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Imported Disease Screening Prior to Chemotherapy and Bone Marrow Transplantation for Oncohematological Malignancies

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Abstract. Reactivation of latent imported infections has been periodically reported in migrant patients undergoing immunosuppression. We performed a prospective study at Vall d'Hebron University Hospital (Barcelona, Spain). Migrant patients over 16 years with the diagnosis of any oncohematologic disease were included. Patients were tested for soil-transmitted helminths, hepatitis virus, and human immunodeficiency virus, *Treponema pallidum*, human T-cell lymphotropic virus, latent tuberculosis infection, *Toxoplasma* spp., *Plasmodium* infection, *Schistosoma* spp., *Trypanosoma cruzi* infection, *Leishmania* spp., and dimorphic fungi. Patients were treated and followed for 1 year to assess reactivation. A total of 42 patients were included in this study. Median age was 39 (31–51) years. Twenty-five (59.5%) patients were women. More than half of the patients were of Latin American origin. Sixteen patients (38.1%) underwent hematopoietic stem cell transplantation. Of the patients, 71.4% had at least one imported infection. Patients with at least one positive result in the screening did not show any statistically significant association with the studied variables. We did not find any reactivation of the treated latent infections. After specific treatment we did not observe any reactivation. Screening of latent imported infections previous to an immunosuppressive treatment is easy to perform and it may be lifesaving.

INTRODUCTION

Reactivation of latent diseases or worsening of paucisymptomatic infections have been periodically reported in the literature in patients undergoing immunosuppression, including chemotherapy, and bone-marrow transplantation.[1–3] Sometimes these infections may lead to fatal outcomes, and in many cases they hinder the appropriate progress of the disease that lead to immunosuppression.

Migratory flows have increased in the last decades worldwide. In January 2014, there were 33.5 million people living in the European Union (EU)-28, who had been born outside of the EU.[4] More concretely, in 2015, the migrant population in Spain represented 10.13% of the total population.[5] Despite the proportion of migrants with oncohematologic diseases being unknown, it is likely to be similar or slightly inferior to that of the receiving country.[6] Besides, until recently, Spain has had a universal and costless health system, ensuring medical care for all patients independent of their origins or incomes.[7]

On the other hand, oncohematologic treatments have evolved rapidly in the last few years and new and more immunosuppressive agents are being used; among them allogenic hematopoietic stem cell transplantation (HSCT) is the paradigm of immunosuppression.[8] Higher degree of immunosuppression usually means higher risk of reactivation or acquisition of infection. Therefore, screening before immunosuppression is adopted to avoid infection-related complications. However, little attention is given to imported infections, despite systematic screening being recommended for people at risk of imported disease.[9]

Data regarding imported infection reactivations in patients receiving steroid therapy, chemotherapy, and bone marrow transplantation are scarce. Unfortunately, the reactivation of imported diseases in this population is usually life threatening. A screening strategy used to diagnose imported diseases preceding immunosuppressive treatment may reduce associated morbidity and mortality.

For this purpose, we designed a prospective study to determine the prevalence of imported infections in patients before drug-induced immunosuppression and the incidence of reactivation of imported infections during the follow-up.

METHODS

Patients and study design. We performed a prospective study at Vall d'Hebron University Hospital (Barcelona, Spain) from March 2011 to August 2015. All patients over 16 years currently living in Spain, having migrated from a developing country, diagnosed of any oncohematologic disease and that were about to receive or were already under immunosuppressive treatment (including corticosteroids), were offered to participate in the study. Patients with previous known human immunodeficiency virus (HIV) infection were excluded.

All patients had a 1-year follow-up to assess the reactivation of the latent or imported disease. The last patient was included in August 2014. Every latent or imported disease was treated according to international guidelines or expert recommendations (Supplemental Appendix). Treatment of the imported diseases was initiated as soon as the investigators were aware of the results. Immunosuppressive therapy or chemotherapy was started according to the hematology or oncology specialist.

Screening process. All assays were ideally performed before the immunosuppressive condition began. In some cases, the diagnosed disease is per se an immunosuppressive condition and the patient had been suffering the illness before the screening. In any manner, the screening was conducted as soon as the patient was identified to comply with the inclusion criteria. Diagnostic techniques for commercial tests were performed according to the manufacturer instruction. The

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TABLE 1
Screening process according with geographic area

	Latin America	North Africa and Middle East	Asia	Sub-Saharan Africa
Human immunodeficiency virus	x	x	x	x
Hepatitis	x	x	x	x
Human T-cell lymphotropic virus-1	x	x	x	x
Strongyloides stercoralis	x	x	x	x
Schistosoma spp.	x*		x*	x
Parasites in feces	x	x	x	x
Treponema infection	x	x	x	x
Latent TB infection	x	x	x	x
Toxoplasmosis	x	x	x	x
Chagas disease	x			
Dimorphic fungi	x		x*	x
Leishmania	x	x	x	x
Malaria	x†		x†	x†

*Apply to specific areas within the region.
†Apply for patients living for more than 1 month in a malaria-risk area.

screening process according to the geographic area is summarized in Table 1.

