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Leishmaniasis: Is it Treatment Failure or Drug Resistance?

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ABSTRACT

The term leishmaniasis defines a wide range of diseases caused by leishmania parasites that are transmitted by infected sandflies while sucking blood from the skin. The World Health Organization reports that there are more than 20 million leishmaniasis patients in around 80 countries. Pentavalent antimony compounds have been the basis of anti-leishmanial therapy since the 1940s. Although primary resistance up to 15% has been reported against pentavalent antimony compounds in different geographical regions, these compounds are still the most effective drugs for many types of leishmania. Treatment failure and drug resistance are different concepts. We wanted to mention this difference in our case, which we treated with meglumine antimonate, although it did not benefit before.

Keywords: Leishmania, Treatment, Drug resistance

Introduction

The term leishmaniasis defines a wide range of diseases caused by leishmania parasites that are transmitted by infected sandflies while sucking blood from the skin. Depending on the type of the parasite and the immune response of the host, the disease may present in three basic forms: cutaneous, mucocutaneous and visceral leishmaniasis [1].

The World Health Organization reports that there are more than 20 million leishmaniasis patients in around 80 countries, and an estimated 1.5-2 million new patients of leishmaniasis, including 1-1.5 million cutaneous cases, and 500 thousand visceral and mucocutaneous cases, is observed every year [2]. The mortality and morbidity caused by Leishmaniasis lead to an estimated 2-4 million "years of unhealthy life" worldwide [3].

Pentavalent antimony compounds have been the basis of anti-leishmanial therapy since the 1940s. They include meglumine antimonate (glucantime) and sodium stibogluconate (pentostam). However, in recent years, further reports demonstrating different

clinical responses to the treatment of leishmania have been submitted from various parts of the world. Such difference may be related to drug resistance or treatment failure. Although primary resistance up to 15% has been reported against pentavalent antimony compounds in different geographical regions, these compounds are still the most effective drugs for many types of leishmania [4].

Treatment failure and drug resistance are different concepts. In this case report, we aimed to place emphasis on this difference, presenting a patient whose leishmania treatment continued.

Case Report

A 61-year-old female patient. In October 2020, she presented to the Erciyes University Faculty of Medicine Skin and Venereal Diseases Polyclinic with the complaint of a 1-year wound on the forehead, hands and arms. Our patient had emigrated from Syria and she had been living in Turkey for five years. She had a history of travel to Syria one year ago and her complaints started after this travel. At first, acne occurred on the forehead. Then, it gradually spread out, and



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similar lesions appeared on the hands and arms. The lesions caused pain and sometimes itching symptoms. The patient presented to the hospital about five months ago with these complaints, but could not be diagnosed and treated because she had to be hospitalized due to chronic kidney failure. Two months ago, she presented to the hospital again with the same complaints. A pre-diagnosis of leishmaniasis was considered in the patient, and necessary samples were taken and sent to the microbiology laboratory. Then, the patient was diagnosed with cutaneous leishmaniasis upon the presence of leishmania amastigotes observed by direct microscopy. She began to receive intralesional meglumine antimonate treatment once a week. However, since the patient did not benefit from this treatment, she presented to Erciyes University.

When the patient presented to us, she had one erythematous, soft consistency, 3x4 cm nodular lesion with yellow crusts and local hemorrhagic crusts, extending from the glabella region to the right frontal area. She also had marked edema, erythema and scaling on the whole fifth finger of the right hand, along with purplish, centrally scaled plaques, two on the right forearm, and one on the left forearm (Figure 1, 2).



Figure 1. Lesion in the facial area before treatment

Due to the presence of amastigote forms in her samples examined in an external center and their clinical compatibility, the patient was considered to have cutaneous leishmaniasis. Seeking further details of the patient's history by the help of an interpreter revealed that she had not continued her treatment regularly. Therefore, the patient was not considered to have meglumine antimonate resistance. Since the lesions were large and numerous, systemic meglumine antimonate treatment was planned for the patient. We consulted with the nephrology department about the appropriateness of systemic treatment because the patient had chronic renal failure and underwent dialysis. Upon receiving the response that systemic therapy would not be appropriate due to the patient's existing kidney disease, intralesional meglumine antimonate treatment was initiated 3 days a week, along with additional cryotherapy for lesions on the arms and fingers. The treatment days and hours of the patient were arranged in accordance with the dialysis hours in order to ensure the continuity of the treatment. The treatment and follow-up of our patient continue and she has benefited significantly from the treatment (Figure 3, 4).

Discussion

Cutaneous leishmaniasis is a disease that can be seen all over the world except the Antarctic continent, especially with a quite high incidence in countries bordering the Mediterranean [5]. It has been a serious public health problem for many years also in Turkey, particularly in the Southeastern Anatolia region [6].

Two equivalent antimony compounds form the basis of the treatment of cutaneous leishmaniasis. These drugs can be used



Figure 2. Lesion on the fifth finger of the right hand before treatment

systemically or intralesionally (IL). IL treatment is done using a fine-tipped syringe. The drug is applied into the lesion without any dilution. The entire lesion should become white in order for the drug to reach an effective dose within the lesion. The injection is applied 1-3 times a week until the lesion is completely healed. The descent of the lesions in the form of puffy papules, nodules or plaques to



Figure 3. Lesions in the facial area during treatment



Figure 4. Lesion on the fifth finger of the right hand before treatment

the skin level, and complete closure of ulcerated lesions are the criteria for healing, and therefore, termination of the treatment [7]. Drug resistance can be defined as a decrease in the effectiveness of a drug in ameliorating a disease or a condition. In order for antimony to be effective on amastigote and promastigote forms of leishmania species, it must be reduced to the trivalent antimony form. The reduction reaction of antimony to trivalent occurs in both parasite and macrophage cells. In our country, enolase, EF-2, HSP-70, trypanothion reductase, protein kinase c receptor and metallo-peptidase genes have been found to play a role in the resistance development of *L. tropica* isolates against antimony compounds [8]. Treatment failure, however, is a concept different from drug resistance. Failure in treatment can occur due to several reasons other than drug resistance, depending on the host (immune status of the host, etc.), parasite (parasite settling in tissue areas where the drug cannot reach, etc.), environmental and socio-economic factors (continuity of treatment, etc.), and drug (staying below therapeutic dose or duration, etc.).

In this case, the patient did not take the initial treatment regularly. Since she did not have a good command of Turkish, this situation was initially considered to be treatment resistance. However, when the history was sought again through an interpreter, it was thought that the situation was more associated with treatment failure than drug resistance. The number of cutaneous leishmaniasis cases in Turkey has increased, especially in recent years and most of these patients are refugees. Inadequate communication causes treatment failure to be perceived as drug resistance. However, it should not be forgotten that the number of resistant strains and cases may increase rapidly if CL patients receive inadequate and incomplete treatment. In this case report, we aimed to draw attention to the need for being more careful about this distinction.

Ethics

Informed Consent: Consent form was filled out by all participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: F.C.A., Concept: F.C.A., D.K., Design: D.K., F.C.A., E.Ö.S., Data Collection or Processing: F.C.A., D.K., Analysis or Interpretation: F.C.A., D.K., Literature Search: F.C.A., D.K., Writing: F.C.A., D.K.

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