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Review

Anti-OJ autoantibodies: Rare or underdetected?

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ABSTRACT

Anti-OJ autoantibodies are rare myositis-specific autoantibodies that have been described to target isoleucyl-tRNA synthetase. Routinely used multiplex assays perform poorly in detection of anti-OJ antibodies. In this manuscript, we review the existing literature on critical issues in detection of anti-OJ and the clinical features associated with anti-OJ. The challenging detection with line/blot immunoassays and ELISAs is most likely related to the characteristics of the autoantigen involved, which is part of a multi-enzyme synthetase complex. Anti-OJ autoantibodies might therefore be more aptly termed anti-OJ complex autoantibodies. Anti-OJ autoantibodies are associated with the anti-synthetase syndrome, with interstitial lung disease (ILD) frequently being the sole manifestation. Myositis, present in the majority of patients with anti-OJ antibodies, is more severe than in patients with other anti-aminoacyl-tRNA synthetases. Most patients respond to glucocorticoid therapy. As detection of anti-OJ is relevant for treatment, reliable and practical detection is needed. Meanwhile, clinicians need to be aware of the possibility of anti-OJ in patients with ILD, isolated or in combination with myositis.

1. Introduction

Anti-OJ autoantibodies are myositis-specific autoantibodies (MSAs) that can be found in < 5% of patients with idiopathic inflammatory myopathies (IIMs) [1,2]. They presumably target isoleucyl-tRNA synthetase and, as such, are part of the group of the anti-aminoacyl-tRNA synthetases (anti-ARS, Table 1), of which anti-Jo-1 is the most prevalent [1,3]. Collectively, anti-ARSs can be found in 11–40% of patients with IIM, depending on the detection method and the examined cohort [1,4].

The anti-ARSs are associated with the anti-synthetase syndrome (ASS), a subtype of IIM. ASS consists of the triad of myositis, interstitial lung disease (ILD) and arthritis, with mechanic's hands, Raynaud phenomenon and unexplained fever as frequently accompanying manifestations [3,5–7]. In addition to ASS, which is sometimes seen as a form of overlap myositis (OM), four more IIM subtypes are recognized: dermatomyositis (DM), immune-mediated necrotizing myopathy (IMNM), inclusion-body myositis (IBM) and polymyositis (PM) [8]. Within these subtypes, other autoantibody-defined syndromes are being considered, highlighting the relevance of reliable autoantibody detection [9,10].

Although the detection methods for autoantibodies in IIM are evolving rapidly, detection of anti-OJ autoantibodies with newer immunoassays proves to be especially difficult. Therefore, knowledge of the clinical features associated with anti-OJ is relevant for the physician in order to avoid misdiagnosis or misclassification. To this end, we provide an overview on the detection, with emphasis on the target of anti-OJ, and associated clinical features of anti-OJ autoantibodies.

2. Methods

In PubMed and Embase the following search was performed: “Anti-OJ” OR ‘OJ autoantibodies” OR “anti-isoleucyl-tRNA synthetase”. After removal of duplicates and exclusion of articles based on article type (reviews and conference abstracts were excluded) and content (as based on abstract) a full-text review was performed for articles available in English. Additional articles were hand searched. Patients described in multiple articles, if explicitly stated, were only included once for review of associated clinical features.

Antigens recognized by sera were analyzed by immunoprecipitation (IP) of radiolabeled K562 (human erythroleukemia) cell extract and

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Table 1
Autoantibodies targeted at aminoacyl-tRNA synthetases or proteins associated with translation.

