Anterior Non-granulomatous Uveitis: Differential Diagnosis

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Introduction

The anatomical classification of uveitis into anterior, intermediate, and posterior forms is very useful to conduct the work-up and eventually to reach a diagnosis, even though inflammation does not always respect these anatomical boundaries. Anterior uveitis is the term used for the group of inflammatory disorders for which the preponderant part of the inflammation is situated at the level of the pars plicata of the ciliary body, the retroiridal space, the iris, and the anterior chamber.

The anatomical diagnosis of anterior uveitis should first be verified by excluding spillover inflammation associated with uveitis of the posterior segment (intermediate or posterior uveitis). To exclude posterior involvement, pupil dilatation is mandatory in all cases. Secondly, the type of clinical presentation has to be characterized as non-granulomatous or granulomatous in order to correctly orient work-up and differential diagnosis.

Characteristics of Non-granulomatous Versus Granulomatous Uveitis

Non-granulomatous uveitis is characterized mainly by the type of keratic precipitates (KPs) that present as fine KPs producing endothelial dusting. In severe cases fibrinous clotting or hypopyon can occur depending on whether protein influx or cellular infiltration is predominant (Figs. 1, 2, and 3). In case of severe inflammation, it is also common to find posterior synechiae, and pressure tends to be more often decreased than increased (Fig. 2).

In contrast, granulomatous uveitis is characterized by KPs that are larger than the dusty KPs of non-granulomatous uveitis. These KPs are better individualized but their size varies depending on the inflammatory process. The medium- and large-size granulomatous KPs are called mutton-fat KPs. Other characteristic features of granulomatous uveitis are Koeppe and Busacca nodules made of inflammatory cells at the pupillary margin (Koeppe) or within the iris stroma (Busacca).

Synechiae are common in more pronounced inflammation. Pressure changes when present are usually characterized by increased intraocular pressure. In this context it is important to insist on the fact that Fuchs’ uveitis is a granulomatous uveitis unlike what is written in several textbooks. Fuchs KPs are structured, usually in a stellate fashion; they can be easily individualized and are larger than just dust (Fig. 4). The presence of Koeppe nodules in a substantial number of cases is further confirming the granulomatous character of Fuchs’ uveitis. The term of granulomatous...
uveitis is in fact a misnomer because a histopathologic term is used to describe clinical conditions based on certain clinical features including specific KPs and iris nodules, among other clinical signs. Originally the clinical term of granulomatous uveitis was still based on the histopathologic presence of granulomatous lesions which today is no more always the case. It has become a clinical category, a clinical terminology for which in some cases an underlying granulomatous histopathology can be found such as in sarcoidosis and tuberculosis, but this clinical terminology has extended to other conditions where the underlying histopathology is not granulomatous such as in Fuchs’ uveitis or birdshot retinochoroiditis or not always granulomatous such as in Vogt-Koyanagi-Harada disease.

Although this clinical distinction between granulomatous and non-granulomatous is a very useful classification, the subdivision is not an absolute one. A granulomatous uveitis may initially present as non-granulomatous before taking its granulomatous aspect. On the other hand, when dusty KPs are very numerous and thick, they may be mistaken as granulomatous (Table 1).

### Symptoms and Signs of Non-granulomatous Anterior Uveitis

The severity of symptoms in anterior uveitis ranges from no symptoms in chronic disease such as anterior uveitis related to juvenile idiopathic arthritis (JIA) to very severe symptoms in acute uveitis such as HLA-B27-related uveitis. Symptoms of acute anterior uveitis include photophobia, redness, pain, decreased vision, and tearing in the absence of discharge.
The Signs of Anterior Non-granulomatous Uveitis (Listed in Table 2)

1. Conjointival injection in anterior uveitis can be diffuse or localized circumferentially at the limbus (perikeratic injection) or mixed (diffuse and perikeratic injection).

2. Keratic precipitates (KPs) are small and diffuse causing dusting of the endothelium. If KPs are larger than dust and can easily be individualized, even if they are small, they should be considered as granulomatous such as in Fuchs' uveitis presenting microgranulomatous stellate KPs.

