Original article:

Study of Lepra reactions in Leprosy

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ABSTRACT:

In the current scenario of leprosy elimination, lepra reactions (LRs) remain a major persistent problem. Type 1 LR (T1LR) and type 2 LR (T2LR) are the major causes of nerve damage and permanent disabilities. The immunopathogenesis of LR have recently become an important field of research, since it may provide the relevant targets for the early detection and control of these episodes. Presently, there are no uniformly acceptable laboratory markers for LR.Genetic and serum markers in human host may predict susceptibility to reactions as well as progression of nerve damage in leprosy. Therefore, a deeper understanding of the molecular mechanisms involved in LR may provide a rational strategy for early diagnosis and prevention of the catastrophic consequences of LR. Leprosy is a chronic granulomatous disease caused by mycobacterium leprae with wide spectrum of clinical, histopathological and immunological characteristics. Leprosy reactions mainly encountered are type 1 and type 2 lepra reactions. The present work was carried out in our hospital. Type 2 lepra reaction, otherwise termed erythema nodosum leprosum, is an acute inflammatory reaction seen in patients with lepromatous leprosy or occasionally in borderline lepromatous leprosy. Rarely in severe type 2 leprosy reaction nodular lesions breakdown to form ulcers. This severe type 2 reaction with ulceration is called erythema necroticans.

INTRODUCTION:

A major problem in the management of leprosy patientsis the occurrence of “reactions.” These reactions are the consequences of the dynamic nature of theimmune response to Mycobacterium leprae (M. leprae)that may occur before, during, or following the completion of multi-drug therapy (MDT). There are two major types of lepra reactions (LR). Type 1LR (T1LR), also described as “reversal” reaction, is a type IV hypersensitivity reaction, that occurs in borderline leprosy patients with cellular immune responses to M. leprae antigenic determinants,[1] a n dis characterized by acute inflammation of pre-existing skin lesions or by the appearance of new lesions and/or neuritis.[2] Approximately 95% of T1LR cases are diagnosed simultaneously with leprosy or during the first 2 years of MDT.[3] Erythema nodosum leprosum (ENL), the most common manifestation of type 2 LR (T2LR), is an immunecomplex mediated complication of lepromatous leprosy (LL). T2LR presents with skin lesions (red, painful, and tender subcutaneous lesions),fever, and systemic inflammation that may affect the nerves, eyes, joints, testes, and lymph nodes. Most of the T2LRs occur during the first year of MDT.[4] Reactions are responsible for most of the permanent nerve damage, deformity, and disability.[1,5] Clinically detectable nerve function impairment (NFI) occurs in approximately 10% of paucibacillary and 40% of multibacillary leprosy patients, particularly inpatients with T1LR.[6] It has, however, been suggested that “silent neuropathy” due to sub-clinical neural involvement may take place in virtually all leprosypatients and that 30% of the nerve fibres need tobe destroyed before sensory impairment

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becomes detectable.[1]

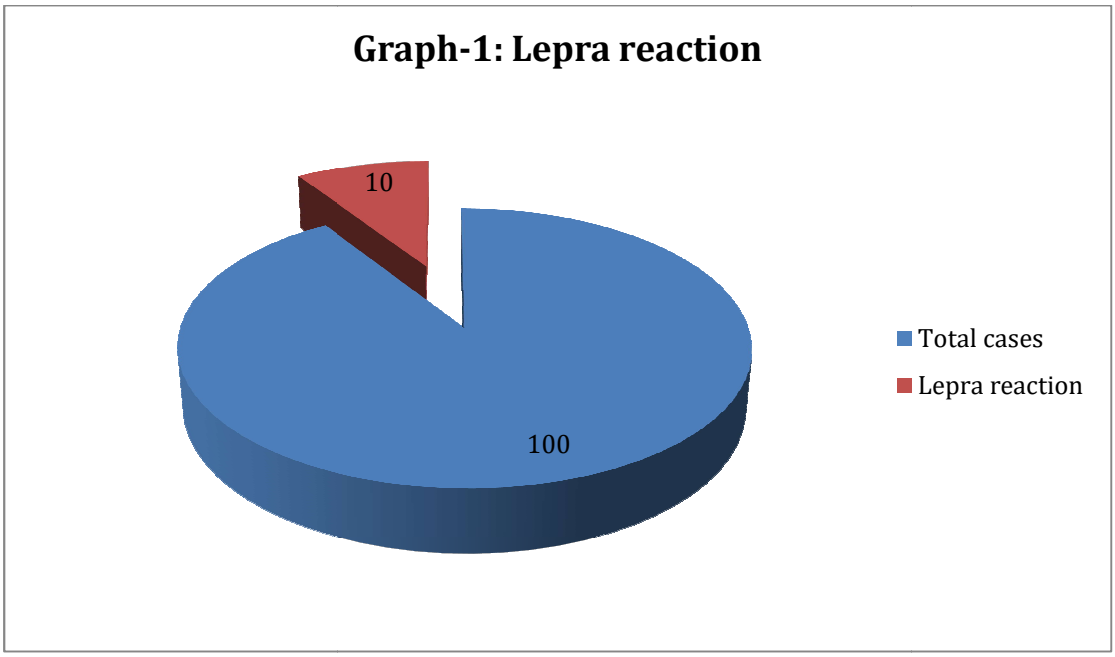
MATERIALS AND METHODS:

