

CUTANEOUS LEISHMANIASIS IN PAKISTAN; HOW TO GO ABOUT IT

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INTRODUCTION

Leishmaniasis is a major health problem worldwide. It is also a problem especially of the rural Pakistan. It occurs in varying presentations, from the self-limiting, even self-healing cutaneous to fatal systemic disease. The disease can manifest itself in two forms, Cutaneous and Systemic Leishmaniasis. Cutaneous Leishmaniasis, can cause a lesion anywhere on the body but the most likely sites for these lesions are the exposed parts. The lesion rapidly gives rise to a harsh-looking large ulcer. Systemic Leishmaniasis is rarer in Pakistan and invariably fatal if not treated promptly. It affects the internal body organs, particularly the spleen and the liver. Leishmaniasis is transmitted by an infected female sandfly. Patients usually have a single self healing ulcer which may sometimes need local treatment. Multiple ulcers due to multiple bites from the sandfly is not a rare presentation in Pakistan. *Leishmania Braziliensis* may give rise to the mucocutaneous form "Espundia" which need systemic antimony. Mucocutaneous Leishmaniasis is almost unknown in Pakistan due to its aetiological factor. Sodium Stibogluconate 20mg/kg/day i.v for 20 days is the appropriate therapy. It is a safe drug although rarely it may cause bone marrow suppression, liver damage, pancreatic and arrhythmias. Patient

should be seen six weeks and then six months after the completion of therapy to access success. The disease has a very old history and lesions like Leishmaniasis have been described dating back to the 9th century (Balkan sore) and has been given various names in various civilizations by various names like Delhi boil in India, Baghdad sore in Iraq and Saldana in Afghanistan. The leishmaniasis has been discovered 100 years back but has not been eradicated; rather it is on rise in many parts of the world. If control measures are not taken it might become a major health problem.

Pakistan has a burdon of cutaneous and visceral Leishmaniasis, mucocutaneous form being almost nonexistant. The physicians need to know the diagnostic criteria as well as the treatment of the disease. Due to scarcity of dermatologists in the rural areas most of these cases present to the general practitioners and physicians. This is further complicated by the inadequate supply of appropriate drugs.

EPIDEMIOLOGY OF THE DISEASE

There are about 1.5 million cases of cutaneous Leishmaniasis each year worldwide with the bulk reported from Afghanistan, Iran, Iraq, Algeria, Saudi Arabia, Peru and Pakistan. According to WHO the leishmaniasis is now endemic in 88 countries, with a total of 350 million people at risk. It

is believed that worldwide 12 million people are affected by leishmaniasis. It is very prevalent in Pakistan and manifests in almost all forms and has been reported from all the provinces and almost all the major cities. It is endemic at Baluchistan, Interior Sind, and Multan^{1,2,3,4,5,6,7}. It has also been reported in Pakistanis working abroad⁸. In Pakistan the disease has been described in its classical form and as variants of the classical variety. Some rare manifestations have also been described. These include acute paronychia, chancriform, annular, palmo-plantar, zosteriform and erysipeloid forms⁹. Careful review of the literature confirms that it is present in almost all parts of Pakistan but is more prevalent in the hilly areas^{10,11,12}. The World Health Organization has been working with local health authorities in the Northwest Frontier Province of Pakistan to control an outbreak of Leishmaniasis. It has reported a total of 738 cases, mostly in children under the age of 15, these cases have been found in Kurram agency. These cases are amongst the local population and are in addition to 1500 cases in Afghan refugee camps^{13,14,27}.

At least 72% of the affected are unable to access medical treatment due to multiple factors like poverty, lack of health education, lack of health facilities etc. Leishmaniasis is caused by a parasite transmitted by the sand fly. There are two types of the disease: urban and rural. The most common type in Pakistan is called urban or Anthroponotic Leishmaniasis. The disease is transmitted from humans to humans. Rural or Zoonotic Leishmaniasis comes from the interaction of man with animal. The cutaneous variety can present in various unusual clinical variants which can be difficult to diagnose like paronychia, chancriform, annular, palmo-plantar, zosteriform and erysipeloid forms^{9,15}.

