male child.

Our patient had PWS, hypertrophy of left half of the face, trunk, extremities and external genitalia with venous engorgement on left lower abdomen and history of seizures. The color Doppler studies of lower limb showed chronic thrombosis of left deep venous system. MRI of the brain showed cerebral hemiatrophy on left side with loss of white matter more significant in temporo-parieto-occipital region. The case is being reported for its rarity and unusual presentation.

How to cite this article:
Gupta R, Wadhwani AR, Singh K, Kanodia SK. A case of Phakomatosis Pigmentovascularis type IIb with seizures. JDA Indian Journal of Clinical Dermatology 2018;1: 30-31.

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CASE REPORTS
Year: 2018 I Volume: 1 I Issue: 1 I Page: 32-33

INSULIN RESISTANCE SYNDROME: A CASE REPORT

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Abstract

Insulin resistance is impaired ability of plasma insulin to perform its actions at usual concentrations. It can be acquired or genetic. Here we report a case of insulin resistance.

Key words: insulin resistance syndromes, acanthosis nigricans

Introduction

Insulin resistance is defined as an impaired ability of plasma insulin at usual concentrations to adequately promote peripheral glucose disposal, suppress hepatic glucose, and inhibit very low density lipoprotein (VLDL) output. It can be acquired or genetic. Insulin resistance is associated with many cutaneous and systemic manifestations[1]. Here we report a case of insulin resistance.

Case Report

A 12 year old male boy born of non consanguineous marriage presented to our OPD with hypertrichosis and severe acanthosis nigricans. On examination, there was abnormal facies with low frontal hair line, large ears with hypertrichosis, large lips, prognathism, hypertelorism. There was severe acanthosis nigricans involving the neck, axillae and flexures with blackening and thickening of skin over trunk. There was generalized hypertrichosis (fig 1-4). Oral mucosa, nails and teeth were normal.

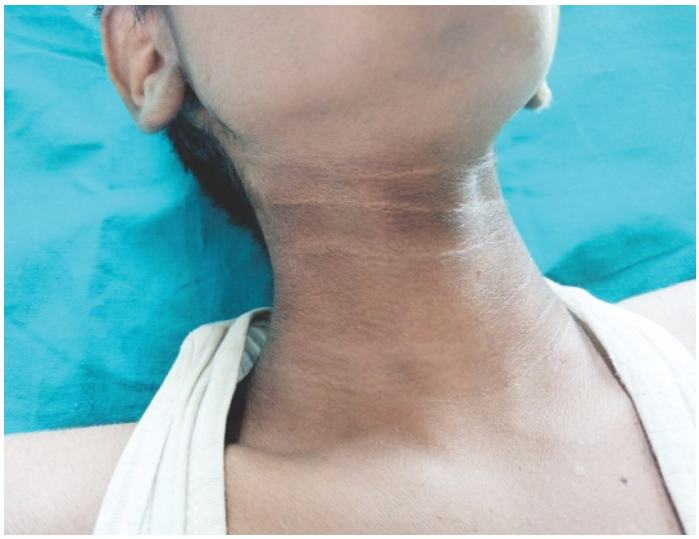

Figure 1 : Acanthosis nigricans over neck and hypertrichosis over ear

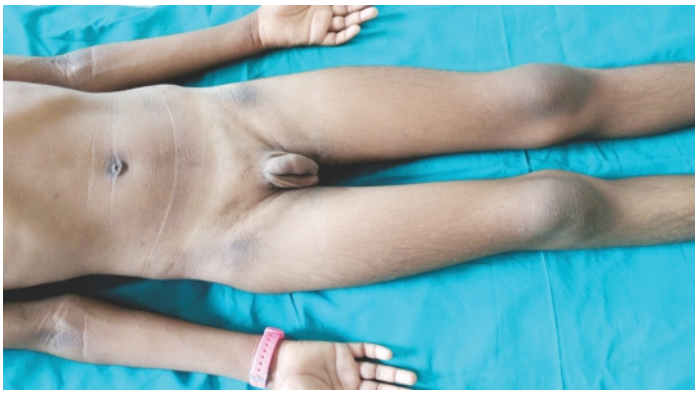

Figure 2 : Acanthosis nigricans over flexor aspect of elbow and blackening and thickening of skin over trunk

A primary diagnosis of insulin resistance syndrome was kept and patient was worked up. His complete blood count, urine examination, renal function test were normal. Liver function test showed elevated enzymes and fasting insulin was remarkably raised with values 65.60 µIU/ml. His fasting blood sugar was 108mg/dl, Hb1Ac was 9.34% and lipid profile was normal. On USG of abdomen there were bilateral bright kidneys. His echocardiography was normal.

