Measles in bone marrow transplant recipients during an outbreak in São Paulo, Brazil

Clarisse M. Machado, Flávio B. Gonçalves, Cláudio S. Pannuti, Frederico L. Dulley, and Vanda A. U. F. de Souza

In 1997, a measles outbreak was identified in São Paulo. Between February and December, 20 185 cases were confirmed. From April to July 1997, a seroepidemiologic survey was conducted to identify the recipients of bone marrow (BM) transplants who were susceptible to measles and the occurrence of measles in this population. A total of 156 patients were screened by enzyme immunoassay (EIA). Patients with IgG titers more than 100 mL/mL were considered immune. Measles reimmunization records were also reviewed. Thirty-two vaccinated patients underwent serologic evaluation. Six of 22 patients (27.3%) within 3 years after vaccination lost measles immunity, in contrast to 7 of 10 patients (70%) vaccinated longer than 3 years previously (P = .049). Among the 122 nonvaccinated patients, 41 (33.6%) were susceptible to measles: 4 of 47 patients (8.5%) within the first year after BM transplantation (BMT), and 37 of the 75 patients (49.3%) after the first year after BMT (P < .001). Eight recipients acquired measles, confirmed by serology (EIA). High-avidity IgG antibodies were observed in the acute phase of measles, suggesting a secondary immune response. Measles interstitial pneumonia was observed in one patient. Seven patients had mild symptoms. Exanthema was present in all patients. All but one patient had fever and nonproductive cough. Koplik spots could be observed in 5 patients. Measles can be mild in BM transplant recipients. Exanthema is frequently present but not often typical. Immunity to measles decreases after day +365 after BMT. Additional studies are needed to evaluate the safety of measles vaccine after the first year of BMT, mostly during outbreaks. (Blood. 2002;99:83-87)
Serology
Measles IgM antibodies were detected by a monoclonal-based capture enzyme immunoassay (EIA), provided by the Centers for Diseases Control and Prevention.9
Measles IgG antibodies were detected by an in-house EIA. Standard serum (National Institute for Biological Standards and Control, Hertford, United Kingdom) was included in each set of tests for the estimation of antibody titers expressed in mIU/mL, which were calculated by a linear regression analysis. Patients with EIA titers more than 100 mIU/mL were considered immune to measles.10

In patients with measles, the IgG avidity test was performed using the urea method11 to characterize the type of infection, if primary or secondary. Briefly, after incubation with diluted serum for 1 hour at 37°C, the wells were washed twice with phosphate-buffered saline-Tween (PBST). Half the wells were soaked for 10 minutes with 7 M urea in PBS containing 0.05% Tween 80 (PBST) and half with PBST without urea. After 2 additional washes, the antibodies were detected by conventional EIA. The result for each serum, expressed as difference in optical density (ΔOD), was obtained by subtracting the absorbance of the control antigen from the absorbance of the measles virus antigen. The avidity index was calculated by (ΔOD with urea/ΔOD without urea) × 100 and a value of 30% or less was considered indicative of primary infection.

Statistical analysis
Statistical significance was determined using the χ² test.

Results
Patient characteristics

The study included 2 syngeneic BMTs, 25 autologous BMTs, and 129 allogeneic BMTs (one unrelated). The median age of the patients was 27 years (range, 4-58 years). At the evaluation for measles antibodies, 15 of the 129 allogeneic recipients were within the first 100 days after BMT and 10 of them (66.6%) had acute graft-versus-host disease (GVHD) grade 2 or higher. The remaining 114 had undergone BMT longer than 100 days previously and active chronic GVHD was present in 28 patients (24.5%). Twenty-six had extensive chronic GVHD and 2 had limited chronic GVHD. Among the 129 recipients of allogeneic transplants, 34 (26.4%) were receiving immunosuppressive drugs (prednisone or cyclosporin A or both; Table 1).

Vaccination and immunity to measles

Thirty-four patients had already received measles vaccination and 122 patients had not been vaccinated. Of the 122 not vaccinated, 76 were not eligible because they were less than 2 years from BMT, 8 were on immunosuppression regimens, and 38 were not compliant with the vaccines scheduled in the second year after BMT. During the outbreak, 32 of the 34 vaccinated patients underwent serologic evaluation by EIA and 13 (40.6%) were susceptible to measles despite previous vaccination. A significant loss of measles immunity was observed after the third year after vaccination. Only 6 of 22 patients (27.3%) who were vaccinated less than 3 years previously were deemed susceptible to measles (EIA titers ≤ 100, as previously defined), in contrast to 7 of 10 patients (70%) vaccinated 3 or more years previously. (Table 2, P = .049).

