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ORIGINAL ARTICLE

Purtscher-like Retinopathy Associated with Systemic Lupus Erythematosus

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ABSTRACT

Purpose: To report on clinical manifestations of Purtscher-like retinopathy (PLR) associated with systemic lupus erythematosus (SLE) and visual outcomes.

Methods: We performed a retrospective cohort study of 11 patients (21 affected eyes) with PLR in SLE.

Results: All patients were treated with systemic corticosteroids ± immunosuppressive agents. Ocular therapy included intravitreal injections with bevacizumab in 18/21 eyes and posterior sub-Tenon injections with triamcinolone acetonide 13/21 eyes. Panretinal photocoagulation (PRP) was performed in 19/21 eyes and pars plana vitrectomy was required in 5/21 eyes. Visual improvement was found at follow-up of 3 and 6 months ($p=0.05$). Poor visual outcome was associated with presence of neovascularizations at onset ($p=0.009$), development of vitreous hemorrhage during PRP ($p=0.015$), and active status of SLE after onset of PLR ($p=0.029$).

Conclusions: PLR might manifest as a devastating complication of SLE. We recommend treating any systemic activity of SLE and starting an early ocular treatment.

Keywords: Bevacizumab, complication, purtscher-like retinopathy, systemic lupus erythematosus, treatment

Purtscher's retinopathy is a clinical syndrome characterized by ischemic changes of the posterior pole associated with multiple areas of whitening of inner retina (Purtscher flecken), optic disc swelling, cotton wool spots, and hemorrhages usually concentrated around the optic disc. Purtscher's retinopathy is a mostly bilateral disorder and was originally described after various types of trauma. Pathogenesis of this syndrome was attributed to embolic occlusions of the precapillary arterioles and/or impaired venous return from raised intracranial/intrathoracic pressure and secondary extravasation of fluid.^{1–3}

Purtscher-like retinopathy (PLR) represents a clinical syndrome with manifestations similar to the original Purtscher's retinopathy but related to causes other than trauma.³ PLR was reported in various conditions such as acute pancreatitis,^{4–6} fat embolism,⁷ chronic renal failure,⁸ hemolytic uremic syndrome,^{9,10} after childbirth,¹¹ weight lifting,¹² battered

child syndrome,¹³ and several autoimmune diseases.^{14,15} The visual prognosis of PLR in general is poor and the secondary development of neovascularizations and glaucoma might even destroy the eye.

Herein we report on PLR in 11 patients with systemic lupus erythematosus (SLE) and refer to its management and visual outcomes.

MATERIALS AND METHODS

In this series we included 11 consecutive patients with PLR associated with SLE from the ophthalmological department of Chiang Mai University Hospital in Thailand between September 2006 and September 2012. We performed a retrospective study of their clinical, laboratory, and imaging data. We registered clinical ocular manifestations, development of visual acuity (VA) over time, complications, and SLE activity,

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as well as systemic and ocular treatment regimens employed. Mean follow-up time was 19 months (median 10 months; SD 20.051; range 3–72 months).

The diagnosis of SLE was based on the American College of Rheumatology criteria in all cases.¹⁶ The SLE disease activity was determined using the MEX-SLEDAI score.¹⁷ PLR was defined as ischemia of the posterior pole associated with multiple areas of whitening of inner retina with optic disc swelling, cotton wool spots, and hemorrhages in the absence of previous trauma.

All patients were treated with a combination of systemic (oral or intravenous corticosteroids, sometimes with addition of other immunosuppressive agents) and local treatment (posterior sub-Tenon corticosteroid and/or anti-vascular endothelial growth factor (anti-VEGF) intraocular injections, panretinal photocoagulation, and occasionally pars plana vitrectomy), depending on the clinical condition of the patients. First, we attempted to control the activity of systemic SLE and PLR with a combination of systemic and local treatment, then we applied anti-VEGF injections in patients with neovascularizations, large areas of nonperfusion on fluorescein angiography (FA), and/or macular edema. Panretinal photocoagulation (PRP) was performed in all cases with neovascularizations and/or large area of nonperfusion on FA. Pars plana vitrectomy (PPV) was performed in cases resistant to the above indicated treatment or in patients with vitreous hemorrhage. During follow-up, all patients were regularly evaluated by gonioscopy for the presence of neovascularizations.

