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Azathioprine as a Steroid Sparing Agent in Recalcitrant Type 2 Reaction

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Abstract: ***Introduction: Severe recalcitrant Type 2 Leprosy reaction (ENL) is recalcitrant to conventional therapy & characterized by ulcerative necrotic skin lesions, known as Erythema Nodosum Necroticans and required long term systemic glucocorticoid therapy which leads to serious complications. To prevent serious side effects of ENL one should consider steroid sparing agents. Azathioprine is generally well tolerated and has a favourable therapeutic index compared with other traditional immunosuppressant. In our study, severe ENL patients recalcitrant to conventional therapy were successfully managed with Azathioprine monotherapy. Objective: To evaluate Azathioprine as a steroid sparing agent. To prevent serious side effects of Glucocorticoids and to prevent systemic complications of severe Type 2 leprosy reaction. Methods: Total 14 cases of severe recalcitrant T2R were enrolled in study. We started Azathioprine average 100 mg per day in all 14 patients for total period of 12 months along with oral. Prednisolone and anti leprosy treatment (MB Adult Pack). Clinical & laboratory evaluations were done at baseline (0), 3, 6, 9 & 12th month. Results: At the end of 12 months, only one patient showed recurrence of ENL & remaining 13 patients (92.85%) were absolutely fine & they didn't require any immunosuppressive. We found serious side effects of Glucocorticoids before treatment which were prevented at the completion of study, as early as at 6 months & serious necrotic skin lesions before treatment were healed with Azathioprine & Prednisolone combination. In our study we found 92.85% success rate in Azathioprine treatment in severe recalcitrant T2R. Conclusion: Azathioprine is a good adjuvant immunosuppressive drug in the control of recalcitrant Type 2 reactions, and especially as a GCS sparing agent with minimum side effects.***

Keywords: Recalcitrant Type 2 Leprosy Reaction, Azathioprine, Steroid Sparing Agent

1. Introduction

T2R is immune complex syndrome secondary to the presence of Leprosy bacilli and is observed mostly in LL with high bacillary index & rarely in BL. [(1)] Hospital based study from Nepal showed high incidence of ENL reaction in 28.6% in LL & 7.5% in BL cases. [(2)] Other study from north India reported 47.4% in LL and 10.5% in BL cases. [(3)]

Skin lesion of T2R is known as ENL. Clinically it is characterized by crops of brightly erythematous slightly raised subcutaneous nodules or plaques of variable sizes, occur mostly on face, arm, thighs & flexors without changes in original skin lesions of leprosy.In severe form of T2R the skin lesions may become vesicular, pustular, bullous, gangrenous and break down, known as Erythema Nodosum Necroticans.T2R may be accompanying with neuritis, bone & joint pain, dactylitis, rhinitis, lymphadenitis, epididymoorchitis, fever & malaise. Histopatholgy of ENL shows dense neutrophilic infiltrate with existing lepromatous granuloma. Necrotic lesion shows changes of vesiculation and damage to collagen & elastic fibers. [(1)]

Mild form of ENL can be treated symptomatically with anti-inflammatory agents and usually resolves spontaneously.Severe form of ENL requires systemic therapy to prevent permanent complications.Prednisolone and thalidomide have been traditionally used in treatment of severe ENL in absence of contraindications, as a second line of treatment with high dose of clofazimine. Clofazimine has been used for ENL for its unknown immune suppressive action but high dose is require for severe ENL. Clofazimine is associated with a cosmetically problematic deposition of pink-brown pigments in the skin and eyes that can take months to years to resolve after discontinuation of the drug. Severe ENL requires long term of high dose of glucocorticoid therapy which can cause serious complications.Thalidomide is the drug of choice for the management of ENL in response to Prednisolone. Currently severely restrict the use of thalidomide for its teratogenic effect & it should not be given to women of child-bearing age without reliable forms of birth control.

