

Paradoxical reaction associated with cervical lymph node tuberculosis: predictive factors and therapeutic management



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SUMMARY

Objectives: The aims of this study were to determine predictive factors of paradoxical reaction in patients with cervical lymph node tuberculosis (TB) and to discuss the therapeutic management of this condition. **Materials and methods:** A retrospective study was performed of 501 patients managed for cervical lymph node TB over a period of 12 years (from January 2000 to December 2011). Statistical data were analyzed using IBM SPSS Statistics version 20.0.

Results: Paradoxical reaction occurred in 67 patients (13.4%), with a median delay to onset after starting TB treatment of 7 months. Lymph node size ≥ 3 cm and associated extra-lymph node TB were independently associated with paradoxical reaction. Treatment consisted of surgical excision (71.6%), restarting quadruple therapy (10.4%), reintroduction of ethambutol (23.8%), and addition of ciprofloxacin (20.8%); steroids were given in two cases. All patients recovered after an average treatment duration of 14.91 ± 7.03 months.

Conclusion: The occurrence of paradoxical reaction in cervical lymph node TB seems to be predicted by associated extra-lymph node TB and a swelling size ≥ 3 cm. The treatment of paradoxical reaction remains unclear and more randomized trials are necessary to improve its management.

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1. Introduction

Paradoxical reaction (PR) during tuberculosis (TB) treatment is defined as a transient worsening of pre-existing clinical and/or radiological lesions, or as the formation of a new tuberculous location, during appropriate treatment that is being taken correctly.¹ It occurs in about 20% of patients, with an average delay to onset of 2 to 3.5 months after the initiation of TB treatment.² The delay to occurrence is unpredictable, as are its duration and severity.

Limited information is available regarding the risk factors of PR associated with peripheral cervical lymph node TB and controversy remains about its therapeutic management. The aims of this study were to determine the predictive factors of PR in patients with cervical lymph node TB and to discuss the therapeutic approaches.

2. Materials and methods

This was a retrospective study involving 501 patients diagnosed with cervical lymph node TB at Rabta Hospital, a tertiary teaching hospital in Tunis, Tunisia. Patients were managed in the departments of otorhinolaryngology and infectious diseases over a period of 12 years (From January 2000 to December 2011). Lymphadenectomy was performed for diagnosis in 84.8% of cases. The diagnosis was made by fine-needle aspiration cytology in the remaining 15.2% of patients. Cases were defined as confirmed following the identification of *Mycobacterium tuberculosis* in lymph node and/or another biological fluid. Cases were defined as probable in the presence of typical histological findings (granuloma with caseating necrosis), or necrosis on histology with healing under TB treatment. TB treatment was performed as recommended by the World Health Organization. Four drugs (isoniazid, rifampicin, ethambutol, pyrazinamide; HRZE) were administered for 2 months, followed by a two-drug regimen (isoniazid and rifampicin) for a variable duration. Two major drugs were used in all cases: isoniazid and rifampicin.

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All patients who showed poor adherence to the initial anti-TB treatment, were transferred to another hospital during treatment, had incomplete medical records, or were lost during the follow-up period were excluded.

All tests of significance were conducted using IBM SPSS Statistics version 20.0 software (IBM Corp., Armonk, NY, USA). Univariate and multivariate analyses were performed using logistic regression. A p -value of <0.05 was considered statistically significant.

3. Results

Over the study period, 501 patients were diagnosed with lymph node TB; 185 were male and 316 were female, giving a sex ratio of 0.37. The median age of the patients was 33 years (interquartile range (IQR) 21–46 years). HIV testing was performed in only four cases and was negative. TB was confirmed in four cases and was probable in 497 cases. A past TB treatment was noted in 14 cases. The tuberculin skin test (TST) was positive in 77.6% of cases.

PR occurred in 67 patients (13.4%), with a median delay to onset after starting TB treatment of 7 months (IQR 4–9 months). The median age of the patients was 30 years (IQR 21–46 years). The same female predominance was noted, with a sex ratio of 0.39. Diabetes was noted in three patients, with associated Henoch-Schönlein disease in one case. A past medical history of treated TB was reported in two cases. Extra-lymph node TB was found in six cases. All patients reported regular intake of their medications. Of these patients, 44.8% presented with enlarged lymph nodes at previous sites. On clinical examination, new lymph nodes had appeared in 32.8% of patients. Fluctuation and