We defined the progression of PLR as the ongoing development of one or more of following characteristics: retinal neovascularization, vitreous hemorrhage, neovascular glaucoma, progression of retinal ischemic areas, and increase of macular edema. Stabilization of PLR was defined as a situation in which no progression occurred and hemorrhages and neovascularization diminished.

For all calculations with VA data, we converted Snellen VA to the logarithm of the minimum angle of resolution (logMAR). For easier understanding the logMAR results were converted back to Snellen VA and presented in this report. We included only right eyes of affected patients for all calculations to prevent the bias of similar manifestations in bilateral cases.

This study was approved by a suitably constituted ethics committee of the institution within which the work was undertaken and conforms to the provisions of the Declaration of Helsinki.

RESULTS

General characteristics of the patients are given in Table 1. All patients except one were females

TABLE 1. General features of 11 patients with Purtscher-like retinopathy associated with systemic lupus erythematosus.

| | |
|--|---------------------|
| Median age (years) | 29.0 (range 15–44) |
| Female gender | 10 (91%) |
| Bilateral involvement | 10 (91%) |
| Known with SLE before the onset of PLR | 5 (45%) |
| Active systemic SLE at onset of PLR | 7 (64%) |
| Systemic medication at onset of PLR | 6 (55%) |
| Positive anticardiolipin antibodies | 1 (9.5%) |
| Median ESR | 56.0 range (16–118) |
| Median follow-up time (months) | 10.0 range (3–72) |

SLE, systemic lupus erythematosus; PLR, Purtscher-like retinopathy; ESR, erythrocyte sediment rate.

(10/11 patients; 91%) with a mean age of 31 years (median 29 years; SD 9.792; range 15–44 years). Before the onset of PLR, 5/11 (45%) patients were already known to have SLE and the remaining 6/11 (55%) were diagnosed with SLE after the onset of PLR. At the time of PLR onset, active SLE was observed in 7/11 patients (64%) and the remaining 4 were considered to be in the inactive stage. Anticardiolipin antibodies were positive only in 1 patient (9.5%). None had additional risk factors for retinal ischemia, such as diabetes mellitus, hypertension, dyslipidemia, or nephropathy.

Bilateral ocular involvement was present in 10/11 (91%) patients, resulting in 21 affected eyes. FA was performed in 9/11 patients (out of 2 missing cases, one had known allergy to fluorescein and the other had dense vitreous hemorrhages, which prevented view of the fundus). Macular ischemia and a nonperfusion area of more than 10 disc diameters were noted at onset in 16/18 (89%) evaluable eyes (Figures 1, 2). Retinal neovascularization at initial presentation was demonstrated in 4/11 (36%) patients (7/21; 33% affected eyes).

After the onset of PLR, all patients were treated with systemic steroids (1 mg/kg/day), and additional immunosuppressive treatment was initiated in 6 patients, resulting in 7 patients being on immunosuppressive therapy (Table 2). Severe systemic complications caused by either SLE or its treatment developed in 3 patients (sepsis in all, Table 2).

Ocular treatment included intravitreal injections with bevacizumab (Avastin 1.25 mg/0.05 mL) and posterior sub-Tenon injections with triamcinolone acetonide (Kenakort 20 mg/0.5 mL) (18/21; 86% and 13/21; 62% of affected eyes, respectively). Panretinal photocoagulation (PRP) was performed in 19/21 (91%) of affected eyes. Pars plana vitrectomy (PPV) was performed in 4 patients; 5/21 (24%) of affected eyes, which was 1/5 eyes (case 7), had severe vitreous hemorrhage at the initial presentation.

