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PERSPECTIVE

Etiology of Yan (Morgellons) Disease: A New Plant-Like Infectious Organism from Brazil and Its Skin Manifestations

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Abstract: This paper describes the etiological organism causing a new human infection, ie, Yan (also known as Morgellons) disease. Colored threads, black speck-like material, and granules are formed within and/or on the skin surface. The organism has four main morphological forms, ie, tube-shaped fibers, amorphous tuber masses, fibrous roots, and seeds. Brilliant red and blue autofluorescent pigments similar to phycobiliproteins have been observed. The seed form of the organism grows in solid potato and blood agar as pointed masses, and in potato broth as interconnecting bundles of fibers. The seed form of the organism was grown in a hamster/mouse model as light brownish tuber masses interconnecting with fibrous roots. The main symptoms for the patient are of biting, stinging, and a "shooting" sensation from the skin caused by the sharp and pointed ends of the seed form of the organism.

Keywords: etiology, Morgellons, infectious, Brazil

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Introduction

This article describes the etiological organism causing a new human infection, ie, Yan (Morgellons) disease.[1–5] The main symptoms reported by patients are crawling, biting, stinging, and "shooting" sensations from the skin. Colored threads, black speck-like material, and granules found in and on the skin have been reported as unexplained cutaneous syndromes.[1,5] The US Centers for Disease Control and Prevention launched an investigation into the "unexplained dermopathy (also called 'Morgellons')", but no common underlying medical condition or infectious source was identified.[5]

The term "Morgellons" was first used in 1674 by Sir Thomas Browne to describe harsh hairs breaking out from children's backs accompanied by sensations of movement.[1,3] The term "Morgellons disease" and/or "Morgellons syndrome" was coined in 2002 by Mary Leitao,[1,3] as a practical "place holder" because of its dermal similarity to the Morgellons disorder described by Browne.[3] However, the exact relationship between the Morgellons described by Browne and the term Morgellons disease as a practical "place holder" used today is unknown. Certainly, the Morgellons fibers drawn by Ettmuller in 1682[1] looked quite different from the organism described in this paper. They are not the same organism and thus are not the same disease.

Case Report

In 1992, a 33-year-old Chinese male from Hong Kong studying in the US, traveled in South America and was infected with Morgellons disease in southern Brazil. His symptoms included a range of cutaneous problems, including crawling, biting, and stinging sensations, finding fibers on or under the skin, and a persistent skin rash and sores. Initially he had developed small lesions on his legs, and multiple skin lesions without ulceration subsequently appeared at various sites over his body. Surgical biopsies yielded relatively nonspecific pathological findings, including for a series of special stains for exotic infectious organisms. They did show some mild inflammation, a mild increase in mast cells, and subtle changes in the nerves which could have accounted at least in part for his symptoms, and recent significant fibrosis. A lesion on his right palm showed central atrophy surrounded by a rim of marked hyperkeratosis. KOH digestion of the hyperkeratotic surface was negative for fungus but did show some microhemorrhages. There was hyperpigmentation of the epidermis in some areas.

The patient was diagnosed as having a fungal infection of unknown origin and was treated empirically with antifungal azole drugs, even though serology for histoplasma antibody, coccidioides antibody, and latex agglutination test for cryptococcal antigens were negative. The antifungal drug, fluconazole, was initially prescribed at 200 mg once a day and was then increased to 400 mg once a day for 2–3 months. Most of the lesions cleared up and the skin changed from a deep color back to his normal color. The itchy feeling was not as intense or as frequent. Unfortunately, the patient became sensitive to fluconazole, the treatment had to be stopped, and the symptoms returned within a few months but to a lesser degree. The newer antifungal azole drug, voriconazole, might have been a better choice than fluconazole for suppressing the organism, given that the azole antifungal drugs have the adverse effect of driving the fibrous root form of the organism onto the skin surface (Fig. 1A), putting others at risk of infection by the seed form produced by the fibrous

