



Tb or Not Tb: Paradoxical Response and The Role of Selective Lymphadenectomy in Tuberculous Cervical Lymphadenitis.

KEYWORDS

Tuberculous lymphadenitis, Paradoxical response, Selective lymphadenectomy

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ABSTRACT *Introduction: Worsening of symptoms, a paradoxical response during anti-tuberculous therapy is a known phenomenon. There is an imbalance in responses that restrain inflammation and pro-inflammatory T cells.*

Additionally, granuloma formation occurs as a result of increased IFN- . The role of surgical treatment in tuberculous cervical lymphadenitis is not well-defined. We report a series of symptomatic cases of tuberculous cervical lymphadenitis on anti-tubercular treatment that underwent surgical intervention to treat.

Methods: A retrospective review of medical records of 19 patients diagnosed to have tuberculous cervical lymphadenitis over a 15-month period from June 2012 to August 2013 was done. Pre-operative diagnosis of tuberculosis was made based on FNAC, mycobacterial culture of aspirated fluid or histopathological examination of lymph nodes. All patients underwent excision of one or more groups of lymph nodes. Specimens were subjected to histopathological examination, MGIT culture and sensitivity and Xpert MTB/RIF tests. Rifampicin resistance on Xpert was diagnostic of drug-resistant tuberculosis while the absence of rifampicin resistance with documentation of acid-fast bacilli by either of the diagnostic modalities was considered as an evidence of paradoxical response.

Results: Fourteen patients were diagnosed to have cervical tuberculous lymphadenitis were retrospectively analysed while on anti-tubercular treatment for 3 months or more. All patients presented with a swelling while, 6 (42.9 %) patients presented with a discharging sinus or the constitutional symptoms. Disseminated tuberculosis was present in 3 patients (21.4 %). All patients underwent excision of lymph nodes while 42.1% patients underwent selective neck dissection. The incidence of tuberculous infection was 85.7% by Xpert TB PCR and 31.6%. Drug-resistance was noted in 14.3% of the patients while paradoxical response to anti-tubercular treatment was made in 85.7% of the patients.

Conclusion: Paradoxical response in tuberculous cervical lymphadenitis receiving anti-tubercular treatment is common in patients with persistent symptoms. There appears to be a definite beneficial role of selective neck dissection in a significant number of patients.

Introduction

Worsening of symptoms during antituberculosis therapy is a clinical challenge to the treating physicians. Paradoxical response is defined as the clinical or radiological worsening of pre-existing tuberculous lesions or the development of new lesions not attributable to the normal course of disease. The patient initially improves with antituberculosis therapy with the onset of paradoxical response at least 2 weeks after the initiation of treatment.(1)

Paradoxical response is a well-known phenomenon in HIV-positive patients with significant reductions in viral load and increases in CD4+ lymphocyte counts when anti-retroviral treatment is administered within 2 months of antituberculosis therapy.(2) A similar response has been noted in HIV-negative patients receiving anti-tubercular treatment although the incidence, clinical spectrum and risk factors of paradoxical response in HIV-negative patients is lacking.(1) Immunopathological damage has been suggested as a possible explanation for the paradoxical worsening of tuberculosis after initiation of treatment. Immune reconstitution inflammatory syndrome (IRIS) is an exaggerated dysregulated inflammatory response with an abrupt shift of host immunity from an anti-inflammatory and immunosuppressive status towards a pathogenic pro-inflammatory state. There is a shift in the dominant T-helper responses that restrain inflammation (Treg and Th2) towards generation of proinflammatory T cells (Th17 and Th1). Further, rebound in IFN-g, a Th1 cytokine, results in granuloma formation. (3)

Traditionally, the role of surgical intervention in tuberculous cervical lymphadenitis is that of providing diagnostic sample or to address one of its complications. Due to bulky adenopathy, patients were treated with limited neck dissection. A retrospective review of HIV-negative patients' records was done to note the findings and study the profile of the patients on anti-tubercular treatment with regard to drug resistance and paradoxical response.

Methods

Medical records of 14 patients diagnosed to have tuberculous cervical lymphadenitis over a 15-month period from June 2012 to August 2013 were retrospectively reviewed. All symptomatic patients on anti-tubercular treatment for at least 3 months were included in the analysis. The indication for additional surgical intervention was either for diagnosis or treatment. The symptoms were defined as refractory or new neck swellings and/or discharging sinuses that were seen initially in the department of infectious diseases. Following a detailed clinical work-up, basic laboratory parameters were evaluated and patients underwent an imaging of the neck and chest X-ray. The laboratory investigations included complete blood count, erythrocyte sedimentation rate, C-reactive protein levels, liver function tests and renal function tests.

