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Association between Piscine Mycobacteriosis and Morgellons Disease: A Review of Literature

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Abstract

Piscine mycobacteriosis is a fatal fish illness that affects a variety of species globally. It affects over 200 species of freshwater and marine fish. Several species of *Mycobacterium* are responsible among them *Mycobacterium marinum* is the comment. It also affects humans when exposed to contaminated water. In fishes, the symptoms include eroded fins, body surface coated with heavy mucus, changing pigmentation, swelling of abdomen, ulcerative dermal necrosis, and scale loss. In humans, the infection is classified into three clinical groups. Type I is a self-limiting, verruca lesion. Type II is single or numerous subcutaneous granulomas in the presence or absence of ulceration. Type III is deep infections of the tenosynovium, bones, bursa, or joints, resulting in tenosynovitis, osteomyelitis, and septic arthritis. The diagnosis is made by Ziehl-Neelsen acid-fast staining, culture, biochemical reaction, and PCR being the most reliable approach. Piscine mycobacteriosis is treated by antibiotics and vaccination has been considered for its long-term prevention in order to reduce morbidity and mortality. Morgellons disease (MD) is a filamentous dermopathy in which lesions with strange filamentous inclusions appear out of nowhere. Furthermore, formication may accompany dermopathy. The identification of *Borrelia spirochetes* directly in Morgellons disease patient specimen is constant and repeatable when sensitive and precise detection techniques are utilized. It has been diagnosed by microscopy, histology and molecular diagnostic techniques which are highly sensitive and specific. Morgellons disease is still a myth therefore its treatment is evolving, up to date it has been treated symptomatically.

Keywords

Piscine Mycobacteriosis, Fish Tuberculosis, *Mycobacterium marinum*, Morgellons Disease, *Borrelia* Infection

1. Introduction

Piscine mycobacteriosis (fish tuberculosis) is a zoonotic illness that affects both freshwater and marine fish globally. More than 20 strains of *Mycobacterium* species have been found in fish, although the pathogenesis of the majority of them is unclear [1]. Fish tuberculosis is caused by *Mycobacterium marinum*, and *Mycobacterium fortuitum* [2]. According to Runyon's classification, *Mycobacterium marinum* is an environmental, waterborne aerobic bacterium that belongs to the photochromogenic Group I non-tuberculous Mycobacteria [3]. *Mycobacterium marinum* is an opportunistic infection responsible for tuberculosis-like disease in fish and can infect people when damaged skin is exposed to a polluted aquatic environment. In immunocompetent patients, the infection manifests as a nodular granulomatous illness that can spread along the lymphatic system's distribution and is generally restricted to the skin and soft tissues [4]. Morgellons disease (MD) is a skin disorder in which lesions with strange filamentous inclusions and/or projections appear out of nowhere. Furthermore, formication (feeling of something crawling across or underneath skin) may accompany the dermopathy [5]. *Borrelia spirochetes* causative agent of Lyme disease such as *B. sensu lato* (Bbsl), *Bb sensu stricto* (Bbss), Relapsing Fever *Borrelia* (RFB) and *Borrelia burgdorferi* (Bb) species, have been found in Morgellons disease patient's bodily fluids and/or tissue samples. Other infections found in Morgellons disease patient's tissues include *Helicobacter pylori* (Hp), *Treponema denticola*, *Bartonella henselae*, and *Rickettsiae* species, suggesting that these pathogens may be involved in the development of the dermopathy [6]. The infectious agent in the majority of the Morgellon skin specimens examined was *Borrelia burgdorferi sensu stricto*. Some other *Borrelia* species have been found in Morgellons disease patients' skin samples such as *Borrelia garinii*, *Borrelia hermsii* and *Borrelia miyamotoi* [7].

2. Piscine Mycobacteriosis

2.1. Epidemiology

Piscine mycobacteriosis is a widespread illness of marine, freshwater, and brackish fish that affects over 200 species of freshwater and marine fish throughout a large area that ranges from the subarctic to the tropics. This illness affects tropical aquarium fish as well, and it is a leading cause of morbidity and mortality in free-living fish [3].

