

Metallopharmaceuticals as possible treatment for an uncharacterized parasitosis

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Abstract- In the last 10 years, several parasitosis have been emerged, particularly, the Morgellons disease which has emerged as a highly controversial disease. Is usually associated to a mental illness and because of this, has been defectively characterized and there is a small evidence of whether or not the disease really exist. However, because of the increasing number of patients, in 2012, the Center for Disease Control (CDC) has begun to study this phenomenon. Further studies have to be developed in order to collect evidence and study possible treatments. The present work is a proposal, of a possible treatment that could be applied to a patient with the Morgellons disease or with an aggressive infection of parasite or bacteria. Further studies should evaluate if this is a viable treatment.

Index Terms- Uncharacterized Parasitosis; Metallopharmaceuticals; Morgellons

I. INTRODUCTION

Morgellons is a controversial term, used to describe a collection of unexplained symptoms, such as the initial manifestation of non-healing skin lesions, solid material or fibers emerging from the skin, pruritus, formication and a stinging or biting sensation. These symptoms are usually chronic and recurrent. Other symptoms can be present as well, for example: generalized fatigue, cognitive problems, difficulty concentrating, short-term memory loss, depressed mood, chronic fatigue syndrome, fibromyalgia, neurocognitive deficits, neurological conditions, particularly multiple sclerosis and psychiatric disorders.[1-3] Also, the patient is intensely anxious and obsessive with their symptoms. As the condition progresses, paranoia and depression are common, in some cases leading to suicidal tendencies.[2, 4] Although no fatalities have been proven resulting directly from this condition, some reports suggest that persons with this condition have experienced substantial decline in quality of life, including social disruption, isolation, decreased work productivity or job loss and total disability.[1] Morgellons disease is highly debatable, many dermatologists and psychiatrists consider that this condition is synonymous of delusional parasitosis or infestation.[1, 5-12] Delusional infestation, delusional parasitosis or Ekbom syndrome, is a psychiatric disorder characterized by the patient belief that they are infested with a skin parasite. The delusion is often sustained with tactile hallucinations, sensations of itching and crawling. This condition usually occurs in people with other psychiatric conditions such as bipolar disorder, paranoia, schizophrenia or in individuals with addiction to cocaine and amphetamine.[2, 4, 9, 12-16] Patients with the symptoms of delusional parasitosis, present cutaneous pruritus that causes that the patient pick at their skin continuously, to extract a foreign body or organism they believe they have.[12] Because of this, Morgellons disease is not currently recognized as a clinical disorder and is not accepted yet by the medical community.[13]

Instead, a variety of potential infectious diseases have been postulated as a cause of Morgellons as the parasitic Lyme disease[1] or bed bug infestations[5], but the etiology of this condition remains unknown and there have been no proven effective medical therapies.[1] On the other hand, Morgellons disease could be an old syndrome. Using a different name for the disease (Dracontia), this condition was first described in 1544 by Leonellus Faventinus de Victoriis[17], and later an English physician Sir Thomas Browne, in 1675 made mentions of a pediatric medical condition that he called “the Morgellons”. Describing fibers in the back in children.[3, 4, 13, 14, 17] Throughout its history, this condition was sporadically mentioned and could have been named as Les Crinons, Masclous, Masquelons and finally Morgellons. However, there were notable differences in the symptoms and is not clear if could be the same disease.[17] Yet, Morgellons was mentioned again until 2002 by Mary Leitao to describe the symptoms of her son.[2, 13, 14, 17]

Skin biopsies of individuals with Morgellons disease normally reveal nonspecific pathology or an inflammatory process without observable pathogens with fibrous materials projecting from inflamed epidermal tissue[14, 18] and recently, oral complications as fibers in oral ulcerations[19]. Several bacteria have been mentioned as responsible for Morgellons disease, in which could be present some spirochaetes infection[18] or some other organism, specifically *Stenotrophomonas maltophilia*, nematodes (causal agent of Filariasis), *Strongyloides stercoralis*, *Cryptococcus neoformans*[17], and recently *Agrobacterium* spp. [17, 20]. Nevertheless, Many patients with Morgellons disease have positive Western blot for *Borrelia burgdorferi* the causative agent of Lyme disease [14, 18].