Azathioprine is generally well tolerated and has a favorable therapeutic index compared with other traditional immunosuppressants. It has been utilized as a corticosteroid sparing agent and as monotherpy.[(4)]

In our study we used Azathioprine because of its immunosuppressive effect as well as its effect on vasculitis[(5)], the initial findings of histopathology of ENL. We present patients with severe ENL, recalcitrant to conventional therapy that was successfully treated with Azathioprine.

2. Materials and Methods

Total 14 out of 22 T2R patients(Pts) were selected.All baseline clinical & laboratory investigations were done.Skin Slit-Smear (SSS) was taken in each patient for BI calculation.In our study we continued MB adult Anti Leprosy Treatment (ALT) for total period of two years.

We started Azathioprine in dose of 1-2 mg per kg, average 100 mg per day in two divided doses from baseline to total 12 months therapy. TMPT was avoided due to cost.We started Prednisolone 40-60 mg per day at baseline and gradually tapered according to clinical response. Clinical & laboratory evaluation were done at baseline (0), 3, 6, 9 & 12th month.

Treatment Regimen:

Continued MB ALT for total period of 2 years.

Oral Prednisolone 40 to 60mg per day at baseline then tapered 5-10mg per week according to clinical response. Oral Azathioprine 100 mg per day in two divided doses at

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baseline and continued up to 12 months.

3. Results

Table 1: Year wise distribution of T2R

Year	Total No of Patients of Leprosy	BL	LL	T2R
2008	28	7	10	8
2009	25	6	5	4
2010	23	4	4	3
2011	22	2	12	7
TOTAL	98	19	31	22

Table 2: Type of leprosy

Type of Leprosy (Out of 98 Leprosy Pts)	*Total No of Patients (Out of 98 Leprosy Pts)*	*No of Patient With T2R(Out of 98 Leprosy Pts)*	*Percentage Of Patient With T2R(Out of 98 Leprosy Pts)*
BL	19	4	4.08%
LL	31	18	18.36%
---	40	22	55%

Total 98 patients of leprosy attended skin OPD from 2008 to 2011.T2R occurred in 4 patients (4.08%) of BL & 18 patients (18.36%) of LL.

Table 2: Age

Age Group	**T2R**
0-10	-
11-20	1
21-30	14
31-40	4
41-50	2
51-60	1
>60	-

Maximum number of patients were found between 21-30 years of age group.

Table 4: Sex

Sex	**T2R**
Male	13
Female	9

In our study male more suffered than female.

Table 5: Relation with duration of ALT &T2R

Time Interval	T2R IN BL	T2R IN LL
No Prior Treatment	1	4
<3 Months	-	-
3-6 Months	3	1
7-12 Months	0	7
13-24 Months	0	4
>24 Months	0	2
Total	4	18

Total 5 pts 1 from BL & 4 from LL directly presented with T2R in skin OPD.T2R occurred in 7 patients after seven months of ALT.

Table 6: Recurrent episodes (>4 episodes)

	BL(total 4 pts of T2R)	LL(total 18 pts of T2R)	TOTAL=22
Recurrent Episodes (More than 4 episodes)	2 pts out of 4	12 pts from 18	14 pts out of 22

Pattern of Skin Lesion	ENL	1	2	3
	Ulceration & Necrosis	1	10	11

Nerve	Nerve Pain	1	2	3
	Nerve Tenderness	1	10	11
	Nerve Abscess	-	-	

14 pts out of 22 showed recalcitrant recurrence ENL were included in study group.

Table 7: Systemic Complaints

Complaints	*No of Patients inBL(2)(T2R)*	*No of Patients in LL(12)(T2R)*
Fever	2	10
Malaise	3	12
Bone		
-Arthralgia	3	12
-Arthritis	-	-
-Bone Pains	-	-
-Dactylitis	-	-
Peripheral Oedema		3
Lymphadenopathy	1	2
Eye Involvement	-	-
Nose(Rhinitis And	-	1
Epistaxis)		
Epididymo-Orchitis	-	1

All 14 pts had history of systemic complaints.