2.2. History and Classification

Piscine mycobacteriosis is a dangerous and sometimes fatal fish illness that affects a variety of species worldwide [8]. Several species of the genus *Mycobacterium* are responsible. *Mycobacterium* species are members of the Mycobacteriaceae family, which is part of the Actinomycetales order. Despite their mycolic cell wall's poor fixation of the Gram stain, these aerobic, non-motile pleomorphic bacilli are Gram+ve and are generally stained with Zeihl-Neelsen method.

In 1897 *Mycobacterium* specie was initially isolated from granulomatous lesions in common carp (*Cyprinus carpio*), which led to the first report of the bacteria in fish. This bacterium was given the name *Mycobacterium piscium*, and it has subsequently been found in frogs and other animals [9]. In 1903 *Mycobacterium chelonae* was initially discovered from two sea turtles (*Chelona corticata*) with pulmonary illness [10]. *Mycobacterium fortuitum* was discovered from neon tetra (*Paracheirodon innesi*) in 1953 [11]. In ornamental fish, *M. avium* subspecies hominissuis is found. In Netherlands *M. avium* was recently isolated in public aquarium from an epaulette shark [12]. *Mycobacterium stephanolepidis*, novel *Mycobacterium* specie, was discovered in the thread sail filefish (*Stephanolepis cirrhifer*) in 2017 [13]. Four *Mycobacterium* species (*M. marinum*, *M. chelonae*, *M. fortuitum* and *M. gordonae*) dominate the clinical landscape. *Mycobacterium platypoecilus*, *Mycobacterium balnei*, and *Mycobacterium anabanti* are now known as *Mycobacterium marinum*. *Mycobacterium ranae* has been categorized as *M. fortuitum*, whereas *Mycobacterium runyonii* and *Mycobacterium borstelence* have been classified as *M. chelonae* species [14]. Table 1 shows the aquatic host and environment of *Mycobacterium* species responsible for piscine mycobacteriosis [14].

2.3. Etiology

Table 1. *Mycobacterium* species responsible for piscine mycobacteriosis (Delghandi, M.R., *et al.*, 2020) [14].

Species	Aquatic Host	Environment
M. septicum	Zebrafish (*Danio rerio*), Cichlid (*Pseudotopheus lombardoi*), Koi fish	Fresh water
M. peregrinum	*Labidochromis caeruleus*, *Black mollies* (*Poecilia sphenops*), guppies (*Poecilia reticulata*), green swordtails (*Xiphophorus hellerii*), catfish (*Pangasius hypophthalmus*)	Fresh water
M. chelonae	Multiple	Fresh and marine
M. avium	Dwarf Cichlid *(Apistogramma cacatuodes*)	Fresh water
M. haemophilum	Zebrafish (*Danio rerio*)	Fresh water
M. lentiflavum	Swordtail (*Xiphophorus hellerii*)	Fresh water
M. gordonae	Goldfish (*Carassius auratus*), Guppy (*Poecilia reticulate*), Angel fish (*Pterophyllum scalare*)	Marine water
M. chesapeaki	Striped bass (*Morone saxatilis*)	Marine water
M. marinum	Multiple	Fresh and marine
M. fortuitum	Neon tetra (*Paracheirodon innesi*)	Fresh water
M. pseudoshottsii	Yellow tail (*Seriola quinqueradiata*), Greater amberjack (*Seriola dumerili*), Striped jack (*Pseudocaranx dentex*)	Marine water
M. shottsii	Striped bass (*Morone saxatilis*)	Fresh water