Figure 1. Infected lower arm, thumb, and a biopsy of the right upper thigh. (**A**) An infected inner right lower arm showed white or colorless fibrous materials, some rolled up as fiber balls or threads after slightly rubbing the skin with the fingers. **^**Focused area of the arm with rolled up fiber threads. X marks the upper limit of the focused area with rolled-up fiber threads. (**B**) Infected right thumb showing numerous colorless/white/opaque tuber mass forms of the organism on the skin surface. (**C**) Infected right upper thigh with numerous brown spots, and a black-colored biopsy spot with red patches around it. Biopsy shows a probably infectious granuloma.

root form of the organism. Other classes of medication with different antimicrobial mechanisms should be used, if possible. Atypical antipsychotic drugs quetiapine and olanzapine show activity against the organism with unknown mechanism. Direct skin-to-skin contact should be avoided as far as possible.

At the start of antifungal treatment with fluconazole, numerous brownish spots appeared on the skin of the thighs, which had previously been itchy (Fig. 1C). A detailed biopsy study was done on one of these spots and a diagnosis was made of chronic dermatitis with granuloma, probably infectious, with the cause not determined. It was reported that "... a few fine black round-to-rod-shaped bodies were also noted in the H&E sections only, of uncertain significance". These round/rod-shaped bodies might have been related to the tube-shaped fibrous form of the organism. There was also "focal necrosis and multiple apparently empty spaces". These spaces might reflect the organism having migrated to the skin surface and left behind multiple apparently empty spaces within the skin tissue.

Discussion

Samples of the organism can be recovered from an infected individual by simply picking specimens from the skin surface. No special instruments need to be used when collecting the samples. Figure 1A shows the white fibrous root form of the organism on the patient's lower arm and Figure 1B shows the tuber mass form of the organism on one of the patient's thumbs. The organism appeared to evade the effects of the antifungal drug by migrating onto the skin surface from the underlying dermis. The effectiveness of antifungal azole drugs in decreasing the number of organisms might relate to the reported cellulose structure of Morgellons fibers.[1,5]

The organism has brilliant blue and red pigments which autofluoresced under ultraviolet light, a characteristic similar to that found for phycobiliproteins. The bluish phycocyanin and reddish phycoerythrin phycobiliproteins can be found in four types of organisms, ie, cyanobacteria (formerly called blue-green algae) and rhodophyte, cryptomonad, and glaucocystophyta algae.[6] The red and blue pigments observed in the organism might be related to the phycobiliproteins, which aid photosynthetic processes for the above organisms. However, based on other observed characteristics of the organism, it is unlikely to be related to algae.[7,8] The multicellular nature of the organism also rules out any possible relationship with cyanobacteria, cryptomonads, or glaucocystophyceae.[8] The existence of possible photosynthetic pigments in the organism rules out the possibility of a fungal relationship. Thus, Morgellons might be the first report of an organism undergoing a photosynthetic process in humans.

Results

The organism can be divided into four main morphological forms, ie, tube-shaped fibers, amorphous tuber masses, fibrous roots, and seeds. The interrelationships between these four forms are based on a limited number of samples in which more than one form of the organism is present and their interrelationship can thus be observed and established. Aspects of the characteristic features and morphologies of the organism to be described and discussed here are based on observations of samples under both light and electronic microscopes.

The tube-shaped fiber form has the appearance of individual blue, red, or dark fibers under the epidermis.[1,2] Some tube-shaped fibers formed a network of blue fibers under the skin and blue and white fibers protruding from lesions.[1,2,5] Biopsies of infected skin samples were found with "fibrous material revealed nothing specific but an inflammatory process with no observable pathogens".[1,2] The colorless, blue, and red amorphous tuber masses are usually found as individual small dark specks and granule-like objects on an intact skin surface.[1,2] The seed form of the organism forms simple or complex structures with sharp and pointed ends which causing the stinging, biting, and shooting sensations from the skin. The movements of the very fine roots of the more mature seed form of the organism might account for the crawling sensation on the skin.

