IOII #1522356, VOL 00, ISS 00

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Ocular Immunology & Inflammation, 2018; 00(00): 1–8

ISSN: 0927-3948 print / 1744-5078 online
DOI: 10.1080/09273948.2018.1522356

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Uveitis of Unknown Etiology: Clinical and Outcome features. A Retrospective Analysis of 355 Patients

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ABSTRACT

Purpose: Despite the huge advance in diagnostic technics, about one-third of uveitis is still considered of unknown etiology. In this study, we aimed to report their clinical features and to describe how a diagnosis has been finally reached for some patients.

Methods: We retrospectively reviewed all patients with uveitis referred to our tertiary center between 2002 and 2016. The unknown etiology was admitted after a new ophthalmologic examination and a full work-up in internal medicine in our tertiary center.

Results: Among 957 patients with uveitis, 355 had uveitis of unknown etiology. The clinical and epidemiological characteristics of this subgroup were no different from those with a known etiology. Out of 104 patients who were followed-up for more than 1 year, a diagnosis was finally achieved in 20 patients. The diagnosis was determined either because of the occurrence of a new clinical symptom (n = 10), a new/repeated non-ophthalmologic investigation (n = 7), or a new/repeated ophthalmic exam (n = 3).

Conclusion: A prolonged follow-up, with repeated exams, may allow the determination of an etiology in about one-fifth of uveitis initially considered as idiopathic.

Keywords: Diagnosis, epidemiology, uveitis

Uveitis has a prevalence of 17–52/100,000 person-years and is responsible for 15% of preventable blindness in the Western world.[1] Uveitis mainly affects young adults, as 70–90% of patients suffering from uveitis are aged between 20 and 60 years. Uveitis leads to a significant economic cost and to a significant number of years of visual loss.[2,3]

Uveitis etiologies can be separated into several subgroups: (i) purely ophthalmic causes, such as Birdshot chorioretinopathy; (ii) linked to a general inflammatory disease, such as spondyloarthritis, sarcoidosis, Behcet's disease, or Vogt–Koyanagi–Harada syndrome; (iii) infections, such as syphilis, tuberculosis, or viral causes; (iv) neoplastic causes, such as cerebral lymphoma; (iv) iatrogenic causes; and (v) idiopathic uveitis.[4]

About one-third of uveitis remains of unknown etiology (i.e., idiopathic).[2] In some series, idiopathic uveitis represents the most frequent etiology.[2,5] To date, there is no clear definition of what an idiopathic uveitis is, neither are determined the specific etiologies that must be ruled-out before uveitis can be categorized as idiopathic. The proportion of idiopathic uveitis tends toward a decrease over the last few decades, but there is still a significant proportion of undiagnosed uveitis.[6] To our knowledge, there is no data in the literature regarding the evolution or the recommended follow-up for patients suffering from idiopathic uveitis. Considering the morbidity of blindness in a young, age class of working people, and the cost of treatment (economic, microbial resistance, iatrogenic effects, immune defect), it seems

Received 5 December 2017; revised 29 August 2018; accepted 7 September 2018; published online xx xxx xxxx

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important to know whether a diagnosis could be reached during the follow-up of these patients.

We therefore aimed to describe, in our tertiary center, the clinical and epidemiological profile of these patients with idiopathic uveitis. Another purpose was to determine if a diagnosis could be acquired during the follow-up and how it was achieved.

PATIENTS AND METHODS

Patients

The study was a retrospective analysis of records from patients with a diagnosis of "uveitis" referred to the Department of Internal Medicine (Hôpital de la Croix-Rousse, Hospices Civils de Lyon, Lyon, France) between July, 2002 and August, 2016. The uveitis diagnosis was achieved after an ophthalmologic exam. According to the French law (no. 2004–806, August 9, 2004), and because the data were collected retrospectively and patient management was not modified, this study did not require research ethics committee approval.