Table 1
Predictive factors for paradoxical reaction: univariate analysis

Variable	Number	OR	95% CI	p -Value
Age	≤30 years: 35 >30 years: 32	0.746	0.446–1.249	0.265
Sex	Male:19 Female:48	1.060	0.598–1.877	0.842
Immunological deficiency	Yes: 3 No: 64	1.224	0.347–4.321	0.753
Fever	Yes: 14 No: 53	1.646	0.860–3.150	0.132
Emaciation	Yes: 8 No: 59	1.018	0.460–2.252	0.964
Sweating	Yes: 15 No: 52	1.987	1.047–3.770	0.035
Number of lymph nodes	Multiple: 42 Single: 25	1.649	0.971–2.801	0.064
Bilateral cervical lymph nodes	Yes: 7 No: 60	0.7	0.305–1.061	0.398
Mobility	Fixed: 25 Mobile: 42	1.376	0.805–2.352	0.242
Local tenderness	Yes: 13 No: 54	1.5	0.772–2.915	0.229
Skin appearance	Inflammatory: 20 Normal: 47	1.223	0.694–2.154	0.485
Node size	≥3 cm: 34 <3 cm: 33	1.232	1.127–3.176	0.016
Consistency	Soft: 8 Firm: 59	1.2/32	0.552–2.751	0.609
Extra-lymph node TB	Yes: 6 No: 61	4.644	1.597–13.504	0.004
Elevated WBC count	Yes: 5 No: 62	4.644	0.604–4.609	0.323
Anemia	Yes: 18 No: 49	1.423	0.790–2.564	0.238
Treatment	Standard: 57 Combined: 10	1.327	0.650–2.710	0.436
Treatment complications	Yes: 15 No: 52	1.735	0.916–3.285	0.090

OR, odds ratio; CI, confidence interval; TB, tuberculosis; WBC, white blood cell.

Table 2
Predictive factors for paradoxical reaction: multivariate analysis

Variable	OR	95% CI	p -Value
Extra-lymph node TB	6.510	1.597–3.504	0.003
Node size	1.811	1.060–3.092	0.030
Sweating	1.779	0.792–3.995	0.163
Complications of medical treatment	1.732	0.905–3.392	0.096
Number of lymph nodes	1.468	0.848–2.539	0.170
Fever	0.946	0.402–2.224	0.898

OR, odds ratio; CI, confidence interval; TB, tuberculosis.

fluctuation were observed in 16.4% and 6% of patients, respectively. New bacteriological smears were not performed.

Univariate analysis of predictive factors of PR revealed that sweating, a lymph node size ≥ 3 cm, and associated extra-lymph node TB were associated with a high risk of PR (Table 1). On multivariate analysis, a lymph node size ≥ 3 cm and associated extra-lymph node TB were independently associated with PR (Table 2).

The management of PR varied depending on the case and the doctors involved (Figure 1). Two patients received systemic steroids for a large fluctuant swelling, without any improvement. Quadruple therapy (HRZE) was reinitiated in 10.4% of patients. *Mycobacterium bovis* was suspected in 13.4% of patients, and ethambutol was added to isoniazid and rifampicin. Because of gastric pain and to avoid optic toxicity, ciprofloxacin was added to the TB treatment in 19.4% of cases (the only oral fluoroquinolone used at the hospital during that period) (Table 3). Surgical excision of the lymph node was performed in 71.6% of cases (Figure 2). All patients recovered after a median duration of TB treatment of 14.91 ± 7.03 months. The duration was significantly longer in the PR-

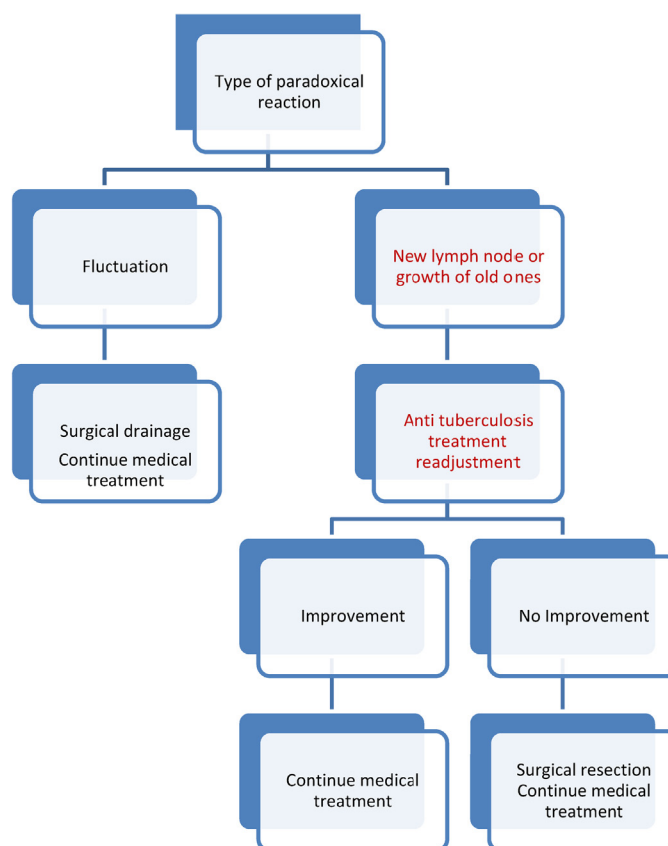


Figure 1. Therapeutic algorithm for paradoxical reaction in patients with cervical lymph node tuberculosis.

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