Epidemiological profile of non-infectious uveitis from the rheumatologist's perspective: a survey from two tertiary referral centres in Italy

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ABSTRACT

Objective. *To describe the epidemiology of non-infectious uveitis (NIU) in two tertiary referral rheumatology units in Central and Southern Italy.*

Methods. *Two hundred and seventy-eight consecutive NIU patients (417 eyes) evaluated between January 2016 and January 2017 were enrolled. Collected data were analysed in accordance with the primary anatomic site of inflammation, clinical course, and laterality.*

Results. *The mean age at NIU onset was 36.92±18.30 years with a female-to-male ratio of 1.34:1. Anterior uveitis (AU) was identified in 151 (54.32%), posterior uveitis (PU) in 67 (24.10%), intermediate uveitis (IU) in 5.40% and panuveitis (PanU) in 16.19% patients. Bilateral involvement was identified in 50% of our cohort. Uveitis was acute in 33.81% of patients, while 24.46% and 41.73% had a chronic and recurrent course, respectively. Gender and laterality did not influence the anatomical pattern, while disease course was significantly more acute or chronic in AU ($p<0.05$) and chronic in IU ($p<0.05$). An associated systemic disease was identified in 116 patients (41.73%). Twenty-seven patients (9.7%) had a specific isolated eye disease, 135 patients (48.56%) had idiopathic NIU. Uveitis associated with a systemic disease was significantly bilateral ($p=0.01$) and acute or chronic ($p<0.0001$), while the isolated form showed an association with chronic course ($p<0.0001$) and unilaterality ($p=0.01$).*

Conclusion. *The most common anatomic pattern of NIU has been AU, followed by PU, PanU and IU. A systemic disease (mainly Behçet's disease, ankylosing spondylitis and juvenile idiopathic arthritis) has been recognised in a fair proportion of the entire cohort. The rheumatologist should remain a central professional figure in the multidisciplinary team dealing with intraocular inflammation on a daily basis.*

Introduction

The term "uveitis" refers to a broad spectrum of infectious and non-infectious ocular disorders basically defined by intraocular inflammation. Structural complications of uveitis, including macular oedema, epiretinal membranes, glaucoma and cataract, are of deep concern in the management of patients, since they are intimately connected with a poor visual prognosis (1). Given the substantial impact on disability among working-age groups and its contribution to a considerable percentage on legal blindness worldwide, this high-morbidity condition results in a marked social and economic burden (2, 3). Epidemiologic data represent a crucial instrument for clinicians during the diagnostic work-up of uveitis as well as they might have favorable relevant implications in helping physicians during differential diagnosis.

Many epidemiologic studies have been widely reported in the medical literature (4-10), even though with a variation in quality due to the lack of a standardised nomenclature, which only recently has been taxonomically improved.

The anatomic pattern and aetiology of uveitis differ according to patient's geographical region because of ethnic, environmental and genetic background influences (4). Additionally, in the context of increased migratory fluxes, uveitis anatomical and aetiological pat-

terns can be considered dynamic rather than static (5). We also presume that epidemiologic findings reported in the literature mainly by ophthalmologic departments may not necessarily reflect the experience on uveitis of referral rheumatologic centres. Therefore, we herein present a retrospective review of non-infectious uveitis (NIU) cases attending two referral rheumatology centres in Italy during a 12-month working period.

Patients and methods

We conducted a retrospective review related to 278 cases of NIU attending two tertiary referral rheumatologic centres in Central and Southern Italy: in particular, all data from these consecutive patients affected by NIU admitted between January 2016 and January 2017 were retrospectively collected and examined.

Demographic information included gender, age, age at onset, family history and ethnicity. Ocular findings were extracted in accordance to the Standardization of Uveitis Nomenclature (SUN) criteria (11). Laterality was defined either mono or bilateral. Alternated uveitis was classified as bilateral. Cases with no systemic or isolated ocular diagnosis were deemed as idiopathic. Ophthalmologic examinations included Best Corrected Visual Acuity (BCVA), slit-lamp examination, applanation tonometry, fundus biomicroscopy. Optical coherence tomography (OCT) and fluorescein angiography (FA) were also employed as requested by medical discretion in selected cases.

