



Importance of Chemical Therapy in Relapsing Polychondritis – a Disease with Impact on the Eye Tissues

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Abstract: *Relapsing polychondritis (RP), falls into the category of rare diseases. The true incidence and prevalence of this rare disease is unknown. The ocular implications in relapsing polychondritis (RP) are numerous and variable, including mainly inflammation in different structures of the eye. As a complication of this inflammatory condition, a closed secondary angle glaucoma has been described. The purpose of our work is to highlight the diversity of ocular determinations of the same rare disease, including different types of glaucoma that may occur under the same circumstances and to make a detailed analysis of chemical therapies based on drug treatment pathways. The paper includes a report of the cases series admitted to the Clinic of Ophthalmology in St. Andrew Emergency Clinical Hospital, Constanța, between 2007 and 2018, cases analyzed and compared with international literature. One of the cases is a 43-year-old male patient with bilateral open-angle bilateral glaucoma. Other cases with RP, are patients of 41 and 46 years old, respectively, presented with unilateral episcleritis. This case series report aims to show that RP can associate even more protean ocular manifestations than already discussed in the literature, with specific chemical therapies and to emphasize the need for team approach and ophthalmological monitoring in the care of RP patients with chemical therapy (drug treatment) for each patient.*

Keywords: *chemical therapy, steroid, relapsing polychondritis, inflammation, glaucoma*

1. Introduction

Relapsing polychondritis (RP) is a severe, episodic, rare, progressive and potentially fatal multi-systemic autoimmune granulomatous inflammatory condition involving cartilaginous structures and proteoglycan-rich structures, more often those of the ears, nose, laryngo-tracheo-bronchial system, but also those in joints, skin, epiglottis and eye [1]. For the first time, in 1923 this condition was described by Jaksch-Wartenhorst as "polychondropathy" [2]; in 1960, Pearson et al. introduced the term "relapsing polychondrite", to highlight the particular intermittent observing course in 12 patients [3]. The diagnostic criteria for RP were initially established in 1976 by Mc Adam et al. based on the clinical presentation observed in patients [4], but at a later date they were modified by Damiani and Levine [5] and Michet et al. [6]. RP is a rare disease (Orpha code: 728), with a large number of unique case reports, but few patient series reported in the literature [6]. An incidence of 3.5 / 1,000,000 / year has been estimated [7, 8], but in a recent study, in the UK, an even lower incidence was reported [9]. The average age of disease onset is between the fourth and fifth decade of life, in the majority of patients aged between 44 and 51 years at the time of diagnosis [10]; however, RP can occur at any age. The literature studies [11] show that the clinical presentation of RP in children is similar to that of the adult. Neonatal cases are not described [12]. This condition (RP) occurs with a similar frequency in both sexes [13], may affect populations from all ethnic groups with very high variability in clinical presentations [14]. Ocular involvement occurs in 14 – 24% of patients at presentation, and eventually the eye is involved in 51-65% of cases. Other studies revealed 50-60% of the cases of RP with ocular manifestations, but rarely as inaugural phenomenon [14].

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Although the most common sites of involvement are the conjunctiva, episclera and sclera (each involved in nearly 10% of the patients), almost any part of the eye can be involved in the disease [15]. As a complication, secondary angle-closure glaucoma was also described [16].

2. Materials and methods

Three male RP patients presented in the Clinic of Ophthalmology of Sf. Andrew's Emergency Clinical Hospital, Constanta. They were diagnosed and followed between 2007 and 2018; during this time their clinical manifestations were analysed. Research methods and specific ocular therapy investigation techniques were used. Patients were 43, 41 and 46 years old (Table 1).

