

CASE REPORT

Mycobacterium avium Complex Cervical Lymphadenitis in an Immunocompetent Adult[∇]

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Nontuberculosis mycobacterial cervical lymphadenitis is a relatively common disease in immunocompetent children but a rare disease in immunocompetent adults. We report the diagnosis and treatment of *Mycobacterium avium* complex cervical lymphadenitis in an adult female. Our evaluation of immune competence, including gamma interferon (IFN- γ) and interleukin-12 (IL-12) signaling, found no evidence of deficiency.

CASE REPORT

A 54-year-old female with well-controlled hypothyroidism presented with a gradually enlarging right submandibular mass of several months' duration. She was otherwise asymptomatic and was treated with two courses of oral cephalexin with no discernible improvement. A fine-needle aspiration was performed that was nondiagnostic, and she subsequently developed a fistulous tract. Excision of the mass was undertaken, and a necrotic mass was found adjacent to the right submandibular gland. This was treated with an excision of the fistulous tract, right submandibular gland, and surrounding lymph nodes. Two of the five excised nodes and the fistula tract exhibited mixed necrotizing granulomatous inflammation. A Gram stain revealed heavy mononuclear cells, few polymorphonuclear white blood cells, and no organisms. Gomori methenamine silver and acid-fast bacilli stains were negative. Specimens were sent for culture, and standard aerobic and anaerobic bacterial cultures and fungal cultures were negative.

Both a Mantoux skin test and a Quantiferon TB Gold test were negative. No antibiotics were initiated, pending the results of the mycobacterial culture. At 2 weeks, the culture became positive with acid-fast bacteria. This was ultimately identified as *Mycobacterium avium* complex, by means of a *Mycobacterium avium* complex AccuProbe (Gen-Probe, San Diego, CA), which, while unable to differentiate between *M. avium* and *M. intracellulare*, is otherwise quite specific; most clinical laboratories do not differentiate these species due to the cost and the lack of difference in treatment between species (3, 9). The isolate was susceptible to clarithromycin and clofazimine, intermediate to ciprofloxacin, rifabutin, ethambutol, streptomycin, and amikacin, and resistant to rifampin. As the patient's incision had healed well and a follow-up computer-

ized tomography scan noted no clear evidence of a mass or infection, no antimicrobial treatments were initiated.

An immunologic workup was undertaken given the rarity of this infection in adults. The patient's complete hematology profile was normal, with a normal differential of her white blood cells. A comprehensive metabolic panel, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), thyroid-stimulating hormone (TSH), and vitamin D level were normal. She was HIV antibody negative, and flow cytometry of T and B lymphocytes was normal, with results as follows: number of TCD3 cells, 1,743 (83%); number of CD4 cells, 1,071 (51%); number of CD8 cells, 630 (30%); CD4/CD8 ratio, 1.7; and number of CD19 cells, 189 (9%). Immunoglobulin levels were as follows: IgG, 1,633; IgA, 218; and IgM, 92; all were within normal limits. Neutrophil function testing with nitroblue tetrazolium was performed, with 100% of neutrophils reducing nitroblue tetrazolium, as is normal. The gamma interferon (IFN- γ) receptor index was 4.3, with a reference range of >2.1, and an interleukin-12 (IL-12) receptor assay was reported as qualitatively present, with a mean fluorescence intensity (MFI) index of 3.6. P-STAT1 expression was normal by flow cytometry, with a fold increase of 6.2 with IFN- γ stimulation. These results are indicative of normal IFN- γ and IL-12 signaling. Thus, no immunologic defect was detected with the performed assays. She had no recurrence of her neck mass at 6 months.

Cervical lymphadenitis is the most common presentation of nontuberculosis mycobacterial (NTM) infection in children, with the predominant etiologic agent being *Mycobacterium avium* complex (17, 18). Conversely, in adults cervical lymphadenitis is almost exclusively caused by *Mycobacterium tuberculosis*, except for immunocompromised patients, such as those with AIDS or lymphoma (13, 15, 17, 18, 24, 26). More recently, extrapulmonary NTM infections have been associated with defects in IFN- γ and interleukin-12 signaling (2, 10, 12). Antitumor necrosis factor alpha (TNF- α) therapy has also been associated with NTM infection, particularly with *Mycobacterium avium* (27). Cervical lymphadenitis in an immunocompe-

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tent patient remains a rare entity, with few well-documented cases previously reported (1, 6). *Mycobacterium avium* complex cervical lymphadenitis has not been reported in an adult with documentation of normal IFN- γ and IL-12 signaling.

