

Contribution of Nail Fold Videocapillaroscopy in Patients with Early Inflammatory Arthritis

M. FLOREA¹, ANCA ROȘU¹, F.A. VREJU¹, ANCA EMANUELA MUȘETESCU¹,
CRISTINA CRIVEANU¹, PAULINA CIUREA¹

¹Rheumatology Department, University of Medicine and Pharmacy of Craiova, Faculty of Medicine, Romania

ABSTRACT: Background: Early inflammatory arthritis (EIA) a condition defined by joint swelling, with or without morning stiffness, and/or swelling of metacarpophalangeal and/or metatarsophalangeal joints. Nail fold videocapillaroscopy (NVC) is important for the evaluation of microcirculation in vivo. There are limited data about the role of NVC in EIA. **Objectives:** To study the capillaroscopic pattern in patients with EIA. **Patients and methods:** 27 patients with EIA - 21 women, 6 men, mean age of 41.6±4.2 yrs, mean disease duration of 6.9±3.1 months. Anamnesis and clinical examination were performed to identify clinical signs associated with connective tissue diseases. All the patients were nonsmokers and had no personal medical history of diabetes or non-immune mediated occlusive vascular disease. Blood and urine samples were collected for bio-chemical and immunological evaluation. All the patients were interrogated by NVC. **Results:** Raynaud's phenomenon was found in 9 patients, puffy fingers in 2 pts, telangiectasia in 2 pts, Sicca symptoms in 6 pts, malar rash in 2 pts, photosensitivity and psoriasis plaque in one patient. Combined information from clinical exam, NVC and immunological assessment allowed a specific diagnosis in 5 patients. **Conclusions:** Nail fold capillaroscopy assessment can provide further information and has diagnostic value in some cases of early arthritis. Nail fold capillaroscopy assessment contribution to the differential diagnosis in patients with early arthritis is sometimes significant, especially in poorly clinical and immunological defined cases.

KEYWORDS: early inflammatory arthritis, antinuclear antibodies, Raynaud's phenomenon, capillaroscopy

Introduction

Early inflammatory arthritis (EIA) is the currently used term for a pathological condition clinically defined by joint swelling, preferably at least two joints, not caused by local trauma or bony swelling, with or without morning stiffness of more than 30 minutes, and/or swelling of metacarpophalangeal and/or metatarsophalangeal joints [1]. There is no stated consensus regarding the time interval defined by the term early, but the general opinion of the experts is to consider this interval at 12 months. In practice, EIA is sometimes undifferentiated, thus, the terminology early undifferentiated arthritis/synovitis or early undifferentiated inflammatory arthritis is often used [2].

Joint swelling, as a first relevant symptom for the patient and a frequent reason for addressing a rheumatologist, can have multiple causes and, among other signs and symptoms such as Raynaud's phenomenon (RP), sicca symptoms, skin lesions (rash, purpuric lesions, puffy fingers, digital ulcers, etc.), is a frequent clinical finding in various immune mediated arthropathies or connective tissue diseases, such as rheumatoid arthritis, psoriatic arthritis, spondylarthritis, systemic lupus erythematosus,

systemic sclerosis, polymyositis, Sjögren syndrome, etc. [3, 4].

Nail fold video-capillaroscopy (NVC), a noninvasive and reproducible technique, is very important for the evaluation of microcirculation in vivo. Its main indication is the presence of Raynaud's phenomenon [5]. NVC allows identifying characteristic patterns of microvascular alterations, especially in scleroderma spectrum disorders – Systemic Sclerosis, Mixed connective tissue disease, Dermatomyositis. Also NVC may be useful for the diagnosis and follow-up of autoimmune rheumatic diseases [6, 7, 8, 9, 10].

The first steps that should be performed in the management of patients presenting with joint swelling are the recognition of inflammatory arthritis and identifying its cause. Differential diagnosis should be based on a thorough anamnesis and clinical exam and the evaluation should include a complete blood cell count (CBC), urinary analysis, aminotransferases and antinuclear antibodies (ANA) [1].

