Hansen’s disease: clinical characteristics, oral lesions and periodontal disease: A review and update

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Abstract
Introduction: Hansen’s disease is still a prevalent disease in many countries of the world. A number of peripheral pathological manifestations of the disease including those in the oral mucosa have been described in the medical and dental literature.

Goals: Describe the mechanism of the disease, oral, clinical manifestations and the potential relationship with periodontal disease. Methods: Using a number of descriptors including Leprosy; periodontal disease, clinical manifestations, mechanisms and oral lesions entered into www.google.com, a number of reviews and experimental studies were found and used to summarize to prepare the current investigations. Only this database was used to collect scientific papers. Outcome: About 60 papers were used. However, because the focus of this investigation was oral lesions and periodontal disease, 17 papers were discarded and the other 47 studies were used to summarize papers to prepare the current study. Conclusion: Leprosy is still a serious health problem in some countries in South America, Asia and Africa. The orofacial structures including the mouth are frequently affected by leprosy leading to a number of intraoral lesions that complicate treatment of this clinical process. Many types and subtypes of leprosy with different clinical and histological characteristics can be observed. To a certain extent Hansen’s disease represents a failure of the immune system to successfully combat infection directly favoring the transmission of the disease from one subject to the other. Key Words: Hansen’s disease. Leprosy. Mechanisms. Oral Lesion. Periodontal Disease. Diagnose. Treatment.

I. Introduction

Leprosy is a chronic, contagious and infectious disease caused by the microorganism Mycobacterium leprae that predominantly affects the skin, peripheral nerves, internal organs and mucosa of the body[1]. Signs and symptoms of this disease in actuality represents sudden acute immune and inflammatory reactions against Mycobacterium leprae superimposed on the chronic course of the disease[2] that predominate in individuals classified as multibacillary, being responsible for irreversible nerve damage, increasing the disease burden and associated prejudice on affected individuals[3]. Leprosy is a clinical diagnosis usually confirmed with the use of bacilloscopy of the skin slit smears and biopsy[4]. Mycobacterium leprae is an acid-fast bacteria and the infection is characterized by cutaneous, neural and constitutional symptoms and by the production of numerous disfiguring deformities.

The infection takes different clinical forms depending on patterns of host response to the bacteria[5]. Hansen’s disease is also defined as a chronic granulomatous disorder caused by an acid fast bacillus, an obligate intracellular mycobacterium that was first identified by Hansen in 1873[6]. The cell wall of the microorganism is Gram positive, highly complex and contains proteins, phenolic glycolipids, arabinoglycan, peptidoglycan and mycolic acid[7]. Mycobacterium Leprae, the microorganism that transmits the disease and produces the clinical manifestations, has a strong preference for peripheral tissues as it appears to survive better at a temperature close to 30°C rather than 37°C, which explains a number of lesions preferentially observed on the skin, peripheral nerves and mucosa and on the upper respiratory tract[8], de Macedo and associates[9] define leprosy as a chronic infectious disease that affects the skin and peripheral nervous system and is caused by an intracellular microorganism.
II. Methods
The terms “Hansen’s disease”, leprosy, periodontitis and oral lesions were entered into the database www.google.com in order to get scientific papers about this condition. No other databases were searched and only papers written in English were accepted in order to carry out this review.

III. Outcome
Sixty papers on “leprosy” or “Hansen’s disease” were found. However many of them present insufficient or repetitive information about this disorder. Thus, seventeen (n=17) papers were discarded and forty-three (n=43) papers were reviewed and summarized in order to carry out the current review.

IV. Literature Review
Prevalence and epidemiology
Leprosy is an infectious disease and even though its presence has been documented since antiquity, the disease continues to be present even in the endemic form in some underdeveloped and developing countries, most of them located in tropical and sub-tropical zones. For a long time, the disease has been considered as incurable and fear of the disease is associated with a number of superficial deformities in some parts of the body and the fact that diseased people are discriminated by the public and society in general. Even though it has been claimed that leprosy has a definitive cure, the disease is still present in many regions and countries being a major reason for serious concerns to governments and health authorities. Hansen’s disease is still endemic in some countries including Brazil and India where some endemic pockets of the disease have been identified. Brazil has the second highest number of cases in the whole world. Leprosy is still a significant health, social and economic problem in many areas of the world. It has been reported that about 80% of all reported cases are restricted to a group of countries including Brazil, India, Indonesia, Madagascar, Myanmar, Nepal and Nigeria. Leprosy is an extremely rare disease in Central and North America. The worldwide prevalence of Hansen’s disease is reported to be just one case per a group of 10000 inhabitants. However, it is known that the prevalence of the disease has decreased since the introduction of short course multiple drug therapy in 1982. It is believed that approximately 10-15 millions of people around the world have been infected with the microorganism and present with clinical signs and symptoms. Leprosy is considered endemic in some countries, for instance, Brazil and India and about 266000 subjects in Brazil have been infected by the microorganisms and present with clinical signs and symptoms. It is believed that India has the highest number of leprosy cases and the disease occurs in all races. African blacks have a higher incidence of the tuberculoid form of leprosy, whereas light skin people and Chinese tend to have the lepromatous form of the disease.