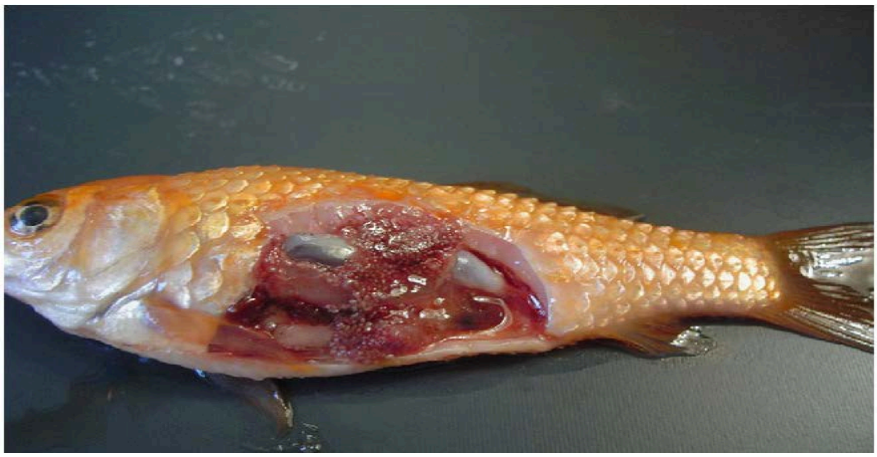


Figure 1. White tubercles present in internal organs (Passantino, A., *et al.*, 2008) [15].

2.4. Clinical Signs and Symptoms

The first outward signs include eroded fins and tail rot. Body surface coated with heavy mucus, as well as a changing pigmentation and bleaching have been observed, nonspecific outward symptoms that are frequently quite similar to those of other diseases, such as swelling of abdomen, ulcerative dermal necrosis, and scale loss. White tubercles within internal organs are also seen, as shown in **Figure 1** [15]. There have also been reports of external red lesions on the lateral line and shallow asymmetrical ulcers. Exophthalmia, vision loss, pale gills and ascites as well as skeletal abnormalities including spinal curvature or restricted growth, aberrant behavior such as lethargy, poor appetite, and the resultant emaciation, can also be seen [14].

In humans, infections are classified into three clinical groups that have historically been used to guide therapy. Type I is a self-limiting, verruca lesion. Type II is single or numerous subcutaneous granulomas in the presence or absence of ulceration. Type III is deep infections of the tenosynovium, bones, bursa or joints, resulting in tenosynovitis, osteomyelitis and septic arthritis. The lesions are generally 1 - 2.5 cm in diameter after 3 - 5 weeks of infection. The spread of lesions is in a proximal manner along the course of the lymphatics is a typical characteristic, albeit it seldom causes axillary discomfort or lymphadenopathy. It is recognized that the illness is rapidly progressing [16].

2.5. Methodology

Ziehl-Neelsen acid-fast stain

After staining with carbolfuchsin, mycobacterial cell wall is resistant to acid-alcohol decolorization. Thus Ziehl-Neelsen acid-fast stain is used to stain fish tissue sections to examine the presence of mycobacteria [14].

Isolation and Culture:

Mycobacteria are picky and slow growing, and they are prone to be overtaken by rapidly growing organisms on non-selective media. Löwenstein-Jensen (solid medium), Middlebrook 7H10, Middelbrook 7H9 (broth medium), Dorset egg

media and Petragnani agar are examples of these. *Mycobacterium* is also resistant to acid and basic compounds, as well as other combinations like benzalkonium chloride and hypochlorite [17].

Depending on the species, *Mycobacterium* species can be cultured at room temperature or at ambient temperature, and clear colonies can take somewhere between 2 to 28 days to develop [18]. *Mycobacterium marinum*, for instance, will grow at 30 degrees Celsius, but *Mycobacterium shottsii* and *Mycobacterium pseudoshottsii* will grow at 23 degrees Celsius [19]. *Mycobacterium salmonifilum* may develop at 20˚C - 30˚C on particular medium, and after 4 - 6 days, smooth colonies can be seen [20]. *Mycobacterium haemophilum* can be cultured at 29 degree Celsius on Middlebrook 7H10 agar [21].

The interference of *Mycobacterium* growth on conventional medium complicates culture-based identification of *Mycobacterium* species from fish skin or gills due to the background presence of microbiota.