Diagnosis Work-Up and Definitions

The *unknown etiology* was admitted after a new ophthalmologic exam and a full work-up in internal medicine were performed in our tertiary center. Depending on the anatomical classification, patients underwent a screening protocol for uveitis, which included tuberculosis skin test, determination of C-reactive protein level and erythrocyte sedimentation rate (ESR), complete blood cell count (CBC), serological tests for HIV and syphilis, and radiological chest examination. Human leucocyte antigen (HLA)-B27 typing was performed in patients with acute anterior uveitis. In cases of chronic anterior uveitis or granulomatous uveitis, angiotensin-converting enzyme (ACE) dosage and chest CT scan were performed. Serological tests for *Toxoplasma gondii*, chest CT scan, and cerebral MRI were performed in patients with posterior uveitis or panuveitis.

The diagnostic battery for sarcoidosis also included conjunctiva or skin biopsy, if clinically suspicious features were present. Some patients underwent minor salivary gland biopsy, transbronchial lung biopsy, bronchoalveolar lavage (BAL), or nuclear imaging. This work-up was completed in some patients by anterior chamber paracentesis (with polymerase chain reaction (PCR) for Herpesvirus, *Toxoplasma*, or RNA16S and sometimes Interleukin-10 measurement), vitreous biopsy, and/or cerebrospinal fluid analysis if appropriate.

This protocol was not mandatory, and each physician could choose to adapt it if necessary. Therefore, some patients may not have been fully screened at the first visit in our center.

We then focused on patients with uveitis of unknown etiology who had been followed-up for more than 1 year and noted whether an etiology was found or not. For those with a diagnosis, we recorded the final diagnosis, the means to achieve it (new medical opinion, occurrence of a new clinical sign, new/repeated ophthalmologic or paraclinical exam), and the treatment.

The Standardization of Uveitis Nomenclature was used throughout this study for the anatomic classification of uveitis.[7] We used the following criteria for patients with idiopathic uveitis who finally achieved a diagnosis during follow-up:

- Gupta *et al*. criteria[8] for the diagnosis of intraocular tuberculosis,
- Assessment of SpondyloArthritis international Society (ASAS) criteria[9] for spondyloarthritis,
- the international study group for Behcet's disease criteria,[10]
- the revised diagnostic criteria for Vogt–Koyanagi–Harada syndrome,[11]
- the 2010 revised McDonald criteria for multiple sclerosis,[12]
- the International criteria for the diagnosis of ocular sarcoidosis[13] (with use of Zajicek's classification for neurosarcoidosis.[14]) We also used Abad's criteria[15] in the absence of histological proof. Patients had presumed sarcoidosis if they had at least two of the following four criteria: typical changes on a chest radiograph or CT scan, predominantly CD4 lymphocytosis on BAL fluid, elevated ACE levels, or high gallium or 18-fluorodeoxyglucose positron emission tomography (18-FDG PET) uptake.

Data Collection

We collected patient's demographic data, follow-up duration, and the following ophthalmologic characteristics at diagnosis: localization of the inflammation (anterior, intermediate, posterior, panuveitis) and anterior segment examination (tonometry, slit lamp biomicroscopy to assess whether the uveitis was granulomatous or not). We also noted whether the uveitis was acute or chronic, uni- or bilateral.

Statistical Analysis

Data are described as frequencies and percentages for categorical variables and as medians and 25th–75th percentile range for quantitative variables. Categorical

variables were compared using Fisher's exact test and quantitative variables using Wilcoxon's ranked-sum test. All tests were two-sided and statistical significance was set at the $p = 0.05$ level. All analyses were performed using R-software, version 3.1.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Study Population

957 patients were included (Table 1), of which 362 had a uveitis of unknown etiology. As 7 patients were excluded because of insufficient data, the full analysis set population comprised 355 patients, including 227 (64%) women. Overall, the mean age at diagnosis was 49.8 [5–92] years. Sixty-five (19%) patients were non-Caucasian: 16% were Maghrebin, 3% were African, and 0.5% were Asian.

