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Outcome of Unclassified Inflammatory Rheumatism: Observation of 7 Cases in Dakar

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Abstract

Introduction: Unclassified inflammatory rheumatism is persistent inflammatory arthralgias with or without synovitis without sufficient classification criteria for an inflammatory rheumatism or a well-defined connective disease. Their outcome is variable and has been little studied in Africa. We report the epidemiological, paraclinical and evolutionary characteristics of seven cases of indeterminate polyarthritis. **Material and Method:** From January 2012 to May 2021, we selected all the files of patients followed up for unclassified inflammatory rheumatism and in whom a precise diagnosis was retained during the course of the disease. The diagnosis of unclassified inflammatory rheumatism was retained after biological, immunological and radiological explorations without specificities. Our study took place in the Internal Medicine Department of Aristide Le Dantec Hospital (HALD). **Results:** Seven cases out of 274 consulted were collected. They consisted of seven women with an average age of 39 years at the time of the first consultation (extremes: 19 and 67 years). All seven patients presented with inflammatory polyarthralgia or non-deforming, non-erosive peripheral polyarthritis, without extra-articular manifestations. A biological inflammatory syndrome was present in all seven patients. Autoantibodies (rheumatoid factor, ANA, anti-ENA and ACPA) were negative in all patients. The first-line treatments in all seven cases were hydroxychloroquine (200 - 400 mg/day) and prednisone (5 - 10 mg/day). Methotrexate was added in 3 cases. During follow-up, 2 cases progressed to Polyarthritis Rheumatoid (PR) after 3 and 4 years. Two cases progressed to Sjögren's syndrome after 4 and 5 years. Two patients progressed to systemic scleroderma after 5 and 8 years. One patient progressed to lupus after 5 years. **Conclusion:** Regular follow-up is essential in IAN. It allows the early diagno-

sis of IJR or a well-differentiated connective tissue disease and ensures adequate management, especially early.

Keywords

Rheumatic Unclassified, Rheumatoid Arthritis, Connective Tissue Disease

1. Introduction

Unclassified inflammatory rheumatism is characterised by a pattern of persistent inflammatory arthralgias or arthritis without sufficient classification criteria for a well-defined inflammatory rheumatism or a specific connective tissue disease. Their outcome is variable and sometimes unknown. It may progress to complete remission, to the development of a well-individualised clinical entity or remain undifferentiated. These unclassified inflammatory rheumatism are poorly studied, especially in Africa. Several studies have been carried out on cases of chronic indeterminate monoarthritis [1] [2] [3]. Other studies have focused on undifferentiated polyarthritis [4] [5]. Their results are not always unambiguous. In this work, we describe the outcome of seven cases of IAM in the Internal Medicine Department of Aristide Le Dantec Hospital.

2. Material and Method

This was a retrospective and descriptive study from 1 January 2012 to 31 May 2021. The selected files concerned patients with inflammatory polyarthralgia or polyarthritis evolving for more than three months without a precise etiology, despite indicated paraclinical explorations and in whom a diagnosis of well-determined chronic inflammatory rheumatism or connectivities was retained during follow-up. The minimum laboratory tests performed in these patients were blood count, erythrocyte sedimentation rate, C-reactive protein, rheumatoid factors, antinuclear antibodies (ANA) with or without anti-ENA antibodies, ACPA antibodies, transaminases, HBsAg, serum creatinine, 24-hour proteinuria, standard X-rays of the hands, wrists, feet, and chest, and joint ultrasound in one case. The diagnosis of unclassified inflammatory rheumatism was retained if this first-line work-up did not point to a well-defined inflammatory rheumatism disease or a specific connective tissue disease. Patients with extra-articular signs suggestive of a specific disease were not included. Incomplete records were also not included. Confidentiality criteria were respected. The authors have no conflict of interest in this work.

3. Results

Of the 274 cases consulted, seven were selected, representing a frequency of 2.55%. All seven cases involved women with an average age of 39 years (extremes 19 and 67 years) at the time of first consultation. The reasons for consul-

tation were peripheral polyarthritis in all cases and the latter was polysynovial in 5 cases with involvement of the proximal interphalangeal joint (6 patients), the metacarpophalangeal joint (6 patients), the metatarsophalangeal joint (3 patients), the wrists (7 patients), the ankles (7 patients), the knees (5 patients), the elbows (3 patients), the shoulders (4 patients), the hips (3 patients) and the cervical spine (1 patient).

The affected joints were free of deformity and radiological abnormalities. The seven patients had no extra-articular manifestations. The duration of the pain ranged from 4 to 72 months. There was a non-specific inflammatory syndrome in all cases and autoantibodies were negative in all patients.

