Review

Rare within rare. Necrotising scleritis and peripheral ulcerative keratitis: eye-threatening complications of relapsing polychondritis

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Received on November 29, 2021; accepted in revised form on February 7, 2022.

Clin Exp Rheumatol 2022; 40 (Suppl. 134): S86-S92.

Key words: relapsing polychondritis, necrotising scleritis, peripheral ulcerative keratitis, rare connective tissue diseases

Funding and disclaimer: page S91.

Competing interests: none declared.

ABSTRACT

Objective. *Relapsing polychondritis (RP) evolves with variable and intermittent involvement of cartilage and proteoglycan-rich structures. Ocular manifestations are present in up to two-thirds of RP patients. Necrotising scleritis (NS) and peripheral ulcerative keratitis (PUK) may be inaugural and may lead to eye perforation and vision loss. We aimed to review NS and PUK in RP, in order to characterise them, to identify successful treatment options and unmet needs.*

Methods. *A systematic review of the currently available evidence in PubMed, EMBASE and Scopus was performed according to PRISMA, including observational studies, single case reports and case series of NS/PUK in RP. Study design, number of patients, age, gender, treatment and outcome, were extracted. Two RP patients also provided their opinion.*

Results. *Five case reports and two case series were eligible for inclusion. We identified 10 RP patients with eye-threatening complications (NS and/or PUK), 9 adults (2 males, 7 females, aged 35-72, median age 57.6 years) and one paediatric patient (F, 11 years). Apart from glucocorticoids, cyclophosphamide was effective in 4 patients; infliximab, high-dose immunoglobulins, dapsone, or cyclosporine were also successfully employed in a case each. Surgical repair was reported in 2 cases.*

Conclusions. *Ocular inflammation is often bilateral and recurring in RP; NS/PUK are rare complications. All patients who develop NS/PUK should be specifically questioned for RP signs and symptoms. Early institution of immunosuppressive therapies is mandatory. Increasing awareness, physicians' and patients' education and a multidisciplinary approach may help improve the prognosis of these serious complications of RP.*

Introduction

Relapsing polychondritis (RP) is a systemic immune-mediated disease that evolves with variable and intermittent involvement of cartilage and proteoglycan-rich structures, including the eye. Ocular manifestations are present in up to two-thirds of RP patients (1). Of these, episcleritis and scleritis are the most common ocular manifestations of RP and occur in nearly half of patients during the disease course (1). Less commonly, proptosis, eyelid or periorbital oedema, keratoconjunctivitis sicca, dacryocystitis, extraocular muscle palsy, choroiditis, corneal infiltrate, peripheral ulcerative keratitis (PUK), iridocyclitis, anterior and posterior uveitis, cataract, retinal vein/artery occlusion, retinopathy, exudative retinal detachment, papilledema, and optic neuritis are seen (1, 2).

A unilateral painful diffuse red eye in RP primarily suggests scleritis. The eye in scleritis is tender to palpation, and topical epinephrine does not improve the ocular congestion. By contrast, episcleritis is less painful and eye congestion improves with vasoconstrictor instillations. Anterior scleritis may be diffuse, nodular, or necrotising. Posterior scleritis is rare and may manifest as ptosis or periorbital swelling (3). Posterior scleritis is generally diagnosed by B-scan ultrasonography, which identifies a T sign created by the hypoechogenic fluid between the sclera and the optic nerve (3). The subtypes of scleritis are distinct

and may progress exceptionally from one type into another (3). Importantly, ocular symptoms, reflecting recurrent episcleritis or scleritis, may occur early and could be the first manifestation of RP. Nevertheless, the most severe complications of RP are necrotising scleritis (NS) and PUK, which may lead to eye perforation and vision loss.

