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Vector borne disease: Leishmaniasis

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Abstract
Leishmaniasis is a parasitic illness that is spread by female sandflies from the genus Phlebotomus. It is communicated by sandflies phlebotomine and occurs in four main clinical conditions. The sign and symptoms of leishmaniasis disease are fever, weight loss, loss of appetite, papules formation. The life cycle of Leishmania switches between two different forms i.e. intracellular and extracellular. Leishmaniasis in humans has anthroponotic and zoonotic transmission patterns. The leishmaniasis disease is endemic in the region of South America, Asia, and Europe. In Pakistan, it is more common in the south, and mostly present in rural and semi-urban areas of Baluchistan, Sindh, and Punjab, province. The medications used for the treatment of leishmaniasis may include first-line medicines such as pentavalent antimonial and second-line drugs such as "paromomycin, pentamidine and miltefosine", for cases that are resistant. Further studies are needed to understand the pathology of this illness. This short review will help the researchers to understand and diagnose this disorder easily.

Keywords: Leishmania, Pakistan, antimonial, and anthroponotic

Introduction
Leishmaniasis, a parasitic disease that is caused by a genus of protozoa called Leishmania, spread by female sandflies from the genus Phlebotomus (related to flagellated trypanosomes). This genus, as well as the disease, were named by William B. Leishman, early in the 19th century [1]. There are two types of leishmania (a) Visceral leishmaniasis (VL) (b) Cutaneous leishmaniasis (CL)
It is widespread in southern Europe. The two common appearances of the disease are cutaneous form, which is mostly self-healing but often leaves defacing scars, and the usually incurable visceral form [2].

Fig 1: Leishmaniasis is a parasitic disease [2]

History
The environmental science of leishmaniasis is varied in diverse geographic areas. In Asia, leishmaniasis occurs in arid as well as semi-arid conditions. In Mediterranean regions and the Middle East, it is typically urban, while in Africa it is principally rural. In tropical areas of America, it customarily is a forest disease but is proceeding into inner-city areas. It occurs in small towns in Peru, and farmhouses of high mountain valleys. The only sand fly confirmed vectors of species Phlebotomus are human disease in Old World (Africa, Asia, and Europe)

while Lutzomyia in New World (the Americas) [3]. Like the chikungunya virus, the leishmaniasis parasite is also widespread in Africa and South-East Asia. In African countries, the leishmaniasis parasite has been found to circulate in a "sylvatic cycle" among the dwelling of forest [4, 5].