With a combined systemic and ocular treatment, the progression of PLR was stopped in all patients. There were 2/11 patients (18%; 4/21 affected eyes,

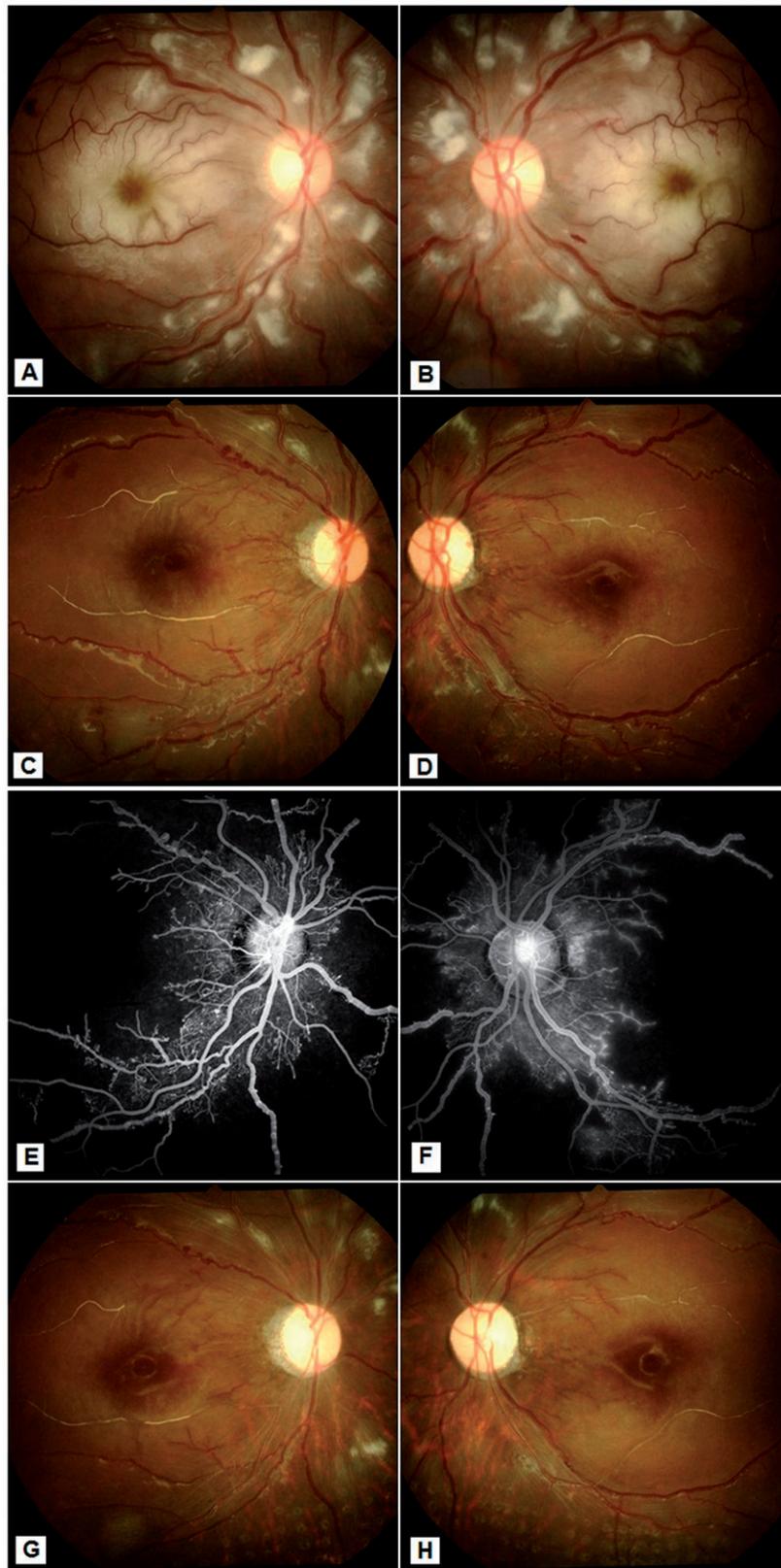


FIGURE 1. Ocular manifestations of Purtscher-like retinopathy associated with systemic lupus erythematosus (Table 2, case 2). (A, B) Fundus photographs of both eyes at presentation demonstrate extensive cotton wool spots and occlusions of multiple arterioles, including the macular area, which exhibits cherry red spots. (C–F) Fundus photographs and fluorescein angiography at 3 months follow-up, after treatment with oral prednisolone and cyclophosphamide, the cotton wool spots subsided but disc and retinal neovascularizations developed. Fundus fluorescein angiography shows extensive ischemia involving macula and neovascularizations. (G, H) Fundus photographs at 9 months follow-up. After panretinal laser photocoagulation as well as intraocular injections with bevacizumab, the neovascularizations regressed and the situation stabilized with bilateral pale optic discs.