Pre-operative diagnosis of tuberculosis was made based on FNAC suggestive of granulomatous inflammation, positive mycobacterial culture of aspirated fluid or caseating granulomatous inflammation on histopathological examination of lymph nodes.

The type of anti-tubercular treatment being received by the patients was noted. The patients were evaluated for fitness for surgery under general anesthesia.

Surgical treatment: The patients underwent limited neck dissection of at least one involved nodal level. Transverse cervical skin crease incisions were modified (as necessary due to previous scarring) with excision of sinuses or overlying devitalized skin when present. Excision of lymph node group(s) was done based on clinical and radiological findings. All attempts were made to preserve vital neurovascular structures. Surgical specimens were sent for microbiological and histopathological examination. Smears using Zeil Neelsen stain and culture/sensitivity using LJ media, MGIT and Xpert TB gene PCR analyses were requested.

The patients were categorized into the following groups:

Drug-resistant tuberculosis: *Mycobacterium tuberculosis* detected and/or features suggestive of tuberculous lesions on histopathological examination, MGIT examination with culture positive but resistant MTb and Xpert TB gene PCR with rifampicin resistance.

Paradoxical response: *Mycobacterium tuberculosis* detected and/or features suggestive of tuberculous lesions on histopathological examination, MGIT examination with culture positive but non-resistant MTb and Xpert TB gene PCR with no rifampicin resistance.

No laboratory evidence of tuberculosis: lymphadenopathy with negative histopathological, microbiological, and gene PCR assays for MTb.

Data entry was done using Microsoft office Excel 2010 and analysis was done using SPSS 11.

Results

Demographics: Medical case records of 19 patients that were diagnosed to have cervical tuberculous lymphadenitis were retrospectively analysed. Fourteen patients were on anti-tubercular treatment for 3 months or more. The youngest patient was 15 years old while the eldest patient was 40 years old. The mean age was 26.1 years (s.d. 7.9). Women constituted 92.9% of the cohort. Native state (Tamil Nadu) accounted for 14.3 % of the patients while 78.6 % hailed from other states (West Bengal – 21.4 %; Jharkhand – 21.4 %; 7.1 % each from Andhra Pradesh, Assam, Kerala, Chhattisgarh, and Karnataka) and 7.1 % patients came from the overseas (Bangladesh).

Presentation: All 14 patients presented with a swelling. Among other presenting complaints, 6 (42.9 %) patients presented with a discharging sinus while the constitutional symptoms were present in the same number of patients (6 patients). Features suggestive of disseminated tuberculosis were present in 3 patients (21.4 %). The duration of symptoms ranged from 2 to 24 months (mean - 6.8; s.d - 5.6, respectively). There was a history of exposure to tuberculosis in 2 patients (14.3%).

Previous treatment history: Minimum duration of previous treatment was 3 months while the maximum duration was 15 months (mean – 7.36 months). The details for previous treatment drugs and regimen were known only in 7 patients (50%). **Table1.**

Age	
Mean age (years)	26.1
Range	15-40
Sex (Male:Female)	
	1:13
Presentation	
Swelling	14 (100)
Sinus	6 (42.9)
Constitutional symptoms	6 (42.9)
Disseminated Tb	3 (21.4)
Mean duration of symptoms (months)	6.8
Duration of ATT (months)	7.4

Table 1: Baseline characteristics

Treatment: All 14 patients were referred for the surgical relief of the symptoms. Based on the clinical and radiological findings, 10 patients (71.4 %) underwent lymph nodal excision, 3 patients (21.4 %) underwent excision along with incision & drainage of the cold abscesses, and 1 patient (7.1 %) underwent incision & drainage with debridement. Of the 10 patients who underwent nodal excision, 5 patients (35.7%) were treated with selective neck dissection.