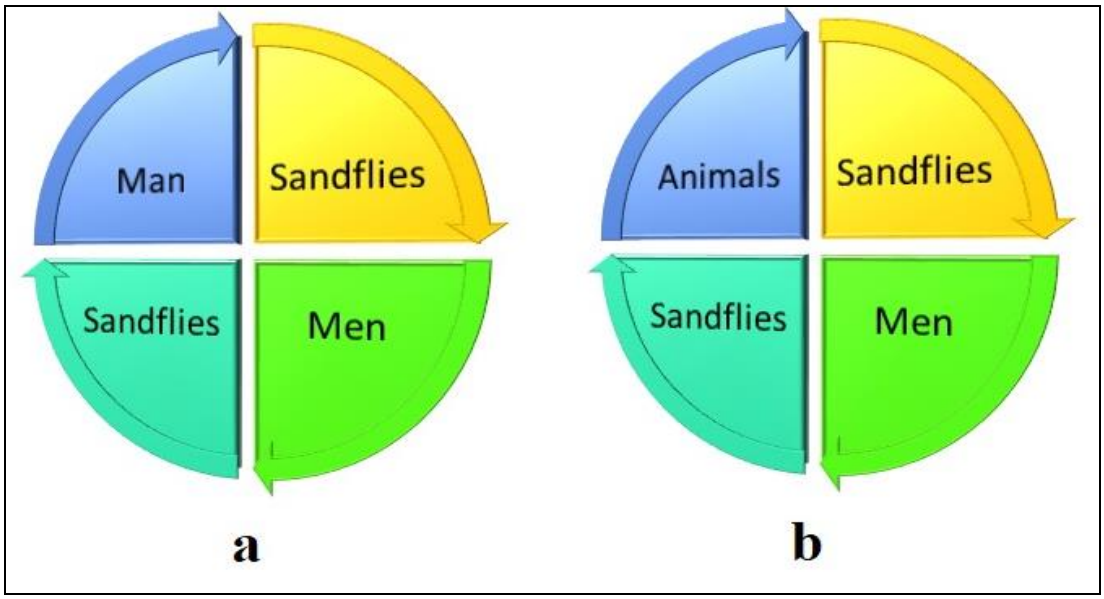

Fig 2a): Common Urban Life Cycle (b) Sylvatic Life cycle

Worldwide, 200 million people are at high risk of leishmaniasis in 98 countries with an assessed rate of 12 million affected people, and 2 million additional cases each year (Table 1) [6].

Table 1: Diseases of Humans caused by Sand-Fly (adopted from Ferreira *et al*., 2018)

Disease	Causative agent	Distribution	Reservoir	Vector
Sand-fly fever (New World)	Sand-fly fever virus	Colombia Panama	Primates rodents	*Lu. Ylephiletor Lutzomyia trapidoi*
Sand-fly fever (Old World)	Sand-fly fever virus	Northern America, Europe, Asia	Rodents	*P. perniciosus P. perfiliewi Phlebotomus papatasi*
Changuinola virus disease	Changuinola fever virus	Central and South America	Sloths	*Lutzomyia umbratilis*
VS (Vesicular stomatitis) virus disease	VS virus	North and South America	Monkeys Opossums Raccoons Swine Horses Porcupines	*Lu. Ylephiletor Lu. Trapidoi Lutzomyia shannoni*
Chandipura virus disease	Chandipura virus	India, West Africa	Hedgehogs	*Phlebotomus papatasi*
Bartonellosis	*Bartonella bacilliformis* (bacterium)	Colombia, Ecuador, Peru	Rodents (Rattus)	*Lu. Columbiana Lutzomyia verrucarum Lu. peruensis*

Leishmaniasis is communicated by sandflies phlebotomine and occurs in 4 main clinical conditions: cutaneous leishmaniasis (CL), seems as single and multiple cutaneous lesions; mucocutaneous leishmaniasis (MCL), offering in mucosal tissue; diffuse cutaneous leishmaniasis (DCL), seems as multiple nodular cutaneous scratches cover the body; and visceral leishmaniasis (Kala-Azar), affecting internal organs. The disease incidence per year is at 0.9-1.6M new cases, generally of CL, and up to 90033 new cases per year of VL are linked with an 11% mortality rate. The disease form is largely determined by the species of Leishmania that causing the infection but is influenced by biological vector and host factors, significantly by host immune status. In the host of mammalian, the parasites were intracellular, residing mostly in long-lived macrophages. In the severe visceral form, the parasites cause infection in the liver, lymph nodes, spleen, bone marrow, and hepatomegaly [7].

Sign and symptoms

The sign and symptom of leishmaniasis disease is the fever, weight loss, loss of appetite, papules (A), non-itchy lesions nodule (B) often conveyed by pancytopenia, Ulcer (C), dermal plaques (D), lymphadenopathy may occur, the involvement of mucosal tissue, hepatosplenomegaly and raised liver enzymes [8, 9]. The most common form is "Cutaneous leishmaniasis" (CL) which causes lesions in the skin, leaves scars, and causes disability that's is lifelong. VL is the most serious form that has a case of fatality rate >95%

in crude cases. The infection might mimic the leukemia and infections of a virus. Through B-cell activation, numerous +ve serologic tests may appear as in figure 3 [10].