Although NVC at this time is not part of the recommended protocol for evaluation of patients with early inflammatory arthritis, some authors, proposed to include it, arguing that capillaroscopic examination may facilitate differential diagnosis [11, 12, 7].

Patients and Methods

Study group included 27 consecutive patients with early arthritis defined according to EULAR 2007 recommendations. In the absence of a consensus on the time period defined by the term “early” we decided to establish it at 12 months. Study group included 21 women and 6 men with a mean age of 41.6 ± 4.2 years and mean disease duration of 6.9 ± 3.1 months. None of the patients was treated with disease modifying anti-rheumatic drugs (DMARDs) or systemic corticosteroids for the clinical condition. All the patients were nonsmokers and had no personal medical history of diabetes or non-immune mediated occlusive vascular disease such as atherosclerotic vascular disease, thromboangiitis obliterans or severe arterial hypertension.

Ethics committee approval was obtained to conduct this research. All study procedures complied with the requirements of 2013 WMA Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects.

A thorough anamnesis and clinical examination were performed in each patient in order to identify clinical signs that may be associated with various immune mediated connective tissue diseases or specific arthropathy. Because of their particular association with connective tissue diseases or specific arthropathy, the following clinical signs and symptoms were of special interest: RP [13], puffy fingers, digital ulcers and fingertip scars, telangiectasia, sicca symptoms, malar rash, discoid rash, photosensitivity, oral ulcers, Still’s rash (salmon like maculopapular rash with Koebner phenomenon), psoriasis plaque, and psoriasis nail dystrophy. Blood and urine samples were collected for bio-chemical and immunological evaluation. Complete blood count (CBC), erythrocyte sedimentation rate (ESR), C reactive protein (CRP), ANA, aspartate transaminase, alanine transaminase, rheumatoid factor, anti-cyclic citrullinated antibodies (anti-CCP), glucose, serum creatinine, and a complete urine analysis were performed in each patient. In addition in patients showing ANA positivity a complete qualitative assessment of ANA profile was performed in order to identify disease specific ANA antibodies (U1-nRNP, Sm, SS-A, Ro-52, SS-B, Scl-70, PM-Scl, Jo-1, Centromere B, PCNA, dsDNA, nucleosome, histone, P ribosomal protein, AMA M2).

Nail fold videocapillaroscopy was performed at the Rheumatology Research Center,

Department of Rheumatology, University of Medicine and Pharmacy, Craiova, Romania, using a high performance video-capillaroscope – Videocap 3.0 (DS Medica, Italy) after acclimatization in a relative constant temperature environment ($20 - 22^{\circ}\text{C}$) [10]. Capillaroscopic evaluation was performed by trained study staff without having access to patient records in order to minimize bias. Nail folds from fingers 2 to 5 (right and left hands), were examined.

The following capillaroscopic parameters were evaluated: shape, width, length, capillary density, presence of avascular areas, hemorrhages, neoangiogenesis and visibility of sub-papillary plexus [10]. Measurements were performed using device software installed on PC and were expressed in millimeters.

All the information obtained from clinical, biological, immunological and imaging (NVC) evaluation and also the final diagnosis were recorded for each patient in the study database. Final diagnosis was made according to the criteria in use. Patients with features of immune mediated connective tissue disease but who do not fulfil current criteria for a specific connective tissue disease are diagnosed as having undifferentiated connective tissue disease [14]. Patients with features that could satisfy the classification criteria of at least two connective tissue diseases were classified as Overlap syndrome [15].

Results

After anamnesis and clinical examination, in addition to joint swelling, the following clinical sign and symptoms were recorded: Raynaud’s phenomenon (9 patients – 33.33%), puffy fingers (2 patients - 7.40 %), telangiectasia (2 patients - 7.40 %), Sicca symptoms (6 patients - 22.22 %), malar rash (2 - 7.40 %), photosensitivity (one patient – 3.70%), psoriasis plaque (1 patients – 3.70%). Biochemical and immunological evaluation results are shown in the table below (Table 1).