The whole prevalence of the disease is much higher in Africa (3.14/1000 habitants) as compared to 1.56/1000 for Asia; 0.46/1000 in the Americas and 0.02/1000 for Europe. The prevalence of the disease has declined dramatically in Asia in the last 55 years from 8/100000 to 0.2/100000. Clusters or pockets with high prevalence of the disease can still be observed in some areas of Africa, Asia, South America, more specifically in India and Brazil. Based on data from the World Health Organization (WHO), it seems that the global number of cases of leprosy decreased from 2003 to 2009, but the total prevalence is still very high in some countries including India and Brazil. In Brazil, a reduction in new cases from 2006 to 2011 has been documented but the country still has a prevalence of 2 or more cases per 10000 inhabitants.

Etiology, characteristics of Mycobacterium leprae and transmission of the microorganism
In terms of taxonomy, the microorganism Mycobacterium leprae belongs to the genus Mycobacterium, which is a single genus of the family Mycobacteriaceae, in the order Actinomycetales. The microorganism is an obligate intracellular parasite which multiplies very slowly, with a generation time of 120-14 days, that grows optimally at a temperature of more or less 30°C and thus, it prefers the cooler areas of the human body. The Gram-positive type of the cell wall is highly complex and contains proteins, phenolic glycolipid, arabinoglycan, peptidoglycan and mycolic acid. M. leprae invades and survives in the organism within some specialized cell types including macrophages, dendritic and Schwann cells. Penetration in the host is the first step in the intracellular life cycle of M. leprae, which is achieved via several different methods.

The microorganism is transmitted to other individuals through secretions including semen, saliva, and sweat or tears of patients with infectious forms of the disease and/or by direct contact with the skin through open wounds. It is generally accepted that Mycobacterium leprae are transmitted during close contact between an infected patient and a uninfected individual. If the contact is intimate and prolonged, the probabilities of contracting the disease are increased. It has been reported that more vulnerable anatomic areas allowing the entry of the microorganism are the skin, upper and lower respiratory tract and the gastrointestinal tract.
Temperature seems to play a key role in the survival of the mycobacterium leprae and in its capacity to cause a disease within body tissues. It is clear that the leprosy bacilli appear to be excessively temperature dependent, for it produces lesions mainly in cooler parts of the body. Thus, the mycobacterium has a strong preference for peripheral nerves as it appears to better survive at a temperature close to 30 degrees C. This preferential peripheral location of the bacilli facilitates the development of numerous deformations in the skin, peripheral nerves and mucosa of the upper respiratory tract.[8]

There is strong evidence indicating a greater risk to acquire the disease in individuals living in close contact with leprosy patients. However, many new cases cannot identify an index case from whom they may have acquired the infection. Strong evidence suggests a “clustering” of leprosy cases and there is elevated risk of leprosy among contact of index cases both within the household and in social contact. Transmission may occur in the absence of overt disease and/or in the presence of many undiagnosed cases.[20]. The studies carried out by Andrew and Kadala[21] indicate that the skin and the upper respiratory tract constitute the most common routes of transmission of the disease.

It is believed that droplets from humans with leprosy expelled during breathing can be inoculated into the nasal mucosa of healthy individuals allowing the bacteria to safely colonize the mucosa and initiates its reproduction and potential dissemination to other anatomic sites. Mycobacterium Leprae displays a very low genetic variability allowing researchers to more easily trace the dissemination of the disease by the great human migratory movements around the world. Most ancient strains infecting humans are typical from Eastern Asia and M. lepromatosis, a microorganism sharing about 87% genome homology with M.leprae was identified as the etiologic agent of a diffuse clinical form of leprosy[9].

Clinical presentation

In leprosy, the cooler tissues of the body are more severely affected when the organism has colonized completely some anatomic areas. Many researchers have described that the most commonly affected areas of the body are the skin, superficial courses of the peripheral nerves,[22] for example, the seventh and fifth cranial nerves and the nasal passages. It is generally accepted that most individuals consider leprosy as an incurable disease usually associated with a number of severe deformities and disabilities resulting in stigmatization and thus, the victims suffer of frequent humiliations and discriminations[7]. Resorption of the anterior nasal spine in patients with leprosy was first observed almost seventy years ago. Researchers at that time, found that resorption of nasal spine and maxillary alveolar process occurred more frequently in patients with long-standing leprosy. Such pathological alteration was more frequently observed in those with the lepromatous leprosy type[25]. Cutaneous manifestations of lepraes are well known and have been described in numerous investigations.