3. Anterior chamber flare is caused by exudation of proteins into the normally clear aqueous humor from iris vessels or across the ciliary body epithelium following the breakdown of the blood-aqueous barrier. The intensity of flare is measured in a standard fashion following the grading system proposed by the Proctor Group in San Francisco in 1959 (Table 3). This grading system is however only qualitative. When the concentration of proteins in the aqueous is very high, they agglomerate and form fibrinous clots, a finding more common in acute non-granulomatous uveitis (Fig. 1).

4. Posterior synechiae: Depending on the amount and composition of aqueous inflammatory proteins, adherences between the iris and anterior capsule of the crystalline lens can form (posterior synechiae) (Figs. 1–3).

   Since a few years, it is now possible to measure flare in a quantitative and objective fashion, using laser flare photometry (LFP) (Fig. 5). This new technology makes flare the only quantitative parameter to measure intraocular inflammation. So far cells were estimated to be more accurate to measure inflammatory activity in uveitis. At best this measurement is however only semiquantitative. LFP was shown to be more sensitive than slit-lamp assessment of cells to measure the evolution of inflammatory activity, making flare the new gold standard to assess intraocular inflammation. LFP allows to detect subclinical flare intensities and changes that can be predictive of clinical recurrence. A closer follow-up of therapy is possible, leading to increase of treatment in case of resistance to therapy but often also leading to corticosteroid sparing in case of lowered and stabilized LFP values. When available, laser flare photometry certainly allows improved management of uveitis and should be acknowledged as such.

5. Aqueous cells used to be the reference parameter for inflammatory activity because their evaluation was somewhat quantifiable by slit-lamp examination. Nowadays this is no longer true, when LFP is available. LFP is now the quantifiable gold standard to measure inflammatory activity even in chronic inflammation with chronic breakdown of the hemato-ocular barriers; LFP can detect active inflammation that responds to therapy. The notion that cells are no longer the hallmark of activity will take time to be acknowledged as, unfortunately, LFP is still not used universally in uveitis centers. Until then textbooks will continue to present cells as the sign of activity. Grading of cells in the anterior chamber has been standardized by Hogan et al. at the Proctor Foundation in 1959 (Table 4).

   It is important to make the difference between pigment clumps and inflammatory cells and to examine the anterior chamber.

### Table 2 Signs of anterior uveitis

| 1.1. Conjunctival and perikeratic injection |
| 1.2. Keratic precipitates (dust) |
| 1.3. Aqueous flare/fibrinous clots (Fig. 1) |
| 1.4. Posterior synechiae between the iris and capsule of the lens (Fig. 2) |
| 1.5. Aqueous cells/hypopyon (Fig. 3) |
| 1.6. Iris rubeosis |
| 1.7. Intraocular pressure changes (hypotony in severe acute anterior non-granulomatous uveitis) |

### Table 3 Slit-lamp grading of aqueous flare (1 mm x 3 mm beam)

<table>
<thead>
<tr>
<th>Flare</th>
</tr>
</thead>
<tbody>
<tr>
<td>No flare</td>
</tr>
<tr>
<td>Faint, just detectable</td>
</tr>
<tr>
<td>Moderate, iris details clear</td>
</tr>
<tr>
<td>Marked, iris details hazy</td>
</tr>
<tr>
<td>Intense, fibrin</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Grading</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
</tr>
<tr>
<td>+</td>
</tr>
<tr>
<td>++</td>
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<tr>
<td>+++</td>
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<tr>
<td>++++</td>
</tr>
</tbody>
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prior to mydriasis as cells and especially pigment dispersion can sometimes be seen after pupillary dilatation.

When the quantity of cells is very dense, they sediment and cause a hypopyon, a sign more often seen in HLA-B27-related uveitis, Behçet’s uveitis, and uveitis related to juvenile idiopathic arthritis (JIA) (Fig. 3).

6. In severe and long-standing uveitis, iris rubeosis can develop. It is in fact most often a pseudo-rubeosis that is reversible after introduction of anti-inflammatory treatment. Even when a real rubeosis has developed, it is usually situated at the pupillary border of the iris and is much less aggressive and proliferative than ischemic rubeosis iridis.

