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Contents

Original Articles

Review Articles

Intralesional Immunotherapy in Palmo-plantar Warts using Mumps, Measles and Rubella vaccine: A Case-Control Study

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Abstract

Background: Palmoplantar warts are always challenging to the treating dermatologist because of their high rates of failures and recurrences. First line treatment modalities available currently are associated with recurrences and second line modalities are associated with scarring. Clinical trials with MMR suggests that this approach could speed up the resolution of recalcitrant warts.

Objective: To evaluate efficacy and safety of intralesional MMR vaccine in treatment of recalcitrant palmoplantar warts by comparing it with intralesional distilled water.

Materials and methods: Seventy clinically diagnosed patients were divided into a study group and a control group. MMR injections (0.5 ml) were administered to the study group patients every 3 weeks to the single largest wart. Distilled water (0.5 ml) was administered to the control group at similar intervals. Follow up of patients in both groups were done every month after completion of treatment for 9 months for result, side effects and recurrence.

Result: Among 64 patients who completed the study, 32 patients received MMR and 32 patients received distilled water. An 81.30% reduction of wart size and number was noted in study group were as only a 18.80% reduction was seen in control group which was statistically highly significant (p value < 0.001).

Keywords: Warts; MMR vaccine; Distilled water.

Introduction

Skin warts are benign tumours caused by infection of keratinocytes with Human Papilloma Virus (HPV), visible as well-defined hyperkeratotic protrusions.[1]

Cutaneous warts are caused by a small group of specific HPV types, with an overall prevalence of 20% in schoolchildren and a decline thereafter with increasing age. Patients living in larger households often report an infected cohabitant, supporting the concept of person-to-person transmission. Majority of warts will regress spontaneously within 1–2 years. Reinfection with the same HPV type appears uncommon after clearance, suggesting that protective type-specific immunity may develop.[2]

There are different types of cutaneous warts such as common, plain, filiform/digitate, anogenital and palmoplantar.[3] Treatment of warts are often difficult despite availability of several modalities, more so of warts affecting periungual area and over soles.[4] The treatment of warts depends on two main therapeutic options: the first is the conventional destruction and aggressive method which includes treatment with chemical cautery, cryotherapy, electrocautery, surgical excision, and laser ablation and the second is immunotherapy, based on the activation of the immune system to deal with the virus and suppress its activity. Such immunotherapy may be applied either topically or through intralesional injection or through systemic administration.[5]

Intralesional immunotherapy utilises the ability of the immune system to mount a delayed type hypersensitivity response to various antigens and also to the wart tissue. This therapy has been found to be associated with the production of Th1 cytokines which activate cytotoxic and natural killer cells to eradicate HPV infection. This clears not only the local warts unlike traditional wart therapies, but also distant untreated warts.[6]

Increasing evidence of cellular immunity playing a vital role in wart clearance supports the use of intralesional MMR vaccine. Open labelled studies have also shown to have a positive result. Lack of enough randomised control studies reporting efficacy of intralesional MMR limits its use to some extent. So, in our study we attempted to prove the efficacy and safety profile of MMR in treatment of palmoplantar warts comparing it with distilled water.

Materials and Methods

Seventy consecutive patients with palmoplantar warts presenting to skin department, VIMS, Ballari were selected. Patients were randomised using block technique. Study design was double blinded and placebo controlled, conducted from January 2016 to December 2016. The study was approved by institutional ethics committee.

Patients with palmoplantar warts with or without warts at distant sites (warts present at sites other than palms and soles) were included in the study. Exclusion criteria were age less than 18 years, prior allergic response to MMR vaccine, acute febrile illness, history of atopy, pregnancy/ lactation and immunosuppression. Written informed consent is taken before starting the study. Patients' details including demographic data and clinical details were taken in a prescribed proforma. Photographs were taken at baseline and before each subsequent injections. Patients were divided using block randomisation technique into a study Group (Group A) and a control group (Group B). MMR vaccine available as single dose vial of freeze dried vaccine with diluent (0.5 ml) is purchased as necessary. This is given at base of largest wart at each visit for a maximum of 3 doses with 30G insulin syringe, each dose 3 weeks apart for patients enrolled in Group A. Group B patients received 0.5 ml of distilled water at same intervals. Patients were followed up every month for a period of 9 months after completion of treatment for results, side effects and recurrences. Data obtained was tabulated and analysed using suitable statistical tools.

The response was evaluated as follows:

1. *Complete:* disappearance of the wart(s) and return of normal skin markings.
2. *Partial:* regression in size by 50% to 99%.
3. *No response:* Zero to 49% decrease in wart size.

Results

Sixty four patients completed the study out of 70 enrolled patients. Thirty two patients were included in group A and the rest 32 in Group B. Table 1 is showing the baseline demographic characters of study as well as control groups. No statistically significant differences were observed with respect to age, gender, number of warts, distant warts, recalcitrant warts and number of previous treatments. Majority of the patients were in 21-30 years age group.

Table 2 is showing the treatment outcomes among study subjects in Group A and B. At 42 days, 20 patients showed partial response and 4 patients showed complete response in study group and 4 patients showed partial response and 2 patients showed complete response in control group. This resolution of warts at 42 days is statistically significant with a p value less than 0.001. Again at 63 days 16 patients showed complete response in study group against 3 patients in control group which is also statistically highly significant ($p < 0.001$). Response of distant warts to MMR injections did not differ much from that of distilled water. Side effects like pain, erythema, edema and flu like symptoms did not show a statistically significant difference between both groups.

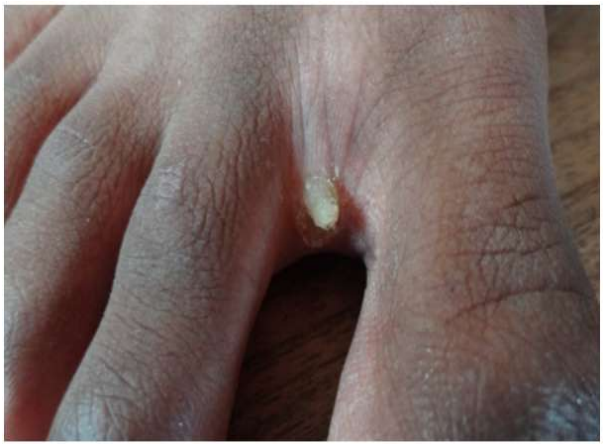

Fig. 1: Plantar wart before MMR injection

Table 1: Clinical Profile of the study subjects among the two treatment Groups

Variable	MMR Group (N = 32) n (%)	NS Group (N = 32) n (%)	*p* value
Age group			
≤ 20 years	7 (21.9)	8 (25.0)	0.424
21–30 years	17 (53.1)	12 (37.5)	
31–40 years	7 (21.9)	8 (25.0)	
> 50 years	1 (3.1)	4 (12.5)	
Mean ± SD	27.31 ± 7.32	28.75 ± 9.44	0.499
Sex			
Female	12 (37.5)	14 (43.8)	0.799
Male	20 (62.5)	18 (56.3)	
Skin leisons			
Single	8 (25.0)	12 (37.5)	0.282
Multiple	24 (75.0)	20 (62.5)	
Distant leisons			
Yes	5 (15.6)	3 (9.4)	0.708*
No	27 (84.4)	29 (90.6)	
Recalcitrant			
Yes	8 (25.0)	2 (6.3)	0.08*
No	24 (75.0)	30 (93.8)	
Previous treatment			
Yes	8 (25.0)	2 (6.3)	0.08*
No	24 (75.0)	30 (93.8)	

*Fisher Exact test

Table 2: Treatment outcome among the study subjects within the two Groups

Variable	MMR Group (N = 32) n (%)	NS Group (N = 32) n (%)	*p* value
Cycles of treatment			
Two cycles	4 (12.5)	2 (6.3)	0.672
Three cycles	28 (87.5)	30 (93.8)	
Response at 21 days	*Cases*	*Controls*	
No response	25 (78.1)	30 (93.8)	0.148
Partial response	7 (21.9)	2 (6.3)	
Response at 42 days			
No response	8 (25.0)	26 (81.3)	<0.001
Partial response	20 (62.5)	4 (12.5)	
Complete response	4 (12.5)	2 (6.3)	
Response at 63 days			
No response	6 (18.8)	26 (81.3)	<0.001
Partial response	10 (31.3)	3 (9.4)	
Complete response	16 (50)	3 (9.4)	
Response of distant wart			
No response	0 (0.0)	2 (6.3)	0.261
Complete response	2 (6.3)	0 (0.0)	
Recurrence			
Yes	3 (9.4)	1 (3.1)	0.223
No	29 (90.6)	29 (90.6)	
Side effects			
No side effects	5 (15.6)	3 (9.4)	0.125
Pain	18 (56.3)	26 (81.3)	
Pain, dizziness	0 (0.0)	1 (3.1)	
Pain, Flu	3 (9.4)	0 (0.0)	
Pain, Erythema	2 (6.3)	0 (0.0)	
Pain, Erythema, Oedema	4 (12.5)	2 (6.3)	