All patients regardless of their countries of origin were tested for:

Soil-transmitted helminthes. Stool samples of 3 different days were collected from recipients containing 10% formalin. All feces samples were microscopically examined by an expert microbiologist using Ritchie's formalin-ether concentration technique. Moreover, the patient stored the latest sample also in a sterile pot to perform culture of *Strongyloides* spp. larvae (charcoal culture).

Strongyloides spp. infection (SI) was also investigated by means of serologic assay (*Strongyloides* serology microwell enzyme-linked immunosorbent assay (ELISA; Scidmex, the Hague, the Netherlands). The test was deemed positive if the index (ratio of optical density measurement of the sample) was higher than 1.1.

Hepatitis virus and HIV. A blood sample was analyzed for antibodies against the surface antigen (Elecsys HBsAg II, Roche diagnostics, Mannheim, Germany) and anti-core antibodies (Elecsys HBcAc, Roche diagnostics) for hepatitis B, and antibodies against hepatitis C by chemiluminescence immunoassay from 2011 to 2012 VITROS anti-hepatitis C virus assay (Ortho Clinical Diagnostics Inc., High Wycombe, United Kingdom), and from 2012 to 2015 Cobas anti HCV® (Roche diagnostics). Viral load was performed for all patients testing positive in any of the aforementioned tests for hepatitis (for HCV COBAS® AmpliPrep/COBAS® Taqman® HCV Test v2.0, and for HBV COBAS® AmpliPrep/COBAS® Taqman® HBV Test v2.0, Roche diagnostics). HIV was discarded by a fourth-generation ELISA (Enzygnost HIV Integral II, Siemens, Marburg, Germany) and diagnosis confirmed by viral load test (NASBA method Nuclisens EasyQ HIV–1, Biomerieux®, Marcy l'Etoile, France).

***Treponema pallidum* spp.** A sequential two-step algorithm was used. First, a treponemic assay was performed by enzyme immunoassay (EIA; Enzygnost Syphilis, Siemens). Reactive specimens were tested by rapid plasma reagin and treponema pallidum hemagglutination assay (TPHA) tests. Discordant EIA and TPHA results were resolved using and fluorescent treponemal antibody absorption test. Patients were classified based on the results and the anamnesis in primary, secondary, latent, and cured infection (serological scar).

Human T-cell lymphotropic virus. Serum sample was tested for human T-cell lymphotropic virus (HTLV) antibodies (EIA Murex HTLV I+II; Diasorin, Saluggia, Italy). The seropositivity for HTLV was confirmed by line immunoassay (INNO-LIA HTLVI/II Score; Innogenetics, Zwijnaarde, Belgium).

Latent tuberculosis infection. When possible, patients were evaluated with both the tuberculin skin test (TST) and one interferon gamma release assay (IGRA; Quantiferon®-TB Gold In-Tube, Cellestis, Victoria, Australia). Latent tuberculosis infection was considered when one of the tests was positive (TST > 5 mm; interpretation of the IGRA results were done according to the manufacturer instructions. We considered the indeterminate results as positive). Anamnesis, sputum samples, and chest X-ray were used to discard active pulmonary tuberculosis.

***Toxoplasma* spp.** Immunoglobulin G against *Toxoplasma gondii* was detected through an ELISA (Enzygnost Toxoplasmosis IgG, Siemens).

Other diseases were evaluated according to geographic distribution of the disease.

***Plasmodium* infection.** A real-time polymerase chain reaction (RT-PCR) of *Plasmodium* spp. and four different species (*Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium ovale*, and *Plasmodium malariae*) was performed using Taqman according to Rougemont and others in patients that were living for at least 1 month in a malaria-risk area at any time.[10]

***Schistosoma* spp.** Patients from sub-Saharan Africa, south Asia, Caribbean region, and the north of Brazil were screened for schistosomiasis with a *Schistosoma mansoni* serology (Novagnost *S. mansoni* IgG, Siemens, Germany). When the serology was positive, the feces samples were also re-examined for *S. mansoni*, *Schistosoma intercalatum* ova, and others. Moreover, all patients from sub-Saharan Africa collected, after a mild exercise (climbing stairs), a urine sample that was processed through urine concentration technique to detect eggs of *Schistosoma haematobium*.

