Infection and Drug Resistance

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PERSPECTIVES

Buruli Ulcer and Medical Geo-Microbiology

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Abstract: Buruli ulcer is a chronic debilitating infectious disease caused by the pathogen *Mycobacterium ulcerans*, which can be cured if diagnosed and treated in an early stage. However, advanced cases need antibiotic treatment followed by surgical interventions. In this context, an extremely effective and less expensive treatment modality can be developed by means of an extended topical application of certain selected natural clay minerals, most of the time containing illite-smectite having some iron content. There is a scope for developing the speciality, medical geo-microbiology, which is truly a multidisciplinary one, for finding a cure for the severe and advanced cases of BU.

Keywords: Buruli ulcer, clay minerals, drug resistance

Perspective

Buruli ulcer (BU) is a debilitating neglected tropical disease, first reported in Kampala, Uganda, by an English physician Albert Cook, in the late nineteenth century.[1] It is a destructive infection affecting the skin and soft tissues, resulting in extensive skin loss and severe tissue damage followed by scarring and contracture,[2] and anyone can contract it irrespective of sex and age, although the highest incidence was seen in children aged between 5 and 15.[3] Buruli ulcer exists in more than thirty countries with tropical, subtropical, and temperate climate zones, including Africa, South America, and the western Pacific region; it is a disease of particular concern in some areas of Africa and Victoria in Australia.[2] However, there exists a sharp contrast in the epidemiology of BU between Africa and Victoria.[4,5]

Buruli ulcer is the third most common human mycobacteriosis caused by an environmental mycobacterium called *Mycobacterium ulcerans*, which has a predilection for dermal and bone tissues.[6] As per the World Health Organization, there is some ambiguity in the transmission mode, and there exist some ignorance and negligence of effective primary preventive measures supposed to be taken, such as the use of protective clothing during exposure to vectors.[7] There are many suspected vectors, such as aquatic insects (biting water bugs belonging to the families Naucoridae, the creeping water bugs and Belostomatidae, the giant water bugs), adult mosquitoes, or other biting arthropods.[8] Frequent contacts with swamps and slow-moving water bodies facilitates contracting BU.[8]

Mycobacterium ulcerans produces a unique exotoxin, mycolactone (a polyketide-derived macrolide), which leads to heavy tissue damage if left untreated. Specifically, mycolactone provokes apoptotic cell death by driving the expression of pro-apoptotic proteins, BCL 2L11 and Fas and inhibiting cell cycle progression.[9] The clinical manifestations of BU include relatively unspecific and non-ulcerative lesions such as nodules, papules, plaques, and oedema, which may eventually progress to necrotic ulcers.[7] Earlier research reported that nodules were associated with higher interferon-γ and lower interleukin-10 (IL-10) productions, and ulcers were associated with higher IL-10 production.[10] Rarely nodular lesions can be misleading, and wrong diagnoses can happen, interpreting the condition as lymph node tuberculosis. Human Immunodeficiency Virus infection complicates the management of BU patients, and the treatment outcomes will be always poor.[7]

Buruli ulcer can be co-infected with an array of wound bacteria. The diversity of species isolated from BU wounds represents a broad spectrum that is similar to those isolated from other wound types, such as burns and infected diabetic

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foot ulcers. However, the predominant bacteria co-existing with *M. ulcerans* in the wounds of BU patients are *Staphylococcus aureus, Pseudomonas aeruginosa* and β-hemolytic streptococci, which delay the healing.[11–13]

Of late, there has been a waxing and waning in the overall number of reported BU cases, attributed to various reasons, including COVID-19, which intervenes with the active detection programs.[7] Diagnosis of BU-associated lesions is a bit difficult. It is often confused with skin conditions with similar presentations ranging from cysts, lipoma, psoriasis, skin lymphomas, tropical ulcers, ulcerated skin malignancies, venous or vascular ulcers, bacterial skin infections such as actinomycosis, boils, cellulitis, ecthyma, folliculitis, furuncle, impetigo, noma, treponematosis, parasitic infections including cutaneous leishmaniasis, myiasis, cutaneous tuberculosis, leprosy, and atypical mycobacteriosis.[14] Nevertheless, highly experienced professionals in the endemic area can make an early, precise and reliable diagnosis.