Table 1. Biochemical and immunological

Parameter	No of patients (%)
<i>Non-specific markers of inflammation – ESR, CRP</i>	19 (70.37 %)
<i>RF</i>	12 (44.44%)
<i>Anti-CCP atb.</i>	2 (7.40%)
<i>ANA</i>	6 (22.22 %)
<i>CBC abnormalities</i>	2 (7.40 %)

Nineteen patients (70.37 %) shown non-specific markers of inflammation, 12 patients (44.44%) shown RF positivity and only in 2 patients (7.40%) anti-CCP have been identified. Both patients with anti-CCP showed also RF positivity. ANA (screening) positivity was identified in 6 patients (22.22%). Complete blood count abnormalities have been found in 2 patients (7.40 %) one patient with mild thrombocytopenia who was diagnosed with early RA (elevated ESR, CRP, high titers of RF and anti-CCP, ANA positive, ANA qualitative

profile negative for all subset of tested autoantibodies) and one with mild leukopenia who was classified as Sjögren syndrome.

In patients showing ANA (screening) positivity a complete qualitative assessment of ANA profile was performed. Five patients (18.51%) with ANA positivity showed abnormalities on qualitative assessment of ANA profile. Clinical, bio-chemical, immunologic, capillaroscopic patterns and final diagnosis of those patients are listed in the table below (Table 2).

Table 2. Clinical, bio-chemical, immunologic, capillaroscopic patterns and final diagnosis of the patients with abnormalities on qualitative assessment of ANA profile.

Case no	Features	ANA profile	Capillaroscopy findings	Classification
1	chronic guttate psoriasis sicca symptoms elevated ESR RF positivity Mild leukopenia	SS-A SS-B Ro-52	Non-specific pattern: frequent dilated capillaries, frequent capillaries with altered morphology, bizarre capillaries, tortuous capillaries. No hemorrhages, no avascular areas, visible venous plexus, preserved number of capillaries, no tight terminal convolutions [Fig. 1, Fig .2]	Sjögren syndrome
2	Raynaud's phenomenon puffy fingers telangiectasia ESR and CRP RF and anti-CCP	PM-Scl	Early scleroderma-like pattern: frequent dilated capillaries, giant capillaries and isolated hemorrhage / thrombosis; frequent tortuous capillaries showing simple and complex tortuosity [Fig. 3, Fig .4, Fig. 5]	Overlap syndrome
3	puffy finger telangiectasia persistent elevated ESR	Scl-70	Active scleroderma-like pattern: frequent giant capillaries and hemorrhages, moderate loss of capillaries, isolated bushy capillaries [Fig. 6, Fig .7, Fig. 8]	Systemic sclerosis
4	Raynaud's phenomenon sicca symptoms elevated ESR, CRP RF positivity	U1-RNP	Early scleroderma-like pattern: frequent dilated capillaries, giant capillaries and tortuous capillaries showing simple and complex tortuosity [Fig. 9, Fig. 10, Fig. 11]	Mixed connective tissue disease
5	Raynaud's phenomenon RF positivity Elevated ESR	U1-RNP	Early scleroderma-like pattern: frequent dilated capillaries, giant capillaries and tortuous capillaries showing complex tortuosity.	Mixed connective tissue disease

All the 21 remaining patients showed a non-specific capillaroscopic pattern. Clinical, bio-chemical, immunologic and diagnosis of the remaining 21 patients are the table below (Table 3)

Table 3. Clinical, bio-chemical, immunologic and diagnosis of the remaining 21 patients

Features	No of patients	Classification
Raynaud's phenomenon	6	Undifferentiated connective tissue disease
Sicca symptoms	4	Undifferentiated connective tissue disease
Malar rash	2	Undifferentiated connective tissue disease
Malar rash	1	Undifferentiated connective tissue disease
RF positivity	7	Early undifferentiated arthritis
No feature	1	Early undifferentiated arthritis

Discussion

By identifying specific and non-specific microvascular abnormalities, NVC evaluation had a significant contribution regarding diagnostic decision in 5 (18,51 %) patients. (Table 2).