Autoantibody	Autoantigen	ARS class	Molecular weight in kDa (IP)	Clinical phenotype	Prevalence in IIM (%)
Aminoacyl-tRNA synthetases					
Anti-Jo-1 [55]	Histidyl-tRNA synthetase (HARS)	II	50	ASS/ILD	25–30%
Anti-PL-12 [56]	Alanyl-tRNA synthetase (AARS)	II	110	ASS/ILD [57]	2–5%
Anti-PL-7 [58]	Threonyl-tRNA synthetase (TARS)	II	80	ASS/ILD [59]	2–5%
Anti-EJ [11]	Glycyl-tRNA synthetase (GARS)	II	75	ASS/ILD	< 2%
Anti-KS [60]	Asparaginyl-tRNA synthetase (NARS)	II	65[60]	ILD, arthritis, sicca syndrome [60,61]	< 2% [60]
Anti-OJ [11]	Components of the MSC	I (IRS)	150 + 170/130/75	ASS/ILD	< 5% [1,2]
Anti-YRS/Anti-Ha [62]	Tyrosyl-tRNA synthetase (YARS)	I	59	ASS/ILD	Rare
Anti-Zo [63]	Pheynlalanyl-tRNA synthetase (FARS)	II	60/70	ASS/ILD	Rare
Anti-WRS [64]	Tryptophanyl-tRNA synthetase (WARS)	I	120	SLE, RA, malignancy [65,66]	NA
Proteins associated with translation					
Anti-Mas [67]	Selenocysteine-seryl-tRNA-protein complex	NA	48	AIH, IIM	2% [68]
Anti-KJ [69]	Translocation factor	NA	30/43	ASS-like syndrome	Rare
Anti-Wa [70]	NEFA/nucleobindin-2 [71]	NA	48	ASS-like syndrome	Rare
Anti-Fer [72]	Eukaryotic elongation factor Ia [73]	NA	Unknown	ASS-like syndrome	Rare

ASS antisynthetase syndrome, IIM idiopathic inflammatory myopathy, IP immunoprecipitation, IARS isoleucyl-tRNA synthetase, MSC multienzyme synthetase complex, NA not applicable, NEFA DNA binding/EF-hand/acidic amino acid rich region.

SDS-PAGE. In brief, cells were labeled for 14 h with 35S-L-methionine and 35S-L-cysteine (NEG772, PerkinElmer, Waltham, MA, USA) and lysed in NET/IGEPAL CA-630 buffer (500 mM NaCl, 2 mM EDTA, 50 mM Tris-HCl pH 7.5, 0.3% IGEPAL CA-630) containing 0.5 mM PMSF and 0.3 TIU/ml aprotinin. Cell extract was cleared by centrifugation and immunoprecipitated on Protein A Sepharose beads (17-0780-01, GE Healthcare, Marlborough, MA, USA) coated with antibodies from 8 µl of human serum. Beads were then washed with 0.5 M NaCl NET/ IGEPAL CA-630 buffer (500 mM NaCl, 2 mM EDTA, 50 mM Tris-HCl pH 7.5, 0.3% IGEPAL CA-630). Immunoprecipitated proteins were subjected to 8% and 12.5% SDS-PAGE followed by autoradiography.

3. The anti-OJ target

Anti-OJ autoantibodies were, concurrently with anti-EJ autoantibodies, discovered by IP and aminoacylation inhibition experiments by Targoff in 1990 (Fig. 1) [11]. The immunoprecipitate of sera of two patients, who had the initials OJ and EJ, revealed identical patterns of tRNA, which co-immunoprecipitated with the ARS, and a distinct protein pattern, consistent with the multi-enzyme synthetase complex (MSC). These sera inhibited the enzymatic activity of isoleucyl-tRNA synthetase (IARS), a component of the MSC, most strongly in an aminoacylation assay, though reactivity with other components of the MSC were noted in the initial and subsequent study by Targoff [11,12]. Interestingly, immunoblotting with anti-OJ positive sera did not show reaction with the presumed main target IARS in most cases. These findings challenge the notion of IARS as a singular isolated target and points to considering IARS as a part of the MSC if we want to further elucidate the target.

The MSC consists of 9 synthetases, including IARS, and 3 non-catalytic components (Fig. 2a) [13,14]. It has a key role in protein synthesis but is a central hub for many signaling pathways as well [14]. In addition to IARS, anti-OJ autoantibodies have shown reactivity with lysyl-tRNA synthetase (KARS), a 160 kD synthetase protein that most likely corresponds to the bifunctional glutamyl-prolyl-tRNA synthetase (EPRS) or glutaminyl-tRNA synthetase (QARS), and possibly leucyl- (LARS) and arginyl-tRNA synthetase (RARS) [12,15]. No reactivity with methionyl-, arginyl- and asparaginyl-tRNA synthetases, the remaining synthetases of the MSC, has been described. The 3 non-catalytic components, p43, p38 and p18, are instrumental for stabilization of the interactions between the components [14,16]. Next to these established components, additional components have been suggested, such as threonyl-tRNA synthetase like-2 (TARSL2), an enzyme with similar aminoacylation activity to threonyl-tRNA synthetase (TARS) [17], which is a known autoantigen for anti-PL-7 autoantibodies [18].

