Introduction

Atypical mycobacterium infections commonly manifest as cervicofacial lymphadenitis in pediatric patients. The following is a discussion on the clinical manifestations, diagnostic methods and an update on the treatment of this disease process.

History

Hippocrates first coined the term “scrofula” around 400 BC in his writing *Aphorisms*. Scrofula now refers to a tuberculous infection of the cervicofacial lymph nodes. During the Middle Ages in England and France, royalty was believed to heal scrofula with a touch. This began with King Edward the Confessor in England around 1003 AD and Philip I in France in 1052. This disease process was called the “King’s Evil.” This showed that their right to rule was God-given.

In 1951, Prissick and Masson presented to the Canadian Public Health Association a new etiology of scrofula by chromogenic or non-tuberculous mycobacterial. They published their findings in their paper in 1956 and later coined the term *Mycobacterium scrofulaceum* in 1957. In 2 subsequent papers, *Mycobacterium avium*, previously described as virulent in chicks, was described in 2 children.

About Atypical Mycobacterium

Atypical mycobacterium is found naturally in soil and water environments. As opposed to tuberculous mycobacterium, atypical mycobacterial are not transferred from human-to-human from airborne contact. The most common single organ they affect are lungs, especially of immunocompromised adults. They have other manifestations such as skin disease manifested as subcutaneous nodules, cellulitis or abscesses. They can involve the eye as keratitis, scleral buckle infections and peri-ocular tissue.

The pathophysiology of mycobacterium comes mostly from studies immunocompromised adult so the exact pathophysiology of this topic can only be extrapolated from these studies and hypothesis. Mycobacterium avium complex (MAC) infections first adhere
to the mucosal surface, i.e. intestinal mucosa. Macrophages phagocytose these organisms, where they survive within a vacuole and replicate. When the host’s defense weakens, the host cell ruptures and spills replicate organisms. For atypical neck disease, this bacterium is suspected to be in secretions of the oral cavity and pharynx and go to anterior cervical lymph nodes, especially in the submandibular area. Children aged 2-5 years old are thought to have a higher prevalence of neck disease because they commonly place non-sterile objects from the environment in their mouths and also because of the eruption of deciduous teeth. For these reasons, the gingiva and oropharyngeal mucosa are thought to be portal sites for children. For tuberculous disease, the palatine tonsils are considered a portal site but there is no evidence for atypicals. Atypical infections of children usually do not disseminate to the lungs.

Atypical mycobacterial lymphadenitis in the head and neck is more common than tuberculous disease in children aged 1-12 year old. Lai et al. from Boston showed that atypicals accounted for 55 out of 60 mycobacterial infections in a retrospective review from 1972-1982. However, in children ages over 12 year old, 147 out of 154 mycobacterial infections were by tuberculous mycobacterium. In addition, this disease is more common in females ranging from 1.1:1 to 1.7:1 female to male ratio in studies from Wolinsky, Fraser et al., Tunkel et al., Robson et al., Kuth et al. As far as commonly affected ages of children, Tunkel et al. and Wolinsky et al. also showed the median age to be 2.33 and 2.92 years old. Kuth et al. and Fraser et al. showed mean ages of 2.2 and 4.2 years old respectively.

The most common pathogens of atypical mycobacterial lymphadenitis is MAC and M. scrofulaceum. Wolinsky showed a change in the most common pathogen from M. scrofulaceum to MAC. In 1958-1972, M. scrofulaceum was isolated in 35 specimens and MAC was isolated in 7 specimens. However in 1979-1990, M. scrofulaceum was isolated in only 9 specimens and MAC was isolated in 26 specimens. Lindeboom et al. also showed a MAC prevalence showing that 71 out of 100 children had MAC; 22 out of the 100 children were of M. haemophilum origin

Clinical Presentation

Atypical mycobacterial in children usually present as a firm, painless cervicofacial mass. The patient usually has taken 1 or more courses of antibiotics without much response. These masses may enlarge and become fluctuant. They have a characteristic violaceous hue. The overlying skin may become necrotic adding to the discoloration. They may have already started draining which can continue chronically with potential sinus tract formation. The most common area that the disease manifests is the submandibular region followed by the pre-auricular and parotid region. The diagnosis is more clinical so having a good differential is key for elucidating etiology. The differential for infectious neck disease includes tuberculous disease, cat scratch disease, toxoplasmosis, cytomegalovirus, Epstein Barr virus, staphylococcus and streptococcus species, Lyme disease, Brucellosis and HIV. Differential also includes malignancies like lymphoma, Kawasaki disease, and congenital neck masses. Diagnostic procedures may be undertaken including ultrasound guided fine needle aspiration or wound culture but the provider must be aware of the high incidence of chronic sinus tracts once the inner contents commence drainage.
Laboratory Work-up

To assist in diagnosis of mycobacteria, a Mantoux screening test with purified protein derivative (PPD) of 5 tuberculin units (TU) may be injected intradermally. Most children with atypical mycobacterial infections are negative or weakly reactive. If tuberculous disease is suspected after results of PPD test, some authors recommend getting a chest plain film.