Figures 1 & 2

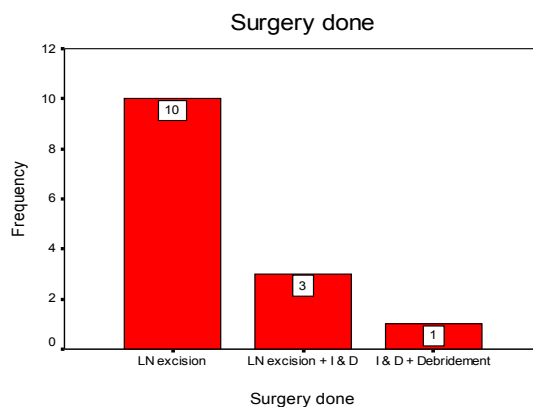


Figure 1: Surgical procedures performed

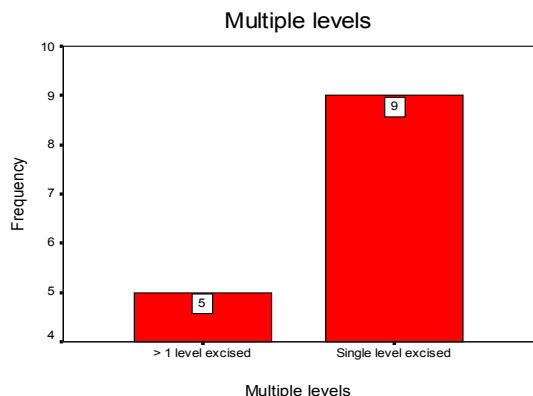


Figure 2: Type of lymphadenectomy

Diagnosis: Surgical specimens from all the patients were reported as chronic granulomatous inflammation on histopathological evaluation. MGIT and Xpert gene PCR reports were available for 13 patients. Mycobacterium tuberculosis was detected by MGIT in 6 patients (42.9 %). Mycobacterium tuberculosis was detected by Xpert gene PCR in 12 patients (85.4 %). Drug resistance was noted in 2 patients (14.3%) by Xpert gene PCR. Based on the above findings and the guidelines to diagnose paradoxical response, 2 patients (14.3%) were diagnosed to have drug resistant tuberculosis and 10 patients (71.4%) were diagnosed to have a paradoxical response to the anti-tubercular treatment.

Table 2

Mycobacterium detection	
MGIT	
Performed	13
MTB detected	6 (42.9)
Xpert PCR	
Performed	13
MTB detected	12 (85.4)
Rifampicin resistance	2 (14.6%)
Histopathology	14

Table 2. Laboratory results

Discussion

In this retrospective chart review, 14 patients while receiving anti-tubercular treatment for more than 3 months were found to have swellings or discharging sinuses in the neck. The mean age was 26.1 years and there was a strong female preponderance in this cohort (92.9%). Inherent in the design, all patients presented with a swelling while 42.9 % patients presented with a discharging sinus and the constitutional symptoms. Disseminated tuberculosis was present in 21.4 %. The mean duration of symptoms was 6.8 months while the maximum duration of being on anti-tubercular treatment was 15-months. All patients underwent lymph node excision of varying magnitude, 42.1% patients underwent selective neck dissection. All the patients were reported as chronic granulomatous inflammation on histopathological evaluation. Mycobacterium tuberculosis was detected by Xpert gene PCR and MGIT in 85.7 % and 31.6% of patients, respectively. Drug resistance was noted in 14.3% of patients by Xpert gene PCR. Multi-drug resistant tuberculosis and paradoxical response were diagnosed in 14.3% and 85.4% of patients, respectively.

A certain number of patients with tuberculous cervical lymphadenitis do not respond completely to the anti-tubercular treatment. In fact, there may be initial partial or complete regression of the node(s) followed by recrudescence of the same node or appearance of an altogether different node(s). Often labeled as refractory or drug resistant tuberculosis, many patients undergo repeated lymph node biopsies and AFB cultures and sensitivities. This is compounded by the fact that the usual acid-fast bacilli culture and sensitivity in Lowenstein-Jensen medium takes 6 weeks or more. Consequently, the patient may empirically be subjected to a second-, or even third-line anti-tubercular treatment with the same results over and over again.

Traditionally, the role of surgery has been limited to diagnose or treat the complications of tuberculosis although non-tuberculous mycobacterial infection is essentially treat-

ed with complete surgical excision of nodes augmented with antibiotics.(4) Diagnosis has been through fine-needle aspiration cytology (FNAC), incisional or excisional biopsy of a cervical lymph node, and detection of acid-fast bacilli in the tissue samples or on histopathological examination.

Complications of cervical tuberculous lymphadenitis include formation of cold abscess, collar stud abscess or tuberculous sinus. In all these, the excision of the subcutaneous abscess or sinus with the underlying node has been the usual recommendation.(5) In the past few years, it has been noted that after such excisions, it was not uncommon to find lymph nodal enlargement in the nearby nodes or groups often needing repeated excisions.

