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Paradoxical Reaction in Tuberculous Meningitis: Clinical Insight and Management, a Literature Review

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Abstract: Tuberculous meningitis (TBM) is a type of TB with the most severe clinical symptoms of extrapulmonary tuberculosis, with high mortality and neurological morbidity rates. Paradoxical reaction (PR) are clinical symptoms characterized by the worsening of existing tuberculosis lesions or the emergence of new lesions despite receiving appropriate antituberculosis therapy (ATT), often leading to diagnostic confusion and management challenges for patients. This study aims to explain the definition, epidemiology, mechanism, clinical manifestations, diagnosis, and management of PR in TBM, based on various literature reviews. This study is a literature review using basic data from databases such as Google Scholar, PubMed, ScienceDirect, EuroPMC, and Cochrane Library, collecting relevant studies from 2015 to 2025. The main findings show that PR is triggered by complex immune mechanisms, often involving an excessive inflammatory response to mycobacterial antigens and known as Immune Reconstitution Inflammatory Syndrome (IRIS) in HIV patients. Paradoxical reaction (PR) presents with varying clinical symptoms, including fever, headache, impaired consciousness, as well as hydrocephalus and tuberculoma on radiological examination. Therefore, clear clinical guidelines are needed to optimize the diagnosis and management of PR in TBM.

Keywords: Tuberculous meningitis, paradoxical reaction, IRIS

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Introduction

Tuberculosis (TB) is an infectious disease that is the leading cause of death worldwide.(Chandrasiri, 2025; Ishikawa & Mori, 2025; Singh et al., 2016) In 2022, approximately 10 million people were infected with TB, and of these, approximately 1.3 million deaths were caused by infectious diseases, second only to COVID-19.(Ishikawa & Mori, 2025). Tuberculous meningitis (TBM) is the most severe form of extrapulmonary TB, with high mortality and significant neurological morbidity. Although Central Nervous System (CNS) TB is relatively rare, representing about 1% of all TB cases, TBM and intracranial tuberculoma account for about 3.67% and 0.52% of TB cases, with reported mortality rates ranging from 20% to over 40% in some cohort studies.(Chandrasiri, 2025; Ishikawa & Mori, 2025; Perera, 2023; Singh et al., 2016)

The most challenging aspect of treating TBM is the occurrence of PR. Paradoxical reaction (PR) is a symptom characterized by the worsening of pre-existing tuberculosis lesions or the appearance of new lesions, even though the patient has shown initial clinical improvement and has received appropriate antituberculosis therapy (ATT) for at least 10 days.(Chandrasiri, 2025; Ishikawa & Mori, 2025; Perera, 2023; Singh et al., 2016)This reaction is referred to as a

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complication caused by an excessive immune response to residual mycobacterial antigens. 1,2, 5 In HIV-positive patients, this phenomenon is specifically called Immune Reconstitution Inflammatory Syndrome (IRIS), which occurs after the initiation of antiretroviral therapy (ART).2–4,6 However, PR are also common in HIV-negative patients with TBM.(Ishikawa & Mori, 2025; Liu et al., 2019)

Distinguishing the clinical symptoms of PR from complications caused by other diseases is a difficult diagnostic challenge. The worsening of clinical symptoms in PR can resemble drug resistance, treatment failure, or other diagnoses, such as new infections, drug toxicity, or even cancer. This diagnostic uncertainty can lead to misdiagnosis and inappropriate changes in ATT regimens. Given this complexity, this review aims to provide current insights into the definition, epidemiology, underlying mechanisms, diverse clinical manifestations, diagnostic approaches, and management strategies for PR in TBM. The primary objective is to enhance clinicians' understanding of this phenomenon and evaluate new treatments to improve treatment outcomes in PR cases.(Chandrasiri, 2025; Gooding et al., 2024; Ishikawa & Mori, 2025; Liu et al., 2019; Perera, 2023; Singh et al., 2016)

Definition of Paradoxical Reaction (PR)

