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Epidemiological and clinical profile of immunosuppressed patients with imported strongyloidiasis: a substudy from a larger cohort of the +REDIVI Spanish Collaborative Network.

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ABSTRACT

The aim of this study was to describe the clinical and epidemiological profile of immunosuppressed patients with imported strongyloidiasis in a non-endemic setting, and to compare these results with non-immunosuppressed patients. This is a case-control substudy from a larger observational retrospective study that included all patients with strongyloidiasis registered in the +REDIVI Spanish Collaborative Network. Overall, 1245 patients with imported strongyloidiasis were included. From these, 80 (6.4%) patients had some kind of immunosuppression. Three (3.8%) patients had a hyperinfection syndrome, and 34 (52.3%) patients had eosinophilia. The percentages of positive results of the formalin-ether technique, the fecal culture and serology were 12.3%, 21.1% and 95.4%, respectively. When comparing the main characteristics, immunosuppressed patients had higher proportion of severe clinical manifestations and lower proportion of eosinophilia. No differences were found regarding yield of microbiological techniques and treatment response. These results stress the importance of strongyloidiasis screening among immunosuppressed patients coming from endemic areas. Serological tests have an acceptable sensitivity to be used as a screening tool.

KEYWORDS

Strongyloides stercoralis; strongyloidiasis; immunosuppression; HIV

Introduction

Human strongyloidiasis, caused by the soil-transmitted nematode *Strongyloides stercoralis* (and sporadically by *S. fuelleborni*), affects an estimated 370 million people worldwide, especially in the tropics and sub-tropics [1]. The infection is asymptomatic most of the times, but patients may present digestive, respiratory and cutaneous symptoms. Moreover, chronic strongyloidiasis in schoolchildren has been associated with malnutrition and stunting [2].

However, it is in immunosuppressed population where severe clinical presentations usually take place: *S. stercoralis* hyperinfection syndrome and disseminated strongyloidiasis, with high mortality rate, ranging from 10% to 70% depending on the studies [3]. Most common immunosuppressant-related conditions are corticosteroid therapy, solid organ or bone marrow transplantation, and human T-lymphotropic virus 1 (HTLV-1) infection [4]. The risk associated with HIV infection is not well established; it seems that the risk factor for dissemination is the recovery of the CD4 cell count (after initiation of antiretroviral therapy) more than the immunosuppression itself [5].

The aim of this study was to describe the clinical and epidemiological profile of immunosuppressed patients with imported strongyloidiasis in a non-endemic setting, the yield of the different microbiological diagnostic techniques, and to compare these results with a group of non-immunosuppressed patients.

Material and methods

This is a case-control substudy from a larger observational retrospective study that included all patients with strongyloidiasis registered in the +REDIVI Spanish Collaborative Network from January 2009 to February 2017. The methods are described elsewhere [6]. Briefly, demographic and clinical information of immigrants and travelers with strongyloidiasis were collected from the +REDIVI online database (22 Spani sh participant centers). Microbiological techniques included: the Ritchie's formalin-ether technique,

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specific fecal culture for *S. stercoralis* larvae, and serum anti-*S. stercoralis* IgG detection through different serological techniques depending on the center: SciMedx *Strongyloides* serology microwell ELISA (SciMedx Corporation, Denville, NJ, United States), NovaLisa Strongyloides (NovaTec Immunodiagnostica GmbH, Dietzenbach, Germany), AccuDiag *Strongyloides* IgG ELISA Kit (Diagnostic Automotion/Cortez Diagnostics Inc, CA, United States). Eosinophilia was defined as eosinophil cell count ≥450 cells/mm^3 and/or a percentage ≥5% following the Spanish Society of Tropical Medicine and International Health recommendations [7]. We considered severe clinical presentation: hyperinfection syndrome (infection confined to lungs and gastrointestinal tract, but symptoms of severe disease related to elevated number of larvae) and disseminated strongyloidiasis (larvae found in any organ other than the lungs and gastrointestinal tract). Strongyloidiasis diagnosis was classified into three groups: confirmed (detection of larvae by any parasitological technique), probable (positive serological result and presence of eosinophilia), and possible (positive serological result without presence of eosinophilia). Treatment outcome was classified into four categories: cure (when patients had negative conventional methods after treatment, disappearance of the eosinophilia, and negative serology or at least a 60% decrease in the OD ratio), probable cure (the same as cure criteria but with eosinophilia persistence, or negative parasitological test and no eosinophilia in the absence of serological control), failure (larvae detection through parasitological tests, or cure criteria not reached after 6 months of follow-up), and not enough information (cure criteria not reached with a follow-up period less than 6 months). Cure and probable cure were considered 'treatment success' outcome.