Biochemical reaction:

Numerous biochemical tests are used to identify non tuberculous mycobacteria, this includes Arylsufatase test which is negative and becomes weak positive after 3 days, Nitrate reduction test which is also negative, Catalase test is positive, doesn't grow in the presence of 5% NaCl and Urease is positive [14].

Molecular Diagnosis:

For detection and identification of *Mycobacterium* spp. that pose a public health risk, a number of molecular diagnostic techniques have been developed. The small subunit, 16S rRNA gene is a preferred target for precise diagnosis, Owing to the accessibility of *Mycobacterium* 16S gene sequences in archives like as GenBank and the Ribosomal Differentiation Database of Microorganisms. In 1997, restriction fragment length polymorphism analysis of the 16S rRNA gene (PCR-RFLP) was used to identify *Mycobacterium marinum*, *Mycobacterium fortuitum*, and *Mycobacterium chelonae* [22]. DNA probe and gene sequencing have also been developed to evaluate *Mycobacterium* to the species level [23] [24].

When Mycobacteria culture fails, direct sequencing from fish tissues serves as a good alternative [25]. FRET (fluorescence resonance energy transfer) has recently been shown to have excellent specificity when used in conjunction with melting curve analysis to successfully differentiate and identify *Mycobacterium marinum* from other mycobacteria [26]. A first PCR using SYBR green (at a detection limit of 102 *Mycobacterium* DNA copies) and then a secondary amplification utilizing FRET in real-time PCR describe this diagnostic approach. **Figure 2** shows Micobacterium phlei colonies in Middlebrook agar [14].

2.6. Treatment

Antibiotic Therapy:

M. marinum infection must be treated properly for a quick recovery and to prevent the infection from spreading to deeper tissues and causing permanent

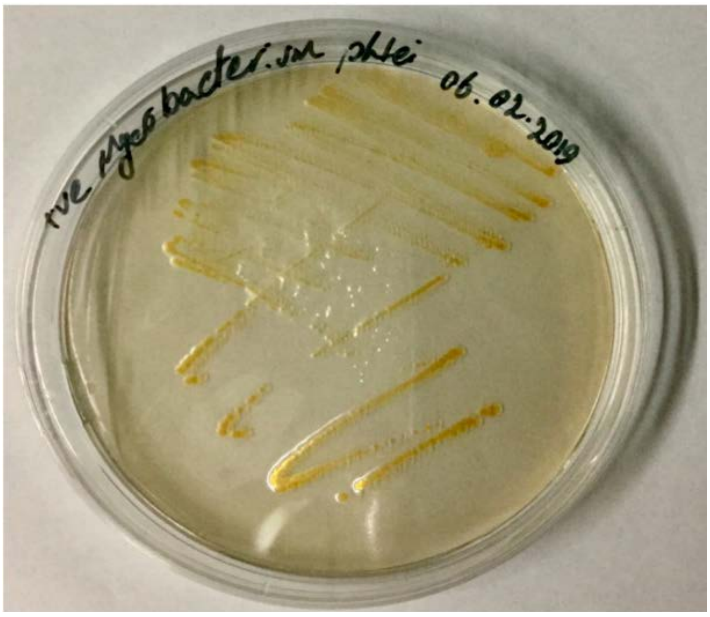


Figure 2. *Mycobacterium phlei* colonies on Middlebrook 7H10 agar (Delghandi, M.R., *et al.*, 2020) [14].

damage to them. Antibiotics such as rifampicin, erythromycin, streptomycin, ethambutol, kanamycin, isoniazid, minocycline, doxycycline, ethionamide and tetracycline have been used to treat Mycobacteriaceae infections in the past, with some effectiveness [27]. Furthermore, acquired antibiotic resistance is a problem in most genera of harmful bacteria. *Mycobacterium marinum* strains (AR103K, OR932, TG19, and ATCC927) resistant to sulfamethoxazole and trimethoprim were identified from zebra fish [28].