NS is a rapidly progressive, devastating complication of RP. Clinically, patients often experience harrowing pain (4). In NS, the severe immune-mediated scleral inflammation progresses to avascular necrosis of the sclera, which can extend to the episclera and other ocular structures. Eye examination reveals dilation of the deep episcleral vessels, along with areas of white sclera surrounded by oedema and congestion, reflecting vascular infarction and necrosis of the sclera. The involvement of adjacent tissues, with secondary corneal ulceration or uveitis, is a frequent concomitant finding. In a further phase, scleral thinning after the resolution of scleritis allows for the choroidal hue to become visible (5).

PUK is, at its turn, a notably destructive ophthalmological manifestation of autoimmune diseases. Clinical features of PUK are ocular irritation and pain, redness, photophobia, and corneal opacity (6). Upon examination, PUK presents as an area of crescent-shape necrotising inflammation in the peripheral cornea, combined with epithelial defects and disorganisation of the perilimbic stroma, a structure rich in proteoglycans. PUK may be associated with NS, and their association often suggests a systemic autoimmune disease, including RP, for which it may be inaugural (5). This type of eye involvement requires rapid recognition and prompt therapy to prevent the eye loss.

We aimed to review the eye-threatening complications of RP, respectively NS and PUK, in order to characterise these manifestations and to identify successful treatment options and unmet needs.

Material and method

This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist 2020 (7) (Fig. 1).

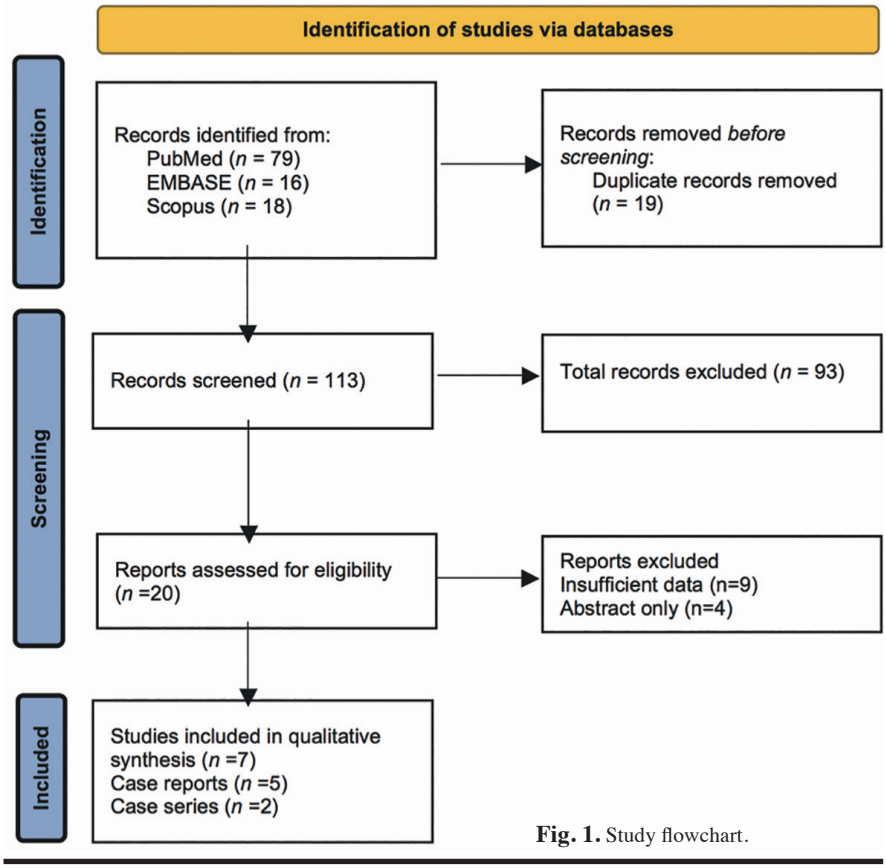

Fig. 1. Study flowchart.

