

Idiopathic inflammatory myopathies: Not nearly the end of the road

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The clinical spectrum of idiopathic inflammatory myopathies (IIM) has broadened over the past half century from a simple disease characterised primarily by muscle and skin manifestations, to a potentially life-threatening complex condition of multiple organ involvement. In the recent decade, the discovery and addition of novel autoantibody profiles including the myositis-specific autoantibodies (MSAs) and myositis-associated autoantibodies (MAAs) have led to considerable advances in our understanding of the clinical and pathological heterogeneity of IIM. The knowledge and interpretation of the presence of an MSA enable the identification of distinct clinical phenotypes and facilitate early diagnosis of IIM, obviating the need for invasive tests such as muscle biopsy in some cases. Serologically defined subgroups of IIM provide valuable insights into the genetic susceptibility factors, and oncogenic as well as environmental triggers of the disease.¹ More importantly, these autoantibodies have allowed physicians to ascribe prognosis.

The conventional screen for the presence of an autoantibody, in patients with a suspected systemic autoimmune rheumatic disease, is the anti-nuclear antibody (ANA) test. ANA is an array of autoantibodies that direct against nuclear constituents such as single- or double-stranded deoxyribonucleic acid (dsDNA), centromeres, proteins complexed with ribonucleic acid (RNA), and enzymes such as topoisomerase. ANA screen is usually performed by indirect immunofluorescence (IIF) using rodent tissues or a human cell line (usually HEp-2 cells) as the substrate. While it is useful in the diagnosis of most connective tissue diseases such as systemic lupus erythematosus (SLE) and systemic sclerosis, it is not so in IIM. MSAs and MAAs yield a cytoplasmic rather than a nuclear staining pattern on IIF, often leading to a negative ANA test result. Myositis autoantibody testing must therefore be specifically requested in addition to an ANA screen when the pre-test probability of IIM is high.

Approximately 50–60% of adults and children with IIM

carry an identifiable MSA.^{2,3} MAAs are less specific to IIM, and may be found in other autoimmune conditions that overlap with myositis such as SLE and systemic sclerosis. Classic MSAs include antibodies to Jo-1 such as histidyl transfer RNA (tRNA) synthetase, and other aminoacyl tRNA synthetases (ARS), anti-nucleosome remodelling deacetylase complex (Mi-2), anti-signal recognition particle (SRP), anti-3-hydroxy-3-methylglutaryl coenzyme A reductase (HMGCR), anti-melanoma differentiation-associated gene 5 (MDA5), anti-transcription intermediary factor 1 γ (TIF1- γ), anti-nuclear matrix protein 2 (NXP2), anti-small ubiquitin-like modifier activating enzyme (SAE), and anti-cytosolic 5'-nucleotidase 1A (cN1A).

The association between MSAs and clinically important disease features—such as interstitial lung disease and malignancy—makes the autoantibody profile a useful tool to guide further investigations and appropriate monitoring. Paramount to the finding of anti-TIF1- γ or anti-NXP2 in adult-onset IIM is their strong correlation with cancers, with a 38–71% risk of malignancy occurring within 3 years prior to or following an IIM onset.⁴ Children with anti-TIF1- γ or anti-NXP2 antibodies, on the contrary, are at risk for severe skin diseases including calcinosis, rather than that of cancers.¹

In this issue of the *Annals*, Chua et al.⁵ describe and compare the main clinicopathologic features and outcomes between 36 patients with dermatomyositis who were positive for anti-TIF1- γ antibody and 60 counterparts negative for the antibody at a tertiary institution in Singapore. The study revealed a higher prevalence of cancers among dermatomyositis patients with anti-TIF1- γ antibody compared with those without (63.9% versus 8.3%; odds ratio 19.1, 95% confidence interval 6.1–59.8, $P < 0.001$), with nasopharyngeal carcinoma and breast cancer being the most common malignancies (26.1%) in these patients. Previous local studies^{6,7} predating the advent of most MSAs established a similar link between these malignancies and dermatomyositis in adults.

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The data and recommendations by Chua et al. are timely and complement the recent evidence and consensus-based cancer screening guideline issued by the International Myositis Assessment and Clinical Studies Group (IMACS) at the American College of Rheumatology Convergence 2022.⁸ Most cancers are diagnosed simultaneously with IIM, or during the first year after the diagnosis of IIM.^{9,10} The absence of cancer at IIM onset does not negate the likelihood of its future occurrence; surveillance of malignancy is therefore required. The intensity of cancer surveillance can vary, depending on various clinical and epidemiological factors. All adult IIM patients should undergo basic laboratory testing and country/region-specific age and sex-appropriate cancer screening at diagnosis of IIM.⁸ The IMACS further recommends stratifying cancer risk according to disease subtypes, autoantibody status and clinical features. Patients with an increased risk of developing cancer should undergo enhanced screening. This includes basic and sex-based screening, as well as computed tomography (CT) scanning of the thorax, abdomen and pelvis; cancer antigen 125 (CA 125) test; abdominal or transvaginal ultrasound for ovarian cancer evaluation; and prostate-specific antigen test. In addition to these recommendations by IMACS, Chua et al.⁵ propose magnetic resonance imaging of the neck and posterior nasal space and otolaryngology assessment for all patients with dermatomyositis in accordance with the high prevalence of nasopharyngeal carcinoma in Singapore.^{6,7} Patients with 2 or more of the following features including (1) dermatomyositis, (2) anti-TIF1- γ antibody positivity, (3) anti-NXP2 positivity, (4) aged more than 40 years at onset, (5) persistent high disease activity despite immunosuppressive therapy, (6) moderate to severe dysphagia, and (7) cutaneous necrosis, are encouraged to undergo cancer surveillance for up to 3 years after the onset of IIM.⁸

Glucocorticoids are the first-line therapy for IIM. In most cases, additional immunosuppressive agents are required for patients with IIM, and introducing them early in the course of the illness can attenuate glucocorticoid toxicity and facilitate rapid resolution of disease features. Combination therapy with different immunosuppressants and the use of intravenous immunoglobulin, an immunomodulatory agent, are

considered in certain disease subtypes. Patients with cancer-associated myositis should be managed from the perspective of both their cancers and myositis. Physicians who manage IIM often closely collaborate with oncologists to devise individualised therapy plans, taking care to mitigate potential drug interactions.

In recent years, substantial work has been undertaken towards establishing the epidemiology, genetic associations, disease subtype classification of IIM and novel therapeutic strategies. Despite these significant advances, major unmet needs endure. The establishment of personalised medicine in IIM, while tantalising, requires better data harmonisation and international collaborations. We remain optimistic, fully cognisant of the sinuous path that accompanies this odyssey.

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