Table 8: Clinical Assessment T2R at 0,3,6,9 & 12months

Parameters	No. of Pts at 'O' Baseline	No. of Pts at '3' Months	No. of Pts at '6' Months	No. of Pts at '9' Months	No. of Pts at '12' Months
Recurrent Enl	14	8	2	2	1
Skin Lesion	14	8	2	2	1
Nerve Pain &Tenderness	14	8	4	-	-
Systemic Complaints	14	8	4	-	-
Requirement Of Steroids					
-60 mg	10	-	-	-	-
-40 Mg	4	4	2	-	-
-30 Mg	-	3	1	1	-
-10 Mg	-	4	1	1	-
AZATHIOPRINE(100 Mg)	14	14	14	14	0

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Table 9: Clinical outcome (percentage)

	At 0 month		At the end of 3 months		At the end of 6 months		At the end of 9 months		At the end of 12 months	
	No of Pts	%	No of Pts	%	No of Pts	%	No of Pts	%	No of Pts	%
Recurrent ENL	14	100	8	57.14	2	14.28	2	14.28	1	7.14
No skin Lesions	0	0	6	42.85	12	85.71	12	85.71	13	92.85

In our study we enrolled 14 out of 22 T2R cases of severe recalcitrant T2R.Clinical & laboratory evaluations were done including SSS at baseline (0), 3, 6, 9 & 12th months.Initially for early control of reaction we started GCS in form of Prednisolone 40 to 60 mg per day (according to skin lesion) along with Azathioprine.Azathioprine was given up to total 12 months along with Prednisolone and anti leprosy treatment (MB Adult Pack).Laboratory evaluation was done according to Azathioprine monitoring guidelines. At the end of 3 months, out of 14 patients, 6 patients (42.85%) showed no recurrence, remaining patients showed recurrence of skin lesions but less severe in nature & no necrotic ulceration seen in crops of ENL

At the end, at 6 month evaluation we found 12 patients (85.71%) were managed successfully with Azathioprine and Prednisolone was tapered and discontinued.They didn't required GCS & didn't show any relapses and recurrence of ENL at the end of 6 month evaluation.Remaining 2 patients, in spite of Azathioprine, still developed recurrent ENL & they required additional dose of steroids even at 6 month of combination therapy. At the end of 9 months only 2 patients showed recurrence of ENL & required steroids.

At the end of 12 months we stopped Azathioprine in all patients; only one patient showed recurrence of ENL & all 13 patients (92.85%) were absolutely fine & they didn't require any immunosuppressive.We would like to screen this patient for other alternative management but unfortunately that patient was lost to follow up for further management.

We found serious side effects of Glucocorticoids before treatment (fig-1a,2a) which were prevented at the completion of study, as early as at 6 months (fig-1b,2b) & serious necrotic skin lesions before treatment (fig-3a,4a) were healed (fig-3b,4b) with Azathioprine & Prednisolone combination.

Discussion:

Leprosy is an ancient infectious disease caused by Mycobacterium leprae that affects the skin and peripheral nerves.A wide clinical spectrum of disease exists, from the tuberculoid pole (associated with a vigorous Th1 response, relatively few bacilli, and limited well-defined lesions) to the lepromatous pole (associated with aggressive Th2 response, many bacilli, and diffuse symmetric lesions) [(1)].According to WHO, the number of new cases detected during the year 2011, as reported by 105 countries, was 219 075.The registered prevalence globally at the beginning of 2012 was 181 941. [(6)] The underlying immunologic mechanisms for ENL remain unclear.Beginning with thepioneering work of Wemambu et al in 1969, ENL has traditionally been considered an immune complex–mediated phenomenon with an accompanying vasculitis.[(7,8,9)] However, high levels of TNF-a and interleukin-6 are consistently found in patients with more severe disease, which suggests that a cell-mediated immune response also plays a role. [(10)]

Over all the pathology of ENL is poorly understand involving immune complex deposition as well as a localized cell mediated immune response with vasculitis.

