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# **Paradoxical reaction in peripheral lymph node tuberculosis: a review for its prevalence, clinical characteristics, and possible treatment**

Deependra Kumar Rai,<sup>1</sup> Surya Kant,<sup>2</sup> Vatsal Bhushan Gupta<sup>1</sup>

<sup>1</sup>Department of Pulmonary Medicine, All India Institute of Medical Sciences, Patna

<sup>2</sup>Department of Respiratory Medicine, King George Medical University, Lucknow, India

Correspondence: Dr Vatsal Bhushan Gupta, Department of Pulmonary Medicine, All India Institute of Medical Sciences, Patna, Bihar, India, Phone No. +91 9953510274

Email id - [vatsalgupta.gkp@gmail.com](mailto:vatsalgupta.gkp@gmail.com)

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## **ABSTRACT**

The paradoxical reaction (PR) is a transient worsening following tuberculosis treatment and it is not uncommon in lymph node tuberculosis (LNTB). PR in LNTB maybe wrongly considered as treatment failure or relapse. This review was undertaken to address various aspects of PR associated with lymph node tuberculosis prevalence, underlying mechanism, clinical pattern, predictors, and possible treatment in an immunocompetent individual. A literature review was performed using various databases (PubMed, Scopus, Science Direct, and Google Scholar) to identify relevant articles for review. The prevalence of paradoxical reactions associated with LNTB varies from as low as 13.3% to as high as 35.3% PR may occur during antitubercular treatment or be reported even after completion of treatment called post-therapy PR. An onset of PR may occur within a month of therapy to even 12 months from the initiation of an anti-tubercular drug. Delayed hypersensitivity reaction and reduction in immune suppression is believed to be possible mechanism leading to a paradoxical reaction.

PR in LNTB is characterized by either progression of pre-existing nodal enlargement or formation of abscess, sinus formation, or appearance of new nodal enlargement or rarely extra-nodal involvement. PR is a diagnosis of exclusion and may show granuloma, positive AFB smear, or positive GeneXpert but AFB culture is always negative. Younger age, lymph node size of equal to or more than 3 cm, female gender, unilateral lymphadenopathy, and those with positive AFB on initial examination are predictors for PR in peripheral LNTB. The majority of PR in LNTB have a mild course and are generally self-limited.

**Key words:** paradoxical reaction, lymph node tuberculosis, surgical excision

## **Introduction**

A paradoxical reaction (PR) in patients with lymph node tuberculosis (LNTB) is defined by either the worsening of pre-existing tuberculous lesions or the appearance of new tuberculous lesions in patients who show initial improvement with anti-tuberculosis treatment [1]. In general, a paradoxical reaction refers to a substance's effect that is opposite to what is typically anticipated. PR is a transient worsening that occurs more commonly with neurological than lymph node TB and HIV-positive patients than HIV-negative patients [2]. But PR in lymph node TB is not uncommon in immunocompetent individuals [3,4]. Worsening of lymph node TB lesions may occur during or even after the completion of treatment, which is called post-therapy PR. PR during therapy was defined as the worsening of lymph node TB in patients who improved initially and received at least 2 weeks of anti-tubercular treatment. Post-therapy PR is defined as the worsening of lymph nodes after completion of anti-TB treatment, along with a sterile sample from worsened lymph nodes, and there should be spontaneous regression of TB lesions without further anti-TB therapy [5]. PR is a diagnosis of exclusion, and it is very important to rule out factors such as poor compliance, drug resistance, primary disease progression, or alternative diagnoses before labelling PR. The diagnostic approach to worsening lymph nodes following TB treatment is summarised in Figure 1.

This review was performed to address various aspects of PR associated with Lymph node tuberculosis like prevalence, underlying mechanism, clinical pattern, and possible treatment.

## **Methods**

A literature review was performed using different databases (PubMed, Scopus, Science Direct, and Google Scholar) to identify relevant articles published in English. The search included various combinations of terms like paradoxical reaction, lymph node tuberculosis, prevalence,

the pattern of PR, mechanism, HIV negative, immunocompetent, and treatment. We have included the original article, review article, case report, correspondence, etc. We reviewed here PR associated with peripheral lymph node tuberculosis in immunocompetent individuals. PR associated with pulmonary tuberculosis or other extrapulmonary tuberculosis was not included in the review. The authors independently reviewed the titles and abstracts for inclusion.

### **Prevalence**

Few studies have assessed the prevalence of paradoxical reactions associated with lymph node tuberculosis [4-9]. It varies from as low as 13.3% [8] to as high as 35.3% [9]. PR may occur during therapy antitubercular treatment or be reported even after completion of therapy called post-therapy PR. An onset of PR may occur within a month of therapy to even 12 months from the initiation of an anti-tubercular drug. Park *et al.* [5] prospectively analyzed 75 patients with LNTB and found that 8 (10.6%) patients developed PR during therapy and 18 (24%) patients after completion of therapy (Table 1). PR may occur on more than one occasion in patients reported by few studies [4,6].

