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Review

Clinical follow-up predictors of disease pattern change in anti-Jo1 positive anti-synthetase syndrome: Results from a multicenter, international and retrospective study

Elena Bartoloni [a,*], Miguel A. Gonzalez-Gay [b], Carlo Scirè [c], Santos Castaneda [d], Roberto Gerli [a], Francisco Javier Lopez-Longo [e], Julia Martinez-Barrio [e], Marcello Govoni [f], Federica Furini [f], Trinitario Pina [b], Florenzo Iannone [g], Margherita Giannini [g], Laura Nuño [h], Luca Quartuccio [i], Norberto Ortego-Centeno [j], Alessia Alunno [a], Christopher Specker [k], Carlomaurizio Montecucco [l], Konstantinos Triantafyllias [m], Silvia Balduzzi [l], Walter Alberto Sifuentes-Giraldo [n], Giuseppe Paolazzi [o], Elena Bravi [p], Andreas Schwarting [q], Raffaele Pellerito [r], Alessandra Russo [r], Carlo Selmi [s], Lesley-Ann Saketkoo [t], Enrico Fusaro [u], Simone Parisi [u], Nicolò Pipitone [v], Franco Franceschini [w], Ilaria Cavazzana [w], Rossella Neri [x], Simone Barsotti [x], Veronica Codullo [l], Lorenzo Cavagna [l]

[a] Rheumatology Unit, Department of Medicine, University of Perugia, Perugia, Italy
[b] Division of Rheumatology, Hospital Universitario Marqués de Valdecilla, IDIVAL, University of Cantabria, Santander, Spain
[c] Epidemiology Unit, Italian Society for Rheumatology, Milano, Italy
[d] Rheumatology Department, Hospital Universitario de la Princesa, IIS-IP, Madrid, Spain
[e] Servicio de Reumatología, Hospital General Universitario Gregorio Marañón, Madrid, Spain
[f] UOC Reumatologia, Azienda Ospedaliero Universitaria S. Anna, University of Ferrara, Ferrara, Italy
[g] Interdisciplinary Department of Medicine (DIM), Rheumatology Unit, University of Bari, Bari, Italy
[h] Servicio de Reumatología, Hospital Universitario La Paz, Madrid, Spain
[i] Clinic of Rheumatology, Department of Medical and Biological Sciences (DSMB), Santa Maria della Misericordia Hospital, Udine, Italy
[j] Systemic Autoimmune Diseases Unit, Hospital Clínico San Cecilio, Granada, Spain
[k] Department for Rheumatology and Clinical Immunology, St. Josef Krankenhaus, University Clinic, Essen, Germany
[l] Division of Rheumatology, University and IRCCS Policlinico S. Matteo Foudation, Pavia, Italy
[m] ACURA Rheumatology Center, Bad Kreuznach, Germany
[n] Department of Rheumatology, University Hospital Ramón y Cajal, Madrid, Spain
[o] Rheumatology Unit, Santa Chiara Hospital, Trento, Italy
[p] Rheumatology Unit, Ospedale Guglielmo da Saliceto, Piacenza, Italy
[q] Department of Internal Medicine, Rheumatology and Clinical Immunology, University Hospital Johannes-Gutenberg, Mainz, Germany
[r] Division of Rheumatology, Mauriziano Hospital, Turin, Italy
[s] Division of Rheumatology and Clinical Immunology, Humanitas Research Hospital, Rozzano, Milano, Italy
[t] Tulane University Lung Center Tulane/UMC Scleroderma and Sarcoidosis Patient Care and Research Center New Orleans, New Orleans, LA, USA
[u] Rheumatology Department, Città Della Salute e della Scienza, Torino, Italy
[v] Rheumatology Unit, Department of Internal Medicine, Azienda Ospedaliera ASMN, Reggio Emilia, Italy
[w] Rheumatology Unit, University and AO Spedali Civili, Brescia, Italy
[x] Division of Rheumatology, Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy

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ABSTRACT

Objective: Arthritis, myositis and interstitial lung disease (ILD) constitute the classic clinical triad of anti-synthetase syndrome (ASSD). These patients experience other accompanying features, such as Raynaud's phenomenon, fever or mechanic's hands. Most ASSD patients develop the complete triad during the follow-up. In the present study we aimed to determine whether the subsequent appearance of accompanying features may suggest the development of triad findings lacking at the onset in anti-Jo1 positive ASSD patients.
Methods: Anti-Jo1 positive patients presenting with incomplete ASSD (no >2 classic triad features) were assessed. Clinical characteristics and clusters of disease manifestations were retrospectively collected and analyzed in a large international multicenter cohort of ASSD patients.

* Corresponding author at: Rheumatology Unit, Department of Medicine, University of Perugia, Via Enrico dal Pozzo, I-06122 Perugia, Italy.
E-mail address: elena.bartolonibocci@unipg.it (E. Bartoloni).

