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Abstract
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Reference

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Persistent Intraocular Rubella Infection in a Patient with Fuchs’ Uveitis and Congenital Rubella Syndrome

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There is growing evidence for the role of rubella virus in Fuchs’ uveitis syndrome (FUS). This report is the first to show persistent intraocular rubella virus in a 28-year-old man with congenital rubella syndrome (CRS), who presented with blurred vision and was diagnosed with FUS.

CASE REPORT

A 28-year-old man of Afro-Caribbean descent was referred to a tertiary hospital in 2006 with progressively worsening vision in both eyes. There was no history of pain, conjunctival injection discharge, photophobia, photopsia, or floaters. He had been diagnosed at birth with congenital rubella syndrome (CRS), following a clinical diagnosis of maternal rubella in pregnancy and presentation with profound deafness and cataracts. He did not have any cardiac defects. His visual acuities on presentation in 2006 were 6/36 and 6/12 in the right and left eye, respectively. Examination revealed bilateral anterior uveitis with stellate keratic precipitates as well as bilateral posterior subcapsular lens opacities. Intraocular pressures were within normal limits in both eyes. Dilated fundus examination was normal.

The clinical diagnosis of Fuchs’ uveitis syndrome (FUS) was made based on the presence of a bilateral low-grade anterior uveitis with typical keratic precipitates and the absence of posterior synechiae or acute symptoms of pain, redness, and photophobia. Investigations for other causes of uveitis were carried out, including serum angiotensinogen-converting enzyme, syphilis serology, and antinuclear antibody titers, which were all negative. The full blood count, renal and liver function tests, and erythrocyte sedimentation rate (ESR) were normal, and the sickle cell screen was negative. The serum rubella IgM was negative, and the rubella IgG was positive.

His reduced visual acuity was attributed to his bilateral lens opacities, which is a common feature of FUS. Right followed by left eye phacoemulsification cataract extraction and intraocular lens implantation were performed under general anesthesia to improve vision. One-hundred-microliter samples of aqueous humor (AH) were aspirated through a paracentesis prior to both cataract surgeries. The rest of the operations were performed in a standard manner and without complications. The postoperative treatment regimen consisted of hourly dexamethasone as 0.1% drops that were tapered over 6 weeks and with chloramphenicol as 0.5% drops 4 times a day (q.d.s.) for 1 week.

A venous blood sample, urine sample, and throat swabs were collected for serological and microbiological investigations. The serum sample confirmed serological evidence of past rubella infection with an unusually high titer (Table 1). Samples of aqueous fluid were sent to the national rubella reference laboratory at Colindale, United Kingdom, for detection of rubella RNA and intraocular antibody production, by calculating the rubella-specific antibody index ($A_{I_{Rub}}$) based upon the Goldmann-Witmer index (GW-I) (1). This compares the relative levels of specific antibody in aqueous and serum samples and compares them with the relative levels of total IgG as follows: (i) total IgG ratio ($Q_{IgG}$) = aqueous humor total IgG/serum total IgG, (ii) rubella ratio ($Q_{Rub}$) = aqueous humor rubella IgG/serum rubella IgG, and (iii) rubella antibody index ($A_{I_{Rub}}$) = ($Q_{Rub}$)/($Q_{IgG}$).

There was evidence of intraocular antibody synthesis against rubella virus from the right and left eye AH samples (Table 1). An $A_{I}$ of $>$3 is considered consistent with local antibody production. It should be noted that the $A_{I_{Rub}}$ from the left eye AH sample was calculated from the previously obtained serum IgG, which could have changed during this time. Antibodies for herpes simplex virus and varicella zoster viruses were tested as control antibodies and were within normal limits. There was no evidence of intraocular antibody synthesis for herpes simplex virus or varicella zoster viruses as no antibodies toward these viruses were detected. There was no rubella virus RNA detected in serum, plasma, whole blood on EDTA, throat swabs, or urine samples by rubella nested reverse transcriptase-PCR (RT-PCR) (2). Rubella virus RNA was detected, but at a low level (based on the intensity of the band) in both eyes, and was confirmed on sequencing of a 252-bp portion of the rubella virus glycoprotein E1. Although the sequence from both eyes (right eye, GenBank accession no. EF210070; left eye, GenBank accession no. EU240897) revealed the rubella virus was of the same genotype (1g), the sequences were not identical: there were 5 differences in the region sequenced. This variation is most likely explained by independent evolution in the left and right eyes and is unlikely to represent a sequencing artifact.