More recently on the web site of the Morgellons disease foundation, there has been indicated that *Agrobacterium* is the responsible infectious pathogen.[17] Additionally, Fiber formation in Morgellons disease is stated to be cellulose [1, 14, 17] or a cellulose-protein complex of mammalian connective tissue produced by certain gram-negative bacteria.[1, 14, 17] Several medications have been used for Morgellons disease; which goes from antiparasitic therapy (which does not appear to be useful) to antibacterial therapy.[2, 14] When patients are treated with antibacterials for Lyme disease, remission of Morgellons symptoms is seen in most.[14] Some other medication have been used, specially tetracycline which causes no improvement of reported symptoms.[19] In the case of dermatologic symptoms, fluocinonide gel could be active for the Morgellons ulcers.[19] Also Morgellons may cause chronic pruritus, which in some cases can lead to depression or anxiety, this is usually treated with antidepressants and anticonvulsants.[21, 22] Also, Pimozide is usually prescribed.[4, 10]

Morgellons remains controversial because the mental and physical symptoms that generates. Nevertheless, the associated symptoms for Morgellons can be explained in several ways. Some theories indicate that, in diseases as hepatitis C and Lyme disease, the body's reaction to infection is well-known to produce a mental illness.[2] These could be explained considered that if a parasite is involved, physical symptoms are justified because the host immune system, unleashes an inflammatory response, mediated in part by some protein messengers such as cytokines. Cytokines also produce symptoms in the host such as fever, aches, pains and fatigue.[2] Still, some authors believe that the first step to unlocking this medical mystery of the Morgellons disease is to recognize it is a real somatic condition. In which the patient should not be conferred to a stigmatizing and psychiatric diagnosis, without a thorough and proper history and examination. [23]

II. HYPOTHESIS

It is hypothesized that Morgellons disease could be caused by an infection of an *agrobacterium*-like organism.

III. INHIBITION OF AGROBACTERIUM

Recently, *Agrobacterium* is considered the organism that could be responsible for the Morgellons disease.[17, 20] *Agrobacterium* spp. are phytopathogens usually in soil, that causes neoplastic growths on the host plant species (crown gall). In nature, *Agrobacterium* also may encounter organisms belonging to other kingdoms such as insects and animals that feed on the infected plants. Several studies have been carried out to evaluate in what way the *Agrobacterium* can infect animal cells.[24, 25] *Agrobacterium* could attach to a human host and genetically transforms several types of human cells by a mechanism similar to that which it uses for transformation of plants cells. Some studies suggest that *Agrobacterium* can transport its T-DNA to human cells and integrate it into their genome.[2, 24] Nevertheless, *Agrobacterium* is currently recognized as an opportunistic pathogen affecting mostly immunocompromised and chronically ill patients. A few cases of *Agrobacterium* infection in humans have been reported, for example Chronic Endophthalmitis[26], also *Agrobacterium* was found present in chronic ulcerous inflammation[27] and bacteraemia[28]. *Agrobacterium* is usually found in crops, where has many potential agricultural applications. Is usually used to modify crops. Nevertheless, in order to contain the infection, several growth-inhibiting agents have been developed and patented. Because *Agrobacterium* is highly sensitive to heavy metals, some of them are heavy metal such as silver, silver nitrate, silver thiosulfate, silver nitrite, silver dithionate, silver stearate, silver selenate, silver salicylate, silver oxalate, silver phosphate, silver metaphosphate, silver orthophosphate, silver carbonate, silver propionate, silver acetate, silver citrate, silver laurate, silver levunilate, silver pyrophosphate or other silver-containing compounds. Also other chemicals are used as compounds with potassium, manganese, or cadmium, proteins, nucleotides, and cell extracts, cell exudates, secondary metabolites, sulfa drugs, and growth regulators. These are capable of inhibiting *Agrobacterium* growth. Between the usual inhibiting agents are silver nitrate, silver thiosulfate, and penicillins such as carbenicillin, ampicillin, and cloxacillin, cephalosporins such as cefotaxime and cefoxitin, or a combination antibiotic such as a penicillin plus clavulanic acid such as augmentin and timentin.[29]

In individuals, *Agrobacterium* infection can be sensitive to cefepime, carbapenems, tetracyclines, piperacillin/tazobactam and ciprofloxacin, and probably this medication could be tested as first option.[27] Also, have been used amikacin and piperacillin/tazobactam.[28] Finally, other studies mention cefepime, carbapenems, tetracyclines, piperacillin/tazobactam and also ciprofloxacin, whereas resistance to other antibiotics is common and variable. However, *Agrobacterium* could possess antibiotic inactivating mechanisms.[28]