Clinical Characteristics

The anatomical forms were as follows: anterior uveitis (AU, $n = 150$, 42.3%), intermediate uveitis (IU) ($n = 48$, 13.5%), posterior uveitis (PU) ($n = 71$, 20%), and panuveitis (PAU) ($n = 86$, 24.2%).

Patients with a Final Diagnosis after a 1-Year Minimum Follow-Up

For the overall population, the mean follow-up was 16 months (range, 0–144). 251 patients were followed-up for less than 1 year. Precisely, 104 patients were followed-up for more than 1 year; their mean follow-up time was 50 months (range, 12–144). The comparison between these two subgroups did not show any difference in demographic, clinical, or paraclinical data (Table 3), although there was a trend toward more acute anterior uveitis in the less than 1-year follow-up group (32 vs 20%, $p = 0.08$).

A diagnosis was finally achieved in 20 (18%) patients with idiopathic uveitis who had a follow-up >1 year (Table 3). In this subgroup, the median follow-up duration was 54 months (range, 38–121). In 10 cases, the diagnosis was achieved thanks to the occurrence of new symptoms. Three patients had inflammatory arthralgia, and were finally diagnosed with spondyloarthritis. They were all secondarily tested positive for HLA-B27. One patient presented with chronic diarrhea, and the final diagnosis was Crohn's disease. Another patient presented with focal neurological deficit and was finally diagnosed with multiple sclerosis. Two patients presented leg pains associated with dysuria due to myelitis leading to the diagnosis of possible neurosarcoidosis according to Zajicek's criteria. One patients developed

TABLE 2. Comparison of patients with idiopathic uveitis followed for more or less than 1 year.

	Follow-up > 1 year	Follow-up < 1 year	P value
Patients (n)	104	251	
Age (median, years)	45.3	50.4	
Male (%)	41 (42%)	86 (35.5%)	0.35
Median follow-up (months)	50	3	
Anterior uveitis (n, %)	47 (45%)	108 (43%)	0.7
Intermediate uveitis (n, %)	25 (24%)	50 (19.9%)	0.38
Posterior uveitis (n, %)	18 (17%)	61 (24%)	0.56
Panuveitis (n, %)	23 (22.1%)	60 (23.9%)	0.65
Acute (n, %)	39 (37.5%)	83 (33%)	0.42
Unilateral (n, %)	52 (50%)	112 (44%)	0.35
Granulomatous (n, %)	27 (25.9%)	60 (23.9%)	0.68
Hypertensive (n, %)	9 (8.6%)	28 (11.2%)	0.48

TABLE 1. Comparison of the clinical features of the study patients (20 patients initially classified as unknown etiology were finally excluded).

	Uveitis of known etiology	Uveitis of unknown etiology	P value
Patients (n)	595	335	
Age (years, mean)	46.3	49.1	
Mean follow-up (months)	25.9	16.2	
Median follow-up (months)	6.5	3.8	
Male (n, %)	270 (45.4%)	126 (37.6%)	**0.02**
Anatomical forms			
- Anterior uveitis	218 (35.3%)	144 (42.9%)	0.056
- Intermediate uveitis	102 (23.7%)	46 (13.7%)	0.17
- Posterior uveitis	110 (23.0%)	66(19.7%)	0.65
- Panuveitis	165 (29.8%)	79 (23.6%)	**0.16**
Acute (n, %)	198 (33.3%)	119 (35.5%)	0.6
Granulomatous (n, %)	183 (30.7%)	69 (20.6%)	**0.014**
Unilateral (n, %)	243 (40.8%)	159 (47.5%)	0.10
Hypertensive (n, %)	58 (9.7%)	28 (8.3%)	0.33

TABLE 3. Description of the cases with a secondary diagnosis.

