Current Diagnosis and Management of Peripheral Tuberculous Lymphadenitis

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Peripheral tuberculous lymphadenitis accounts for ~10% of tuberculosis cases in the United States. Epidemiologic characteristics include a 1.4:1 female-to-male ratio, a peak age range of 30–40 years, and dominant foreign birth, especially East Asian. Patients present with a 1–2 month history of painless swelling of a single group of cervical lymph nodes. Definitive diagnosis is by culture or nucleic amplification of *Mycobacterium tuberculosis*; demonstration of acid fast bacilli and granulomatous inflammation may be helpful. Excisional biopsy has the highest sensitivity at 80%, but fine-needle aspiration is less invasive and may be useful, especially in immunocompromised hosts and in resource-limited settings. Antimycobacterial therapy remains the cornerstone of treatment, but response is slower than with pulmonary tuberculosis; persistent pain and swelling are common, and paradoxical upgrading reactions may occur in 20% of patients. The role of steroids is controversial. Initial excisional biopsy deserves consideration for both optimal diagnosis and management of the otherwise slow response to therapy.

Peripheral tuberculous lymphadenitis—previously termed "scrofula"—is a unique manifestation of disease due to organisms of the *Mycobacterium tuberculosis* complex. Epidemiologic characteristics differ from those of pulmonary tuberculosis, clinical manifestations are variable, and diagnosis may be challenging. Of most importance for the clinician, response to therapy may be slow or paradoxical, with the frequent development of enlarging or new lymph nodes during and even after effective treatment in HIV-negative patients and of immune reconstitution inflammatory syndrome (IRIS) in HIV-positive patients. The optimal approach to management of such responses deserves reconsideration in light of newer studies in both HIV-negative and HIV-positive patients.

Received 1 April 2011; accepted 7 June 2011.

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Clinical Infectious Diseases 2011;53(6):555–562

1058-4838/2011/536-0009$14.00
DOI: 10.1093/cid/cir454

Recent studies have helped define the contemporary presentation of tuberculous lymphadenitis and its epidemiology. In addition, more extensive data are now available on both standard and novel diagnostic methods and the optimal management of complications during treatment. We searched Medline for English articles with use of the Medical Subject Heading term "Tuberculosis, Lymph Node" as a major topic from 1990 through 2011 to provide the clinician a contemporary perspective on these issues from both developed and developing countries.

EPIDEMIOLOGY

While overall rates of pulmonary tuberculosis have continued to decrease in the United States, the proportion of extrapulmonary cases, with their principal subset, lymphadenitis, has increased. Of the 12 904 cases of tuberculosis in the United States in 2008, 1103 (8.5%) represented lymphadenitis [1]. Epidemiologic characteristics from 14 studies on tuberculous lymphadenitis are shown in Table 1 and are separated into reports from countries where tuberculosis is endemic (>40 cases/100 000 population) and from countries where it is not

endemic. In most series, tuberculous lymphadenitis is more common among women than among men (composite ratio, 1.4:1)—a different pattern than for pulmonary tuberculosis, for which disease is more common among men [13]. Although formerly a disease of children, the peak age range in recent series has been 30–40 years. In countries where tuberculosis is not endemic, the majority of patients are foreign-born, with a pattern consistent with reactivation disease.

A consistent observation in studies from nonendemic countries is that immigrants from Southeast Asia and India appear to have a special predilection for tuberculous lymphadenitis [4, 5, 8, 11]. In a study from Texas, the odds ratio (OR) was 11.3 for patients from Southeast Asia ($P < .01$) and 12.7 for patients from India ($P < .01$), compared with other ethnicities [4]. In a study involving HIV-negative Somalis in Minnesota [6], 30% of 407 patients with tuberculosis had lymphadenitis, which suggests that Africans may also have an increased risk of lymph node tuberculosis.

The basis for enhanced risk among women and Asians and, possibly, Africans is not known. Possible host factors include occupations or cultural practices favoring oropharyngeal exposures to *M. tuberculosis* complex (eg, exposure to *Mycobacterium bovis* or *M. tuberculosis* from milking cows), genetically determined organ tropism, hormonal influences, effects related to bacillus Calmette-Guérin (BCG) immunization, and differences in health-seeking behavior.