Mycobacterium avium complex is an unusual cause of extrapulmonary infection in immunocompetent adults, particularly cervical lymphadenitis. The prevalence of *Mycobacterium avium* complex cervical lymphadenitis in large surveys of mycobacterial infections has ranged from less than 1% to 3% in adults (11, 17, 20, 24). In a small survey on NTM lymphadenitis, two of seven cases in adults were attributed to *Mycobacterium avium* complex (7). However, these studies did not address underlying immunocompromise or disease. A case report from 1969 with a Runyon group III, which includes *Mycobacterium avium* complex, cervical lymphadenitis (25) and a 1980 case report (5) detail infections in a previously healthy adult but do not report any other evaluation of the patients' immune status. In 2000, Asensi et al. reported *Mycobacterium avium* complex cervical lymphadenitis in a 52-year-old male with normal immunoglobulin, complement, and granulocyte levels, normal FACS lymphocytic subpopulations, normal lymphocyte and granulocyte function, and HIV antibody and viral load negativity (1). Likewise, in 2007, de Pedro et al. reported an 18-year-old male with *Mycobacterium avium* complex cervical lymphadenitis with a negative HIV antibody level, normal CD4 count and CD4/CD8 ratio, and normal immunoglobulin and complement levels (6). IFN- γ and IL-12 signaling was not documented in any of the reports.

Mycobacterial infection ultimately leads to macrophage engulfment of the mycobacteria, resulting in macrophage production of IL-12. IL-12 then stimulates NK and T cells to produce IFN- γ ; IFN- γ then activates innate and adaptive immune response to the infection, primarily through the Jak-Stat signaling pathway (14, 23). IFN- γ and Stat-1 signaling dysregulation, while rare, causes selective holes in immunity that predispose patients to infection with NTM. This has been well illustrated in several cases of severe atypical mycobacterial infections in patients with IFN- γ receptor deficiency and IFN- γ autoantibody and Stat-1 defects and IL-12 receptor deficiency (2, 10, 13, 14). Additionally, these or similar defects may be more common than have been reported. A study from Thailand noted 128 cases of disseminated NTM infection in adults (9 with *M. avium* complex infection), with only 15 of the patients having a diagnosed underlying disease, suggesting a cell-mediated immune defect (4).

Immunomodulating medications have been implicated in mycobacterial infections. TNF blockade interferes with chemokine induction for cell recruitment, granuloma formation in response to mycobacterial infection, and maintenance of granulomas and potentially impairs T-lymphocyte control of the infecting mycobacteria. Patients using TNF- α inhibitors are at increased risk for mycobacterial infections (19, 22, 27).

Identification of these defects has significant clinical implications. Partially deficient patients respond to treatment with antimicrobials and IFN- γ therapy. These patients will always be at risk of recurrence or repeat mycobacterial infections and are often given prophylaxis indefinitely. Another approach favored by some is aggressive diagnosis of the immune defect, close monitoring, and early treatment of infection (14).

Diagnosis of the infection itself is not without pitfalls. Fine-

needle aspiration (FNA) is used extensively in the evaluation of cervical lymphadenitis. The presence of acid-fast bacilli on stains or growth on culture is, of course, highly specific, though not sensitive, and granulomatous inflammation without evidence of bacteria must be interpreted with caution (8, 12). Fistula formation, at least in children, is a common complication (28). Molecular methods such as DNA probes and PCR are also being used to increase the sensitivity of biopsy specimen testing. Skin testing with PPD frequently results in induration of 5 to 10 mm due to cross-reactivity, though skin testing with protein extracts of various NTM has been found to be much more sensitive, up to 90% (16). Due to the limitations of FNA and skin testing, excision of the entire node is often undertaken. Excision should be done with caution, as there is risk of injury to the facial nerve (12, 16).

There are few data beyond case reports on treatment of adults with *M. avium* complex cervical lymphadenitis. Of the four well-documented case reports, excision of the lymph node was undertaken in all cases. Antimycobacterial therapy was given in three of the cases, though in the case reported by de Pedro et al., it was stopped, as the isolate was resistant to the antimycobacterial drugs used. All patients were cured (1, 5, 6, 25). While NTM cervical lymphadenitis has been successfully treated in children with antimicrobials, surgery, or both, as well as observation alone, current ATS/IDSA guidelines recommend complete surgical excision in immunocompetent patients and antimicrobial therapy based on NTM species (12, 21, 28).

In light of recent data regarding host genetic factors in *Mycobacterium avium* complex infection, patients presenting with extrapulmonary *Mycobacterium avium* complex infections, in the context of no previous known immune deficiency or immune-modulating drug exposure, should be evaluated for IFN- γ , IL-12, and Stat-1 function. The presence of an immunologic defect may significantly alter management. Our experience and literature review suggest that treatment with excision alone may be adequate to treat *Mycobacterium avium* complex cervical lymphadenitis in an apparently immunocompetent adult, sparing the need for prolonged and complicated antimycobacterial chemotherapeutic regimens.

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