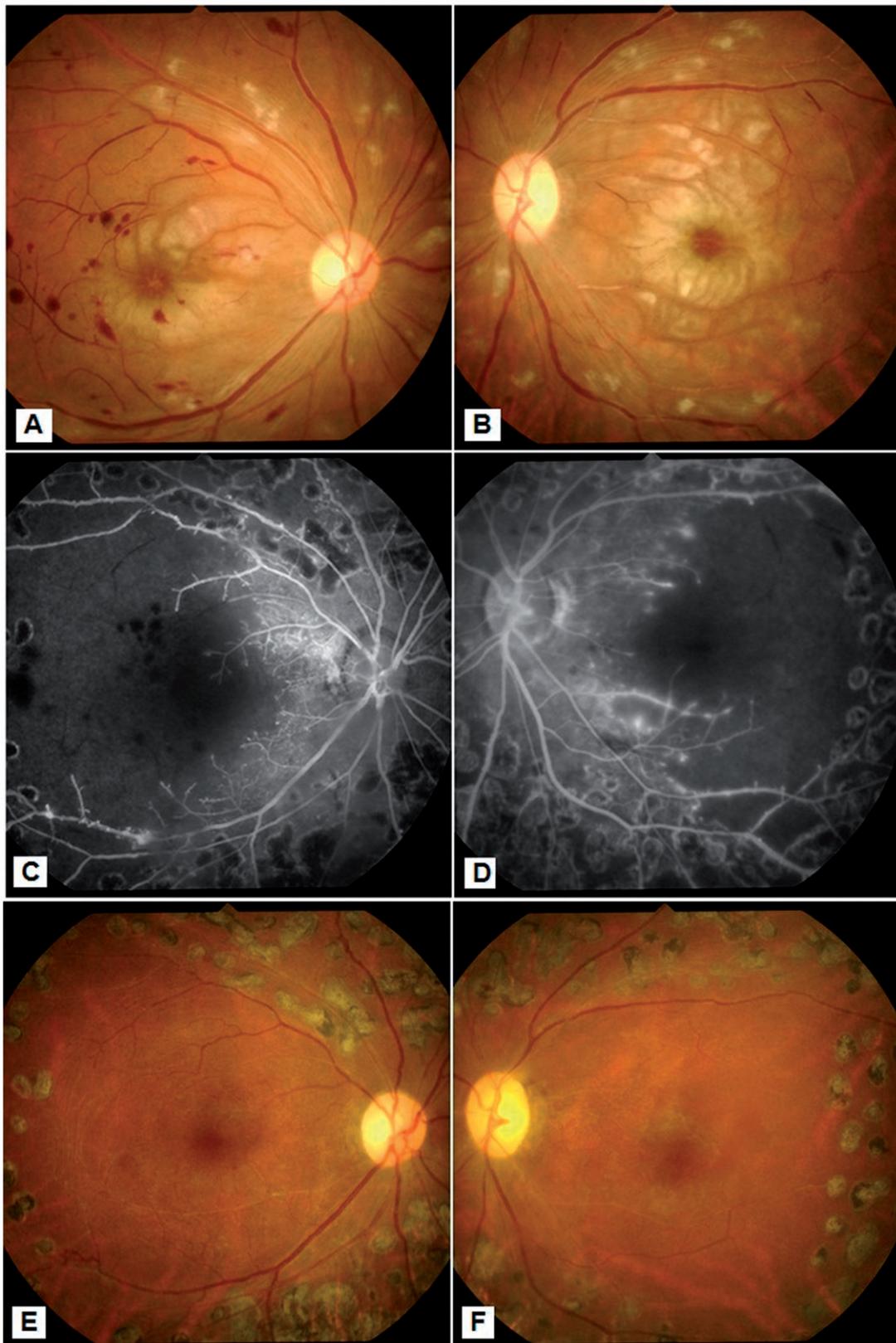


FIGURE 2. Ocular manifestations of Purtscher-like Retinopathy associated with systemic lupus erythematosus (Table 2, case 3). (A, B) Fundus photographs of both eyes at presentation demonstrate extensive cotton wool spots and occlusions of multiple arterioles, including macular area, which exhibits cherry red spots. (C, D) Fundus fluorescein angiography at 5 months follow-up, after panretinal laser photocoagulation as well as intraocular injections with bevacizumab, shows large areas of nonperfusion, vascular leakage, and macular ischemia without neovascularization. (E, F) Fundus photographs at 1 year follow-up, when retinal situation became quiescent.

TABLE 2. Treatment and systemic complications of 11 patients with Purtscher-like retinopathy associated with systemic lupus erythematosus.

| Patient no. | SLE diagnosed before onset of PLR | Treatment before onset of PLR | Treatment after the diagnosis of PLR has been made | | | | | | Systemic complications | |
|----------------|-----------------------------------|---|--|---------------|--|--------|-------------|-----------------------------|------------------------|-----------------------------|
| | | | Active SLE after onset of retinitis | Oral steroids | Immunosuppressive treatment after the onset of PLR | PST-TA | Bevacizumab | Panretinal photocoagulation | | |