Paradoxical reaction (PR) is worsening clinical symptoms due to existing tuberculosis lesions or the appearance of new lesions in patients who have received appropriate antituberculosis therapy (ATT) and have shown clinical improvement, usually occurring after at least 10 days of treatment.(Chandrasiri, 2025; Ishikawa & Mori, 2025; Singh et al., 2016) This can manifest clinically, radiologically, or in cerebrospinal fluid (CSF) parameters.(Liu et al., 2019; Perera, 2023; Singh et al., 2016) These clinical symptoms are mediated by the immune system's excessive inflammatory response to mycobacterial antigens released by dead bacteria. These symptoms can confuse the diagnosis of whether it is a treatment failure or drug resistance. In patients with HIV, this similar reaction is known as Immune Reconstitution Inflammatory Syndrome (IRIS).(Chandrasiri, 2025; Gooding et al., 2024)

Epidemiology

A prospective cohort study showed that approximately one-third of TBM patients (31.2%) experienced PR, a higher rate than other types of TB such as pulmonary TB or lymph node TB. Several studies also show higher incidence in certain subpopulations, for example, 52% in HIV-negative TBM patients with vertebral bone disorders and up to 56% in other cohort studies on TBM.(Chandrasiri, 2025; Liu et al., 2019; Singh et al., 2016)

The time of occurrence of PR varies among patients, although most symptoms appear within the first three months after antituberculosis therapy (ATT) begins. The time to onset of clinical symptoms ranges from 30 to 37 days, with a wide range from 15 to 330 days, while central nervous system tuberculosis tends to have a longer time to onset of approximately 63 days. Cases that emerged long after treatment, approximately ten years later, have also been reported. Additionally, RP can recur, with an incidence rate of up to 30% in HIV-negative patients, indicating that this complication requires long-term monitoring and appropriate treatment management.(Chandrasiri, 2025; Liu et al., 2019; Machida et al., 2018; Singh et al., 2016)

Risk Factors

There are several risk factors that can cause PR, including host factors, disease characteristics, and treatment factors. Host factors can include female gender, concurrent HIV infection, and young age (especially under 40 years) as significant predictors. Low lymphocyte counts in HIV-negative patients have also been reported as a major risk factor. Furthermore, a shorter disease onset time before starting treatment and vertebral involvement in patients also contribute to a higher risk. In addition, low-dose antituberculosis drugs (e.g., rifampin) at the start of treatment can increase the occurrence of PR. (Liu et al., 2019; Singh et al., 2016)

Pathophysiology

The pathogenesis of PR is mediated by a complex immune response. This theory explains that the rapid killing of bacteria by antituberculosis drugs can trigger an excessive inflammatory reaction due to the mass release of microbial antigens. This is also supported by the "immunological paradox," in which mycobacterial-specific T cell activity increases significantly even though the patient initially reported clinical improvement.(Chandrasiri, 2025) The main mechanisms include the following:

• T Cell Activation: CD4+ Th1 T cells play a major role. When a PR occurs, there is an increase in the number of activated T cells (HLA-DR+CD38+) in the cerebrospinal fluid (CSF), as well as a multifunctional cytokine response to the TB antigen.(Chandrasiri, 2025; Gooding et al., 2024)

• Cytokine Release: The inflammatory chain is triggered by pro-inflammatory cytokines. Tumor necrosis factor alpha (TNF-α) is a mediator whose excessive production can aggravate the disease. Levels of other cytokines such as interferon-gamma (IFN-γ), IL-6, and IL-8 also increase in CSF during a PR.(Chandrasiri, 2025; Marais et al., 2021)

• Immune Recovery: The initiation of antituberculosis therapy (ATT) causes an irregular and excessive inflammatory response, a mechanism considered similar to IRIS triggered by antiretrovirals.(Chandrasiri, 2025; Perera, 2023)

Diagnosis

Paradoxical reaction (PR) are an exclusionary diagnosis, due to the lack of rapid and accurate diagnostic tests or biomarkers. The challenge lies in distinguishing PR from treatment failure, drug resistance, or other diagnoses such as new infections, drug toxicity, or malignancy. A case suspected to be a PR was reported to be multidrug-resistant tuberculosis, which highlights the need for heightened vigilance in establishing an accurate diagnosis.(Gooding et al., 2024; Liu et al., 2019; Siahaan et al., 2022; Singh et al., 2016)

