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Antibiotic Therapy for Nontuberculous Mycobacterial Cervicofacial Lymphadenitis

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Objectives/Hypothesis: **To evaluate the efficacy of antibiotic treatment of nontuberculous mycobacterial (NTM) cervicofacial lymphadenitis, both as an alternative and as adjuvant to surgical excision.** ***Study Design:*** **Retrospective chart review of pediatric patients with NTM cervicofacial lymphadenitis treated from January 1993 to November 2003 at an academic tertiary care children's hospital.** ***Methods:*** **Fifty-five patients (age range, 15 mo–16 y) with the diagnosis of NTM cervicofacial lymphadenitis by fine-needle aspiration biopsy that had 1) lymph node culture positive for an atypical mycobacteria, 2) histological findings consistent with mycobacterial infection (granulomas) with negative bartonella serological titers, 3) histological stain positive for the presence of acid-fast bacillus in the absence of tuberculous infection, or 4) positive Mantoux tuberculin skin test result with a negative finding on polymerase chain reaction for tuberculous mycobacteria. Clinical response was defined as complete or partial resolution of skin changes and palpable lymphadenopathy in response to antibiotic therapy consisting of macrolide therapy alone or in combination with other antimycobacterial pharmaceuticals.** ***Results:*** **Of the 55 children studied, 45 of 55 (82%) with both single and multiple lesions underwent a trial of medical therapy, and 30 of 45 lesions (67%) ranging in size from 1 × 1 to 6 × 5 cm achieved resolution without surgical excision. Of the other 15 patients treated initially with medical therapy, 6 of 15 (40%) responded well to a course of antibiotic therapy before undergoing surgical excision, and 7 of 15 (47%) patients were nonresponsive to antibiotic therapy and required surgical excision to resolve the neck mass. The remaining 2 of 15 patients (13%) proceeded to surgery only after a course of antibiotics of 3 weeks or less. Ten of the 55 patients (18%) underwent surgical excision initially, with 5 of 10 patients (50%) receiving postoperative antibiotics for treatment of residual disease or prevention of recurrence.** ***Conclusion:*** **Some NTM cervicofacial lymphadenitis infections appear to respond to medical therapy alone. A trial of antibiotic therapy might be considered in patients with NTM cervicofacial lymphadenitis before surgical excision or as an adjuvant to surgical excision.** ***Key Words:*** **Nontuberculous mycobacteria, lymphadenitis.**

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INTRODUCTION

Nontuberculous mycobacterial (NTM) infections commonly present as a chronic cervical lymphadenitis in immunocompetent children under the age of 5 years.[1–3] Typically affecting the levels I and II nodes, these infections begin as slowly enlarging, painless neck masses. Untreated, the infected nodes surface to the skin and erupt. This progression often takes place over several months.[1,4] The diagnosis is often delayed and made after several failed treatments with anti-streptococcal and anti-staphylococcal antibiotics. Atypical mycobacteria, the bacteria responsible for NTM infections, are ubiquitously found in the soil, food, and various animals.[5] More than 50 species of mycobacteria have been described; approximately 50% of these species are pathogenic.[6]

Surgical excision through complete resection or curettage is the gold standard for treatment of NTM infections. It has been shown to be associated with low recurrence and little morbidity. [2,7] In fact, in a recent review by Panesar et al.,[7] 55 patients with a cervicofacial NTM infection underwent total excision with only one recurrence. However, when these infections were treated only with an incision and drainage, 20 of the 21 patients developed a recurrence.[7] Tunkel[8] and Saggese et al.[9] also noted a low recurrence rate associated with surgical resection and curettage. Therefore, the current surgical recommendation is complete resection of NTM infections by excision or curettage.

The role of medical management remains unclear for NTM infections. Several studies have shown poor responses to anti-tuberculous medications.[3,10] However, more recent studies using macrolides such as clarithromycin (Braxin) have reported successful treatment with antibiotic therapy alone.[11–14] Specifically, Harza et al.[13] reported a 50% complete resolution of NTM infection without requiring surgical excision. Berger et al.[14] discussed the resolution of chronic drainage and lymphade-

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nitis with Biaxin and rifabutin in eight patients. These have all been small studies involving 10 or fewer patients.

With the emerging data of successful treatment of NTM infections with antimicrobial therapy, our institution has recently trended toward initiating treatment of NTM infections with a trial of medical management. In the present study, we review our experience with NTM infections since 1993, emphasizing the effect of antimicrobial therapy.