Data sources and search strategy

We aimed to review the currently available evidence published on PubMed, EMBASE, and Scopus. We included observational studies and case reports/case series, reporting information on NS and/or peripheral ulcerative keratitis associated with RP. A description of the search strategy is provided in the Supplementary material. We searched all published articles from database inception up to 13 October 2021. No search filters or restrictions were applied regarding duration, country, or language. Moreover, we performed a manual search for relevant missed publications by screening the references of included articles to minimise results bias. Afterwards, a screening assessment was conducted by evaluating titles and abstracts for appropriateness. Articles that could not be included/excluded based on information from the abstract were evaluated through a full-text review.

Study selection and eligibility criteria

Eligibility of the evaluated studies and data extraction were performed independently by three authors (LD, CP and CB), while resolving any discrepancies by mutual consensus. Inclusion criteria were as follows: (a) observational studies (observational cohort population-based/hospital-based, cross-sectional, or case-control designs) and (b) single case reports, case series, reporting patient-level information on NS associated with RP. Reviews, editorials, and guidelines were excluded.

Data extraction

The following data were extracted from each selected study: study design, number of RP patients with NS and/or PUK, age of patients at inclusion, gender, treatment, and treatment outcome when available. Also, two patients participated by providing their perspective on unmet needs in RP.

Results

Five case reports and two case-series were eligible for inclusion in the review; the cases are depicted in Table I. These papers were published between 1984 and 2017 and included between one and four eligible cases. From the two case-series we selected the report-

Table I. Characteristics and outcomes of patients from included studies.

Author, year	Case report/ case series	Sex/age	Type of eye involvement	Associated disease	Effective systemic therapy	Failed remissive therapies	Other therapies	Eye disease outcome	Observations
Lai *et al*., 2017	CR	M, 43	PUK with perforation, iris prolapse	NA	MP IVIG	AZA, CyA, CP, MTX	Cyanoacrylate glue	controlled	Demise (respiratory failure)
Loeffler *et al*., 2000	CR	M, 66	Diffuse NS, uveitis Retinal detachment	Myelodysplastic syndrome, lymphoma	MP	-	NA	not controlled	Bilateral blindness, bilateral deafness, demise
Matoba *et al*., 1984	CR	F, 11	PUK with perforation	Juvenile idiopathic arthritis	DPA	-	Surgical repair	resolved	
Jabbarvan *et al*., 2010	CR	F, 60	NS, PUK	NA	IFX	MTX, CP	NA	controlled	
Priori *et al*,. 1993	CR	F, 54	NS, relapsing nodular scleritis, corneal infiltration	NA	CyA	AZA	NA	controlled	
Sainz-de-la-Maza *et al*., 2016	CS	F, 35	NS bilateral, uveitis Posterior scleritis, vitritis	Ankylosing spondylitis	CP+MP	MTX, IFX ADA+MP	NA	controlled MTX+IFX	NS while under
Hoang-Xuan *et al*., 1990	CS	F, 65	PUK, diffuse scleritis, episcleritis, iritis, muscle palsy	NA	NSAIDs	-	NA	resolved	
Hoang-Xuan *et al*., 1990	CS	F,46	NS	NA	CP	DPA, MTX	NA	controlled	
Hoang-Xuan *et al*., 1990	CS	F, 57	NS, PUK	NA	CP	MTX, DPA	NA	controlled	
Hoang-Xuan *et al*., 1990	CS	F, 72	NS bilateral	NA	CP	DPA	NA	controlled	

CR: case report; CS: case series; M: male; F: female; PUK: peripheral ulcerative keratitis; NS: necrotising scleritis and peripheral ulcerative keratitis; MP: methylprednisolone; IVIG: intravenous immunoglobulin; IFX: infliximab; CyA: cyclosporine A; NSAIDs: non-steroidal anti-inflammatory drugs; CP: cyclophosphamide; AZA: azathioprine; MTX: methotrexate; ADA: adalimumab; DPA: dapsone; GC: glucocorticoids; NA: not available; MDS: myelodysplastic syndrome; ENT: ears-nose-throat.
For case series Hoang-Xuan *et al*. and Sainz-de-la-Maza M *et al*. we were able to include only part of the described cases, according to the availability of information.