In addition, genetic differences in the virulence of organ tropism of different strains of *M. tuberculosis* may play a role [18, 19]. Extrapulmonary tuberculosis, including lymphatic tuberculosis, is more common among immunocompromised patients, including those with HIV infection [20, 21]. Although diabetes mellitus is a risk factor for pulmonary tuberculosis, studies suggest that it may reduce the relative risk of tuberculous lymphadenitis [4, 5]. In a review of extrapulmonary tuberculosis in the United States, traditional risk factors for pulmonary tuberculosis, such as homelessness and excess alcohol use, were associated with a lower risk of disease [7].

MICROBIOLOGY

Many studies of tuberculous lymphadenitis do not report speciation of the causative organism in the *M. tuberculosis* complex. *M. bovis* was historically a common cause of tuberculous lymphadenitis, but pasteurization and bovine tuberculosis programs have virtually eliminated this source of human infection in developed countries; risk remains with consumption of unpasteurized milk [22]. *M. tuberculosis* is the usual cause of tuberculous lymphadenitis [23]. Other infectious causes of chronic lymphadenitis include nontuberculous mycobacteria (including *M. scrofulaceum, M. avium,* and *M. haemophilum*), *Toxoplasma* species, *Bartonella* species, and fungi. Noninfectious causes include

Table 1. Epidemiology of Tuberculous Lymphadenitis

Location	Date	N	Mean Age	Female %	Foreign-born %	HIV+ (*n*)	Pulmonary involved* (%)
Non–TB-Endemic							
California [2]	1992	40	38	52	82	11	28
Washington DC [3]	1995	8	30	62	NA	0	0
Texas [4]	2003	73	41	62	68	0	0
California [5]	2005	106	34	66	92	5	0
Minneapolis [6]	2006	124	25	57	100	0	0
US [7]	2009	19 107	38	58	61	2102	0
Australia [8]	1998	31	35	NA	87	0	3
France [9]	1999	59	38	52	69	0	0
Germany [10]	2002	60	41	68	70	0	0
UK [11]	2007	128	41	53	90	2	17
UK [12]	2010	97	14–89⊥	59	90	4	NA
TB-Endemic							
Taiwan [13]	1992	71	42	59	0	0	42
Zambia [14]	1997	28	24	54	0	0	32
Taiwan [15]	2008	79	37	58	0	0	0
India [16]	2009	893	20	58	0	0	18
Qatar [17]	2009	35	29	20	86	0	9

NOTE. NA, not available; TB, tuberculosis.

* In some cases, pulmonary tuberculosis is inferred from a positive chest radiograph, but not proven by culture.

⊥ Reflects age range, 57 of 97 patients were between 20 and 39 years old.

Table 2. Presenting Signs and Symptoms of Tuberculous Lymphadenitis

Location (Year)	N	*n*		Fever		Cough		Cervical Involvement		Abscess formation (%)		Sinus drainage (%)	
		HIV(-)	HIV(+)	HIV(-)	HIV(+)	HIV(-)	HIV(+)	HIV(-)	HIV(+)	HIV(-)	HIV(+)	HIV(-)	HIV(+)
Non–TB-endemic													
California (1992) [2] *	40	29	11	18%	63%	NA	NA	58%	36%	NA	NA	NA	NA
California (2005) [5]	106	101	5	18%	80%	19%	100%	57%		13%		8%	
UK (1996) [25]	23	NA		52%		NA		40%		30%		23%	
UK (2007) [11]	128	126	2	26%		NA		87%	100%	21%		NA	
TB-endemic													
Zambia (1997) [14]	185	28	157	32%	44%	NA	NA	96%	99%	0%	4%	7%	3%
India (2007) [26]	121	45	20	23%		NA		69%		NA		4%	
India (2009) [16]	893	893	0	4%	0%	10%	0%	89%	0%	4%	0%	2%	0%

NOTE. NA = data not available.

* Reference includes 2 cases of nontuberculous mycobacteria, symptoms seen during paradoxical response not included.

neoplasms, sarcoidosis, Castleman disease, drug reactions, and nonspecific reactive hyperplasia.

CLINICAL FEATURES

Tuberculous lymphadenitis usually presents as a slowly progressive, painless swelling of a single group of lymph nodes [3, 24]. The duration of symptoms at the time of presentation is typically 1–2 months, varying from 3 weeks to 8 months [3, 5, 24]. In a series of patients in India, the mean duration of symptoms was significantly longer in men than in women [24].