Immunosuppression was considered in the following situations: HIV infection, solid organ and bone marrow transplantation, cancer under adjuvant or neoadjuvant chemotherapy, corticosteroid therapy with an accumulated dose over 20 mg/day during 2 weeks or more, treatment with other immunosuppressive drugs (cytotoxics, antimetabolites, and biological drugs), and hypogammaglobulinemia. Epidemiological and clinical characteristics of immunosuppressed patients (cases) were described. To compare the results with those from non-immunosuppressed patients (controls), two controls for every case were randomly selected from the +REDIVI database, paired by age, gender, and center. For the comparison of the serological optical density (OD) levels between groups, only patients in whom the SciMedx serology was performed were analyzed (it was the most frequently used serological test). Categorical data are presented as absolute numbers and proportions, and continuous variables are expressed as means and standard deviations (SD) or medians and interquartile ranges (IQR) depending on the distribution. The χ^2 test or Fisher exact test, when appropriate, was used to compare the distribution of categorical variables, and the t-Student test for continuous variables. Results were considered statistically significant if the 2-tailed P value was <0.05. SPSS software for Windows (Version 19.0; SPSS Inc, Chicago, IL, USA) was used for statistical analyses.

The STROBE statement guidelines were used to improve the quality of the study. Procedures were performed in accordance with the ethical standards laid down in the Declaration of Helsinki as revised in 2013, and the study protocol was approved by the Ethical Review Board of the Vall d'Hebron University Hospital (Barcelona, Spain).

Results

During the study period, 1245 patients with imported strongyloidiasis were registered in the +REDIVI database. From these, 80 (6.4%) patients had some kind of immunosuppression and were included in the substudy. Overall, 48 (60%) patients were men, with a mean age of 39.9 (SD 10.4) years. The main reason of immunosuppression was HIV infection (56 patients, 70%); at the time of strongyloidiasis diagnosis, the median CD4+ cell count was 435 (IQR 248–587) cells/mm^3, 16.1% patients had a CD4+ cell count <200 cells/mm^3, and 46.4% of the patients had a detectable (>50copies/mL) viral load. When strongyloidiasis was diagnosed and treated, 22 (39.2%) patients were naïve for antiretroviral therapy, and from them 8 (36.4%) patients had a CD4+ cell count <200 cells/mm^3; the other 34 (60.8%) patients were already under antiretroviral therapy, with a median time of treatment duration of 38 (IQR 14.5–80.5) months.

Other causes of immunosuppression were: 19 (23.7%) patients receiving immunosuppressive therapies (11 of them receiving corticosteroids), and 5 (6.3%) patients with solid organ transplantation (4 kidneys and 1 lung; 4 of them under corticosteroid therapy). HTLV-1 serology was performed in 32 patients, with one positive result (3.1%).

The vast majority were immigrants (78 patients, 97.5%). Main regions of origin were South America (45 patients, mainly coming from Ecuador, Bolivia and Colombia), and Sub-Saharan Africa (22 patients, mainly from Equatorial Guinea). Only two (2.5%) patients were travelers. Regarding clinical presentation, 19 (23.8%) patients were symptomatic, and 3 (3.8%) patients had a hyperinfection syndrome.

At the time of diagnosis, eosinophilia was observed in 34/65 (52.3%) patients, and these patients had a median eosinophil count of 940 (IQR 600–1400) cells/mm^3. Regarding microbiological techniques, positive results were as follows: 8 positive Ritchie's formalin-ether technique out of 65 (12.3%), 11 positive fecal cultures out of 52 (21.1%), and 63 positive serological tests out of 66 (95.4%). These results allowed classifying the diagnosis in: 13 (19.1%) confirmed cases, 24 (35.3%) probable cases, and 31

(45.6%) possible cases. All patients received treatment with 200 mcg/kg/day ivermectin orally for 2 days, except for two patients that received a combined treatment: one patient received ivermectin (200 mcg/kg/day) and albendazole (400 mg/12 hours) for 7 days, and one patient received ivermectin orally and subcutaneous (200 mcg/kg/day) for 10 days (both of them had a severe clinical presentation). Follow-up information was available from 61 patients, with a mean time of follow-up of 10.1 (SD 9) months. The treatment outcomes were as follows: 24 (39.3%) patients with cure, 18 (29.5%) with probable cure, 5 (8.2%) with treatment failure and 14 (23%) with no enough information. Treatment success was achieved in 42 (68.9%) patients.