In humans, monotherapy with clarithromycin, ciprofloxacin and trimethoprim was found to be beneficial in treating superficial cutaneous infections, whereas combination therapy with two medicines may be more successful in treating deeper infections. Combination therapy *i.e.*, rifampicin and ethambutol are indicated in the case of sporotrichoid distribution pattern. *Mycobacterium marinum* is more resistant to streptomycin, pyrazinamide, and isoniazid therefore they shouldn't be included in the treatment regimen. Several other therapeutic options have been documented and recommended, which includes electrodessication, treatment with X-ray, photodynamic therapy, cryotherapy and local hyperthermic therapy [17].

Vaccination:

Vaccination for fish mycobacteriosis would be extremely beneficial in terms of illness prevention and control, and numerous attempts have been made throughout the years. In the Japanese flounder (*P. olivaceus*), the BCG vaccination (Bacillus Calmette and Guerin) was shown to boost the production of numerous immune genes, including IL-1, IL-6, IFN, and TNF-α, and this vaccination was linked to improved survival after exposure [29].

Injecting European Seabass (*Dicentrarchus labra*) with heat killed *Mycobacte-*

rium marinum causes the production of IgM and TNF-*α*, which is associated with lower fatality from mycobacteriosis in fish [30].

In zebrafish, the infusion of heat killed *Mycobacterium bovis* provided cross-protection. Furthermore, immunizing fish with the mycobaterial enzyme RpfE increased the survival rate of fish when high dose of *Mycobacterium marinum* was injected intraperitoneally [31].

DNA vaccines targeting *Mycobacterium* spp. Ag85A secreted fibronectin-binding protein have been developed, and hybrid-striped bass (Morone saxatilis Morone chrysops) have been protected against *Mycobacterium* species, including *Mycobacterium marinum*. The establishment of an immune response against *Mycobacterium marinum* by using a DNA vaccine can lower the fatality of vaccinated fish. Furthermore, in zebrafish, the administration of a live attenuated *Mycobacterium marinum* mutant (L1D) resulted in improved survival greater than 70% survival rate after 50 days following *Mycobacterium marinum* injection [14].

3. Morgellons Disease

3.1. History and Background

Morgellons disease is a rising dermopathy with a global reach. In the 17th century, Sir Thomas Browne identified an illness in French children and named it "Morgellons". It was noticed that the backs of these children had "coarse hairs" sprouting from them. In 1674, Sir Thomas Browne described cutaneous hair like extrusions accompanied by movement sensations [32]. Ekbom's foundational description of delusional parasitosis with perception of insects crawling on or beneath the skin along with feeling of biting and stabbing was seen. Patients would occasionally bring specimens to show doctors in such situations, and these collections comprised of "tiny hairs, grains of sand, little threads and skin scales." He noticed that there were no constant mental disorders evident, aside from delusional ideas of infestation was published in 1938 [7].

3.2. Etiology

In recent times Spirochetal infection was first suggested as an etiologic cause for Morgellons disease in 2006. The identification of *Borrelia spirochetes* directly in Morgellons disease patient specimen is constant and repeatable when sensitive and precise detection techniques are utilized. Even though spirochetal infection appears to be the most important etiologic component in Morgellon disease progression, Morgellons disease patients have a high prevalence of various co-infections including tick-borne illnesses, with Babesia infection being the most common. Other microorganisms have been found directly in Morgellons disease skin specimens, although they have been found less frequently and reliably than *Borrelia* species. The co-infecting *Rickettsia* and *Bartonella henselae* as well as the common human pathogens *H. pylori* and *T. denticola*, are among these pathogens [5].