PATIENTS AND METHODS

The medical records of all available children under the age of 18 years who were given a diagnosis of NTM cervicofacial lymphadenitis and treated by at least one of the authors from January 1, 1993, to November 1, 2003, were retrospectively reviewed. The criteria for the diagnosis of NTM adenitis was based on a history of chronic cervicofacial lymphadenitis with either a fine-needle aspiration or excisional biopsy that met one or more of the following criteria: 1) lymph node culture positive for an atypical mycobacteria, 2) histological findings consistent with mycobacterial infection (granulomas) with negative bartonella serological titers, 3) histological stain positive for the presence of AFB in the absence of tuberculous infection or 4) positive Mantoux tuberculin skin test with a negative PCR for tuberculous mycobacteria.

Data reported were extracted from review of notes from hospitalizations, laboratory reports, surgery dictations, and clinical notes. Follow-up was obtained by chart review. The present study was approved by the University of Texas Southwestern Medical Center (Dallas, TX) Institutional Review Board for research.

RESULTS

Fifty-five patients were diagnosed with NTM cervicofacial lymphadenitis during the 10-year period. Forty-five of the 55 patients had an initial trial of medical therapy. Patients were retrospectively divided into four groups based on the treatment and response to treatment (Table I). Group 1 had resolution with antibiotic treatment alone. The antibiotics usually included a macrolide with a possible addition of anti-tuberculous antibiotics or multidrug anti-tubercular therapy (n = 30). The choice of antibiotics was physician dependent. Group 2 was treated with antimicrobials followed by surgical excision (n = 15). Group 3 was treated with surgical excision followed by adjuvant antibiotic therapy (n = 5). Group 4 had only surgical intervention with either total excision or curettage (n = 5). Of the patients who were initially treated with medical therapy, 30 of 45 (67%) had resolution with only antibiotic therapy (Table I).

Of the patients treated with antibiotics alone, 11 of 30 (37%) had documented improvement within 1 month (Table II). Given the retrospective nature of the study, not all of the patients had documentation of node size after 1 month of treatment. Of the remaining 19 patients, 12 (63%) showed response to antibiotic treatment by the second month. Ultimately, 77% (23 of 30) of the cases of NTM cervicofacial lymphadenitis in these children had begun to regress by 2 months of treatment. By 6 months, all but one patient (patient 14) (Table III), had resolution of the lymphadenitis. Patient 14 had four separate nodes within her parotid and submandibular gland that resolved after receiving treatment for 1 year.

Although the medical regimen was not standardized, 22 of the 30 patients were initially started on a regimen of Biaxin, either alone or in combination with an antimycobacterial antibiotic such as ethambutol or rifampin. Within this group, 40% (9 of 22 patients) had documented improvement within the first month. By the second month, 18 of the 22 patients (82%) had responded to the antibiotics (Table II). Of the 19 patients treated with antibiotics alone who did not respond within the first month of antibiotic therapy, 15 continued with their current therapy and began to respond by the second month. Four patients underwent a change in their therapy regimen (Table III). All three were initiated with rifampin in combination with either Biaxin (2 of 4) or isoniazid (1 of 4) or both (1 of 4). In summary, 15 of 30 children were started on a regimen of Biaxin alone and 13 of the 15 children responded by 2 months of treatment (Table II). The other patients responded to therapy involving a combination of drugs. Only one recurrence of infection was noted after antibiotic therapy was stopped. This recurrence was successfully treated with a 1-month treatment with Biaxin (Tables IV).

Of the 15 patients who initially received antibiotics followed by surgical excision, 6 patients responded well to 2 months of treatment (Table V). In these patients, the nodes decreased in size or ceased to enlarge. None of these patients underwent a change in the drug regimen. Despite this positive response to medical therapy, surgical excision or curettage was pursued with ultimate resolution, except in one case. For patient 11 (Table V), a recurrence was noted after surgical excision. The infection was ultimately resolved with 3-month course of postoperative antibiotics.

Our institution has also had experience with the use of antibiotics as adjuvant therapy to surgical excision (Table I). Five patients initially underwent surgical excision

TABLE I.
Retrospective Categorization of Patients Based on Response to Treatment (n = 55).

Group	Therapy	No. of Patients	Median Age (yr)	Smallest Node (cm)	Largest Node (cm)	% $< 2 \times 2$ cm	% $> 2 \times 2$ cm
1	Antibiotics Alone	30	2.0	1×1	6.5×5	47	53
2	Antibiotics Followed by Surgical Excision	15	2.0	1×1	6×4	40	60
3	Surgical Excision Followed by Antibiotics	5	1.8	1×0.5	3.5×2	20	80
4	Surgical Excision Alone	5	1.4	1.5×1.5	1.5×5	20	80

TABLE II.
Time of Response in Patients Treated Only with Antibiotics (n = 30).

