Original article

Treatment of presumed tuberculous uveitis affecting the posterior segment: Diagnostic confirmation and long term outcomes

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A B S T R A C T

Objective: To determine the level of agreement with the presumed diagnosis and long term clinical outcomes after antituberculous therapy (ATT) in a group of patients with presumed tuberculous uveitis (PTU) affecting the posterior segment.

Methods: Retrospective case series.

Results: A total of 17 patients with chronic refractory or newly diagnosed uveitis affecting the posterior segment were included. All included patients were diagnosed with PTU and received ATT. Median follow-up after ATT was 34 months (range 2–60). Complete control of inflammation was observed in 14/17 patients (82.3%) during the treatment period, and only 4/17 patients (23.5%) had a uveitis relapse over the entire follow-up period after ATT. All patients who had uveitis relapses (4/4), but none from the remaining group (0/13), required immunosuppressive therapy of some kind after ATT. The response to ATT was able to confirm diagnosis of PTU in 14/17 (82.3%) included patients.

Conclusion: When a clinical suspicion of PTU affecting the posterior segment exists, ATT may be highly effective for both confirming the diagnosis and resolving the inflammatory process. Thus, ATT may offer additional advantages, such as preventing latent-tuberculosis reactivations due to immunosuppressive therapy, and decreasing the number and/or severity of uveitis relapses in some patients. Prospective, randomized studies including a larger number of patients are required to support these and other potential advantages of ATT in such patients.

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Tratamiento de las uveítis tuberculosas presuntas del segmento posterior: confirmación diagnóstica y resultados a largo plazo

RESUMEN

Objetivo: Describir el grado de coincidencia con el diagnóstico de presunción así como los resultados clínicos obtenidos a largo plazo tras el tratamiento antituberculoso (ATT) en un grupo de pacientes con uveítis tuberculosas presuntas (UTBP) que afectaban al segmento posterior.

Métodos: Estudio retrospectivo. Serie de pacientes.

Resultados: Se incluyeron a 17 pacientes con distintos tipos de uveítis del segmento posterior, crónicas, refractarias o de reciente diagnóstico y diversas manifestaciones clínicas, en los que, tras establecerse el diagnóstico de UTBP, se completó ATT. La media de seguimiento fue de 34 meses (rango 2-60). Hubo control de la inflamación en 14/17 pacientes (82,3%) durante el periodo de tratamiento y solo 4/17 pacientes (23,5%) experimentaron una recidiva de su enfermedad a lo largo del periodo de seguimiento tras ATT. Todos los pacientes que sufrieron recidivas (4/4), pero ninguno de los que no las sufrieron (0/13) requirieron terapia inmunosupresora de algún tipo tras ATT. La respuesta al ATT sirvió para confirmar el diagnóstico de UTBP en 14/17 pacientes (82,3%).

Conclusions: En pacientes con sospecha de UTBP que afecta al segmento posterior, el ATT puede ser una eficaz medida para confirmar el diagnóstico y resolver el cuadro inflamatorio. En este contexto, el ATT puede ofrecer otras potenciales ventajas como prevenir futuras reactivaciones de tuberculosas secundarias a tratamiento inmunosupresor o disminuir la frecuencia o la severidad de recaídas en algunos pacientes. La confirmación de estas y otras ventajas requiere trabajos prospectivos, aleatorizados con mayor número de pacientes.

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Introduction

Tuberculosis (TB) subsists as a significant world health problem which causes about 3,000,000 deaths every year. Ocular involvement associated to TB can appear in up to 18% of cases. Among these, tuberculous uveitis (TBU) is the most frequent expression. In recent years, several publications have emphasized the increase in UTB cases even though numbers can vary considerably due to numerous factors including genetic and ethnic influence, geographical location, socioeconomic level, as well as multiple environmental factors. Therefore, the incidence of TB between uveitis patients is highly variable not only due to the above factors but also mainly due to the absence of standardized diagnostic criteria and the serious difficulties involved in the diagnostic confirmation in cases without other systemic involvements.