Table 1. Cases diagnosed with pr, analyzed

| No. crt. | Age / Sex | Diagnosis stage with PR | Patient History Data |
|-----------|---------------------|------------------------------|---|
| Patient 1 | 43 years old, male, | diagnosed with RP 1 year ago | as suffering from type II diabetes, stage III hypertension, |
| Patient 2 | 41 years old, male, | diagnosed with RP 2 year ago | did not show glaucoma or vision disorders |
| Patient 3 | 46 years old, male, | diagnosed with RP 3 year ago | did not show glaucoma or vision disorders |

Each of the 3 cases had particularities and diagnostic dilemmas and required a careful analysis of all the results of the investigations, in order to choose the most effective and harmless therapeutic methods, in an effort to provide the best possible management of the disease, with the fewest possible side effects.

3. Results and discussions

The real incidence and prevalence of this rare disease are unknown. Various treatment pathways are described in the literature. The chemical therapy treatment has been applied according to the indicators obtained from the patient's anamnesis. In case of pain control and inflammation in non-severe forms, non-steroidal anti-inflammatory drugs (NSAIDs) were used [14, 17-19]. For mild manifestations chemical treatment is with Dapsone or Colchicine [20-22]. Most frequently the therapy consisted of orally given prednisone and intravenous administration of methylprednisolone for rapid effect [23-24].

The second treatment option for this serious disease, or in patients which are intolerant to corticosteroids, those who become addicted to corticosteroids or have a lack of response to corticosteroids, consisted of other classes of pharmaceutical compounds. For example, drugs such as Cyclophosphamide, Azathioprine, Cyclosporine or Methotrexate (alone or in association with systemic corticosteroids) were used in the pharmaceutical protocols [25-29]. Other proposed treatments included the following drugs: 6-mercaptopurine, plasmapheresis, anti-CD4 monoclonal antibody, penicillamine, minocycline, high-dose intravenous immunoglobulins, leinflamide [24,30-34]. However, there is limited experience in the specialized literature. There were also selected, complicated cases of severe bronchial stenosis or intractable heart failure due to the regurgitation of the valve and in case of aortic aneurysms, in which surgical procedures were applied [17, 33]. The challenges of understanding the disease remain [5]. In our paper we focused on ocular parameters in our patients with PR and compared them with 20 healthy control eyes (Table 2).

The first male patient, aged 43, came to the emergency department for bilateral blurred vision, tears, photophobia, painful red eyes and headaches (Figure 1a and Figure 1b).

The symptoms started 10 days previously and progressively increased in intensity, forcing the patient to attend the hospital for urgent diagnosis and therapy. As personal history, the patient was known as suffering from type II diabetes, 1 year ago at presentation time, arterial hypertension stage

III, discovered three years ago, both compensated at the moment under therapy. Also the patient was diagnosed with RP 1 year previously, when he visited an otorhinolaryngologist because of red, swollen and painful pinnae of ears, non-responsive to antibiotic and nonsteroid anti-inflammatory (NSAI) treatment. During first hospitalization, the patient also complained about fingers, spine and neck pains, and blood tests revealed strong increased values in inflammation tests. The patient was at third similarly episode during last year, mentioning that under those circumstances he had taken some NSAI medication on his own, and symptoms disappeared, but this time the same medication didn't provide any relief.