Mycobacteria are known to be “acid-fast” bacilli (rod-shaped). Their lipid-rich and mycolic acid-containing cell walls allow for low permeability of basic dyes. The Ziehl-Neelson method is the most common way to stain for these organisms. Fuschsin and phenol is used for the reddish staining of the organisms suspected and then counterstained with methylene blue for a blue background. Another method is the Kinyoun stain, which is less used. Organisms are stained with auramine-rhodamine dye. This treatment shows bright yellow rods against a dark background under fluorescent microscopy. This is more sensitive than the Ziehl-Neelson method but has more false positives.

Cultures can be obtained for further diagnosis. Special solid agars are used, most commonly Lowenstein-Jensen medium. Ferric citrate can be added to search specifically for *M. Haemophilum*. Middlebrook 7H-11 agar plates are also commonly used. Specimens need at least 2-8 weeks incubation for adequate growth. This can render cultures of minimal use as results will likely come after treatment is completed. Liquid cultures can also be obtained with 7H-9 broth. The CDC recommends both solid and liquid methods for clinical specimens. The Runyon criteria can be used after culture growth further distinguishing the pathogen; this criteria uses pigment color with and without light exposure as well as rapidity of growth to classify different mycobacterial species. Species identification can be undertaken using nucleic acid probes and polymerous chain reaction (PCR).

Radiological Studies

With regards to children, minimizing radiation exposure is in the best interest of the patient. Ultrasound is a good study for this patient population for qualitative data about the size and numbers of affected lymph nodes, as well as anatomical planning for possible excision. A study to keep in mind is a chest plain film. When there is a strong suspicion for atypicals, chest films are generally not recommended; however, when tuberculous disease is high on the differential, chest films are a good way to screen for pulmonary involvement.

Computed tomography (CT) is study with relatively higher radiation exposure but allows for good details of anatomy surrounding the affected lymph node. There are some findings on CT that allow the ordering physician to strengthen a diagnosis. These findings include a ring enhancing lesion with skin extension, minimal or no fat stranding and intramedullary necrosis. As opposed to pyogenic lymphadenitis which may have significant fat stranding, atypical lymphadenitis has minimal fat stranding. Calcifications are more suggestive of tuberculous lymphadenitis. CT is not always recommended nor necessarily needed in surgical planning but may add light on diagnosis and surgical planning.

Medical Therapy

Antibiotic therapy may be used to treat atypical lymphadenitis, but there is no standard of therapy with these. Traditional tuberculosis antibiotic therapy has been used but is generally not
given if atypical mycobacterium is suspected. Some examples of these include Isoniazid, rifampin, rifabutin and ethambutol. Isoniazid is a bactericidal antibiotic which works through inhibition of cell wall mycolic acid synthesis. Liver function test must be monitored for possible hepatotoxicity, and pyridoxine is administered together to minimize neurotoxicity. Rifampin and rifabutin are anti-mycobacterial drugs that are notorious for changing bodily fluids including urine and sweat to an orange color. Ethambutol works by inhibits RNA synthesis; the most common complication is optic neuritis.

Macrolides are front line drugs in MAC infections of adult immunocompromised patients with pulmonary involvement. Clarithromycin is commonly used for these infections while azithromycin is used as prophylaxis for MAC infections. Macrolides are primarily metabolized in the liver. A common side effect is GI intolerance as they have agonistic effects on motilin receptors.

A common regimen for MAC caused atypical lymphadenitis is a combination of clarithromycin and ethambutol with possible rifabutin. A regimen for *M. scrofulaceum* that has been mentioned is Isoniazid and rifampin with possible clarithromycin. Hazra et al. and Fraser et al. reported using triple therapy with clarithromycin, ethambutol and rifampin with 5 out of 10 not needing further therapy and 4 out of 4 respectively. Other antibiotics that have been used but not commonly used are fluoroquinolones, Aminoglycosides, tetracyclines and beta-lactams.