3.3. Clinical Features

Clinical signs and symptoms include poor or non-healing dermal lesions, pruritus, sprouting of fibers or excretion of solid particles from the skin; other distressing cutaneous perceptions include stinging, needles, biting sensations and formication. Chronic and recurring symptoms are the most common descriptions for these symptoms [33]. **Figure 3** shows multiple lesions in hands and buttocks of a Morgellons patient [7]. Fatigue, trouble concentrating, short-term memory loss, and a low mood are all other symptoms associated with Morgellons disease. Some people have chronic fatigue syndrome, neurocognitive impairments, fibromyalgia, neurological diseases including multiple sclerosis, and mental problems as co-morbid conditions [34]. Healthcare practitioners commonly and incorrectly identify the illness as a type of delusional infestation (DI) or the heritage names delusional parasitosis (DP) and delusions of parasitosis (DOP) due to the false idea that the fibers are generated from textiles [5].

3.4. Classification

A classification system for Morgellons disease lesions that takes into account the duration and site of the lesions have been proposed:

- **Early localized**: Lesions or fibers that have been present for >3 months and are limited to a single region *i.e.* (head, trunk, and extremities).
- **Early disseminated**: Lesions or fibers that have been present for >3 months and affect more than one part of the body are considered early disseminated.
- **Late localized**: Lesions or fibers that have been present for <6 months and are restricted to a single part of the body.
- **Late disseminated**: Lesions or fibers that have been present for <6 months and affect more than one part of the body are classified as late disseminated [7].

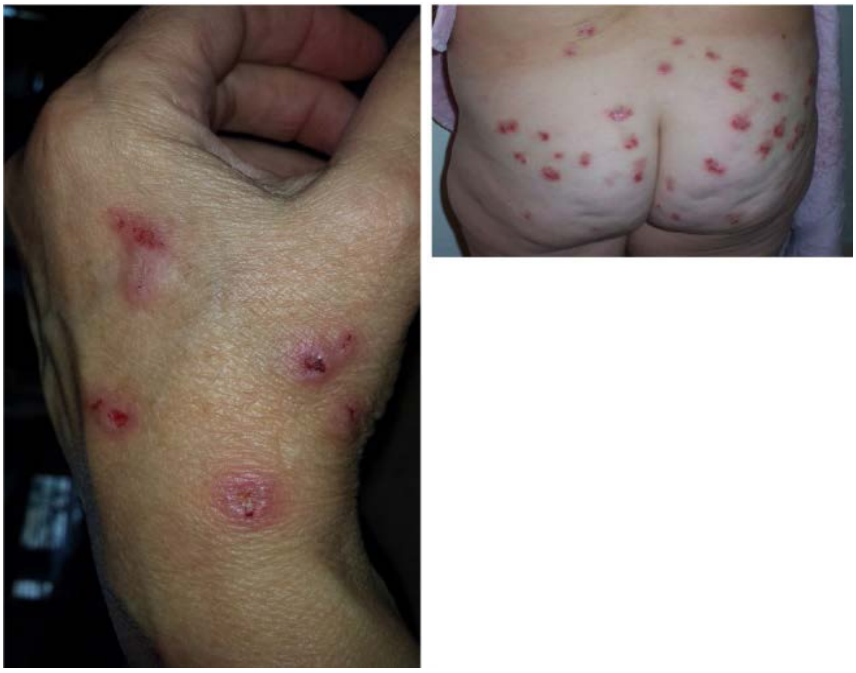
3.5. Classification

Borrelia spirochetes have been found in skin and body fluid samples from Morgellons disease patients.

Histology and Microscopy:

Morgellons disease filaments are not textile fibers, according to histological investigations. Biofilaments of human cellular origin are generated by epithelial cells and originate in the epidermis' deeper layer, the dermis' and from the hair follicles root sheath. Human cellular origin was confirmed by histological investigations, which revealed that these filaments are made mostly of keratin and collagen, and are nucleated at the base of attachment to epithelial cells [35].

On Electron microscopy hair like scales were observed on blue filament, indicating that some fibers of the disease are hair like in structure [36]. **Figure 4** shows positively stained filaments which reveal basal layer origin [5]. Fontana Masson staining positive result revealed blue color pigment in fibers due to the melanin production [35].