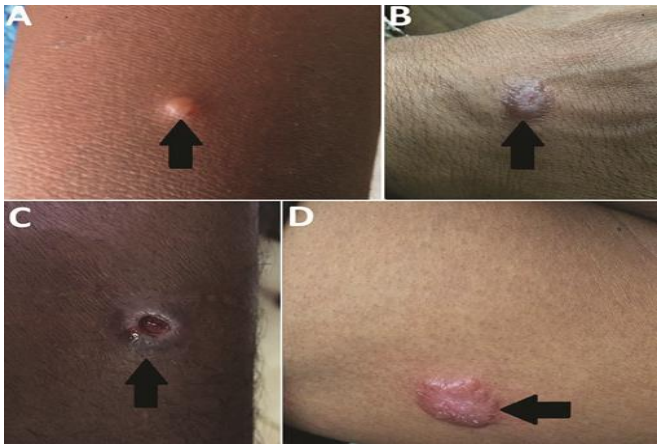

Fig 3: A) papule, B) nodule, C) ulcer, D) plaque [8, 9, 10]

The life cycle of Leishmania switches between 2 different forms, which is better to adapt to each host. There are two forms of life cycle 1 intracellular and 2 extracellular. These parasites (protozoan) live moreover as intracellular amastigotes in human phagolysosome whereas extracellular promastigotes occur in different species of sand fly (e.g. Lutzomyia or Phlebotomus). In the gut vector of insect, after a meal of blood (blood meal required for the developmental egg) Leishmania converts from non-flagellated amastigotes into proliferating procyclic promastigotes, and then further distinguish into metacyclic promastigotes stationary infectious [11]. Due to cycling between the two hosts, the exposure of parasites into major changes of the environment such as temperature, pH, nutrient reactive oxygen species, and availabilities of oxygen. Inorganic phosphate Polymers (polyP) play an important role in the adaptation to these extreme environment changes as they have concerned intolerance of stress in numerous other organisms [12]. The Leishmania species having a generalized life cycle and the complexity in their developmental stages as in Figure 4.