| 1 | No | None | Yes | 1 MKD | Oral cyclophosphamide 50 mg per day | Yes | Yes | Yes | Yes | None |
| 2 | No | None | Yes | 1 MKD | IV cyclophosphamide 800 mg | No | Yes | Yes | Yes | None |
| 3 | No | Prednisolone 45 mg per day Azathioprine 50 mg per day ^b | Yes | 1 MKD | Azathioprine 50 mg per day | No | No | Yes | Yes | None |
| 4 | Yes | Prednisolone 20 mg per day | Yes | 1 MKD | IV cyclophosphamide 600 mg | Yes | Yes | Yes | Yes | Sepsis (death) ^a |
| 5 | Yes | Prednisolone 10 mg per day Hydroxychloroquine 400 mg per day | Yes | 1 MKD | None | Yes | Yes | Yes | Yes | None |
| 6 | No | None | No | 1 MKD | Methotrexate 7.5 mg per week | No | No | No | No | None |
| 7 | Yes | Prednisolone 5 mg per day | No | 1 MKD | None ^c | No | No | No | Yes | None |
| 8 | Yes | Prednisolone 30 mg per day | Yes | 1 MKD | None | Yes | Yes | Yes | Yes | Sepsis ^a |
| 9 ^d | Yes | Prednisolone 10 mg per day | No | 1 MKD | Azathioprine 50 mg per day | No | Yes | Yes | Yes | None |
| 10 | No | None | No | 1 MKD | None | Yes | Yes | Yes | Yes | None |
| 11 | No | None | Yes | 1 MKD IVMP | Azathioprine 100 mg per day | Yes | Yes | Yes | Yes | Sepsis ^a |

SLE, systemic lupus erythematosus; PLR, Purtscher-like retinopathy; PST-TA, posterior subtenon triamcinolone acetate (Kenakort) 20 mg per injection; bevacizumab (Avastin) 1.25 mg per injection; MKD, milligram per kilogram per day; IVMP, intravenous methylprednisolone.