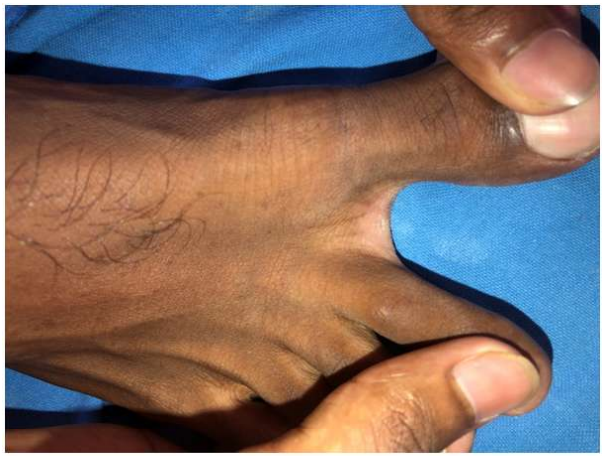

Fig. 2: Plantar wart after single dose of MMR

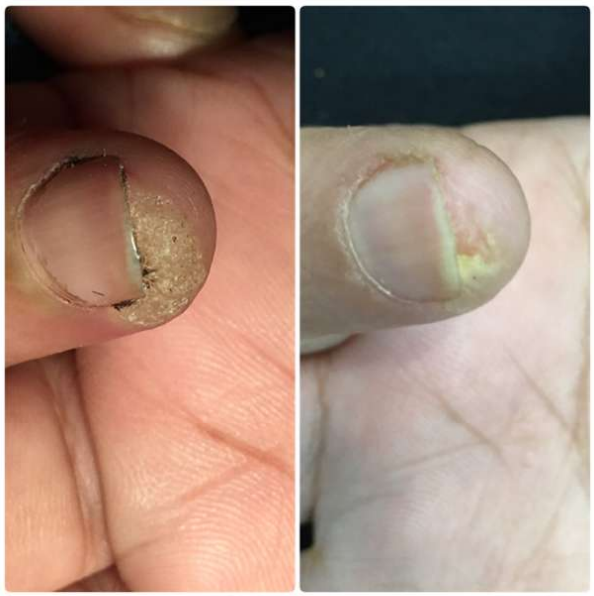

Fig. 3: Periungual wart showing improvement after MMR injection

Discussion

The never ending list of treatment for warts is an evidence to show that no treatment is specific and complete and treatment should be modified accordingly depending on patients' expectations. First line agents are those which can be applied by patients and second line are those modalities which require expertise but is almost always associated with scarring. Those agents which are not studied completely for their efficacy and safety are included in third line therapy. Immunotherapy is one among these third line agents.

Manipulating the immune system to achieve a therapeutic or protective response against diseases caused by HPV is an active field of investigation.[7] It can be achieved by various topical, intralesional, and systemic agents. MMR vaccine accelerates the clearance of virus and viral infected cells by stimulation of cell mediated and humoral immunity. Recently, better results with minimal adverse effects and lower recurrence rates have been reported with this therapy.[8]

In this study including 64 patients, we could obtain a statistically significant difference in the rate of wart resolution as well as in the end result in the group treated with MMR compared to distilled water group. In the study group 12.5% of patients showed complete response after two doses with a total of 75% patients responding to therapy while only 6% patients showed response in the control group. At the third follow up, that is at 63 days, 81.3 patients in the study group showed response to therapy with 50% patients showing complete clearance of the wart with partial return in skin markings. On the contrary in control group 18.8% patients were showing response with 9.4% patients showing complete response.

In an open labelled study on intralesional MMR for cutaneous warts by Saini P et al.[9], a complete clearance of 46.5% was seen with a partial clearance of 20.9%. In a case control study by Dhope A et al.[10] a complete clearance of 65% is noted with a 10% partial response in the study group. Awal G et al.[11] in his case control study showed a 68% complete response and 31.8% partial response to MMR vaccine. A complete response of 81.4% and a partial response of 10% was seen in study by Nofal et al.[12]

The slightly higher responses in these studies may be because these studies were done on common warts and not on palmoplantar warts alone. Palmo-plantar lesions can be harder and inaccessible in some of the patients for intralesional injection. Response of distant warts were also seem to be better with MMR vaccine than distilled water in this study.

In the present study 3 patients (9.4%) showed a recurrence of warts with MMR vaccine during the 9 month follow up period more so with increased duration and number of warts.

In study by Dhope et al.[10] recurrences were noted in 9.1% of patients. Saini et al.[9] showed a recurrence of 5% in the 6 month follow up period in their study.

Side effects associated with MMR vaccine are pain, erythema, edema and flu like symptoms affecting 84.4% of patients in study group. Of which 56.3% of patients had only pain as side effect. This observation is in accordance with other similar studies as well.[13-14]

According to the availability and patients' consent different authors have used different immunotherapeutic agents for intralesional injection for the treatment of warts. These are mainly autologous vaccine[15] candida antigen,[16] trichophytin skin test antigen,[7] tuberculin,[17,18] BCG vaccine,[19] Mycobacterium w vaccine,[20] and IFN-α and IFN-γ injection.[6]

Depending on the antigens the responses varied in different studies. It is difficult to conclude which antigen is efficient and safe. When the side effect profile is compared, intralesional MMR injection is found to be slightly superior than most of the above mentioned antigens.

Limitations of the Study

Increased number of consultations affected compliance of patients which was a major limitation. So was the lesser number of patients in study and control group.

Conclusion

This randomised placebo controlled study further strengthened the efficacy and safety of intralesional immunotherapy in the form of intralesional MMR injection for the treatment of difficult to treat or recalcitrant palmoplantar warts. If return of normal skin markings is taken as the sign of complete cure wen treating warts, intralesional MMR is a promising, safe, simple as well as inexpensive modality with lesser side effects and lower relapse rates compared to other treatment modalities. If enough evidences are available about the safety and efficacy of the MMR immunotherapy, this can be considered as a first line modality for the treatment especially of palmoplantar warts.

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Original Article

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A Retrospective Study to Evaluate the Clinicopathological Correlation of Skin Biopsies Done in a Tertiary Care Centre in South India

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Abstract

Background: Skin biopsy is one of the most commonly used diagnostic tests in dermatology to achieve accurate and rapid diagnosis. However, it is important to incorporate detailed clinical information for histopathological evaluation.

Aims: To retrospectively evaluate the quality of data entered in the histopathology request forms and biopsy reports and to investigate the consistency between clinical and pathological diagnoses in the reported biopsy specimens.

Methods: A retrospective analysis of histopathology request forms and their corresponding skin biopsy reports done over a period of two years was undertaken. Details like clinical history, examination findings, biopsy site and technique, purpose of biopsy, number of differential diagnosis, microscopic description, pathologist's diagnosis, duration of reporting and level of clinicopathological correlation were analyzed. Statistical analysis was carried out for two-tailed significance, and $p < 0.05$ was considered significant.

Results: A total of 456 biopsy reports were analyzed. On assessing the clinicopathological correlation, we observed a concordance rate of 70.2% and discordance rate of 29.8%. No correlation was observed between clinicopathological consistency and inadequate clinical history, inadequate examination findings and number of differential diagnosis. However, correlation was observed between clinicopathological consistency and inadequate clinical history and examination findings, when both were clubbed together. Clinicopathological consistent reports had a significantly higher rate of definitive pathologist's diagnosis and a significantly shorter duration for issuing the histopathology reports.

Conclusions: Several shortcomings were identified in the histopathology request forms during the review. Standardising the methodology of including all details in histopathology request forms would be useful.

Key words: Biopsy; Clinicopathological correlation; Consistency.

Introduction

Histopathology remains the gold standard for most dermatologic diagnoses. Dermatopathology plays an important and integral role in dermatology, aiding in the confirmation of clinical suspicions, helping to arrive at a diagnosis or to narrow the differential diagnoses in challenging cases.[1] However, every specimen submitted for histological diagnosis should be accompanied by detailed clinical information, including a differential diagnosis. The histopathologist's ability to render an accurate diagnosis often depends on the available clinical information, and clinicopathological correlation is

the key to providing optimal patient care. Hence, the histopathology request form becomes the crucial link between the treating dermatologist and the pathologist. Studies auditing the consistency between clinical and histopathological diagnoses of skin disorders are few.[2,3] An audit is a quality improvement process that seeks to improve the quality of existing healthcare facilities through a systematic review of care against explicit criteria and implementation of changes for its betterment.[4] We sought to evaluate the correlation between the clinical diagnoses rendered on the biopsy request form with the subsequent histological diagnoses and factors affecting consistency by reviewing the quality of data included in the dermatopathology request forms and reports in this retrospective study.