Treatment of non-responsive ENL is challenging.Mild form of ENL can be treated symptomatically with anti-inflammatory agents and usually resolves spontaneously.Severe form of ENL requires systemic therapy to prevent permanent complications.Prednisolone and high dose of clofazimine & thalidomide have been traditionally used in treatment of severe ENL in absence of contraindications. [(11, 12)] Infliximab[(13)] and etanercept[(14)] have been found useful, but they are expensive and their long term complications have not been assessed. Oral zinc,[(15)] & methotrexate[(16)] have also been found helpful but are far from ideal and have their own limitations.

To keep in mind of serious complication of long term corticosteroids in T2R and teratogenicity of thalidomide as a dermatologist one should think of alternative immunosuppressive drugs in recalcitrant T2R.Azathioprine is generally well tolerated and has a favorable therapeutic index compared with other traditional immunosuppressants. It has been utilized as a corticosteroid sparing agent and as monotherpy. [(4)]

There are few reports on the use of Azathioprine in leprosy reactions.The only controlled study was carried out with Type 1 reactions, in which Azathioprine was used in an 8 week course with Prednisolone, and was as effective in the reaction management as Prednisolone alone.[(17)] In type 2 reactions, 3 case descriptions reported a better control of reactions when Azathioprine was added to GCS therapy.[(18)] Also reported in the management of intractable T2R that don't response to Prednisolone and clofazimine. [(19)] The role of Azathioprine in preventing recurrence was reported by Verma et al. [(20)] Sandra et al reported Azathioprine as a steroid sparing agent in T2R in nine cases.[(21)]

In our study we used Azathioprine because of its immunosuppressive effect as well as its effect on vasculitis which are initial findings of histopathology of ENL.

In our study we enrolled 14 out of 22 T2R cases of severe recalcitrant T2R.Clinical & laboratory evaluations were done including SSS at baseline (0), 3, 6, 9 & 12th months.Initially for early control of reaction we started GCS in form of Prednisolone 40 to 60 mg per day(according to skin lesion) along with Azathioprine. Azathioprine was given up to total 12 months along with Prednisolone and anti leprosy treatment (MB Adult Pack).

Over all at the end of completion of study we found 92.85% (13 patients) of success rate in Azathioprine treated

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recalcitrant T2R.Only one patient showed recurrent ENL & unfortunately patient was lost to follow up for further management.

We observed that prolonged maintenance dose of Prednisolone along with Azathioprine and subsequent very slow tapering of Prednisolone prevented serious side effects of Glucocorticoids and further relapses of ENL.All patients were better managed and more chronic complications of iritis, orchitis, arthritis and neuritis were prevented.Initial SSS (more than four) results fell to zero at the end of twelve months of treatment.The progression of neural damage was inhibited but there was no recovery of lost of neural functions.

A TPMT value is recommended before introducing Azathioprine to avoid potentially fatal myelotoxicity.TPMT enzyme activity may also be useful to determine the initial dose. [(4)] Unfortunately we were unable to perform this test.In the evaluation of Azathioprine effectiveness, its late onset of action must still be taken into account.

The most common side effects of Azathioprine are nausea, vomiting, diarrhea, fatigue, malaise usually occur within first 4 weeks of therapy.Hypotension, shock and even death are reported as a serious systemic hypersensitivity to Azathioprine.In our study none of patient showed any liver functions abnormalities.Only 3 patients had complaints of nausea after 1 week of Azathioprine therapy.

From our study, we concluded that Azathioprine is a good adjuvant immunosuppressive drug in the control of recalcitrant Type 2 reactions, and especially as a GCS sparing agent with minimum side effects. As a dermatologist we should consider Azathioprine as a good alternative immunosuppressive drug in severe recalcitrant T2R.Still basic research work in pathogenesis of T2R is required because it is very important for development of more powerful drugs for control & prevention of recalcitrant T2R.