The geographical distribution of Cutaneous Leishmaniasis is mainly determined by the sandfly vectors (*Phlebotomus* species

and *Lutzomyia* species¹⁶. They live in dark, damp places; these vectors do not fly high or far and have a range of only 50 meters from their breeding site. Sandflies become infected through feeding on infected animals. Once a sandfly is infected, it can transmit the parasite to both humans and animals for the rest of its life span¹⁷. Unlike mosquitoes, they fly silently and their small size (2-3mm long) allows them to penetrate through mosquito nets. They are most active in the evening and at night. Most infections exist as zoonoses amongst wild animals, such as rodents and dogs, and are most prevalent in rural or forest areas. Whilst man is usually an incidental host, such infections are by no means uncommon. In endemic areas up to 9% of the healthy population may have positive Leishmanin skin test, indicative of an earlier, often asymptomatic infection. In India and Pakistan simple Cutaneous Leishmaniasis is usually due to *Leishmania tropica*¹⁸ and man is the most common reservoir.

Leishmaniasis usually present to the general practitioner or physician most probably due to lack of experienced dermatologists in far flung rural areas where this disease is most prevalent. It is therefore essential for the GP's and physicians to have a clear idea about the diagnosis and treatment besides a fair knowledge about its pathophysiology. The drugs used for the cure are not available usually in open market. It is an interesting fact that till very recently, despite the surge of this disease in various areas from all over Pakistan, antimony compounds was rarely available. These drugs were smuggled from Iran and was such scarce that they would not suffice for the needs of the community. The new drugs are not available in Pakistan and therefore there are no local studies on those drugs making their efficacy questionable. These new compounds have no acquaintance with the health care system.

It is the need of the day to have a working knowledge about leishmaniasis and its treatment^{22,23,24}.

PATHOLOGY

The life-cycle starts with inoculation by promastigotes which are phagocytosed by macrophages, once inside they shed their flagella and become amastigotes which multiply by binary fission. Infected macrophages are destroyed physically by these rapidly dividing amastigotes. After a macrophage breaks down these amastigotes are released which enter other macrophages and divide and re divide unabated destroying these immunocompetent cells and leading to immunosuppression as well. The subsequent fate of the amastigotes depends upon parasite and host factors, which are poorly understood. Viscerotropic species, such as *Leishmania donovani*, migrate throughout the reticulo-endothelial system, giving rise to visceral Leishmaniasis; whereas dermatrophic species, such as *Leishmania major*, usually remain close to the inoculation site, causing cutaneous disease. The skin variety can disseminate however and can lead to systemic manifestations. Any spread of dermatrophic species tends to be late, however, and only to adjacent skin (producing satellite lesions), or to lymphatics only to get trapped at regional lymph nodes¹⁹. *Leishmania Braziliensis* is able to migrate to the oropharyngeal mucosa where it may remain dormant for many years before reactivating to cause the destructive Mucocutaneous form 'espundia'²⁰. There are reports of *Leishmania tropica* causing visceral disease. In post-kala-azar dermal Leishmaniasis the viscerotropic parasite becomes dermatrophic as a consequence of treatment.