Materials and Methods

This study was conducted at a tertiary care referral hospital in South India. A retrospective analysis of histopathology request forms and their corresponding skin biopsy reports done over a period of two years (January 2014 to December 2015) in the Department of Dermatology was undertaken. Histopathology request forms and reports in the Department of Pathology and biopsy records in the Department of Dermatology were reviewed. Two histopathologists with experience in Dermatopathology for more than ten years were reviewing the slides. Each patient's age and gender were recorded. Other details like clinical history, examination findings, biopsy site and technique, purpose of biopsy, number of differential diagnosis, microscopic description, pathologist's diagnosis, duration of reporting and level of clinicopathological correlation were analyzed. The clinical findings were reviewed after the histology diagnosis and histology diagnosis reviewed in relevant cases. The relationships between clinical and pathological diagnoses were studied in 4 groups, namely: (1) definite pathological diagnoses consistent with the clinical diagnoses, (2) descriptive pathological diagnoses consistent with the clinical diagnoses, (3) definite pathological diagnoses inconsistent with the clinical diagnoses, and (4) descriptive pathological diagnoses inconsistent with the clinical diagnoses. The first two groups were taken as evidence of clinicopathological consistency, whereas the latter two groups were taken as evidence of clinicopathological inconsistency between the diagnoses. The data were analyzed using IBM SPSS statistics version 20 for windows. All categorical and quantitative variables were presented as frequencies and percentages and were compared by chi-squared test for trend. All statistical analysis was carried out for two-tailed significance, and $p < 0.05$ was considered significant.

Results

A total of 456 biopsy reports were analyzed, among them 258 (56.6%) were of male patients and 198 (43.4%) were of female patients. The sample size was small considering the fact that, routinely biopsies were not done for all clinically evident cases. Biopsies were done only in suspected cases where clinical diagnosis was not straightforward. Only in Hansen's disease biopsies were done in all cases before starting them on treatment. Mean age recorded in 456 reports was 36.5 years. Proportion of biopsies from different body sites were: lower limbs 32%, upper limbs 26%, back 20%, chest and abdomen 15%, head and neck 6% and mucosa 1%. The biopsies were categorized by type as follows: 444 punches, 10 excisional, and 2 incisional. Majority (452, 99.1%) of the biopsies were performed for diagnostic purposes, and the remaining (4, 0.9%) were done for both diagnostic and therapeutic purposes. Out of these four cases, two cases were melanocytic naevus and one case each of dermatofibroma and pilomatricoma. In these cases, clinicopathological correlation was required to rule out any malignancy and also to confirm the diagnosis.

The deficiencies observed in the histopathology request forms included the following: inadequate clinical history in 36 (7.9%) forms, inadequate examination findings in 86 (18.9%) forms and site of biopsy not mentioned in 10 (2.2%) forms. The number of clinical differential diagnosis varied between 1 and 7. No correlation was observed between clinicopathological consistency and inadequate clinical history, inadequate examination findings and number of differential diagnosis (Table 1). However, when we clubbed together the inadequate clinical history and examination findings, the association between clinicopathological consistency and inadequate clinical details was statistically significant (Table 1). Among 48 biopsies with discordant histopathology reports and inadequate clinical history and clinical findings, the histological diagnosis changed in 10 (20.8%) biopsies after providing the adequate clinical history and findings.

The association between clinicopathological consistency and adequate clinical details for individual groups of disorders was found to be statistically significant (Table 2).

Also, when we separated the definitive diagnosis and descriptive reports in the concordant group, the association between adequate clinical details and definitive diagnosis was statistically significant (Table 3).

Definite diagnosis was recorded in 336 (73.7%) reports, and descriptive diagnosis in 120 (26.3%) reports. Of the 456 reports examined, 296 (64.9%) had a definite pathological diagnosis consistent with the clinical diagnosis, 24 (5.3%) had a

Table 1:

Factors	Biopsy report Concordant n (%)	Discordant n (%)	Total	*p* value
Clinical history				
Adequate	296 (70.5)	124 (29.5)	420	0.63
Inadequate	24 (66.7)	12 (33.3)	36	
Examination findings				
Adequate	256 (69.2)	114 (30.8)	370	0.33
Inadequate	64 (74.4)	22 (25.6)	86	
History and Examination clubbed together				
Adequate	256	88	344	0.014
Inadequate	64	48	112	
Number of diagnosis				
≤2	230 (71)	94 (29)	324	0.55
>2	90 (68.2)	42 (31.8)	132	
Microscopic details				
Mentioned	320 (70.2)	136 (29.8)	456	0.001
Not mentioned	0	0	0	
Pathologists diagnosis				
Definitive	296 (88.1)	40 11.9)	336	0.001
Descriptive	24 (20)	96 (80)	120	
Reporting time				
≤1 week	228 (74)	80 (26)	308	0.009
>1 week	92 (62.2)	56 (37.8)	148	

Table 2: Correlation of clinical details in different group of disorders

Group of disorders	Clinical details	Concordant	Discordant	Total	*p* value
Hansen's disease	Adequate	36	18	54	0.003
	Inadequate	4	12	16	
Psoriasis	Adequate	30	14	44	0.03
	Inadequate	6	10	16	
Lichen planus and lichenoid disorders	Adequate	22	12	34	0.12
	Inadequate	6	12	18	
Connective tissue diseases	Adequate	11	7	18	0.02
	Inadequate	1	7	8	
Vasculitis	Adequate	13	3	16	0.005
	Inadequate	1	5	6	
Pigmentary diseases	Adequate	6	4	10	0.02
	Inadequate	2	6	8	
Vesiculobullous disorders	Adequate	10	1	11	0.03
	Inadequate	2	3	5	
Granulomatous diseases	Adequate	7	2	9	0.009
	Inadequate	0	4	4	
Cutaneous malignancies	Adequate	2	4	6	0.10
	Inadequate	2	0	2	
Adnexal tumors	Adequate	2	4	6	0.35
	Inadequate	0	2	2	

descriptive pathological diagnosis consistent with the clinical diagnosis, 40 (8.8%) had a definite pathological diagnosis inconsistent with the clinical diagnosis, and 96 (21.1%) had a descriptive pathological diagnosis that was inconsistent with the clinical diagnosis.

Time taken for issuing the histopathology report was ≤ 7 days in 316 (69.3%) forms and > 7 days in 140 (30.7%) forms. On assessing the clinicopathological correlation, we observed a concordance rate of 70.2% (320 reports) and discordance rate of 29.8% (136 reports). Maximum concordance was observed among vesiculobullous and vasculitic disorders and maximum discordance among adnexal tumours, pigmentary disorders and cutaneous malignancies. Cutaneous malignancies reported were melanocytic melanoma (1 case), squamous cell carcinoma (2 cases), basal cell carcinoma (1 case) and adenexal carcinoma (0). There were 18 cases in the benign neoplasia group with a concordance of 37.5%. Clinicopathological concordance among various groups of disorders are summarized in Table 4.

Table 3: Comparision of clinical details of concordant reports between definitive diagnosis and descriptive reports

Clinical details	Definitive diagnosis	Descriptive reports	*p* value
Adequate	286	10	<0.001
Inadequate	10	14	
Total	296	24	

Table 4: Group of disorders and rates of clinicopathological consistencies

Group of disorders	Number of biopsies	Clinicopathological concordance (%)
Hansen's disease	70	57.1
Psoriasis and psoriasiform dermatitis	60	60
Lichen planus and lichenoid disorders	52	57.7
Connective tissue diseases	26	46.2
Vasculitis	22	63.6
Pigmentary diseases	18	44.4
Vesiculobullous disorders	16	75
Granulomatous diseases	13	53.8
Cutaneous malignancies	8	50
Adnexal tumors	8	25

Table 5: Comparison of level of clinicopathological correlation of various groups of disorders in different studies

Group of disorders	No. of biopsies in our study	Concordance (%)	Other studies	No. of biopsies in their study	Concordance (%)
Hansen's disease	70	57.1	Bhatia et al.[16]	1351	89
			Moorthy et al.[15]	372	62.6
			Rao et al.[18]	108	95
			Balasubramanian et al.[3]	454	58.8
			Shivaswamy et al.[17]	182	74.7
Psoriasis and psoriasiform dermatitis	60	60	Mehta et al.[14]	100	81
			Aslan et al.[2]	Not mentioned	96.8
			Balasubramanian et al.[3]	274	68.2
Lichen planus and lichenoid disorders	52	57.7	Aslan et al.[2]	Not mentioned	94.6
			Balasubramanian et al.[3]	286	70.6
Vasculitis	22	63.6	Khetan et al.[20]	80	77
			Balasubramanian et al.[3]	160	56.3
Pigmentary diseases	18	44.4	Aslan et al.[2]	202	87.6
Vesiculobullous disorders	16	75	Aslan et al.[2]	Not mentioned	94.6
			Balasubramaniam et al.[3]	204	71.1
Cutaneous malignancies	8	50	Aslan et al.[2]	Not mentioned	89.6
			Balasubramaniam et al.[3]	55	52.7
			Tan et al.[7]	78	91

Further we categorized our cases into broad groups such as inflammatory and neoplastic. In the inflammatory group, there were 432 cases with a concordance of 71.8% and in the neoplastic group there were 24 cases with a concordance of 41.7%.

Clinicopathological consistent reports had a statistically significant (p = 0.001) higher rate of definitive pathologist's diagnosis and a statistically significant (p = 0.009) shorter duration for issuing the histopathology reports (Table 1).