The term "Morgellons" was first used by Sir Thomas Browne in 1674 to describe harsh hairs breaking out of the skin on children's backs and sensations of cutaneous movement.[1,3] The name "Morgellons disease" or "Morgellons syndrome" was created in 2002 by Mary Leitao,[1,3] as a practical place holder because of its dermal similarity to the Morgellons described by Browne in particular.[3] The label "Morgellons disease" was also intended to be an alternative to decades of clinical use of the label "delusions of parasitosis",[9,10] also known as Ekbom syndrome, which is a form of psychosis including a strong delusional belief of infestation with parasites. Very often the imaginary parasites are reported as being "bugs" or insects crawling on or under the skin.[9,10] Many medical doctors still believe that Morgellons disease is a mental disorder and is not caused by a living organism, as suggested in this paper.

The US Centers for Disease Control and Prevention understandably has not wanted to use a term coined in 1674 more than 300 years later to characterize a range of cutaneous symptoms including crawling, biting, and stinging sensations, finding fibers on or under the skin, and persistent skin lesions. Most patients in the 21st century do not fit the descriptions from 1500–1800.[3] The US Centers for Disease Control and Prevention thus came up with the term "unexplained dermopathy (also called 'Morgellons')" to distinguish an entity separate from Morgellons disease or Morgellons syndrome.[5] In this paper, the new term "Yan disease" is used as a synonym for Morgellons disease/unexplained dermopathy. The author coined the term in order to distinguish the disease from both the Morgellons described in 1674 and the Morgellons disease identified in 2002, both of which are still of unknown etiology. In the absence of the term "Yan disease", others would need to use a term of unknown etiology and more than 300 years old for a present day disease caused by a new organism, as described in this paper. The place holder term will become an official term in the future no matter whether the two diseases, more than 300 years apart, were caused by the same organism as described in this paper or not.

Tube-shaped fiber form

Most samples of the tube-shaped fibers were collected from the fingers' skin surface. The tube-shaped fibers were usually 0.1–0.01 mm in width and of variable length, which could be over a few centimeters. At the root end, the colors became lighter and the structure showed a distinct cap where short roots were extruded, either in clusters or individually (Fig. 2A). Another sample of the tube-shaped fiber formed fibrous roots at the top and a type of banding at the lower end (Fig. 2B). Scanning electron micrographs showed tube-shaped fibers (Fig. 3A) with smooth, rounded outer surfaces which did not collapse as did the fibrous root form after exposure to high temperature treatment for electron microscopy. A more thorough analysis of the fibers performed by the forensics laboratory at the Federal Bureau of Investigation revealed that "the fibers do not resemble textiles or any other man-made substance".[2] The fibers were reported to be "indestructible by heat or chemical means, making analysis difficult by conventional method".[2]

There was a sample identified with a reddish-brown, short tube-shaped fiber connected to a triangular-shaped bluish tuber mass form of the

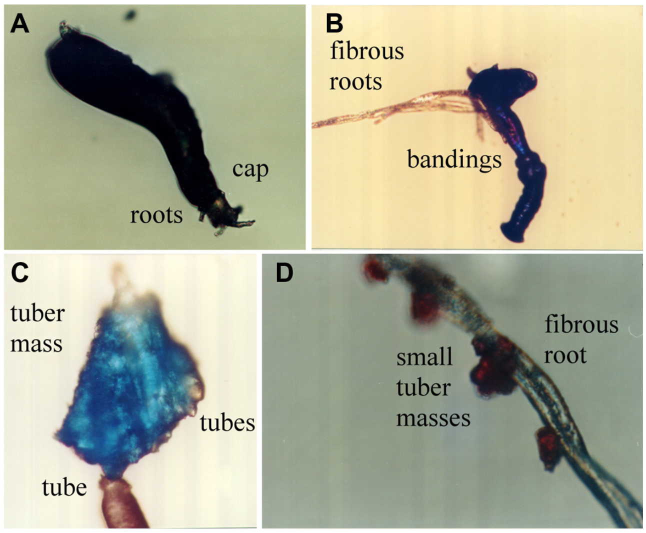

Figure 2. Samples of tube-shaped fibers and fibrous roots from fingers. (**A**) Tube-shaped fibers with larger bulging end, and a smaller cap end with short roots at bottom right. (**B**) Tube-shaped fiber with fibrous roots and bandings. (**C**) Amorphous tuber mass form of the organism, note tube-shaped fibers extruded as short cone-shaped extrusions on the lower right. The lighter colored tube-shaped fiber on the top could be traced through the semitransparent amorphous tuber mass all the way to one of the cone-shaped extrusions on the lower right. (**D**) A fibrous root is shown with small reddish amorphous irregular tuber masses. Original magnification 20×.