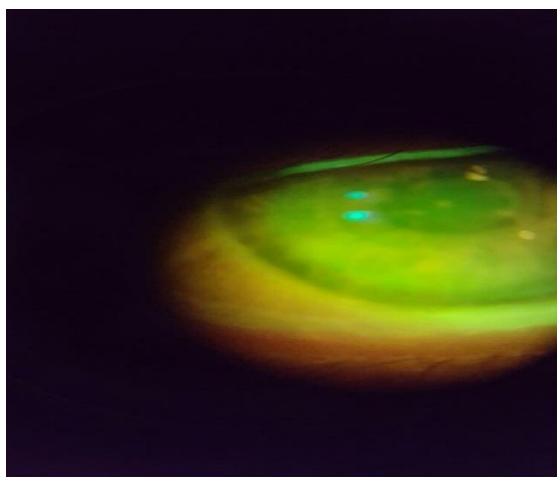
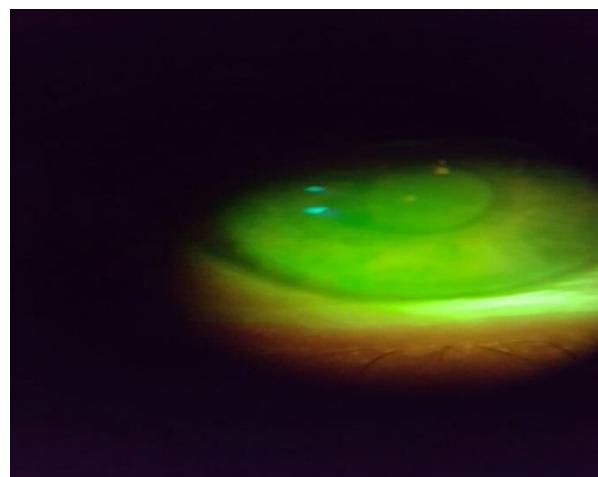
Table 2. Ocular parameters in our rp patients and control eyes

| | Patient 1 | Patient 2 | Patient 3 | Controls ($n = 20$) |
|-----------------------------|-----------|-----------|-----------|-----------------------|
| Age (years) | 43 | 41 | 46 | 45.2 ± 3.2 |
| Refractive error (diopters) | + 1 | + 1 | +0.5 | $+0.75 \pm 0.25$ |
| Corneal diameter(mm): | | | | |
| Horizontal | 11.06 | 11.26 | 11.37 | 11.42 ± 0.28 |
| Vertical | 10.59 | 10.68 | 11.15 | 11.26 ± 0.15 |
| Keratometry: | | | | |
| Central | 45.29 | 44.54 | 44.89 | 43.71 ± 0.65 |
| Peripheral | 45.14 | 44.28 | 44.63 | 44.05 ± 0.82 |
| Pachymetry: | | | | |
| Central | 581.1 | 529.2 | 534.1 | 526.4 ± 11.9 |
| Peripheral | 690.1 | 669.0 | 692.1 | 695.8 ± 13.1 |
| Corrected AC depth (mm) | 1.527 | 1.799 | 1.999 | 2.289 ± 0.19 |
| Lens thickness (mm) | 4.905 | 4.599 | 4.612 | 4.428 ± 0.18 |
| Axial length (mm) | 22.31 | 22.49 | 22.71 | 22.99 ± 0.68 |
| Relative lens position | 0.199 | 0.201 | 0.214 | 0.213 ± 0.015 |

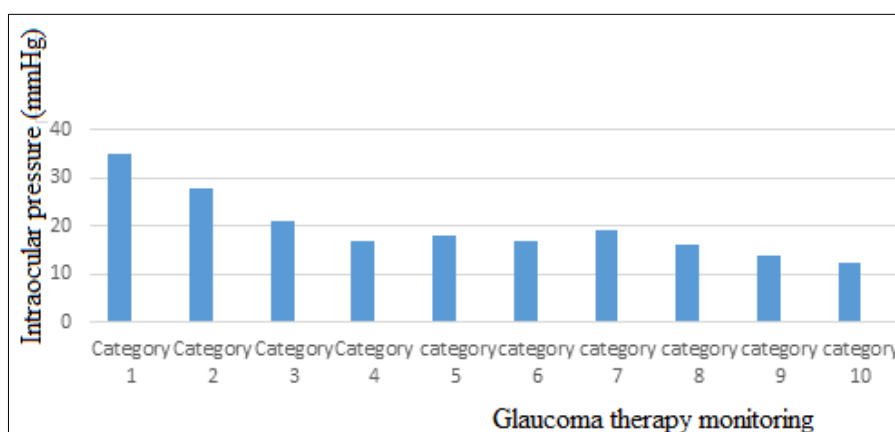
Due to this new different evolution, the patient attended hospital for the first time. During that same first hospitalization, clinical aspect correlated with paraclinic tests led to diagnosis of RP and general steroid therapy was initiated.