These components are assembled into multiple subcomplexes and ultimately into the MSC, which has an estimated weight of 1.5 MDa [14]. Cryogenic electron microscopy [19] and small angle X-ray scattering [20] has allowed the construction of a low resolution model of the entire native MSC. These structural studies reveal a large and elongated, but probably flexible, structure. This organization befits the dual role of the MSC in protein synthesis and signaling.

Considering the confounding results in defining the primary target (s) of anti-OJ and the expanded knowledge of the components and structure of the MSC, the epitope might be based on quaternary interactions between MSC components. If the binding of autoantibody and the OJ epitope would indeed be dependent on quaternary interactions, anti-OJ autoantibodies may rather be seen as anti-OJ complex autoantibodies. Viewing anti-OJ autoantibodies as targeted at a complex has direct implications for the development of an assay for detecting anti-OJ autoantibodies.

4. Detection of anti-OJ autoantibodies

In current clinical practice detection of anti-OJ autoantibodies is problematic. IP is the preferred method as sera with anti-OJ autoantibodies have a specific pattern on RNA and protein IP (Fig. 2b). However, differences between direct antigen-antibody interactions that can be detected by solid phase assays vs. direct, indirect and quaternary interactions captured by IP could negatively impact the agreement between these methods. Furthermore, IP is laborious and technically demanding, leading to increasing use of other assays in routine practice.

Line immunoassays (LIA) and dot blot assays (DBA) are the current detection method for MSAs in many hospitals. These multiplex assays, which are based on immunoblotting, agree only for some MSAs with IP [21]. For anti-OJ, they perform poorly. In a comparison of a LIA (Euroimmun Myositis profile, Lübeck, Germany) with IP in three studies, none of the 25 anti-OJ-positive sera (all three studies combined), as confirmed by RNA and protein IP [1,22] or protein IP alone [21], were positive on the LIA. Moreover, in large cohorts tested with LIA or DBA, detection of anti-OJ was exceedingly rare, even more so than in cohorts tested with IP with a similar number of patients [4,23–25].

Few other methods besides LIA and DBA have been investigated. In a study of an ELISA for a mixture of 6 anti-ARSs, anti-OJ was the only anti-ARS that could not be detected in RNA IP-confirmed anti-OJ positive sera [26]. The recombinant antigen was expressed in insect cell expression system (Hi-5 cells). A novel detection technique called