Discussion

The pathogenesis of insulin resistance is multifactorial. Thus, several molecular pathways in energy homeostasis, lipid metabolism, insulin receptor signaling pathway, cytokines, hormone-binding proteins including those that are serine protease inhibitors (SERPINS), and other protease regulators are responsible for the development of IR, obesity, or lipodystrophy. On review of literature the above patient seemed to be affected by defect in the insulin-signaling pathway, which may cause mutations in insulin receptors, development of insulin receptor autoantibodies or defects in plasma cell membrane glycoprotein-1 and glucose transporter 4 (GLUT4) molecules are reported. The syndromes reported with this pathway defect are Type A syndrome, Donohue syndrome

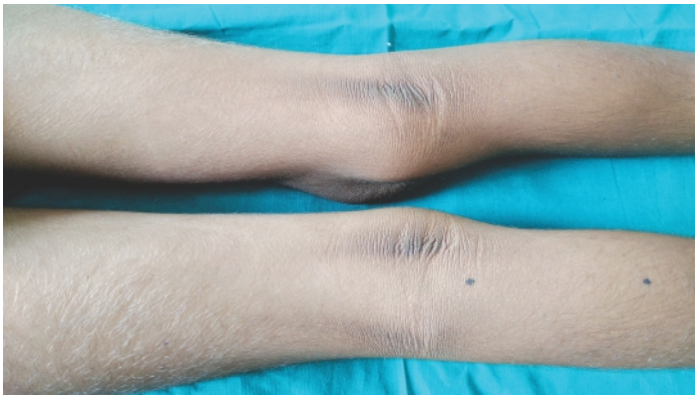

Figure 3 : Acanthosis nigricans over flexor aspect of knee

(Leprechaunism)[2], Rabson-Mendenhall syndrome[3] and Polymorphism in plasma cell membrane glycoprotein-1 (PC-1)[1].

The features present in this patient suggestive of insulin resistance were acanthosis nigricans, hypertrichosis, hypertelorism, large ears, prominent lips, prognathism, steatohepatitis and bilateral bright kidneys which might be due to glomerulonephritis. The patient also had very high fasting insulin although his blood sugar was normal.

In children, insulin resistance is usually well compensated by hyperinsulinemia. However it increases risk for fatty liver, atherosclerosis and increased cancer risk. Thus an early intervention is necessary. This involves regular exercise, restricted calorie, carbohydrate and triglyceride dietary intake. Fibrates may be required, especially when TG levels exceed 500 mg/dl, at which point acute pancreatitis and gall bladder disease become real risks. Metformin can also be used for prophylaxis. Laparoscopic surgery can be used in obese cases.

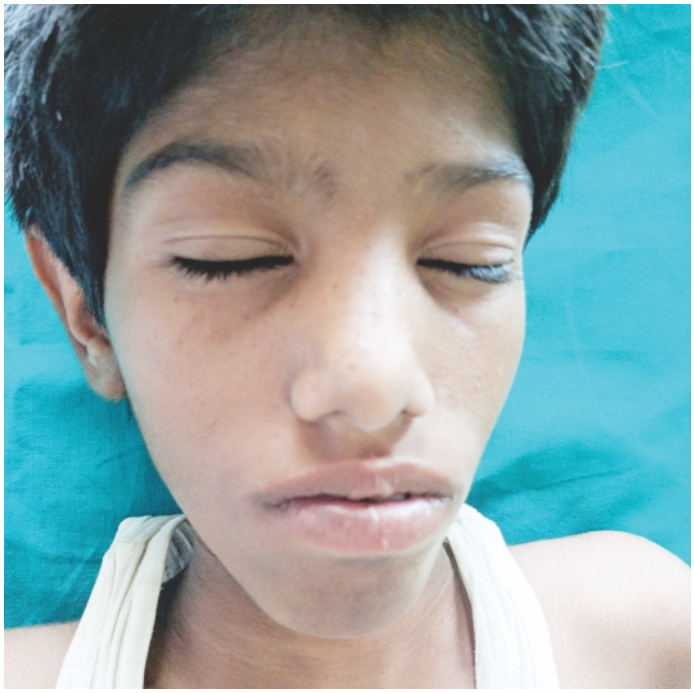

Figure 4 : Showing thick lips, prognathism, hypertrichosis over scalp, hypertelorism