Median lymph node size is 3 cm, but nodes may be up to 8–10 cm in diameter [15]. Patients do not generally report significant pain at presentation, and node tenderness during examination is noted in only 10%–35% of cases [3, 15, 17]. A draining sinus may be present in 4%–11% of cases [3, 17, 24]. Unilateral involvement of 1–3 nodes has been noted in 85% of cases [8]. Cervical chain involvement is most common and is reported in 45%–70% of cases, with 12%–26% in the supraclavicular region; ~20% of cases are bilateral [2, 5, 15, 17]. In a study from Zambia, symmetrical adenopathy with nodes typically <3 cm was reported in 94% of patients with HIV-induced lymphadenopathy, compared with 29% of patients with HIV-associated tuberculous lymphadenitis. In contrast, symmetrical adenopathy was observed in only 11% of HIV-negative patients with tuberculosis lymphadenitis, and nodes in this group were typically >3 cm [14].

Rates of systemic symptoms reported in different series vary depending in part on geographic origin and case selection (Table 2). In a series of 104 predominantly HIV-negative patients from California, fever was reported in 19% and weight loss in 16% [5]. In contrast, fever and weight loss were reported in 40%–60% of HIV-negative patients in series from Qatar and India [17, 24]. Systemic symptoms are reported more frequently in HIV-positive patients than in HIV-negative patients (76% of 21 vs 12% of 43 in a report from Taiwan) [15]. Concomitant pulmonary tuberculosis is reported in 18%–42% of patients (Table 1), with higher rates among HIV-positive patients than among HIV-negative patients (90% of 10 vs 28% of 25 in a study from Los Angeles) [2]. HIV-positive patients with tuberculous lymphadenitis typically have a higher rate of disseminated disease than do HIV-negative patients (38% vs 8%; $P < .001$) [27].

PRIMARY DIAGNOSTIC STUDIES

A definitive diagnosis of tuberculous lymphadenitis can be made by culture or polymerase chain reaction demonstration of *M. tuberculosis* in an affected lymph node, thereby permitting distinction from other mycobacteria that may cause lymphadenitis. Culture remains the gold standard for diagnosis, but may take 2–4 weeks to yield results. A positive acid-fast bacilli (AFB) stain result indicates a mycobacterial etiology and has excellent specificity for *M. tuberculosis* in adults. Histologic features, such as nonspecific lymphoid infiltrates, noncaseating granulomas, or Langerhan giant cells in areas of extensive caseous necrosis, support a diagnosis of probable tuberculosis in AFB-negative, culture-negative cases.

The relative sensitivities of different procedures (Table 3) and the potential therapeutic benefits should be considered in making the choice of diagnostic approach. Excisional biopsy is the most invasive approach to diagnosis; however, it has the highest sensitivity and may produce a more rapid and favorable symptomatic response [3] and has been recommended in cases involving multiple nodes [31]. Rare complications of biopsy include postsurgical pain, wound infection, sinus formation, and scar [28]. In a study from Hong Kong, 80% of specimens from excisional biopsy yielded positive culture results, compared with 17% from fine-needle aspiration (FNA) specimens [32].

Table 3. Primary Diagnostic Tests in Tuberculous Lymphadenitis

Location (Year)	Culture (+)	AFB (+)	GI (+)	Culture + GI (+)	NAAT (+)
California (1992) [28]					
Excisional Biopsy	28/30 (93%)	11/30 (37%)	23/30 (77%)	N/A	N/A
FNA	18/29 (62%)	10/29 (35%)	16/29 (55%)	N/A	N/A
France (1999) [9]					
Excisional Biopsy	12/39 (31%)	2/39 (5%)	32/39 (82%)	N/A	N/A
FNA	8/26 (31%)	2/26 (8%)	N/A	N/A	N/A
California (1999) [29]					
FNA	44/238 (18%)	58/238 (24%)	84/238 (35%)	N/A	N/A
India (2000) [30]					
Excisional Biopsy	4/22 (18%)	5/22(23%)	13/22 (59%)	17/22 (77%)	15/22 (68%)
FNA	2/22 (10%)	4/22 (18%)	7/22 (32%)	9/22 (41%)	12/22 (55%)
California (2005) [5]					
Excisional Biopsy	24/34 (71%)	15/39 (38%)	36/31 (88%)	N/A	N/A
FNA	48/77 (62%)	5/19 (26%)	47/76 (62%)	N/A	N/A
UK (2010) [12]					
FNA	65/97 (67%)	22/97 (23%)	77/97 (79%)	88/97 (91%)	N/A

NOTE. NA, not available; AFB, acid-fast bacilli; GI, granulomatous inflammation; NAAT, nucleic acid amplification test; FNA, fine-needle aspiration.