Infiltration of any peripheral nerve trunk may give rise to severe and disabling visible deformities associated with facial paralysis caused by dysfunction of the seventh cranial nerve, hypoesthesia or anesthesia resulting from involvement of the fifth cranial nerve in leprosy patients[9]. These pathological changes indicate the presence of a neuropathic peripheral disorder. Peripheral leprosy neuropathy is caused by invasion of superficial peripheral nerves by leprosy bacilli. Leprous neuropathy is characterized by involvement of superior nerve trunks such as the ulnar, radial cutaneous, median common peroneal, supra-orbital and greater auricular[20][24]. Peripheral nerve injury is the most severe symptom affecting patients with leprosy. Nerve impairment may become irreversible when the diagnosis is late, resulting in permanent disability and physical deformities[9] which to a certain extent are used to recognize the presence of the disease.

The indeterminate leprosy type is the earliest manifestation of leprosy being characterized by poor delimited hypo-pigmented macules which can be smooth or scaly, sensory loss over macules in some patients and thickened peripheral nerves. The tuberculoid leprosy type is characterized by asymmetrically distributed plaques and papules on the extremities, formation of erythematous plaques with central atrophy and hypopigmentation, alopecia, anhidrosis, loss of pain and temperature sensation and loss of fine touch sensation over skin lesions in some patients[21]. The lepromatous type is characterized by multiple asymmetric papules and nodules on the skin and mucosa membranes, involvement of the nasal mucosa, destruction of the nasal septum and nasopharynx with associated ulcerations of the palate and larynx, occasional visual loss with complete blindness in 10% of the cases. The borderline/tuberculoid leprosy form of such disease presents with numerous skin lesions, annular plaques and papules sharply demarcated and asymmetrically arranged. The borderline/lepromatous leprosy is characterized by symmetrically arranged multiple and hypo-pigmented papules, nodules and plaques, poorly demarcated with small islands of normal skin[21].

Classification or Hansen’s disease types

Leprosy is a pathological disorder with many and different clinical and histological characteristics and consequently it has been classified in various types and even subtypes. The most used and accepted classification system in leprosy is one based on Ridley and Jopling criteria and accepted in the whole world:
1. Indeterminate: Is the initial form of the disease which in many cases can cure spontaneously or evolve to a broad spectrum of clinical manifestations in different anatomic structures of the body. This leprosy type is characterized by the presence of hypopigmented lesions with sensory disturbances, loss of hair and absence of horripilation.

2. Borderline form: This leprosy type usually involves a combination and/or a predominance of the lepromatous form or the tuberculoid form of leprosy. Patients with high immune resistance and favorable immune response predominantly present with tuberculoid characteristics of the disease, that is, frequent nerve trunk involvement with severe destruction of nerve elements by an epithelioid granuloma with the presence of skin lesions and nerve trunk destruction. Skin lesions in this subtype of borderline leprosy, are more numerous, but less indurated when compared to tuberculoid leprosy. In borderline leprosy with a lepromatous predominance, early axonal damage is present. Further, axonal regeneration, symmetrical involvement of nerve networks and trunks, preservation of nerve architecture, infiltration of foamy histiocytes and great number of bacilli are some reported characteristics. This subtype of leprosy is also characterized by symmetrically distributed, multiple hypo-pigmented papules, nodules and plaques. This lesions are poorly demarcated.

3. Tuberculoid type: This form of leprosy usually begins with a slightly elevated macular lesion on the skin that advances centrifugally with a central portion that becomes flat and pale while the periphery remains erythematous and irregular. Other characteristics of such leprosy type include hyperesthesia at the periphery and anesthesia in the center of the lesion and presence of adjacent lesions that usually coalesce. Further, larger nerves of the extremities are frequently affected by Mycobacterium leprae in the form of infiltration that gives rise to painful neuritis, anesthesia, paralysis and trophic changes in the hands and feet usually associated with loss of light touch, pain, and thermal sensations usually associated with increased vulnerability to trauma in the affected extremities or regions. Patients with tuberculoid leprosy frequently have a large macular hypopigmented or erythematous anaesthetic lesions with a well defined, often raised margin or occasionally are scaly plaques.

