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Non-Tuberculosis Mycobacterial Lung Disease and Infection

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Abstract

Mycobacterial infections are complex diseases and are even more in individuals suffering from immune-mediated inflammatory diseases (IMIDs). They can cause tuberculosis, nontuberculous mycobacteria (NTM) pulmonary infections, other localized NTM or disseminated infections, leprosy, and chronic ulcers (Buruli ulcer) [1]. IMID-afflicted patients are at increased risk; often have atypical clinical presentations and unusual or complicated clinical courses during therapy. Providers taking care of individuals with IMID must have some knowledge about mycobacterial infections to recognize and diagnose the disease [2]. They should not treat those infections alone and should look for expert guidance. Treatment usually implies multiple drugs that can cause severe side effects. This hazard can be reduced with judicious selection of therapeutic agents and close monitoring. Prevention of disease acquisition, reactivation, and recurrence should also be sought.

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Introduction

Ocular mycobacterial infection represents an important form of extra pulmonary infection which encompasses tubercular (TB) as well as nontubercular mycobacterial (NTM) diseases in and around the eye. It presents with diverse clinical manifestations because of a number of factors that are related to the microbe and the host [3]. In spite of recent revolutionary advances in diagnostic technologies, establishing the diagnosis as well as treating the disease is clinical challenges. Mycobacterial disease is known to have affected humans for more than a century and still it continues to be a global health concern. There are several challenges as far as TB is concerned. To list a few, TB stands as the most common opportunistic infection in HIV-positive patients in many developing countries. In 2009, 1.7 million people died from TB, including 380 000 people with concomitant HIV infection, which equates to about 4700 deaths a day.1 Yet another global threat is the emergence of multidrug-resistant (MDR-TB) and extensively drug-resistant strains of tuberculosis (XDR-TB). The World Health Organization has estimated there are 11.1 million patients with tuberculosis worldwide, of which 440 000 cases are due to MDR-TB. XDR-TB cases have been confirmed in 58 countries [4]. 1 a second important concern is the emergence of NTM infections, both in immune-competent and immune-compromised individuals in previously unrecognized settings and with new clinical manifestations.2 Clinical manifestations of NTM simulate typical tuberculosis. Lack of better laboratory tools for differentiation, lack of treatment guidelines, and resistance to routine antitubercular treatment challenge the early management of mycobacterial infections.

Mycobacterial Infections

Mycobacterial infections, cat-scratch disease, and toxoplasmosis are more common entities presenting as subacute or chronic lymphadenitis. The epidemiologic and clinical features that aid in the differentiation of typical and nontuberculous mycobacterial infections are summarized. The clinical manifestations virtually are identical. Typically, a child presents with a history of painless, (so-called cold) cervical node swelling. The submandibular cervical nodes usually are involved in nontuberculous mycobacterial infection, whereas other cervical nodes are involved more frequently with M [5]. tuberculosis. As the infection progresses, the skin overlying the node may develop a pinkish or violaceous discoloration caused by increased vascularity, although the skin temperature is not increased. This finding may be followed by

A patient with M. tuberculosis is more likely than one with atypical mycobacterial disease to be older than 4 years of age and to have generalized lymphadenopathy (10-20% of cases), bilateral node enlargement (10% of cases), a history of exposure to tuberculosis (93% of cases), and an urban residence. No differences have been noted, however, with regard to duration of adenopathy, fever, and presence or absence of constitutional symptoms. An abnormal chest radiograph has been noted in 28 to 71 percent of cases