Discussion

Skin biopsy is one of the most commonly used diagnostic tests in dermatology and an invaluable tool in the dermatologist's diagnostic armamentarium.[3] Previous studies have observed that providing a good clinical description in histopathology requisition forms increased the diagnostic accuracy.[2,5,6] Tan et al.[7] in their study on inflammatory and malignant disorders have highlighted the utility of the Clinico-Pathological Correlation (CPC) score, and demonstrated how this scoring system could provide a form of communication between clinicians and dermatopathologists. In our study, no significant association was observed between clinicopathological consistency and inadequate clinical history and examination findings provided. Similar findings have been reported by Balasubramanian et al.[3] in their retrospective audit of 3006 pathology requisition forms and reports. However, when we clubbed together the inadequate clinical history and examination findings, the association between clinicopathological consistency and inadequate clinical details was statistically significant. Among 48 biopsies with discordant histopathology reports and inadequate clinical history and clinical findings, the histological diagnosis changed in 20.8% of biopsies after providing adequate clinical history and findings. This may be due to the fact that, the histological or tissue responses may be similar or overlap and the histological diagnosis changed after providing the necessary clinical details. These findings reiterate the importance of filling the requisition forms with detailed clinical history and examination findings.

Aslan et al.[2] in their study reported that no correlation was observed between clinicopathological consistency and type of biopsy or number of differential diagnosis. Our results also did not show any correlation with respect to number of differential diagnosis and majority of our biopsies were punch biopsy.

Our study demonstrated a clinicopathological concordance rate of 70.2% and discordance rate of 29.8% in diagnosing dermatologic diseases. This correlates well with literature accuracy rates where Balasubramanian et al.[3] and Aslan et al.[2] found 59.8% and 76.8% concordance rate, and 30.9% and 23.2% discordance rates respectively. Both these studies evaluated skin biopsies of all types of dermatological diseases. The diagnostic accuracy rate in prior clinicopathological consistency studies looking at single lesions, benign tumors and malignancy such as basal cell carcinoma and melanoma, has ranged from 44% to 96.5%.[8-13]

Comparision of clinicopathological concordance among various groups of dermatological disorders in our study with other studies are summarized in Table 5. Psoriasiform and lichenoid disorders had a low degree of concordance in our study which was relatively close to another Indian study by Balasubramanian et al.[3] However, studies by Mehta et al.[14] and Aslan et al.[2] had a higher degree of concordance in these groups of disorders. This dichotomy in concordance rates could be due to improper biopsy site selection, lack of standardized criteria for reporting and could be that biopsies were done only in suspected but not clinically evident cases. Also, in other studies, biopsies could have been done in the clinically evident cases also for documentary evidence.[3]

Clinicopathological correlation in Hansens disease in our study (57.1%) was similar to that observed by Balasubrmanian et al.[3] (58.8%) and Moorthy et al.[15] (62.6%). However, higher clinicopathological concordance rates have been reported by Bhatia et al.[16] (69%), Shivaswamy et al.[17] (74.7%), and Rao et al.[18] (95%). Correlation was maximum in lepromatous leprosy followed by tubeculoid and borderline tuberculoid leprosy in our study, which is in agreement with those reported by Balasubramanian et al.[3], Shivaswamy et al.[17] and Bhatia et al.[16] Maximum correlation with borderline tuberculoid leprosy followed by borderline lepromatous type has been reported by Manandhar et al.[19] Discordance between clinical and histopathological diagnosis can be explained on the basis that generally the diagnosis is made on clinical grounds alone, awaiting histopathological confirmation. It is possible that there is an individual observer bias also. Variation in different studies may be related to different criteria used to select the cases: choosing the biopsy site, age of the lesion, morphology of the lesion, immunological and treatment status of the patient, retrospective versus prospective studies.

Clinicopathological correlation of cutaneous malignancies in our study was 50% which is almost similar to that reported by Balasubramanian et al. (52.7%).[3] On the contrary, Aslan et al.[2] and Tan et al.[7] have reported it to be 89.2% and 91% respectively. This could be because of the infrequent occurrence of skin cancers in the Indian subcontinent compared to white skinned individuals and our high index of clinical suspicion.

Concordance rate was minimum in adnexal tumors group (25%). This may be due to the fact that, these present with cutaneous/subcutaneous swellings and specific clinical diagnosis is difficult to make.

Balasubramanian et al.[3] documented that concordant reports had a significantly higher rate of definitive pathologist's diagnosis and a significantly shorter duration for issuing the histopathology reports. Our study also documented the same findings. This could be due to the fact that, when pathological diagnoses are inconsistent with the clinical diagnosis, the pathologist can apply additional procedures such as histochemistry, immunohistochemistry and serial sections to establish a definite diagnosis which may prolong the duration of the reports.

Limitation of this study was sampling bias, as all cases of Hansen's disease were preferentially biopsied whereas other diseases were biopsied only when there was clinical difficulty.

Conclusion

The rate of clinicopathological consistency in our study was 70.2%. Several inadequacies were identified in the histopathology request forms during the review. Review of discordant slides is required to reduce the clinic-pathological inconsistency. It would be useful to have a standardised histopathology request forms which includes all the clinical details. Also, a clinicopathological correlation scoring system would be beneficial in improving the communication between dermatologists and pathologists.

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Original Article

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Pattern of Inpatient Referrals to Dermatology OPD at a Tertiary Care Centre, VIMS, Ballari

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Abstract

Background: Dermatology is a department mainly concerned without patients examination and treatment. But sometimes dermatologists expertise is sought for by the inpatients who are admitted in wards of other specialities.

Aims: The aim of the study is to know from which departments the referrals are commonly sought for from department of dermatology and their cutaneous diagnosis and to analyse the knowledge of non-dermatologists on various common dermatoses.

Materials and Methods: The study included all in patients referred to dermatology department in a tertiary care centre between January 2018 to December 2018. *Results:* A total of 215 referrals with dermatological diagnosis were recorded. Internal medicine (70; 32.55%), topped the number of referrals to dermatologists department followed by paediatrics (56; 26.04%), obstetrics and gynaecology (20; 9.30%), ENT (20;9.30%) and surgery (19; 8.83%). Infectious skin diseases were most common (42.79%) followed by eczema (5.58%) and drug reactions (5.11%). Before referral to the dermatology opd, a tentative dermatological diagnosis was made in 30% patients only by the referring department, and it was found to be correct in 20% of the patients, common skin conditions like scabies, psoriasis were missed.

Conclusion: Maximum referrals to Dermatology department were from department of internal medicine and infectious dermatoses were the most common cause. Prompt dermatology referral from other departments helps in better patient management and there is a need for better training of non-dermatologists to recognise and treat common skin disorders.

Key Words: Referral; Inpatients; Dermatology.

Introduction

Dermatology practice takes place mainly in the outpatient setting but a substantial part represents inpatients referrals from other specialists in a large hospital.[1] Patients admitted to non-dermatology departments may often have numerous skin lesions besides the systemic disease for which they are hospitalised.[2,3] Several inpatient referrals are made to dermatology department by other specialities on a daily basis for proper patient management in the hospital settings.[1] References from other departments to the dermatology department helps in better diagnosis and management of cutaneous condition of the patient and also helps in improving the clinical knowledge of the treating dermatologist and of the referring doctor.

This study was conducted to determine the pattern of inpatient referrals to dermatology department among patients admitted in other wards at a tertiary care teaching institute of VIMS, Ballari.

Materials and Methods

This observational study was undertaken at a tertiary care teaching institute, VIMS, Ballari, between January 2018 to December 2018. All the in patients referred from non-dermatology wards to dermatology department were initially evaluated by a dermatology resident, the case was then discussed with the attending consultant to arrive at a clinical diagnosis. Whenever necessary, specific investigations such as KOH preparation, grams smear, Tzanck smear, slit skin smear, skin biopsy and blood and radiological investigations were done to substantiate the clinical diagnosis. Bed side referral services were also provided for non-ambulatory sick patients in intensive care units and other wards. Details of the referring department, patients demographic profile and diagnosis of the dermatoses by dermatologist were recorded in a proforma for analysis and interpretation. Institutional Ethics Committee approval was obtained for the study.

Results

During the 1 year period, a total of 215 referrals were received. The average number of patients seen per month was 18, with a range of 16–20. There were 132 males (61%) and 83 females (39%) with a M:F ratio of 1.59.

The department of internal medicine accounted for the highest dermatologic referrals (70 cases, 32.55%) followed by the department of paediatrics (56 cases, 26.04%), obstetrics and gynaecology and ENT (20 cases, 9.30%), and surgery (19 cases, 8.83%). The dental department accounted for the least number of referrals. The different specialities requesting Dermatology consultation have been shown in Table 1.

The different diagnosis made by the dermatologists after examining the referred patients has been tabulated in Table 2. Cutaneous infection was the most commonly diagnosed condition (42.79%), followed by eczemas/dermatitis (5.58%) and drug reactions (5.11%) (Fig. 1, Fig. 2, Fig. 3). Dermatophytosis was the most common diagnosis among the skin infections followed by cutaneous bacterial infection. Maculo-papular rash was the commonest type of reaction caused by drugs.

