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

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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 may be wrongly considered as treatment failure or relapse. This review was undertaken to address various aspects of PR associated with LNTB prevalence, underlying mechanisms, clinical patterns, 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 PR 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 are believed to be possible mechanisms leading to a PR. 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 acid-fast bacilli (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.

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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 (TB) treatment [1]. In general, a PR 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 LNTB and HIV-positive patients than HIV-negative patients [2]. However, PR in LNTB is not uncommon in immunocompetent individuals [3,4]. Worsening of LNTB 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 LNTB in patients who improved initially and received at least 2 weeks of anti-tubercular treatment (ATT). 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 ATT 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 labeling PR. The diagnostic approach to worsening lymph nodes following TB treatment is summarized in Figure 1.

This review was performed to address various aspects of PR associated with LNTB like prevalence, underlying mechanisms, clinical patterns, and possible treatment.

Methods

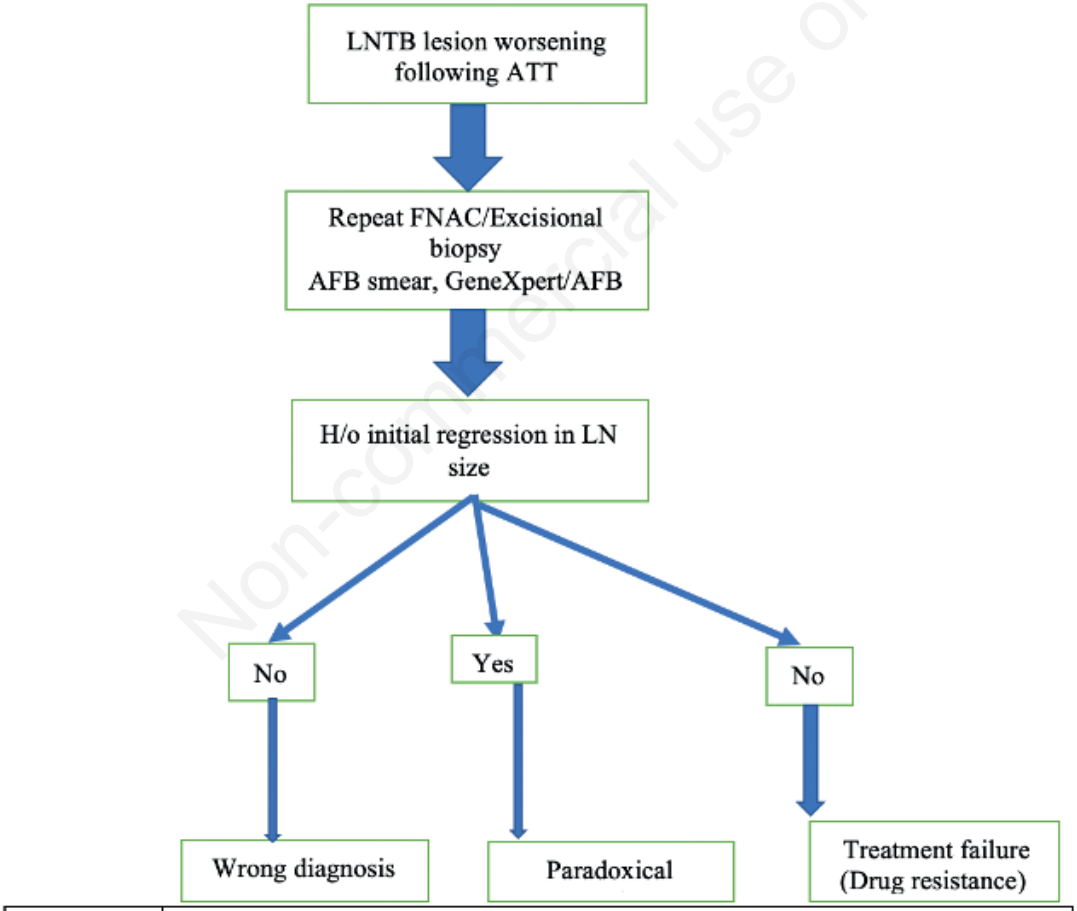
A literature review was performed using different databases (PubMed, Scopus, Science Direct, and Google Scholar) to identify relevant articles published in English. The search included various combinations of terms like paradoxical reaction, lymph node tuberculosis, prevalence, the pattern of paradoxical reaction, mechanism, HIV negative, immunocompetent, and treatment. We have included original articles, review articles, case reports, correspondence, *etc*. We reviewed here PR associated with peripheral LNTB in immunocompetent individuals. PR associated with pulmonary TB or other extrapulmonary TB was not included in the review. The authors independently reviewed the titles and abstracts for inclusion.

