International Journal of Infectious Diseases 54 (2017) 4–7

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

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

Houda Chahed [a,b,*], Hela Hachicha [a,b], Aida Berriche [a,c], Rim Abdelmalek [a,c], Azza Mediouni [a,b], Badreddine Kilani [a,c], Mohamed Ben Amor [a,b], Hanene Tiouiri Benaissa [a,c], Ghazi Besbes [a,b]

[a] Faculty of Medicine, Université de Tunis El Manar, Tunis, Tunisia
[b] Otorhinolaryngology Department, Rabta Hospital, Jebel Lakhdar Bab Saadoune, 1007 Tunis, Tunisia
[c] Infectious Diseases Department, Rabta Hospital, Tunis, Tunisia

ARTICLE INFO

Article history:
Received 3 July 2016
Received in revised form 23 October 2016
Accepted 24 October 2016

Corresponding Editor: Eskild Petersen, Aarhus, Denmark

Keywords:
Tuberculosis
Cervical lymph node
Paradoxical reaction
Treatment

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.

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.

* Corresponding author. Tel.: +216 22479844; fax: +216 71561889.
E-mail address: houda.chahed@gmail.com (H. Chahed).

http://dx.doi.org/10.1016/j.ijid.2016.10.025

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

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.

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-

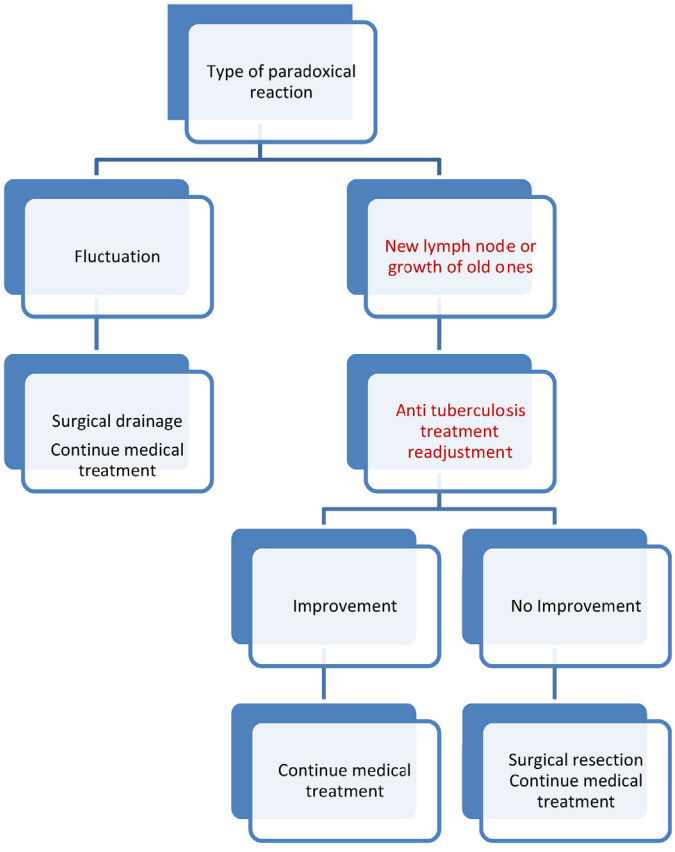

Figure 1. Therapeutic algorithm for paradoxical reaction in patients with cervical lymph node tuberculosis.

Table 3
Paradoxical reaction: treatment decision

Treatment	Number (%)	Treatment duration, months (IQR)
Steroids	2 (3%)	2.5
Ciprofloxacin	13 (19.4%)	5 (3–18)
Restarting quadruple therapy	7 (10.4%)	3.87 (3–4)
Addition of ethambutol	9 (13.4%)	3.2 (1–9)
Surgical excision	48 (71.6%)	
Continuation of classic treatment	2 (3%)	

IQR, interquartile range.

positive group compared to the PR-negative group (14.91 months vs. 8.48 months; $p < 0.001$). No recurrence was detected in this study.

4. Discussion

Lymph node TB is the most common extra-pulmonary location of TB. In Tunisia, its prevalence is estimated to be 23–29.9% of all TB and is increasing.[3] It is the second most common form after pulmonary TB.[3] With appropriate treatment, the outcome of lymph node TB is usually favorable, but worsening can occur under effective treatment, resulting in a PR.[4]

The pathogenesis of PR remains unclear, but it is probably due to an immunological response.[5] Two different hypotheses have been put forward. The first is that PR is caused by delayed immune activation. This is supported by the fact that patients with PR generally have a negative TST and decreased lymphocyte blastogenesis at the time of diagnosis, but a positive TST and increased lymphocyte blastogenesis after the initiation of therapy.[6,7] The second is a hypersensitivity reaction to the antigen released from dying mycobacteria.[2,8,9]

The prevalence of PR is variable. It has been reported to occur in 5–35% of patients receiving TB treatment.[5] Cheng et al. found that only 2.4% of pulmonary TB patients developed PR.[10] Its prevalence in lymph node TB seems to be higher, ranging from 12% to 23%.[2,3] These differences may be due to the infection site.[4] In the present study, the prevalence of PR was 13.4%.