FNA has emerged as a first-line diagnostic technique, especially in tuberculosis-endemic countries, where the test is both sensitive and specific [29, 33]. FNA is safer, less invasive, and more practical than biopsy, especially in resource-limited settings. However, of note, in the majority of FNA studies from these regions, the diagnosis of tuberculosis was based on detection of granulomatous inflammation (GI). In settings where tuberculosis is not endemic, the finding of GI may not be as specific for tuberculosis. In a study of 97 cases from the United Kingdom (90% of which were in foreign-born patients), 67% of FNA specimens had positive culture results, and 79% had GI. Fifty-four (70%) of 77 FNA specimens with GI had cultures positive for *M. tuberculosis* [12]. In a study from California, 18% of FNA specimens from 180 patients (106 HIV-positive) yielded positive culture results. When positive culture results were combined with detection of AFB, the sensitivity of FNA specimens was 46% and specificity was 100% [29]. Among 106 predominantly HIV-negative cases from California, the rate of culture positivity from excisional biopsy and FNA specimens was similar (71% and 62% respectively; $P = .4$) [5]. Fluorescence microscopy using light-emitting diodes is an inexpensive and robust method of AFB smear analysis of FNA specimens from children with tuberculous lymphadenitis in South Africa [34].

Nucleic acid amplification tests (NAATs) may provide a rapid, specific, and sensitive means of diagnosis. In a study from India, 17 (77%) of 22 cases diagnosed by culture and detection of GI were detected by testing of excisional biopsy samples, compared with 9 (41%) of 22 by testing of FNA samples. With the addition of NAAT of the FNA specimens, 18 (82%) of 22 cases were detected [30]. A systematic review of NAAT in tuberculous lymphadenitis revealed highly variable and inconsistent results (sensitivity, 2%–100%; specificity, 28%–100%), with more favorable performance from commercial assays and with sample sizes >20 uL [35]. In a study from Germany, 6 of 10 tuberculous lymphadenitis cases confirmed by culture were detected by the newer GeneXpert test; 3 cases with positive results had negative culture results, but subsequent investigation suggested that these were true cases [36].

ANCILLARY DIAGNOSTIC TESTS

Ancillary diagnostic tests may be useful in raising the suspicion of tuberculous lymphadenitis before definitive diagnosis or in supporting the diagnosis of cases with nondiagnostic microbiologic or histologic findings (Table 4). In the United States, 90 (98%) of 92 HIV-negative patients with tuberculous lymphadenitis had a positive tuberculin skin test (TST) result [5]. TST reactions may be falsely positive in persons with prior BCG or prior infections with nontuberculous mycobacteria (which may produce TST reactions of 5–14 mm) [38]. Because interferon-γ release assays (IGRAs) are not affected by BCG or nontuberculous mycobacteria other than *M. marinum*, *M. kansasii,* and *M. szulgai,* they are more specific than the TST [39]. In a study of tuberculous lymphadenitis from South Korea, the sensitivity and specificity of TST were 86% and 67%, respectively, and of IGRAs, 86% and 87%, respectively [37].

Chest radiograph findings may be positive in 10%–40% of patients, and positive sputum AFB stains or culture results may

Table 4. Ancillary Diagnostic Tests in Tuberculous Lymphadenitis

Location (Year)	N (HIV+)	Sputum culture positive (%) (HIV+%)	AbnormalCXR (%) (HIV+%)	TST positive (%) (HIV+%)	IGRA positive (%)
Non–TB- endemic					
California (1992) [2]	40 (11)	NA	45 (90)	70 (0)	NA
California (2005) [5]	106 (5)	18 (100)	39 (60)	91 (20)	NA
UK (1996) [25]	23	NA	55	NA	NA
TB-endemic					
Zambia (1997) [14]	185 (157)	NA	3 (0)	13 (0)	NA
India (2009) [16]	893	4	10	89	NA
Korea (2009) [37]	21	NA	NA	86	86

NOTE. NA, not available; TST, tuberculin skin test; CXR, chest X-ray; IGRA, interferon-gamma release assay.

be present for a small proportion of HIV-negative cases. Tuberculous lymphadenitis was associated with higher incidence of surrounding soft-tissue edema, homogeneity, intranodal cystic necrosis, matting, and posterior enhancement, compared with lymph node metastases on neck ultrasound [40]. In the evaluation of abdominal lymph nodes by contrast-enhanced CT, tuberculous lymphadenitis was associated with higher incidence of peripheral enhancement with multilocular appearance and heterogeneous attenuation, compared with lymphoma [41].

