Figure. Pulsed-field gel electrophoresis (PFGE) banding patterns of chromosomal DNA of 26 isolates of vancomycin-resistant enterococci. There is a clear predominant type, classified as type A (≥80% similarity), composed of 18 isolates of Enterococcus faecium. There are at least 3 subtypes that display a 100% similarity.

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References

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Disseminated Bacillus Calmette-Guérin Infection and Immunodeficiency

To the Editor: Disseminated bacillus Calmette-Guérin (BCG) infection has been noted in patients with primary immunodeficiency. Incidence rates have ranged from 0.06 to 1.56 cases per million vaccinated, and mortality rates have remained at ≈60% (1–7). Of 946 patients with primary immunodeficiency, including 29 with severe combined immunodeficiencies, diagnosed from 1980 through 2006 at the Children’s Memorial Health Institute in Warsaw, adverse events after BCG vaccination were observed in 16 (8,9). All 16 were children who had been vaccinated at birth with BCG, Brazilian strain (Biomed, Lublin, Poland).

Four patients with severe combined immunodeficiency showed adverse reactions to BCG. Patient M.K. had mild inflammation at the site of the BCG injection and was successfully treated with rifampin. The patient subsequently received a bone marrow transplant, and 2 months later poor appetite, failure to thrive, and subfebrile condition were noted. Disseminated skin changes (with pus formation in the subcutaneous layer), osteomyelitis, and multiple lesions in the liver were found. A skin biopsy showed tuberculosis formations, which were PCR-positive for Mycobacterium tuberculosis complex (Amplified Myco-
bacterium Tuberculosis Direct [MTD] Test, Gen-Probe, Inc., San Diego, CA, USA) but had negative culture results. Complete recovery, including full immunologic reconstitution, was reached after 12 months of treatment with triple antituberculosis (TB) therapy (rifampin, isoniazid, and ciprofloxacin). Patient M.C., a 6-month-old boy, was admitted to an intensive care unit because of respiratory insufficiency. An unhealed BCG vaccination site was noted. Bronchopulmonary lavage samples were tested for M. bovis; positive PCR and culture results led to the diagnosis of disseminated BCG infection. Despite intensive anti-TB therapy, the child died of multiple organ failure. Autopsy showed typical granuloma formations and a hypoplastic thymus, typical for severe combined immunodeficiency. Male patients S.D. and C.G. were admitted to intensive care units at 6 and 8 months of age, respectively, with lymphadenopathy and multiple organ insufficiency. Each boy died of multiple organ failure; postmortem examination found granuloma formation and a hypoplastic thymus in each (8).

Eight patients with severe combined immunodeficiency had local adverse events after vaccination with BCG. Inflammation at the vaccination site was observed for all 8. For all except 1, dual anti-TB therapy (rifampin, isoniazid) or monotherapy was successful. For 1 of these patients, anti-TB treatment was stopped 3 months after bone marrow transplant, but increasing inflammation and lymphadenitis appeared 1 month later, with positive PCR and negative culture results for Mycobacterium spp. After 12 months of triple anti-TB therapy, this patient recovered, including full immunologic reconstitution, was reached. Bronchopulmonary lavage samples were tested for M. bovis; positive PCR and culture results led to the diagnosis of disseminated BCG infection. Despite intensive anti-TB therapy, the child died of multiple organ failure. Autopsy showed typical granuloma formations and a hypoplastic thymus, typical for severe combined immunodeficiency. Male patients S.D. and C.G. were admitted to intensive care units at 6 and 8 months of age, respectively, with lymphadenopathy and multiple organ insufficiency. Each boy died of multiple organ failure; postmortem examination found granuloma formation and a hypoplastic thymus in each (8).

In 2-month-old female patient, W.M., who had interferon-γ–receptor deficiency, axillary lymphadenopathy with normal healing of the vaccination site was noted 7 weeks after BCG vaccination. Tuberculous lymphadenitis was diagnosed by histopathologic methods. Despite dual anti-TB therapy and streptomycin administration, the girl died. At autopsy, multiple tuberculous granulomas were found (5).

In 4-month-old female patient M.K., who had interleukin-12–receptor deficiency, axillary lymphadenopathy with positive results from Mycobacterium typing was noted. Dual anti-TB therapy for 12 months produced good results.

In 7-month-old female patient B.B., who also had interleukin-12–receptor deficiency, axillary lymphadenopathy was noted. Mycobacteria PCR-positive for the M. tuberculosis complex were found in the purulent secretion. Despite dual anti-TB therapy, the patient experienced 2 episodes of relapse. After another 2 years of anti-TB therapy, disseminated BCG infection, with pulmonary consequences, developed.

In patient R.C., a 6-month-old boy, osteomyelitis was diagnosed, and delayed healing of the BCG vaccination scar was noted. Investigation of his immunologic status showed no abnormalities. However, because granulomatous inflammation was present in a bone biopsy sample and staining for BCG produced a positive result, triple anti-TB therapy was provided for 12 months, with good results.