Among the 122 unvaccinated patients, 41 (33.6%) had antibodies titers lower than 100 mIU/mL. Only 4 of 47 (8.5%) patients in the first year after BMT were susceptible to measles, whereas 37 of 75 (49.3%) patients were susceptible after the first year after BMT (Table 3, P < .001). No statistical difference was observed between susceptibility to measles and type of transplant (allogeneic, syngeneic, or autologous), presence of acute or chronic GVHD, or the use of immunosuppressive drugs (Table 3).

Acquisition of measles and patient outcomes

Eight of the 54 susceptible patients (IgG titers ≤ 100) contracted measles, for an attack rate of 14.8%. Five had undetectable titers, whereas 2 had detectable titers less than 100 mIU/mL. The remaining patient was not tested at the start of the survey. This patient (Table 4, patient no. 8) had seroconverted after being vaccinated in 1994, but probably lost specific immunity and acquired measles. In the 7 unvaccinated patients, high-avidity IgG antibodies were observed in the acute phase of measles, suggesting a secondary immune response.

Two patients were within the first year after BMT and were not eligible for vaccination. Four patients had not been vaccinated due to lack of compliance and one due to chronic GVHD and use of immunosuppressive drugs until 3 months before acquiring measles (patient no.1). All patients who contracted measles were allogeneic transplant recipients. Chronic GVHD was present in patient no. 1 (limited GVHD) and in patient no. 6 (extensive GVHD). This patient was receiving cyclosporin A (300 mg) and prednisone (60 mg) every other day. Patient no. 7 had no chronic GVHD at evaluation and was tapering immunosuppressive drugs (cyclosporin A 200 mg) when he contracted measles.

All patients had coldlike prodomes. All patients but one had rash, which was generally mild, except in 3 adults, who
received a transplant longer than 3 years 6 months previously and who had typical rashes and higher fever. In younger patients (patients no. 4 and 7) the rash was mild and without desquamation. The only complication observed in the present series, measles interstitial pneumonia, was seen in patient no. 6 who had an extremely mild rash, only in the face, trunk, and arms, which faded in 18 hours. The latter patient was receiving cyclosporin A (300 mg) and prednisone (60 mg) every other day and was hospitalized for 5 days (Table 4). The patients received vitamin A, 400 000 IU, and in 2 patients receiving ongoing immunosuppression; Table 4).

### Discussion

Few data are available concerning the occurrence and the severity of measles in BMT recipients.3

The serologic survey that we conducted at the beginning of the outbreak showed that 91.5% of the unvaccinated patients within the first year after BMT retained measles immunity, whereas only 50.7% of the patients receiving a transplant longer than 1 year previously were immune to measles. These data confirm reported data about the persistence of host-derived humoral immunity for at least 6 months after grafting, fading thereafter.12 The persistence of host B cells producing antibodies, passively acquired antibodies via blood transfusion, and the stimulation of already precommitted memory B cells transferred from the donor may also contribute to the presence of specific antibodies after transplantation.12

Ljungman and coworkers observed a 27% probability of measles immunity in patients in the fifth year after BMT.13 Therefore, an increasing number of susceptible patients are expected after the first year after BMT and measles vaccination should be considered earlier for these patients, especially if an outbreak emerges in countries that have not achieved measles elimination.

No data are available concerning the safety and effectiveness of measles vaccination before the second year of BMT. Due to the potential risk of complications of live attenuated virus vaccines in the immunocompromised host,14 the safety and efficacy of measles vaccination have only been evaluated in patients not receiving immunosuppressive drugs and after the second year following BMT.5-6

Among the vaccinated patients, the serologic survey demonstrated that a significant loss of measles immunity occurred after the third year after vaccination (70% versus 27.3%), suggesting that serologic surveillance to check for immunity should be conducted in patients during long-term follow-up. Moreover, the value and the frequency of booster doses of measles vaccine in patients who lost measles immunity should be better investigated in this population.

Measles susceptibility among immunocompromised patients may not represent a major problem in countries that have achieved measles elimination and have maintained high levels of immunity among children. However, if measles virus recirculates and the numbers of susceptible persons are significant, an outbreak can emerge as happened in the city of São Paulo.