CLINICAL FEATURES

Most Infections, following a bite from an infected sandfly, remain sub-clinical. Then develops, after an incubation period of

1 to 12 weeks, a papule that enlarges and then ulcerates. A typical lesion is a painless ulcer with a raised, indurated, margin and a necrotic base. Most patients have 1 or 2 lesions but may be multiple and in crops. They are usually present on the exposed sites Their sizes also vary from 0.5 to 3 cm in diameter. Some lesions do not ulcerate at all and remain as a bluish papule, others develop sporotrichoid nodular lymphangitis. Secondary bacterial infection is common and must always be suspected if the painless lesion becomes painful. Most lesions heal over months or years, leaving an atrophic scar. In general 50% of those lesions caused by *Leishmania major* will have healed in 3 months, those caused by *Leishmania tropica* take longer – about a year and those due to *Leishmania braziliensis* persist much longer. Natural resolution leads to partial resistance to re-infection. This is why certain clinicians avoid therapy early and do a "wait and see" policy as resolution with drugs does not provide an immunity, at least as amicable as that provided by natural and spontaneous resolution.

DIAGNOSIS

The diagnosis is often made by the wary eye of a careful physician based on the typical lesion in conjunction with an appropriate history of exposure, usually in an endemic area. However, to the unwary, there are a number of mimics and it may be underdiagnosed or over diagnosed and treated un-necessarily. The treatment is toxic, so pathological confirmation should be sought - preferably by demonstrating the organism in tissue and culture²¹.

Easily said, unfortunately this is not always possible in clinical practice. The parasite may not be found by the most adequate methods.

A full thickness biopsy is taken from an infiltrated margin of the lesion and divided into 3 parts: to prepare an impression smear,

for histological examination and for culture. Usually a lesion is selected which is not secondarily infected and cleaned with 0.9% saline or 70% ethyl alcohol. If a lesion uninfected secondarily can not be found a second cleanse is given with 6% hydrogen peroxide. These cleansing agents will remove any scab from the lesion. After this 2% lignocaine with adrenaline is injected around the lesion and biopsy taken. Although a punch may be used, an elliptical biopsy taken with a scalpel is much handy.

Impression smears are made by gently pressing the skin biopsy against a glass microscope slide 4-5 times after which the slide is dried in air then fixed in 95% ethanol for 3 minutes. They can then be stained with Giemsa or H & E and examined for the presence of amastigotes.

Specimens for culture should be transported in 'sloppy Evans' media and subsequently cultured on Evans Modified Tobies media or NNN media. Cultured organisms may be typed by isoenzyme analysis.

Alternatively needle aspirates and slit skin smears may be useful. A needle aspirate is obtained by using a 2ml leuc lock syringe with a 20 gauge needle, containing 0.3ml 0.9% saline. The needle is inserted through intact skin and 0.1 ml is injected into the edge of the lesion. The needle is then moved back and forth rotating it and applying suction at the same time to cut small pieces of tissue from the edge of the needle track, which are then aspirated. The aspirate can be used to inoculate cultures and prepare smears. Slit-skin smears are made by squeezing the edge of the lesion between thumb and forefinger, making a shallow slit 1mm deep in the pinched skin with a scalpel and then scrapping the cut edge. A sharp lancet may be all that is needed to obtain a small tissue from the edge of the lesion.

Monoclonal antibodies can demonstrate parasites .PCR methods are useful for

confirming the diagnosis and are more sensitive than microscopy and culture, however, problems exist with the identification of individual species.

Serology is unhelpful for cutaneous disease because antibodies tend to be undetectable or present in low titer. The Leishmanin skin test is an old test, which is analogous to the tuberculin test, detects cell-mediated immunity; becomes positive once the lesions begin to crust and remains so indefinitely. It cannot distinguish between past and present infection and may be useful only for epidemiological studies.

TREATMENT

Due to the diverse and varied presentation there is no single optimal treatment for all forms of Cutaneous Leishmaniasis^{22,23}.

The situation is complicated by the self-healing nature of Cutaneous Leishmaniasis. Adequately controlled therapeutic trials are therefore essential to assess the efficacy of any new treatment. Unfortunately the trials done on drugs are few and inconsistent, uncontrolled and sometimes biased. Furthermore, the drugs which work reasonably well in one endemic area may not be efficacious in another one. Natural healing is so likeable and beneficial that certain times it is unpredictable if therapy will be justified at all at some stage.