In case no. 1 (Fig.1,2) the clinical pattern consisting in of chronic psoriasis and arthritis would lean to the diagnosis of psoriatic arthritis even in the context of positivity FR [16]. The capillaroscopic pattern observed in this case was not similar with the one that other authors have found in patients with psoriatic arthritis, but rather similar with the non-specific pattern sometimes observed in patients with Sjögren syndrome, especially in those without Raynaud's phenomenon [11, 12, 17].



Fig.1. Case 1 - Non-specific pattern: frequent dilated capillaries, frequent capillaries with altered morphology, bizarre capillaries, tortuous capillaries. No hemorrhages, no avascular areas, visible venous plexus, preserved number of capillaries, no tight terminal convolutions



Fig.2. Case 1 - Non-specific pattern: frequent dilated capillaries, frequent capillaries with altered morphology, bizarre capillaries, tortuous capillaries. No hemorrhages, no avascular areas, visible venous plexus, preserved number of capillaries, no tight terminal convolutions

In regards to case no. 2 (Fig.3,4,5), capillaroscopic assessment brought useful information on etiology and substrate of Raynaud's phenomenon. Identifying early scleroderma-like capillary changes in the context of hands symmetric arthritis, telangiectasia, RF, anti-CCP and PM-Scl positivity made possible disease classification.



Fig.3. Case 2 - Early scleroderma-like pattern: frequent dilated capillaries, giant capillaries and isolated hemorrhage / thrombosis; frequent tortuous capillaries showing simple and complex tortuosity



Fig.4. Case 2 - Early scleroderma-like pattern: frequent tortuous capillaries and simple tortuosity



Fig.5. Case 2 - Early scleroderma-like pattern: frequent tortuous capillaries showing simple and complex tortuosity

In case no. 3 (Fig.6,7,8) the lack of obvious signs and patient complaints characteristic for Raynaud's phenomenon in the context of persisting RF negative anti-CCP negative symmetric arthritis involving the small joints of the hands the initial diagnosis was early RA. The rapid addition of puffy fingers sign and the absence of clinically obvious Raynaud's phenomenon raised some suspicions regarding the initial diagnosis. Results obtained from capillaroscopic evaluation and ANA profile testing allowed diagnosis reconsideration.



Fig.6. Case 3 - Active scleroderma-like pattern: giant capillary moderate loss of capillaries



Fig.7. Case 3 - Active

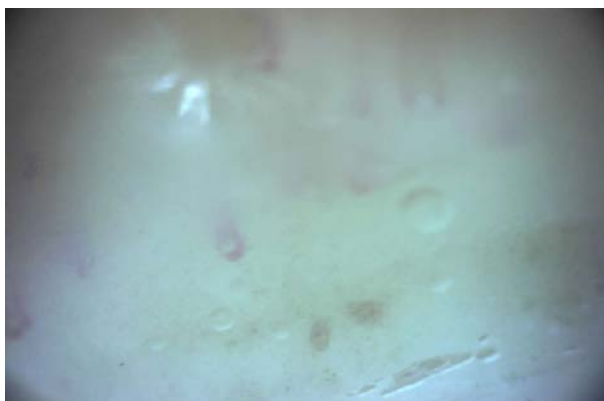


Fig.8. Case 3 - Active scleroderma-like pattern: moderate loss of capillaries

Cases no. 4 and 5 (Fig.9-11) were somewhat similar. Both patients had early arthritis involving small joints of the hands, mainly metacarpophalangeal and proximal interphalangeal joints, Raynaud's phenomenon and mild RF elevation. Both patients shown similar pattern at NVC evaluation consisting of microvascular abnormalities highly specific for early scleroderma-like pattern. ANA profile testing allowed identifying specific mixed connective tissue disease and proper classification.

