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Preface

How to investigate: Very early inflammatory rheumatic diseases

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Window of opportunity
Early inflammatory back pain

In this issue of Best Practice and Research Clinical Rheumatology, we are delighted to introduce an outstanding selection of reviews about how to investigate patients presenting with manifestations suggestive of early inflammatory rheumatic diseases. Following the aim of this series, authors of the eleven topics devised practical, evidence-based review articles that seek to address the key clinical issues, integrating the results from the latest original research articles. These reviews are primarily aimed at providing clinically useful insights and investigation strategies for practising and trainee rheumatologists or others involved in the management of inflammatory rheumatic diseases.

Investigation and diagnosis of inflammatory rheumatic diseases is usually a challenging task, even for experienced specialists. To identify the correct diagnosis at very early stages, when the manifestations are limited and mostly unspecific is even more daunting. However, the importance of early diagnosis can not be overstated. Very early diagnosis offers to our patients the best chance for intervention during a *window of opportunity* when treatment may allow optimal clinical responses, better chances of achieving sustained remission, preventing irreversible organ damage and ultimately optimising long-term outcomes. It was hypothesised that there is potential for aborting the disease process altogether, if truly disease-modifying treatment is initiated early enough to avoid progression to chronicity. With this goal, in recent years clinical and translational research focused on identifying patients in ever earlier disease states. These include healthy carriers of genetic risk factors for inflammatory rheumatic diseases, individuals with pre-clinical autoimmune and inflammatory abnormalities, and patients with mild clinical manifestations not fulfilling disease classification criteria. The value of early markers and manifestations to stratify risk for disease progression of pre-clinical and early disease is reviewed in this issue.

For achieving an early diagnosis of inflammatory rheumatic diseases, it is fundamental that patients seek timely advice in primary care and that appropriate early referral to rheumatology is provided. In their review, Dr. Warburton et al. discuss current barriers to achieving early referral from primary to

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secondary care of patients with suspected new-onset inflammatory arthritis and discuss strategies to overcome these challenges. Regarding rheumatoid arthritis, Dr. Martins and Prof. Fonseca present an overview of the most recent advances on markers of *pre-clinical arthritis* and how to investigate and stratify risk of progression of patients presenting with *clinically suspect arthralgia* or with *undifferentiated arthritis*. Early diagnosis of axial spondyloarthritis is still an unmet need in most cases, with over 6 years of average delay in current practice, as reported by Dr. Carvalho and Prof. Machado in their review. Aiming for an earlier diagnosis, they propose an algorithm to investigate early inflammatory back pain in clinical practice.

In their viewpoint, Dr. Gatto et al. discuss the investigation and management approach to *preclinical lupus*, defined as asymptomatic immunological abnormalities potentially heralding development of Systemic lupus erythematosus (SLE), and *early lupus*, defined as clinical manifestations consistent with SLE but not yet fulfilling classification criteria. In their review, Dr. Bellando-Randone and Prof. Matucci-Cerinic discuss *very early Systemic sclerosis*, characterized by Raynaud's phenomenon, puffy fingers, disease-specific autoantibodies and microvascular alterations detected by capillaroscopy and provide an algorithm for investigating these patients. Besides the typical pattern of Giant cell arteritis with cranial ischemic manifestations, which is the prototype of large vessel vasculitis (LVV) in adults, extra-cranial involvement has emerged as a common feature of LVV. Patients with predominant extra-cranial LVV often present with non-specific manifestations and have longer delay for diagnosis. Prof. González-Gay et al. focused in their review on the work-up suggested for an early diagnosis of LVV.

Patients often present with manifestations that may not include prominent musculoskeletal features, but that should elicit the hypothesis of early systemic rheumatic diseases. The investigation of these cases can be particularly challenging, leading to longer diagnosis delay. Patients presenting with fever represent a frequent example of these difficult clinical scenarios. Dr. Ludwig et al. propose in their article an evidence-based algorithm for investigating fever of unknown origin from a rheumatological perspective. Reduced blood cell counts are a common presenting feature of various systemic rheumatic diseases, often years before patients fulfil classification criteria, such as in SLE. Dr. Nikolopoulos et al. discuss the diagnostic work-up of cytopenias in suspected early systemic rheumatic diseases, that should aim to exclude non-rheumatic mimickers such as drug toxicity, infections or hematological/myelopoiesis disorders, and provide guidance regarding their investigation in routine clinical practice. Skin rashes are frequently the earliest and most evident sign leading to a suspicion of a variety of inflammatory rheumatic diseases. However, differential diagnosis is extensive and includes many challenging mimickers. Dr. Alves and Prof. Gonçalo provide practical guidance on how to investigate skin rashes for helping in the early diagnosis of rheumatic diseases. Muscle complaints are another common early presenting feature of inflammatory rheumatic diseases. The scope of differential diagnosis to consider is wide, including myositis, neuromyopathies, polymyalgia rheumatica, as well as fibromyalgia. In their review, Dr. Altabás-González et al. discuss how to investigate these clinical scenarios.

Digital health or eHealth technologies are changing established medical practices. Notably, big-data, wearables, machine learning, and artificial intelligence are opening unprecedented opportunities as to how the diseases are investigated, diagnosed and managed with more active patient engagement. The review by Dr. Kataria and Dr. Ravindran focuses on these recent technological advances and highlight their immense potential to enable earlier diagnosis of inflammatory rheumatic diseases.

We hope you enjoy these reviews and that this publication proves helpful for clinicians in daily clinical practice. Furthermore, we are grateful and would like to thank all authors for their outstanding contributions to this issue of Best Practice and Research Clinical Rheumatology.

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