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Letter to the Editor (Case report)

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Detection of anti-Mi-2 autoantibodies before dermatomyositis-specific manifestations

Rheumatology key message

- Anti-Mi-2 autoantibodies can be detected before DM-specific manifestations.

Sir, There is intensifying interest in myositis-specific autoantibodies (MSAs) and in methods for their detection [1, 2]. The expanding availability of dot/line immunoassays almost certainly will result in increased detection of MSAs, in some cases even in absence of clinical features specific for idiopathic inflammatory myopathy (IIM). It is unclear how to monitor these patients. In other systemic autoimmune rheumatic diseases such as SLE and SS, presence of autoantibodies before symptom onset has been described [3, 4]. For MSAs, detection of MSAs at a significant titre before a definite diagnosis of IIM has only been documented in a handful of cases with anti-Jo-1 (one patient [5]), anti-melanoma differentiation-associated gene 5 (two patients [6, 7]) and anti-EJ (one patient [8]) autoantibodies, but not for anti-Mi-2.

We present a case of a 17-year-old Caucasian female in whom anti-Mi-2 autoantibodies were detected 3 months before IIM-specific symptom onset. ANA by indirect immunofluorescence assay testing was prescribed by her primary care provider as part of a general diagnostic work-up for evaluation of chronic mechanic polyarthralgia (both wrists and knees). ANA immunofluorescence assay testing was positive with a titre of 1/1280 and a nuclear speckled pattern. After initial positive reflex testing by the clinical laboratory with EliA CTD Screen (Thermo-Fisher, Germany), subsequent subtyping with a dot immunoassay (ANA + DFS70 IgG Dot, Alphadia, Mons, Belgium) was positive for anti-Mi-2 autoantibodies (71 arbitrary units, reference value <10). Three months later, she developed a heliotrope rash and Gottron's papules. At referral, 4 months after the detection of anti-Mi-2, she had subclinical myositis with normal muscle strength but elevated creatinine kinase levels (Table 1). Presence of anti-Mi-2 autoantibodies was confirmed with a dot immunoassay (63 arbitrary units; Myositis 12 SAE IgG Dot, D-tek, Mons, Belgium) She was diagnosed with anti-Mi-2-positive DM and treatment with methylprednisolone was subsequently started.

Anti-Mi-2 autoantibodies are associated with the classical cutaneous features of DM, muscle involvement and good prognosis [9]. Detection of anti-Mi-2 autoantibodies before presence of IIM-specific features points to an early presence of anti-Mi-2 autoantibodies in the autoimmune process. Whether MSAs such as anti-Mi-2 are mere bystanders or active participants in IIM pathogenesis is unclear. A direct pathogenic role is suspected, but highly debated, for anti-hydroxy-3-methylglutaryl-coenzyme A reductase, anti-signal recognition particle and anti-Jo-1 autoantibodies [10, 11]. While there is no evidence for such a role for anti-Mi-2 autoantibodies as yet, production of these autoantibodies may be fuelled by the increased expression of Mi-2 in regenerating muscle cells and ultraviolet light-exposed keratinocytes [12]. Interestingly, Mi-2β has recently been described to repress pro-inflammatory genes in keratinocytes [13]. In this case, the short time interval to appearance of overt manifestations suggest an active disease process at the moment of anti-Mi-2 detection.

Reflex testing with an assay including MSAs in ANA-positive patients with non-specific symptoms is expected to lead to more 'incidental' findings. For a correct interpretation of such a finding, the prescribing physician should be aware of varying diagnostic accuracy between detection methods [14]. These detection

Table 1 Overview of laboratory data obtained before symptom onset and at referral to a rheumatology clinic

	Reference range	Before symptom onset	At referral (4 months later)
White blood cell count (/μl)	4900–9100	4640	2890
CK (U/l)	<170	105	2946
AST (U/l)	<25	21	158
ALT (U/l)	<22	25	84
LDH (U/l)	<210	216	NA
ANAs	<1/80	1/1280, nuclear speckled	1/2560, nuclear speckled
CTD screen (U/l) (EliA, Thermo Fisher)	<1.0	6.9	6.1
Dot immunoassay	<10 arbitrary units	Anti-Mi-2: 71 arbitrary units	Anti-Mi-2: 63 arbitrary units

CK: creatine kinase; AST: aspartate aminotransferase; ALT: alanine aminotransferase; LDH: lactate dehydrogenase; NA: not available.

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methods include immunoprecipitation, ELISA, fluorescence enzyme immunoassays, chemiluminescence assays and line/dot immunoassays. For instance, there is only weak to moderate agreement between line immunoassays and immunoprecipitation for detection of anti-Mi-2 autoantibodies [14, 15]. In addition, the diagnostic performance of commercially available assays varies between manufacturers for each individual MSA [1]. The positive likelihood ratio for IIM for positive anti-Mi-2 on the specific assay used in this case is very high. Though it is uncertain whether in quantitative assays the titre of anti-Mi-2 autoantibodies accurately reflects disease activity, a high result does make a false-positive less likely. Furthermore, the ANA pattern (nuclear speckled) was consistent with anti-Mi-2 autoantibodies. These three laboratory parameters [ANA pattern concordance (if ANA is positive), autoantibody titre and assay characteristics] should be reviewed if an MSA is detected 'incidentally'. Given the possibility of an incipient IIM, it seems prudent to refer each case with a detectable MSA to a physician with experience in diagnosis and management of IIM.

How long MSAs can be present before symptom onset is unknown. In this case the detection of anti-Mi-2 only predated the first DM-specific symptoms (heliotrope rash) by 3 months, though polyarthralgia (which was deemed mechanic) was present. SLE-associated autoantibodies can be present years before clinical manifestations. The previously described patient with anti-Jo-1-positive IIM had detectable autoantibodies 5 months before IIM-specific symptoms. The other patients (two with anti-MDA5 and one with anti-EJ) already had non-IIM-specific features suggestive of a systemic autoimmune rheumatic disease or diagnosis of a different systemic autoimmune rheumatic disease. A systematic study on presymptomatic samples of patients with IIM would provide insight into the temporal relationship of autoantibody production and symptom onset, although retrieval of sufficient presymptomatic samples would be logistically exceedingly difficult.

To conclude, this case report illustrates the detection of anti-Mi-2 autoantibodies before DM-specific symptoms. In patients with a detectable MSA in the absence of IIM-specific features, the autoantibody titre, ANA pattern concordance and assay characteristics should be reviewed, and referral to a physician with experience in diagnosis and management of IIM should be considered.

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