4. Lepromatous type:
The lepromatous leprosy type is characterized by the presence of infiltrates in the deeper cutaneous layers forming nodular masses in the superficial skin. This leprosy type is also characterized by the presence of a chronic subtype with a quiescence period and by an acute or spreading type in which a breakdown of lesions, presence of fever and formation of new lesions can be observed. In lepromatous cases, there is a strong trend for the presence of caries, gingivitis and periodontitis with significant alveolar bone loss and subsequent loss of dental elements initiating in the maxillary interincisal bone crest. In a study of 40 leprosy patients, researchers reported that lepromatous lepra was the most common form of the disease and the hard palate was the most common anatomic site affected in the masticatory structures. The lepromatous type of leprosy is known to result in a variety of clinical manifestations in the oral mucosa. Symptoms may be or may not be present.

Lepromatous leprosy is usually widespread and frequently consists of erythematous macules, papules or nodules. Sometimes the disease has a diffuse character and distinct lesions are not observed.

5. Paucibacillary leprosy is one type characterized by the presence of one to five lesions.

6. Multibacillary leprosy is the one characterized by the presence of more than five lesions.

Pathophysiology

M. lepraegrows and multiplies preferentially in anatomic areas where the local temperature is a little bit lower as compared to the rest of the body. Recently, a pathophysiological mechanism for oral involvement of the microorganism has been postulated: Supposedly, a nasal lesion in which the air flow is obstructed, favors another mechanism of oral or mouth breathing, which is very common in lepromatous individuals. Such change causes a decrease in the intraoral temperature most frequently in some anatomic areas in contact with the air flow, for instance, the epithelium of the upper respiratory tract including the oral epithelium. The upper airways constitute the most important point of entry for the bacillus and a main source for bacillary elimination in leprosy. The oral mucosa is apparently a secondary site for M. leprae infection and transmission. Further, the involvement of the oral mucosa may have a major role in the transmission of the disease from adults to children. Further, Mycobacterium leprae invades and survives within macrophage, dendritic and even within Schwann cells even when some interleukins are expressed to combat the microorganism.

According to Salgame and colleagues, interleukin 2 and interferon gamma predominate in the tuberculoid type of lesion whereas interleukin 4, interleukin 5 and interleukin 10 predominate in lepromatous lesions. M. leprae has the capacity to induce lipid accumulation in infected cells in the form of lipid droplets.
which are storage organelles of the cells\textsuperscript{[9]}. These lipid droplets may migrate to the phagosomes of the bacteria. It has been reported that lipid accumulation enhances the killing capacity of the bacteria. As mentioned before, M. leprae has a special predilection to colonize the peripheral nerves causing severe motor and sensory changes including neuropathic disorders. In the context of Schwann cells, it has been shown that M. leprae is capable of altering host cell energy metabolism at several points thus resulting in lipid accumulation, decrease of the mitochondrial action potential, exacerbation of lipid accumulation in the host cell cytosol, reduction in the generation of reactive oxygen species and lowering of the reduction power consumption from glucose oxidation\textsuperscript{[9]}.

The pathogenesis of nerve destruction depends largely on the clinical form of the disease. In multibacillary cases in which macrophages are found profusely within the nerve, bacilli can be found in greater numbers, often as large bundles or globi. Ultrastructural analysis indicates that borderline and lepromatous leprosy with foamy macrophages and vacuolated Schwann cells contain numerous electrodense structures of deteriorated and fragmented M. leprae\textsuperscript{[18]}. It has been accepted in the medical literature that major defense mechanisms against M. leprae are established by cell mediated immune responses. Thus, the success or failure of such bacteria to colonize and produce a clinical infection depends primarily on the host response to the pathogen and the magnitude of the cell mediated immune reaction. Thus, to a certain extent, these variables may determine the presence of absence of clinical signs and symptoms\textsuperscript{[7]}. The disease adopts different clinical forms depending on patterns of host response to the bacteria, especially the perturbation of cell mediated immunity. It is very likely that there is a direct relationship between the capacity to combat the presence of the M. leprae and the development of a specific infection, for instance, the lepromatous or the tuberculoid form of the disease\textsuperscript{[5]}.

It has been reported that in the presence of established leprosy, to a certain extent there is a cytokine profile dominated by the presence of IL-2, interferon gamma, mostly present in the tuberculoid leprosy type lesions, and II-4, II-5, and II-10 predominating in the presence of lepromatous lesions\textsuperscript{[31]}. T cell subsets forming part of the immune defensive system are of paramount importance in the defense mechanisms mounted against invasion by M. leprae. Recently, it has been reported that T cells contribute to host defense mechanism against the intruder (M. leprae) using granulosyn (an antibacterial protein) which is predominantly expressed and released by T cells in tuberculoid lesions but not in lepromatous lesions. It has been found that this protein is capable of reducing the availability of mycobacteria\textsuperscript{[7]}.