(a) (b)

Figure 3. (a) Morgellons disease lesion on hand. (b) Skin lesion on buttocks (Middelveen, M.J., *et al.*, 2016) [7].

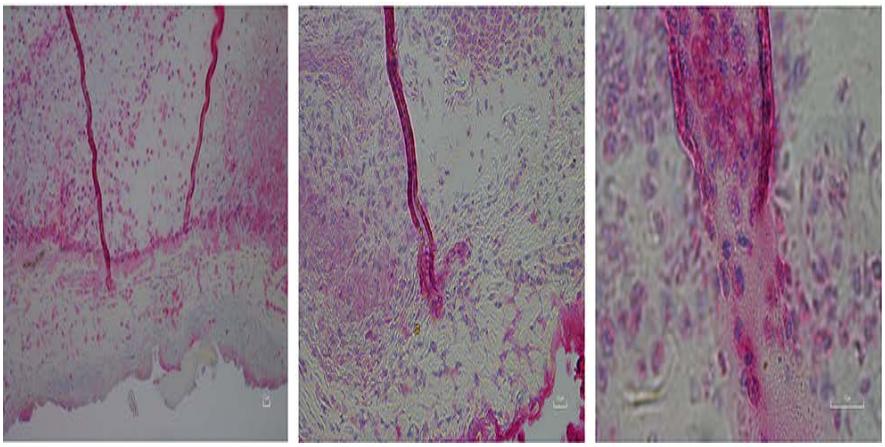


Figure 4. Positively stained filaments revealing basal cell layer origin (Middelveen, M.J. *et al.*, 2020) [5].

Molecular Diagnosis:

Borrelia DNA was identified by polymerase chain reaction (PCR) and Sanger sequencing. Motile spirochetes *i.e.*, *Borrelia* species were cultured in Barbour-Stoenner-Kelly (BSK)-H medium and inoculated with Morgellons disease skin tissue. The presence and molecular identification of live *Borrelia spirochetes* in Morgellons disease skin specimen was confirmed by PCR amplification of cultured spirochetes. *Borrelia* culture and PCR altogether provide significant evidence for a clinical link between spirochetal infection and Morgellons disease [7].

3.6. Treatment

Because a clinical categorization for Morgellons disease has yet to be agreed upon, the best treatment for the condition is unknown. Several therapeutic concepts have evolved.

1) The earlier the treatment begins in the course of morgellons disease, the better the outcome seems to be.

2) The therapy should target the underlying tick-borne disease.

3) Prolonged antibiotic combination therapy may be required to eliminate dermopathy.

4) Antiparasitic medication may be beneficial in some Morgellons disease patients [37].

5) Patients with neuropsychiatric illness have been suggested to be treated with antipsychotic drugs [38].

4. Conclusion

Piscine mycobacteriosis is a zoonotic illness that affects both freshwater and marine fish globally. The etiological factor for piscine mycobacteriosis is *Mycobacterium* species; more than 20 strains of *Mycobacterium* species have been found in fish. Humans get infected by *Mycobacterium marinum* via contaminated water. *Mycobacterium marinum* is an opportunistic infection in fishes its control prophylactically and prevention by vaccination is the need of hour and because of the communicable nature of the disease, precautions should be taken *i.e.*, by avoiding swimming in fish pools and using gloves while handling and preparing fish. While on the other hand Morgellons disease is a new kind of dermopathy linked to *Borrelia* infection, and the rising number of Morgellons disease patients parallels the global rise in tick-borne illnesses. Sometimes Medical practitioners misdiagnose it as a delusional disorder due to the false idea that the fibers are generated from textiles. According to the previous studies Morgellons disease is a somatic disease that seems to be induced by *Borrelia* infection. The best therapy for this illness has yet to be discovered. Thus, on the basis of the available data, it can be concluded that there is no evidence of correlation between *Mycobacterium marinum* and Morgellons disease. Further research is required to understand the disease process of these complex entities and to evaluate the best therapy for both of the diseases.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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