ed patients with sufficient details to allow inclusion (12, 13). We identified 10 RP patients with eye-threatening complications, respectively 9 adults and one paediatric patient (2 female, 8 male, ages 11-72, median age 51 years) (8-14). Apart from glucocorticoids, some RP cases responded to cyclophosphamide (which was employed in 4/10 patients). Infliximab, high-dose immunoglobulins, dapsone, or cyclosporine A were also successfully used in single cases. Surgical repair, including cyanoacrylate glue was reported in 2 cases (8, 9).

Epidemiology

In RP, the perforating eye-threatening complications such as NS and PUK truly deserve the name "rare within rare". In a large series of 112 RP, 18% had ocular symptoms at RP onset, while half of the patients developed ocular symptoms during the disease course (15, 16). Eye inflammation was the initial symptom reported by RP patients in 40% of cases (17). Inflammation of the eye occurred in 53% of RP patients in an international cohort during the disease course (17). Scleritis led to a diagnosis of RP in 61.5% of cases (12). The mean age at diagnosis was 51 years, and episcleritis or scleritis occurred in 56% of men and in 29% of women (15, 16). NS is reported to occur more often in older patients (18).

About half of the non-infectious PUK cases are inaugural manifestations of collagen-vascular diseases (1, 16, 19). Likewise, a first presentation of NS is in 70–80% of cases a sign of an underlying disease, compared to other types of scleritis, in which systemic disease is present in only 8% (20). PUK may complicate NS, mostly in systemic rheumatic diseases (5, 18, 21). The prevalence of PUK in RP was reported as 4–10% (16, 21, 22), while the prevalence of NS in RP was 18.7% in a recent Chinese series (23). About two-thirds of patients with NS and RP had another concomitant disease, mainly systemic vasculitis, cutaneous vasculitis, systemic lupus erythematosus, rheumatoid arthritis, thyroid disease, or ankylosing spondylitis (12).

Pathogenesis

The sclera is an opaque protective coat for the intraocular tissue which is composed predominantly of collagen types I and II, as well as small amounts of collagen V and VI, elastic fibres and proteoglycans (24). The sclera starts at the eye limbus, where it is continuous to the cornea, and ends at the optic canal, where it continues with the dura. Although avascular, the sclera is irrigated by the choroidal plexus beneath and the episcleral plexus above, from anastomoses in which the blood oscillates rather than flows rapidly (3, 24). The perilimbal cornea has distinct morphologic and immunologic characteristics, as it allows the deposition of circulat-

ing immune complexes in the terminal ends of the limbal vessels, initiating the immune-mediated damage of the vessel wall (5). Notably, the peripheral cornea is near the capillary bed, in proximity to the capillary and lymphatic arcades, making this area vulnerable to inflammatory mediators in systemic inflammation (6).

In PUK, deposition of circulating immune complexes in the limbal vessels activate the classical complement pathway, resulting in an immune-mediated vasculitis, with increased endothelial permeability and leakage of inflammatory cells and proteins (25, 26). Inflammatory cells, mainly neutrophils and macrophages in the peripheral cornea, release IL-1 and other proinflammatory cytokines and enable stromal keratinocytes to produce matrix metalloproteinases (MMPs) (5, 18). In PUK, an imbalance between the MMPs and the tissue inhibitors of proteinases also contribute to the rapid keratolysis, breaking down proteoglycans and collagens (3, 27-29). Similar findings are encountered in NS, where MMP-3 and MMP-9 are involved (28, 29). Histopathological examination in NS shows complement C3 and immunoglobulin deposition, vasculitis, perivascular mast cell degranulation, and massive mononuclear cell infiltrate (plasma cells, lymphocytes) (13). Trauma or chronic infection may trigger the inflammatory microangiopathy of the sclera, especially in an already predisposed patient with an immune-mediated disorder (12).