7. Intraocular pressure changes due to uveitis can present either as hypotension or hypertension. Hypotony is usually measured in severe uveitis involving the ciliary body such as acute anterior non-granulomatous HLA-B27-related uveitis, hypertony being usually associated with granulomatous uveitis, especially herpes simplex or herpes zoster uveitis, where a trabeculitis is associated.

Differential Diagnosis of Non-granulomatous Anterior Uveitis

1. In case of simple, fibrinous, or hypopyon non-granulomatous unilateral uveitis, the only first-line work-up test we presently perform is the detection of the HLA-B27 antigen. HLA-B27 testing is performed even if the inflammation is only moderate. If the test is positive, it will avoid further unnecessary testing during a subsequent episode, and it is reassuring for the patient and the doctor to know the specific diagnosis, especially when it is a benign disease. In case of a positive result, no further investigation is performed at the ophthalmological level. It is however recommended to take an oriented history that will allow, with the help of the internist or rheumatologist when necessary, to subclassify the affection into ankylosing spondyloarthritis, Reiter’s syndrome, Crohn’s disease, ulcerative colitis, or simply HLA-B27 uveitis without systemic associated disease.
About 50–55 % of acute anterior non-granulomatous uveitides are HLA-B27 positive in Europe. In different parts of the world, B27 positivity varies from one geographical area to another, being, for instance, quite low in Japan. In the remaining 45–50 % of cases, a specific diagnosis is more difficult to establish.

If the episode of B27-negative non-granulomatous uveitis is of limited severity and/or responds readily to classical topical corticosteroid therapy, no other investigation than to search for the HLA-B27 antigen is performed.

2. In case of an anterior uveitis with hypopyon (Fig. 6), signs and symptoms found in Behçet’s syndrome should be searched for, in particular oral and/or genital ulcerations (Fig. 7), cutaneous signs such as erythema nodosum and pustules, arthralgias, thrombophlebitis, and cardiovascular, pulmonary, gastrointestinal, or central nervous system involvement. If Behçet’s uveitis is suspected, we find it useful to look for the HLA-B51 antigen that, when present, represents an additional argument for the diagnosis of Behçet’s uveitis (but is not diagnostic), especially in the milder forms of Behçet’s uveitis seen in the European Caucasian population. Isolated anterior Behçet’s uveitis can occur, but posterior involvement should be searched for by fundoscopy and is best investigated by performing a fluorescein angiography looking for retinal vasculitis (Fig. 8) (Table 5).

3. In case of non-granulomatous uveitis in children (with or without band keratopathy), history should be directed toward juvenile idiopathic arthritis (JIA). Inflammatory symptoms can be completely absent, contrasting with the severe signs of uveitis such as hypopyon and synechiae that can occur in a white externally non-inflamed eye, features of JIA-related uveitis (Fig. 9). Uveitis is usually associated with the oligoarticular form of JIA, and testing should include antinuclear antibodies (ANA) that are present in up to 70 % of JIA patients with uveitis (Jones NP, an illustrative manual). In elderly children it is also useful to test for the presence of HLA-B27 antigen.
A bilateral non-granulomatous uveitis in children, but also in adults, should prompt to search or exclude tubulointerstitial nephritis and uveitis (TINU) syndrome, an often neglected diagnosis. Renal function should be tested, starting with the dosage of creatininemia requiring sometimes renal biopsy, and urinalysis should be performed looking for glucosuria and dosage of beta-2-microglobulin which is found to be elevated in the urine in TINU.

In children pars planitis can initially present with an anterior participation and can be mistaken for an anterior uveitis if the posterior segment is not carefully examined.

In case of non-responding HLA-B27-negative anterior uveitis or in case of recurrence, we pursue the work-up in the same fashion as for a granulomatous uveitis.