Macrophages are especial cells that belong both to the anti-inflammatory and to the immune system. Their major functions include travelling in the blood vessels, watch and identify foreign bodies including cell residues, dead cells, bacteria, fungi and virus the third function is the presentation of the antigen to the antibody. It has been established that M. leprae infected macrophages present in skin lesions of patients with lepromatous leprosy are capable of producing both prostaglandins and IL-10. II-10 has an important role inducing high levels of phagocytic activity concomitant with the obstruction in the antimicrobial pathways resulting in the multiplication of the pathogens\textsuperscript{[9]}. Recent studies evaluating the relationship between inflammatory mediators and leprosy have reported a high incidence of pathological reactions in the oral structures. In this regard, it has been reported that leprosy reactions and dental or oral infections (for instance gingivitis and periodontitis) have some common characteristics as in both the chronic infection evolves slowly and inflammatory and immune factors modulate the host response\textsuperscript{[2]}.

When the oral mucosa is overtly exposed to M. leprae antigens, innate immune mechanisms are immediately activated so as to prevent the adhesion of Mycobacterium leprae to the oral epithelium and at the same time the production of IgA and IgM antibodies is stimulated and both can be found in free saliva\textsuperscript{[13]}. As the presence of M. leprae in the body tissues largely on established bacteremia, it has been indicated that the presence of the bacilli in the oral cavity may be closely associated with an infection of greater severity\textsuperscript{[1]}. With the discovery in the last century that leprosy could be associated with mechanisms responsible for bone resorption in the anterior nasal spine and maxillary alveolar bone, such observation opened a new avenue of research regarding leprosy. Such bone destruction in specific anatomic sites was confirmed many years later in a study of 44 patients presenting with lepromatous, borderline and tuberculoid leprosy. It was observed that resorption of nasal spine and maxillary alveolar process was greater in patients with long standing disease and in those patients with lepromatous leprosy\textsuperscript{[23]}.

\textbf{Immune host response}

The chain of body tissue reactions once M. leprae has colonized the tissue and is fully established within the cell, depends largely on the immune status of the invaded host. The course of the disease is also dependent on individual factors that influence the host immunologic response. Genetic, environmental and nutritional factors also influence not only the probability of infection but the course of the disease as well. Nutritional deficiencies are observed frequently in countries in which leprosy is endemic, for instance, northern Brazil, India and some countries in Africa. The course of the disease may be influenced by the body
concentrations of some ions and vitamins including iron, selenium, zinc, vitamins C, A and D\[^{16}\]. The host immune system affects the clinical manifestation of leprosy. Strong cell-mediated immunity mechanisms and humoral immunity characterize the response to tuberculoid leprosy, whereas in lepromatous leprosy, the opposite is true\[^{17}\].

It has been established that the different degrees of cellular immune responses of the host to the invader is responsible for different types of granulomatous reactions. Epithelial cells are usually found in the tuberculoid and borderline tuberculoid whereas foamy macrophages are frequently observed in multibacillary cases\[^{18}\]. The body immune response may be activated rapidly when M. leprae overcomes the natural barriers of the organism including tissues, epithelia, superficial lipids and acidity. The infection or control of the pathogen depends on the host ability to produce a positive response against the infectious agent\[^{16}\]. It has been reported that some products including TNF-alpha, nitric oxide, and reactive oxygen species (ROS), although are capable of displaying key microbicidal action, they also induce tissue damage\[^{16}\].

It has been reported that the TH1 subset of lymphocytes characterized by the predominant secretion of IL-2 and interferon gamma preferentially induces cell-mediated immunity whereas Th2 cells, which express interleukin 4, interleukin 5 and interleukin 10, enhance the humoral immune response\[^{17}\]. Mycobacterium leprae activates TLR2 and TLR1 in Schwann cells which specifically trigger a chain of reactions leading to tuberculoid type leprae. It has also been found that the alpha-2 laminin receptors found in the basal lamina of Schwann cells are also an entry target for M. leprae. The activation of macrophages and dendritic cells which are characterized by their capacity to present antigens to cells, is associated with the initiation of the host immune response to the microorganism\[^{17}\].