How to cite this article:
Garg V. Insulin resistance syndrome: A case report. JDA Indian Journal of Clinical Dermatology 2018;1:32-33.

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Year: 2018 I Volume: 1 I Issue: 1 I Page: 34-36

INVASIVE ASPERGILLOSIS PRESENTING AS SCALP OSTEOMYELITIS: A RARE CASE REPORT

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Abstract

Aspergillus is a mold whose spores are commonly found in air. It primarily causes infection in immunocompromised individuals. We report a rare case of osteomyelitis due to Aspergillus niger in an immunocompetent patient.

Key words: Fungal Osteomyelitis, Invasive Aspergillosis

Introduction

Aspergillus is a mold whose spores are commonly found in air. It primarily causes infection in immunocompromised individuals.[1] Three types of aspergillosis are seen: invasive aspergillosis, chronic (and saprophytic) forms of aspergillosis; and allergic forms of aspergillosis. Invasive aspergillosis (IA) usually involves the sinopulmonary tract, with the lung being the most common site of infection, while osteomyelitis due to Aspergillus species is rare.[2] We report a rare case of osteomyelitis due to Aspergillus niger in an immunocompetent patient.

Case Report

A 45 year old male, manual laborer by occupation presented to the OPD with complaint of sinuses over scalp for four years associated with bilateral hearing loss and loss of vision from right eye. According to his wife, he had headache predominantly on right side four years back which was followed by redness and swelling of right eye after 15 days. He took some treatment and when the swelling resolved there was corneal opacity and loss of vision. Over the next 5-6 months the pain persisted. Then he had difficulty in hearing from left ear followed by right leading to complete hearing loss in both ears. For the next one year there was no complaint except pain in the right frontal area. Thereafter an ulcerated nodule developed over occipital area with pus discharge. It was followed by formation of multiple nodules over occipito- frontal area of scalp and the mastoid area over the next 6-7 months. The nodules eventually became non-healing ulcers. Later on, the patient had discharge of pus from both ears and lateral margin of the left eye. These sinuses persisted for next one and a half years with on and off pus discharge. There was a history of weight loss of 7- 8 kg over the course of the illness. There was no history of any trauma, surgical intervention, cough, fever, night sweats and ear, nose or oral cavity infection prior to onset of symptoms. He had an MRI (brain and orbit) done in November 2013 suggesting ill defined diffuse lesion in the orbital fat in right retrobulbar region surrounding the extraocular muscles and the optic nerve and bilateral mastoiditis.

On examination there were multiple draining sinuses present over scalp with necrotic edges (Fig. 1-3). There was a greenish waxy discharge. The discharge was also coming through auditory meatus. In the right eye corneal opacity was seen. A sinus was also present over left cheek with discharge of clear fluid on mastication and talking. The patient was pale and had bilateral mobile, slightly tender posterior cervical lymph nodes.

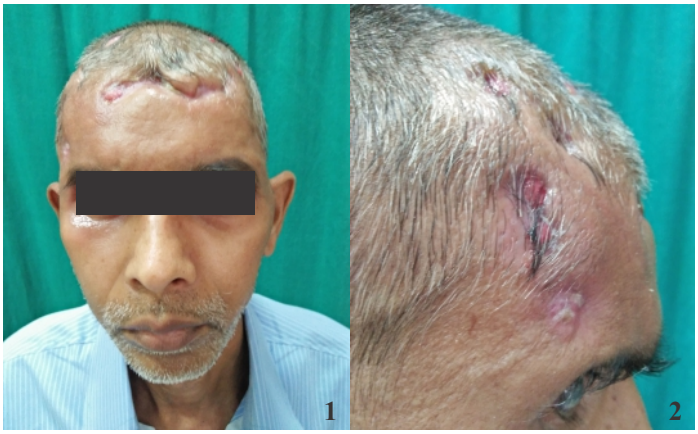

Figure 1 & 2 : 1: Multiple draining sinuses over frontal and temporal area of scalp with corneal opacity in right eye.
2: Multiple draining sinuses over frontal and temporal area of scalp