Life cycle

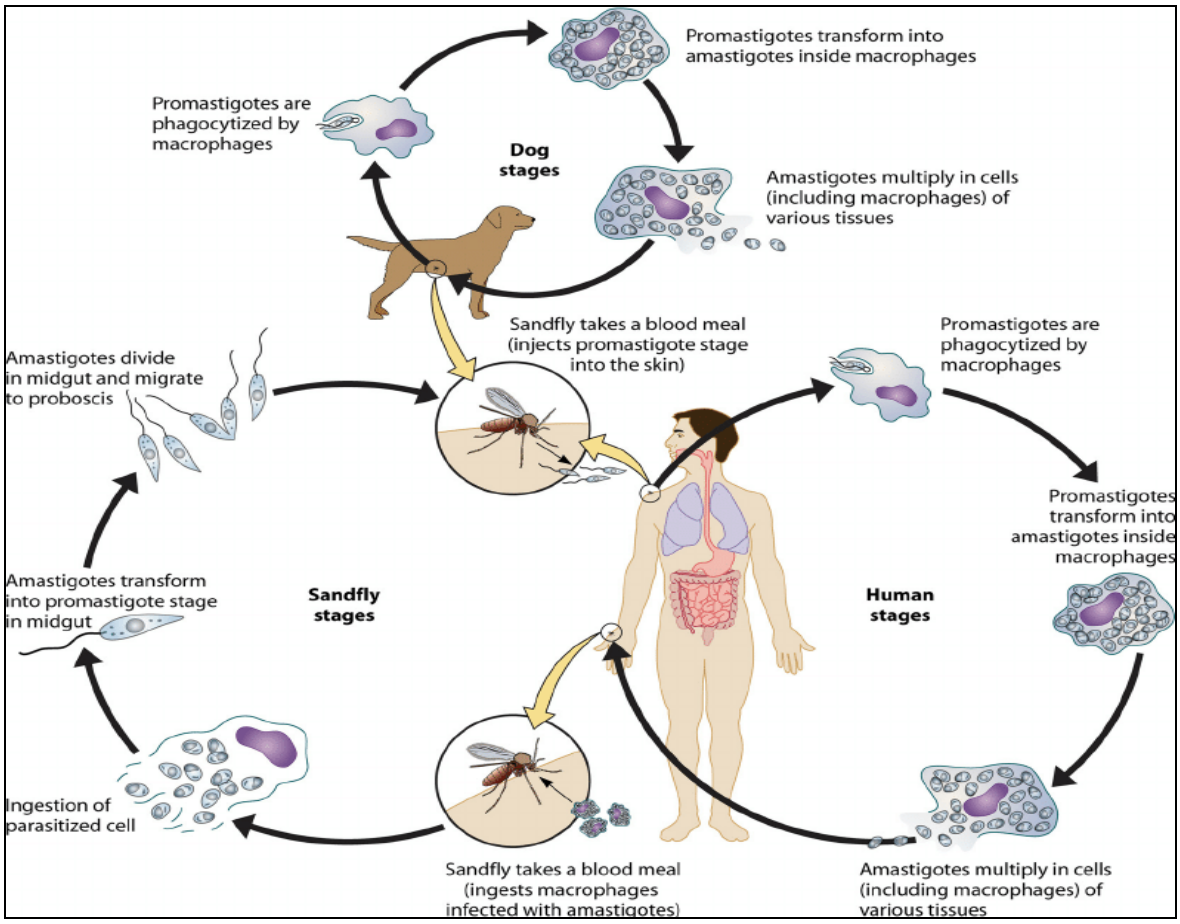

Fig 4: Life cycle of Leishmania in sand fly host and in the vertebrate host [12]

Transmission

There is a wide range of hosts for sand flies including marsupials, hyraxes, and rodents while others feed on humans. Hence, leishmaniasis in humans has anthroponotic and zoonotic transmission patterns. In host mammalian, Leishmania lives and reproduces intracellular in phagolysosomes. At present, there are eighteen species of Leishmania are designated to be infectious for humans as in figure 5 [13].

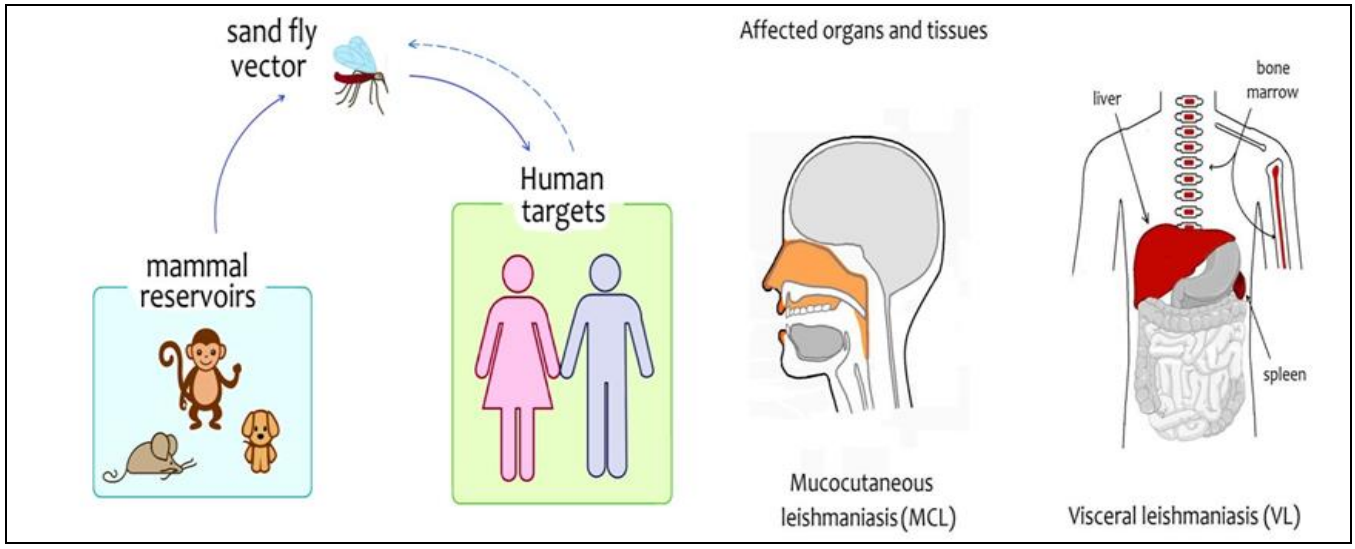

Fig 5: Transmission of leishmaniasis to human subjects [16].