Initial Antibiotic Course	N	Initial Improvement by 1 Month (%)	Improvement Noted by 2 Months (%)	Resolved by 6 Months (%)
Biaxin Alone	15	6 (40)*	13 (87)	15 (100)
Biaxin with Other Antibiotics	8	3 (38)	6 (75)	7 (88)[+]
Others	7	2 (29)	4 (57)	7 (100)

*Absolute number (Percentage of total number within group).
[+] The one child, Patient 14, did not respond by 6 months but responded within one year.

followed by several months of antibiotic therapy. Three of the five patients (60%) had either known multiple lymphadenitis preoperatively or residual lymphadenitis after surgery. The other two patients received postoperative antibiotics for recurrent lymphadenitis (Table IV). Both were successfully treated with medical therapy alone.

Of the patients who underwent surgical excision initially (groups 3 and 4), 3 of 10 (30%) required additional treatment for recurrence. As described earlier in the present study, two of the recurrences occurred in the group treated initially with surgery. The recurrences were managed medically. The other recurrence was treated with surgical resection with resolution. Table IV lists all four groups and the number of recurrences in each group.

Of the 55 patients, 9 had involvement of the parotid gland. Of these patients, 6 of 9 (67%) of the patient's infections were resolved with antibiotic treatment alone. Two patients' lesions were initially treated with antibiotics with some decrease in lesion size before proceeding with surgical excision. One patient underwent surgical excision but had a recurrence of the infection at the same location. Biaxin was given for 1 month to help reduce the active infection followed by a superficial parotidectomy. No facial nerve paresis was noted in any of the patients.

DISCUSSION

Although surgical excision remains the gold standard for the treatment of NTM infections, the introduction of new antibiotics such as the macrolides present new treatment options. Pharmacological studies on clarithromycin showed good antimicrobial activity against atypical mycobacteria.[15] This first translated clinically into the successful treatment of Mycobacterium avium-intracellulare complex infections in patients with acquired immune deficiency syndrome (AIDS).[16] With the relatively benign pharmacological profile of the macrolides, small case reports eventually emerged revealing successful treatments of Mycobacterium avium-intracellulare complex infections in children.[11,12,14] Lindeboom et al.[12] discussed the treatment of two immunocompetent children with NTM cervicolymphadenitis. The children both underwent a 2-month treatment with a single modality of Biaxin only. The infections began responding within the first month of treatment, with complete resolution noted by 2 months. There were no complications of the treatment. Macrolide treatment was proving to be a possible alternative to surgical excision.

Similar to the pilot studies treating NTM infections with macrolides, our experience suggests that antibiotic therapy can resolve or at least ameliorate NTM infections. Of the 45 patients who were initially treated with antibiotics, 30 patients (67%) had resolution without surgical excision or curettage, a percentage similar to that published by Harza et al.[13]

Fifteen of the 45 patients who initially were treated with antibiotics underwent surgical excision for complete resolution of their lymphadenitis. Three categories of these patients were recognized. The first group, which consisted of only 7 patients (47%), showed no response to the antibiotics or continued to have progression of the infection while on a regimen of antibiotics. The second group (2 of 15 patients [13%]) received only a limited trial of antimicrobial therapy consisting of a period of 3 weeks or less. The third group (6 of 15 [40%]) showed some improvement or cessation of disease progression while on a regimen of antibiotics. The third group proceeded to surgery as either the parents' or the surgeons' choice, despite showing improvement. Therefore, even in the third group of patients who seemingly failed antibiotic treatment, a closer evaluation revealed that many responded positively while on a regimen of antibiotics.

The present retrospective review identified several cases in which treatment with antibiotics was a successful adjuvant therapy to surgical excision. In cases in which multiple lymph nodes were involved and not completely removed or in which there was recurrence after surgical intervention, addition of antibiotic treatment can complement surgical excision.

One argument against the benefit of antibiotic therapy is that the resolution of disease while on a regimen of antibiotics may represent the natural history of the infection. For NTM infections, duration of antibiotic treatment ranges from a minimum period of 2 months to a maximum period of 6 months. The studies evaluating the natural history of NTM infections have shown that these infections undergo a predictable progression starting with lymphadenitis. Then, the lymph node surfaces to the skin and erupts, which leads to resolution of the infection. In the present study, antibiotic therapy seemed to interrupt this natural progression in a majority of patients and resulted in minimization of the palpable lymph node and/or prevention of fistulization of the infected nodes.