Of interest, an underlying, not always apparent vasculitis seems to underlie the pathogenesis of NS, as opposed to non-necrotising scleritis (24). Moreover, in NS the $CD20^+$ B cells were predominant, as in vasculitis, in the immunohistology of enucleated eyes, whereas in non-necrotising scleritis macrophages were the main cells found (30). This could have therapeutic consequences.

Also, the peripheral regulatory T cells (Tregs) are reduced in RP, their imbalance with T helper cells contributing to RP pathogenesis (31). Tregs are also reduced in PUK (6). Common genetic predisposing factors may play a role. Scleritis is associated with HLA-DRB1, whereas RP is associated with HLA-DRB1*16:2 (along with HLA-DQB1B1*05:02 and HLA-B*67:01, in linkage disequilibrium with each other) (24, 32). A variant of the protein thyrosine phosphatase non-receptor type 22 (PTPN22) gene, 1858C/T, is associated with an increased risk for RP (33). A PTPN22 haplotype (TTATACGCG) is associated with scleritis in Han Chinese (34). PTPN22 polymorphism contributes to the breeching of immune tolerance during the earliest phases of autoimmunity (35).

Clinical clues

In NS, the pain is often very severe, sometimes irradiating to the forehead, ear, face or jaw; the pain may worsen in the morning and awakens the patient from sleep (36). The eye pain responds poorly to analgesics and aggravates with eye movements. Other signs of NS are decreased vision, tearing, and photophobia (3, 18). In PUK, a crescent-shaped corneal ulcer is found within 2 mm from the limbus, often with an inflammation involving the contiguous conjunctiva and sclera (27).

The scleritis in RP is typically anterior and unilateral, and usually parallels the nasal or joint chondritis (1, 16, 19). The great majority of patients with RP have non-erosive seronegative inflammatory polyarthritis, mainly of the metacarpal, proximal interphalangeal, and knee joints (12, 13). Also, otolaryngeal involvement (impaired hearing, tinnitus, vertigo) is present in 85% of patients (12). In Chinese patients, the prevalence of arthritis and ear involvement is probably lower than in Caucasians (23).

Differential diagnosis

The most important differential diagnosis of the unilateral red eye is between NS and eye infection. While most cases of NS are autoimmune, there are also reports of infections scleritis. Importantly, keratouveitis with hypopyon in RP may mimic the presence of an infection (37). Reversely, systemic infections such as syphilis or tuberculosis may imitate non-infectious NS (36).

PUK may be associated with ocular and systemic infections: bacterial (most frequent Staphylococcus), mycobacterial, spirochetal, Chlamydiae, viruses (herpes simplex, varicella zoster virus, hepatitis C), amoebae or fungi (3). NS in the context of fungal infections has also been described (38, 39).

Infections should be suspected in patients with underlying risk factors such as dry eye, chronic use of topical glucocorticoids, ocular trauma, recent eye surgery, severe systemic immunosuppression, local radiotherapy, recurrent herpetic keratitis, occupational exposure to soil and contaminated water, etc (36). Clinical findings suggestive of infection include yellowish or reddish scleral hue of the nodules, purulent exudates, a pus appearance, hypopyon or the spread of lesions to adjacent tissues (40). The healing with a fibrous tissue band along with the scleral thinning suggests a previous infection, while isolated scleral thinning is indicative of an autoimmune aetiology (36).

To rule out an infectious aetiology of PUK and NS, corneal scrapings, cultures, and a viral infectious screen should be performed prior to starting aggressive therapy, especially when the eye involvement is a presenting feature that precedes the diagnosis of systemic disease. Further serological testing, blood, urine or other cultures of biologic fluids may be performed according to the clinical picture (36). Other clinical clues for infections may be obtained from chest X-rays and CT (for tuberculosis, nocardiosis, etc). Scleral biopsy should be avoided if a systemic aetiology such as RP is suspected (40); nevertheless, a scleral biopsy may be considered when an infection is highly probable (36).