While different species of Leishmania are morphologically identical, which cause three main clinical forms, 1) CL 2) VL 3) MCL dependent on types that which phagocytic cells are attacked [14]. In cutaneous leishmaniasis, the parasites affect the macrophages in the skin. When the parasite is full in the host cell, it ruptures and then free amastigotes that will contaminate neighboring macrophages. While in visceral leishmaniasis, the free amastigotes are then spread by the flow of blood and infect the cells of the mononuclear phagocyte system of bone marrow, liver, lymph nodes, spleen and the intestine [15]. Leishmania species Identification usually requires pathogenic culture followed by molecular assay, immunological, and biochemical though PCR and additional diagnostics assay are in the development stage as in figure 5 [16].

Developmental stage

In the host of vertebrate, Leishmania is an intracellular parasite of macrophages. These forms characterize the development stage of amastigote (Figure 6 A-B). Amastigotes are oval and round, the diameter is 3 to 7 mm, along with a round nucleus, rudimentary, internal undulipodium, and pole like kinetoplast (mitochondrion). In the macrophage, the parasites are multiplying through binary fission and producing 50 to 300 new parasites [3]. The Leishmania is invaded into other cells where host cell ruptures. The parasites (sand fly), develop extracellular from amastigotes ingestion as it enters the alimentary canal. Two morphological types called the promastigote and promastigote. Promastigotes are different in shape, having a free undulipodium anteriorly rising. Promastigotes are pear-shaped and 5 to 24 mm long, while the kinetoplast located to the nucleus anteriorly (Figure 6 C, E, and G). Promastigotes are oval and 3 to 7 mm in diameter, while kinetoplast located to the nucleus laterally. Promastigotes and Promastigotes maybe attach to alimentary tract or persist free-swimming [17].