***Trypanosoma cruzi* infection.** All patients from Latin America were screened for CD, with the exception of patients coming from the Caribbean islands. The diagnosis of the disease was based on two positive serological ELISA test, one with recombinant antigen (Bioelisa Chagas, Biokit, Lliçà d'Amunt, Spain) and the other with crude antigen (Ortho *T. cruzi* ELISA; Johnson and Johnson, High Wycombe, United Kingdom). Furthermore, *T. cruzi* DNA was assessed in the peripheral blood by qualitative PCR when both ELISA tests were positive. RT-PCR assay was performed according to Piron and others.[11]

***Leishmania* spp.** Previous infection by *Leishmania* spp. was ruled out through serological test (Novagnost Leishmania sp IgG, Siemens, Germany). It was studied in patients from Latin America, north Africa, Middle East, and Asia with compatible epidemiological context.

Dimorphic fungi. A serological test covering *Coccidioides* spp., *Paracoccidioides* spp., and *Histoplasma* spp. (Ouchterlony double immunodiffusion technique) was performed in patients from Latin America, sub-Saharan Africa and some regions of Asia with compatible epidemiological context.

Ethical considerations. The study protocol was approved by the Ethical Review Board of Vall d'Hebron University Hospital. All patients received oral and written information of the study and signed the informed consent. Procedures were in accordance with the ethical standards laid down in Helsinki Declaration, as revised in 2000.

Statistical analysis. Data were analyzed with IBM® SPSS® Statistics (v.21.0.0.0) software (IBM, Armonk, NY). Median and interquartile range were calculated for quantitative variables; frequencies and percentages were calculated for qualitative variables. Analysis for comparing variables associated with the risk of any latent or imported infection was performed using Student's t test or Mann–Whitney U test for quantitative variables and χ^2 test or Fisher's test for qualitative variables when appropriate. Risk of reactivation and time to reactivation according to screening results were estimated with a proportional risk regression. Multiple comparison corrections were performed. Tests were considered significant when two-tailed P value was < 0.05.

RESULTS

Forty-seven patients were offered to participate and a total of 42 patients were finally included in the study. Of the five patients not included, one patient died of his underlying condition before the samples could be collected, two patients were transferred to other centers on their request, one patient declined to participate in the study, and one had a known HIV infection.

The median age of the study cohort was 39 (31–51) years. Twenty-five (59. 5%) patients were women. More than half of the patients were of Latin American origin. Thirty-three out of 42 patients were diagnosed of oncohematologic diseases in the host country, whereas nine had traveled from their country of origin to receive specific treatment. The underlying diseases of the study cohort are described in Table 2. One-third of the patients were screened before the immunosuppressive therapy was started or were on it for less than 1 month. Sixteen patients (38.1%) underwent HSCT, 12 of them being allogenic. The most frequent disease in patients receiving HSCT was acute leukemia, followed by multiple myeloma, lymphoma, chronic myeloid leukemia, and severe aplastic anemia.

When all the imported or latent infections (syphilitic serological scar, *Blastocystis hominis*, and *Entamoeba coli* were not included in the analysis) were taken into account, 71.4% of the patients had at least one positive result. Results according to the country of origin of the patients are shown in Table 3. Patients with at least one positive result in the screening did not show any statistically significant association with the studied variables (Table 4).

During the follow-up, one patient with positive *Toxoplasma* spp. serology suffered a disseminated toxoplasmosis with fatal consequences shortly after the transplantation. We did not find any reactivation of the treated latent infections. All treatments for the latent infections were well tolerated. We did not find important side effects, even for the 6-month treatment with isoniazid for the latent tuberculous infection. There were 10 deaths, seven due to underlying disease progression, and three due to infectious complications, including the patient with disseminated toxoplasmosis. Two patients were transferred or lost to follow-up.