Mycobacterial adenitis, caused by nontuberculous mycobacteria, such as *M. avium* complex, is typically seen in non-BCG immunized children in developed countries [42]. The indolent presentation is similar to that seen with *M. tuberculosis*, although other diagnostic features may differ (Table 5). Treatment of nontuberculous mycobacteria adenitis is surgical and achieves resolution rates >70% [43].

ANTIBIOTIC TREATMENT

The Infectious Disease Society of America (IDSA) recommends 6 months of the following treatment for lymphadenitis caused by drug-susceptible organisms [44]: isoniazid, rifampin, pyrazinamide, and ethambutol for 2 months, followed by isoniazid and rifampin for another 4 months. The 6-month recommendation is supported by studies that showed no difference between 6 and 9 months of treatment in cure rates (89%–94%) [45, 46] or relapse rates (3%) [47].

STEROID THERAPY

The benefit of routine corticosteroid therapy for peripheral tuberculous lymphadenitis is unknown. A double blind, placebo-controlled trial involving 117 children with lymph node

Table 5. Features of Peripheral Lymphadenitis Due to *M. tuberculosis* vs. Nontuberculous Mycobacteria

	TB	NTM
Age range (years)	20–40	1–6
Sex distribution	F>M	F≥M
Birth country	TB-endemic	Non–TB-endemic
HIV infection	Common in HIV-endemic countries Uncommon in developed countries	Rare
Clinical features	Indolent painless swelling Systemic symptoms: uncommon in HIV-negative, common in HIV-positive	Indolent painless swelling Systemic symptoms: uncommon
Location	Cervical	Cervicofacial
Pulmonary disease	Common	Absent
Tuberculin skin test	Positive	Occasionally positive
IGRA	Positive	Negative
Histology	Reactive adenitis	Caseating granuloma
Treatment	Antibiotics +/− excision	Excision +/− antibiotics
Paradoxical reactions	Common	Absent

NOTE. TB, tuberculosis; NTM, nontuberculous mycobacteria,
IGRA, interferon gamma release assay; TM, non-tuberculous; TB, tuberculosis.

endobronchial tuberculosis revealed a significantly greater improvement in those who received a 37-day tapering course of steroids ($P < .05$) [48]. Only uncontrolled studies are available on treatment outcomes in adults with peripheral lymphadenitis [49, 50]. Steroids have been used selectively for local discomfort [31], a significant issue for some patients in our experience. IDSA guidelines do not recommend the use of steroids in the treatment of tuberculous lymphadenitis [44]. Adjuvant immunotherapy with anti–tumor necrosis factor agents has been studied in small numbers of patients for routine treatment of all forms of tuberculosis, but available data are insufficient to make a recommendation [51].

PARADOXICAL UPGRADING REACTIONS

A unique and disturbing feature of successful treatment of drug-susceptible tuberculous lymphadenitis is the frequency with which patients experience worsening of symptoms during treatment (ie, paradoxical upgrading reaction [PUR]). Reported rates of PUR vary and depend, in part, on the definition that has been applied. One definition is the development of enlarging nodes, new nodes, or a new draining sinus in patients who have received at least 10 days of treatment [50]. A narrower definition excludes earlier cases because it requires initial clinical improvement before worsening and does not include draining sinuses [52].

PUR has been reported in 20%–23% of HIV-negative patients [5, 49, 50]. It occurred at a median of 1.5 months (46 days; interquartile range, 21–139 days) after initiation of treatment in a study from London and persisted for a median of 2 months (67 days; interquartile range, 34–111 days) [50]. In reports from California and South Korea, onset occurred at a mean of 2–3.5 months after initiation of treatment and resolved at a mean of 3.9 additional months [5, 49]. Manifestations of PUR have included enlarging lymph nodes in 32%–68% of cases [50], new nodes in 27%–36%, pain in 60%, and draining sinuses in 12%–60% [5, 49, 50]. In addition, increased adenopathy has also been reported in 9%–11% of patients a mean of 27 months after successful treatment [5, 53].