The present work was carried out in our hospital.

Three types of reaction are recognized:

- Type1 reaction
- Type 2 reaction
- Lucio phenomenon

RESULTS:



Of the 100 skin biopsies, there were 10 (10%) biopsies with features suggestive of lepra reaction. Among the 10 biopsies of lepra reaction, 2(20%) were diagnosed as BL with Type 1 Downgrading reaction . Both showed BI of 5+ . 1 (10%) case was diagnosed as BL with Type 2 ENL reaction. It had BI of 4+. Remaining 7 (70%) cases were diagnosed as LL with Type 2 ENL reaction. BI for six was 6+ and for one was 5+.

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Clinical Diagnosis	HP Diagnosis	Changes in Epidermis			Changes in Dermis								BI	Type of Reaction
		U	A	BME	Edema	IGE	Lymphocytes	Giant Cell	Plasma Call	Necrosis	Epithelioid	Macrophages foamy		
BL	BL	-	+	-	+	-	+	+	-	-	+	+	5+	Type 1-DG
BL	BL	-	+	--	+	-	+	+	-	-	+	+	5+	Type 1 - DG

Table 1) Of 2 biopsies in this category, both (100%) were BL with reaction downgrading type. Epidermal atrophy was present in both. Both biopsies showed presence of dermal edema, lymphocytes, giant cells, epithelioid granulomas and macrophages.

Clinical Diagnosis	HP Diagnosis	Changes in Epidermis			Changes in the Dermis				Adenexal structure			BI	Type of Reaction
		UN	A	BME	Grenze zone	Foamy Macrophage	Necrosis	Neutrophils infiltration	I	D	Both		
BL-ENL	BL		+		+	+		+				4+	ENL
LL-ENL	LL		+		+	+		+				5+	ENL
LL-ENL	LL		+		+	+		+				6+	ENL
LL-ENL	LL		+		+	+		+				6+	ENL
LL-ENL	LL		+		+	+		+				6+	ENL
LL-ENL	LL		+		+	+		+				6+	ENL
LL-ENL	LL	+			+	+		+				6+	ENL
LL-ENL	LL	+			+	+		+				6+	ENL

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I –Intact

D – Destroyed

UN –unremarkable

BME – Basement membrane erosion

A – Atrophic

Table 2) Of the 8 biopsies(80%) in this category, 1(12.5%) was BL. It had BI of 4+ . Remaining 7 (87.5%) were LL type. Grenz zone, foamy macrophages and neutrophilic infiltration and vasculitis was present in all 7 biopsies . BI in six biopsies was 6 + each and in one was 5+.