Prevalence

Few studies have assessed the prevalence of PR associated with LNTB [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-TB drug. Park *et al*. 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) [5]. PR may occur on more than one occasion in patients reported by few studies [4,6].

Mechanism

The exact mechanism for PR associated with TB infection is not known, but it is well described when it occurs in a patient with



Granuloma	+/-	+/-	+/-
AFB smear	-	+/-	+/-
GeneXpert	-	+/-	+/-
AFB culture	-	-	+

Figure 1. Diagnostic algorithm for worsening lymph node after initiation of anti-tubercular treatment. + means positive, - means negative. ATT, anti-tubercular treatment; FNAC, fine needle aspiration cytology; AFB, acid-fast bacilli; LN, lymph node.

HIV infection. Immune restitution is believed to be a possible mechanism leading to a PR [10]. PR during TB treatment is a well-known phenomenon first described by Chloremis in 1955 [11]. PR is referred to as immune reconstitution inflammatory syndrome when it occurs in HIV-infected patients who have recently started on highly active anti-retroviral therapy (HAART) [12]. PR might reflect abnormal host immunologic reactions to antigens from dying *Mycobacterium tuberculosis* organisms. PR, also called the Jarisch-Herxheimer reaction, 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. However, 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 as tuberculoprotein or other cell wall components [14,15]. The presence of acid-fast bacilli (AFB) on the initial diagnostic aspirate smear on examination was associated with the development of PR, which could be due to hypersensitivity to persistent antigens [4,6]. Since these reactions occur even during the delayed phase of treatment, it suggests antigenic stimulus may be poorly cleared from the disease site [6]. Vitamin D supplementation at baseline resulted in the enhancement of toll-like receptor signalling, leading to an 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 PR in HIV-negative patients with peripheral tuberculous lymphadenitis [4]. A possible explanation for its occurrence at a 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 PR 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 PR, such as axillary lymph node or inguinal lymph node enlargement. Enlargement of the primary lesion is the most common presentation of a PR, 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 had enlargement only, 16 had enlargement and rupture, and 16 had new nodal enlargement. Rajendra *et al*. found primary nodal enlargement, abscess, or sinus formation in 22 out of 32 patients with PR [7]. Rarely does PR involve different organs than nodal involvement. Bhattacharya *et al*. described the occurrence of pleural effusion as PR in LNTB [19]. Another case report showed loss of vision and hearing as PR, which occured due to progression in the size of tuberculoma [20]. Another study [21] showed uveitis as PR in LNTB following 2 months of ATT for cervical LNTB. There is also a 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 there are limited studies for PR in HIV-negative patients with LNTB. Both Cho *et al.* and Hawkey *et al.* concluded that younger age, male gender, and local tenderness at the time of diagnosis could be risk factors for PR in HIV-negative patients with LNTB [3,4]. Chahed *et al.* found that lymph node size equal to or more than 3 cm and the presence of TB in another organ could be associated with the occurrence of PR [8]. Batra *et al.* showed that younger age, female gender, unilateral lymphadenopathy, and those with positive AFB on initial examination are predictors for PR in peripheral LNTB [6]. Extrapulmonary TB and lower baseline lymphocyte count could be risk factors for PR in HIV-negative patients with TB [15].

Treatment

The majority of PR in LNTB has a mild course, and it generally resolves on its own. Prior warning about the possibility of a PR may improve patient satisfaction and adherence to ATT [4]. According to index TB guidelines, deterioration in the first 3 months may be due to PR, 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 TB [25]. The treatment options could be a simple observation, a short

Table 1. Summary of various studies that assessed the incidence of paradoxical reactions.

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

PR, paradoxical reaction.

course of steroids, an aspiration, and/or a surgical excision of the lymph node [27-29]. Post-therapy PR does not require further ATT as it is immunologically mediated rather than microbiologically relapsed [5].

Rajendra *et al.* showed surgical excision was required in almost half of the patients; few patients had been given oral corticosteroids and pentoxifylline [7]. In a study by Chahed *et al.*, a surgical approach was adopted in nearly 71.6% of patients [8]. Simple aspiration of the enlarged lymph nodes is an important strategy in the treatment of PR, as it reduces the unwanted side effects of steroids [4,30,31]. It shortens the duration of TB treatment and improves the healing processes [8]. Anti-tumor necrosis factor-α inhibitor (infliximab) has been evaluated for PR and found useful in the resolution of symptoms of PR by inhibiting granuloma formation and interfering with the penetration of TB treatment [8,32]. The definite role of corticosteroids or any other therapy can only be established after a randomized placebo-controlled trial.

Conclusions

PR in LNTB may occur during therapy, where it mimics treatment failure, and it 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, it is important to always get an 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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