	Clinical characteristics	Demographics	Diagnostic tool	Final diagnosis	Treatment
Case 1	Chronic granulomatous, non-hypertensive bilateral panuveitis	46 years Female North Africa	New clinical sign: focal neurologic symptoms	Probable sarcoidosis	Mycophenolate mofetil Steroids
Case 2	Acute non-granulomatous Non-hypertensive bilateral anterior uveitis	38 years Female North africa	New clinical sign: arthralgia	Spondyloarthitis	Topic steroids
Case 3	Chronic non-granulomatous non-hypertensive unilateral posterior uveitis	34 years Female Caucasian	New clinical sign: oral aphtosis	Behcet's disease	Colchicine Steroids
Case 4	Chronic non-granulomatous, non-hypertensive bilateral panuveitis	62 years Female Caucasian	New clinical sign: peripheral arthralgia	Spondyloarthitis	Salazopyrine
Case 5	Acute non-granulomatous non-hypertensive bilateral anterior uveitis	19 years Female Caucasian	New clinical sign	Spondyloarthritis	Salazopyrine Topic steroids
Case 6	Chronic granulomatous non-hypertensive bilateral Posterior uveitis	60 years Female Caucasian	New clinical sign: mnesic impairment (steroids given)	Lymphoma	Aracytine, methotrexate, bone marrow transplant, rituximab radiotherapy
Case 7	Chronic non-granulomatous Non-hypertensive bilateral panuveitis	35 years Female North Africa	New clinical sign: optic neuritis	Multiple sclerosis	Steroids azathioprine
Case 8	Chronic granulomatous, hypertensive bilateral panuveitis	72 years Female Caucasian	New clinical sign: myelitis	Probable Sarcoidosis	Steroids cyclphospahmide
Case 9	Chronic non-granulomatous, non-hypertensive bilateral panuveitis	66 years Female North Africa	New clinical sign: ulcerative granulomatous skin lesion	Crohn's disease	Steroids
Case 10	Chronic non-granulomatous, hypertensive bilateral posterior uveitis	28 years Female North Africa	New clinical sign: oral aphtosis	Behcet's disease	Steroids colchicine azathioprine
Case 11	Chronic non-granulomatous, non-hypertensive bilateral panuveitis	14 years Female Caucasian	New ophtalmologic exam	Vogt-Koyanagi Harada syndrome	Steroids
Case 12	Chronic non-granulomatous hypertensive unilateral intermediate uveitis	30 years Male Caucasian	New ophtalmologic exam	Fuchs uveitis	Steroids methotrexate
Case 13	Chronic granulomatous hypertensive unilateral Posterioir uveitis	53 years Female Caucasian	New ophtalmologic exam	Irvan syndrome	Steroids infliximab
Case 14	Chronic granulomatous non-hypertensive bilateral intermediate uveitis	48 years Female Caucasian	New paraclinical exam: anterior chamber paracenthesis	Lymphoma	Radiotherapy rituximab aracytine methotrexate
Case 15	Acute granulomatous, non-hypertensive bilateral anterior uveitis	42 years Male Caucasian	New paraclinical exam: PET scan	Probable Sarcoidosis	Hydroxychloroquine steroids
Case 16	Chronic granulomatous hypertensive bilateral posterior uveitis	61 years Female Caucasian	New paraclinical exam: PET scan	Proven sarcoidosis	Steroids
Case 17	Acute granulomatous, non-hypertensive unilateral anterior uveitis	38 years Female Caucasian	New paraclinical exam: PET Scan	Proven Sarcoidosis	Hydroxycholoroquine
Case 18	Chronic granulomatous hypertensive bilateral anterior uveitis	66 years Female Caucasian	New paraclinical exam: anterioir chamber punction	HSV infection	Aciclovir
Case 19	Acute granulomatous, hypertensive bilateral anterior uveitis	54 years Female North Africa	New paraclinical exam: interferon gamma dosage	Tuberculosis	Isoniazide pyrazinamide rifampicine ethambutol
Case 20	Chronic granulomatous hypertensive bilateral pan uveitis	56 years Female Caucasian	New paraclinical exam: PET scan	Probable sarcoidosis	Steroids

central neurologic deficit, which led to the diagnosis of primary vitreoretinal lymphoma (PVRL). This patient was treated with corticosteroids before the diagnosis was reached. This may have delayed the diagnosis of lymphoma. One patient presented genital aphtosis and another one buccal aphtosis leading to the diagnosis of Behcet's disease.