**Case 1: HLA-B27 Uveitis**

Case 1a. A 33-year-old man consulted for a red painful right eye since 2 days. He said that he had previous episodes sometimes in the right and sometimes in the left eye but never in both eyes at the same time. Visual acuity was conserved and uncorrected VA in both eyes was 1.0. At the slit lamp, there were fine KPs not exceeding dust on the endothelial surface predominant inferiorly. In the anterior chamber, there was a 3 to 4+ flare and fibrin with posterior irido-lenticular synechiae on nearly 360º. Laser flare photometry was increased to 433 ph/ms in the right eye and was normal (3.8 ph/ms) in the left eye. Aqueous cells amounted to 2+. Pressure was reduced to 5 mmHg on the right, while the left contralateral eye had a normal pressure of 12 mmHg. Treatment was started immediately applying prednisolone acetate 1 % drops every 10 min, alternating with a dilating cocktail containing 2.5 % phenylephrine, 0.5 % tropicamide, and 0.25 % scopolamine. The synechiae were broken after 2 h (Fig. 10), and the patient was dismissed with the treatment including hourly 1 % prednisolone acetate drops and prednisolone 0.5 % ointment at night, as well as tropicamide 0.5 % ten times per
When the patient came back on the following morning, slit-lamp flare and cells were estimated at 2+. LFP values decreased to 98.7 ph/ms, showing that the treatment was efficient. After 1 day LFP values went down to 25.8 ph/ms and to 14.3 after 2 days (Fig. 11). Dilatation was stopped on the second follow-up day, as synechiae usually do not develop with LFP values under the value of 30 ph/ms. Prednisolone drops were tapered and finally stopped after 16 days with nearly normal LFP values of 6.1 ph/ms indicating good recovery of blood-ocular barrier (BOB) HLA-B27 antigen, never tested before, was searched and came back positive.

Case 1b. A second patient consulted our emergency ward with the same type of presentation. He was seen for a left red eye and presented anterior chamber cells (2+), slit-lamp flare (3+), and fibrin, synechiae, and hypotony (Fig. 12). Laser flare photometry values were very elevated up to 298.7 ph/ms. The same therapy as in the first patient was applied, and the inflammation seemed to improve at the slit lamp showing release of synechiae but the eye was still painful after 2 days. After 12, 24, and 48 h, the LFP values remained high around 295 ph/ms and even increased to 309 ph/ms at 48 h indicating resistance to the classic topical treatment applied for acute anterior HLA-B27 uveitis (Fig. 11). It was then decided to perform an orbital floor injection of aqueous betamethasone 4 mg (Celestone®). Twelve hours after the periocular injection, LFP value decreased to 14.8 ph/ms (Fig. 11), and all topical treatment could be stopped after 19 days with an LFP value of 8.1 ph/ms showing a slight residual BOB, in accordance with standard evolution of HLA-B27-related acute anterior uveitis (Fig. 13).

These two typical HLA-B27 uveitis cases optimally benefit from LFP. Without LFP it is not possible to follow flare changes in such high flare situations; it would have been impossible to detect that case 2 was resistant to standard topical therapy. In such cases it is necessary to give additional orbital corticosteroid injections. It was shown that in nine resistant cases, periocular aqueous corticosteroid injection led to a 50 % flare reduction after only 12 h (Herbort et al. 1997) (Fig. 14). On the other hand, in low
flare situations, at the end of an episode, it would not be possible to determine the end of dilatation when LFP reaches values below 40 ph/ms, a value under which synechiae formation is improbable.

**Case 2: Uveitis Associated with Juvenile Idiopathic Arthritis**

An 8-year-old patient came to see us for second opinion. She had presented uveitis and an initial attack of juvenile idiopathic arthritis of the oligoarticular at 2 years of age. At age 7 a bilateral cataract operation with intraocular lens implantation was performed. We saw the patient 1 year after cataract surgery with a vision reduced to fingercounting on the right and 3/60 on the left, and the patient was already registered in a special school for visually impaired persons. Slit-lamp examination showed complete pre- and retro-IOL opacification and band keratopathy on both sides (Figs. 15 and 16). The patient was merely under topical treatment, receiving one single daily drop of prednisolone acetate 1 %. This minimalistic treatment was justified by the fact that there were no aqueous cells; hence there was no active inflammation. Slit-lamp examination
of the anterior segment showed no cells but a 3+ flare ODS. The posterior segment was barely visible but no major lesions could be seen, and OCT showed that there was no major loss of architecture of the macular retina. Visual fields showed a nearly total loss of mean sensitivity ODS (Fig. 17). Laser flare photometry (LFP) values were very elevated up to 435 ph/ms on the right and 292 ph/ms on the left. Intraocular pressure (IOP) was 6 mmHg on the right and 11 mmHg on the left, and phthisis bulbi was feared OD.