### **Mechanism**

The exact mechanism for PR associated with tuberculosis infection is not known, but it is well-described when it occurs in a patient with HIV infection. Immune restitution is believed to be a possible mechanism leading to a paradoxical reaction [10]. PR during tuberculosis treatment is a well-known phenomenon first described by Chloremis in 1955 [11]. PR reactions are referred to as immune reconstitution inflammatory syndrome (IRIS) when it occurs in HIV-infected patients who have recently started on HAART (highly active anti-retroviral therapy) [12]. PR might reflect abnormal host immunologic reactions to antigens from dying *Mycobacterium tuberculosis* organisms. The paradoxical reaction, also called the Jarisch-Herxheimer reaction (JHR), occurs in patients receiving treatment for syphilis. It is self-limited in response to endotoxin released from dead bacteria, cytokines, and immune complexes [13]. It primarily occurs due to an exaggerated restoration of host immunity against live or dead pathogens that leads to an uncontrolled inflammatory response. But limited information is available on the underlying mechanism or risk factors for the PR of peripheral tuberculous lymphadenitis in HIV-uninfected patients. PR has been linked to host immunologic responses, with potential mechanisms including a delayed hypersensitivity reaction, a reduction in immunological suppression, or a response to mycobacterial antigens such tuberculoprotein or other cell wall components [14,15]. Presence of acid fast bacilli (AFB) on the initial diagnostic

aspirate smear on examination was associated with development of PR which could be due to hypersensitivity to persistent antigen [4,6]. Since these reactions occur even during delayed phase of treatment, it suggests antigenic stimulus may be poorly cleared from the disease site [6]. Vitamin D supplementation at baseline resulted in enhancement of toll like receptors signalling (TLR) leading to upgraded immune response [16]. Few studies observed that younger age, male gender, local tenderness of lymph nodes, and higher peripheral blood monocytes at baseline, might be predictive for the PR in HIV-negative patients with peripheral tuberculous lymphadenitis [4]. Possible explanation for its occurrence in younger age could be better immunologic status which decreases with advancing age [17]. One study reported the occurrence of PR in cases of unilateral lymphadenopathy [6]. It has also been observed that the majority of PR has been associated with raised inflammatory markers, tuberculin conversion during the treatment course, and the presence of disseminated infections [18].

### **Clinical patterns and predictors**

A paradoxical reaction in LNTB is characterized by either the progression of pre-existing nodal enlargement or the formation of an abscess, fistula, or sinus formation, the appearance of new nodal enlargement, or rarely extra-nodal involvement. The new nodal enlargement may be on the same site or a different site, ipsilateral or contralateral. Cervical LNTB may have a paradoxical reaction, such as axillary lymph node or inguinal lymph node enlargement. Enlargement of the primary lesion is the most common presentation of a paradoxical reaction, followed by new nodal enlargement or progression to the formation of an abscess, rupture, and sinus formation [6-9]. In a recent study by our group [9], out of 46 patients with PR, 14 patients had enlargement only, 16 had enlargement and rupture and 16 patients had new nodal enlargement. Rajendra *et al.* [7] found primary nodal enlargement, abscess, or sinus formation in 22 out of 32 patients with PR. Rarely does PR involve different organs than nodal involvement. Bhattacharya *et al.* [19] described the occurrence of pleural effusion as PR in LNTB. Another case report showed loss of vision and hearing as PR which occur due to progression in the size of tuberculoma [20]. Another study [21] showed uveitis as PR in LNTB following 2 months of anti-tubercular treatment for cervical LNTB. There is also described occurrence of PR as shoulder osteomyelitis following treatment of LNTB [22].

Several studies explored predictors of PR during TB treatment in HIV-infected patients on HAART [14,23,24], but limited studies for PR in HIV-negative patients with LNTB. Both Cho *et al.* [3] and Hawkey *et al.* [4] concluded that younger age, male gender, and local tenderness at the time of diagnosis could be a risk factor for PR in HIV-negative patients with LNTB.

Chahed *et al.* [8] found that lymph node size equal to or more than 3 cm and the presence of tuberculosis in another organ could be associated with the occurrence of PR. Batra *et al.* [6] showed that younger age, female gender, unilateral lymphadenopathy, and those with positive AFB on initial examination predictors for PR in peripheral LNTB. Extrapulmonary TB and lower baseline lymphocyte count could be risk factors for PR in HIV-negative patients with tuberculosis [15].