In seven patients, the final diagnosis was achieved thanks to a new or repeated paraclinical exam. One tuberculosis was suspected with an interferon gamma release assay (3.28 UI/L) leading to a successful antibiotherapy. Four patients underwent 18-FDG PET and were finally considered as suffering from sarcoidosis. One patient had Herpesvirus-related uveitis, which was diagnosed thanks to anterior chamber paracenthesis. Another patient who underwent vitrectomy was finally diagnosed with PVRL.

Three patients were diagnosed after repeated ophthalmologic exam; one had Fuchs uveitis syndrome (FUS), one had Vogt-Konayagi-Harada syndrome, and one had IRVAN syndrome.

DISCUSSION

The present study describes for the first time the long-term follow-up of a large cohort of patients with uveitis of unknown origin. Eighteen percent of these patients who were followed-up for more than 1 year acquired a diagnosis. Nevertheless the demographical, clinical and ophthalmologic features were no different in this subgroup when compared with patients with uveitis of known etiology.

In our series, about 30% of patients had uveitis of unknown etiology, whereas most series have 40–50% of them.[2,5,16] This discrepancy may be explained by the monocentric design of our study. Indeed, we collected data from our tertiary center, whose aim is to find an etiological diagnosis and where we apply a strict diagnosis work-up before uveitis is considered as idiopathic.

In line with previous series, there was a female predominance in our cohort of patients with uveitis with a female-to-male sex ratio of 2.[3,16] Moreover, although no previous study has specifically focused on the demographics of patients with idiopathic uveitis, our data were in line with reports of uveitis in Western world tertiary centers, as far as clinical and epidemiologic characteristics are concerned.[4]

Interestingly, patients with idiopathic acute anterior uveitis had a shorter follow-up duration than other patients. It is likely that most of them had only one occurrence of the disease without recurrent manifestation, and therefore no longer required medical care. Because the follow-up was not mandatory for these patients, we were not able to analyze their data, which is one of the limitations of our work

About one-fifth of the patients with uveitis of unknown etiology, who were followed-up for more than 1 year, were finally diagnosed with a specific etiology. We have identified three settings. First, some patients developed a new clinical symptom that led to the diagnosis. Three of our patients developed neuropathic pains leading either to the diagnosis of multiple sclerosis or to neurosarcoidosis with spinal cord involvement. In previous studies, the prevalence of uveitis in the setting of multiple sclerosis has been reported at about 1% while the prevalence of multiple sclerosis among patients with uveitis was also 1%.[17] Intermediate uveitis is most commonly associated with multiple sclerosis[18] and uveitis can precede the onset of multiple sclerosis for several years.[18] Le Scanff *et al.* have reported uveitis prevalence in multiple sclerosis at 0.65%, with uveitis preceding multiple sclerosis in 46% of the cases while it occurred simultaneously in 18% of the cases.[19]

Series dealing with sarcoidosis, have reported symptomatic uveitis in 20–50% of the patients with 80% of the cases being diagnosed within the first year (of which 30% had uveitis as the presenting complaint).[20] No specific extraocular manifestation of sarcoidosis has been associated with the development of ocular involvement or uveitis. Spinal cord sarcoidosis is a rare manifestation of sarcoidosis that occurs in <1% of patients. In a series of 21 spinal cord sarcoidosis, uveitis was reported either before, simultaneously, or after neurological involvement.[21]