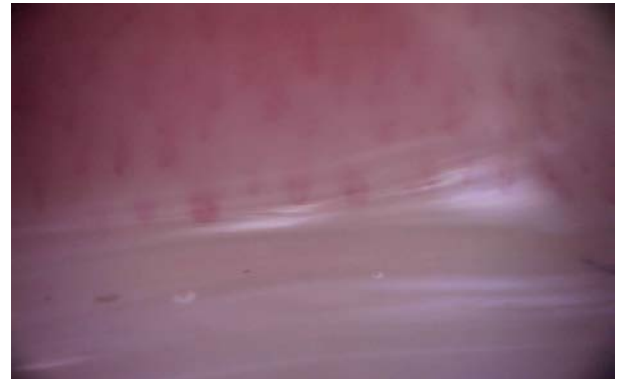


Fig.9. Case 4 - Early scleroderma-like pattern: frequent dilated capillaries, giant capillaries



Fig.10. Case 4 - Early scleroderma-like pattern: frequent tortuous capillaries showing simple and complex tortuosity

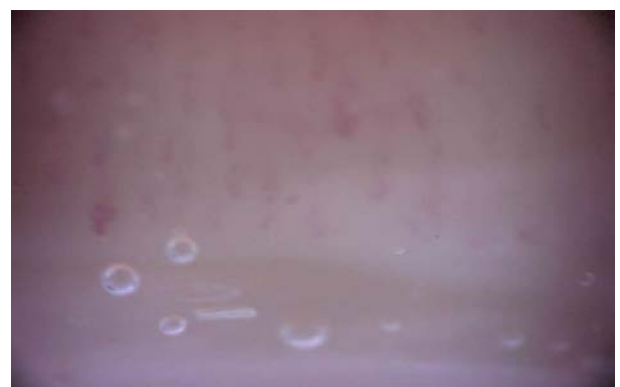


Fig.11. Case 4 - Early scleroderma-like pattern: frequent dilated capillaries and tortuous capillaries showing simple tortuosity

In regards to other 21 patients (77,77%) classified as undifferentiated connective tissue disease or early undifferentiated arthritis, non-specific microvascular abnormalities identified by NVC corroborated with clinical and immunological findings did not allowed specific connective tissue disease diagnostic. In these patients close monitoring by means of biochemical and immunological assessment at regular intervals including NVC evaluation is the proper monitoring protocol that may allow early and accurate diagnosis. In these patients, contribution of the NVC monitoring could be highlighted by early identification of microvascular abnormalities that may have a predictive value for developing specific connective tissue diseases.

Conclusions

Nail fold capillaroscopy assessment can provide further information and has diagnostic value in some cases of early arthritis. Nail fold capillaroscopy assessment contribution to the differential diagnosis in patients with early arthritis is sometimes significant, especially in poorly clinical and immunological defined cases.

Acknowledgements

Dr. Florea Marius was supported by the Project "Excellence program for multidisciplinary research in chronic disease", grant no. POSDRU/159/1.5/S/133377 partially supported by the Sectoral Operational Programme Human Resources Development 2007 -2013, financed from the European Social Fund.