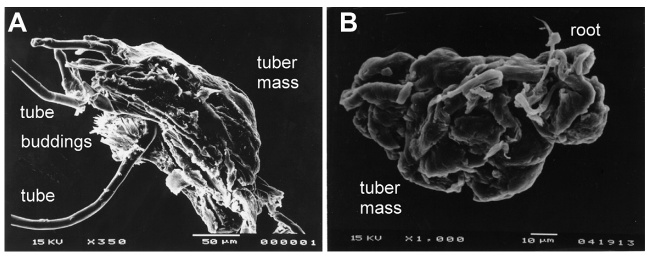

Figure 3. Scanning electron micrographs of samples of amorphous tuber masses from fingers. (**A**) Amorphous tuber mass form of the organism with tube-shaped fibers and budding extruded from the top left end. The underside of the tuber mass seemed to crack open with tube-shaped fibers and buddings extruded from either ends. (**B**) Smaller "speck" with fine roots extends to the top right side.

organism (Fig. 2C). The bluish tuber mass was observed to be composed of two or three internal tube-shaped structures that could be traced within the tuber mass to cone-shaped extrusions along the edges of the sample.

Amorphous tuber mass form

Most of the amorphous tuber mass samples were collected from the palms. There was no definite shape or structure to the amorphous tuber mass form of the organism. This form might be a type of energy storage aggregate similar to that in the potato, which is also a tuber plant. Tube-shaped fibers and/or fibrous roots were observed to originate from and extend into various parts of the tuber mass (Fig. 4A). Budding similar to that observed in potatoes sprouted from various parts of the tuber mass (Fig. 4A–C). A sample of a fibrous root showed four small reddish masses that grew along its length (Fig. 2D). These fibers might represent a backbone or conduits via which some form of energy could be stored within the tuber mass.

Under electron microscopy, a sample of a large tuber mass (about 0.21 mm in length) showed budding and a smooth outer surface. The bodies seemed to be cracked open on one side, from which tube-shaped fibers extended outwards from the inside and to either ends along the length of the tuber mass (Fig. 3A).

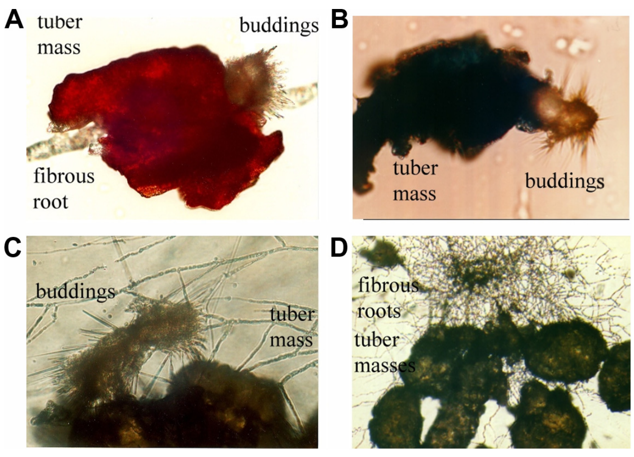

Figure 4. Samples of amorphous tuber masses from both palms. (**A**) Brilliant red color tuber mass form of the organism with fibrous roots extended along the length of it. (**B**) Dark blue-colored amorphous tuber mass with budding forming a cap, where long, sharp, narrow pointing ends extended outwards. (**C**) Colorless tuber mass form of the organism with a large budding forming an arm-shaped extension within a network of thin fibrous roots. (**D**) Collection of 5–6 colorless tuber mass form of the organism is shown, which forms a root system network. The masses might have been infected with Agrobacterium and thus their lumpy surfaces, relatively large in size, and numerous in number. Original magnification 20×.

