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

Adrián Sánchez-Montalvá,1* Fernando Salvador,1 Isabel Ruiz-Camps,1 Pere Barba,2 David Valcárcel,1 Elena Sulleiro,3 Enrique Sanz-García,4 and Israel Molina1

1Infectious Disease Department, Vall d’Hebron University Hospital, PROSICS Barcelona, Universitat Autònoma de Barcelona, Barcelona, Spain; 2Hematological Department, Vall d’Hebron University Hospital, Universitat Autònoma de Barcelona, Barcelona, Spain; 3Microbiology Department, Vall d’Hebron University Hospital, PROSICS Barcelona, Universitat Autònoma de Barcelona, Barcelona, Spain; 4Medical Oncology Department, Vall d’Hebron University Hospital, Universitat Autònoma de Barcelona, Barcelona, Spain

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, Trypanosoma cruzi, 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 pauci-symptomatic 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.5 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
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 HBeAg, Roche diagnostics) for hepatitis B, and antibodies against hepatitis C by chemiluminescence immunoassay from 2011 to 2012 VITROS anti-hepatitis C and antibodies against hepatitis C by chemiluminescence immunoassay (Elecsys HBcAg, Roche diagnostics) for hepatitis B, and antibodies against hepatitis C by chemiluminescence immunoassay.

**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.

**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, sub-Saharan Africa, Middle East, and 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 χ² 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.

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

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**Table 2**

Baseline characteristics of the study cohort (N = 42)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Count (Percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), median</td>
<td>39 (31, 51)</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>25 (59.5%)</td>
</tr>
<tr>
<td>Geographical area of origin</td>
<td></td>
</tr>
<tr>
<td>Latin America</td>
<td>24 (57.1%)</td>
</tr>
<tr>
<td>Sub-Saharan Africa</td>
<td>7 (16.7%)</td>
</tr>
<tr>
<td>North Africa and Middle East</td>
<td>7 (16.7%)</td>
</tr>
<tr>
<td>Asia</td>
<td>4 (9.5%)</td>
</tr>
<tr>
<td>Time from arrival to diagnosis (days)</td>
<td></td>
</tr>
<tr>
<td>Diagnosis after arrival (N = 33)</td>
<td>3,465 (1751,4444)</td>
</tr>
<tr>
<td>Diagnosis before arrival (N = 9)</td>
<td>−909 (~2998, −164)</td>
</tr>
<tr>
<td>Time from arrival to screening (days)</td>
<td>2266 (483,4355)</td>
</tr>
<tr>
<td>Time from diagnosis to screening (days)</td>
<td>72 (9,728)</td>
</tr>
<tr>
<td>Infectious symptoms at screening</td>
<td>5 (11.9%)</td>
</tr>
<tr>
<td>Underlying disease</td>
<td></td>
</tr>
<tr>
<td>Acute leukemia</td>
<td>10 (23.8%)</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>10 (23.8%)</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>5 (11.9%)</td>
</tr>
<tr>
<td>ITP or IHA</td>
<td>4 (9.5%)</td>
</tr>
<tr>
<td>Chronic myeloid leukemia</td>
<td>2 (4.8%)</td>
</tr>
<tr>
<td>Severe aplastic anemia</td>
<td>1 (2.4%)</td>
</tr>
<tr>
<td>Hemophagocytic syndrome</td>
<td>1 (2.4%)</td>
</tr>
<tr>
<td>Solid tumor</td>
<td>9 (21.4%)</td>
</tr>
<tr>
<td>Eosinophils count &gt; 700 x 10⁹/L</td>
<td>3 (7.1%)</td>
</tr>
<tr>
<td>&lt; 1 month of immune suppressive treatment</td>
<td>14 (33.3%)</td>
</tr>
<tr>
<td>Use of steroids</td>
<td></td>
</tr>
<tr>
<td>Use of steroids</td>
<td>20 (47.6%)</td>
</tr>
<tr>
<td>Hematopoietic stem cell transplantation</td>
<td>16 (38.1%)</td>
</tr>
<tr>
<td>Allogeneic (donor)</td>
<td>8</td>
</tr>
<tr>
<td>Allogeneic (umbilical cord)</td>
<td>4</td>
</tr>
<tr>
<td>Autologous</td>
<td>4</td>
</tr>
<tr>
<td>Patients with at least one infection including Toxoplasma sp.(^a)</td>
<td>30 (71.4%)</td>
</tr>
</tbody>
</table>

\(^a\) Syphilitic serological scar, Blastocystis hominis, and Entamoeba coli were not included in the analysis.
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%. Usually, a delay of 2–5 months is seen between the diagnosis of Strongyloides spp.-disseminated infection and the initiation of the immunosuppressive therapy.

In a prospective study carried out in Brazil, an incidence of 7% infections constituted a highly hazardous situation to develop disseminated SI. Of course, autologous and allogenic bone marrow transplantation have been widely associated with disseminated SI. 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. A reactivation rate of 27.3% was seen in a prospective study in patients undergoing bone marrow transplantation. However, how to tackle a patient with chronic T. cruzi infection who is under immunosuppressive therapy is still a matter of debate. 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. 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 under chemotherapy. Moreover, chemotherapy may reduce the amount of excreted eggs by the parasite, hindering the diagnosis of the disease. 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. A reactivation rate of 27.3% was seen in a prospective study in patients undergoing bone marrow transplantation. However, how to tackle a patient with chronic T. cruzi infection who is under immunosuppressive therapy is still a matter of debate. In our case, we decided to treat patients with benznidazole and perform close T. cruzi PCR monitoring to promptly diagnose a reactivation.

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Toxoplasma spp. infection and a high degree of immunosuppression are key factors implicated with an increased risk of Toxoplasma spp. infection. 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, 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. Histoplasma spp. occurs mainly in immunosuppressed patients, with a mortality rate of about 6%. Severe infections have been associated with steroid use and the burden of the disease. 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. Other dimorphic fungus infections have been reported in HSCT recipients.

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.

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 recommended, but scanty 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.

REFERENCES


