CLINICAL SCIENCE

Is granuloma annulare related to intermediate uveitis with retinal vasculitis?

B van Kooij, M Canninga van Dijk, J de Boer, V Sigurdsson, A Rothova

See end of article for authors' affiliations

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Correspondence to:
Bram van Kooij, FC
Donders Institute,
Department of
Ophthalmology, University
Hospital Utrecht, PO Box
85500, 3508 GA Utrecht,
Netherlands;
b.vankooij@oogh.azu.nl

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Aim: To report on eight patients with severe idiopathic intermediate uveitis (IU) and granuloma annulare (GA), a self limiting cutaneous condition of unknown aetiology.

Methods: Retrospective case series. Clinical ophthalmic and dermatological data were studied and fluorescein angiography and skin biopsies were reviewed.

Results: All patients with idiopathic IU had similar ocular features (eight with vitritis, seven with retinal vasculitis) and developed complications such as cystoid macular oedema (n=5), cataract (n=4), and glaucoma (n=3). Systemic diseases were not found, but a localised type of GA was observed in all.

Conclusion: Seven out of eight patients with IU and GA developed severe retinal vasculitis. Further studies are needed for a better understanding of this association, a common pathogenesis, and its eventual clinical consequences.

Intermediate uveitis (IU) is a chronic intraocular inflammation of the vitreous and the peripheral retina. This uveitis is usually a bilateral disease with the onset mostly in the teenage or young adult years. Complications include cystoid macular oedema (CMO), peripheral retinal vasculitis, and cataract.¹ The aetiology is of unknown origin in the majority of cases, although an occasional association with systemic diseases such as sarcoidosis, multiple sclerosis, and inflammatory bowel disease is described.²⁻⁵

Granuloma annulare (GA) is a self limiting cutaneous condition of unknown aetiology. GA is characterised by smooth, skin coloured annular plaques and papules and affects mainly children and young adults. Associations of generalised GA with sarcoidosis and diabetes mellitus are reported.⁶⁻⁹

We describe eight patients with IU who also suffered from GA.

PATIENTS AND METHODS

Diagnosis of IU was based on the IUSG criteria.¹⁰ All patients underwent complete clinical examination, fluorescein angiography, and the standard screening protocol for intermediate uveitis, which included erythrocyte sedimentation rate, red and white blood cell counts, glucose levels, determination of serum angiotensin converting enzyme levels and serological tests for syphilis, borreliosis, bartonellosis, and chest radiography. HLA typing was performed in three cases. The presence of systemic diseases was assessed according to current diagnostic criteria. All patients were examined by dermatologists and skin biopsies of all patients were consistent with the diagnosis of GA and were, in addition, revised by an independent dermatopathologist.

RESULTS

The clinical features of our patients are given in Table 1. Our series included five female and three male patients. Mean age at onset of IU was 28 years with a range of 8-60 years. Mean follow up was 7.1 years with a range of 1-17 years. The results of uveitis screening were within normal limits for all (except one case with high erythrocyte sedimentation rate (ESR)). Detailed examinations by an internist or paediatrician revealed no indications suggestive of sarcoidosis, multiple sclerosis, or diabetes mellitus. The patient with elevated ESR

disclosed monoclonal paraproteinaemia, but progression did not occur during follow up. During the follow up, none of the remaining patients developed associated systemic disease. HLA typing disclosed positivity for HLA B8 in two of four patients examined.

Eight patients presented with similar manifestations of ocular disease, which consisted of bilateral, chronic IU. Seven out of eight exhibited severe retinal vasculitis (periphlebitis; Figs 1 and 2). The only patient without retinal vasculitis was a 8 year old child. Ocular complications developed in 7/8 patients and included CMO, cataract, and glaucoma. Visual acuity at onset ranged from 0.02-0.8 and final visual acuity ranged from 0.1-1.25. Patients were initially treated topically, but the severity of the inflammation required periocular triamcinolone injections in three patients and systemic corticosteroids in three. One patient was treated with laser because of peripheral ischaemic retinopathy. Of seven patients with retinal phlebitis four developed CMO. The causes of definitive visual loss included CMO in four patients (six eyes) and vasculitis in one patient (two eyes; in two eyes a temporary visual loss was attributed to cataract).