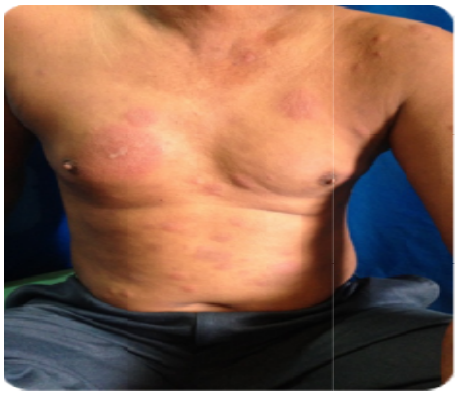

Fig 1 : erythema nodosum leprosum

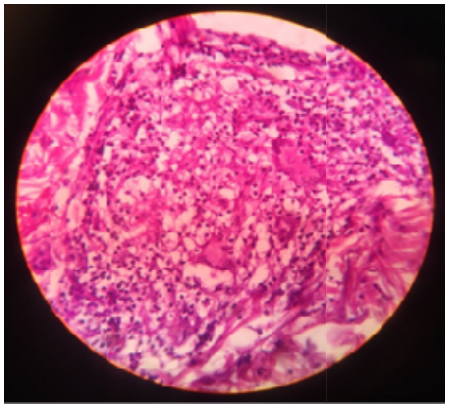

Fig 2 : Type 1 downgrading reaction showing foamy histiocytes with langhans giant cells

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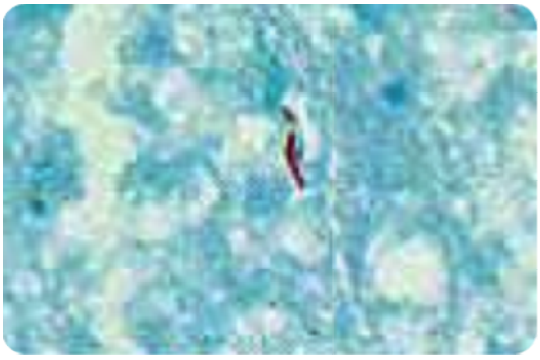

Fig.3: BT-Bacillary index 1 +

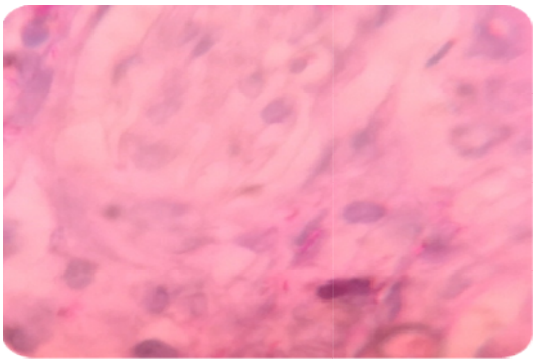

Fig.4: BB-Bacillary index 2 +

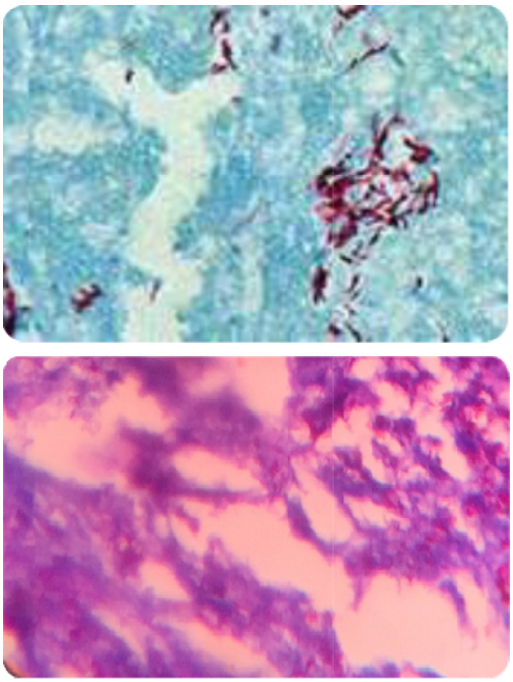

Fig 5 : BL- Bacillary index 3 +

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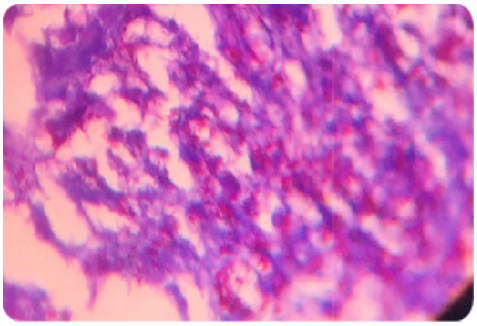