The following are several things that need to be considered in establishing a PR in patients with TB meningitis, namely: (Chandrasiri, 2025; Gooding et al., 2024; Singh et al., 2016)

1. Improvement in clinical condition at the start of appropriate anti-tuberculosis drug treatment.
2. Worsening of clinical symptoms or radiological findings, either in existing lesions or the emergence of new TB lesions.
3. Exclusion of other factors that may reduce the effectiveness of ATT (e.g., drug resistance, non-compliance).
4. Absence of other possible causes leading to clinical deterioration.

Supporting Tests

Supporting tests performed include neuroimaging (MRI/CT): These tests can reveal the presence of new tuberculomas or the spread of existing lesions, hydrocephalus, increased basal exudate, infarction, and optic arachnoiditis (SAHARA et al., 2024; Singh et al., 2016). Additionally, cerebrospinal fluid (CSF) analysis is required: CSF shows an increase in cell count and/or protein levels. The pattern of change is a shift from lymphocytic dominance to polymorphonuclear dominance. (Ishikawa & Mori, 2025; Singh et al., 2016) Potential biomarkers are also needed, as they serve to identify increased levels of interferon-gamma (IFN-γ) and ferritin in plasma. CSF findings indicate increased T cell activation and inflammatory biomarkers such as IL-6, IL-8, IFN-γ, and TNF-α during the PR. However, these tests are not yet routine diagnostic tests. (Chandrasiri, 2025; Gooding et al., 2024)

Management and Treatment

Currently, there are no official guidelines for treating patients experiencing PR.(Perera, 2023) The following are some important points in providing therapy to patients suspected of experiencing PR:

1. Anti-tuberculosis therapy (ATT). The main thing to note is to continue administering the ATT regimen without changing the dosage. This is considered because RP is not a treatment failure, but it is also necessary to rule out a diagnosis of drug resistance in these patients.(Perera, 2023; Siahaan et al., 2022)
2. High-dose corticosteroids are the treatment of choice for managing the inflammatory response in PR. Treatment typically involves intravenous dexamethasone followed by gradual tapering of the oral dose. However, a randomized controlled trial has shown that some patients are resistant to steroids. Long-term steroid use can also lead to osteopenia, uncontrolled diabetes, and hypertension.(Chandrasiri, 2025; Perera, 2023; Singh et al., 2016)
3. Surgical intervention may be performed if complications such as hydrocephalus are present. Procedures such as ventriculoperitoneal shunting (VP) or external ventricular drainage (EVD) can reduce intracranial pressure and improve survival rates.(Ishikawa & Mori, 2025; Siahaan et al., 2022)
4. New immunomodulators have been used as immunomodulatory agents for patients with severe PR who do not respond to steroid treatment. Administration of TNF-α antagonists (e.g., Infliximab) has shown improvement in clinical and radiological conditions in patients with severe cases. Thalidomide has also shown clinical improvement in children with central nervous system TB, and other agents such as cyclophosphamide and intrathecal hyaluronidase are also being studied for the treatment of drug-resistant arachnoiditis.(Donovan et al., 2021; Husic et al., 2024; Marais et al., 2021)

Materials and Methods

This research will talk about the PR in TB meningitis, including clinical insights and management. This study is a literature review using basic data from databases such as Google Scholar, PubMed, ScienceDirect, EuroPMC, and Cochrane Library, collecting relevant studies from 2015 to 2025. Articles were selected based on the following inclusion criteria which were studies discussing PR in tuberculosis meningitis in both HIV and non-HIV populations, publications available in full-text PDF format, open access, and written in English. Exclusion criteria were articles published before 2015, literature not in English, sources without free full-text access, as well as duplicates, editorials, conference abstracts, and opinion articles that did not have primary data or comprehensive reviews. All studies were filtered for relevance by examining the title, abstract, and full text. Data from eligible articles were then extracted and synthesized

narratively, focusing on definitions, pathophysiological mechanisms, clinical features, diagnostic approaches, and management strategies for PR in TBM.