TABLE 2
Baseline characteristics of the study cohort ($N = 42$)

Age (years), median	39 (31, 51)
Sex (male)	25 (59.5%)
Geographical area of origin	
Latin America	24 (57.1%)
Sub-Saharan Africa	7 (16.7%)
North Africa and Middle East	7 (16.7%)
Asia	4 (9.5%)
Time from arrival to diagnosis (days)	
Diagnosis after arrival ($N = 33$)	3,465 (1751,4444)
Diagnosis before arrival ($N = 9$)	−909 (−2998, −164)
Time from arrival to screening (days)	2266 (483,4355)
Time from diagnosis to screening (days)	72 (9,728)
Infectious symptoms at screening	5 (11.9%)
Underlying disease	
Acute leukemia	10 (23.8%)
Lymphoma	10 (23.8%)
Multiple myeloma	5 (11.9%)
ITP or IHA	4 (9.5%)
Chronic myeloid leukemia	2 (4.8%)
Severe aplastic anemia	1 (2.4%)
Hemophagocytic syndrome	1 (2.4%)
Solid tumor	9 (21.4%)
Eosinophils count $> 700 \times 10^9$/L	3 (7.1%)
< 1 month of immune suppressive treatment before screening	14 (33.3%)
Use of steroids	20 (47.6%)
Hematopoietic stem cell transplantation	16 (38.1%)
Allogeneic (donor)	8
Allogeneic (umbilical cord)	4
Autologous	4
Patients with at least one infection including *Toxoplasma* sp.*	30 (71.4%)

ITP = immune thrombocytopenia; IHA = immune hemolytic anemia. Quantitative variables are shown as total number and frequencies and qualitative data are shown as median and interquartile range.
*Syphilitic serological scar, *Blastocystis hominis*, and *Entamoeba coli* were not included in the analysis.

DISCUSSION

This is a prospective study that screens imported or latent infections in a cohort of patients with underlying oncohematologic diseases. We studied 42 patients from different origins and found that more than half of the patients had a latent imported infectious disease susceptible of being treated or closely followed up. Although one patient suffered a disseminated toxoplasmosis, we did not find any reactivation in imported infections that received treatment.

Migrant population from developing countries is increasingly growing in many countries. When attending patients susceptible to receiving immunosuppressive treatment or chemotherapy, it is important to assess their country of birth and travel history, since many neglected diseases are inalienably associated with poverty and thus more frequent in developing countries. Physicians in developed countries are not used to deal with some of these neglected diseases, so it is important to highlight their potential to cause devastating consequences in patients with immunosuppressive treatment and design protocols to help physicians. Many medical guidelines agree to screen for infectious diseases, including neglected diseases according to place of birth and travel history before immunosuppressive therapy is started.[9,12]

Data regarding SI in patients with hematological dyscrasias, solid organ transplantation, or solid organ cancer are scant, yet it is by far the most reported. In our cohort, 8.8% of the patients had a SI, similar prevalences have been described in endemic countries in patients with solid or hematological malignancies.[13–16] In a study performed on healthy migrants, detection of SI using only microscopic methods was 3.25%.[17] Fortunately, serologic methods have shown to improve the diagnosis of SI.[18–21] SI can be a lifelong infection and patients

TABLE 3
Imported or latent infections of the study cohort according to geographic area

	Total	Latin America	Sub-Saharan Africa	North Africa and Middle East	Asia
Human immunodeficiency virus	1/42 (2.4%)	0/24	1/7 (14.3%)	0/7	0/4
Hepatitis C infection	3 (7.1%)	0/24	1/7 (14.3%)	1/7 (14.3%)	1/4 (25%)
Hepatitis B infection					
HBsAg (+) and anti-HBc (+)	1 (2.4%)	0/24	0/7	0/7	1/4 (25%)
HBsAg (−) and anti-HBc (+)	9 (21.4%)	0/23	6/7 (85.7%)	2/7 (28.6%)	0/4
Human T-cell lymphotropic virus-1	1/18 (5.6%)	1/8 (12.5%)	0/6	0/2	0/2
Strongyloides stercoralis (by any mean)	3/34 (8.8%)	3/21 (14.3%)	0/7	0/6	0/3
Schistosomiasis (serologic results)	0/14	0/5	0/7	N/A	0/1
Parasites in feces (other than *Strongyloides*)					
Blastocystis hominis	5/33 (15.2%)	4/20 (20%)	1/7 (14.3%)	0/5	0/3
Entamoeba coli	1/33 (3%)	0/20	1/7 (14.3%)	0/5	0/3
Treponema pallidum infection					
Latent syphilis	1/39 (2.6%)	1/22 (4.5%)	0/6	0/7	0/4
Syphilitic serological scar	3/39 (7.7%)	2/22 (9.1%)	0/6	1/7 (17.3%)	0/4
Latent tuberculosis infection*	13/36 (36.1%)	4/19 (21.1%)	4/7 (57.4%)	5/7 (71.4%)	0/3
Toxoplasma (positive IgG serology)	21/35 (60%)	13/21 (61.9%)	4/4 (100%)	4/6 (66.7%)	0/4
Chagas disease	2/20 (10%)	2/20 (10%)	N/A	N/A	N/A
Dimorphic fungus	0/20	0/18	0/2	N/A	N/A
Leishmania	0/23	0/13	0/4	0/4	0/2
Malaria	0/21	0/13	0/6	N/A	0/2