During last year, general state of our patient was good, without any inflammations or pains. He was under steroid maintenance therapy, with 20 mg Prednisolone daily. But 10 days ago, ocular symptoms appeared, so that the patient attended Ophthalmology service. Complete ophthalmological examination was performed, revealing intense perikeratic congestion, diffuse corneal epithelium edema, normal depth anterior chamber, circular and reactive pupils, clear crystalline lens.

Visual acuity was 0.3 BCVA bilateral. Goldmann tonometry revealed intraocular pressure of 35 mm Hg bilateral. Ophthalmoscopy showed well defined outline optic disks, slightly discolored in temporal sector, with blood vessel moderately deviated toward medial, the rest of retina looking normal. Gonioscopy showed open angle and of normal width. The patient received fixed combination Timolol maleat 0.5% and Dorzolamide eye drops twice daily, Brimonidine tartarate 0.2 % drops thrice daily, Furosemide 40 mg daily, Ketoprofene 200 mg orally once daily, Acetazolamide 250 mg every 8 h. Prednisolone dosage was reduced to 10 mg daily.

**Figure 1a.** Painful red right eye**Figure 1b.** Painful red left eye

After two days therapy, intraocular pressure decreased to 21 mm Hg bilateral, and the third day reached 17 mm Hg. One week later, patient state improved significantly, congestion and edema were resolved; visual acuity recovered to 1.00 bilateral, and IOP was 12 mm Hg in right eye and 13 mm Hg in left eye. Systemic anti-glaucoma medication was discontinued, topical anti-glaucoma medication was partially discontinued; one month later the patient was prescribed only Timolol maleate 0.5 % eye drops twice daily (Figure 2).

**Figure 2.** Intraocular pressure evolution under glaucoma therapy

Despite intraocular pressure reduction, headache persisted. We asked for neurological examination. The neurologist suggested perform brain tomography, which looked normal, so Quarelin 3 tablets daily were indicated [34]. The final diagnosis was steroid-induced glaucoma. It was not possible to stop steroid therapy to our patient, because of RP; steroids and same Timolol maleate 0.5 % eye drops were indicated after hospitalization period. Maintenance steroid dosage was kept 10 mg Prednisolone daily. During 1year follow-up, until now, IOP remained normal, there was no glaucoma progression and no other ocular discomfort. The other two cases were 2 male patients, 41 and 46 years of age, diagnosed with RP 2 and respectively 3 years previously to their presentation in the Ophthalmology service. The eye impact was much less severe than in the first case, consisting of unilateral scleritis, without other ocular tissues determinations (Figure 3a and Figure 3b).