The impact of the outbreak in the BMT population could soon be observed. None of 100 patients with EIA titers more than 100 contracted measles. Among the 54 susceptible patients (13 vaccinated, 41 nonvaccinated), 8 acquired measles (measles attack rate = 14.8%). The number of cases could indeed have been higher because asymptomatic measles could have occurred but was not investigated in the present study. Among the patients in whom measles was confirmed, 7 were susceptible to measles (EIA \(\leq 100\) mIU/mL). The remaining patient was not tested at the beginning of the survey. An IgG titer more than 100 mIU/mL establishes immunity in immunocompetent hosts10 and we could

### Table 3. Measles serologic status in 122 nonvaccinated patients after BMT

<table>
<thead>
<tr>
<th>Time after BMT, y</th>
<th>Susceptible</th>
<th>Immune</th>
<th>Total</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\leq 1)</td>
<td>04 (8.5)</td>
<td>43 (91.5)</td>
<td>47 (100)</td>
<td></td>
</tr>
<tr>
<td>1-2</td>
<td>11 (36.6)</td>
<td>19 (63.3)</td>
<td>30 (100)</td>
<td></td>
</tr>
<tr>
<td>(\geq 2)</td>
<td>26 (57.7)</td>
<td>19 (42.3)</td>
<td>45 (100)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>41</td>
<td>81</td>
<td>122</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

- **Type of BMT**
  - Allogeneic
    - 37 (37.4)
    - 62 (62.6)
    - 99 (100)
  - Autologous or syngeneic
    - 06 (26.1)
    - 17 (73.9)
    - 23 (100)
  - Total
    - 43
    - 79
    - 122

- **Acute GVHD†**
  - Grade 1 or absent
    - 0 (0)
    - 5 (100)
    - 5 (100)
  - Grade \(\geq 2\)
    - 2 (20)
    - 8 (80)
    - 10 (100)
  - Total
    - 2
    - 13
    - 15

- **Chronic GVHD‡**
  - Absent
    - 27 (48.2)
    - 29 (51.8)
    - 56 (100)
  - Present
    - 10 (35.7)
    - 16 (64.3)
    - 26 (100)
  - Total
    - 37
    - 47
    - 84

- **Immunosuppressive drugs**
  - With
    - 10 (29.4)
    - 24 (70.6)
    - 34 (100)
  - Without
    - 27 (41.5)
    - 38 (58.5)
    - 65 (100)
  - Total
    - 37
    - 62
    - 99

**NS** indicates not significant.

*Refer to definition in text.

†In 84 allogeneic patients after day 100.

‡In 15 allogeneic patients within the first 100 days after BMT at evaluation.

### Table 4. Clinical findings in transplant recipients with measles

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age</th>
<th>BMT type</th>
<th>Time after BMT</th>
<th>GVHD at evaluation</th>
<th>GVHD treatment</th>
<th>Serologic status</th>
<th>Duration of rash</th>
<th>Koplik spots</th>
<th>Fever cough</th>
<th>IgM</th>
<th>IVIg</th>
<th>Complication</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>42</td>
<td>Allo</td>
<td>3 y 9 m</td>
<td>CL</td>
<td>None</td>
<td>Neg</td>
<td>7 d</td>
<td>No</td>
<td>Yes</td>
<td>Pos</td>
<td>Yes</td>
<td>None</td>
</tr>
<tr>
<td>2</td>
<td>28</td>
<td>Allo</td>
<td>6 y 9 m</td>
<td>None</td>
<td>None</td>
<td>Neg</td>
<td>12 d</td>
<td>Yes</td>
<td>Yes</td>
<td>Pos</td>
<td>No</td>
<td>None</td>
</tr>
<tr>
<td>3</td>
<td>25</td>
<td>Allo</td>
<td>3 y 1 m</td>
<td>None</td>
<td>None</td>
<td>&lt;100 mIU/mL</td>
<td>5 d</td>
<td>No</td>
<td>No</td>
<td>Pos</td>
<td>No</td>
<td>None</td>
</tr>
<tr>
<td>4</td>
<td>17</td>
<td>Allo</td>
<td>4 y 10 m</td>
<td>None</td>
<td>None</td>
<td>Neg</td>
<td>6 d</td>
<td>Yes</td>
<td>Yes</td>
<td>Pos</td>
<td>No</td>
<td>None</td>
</tr>
<tr>
<td>5</td>
<td>45</td>
<td>Allo</td>
<td>4 y 9 m</td>
<td>None</td>
<td>None</td>
<td>Neg</td>
<td>10 d</td>
<td>Yes</td>
<td>Yes</td>
<td>Neg</td>
<td>Yes</td>
<td>None</td>
</tr>
<tr>
<td>6</td>
<td>27</td>
<td>Allo</td>
<td>Day (+373)</td>
<td>CE</td>
<td>CyA/PDN</td>
<td>Neg</td>
<td>18 h</td>
<td>Yes</td>
<td>Yes</td>
<td>Pos</td>
<td>Yes</td>
<td>MIP</td>
</tr>
<tr>
<td>7</td>
<td>10</td>
<td>Allo</td>
<td>Day (+257)</td>
<td>No</td>
<td>CyA</td>
<td>100 mIU/mL</td>
<td>7 d</td>
<td>No</td>
<td>Yes</td>
<td>Pos</td>
<td>Yes</td>
<td>None</td>
</tr>
<tr>
<td>8</td>
<td>38</td>
<td>Allo</td>
<td>6 y 7 m</td>
<td>None</td>
<td>None</td>
<td>Not done</td>
<td>6 d</td>
<td>Yes</td>
<td>Yes</td>
<td>Neg</td>
<td>No</td>
<td>None</td>
</tr>
</tbody>
</table>