HBsAg = Hepatitis B surface antigen; anti-HBc = hepatitis B core antibody; N/A = not applicable. Quantitative variables are shown as total number and frequencies.
*Any positive purified protein derivative or interferon gamma release assay was considered as latent tuberculosis infection. Interferon gamma release assays indeterminate results were considered positive. PPDs were considered positive if the induration was higher than 5 mm.

are usually asymptomatic. Notwithstanding, when an immunosuppressive condition misbalances the host–parasite equilibrium, a fatal disseminated infection may occur with a mortality rate approaching 90%.[3,22] Usually, a delay of 2–5 months is seen between the diagnosis of *Strongyloides* spp.-disseminated infection and the initiation of the immunosuppressive therapy.[2] In a prospective study carried out in Brazil, an incidence of 7% was seen in patients with hematological diseases.[23] Despite this, not all immunosuppressive conditions have the same risk of triggering a disseminated infection.[19] Some therapies, such as steroids, have been widely associated with disseminated SI. Other immunosuppressive agents, such as cyclosporine and tacrolimus, may also increase the risk of disseminated infection. Of course, autologous and allogenic bone marrow transplantation constituted a highly hazardous situation to develop disseminated SI. Many clinicians rely on eosinophil count to rule out nematode infection, yet patients with hematological conditions or with previous corticoid therapy may have a reduced eosinophil count.[2,24] In our experience, all patients with positive microscopic diagnosis of SI were detected by serologic tests, and despite the small number of patients, we think serologic test can be used as the only test. However, by doing this, other intestinal parasite infections may go undetected.

Schistosoma spp. infection is prevalent in many countries of the world, but the main burden of the disease is found in sub-Saharan Africa. Severe visceral involvement due to *Schistosoma* spp. has been previously described in patients under chemotherapy.[1] Moreover, chemotherapy may reduce the amount of excreted eggs by the parasite, hindering the diagnosis of the disease.[25] The screening may detect the disease before the initiation of the chemotherapy and specific treatment may avert any severe complication.

Patients with an asymptomatic *T. cruzi* infection can develop an acute Chagas reactivation with positive parasitemia in peripheral blood if they undergo immunosuppressive therapy. Acute Chagas reactivation can be fatal if untreated, with myocarditis and meningoencephalitis being the most fearful complications. As with other parasitic infections, a malignant hematological condition is a trigger for an acute Chagas reactivation.[26] A reactivation rate of 27.3% was seen in a prospective study in patients undergoing bone marrow transplantation.[27] However, how to tackle a patient with chronic *T. cruzi* infection who is under immunosuppressive therapy is still a matter of debate.[28] In our case, we decided to treat patients with benznidazole and perform close *T. cruzi* PCR monitoring to promptly diagnose a reactivation.

Other intracellular parasites such as *Toxoplasma* spp. and *Leishmania* spp. can also cause reactivations in immunocompromised patients. Reports of disseminated *Leishmania* spp. infection in patients with oncohematologic diseases have been described.[29] Incidence of disseminated toxoplasmosis is 1.4/100 bone marrow transplantations. Unfortunately, most of the diagnoses are made in the necropsy, as it was in our study. The positivity of the serological tests indicating

TABLE 4
Result of the screening according with epidemiological and clinical characteristics

	Negative screening ($N = 12$)	Positive screening ($N = 30$)	P value
Sub-Saharan Africa origin	0 (0%)	7 (23.3%)	0.164
Sex, Male	8 (66.7%)	17 (56.7%)	0.731
Steroid use	6 (50%)	14 (46.7%)	> 0.99
< 1 month of therapy	4 (33.3%)	10 (33.3%)	> 0.99
Age (years)	33 (26–46.75)	42 (34–55.75)	0.733
Days from arrival to screening	1897 (410–3501.5)	3533.5 (482.75–4396.25)	0.306

Toxoplasma spp. infection and a high degree of immunosuppression are key factors implicated with an increased risk of *Toxoplasma* spp. infection.[30] Nonetheless, a high level of suspicion is needed to initiate the treatment in a timely manner. *Toxoplasma* spp. PCR may help to identify patients at high risk of reactivation,[31] however, further research is needed. To date, standard recommendations are hard to perform, nevertheless, we plead that the knowledge of the serological status may enhance the alertness of physicians.