Scleromalacia perforans, also called "NS without inflammation", is an important differential diagnosis of NS. In scleromalacia perforans, the scleral thinning may progress slowly and painlessly; against its name, it rarely leads to perforation (8, 16, 41). Other causes of NS include post-surgery NS, which is especially suspected after pterygium surgery, or granulomatosis with polyangiitis (36).

PUK should be differentiated from Mooren's ulcer (MU), a peripheral corneal ulcer lacking systemic signs (26). MU is a diagnosis of exclusion, following a thorough workup aimed to rule out an underlying systemic disease.

The MU lesion starts in the peripheral cornea with a steep, undermined edge that spreads centrally and peripherally and may involve the whole cornea; compared to PUK, MU occurs slightly more central to the corneoscleral limbus and has an overhanging edge (26).

Treatment

The management of NS and PUK is not standardised; however, timely recognition and early treatment improve prognosis and prevent permanent damage. Regardless of aetiology, systemic oral glucocorticoids are more often employed in the treatment of anterior NS, compared to diffuse and nodular scleritis (20, 41). Pulse methylprednisolone may be initiated in patients threatened by vision loss (1g/day for three consecutive days) (8). In several case reports, intravenous immunoglobulins were used successfully for NS in RP (8, 42).

Besides glucocorticoids, severe PUK associated with RP may respond to cyclophosphamide, chlorambucil, azathioprine, or cyclosporine (8). The current management strategy for PUK in the context of a systemic diseases is systemic glucocorticoids plus a cytotoxic agent in the acute phase of disease (5). Most corneal lesions resolve after therapy of accompanying scleritis (5). In a case series, dapsone was employed for the treatment of RP-associated NS, with limited success (13).

While diffuse or nodular scleritis associated with RP may be treated with immunosuppressants, mainly antimetabolites or TNF inhibitors, NS requires the administration of alkylating agents (cyclophosphamide), while biologics may be an alternative (12, 13). Most often TNF inhibitors (mainly infliximab and adalimumab) were used in this setting; however, cases of NS have also been reported to occur during anti-TNF therapy (12). Other biologics that have been employed in NS and PUK are tocilizumab, rituximab, abatacept and JAK-inhibitors (6, 43, 44). Importantly, as these complications may be difficult to treat, early diagnosis and vigorous therapy are imperative (12).

Amongst local therapies, preservative-free lubricating agents are used to lubricate the eye surface and to dilute inflammatory mediators. Collagenase inhibitors or collagenase synthetase inhibitors, such as acetylcysteine, have been administered with limited benefit, while topical glucocorticoids are not recommended, as they increase the risk of perforation by inhibiting new collagen production (5). In the same line, local injections of glucocorticoids in NS and PUK are to be avoided (41). Oral tetracycline derivatives may inhibit metalloproteinase synthesis (5).

Tissue adhesives such as cyanoacrylate or fibrin glues may be used for the emergency repair of peripheral corneal ulceration, along with systemic therapy (8). In mild cases of PUK, cyanoacrylate glue patches were used (9). Surgery is reserved for corneal perforations and includes amniotic membrane transplantation and corneal transplantation (27, 45). Lamellar keratectomy, keratoepitelioplasty or lamellar keratoplasty with lenticular graft may be employed in PUK in RP (46, 47). In imminent perforations, corneal/scleral repair using fascia lata, GoreTex, autologous/homologous scleral tissue, or others have been employed, along with the systemic control of inflammation (48). Nevertheless, surgical trauma may trigger immune-complex vasculitis in collagen-vascular diseases and further aggravate the ocular pathology (5, 12).