For the above reasons, even at this date many ocular TB cases still remain as presumptive diagnostic. In many cases the term “presumptive” is added to the acronym (PTBU) after excluding other etiologies but without demonstrating beyond doubt that the cause is tuberculosis. In said PTBU cases the diagnostic would be based on the presence of several indicators which could be summarized as: (1) compatible clinical expressions, (2) tuberculosis infection data, (3) absence of better diagnostic hypotheses.

Patients with PTBU and particularly those having the posterior segment affected by uveitis (which involves a higher rate of complications and therefore a poor prognosis) represent a diagnostic and therapeutic nightmare due to the scarcity of references on which to base an action algorithm.

In this retrospective study derived from the uveitis unit of a single third level health facility, the authors present the long-term results of the application of antituberculosis treatment (ATT) for treating patients with PUTB involving the posterior segment.

Materials and methods

This study included all the patients of the Uveitis Unit of our hospital with uveitis involving the posterior segment (intermediate and posterior uveitis as well as panuveitis) and diagnosed with PUTB, who completed ATT from 2006 up to 3 months prior to the preparation of this study. Table 1 shows the demographic and clinical characteristics as well as the previous treatments taken by all the patients included in the study. Chronic uveitis patients had received some type of systemic immunosuppressant treatment which failed to cause the remission of the inflammatory condition. Only patients 5 and 14, who were recently diagnosed, had not received any systemic immunosuppressant treatment. Patients were diagnosed with PUTB if the following 4 premises were fulfilled: (1) presence of recent onset active uveitis or pre-existing uveitis resistant to immunosuppressive treatment; (2) previous infection data by M. tuberculosis (latent tuberculosis) expressed as positive result of tuberculine/Mantoux test (according to the criteria of the Centers for Disease Control and Prevention) or positive result of the QuantiFeron-TB-Gold (QFN-TB Gold, Cellestis, Carnegie, Australia) test; (3) evidence for reasonably excluding other causes of uveitis of immune or infectious origin after appropriate clinical and serological screening.
The Quantiferon-TB-Gold was performed on all patients. In order to maximize sensitivity to tuberculosis infection tests, the Mantoux test was repeated (booster) in all the patients with immunosuppressant treatment who gave negative results in the first test.

All the patients included in the study underwent ATT for a minimum period of 9 months (except in patient 16 who had to suspend treatment due to severe lymphangitis). Two patients (# 2 and 11) received 2 cycles of treatment due to the insufficient length of the first cycle. All the treatment data (number of drugs, overall treatment time and secondary events) as well as the data referring to tuberculous infection diagnostic and epidemiology are shown in Table 2. Three of the patients had suffered pulmonary tuberculosis (# 8 and 15) or tuberculous meningitis (# 4) and had been treated previously with antituberculosis monotherapy, for which reason it was considered they were partially treated. All the patients of the study (with the exception of patient # 17) also received adjuvant systemic steroid treatment (prednisone) during the first 3 months of ATT at a maximum dosage of 0.5 mg/kg/day and for a maximum period of 3 months. Data on the clinical evolution and subsequent treatments were recorded for all the patients included in the study following a preestablished protocol. All the patients were assessed in our unit with at least a quarterly interval during the follow-up period of the study. All the procedures followed for the study were in accordance with the ethical rules of the 1975 Helsinki Declaration.

**Results**

Overall, 17 patients were included in the study. Table 3 illustrates the follow-up time, the clinical evolution and the subsequent treatments of the study patients. The mean follow-up, after completing at least one ATT cycle, was of 34 months with a range between 3 and 60 months. For the patients who received more than one treatment cycle only the follow-up months after completing the second treatment cycle were accounted. All the patients experienced improvements (according to the criteria posed by the SUN group) in inflammatory activity during ATT, even though only 14/17 patients (82.3%) exhibited complete inflammatory control during the treatment. All the patients with controlled inflammation during treatment achieved remission of the disease, which became inactive 3 months after completing the treatment (Figs. 1 and 2). Of said 14 patients, 13 (92.8%) remained in remission throughout the period of the study. The 13 patients who achieved complete remission without relapses during the period of the study did not receive any type of systemic immunosuppressant treatment (including corticosteroids) during the follow-up period. Patients who did not achieve remission (# 3, 10 and 11) and the patient who subsequently experienced a relapse (#12) had to be treated with the systemic immunosuppressant therapy specified in Table 3. The PUTB diagnostic was confirmed by therapeutic test response in 14 patients following the criteria of Gupta et al.1 The patients with active TB systemic expressions (patients 1 and 11) achieved complete resolution of the clinical condition.