A preliminary diagnosis of scrofuloderma, actinomycetoma and subcutaneous mycosis were kept and all routine investigations of the patient were sent along with Mantoux test (MT), sputum for AFB, skin biopsy for histopathology and tissue culture. The pus was also sent for culture and KOH examination. Cartridge based nucleic acid amplification test (CBNAAT) was done from pus for tuberculosis. A contrast-enhanced magnetic resonance imaging (CEMRI) of brain and orbit was advised to assess the extent of the lesion. Patient was found to be severely anemic with

Haemoglobin 4.3g/dL and total red blood cell count 2.11*106/µL. His MT and CBNAAT were negative, chest X ray did not reveal any lesion and the KOH mount was negative for fungal hyphae. Histopathology showed granulomatous inflammatory lesion but no organism was seen on Periodic acid Schiff (PAS) and Ziehl-Nielson (ZN) stain. His CEMRI (brain) suggested multiple bilateral frontal and occipital cutaneous-subcutaneous lesions involving underlying bones with no gross intra cranial extension. There was soft tissue mucosal thickening in bilateral ethmoid air cells, frontal and sphenoid sinuses, suggestive of sinusitis and also there was evidence of bilateral mastoiditis. His CEMRI (orbit) suggested enopthalmos of right eye ball with loss of normal right retrobulbar fat. Skull X-ray showed osteolytic changes with destruction of outer and inner table of skull involving frontal and occipital bones. The pus culture grew Aspergillus niger. An ENT opinion was sought for ear discharge and hearing loss. His ear examination showed bilateral subtotal tympanic membrane perforation with polypoidal mucosa and was advised contrast-enhanced CT scan of temporal bone and audiometry. CECT (temporal bone) suggested multiple lytic lesions in frontal, left sided sphenoid, bilateral petrous and occipital bones along with sphenoid and maxillary sinusitis. A mass was seen causing encasement of petrous part of bilateral internal carotid arteries also causing destruction of bone forming inner ear. Also there was thickening of mucosa of middle ear cavity and epitympanum. The audiometry suggested bilateral hearing loss. Since skin biopsy was inconclusive and no conclusion could be reached about etiology on culture, a biopsy was planned from the mass seen in CECT (temporal bone). Histopathology revealed many bony trabeculae with focal presence of mucosal lining. Intertrabecular spaces showed mixed inflammatory infiltrate with presence of giant cells. On PAS stain, at one focus a single fungal colony was seen with few branching, septate hyphae, branching at acute angle [Fig. 4,5]. Due to presence of fungal hyphae in histopathology, Aspergillus niger was considered to be the causative organism as it was grown on culture.

