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Review

Epidemiology of cervico-facial pediatric lymphadenitis as a result of nontuberculous mycobacteria

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ABSTRACT

Cervical lymphadenitis as a result of nontuberculous mycobacteria, otherwise known as scrofula, is a disease occurring almost exclusively in immunocompetent young children. The most frequent mycobacterial species responsible is *Mycobacterium avium*, but a large number of other species may also be involved. The epidemiology of such disease is revised here, and the impact of different species as causative agents of adenitis is also discussed.

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Introduction

Scrofula is a mycobacterial disease of the lymph nodes of the head and neck well known during ancient times; in the Middle Ages, it was also called the "king's evil," as it was believed the disease could be healed by the touch of royalty. Both tuberculous and nontuberculous mycobacteria (NTM) can be responsible for cervical lymphadenitis.

The cases of scrofula, which were very common in the past, are, at least in the great majority, imputable to *Mycobacterium tuberculosis* and *Mycobacterium bovis*; in the xx century this kind of disease has steadily decreased and is now very rare in developed countries, but, starting with the 1950s, an increasing number of cases as a result of NTMs have been reported [1].

Scrofula is typically a disease of childhood, but rare cases in adults have also been documented. The focus of this review is on the epidemiology of cervical lymphadenitis of otherwise healthy children, with the exclusion therefore of cases affecting immunocompromised patients.

Clinical notes

The disease typically affects immunocompetent children, most prevalent in those between the ages of 1 and 5 years old. It is hypothesized that NTMs present in the environment are ingested and enter the body through lesions in the oral mucosa (e.g. in concomitance with dental eruption), or by way of the lymphatic vessels that drain the mouth and pharynx. The lymph nodes most commonly affected include the jugulodigastric, submandibular, parotid/pre-auricular, submental and posterior triangle. In most of the cases, the patient is asymptomatic; less frequent symptoms can include a slight fever and malaise. The first manifestation is a nontender, indolent, mostly unilateral swelling (1–6 cm) which subsequently enlarges and, in consequence of the necrosis of the central part of the granulomatous lesions, liquefies becoming fluctuant. The skin becomes often violaceous as a consequence of the inflammatory reaction, and frequently the necrotic collection fistulizes.

In a limited number of cases, spontaneous healing occurs by fibrosis and calcification; regression is quite rare.

The initial stages of the disease are frequently interpreted as an incidental upper respiratory tract infection and antibiotics are prescribed which, however, prove to be ineffective. Differential diagnosis with tuberculous or pyogenic adenitis is needed, and the isolation of the agent in a culture is of paramount importance. For this purpose, the use of a liquid media is advisable to reduce the burden of cases with positive acid-fast microscopy which fails to grow if cultured on solid media only.

The skin test based on intradermal inoculation of sensitins, tuberculin analogs specific from the most common NTMs, has been used for many years to diagnose, in absence of a culture, NTM lymphadenitis; the diagnostic accuracy of such tests is at least questionable because of the high level of cross-reactions between the different antigens and with the tuberculin skin test itself. The discontinuation of commercialization of sensitins, despite the regret of some pediatricians, confirms their limited value.

The most resolutive intervention is nowadays considered the complete excision of the affected lymph nodes before the suppuration occurrence; the healing is obtained in a large proportion of cases, but recurrences are not exceptional. Other less usual possibilities include no intervention, antimicrobial therapy alone, fine needle aspiration and incision followed by drainage or curettage.

Epidemiology

Differently from NTMs isolated from pulmonary specimens – which only in a limited number of cases are clinically significant – the mycobacteria isolated from lymph nodes can never be considered contaminants or colonizers. The number of NTM species responsible for cervical lymphadenopathy is very high, and so far some of them have only been isolated from lymph nodal biopsies.

Mycobacterium scrofulaceum

M. scrofulaceum is one of the oldest of the NTM species; it was described in 1956 by Prissick and Masson in a report concerning ten cases of a new variant of scrofula presenting with a nontuberculous etiology [2]. Major emphasis is placed in this paper on the slow growth and the yellow pigmentation of the newly detected mycobacterium. The vagueness of such features, compatible with many mycobacterial species, were, along with the name "scrofulaceum", destined to influence the identification of mycobacteria isolated from adenitis over a long period of time.