In Europe, *Histoplasma* spp. cases are due to reactivations of latent infections in patients coming from endemic countries.[32,33] *Histoplasma* spp. occurs mainly in immunosuppressed patients, with a mortality rate of about 6%.[34] Severe infections have been associated with steroid use and the burden of the disease.[35] Currently, there is no proper diagnostic test to use as screening for *Histoplasma* spp. latent infection. Serological studies have high specificity at the expense of a low sensitivity.[36] Other dimorphic fungus infections have been reported in HSCT recipients.[37,38]

In our study, we assessed patients at risk of asymptomatic malaria with peripheral *Plasmodium* spp. PCR. We are aware of the rarity of this event in migrant population, but reactivation, especially of non-*P. falciparum*, has been described in immunocompetent patient many years after their arrival. We did not find any patient with malaria infection, but due to its potential for causing severe complications, we think it should be ruled out in patients who had been living in a high-incidence malaria area.

Our research has some limitations. Although, the number of patients is small and they are coming from different countries and socioeconomic backgrounds, we think the results are representative of the migrant population found in many European countries. We are aware that the grade of immunosuppressant therapy varies extensively among the study cohort. However, 16 patients in the study underwent HSCT, which is considered as one of the most immunosuppressive conditions. Also, some patients in our study were under immunosuppressive treatment long before screening was performed; we think that this fact could reduce our chances of finding latent imported diseases because patients with latent infection could have had lethal reactivations shortly after the initiation of the chemotherapy, and thus not being included in our cohort. Despite reactivation of a latent imported disease can occur at any time, we think that 1 year is a cautious follow-up time. We are aware that the diagnostic methods used in immunocompetent patients may work differently in immunosuppressed patients.[25]

Some diagnostic tests, such as *Leishmania* spp. serology and dimorphic fungi serologies, are of limited access in many settings. In addition to the above, their power to predict reactivation in immunosuppressed patients is unknown. We included them in the study because of research purposes; however, we recommend using them with caution.

To date, the screening of the migrant population previous to the initiation of immunosuppressive therapy is highly recommendable, but scantly performed. Physicians should be aware of the lethal potential of many of the latent imported disease if reactivation occurred. However, not all of the latent imported diseases have the same world prevalence or reactivation potential. We think that some diseases deserve special attention because their diagnoses are simple and highly reliable, and their treatments are safe and effective. In our opinion, SI, *T. cruzi* infection, and *Schistosoma* spp. infection meet these conditions.

The screening for HIV, hepatitis, and tuberculosis infection in the immunosuppressed patients is recommended beyond any doubt. Concerning tuberculosis infection screening, there is still no consensus on what diagnostic strategy should be followed.

In summary, our study detected a high rate of latent imported infection in migrant patients with oncohematologic diseases. After specific treatment of the latent imported infections, we did not observe any reactivation. Screening for latent imported infections previous to an immunosuppressive treatment is easy to perform and it may be lifesaving. The cost-effectiveness of this screening strategy should be further investigated.

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REFERENCES

1. de Górgolas M, Casado V, Renedo G, Alen JF, Fernández Guerrero ML, 2009. Nodular lung schistosomiais lesions after chemotherapy for dysgerminoma. *Am J Trop Med Hyg 81:* 424–427.
2. Aydin H, Doppl W, Battmann A, Bohle RM, Klör HU, 1994. Opportunistic *Strongyloides stercoralis* hyperinfection in lymphoma patients undergoing chemotherapy and/or radiotherapy—report of a case and review of the literature. *Acta Oncol 33:* 78–80.
3. Wirk B, Wingard JR, 2009. *Strongyloides stercoralis* hyperinfection in hematopoietic stem cell transplantation. *Transpl Infect Dis Off J Transplant Soc 11:* 143–148.
4. Eurostat, 2015. *Migration and Migrant Population Statistics: Statistics Explained*. Available at: http://ec.europa.eu/eurostat/statistics-explained/index.php/Migration_and_migrant_population_statistics. Accessed September 2, 2015.
5. *Sección Prensa/Cifras Oficiales de Población. Explotación Estadística del Padrón*. Available at: http://www.ine.es/prensa/padron_prensa.htm. Accessed August 27, 2015.
6. McDermott S, Desmeules M, Lewis R, Gold J, Payne J, Lafrance B, Vissandjée B, Kliewer E, Mao Y, 2010. Cancer incidence among Canadian immigrants, 1980–1998: results from a national cohort study. *J Immigr Minor Health 13:* 15–26.
7. Vázquez M-L, Terraza-Núñez R, Vargas I, Rodríguez D, Lizana T, 2011. Health policies for migrant populations in three European countries: England; Italy and Spain. *Health Policy Amst Neth 101:* 70–78.
8. Kindwall-Keller T, Isola LM, 2009. The evolution of hematopoietic SCT in myelodysplastic syndrome. *Bone Marrow Transplant 43:* 597–609.
9. Tomblyn M, Chiller T, Einsele H, Gress R, Sepkowitz K, Storek J, Wingard JR, Young JA, Boeckh MJ, Center for International Blood and Marrow Research, National Marrow Donor program, European Blood and Marrow Transplant Group,