Standard radiographs of the hands, wrists and feet were normal in all patients. Ultrasound of the joints in one patient showed tendonitis of the extensors of the left wrist without evidence of synovitis or erosion. All patients were started on hydroxychloroquine 200 - 400 mg/day and prednisone 5 - 10 mg/day. Three patients were additionally treated with methotrexate due to persistent symptomatic polyarthritis.

During the follow-up, RA was retained in two patients with secondary ACPA positivity after 4 years of evolution in one of the patients, giving her a score of 8 points out of 10 using the ACR/EULAR 2010 criteria; and the presence of bilateral synovitis of the metacarpophalangeal joint, the proximal interphalangeal joint associated with erosion of the head of the 2nd right metacarpal on the control ultrasound scan of the hands carried out 4 years later in the other patient (Table 1).

The occurrence of oculo-buccal dry syndrome and isolated dry mouth after 4 and 5 years of evolution in 2 patients led to the diagnosis of primary Sjögren's syndrome with a positive Schirmer's test and Chisholm and Masson grade III and IV sialadenitis respectively at accessory salivary gland biopsy according to ACR/EULAR 2016 criteria (Table 1).

Scleroderma was diagnosed in two patients with the appearance of skin sclerosis of the fingers, hands, forearms, feet and legs with a Rodnan score of 18/51 and 21/51. A limitation of mouth opening, hypochromic macules in speckles on the anterior aspect of the thorax and retraction of the proximal interphalangeal joint were noted in one patient. In one of the patients, repeat immunological investigations showed ANA positivity at 1/100 with speckled fluorescence and the presence of anti-SSA/Ro > 8 IU/mL on identification. In the latter, radiography noted multiple periarticular calcifications at the elbows and opposite the right metacarpophalangeal joint 1 and the left thumb interphalangeal (Table 1).

After five years, the diagnosis of lupus was considered probable in one patient due to the persistence of relapses/remissions of polyarthritis, the absence of destructive lesions on the control radiographs of the hands, wrists and feet and the positivity of antinuclear cells at 1/160 IU/L with homogeneous fluorescence, whereas the assay at the beginning was negative (Table 1). Anti-ENA and anti-DNA were not obtained in this patient due to financial constraints.

Table 1. Characteristics of the seven patients followed for unclassified inflammatory rheumatism.

Patients, age	Signs of onset	New clinical signs	New paraclinical signs	Retained diagnosis	Duration of follow-up
P1, 54 years	- Chronic symmetrical peripheral polyarthritis without deformity, without extra-articular signs - Biological inflammatory syndrome - X-ray of hands, wrists and feet: normal - Immunology: negative (rheumatoid factors, ACPA, ANA, anti-ENA, anti-DNAn)	0	ACPA (+) at 7.7 IU/mL	RA	3 years
P2, 67 years		0	Ultrasound of the hands: bilateral synovitis of the MCP and PIP; erosion of the head of the right 2nd metacarpal	RA	4 years
P3, 28 years		Oculo-buccal dry syndrome	Schirmer's test: positive Accessory salivary gland biopsy: grade III sialadenitis	Sjögren's syndrome	4 years
P4, 43 years		Dry mouth	Accessory salivary gland biopsy: sialadenitis grade IV	Sjögren's syndrome	5 years
P5, 33 years		0	ACPA: (−) ANA: 1/160	SLE	5 years
P6, 32 years		Skin sclerosis (Rodnan score 21/51) PIP shrinkage Hypochromic macules in speckles	No further explorations	Systemic scleroderma	5 years
P7, 19 years		Skin sclerosis (Rodnan score 18/51)	ANA: 1/100 Anti-SSA: 8 IU/mL ACPA: (−) X-ray: periarticular calcifications in hands and elbows	Systemic scleroderma	8 years

MCP: Metacarpophalangeal joint, PIP: Proximal interphalangeal joint.

Once a positive diagnosis was made, azathioprine was prescribed in one patient, methotrexate in four patients. Hydroxychloroquine and prednisone were continued in five patients.

4. Discussion

The diagnosis of unclassified inflammatory rheumatism may be made in the presence of isolated inflammatory joint pain, *i.e.*, not associated with other clinical and/or paraclinical manifestations suggestive of a well-defined disease. Isolated polyarthritis may precede other signs of connective tissue disease by several years. Our seven cases had in common a "naked" polyarthritis associated with a biological inflammatory syndrome. According to the literature, the frequency of undifferentiated rheumatism varies around 30% with extremes ranging from 23% to 81% [6]. In Morel's study of 43 patients followed for unclassified inflammatory rheumatism, a precise diagnosis was made after a mean delay of 38.2 months in 24 patients with benign, non-erosive RA without extra-articular signs in 18 patients; peripheral psoriatic arthritis in 2 patients; SS in 2 patients, one

patient had lupus, one patient had a paraneoplastic syndrome, 7 patients remained unclassifiable, and 12 patients had progressed to complete remission [4]. In undifferentiated monoarthritis, the most common diagnoses were RA, ankylosing spondylitis, and no connectivity diseases were identified [3].

