Several subtypes of TBEV cause disease: European, Siberian, and Far Eastern (1). Siberian and Far Eastern have been associated with worse outcomes (1), but the potentially fatal neurologic complications in this patient are consistent with emerging data indicating that the European subtype causes more severe disease than previously thought (4–6). In <10% of cases, TBEV targets the anterior horn of the spinal cord, resulting in flaccid poliomylitis-like paralysis (3,7), or, rarer still, as in this case, in paralysis of respiratory muscles, requiring artificial ventilation (3,8,9).

Treatment of TBEV is supportive only; vaccination and avoiding mosquito bites are key to disease prevention and control. Although some TBEV-endemic countries have vaccination programs, level of uptake varies (10). Public health experts recommend that travelers undertaking high-exposure activities in endemic countries get vaccinated. This case underscores the importance of vaccination among groups of susceptible people and improved awareness of this emerging disease.

About the Author
Dr. Neill is a junior doctor currently working at University College Hospital London. Her research interests include infectious diseases and hematological malignancy.

References

Aspergillus felis in Patient with Chronic Granulomatous Disease

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We report a case of *Aspergillus felis* infection in a patient with chronic granulomatous disease who had overlapping features of invasive pulmonary aspergillosis and allergic bronchopulmonary aspergillosis. Identifying the species responsible for aspergillosis by molecular methods can be crucial for directing patient management and selection of appropriate antifungal agents.

A 42-year-old man with X-linked chronic granulomatos disease (CGD) sought care at a hospital in Paris, France, for a 2-week history of cough and night sweats. He had been receiving long-term prophylaxis with itraconazole (400 mg/d) and had normal trough levels (1.240 µg/L) 1 month before his hospital visit.

At admission, blood counts showed mild leukocytosis (leukocytes 9.6 × 10⁹ cells/L, reference range 4–10 ×
10^6 cells/L), with neutrophils at 6.1 × 10^6 cells/L (reference range 1.5–7 × 10^6 cells/L) and eosinophils at 2 × 10^6 cells/L (reference <0.5 × 10^6 cells/L). Computed tomography (CT) revealed an upper left lobe consolidation (Appendix Figure, https://wwwnc.cdc.gov/EID/article/25/12/19-1020-App1.pdf). We administered broad-spectrum antimicrobial drugs (2 g meropenem 3×/d and 20 mg/kg/d amikacin). Results of bacterial and mycological cultures yielded a mold morphologically consistent with Aspergillus fumigatus (10^9/10^9 cells/mL) as the partial sequence of the internal transcribed spacer 2, and Antifungals (Paris). Molecular identification based on the partial sequence of the internal transcribed spacer 2, 5.8S ribosomal RNA gene, and internal transcribed spacer 2, and Antifungals (Paris). Molecular identification based on the partial sequence of the internal transcribed spacer 2, 5.8S ribosomal RNA gene, and internal transcribed spacer 2 (102 bp; 100% similarity to the type strain, CBS DTO_131-E3). The European Committee for Antimicrobial Susceptibility Testing (EUCAST) MICs with broth microdilution methods (1) were 4 µg/L for voriconazole, 4 µg/L for itraconazole, 0.25 µg/L for posaconazole, 2 µg/L for caspofungin, and 4 µg/L for amphotericin B. Based on EUCAST MIC breakpoints for A. fumigatus (2), we switched treatment to oral posaconazole (loading dose of 300 mg 2×/d, followed by 200 mg 2×/d). Eosinophilia persisted (1.8–2 × 10^6 cells/L) despite antiparastic treatment with ivermectin (5 mg/kg/d at days 1 and 7) and albendazole (400 mg/d for 7 d). Pathology findings from a transbronchial percutaneous biopsy revealed granulomas with Grocott-positive septated hyphae. Result of an Aspergillus section Fumigati PCR on a biopsy specimen were positive, and mycological cultures yielded a mold morphologically identified as Aspergillus. After 5 weeks of liposomal amphotericin B therapy (including 2 weeks of combination therapy with caspofungin), we switched treatment to oral voriconazole (loading dose of 400 mg 2×/d, followed by 200 mg 2×/d). Normalization of eosinophilia occurred at 6 weeks.

We sent mycological cultures from the biopsy specimens to the French National Center for Invasive Mycoses and Antifungals (Paris). Molecular identification based on the partial sequence of the internal transcribed spacer 2, 5.8S ribosomal RNA gene, and internal transcribed spacer 2 (525/526 bp; 99% similarity to the type strain, CBS 103245; GenBank accession no. KF558318.1) and the β-tubulin target gene enabled the identification of Aspergillus fumigatus (109/109 bp; 100% similarity to the type strain, CBS DTO_131-E3). The European Committee for Antimicrobial Susceptibility Testing (EUCAST) MICs with broth microdilution methods (1) were 4 µg/L for voriconazole, 4 µg/L for itraconazole, 0.25 µg/L for posaconazole, 2 µg/L for caspofungin, and 4 µg/L for amphotericin B. Based on EUCAST MIC breakpoints for A. fumigatus (2), we switched treatment to oral posaconazole (loading dose of 300 mg 2×/d,

### Table. Defining features of invasive pulmonary aspergillosis and allergic bronchopulmonary aspergillosis in a 42-year-old man with X-linked chronic granulomatous disease, Paris, France