Most of the masses collected were relatively large (about 1 mm) and colorless or opaque under the light microscope. These colorless masses turned an opaque dark color when put under sunlight for an extended period of time. The darker color might relate to generation of a large quantity of phycobiliproteins after stimulation by sunlight, a process similar to photodestruction of phycoerythrin in red algae.[7,8]

We speculated that the relatively more abundant and smaller-sized brilliant bluish tuber masses might have originated from the upper skin where the longer spectrum of sunlight penetrates and reflects blue light. The less common and larger-sized reddish tuber masses might have originated from deeper parts of the skin where blue light with a shorter wavelength penetrates and reflects red light. The colorless tuber masses (Fig. 4C and D) might have originated from relatively deeper parts of the skin where little sunlight penetrates. This is similar to chromatic adaptation[6,7] of red algae whereby the proportion and/or the nature of the different pigments is varied in response to differing qualities of incident light.

A network of very small roots with relatively extensive budding (Fig. 4C) was observed to grow from these colorless tuber masses (Fig. 4C and D) after a period of a few months with or without sunlight. These tuber masses were observed to have a lumpy surface, with budding and a root system. There has been a report of "virulence (vir) genes derived from chromosome and from the Ti plasmid, including the T-DNA" in Agrobacterium tumefaciens based on polymerase chain reaction study of samples from patients with Morgellons disease.[11] The most likely reason is that the plant-like organism was infected with Agrobacterium and formed lumpy tumors which were larger and more numerous than the blue or red tuber masses or black speck-like material. The tumors forming the tuber mass form of the organism appear as granule-like objects on an infected skin surface (Fig. 1B).

Fibrous root form

Most fibrous root samples were collected from the lower arm in the form of colorless or white fibrous roots with a great variety of lengths (from about 0.1 mm to several millimeters). Most of the fibers were short, about a few millimeters in length, with a width of one tenth of a millimeter. In heavily affected areas, the fibrous roots could be rolled into threads or strands by rubbing the skin surface with the fingers (Fig. 1A). The unusual nature of the fibrous roots could be recognized when associated with the tube-shaped fiber and/or colored tuber masses described above (Figs. 2B, D, and 4A).

The fibrous root samples were shown to autofluoresce under ultraviolet light and collapsed in form when exposed to high temperature treatment for electron microscopy (Fig. 3A and B). The fibrous root samples were also viewed under a light microscope (Figs. 2 and 4).

Seed form

The seed form of the organism causes the characteristic symptoms of crawling, biting, stinging, and shooting sensations when emerging from the skin en masse or individually. The seed form of the organism can be divided into simple and complex forms (approximately 0.1 mm in size). The simple form was comprised of interconnecting branches in various configurations. The branches had shapes similar to long, narrow blades, with the pointed ends facing away from the interconnecting central parts (Fig. 5B and D). The sharp and pointed ends were the major cause of the cutaneous symptoms of crawling, biting, stinging, and shooting sensations.

The complex seed form of the organism formed more or less circular patterns with branches radiating outwards (Fig. 5A and C). The center formed a high dome shape (Fig. 5A), suggesting that the branches might grow from a single seed or from the end of a fibrous root. Figure 5C shows a more mature seed form of the organism, with the sharp and pointed ends changing to very fine fibrous roots connected to a central tuber mass. Movement of these fine fibrous roots could account for the reported crawling sensations.

The fibrous root and seed forms of the organism have a chemical ability to deform (Fig. 6A) plastic and cut very small holes (Fig. 6B) on thin plastic, an ability also found in some fungi. These abilities enable the organism to puncture healthy skin, which is thought to be a major factor in infection of the host.