Before referral to the dermatology opd, a tentative dermatological diagnosis was made in 30% patients only by the referring department, and it was found to be correct in 20% of the patients (Table 3). Woods lamp examination, skin biopsies, dermatoscopic examination, grams stain, potassium hydroxide examination etc, were some of the additional investigations done in 20% of

Table 1: Distribution of interdepartmental consultations

Department	Male	Female	Total No	%
Medicine	60	10	70	32.55
Paediatric	39	17	56	26.04
OBG	0	20	20	9.30
ENT	12	8	20	9.30
Surgery	16	3	19	8.83
Orthopaedic	5	3	8	3.72
Psychiatry	3	3	6	2.79
Oncology	2	3	5	2.32
Ophthalmology	3	2	5	2.32
Urology	3	2	5	2.32
Dental	0	1	1	0.46
Total	143	72	215	100

Table 2: Dermatological diagnosis made in referred patients (n = 215)

Dermatological diagnosis	n(%)
1. Infections and Infestations	92 (42.79)
a. Viral	37 (17.20)
b. Bacteria	20 (9.3)
c. Fungal	19 (8.83)
d. Parasitic	7 (3.25)
e. Mycobacterial	9 (4.18)
2. Eczema	12 (5.58)
3. Drug reactions	11 (5.11)
4. Hansen's disease	9 (4.18)
5. Oral lesions	9 (4.18)
6. Miliaria	8 (3.72)
7. Icthyosis	6 (2.32)
8. Benign skin tumours	6 (2.32)
9. Psoriasis	5 (2.32)
10. Xerosis	5 (2.32)
11. Pregnancy related	5 (2.32)
12. Non specific dermatosis	5 (2.32)
13. STD's	4 (1.86)
14. Pruritus of systemic origin	4 (1.86)
15. Acute urticaria	3 (1.39)
16. Pigmentary disorders	3 (1.39)
17. Nutritional disorders	3 (1.39)
18. Psychocutaneous	3 (1.39)
19. Neoplasms	3 (1.39)
20. Papular urticaria	3 (1.39)
21. Ecchymois/purpura	2 (0.93)
22. Vasculitis	2 (0.93)
23. Postherpetic neuralgia	2 (0.93)
24. Keratoderma	2 (0.93)
25. Immunobullous	2 (0.93)
26. Exfoliative dermatitis	2 (0.93)
27. Hair and nail disease	2 (0.93)
28. Acne /acneiform eruption	1 (0.46)
29. Subcutaneous necrosis of new born	1 (0.46)
Total	215

the cases referred, for confirmation of the clinical diagnosis. In 150 (70%) of cases referrals resulted in an alteration or additional treatment in the form of either stopping of the treatment for the cutaneous infection and/or addition of new oral or topical medication. For better management of some of the referred cases, they were asked to be transferred to dermatology ward for further management.

Table 3: Dermatological diagnosis wrongly diagnosed by referring doctors (n=52)

Dermatological diagnosis	n(%)
1. Infections and Infestations	30 (57.69)
a. Viral	16 (30.76)
b. Bacteria	6 (11.53)
c. Fungal	4 (7.69)
d. Parasitic	2 (3.84)
e. Mycobacterial	2 (3.84)
2. Eczema	4 (7.69)
3. Drug reactions	3 (5.76)
4. Hansen's disease	3 (5.76)
5. Oral lesions	3(5.76)
6. Miliaria	3(5.76)
7. Icthyosis	2 (3.84)
8. Benign skin tumours	2 (3.84)
9. Psoriasis	2 (3.84)
Total	52(100)

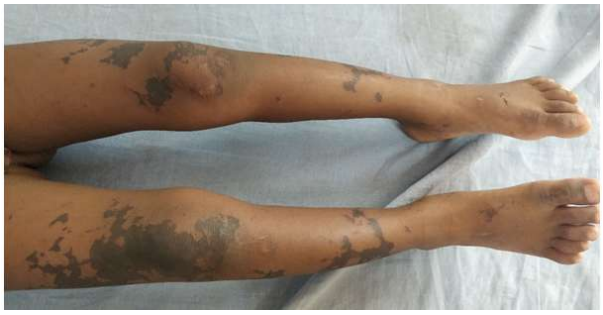

Fig. 1: Purpura Fulminans

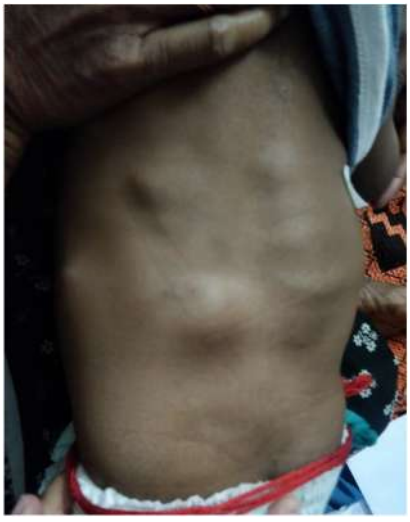

Fig. 2: Subcutaneous necrosis of newborn

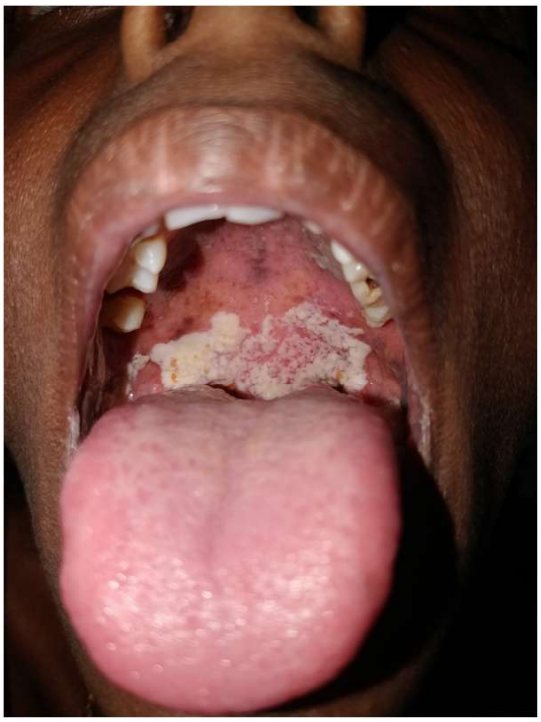

Fig. 3: Oral candidiasis in an immunosuppressed patient

Discussion

The knowledge of dermatology among non-dermatologists is believed to be very poor.[4-6] At times, the dermatoses, for which referral to dermatologic department is sought by the other departments may be associated with significant morbidity and at times mortality.[7] These dermatology lesions could be detected as a coincidental finding during examination or develop during their stay in the hospital.[8] Often, expert dermatological opinion is required for the patient with coexisting cutaneous problem. Here in this study we analyse the various reasons for dermatology referrals and their impact on patient care. In our study, most of the dermatology consultations were sought for patients above 18 years. similar results were obtained in a study by Chowdhury SN et al.[9] In most of the published works males have outnumbered females, and the same pattern of distribution was seen in this study as well.[10]

In the present study, internal medicine accounted for the highest proportion of dermatological consultations (32.55%), in concurrence with several other studies.[11-14] The reason for this could be due to increased number of admissions in medicine wards. Another reason could be that many medical disorders are associated with dermatological manifestations which may sometimes serve as

important clues for the diagnosis of the underlying medical conditions. Paediatrics (26.06%) referrals were more in our study as compared to other studies.[15,16] The reason for this could be due to increase number of paediatric fevers associated with cutaneous rash. And also more number of children developed miliaria because of hot and humid conditions in the wards. From general surgery the percentage of referrals was 8.83%. Similar percentage was seen in other studies as well.[15,16] Surgical references mainly consisted of stasis dermatitis and infective eczemas. Among the obstetrics and gynaecological referrals (9.30%), most of the patients had specific dermatoses of pregnancy. Other common conditions seen were dermatophytosis and patients with VDRL positivity to rule out syphilis.

The final diagnosis made by the dermatologists in this study revealed infections (42.79%), eczema/ dermatitis (5.58%) and drug reactions accounting for (5.11%) cases. Similar findings were seen in the study by Chowdary et al.[9] where in infections (35%), drug reactions (12.6%) and eczema/ dermatitis (8.6%) constituted the referrals and also in studies by Davila et al.[10] and Balai et al.[15]Among the infections fungal cases dominated reflecting the general trend of increase in the incidence of fungal infections in this part of the world where hot and humid climate predominate. The common drugs causing drug rash in our study were phenytoin, carbamazepine and cotrimoxazole, mainly causing Stevens Johnsons syndrome and penicillins and non-steroidal anti-inflammatory drugs causing maculopapular rash.