Allo indicates allogeneic; CL, chronic limited; CE, chronic extensive; MIP, measles interstitial pneumonia; CyA, cyclosporin A; PDN, prednisone; Pos, positive; and Neg, negative.
observe that this cut-off value is also valid in immunocompromised hosts.

The fact that all 7 unvaccinated patients had high-avidity antibodies, during the acute phase of measles (indicating secondary immune response), can explain the mild presentation of measles in this population as observed in secondary vaccine failures.15

A T-cell response seems also to be important for the control of an established infection as suggested by the occurrence of severe measles in immunocompromised patients.2 We did not evaluate the presence of specific T-cell immunity to measles but some studies have demonstrated that it can also persist16,17 and may also have contributed to the benign course of the infection in the present study.

Except for 2 patients, who were 10 and 17 years old, the other 6 patients were adults. In addition to their immunocompromised status, we expected that measles would be severe and with more complications because measles symptoms are more intense in adults.18 However, in the present series, we observed mild symptoms, slightly more intense in 3 patients who were older than 40 years and received their transplant longer than 3 years previously. Younger patients and those within the first year after BMT had an atypical presentation of measles, with low fever and subtle rash.

Concerning the measles presentation in immunocompromised patients, the atypical course of the disease related to the rash should be emphasized. The data reported in the literature and shown here suggest that the more immunosuppressed the patient, the more atypical and faint the rash. Therefore, susceptible patients within the first year after BMT are at greater risk of atypical and complicated measles. Clinicians should be aware that the rash may be absent and diagnosing measles in this situation is not an easy task. In addition, the presence of IgM antibodies can be of limited help. In 2 of the 8 patients (25%) who seroconverted or had a 4-fold IgG rise, IgM antibodies were absent. Polymerase chain reaction has been used to diagnose subacute measles encephalitis in immunocompromised hosts,19 but its value in diagnosing acute measles needs further studies.

Treatment of measles has been mainly supportive. Intravenous ribavirin has been used successfully in some circumstances,19 but its role in the treatment of measles has not been established. Many studies have shown that administration of high doses of vitamin A during the acute phase of measles decreases morbidity and mortality even in the absence of clinical evidence of vitamin A deficiency.20 The World Health Organization recommends high-dose vitamin A supplementation for all children with measles in countries where the fatality rate is 1% or higher.21 A dose of 400 000 IU for all ages has been advised.11 All patients received vitamin A, and IVIg was added in 4 cases. Nevertheless, their role could not be evaluated in the present series.

Live attenuated measles vaccination is indicated for susceptible immunocompetent hosts who have contact with a person with measles.22 In the setting of BMT, due to the limited use of live attenuated virus vaccines in patients undergoing immunosuppression, the alternative would be IVIg. The rational for administering IVIg to the susceptible patients is to provide adequate levels of antibodies to abort natural infection. However, the control of an outbreak can last several months and, consequently, IVIg would have to be administrated every 40 days for all susceptible patients until the end of the outbreak.

The high cost of this approach, in addition to an increasing number of transplant recipients acquiring measles and the observation of mild symptoms in patients exposed to the wild virus, led us to extend the use of the measles attenuated virus vaccine to all susceptible patients after the first year following BMT. The safety and effectiveness of such an approach are being evaluated in a prospective trial.

We concluded that measles is not necessarily a severe disease in transplant recipients. Most of the patients who acquired measles had high-avidity antibodies indicating secondary immune response and this fact can explain the benign course of measles observed in the majority of the patients in the present series. We concluded also that immunity to measles decreases after the first year following BMT. The cut-off level of IgG titers that establishes immunity in immunocompetent hosts (> 100 mIU/mL) is also valid in immunocompromised patients. Patients at long-term follow-up after BMT are more likely to lose specific immunity after the third year of measles vaccination. The need and the frequency of booster doses of measles vaccine should be better investigated in these transplant recipients.

Acknowledgments

We would like to thank the nurses (Isamar Ferreira Rocha and Beatriz B. Diomede) and the physicians (Carlos Dzik, Maria Cristina A. Macedo, Roberto L. Silva, Ronald P. Filho, and Rosaura Saboya) for excellent patient care.

References


Measles in bone marrow transplant recipients during an outbreak in São Paulo, Brazil