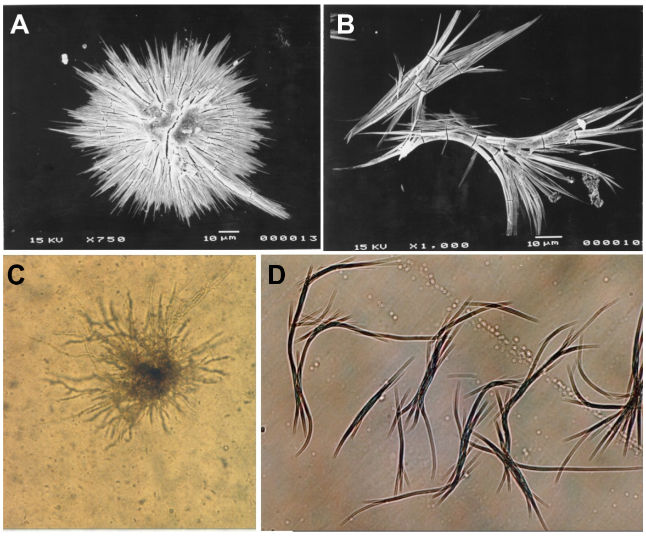

Figure 5. Scanning electron and light micrographs of seed form of the organism. (**A**) Complex seed forms (approximately 0.1 mm) have circular patterns with sharp pointing ends extending from various parts of the perimeter facing outward. (**B**) Simple seed forms (under electron microscopy) show long, sharp, and narrow pointing ends extending from interconnecting centers. The sharp and pointed ends cause the characteristic symptoms of biting, stinging, and shooting sensations in the skin. (**C**) Shows the more mature seed form which was changed from sharp and pointed ends into very fine roots causing the sensation of something crawling on top of the skin. (**D**) Simple seed forms (under light microscope) showed long, sharp, and narrow pointed ends extend from interconnecting centers.

Culture growth in agar and animal model of infection

The seed forms of the organism were found to grow in fungal media of solid potato dextrose agar culture, potato broth culture, solid blood agar culture, and in hamster and mouse models, albeit very slowly (over months) in a normal environment. Solid agar and broth cultures were inoculated at room temperature for about two years using the seed form of the organism. The organism formed circular patterns on the medium surface, but three or four pointed masses were also seen deep within the solid agar medium (Fig. 7A). The organism also grew as numerous tuber masses interconnecting with the root form of the organism (Fig. 7B), and the tuber masses could be quite large (about 2–3 mm). In potato broth culture, the fibrous root form of the organism emerged

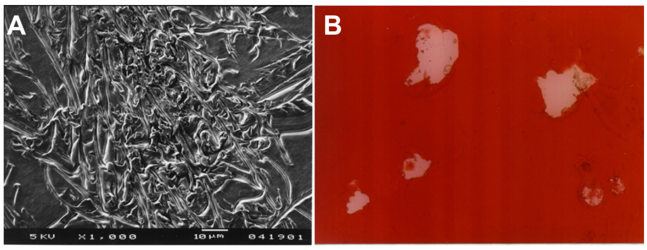

Figure 6. Thin plastic deformation and cutting holes. (**A**) The fibrous root and seed forms of the organism were observed to have the ability to deform thin plastic with some kind of chemical reactions. (**B**) It also made very small cutting holes ($<$0.5 mm) on thin plastic. The red area is about 3 mm across on thin plastic.

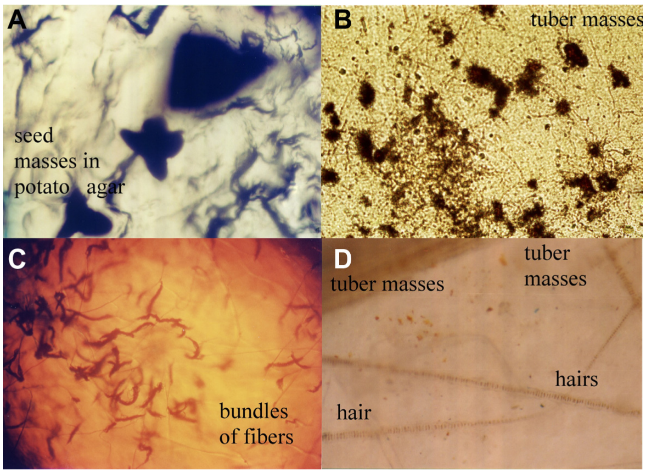

Figure 7. Culture growth and mouse subcutis plain view. (**A**) Seed form of the organism grew into 3–4 points masses in potato dextrose agar medium in 2–3 years. (**B**) Tuber masses form of the organism grew as numerous tuber masses interconnecting with fibrous root form in potato dextrose agar medium. (**C**) Fibrous root form as a number of interconnecting fibrous bundles grew in potato broth medium. (**D**) Tuber masses form as a number of light brownish small tuber masses grew in a mouse's subcutis with two hairs running across (in plain view).