**Discussion**

Definitive ocular TB diagnostic is infrequent for several reasons, including the difficulty to obtain sufficient sample size to isolate the pathogen, the time required to obtain results in conventional culture media (between 4 and 8 weeks in the Löwestein-Jensen medium), as well as due to the potential morbidity associated to the obtention of tissue samples by means of VFP. In addition, most patients do not exhibit TB history and over half have absolutely normal chest X-rays. In these patients with active uveitis who meet the PUTB
criteria, it has been postulated that ATT provides a significant reduction in the number of recurrences. This study presents the long-term results of a diagnostic-therapeutic algorithm for managing PUTB patients with posterior segment involvement.

ATT has demonstrated to be an effective therapy which achieved long-term remission in 13 out of the 17 patients (76.4%) who were part of the study. It should be noted that 11 of 13 patients had exhibited resistance to systemic immunosuppressant treatment for the inflammatory condition which, in some cases, was long-lasting and had been assessed in different hospitals without being offered an efficient therapeutic alternative.

In addition, ATT enabled an improvement of the intraocular inflammation and a reduction in the number and severity of relapses and all the study patients. This leads us to question the etiology of the inflammatory condition in the cases in which complete remission was not achieved. It is known that M. tuberculosis is a bacteria with a special tropism for the eyes and a particular tendency to produce (mainly posterior) uveitis, as can be seen in

Table 3 – Evolution of patients included in the study after ATT.

<table>
<thead>
<tr>
<th>Patient #</th>
<th>Follow-up after anti-TB trt. (months)</th>
<th>Relapse after ATT</th>
<th>IS Trt. after anti-TB trt.</th>
<th>Final diagnostic after anti-TB trt.</th>
<th>Eye</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>32</td>
<td>N</td>
<td>N</td>
<td>RV TB</td>
<td>B</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>N</td>
<td>N</td>
<td>PU TB</td>
<td>U</td>
</tr>
<tr>
<td>3</td>
<td>21</td>
<td>Y</td>
<td>MFM, CSa</td>
<td>Idiopathic PU</td>
<td>B</td>
</tr>
<tr>
<td>4</td>
<td>18</td>
<td>N</td>
<td>N</td>
<td>PU TB</td>
<td>U</td>
</tr>
<tr>
<td>5</td>
<td>38</td>
<td>N</td>
<td>N</td>
<td>MFSCL TB</td>
<td>B</td>
</tr>
<tr>
<td>6</td>
<td>3</td>
<td>N</td>
<td>N</td>
<td>PU TB</td>
<td>U</td>
</tr>
<tr>
<td>7</td>
<td>40</td>
<td>N</td>
<td>N</td>
<td>Chor TB</td>
<td>U</td>
</tr>
<tr>
<td>8</td>
<td>58</td>
<td>N (NVCM)</td>
<td>N</td>
<td>Chor TB</td>
<td>B</td>
</tr>
<tr>
<td>9</td>
<td>60</td>
<td>N (NVCM)</td>
<td>N</td>
<td>Chor TB</td>
<td>B</td>
</tr>
<tr>
<td>10</td>
<td>53</td>
<td>Y</td>
<td>MFM, ADA, CSa</td>
<td>PU-(LES)</td>
<td>B</td>
</tr>
<tr>
<td>11</td>
<td>33</td>
<td>Y</td>
<td>MFM, MFS, CSa</td>
<td>Idiopathic PU</td>
<td>B</td>
</tr>
<tr>
<td>12</td>
<td>56</td>
<td>Y</td>
<td>MFM, MFS, ADA, CSa</td>
<td>PU + Idiopathic RV</td>
<td>B</td>
</tr>
<tr>
<td>13</td>
<td>33</td>
<td>N</td>
<td>N</td>
<td>PS TB</td>
<td>U</td>
</tr>
<tr>
<td>14</td>
<td>3</td>
<td>N</td>
<td>N</td>
<td>CSL TB</td>
<td>U</td>
</tr>
<tr>
<td>15</td>
<td>45</td>
<td>N</td>
<td>N</td>
<td>RV TB</td>
<td>U</td>
</tr>
<tr>
<td>16</td>
<td>48</td>
<td>N</td>
<td>N</td>
<td>CSL TB</td>
<td>B</td>
</tr>
<tr>
<td>17</td>
<td>24</td>
<td>N</td>
<td>N</td>
<td>Ea-TB</td>
<td>B</td>
</tr>
</tbody>
</table>