Systemic involvement was investigated in a tailored case-by-case manner and not by protocol with one or more of the following examinations: clinical history; complete blood chemistry; erythrocyte sedimentation rate; C-reactive protein; angiotensin-converting enzyme (ACE) or lysozyme and/or alpha-chitotriosidase in patients using ACE inhibitors; human leukocyte antigen (HLA) haplotype typization; anti-nuclear antibodies and anti-extractable nuclear antigen antibodies; *Toxoplasma gondii* and syphilis serology; *Borrelia burgdorferi* specific immunoglobulins IgM/IgG; specific test for HIV; purified protein derivative (PPD) or QuantiFERON test; urinalysis; chest X-ray; plain X-ray and/or magnetic resonance imaging of the sacroiliac joints; high-resolution computed tomography of the chest. Patients recognised as having infectious uveitis, uveitis secondary to surgical treatment, or traumatic-induced uveitis were excluded from the study.

The study conformed to the Declaration of Helsinki and both tertiary referral rheumatologic centres obtained a formal approval from their respective ethic committees.

Statistical analysis

Statistical analysis was performed using Stata 14.2 (Statacorp, USA, TX). A descriptive statistics was employed for continuous variables expressed as mean and standard deviation, while absolute frequencies with their relative percentages describes categorical data. Cross-tables were analysed by Pearson's Chi square test and post hoc test with adjusted residuals in case of contingency tables with dimensions greater than 2x2. A p value lower than 0.05 was considered statistically significant.

Results

Demographic characteristics

Two hundred and seventy-eight patients (119 males, 159 females, 417 eyes) diagnosed with non-infectious uveitis were enrolled during the 12 months of the study. The female-to-male ratio was 1.34:1 with a mean age at onset and a mean age at diagnoses of 36.92±18.30 years and 42.00±18.17 years, respectively. Paediatric patients (defined as subjects with less than 16 years) with uveitis represented 11.87% of our cohort (33/278), while 10.07% (28/278) of patients were ≥65 years of age. All but one patient were of Caucasian ancestry.

With regard to laterality, uveitis was deemed as bilateral in 50% of cases. A detailed description of demographic features and location of ocular inflammation is provided in Table I.

In our population of patients with NIU a specific diagnosis was established in 143/278 (51.44%), whereas the remaining 135 uveitis cases were classified as idiopathic.

Anatomic and aetiologic subgroups

With regard to the anatomical pattern classified according to the SUN criteria, the majority of patients had anterior uveitis (AU), which was identified in 151/278 patients (54.32%), followed by posterior uveitis (PU) in 67 (24.10%), panuveitis (PanU) in 45 (16.19%) and intermediate uveitis (IU) (15/278 patients; 5.40%). No statistical significance was found for laterality and gender between AU, PU, PanU and IU, while the clinical course was significantly non-recurrent (acute or chronic) in AU ($p<0.05$) and chronic in intermediate uveitis ($p<0.05$).

AU had an aetiologic diagnosis in 83/151 cases (54.97%): specifically, the most represented diagnoses were ankylosing spondylitis (AS, 16/83 patients; 19.28%), followed by juvenile idiopathic arthritis (JIA, 13/83 patients; 15.66%), HLA-B27-related uveitis (12/83 patients; 14.46%), Fuchs' heterochromic iridocyclitis (12/83 patients; 14.46%) and Behçet's disease (BD, 9/83 patients; 18.84%). Intermediate uveitis had a definite diagnosis in 4/15 cases (26.67%). In our population, among intermediate uveitis, BD was the most common associated diagnosis (3/4 patients; 75.00%) with the remaining case being related to AS (1/4 patients; 25%). Posterior uveitis had a definite diagnosis in 33/67 cases (49.25%). BD was the prevalent diagnosis (16/33 patients; 48.48%) in patients affected by posterior uveitis. An aetiological diagnosis of PanU was established in 23 out of 45 patients (51.11%), with BD being the most frequent diagnosis (12/23 patients; 52.17), followed by AS (4/23 patients; 17.39%). A comprehensive information on different diagnosis for each anatomical pattern is provided in Figure 1.

With regard to uveitis diagnosed in the context of a systemic inflammatory disease, BD-related uveitis was by far the most common recognised ocular entity (40/116), followed by AS (22/116) and JIA (14/116). Together, these aetiologic entities accounted for 65.5% of all cases of uveitis related to systemic inflammatory disorders. Notably, isolated uveitis such as HLA-B27-related uveitis and Fuchs' heterochromic iridocycli-

Table I. Clinical and demographic characteristics of 278 patients with non-infectious uveitis according to the anatomic location of inflammation.

