Visceral Leishmaniasis in COVID-19

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Leishmaniasis is a zoonosis that may present general symptoms, including fever, malaise, and arthralgia, rendering it indistinguishable from COVID-19.

visceral leishmaniasis COVID-19 coinfection

1. Introduction

The ongoing COVID-19 pandemic represents an unprecedented global health challenge. Currently, health systems worldwide are engaged in unparalleled efforts, and physicians continue to play a critical role in the early detection and clinical management of the COVID-19 pandemic. COVID-19 infection in children is usually mild with low numbers of severe cases compared with adults [1].

However, in children, SARS-CoV-2 infection can frequently involve multiple body tracts, including the respiratory, gastrointestinal, musculoskeletal, and neurological systems [2][3][4]. In children, co-infections represent a particular challenge for clinicians because the current focus on the management of COVID-19 may, in part, lead to the inappropriate diagnosis and management of other life-threatening febrile medical conditions [5]. An appropriate epidemiological approach and a differential diagnosis are critical for selecting the most appropriate clinical intervention. Visceral leishmaniasis (VL) is an anthropozoonosis endemic in areas surrounding the Mediterranean Sea. In these areas, VL is caused by the protozoan *Leishmania infantum* and is transmitted through the bite of hematophagous sandflies belonging to *Phlebotomus* spp. Sicily is the largest island in the Mediterranean Sea, where VL is endemic [6].

2. Children with Visceral Leishmaniasis in COVID-19

Most children with SARS-CoV-2 infection develop no symptoms or mild symptoms, requiring only supportive care [7]. Coinfections with other pathogens, viruses, bacteria, and protozoa, should always be investigated, especially in cases, such as the one reported here, that present with a long-lasting fever [8][9][10]. In the diagnostic process of fevers of unknown origin, Leishmania infection should always be investigated in Sicily, the largest island in the Mediterranean and an endemic area for this zoonosis. It has been estimated that approximately half of the Sicilian population lives in areas at risk of Leishmania infection (rural areas, small villages or suburbs of cities), where sandfly vector species are more prevalent [6].

In contrast with the past, when VL was typically observed more commonly in children, the current age-related epidemiologic features observed in Sicily are consistent with reports from other Mediterranean regions of Europe, such as France, Spain, and Greece, where the ratio of childhood to adult cases is approximately 1:1 [11].

Typical clinical features of VL in children include fever, pallor, weakness, hepatosplenomegaly, and pancytopenia. As the case, fever may be intermittent at first and then become continuous. Non-tender splenomegaly and hepatomegaly are caused by infection of the reticuloendothelial system. Pancytopenia caused by parasites invading the bone marrow is responsible for pallor due to anaemia and may subsequently cause haemorrhages due to thrombocytopenia and concomitant infections due to leukopenia. Anorexia and weight loss can lead to a wasting syndrome in misdiagnosed cases. Lymphadenopathy is found in some geographic areas, such as Sudan, but is less common in the Mediterranean region where it is an occasional finding unrelated to the disease [6][12]. Slightly latero-cervical lymphadenopathy was present here.

COVID-19, by contrast, is an emerging infection with clinical manifestations in children ranging from the most frequent mild cold to the rarest life-threatening, rapidly progressing, systemic disease that can lead to multi-organ failure [13]. During the current pandemic, the pathways of these two infections have inevitably crossed, with consequences that are not yet fully understood. Moreover, the early clinical symptoms (fever and asthenia) and laboratory parameters (e.g., leukopenia, thrombocytopenia, and elevated transaminases) might be similar in patients infected with SARS-CoV-2 and those with VL. Overlapping SARS-CoV-2 and Leishmania infection could lead to misdiagnosis, because leishmaniasis shares clinical and laboratory features with SARS-CoV-2 during the onset of the infection, making it difficult to determine which etiologic agent causes the disease.

One of the other two cases of Leishmania-COVID-19 coinfection reported in the literature is that described by Miotti et al. [14] in an immunocompromised adult patient. Protozoa persistence appears to be very common in infected individuals, and the development of an immunocompromised or immunosuppressive state affects various activities of innate and adaptive immunity in patients with VL. This is evidenced by the inability of peripheral blood mononuclear cells stimulated with leishmanial antigens to produce antibodies [15]. As a result, chronic infection may reactivate years after the initial contact with the parasite. The clinical presentation of VL in immunocompromised patients is similar to that observed in immunocompetent individuals. The main difference is the lower rate of response to treatment and the subsequent high rate of disease relapse [11][16][17][18][19].

In the case described by Miotti et al., although amphotericin therapy was well-tolerated and resulted in defervescence with a mild to moderate improvement in clinical conditions and laboratory tests, the concomitant VL and COVID-19, burdened by several comorbidities, was fatal.

The leishmaniasis-COVID-19 coinfection reported by Antonis Pikoulas may also have led to the reactivation of previously asymptomatic leishmaniasis [20]. Repolarization toward Th1 to deal with the virus may have allowed the parasite to escape immune surveillance, leading to symptomatic VL. There are many cases reporting that COVID-19 led to the reactivation of chronic, asymptomatic infections caused by viruses such as VZV (varicella-zoster virus), EBV (Epstein–Barr virus), CMV (cytomegalovirus), HSV (herpes simplex virus), HHV6 (human herpes virus

6), HBV (hepatitis B virus), protozoa, and fungi [21][22][23][24]. By contrast, VL may have led to a specific polarization of the immune response, making the patient more susceptible to viral infections, such as the widely circulating COVID-19, which was transmitted to the patient during the pandemic. Currently available data do not allow us to decide which scenario might be correct. Whatever the case, there are clear indications that the two infections likely result in complex immunologic interactions when their pathways cross [25].

Interactions between parasitosis and coronaviruses were extensively studied during the early stages of the pandemic, and the presence of a cross-talk between the two types of infection is confirmed. Researchers attempted to determine the relationships between the higher mortality observed in northern regions compared with Southern Europe and Africa with the lesser incidence of parasitosis and vector-borne diseases in the colder region. Indeed, following the first wave of COVID-19 in Europe in summer 2020, the possibility of herd immunity mediated by sandflies in Southern Europe was theorized by observing the distribution of arthropods and the lower impact of COVID-19 in these regions (most evident in Sicily, Cyprus, and Malta) [1][5]. Furthermore, an Iranian study carried out on 1.010 patients with a positive history of Cutaneous Leishmaniasis (CL) and 2.020 with no history of CL found a strong negative association between CL and severe COVID-19 [25]. Thus, despite the presence of an interaction between the immunological responses in these two conditions, the relevance of this needs to be better studied in the future.

Liposomal amphotericin B (AmBisome) is nowadays considered the first-line treatment for VL. The efficacy and safety of a six-dose regimen of L-AmB is demonstrated by Cascio et al., who validated this first-line treatment for Mediterranean VL in children [26][27].

To summarize, the present case is the third case of Leishmania-SARS-Cov2 coinfection, the first in a child, and the first during the Omicron variant. The need for a thorough understanding of the relationship between neglected endemic diseases such as VL and pandemic SARS-CoV-2 infection was highlighted. In particular, the complex immunology behind COVID-19 and rapidly changing pandemic scenarios force clinicians to deal with clinical conditions that are difficult to define at the first approach. Therefore, the complex interaction between parasites and the immunology of COVID-19 needs to be better explained in the future and forms an extremely interesting body of research that supports the “old friendly hypothesis” postulated by Rook [28].

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