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Results: 165 patients (123 women) with incomplete ASSD were identified. Ninety-five patients (57.5%) developed new classic triad manifestations after 15 months median (IQR 9–51) and 40 (24%) developed new accompanying features after 19 months median (IQR 6–56) from disease onset. During the follow-up, the ex-novo occurrence of triad features was observed in 32 out of 40 patients (80%) with new accompanying findings and in 63 out of 125 patients (50.5%) without new accompanying findings ($p = 0.002$). In patients with at least one new accompanying feature the odds ratio for the occurrence of new triad manifestations was 3.94 with respect to patients not developing ex-novo accompanying findings (95% CI 1.68–9.21, $p = 0.002$).
Conclusion: Anti-Jo1 ASSD patients with incomplete forms at disease onset are at high risk for the subsequent occurrence of lacking classic triad findings. Although all ASSD patients should be carefully assessed for the occurrence of new triad features, a closer follow-up should be considered in the subgroup of patients developing ex novo accompanying findings. These patients, indeed, have near four-fold increased risk for new classic triad manifestation occurrence with respect to patients not presenting ex novo accompanying findings.

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1. Introduction

Anti-synthetase syndrome (ASSD) is a connective disease mainly affecting adults at any age, characterized by a strict association with aminoacyl-transfer RNA synthetase (ARS) antibodies and by a highly variable clinical picture [1]. Interstitial lung disease (ILD), myositis and arthritis represent the classic clinical triad of the disease, with frequencies ranging from 60% to 95% of cases [2–8]. Recently, it has been shown that in anti-Jo1 positive ASSD, the clinical triad of the disease is rarely observed at disease onset, and that patients presenting with just one or two classic triad findings (for a practical purpose defined as incomplete forms) frequently will develop additional triad features during the follow-up [9–11]. The later appearance of initially absent classic triad findings during the follow-up is common and, of interest, is particularly increased in patients with a single triad finding onset, depicted in up to 50% of anti-Jo1 positive ASSD [10]. Other ASSD typical clinical features, like fever, Raynaud phenomenon (RP) and mechanic's hands (MHs), are less frequently observed in comparison to the classic triad findings and have been reported in approximately 40% of cases [10–12]. Although the presence of MHs is a relevant clinical clue for the diagnosis of ASSD [13], the implications and clinical predictive value of the development of fever, MHs and RP during the course of the disease in patients without the classic triad at disease onset have not been evaluated yet. Thus, the aim of this multicenter, international and retrospective study was to assess whether the development of RP, fever or MHs during the follow-up may predict the subsequent occurrence of the baseline absent classic triad manifestations in one of the largest cohort of anti-Jo1 positive ASSD [10].

2. Patients and methods

Patients were selected from a retrospective large database of ASSD patients regularly followed at twenty-four Rheumatology centers from Italy (14), Spain (6), Germany (3), and USA (1), as previously described [10]. Patients were eligible if they had at least two anti-Jo1 positive tests and presented, at disease onset, with an incomplete ASSD (just one or two findings between arthritis, myositis and ILD). Signed informed consent as approved by the local Institutional Ethics Board was required and collected at enrollment, when possible, in all cases according to national rules. Type and characteristics of clinical features, different clusters of disease manifestations, outcomes, laboratory and instrumental investigations at the onset and during follow-up, were retrospectively collected for all patients by reviewing their clinical charts. The onset of ASSD was considered from the first pulmonary, muscular or joint symptom. Clinical features onset was considered concurrent in case of <-3 months of delay between manifestations' presentation.

As previously described [10], ILD was defined instrumentally by a restrictive pulmonary function test pattern (FVC ≤ 80%, FEV1/FVC ≥ 70%, decreased or normal FEV1, and/or >20% reduction in DLCO), after excluding other causes different from ILD, and/or by signs of alveolitis/fibrosis on high-resolution computed tomography (HRCT). Screening for ILD occurrence was regularly performed during the follow-up (PFTs + DLCO every 6–12 months, lung HRCT at baseline and then on annual or biannual basis thereafter) or in case of respiratory symptoms appearance. Patients with muscle enzyme elevation (creatinine phosphokinase and/or aldolase) and the presence of typical electromyography alterations and/or compatible muscle biopsy findings were considered as having muscle involvement. Muscle enzymes were routinely assessed at baseline and during follow-up (in general every 6 months). Arthritis occurrence (joint swelling and tenderness required) was assessed clinically by the clinician in charge of the patient at each visit. Patients were periodically evaluated for the presence of fever, MHs and RP (for a practical purpose defined as accompanying features) during all disease course. The occurrence of these accompanying features was assessed clinically. In particular, fever was defined related to ASSD in case of a body temperature ≥ 38 °C for >10 days without the evidence of other possible causes. MHs were defined as the occurrence of a thickened, hyperkeratotic, and fissured aspect of the radial sides of the hands' fingers, without any other possible explanation. RP was intended as the occurrence of a transient fingers' ischemia after cold