Massive inflammation-suppressive treatment (IST) was started including dexamethasone 0.1 % drops and nonsteroidal drops six times daily, prednisone 1.7 mg/kg with subsequent slow tapering, and azathioprine 2.5 mg/kg. After 1 month, visual acuity (VA) improved from fingercounting to 0.1 OD and from 3/60 to 0.15 OS. LFP values decreased to 261 ph/ms OD and 124 ph/ms OS. Band keratopathy was removed using EDTA 2 % drops together with milling and scratching of calcium deposits. YAG laser capsulotomies were performed ODS. After 6 months BCVA improved to 0.2 OD and 0.6 OS (Figs. 18 and 19). LFP values decreased to 226 OD and 99.6 OS. Intraocular pressure stabilized around 9–10 mmHg OU. After 24 months BCVA increased to 0.7 OD and 0.8 OS. Visual field improved substantially on both sides (Fig. 17). After 11 years under several ISTs, including immunosuppressants such as mycophenolic acid and cyclosporine as well as biologics such as infliximab and adalimumab, the situation stabilized in this patient that finally could follow a normal school and was employed as a medical assistant. BCVA was 0.2 OD and 0.8 OS. LFP values stabilized at 95.3 ph/ms OD and 39.7 ph/ms OS with IOP values of 7 mmHg OD and 12 mmHg OS.

This case shows that the axiom “no aqueous cells means no active inflammation” has to be revised especially in non-granulomatous uveitis. It is shown here that very high LFP values do not necessarily mean irreversible BOB breakdown. A substantial proportion of BOB in chronic
inflammation corresponds to active inflammation even though there are no inflammatory cells present and maximal IST has to be applied to determine which part of BOB can be reversed and which proportion is truly irreversible BOB. Improvement of LFP values clearly here had a tremendous impact on visual function. Obviously close monitoring of the level of BOB and evolution of aqueous flare can only be performed with LFP, today the only quantitative and precise modality to exactly measure the level of intraocular inflammation.

**Case 3: Uveitis Mistakenly Described as Non-granulomatous with Very Deleterious Consequences**

A 19-year-old lady complained of headaches with slightly fuzzy vision. She consulted her eye doctor, who described bilateral non-granulomatous
uveitis with fine KPs, vitritis, and hot hyperfluorescent disks. The best corrected visual acuity was 0.9 ODS. The ophthalmologist sent the patient for internal medicine work-up where she revealed to the internist that she presents oral aphthae four to five times a year. The search for HLA-B51 was positive and the diagnosis of Behçet’s uveitis is made. The patient was treated with systemic corticosteroids with an initial dosage of 60 mg of prednisone tapered down to 10 mg after 8 months. In addition the patient was given 15 mg of methotrexate orally once a week that subsequently had to be stopped because of suspected liver toxicity. We saw the patient 3 years later when the patient had put 8 kg of weight.

BCVA was still 0.9 ODS. On the endothelium on both sides, very fine however well-identifiable stellate KPs could be seen (Fig. 20). Laser flare photometry values were 9.7 ph/ms OD and 10.3 ph/ms OS. The brown iris showed a slight degree of atrophy (Fig. 20). There were 1–2+ cells in the anterior vitreous. On the right there was small posterior subcapsular cataract (Fig. 20). The patient brought with her the fluorescein angiographies performed elsewhere that showed bilateral disk hyperfluorescence without significant vasculitis (Fig. 21) that is classically seen in Fuchs’ uveitis, which obviously was the diagnosis in this patient. Treatment was discontinued after which the situation remained stable. Such a misdiagnosis would never have happened if the KPs would have been interpreted as granulomatous, a definition which applies to all KPs that are more than dust, that can be individualized. Such granulomatous KPs are an absolute exclusion criterion of Behçet’s uveitis.