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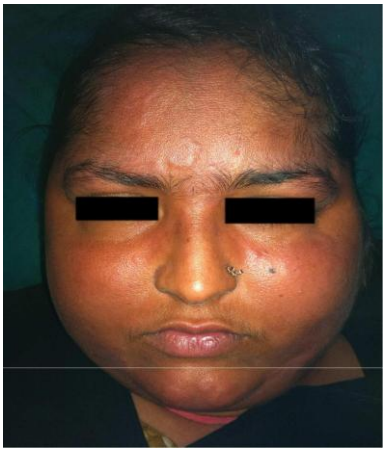
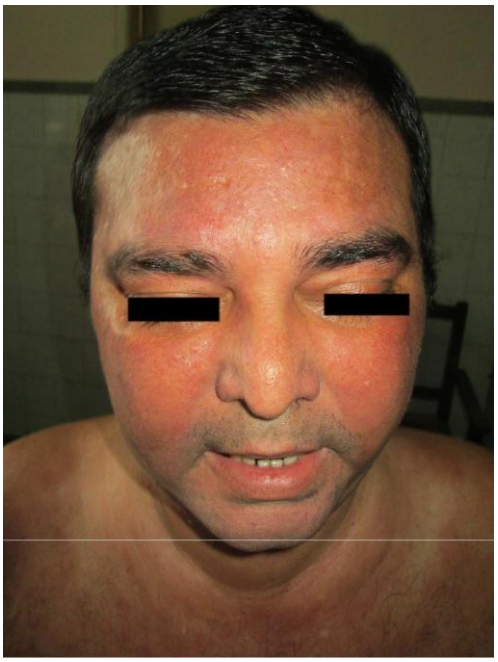
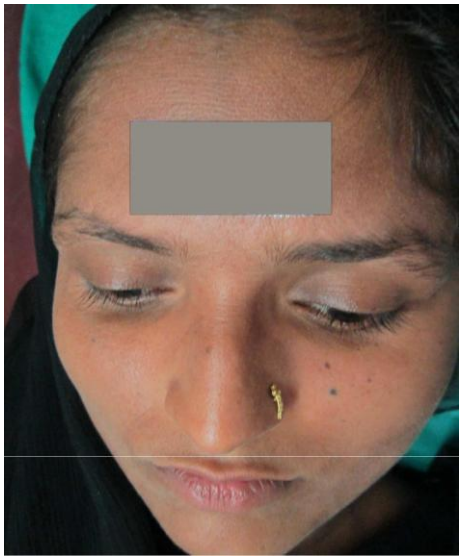


