



Case report

Good's syndrome and recurrent leishmaniasis: A case report and review of literature

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ARTICLE INFO

Keywords:

Infectious disease
 Immunology
 Intensive care medicine
 Internal medicine
 Laboratory medicine
 Good's syndrome
 Leishmaniasis
 Liposomal amphotericin B
 CD4+ T cells
 IFN γ

ABSTRACT

We report the case of a 56-year-old Caucasian male affected by thymoma and myasthenia gravis that developed recurrent visceral leishmaniasis 11 years after thymectomy. After treatment of each relapse with liposomal amphotericin B the PCR-*Leishmania* was negative and the patient showed clinical improvement. An immunologic work-up was performed showing lymphopenia with an important decrease in CD4+ T cells (52 cells/ μ) and CD4/CD8 ratio (0.2). HIV test was negative. On the basis of previous thymoma and myasthenia gravis and on the basis of the immunological profile a diagnosis of Good's syndrome was made. Since IFN γ plays a main role in the control of *Leishmania* infection the production of IFN γ was evaluated. After mitogen stimulation of peripheral blood mononuclear cells the production of IFN γ was lower than normal. This is the second reported case of Good's syndrome with recurrent leishmaniasis and indicates that a definitive cure for leishmaniasis in patients with Good's syndrome is not possible. Immunologic work-up in our patient strongly suggests that relapses could be correlated with the low CD4+ T cell number and with the low IFN γ production. Immunotherapy with IFN γ or with compounds able to block the Th2 interleukin production could be a therapeutic option in these patients.

1. Introduction

Good's syndrome is a rare acquired immunodeficiency syndrome that can occur in patients with thymoma. It is characterized by an increased susceptibility to infections caused by a B- and T-lymphocytes immunodeficiency. This syndrome was first recognised in 1954 by Robert Good, who described a case of thymoma associated to hypogammaglobulinemia (Good, 1954). The main immunological alterations in Good's syndrome are: i) important decrease or absence of B cells, ii) abnormal reduction in CD4+/CD8+ T cell ratio caused by severe CD4 T cell lymphopenia, and iii) reduced T cell mitogenic responses. Frequently the serum IgG, IgA, and IgM levels are decreased although there are reports of patients with normal IgA values (Tarr et al., 2001) and raised IgM concentrations (Jeandel et al., 1994).

The diagnosis is based on clinical criteria and the clinical outcome depends on the severity of infections. Sinopulmonary infection secondary to encapsulated organisms, bacterial urinary tract and skin infections are the most frequent infections in patients affected by Good's syndrome. Opportunistic infections such as *cytomegalovirus* (CMV) colitis, CMV retinitis and mucocutaneous *candida* are common (Tarr et al., 2001).

Moreover, opportunistic infection caused by *herpes simplex* (Beck et al., 1981), *varicella zoster* (Watts and Kelly, 1990) and *Pneumocystis carinii* pneumonia (Souadjan et al., 1974) have also been described.

The etiological agent of leishmaniasis is an obligate intracellular protozoa of the genus *Leishmania*. It is transmitted by the bite of a sandfly. There are 3 different clinical forms of leishmaniasis: i) cutaneous, characterized by skin ulcers, ii) mucocutaneous with ulcers in the mucous membranes of the mouth, nose, and throat, and iii) visceral characterized by fever, anemia and hepatosplenomegaly. Leishmaniasis is diagnosed by microscopic identification of amastigotes from bone marrow, spleen, lymph nodes, or skin lesions and by polymerase chain reaction (PCR). Liposomal amphotericin B is the treatment of choice in both immunocompetent and immunodeficient patients affected by visceral leishmaniasis. Rates of cure with a single dose of amphotericin have been reported as 95% (Barrett and Croft, 2012) and the relapse is no common in immunocompetent patients.

To our knowledge, only one case of Good's syndrome with recurrent leishmaniasis have been currently reported showing that a definitive cure for leishmaniasis in these patients is not possible (Stoeckle et al., 2013). We focused the attention in our case on the very low number of CD4+ T

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cells and on the low level of IFN γ that represent the most important cytokine for the control of *Leishmania* infection.