Macrophages: As mentioned before, circulating or tissue macrophages has a pivotal role in the defense or immune mechanism mounted against the M. leprae. Such cells can be found passively on the connective tissue, in the circulating blood and or forming part of the immune and/or hematologic system. Macrophages are multifunctional cells endowed with enormous capacity to combat the invader and even function as a cell presenting the antigen to the antibody. The bacilli has a special predilection to invade and establish within the tissue macrophage which may present a granular eosinophilic cytoplasm with larger numbers of bacilli in early and active lesions and the cytoplasm has a foamy appearance derived from lipid bodies accumulation induced by M leprae\[^{32}\]. It has been demonstrated that during an inflammatory response state, monocytes derived from the bone marrow enter the tissue in large numbers and take part in the defense against the pathogens. Further, it has been found that non stimulated endothelial cells trigger monocytes to become M2 macrophages and that interferon gamma activate endothelial cells to induce monocytes to differentiate into M1 macrophages\[^{18}\].

Macrophages found in skin lesions are capable of expressing galactin-3 in patients with the lepromatous type. This molecule is thought to contribute reducing T cell activation in infected patients. In Mycobacterium leprae, activation of infected macrophages is crucial for the control of the invading microorganism in which the main mechanism of destruction is mediated by oxygen reactive species (ROS) and nitric oxide\[^{18}\]. Virchow, the famous German histologist was a pioneer in the study of the molecular and histologic mechanisms in leprosy. He observed that macrophages from skin lesions of leprosy patients had a foamy appearance which were later known as "Virchow cells". This phenomenon was later observed in Schwann cells present in nerves from patients with leprosy\[^{9}\]. Furthermore, it has been reported that M. leprae infected macrophages have been shown to be good producers of both prostaglandin E2 and interleukin 10. IL-10 plays a relevant impairing antimicrobial activity, thus allowing pathogens to multiply and reach high number within the invaded macrophage\[^{9}\].

Another cell rarely mentioned in the literature about leprosy and the skin, is the keratinocyte. This cell is not only a source of cytokines and chemokines which are critical for recruiting dendritic cells, T cells and neutrophils to the site of infection, but such cell is very effective in the phagocytosis of M leprae in vitro. Such cell has a major role in inducing changes in the expression of surface molecules and cathelicidin as well as in the secretion of tumor necrosis factor (TNF) alpha and interleukin-1 beta\[^{33}\]. Furthermore, keratinocytes play a relevant and unique role in the immune response to M. leprae\[^{17}\].

It has been reported that keratinocytes express mannose-binding receptors (MBR), TLRs, and class II MHC antigens. They have also been identified as a source of cytokines, chemokines and antimicrobial peptides. Further, keratinocytes participate in the epidermal immune response to M. leprae, they possess a highly efficient innate pattern recognition system in which the simultaneous recognition of a pathogen by different classes of pattern recognition receptors can provide a specific immune response. Moreover, keratinocytes are capable of distinguishing between pathogenic and commensal microorganisms. Because there is a close relationship between the presence of keratinocytes in the skin and its capacity to recognize and combat M. leprae\[^{17}\], it follows that the skin is a potential route of leprosy transmission and this mechanism has been mentioned in many other studies.
Oral manifestations

Only in the last decades has there been of body of evidence, demonstrating the pathological effects of Hansen’s disease in both internal and internal structures of the masticatory system. It seems that there is a preferential localization of lesions in the hard palate and in symmetrical regions inside the mouth. Further, the rather specific distribution of the oral lesions has been attributed to the preference of the leprosy bacillus to colonize areas with temperatures below 37 °C. “Facial Leprosa” is the terminology used to denote the pathological alterations as a consequence of a series of events associated with Hansen’s disease in the facial structures. These pathological associated deformities changes include atrophy of the anterior nasal spine, atrophy and recession in the anterior part of the maxilla, and endonasal inflammatory changes.

Oral manifestations are observed most frequently in lepromatous leprosy. They occur with a prevalence of about 20% -60% and take the form of multiple nodules or lesions, necrosis, ulcerations, atrophic scarring and even tissue destruction. Further, the lesions are usually located in the hard and soft palate, uvula, underside of the tongue, lips and gums. Loss of teeth does not occur rarely. It has been reported that lesions in the soft oral tissues may involve a reduced sensitivity of the oral mucosa, lepra formation, ulceration and complete loss of oral soft tissue structures such as the soft palate. There are some reasons to believe that there is a close and direct relationship between the severity of the disease and the chronicity of the disease, indicating that the likelihood of the observations of these oral alterations is largely influenced by the duration and severity of the disease.

As mentioned in other sections of this investigation, oral lesions are considered to be manifestations of advanced stages of the disease with a preference of occurrence in males probably associated with females seeking diagnosis and treatment earlier as compared to males. Further, there seems to be a family predisposition for the occurrence of the disease. One investigation evaluated pathological oral alterations in a set of 40 consecutive, untreated, multibacillary, lepromatous and borderline leprosy patients in a medical facility for the diagnosis and treatment of infectious diseases. Researchers reported that the palate was the most frequently affected anatomic site in 57.2% of all cases. Lesions of the oral mucosa were very common. However, the uvula and the soft palate were also affected by the disease. Multiple papules and nodules were observed in 10 clinical cases over the hard palate. Researchers reported that the uvula was involved in 10 cases and complete destruction of the uvula was observed in 3/10 cases. Lesions were also observed in the tonsillar pillars and posterior pharyngeal wall. Lesions or malformations were also reported in the gums, buccal mucosa and tongue.