Result and Discussion

Clinical Manifestations

Paradoxical reaction (PR) in patients are characterized by a wide variety of clinical symptoms and radiological findings, resulting in significant neurological dysfunction.(Chandrasiri, 2025; Singh et al., 2016)

Neurological Deterioration

The clinical symptoms commonly experienced by patients are fever, headache, impaired consciousness, decreased vision, and seizures. This was demonstrated in a study in which 44 patients experienced PR with symptoms of fever, headache, impaired consciousness, decreased vision, and seizures. Other neurological deficits that often occur are hemiparesis due to new infarcts.(Chandrasiri, 2025; Siahaan et al., 2022; Singh et al., 2016) Meanwhile, cranial nerve weakness often occurs due to inflammation of the leptomeningeal. In another research study, it was reported that patients experienced decreased vision and clinical symptoms consistent with weakness of the third and sixth cranial nerves on the left side. Recurrent attacks with clinical manifestations of fever, decreased vision, and headache occurred after a reduction in the dose of corticosteroids.(Donovan et al., 2021; Gooding et al., 2024)

New Intracranial Lesions (Tuberculoma, Abscess, Hydrocephalus)

Paradoxical reaction (PR) often cause new lesions to appear or existing lesions to spread. The most common manifestation is hydrocephalus. In one study, 20 patients were reported to have newly identified hydrocephalus and 7 patients had ventricular enlargement. In addition, tuberculoma was also reported in 26 patients (59%), with 15 patients having new manifestations of tuberculoma. Other clinical manifestations include optochiasmatic arachnoiditis, which occurred in 12 patients in one cohort. Furthermore, spinal arachnoiditis was experienced by 4 patients. These lesions can also cause conditions such as brain abscesses and complications in the spinal cord, namely myeloradiculopathy and spinal epidural abscesses. (Chandrasiri, 2025; Singh et al., 2016)

Characteristic Neuroimaging Findings

Neuroimaging such as MRI and CT scans are the gold standard for identifying a PR in patients with TB meningitis. Typical findings include clear basal exudate, expansion of existing tuberculomas, expansion of infarcts, and increased ventriculomegaly.(Chandrasiri, 2025; Singh et al., 2016) Meanwhile, optochiasmatic arachnoiditis shows thickened lesions in specific cisterns such as the interpeduncular, pontine, perimesencephalic, and suprasellar fossae. In spinal TB, MRI shows spinal arachnoiditis or tuberculoma, characterized by nerve root clumping and vertebral bone involvement. In addition to radiological findings, cerebrospinal fluid also shows characteristic findings in the form of increased cells and/or protein levels. Shift to dominance, increased CSF pleocytosis, increased protein levels, and decreased glucose concentration.(Chandrasiri, 2025; Donovan et al., 2021)

Diagnosis

Difficulties in diagnosing PR pose a significant challenge because they are difficult to distinguish from the clinical symptoms of other complications.

Challenges in Differentiating PR from Relapse/Drug Resistance

Knowledge and awareness of PR in TBM patients are very important because they can lead to misdiagnosis and incorrect treatment of patients. This is because the clinical symptoms can resemble drug resistance, treatment failure, or other diagnoses. For example, a patient who appears to be experiencing a PR may actually be suffering from multidrug-resistant tuberculosis. There are no rapid diagnostic tests or biomarkers for PR. This uncertainty is also influenced by the time required for TB cultures to grow and the difficulty of growing extrapulmonary TB, which can make it difficult to rule out the possibility of treatment failure. Clinical deterioration can also be misinterpreted as a relapse of the disease. Clinicians must consider drug toxicity, new infections, or unrelated causes as differential diagnoses to establish a PR.(Gooding et al., 2024; Siahaan et al., 2022; Singh et al., 2016)