We report herein two cases of PVRL that were initially misdiagnosed as idiopathic uveitis. One of them presented with neurological symptoms during the follow-up, which led to perform a cerebral MRI. The other diagnosis was made thanks to vitrectomy, ordered as a second line test in our tertiary center. The median time between the onset of symptoms and definitive diagnosis of PVRL reported in the literature ranges from 0–144 months with a mean of 4–40.[22] Nowadays, the delay is reported from 4 to 8 months in specialized tertiary centers.[23,24] Approximately one-third of PVRL patients will have concurrent cerebral involvement at presentation, and 42–92% will develop central nervous system involvement within a mean delay of 8–29 months.[25] As for one of our patient, treatment with steroids may delay the correct diagnosis.[22] The diagnosis of PVRL is usually based on the analysis of vitreous biopsy material. In addition to cytological and immunocytochemical examination, measurement of cytokine levels and molecular determination of B-cell clonality increase the diagnostic yield.[26] Appropriate evaluation may prompt to a timely vitreous sampling and therefore to a faster diagnosis. We suggest to perform cerebral MRI in patients with uveitis older than 50 at the initial evaluation and to repeat this exam.

Two patients developed aphtosis that led to the diagnosis of Behcet's disease. Ocular manifestations are the presenting symptom in 10–20% of the patients and are often present at the onset of the disease or within the first 2 years.[27] The main ocular manifestation in Behcet's disease is posterior uveitis. It can be associated with arterial or venous vasculitis. Both patients who were finally diagnosed with Behcet's disease presented with posterior uveitis, one of them had active vasculitis. Both patients presented with aphtosis and were positive for HLA B51. One of them also presented repeated erythema nodosum and superficial veins thrombosis. As a result of the low sensibility of the International Study Group for Behcet's disease criteria published in 1990[11], an international group has proposed a new set of criteria, which include vascular manifestations, skin lesions, and neurological manifestations, and have an improved sensitivity.[28,29]

Three patients developed arthralgia that led to the diagnosis of either axial or peripheral spondyloarthritis according to the ASAS criteria.[10] All had not been tested immediately for HLA B27. This is due to the retrospective design of this work and to the fact that data have been collected over several years. We now recommend testing all patients who present with acute anterior uveitis for HLA 27. Most patients have also imaging tests, such as MRI to look for sacroiliitis. Uveitis is the most common non-rheumatic manifestation of spondyloarthritis. Indeed, 25% of patients with spondyloarthritis experience uveitis at some point in the course of their disease.[30] Several studies have shown that at the time of uveitis, 20–40% of patients had preexisting, undiagnosed joint or back pain, and that the onset of the uveitis allowed the spondyloarthritis diagnosis.[31] The first attack of acute anterior uveitis often precedes rheumatologic symptoms (18% of the cases).[32] Most SPA-related uveitis are non-granulomatous[33] and are never granulomatous when the patient is positive for HLA B27. However, granulomatous uveitis can be associated with psoriatic arthritis.

Finally, one of the patients had diarrhea during the follow-up, leading to the diagnosis of Crohn's disease. Uveitis is one of the extraintestinal manifestations that are commonly seen in association with inflammatory bowel diseases (both ulcerative colitis and Crohn's disease). Ocular manifestations (anterior uveitis, episcleritis, more rarely scleritis, conjunctivitis, posterior uveitis) associated with inflammatory bowel diseases are reported in 1.6–4.6% of patients with ulcerative colitis and in 3–6.3% of patients with Crohn's disease.[34]

Besides the group of patients with new clinical symptoms, seven patients were diagnosed thanks to a new or repeated paraclinical exam. Four patients underwent 18-FDG PET that revealed hypermetabolism in the mediastinal and hilar lymph nodes. We have previously reported on 54 patients with chronic uveitis who underwent an 18-FDG PET; 17 had an exam suggestive of sarcoidosis, including 10 patients with normal chest CT scan.[35] An older age at diagnosis of uveitis and the presence of posterior synechiae were significantly associated to an abnormal 18-FDG PET.