^aCase 4 suffered from repeated periods of sepsis; onset of the first sepsis period dated before onset of PLR and start of immunosuppressive administration; second sepsis period started 4 months after the onset of PLR (3 months after start of cyclophosphamide) and third period 6 months after PLR. Patient died with a concurrent medication of 5 mg prednisolone per day and 6 days after 5th intravenous cyclophosphamide due to coagulation negative staphylococcus sepsis. Case 8 manifested with sepsis 4 months after the onset of PLR with concurrent medication of 50 mg prednisolone per day for her active SLE. Case 11 developed sepsis 5 weeks after the onset of PLR (10 days after start of azathioprine with concurrent medication of 30 mg prednisolone and azathioprine 100 mg per day).

^bDue to initial idiopathic thrombocytopenic purpura presentation.

^cCase 7 decreased the initial steroid dosage very quickly to 5 mg/day.

^dUnilateral case (right eye).

19%) who stabilized within 3 months and 9 patients (82%; 15/21 eyes; 71%) reached a stabilized situation within 6 months. During PRP, vitreous hemorrhage occurred in 4/11 patients (7/21 eyes, of whom 4 required PPV and additional laser coagulation), but retinal detachments did not develop. Additional complications included ocular hypertension in 3/11 patients (4/21 eyes), which could be controlled with one or two topical anti-glaucoma medications, but none of the patients developed neovascular glaucoma.

At onset, visual acuity (VA) of less than 0.1 was found in the majority of patients (8/11; 73%; 14/21; 67% eyes). At 6 months follow-up, VA of less 0.1 was noted in 5/9 (56%) patients (8/17; 47% eyes). After treatment, the most affected eyes (14/21; 67%) had improved visual acuity while 4/21 (19%) had stable VA and 3/21 (14%) decreased. While we observed significant visual improvement at 3 and 6 months of follow-up ($p=0.05$, Wilcoxon signed rank test), the number of eyes with VA of less than 0.1 at onset and at 6 months follow-up did not differ (14/21; 67% versus 8/17, 47%, $p=0.324$). VA of less than 0.1 at 6 months follow-up was associated with following characteristics: the presence of neovascularization at onset of PLR ($p=0.009$ Fisher's exact test), the development of vitreous hemorrhage during PRP ($p=0.015$ Fisher's exact test), and active status of SLE after the onset of PLR ($p=0.029$ Fisher's exact test). No associations were observed between the visual outcomes and activity of SLE at onset of PLR, medications at onset, presence of anticardiolipin antibodies, treatment with immunosuppressive agents, area of nonperfusion, presence of macular ischemia, and initial VA.

Since our treatment induced stabilization in all eyes, oral prednisolone medication could be gradually decreased and/or tapered off in all patients. Six out of 11 patients could stop prednisolone medication entirely (mean 21 months; median 13 months; range 8–60 months) and the remainder could decrease their daily dosage. During the follow-up, 3 out of 11 patients developed sepsis at various intervals after the onset of PLR (Table 2) and 1 of these patients died. The septic periods developed at variable times after the onset of PLR in patients with different therapeutic regimens and, moreover, 1 patient suffered from septic phases even before the onset of PLR.

DISCUSSION

We report on severe PLR in 11 patients with SLE and point out that stabilization of PLR occurred in all cases with a combination of systemic and local treatment regimens. All but 1 patient had bilateral PLR and a majority of patients (73%) had visual acuity at onset of less than 0.1. During follow-up, none of the patients developed retinal detachment or neovascular glaucoma, which might be caused by an aggressive

treatment including the early local application of bevacizumab.

Ocular complications of SLE are generally associated with active systemic disease and the pathogenic mechanism of the SLE retinopathy has been attributed to the immune complex-mediated vasculopathy.^{18–20} Therefore, control of the systemic disease is a primary goal of the treatment. The aggressive immunosuppression was recommended, which seemed to improve the systemic disease and the status of retinopathy but visual outcome was generally unaffected due to persistent arteriolar attenuation and subsequent progression of retinal vascular occlusions.^{21–24}