The diagnosis of PR is not easy since the results of bacteriology are usually negative, making it difficult to rule out drug resistance. In the present study, the TST was not performed again to identify any new positive result. The TST was positive in 73.3% of PR patients and in 77.9% of the remaining patients, with no difference between the two groups.

Risk factors for PR during TB treatment have been explored mainly in HIV-infected patients. However, limited data are available on the risk factors for PR in immunocompetent patients with lymph node TB.[2]

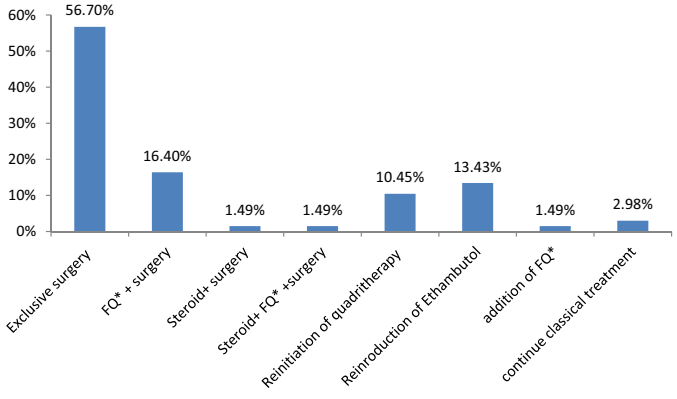

Figure 2. Therapeutic management of paradoxical reaction in the present series (FQ, fluoroquinolone).

Cheng et al. found that baseline anemia, hypoalbuminemia, lymphopenia, and a greater change in lymphocyte count were independent risk factors for developing PR in pulmonary TB.[10] Anemia and a lower lymphocyte count at baseline have been described as biological predictors of PR.[11–13] Hawkey et al. found that a higher peripheral blood monocyte count at baseline might be predictive of PR in HIV-negative patients with peripheral lymph node TB.[14] Jung et al. concluded that a high baseline albumin level in serum was a risk factor for PR in pleural TB.[4] In the present study, neither anemia nor leukocytosis were predictive of PR. No other biological abnormalities were observed.

Cho et al. and Hawkey et al. found that younger age, male sex, and local tenderness at the time of diagnosis were independently associated with PR in HIV-negative patients with peripheral lymph node TB.[2,14] Several case–control studies have demonstrated that PR occurs more frequently in patients with extrapulmonary involvement.[11,12] However, none of the factors have been shown to be clinically useful to date. In the present study, none of the biological criteria were associated with PR; only extra-lymph node TB and a swelling size ≥3 cm were independent risk factors for developing PR.

PR is usually a mild, transient, and self-limited phenomenon. No consensus on the therapeutic management of this entity has been reached to date, but many authors propose an extension of TB treatment, a short course of steroids, and aspiration puncture and/or surgical excision of the lymph node.[1] The value of steroid therapy in the management of PR has been emphasized mainly in cases of intracranial tuberculoma.[1,14] Jung et al. demonstrated an improvement in 71% of patients with PR in pleural TB after steroid therapy; they found that steroid responders showed a more rapid improvement than the non-steroid group.[4] Recent studies have suggested that immunotherapy with steroids or an anti-tumor necrosis factor alpha (anti-TNF-α) inhibitor may help to resolve PR by inhibiting granuloma formation interfering with the penetration of TB treatment.[3,14,15] In the study by Geri et al., the use of adjunctive steroids in the management of PR was not associated with a significant clinical improvement.[13] In the present study, the number of patients treated with steroids was limited, so conclusions cannot be drawn.

The surgical approach was adopted in 71.6% of cases in this study. It is believed that the excision of large lymph nodes and drainage of cold abscesses could shorten the duration of TB treatment and improve the healing processes. Surgery was useful when the PR did not improve 4–8 weeks after the adjustment of TB treatment. Needle aspiration and a prolongation of the TB treatment is a common alternative to surgical excision, but there is a higher risk of fistulization or poor wound healing with this method.[12]

The main limitation of this study was a lack of positive culture. Thus drug resistance could not be eliminated. The diagnosis of PR was made retrospectively when patients healed after the use of a steroid, surgical treatment, or prolonged TB treatment.

In conclusion, PR is not uncommon in patients with cervical lymph node TB. Its occurrence seems to be predicted by associated extra-lymph node TB and a swelling size ≥3 cm. Resorting to surgery to shorten the course of medical treatment will hinder the clarification of a strategy for the management of treatment. Randomized trials are required to determine the pathogenesis of PR and improve its management in cervical lymph node TB.

Funding: This research did not receive any specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest: None.

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