RA, the most common inflammatory rheumatic disease, is characterised by heterogeneity ranging from benign forms with good prognosis to severe, deforming, rapidly destructive forms [7]. It is in these benign forms that radiographs may remain normal or show minimal erosions even after several years. This was probably the case in our patients as they did not show any deformities or extra-articular signs and the ACPA was weakly positive after a long evolution. ACPA testing is particularly useful in the diagnosis of RA, as its positivity is highly specific [8] and its level varies little over time. ACPA is usually present before the onset of RA symptoms and is also highly predictive of progression from undifferentiated arthritis to RA [9].

Sjögren's syndrome (SS) is manifested by the triad of dryness, fatigue and pain. The pain is often related to non-destructive polyarthritis or more often to peripheral inflammatory polyarthralgia. Although the anti-SSA and anti-SSB assays were not performed again in our patients, the diagnosis of SS was made in the presence of chronic grade III and IV sialadenitis. Accessory salivary gland biopsy is an essential test for the diagnosis of SS, especially in the absence of anti-SSA/Ro or anti-SSB/La [10], which may be absent in up to 1/3 of SS cases.

In systemic scleroderma (SSc), the appearance of sclerosis is sufficient to make the diagnosis according to the classification criteria of both the ACR in 1980 and the ACR/EULAR 2013 [11] [12]. This criterion allowed us to retain SSc in two of our patients associated with hypochromic speckled macules in one and periarticular calcifications on radiography in the other. NAAs are present in more than 90% of cases of SSc [13], which was the case in one of our patients with a speckled fluorescence, but the identification showed anti-SSA/Ro and not the more specific SSc autoantibodies.

Joint involvement is very common in SLE. It occurs at the beginning of the disease in one out of two cases and at some point during the course of the disease in eight to nine cases [14]. Like joint involvement, mucocutaneous manifestations are very common in SLE [15], initiating the disease one in four times, but may also be missed throughout the course of the disease one in four times. Our patient had only clinical joint damage. Immunologically, NAAs are detectable in almost all cases. The fluorescence is most often homogeneous, sometimes mottled or peripheral, and rarely nucleolar. The homogeneous appearance was observed in our patient. The patient did not have enough criteria to classify her as lupus, as these are classification criteria and not diagnostic criteria [16]. Their use as a diagnostic tool makes them less sensitive mainly at the time of diagnosis and initial presentation. It may take many years for the last criterion to appear to classify the patient "correctly".

Various studies have been carried out in search of factors predictive of a progressive mode in inflammatory rheumatic diseases. However, no clinical, bio-

logical, radiographic or histological parameter was predictive of a particular disease pattern. The only prognostic factor for the outcome of monoarthritis in Inaoui's study was the presence of the HLA group, and patients in this group more frequently progressed to ankylosing spondylitis [3]. Clinical suspicion, initial presence of rheumatoid factor and HLA DRB1 * 04 allele were predictive of progression to definite PR in Morel's study of unclassifiable rheumatism [4]. Nevertheless, this unclassified inflammatory rheumatism may remain unclassified despite long-term follow-up [4]. In our work, no clinical or paraclinical factor predicted progression to a definite disease; except for HLA typing, which was not done in our patients.

Thus, in the absence of any predictive factor, regular follow-up is necessary in case of IAM and the request for paraclinical explorations must be renewed, especially if there are elements of orientation over time in order to establish a diagnosis of certainty.

In terms of treatment, we started hydroxychloroquine and prednisone at the initial stage in all patients and with the persistence of polyarthritis, methotrexate was instituted in three patients. Once the final diagnosis was made, treatment was based on azathioprine, methotrexate, hydroxychloroquine and prednisone. According to the EULAR 2016 recommendations, patients at risk of persistent arthritis should receive a DMARD as soon as possible, even if they do not meet the classification criteria for a defined inflammatory rheumatism. Among DMARDs, methotrexate is considered the anchor drug and, in the absence of contraindications, should be part of the first treatment strategy in patients at risk of persistent arthritis [17].

Our study has certain limitations, in particular the small size of our cohort and the non-exhaustiveness of the initial paraclinical investigations, which did not allow us to analyse the existence of possible predictive factors.