As in the cases of leprosy, BCG vaccination appears to provide some protection against BU; WHO is very much committed to providing technical support, implementing policies, and regularly coordinating various measures related to the control and research efforts to curb BU.[8] The policies of WHO in managing BU center around understanding the mode of transmission, developing quicker diagnostic tools and tests, and assuring the best case-antibiotic treatment. Recently, WHO has developed a skin app to aid health workers in this field.[8]

The current treatment options for BU are lengthy and consist of antibiotics developed for tuberculosis. However, considering the history of antibiotic resistance in other bacterial pathogens, such as *M. tuberculosis*,[14] concerns have arisen that inappropriate use of antibiotics may lead to similar resistance patterns in the case of *M. ulcerans* too. To prevent the emergence of resistant strains, a combination of antibiotics was suggested by WHO, including rifampicin, clarithromycin, as well as intramuscular injection of streptomycin even though moxifloxacin is recommended instead of clarithromycin.[7] In extreme cases, surgery is an option used to hasten the healing of ulcers bigger than 5 cm in diameter, prior to which and also after which a combined antibiotic therapy for four weeks is practiced. However, surgical facilities are not available or not practical in highly endemic rural regions of Africa, and there can be other infections occurring during surgery and also there will be excessive loss of healthy tissues.[15] This scenario demands a new treatment modality and is a research priority for the strict control of BU; medical geo-microbiology can be considered as a silver line, which appears to be a fascinating and innocuous option. It is an interdisciplinary branch of studies on clay mineralogy, geochemistry, microbiology, statistics and therapeutic response to clay applications.[15] In fact, clinical microbiology research on antibacterial minerals comprises the basis of the branch of medical geo-microbiology.[16] Application of selected clay minerals in the necrotized ulcers of BU patients can result in continued debridement of affected tissues and regeneration of healthy tissues, ultimately resulting in healing.[16]

An extremely effective, non-conventional and less expensive treatment of severe BU cases was initiated more than two and a half decades ago in Ivory Coast among women and children, and the work lasted for a decade.[17,18] Advanced cases of BU have been treated and cured by the topical applications of selected wet clays of volcanic origin (bentonite) from France. This treatment intervention provided the ultimate cure and relief within a short period (approx. 3 months) for the patients who were suffering from necrotized wounds. The remarkable therapeutic utility of a particular French clay was illustrated by the rapid, non-surgical elimination of necrotized tissues.[17,18] An extended treatment via the daily topical applications of this clay mineral resulted in very effective debridement of ulcer tissues, regeneration of healthy tissues and ultimately the wound healing. After two to three months of daily application of clays on the affected area, the BU wounds healed perfectly with the re-installation of normal motor function. These observations had brought in far-reaching consequences, hope and high relevance with regard to the failed cases of severely ulcerated patients, mostly belonging to category 3 cases of BU. The only accepted treatment for the advanced cases of BU till then is antibiotic therapy clubbed with the surgical ablation of ulcerative lesions, most often involving the elimination of even the healthy tissues. In other words, this work initiated by a French humanitarian gave hope, and it substantiated the potential of medical geo-microbiology, which can be further developed as a promising cure for the advanced cases of BU worldwide.[18] Following this effort, there stemmed some opportunities to study the antibacterial activities of several clay minerals from different locations and sources.[15,16] The above-mentioned French clay and several other clay minerals from the US and elsewhere were soon subjected to extensive physico-chemical characterization by the research group of Dr. Lynda B Williams of Arizona State University. They studied the broad spectrum in vitro antimicrobial activities of

several clay minerals against a series of antibiotic-resistant bacterial pathogens, including a couple of mycobacterium species which are the surrogate organism of *M. ulcerans*.[18–21]