## **Treatment**

The majority of PR in LNTB have a mild course and it generally resolves on its own. Prior warning about the possibility of a paradoxical reaction may improve patient satisfaction and adherence to anti tubercular treatment (ATT) [4]. According to Index TB guidelines, deterioration in the first 3 months may be due to paradoxical reaction which does not require repeat diagnostic tests or change of treatment [25]. Steroids may be beneficial in the treatment of peripheral LNTB where they fasten resolution, and early symptomatic benefit but their role in PR is uncertain [26]. Initiation of steroids did not decrease the duration of PR in lymph node TB [4]. The value of steroid therapy in PR management has been found useful in intracranial tuberculoma and pleural tuberculosis [25]. The treatment options could be a simple observation, a short course of steroids, an aspiration, and/or a surgical excision of the lymph node [29]. Post therapy PR do not require further ATT as they are immunologically mediated rather than microbiological relapse [5]. Rajendra *et al.* [7] showed surgical excision was required in almost half of the patients, few patients had been given oral corticosteroids and pentoxifylline. In a study by Chahed *et al.* surgical approach was adopted in nearly 71.6% patients [8]. Simple aspiration of the enlarged lymph nodes is an important strategy in the treatment of PR as it reduced the unwanted side effects of steroids [4,30,31]. It shorten the duration of TB treatment and improve the healing processes [8]. Anti-TNF alpha inhibitor (Infliximab) has been evaluated for PR and found useful in the resolution of symptoms of PR by inhibiting granuloma formation interfering with the penetration of TB treatment [8,32]. The definite role of corticosteroid or any other therapy can only be established after a randomised placebo controlled trial.

## **Conclusions**

PR in lymph node tuberculosis may occur during therapy, where it mimics treatment failure, and can occur after therapy, where it mimics relapse. PR is a diagnosis of exclusion and may show granuloma, positive AFB smear, or positive GeneXpert but AFB culture is always

negative. So always get AFB culture to differentiate from treatment failure of relapse. The majority of PR in LNTB have a mild course, self-limited and limited role of corticosteroids.

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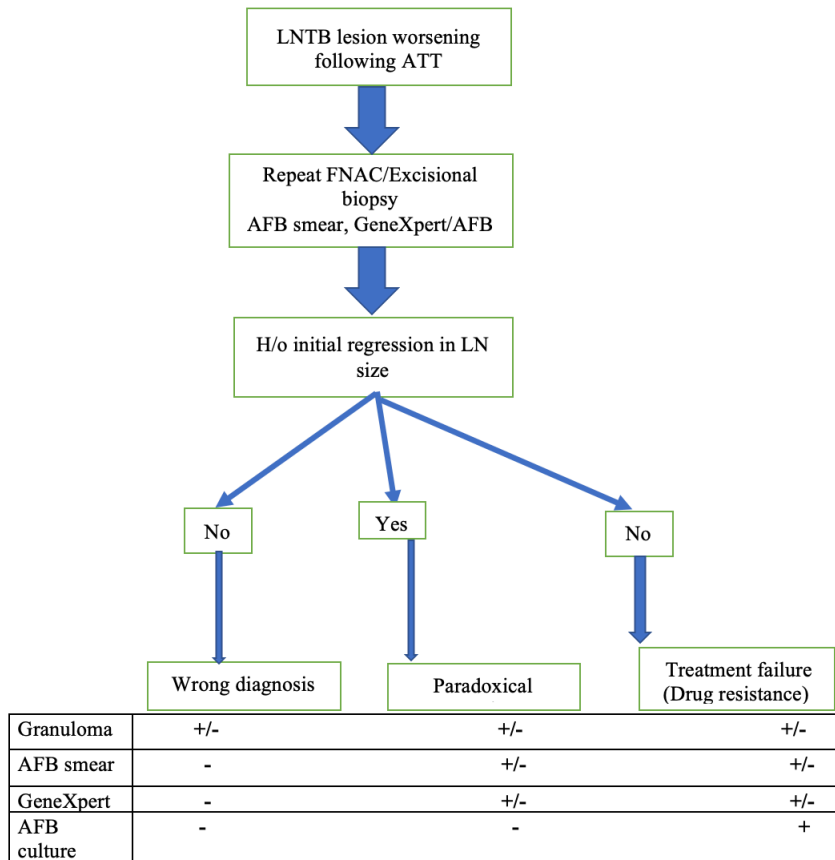


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Table 1. Summary of various studies that assessed the incidence of PR.

Authors	Country/Year	Sample size	Incidence (%)	Onset time (months)	Total PR event/ patients with PR	Primary node worsening (%)	New node (%)	Sinus formation (%)
Batra <i>et al.</i> [6]	India / 2017	110	25	1.5 (0.5-03)	32/28	79	29	7
Rajendra <i>et al.</i> [7]	India / 2016	124	29.03	-		-	-	
Hawkey <i>et al.</i> [4]	South Africa / 2005	109	23	1.5 (1-5)	27/25	68	36	12
Park <i>et al.</i> [5]	Korea / 2010	75	34.6	3 (1-13)	-	57.6	23	50
Chahed <i>et al.</i> [8]	Tunisia / 2016	501	13.4	7(4-9)		44.8	32.8	6
Rai <i>et al.</i> [9]	India /2020	130	35.3	2	-	30.4	34.7	34.7

Figure 1. Diagnostic algorithm for worsening lymph node after initiation of anti-tubercular treatment.



+ means positive, - means negative