Recently, understanding of the pathogenesis of tuberculous cervical lymphadenitis is seen in the light of its association with HIV infection and development of immune reconstitution inflammatory syndrome. In this subset of patients, it has been noted that the patients develop paradoxical response to the treatment which is linked to the release of inflammatory mediators. Typically, this begins after a few weeks of treatments.(1) International Network for the Study of HIV-associated IRIS (INSHI) has defined criteria to diagnose IRIS in HIV infected individuals affected with tuberculosis.(6) At present there are no guidelines to diagnose IRIS in non-HIV infected patients. If the same guidelines are applied to non-HIV, it is possible to segregate the patients with IRIS from multi-drug resistant or extensively drug resistant tuberculosis. While the former may benefit from surgical excision, the latter would obviously need ATT as per the sensitivity, if at all.

Rapid diagnosis of mycobacterial infections is essential to provide appropriate antimicrobial therapy. Automated, non-radiometric culture detection systems have focused on maximizing mycobacterial recovery from clinical specimens and minimizing the time to detection. Mycobacterium growth indicator tube (MGIT) is able to detect Mycobacterium tuberculosis in an average of 13.5 days. MGIT demonstrates sensitivity of 100% for M. tuberculosis.(7)

Polymerase chain reaction (PCR) technique is able to demonstrate mycobacterial DNA fragments in patients with clinically suspected mycobacterial lymphadenitis even with few dead or live microorganisms from materials obtained by FNA or biopsy.(8,9)52,53,54,55. The reported sensitivity is between 43 - 84%, and its specificity is 75 - 100%. (8,10)52,56. The Xpert MTB/RIF assay can detect M. tuberculosis and identify rifampicin resistance as a surrogate for multi-drug resistance (MDR) directly from a patient's sputum in less than 2 hours.(11)

Surgical technique: Neck dissection for tuberculous cervical lymphadenitis is significantly different from the usual oncological indications. Even the incisions for the neck dissection have to be modified according to the seat of pathologic node(s). This may be compounded with presence of previous scars, etc. While the usual non-lymphatic structures are essentially aimed to be preserved, this is by no means as easy due to inflammatory fibrosis and loss of planes. The disease seldom extends beyond two or three lymph nodal groups or levels. There is higher likelihood of injury to the neurovascular structures many of which form the abscess wall. The structures which are particularly at risk are the internal jugular vein, spinal accessory nerve, subclavian vein and brachial plexus. One must know when to stop as some of these nodes can extend behind the clavicle well into the mediastinum, thus justifying the pre-

operative imaging.

It is possible to group patients according to their laboratory results into those with the drug-resistant tuberculosis or paradoxical response. The surgical specimen was sent for routine Hematoxylin & Eosin histopathological examination, MGIT culture and sensitivity and Xpert MTB/RIF PCR for rifampicin resistance. This aims to distinguish the resistant cases from the patients with no documented infection. While the former situation merits administration of the more effective ATT regimens, the latter is a step towards the closure of the persistence of IRIS as ATT course is completed. A surge in the lymphocyte count, associated with a strongly positive tuberculin skin test result may be observed during the paradoxical response.

Further treatment: From the foregoing it is apparent that the post-excisional laboratory findings should be interpreted with caution so as to place the patients in one of the two streams of management: 1) The drug-resistant group and 2) The paradoxical response group. While the former mandates the change-over to more effective, 2nd- or 3rd-line anti-tubercular treatment with nearly no role of surgery in the ultimate cure of the disease, the latter is a step towards the closure of the persistence of IRIS as ATT course is completed.

Limitations: Being a retrospective review of a small subset of patients, the findings of this study need to be interpreted with caution. The diagnostic criteria of paradoxical response in non-HIV infected patients suffering with tuberculous cervical lymphadenitis while on anti-tubercular treatment are still being defined. The diagnosis is, at best, based on the presence of non-drug resistant mycobacterium tuberculosis bacilli in an individual receiving anti-tubercular treatment.

Future directions: Recommendations based on a newly-introduced diagnostic term merit a properly designed prospective study. The role of surgical treatment in tuberculous cervical lymphadenitis needs to be further scrutinized for its benefit and the potential morbidity. Akin to a follow up after the treatment of a malignancy, the patients being treated for tuberculous cervical lymphadenitis need to be followed up even after the completion of anti-tubercular treatment. This is even more relevant in the patients who may manifest paradoxical responses.

Conclusions: Paradoxical response in tuberculous cervical lymphadenitis receiving anti-tubercular treatment is common in patients with persistent symptoms. Selective neck dissection may have a definite beneficial role in the management of persistent symptom.

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