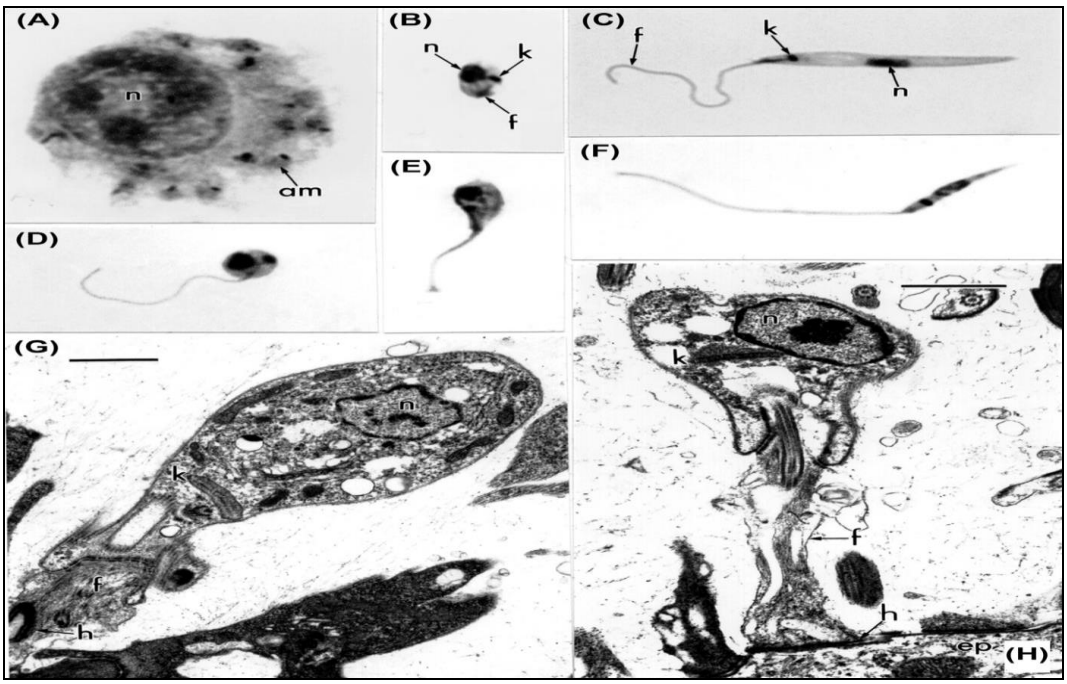

Fig 6: Developmental stages of Leishmania (A) Macrophage comprising of amastigotes (B) amastigote (C) Promastigote (elongated) (D) Paramastigote (E) pear-shaped promastigote (F) metacyclic form (G) promastigote attached to alimentary canal (H) paramastigote attached to foregut [17]

Leishmaniasis in Pakistan

The leishmaniasis disease is endemic in the region of South America, Asia, and Europe. According to the WHO, due to the increase in several various new case every year, it's the utmost serious disease. Ten countries including Algeria, Afghanistan, Iran, North Sudan, Colombia, Brazil, Ethiopia, Syria, Costa Rica, and Peru collectively make up 71–75% of globally valued CL frequency. The blood, sucking sandflies (Phlebotomines) is the main cause of transmitting disease in which 700 species all over the world have been identified, out of which 37 species are recognized in Pakistan. In the old world, the species of genera Phelobotomus which are involved in the transmission of parasites while transmission in new world occurs through species of Lutzomyia correspondingly. These sand flies having a varied range of habitation from steamy forest to dessert and a wide array of hosts including livestock, human, vertebrates, chickens, dogs, as well as some mammals. In KPK, the characterization of disease is credited to L. tropica. The zoonotic (ZCL) is credited to infection by Leishmania major and it is common in the south, and mostly present in rural and urban parts of Baluchistan Sindh and Punjab, province as in figure 7 and 8 [17]