2. Case presentation

We report the case of a 56-year-old Caucasian male affected by Good's syndrome and thymoma with recurrent leishmaniasis treated with liposomal amphotericin B. In 2007, he showed persistent cough and for this performed a chest computed tomography (CT) that suggested the presence of a thymoma and therefore he underwent thymectomy. Thymoma was classified into histological type B3, according to the WHO classification system. On postop follow-up, the patient showed typical symptoms of myasthenia gravis (MG) characterized by weakness and fatigue in the skeletal muscle. In 2009 he was treated with five cycles of chemotherapy with cis-platin and adriamycin and surgery for thymic epithelial tumour recurrence. In April 2018 the patient was admitted for suspected leishmaniasis with the following symptoms: fever, hepatosplenomegaly, weight loss, anaemia, leukopenia, and thrombocytopenia. The diagnosis of visceral leishmaniasis (*L. infantum*) was made by microscopic identification of the intracellular form (amastigote) in stained sections from bone marrow biopsy. Moreover, real-time PCR and serological tests for leishmaniasis were positive. The patient was treated with liposomal amphotericin B (AmBisome®) 3 mg/kg IV once daily days 1–5, 14 and 21. After treatment the PCR-*Leishmania* was negative and the patient showed clinical improvement. The first relapse appeared in December 2018 and was treated with liposomal amphotericin B 3 mg/kg IV once daily days 1–5, 14 and 21. The second relapse appeared in April 2019. We performed an immunologic work-up during the second relapse. Results showed lymphopenia with 400 total lymphocytes/ μ l (normal lower limit 1000 cells/ μ l), CD4+ T cells = 52 cells/ μ l (normal lower limit 580 cells/ μ l), CD8+ T cells = 208 cells/ μ l (normal lower limit 200 cells/ μ l), a CD4/CD8 ratio of 0.2 (normal range 1–1.5), CD19 + CD20+ B-lymphocytes = 12 cells/ μ l (normal lower limit 80 cells/ μ l), CD3+CD16 + CD56 + natural killer (NK) lymphocytes = 49 cells/ μ l (normal range 40–600 cells/ μ l). HIV test was negative and a modest IgG and IgA deficiency was observed. Moreover, PCR was positive for *Cytomegalovirus*, *Epstein Barr virus* and *herpes simplex*. The production of interferon gamma (IFN γ) after mitogen stimulation of peripheral blood mononuclear cells (PBMCs) was 5 IU/ml (normal lower limit 10 IU/ml). On the basis of i) previous thymoma, ii) deficit of B and CD4+T lymphocyte, iii) hypogammaglobulinemia, iv) recurrent infections, a diagnosis of Good's syndrome was made. The patient was started on intravenous immunoglobulin (IVIg 0.5 gr/Kg every 28 days) and *P. jiroveci* and *HSV* prophylaxis. The second relapse was treated with liposomal amphotericin B 4 mg/kg IV once daily days 1–5, 10, 17, 24, 31, 38. The third relapse appeared in December 2019 and treated again with liposomal amphotericin B 4 mg/kg IV once daily days 1–5, 10, 17, 24, 31, 38 followed by amphotericin B 4 mg/kg IV every month. After treatment of each relapse a complete clinical and molecular (PCR) remission was observed. The fourth relapse appeared in May 2020 (Table 1). Table 2 shows the comparison between our case and the only case previously reported of recurrent leishmaniasis in Good's syndrome. Informed consent was obtained for publication of this case report.

3. Discussion

To our knowledge, this is the second reported case of Good's syndrome with recurrent leishmaniasis. The first case was reported by Stoeckle et al. (2013) in a 76-year old patient affected by Good's syndrome with recurrent mucosal localized leishmaniasis (tongue). Multiple treatment regimens were administered. The third relapse was treated with oral miltefosine with complete resolution of the lesions. Christopoulos P. et al. (Christopoulos et al., 2015) reported a case of recurrent visceral leishmaniasis in a patient affected by thymoma. This patient showed cutaneous anergy, even though he had normal number of peripheral blood total lymphocytes as well as CD4+ and CD8+ T cells.

Table 1. Clinic timeline of the case report.