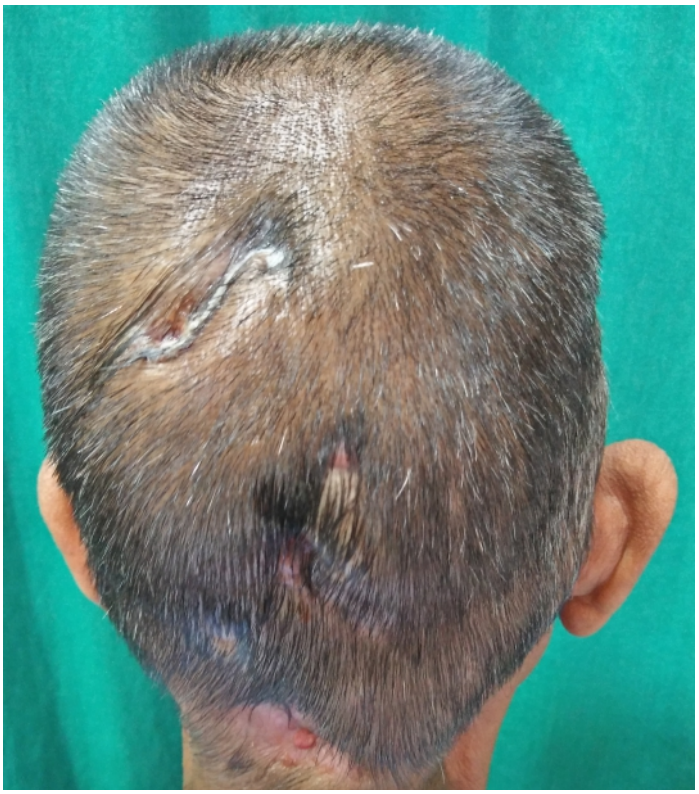

Figure 3 : Multiple draining sinuses over occipital area of scalp.

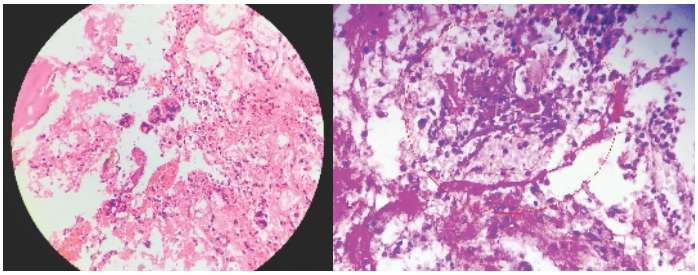

Figure 4 & 5: 4: On histopathology Intertrabecular spaces showed mixed inflammatory infiltrate with presence of giant cells (H&E,10X). **5:** On PAS stain, at one focus a single fungal colony was seen with few branching, septate hyphae, branching at acute angle. [In circle] (PAS, 40X).

The patient was started on liposomal amphotrericin B (1mg/kg/day) intravenously along with itraconazole 200 mg BD. The patient responded dramatically to the treatment with significant reduction in pus discharge after a week. The sinuses began to heal and granulation tissue was seen to grow in the ulcers. The discharge from the ear also reduced significantly.

Discussion

Aspergillus species are ubiquitous saprophytic organisms. More than 300 species are known, but only a few of them cause opportunistic infections.[2] Osteomyelitis due to Aspergillus is rare. It is caused by: [3,4]

(1) Contiguous spread of infection, like from sinus infection affecting cranium or pulmonary infection affecting ribs or vertebrae

(2) Hematogenous spread from a primary focus

(3) Trauma or maybe iatrogenic

The incidence of Aspergillus affecting the bone among all cases of invasive aspergillosis (IA) is estimated to be 3%.[2] Amongst the infective Aspergillus species the most common isolates from osteomyelitis lesions are Aspergillus fumigates followed by Aspergillus flavus and Aspergillus nidulans. Less frequently isolated species included Aspergillus terreus, Aspergillus niger, Aspergillus versicolor and Aspergillus flaviparus.[5]

Clinically IA manifests with pain and tenderness followed by sinus tract formation with purulent discharge (green waxy pus).[6] According to Infectious Diseases Society of America (IDSA), diagnosis of Aspergillosis requires histopathological documentation of infection and a positive microbiological culture from a normally sterile site. Other methods are PCR and detection of Galactomannan and (1-3)-ß-D-Glucan in serum and bronchoalveolar lavage. The IDSA recommended treatment for Aspergillus osteomyelitis is surgical intervention, where feasible, combined with voriconazole. Other useful antifungals

are liposomal amphotericin B, isavuconazole, caspofungin, micafungin, posaconazole and itraconazole. Therapy should be continued for a minimum of 8 weeks, frequently requiring longer courses (> 6 months).[7]

How to cite this article:
Agarwal P, Agarwal US, Thalor SK, MeenaRS, Purohit S. Invasive aspergillosis presenting as scalp osteomyelitis: A rare case report. JDA Indian Journal of Clinical Dermatology 2018;1:34-36.