Moon-face side effect of long term glucocorticoid before study



Resolved moon face at the end of study



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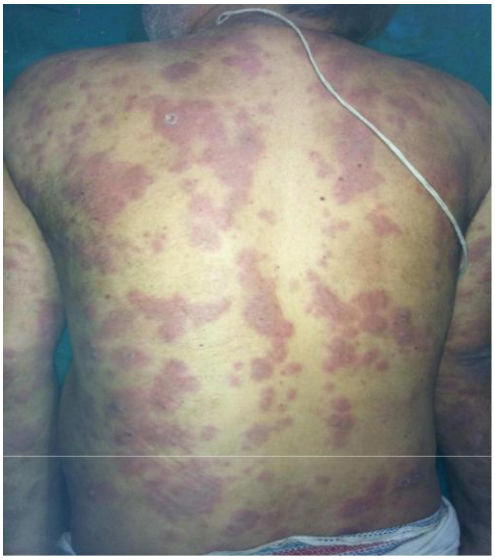
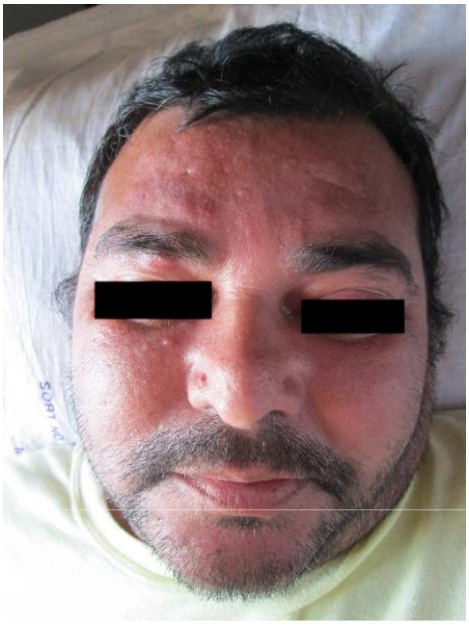
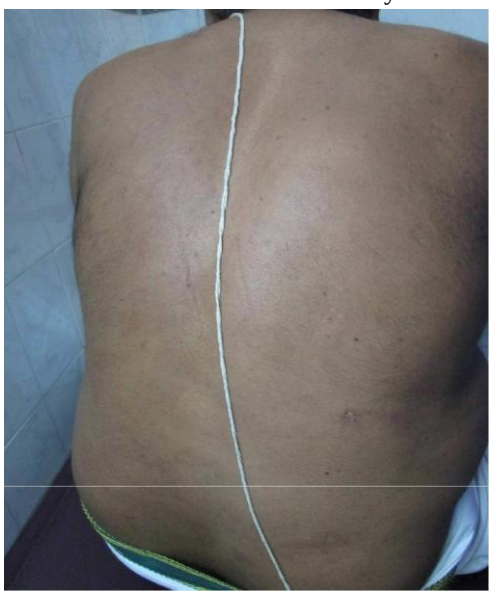


Necrotic lesion before study



"moon face"after long term side effect of steroid



Necrotic lesion after study

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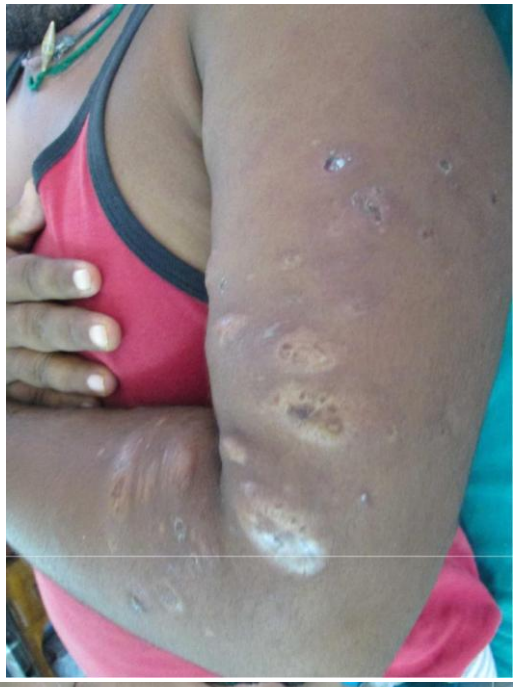

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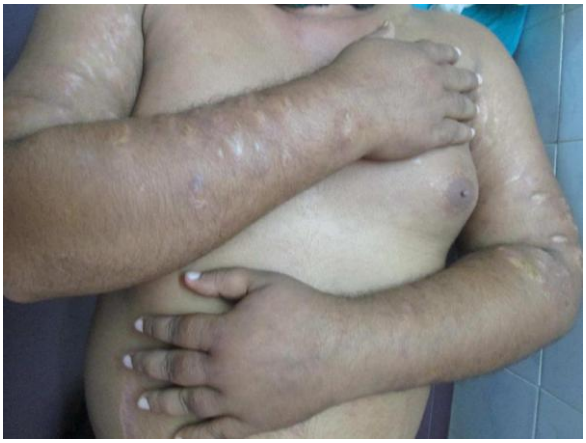

Necrotic lesions after study

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