IV. A POTENTIAL TREATMENT FOR THE MORGELLONS DISEASE OR UNCHARACTERIZED PARASITOSIS

The Morgellons disease treatment can be centered in relief of the symptoms solve the infection, decrease the inflammatory response and anxiety. Because Morgellons disease symptoms require an effective anti-inflammatory activity and an enhanced antibiotic absorption, Morgellons could be treated by high ingesta of proteolytic enzymes, such as bromelain. Bromelain was used by the natives of the tropics before the arrival of Christopher Columbus.[30] Bromelain belongs to a group of protein digesting enzymes obtained commercially from the fruit or stem of pineapple. Fruit bromelain and stem bromelain are prepared differently and they contain

different enzymatic composition.[31] Bromelain is a mixture of different thiol endopeptidases and other components like phosphatase, glucosidase, peroxidase, cellulase, escharase, and several protease inhibitors. In vitro and in vivo studies demonstrate that bromelain exhibits various activities as fibrinolytic, antiedematous, antithrombotic, and anti-inflammatory. Bromelain is considerably absorbable in the body without losing its proteolytic activity and without producing any major side effects. Bromelain accounts for many therapeutic benefits like the treatment of angina pectoris, bronchitis, sinusitis, surgical trauma, and thrombophlebitis, debridement of wounds, and increase the absorption of drugs, particularly antibiotics. It also relieves osteoarthritis, diarrhea, and various cardiovascular disorders. Bromelain also possesses some anticancerous activities and promotes apoptotic cell death.[31] Because the anti-inflammatory treatment should be sustained, a natural anti-inflammatory treatment must be recommended. Also, skin injuries caused by Morgellon disease can be treated by studying the management of difficult healing wounds. The time required for tissue repairing can considerably be reduced and promote the healing process and minimize the risk of infection by using silver compounds, especially silver sulfadiazine. This is often used to prevent or to treat wound colonization, also in presence of antibiotic-resistant bacteria[32].

Because Agrobacterium is sensitive to heavy metals, several prescriptions with heavy metals can be evaluated in order to treat the infection. From 2500 BC, gold drugs have been used to treat different conditions.[33] Nowadays, some medicinal compounds are available and approved by the Federal Drug Administration, which contains heavy metals. Some of them are Gold sodium thiomalate, aurothioglucose or auranofin. Particularly, auranofin was developed for the treatment of rheumatoid arthritis and psoriasis, as a substitution for the injectable gold compounds: aurothiomalate and aurothioglucose. Auranofin is prescribed in the form of oral administration, presents remarkable potent anti-inflammatory effects *in vitro*. Some studies report that this could be an exceptional substitute for the traditional injectable gold compounds. Research on auranofin has continued and new applications have been discovered. Posses the dual inhibition of inflammatory pathways and thiol redox enzymes and is a candidate to be used in cancer therapy, several types of leukemia, carcinomas, parasitic, bacterial and viral infections.[33] Also, Auranofin is about ten times more potent against some parasites than metronidazole. Oral auranofin markedly decreases the number of parasites and the detrimental host inflammatory response and hepatic damage. The auranofin represents a promising therapy for parasites.[34]

In extreme cases, a more aggressive treatment can be considered. In the past century, the infection of an antibiotic-resistant bacteria as Spirochaetes of *Treponema pallidum* which cause syphilis[35], was treated using salvarsan or 3-amino-4- hydroxyphenylarsenic(I). [36] Arsenic has been used in medicine for more than 2400 years for a variety of ailments including ulcers, the plague, and malaria. In 1878, potassium arsenite was reported to have an antileukemic effect and was used for this purpose in the late 19th and early 20th centuries until it was replaced by busulfan in the 1950s. [37] In the modern time, interest in arsenic as chemotherapy was rekindled after it was identified as an active ingredient in traditional medicines in China. [37] Nowadays, arsenic compounds are not used, as far as we know, the only one approved by the Federal Drug Administration is in the form of arsenic trioxide (Trisenox™) which is restricted to be used as a therapeutic medication against hematologic malignancies.[38] Nevertheless, have been reported that therapeutic doses of arsenic trioxide are well tolerated, with no evidence of long-term toxicity. [37]

V. CONCLUSION

Some infectious diseases have been difficultly characterized and still remain very controversial, as the Lyme disease, which was elusive to be characterized until 1980. The Morgellons disease could be one of these diseases. Because of the psychological beliefs that the patients with Morgellons disease can experience, are easily associated to psychological or psychiatric disorders and generates that these symptoms might be confused with some other syndromes, disregarding the unexplainable skin symptoms. This promotes an inaccurate characterization and a missed diagnosis. Nevertheless, keeping the mind open could help to characterize the real syndrome in a detailed way.

Testing new treatments with old active ingredients for the Morgellons disease could help to relief the symptoms. In the history of the medicine, test antibiotic regimens in adult patients before the proper characterization of the disease, has been always present. Hopefully this proposal could be useful to the treatment of the Morgellons disease and other infectious disease.

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