Fig 6 : BL – Bacillary index 4+

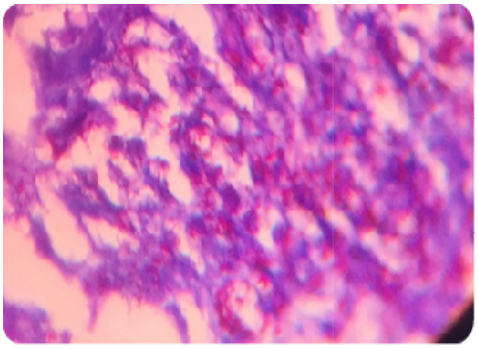

Fig 7 : Bacillary index 5 +

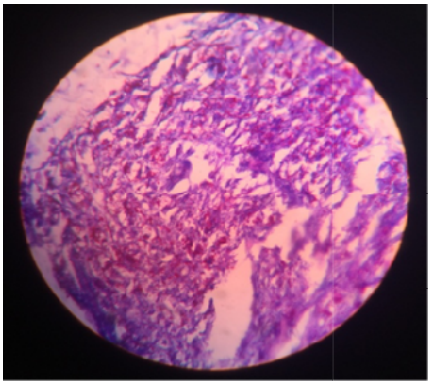

Fig 8 : Bacillary index 6+

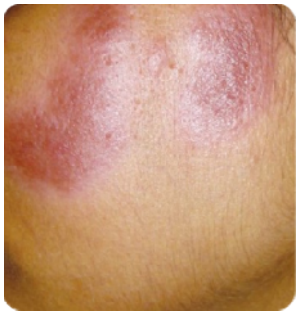

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Fig 9 : Well defined raised patches seen in Type 1 reaction

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Discussion:

Many years after elimination of leprosy has been achieved, the occurrence of reactions in leprosy patients continues to be a formidable challenge mainly owing to its role in causing nerve damage and disability. Because LR may occur months or even yearsafter MDT completion, related disabilities are expected to continue to occur even under the unlikely scenario of leprosy eradication. Cohort studies estimatethat disability in leprosy ranges from 16% to 56%,mainly attributable to the occurrence of reactional episodes. Even with adequate treatment, 40% ofpatients with T1LR may present with permanent nerve damage.[10] A recent study by van Brakel et al.,using nerve conduction studies and quantitative sensory testing, has demonstrated that individuals experiencing neuritis, NFI, or reactional episodes,either alone or in combination, have evidence of

subclinical neuropathy up to 12 weeks prior to clinically detectable changes.[11] This indicates that there is a potential for early diagnosis and intervention for prevention of clinically apparent nerve damage and deformity. In this context, it is pertinent to identify reliable laboratory tests to aid in the early diagnosisof leprosy reactions to monitor efficacy of treatment.[2]

Type I reaction is a naturally occurring delayed-type hypersensitivity response to M. leprae . Clinically, it is characterized by “upgrading” of the clinical picture towards the tuberculoid pole, including a reduction in bacillary load. Immunologically, it is characterized by the development of strong skin test reactivity as well as lymphocyte responsiveness and a predominant Th1 response.[3]

Type 1 have been associated with the infiltration of IFN-γ and TNF-secreting CD4+ lymphocytes in skin lesions and nerves, resulting in edema and painful inflammation.[4]

Pathogenesis of type II reaction is thought to be related to the deposition of immune complexes. [5]

In addition, C-reactive protein, amyloid A protein, and α -1 antitrypsin have also been reported to be elevated in ENL patients’ sera.[6]

A massive infiltrate of polymorphonuclear cells (PMN) in the lesions is only observed during ENL and some patients present with high numbers of neutrophils in the blood as well. Neutrophils may contribute to the bulk of TNF production that is associated with tissue damage in leprosy. More recently, microarray analysis demonstrated that the mechanism of neutrophil recruitment in ENL involves the enhanced expression of E-selectin and IL-1β, likely leading to neutrophil adhesion to endothelial cells again, an effect of thalidomide on PMN function was observed since this drug inhibited the neutrophil recruitment pathway .[7]

RR episodes (reversal reactions type 1) have been associated with the infiltration of IFN-γ and TNF-secreting CD4+ lymphocytes in skin lesions and nerves, resulting in edema and painful inflammation.[8]

Conclusion:

Type 2 lepra reaction, otherwise termed erythema nodosum leprosum, is an acute inflammatory reaction seen in patients with lepromatous leprosy or occasionally in borderline lepromatous leprosy. Rarely in severe type 2 leprosy reaction nodular lesions breakdown to form ulcers. This severe type 2 reaction with ulceration is called erythema necroticans.

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