GA manifested at mean age of 30 years with a range of 5-62 in four before and four after the onset of IU (Table 1, Fig 3). Histological examination of skin biopsies showed abnormalities typical for GA in all patients. The epidermis was normal. In the underlying dermis there were one or more areas of necrobiosis, surrounded by histiocytes (Fig 4). In most biopsies some lymphocytes and eosinophils were also present in the infiltrate. One patient was treated with hydroxychloroquine, two patients with topical corticosteroids, and one patient with cryotherapy and four received no treatment. All skin lesions recovered within 1 year.

Patient 1

An 8 year old boy presented with bilateral IU. Visual acuity was 0.02 in the right eye and 1.25 in the left eye. Both eyes had cells in the vitreous and snowbanking. On funduscopy severe CMO was noted in the right eye, which was confirmed by fluorescein angiography. The patient was treated with periocular steroid injection in the right eye. The activity of inflammation slowly subsided however the final visual acuity remained 0.1 due to CMO. Visual acuity in the left eye was 1.25

Table 1 Patient characteristics

Patient	Sex	Age at onset of IU (years)	Age at onset of GA (years)	Follow up (years)	Bilateral IU	CMO	Vasculitis	Cataract	Glaucoma	Snow banking	Treatment of IU	Intraocular surgery (No of procedures)	Visual acuity at onset	Worst visual acuity	Optimal visual acuity	Cause of permanent visual loss
1	M	8	5	7	+	+	-	-	-	+	Periocular CS, topical NSAID	0	0.02	R 0.02 L 1.25	R 0.1 L 0.25	R CMO L CMO
2	F	50	55	8	+	+	+	+	+	-	Systemic, periocular and topical CS, topical NSAID, acetazolamide	2	0.2	R 1.0 L 0.2	R 1.0 L 0.6	R CMO L -
3	F	23	22	1	+	+	-	-	-	+	Periocular and topical CS, topical NSAID	0	1.0	R 1.0 L 0.5	R 1.0 L 1.0	R - L CMO
4	M	10	9	6.5	+	+	+	+	+	+	Periocular and topical CS, topical NSAID	3	1.0	R 0.02 L 0.2	R 1.0 L 0.8	R CMO L vasculitis
5	F	36	38	7	+	-	+	+	-	+	Systemic, periocular and topical CS, topical NSAID	2	0.8	R 1.0 L 0.5	R 1.0 L 0.6	R - L -
6	F	28	25	8	+	-	+	+	+	-	Topical CS and topical NSAID	0	1.0	R 1.0 L 0.4	R 0.6 L 0.8	R - L -
7	M	60	62	2	+	-	-	-	-	-	Topical CS	0	0.4	R 0.4 L 0.5	R 0.8 L 0.8	R - L CMO
8	F	9	25	17	+	+	-	-	-	+	Systemic and periocular CS, systemic NSAID, acetazolamide	0	0.4	R 0.4 L 1.0	R 0.8 L 1.25	R CMO L -

CS = corticosteroids; NSAID = non-steroidal anti-inflammatory drug.

Figure 1 Segmental vasculitis (periphlebitis) in a patient with granuloma annulare (see Table 1, patient no 5). **Figure 2** Peripheral retina with extended leakage of inflamed vessels (same patient as in Fig 1, Table 1, patient no 5). **Figure 3** Localised form of granuloma annulare. Note the erythematous papules arranged in a ring.

during the follow up of 7 years. Repeated evaluations for systemic diseases were negative. Three years before the onset of IU, he developed skin lesions, which were clinically consistent with GA. Skin biopsy confirmed the suspected diagnosis. The lesions recovered spontaneous within 1 year.

Patient 2

A 50 year old woman presented to our clinic with bilateral IU. Visual acuity was 0.6 in the right eye and 0.2 in the left eye. Both eyes had occasional cells in the anterior chamber and cells in the vitreous. On funduscopy severe CMO was noted. Fluorescein angiography demonstrated active vasculitis and CMO in both eyes. She was treated with periocular steroid injections; however, the CMO persisted and acetazolamide was added. In response to corticosteroids a high intraocular pressure developed and the depot was removed with good effect. However, she developed a severe recurrence and the patient required systemic corticosteroid medication (initial dose 40 mg, slowly tapered to 5 mg a day). Repeated evaluation for systemic disease was negative. After 3 years of treatment she underwent cataract surgery in both eyes. At 8

Figure 4 In the dermis, small zones of necrobiosis are surrounded by a palisade of inflammatory cells.

years of follow up, visual loss due to CMO developed (right eye 0.8 and left eye 0.6). Five years after the onset of IU, she developed skin lesions, which were clinically consistent with GA. Skin biopsy confirmed the suspected diagnosis and the patient was treated with hydroxychloroquine with good effect on GA.