Age at onset (years)	Tot (n=278)	Anterior uveitis (n=151)	Intermediate uveitis (n=15)	Posterior uveitis (n=67)	Panuveitis (n=45)
Mean ± SD (range)	36.91±18.30 (0-87)	36.59±18.45 (2-86)	30.93±15.89 (5-54)	39.10±16.03 (0-81)	36.73±21.50 (1-87)
Gender					
Female, n (%)	159 (57.19)	85 (53.46)	5 (3.14)	37 (23.27)	32 (20.13)
Male, n (%)	119 (42.81)	66 (55.46)	10 (8.40)	30 (25.21)	13 (10.92)
Ethnicity					
Caucasian n (%)	277 (99.65)	151 (54.32)	15 (5.40)	66 (23.74)	45 (16.19)
Asian, n (%)	1 (0.35)	0 (0.00)	0 (0.00)	1 (0.35)	0 (0.00)
Ocular involvement					
Unilateral, n (%)	139 (50.00)	82 (49.64)	6 (86.47)	28 (20.14)	23 (16.55)
Bilateral, n (%)	139 (50.00)	69 (49.64)	9 (6.47)	39 (28.06)	22 (15.83)
Course of uveitis					
Acute, n (%)	94 (33.81)	61 (64.89)	1 (1.06)	23 (24.47)	9 (9.57)
Chronic, n (%)	68 (24.46)	40 (58.82)	8 (11.76)	10 (14.71)	10 (14.71)
Recurrent, n (%)	116 (41.73)	50 (43.10)	6 (5.17)	34 (29.31)	26 (22.41)

tis made up a conspicuous proportion of the non-idiopathic subgroup (24/143, 16.8%). The HLA-B51 haplotype was positive in 61/278 patients (21.94%), and a HLA-B27 positivity was recorded in 44/278 patients (15.83%). The HLA-A29 was negative in all patients. A detailed description of demographic and clinical data for every specific entity encountered in our cohort of patients is provided in Table II.

Concerning treatment strategies, topical medications, either corticosteroids or nonsteroidal antinflammatory drugs, were the most prescribed medications (36.92%) followed by disease-modifying antirheumatic drugs, prescribed as monotherapy (6.15%) or in combination with corticosteroids (17.69%) and anti-tumor necrosis factor (TNF)-α agents (9.23%). Systemic corticosteroids were given in 16.15% of the population, while anti-TNF-α agents were administered as monotherapy in 13.85%. Figure 2 shows the systemic treatment strategies in our patients with NIU.

The subgroup analysis between isolated, systemic and idiopathic NIU showed no statistical differences regarding gender