Male sex (OR, 2.60) and the presence of local tenderness at the time of diagnosis (OR, 2.90) were independently associated with PUR [49]. Biopsy or culture of nodes involved in PUR typically shows granuloma formation and negative culture results with or without positive AFB stains [5, 50]. These features are consistent with a robust immune response to *M. tuberculosis* with initiation of antibiotic therapy and release of mycobacterial antigens.

The pathogenesis of PUR in patients with HIV infection and tuberculous lymphadenitis is more complex, because IRIS from newly initiated antiretroviral therapy (ART) also contributes to the exaggerated inflammatory response, as it does in pulmonary tuberculosis [54]. Definitions of paradoxical IRIS in HIV infection vary but typically require some evidence of response to ART (eg, decreased viral load or increased CD4 cell count) and evidence of a worsening of the complicating infection [55]. IRIS usually develops after at least several weeks of ART, 90% of cases occur within 3 months after starting ART, and rates are higher when ART is started at lower CD4 cell counts [55, 56]. Thus, worsening of tuberculous lymphadenitis in patients with HIV infection and newly initiated ART may reflect the sum of the expected rate of PUR among HIV-negative persons plus an additional contribution from IRIS. Rates of PUR and/or IRIS have ranged from 22% to 60% in reported series involving HIV-positive patients treated for tuberculous lymphadenitis who have initiated ART [5, 54, 57]. Furthermore, HIV-positive patients with apparent sole pulmonary tuberculosis may develop peripheral or central lymphadenitis as the manifestation of IRIS [58].

Steroids have been considered as a means to reduce the robust immune response in PUR, but their use is controversial. Some authors report benefit [52, 53], but retrospective studies have shown that steroids did not prevent PUR in patients who received them from the onset of treatment [59] and had no effect on the duration of PUR [49, 50].

SURGICAL THERAPY

IDSA guidelines recommend surgical excision only in unusual circumstances, and these circumstances are not defined explicitly [44]. Although surgical excision combined with antibiotic therapy has produced favorable outcomes [60], we are not aware of controlled studies that have compared excision plus antibiotic therapy with antibiotic therapy alone. Two considerations suggest that early excisional biopsy be considered more frequently as an adjunct to antibiotic therapy, especially for patients at risk of PUR (eg, those with baseline tenderness) in settings where expert surgical care is available and when cosmetic considerations are not a contraindication. First, some patients who respond to medical treatment have significant baseline and persistent nodal discomfort, which might be ameliorated by excision. Second, paradoxical upgrade reactions are common and uncomfortable and require additional medical visits and consideration of prolonged antibiotic therapy and/or corticosteroids, all of which might potentially be avoided by excision. Surgical excision should also be considered as an adjunct to antibiotic therapy for disease cause by drug-resistant organisms.

Surgical excision has been recommended for PUR and for treatment failure in cases of tuberculous lymphadenitis and for patients who have discomfort from tense, fluctuant lymph nodes [5, 61]. In a retrospective review, aspiration, incision, and drainage or excision were associated with a trend toward a shorter duration of PUR [50]. Surgical excision is the recommended

therapy for cervical lymphadenitis due to nontuberculous mycobacteria in children and has been associated with better outcomes than 3 months of 2-drug antibiotic therapy [62–64].

CONCLUSION

Tuberculous lymphadenitis represents ~10% of cases of tuberculosis in the United States and is frequently the sole manifestation of extrapulmonary tuberculosis. Disease rates are highest among patients aged 30–40 years, and disease is more common among women and patients of Asian descent. Tuberculous lymphadenitis may respond slowly to standard antibiotic treatment, with persistent discomfort and the development of culture-negative paradoxical upgrading reactions in as many as 20% of patients. Frequent patient follow-up during treatment is recommended for reassurance and management of local discomfort. Initial surgical excision has optimal diagnostic sensitivity and deserves both current consideration and further study as an adjunct to standard antibiotic therapy to improve the otherwise slow response to treatment.

Acknowledgments

We thank Fred Pond for his assistance with the literature search strategy.

Potential conflicts of interest. C. F. v. R. has served as a consultant for Oxford Immunotec. J. F. and A. B.: no conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed in the Acknowledgments section.

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