The results in this case show evidence of persistent rubella virus in aqueous humor and localized intraocular rubella antibody synthesis in the anterior chamber of a man with a known history of CRS. The profound deafness since birth and presence of rubella IgG support the diagnosis of CRS. In addition, the diagnosis of CRS is in keeping with the rubella epidemic in 1978, when there were approximately 50 CRS births and 800 terminations of preg-
nancy due to rubella disease in England, Scotland, and Wales (3). Our findings suggest that congenital rubella infection could be the cause underlying this patient’s bilateral FUS.

This is the first report of FUS in a CRS patient with evidence of intraocular rubella virus antibody synthesis, rubella virus RNA, and genotyping of the virus by sequencing. The difference in rubella virus sequence between the eyes is supporting evidence of independent and persistent replication in both eyes since birth. This case adds to the growing body of evidence for the role of rubella virus in the pathogenesis of FUS.

The diagnosis of FUS remains clinical, and its etiology is still uncertain. Several recent observations have been published linking rubella virus to FUS; however, the current evidence is still inconclusive. Rubella virus is a single-stranded positive-sense RNA virus, the only member of the genus Rubivirus, and belongs to the family Togaviridae. The clinical features of rubella are usually an acute exanthematous infection that may be preceded by or occur concurrently with fever and lymphadenopathy; it is usually less severe in children than adults. Systemic manifestations can occur, but complications, including transient thrombocytopenia (1 in 3,500 cases) and postinfection encephalopathy (1 in 5,000 to 1 in 10,000 cases) are not common (4). The initial report on the teratogenic effects of rubella described the association between congenital cataracts and maternal rubella (5). Rubella infection in early gestation was subsequently associated with an array of congenital defects, including cataracts, congenital glaucoma, congenital heart disease, hearing loss, and pigmentary retinopathy. Other clinical manifestations include purpura, splenomegaly, microcephaly, developmental delay, meningo-encephalitis, radiolucent bone disease, and jaundice. Rubella virus has been observed to persist with CRS, in contrast to acute postnatal infection, although the mechanism remains unknown. A distinct cellular response has been suggested as rubella virus was demonstrated to induce apoptosis in differentiated cells (including cytotoxic lymphoblasts), although it was not a sufficient stimulus in fibroblastic dividing cells (6).

FUS has been defined as an intraocular syndrome with characteristic signs that include iris heterochromia, low-grade anterior uveitis, and cataract (7). It has previously been described that infections with herpes simplex virus, toxoplasmosis, and toxocariasis may be associated with ocular disorders with similarity to FUS. In addition to this, a role in the pathogenesis for FUS has been proposed for autoantibodies against the cornea, increased intraocular IgG, retinitis pigmentosa, and trauma (8, 9). However, there is growing evidence within the last 6 years for the role of rubella virus as a specific pathogen responsible for FUS, and FUS has been proposed to occur due to chronic rubella virus persistence following infection. It has been demonstrated that all (52 of 52 [10] and 63 of 63 [11]) or the majority (13 of 14 [12] and 10 of 14 [13]) of patients with ocular characteristics consistent with FUS had evidence of production of intraocular antibody against rubella virus. Furthermore, the rubella virus genome was detected by PCR in a proportion (5 of 28) of patient’s aqueous humor samples in the 2004 study.

There is further evidence to support the association of rubella virus and FUS due to an observed decrease (4.48% down to 0.62%) in the proportion of patients with FUS in a tertiary ophthalmology center since the introduction of the U.S. rubella vaccination program that has led to the virtual elimination of rubella virus (14). This observation was not seen for patients with idiopathic chronic uveitis or idiopathic chronic granulomatous uveitis. Moreover, the proportion of foreign-born patients with FUS who were not likely to be vaccinated increased from 24 to 25% to 42 to 55% following the vaccination program.