Fortunately, there are some guiding principles As most lesions heal rapidly without treatment an expectant approach of "wait and see" for spontaneous cure may be appropriate particularly for those patients living in endemic areas because spontaneous healing is associated with the development of protective immunity. Lesions on cosmetically or functionally important sites, such as the face or hands, those with associated lymphangitis and those with multiple or persistent lesions are best given active treatment. Local treatment is appropriate for those with early non-inflamed lesions

and systemic therapy for those with multiple or more complicated lesions.

The pentavalent antimony derivatives sodium stibogluconate (Pentostam, Glaxo Wellcome, UK) and meglumine antimoniate (Glucantime, Rhone-Poulenc Rorer, France), developed in the 1940s, remain the mainstay of systemic treatment. They are similar in both efficacy and toxicity. Their mode of action is not known, although they inhibit glycolysis and fatty acid oxidation in *Leishmania*. Their efficacy is well established, provided they are given in adequate doses and for an adequate length of time.

Sodium stibogluconate is best given once daily by slow i.v. (or i.m.) injection for upto two weeks depending upon the severity of the lesion. Toxicity is common, and appears dose related, most patients develop malaise, anorexia, myalgia and arthralgia after 14 days treatment. This is associated with elevations in serum aminotransferases, a chemical pancreatitis, a mild leucopenia, thrombocytopenia, and flattening of the T-waves on the ECG. It is therefore advisable to stop therapy once a near adequate response is achieved or toxicity has developed. Treatment should be monitored but in most cases these abnormalities settle rapidly once treatment is stopped. Lesions will become less indurated, flattened and less scarring and will stop growing at the edge with adequate treatment. Healing, however continues after treatment has stopped so the need for additional treatment should be delayed for 4-6 weeks. This allows patients to recover from the toxicity.

Rifampicin has been reported to be efficacious but there are no good controlled trials to support its use and furthermore its use in areas where tuberculosis and leprosy are endemic should be avoided. It should almost never be used in Pakistan for Leishmaniasis for fear of developing resistant and losing this wonderful drug which is still the cornerstone of therapy against Tuberculosis. Alternative systemic agents

include aminosidine²⁴ (paromomycin), pentamidine and ketoconazole. They are not used routinely, though. The most promising oral drug today is miltefosine. In an open label study in Colombia, four weeks treatment with 133 and 150mg of miltefosine daily cured 100% and 89% respectively²⁵.

Local and topical therapy is an important option for those patient not at risk of mucocutaneous disease. Local injection of sodium stibogluconate, or meglumine antimoniate, is useful for early, non-inflamed lesions. The most important thing about local therapy is the technique of administration of these drugs. Infiltrate 1-3ml around the lesion to produce complete blanching at the base of the lesion. It may be repeated on alternate days or given weekly until complete or near complete healing. Aminosidine (paromomycin) ointment (15% paromomycin, 12% methyl benzethonium chloride in white soft paraffin) applied twice daily for 10 days is effective for *Leishmania major* and may also be useful for *Leishmania mexicana*. It causes considerable local irritation, but less irritant derivatives have been less effective. Cryotherapy is also useful for small lesions (<1cm diameter). Lesions can also be treated by local excision, curettage or by electrodesiccation but are probably associated with a higher risk of relapse. The most recent topical agent to be investigated is the topical immunomodulator, Imiquimod, which was developed to treat genital warts. It produced a 90% cure rate in patients who had failed to respond to antimonials alone when it was used in conjunction with antimonials²⁶.

FOLLOWUP

Most relapses occur within 3-6 months after successful treatment, so follow up at 6 months is appropriate. Thereafter patient should be warned that relapse is possible and observe their scar for thickening, crusting or ulceration. Those who relapse should be given a full course of systemic

antimony in the first instance. Patients should be monitored until the lesions have fully healed and the infiltration has resolved.

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