2007	Diagnosis of thymoma (type B3) and thymectomy.
2009	Five cycles of chemotherapy with cis-platin and adriamycin and surgery for thymic epithelial tumour recurrence.
April 2018	Diagnosis of leishmaniasis and treatment with liposomal amphotericin B 3 mg/kg IV once daily days 1–5, 14 and 21.
May 2018	PCR- <i>Leishmania</i> negative and clinical improvement.
December 2018	First relapse with fever, thrombocytopenia, PCR- <i>Leishmania</i> positive. Treatment with liposomal amphotericin B 3 mg/kg IV once daily days 1–5, 14 and 21.
January 2019	PCR- <i>Leishmania</i> negative and clinical improvement.
April 2019	Second relapse with PCR- <i>Leishmania</i> positive. Immunologic work-up and diagnosis of Good's syndrome. Treatment with liposomal amphotericin B 4 mg/kg IV once daily days 1–5, 10, 17, 24, 31, 38.
May 2019	PCR- <i>Leishmania</i> negative and clinical improvement.
December 2019	Third relapse with PCR- <i>Leishmania</i> positive. Treatment with liposomal amphotericin B 4 mg/kg IV once daily days 1–5, 10, 17, 24, 31, 38 followed by amphotericin B 4 mg/kg IV every month.
January 2020	PCR- <i>Leishmania</i> negative.
May 2020	Fourth relapse with fever and PCR- <i>Leishmania</i> positive.

Considering the normal numbers of B cells and CD4+ T cells and the hypergammaglobulinemia observed in this patient clearly did not have Good's syndrome but a generalized T cell activation defect. Recurrent leishmaniasis has been described in other type of immunosuppressed patients such as transplanted patients (Akuffo et al., 2018; Simon et al., 2011).

In our patient the diagnosis of leishmaniasis was made 11 years after the diagnosis of thymoma. The first relapse was observed after 8 months, the second relapse after 15 months, the third relapse after 23 months and the fourth relapse after 28 months from the first diagnosis. After each treatment with liposomal amphotericin B the PCR-*Leishmania* was negative and the patient showed clinical improvement. The complete clinical and molecular (PCR) remission after each treatment and the relapses of the disease months after therapy suggests that recurrence was not dependent on pathogen drug-resistance. Liposomal amphotericin B is one of the most effective drug for the treatment of leishmaniasis (Cascio et al., 2004) and resistance to amphotericin B has been reported only rarely (Purkait et al., 2012; Srivastava et al., 2011; Morizot et al., 2016; Eichenberger et al., 2017).

We focused our attention on CD4+ T cell number and on IFN γ production in our patient. In fact, IFN γ produced by CD4+ TH1 cells plays a main role in the control of *leishmania* infection by increasing the production of reactive oxygen species in macrophages (Saporito et al., 2013). During leishmania infection PBMCs are stimulated by leishmanial antigen and produce IFN γ , IL-2, and IL-12 (Carvalho et al., 1992). Of interest, the use of antibodies neutralizing IL-12 inhibits both PBMCs proliferation and IFN γ production (Ghalib et al., 1995).

Immunologic work-up in our patient showed lymphopenia with an important decrease in CD4+ T-cell number (52 cells/ μ l) and reduced production of IFN γ after mitogen stimulation of PBMCs. Considering the role of CD4+ T cells and IFN γ in the control of *Leishmania* infection the low CD4+ T cell number and the low IFN γ level in our patient could be the main cause of recurrent leishmaniasis.

In contrast, the number of CD8+ T cells and NK was normal. CD8+ T cells are able to directly lyse cells infected by *Leishmania* and can produce high levels of IFN γ contributing to cure the infection. However, it seems that they are not required for secondary immunity (Okwor et al., 2014).

Several subset of CD4+ T cells, such as effector T cells, effector memory T cells, central memory T cells and tissue-resident memory T cells are produced after *leishmania* infection. Effector memory T cells, central memory T cells and tissue-resident memory T cells are mainly involved in resistance to reinfection. The persistence in dendritic cells of a small proportion of parasites seems to be necessary for maintain effector CD4+ T cells, and they are lost in the absence of parasites. In contrast,

Table 2. Comparison between the first case of recurrent leishmaniasis in Good's syndrome reported in literature and our case.