American Society of Blood and Marrow Transplantation, Canadian Blood and Marrow Transplant Group, Infectious Diseases Society of America, Society for Healthcare Epidemiology of America, Association of Medical Microbiology and Infectious Disease Canada, Centers for Disease Control and Prevention, 2009. Guidelines for preventing infectious complications among hematopoietic cell transplantation recipients: a global perspective. *Biol Blood Marrow Transplant 15:* 1143–1238.

10. Rougemont M, Van Saanen M, Sahli R, Hinrikson HP, Bille J, Jaton K, 2004. Detection of four *Plasmodium* species in blood from humans by 18S rRNA gene subunit-based and species-specific real-time PCR assays. *J Clin Microbiol 42:* 5636–5643.
11. Piron M, Fisa R, Casamitjana N, López-Chejade P, Puig L, Vergés M, Gascón J, Gómez i Prat J, Portús M, Sauleda S, 2007. Development of a real-time PCR assay for *Trypanosoma cruzi* detection in blood samples. *Acta Trop 103:* 195–200.
12. *Protocols Clinicos SEIMC*. seimc-procedimientoclinicox.pdf. Available at: http://www.seimc.org/contenidos/documentoscientificos/procedimientosclinicos/seimc-procedimientoclinicox.pdf. Accessed September 4, 2015.
13. Khalil HM, Makled MK, Azab ME, Abdalla HM, el Sherif EA, Nassef NS, 1991. Opportunistic parasitic infections in immunocompromised hosts. *J Egypt Soc Parasitol 21:* 657–668.
14. Graeff-Teixeira C, Leite CS, Sperhacke CL, Fassina K, Petry SM, Mucenic T, Pandolfi C, Barcellos S, Job F, 1997. Prospective study of strongyloidosis in patients with hematologic malignancies. *Rev Soc Bras Med Trop 30:* 355–357.
15. Guarner J, Matilde-Nava T, Villaseñor-Flores R, Sanchez-Mejorada G, 1997. Frequency of intestinal parasites in adult cancer patients in Mexico. *Arch Med Res 28:* 219–222.
16. Schaffel R, Nucci M, Portugal R, Castro MB, Ferreira SB, Almeida L, Spector N, Pulcheri W, 2000. Thiabendazole for the treatment of strongyloidiasis in patients with hematologic malignancies. *Clin Infect Dis Off Publ Infect Dis Soc Am 31:* 821–822.
17. Bocanegra C, Salvador F, Sulleiro E, Sánchez-Montalvá A, Pahissa A, Molina I, 2014. Screening for imported diseases in an immigrant population: experience from a teaching hospital in Barcelona, Spain. *Am J Trop Med Hyg 91:* 1277–1281.
18. Salvador F, Sulleiro E, Sánchez-Montalvá A, Saugar JM, Rodríguez E, Pahissa A, Molina I, 2014. Usefulness of *Strongyloides stercoralis* serology in the management of patients with eosinophilia. *Am J Trop Med Hyg 90:* 830–834.
19. Salvador F, Molina I, Sulleiro E, Burgos J, Curran A, Van den Eynde E, Villar del Saz S, Navarro J, Crespo M, Ocaña I, Ribera E, Falcó V, Pahissa A, 2013. Tropical diseases screening in immigrant patients with human immunodeficiency virus infection in Spain. *Am J Trop Med Hyg 88:* 1196–1202.
20. Schaffel R, Portugal R, Maiolino A, Nucci M, 2004. Strongyloidiasis pre and post autologous peripheral blood stem cell transplantation. *Bone Marrow Transplant 33:* 117.
21. Schaffel R, Nucci M, Carvalho E, Braga M, Almeida L, Portugal R, Pulcheri W, 2001. The value of an immunoenzymatic test (enzyme-linked immunosorbent assay) for the diagnosis of strongyloidiasis in patients immunosuppressed by hematologic malignancies. *Am J Trop Med Hyg 65:* 346–350.