The clinical profile of patients with rubella virus-associated uveitis compared to those with chronic anterior uveitis has shown the patients to be younger at the time of initial ophthalmologic presentation and the disease to occur more frequently with unilateral ocular disease, keratic precipitates, iris atrophy, and/or heterochromia, associated vitreous opacities, and cataracts. In particular, a combination of keratic precipitates, absence of posterior synechiae, cataracts, and vitreous opacities occurred more often in patients with rubella virus (15). In addition, a case report that is in support of FUS due to postnatal rubella virus infection has shown that rubella virus-associated uveitis may present during childhood; this case also demonstrated the susceptibility of an unvaccinated child to uveitis following rubella virus infection (16). However, the variety and combinations of clinical features that are observed with FUS make it difficult to conclusively prove a rubella virus-associated uveitis. Furthermore, the pathogenesis of FUS due to rubella virus and whether it is maintained by the virus or, for instance, is immune mediated remain unclear.

FUS has not previously been reported as a manifestation of CRS, although, cataracts have been observed to occur early in life in 13 patients with CRS in whom glaucoma was diagnosed 3 to 22 years after birth. In addition, keratic precipitates were noted without any other evidence of acute ocular inflammation in 5 of these patients (17, 18). Ernest Fuchs’ hypothesis was based on an observed heterochromia at birth or early childhood (19), whereas

### TABLE 1 Results from patient samples for rubella virus testing

<table>
<thead>
<tr>
<th>Sample</th>
<th>Date</th>
<th>Rubella IgM (Microimmunone)</th>
<th>Rubella IgG (Siemens Enzygnost)</th>
<th>Rubella virus RNA result (nested PCR)</th>
<th>Total IgG concn (mg/liter)</th>
<th>QIgG</th>
<th>QRub</th>
<th>AIRub</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum</td>
<td>November 2006</td>
<td>Negative</td>
<td>15,823.5 (positive)</td>
<td>Not detected</td>
<td>13,387 (positive)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma</td>
<td>November 2006</td>
<td>Negative</td>
<td>Not detected</td>
<td>Not detected</td>
<td>Not detected</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood on EDTA</td>
<td>November 2006</td>
<td>Not detected</td>
<td>Not detected</td>
<td>Not detected</td>
<td>Not detected</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Throat swab</td>
<td>November 2006</td>
<td>Not detected</td>
<td>Not detected</td>
<td>Not detected</td>
<td>Not detected</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urine</td>
<td>November 2006</td>
<td>Not detected</td>
<td>Not detected</td>
<td>Not detected</td>
<td>Not detected</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right eye lens</td>
<td>November 2006</td>
<td>Not detected</td>
<td>Not detected</td>
<td>Not detected</td>
<td>Not detected</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right eye aqueous humor</td>
<td>November 2006</td>
<td>1,703.6 (positive)</td>
<td>Detected</td>
<td>29.5 (positive)</td>
<td>107.66 × 10⁻³</td>
<td>48.94</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left eye lens</td>
<td>March 2007</td>
<td>1,212.8 (positive)</td>
<td>Detected</td>
<td>78 (positive)</td>
<td>76.65 × 10⁻³</td>
<td>13.15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left eye aqueous humor</td>
<td>March 2007</td>
<td>3 76.65</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

EIA, enzyme immunoassay; QIgG, total IgG ratio; QRub, rubella IgG ratio; AIRub, rubella antibody index.
FUS may represent a delayed manifestation of CRS. However, some patients with FUS have been noted to not have heterochromia as infants (12).

Structural eye defects as a result of CRS are understood to be due to the cytopathic effect (20) when maternal infection occurs prior to 8 weeks (21). The evidence to support a direct cytopathic effect is based upon differing grades of rubella virus-induced apoptosis in cell lines in vitro (22) and could account for the discriminatory organ damage observed in CRS. The late ocular complications of CRS and some of the characteristic features observed in patients with FUS could be due to persistence of rubella virus. The mechanism for FUS in patients with CRS is not apparent, though, and the likely incidence is unknown. Overall, the pathogenesis of FUS remains uncertain, and the role of rubella virus is not fully understood.

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The authors of this study have no conflicts of interest.

REFERENCES