as elongating bundles (Fig. 7C). Gram stains for both the solid and broth cultures showed that the samples contained a Gram-negative bacillus. There was also production of a dark pigment that appeared macroscopically to be extracellular.

A hamster and a mouse were subsequently inoculated with the seed form of the organism within the skin for about 2 months. On examination, there were no gross abnormalities of the skin or any other organ. The dermis contained a mild mixed inflammatory infiltrate, not concentrated around vessels or epidermal structures, but included a significant number of eosinophils. The hamster was diagnosed as having mild nonspecific chronic dermatitis. The mouse was noted to have possible thickening of the abdominal wall. An abnormality identified was a focal foreign body granuloma associated with a small amount of brown pigment in the subcutis. Figure 7D shows a plain view of the underside of a subcutis fragment which had a number of light brownish-colored tuber masses formed in between two hairs.

Conclusion

This article describes the likely etiological organism causing a new human infectious condition known as Yan (Morgellons) disease.[1–5] The organism has been described and discussed here based on observation of its morphological characteristics under light and electron microscopes. The organism has four characteristic morphological forms, which might relate to four different stages of development or reflect functional purposes. The four main morphological forms are tube-shaped fibers, amorphous tuber masses, fibrous roots, and seeds. The interrelationship between forms of the organism was based on some important samples where more than one forms were presented.

The patient's main symptoms are crawling, biting, stinging, and shooting out of skin sensations from the skin, which are caused by the sharp and pointed ends of the seed form of the organism. The seed form with sharp and pointed ends/extensions stings the skin when the seeds move on the skin surface. The more mature seed form changes from having sharp and pointed ends into very fine roots, causing the sensation of something crawling on the skin surface. Colored threads, black speck-like material, and granules are found in and on the skin. The white fibrous materials are the most abundant form of the organism on the skin surface. They can be rolled up into fiber balls or threads simply by scratching the skin surface and thus can be mistaken for common clothing fibers. The colorless/opaque tuber mass form of the organism is even harder to recognize as something emerging from the skin. It creates a sensation of sandy or granular objects on the skin surface. The symptoms of the disease are biting, stinging, and a shooting sensation from the skin related to the sharp and pointed ends of the seed form of the organism. Movements of the very fine roots of the more mature seed form of the organism might account for the crawling sensation on the skin. The seed form of the organism can grow in solid potato and blood agar as pointed masses and in potato broth as interconnecting bundles of fibers. The seed form of the organism grows in a hamster/mouse model as light brownish tuber masses.

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Author Contributions

Conceived and designed the experiments: CYY. Analysed the data: CYY. Wrote the first draft of the manuscript: CYY. Contributed to the writing of the manuscript: CYY. Agree with manuscript results and conclusions: CYY. Jointly developed the structure and arguments for the paper: CYY. Made critical revisions and approved final version: CYY. All authors reviewed and approved of the final manuscript.

Competing Interests

Authors disclose no potential conflicts of interest.

Disclosures and Ethics

As a requirement of publication author(s) have provided to the publisher signed confirmation of compliance with legal and ethical obligations including but not limited to the following: authorship and contributorship, conflicts of interest, privacy and confidentiality and (where applicable) protection of human and animal research subjects. The authors have read and confirmed their agreement with the ICMJE authorship and conflict of interest criteria. The authors have also confirmed that this article is unique and not under consideration or published in any other publication, and that they have permission from rights holders to reproduce any copyrighted material. Any disclosures are made in this section. The external blind peer reviewers report no conflicts of interest.

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