Patient 3

A 23 year old woman presented with bilateral IU and visual acuity 1.0 in the right eye and 0.5 in the left eye. Both eyes had occasional cells in the anterior chamber, vitritis, and snowbanking. On funduscopy CMO was seen in the left eye which was confirmed by fluorescein angiography. The patient was treated with periocular steroid injections in the left eye, with good effect on visual acuity (after 1 year of follow up 1.0 in both eyes). Repeated evaluation for systemic disease was negative. One year before the onset of IU she developed skin lesions, which were clinically consistent with GA. Skin biopsy proved the suspected diagnosis. The lesions recovered spontaneously within 1 year.

Patient 4

A 16 year old boy presented to our clinic with bilateral IU. Visual acuity was 0.1 in the right eye and 0.4 in the left eye. Both eyes had cells in the vitreous. On funduscopy CMO and snowbanking were noted. Fluorescein angiography demonstrated severe CMO and vasculitis in both eyes. The patient was treated with periocular steroid injections. This treatment was complicated by a high intraocular pressure. The steroid depot was removed; however, secondary glaucoma developed, requiring filtering surgery. In the following 2 years, the patient underwent cataract surgery in both eyes. Repeated evaluations for systemic diseases were negative. The activity of inflammation slowly subsided and the final visual acuity was 0.8 in both eyes. One year before the onset of IU he developed localised skin lesions, which were clinically consistent with GA. Skin biopsy exhibited a subcutaneous form of GA. The lesion was treated with cryotherapy with good effect.

Patient 5

A 36 year old female patient with bilateral IU presented to our clinic. Visual acuity was 1.0 in the right eye and 0.8 in the left

eye. The left eye had occasional cells in the anterior chamber. Both eyes had cells in the vitreous. On funduscopy, both eyes demonstrated peripheral snowballs. Fluorescein angiography demonstrated extensive vasculitis in both eyes. The patient was initially treated with periocular injections; however, systemic corticosteroids were required 1 year later (initial dose 20 mg, slowly tapered off to 10 mg a day, but complete withdrawal of systemic corticosteroids was not feasible). After 3 years of treatment she developed secondary cataract in both eyes. Snow banking and peripheral ischaemic retinopathy of the left eye manifested after 6 years of follow up and required laser treatment. At the 7 year follow up, visual acuity was 0.4 in the right eye (caused by cataract) and 1.0 in the left eye, despite persistent vitreous inflammation. Repeated evaluations for systemic diseases were negative. Two years after the onset of IU she developed skin lesions, which were clinically consistent with GA. The diagnosis was confirmed by skin biopsy. The lesions recovered spontaneously within 1 year.

Patient 6

A 36 year old woman was referred to our department with a history of IU in both eyes for 8 years treated with corticosteroid drops. On examination, her visual acuity was 0.6 and 0.8; clear anterior chambers and old synechiae in right eye were noted. On funduscopy, she exhibited periphlebitis in the periphery of both eyes. The patient was treated with topical corticosteroids and developed cataract during her follow up of 8 years, which caused a compromised visual acuity. Three years before the onset of uveitis she developed granuloma annulare on her forearms and later on her feet.

Patient 7

A 62 year old man was referred to our department with a history of vitritis in both eyes for 2 years, treated with corticosteroid drops. On examination clear anterior chambers were noted, but slight vitritis was present. His visual acuity was 0.8 and 0.6. On funduscopy, he exhibited periphlebitis of the right eye and small punched out lesions in the periphery of both eyes. On fluorescein angiography leakage of both discs was found, but no CMO. The patient was treated with topical corticosteroids. On systemic examination elevated ESR and monoclonal paraproteinaemia were found. Two years after the onset of uveitis he was diagnosed with granuloma annulare on his back, which was treated with topical corticosteroids and diminished within 1 year.