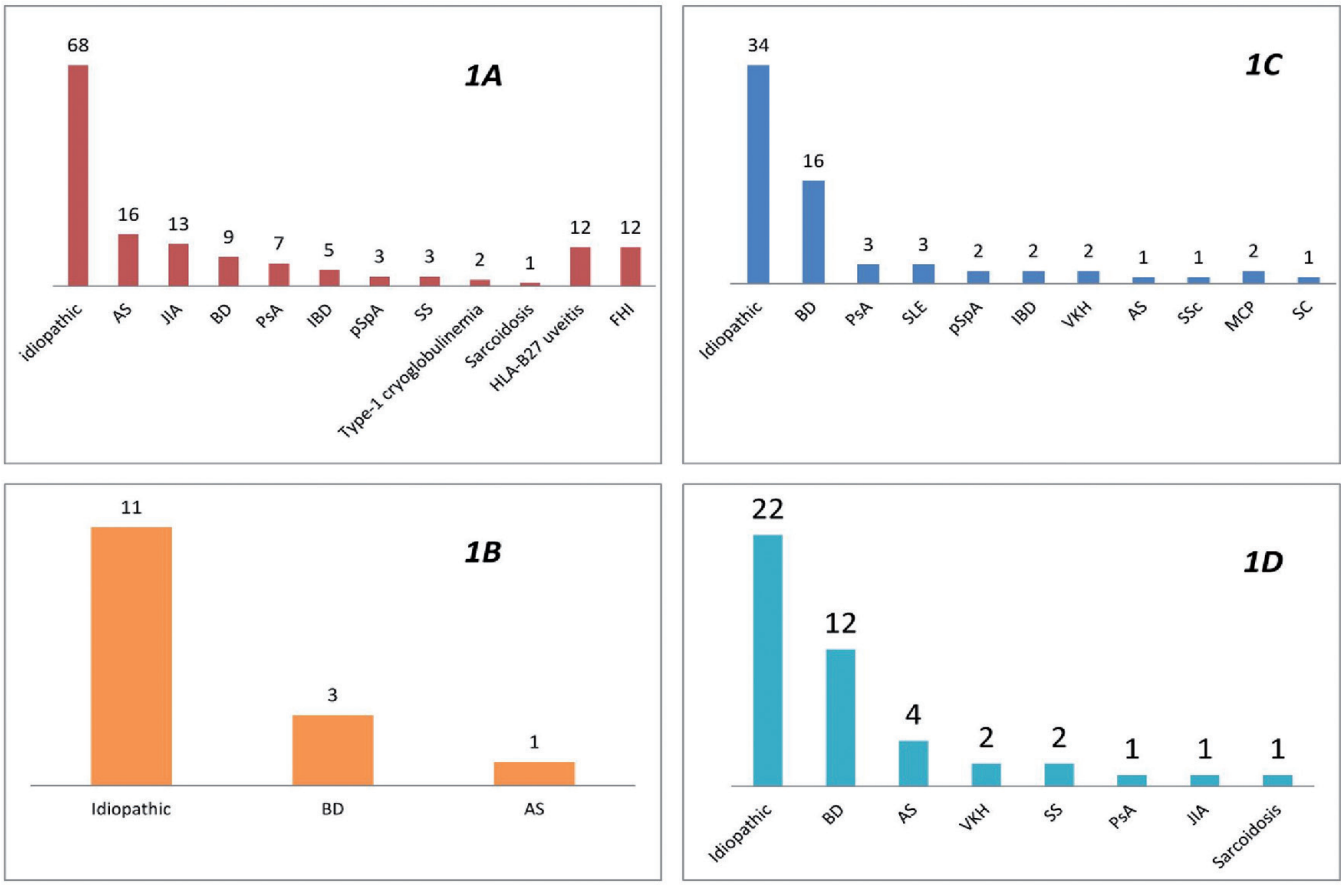

Fig. 1. Absolute frequency of all aetiologies of anterior uveitis (**1A**), intermediate uveitis (**1B**), posterior uveitis (**1C**) and panuveitis (**1D**) in our population of 278 patients with non-infectious uveitis recruited in our study.
AS: ankylosing spondylitis; JIA: juvenile idiopathic arthritis; BD: Behçet's disease; PsA: psoriatic arthritis; IBD: inflammatory bowel disease; pSpA: peripheral spondyloarthritis; SS: Sjögren's syndrome; FHI: Fuchs' heterochromic iridocyclitis; SLE: systemic lupus erythematosus; VKH: Vogt-Koyanagi-Harada disease; MCP: multifocal choroidopathy; SC: serpiginous choroidopathy.

Table II. Demographic and clinical characteristics of 278 patients with non-infectious uveitis according to the specific diagnosis found.

