Drug-Resistant Tubercular Uveitis

Kusum Sharma,a Aman Sharma,b Reema Bansal,c Paul D. Fiorella,d Amod Gupta6
Departments of Medical Microbiology,a Internal Medicine,b and Ophthalmology,c Post Graduate Institute of Medical Education and Research, Chandigarh, India; Bureau of Health Laboratories, Jacksonville, Florida, USAd

Tubercular uveitis (TBU) is a common cause of infectious uveitis in countries where tuberculosis is endemic. Molecular diagnostic techniques are the cornerstone of diagnosis as of now, as culture positivity has never been reported to date. With increasing reports of multidrug-resistant tuberculosis (MDR TB) from various extrapulmonary sites and in the light of a recent case report, there is an urgent unmet need to look for MDR TBU. We report here five such cases of drug-resistant TBU.

Vitreous fluid (VF) samples from 55 clinically suspected cases of TBU, diagnosed according to previously proposed criteria (2), were subjected to multitargeted PCR (MPCR) (3) and the Xpert MTB/RIF assay (GX assay). Forty samples were also subjected to the MTBDRplus line probe assay. Conventional smear and culture examination were not done due to low sensitivity and prolonged turnaround time for culture. Multitargeted PCR was positive for MTB in 39 of the 55 samples tested. Rifampin resistance was detected in five cases by rpoB gene sequencing, with mutations at codon 531 (three patients), codon 516 (one patient), and codon 526 (one patient). Rifampin resistance was also detected in these five cases by MTBDRplus assay and in two of these by GX assay. Two of these cases were also found to have isoniazid resistance by MTBDRplus, confirmed by katG sequencing, with detection of a mutation at codon 315. MTBDRplus had greater sensitivity than the GX assay in detecting rifampin resistance. The clinical profiles, investigation reports, treatment instituted, and clinical outcomes of these five patients are shown in Table 1. All the patients were started on MDR-TB treatment. Corticosteroids were administered as oral or topical treatment or both, as required. Four patients took the treatment and have shown healing of lesions, while one was lost to follow-up.

Molecular methods have been evaluated for timely diagnosis and detection of drug resistance in other paucibacillary conditions, such as tubercular meningitis (TBM) (4) and osteoarticular tuberculosis (OATB) (5). However, these have not been evaluated on VF samples. MDR-TB was diagnosed by MTBDRplus assay in 32.14% of 30 PCR-positive TBM cases (4), and rifampin resistance was detected by rpoB gene sequencing in 13% of OATB cases (5). Mutations for rifampin resistance at codons 531, 516, and 526, as seen in our patients, have been documented from other extrapulmonary sites (4, 5).

The XpertMTB/RIF assay was positive in only two of our five cases (40%). Previous studies have reported low sensitivity (25%) of the GX assay in other paucibacillary conditions, such as pleural TB (6). From our experience of the MTBDRplus assay and of rpoB and katG gene sequencing for the detection of drug resistance in VF samples, we believe that there is a need for the application of rapid molecular techniques for the detection of drug resistance in TBU. Though these diagnostic modalities are relatively expensive (approximate running costs are $25/test for the MTBDR plus assay, $14/test for the GX assay, $9.5/test for rpoB gene sequencing, and $3.5/test for MPCR) and require infrastructure and technical skill, these can be carried out in tertiary care centers in places like India where tuberculosis is endemic.

ACKNOWLEDGMENT
This study was supported by the Department of Biotechnology, New Delhi, India.

REFERENCES

Published ahead of print 3 September 2014
Editor: G. A. Land
Address correspondence to Amod Gupta, dramodgupta@gmail.com.
Copyright © 2014, American Society for Microbiology. All Rights Reserved.
doi:10.1128/JCM.01918-14
**TABLE 1** Clinical profiles, investigation reports, treatment instituted, and clinical outcomes of the five patients

<table>
<thead>
<tr>
<th>Case</th>
<th>Age/sex</th>
<th>TST (mm)</th>
<th>Clinical signs</th>
<th>CXR finding(s)</th>
<th>MPCR</th>
<th>Xpert MTB/RIF</th>
<th>MTBDR plus line probe assay</th>
<th>Visual acuity</th>
<th>Treatment</th>
<th>Length of follow-up (mo)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>28/F</td>
<td>30 by 35</td>
<td>LE choroidal granuloma</td>
<td>Partially healed Koch's lesions</td>
<td>Positive</td>
<td>516 (GAC→TAC)</td>
<td>MTB⁺, RR (codon 516), IR</td>
<td>Hand motion</td>
<td>Hand motions</td>
<td>CS + MDR TB therapy</td>
<td>22</td>
</tr>
<tr>
<td>2</td>
<td>15/M</td>
<td>14 by 16</td>
<td>RE MSC</td>
<td>Normal</td>
<td>Positive</td>
<td>531 (TCG→TTG)</td>
<td>MTB⁺, RR (codon 531), IR</td>
<td>6/9</td>
<td>Counting fingers (significant cataract)</td>
<td>CS + MDR TB therapy</td>
<td>14</td>
</tr>
<tr>
<td>3</td>
<td>26/F</td>
<td>24 by 25</td>
<td>BE anterior uveitis</td>
<td>Bilateral HLP, prominent BV markings</td>
<td>Positive</td>
<td>531 (TCG→TTG)</td>
<td>MTB⁺, RR (codon 531), IS</td>
<td>6/12</td>
<td>6/9</td>
<td>Topical CS and cycloplegics</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>21/F</td>
<td>20 by 20</td>
<td>RE MSC</td>
<td>Normal</td>
<td>Positive</td>
<td>526 (CAC→TAC)</td>
<td>MTB⁺, RR (codon 526), IS</td>
<td>6/6</td>
<td>6/9</td>
<td>CS + azathioprine + MDR TB therapy</td>
<td>8</td>
</tr>
<tr>
<td>5</td>
<td>33/M</td>
<td>15 by 20</td>
<td>BE MSC</td>
<td>Normal</td>
<td>Positive</td>
<td>531 (TCG→TTG)</td>
<td>MTB⁺, RR (codon 531), IS</td>
<td>6/6</td>
<td>6/9</td>
<td>CS + MDR TB therapy</td>
<td>6</td>
</tr>
</tbody>
</table>

*F*, female; *M*, male; TST, tuberculin skin test; MSC, multifocal serpiginous choroiditis; LE, left eye; RE, right eye; BE, both eyes; CXR, chest X-ray; MPCR, multitargeted PCR; HLP, hilar lymphadenopathy; BV, bronchovascular markings; RR, rifampin resistance; MTB⁺, *Mycobacterium tuberculosis* detected; IR, isoniazid resistance; IS, isoniazid sensitivity; CS, corticosteroids; MDR TB therapy, multidrug-resistant tuberculosis treatment, which consisted of five drugs (pyrazinamide, levofloxacin, ethionamide, cycloserine, and streptomycin) for the first 5 months and three drugs (levofloxacin, ethionamide, and cycloserine) for the next 18 months.