When comparing the main characteristics between the 80 immunosuppressed patients (cases) and the 160 non-immunosuppressed patients (controls), immunosuppressed patients had higher proportion of severe clinical manifestations (3.8% vs 0%, p = 0.036), and lower proportion of eosinophilia (52.3% vs 78.5%, p < 0.001) than non-immunosuppressed patients. No differences were found regarding yield of microbiological techniques and treatment response (see Table 1).

parasite by the immunosuppressed host is supposed to be the main cause of these severe clinical presentations [8].

In our cohort of patients, HIV infection was the most common cause of immunosuppression. Although HIV infection induces a Th2 immune response in the host (which usually lead to a rise in the eosinophil cell count), in our study immunosuppressed patients had lower proportion of eosinophilia than non-immunosuppressed patients. This finding has also been observed in two previous studies that compare the eosinophil cell count between HIV infected and non-HIV infected patients who are co-infected with *S. stercoralis* and tuberculosis, respectively [9,10].

When comparing the usefulness of classical parasitological techniques, the proportion of patients with positive Ritchie's formalin-ether technique and fecal culture were low in both groups. Interestingly, when comparing the proportion of positive *S. stercoralis* serology and the median of OD values, no differences were found between groups. Old studies had raised concern about the sensitivity of *S. stercoralis* serology for the strongy-

Table 1. Comparison of clinical and microbiological characteristics between immunosuppressed and non-immunosuppressed patients with imported strongyloidiasis in +REDIVI (2009–2017).

	Immunosuppressed patients (*n* = 80)	Non-immunosuppressed patients (*n* = 160)	*P*-value
Presence of symptoms	19/80 (23.8%)	32/160 (20%)	0.503
Severe clinical manifestations	**3/80 (3.8%)**	**0/160 (0%)**	**0.036**
Presence of eosinophilia	**34/65 (52.3%)**	**106/135 (78.5%)**	**<0.001**
Eosinophil cell count [a], cells/mm^3	870 (590–1600)	990 (600–1400)	0.719
Positive Ritchie's formalin-ether technique	8/65 (12.3%)	14/129 (10.9%)	0.763
Positive fecal culture	11/52 (21.1%)	32/94 (34%)	0.102
Positive *S. stercoralis* serology	63/66 (95.4%)	131/132 (99.2%)	0.109
Serological OD value [b]	2.8 (1.4–6.2)	3.4 (1.8–6)	0.398
Confirmed diagnosis	13/68 (19.1%)	35/135 (25.9%)	0.281
Number of cured patients	24/61 (39.3%)	46/119 (38.7%)	0.929
Number of patients with treatment success [c]	42/61 (68.9%)	80/119 (67.2%)	0.825-
Number of deaths	0/80 (0%)	0/160 (0%)	

Data are reported as number (%) of patients or median (IQR).
[a]Only in patients with eosinophilia.
[b]Only patients in whom the SciMedx serology was performed were analyzed.
[c]Treatment success includes cure and probable cure.

Discussion

We present a cohort of 80 immunosuppressed patients with imported strongyloidiasis in Spain. Most of them had HIV infection, and were young immigrants coming from South America and Sub-Saharan Africa. As it was expected, immunosuppressed patients had higher proportion of patients with severe clinical presentation. From the three cases of hyperinfection syndrome, two patients were receiving immunosuppressive therapies, including corticosteroids, which is the most related risk factor associated to this clinical presentation, and one had HIV infection [4]. The absence of control on the autoinfective life cycle of the

loidiasis diagnosis in immunosuppressed patients [11]. However, using current serological tests as in our study, and given the observed results, this technique has an acceptable sensitivity to be used in immunosuppressed patients. Hence, *S. stercoralis* serology could be used as a screening method for strongyloidiasis diagnosed among immunosuppressed patients, as it has been suggested in other studies [12,13]. This finding is probably the most relevant one in the current study.

This study has some limitations due to the retrospective nature of its design: different microbiological techniques performed, different follow-up schedules, missing information. The majority of the patients were diagnosed through serological tests,

and only three patients had a severe clinical presentation, and it could limit the interpretation of the results. Another point to take into account is the fact that most of the patients had HIV infection (and only a proportion of them with high level of immunosuppression), which may difficult to generalize the conclusions to a more general immunosuppressed population. However, the study brings information from a large cohort of patients with strongyloidiasis and their management in real life.

In summary, immunosuppressed patients with *S. stercoralis* infection had higher risk of having a severe clinical presentation than non-immunosuppressed patients. And most important, no differences were found regarding the percentage of positive serological test when comparing immunosuppressed and non-immunosuppressed patients. This fact stresses the importance of strongyloidiasis screening among immunosuppressed patients coming from endemic areas, and serological tests have an acceptable sensitivity to be used as a screening tool among this population.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Disclosure statement

The authors declare that they have no competing interests.

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