Diagnosis	Number of patients	Mean age ± SD	Gender F/M	Anatomic pattern	Laterality Bilateral (n)	Laterality Unilateral (n)	Course
Idiopathic uveitis	135	38.38±19.36	85/50	68 AU	29	39	20 Acute, 5 Chronic, 43 Recurrent
				11 IU	6	5	7 Chronic, 4 Acute
				34 PU	17	17	10 Acute, 2 Chronic, 22 Recurrent
				22 PanU	8	14	5 Acute, 3 Chronic, 14 Recurrent
Behçet's disease	40	32.73±14.84	18/22	9 AU	6	3	3 Acute, 6 Recurrent
				3 IU	3	-	1 Chronic, 2 Recurrent
				16 PU	9	7	6 Acute, 9 Recurrent, 1 Chronic
				12 PanU	9	3	1 Acute, 10 Recurrent, 1 Chronic
Ankylosing spondylitis	22	44.29±10.33	11/11	16 AU	9	7	16 Acute
				1 IU	-	1	1 Acute
				1 PU	1	-	1 Acute
				4 PanU	-	4	3 Acute, 1 Chronic
Psoriatic arthritis	11	42±22.45	7/4	7 AU	4	3	2 Acute, 5 Chronic
				3 PU	2	1	3 Chronic
				1 PanU	1	-	1 Chronic
Peripheral spondyloarthritis	5	52±7.60	3/2	3 AU	2	1	3 Acute
				2 PU	1	1	2 Acute
Juvenile idiopathic arthritis	14	7.36±4.40	8/6	13 AU	10	3	1 Acute, 12 Chronic
				1 PanU	-	1	1 Acute
Inflammatory bowel disease	7	43±14.48	3/4	5 AU	5	-	5 Acute
				2 PU	-	2	2 Acute
Vogt-Koyanagi-Harada disease	4	25.25±17.86	3/1	2 PU	2	-	2 Recurrent
				2 PanU	2	-	2 Recurrent
Sarcoidosis	2	47.5±6.36	1/1	1 AU	-	1	1 Chronic
				1 PanU	1	-	1 Chronic
Systemic lupus erythematosus	3	38.67±6.66	3/0	3 PU	3	-	2 Acute, 1 Recurrent
Systemic sclerosis	1	16	0/1	1 PU	1	-	1 Chronic
Sjögren's syndrome	5	50±15.30	4/1	3 AU	-	3	3 Chronic
				2 PanU	1	1	2 Chronic
Type 1 cryoglobulinemia	2	35.50±4.95	1/1	2 AU	-	2	2 Chronic
HLA-B27-related uveitis	12	39±14.97	5/7	12 AU	3	9	11 Acute, 1 Recurrent
Fuchs' heterochromic iridocyclitis	12	34.25±8.58	5/7	12 AU	1	11	12 Chronic
Serpiginous choroidopathy	1	51	0/1	1 PU	1	-	1 Chronic
Multifocal choroidopathy	2	49.5±24.75	2/0	2 PU	2	-	2 Chronic

AU: anterior uveitis; IU: intermediate uveitis; PU: posterior uveitis; PanU: panuveitis; F: female; M: male; HLA: Human leukocyte antigen.

(p=0.117). On the contrary, significant statistical differences were found for laterality and disease course. More in detail, idiopathic NIU was found to be more frequently recurrent (p<0.0001) with no predilection on laterality (p=0.07). The isolated and systemic forms showed a preferential chronic (p<0.0001) unilateral (p=0.01) involvement and a bilateral (p=0.01) non-recurrent (acute or chronic) (p<0.0001) pattern, respectively.

Discussion

This retrospective study was arranged to provide a valid epidemiologic overview on 417 eyes (278 patients) with NIU from the rheumatologist's perspective in two tertiary referral centres working in Italy. The mean age at onset was 36.92±18.30 years, which is slightly lower than the mean age at onset reported in other studies (5, 6, 9, 10, 12, 13). This might be partially explained by a higher prevalence in our cohort of BD-related uveitis, a disorder mainly affecting young individuals in their third or fourth decade. Indeed, Llorenç *et al*. identified BD as the aetiology of uveitis with the youngest age at onset (5). An epidemiologic report from Egypt found BD as the most frequent non-infectious aetiology, thus justifying the young mean age (30 years) at presentation and a socio-economic burden on patients in their prime working age (4).

Regarding the anatomical pattern, AU represented the most frequently encountered type (54.13%), followed by PU and PanU. IU was the less commonly diagnosed type of uveitis: this is in line with previous studies describing AU as the prevailing anatomical diagnosis (5, 6, 8-10, 12, 14, 15). However, the tertiary nature of

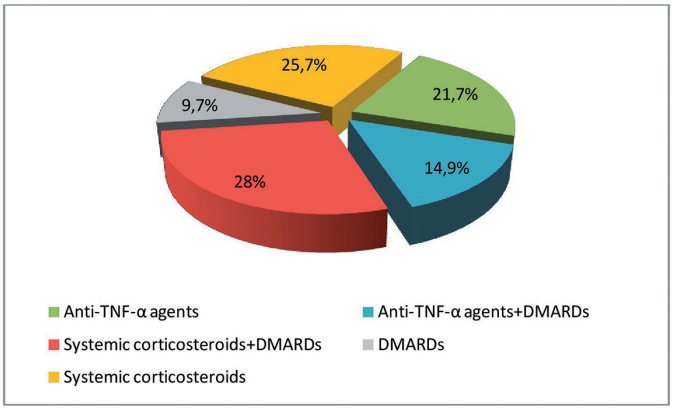

Fig. 2. Treatment overview in the 278 patients with non-infectious uveitis recruited in our study. TNF: tumour necrosis factor; DMARDs: disease-modifying anti-rheumatic drugs.