As with all retrospective studies, the present study has weaknesses in selection and review bias. In addition, we were limited to and dependent on the clinical data that were recorded and available for review. The antibiotic regimen was diverse, making conclusions about specific medical therapies difficult to support definitively. Future

TABLE III.
Patients Treated with Antibiotics Alone (n = 30).

Patient No.	Age (yrs)	Location	Antibiotic Regimen	Length of Tx (mn)	Size (cm)	1 Month	2 Months	6 Months
1	2.1	R superolat	Bia	3.0	3 × 2			nonpalp
2	1.3	R submand	Bia	3.0	2 × 3		nonpalp	nonpalp
3	1.8	R preauricular	Bia	6.0	1 × 1	<1 × 1 cm		nonpalp
		R submand			2 × 2	0.5 × 0.5 cm		nonpalp
4	2.0	R submand	Rif/INH, >keflex	2.5	3 × 2		barely palp	nonpalp
5	2.0	R Preauricular	Bia/Rif	1.0	2 × 3	2 × 2 cm		nonpalp
		and submand			2 × 1	1 × 1 cm		nonpalp
6	1.3	L Level II	Bia/Rif, > biax/etham	4.5	6.5 × 5	4 × 4 cm		nonpalp
7	4.0	L submand	Bia	2.0	1.5 × 1		nonpalp	nonpalp
8	19.0	R parotid and Levels II and III	ethm/INH/Rif/strep	6.0	2.5			nonpalp
9	7.0	L submental	Bia	3.0	1.0		0.8 cm	nonpalp
10	8.0	R preauricular	cef/erythr	1.0	2 × 1.5	1.5 × 1.5 cm	nonpalp	nonpalp
11	9.0	B. coalescent	Bia	6.0	4 × 4	"doing better"		nonpalp
		LAD			3 × 3			nonpalp
12	13.0	Submental	unknown	U	1.5		fistulized	nonpalp
13	3.0	R cervical node	Bia, > recurred, > Bia	3.0	5 × 4.5	2nd inf nonpalp	1st inf nonpalp	nonpalp
14	1.8	Multiple B LAD	Bia/Rif, > Bia/etham, >		2.0	1.5 × 1.5 cm	1 cm	1 cm
		submandibular,	Bia/cipro, > Bia/	12.0	2.5	3 × 2 cm	1.5 × 2 cm	scarred
		parotid	etham/rif					
15	2.0	R parotid	Bia/rif/INH ->Bia	4.5	1.2			nonpalp
		R Level II			2.0			nonpalp
16	2.0	R Level II	Bia/rif	3.0	3 × 3.5		1.5 × 2 cm	nonpalp
		R supraclavicular			2.0			nonpalp
17	4.0	R Level I	INH/pyrid	2.0	2.5 × 1			nonpalp
18	2.0	R submand	Bia	3.0	3 × 2			nonpalp
					0.5 × 0.5			nonpalp
19	2.0	Multilobulated	Clinda/bia ->Bia	4.0	3 × 2		1 × 0.8 cm	nonpalp
		bilateral LAD						
20	2.0	R Level II	Bia	2.0	4 × 2.5	3 × 3 cm	stable and fistulized	sm scar
21	2.0	R submental	Azithr/etham	7.0	3 × 2	3 × 2 cm	1.5 × 0.3 cm	nonpalp
22	2.0	R submand	Bia/etham/rif/INH, >		1.5 × 1.9	2 × 4 cm	1 × 3 cm	0.5 × 0.7 cm
		w bilat LAD	Bia/etham	6.5				
23	2.0	R submand	INH	3.0	2 × 1	1.2 × 1 cm		nonpalp
					non-palp	1 × 1.5 cm		nonpalp
24	4.0	Mult L LAD	Bia	1.0	1.5 × 1	drained	nonpalp	nonpalp
					1 × 1			nonpalp
25	1.1	R submand	Bia/rif	1.5	2 × 1.5			0.5 × 0.5 cm
26	2.0	R submand	Bia	4.5	4 × 2	2 × 1.5 cm	same size	1 × 1 cm
		B nodes			2.0	<1 cm		nonpalp
27	1.4	R submand	Bia	3.0	3 × 2.5		2.5 × 2 cm	2.5 × 1 cm
28	1.5	L submand	Bia	6.0	2.0	<2 × 2 cm	1 × 1 cm	nonpalp
		2 nodes			1.0		1 × 1 cm	nonpalp
29	2.0	L submand	Bia	6.0	3 × 2.5	3 × 2.5 cm	3.5 × 1.5 cm	scarred
30	0.3	L level 2	Bia	2.0	3.2 × 2.7	3 × 2 cm		nonpalp

Tx = treatment; Mo = month; inf = infection; LAD = lymphyadenopathy; R = right; L= left; B = bilateral; Nonpalp = nonpalpable; Bia = biaxin; INH = isonazid; Rif = rifampin; Etham = ethambutal; PZA = pyrazinamide; Azithr = azithromycin; clinda = clindamycin; cef = cefzil; erythr = erythromycin.