ADA: adalimumab; ATT: anti-tuberculosis treatment; B: bilateral; CSa: cyclosporin A; Chor: choroiditis; SC: serpiginous choroiditis; MFSCL: multi-focal serpiginous choroiditis-like; R: right; Ea: Eales disease; PS: scleritis posterior; L: left; IS: immunosuppressant; MFM: mycophenolate mofetil; MFS: mycophenolate sodium; NVCM: neovascular membrane; N: no; PT: panuvelitis; Y: YES; Trt.: treatment; RV: retinal vasculitis.
the experimental self-immune uveoretinitis model (EAU).\textsuperscript{19} Accordingly, in this model the injection of Freund’s adjuvant (comprising M. tuberculosis particles destroyed by heat) in genetically susceptible mice is a sine qua non condition for producing the uveitis condition.\textsuperscript{20} Consequently, the authors consider that in human uveitis M. tuberculosis could be in some cases a “contributing” or “precipitating” factor without being a causal factor (that is, similarly to the events that take place in the EAU model) as this could explain the absence of inflammatory control or remission in some patients. In this context, ATT could continue to play an important role not to heal but to contribute to improving the condition and eliminating the possibility of late reactivation of latent TB (which is present in all the patients of the study) with subsequent immunosuppressant treatments, particularly in the case of tumor necrosis factor alpha (TNF-\(\alpha\)) which, as is known, produces selective immunosuppression against M. tuberculosis.\textsuperscript{21}

For the patients included in the study it was decided to utilize long ATT treatments (initially of at least 9 months) in agreement with the treatments recommended by studies carried out in endemic regions.\textsuperscript{1} The privileged immunology of the eye with extremely difficult to breach blood barriers must be considered when prescribing any type of treatment. In this line and in agreement with the guidelines recommended for other types of infectious uveitis (such as syphilitic uveitis)\textsuperscript{22} in which the intraocular inflammatory condition is seen as the equivalent of SNC expressions, the authors recommend maintaining the same approach with TBU.

Despite the known toxicity of ATT, this study observed how the ATT treatment was perfectly tolerated by the large majority of patients (11/17, 64.7%). Only 6 patients exhibited adverse defects and only in one the ATT had to be called off. However, these good results in what concerns safety do not remove the need of regular examinations for patients receiving this type of treatment.

This study also emphasizes the role of the positive therapeutic response to ATT as a possible solution to the absence of a sufficiently sensitive and efficient method for confirming the tuberculous etiology diagnostic in patients with UTBF. In the experience of the authors, the positive
response to ATT occurred in all patients even though only 14/17 (82.3%) achieved complete control of the inflammation. Of these, only one experienced a relapse in the extended treatment period. This supports the high positive predictive value of complete inflammatory control induced by ATT in patients with PUTB. In case this occurs, it is highly likely (92.8% of probability according to the results of this study) that uveitis is actually secondary to TB.

In summary, this study emphasizes the importance of adequate diagnostic and therapeutic management of patients with posterior uveitis and points to PUTB as a likely diagnostic, above all in patients with long-standing evolution and poor response to immunosuppressant treatment. Establishing ATT in patients fulfilling PUTB diagnostic criteria is an efficient and safe intervention in the vast majority of cases. Even so, prospective studies with higher number of patients are needed to confirm these preliminary data.

Conflicts of interest

No conflicts of interest have been declared by the authors.

REFERENCES