5. Conclusion

The unclassified inflammatory rheumatism requires regular follow-up to look for new clinical or paraclinical findings that may lead to a definite diagnosis. RA was the most frequent diagnosis in this unclassified inflammatory rheumatism.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Blocka, K.L.N. and Sibley, J.T. (1987) Undiagnosed Chronic Monarthritis: Clinical and Evolutionary Profile. *Arthritis & Rheumatism*, **30**, 1357-1361. https://doi.org/10.1002/art.1780301206

[2] Iguchi, T., Matsubara, T., Kawai, K. and Hirohata, K. (1990) Clinical and Histological Observations of Monoarthritis. *Clinical Orthopaedics and Related Research*, **250**, 241-249. https://doi.org/10.1097/00003086-199001000-00033

[3] Inaoui, R., Bertin, P., Preux, P.M. and Trèves, R. (2004) Devenir des mono-arthrites chroniques indéterminées: Étude rétrospective de 46 cas. *Revue du Rhumatisme*, **71**, 372-377. https://doi.org/10.1016/S1169-8330(03)00337-5

[4] Morel, J., Legouffe, M.C., Bozonnat, M.C., Sany, J., Eliaou, J.F., Daurès, J.P. and Combe, B. (2000) Devenir des patients présentant un rhumatisme inflammatoire débutant non classable. *Revue du Rhumatisme*, **67**, 58-63. https://doi.org/10.1016/S1169-8330(00)80047-2

[5] Avenel, G. (2012) Étude longitudinale des rhumatismes inclassés issus d'une cohorte de rhumatismes inflammatoires tout débutants (cohorte VErA). dumas-00745751.

[6] Hazes, J.M.W. and Luime, J.J. (2011) The Epidemiology of Early Inflammatory Arthritis. *Nature Reviews Rheumatology*, **7**, 381-390. https://doi.org/10.1038/nrrheum.2011.78

[7] Raissouni, N., Gossec, L., Ayral, X. and Dougados, M. (2005) Quelles nouveautés dans le diagnostic et le traitement d'une polyarthrite rhumatoïde récente. *Revue du Rhumatisme*, **72**, 195-200. https://doi.org/10.1016/j.rhum.2004.04.011

[8] Avouac, J., Gossec, L. and Dougados, M. (2006) Diagnostic and Predictive Value of Anti-Cyclic Citrullinated Protein Antibodies in Rheumatoid Arthritis: A Systematic Literature Review. *Annals of the Rheumatic Diseases*, **65**, 845-851. https://doi.org/10.1136/ard.2006.051391

[9] Coutant, F. (2018) Pathogénicité des anticorps anti-protéines citrullinées dans la polyarthrite rhumatoïde. *Revue du Rhumatisme*, **85**, A31-A36. https://doi.org/10.1016/S1169-8330(18)30173-X

[10] Shiboski, C.H., Shiboski, S.C. and Seror, R. (2016) ACR-EULAR Classification Criteria for Primary Sjögren's Syndrome: A Consensus and Data-Driven Methodology Involving Three International Patient Cohorts. *Arthritis & Rheumatology*, **69**, 35-45. https://doi.org/10.1002/art.39859

[11] Subcommittee for Scleroderma Criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee (1980) Preliminary Criteria for the Classification of Systemic Sclerosis (Scleroderma). *Arthritis Rheum*, **23**, 581-590.

[12] Van den Hoogen, F., Khanna, D., Fransen, J., *et al.* (2013) Classification Criteria for Systemic Sclerosis: An American College of Rheumatology/European League against Rheumatism Collaborative Initiative. *Annals of the Rheumatic Diseases*, **72**, 1747-1755. https://doi.org/10.1136/annrheumdis-2013-204424

[13] Hachulla, E. and Dubucquoi, S. (2004) Intérêt des anticorps antinucléaires pour le diagnostic, la classification et le pronostic de la sclérodermie systémique. *La Revue de Médecine Interne*, **25**, 442-447. https://doi.org/10.1016/j.revmed.2003.11.012

[14] Wallace, D.J., Hahn, B. and Dubois, E.L. (2007) Dubois' Lupus Erythematosus. 7th Edition, Lippincott Williams & Wilkin, Philadelphia.

[15] Patel, P. and Werth, V. (2002) Cutaneous Lupus Erythematosus: A Review. *Dermatologic Clinics*, **20**, 373-385. https://doi.org/10.1016/S0733-8635(02)00016-5

[16] Bertsias, G.K., Pamfil, C., Fanouriakis, A. and Boumpas, D.T. (2013) Diagnostic Criteria for Systemic Lupus Erythematosus: Has the Time Come? *Nature Reviews Rheumatology*, **9**, 687-694. https://doi.org/10.1038/nrrheum.2013.103

[17] Combe, B., Landewe, R., Daien, C., *et al.* (2016) Update of the EULAR Recommendations for Management of Early Arthritis. *Annals of the Rheumatic Diseases*, **76**, 948-959. https://doi.org/10.1136/annrheumdis-2016-210602