TABLE IV.
Summary of Recurrences in Each Group (n = 55).

Therapy	Number Recurrence	Location of Infection	Recurred After	Treatment of Recurrence
Antibiotics Alone (n = 30)	1	Cervical node	Atbx stopped	Additional atbx
Antibiotics Followed by Surgical Excision (n = 15)	1	Parotid	Excision	3 months atbx
Surgical Excision Followed by Antibiotics (n = 5)	2	Parotid	Excision	1 month atbx followed by total parotidectomy
Surgical Excision Alone (n = 5)	1	Parotid	Excision	Superficial parotidectomy

Atbx = antibiotics.

prospective studies involving more defined medical regimens and closer follow-up may yield better information on the most appropriate medical management of these infections.

CONCLUSION

Some NTM cervicofacial lymphadenitis infections appear to respond to medical therapy alone. A trial of antibiotic therapy might be considered in patients with NTM

TABLE V.
Patients Treated with Antibiotics Followed by Surgery (n = 15).

Patient No.	Age	Location	Antibiotic Regimen	Size (cm)	Clinical Course
1	21 mo	R submand	Rif/INH (1 mo), >fistula	2	Slightly enlarged on meds, > fistula, > resolved with excision
2	4 yrs	R preauricular	Bia/etham (7 mo), >excision, >bia/etham (3 wks)	1.5 × 0.5	Min resolution on meds, > resolution with excision and postop atbx
3	2 yrs	R submand	Bia (5 mo), >fistula	2.5 × 2.5	Reduced to 2.0 cm^2 after 1 mo, > curettage after fistula, > resolution
4	2 yrs	L submand	Bia (1 wk), >excision	2.5 × 1.5	Resolved with excision
5	15 yrs	R Level II	INH/rif/etham/PZA (2 mo), >excision->INH/rif (4 mo)	4.0 × 4.0	Enlarged on 4 drug therapy, > resolved with excisions and post-op atbx
6	12 mo	R infraauricular	Bia (1 mo), >excision	1.0	No change on atbx, > resolved with excision
7	17 mo	L submand.	Bia (3 mo), >excision	3 × 2	Improving on meds, > resolved after excision
				1 × 0.5	
8	2 yrs	R Level II	Bia/rif (5 mo), > fistula-> excision, > bia/rif (1mo)	2	Improving on meds, > fistula, > residual disease after excision, >
				1.1	resolved with postop atbx
9	2 yrs	Bil LAD	Bia/rif (6 mo), >fistula, > curettage	2 and 1.1 × 0.5	Min improvement on atbx, > fistula, > resolved with curettage
				1.8 × 0.5	
10	18 mo	R submand	Bia/etham (3 wks), > excision	2 × 2.5	Unchanged on atbx, > resolved with excision
		R ant cervical		4 × 5	
11	2 yrs	Level II w/parotid	Bia (2 mo), > excision, > azithr/etham (3 mo)	6 × 4	Recurred after excision, > recurrence resolved with atbx
		extension		2	
12	2 yrs	L submand	Azithr/rif (1 mo), > curettage, > rif/etham (3)	3.2 × 2	Residual disease, resolving on antibiotics
13	2 yrs	R Level II	Bia (5 mo), > curettage	2.5	Not resolving on antibiotics
14	2 yrs	L Level III	Bia (1 mo), > excision with residual dz, > restarted	2.3 × 1.5	Residual disease was resolving on antibiotics but
			Bia (3 mo) and rif (1 mo), >excision		parents wanted surgical excision
15	16 mo	R submand	Bia/rif (1 mo), >Bia/etham (1 mo), >excision	2.0	No resolution on antibiotic therapy

R = right; L = left; Submand = submandibular; LAD = lymphadenopathy; mn = month; Rif = rifampin; INH = isonazid; Bia = biaxin; Etham = ethambutal; PZA = pyrazinamide; azithr = azithromycin; atbx = antibiotic; mo = month; yrs = years; dz = disease; Pt = patient.

cervicofacial lymphadenitis before surgical excision or as an adjuvant to surgical excision.

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