Prognosis and complications

NS may occur concomitantly with PUK and sometimes with anterior uveitis (18, 49). In the absence of prompt therapy, scleral inflammation may extend to the contiguous ocular structures (18). Scleritis in RP is often bilateral, recurrent, and necrotising compared to scleritis associated with other connective tissue diseases (12). Similarly, vision loss occurs more often in RP-associated scleritis compared to other autoimmune aetiologies (12).

Recurrence is more frequent in patients with NS compared with diffuse or nodular anterior scleritis (50). Moreover, the resolution of inflammation is longer in patients with NS, respectively 75 days versus 19 days in diffuse and 21 days in nodular scleritis (20). Generally, ocular complications occur more frequently in patients with NS and posterior scleritis (86% and 85% respectively) compared to diffuse (49%) and nodular (40%) anterior scleritis (20). The most common complication is anterior uveitis (20). Other possible complications of NS are cataracts, secondary glaucoma, optic neuritis, or globe perforations (51). Better outcomes were reported in Chinese patients with RP, compared to non-Asian patients (23).

The assessment of NS progression in the context of RP is not standardised. Clinical surveillance is fundamental. Ophthalmological assessment relies on ancillary tests, such as ultrasound biomicroscopy. Anterior optical coherence tomography may quantify the depth and the extension of scleral inflammation and thinning, while fluorescein angiography and indocyanine green angiography show abnormalities of the (epi)scleral vessels (28, 29).

For RP activity (RPDAI) and damage (RPDAM) indexes have been developed (52, 53). In NS complicating RP, a multidisciplinary team approach, using a common language and protocols, is needed. A systematic review protocol for the assessment of pharmacological agents in non-infectious scleritis has been recently published (54). To further aid management, a standardised grading system for scleritis has also been developed (55).

Currently there are no biomarkers of NS and/or PUK in RP, although blood and/or tear fluid markers of severe scleritis have been recently described (28). In-depth characterisation of RP clusters, including their genetic associations (as in the newly described VEXAS syndrome, for instance) will hopefully bring about information regarding early diagnosis, monitoring and best therapy for RP-associated NS and PUK (56, 57).

From patients' perspective

Areas of need for intervention include patients' education to identify alarming signs/symptoms and to photograph the "painful red eye" in order to require an emergency consultation. All patients with NS and/or PUK should undergo a thorough assessment for systemic disease (58, 59). Ancillary techniques, such as colour Doppler ultrasonogra-

phy, computed tomography, magnetic resonance imaging or 18F-fluorodeoxyglucose-positron emission tomography/CT may help identify chondritis in a case of severe NS or PUK (60).

RP has a significant disease burden, and standardisation of treatment approaches and prevention of disease-related complications represent another important unmet need in patients with RP (17). Patients with RP self-report high global assessment scores, discordant from the physician global assessment, likely because of the high physical and psychological disease burden (61).

Conclusions

Early diagnosis and therapy may decrease the risk of eye loss and other complications of RP. Ocular inflammation is often bilateral and recurring in RP. All patients who develop scleritis should be specifically questioned for signs of cartilage inflammation and assessed for signs of chondritis. Alkylating agents, mainly pulse cyclophosphamide, are required in NS and PUK. In case of failure, biologics may be employed as rescue therapy. In the case of NS or PUK, a multidisciplinary targeted approach, including patients' perspective, is needed to improve patient outcomes.

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Co-funded by the European Union

Disclaimer

This publication was funded by the European Union's Health Programme (2014-2020). ERN ReCONNET is one of the 24 European Reference Networks (ERNs) approved by the ERN Board of Member States. The ERNs are co-funded by the EC (European Commission). The content of this publication represents the views of the authors only and it is their sole responsibility; it cannot be considered to reflect the views of the EC and/or the European Health and Digital Executive Agency (HaDEA) or any other body of the European Union. The EC and HaDEA do not accept any responsibility for use that may be made of the information it contains.

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