Before referral to the dermatology opd, a tentative dermatological diagnosis was made in 30% patients only by the referring department, and it was found to be correct in 20% of the patients. This is in concurrence with a study by Balai et al.[15] in which a dermatological diagnosis was made in 33% patients by the referring unit, and it was found to be correct in only 20% of the patients. Other studies from Portugal,[1] US,[11] and Brazil[14] have reported that a correct diagnosis was made in 23.9%, 48%, and 33% of the patients, respectively.

In our study we also observed that some of the common dermatological conditions like scabies, dermatophytosis, herpes zoster, psoriasis, were either missed or misdiagnosed by the referral departments. Similar findings were noted in other studies as well.[9,15] Hence, non-dermatologists should be trained and educated atleast about the common dermatoses and also should be impressed upon early dermatological referrals. This is especially true in cases od adverse drug reactions as immediate suspicion and withdrawl of drug is of atmost importance.

Conclusion

Non-dermatologists often fail to recognise or misdiagnose common cutaneous disorders in our set up. This leads to unnecessary medications and complications in the patients. So the importance of prompt dermatological referrals should be impressed upon non-dermatological staff and basic training should be provided right from the undergraduate level to diagnose simple cutaneous disorders.

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Prevention of Fogging of Magnifying Loupe with Surgical Mask Tying: Our Experience

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Abstract

Fogging of the surgical loupes is a common problem for every surgeon. Not only the surgical loupes, any of the eye protection goggles used during surgery can have fogging. There have been various methods to prevent this like applying adhesive tape over the upper part of the mask, anti-fogging coating over the goggles etc. Recently, we came across an article on a novel method of tying a surgical mask to prevent fogging and tried it. We would like to share our experience.

Keywords: Fogging; Loupes; Surgical mask tying.

Introduction

Magnifying loupes are an important part of armamentarium in an operation theatre for not only plastic surgeons but also cardiothoracic surgeons, urologists etc. Eye protection goggles are a part of universal protection kit.[1] Reports are seen regarding the non-compliance of the use of these due to fogging.[2] There have been various methods of preventing this including use of anti-fogging coating, application of adhesive tape over the upper part of the face mask[3] etc. One of the method we came across recently described a novel method of tying of the surgical mask.[4] In this the author described knotting the superior tie first with it lying directly below the ear. The inferior tie is brought up in front of the ear and knotted over the crown of the head (Figure 1). We would like to share our experience with the use of this method.

Materials and Methods

We have used the above mentioned method of tying surgical mask in six surgeons. Feedback was obtained from them using a proforma (Figure 2).

Fig. 1: Method of tying the surgical mask

Questionnnaire

Feedback form

1. Utility of the mask: Poor/Average/Good
2. Did the mask prevent fogging: Yes/No
3. Comfort of the surgeon: Comfortable/Uncomfortable
4. Would you like to recommend your colleague for usage of this device: Yes/No

Suggestions if any

Fig. 2: Feedback form

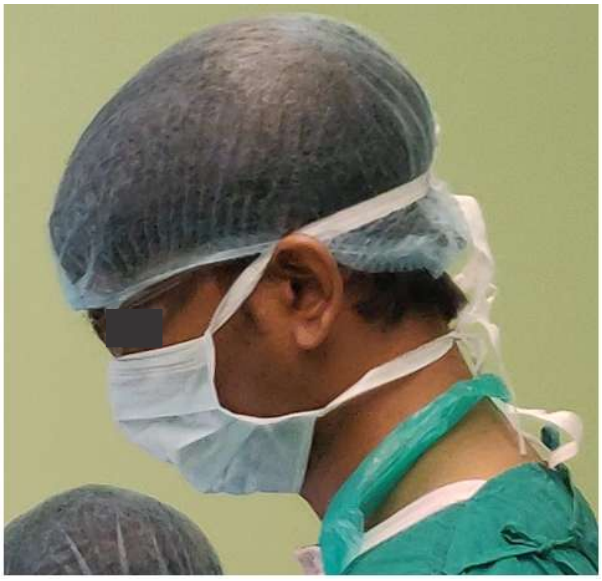

Fig. 3: Conventional method of tying a surgical mask

Discussion

Magnifying loupes and eye protection wear are important in surgery for personal protection and patient safety. Fogging is common problem which leads to reduced visual acuity[5] and leads to reduce compliance for their use.

The conventional method of tying a surgical mask leads to the exhaled air coming out through the mask on the superior aspect leading to fogging (Figure 3). In the method described by Jordan et al. where the surgical mask was tied in a specific way it has lateral vents which caused the exhaled air to come out from the lateral aspect rather than on to the superior aspect towards the loupes. This leads to reduced fogging. We have used this method in 6 plastic surgeons and obtained feedback from them. All the surgeons agreed that this method is effective. However one surgeon felt the tying of the mask in this particular way has led to increase slipping. All surgeons agreed that they would recommend it to other surgeons.

Conclusion

We found the method useful in prevent fogging. However large trials are required to prove its efficacy.

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Update of Treatment Options in Atopic Dermatitis: A Narrative Review

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Abstract

Atopic dermatitis (AD) is a chronic, inflammatory skin disease characterized by pruritus, inflammatory skin lesions. It causes severe impairment of quality of life along with the impairment of physical well of the patient. The management of AD has been always challenging due to its chronic and recurrent course with periods of remission. As the medical science progresses many modalities of treatment have been introduced, beginning from bathing methodology, topical and systemic. This study tries to give a narrative review of the different management options, which clinical dermatologists can use for the management of atopic dermatitis. These options needs to be evaluated and matched according to the age, sex and severity of atopic dermatitis.

Key words: Atopic dermatitis; Treatment; Pruritus.

Introduction

Atopic dermatitis is a type of endogenous eczema. It is common chronic and pruritic skin condition characterised multiple remission and relapse during its course. Itch or pruritus is the hallmark of atopic dermatitis. It has been estimated that around 10–20% of children and 1-3% of adults suffer from this disease.[1] It may be associated with other disease like food allergy, bronchial asthma and allergic rhinitis.[2] Genetic and environment factors resulting in, epidermal barrier dysfunction, immune dysregulation and alteration of the cutaneous microflora has been found as the main factors causing atopic dermatitis.[3-5] Atopic dermatitis due to its chronic course it is associated with psychological stress not only in patients but also in the parents, and resulting in impaired Quality of Life (QoL).[6] Many modalities of treatment are available for the treatment of atopic dermatitis but the treatment of atopic dermatitis is always challenging. This review tries to accumulate the various modalities available for the management of atopic dermatitis.

Management of atopic dermatitis

1. Education and counselling of patients, parents and guardians.
2. Proper bathing.
3. Appropriate use of moisturizers.
4. Use of immunomodulators: phototherapy, topical and systemic medications.
5. Other miscellaneous interventions.
6. Management of coexisting allergies in a patient with atopic diathesis.[7, 8]

Baths

The patient should be advised to have a bath of around five to 10 minutes. It should not be prolonged one as it can remove the skin surface lipids. The water should be just warm not hot.[9] For the bath, the patient should be asked to use a cleanser that is fragrance free and the cleanser should be at neutral to low PH. Syndet bars are preferred than soaps or combars. The syndet bars or the synthetic detergent

bars contain a synthetic surfactant, which is soap free. The synthetic surfactants may consists of fatty acid isothionates, sulfosuccinic acid esters as their principal ingredient. They have the capacity to preserve the skin surface lipids, which is important for maintaining the barrier function of the skin.[10]

Bleach Bath: The bleach bath has the property of prevention of infection and inflammatory cascade, which is an aggravating factor for atopic dermatitis. It is usually advised to have a bleach bath for 2-3 times a week. For the preparation of bleach bath, around 118 ml of household bleach whose active ingredient is NaOCl (Sodium Hypochlorite) is added to 151 litres of water. The patient's body or the affected areas are soaked for around ten minutes and then using a dry towel the body is patted dry. Immediately, the appropriate moisturiser needs to be applied.[11,12]

Oatmeal bath: The oatmeal bath can soothe the skin, maintain the barrier function and reduce the inflammation. For an oatmeal bath one cup, which is 236 ml, of finely powdered colloidal oatmeal is slowly added to the bathtub slowly so that the colloidal oatmeal dissolves evenly. The water of the bathtub should be just warm. The body should be soaked in the bathtub for 10–15 minutes and then dried by just patting.[13,14]

Vigorous rubbing after a bath should be avoided as it can irritate the skin. After the bath the soak and smear, technique can be used to apply the anti-inflammatory medications and/or moisturizers. In this technique the moisturizer is applied liberally shortly after the bath, usually within three minutes. The topical anti-inflammatory agents if indicated should be applied before the application of the moisturizer.[15]

Moisturizers

The cornerstone and agent of choice for management of atopic dermatitis are moisturizers. Moisturizers are available over the counters as well. Before choosing appropriate moisturizer or before prescribing one, certain characteristics need to be taken care of. An emollient for a patient of atopic dermatitis should be free of fragrance, preservatives or other additives, which can act as triggering factor for exacerbation of atopic dermatitis. It should have an occlusive property by which it blocks trans-epidermal water loss, humectant property by which it binds water molecules and emollient property by which it maintains skin barrier function. Certain additives in moisturizers contain substances like parabens, fragrances, tocopherol or other biological additives, which can trigger the inflammatory process and aggravate the disease. The emollient can be topped up with certain additives like aloe vera, coconut oil, ceramide, natural moisturizing factor sand anti-microbial peptides for their better efficacy. Moisturizing creams are preferred over lotions in atopic dermatitis due to their higher proportion of oil in creams than lotions.[16-19] The moisturizers should be applied using the soak and smear technique for better outcome.[15]