Patient 8

A 21 year old woman was referred to our department with a history of IU in both eyes for 12 years, treated with systemic corticosteroids in the past. On examination, her visual acuity was 0.8 and 1.0. Both eyes had cells in the vitreous. On funduscopy, both eyes exhibited peripheral snowbanking. Initially normal fluorescein angiography demonstrated CMO and extensive retinal vasculitis 14 years after the onset of the disease. The patient was treated with periocular steroid injections, acetazolamide, and systemic NSAIDs. Repeated evaluations for systemic diseases were negative. Seventeen years after the onset of IU she developed skin lesions, which were clinically consistent with GA. The diagnosis was confirmed by skin biopsy. The lesions were treated with topical corticosteroids and disappeared within 1 year.

DISCUSSION

This series reveals an association of IU and localised form of GA in eight cases. Seven of these patients had severe retinal vasculitis. These clinical features are strongly similar to variant of IU described by Park *et al.*¹

IU is responsible for about 10% of all uveitis patients; however, in teenagers and young adults this percentage increases up to 15–39%.¹¹ IU may remain active for 5–30 years. So far,

our patients exhibited long term ocular activity and only one patient had remission (Table 1). CMO, vasculitis, and cataract are well known complications of IU and all our patients developed at least one of these complications.^{1,4,12} Seven of our patients had vasculitis (88%), in contrast with 11–55% observed in those with IU.^{4,12} Since GA is common in children, and one patient of our series (child with IU) did not have vasculitis, it is feasible that the combination of localised GA and IU in this child might be a coincidence.

GA is a skin abnormality with an unknown cause, which mainly affects children and young adults. Localised GA is the most common form and resolves spontaneously after 1–2 years. Generalised GA shows a more chronic course, a later age of onset, a rare spontaneous recovery, and poorer response to therapy. Other GA variations include subcutaneous, erythematous, and perforating types.⁷ In our series, all patients had localised GA (one patient had the subcutaneous type). GA was occasionally described following insect bites, trauma, and PUVA therapy.⁷ None of our patients had a history of such a precedent event.

An association between uveitis and GA has to our knowledge never been described. The known relation between granuloma annulare and diabetes mellitus and sarcoidosis has been reported previously.^{6–9} In our patients, despite repeated analyses, these diseases were not observed. The association of IU and GA might be a coincidence; however, this seems improbable. All IU and GA patients presented with uniform clinical features and GA was not reported in patients with other types of uveitis. Secondly, sarcoid associated uveitis and GA share common pathological features. Recent reports have clearly demonstrated GA occurring in association with sarcoidosis.^{6,8,9} In one report it is proposed that GA may act as a precursor lesion to cutaneous sarcoidosis.⁶ Since ocular sarcoidosis, including in those with IU, may precede systemic involvement by many years, it is still feasible that our patients may still develop sarcoidosis in the future. Thirdly, the association of HLA-B8 with pars planitis and also with granuloma annulare with insulin dependent diabetes mellitus has been described.^{1,5,13} These findings suggest that there might exist an immunogenic predisposition to both diseases. HLA B8 was found in two of four typed cases in this study; however, the lack of HLA typing in this study prevents us from drawing the conclusion. Furthermore, several reports have described a correlation of increased matrix metalloproteinase (MMP) 2, 9, and 12 in uveitis and GA with disease activity.^{14–18} MMPs are a family of enzymes that are capable of degrading extracellular matrix proteins. These findings suggest that there might be a common basal defect, which finally leads to both diseases.

The course of IU is variable, ranging from low grade activity and a self limited process to chronic disease with remissions and exacerbations.¹⁹ Long term visual prognosis is usually favourable and depends on the development and severity of associated CMO. Visual prognosis in our patients and in a

similar type of IU (phakic patients with chronic vasculitis) was excellent.¹ Although five of our patients developed CMO, visual acuity of more than 0.5 was retained in all.

In conclusion, we report seven patients with a combination of IU associated with retinal vasculitis and GA. Further studies are needed for a better understanding of this association and its eventual clinical consequences.

Authors' affiliations

B van Kooij, J de Boer, A Rothova, Department of Ophthalmology, FC Donders Institute, University Hospital Utrecht, Netherlands

M Canninga van Dijk, Department of Pathology, University Hospital Utrecht, Netherlands

V Sigurdsson, Department of Dermatology, University Hospital Utrecht, Netherlands

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