<table>
<thead>
<tr>
<th>Category</th>
<th>IPA (oncohematologic setting)</th>
<th>IPA during CGD</th>
<th>Patient in this study</th>
<th>ABPA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underlying disease</td>
<td>Neutropenia</td>
<td>CGD, particularly X-linked CGD</td>
<td>X-linked CGD</td>
<td>Asthma, cystic fibrosis</td>
</tr>
<tr>
<td>Mechanisms of disease</td>
<td>Angioinvasion</td>
<td>Tissue invasion, little or no angioinvasion</td>
<td>No angioinvasion</td>
<td>Exaggerated inflammatory response to Aspergillus</td>
</tr>
<tr>
<td>Course of infection</td>
<td>Acute, single event</td>
<td>Subacute or chronic, single event</td>
<td>Subacute, single event</td>
<td>Chronic with exacerbations</td>
</tr>
<tr>
<td>Radiographic findings</td>
<td>Cavitation, pulmonary infarction, air crescent sign, halo sign</td>
<td>Single or multiple nodules and consolidations</td>
<td>Single consolidation</td>
<td>Central bronchiectasis, pulmonary infiltrates, mucus plugs</td>
</tr>
<tr>
<td>Galactomannan testing</td>
<td>Total serum IgE</td>
<td>Positive or negative</td>
<td>Negative Elevated (1,410 IU/L)</td>
<td>Elevated (&gt;1,000 IU/L)</td>
</tr>
<tr>
<td>Aspergillus species-specific IgE or skin test reactivity</td>
<td>Negative</td>
<td>Negative</td>
<td>Positive (54 IU/mL)</td>
<td>Positive (&gt;10 IU/mL)</td>
</tr>
<tr>
<td>Aspergillus IgG</td>
<td>Negative</td>
<td>Negative</td>
<td>Positive (2 arcs of precipitation)</td>
<td>Positive (&gt;1 arc of precipitation)</td>
</tr>
<tr>
<td>Precipitating antibodies to Aspergillus</td>
<td>Absent</td>
<td>Absent, reported only during &quot;fulminant multihop pneumonia&quot;</td>
<td>Present (2.2 × 10^9 cells/L)</td>
<td>Present (&gt;0.5 × 10^9 cells/L)</td>
</tr>
<tr>
<td>Blood eosinophilia</td>
<td>First-line treatment</td>
<td>Antifungal treatment</td>
<td>Antifungal treatment</td>
<td>Systemic or inhaled corticosteroids</td>
</tr>
<tr>
<td></td>
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</tr>
</tbody>
</table>

*ABPA, allergic bronchopulmonary aspergillosis; CGD, chronic granulomatous disease; IPA, invasive pulmonary aspergillosis.*
followed by 300 mg/d). Chest CT performed 12 months after treatment initiation showed noticeable improvement of pulmonary lesions.

Invasive pulmonary aspergillosis (IPA) remains a leading cause of death during CGD, and typically manifests as subacute pneumonia, with little or no angioinvasion (3). This patient had pulmonary infection caused by *A. felis* with overlapping features of IPA and allergic bronchopulmonary aspergillosis (ABPA) (4). Sensitization to *Aspergillus* spp. in patients with CGD (5) and tissue eosinophilia in lung pathology studies during invasive fungal infections (6) have been reported but do not seem to be common features of IPA in patients with CGD (3,7). There was some uncertainty about whether *A. felis* was responsible for this overlapping phenotype between IPA and ABPA (Table).

*A. felis* is a member of the *A. viridinatus* complex, a group of cryptic species belonging to *Aspergillus* section *Fumigati* (8). Such fumigati-mimetic molds are increasingly being recognized as sporadic causes of IPA (9). *A. felis* has been reported as a cause of sino-orbital aspergillosis in cats, but less frequently in humans (8). In one such case of IPA, and in the few reported cases in patients with CGD of IPA caused by the closely related *A. pseudoviridinutans* and *A. udagawai*, the course of infection was more protracted than for *A. fumigatus* infections, and dissemination occurred in a contiguous manner (10). Nonfumigatus *Aspergillus* spp. exhibit decreased in vitro susceptibility to commonly used antifungal drugs. Most previously reported antifungal susceptibilities from *A. felis* isolates showed high MICs for voriconazole and itraconazole but lower MICs for posaconazole (8).

Because isolates may be misidentified as *A. fumigatus*, culture-based morphological identification of invasive fungal infections in CGD may sometimes be insufficient. In cases of breakthrough fungal infections, or when faced with an atypical or refractory course of infection, identification of the fungus at a species level by molecular methods appears to be critical to guiding proper patient management.

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References

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Aspergillus felis in Patient with Chronic Granulomatous Disease

Appendix

Appendix Figure. Images from a patient with chronic granulomatous disease who had *Aspergillus felis* infection. A) Thin-section (1 mm collimation) CT scan images at admission obtained at the level of the aortic arch showing a parenchymal consolidation of the upper-left lobe. B) Thin-section (1 mm collimation) CT scan images obtained 1 year after initiation of antifungal therapy. Samples of transbronchial biopsy specimens from the patient with *A. felis* infection were sent for pathological analyses. C) Hematoxylin and
eosin staining highlighting multifocal inflammatory lesions, centered on the chorion of a bronchus/bronchiole, with mixed inflammatory infiltrates containing numerous eosinophils and acute necrosis containing Charcot-Leyden crystals (arrowhead) (original magnification 400×). D) Gomori Grocott staining highlighting thin hyaline filamentous fungi with branching, septation, and multifocal distention. The small size of the biopsy did not allow us to adequately assess angioinvasion, but the fungi displayed local aggressiveness with invasion of the respiratory mucosa and chorion (original magnification 400×).