Ischemia and neovascularizations in PLR were regularly reported (in our series illustrated in Figure 1 of case 2) resulting in very poor visual outcomes. Miguel et al. and Sellami et al. compared the visual outcomes of PLR of diverse origins and concluded that SLE-associated PLR had worst visual acuity at presentation (1.7 logMAR) and did not improve with corticosteroid treatment.^{15,25} Previously, approximately 50% of SLE patients with PLR had visual acuity less than 6/20.^{26–29} Jabs et al.²¹ reported on this potentially visually devastating form of retinopathy in SLE in 11 patients (20 involved eyes) and noted the very poor visual outcomes despite the use of different regimens of immunosuppressive drugs, including oral and intravenous corticosteroids, azathioprine, and cyclophosphamide. In his series from the pre-anti VEGF era, approximately 50% of involved eyes had visual acuity less than 6/60, and 45% developed vitreous hemorrhage, which is closely similar to our study (47 and 38%, respectively). In contrast to our series, the authors also observed retinal detachment in 3 eyes (15%), and 1 additional eye (5%) developed ischemia of anterior eye segment. The severity of PLR in our patients seems to be similar to that in previous reports, but might have been also influenced by a late presentation since one-third of the affected eyes had already retinal neovascularizations at first presentation to ophthalmologist. Despite this severe initial presentation, the retinal manifestations stabilized in all patients and lacked severe complications such as neovascular glaucoma, retinal detachment, and anterior segment ischemia.

The role of bevacizumab may explain this difference in outcome. Bevacizumab induces temporary decrease of VEGF levels and reduces retinal nonperfusion, which might cover the time interval until the PRP became effective. Campochiaro et al.³⁰ found that high levels of VEGF result in worsening of retinal ischemia and progressive retinal nonperfusion, including the macular area. Therefore, anti-VEGF medications can reduce the total amount of retinal nonperfusion/macular edema and counteract the neovascular complications.³⁰ Obviously, bevacizumab cannot restore the obliteration of the arteries involved