22. Igra-Siegman Y, Kapila R, Sen P, Kaminski ZC, Louria DB, 1981. Syndrome of hyperinfection with *Strongyloides stercoralis*. *Rev Infect Dis 3:* 397–407.
23. Portugal R, Schaffel R, Almeida L, Spector N, Nucci M, 2002. Thiabendazole for the prophylaxis of strongyloidiasis in immunosuppressed patients with hematological diseases: a randomized double-blind placebo-controlled study. *Haematologica 87:* 663–664.
24. Machado ER, Carlos D, Sorgi CA, Ramos SG, Souza DI, Soares EG, Costa-Cruz JM, Ueta MT, Aronoff DM, Faccioli LH, 2011. Dexamethasone effects in the *Strongyloides venezuelensis* infection in a murine model. *Am J Trop Med Hyg 84:* 957–966.
25. Montes M, White AC, Kontoyiannis DP, 2004. Symptoms of intestinal schistosomiasis presenting during treatment of large B cell lymphoma. *Am J Trop Med Hyg 71:* 552–553.
26. Metze K, Lorand-Metze I, De Almeida EA, De Moraes SL, 1991. Reactivation of Chagas' myocarditis during therapy of Hodgkin's disease. *Trop Geogr Med 43:* 228–230.
27. Altclas J, Sinagra A, Dictar M, Luna C, Verón MT, De Rissio AM, García MM, Salgueira C, Riarte A, 2005. Chagas disease in bone marrow transplantation: an approach to preemptive therapy. *Bone Marrow Transplant 36:* 123–129.
28. Pérez-Molina JA, Perez AM, Norman FF, Monge-Maillo B, López-Vélez R, 2015. Old and new challenges in Chagas disease. *The Lancet Infect Dis 15:* 1347–56.
29. Fakhar M, Asgari Q, Motazedian MH, Monabati A, 2008. Mediterranean visceral leishmaniasis associated with acute lymphoblastic leukemia (ALL). *Parasitol Res 103:* 473–475.
30. de Medeiros BC, de Medeiros CR, Werner B, Loddo G, Pasquini R, Bleggi-Torres LF, 2001. Disseminated toxoplasmosis after bone marrow transplantation: report of 9 cases. *Transpl Infect Dis Off J Transplant Soc 3:* 24–28.
31. Edvinsson B, Lundquist J, Ljungman P, Ringdén O, Evengård B, 2008. A prospective study of diagnosis of *Toxoplasma gondii* infection after bone marrow transplantation. *APMIS 116:* 345–351.
32. Ashbee HR, Evans EGV, Viviani MA, Dupont B, Chryssanthou E, Surmont I, Tomsikova A, Vachkov P, Enero B, Zala J, Tintelnot K, ECMM Working Group on Histoplasmosis, 2008. Histoplasmosis in Europe: report on an epidemiological survey from the European Confederation of Medical Mycology Working Group. *Med Mycol 46:* 57–65.
33. Adderson EE, 2004. Histoplasmosis in a pediatric oncology center. *J Pediatr 144:* 100–106.
34. Assi MA, Sandid MS, Baddour LM, Roberts GD, Walker RC, 2007. Systemic histoplasmosis: a 15-year retrospective institutional review of 111 patients. *Medicine (Baltimore) 86:* 162–169.
35. Vergidis P, Avery RK, Wheat LJ, Dotson JL, Assi MA, Antoun SA, Hamoud KA, Burdette SD, Freifeld AG, McKinsey DS, Money ME, Myint T, Andes DR, Hoey CA, Kaul DA, Dickter JK, Liebers DE, Miller RA, Muth WE, Prakash V, Steiner FT, Walker RC, Hage CA, 2015. Histoplasmosis complicating tumor necrosis factor–α blocker therapy: a retrospective analysis of 98 cases. *Clin Infect Dis 61:* 409–417.
36. Kauffman CA, 2008. Diagnosis of histoplasmosis in immunosuppressed patients. *Curr Opin Infect Dis 21:* 421–425.
37. Glenn TJ, Blair JE, Adams RH, 2005. Coccidioidomycosis in hematopoietic stem cell transplant recipients. *Med Mycol 43:* 705–710.
38. Blair JE, Smilack JD, Caples SM, 2005. Coccidioidomycosis in patients with hematologic malignancies. *Arch Intern Med 165:* 113–117.