Beginning in the 1970s, Wolinsky [3] reported an "abrupt change in the predominant etiologic agent from *M. scrofulaceum* to *Mycobacterium avium* complex" (MAC). Both the prevalent involvement of MAC and the paucity of cases due to *M. scrofulaceum* remain unchanged nowadays.

MAC

The first case of cervical lymphadenitis due to *M. avium* was reported in 1959 [4]; in subsequent years, when the taxonomic status of MAC was still far from being defined and related organisms were referred to as "Battey group", the first case series were published [5,6]. Starting in the 1980s, *Mycobacterium intracellulare* was also beginning to be reported among the agents of lymphadenitis. It remains, however, undistinguished from *M. avium* of which it is considered a variant [7]. The introduction of serotyping made for the first time possible a reliable distinction between *M. avium* and *M. intracellulare*, but, at the same time, produced the ambiguity of the association of such species with *M. scrofulaceum*, in the *M. avium-intracellulare-scrofulaceum* (MAIS) group [8]. With the commercialization of the nucleic acid probes, the definitive distinction of *M. avium* and *M. intracellulare* became within the reach of diagnostic laboratories.

Recently, a large-scale study [9] did not detect any case due to *M. intracellulare* in a group of children with adenitis. The

same study demonstrated furthermore that all the strains of *M. avium* investigated belonged to the subspecies *hominissuis*, with *M. avium* subsp. *avium* being totally absent.

In recent years, MAC has been enriched by several new species; of them, only *Mycobacterium colombiense* has been reported responsible for lymphadenitis [10,11].

Mycobacterium simiae complex

M. simiae, grown for the first time from a monkey, is a multidrug-resistant species frequently isolated in several geographic areas, in particular South-Western USA, Cuba and Israel. It is therefore not surprising that the involvement of this species in cases of adenitis has been reported right in these countries [12,13].

A number of species, genetically related to *M. simiae*, have been described in recent years; many of them have been reported responsible for scrofula. *Mycobacterium genavense*, a species well known for its inability to grow on conventional solid media and for the high number of disseminated infections in severely immunocompromised AIDS patient, is one of them [14]. *Mycobacterium interjectum* was first described following the isolation from a lymph nodal infection in a child [15], and many other isolates have been reported thereafter [16–18]. Two of the strains on which is based the description of *Mycobacterium triplex* [19] had been grown from lymph nodes. Particularly high is the number of cases reported so far related to *Mycobacterium lentiflavum* [20–24]. The papers describing the species *Mycobacterium heidelbergense* [25], *Mycobacterium palustre* [26], *Mycobacterium parmense* [27], *Mycobacterium florentinum* [28] and *Mycobacterium europaeum* [29] all include one isolation from chronic pediatric lymphadenopathy.

Mycobacterium haemophilum

Despite *M. haemophilum* is a fastidious organism which is often missed in culture because of the requirement of particular growth supplements and lower incubation temperatures, the number of pediatric lymphadenitis due to this organism is quite high. A very recent review [30] reports a particularly high frequency in Israel and The Netherlands where the *M. haemophilum* is the second most frequent organism responsible for such disease after *M. avium*. In a Dutch study [31] infections due to *M. haemophilum*, different from those due to *M. avium*, are associated with the involvement of multiple lymph nodes and extranodal areas.

Other slowly growing species

Mycobacterium malmoense is one of the species more frequently isolated from cervical lymphadenitis [32]; in countries where this organism is endemic, mainly the United Kingdom and Sweden, it ranks second after *M. avium*. Similar is the case of *Mycobacterium kansasii*, which in a recent paper [33] is reported to account for 5% of pediatric cervico-facial adenitis; more rare are the cases due to *Mycobacterium celatum* [34,35].

Among the species rarely isolated in clinical laboratories, at least one isolation from cervical lymphadenitis is reported for each of the following: *Mycobacterium heidelbergense* [25], *Mycobacterium mantenii* [36], *Mycobacterium palustre* [26], *Mycobacterium tusciae* [37] and *Mycobacterium asiaticum* [38]. In most cases, such strains were included among the ones characterized for the description of the new species. *Mycobacterium bohemicum*, an uncommon mycobacterium indeed, has been reported responsible for a relatively high number of cases of scrofula [39].

Mycobacterium gordonae and the members of the *Mycobacterium terrae* complex are only exceptionally responsible for disease in humans. Such characteristic is apparently confirmed for adenitis since for the first species, there is only one report present in literature [40], and only two cases – one due to *Mycobacterium arupense* [41] and one to *Mycobacterium terrae* [42] – are reported so far for the *M. terrae* complex.