Role of Imaging and Potential Biomarkers

Neuroimaging such as CT scans and MRIs are very important in confirming a PR and monitoring its development, especially in cisternal tuberculoma. Repeated CT scans or MRIs are performed at specific times or when clinical symptoms worsen. Regarding biomarkers, a study reported higher levels of interferon-gamma (IFN-γ) and ferritin in the plasma of patients with PR compared to the control group in the study. In cerebrospinal fluid (CSF), T cell activation with increased inflammatory biomarkers (including IL-6, IL-8, IFN-γ, MIG, TNF-α, and IL-10) was reported during the recurrence of PR. However, these findings are only

preliminary research and have not yet been applied to routine diagnosis. (Donovan et al., 2021; Gooding et al., 2024; SAHARA et al., 2024)

Management

Management of treatment in patients with PR requires a combination of antituberculosis drugs, corticosteroids, and surgical procedures or immunomodulators currently under development.

Continuation of Anti-Tuberculosis Treatment (ATT)

Although PR do not require discontinuation or dose adjustment of ATT, the cause of drug resistance must first be eliminated. A study has shown that prolonging the duration of treatment or increasing the dose of the drug does not reduce the risk of PR, as these symptoms occur due to an excessive inflammatory response to dead bacteria mediated by the immune system.(Chandrasiri, 2025; Ishikawa & Mori, 2025; Siahaan et al., 2022)

Corticosteroids: Evidence, Dose, and Duration

The use of high-dose corticosteroids remains the standard of care in the management of patients with PR to TBM, which serve to reduce the inflammatory response.(Chandrasiri, 2025)

• Dosage and Duration: The standard regimen uses intravenous dexamethasone for 4 weeks (0.4 mg/kg/day, gradually reduced by 0.1 mg/kg each week) followed by oral corticosteroids for an additional 4 weeks (starting with a dose of 4 mg/day, reduced by 1 mg/week). Another case report states that the intravenous dexamethasone dose used was 20 mg. In patients experiencing a long-onset PR, oral prednisolone (30 mg/day, 0.6 mg/kg/day) was administered, with the dose gradually tapered over 1 year. In severe cases, patients will require long-term corticosteroid treatment; case studies report that medication administration may last for more than 5 years.(Chandrasiri, 2025; Gooding et al., 2024; Singh et al., 2016)

• Evidence and Effectiveness: Although corticosteroids have been used as standard treatment in the management of patients with TB meningitis who experience PR, there have been no specific RCT studies supporting the effectiveness of steroid use. One study reported that clinical deterioration continued despite patients being given high doses of corticosteroids. However, approximately 50% of patients with TB SSP experienced clinical improvement after receiving steroids, and a small proportion of patients with severe symptoms were resistant to corticosteroids.(Chandrasiri, 2025; Husic et al., 2024; Machida et al., 2018)

Surgical Interventions

Surgical interventions such as shunt placement are necessary to treat complications such as hydrocephalus. The type of surgical procedure involving ventriculoperitoneal (VP) shunt placement is a surgical procedure used to reduce intracranial pressure. Other options include external ventricular drainage (EVD) and endoscopic third ventriculostomy (ETV). (Ishikawa & Mori, 2025; Siahaan et al., 2022). Emergency ventriculoperitoneal shunting is indicated in patients who experience acute loss of consciousness and hemiparesis due to hydrocephalus and granuloma. EVD is performed in patients with recurrent PR and non-communicating hydrocephalus. Early VP shunting is highly recommended for patients with non-communicating hydrocephalus and patients with communicating hydrocephalus who do not respond to treatment. However, this procedure still carries risks of infection and bleeding. (Ishikawa & Mori, 2025; Siahaan et al., 2022)

Immunomodulators (Thalidomide, Infliximab)