caused by M. tuberculosis in contrast to the 98 to 100 percent of normal chest radiographs found in patients with nontuberculous mycobacterial adenitis. In a summary of 447 reported childhood cases of nontuberculous mycobacterial infections from 15 countries, Lincoln and Gilbert74 detected only 6 cases of bilateral cervical node involvement, with abnormal chest radiographs, and none with nodal enlargement other than cervical. Similar findings have been reported by other investigators. Intradermal tuberculin skin testing with purified protein derivative uncommonly produces more than 15 mm of induration at 48 hours in a child with nontuberculous mycobacterial infection, but reactions between 5 and 15 mm are common.76,86 Reactions of 10 to 20 mm can occur with Mycobacterium marinum and M. fortuitum infection.114 Tuberculin skin test positivity may persist, even when children are retested many years after infection. Cat-scratch disease may manifest days to weeks after the initial inoculation. Characteristically, a history of contact with a cat or kitten or a scratch is present. Later, when the primary lesion may have healed, tender regional adenopathy appears. Although axillary nodes most frequently are affected, 25 percent of children have isolated cervical node involvement. Middle cervical and parotid nodes are involved more often than are submandibular ones.122 Constitutional symptoms, present early in the course of the illness, usually are mild and may have resolved by the time the adenitis appears. Fever is observed in one fourth of patients and, if present, has a mean duration of 5 to 7 days.85 Nodes suppurate in one tenth to one third of patients.28,29 Rare manifestations include Parinaud syndrome, encephalopathy, exanthems (usually of the erythema nodosum type), and osteolytic lesions. Acquired toxoplasmosis may manifest as regional lymphadenopathy, frequently with posterior cervical node involvement. Most children exhibit few, if any, constitutional symptoms. If present, fatigue and generalized myalgia are prominent. The characteristic location combined with a history of exposure to cats or of eating undercooked meats should raise this diagnostic possibility, and the diagnosis may be confirmed by appropriate serologic testing. It is an uncommon etiology for cervical adenopathy in children living in the United States [6].

Chronic, recurrent cervical adenitis forms part of the periodic fever, aphthous ulcers, pharyngitis, cervical adenitis (PFAPA) syndrome, a chronic syndrome first described in 1987 [7]. It is characterized by periodic episodes of high fever greater than 39° C lasting 3 to 6 days and recurring every 3 to 8 weeks in association with aphthous ulcers, pharyngitis, and cervical adenitis, although symptoms such as abdominal pain, nausea, diarrhea, and headache also are described in 20 to 73 percent of children. In most children, the onset of disease occurs before they reach 5 years of age, the syndrome is self-limited, and recovery without long-term sequelae is the rule [8, 9]. Oral corticosteroids are effective in aborting an attack. Kikuchi-Fujimoto disease, also called subacute necrotizing lymphadenitis, is an uncommon disorder of uncertain etiology that also may manifest as cervical adenopathy, with or without fever. This disorder was described first in 1972 and seems to have a predilection for Asian women 25 to 30 years old, who generally have a benign course with spontaneous resolution over 3 to 4 months. Kikuchi-Fujimoto disease also has been reported in children, typically adolescents, although cases in children 2 years old are documented [10].

Discussion

NTM infection presents a growing global health problem, complicated by ubiquitous exposure to the organisms, incomplete understanding of the immune susceptibility to disease, increasing numbers of immune compromised patients, cumbersome diagnostic tests (with no prognostic tests) and costly, multi drug treatment regimens that often fail to cure. However, we must keep in mind that different disease mechanisms may be operating between different risk groups and preclinical models. NTM disease is frequently slow and progressive, affecting predominantly already vulnerable patient populations. Epidemiological and descriptive studies of patients are many, but gaps in knowledge remain. Foremost among these is a deconstruction of the immune susceptibilities to NTM lung disease. If we can understand potential patient risk profiles, screening tests could be efficiently deployed to identify infection at risk individuals within hours. Such screening tests as well as prognostic tests that can predict outcome (disease remission vs. persistence, optimal treatment course, life changes etc) during early treatment would be extremely beneficial for clinicians to make therapy decisions as soon as possible, with potential improvement of patient outcomes. In the current age of immunotherapy, where targeted augmentation of immune responses is now possible, research into adjuvant immune therapies that could be used to “boost” a weakened immune system would beneficial and could be redeployed from the cancer field. Such immune modulating interventions would go a long way in reducing the global burden of NTM disease. The true level of morbidity caused by NTM lung disease is slowly being revealed, in both developed and developing nations and in both immune competent and immune compromised populations. Disease burden is being documented in both childhood and adulthood disease in terms of both direct and indirect morbidity. A cohesive solution to the global challenge of NTM lung infection requires a multipronged approach involving not just epidemiological data, but also clinical and laboratory-based research for new diagnostics, prognostics, and treatments for use in machine learning. These cohesive approaches are urgent as NTM is more common in the warmer climates. Forty percent of the world's population live in the tropics1 and due to climate change, the tropic are expanding in area.

Acknowledgement

None

Conflict of Interest

None

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