Hansen’s disease and Periodontal disease

Many pathological alterations have been attributed to the presence of Hansen’s disease in the oral structures. Some researchers believe that there is a close association between periodontal disease and Leprosy. For instance, periodontal bone loss, tooth mobility and bleeding gingivitis have been all attributed to the presence of leprosy and no doubt these changes have a close relationship with reactive bone alterations, chronic inflammation, infiltration with large amounts of neutrophils and decrease in local temperature. Based on a study of 47 patients presenting with signs and symptoms of lepromatous, borderline and tuberculoid lepra, and the use of both clinical and radiographic investigations, Subramanian and Marks reported that the majority of patients they evaluated had a normal periodontal condition. Moreover, “some had good gingival conditions and pocket depth of less than 3mm, but 3 patients presented poor gingival conditions and one or more periodontal pockets greater than 3mm”. Findings in this investigation indicates that periodontal conditions in Hansen’s disease patients may vary significantly depending on the quality of oral health care.

In leprosy patients poor oral health may be associated with the severity and or frequency of periodontal conditions including poor oral hygiene due to lack of motivation or disability resulting from advanced mutilation of fingers and hands, unbalanced muscular activity associated with the presence of facial paralysis and asymmetrical function of both masticatory muscles and those of the facial expression. It has been reported frequently that the lepromatous form of the disease is frequently observed and is associated with frequent gingival bleeding even with the slightest touch, papillary hypertrophy of the gums, tooth loss as a result of destruction of the supporting tissues and hypoesthesia at the border at the alveolar mucosa. Subramanian and associates using data from Hansen’s disease patients also reported the presence of blunt maxillary alveolar bone loss and reported that other skeletal deformities could also be observed frequently. These observations indicate that leprosy patients presenting with signs and symptoms of the lepromatous type have increased susceptibility to develop bone loss in the anterior maxillary region.

The prevalence of periodontal disease is very high in leprosy patients. Periodontal disease and loss of alveolar bone in such patients may be attributed to poor oral hygiene, accumulation of salivary calculus around pockets produced by lepromatous infiltrations, some form of more intense occlusal forces (occlusal trauma) on the teeth and periodontal structures facilitated by the paralysis of the facial and masticatory muscles. Some patients develop the habit of thrusting the tongue and apply pressure on the palate and push the anterior inferior teeth as a nervous habit. Thus, such individuals generate abnormal occlusal forces which give rise to tooth

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mobility of the lower incisors, thus, worsening a potential periodontal condition. Studies using proper periodontal measurements\textsuperscript{[37]} reported a high plaque index in the fronto-vestibular areas of the upper dental arches, abundance of soft matter within the gingival pockets on the gingival margin and more frequently on the adjacent tooth surfaces, indicating poor oral hygiene habits and deteriorated periodontal conditions. Such investigation also demonstrated that most cases of leprosy patients presented with mild signs of gingivitis in the upper front and mild to moderate gingivitis in the lower front and molar areas.

Bombach and Reichart\textsuperscript{[38]} evaluated a sample of 110 patients suffering of Hansen’s disease. They used accepted oral hygiene and periodontal measurements including oral hygiene index, sulcus fluid assessment, plaque index, gingival index and calculus index. Researchers reported that there were different types of leprosy in the total group, tooth mobility was present in more than 50% of the sample, and 24.5% of the patients did not perform any oral hygiene care. Further, gingival recession was present in 55.5% of the sample. They concluded their investigation stating that poor oral hygiene habits were responsible for the higher periodontal indexes found in the whole sample. Finally, dental and oral conditions in leprosy patients were also evaluated in another investigation\textsuperscript{[39]} in the city of Serra (Brazil). A subgroup of 99 leprosy patients was examined and researchers reported a prevalence of 80.8% periodontitis and gingival bleeding in 92% of the cases. Additionally, frequent and severe dental loss were observed in the subgroup indicating poor oral health prevention measures and probably difficulties in the access to primary dental and periodontal attention centers. In lepromatous clinical cases, there is a strong tendency for the development of caries, gingivitis and periodontitis with blatant alveolar bone loss initiating in the maxillary bone crest between the incisors. In one study\textsuperscript{[27]} of 100 patients with different leprosy subtypes, researchers reported that periodontal disease was observed frequently among the group they evaluated and manual difficulties as a result of the disease may have significantly hampered the ability of subjects in the sample to implement proper oral hygiene measures to prevent gingivitis and periodontal disease.