both rheumatologic centres could be responsible for an important referral bias. In fact, the proportion of AU may be even higher in the general population due to the often mild inflammatory involvement of anterior chamber, that is mainly managed by primary care ophthalmologists. The effect of referral bias may be even greater as proven by higher percentages of PU or PanU than AU in some studies (4, 7). Almost half of the classified PU and more than half of the classified PanU were attributable to BD (48.48% and 52.17%, respectively). Similar results have been obtained from Amin *et al*., who justified the frequent encounter of BD-related uveitis with the geographical location of their country along the Old Silk Route (4).

Overall, uveitis was idiopathic in 135 patients (48.56%), and this result is not consistent with the current literature reporting lower percentages from 25.4% (4) to 41% (6). A systemic cause was diagnosed in 41.72% (116/278) of cases. Similarly, with the aforementioned discrepancy, this finding also differs from the current literature data, showing different proportions across several studies performed by ophthalmology departments (4-6, 8, 9, 12). The discordant data with previous epidemiologic studies, especially with reference to a greater amount of idiopathic cases, is presumably a result of the exclusion of infectious causes of uveitis, which represent a significant rate among classified cases (4-6, 8, 9, 14, 15). Moreover, a considerable amount of patients was firstly evaluated by trained ophthalmologists, who had excluded any infectious aetiology through an extensive laboratory and clinical examination, and thereafter referred to the rheumatologists. Consequently, the latter professional figure has also been in contact with cases where a systemic diagnosis could not be established.

An interesting finding is the association of uveitis in the context of a systemic inflammatory disorder with a bilateral non-recurrent pattern. Indeed, a systemic diagnosis allows a better and more targeted therapy, increasing the rate of uveitis resolution and at the same time preventing recurrent flares. Additionally, given the particular design of the study, analysing data from a cohort referred to the rheumatologist instead of the ophthalmologist, an effective comparison with other previous studies is unreliable.

The most common systemic disease identified associated with uveitis was BD, which was detected in 14,38% of our total cohort, followed by AS and JIA. All together, these three systemic inflammatory disorders accounted for 53.15% of non-idiopathic cases. The overwhelming prevalence of BD may be related to a referral bias, since both the rheumatology departments of this study are national and regional reference centres for BD. Nevertheless, other systemic disorders, such as PsA, IBD, VKH, sarcoidosis and SLE are to be considered during the diagnostic work-up.

With regard to isolated ocular entities, a relatively high frequency of HLA-B27-related uveitis and Fuchs' heterochromic iridocyclitis were found in 4.3% of the whole population (approximately in 8.3% of the classified diagnosis) for each of them. The relative high prevalence of Fuchs' heterochromic iridocyclitis is consistent with the previous epidemiologic reports carried out in our country (12, 13), and confirms that rheumatologists interested in uveitis should be aware of the clinical presentation and management of this disease.

With reference to the different treatments employed, the majority of our population has been receiving topical treatments. This fact is not surprising, considering that the predominant proportion of intraocular inflammation involved the anterior chamber. However, a consistent number of patients (23.08% of the entire cohort; 36.56% of systemic treatments) were on biologic therapy, especially those patients affected by BD- and AS-related uveitis, for which anti-TNF-α agents have proven to be effective (16-20). In conclusion, the diagnostic frequencies of uveitis is constantly changing over time as a result of both improved knowledge on the different types of uveitis associated with systemic diseases and the evolution of diagnostic techniques. However, a thorough history as well as a solid epidemiology remain a *sine qua non* premise for an efficient diagnostic work-up.

We have herein provided epidemiologic data regarding NIU from a rheumatologic perspective, as a solid epidemiologic background may help the rheumatologist in the management of this sight-threatening disease. The most common anatomic pattern was AU, followed by PU, PanU and IU. The main differentials for NIU in Italy should include BD, AS and JIA, although the rheumatologist must also possess a basic knowledge about other specific isolated ocular entities.

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