**Surgical Therapy**

There have been many different ways to surgically manage atypical lymphadenitis. Needle aspiration has been described by Alessia and Dudley. They treated 9 patients successfully from 1975-1988 with needle aspiration with concomitant antibiotic therapy. Incision and drainage had been tried in the past but is generally frowned upon today. When suspecting an atypical mycobacterial etiology incision and drainage should not be performed specifically for the high risk of chronic local drainage and sinus tract formations; excessive scarring may also occur. For lymph nodes that spontaneously commenced draining, curettage is generally recommended. This is also recommended in cases with skin necrosis, fluctuation and close proximity to the marginal mandibular branch of the facial nerve. Curettage is distinct from incision and drainage in that the approach includes an incision as in surgical excision but there is no formal dissection around the lymph node capsule as it has already started draining.

Although these previously mentioned techniques have been described, complete surgical excision of the affected node(s) is most common today. Because the most common areas affected are the submandibular area and the pre-auricular area, caution should be exercised to protect the facial nerve branches. Surgical lymph node excision has been noted to have a high cure rate with studies in the last couple decades showing better than 90% cure rates with minimal complications (some numbers quoted in following section). Partial parotidectomy has also been described.

**Controversy in Therapy**

Surgical intervention has become the standard for most otolaryngologists as well as pediatric infectious disease specialists. This is because of the efficacy of surgery versus medical treatment. Schaad et al. compiled a review of 380 cases which showed a 92% cure rate in 149
patients as opposed to only 10% cured with medical only treatment in 10 patients. Another 156 patients had combined therapy with surgical excision and antibiotics with a cure rate of 95%. The difference between the surgery alone and the combined therapy was not significant. This study showed how surgical excision alone was more efficacious versus medical therapy alone but not different when adding antibiotics to surgical excision.

One of the few prospective randomized studies by Lindeboom et al. showed superiority of surgical excision alone versus medical therapy alone. 50 patients were randomized to surgical lymph node excision and 50 patients were randomized to 12 week therapy of clarithromycin and rifabutin. There was a 96% cure rate for surgery and 66% cure rate for antibiotic therapy of which the remaining 34% required surgery. Of note is that 1 patient had a permanent facial nerve paresis of a House-Brackmann score of 2 after surgery and another surgical patient had a reoccurrence. Antibiotic therapy was not without side effects which included fever, fatigue, and abdominal pain among others.

The efficacy of antibiotic has been questioned as surgical excision has become the forefront of therapy. The duration of antibiotic therapy usually spans 3 to 6 months in most reviews. Since the natural history of this atypical lymphadenitis has not been extensively studied, antibiotics may in the end not have much benefit from watchful waiting. This remains to be a dilemma in reaching a conclusion of antibiotic therapy.

Conclusion

In the pediatric population, atypical mycobacterium manifests most commonly as a cervicofacial lymphadenitis in the submandibular region. It occurs more commonly in children between 1 to 5 years old with a slight female predilection. The diagnosis is usually clinical. Today, MAC is the most common pathogen isolated ahead of M. scrofulaceum and M. haemophilum. Suspicion of atypical mycobacterial etiology of cervicofacial lymphadenitis should warrant surgical excision of all affected lymph nodes. Medical therapy with antibiotics is inferior to surgery. Incision and drainage should not be done as there is high probability of recurrence and chronic sinus tract with drainage. Adjuvant antibiotic has not proven to improve outcome of this disease.

Faculty Discussion — Shraddha Mukerji, MD

My question to you is what would be the advantage of doing an incision and drainage for a patient whom you suspect has a mycobacterium tuberculosis infection where you know there is a high chance of recurrence and sinus tract formation and the course is going to be more protracted over a period of six months even if you give them antibiotic treatment and you have to remember that these are kids that you are treating and they are not adults. But if you know that it would be likely then why would you perform incision and drainage?

The way that I have been taught is to do curettage as if you plan for an excision. You would actually raise the skin flaps and because the material is so necrotic that you cannot excise it and that is the time you would do curettage to take out all the necrotic tissue and you do that when you know that there is no chance of damage to the facial nerve.
There is an option of doing surgical excision if it’s been treated with antibiotics and is not draining and all the studies have shown that even if it’s close to the facial nerve, if you take all the precautions that you normally do for a submandibular gland excision the rate of facial paralysis is not high. Now studies have shown that you don’t have to remove all the nodes because they are simply reactive to the primary infection.

References