	Case 1: Stoeckle et al. (2013)	Case 2: Tolomeo et al. (2020)
Patient	76-year old man of Sicilian origin.	56-year-old Caucasian male.
Type of leishmaniasis	Mucosal leishmaniasis.	Visceral leishmaniasis.
<i>Leishmania</i> specie	<i>Leishmania infantum</i> .	<i>Leishmania infantum</i> .
Number of relapses	Five relapses.	Four relapses.
Thymoma	Diagnosis of thymoma six years prior to the diagnosis of leishmaniasis	Diagnosis of thymoma eleven years prior to the diagnosis of leishmaniasis
Antileishmanial therapy	Meglumine antimoniate, sodium stibogluconate, liposomal amphotericin B, fluconazole.	Liposomal amphotericin B.
Diagnosis of Good syndrome	Diagnosis of Good's syndrome during the second relapse of leishmaniasis.	Diagnosis of Good's syndrome during the second relapse of leishmaniasis.
CD4+ T cells	424 cells/ μ l	52 cells/ μ l
CD4/CD8 ratio	0.54	0.2
B-cells	59 cells/ μ l	12 cells/ μ l
NK	—	49 cells/ μ l
IFN γ after mitogen stimulation of PBMC	—	5 IU/ml

central memory CD4+ T cells are maintained and after secondary infection they become tissue-homing effector T cells and mediate protection (Zaph et al., 2004). Although we did not study the expression of central memory CD4+ T cells and tissue-homing effector CD4+ T cells in our patient, the very low level of CD4+ T cells suggests that this CD4+ T cell subset could be expressed at very low level.

The reduced production of IFN γ in Good's syndrome affected patients probably represent the effect of a Th1–Th2 unbalanced response. In fact, an excessive Th2 response with an increased IL4 production has been described in Good's syndrome (Di Renzo et al., 2005). Moreover, several studies have demonstrated that IL-10, a Th2 cytokine, plays an important role in many of the immunologic defects associated with *Leishmania* infection (Nylén et al., 2007; Ansari et al., 2006; Gautam et al., 2011). The production of IL-10 in macrophages is induced by *Leishmania* parasites. IL-10 down-regulates the production of IFN γ and inhibits the killing of amastigotes (Nylén et al., 2007). IL-10 neutralization is able to promote parasite killing increasing the levels of IFN γ (Gautam et al., 2011).

Several studies have shown that in Good's syndrome there are both a reduction in Th1 cytokines and an increase in Th2 cytokines (Di Renzo et al., 2005; Kelleher and Misbah, 2003; Tamburello et al., 2019). Differently to HIV infected patients, where antiretroviral therapy can restore the number of CD4+ T cells and leishmaniasis may be kept under control (Colomba et al., 2009), patients with Good's syndrome have persistent impaired cellular immunocompetence. Therefore, immunotherapy with compounds able to modulate the immune response may be the only therapeutic prospective in the future.

Recently, we evaluated the antileishmanial activity of a series of new terphenils derivatives incorporating a phenyl ring as a bioisosteric substitution of the stilbene alkenyl bridge (Castelli et al., 2016). A compound of the series, namely 3,4',5-trimethoxy-1,1':2',1''-terphenyl (TR4) presented the best activity, the safety profiles and a leishmanicidal activity higher than sodium stibogluconate and meglumine antimoniate in the most of *Leishmania* species. This compound was able to markedly decrease the levels of IL-10, increasing the levels of IL-1 β and IL-18, two cytokines involved in the control of *leishmania* infection (Bruno et al., 2018). Considering the imbalance between Th1 and Th2 response in patients affected by Good's syndrome this molecule could be in the future an interesting therapeutic option in patients with recurrent leishmaniasis and Good's syndrome. In vivo studies with 3,4',5-trimethoxy-1,1':2',1''-terphenyl compound are ongoing.

In conclusion and in according with other case reported in the scientific literature, our case shows that a definitive cure for leishmaniasis in patients with Good's syndrome is not possible and relapses are to be expected. Immunologic work-up in our patient strongly suggests that relapses could be correlated with the low CD4+ T cell number and with

the low IFN γ production. However, on the basis of literature data, it is possible that other immunologic alterations such as an excessive Th2 response may play a role in recurrent *Leishmania* infection in Good's syndrome patients. Immunotherapy with IFN γ or with antileishmanial compounds able to targeting the Th2 interleukin production could be a therapeutic option in these patients.

Declarations

Author contribution statement

All authors listed have significantly contributed to the investigation, development and writing of this article.

Funding statement

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Competing interest statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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