The French clay sample initially utilized to cure BU consisted of smectite and illite minerals, with some other minor ancillary minerals, and was iron-rich (6% wt).[17] The clay sample possessed a respectable surface area (90–115 m^2/gm), providing a large reactive surface for ion exchange and the particle size was less than 2 μm. It can be assumed that no complicated processing procedures or modifications were involved in preparing the naturally occurring clay mineral sample for the topical application.[16] The main foci of these studies were the antibacterial activities of clays against a series of drug-resistant bacteria, and maybe in the future, an effective remedy for the advanced cases of BU from antibacterial clays can be anticipated. However, it is to be noted that approximately 5% of the total number of clay mineral samples studied to date only were antibacterial.[15,16] But still, the scope of searching new antibacterial clay minerals is immense.

The mechanism of action of antibacterial clays probably involves toxins that are inorganic in nature and leached out from the clay microstructure in the presence of water, providing bactericidal activity.[16] It has been suggested that physical contact between the bacterial cell wall and the clay particles is not an essential factor for the bactericidal activity to happen. Reports suggest that the Fenton-mediated reaction is the source of the oxidation of mineral-bound Fe^{2+}, generating hydroxyl radicals that can damage and kill bacterial cells.[22,23] Fe^{2+} in excess amount can be toxic to bacterial cells, increasing the oxidative stress and resulting in the damage of the bacterial membranes. This effect, in fact, is related to the binding affinities of Fe^{2+} to biomolecules in the bacterial cell and the production of fatal reactive oxygen species (ROS).[24,25] However, the exact and precise understanding of the antibacterial properties and related mechanisms of natural clay minerals appear to be complex as on today, because they are linked to a blend of several sets of reaction pathways. Extensive research work is to be conducted in this regard. In addition, some other inorganic cations and other species in the leachate of an antibacterial clay mineral can be bactericidal.[16]

A literature survey conducted indicates that natural and cheap ingredients like bentonite (derived from altered volcanic ash beds), Mikulicz ointment (a magistral preparation of 1% silver nitrate and 10% Peru balsam in a cream base), and silver sulfadiazine were used for the treatment of refractory ulcers.[26–29] In addition, the use of silver sulfadiazine in treating venous leg and diabetic foot ulcers infected by biofilm-forming *Staphylococcus aureus* and *Pseudomonas aeruginosa* proved successful.[27,28] There are also cases related to the use of magistral preparations of Mikulicz ointment/cream to treat recalcitrant arteriopathic diabetic foot ulcers.[29]

For the last couple of years, our research group has been engaged in the medical geo- microbiological aspects of selected clay minerals from India and Ethiopia. We have studied the efficacy of several clay samples in curbing the growth of multidrug-resistant bacterial wound isolates (*Staphylococcus aureus, Pseudomonas aeruginosa, Escherichia coli, Klebsiella pneumoniae, Streptococcus pyogenes*), and the preliminary results obtained are encouraging (in vitro studies only). Antibacterial properties of several clay minerals against the surrogates of Mycobacteria, such as *M. marinum* and *M. smegmatis* are currently underway.

Conclusion

Medical geo-microbiology is a promising multidisciplinary and emerging field related to the control and management of several types of wound bacteria, including *M. ulcerans*, an environmental bacteria, utilizing the impressive and varied physico-chemical properties of selected natural clay minerals, some of which contain smectite-illite phases and iron. Recently, the broad-spectrum in vitro antimicrobial activities of some clay minerals against several drug-resistant bacteria have been revealed. This attempt is particularly important in the context of the management of advanced cases of BU, which at present requires surgical interventions.

Disclosure

The authors declare no conflicts of interest in relation to this work.

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