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Quiz
Year: 2018 I Volume: 1 I Issue: 1 I Page: 37

TRICHOSCOPIC FINDINGS IN VARIOUS SCALP ALOPECIAS

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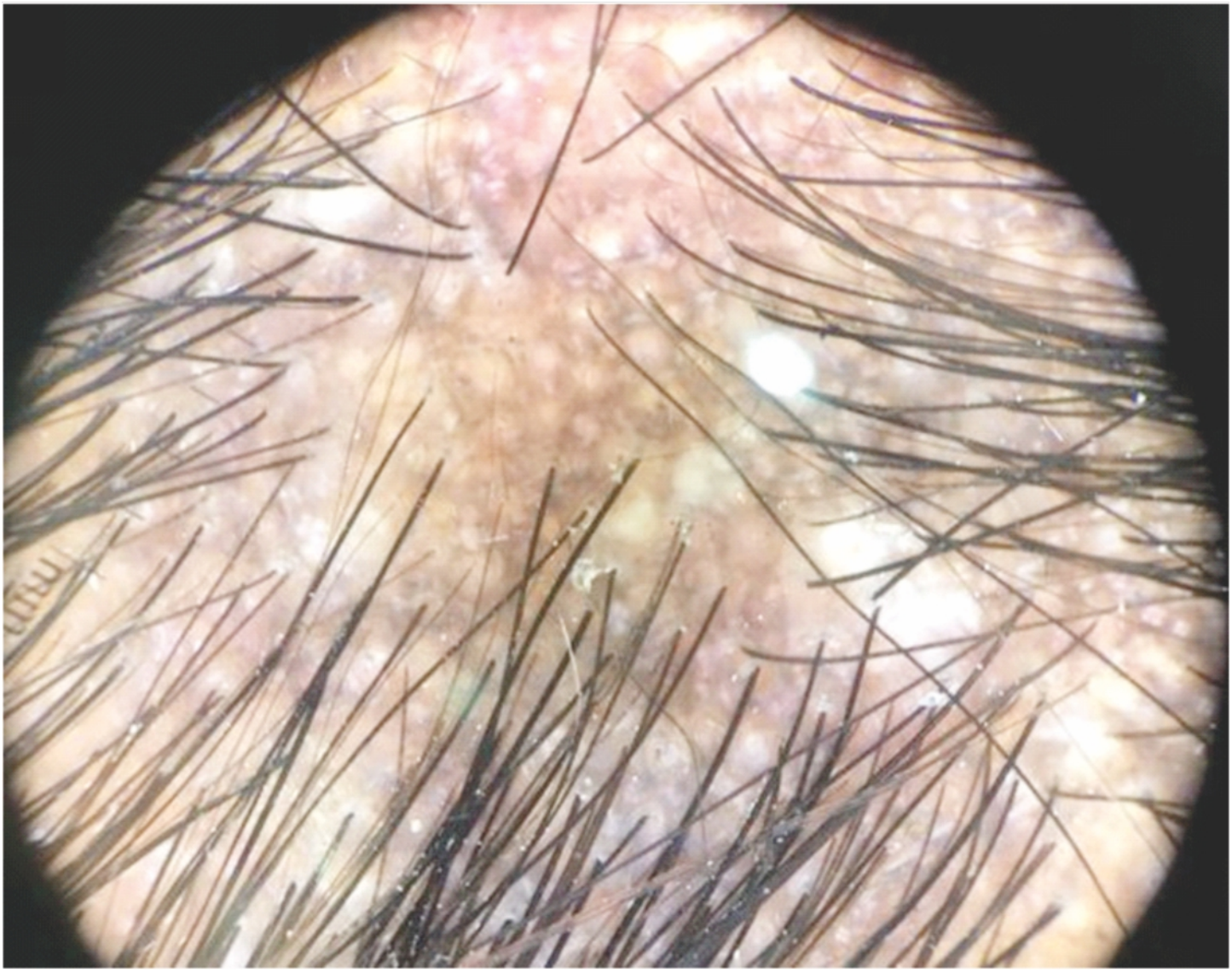

Question

This is the dermoscopic picture of cicatricial alopecia.What is the classical sign seen in the picture and what is the final diagnosis?

(For answer visit PG Quiz section at **www.e-ijcd.in**)

How to cite this article:
Sharma R. Trichoscopic findings in various scalp alopecias. JDA Indian Journal of Clinical Dermatology 2018;1:37.

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