References

1. Combe B, Landewe R, Lukas C, et al, EULAR recommendations for the management of early arthritis: report of a task force of the European Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT), *Ann Rheum Dis.* 2007 Jan;66(1):34-45. Epub 2006 Jan 5
2. Dixon WG, Symmons DP., Does early rheumatoid arthritis exist? *Best Pract Res Clin Rheumatol.* 2005 Feb;19(1):37-53.
3. Gaubitz M., Epidemiology of connective tissue disorders, *Rheumatology (Oxford).* 2006 Oct;45 Suppl 3:iii3-4.
4. Mosca M, Neri R, Bombardieri S., Undifferentiated connective tissue diseases (UCTD): a review of the literature and a proposal for preliminary classification criteria, *Clin Exp Rheumatol.* 1999 Sep-Oct;17(5):615-20.
5. Cutolo M, Grassi W, Matucci Cerinic M., Raynaud's phenomenon and the role of capillaroscopy, *Arthritis Rheum.* 2003 Nov;48(11):3023-30.
6. Cutolo M, Sulli A, Secchi ME, Paolino S, Pizzorni C. Nailfold capillaroscopy is useful for the diagnosis and follow-up of autoimmune rheumatic diseases. A future tool for the analysis of microvascular heart involvement? *Rheumatology (Oxford).* 2006 Oct;45 Suppl 4:iv43-6.
7. Wu PC, Huang MN, Kuo YM, Hsieh SC, Yu CL., Clinical applicability of quantitative nailfold capillaroscopy in differential diagnosis of connective tissue diseases with Raynaud's phenomenon, *J Formos Med Assoc.* 2013 Aug;112(8):482-8. doi: 10.1016/j.jfma.2012.02.029. Epub 2012 Aug 14
8. Souza EJ, Kayser C, Nailfold capillaroscopy: relevance to the practice of Rheumatology, *Rev Bras Reumatol.* 2014 Oct 22. pii: S0482-5004(14)00204-6. doi: 10.1016/j.rbr.2014.09.003.
9. Nagy Z, Czirjak L. Nailfold digital capillaroscopy in 447 patients with connective tissue disease and Raynaud's disease. *J Eur Acad Dermatol Venereol* 2004; 18: 62-8 – abstract
10. M. Cutolo, A. Sulli, M.E. Secchi, M. Olivieri, C. Pizzorni. The contribution of capillaroscopy to the differential diagnosis of connective autoimmune diseases. *Best Pract Res Clin Rheumatol*, 21 (6) (2007), pp. 1093–1108 - abstract
11. Lambova SN, Müller-Ladner U, Capillaroscopic pattern in inflammatory arthritis, *Microvasc Res.* 2012 May;83(3):318-22. doi: 10.1016/j.mvr.2012.03.002. Epub 2012 Mar 9
12. Graceffa D, Amorosi B, Maiani E, et al, Capillaroscopy in psoriatic and rheumatoid arthritis: a useful tool for differential diagnosis, *Arthritis.* 2013;2013:957480. doi: 10.1155/2013/957480. Epub 2013 Dec 12.
13. Maverakis E, Patel F, Kronenberg DG, et al, International consensus criteria for the diagnosis of Raynaud's phenomenon, *J Autoimmun.* 2014 Feb-Mar;48-49:60-5. doi: 10.1016/j.jaut.2014.01.020. Epub 2014 Feb 1.
14. Mosca M, Tani C, Vagnani S, et al, The diagnosis and classification of undifferentiated connective tissue diseases, *J Autoimmun.* 2014 Feb-Mar;48-49:50-2. doi: 10.1016/j.jaut.2014.01.019. Epub 2014 Feb 8.
15. Iaccarino L, Gatto M, Bettio S, et al, Overlap connective tissue disease syndromes, *Autoimmun Rev.* 2013 Jan;12(3):363-73. doi: 10.1016/j.autrev.2012.06.004. Epub 2012 Jun 26.
16. Braun-Falco O, Ruzicka T, Psoriatic arthritis, *Int J Dermatol.* 1994 May;33(5):320-2.
17. Tektonidou M, Kaskani E, Skopouli FN, et al, Microvascular abnormalities in Sjögren's syndrome: nailfold capillaroscopy, *Rheumatology (Oxford).* 1999 Sep;38(9):826-30.

Corresponding author: Florea Marius, University of Medicine and Pharmacy of Craiova, Faculty of Medicine, No 2-4, Petru Rares Street, Craiova, Dolj, Romania; e-mail: dr.mariusflorea@gmail.com