The literature describes >200 cases of disseminated BCG infection in patients with primary immunodeficiency (1–7). The diagnostic difficulties described for 8 of our patients with primary immunodeficiency have been noted by others (1–6, 8–10). In only 2 cases was the Mycobacterium species successfully isolated and identified as the M. bovis BCG strain. We propose novel criteria for the diagnosis of disseminated BCG infection in persons with primary immunodeficiency (Table). These criteria have recently been submitted to the European Society for Immunodeficiencies.

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**Table. Suggested diagnostic criteria for disseminated bacillus Calmette-Guérin (BCG) infection in persons with primary immunodeficiency**

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Clinical</th>
<th>Laboratory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definitive</td>
<td>Systemic symptoms such as fever or subfebrile status, weight loss, or stunted growth, and &gt;2 areas of involvement beyond the site of BCG vaccination†</td>
<td>Identification of Mycobacterium bovis BCG strain from the patient's organs by culture and/or standard PCR, as well as typical histopathologic changes with granulomatous inflammation</td>
</tr>
<tr>
<td>Probable criteria</td>
<td>Systemic symptoms such as fever or subfebrile status, weight loss or stunted growth, and &gt;2 areas of involvement beyond the site of BCG vaccination†</td>
<td>Identification of M. tuberculosis complex from the organs by PCR, without differentiation of M. bovis BCG strain or other members of the M. tuberculosis complex and negative mycobacterial cultures, with the presence of typical histopathologic changes with granulomatous inflammation</td>
</tr>
<tr>
<td>Possible</td>
<td>Systemic symptoms such as fever or subfebrile condition, weight loss or stunted growth, and &gt;2 areas of involvement beyond the site of BCG vaccination†</td>
<td>No identification of mycobacteria by PCR and culture, with presence of typical histopathologic changes with granulomatous inflammation</td>
</tr>
<tr>
<td>Exclusion criteria</td>
<td>Any inflammation without typical histopathologic changes, with no isolation of M. tuberculosis complex by PCR analysis in patient with primary immunodeficiency</td>
<td></td>
</tr>
<tr>
<td>Differential diagnosis</td>
<td>Severe, long-term inflammation with granuloma formation in patient with primary immunodeficiency</td>
<td></td>
</tr>
</tbody>
</table>

*Male or female patient with or without genetic confirmation of severe combined immunodeficiency, interferon-γ–receptor deficiency, interleukin-12–receptor deficiency, or other primary immunodeficiency.
†Areas of involvement may include lymph nodes, skin, soft tissues, lungs, spleen, liver, bones.
We believe that patients with severe combined immunodeficiency and any form of mild local changes at the BCG injection site should be given single or double anti-TB therapy, which should be continued until complete immunologic reconstitution occurs after bone marrow transplant. Severe local BCG infection with regional lymph node involvement needs at least triple anti-TB therapy followed by long-term prophylaxis. Disseminated BCG infection needs anti-TB therapy, including ≥4 anti-TB drugs, until the patient fully recovers.

Acknowledgments

E.A.B. thanks Peter Folb, Dina Pfeifer, and Adwoa Bentii-Enchill for encouragement in writing this article.

The investigation was supported by grant EURO-POLICY-primary immunodeficiency SP23-CT-2005-006411 and national project no. PBZ-KBN-119/PO5/04.

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Clindamycin-resistant Streptococcus pneumoniae

To the Editor: Antimicrobial medications classified as macrolides (e.g., erythromycin) and lincosamides (e.g., clindamycin) show strong activity against streptococci and are commonly used to treat community-acquired infections caused by Streptococcus pneumoniae. Moreover, these drugs are the recommended alternatives for patients who cannot tolerate β-lactams.

Two main macrolide-resistant S. pneumoniae phenotypes have been reported (1). The first has a high level of resistance to all macrolides, lincosamides, ketolides, and streptogramins B due to ribosomal dimethylation, 23S rRNA mutations, or ribosomal protein mutations (MLS, MS, ML, MKS, and K phenotypes). The second is characterized by a low-level resistance (e.g., MIC 2–4 mg/L) to only 14- and 15-member ring macrolides (M phenotype) because of mef gene–mediated active drug efflux mechanism.

In January 2005, an erythromycin-susceptible but clindamycin-resistant pneumococcal strain was obtained from a conjunctival swab of a 10-month-old female outpatient attending the daycare center of the Clinic and Laboratory of Infectious Diseases, Siena University, Siena, Italy. To our knowledge, such a phenotype has not been reported in the international literature for S. pneumoniae, although a similar phenotype of S. agalactiae was described by Malbruny et al. (2).

The S. pneumoniae isolate was identified by standard procedures (3) and confirmed by PCR for the common capsule gene cpsA (4). Serotyping, performed by Quellung reaction, showed a 35F serotype. Susceptibility testing was carried out by disk diffusion and confirmed with E-test according to Clinical and Laboratory