The frequency of tuberculosis in patients with uveitis has been reported from 0.5 (United States) to 11.4% (Iraq).[36] In France, the recent ULISSE study has reported tuberculosis as the cause of uveitis in 11% of 676 patients with uveitis.[37] Interferon-gamma release assay may be helpful for the diagnosis of ocular tuberculosis, when used in conjunction with tuberculin skin test especially in patients who were previously immunized by BCG vaccination. Finally, one patient underwent an anterior chamber paracenthesis with a final diagnosis of Herpesvirus-related uveitis. In cases of suspected Herpesvirus infection, the analysis of aqueous humor by PCR can be very helpful.[38] Currently, infections account for 20–30% of all uveitis causes, with herpesviruses (HSV1/2, VZV, CMV, EBV) being the most common cause of anterior uveitis in Western countries.-[38] However, despite a good sensibility and specificity and a low rate of complications, aqueous humor PCR analysis remains controversial and some authors have reported PCR positivity in only 13% of 53 patients with anterior uveitis, leading to a change in management in only 3% of the total study group, and therefore expressed doubts about PCR usefulness.[39] The last group we identified involves patients who had a new/repeated ophthalmologic exam leading to a diagnosis. One patient presented a unilateral intermediate uveitis resistant to steroids and methotrexate and a new evaluation led to the diagnosis of FUS. Several referral studies suggest that FUS is frequently misdiagnosed.[40] Diffuse small- and medium-sized white round and stellar keratic precipitates, low-grade anterior chamber reaction, iris stromal atrophy without hypochromia, and above all various degrees of vitreous opacities in the absence of macular edema are more often helpful in making the diagnosis than heterochromia.[41] VogtKoyanagi–Harada syndrome accounts for 0.5–4% of all uveitis in Europe depending on the proportion of individuals with pigmented skin, such as Asians, Middle Easterners and Hispanic living in these geographic areas.[42] Contrary to the typical ophthalmic findings seen at the early stage, late ocular manifestations are less specific and may challenge the diagnosis.[43] Depigmentation of the choroid, resulting in the "sunset glow," fibrotic pigmentary changes and complications, such as retinal pigment epithelium proliferation, subretinal fibrosis, and subretinal neovascular membranes, are classical but not always specific in long-standing Vogt–Koyanagi–Harada syndrome.[44] Idiopathic Retinal Vasculitis, Arteriolar macroaneurysm and Neuroretinitis (IRVAN syndrome) is a recently described clinical entity, usually

seen in young women. Its clinical features and etiology are not well known. Chang *et al*. report that most cases involve both eyes, but unilateral cases have been described.[45,46]

Our work has several limitations, as it was a single center study, realized in a tertiary center, with a small number of patients included. Our population might not be representative of all uveitis of unknown etiology. Moreover, it was retrospective, so there are many unavailable data, especially regarding the ophthalmologic exam. Some patients were seen over a short period of time and did not pursue their care in our center and some secondary diagnosis might have been missed. Other did not fully undergo the recommended work-up. Further prospective studies are required to better describe uveitis of unknown etiology and their evolution.

In conclusion, to our knowledge, the present study reports on the largest European series of uveitis of unknown etiology. Physicians should be aware that a prolonged follow-up might lead to a final diagnosis in a significant number of patients. Neurologic symptoms could lead to the diagnosis of neurosarcoidosis, multiple sclerosis or oculocerebral lymphoma, while rheumatic and digestive manifestations, or aphthosis could lead to the diagnosis of spondyloarthritis, inflammatory bowel disease, or Behcet's disease, respectively. The repetition of ophthalmologic exam is also useful in patients with idiopathic uveitis, or initially classified so.

DISCLOSURE STATEMENT

No potential conflict of interest was reported by the authors.

FUNDING

No financial support was received for the study.

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