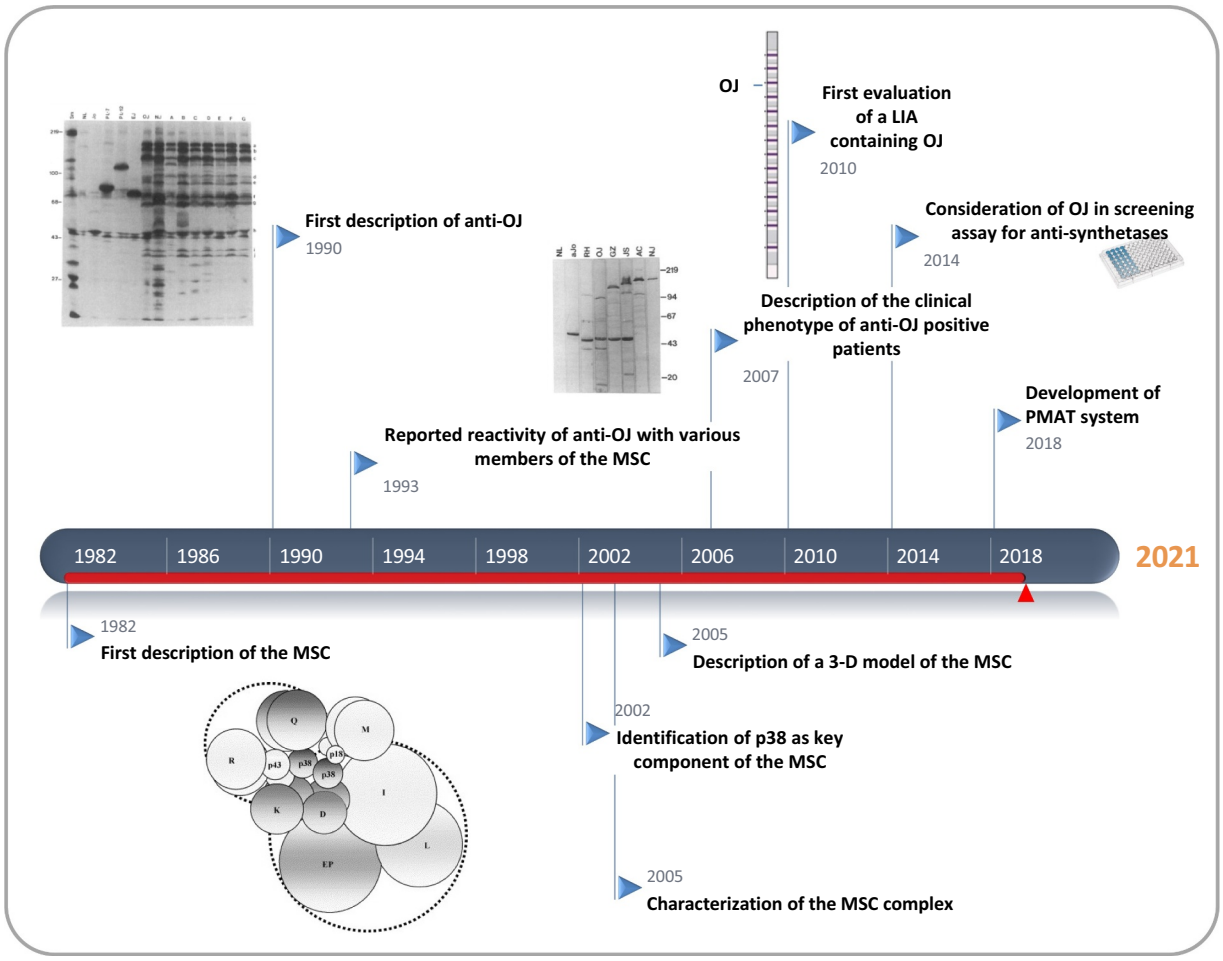

Fig. 1. The history of anti-OJ autoantibodies from biochemical and immunological perspective. MSC = multi-synthetase complex; LIA = Line immunoassay; PMAT = particle-based multi-analyte technology.

particle-based multi-analyte technology (PMAT) has an excellent correlation with IP for the most frequently encountered MSAs, but has not been evaluated with anti-OJ positive sera as detected by IP [27].

The role of indirect immunofluorescence (IIF) in IIM is limited [28]. A cytoplasmic pattern can be seen in a proportion of patients with anti-OJ, as is the case for other anti-ARS [29–31]. Notably, ARSs can also be found in nonconventional localizations such as the nucleus and mitochondria [32]. Lack of sensitivity of IIF on HEp-2 cells for various cytoplasmic antigens, including the ARSs, could be a consequence of low relative antigen concentration, cell preparation or fixation protocols [33]. As such, a negative result on IIF, even with separate reporting of cytoplasmic staining [34], does not exclude MSAs such as anti-OJ. Therefore, IIF alone is not adequate for screening patients with possible anti-OJ or other anti-ARSs. Furthermore, identification of the specific autoantibody is relevant for management of these diseases, even within the ASS, given the heterogeneity in clinical features among anti-ARSs [28,35].

Considering the detection issues with other techniques, IP remains the preferred method for detection of anti-OJ autoantibodies, despite its own limitations. The disappointing results with the other assays reflect the complexity associated with OJ testing and the need to establish the primary target/targets that represent anti-OJ reactivity. This in turn may lead to development of a more practical immunoassay that captures the direct and indirect (quaternary) interactions involving anti-OJ antibodies.

5. Coexistence with other autoantibodies

Of the patients described in literature, only one patient with anti-OJ had coexisting anti-Jo-1 autoantibodies, both detected by RNA IP [15]. This is the only documented case of reactivity with a synthetase that is not a part of the MSC. Furthermore, coexistence of anti-SS-A/Ro60 and anti-SS-B/La, two autoantibodies frequently present in patients with systemic autoimmune rheumatic diseases, have been reported in more than one case [12,36,37]. In patients positive for anti-Jo-1 and other anti-ARS, the anti-Ro52 status delineates a subgroup with more severe muscular, respiratory and articular involvement [38]. The paucity of patients with anti-OJ does not allow a similar analysis. Finally, several patients were positive for rheumatoid factor, though this has no clear relevance in IIMs [39].