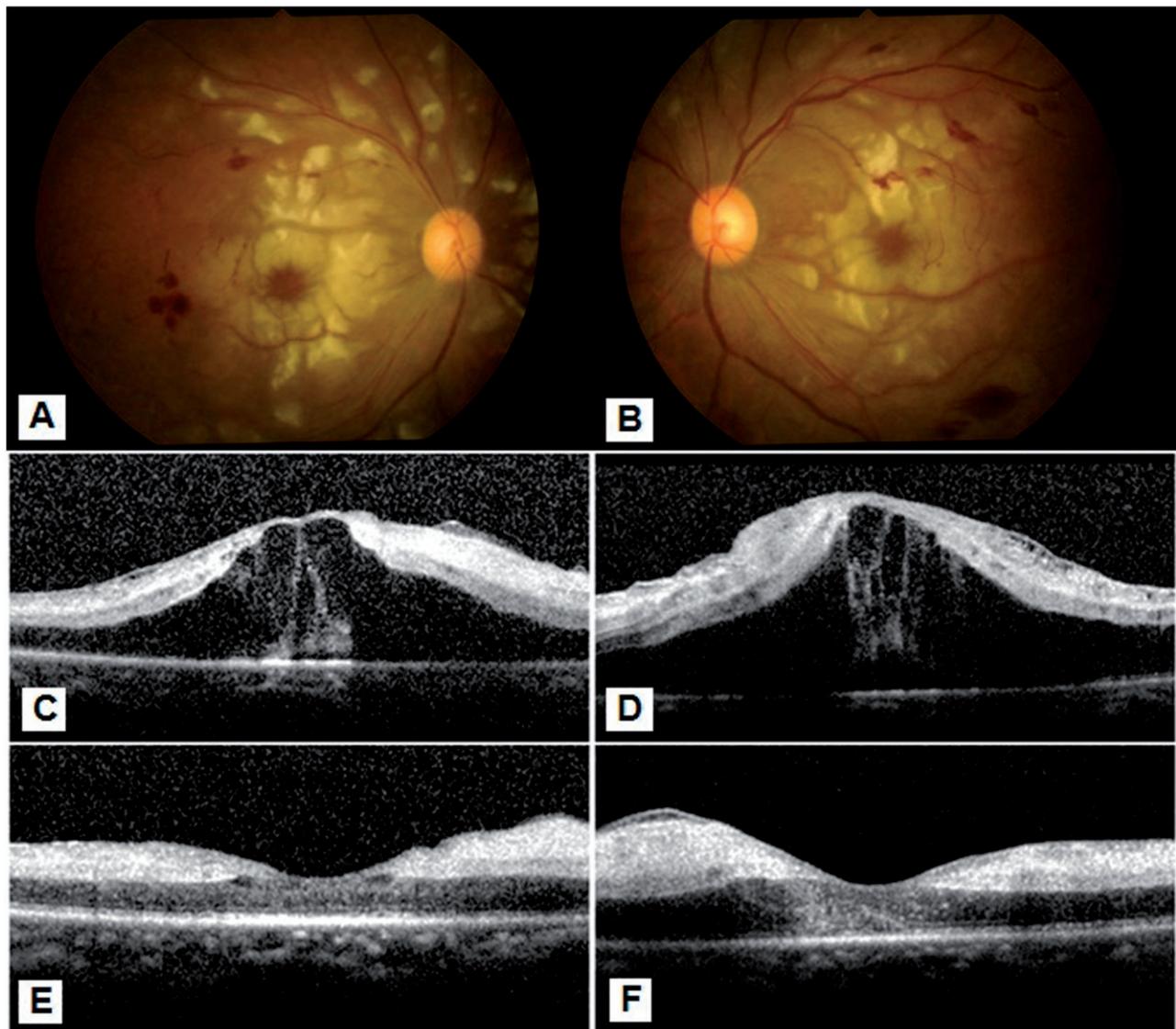


FIGURE 3. Ocular manifestations of Purtscher-like retinopathy associated with systemic lupus erythematosus (Table 2, case 11). (A–D) Fundus photographs and optical coherence tomography at presentation exhibit cotton wool spots, hemorrhages together with bilateral macular edema. (E, F) Optical coherence tomography 3 weeks after intravitreal bevacizumab injection demonstrates the resolution of macular edema. During an additional 3 months follow-up, macular edema did not recur but visual acuity did not improve due to macular ischemia.

and the visual outcome remains dependent of macular ischemic changes (Figure 3, case 11).

Aggressive treatment of SLE has effectively reduced the mortality related to disease activity but also has led to the occurrence of complications that can be related to disease itself or to adverse effects of treatment, especially infections related to severe immunosuppression. Mortality rates in SLE cohorts with follow-up periods ranging from 8 to 14 years varied from 6.8 to 20.2%.^{31–34} The reported causes of death from SLE differ widely. While some studies reported that activity of SLE represented a major cause of death,^{35–37} others found that infections were more common.^{34,38–42} However, most patients who died from infections also had active SLE. Our 3 patients who developed sepsis received different

therapeutic regimens and it was not possible to conclude whether sepsis developed due to severe active SLE or due to its treatment. Two patients had septic periods already before the start of immunosuppressive treatment and moreover developed septic stage during the decreasing medications a long time after the onset of PLR. One patient, however, developed sepsis 10 days after the initiation of azathioprine treatment given because of PLR. In a study of 349 Thai patients with SLE, the patients with infection-related and not infectious causes of death did not differ in the dosages of both prednisolone and/or cyclophosphamide.³⁴

The retrospective nature of the study and the absence of a control group constitute the drawbacks of our study. Based on our results it is difficult to prove

that combination of systemic and aggressive ocular treatment including bevacizumab injection can stop the progression of PLR. However, case-control or randomization trials will probably not be feasible in the uncommon SLE complication. However, the stabilization of PLR and absence of neovascular glaucoma suggest that our treatment approach might be effective.

We conclude that PLR might manifest as a devastating ocular complication of SLE and recommend treating the systemic SLE activity in all affected patients and starting an early local treatment with anti-VEGF medications and PRP in order to retain as much useful vision as possible.

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DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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