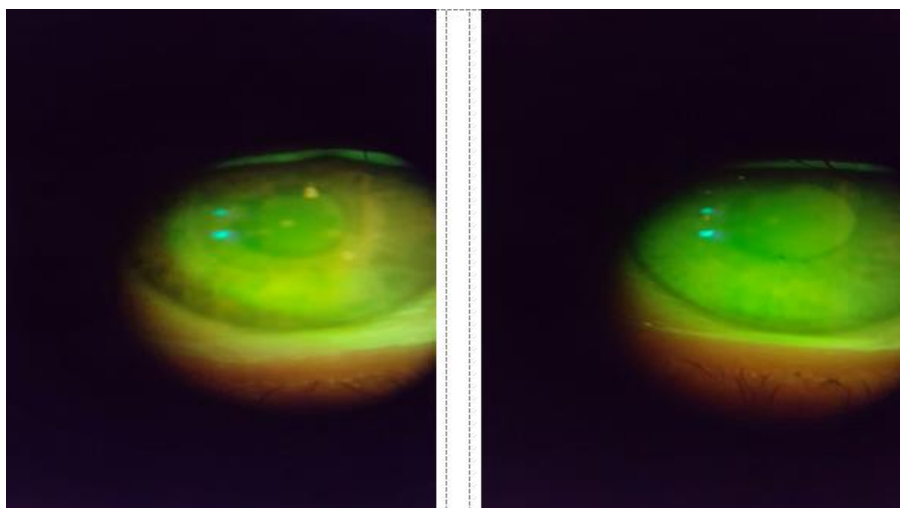


Figure 3a. Unilateral scleritis in right eye

Figure 3b. Normal left eye

None of these two patients developed glaucoma or vision impairment. They had a good outcome with non-steroidic and steroidic anti-inflammatory therapy, as topic and maintenance dosage systemic administration. RP, as inflammatory condition, involving also eye structures, was described as causing sometimes uveitis and scleritis [6], which might lead to secondary angle-closure glaucoma [4]. In our patient, congestion of eye, high IOP, local pain suggested such glaucoma type, but angle was normal, other structures of eye were normal. High IOP in our case had different mechanism. Three previous ophthalmologic examinations during last 2 years before presentation excluded high IOP or glaucoma; no family history of glaucoma either, so we excluded primary open angle glaucoma. Glucocorticoid receptors β and over-expression of FK 506-binding immunophilin 51 may provide molecular explanation for the development of ocular hypertension [7], by formation of fibrils beneath inner wall endothelium of Schlemm's canal [8].

Glucocorticoids also directly alter phagocytic activity, extracellular protease activity and glycosaminoglycan content of trabecular meshwork tissue. [9] Higher protein synthesis after corticosteroids was proven [10].

Anyone can be at risk for steroid induced glaucoma, with higher risk for patients with: relatives with POAG, type I Diabetes Mellitus and connective tissue disease [11, 12].

Association of RP and diabetes mellitus was recognized [12, 16]. Keeping in mind higher risk for diabetic patients to steroid-induced glaucoma, this risk becomes double in patients with both RP and diabetes. Central nervous system manifestations of RP are rare and variable, believed to be caused by underlying vasculitis of small and/or medium sized arteries [13, 35]. Our patient's headache, persisting despite IOP normalization, might be explained by such mechanism. It is interesting that a disorder primarily affecting cartilaginous tissue should involve the eye in such high percentage of cases, maybe because all involved tissues contain large amounts of mucopolysaccharide, particularly glycosaminoglycans; it was demonstrated uniform loss of glycosaminoglycans in affected cartilage and aorta [35-37].

Analogous to the multiple implications that appear in other rare diseases [38] and in RP, there are multiple aspects that need to be analyzed. The deep understanding of RP is the key for a better management and quality of life for the patients. The relative rarity of the disease causes difficulties in evaluating potential therapies. Biologic therapy brings hope in conventional immunosuppressant resistant cases [18, 23, 26]. The anti-TNF- α agents are also of interest in cases with pulmonary involvement, the leading cause of mortality and morbidity in RP. [35, 39].



4. Conclusions

It's important to have in mind all possible complications of such disease, including not only secondary angle-closure glaucoma, but also secondary open angle, steroid-induced glaucoma. Early recognition is a condition to choose best management for the patient.

In RP, corticosteroids are the mainstay of therapy. Continuous use of prednisone decreases severity, frequency and duration of relapses.

RP is a complex condition that requires team approach, in order to provide early diagnosis and prompt therapy for patient care. This would be the way to reach for both complete resolution of ocular manifestations with visual recovery, and a stable course of the general disease, as much as possible.

Another conclusion revealed by our case series is the necessity of having in mind the risk of secondary glaucoma induced by steroid therapy, risk which requires a complete ophthalmological examination at baseline, before starting therapy. The value of teamwork becomes even more obvious under the circumstances of compulsory ophthalmological monitoring, in order to provide to the patient the best possible management of the disease and of its therapy risks. As a last moment idea, considering the COVID-19 pandemic and the higher risk of infection in autoimmune disease patients, corroborated with the international updates regarding conjunctival congestion caused by this virus and the risk of the presence of infectious viral particles in tears and eye secretions, increased protective and disinfection measures during eye examination and care for both patients and doctors are strongly recommended.

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