6. Associated clinical features and treatment experience

Anti-OJ autoantibodies are reportedly associated with the ASS. Within the ASS, there is heterogeneity in clinical features depending on the specific anti-ARS [35,40]. In general, patients with non-Jo-1 anti-ARS have a poorer prognosis than patients with anti-Jo-1 [41,42]. For anti-OJ, we identified 52 published cases with sufficient description of clinical features (summarized in Table 2) [1,12,15,29–31,35–37,43–48]. These patients

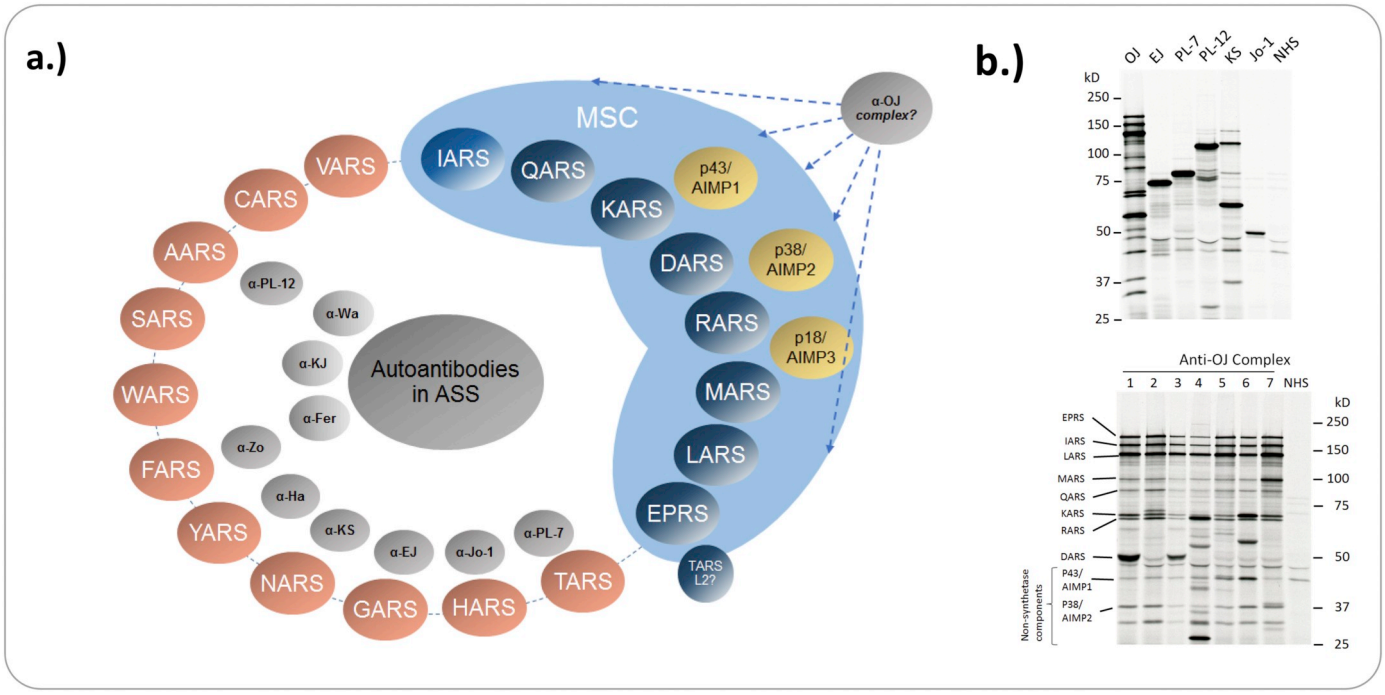

Fig. 2. Autoantibodies associated with the antisynthetase syndrome (ASS) or ASS-like syndrome. In a.) the composition of the multi-synthetase complex (MSC) is illustrated. The panel b.) shows the reactivity profile of anti-synthetase autoantibodies including anti-OJ autoantibodies. α- = anti-, ASS = antisynthetase syndrome, AARS = alanyl-tRNA synthetase, CARS = cysteine-tRNA synthetase, DARS = aspartyl-tRNA synthetase, EPRS = glutamyl-prolyl-tRNA synthetase, FARS = phenylalanyl-tRNA synthetase, GARS = glycyl-tRNA synthetase, HARS = histidyl-tRNA synthetase, IARS = isoleucyl-tRNA synthetase, KARS = lysyl-tRNA synthetase, LARS = leucyl-tRNA synthetase, MARS = methionyl-tRNA synthetase, MSC = multienzyme synthetase complex, NARS = asparagyl-tRNA synthetase, QARS = glutaminyl-tRNA synthetase, RARS = arginyl-tRNA synthetase, SARS = seryl-tRNA synthetase, TARSL2 = threonyl-tRNA synthetase like 2, TARS = threonyl-tRNA synthetase, VARS = valyl-tRNA synthetase, WARS = tryptophanyl-tRNA synthetase.

were between 13 and 79 years old at disease onset and had a female-to-male ratio of 1.7:1. All but one patient, who was diagnosed with systemic sclerosis (SSc), had a primary diagnosis of PM, DM, ILD or ASS. Given the detection issues described in the previous section it is logical that anti-OJ was detected by IP in all but two patients, of which one had confirmation by IP afterwards [36,48].