Immunomodulatory therapy is an alternative for patients with severe symptoms that are resistant to corticosteroids, although clinical evidence is still limited. TNF-α antagonists (Infliximab, Adalimumab) showed good efficacy when first used in 2008, as described in case reports illustrating their effectiveness. This medication is typically a last resort when no other options are available, with a typical dose of 5 mg/kg per month. Infliximab can cross the blood-brain barrier at the meningeal layer. Adalimumab has also been shown to be effective in patients with PR. Therefore, this drug is expected to reduce the long-term use of steroids. However, its use is still off-label and requires strong clinical evidence and institutional approval. (Husic et al., 2024; Marais et al., 2021). In addition, low-dose anti-TNF-α thalidomide showed clinical improvement and neuroimaging findings in children with complex CNS TB. However, high-dose thalidomide RCT studies were discontinued due to side effects and deaths, making this dose unsuitable for patients. Common side effects include rash, peripheral neuropathy, and excessive drowsiness. (Chandrasiri, 2025). Other immunomodulators include cyclophosphamide. It is an immunosuppressive agent that has been proven effective in the management of treatment-resistant SSP arachnoiditis in ongoing randomized controlled trials (RCTs). Intrathecal hyaluronidase (ITH) has also been shown to be effective in the treatment of patients with optochiasmatic and spinal arachnoiditis. Aspirin and interleukin-1 inhibitors are currently undergoing clinical trials. (Chandrasiri, 2025; Ishikawa & Mori, 2025)

Clinical Implications

Importance of Clinician Awareness

Establishing a diagnosis and managing PR in patients with TB meningitis requires expertise and awareness on the part of clinicians that these clinical symptoms are PR. Symptoms to watch out for include headache, nausea, and vomiting during the treatment phase to avoid misdiagnosis such as treatment failure or drug resistance. Paroxysmal sympathetic hyperactivity also needs to be recognized early to reduce the risk of long-term disability.(Ishikawa & Mori, 2025; Siahaan et al., 2022; Singh et al., 2016)

Prognostic Impact of Reaction Paradoxical in TBM Patients

In general, PR do not have a significant effect on the prognosis and disability of patients with TB meningitis. This is evidenced by a study which found that there was no significant difference between the proportion of patients with disability and mortality in the group of patients who experienced PR and those who did not. However, patients with PR require higher treatment and hospitalization costs. Although not significantly affecting prognosis, severe symptoms can cause severe neurological symptoms and even death. Long-term use of corticosteroids can also cause side effects such as diabetes mellitus, hypertension, osteopenia, weight gain, and oral candidiasis.(Donovan et al., 2021; Gooding et al., 2024; Liu et al., 2019; Singh et al., 2016)

Conclusion

Paradoxical reaction (PR) is a problem that needs to be recognized in patients with TBM, as they are experienced by one-third of TBM patients. Several studies report that PR can be 52%–56% higher when accompanied by vertebral involvement. This poses a challenge in diagnosing and providing effective treatment to patients. Worsening radiological findings can even be misinterpreted as a new infection, drug toxicity, cancer, or treatment failure. This can cause confusion in diagnosis and in prescribing the appropriate antituberculosis drugs. Severe symptoms can cause serious neurological deficits that can increase disability and mortality, as well as increase treatment and hospitalization costs.

Therefore, it is essential for medical professionals to make an accurate diagnosis and be alert to symptoms such as nausea, vomiting, fever, and headache during the treatment of patients with TB meningitis. Neuroimaging such as MRI and CT scans are essential to monitor the spread of lesions or the appearance of new lesions. Characteristic findings in cerebrospinal fluid are also frequently observed, such as an increase in cell count, protein levels, and a shift toward more polymorphonuclear cells. Treatment consists of administering high doses of corticosteroids to reduce inflammation while continuing antituberculosis therapy. Steroids are very helpful in severe cases of TB meningitis, but long-term use can also cause side effects such as osteopenia and diabetes. In patients with hydrocephalus, surgical interventions such as ventriculoperitoneal shunting (VP), external ventricular drainage (EVD), or endoscopic third ventriculostomy (ETV) are often required.

Furthermore, additional research is essential to determine the optimal treatment standards for patients with TB meningitis. This is because there are currently no specific guidelines for patients with TB meningitis who experience worsening PR. In addition, strong evidence from RCT studies supporting the effectiveness of corticosteroids in treating PR remains limited, and there is no clear optimal dosage or duration for corticosteroids and immunomodulators. Further research on the immunopathology of PR, as well as large-scale clinical trials to generate strong evidence, is crucial for developing effective guidelines. This will lead to improved treatment for TB meningitis patients experiencing these complex PR.

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