Case 4: Uveitis Related to a Streptococcal Infection/Para-infectious Uveitis

A 9-year-old girl complained of pain in her right eye especially at night with a slightly decreased vision. She had been treated with penicillin since several days for an angina. Visual acuity was 0.9 OD and 1.0 OS. Slit-lamp examination showed a 2–3+ flare and a 1+ cell in the right anterior chamber, while the left eye looked uninflamed. Intraocular pressure was 6 mmHg OD and 10 mmHg OS. There were very few vitreous cells to be seen in the anterior vitreous. Laser flare photometry values were elevated to 176 ph/ms OD and slightly elevated to 15.7 ph/ms. Fundus examination showed a prominent papillitis OD, while the disk was slightly hyperemic at most OS (Fig. 22). Visual fields were normal. Blood laboratory tests showed an elevated sedimentation rate (35/h) and an elevated c-reactive protein (CRP = 24, normal value < 5), and
antistreptolysins were elevated and over 500 (normal value \(< 200\)). Treatment consisted of systemic prednisone (20 mg per day, tapered over 3 months) and topical prednisolone acetate 1 % five times daily ODS, tapered down to zero over a period of 5 months. After 5 months LFP values were down to 7.0 ph/ms OD (slight persistent BOB) and to 3.6 ph/ms (normal value). The papillitis decreased progressively with an almost normal aspect after 5 months (Fig. 22).

Further Comments

Classification of anterior uveitis into granulomatous and non-granulomatous is extremely useful as it allows to orient the clinician in establishing his diagnosis, as long as the criteria distinguishing the two groups are well understood. Indeed some specific entities can be excluded categorically thanks to this differentiation. For instance, the presence of micro-granulomatous KPs as seen in

Fig. 20  Case of bilateral Fuchs’ uveitis that was classified as non-granulomatous leading to misdiagnosis as Behçet’s uveitis. Micro-granulomatous KPs can be seen in both eyes, as well as a posterior subcapsular cataract (middle picture). It has to be noted that Fuchs’ uveitis can be bilateral in about 10 % of cases.

Fig. 21  Case of bilateral Fuchs’ uveitis that was classified as non-granulomatous leading to misdiagnosis as Behçet’s uveitis. Hyperfluorescent is part of the semiology of Fuchs’ uveitis, together with micro-granulomatous KPs and vitreous cellular infiltration.

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Fuchs’ uveitis absolutely allows to exclude Behçet’s uveitis. The problem is that in some textbooks the small KPs seen as Fuchs’ uveitis are described as non-granulomatous and Fuchs’ uveitis is classified into the group of non-granulomatous uveitis entities, leading to the misdiagnosis that happened in case no. 4. Finally there is some confusion in the clinical use of the term granulomatous. This term should not be taken in its histopathologic sense: It is in fact a misnomer as it uses a histopathologic term to categorize a clinical spectrum including diseases that, if histopathology were done, do not have histopathologic granulomatous features.

**Conclusion**

Non-granulomatous anterior uveitis entities can present with very high flare values that however, in general, respond well to corticosteroid therapy, usually topical but that sometimes need to be given by periocular injections and even systemically, sometimes needing to be very aggressive. Evolution of these entities is nowadays best performed using laser flare photometry (LFP) that allows objective and precise measurement of flare. Both in high and low flare situations, LFP can detect slight flare changes imperceptible to the human eye at the slit lamp, allowing to step up with treatment in case of LFP-detected resistance to therapy. On the other hand, in low flare situations, LFP avoids overtreatment if it detects decrease of flare again not perceptible at the slit lamp.

**Key Points**

- Non-granulomatous anterior uveitides are uveitis entities characterized by fine retro-descemetic keratic precipitates (KPs) no larger than dust, associated with hypopyon or fibrin clots in severe forms.
- This distinction allows to orient diagnostic work-up and identify a number of specific entities.
- The more frequent entities include HLA-B27-related uveitis, JIA-associated uveitis predominant in children, and Behçet’s uveitis.
- In the initial stages, granulomatous anterior uveitis can sometimes present itself as non-granulomatous.
- Non-granulomatous entities can often present with high flare and cell values that are still graded using the Proctor grading system taken over by the SUN system. In order to precisely monitor these patients nowadays, however, laser flare photometry is the method of choice, able to detect small flare variations both in high and low flare states.
- In severe cases, hypotony is often found especially in inflammation involving the ciliary body such as acute anterior non-granulomatous HLA-B27-related uveitis.

**Suggested Reading**


![Fig. 22 Papillitis in streptococcal-related para-infectious uveitis](image-url)