Rapidly growing species

The numerous cases reported above – all related to slowly growing species – clearly contrast with the paucity of cases imputable to rapid growers. Their isolation from cervico-facial lymphadenitis is extremely rare and limited to the three most common species: *Mycobacterium fortuitum*, *Mycobacterium chelonae* [43] and *Mycobacterium abscessus* [44].

Discussion

The epidemiologic picture emerging from this review is not exempt from the following biases:

- The high proportion of cases of *M. scrofulaceum* reported until the 1980s is at least in part questionable: a number of species, among which *M. lentiflavum*, *M. tusciae*, *M. bohemicum* and many others, fit the rough characteristics taken into account initially to characterize *M. scrofulaceum*. Furthermore, the term “scrofulaceum” itself may well have played a role in the direct assignment of such species of many of the scotochromogenic slow growers isolated from cases of scrofula.
- The use of biochemical tests, widespread until the end of the last century, leads to wrongly assigning all the less frequently encountered NTMs to just one of the species (usually no more than about 30) present in the identification tables available in microbiological manuals.
- Even the use of more recent and more accurate methods like nucleic-acid probes is not exempt from the incorrect identifications due to cross-reactivity of some of the probes (Table 1).
- The lack of expertise may also lead to incorrect identification even by the users of genetic sequencing once databases that are not exhaustive or are not controlled are used [45].

It seems, therefore, not rash to assert that the role of *M. scrofulaceum* is - in literature related to pediatric cervical lymphadenitis – highly overestimated while, in contrast, is underestimated the involvement of many of the species described in the last 20 years.

It is now generally accepted that NTM species differ in their ability to cause lung disease in humans [46,47]. While

Table 1 – Species whose prevalence in cervical lymphadenitis is underestimated because of cross-reactions of commercial nucleic-acid probes [48] (only the species isolated at least once from cervical lymphadenitis are included).

Species	Misidentifications due to cross-reactions of		
	AccuProbe[a]	INNO LiPA mycobacteria[b]	Genotype mycobacterium CM
M. colombiense			*M. intracellulare*
M. heidelbergense		MAIS	
M. mantenii		MAIS	*M. intracellulare*
M. nebraskense	MAC or *M. intracellulare*	*M. intracellulare*	
M. palustre	MAC		
M. parascrofulaceum		*M. scrofulaceum*	*M. scrofulaceum*
M. sherrisii		*M. simiae*	*M. simiae*

[a] MAC, *M. avium* complex.
[b] MAIS, *M. avium-intracellulare-scrofulaceum* group.

for NTMs of respiratory origin, the problem of distinguishing contaminants from causative agents of disease does exist, the strains isolated from lymphadenitis (from excised lymph nodes, fine needle aspirates, and drainage material) are *ipso facto* clinically significant, thus making easy the speculation on different potentials of single species in infecting lymph nodes.

Although it seems certain that lymph nodal NTM infection originates from the environment, no direct connection exists between the prevalence of different species in the environment and their involvement in cases of adenitis. The case of MAC is striking; the two major species – *M. avium* and *M. intracellulare* – are both very common in the environment, but while the adenitis due to *M. avium* has by far the highest incidence, the cases due to *M. intracellulare* are, if any, extremely rare. *Mycobacterium xenopi*, one of the most prevalent species in many countries of Europe where it is often responsible for severe pulmonary diseases, has never been isolated from lymph nodes. Apart from *M. avium*, only one species among the most frequently isolated is involved in a balanced proportion in pulmonary and lymph nodal diseases: *M. malmo*ense.

It is surprising, in contrast, that species for which little awareness still exists in clinical laboratories are frequently isolated from scrofula: *M. lentiflavum*, *M. bohemicum* and *M. interjectum* are the most striking examples.

The involvement of rapidly growing mycobacteria in pediatric lymphadenitis is restricted to a very limited number of cases.

It seems likely, therefore, that although a ranking in pathogenic potential of different NTMs exists, this is not absolute, but rather organ-specific. Of the top pathogens for the lung, only *M. malmoense* is ranked for lymph nodes too. Other major responsible of lymphadenitis include, in adjunct to *M. avium* and *M. haemophilum*, most of the species of the *M. simiae* complex and *M. bohemicum*.

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