**Diagnosis**

Based on the studies carried out by Alinda and associates\textsuperscript{[39]} leprosy diagnosis is determined when three cardinal signs are present:

1. There is loss of sensation in pale, hypopigmented or reddish skin;
2. There is visible thickening of peripheral nerves in which there is a potential for the development of neuropathic disorders;
3. On scraping and proper laboratory examination of the material, acid – fast bacilli are observed.

Furthermore, some simple or sophisticated laboratory tests are available including, histopathology examination, serology, PGL-1 antibody titer, and polymerase chain reaction or PCR. PCR – based tests provide higher sensitivity and specificity as compared to ELISA or enzyme-linked immunosorbent essay\textsuperscript{[39]}. The cardinal signs for leprosy include the following: hypopigmentation or erythematous skin lesions such as macules or plaques accompanied by loss of sensation in the skin; thickening or enlargement of peripheral nerves and signs of damage such as sensory loss, paralysis or motor dysfunction with or without nerve enlargement, presence of acid-fast bacilli (AFB) on skin lesions, scraping and/or biopsy\textsuperscript{[39]}. In the last decades, molecular techniques to estimate the concentration or presence of M. leprae have been used and are based on the quantitative estimation of RNA levels by direct hybridization with specific probes or by amplification using PCR\textsuperscript{[40]}.

**Therapy**

Multi-drug therapy has become the treatment of choice to eliminate signs and symptoms of Hansen’s disease. Such approach is strongly encouraged by the World Health Organization (WHO). One of the most important drugs accepted in the medical field is the antibiotic Rifampicin, a semisynthetic derivative of Rifamycin which is an antibiotic obtained from Streptomyces mediterranei. Regarding the use of drugs in many fields of medicine, it has been observed that the use of only one drug to treat a particular disease is a common yet undesirable practice. Considering that Hansen’s disease is very resistant to treatment, the use of Rifampicin as the only mode of therapy is strongly contra indicated as may have a negative effect increasing the resistance of the microorganism. According to Alinda and associates\textsuperscript{[39]}, a single dose of 1500 mg or 3–4 doses of 600 mg may be highly effective eradicating more than 99.9% of M. leprae bacteria. Due to its solubility in fat, Rifampicin penetrates through cell membrane, and thus is highly effective eradicating intracellular bacterial\textsuperscript{[41]}.

Another common drug very useful in the treatment of Hansen’s disease is Dapsone, a drug belonging to the sulfa group first synthesized in 1908. Many decades ago, Dapsone was accepted as the main drug against leprosy and continues being used by many practitioners around the world. The drug is prescribed in a concentration of 100 mg given daily. It has to be used for a very long period of time, usually 2–3 years so their clinical effects become visible\textsuperscript{[42]}. Clofazimine has a mild antibacterial capacity against M. leprae and has a
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weaker effect as compared to Dapsone. It is prescribed in a monthly dose of 300mg. It may also be prescribed in a daily dose of 50-100mg. The drug is known for its capacity to inhibit M. leprae multiplication and should not be used neither as the only mode of therapy nor as a substitute for Dapsone.[43] Clofazimine or Lamprene is the only drug available today that has mycobactericidal and anti-inflammatory actions and is able to suppress the signs of acute exacerbation of the disease. Interesting to note is that at the gingiva, the site of constant inflammation which constitutes a serious concern for the periodontist, this anti-inflammatory effect may be the cause of chronic gingival changes.[37] Leprosy management strategies have been devised to attain various objectives: Early detection of patients with the disorder, adequate treatment and provision of adequate comprehensive care for the prevention of physical disabilities and rehabilitation.[7]. Many clinicians defend the notion that monotherapy is not recommended as bacteria easily develops resistance and strategies to prevent the “nocive” effects of the drugs.

V. Conclusions

Based on the review of the current literature to carry out this study, the following conclusions can be drawn:
1. Hansen’s disease is a systemic disorder or infection caused by Mycobacterium leprae, an intracellular parasite that has a predilection to live within and destroy macrophages.
2. Hansen’s disease is also an endemic condition in some countries including India, Brazil, Indonesia, southwest Asia and some countries in Africa;
3. The infection presents different characteristics depending on the form observed during clinical examination and diagnosis: tuberculoid, lepromatous and borderline with its subtypes;
4. Common modes of therapy include the use of Rifampicin, Dapsone and Clofazimine. Drugs should be used for long periods of time to finally destroy bacilli and eradicate the disease.

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