Immunomodulatory Therapy

Phototherapy

Natural sunlight is considered useful for atopic patient. However, sunlight and high temperature can induce pruritus start and itch scratch cycle and can be harmful to patient. UV-B, or UB-A or combined UV-AB phototherapy can be beneficial. The UV rays act by inducing apoptosis of the T-Cells, reduction of Th2 cytokines and reduction of the antigen-presenting cell in the skin. It also reduced microbial colonisation in the skin (like *Staphylococcus aureus*).[20-23]

Topical anti-inflammatory agents

Topical Corticosteroids: Topical corticosteroids is FDA approved for management of atopic eczema and is the first line pharmacologic therapy. The corticosteroids are immunosuppressive, anti-inflammatory, ant proliferative and vasoconstrictive. It also retards the T cell, macrophage and dendritic cell proliferation. Nevertheless, the corticosteroids always remains to be a double-edged sword and proper potency and formulation should be prescribed by the clinician and the adverse effects should be kept in mind. The common side effects consist of skin atrophy, striae, steroid acne, perioral dermatitis, purpura, hypertrichosis, and hypopigmentation. Topical corticosteroids under occlusion can lead to gram-negative folliculitis. Systemic absorption can lead to HPA suppression.[15,24,25]

Topical calcineurin inhibitors: Topical calcineurin inhibitors are FDA approved for the management of atopic dermatitis. Pimecrolimus 1% cream can be used for the management of mild to moderate disease and tacrolimus 0.03% to 0.1% can be used for moderate to severe disease. They work by supressing the T cell activation, reducing the secretion of the

Th2 profile cytokines and by inhibiting release of other proinflammatory mediators. They reduce the mast cell and dendritic cell activity as well. The topical calcineurin inhibitors are particularly useful for skin of face and intertriginous area, which have higher chances of atrophy after prolonged application of topical corticosteroids. The side of topical calcineurin inhibitors include local stinging and burning sensation.[26-28]

Crisaborole: Crisaborole is a phosphodiesterase 4 inhibitor which is FDA approved for the management of mild to moderate atopic dermatitis. Phosphodiesterase 4 leads to degradation of cyclic AMP and results in increased production of pro-inflammatory cytokines.[29-31]

Topical antimicrobials and antihistamines are other topical agents, whichcan be used for the management of atopic dermatitis. Topical antibiotics like fusidic acid 2%, or mupirocin 2% might be required where secondary infection has taken place and for the staphylococcal carrier sites, nasal or extra nasal.[32,33] Topical antihistamines like doxepin can be used for itch relief.[34,35]

Systemic anti-inflammatory agents

The American Academy of Dermatology (AAD) has laid down certain guidelines for the use of systemic immunomodulatory therapy for a patient of atopic dermatitis. According to AAD, systemic immunomodulatory therapy in a case of atopic dermatitis is given for patients in whom optimised topical regimens do not adequately control signs and symptoms of disease and for the patients whose medical, physical and/orpsychological states are greatly affected by their skin disease.[36]

The systemic anti-inflammatory agents for management of atopic dermatitis include:

Corticosteroids: Corticosteroid has multiple mechanism of action leading to final immunosuppression. It leads to NFkB and AP-1 transcription factor inhibition. It also causes apoptosis of lymphocytes and eosinophils. Corticosteroids act on the arachidonic acid pathway by phospholipase A2 and cyclooxygenase inhibition. The resultant effect is reduced activity of inflammatory cells and inhibition of pro-inflammatory cytokines. The corticosteroids also have effects on the dermal vasculature. They inhibit angiogenesis, causes vasoconstriction and reduced vascular smooth muscle response to histamine and bradykinin.[37,38]

The dose of corticosteroid in atopic dermatitis is subjective and depends on clinicians' assessment of the patient. The important side effects of systemic corticosteroids include reactivation of tuberculosis and other infection, impaired wound healing, gastritis and gastric ulcer, electrolyte imbalance, fluid retention and hypertension, iatrogenic diabetes, osteoporosis, myopathy, glaucoma, menstrual irregularities, Cushing syndrome, suppression of HPA axisand Addisonian crisis, even psychosis in rare cases. While prescribing a systemic steroid to a child it should be kept in mind that steroid causes growth retardation. While the patient is on systemic corticosteroid therapy proper monitoring needs to be done including weight and growth chart monitoring, blood counts, infection screening, serum electrolyte levels, blood glucose levels, serum triglyceride levels, cardiac monitoring, bone x-rays, routine ophthalmologic examination and others. After a long course of corticosteroid therapy, serum cortisol level should be checked ideally before steroid withdrawal.[39,40]

Aliretinoin: Alitretinoin or 9-cis retinoic acid is a non-aromatic retinoid. Its special characteristic is that it binds to all the retinoic acid receptors and retinoid X receptors. Upon binding with RAR and RXR it causes reduction in cytokines and chemokines which causes inflammation and mediate apoptotic activity and resulting in antiproliferative effect. Although very less reporting has been done regarding the use of alitretinoin for atopic dermatitis, it can be used in adult with atopic dermatitis at a dose of 30 mg per day. The common side effect include headache, dyslipidaemia, photosensitivity and teratogenicity. It is pregnancy category X drug. If alitretinoin is planned in a case of atopic dermatitis then preliminary investigations must be done like blood counts, liver function tests, fasting lipid profile, renal function tests and most importantly pregnancy test in a female of reproductive age group.[41-43]

Azathioprine: Azathioprine is an immunosuppressant and immunomodulatory substance. After administration of azathioprine it is rapidly converted to 6-mercaptopurine. The active metabolites of azathioprine, 6-thioguanine monophosphate and other 6-thioguanine metabolites are structurally similar to the endogenous purines. They get incorporated into the DNA and RNA and inhibit purine metabolism and cell replication. As a result, they also effect the T cell and B cell and antigen presenting cell function. The empirical dose of azathioprine is 2–3 mg/kg daily but the dose may be needed to adjust according to the thiopurine methyltransferase levels. Thiopurine methyltransferase (TPMT) converts

6-mercaptopurine to inactive metabolites. In case of reduced TPMT levels there can be azathioprine toxicity resulting in myelosupression. Azathioprine is pregnancy category D drug. The important side effects of azathioprine include leucopenia, opportunistic infections, reactivation of latent infections and occasionally lymphoma on long-term usage. Before starting a patient of atopic dermatitis on azathioprine proper risk benefit ratio should be discussed. TPMT levels, pregnancy test, routine blood count, serum biochemistry tests and screening of latent infection should be done.[44-50]

Cyclosporine: This immunosuppressant and immunomodulatory sunstance was originally isolated from the fungus Tolypocladium inflatum. Cyclosporine causes inhibition of the intracellular enzyme calcineurin. As a result, it leads to reduction in pro-inflammatory factors and reduces the langerhans cell function. It leads to suppression of cellular and humoral immunity, mainly T cell function. Cyclosporine A (CsA) is not cytotoxic, does not suppress bone marrow, and is not teratogenic. Cyclosporine is available as two formulations, the original sandimmune and the neoralform. The neural formulationis more absorbed and more bioavailable. The dermatologic dosage of cyclosporine is usually 2.5-5 mg per kilograms of body weight per day. It has the propensity to cause renal dysfunction, hypertension and dyslipidaemia. Other side effects of cyclosporine include tremors, headache, GI intolerance, electrolyte abnormities and even hypertrichosis and hyperplasia of gums. Cyclosporine is contraindicated in extremes of ages, usually in less than 18 years and more than 65 years of age. It is pregnancy category C drug. Before starting a patient on cyclosporine pre-existing renal function, hypertension, malignancy, presence of any active infection should be screened for. A patient on cyclosporine needs to be regularly monitored for alteration in blood pressure and serum creatinine levels. Other relevant investigations like routine blood counts and blood biochemistry tests should always be done at regular intervals and monitored. Intake of grape juice is contraindicated with cyclosporine as it can cause elevation of cyclosporine levels in blood.[5,50-52]

Methotrexate: Methotrexate also known as amethopterincauses inhibition of dihydrofolic acid reductase resulting interference with DNA synthesis, repair, and cellular replication. Methotrexate is specific for S phase of cell cycle. It can be administered orally, intramuscularly or intravenously. The dose and route of administration is subjective to the severity of atopic dermatitis and needs evaluation by the treating doctor. Before administration of methotrexate baseline evaluation for immunosuppressants needs to bedone with special emphasis on, blood counts and liver status. Since methotrexate is a pregnancy category X drug, pregnancy must be ruled out before staring a female of reproductive age group on methotrexate. The tests needs to be repeated at regular intervals for proper monitoring. The important adverse effects of methotrexate include hepatotoxicity like liver fibrosis and cirrhosis, pancytopenia, pneumonitis, pulmonary fibrosis a gastrointestinal upset and teratogenicity. At high doses, methotrexate can cause nephrotoxicity and at long-termusage, lymphoma can occur. Methotrexate overdose can cause toxicity which is manifested as mucositis, stomatitis, oesophagitis, acute renal failure, pancytopenia, neurological dysfunction and diarrhoea. Leucovorin glucarpidase and thymidine are the antidotes, which can be used as an antidote for methotrexate toxicity.[53-57]