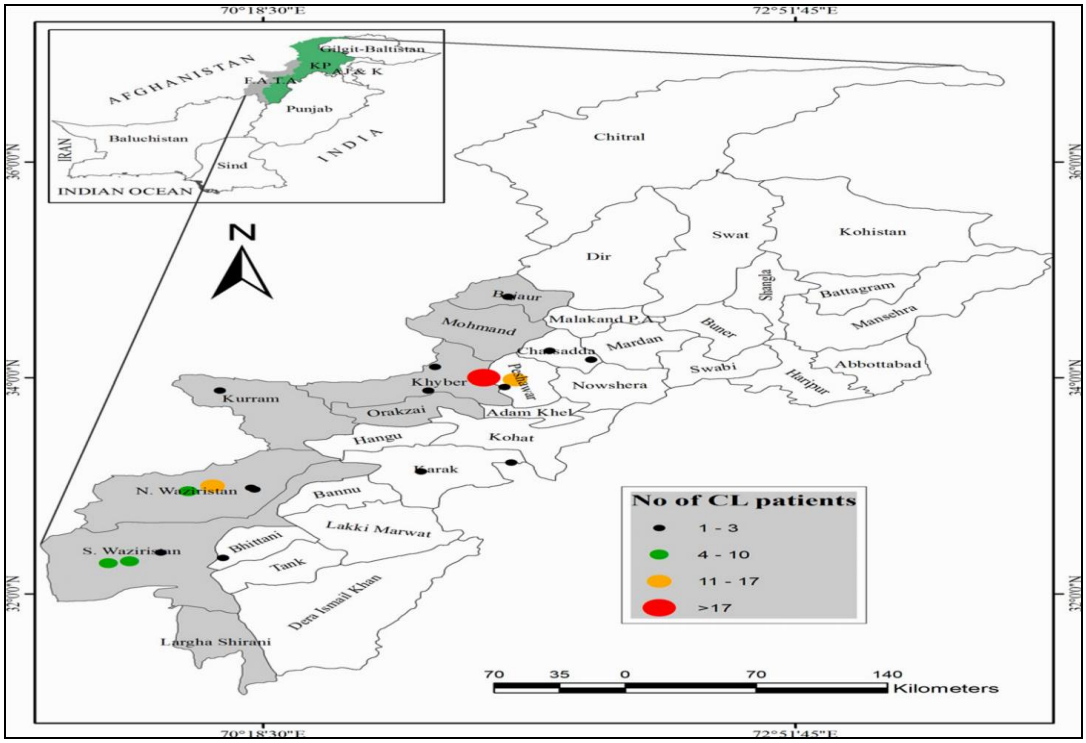

Fig 7: Geographical dispersal of CL cases described in the study. The map shows the connecting regions of KPK Province. Dot on the map represents the isolation site of more than one strain. The dot size is proportional to the strains number represented by it [17]

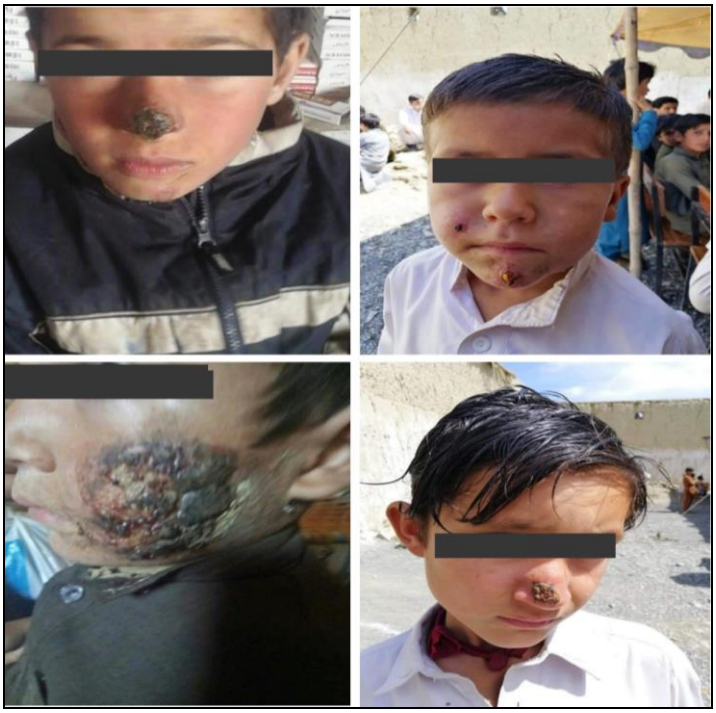

Fig 8: Pakistani Children Affected from leishmaniasis

Detection

Diagnostic methods consist of in vitro culture, histopathology, serologic testing, molecular detection of parasite DNA, and the sensitive assay. Aspiration of bone marrow is the favored taster source; lymph nodes, liver, and blood are also possible. Liposomal amphotericin B treatment is suggested [18].

Treatment

The medications used for the handling of leishmaniasis may include first-line treatments i.e. pentavalent antimonial and second-line drugs (paromomycin, pentamidine, and miltefosine), for tough cases [19]. For visceral leishmaniasis (VL) a new medicine, sitamaquine is now under progress for the possible treatment. The use of these medications for leishmaniasis treatment is affected by some factors such as the appearance of drug resistance, especially with the pentavalent antimonial [20] and short half-life, challenges of toxicity, high cost of drugs, as well as the disappointment of patient to fulfill with treatment [21]

Conclusion

This is concluded from the study that VL and CL are the serious vector-borne disease in KPK Pakistan. It particularly infecting infants and younger children. Cutaneous leishmaniasis has the main health problem in an urban, suburban, and rural area of KPK Pakistan. Some Factors such as global warming. environmental changes and people migration are the main reservoirs at a high prevalence rate.

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