Mycophenolic acid: Mycophenolic acid (MPA) was originally isolated as a fermentation product of Penicillium stoloniferum in 1986 is a class of immunosuppressant. MMA inhibits the de novo pathway of purine biosynthesis, the only mechanism of purine biosymthesis that exists in lymphocytes. It also causes reduced recruitment of pro inflammatory cytokines, reduced expression of adhesion molecules and inhinits ant presenting cells and B cells. The adult dose of MPA for atopic dermatitis varies from 100 to 200 mg per day. MPA is notorious to cause hyperglycemia, hypercholesterolemia, electrolyte imbalance, gastrointestinal complaints, haematological abnormalities, pulmonary toxicities and occasionally flu like syndrome. Before starting MPA baseline investigations must be done to avoid the side effects. MPA has been categorised as pregnancy category D drug.[58-60]

Apremilast: Apremilast is a small molecule, which exerts its mechanism by inhibiting phosphodiesterase-4, and resultant increase of cyclic AMP levels of pro-inflammatory cytokines such as tumour necrosis factor-α, interleukin-23 and Interleukin-12. For adults with atopic dermatitis the dose is 20–30 mg twice daily. Apremilast is comparatively safer drug when compared to other immunosuppressive agents. It is a pregnancy C category drug. The most important side effects include diarrhoea and nausea, which may warrant withdrawal of drug. It is advisable to start with 10 mg once daily dose and gradually increasing the

dose to the upper limit.[61-63]

Dupilumab: Dupilumab is a monoclonal antibody, which got FDA approval for moderate to severe atopic dermatitis in 2017. Dupilumab is fully human-derived monoclonal antibody. Dupilumab binds to the alpha subunit of IL-4 Receptor which is common between IL-4 and IL-13. IL-4 and IL-13 induces differentiation of naïve T cells to Th2 cell line, which is the cornerstone of pathogenesis of atopic dermatitis. Dupilumabis administered subcutaneously. It is available in the market as 200 mg/1.14 ml syringe and 300 mg/2 ml syringe. The dose of atopic dermatitis is 600 mg SC initially followed by 300 mg SC every other week. Dupilumab can cause ocular side effects like conjunctivitis, blepharitis dry eye and keratitis. Injection site reaction and immunosuppression are other side effects. Proper screening should be done before starting Dupilumab as done with every biologics.[64-68]

Other non-immunomodulatory systemic agents for the management of atopic dermatitis include antimicrobials, antihistamines and oral Vitamin D_3.

Systemic antimicrobials: The use of short course of antibiotics can supress the *Staphylococcal* colonization. It is also indicated in a case of a flare of a case of atopic dermatitis.[69,70]

Systemic antihistamines: Antihistamines control pruritus and hence break the itch scratch cycle. It induces sedation and sleep as well.[71,72]

Systemic Vitamin D: Vitamin D has immunomodulatory effects both in the innate and adaptive immune systems, and there is increasing data showing its relevance in inflammatory processes such as AD. In combination with standard therapy, vitamin Dis sufficient to achieve a reduction in severity of AD.[73-76]

Other Therapies

They include interferon gamma which supresses and downregulates Th2 and IgE function, immunotherapy with aeroallergen, passing of psoralen treated WBCs through extracorporeal UV-A light system and Chinese herbal medications.[77-81]

Management of Coexisting Allergies

Around 20–30% of atopic dermatitis is associated with food hypersensitivity and it forms a component of atopic march. Eggs, milk, peanuts, soy, wheat and fish cause around 85–90% of food allergy. Although they mostly cause immediate hypersensitivity, they have the propensity to cause acute flare of atopic dermatitis and such components might need exclusion from diet. Skin prick test can help in finding the agent of exclusion.[82-84] Dust mites, pollen grains, animal dander can cause aeroallergen allergy resulting in AD exacerbation. Use of vacum cleaners, avoidance of furry toys and pets can avoid aeroallergen reactivity.[85-88] Components of topical medications and skin care products can cause an aggravation of AD.[89] Proper patch tests can be done to find the offending agent.[90-92]

Conclusion

Atopic dermatitis has a chronic course and causes a significant distress to the patients and parents in all aspects. Many modalities of treatment and management are available for controlling the acute phase and prevention of exacerbation of atopic dermatitis. Appropriate methods should be selected alone or in combination assessing the status of the patient and calculating the risk and benefits of each modality of management.

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The text of observational and experimental articles should be divided into sections with the headings: Introduction, Methods, Results, Discussion, References, Tables, Figures, Figure legends, and Acknowledgment. Do not make subheadings in these sections.

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The title page should carry

1) Type of manuscript (e.g. Original article, Review article, Case Report)

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The second page should carry the full title of the manuscript and an abstract (of no more than 150 words for case reports, brief reports and 250 words for original articles). The abstract should be structured and state the Context (Background), Aims, Settings and Design, Methods and Materials, Statistical analysis used, Results and Conclusions. Below the abstract should provide 3 to 10 keywords.

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State the background of the study and purpose of the study and summarize the rationale for the study or observation.

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The methods section should include only information that was available at the time the plan or protocol for the study was written such as study approach, design, type of sample, sample size, sampling technique, setting of the study, description of data collection tools and methods; all information obtained during the conduct of the study belongs in the Results section.

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Present your results in logical sequence in the text, tables, and illustrations, giving the main or most important findings first. Do not repeat in the text all the data in the tables or illustrations; emphasize or summarize only important observations. Extra or supplementary materials and technical details can be placed in an appendix where it will be accessible but will not interrupt the flow of the text; alternatively, it can be published only in the electronic version of the journal.

Discussion

Include summary of key findings (primary outcome measures, secondary outcome measures, results as they relate to a prior hypothesis); Strengths and limitations of the study (study question, study design, data collection, analysis and interpretation); Interpretation and implications in the context of the totality of evidence (is there a systematic review to refer to, if not, could one be reasonably done here and now?, What this study adds to the available evidence, effects on patient care and health policy, possible mechanisms)? Controversies raised by this study; and Future research directions (for this particular research collaboration, underlying mechanisms, clinical research). Do not repeat in detail data or other material given in the Introduction or the Results section.

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List references in alphabetical order. Each listed reference should be cited in text (not in alphabetic order), and each text citation should be listed in the References section. Identify references in text, tables, and legends by Arabic numerals in square bracket (e.g. [10]). Please refer to ICMJE Guidelines (http://www.nlm.nih.gov/bsd/uniform_ requirements.html) for more examples.

Standard journal article

[1] Flink H, Tegelberg Å, Thörn M, Lagerlöf F. Effect of oral iron supplementation on unstimulated salivary flow rate: A randomized, double-blind, placebo-controlled trial. J Oral Pathol Med 2006; 35: 540-7.

[2] Twetman S, Axelsson S, Dahlgren H, Holm AK, Källestål C, Lagerlöf F, et al. Caries-preventive effect of fluoride toothpaste: A systematic review. Acta Odontol Scand 2003; 61: 347-55.

Article in supplement or special issue

[3] Fleischer W, Reimer K. Povidone iodine antisepsis. State of the art. Dermatology 1997; 195 Suppl 2: 3-9.

Corporate (collective) author

[4] American Academy of Periodontology. Sonic and ultrasonic scalers in periodontics. J Periodontol 2000; 71: 1792-801.

Unpublished article

[5] Garoushi S, Lassila LV, Tezvergil A, Vallittu PK. Static and fatigue compression test for particulate filler composite resin with fiber-reinforced composite substructure. Dent Mater 2006.

Personal author(s)

[6] Hosmer D, Lemeshow S. Applied logistic regression, 2nd edn. New York: Wiley-Interscience; 2000.

Chapter in book

[7] Nauntofte B, Tenovuo J, Lagerlöf F. Secretion and composition of saliva. In: Fejerskov O,

Kidd EAM, editors. Dental caries: The disease and its clinical management. Oxford: Blackwell Munksgaard; 2003. p. 7-27.

No author given

[8] World Health Organization. Oral health surveys - basic methods, 4th edn. Geneva: World Health Organization; 1997.

Reference from electronic media

[9] National Statistics Online—Trends in suicide by method in England and Wales, 1979-2001. www.statistics.gov.uk/downloads/theme_health/HSQ20.pdf (accessed Jan 24, 2005): 7-18. Only verified references against the original documents should be cited. Authors are responsible for the accuracy and completeness of their references and for correct text citation. The number of reference should be kept limited to 20 in case of major communications and 10 for short communications.

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