ILD is present in 90% of patients and is in most cases the first and presenting clinical feature [35]. Based on the results of high-resolution computed tomography (CT) of chest or open lung biopsy, usual interstitial pneumonia (UIP), organizing pneumonia (OP) and non-specific pneumonia (NSIP) are the most encountered ILD patterns [36,46,49]. Data on respiratory function tests are scarce. In one study there was a statistically significant difference in forced vital capacity between anti-OJ and anti-ARS-negative patients while no difference in CT chest score or diffusion capacity for carbon monoxide was noted. However, only 2 anti-OJ positive patients were included [46]. Death due to respiratory failure was not reported in the studies listed in Table 2. As ILD is the main and frequently sole feature, the possibility of anti-OJ needs to be considered in patients with 'idiopathic' ILD, as is the case for all anti-ARSs [50]. Moreover, follow-up should include regular respiratory function tests and high-resolution CTs of the chest.

The majority of anti-OJ positive patients have muscle involvement. Seventy-five percent of patients described in Table 2 had myositis, but, importantly, muscle weakness was an inclusion criterion in the study by Noguchi et al., which described the largest group of patients with anti-OJ [1]. Interestingly, the prevalence of anti-OJ was higher in this study (14/461) than in other studies, even rivalling the frequency of anti-Jo-1 (15/461 patients), though the frequency of anti-Jo-1 was notably lower than reported in other studies. In a reply to this study, Castañeda et al. stated that in a currently unpublished series of their patients with anti-OJ, 40% had hypomyopathic or amyopathic forms of ASS [6]. If muscle involvement is present, it might be more severe as compared to myositis patients with other anti-ARSs. In the study by Noguchi et al., an increased incidence of severe limb and neck muscle weakness, dysphagia and muscle atrophy on muscle biopsy was noted [1]. Illustrative of this potentially severe muscle involvement is a case report in which the presenting symptom was rhabdomyolysis [48]. Accordingly, clinicians should consider the possibility of anti-OJ autoantibodies in patients with severe muscle involvement, besides anti-SRP and anti-HMGCR autoantibodies or non-immune types of myopathy.

The remaining features of ASS vary in prevalence. Arthritis was present in nearly half of patients, mostly as a polyarthritis. In a limited number of patients arthritis was the presenting symptom, which contrasts with patients with anti-Jo-1 antibodies in whom arthritis is found in a quarter of patients [29]. Several of these patients had a concomitant alleged diagnosis of rheumatoid arthritis [43,44], a finding which has also been noted in patients with other anti-ARSs [51–53]. Fever is regularly present while Raynaud phenomenon occurs in a minority of patients (5/49). Mechanic's hands have not been reported consistently, but they have been described in at least 5 patients [30,35,45]. A complete ASS is hence the exception, rather than the rule.

Skin involvement can occur in anti-OJ positive patients. Approximately 30% of patients had a DM-associated skin lesion. More specifically, heliotrope rash, Gottron's sign or papules, V sign, shawl sign and holster sign have been reported [45]. Other skin lesions include ulceration and sclerodactyly, both described in 3 patients. Two of these patients, who had both ulceration and sclerodactyly, could be classified as both SSc and ASS [5,54].

Few cases of malignancies have been reported in patients with anti-OJ. In one study, there was a history of a malignancy in 2 patients: one with a gastric neuro-endocrine tumor and one with colon cancer [35]. In another study 2 patients with anti-OJ (of 5 in total) died due to cancer without further specification of the type of cancer [41]. Due to the small number of patients with anti-OJ, it is difficult to assess a possible association with cancer.

Most cases of patients with anti-OJ had a good response to

Table 2
Clinical features of patients with anti-OJ autoantibodies described in literature.

Study (authors) (year, reference)	Primary diagnosis	Patients (n)	Myositis (n/n)	DM skin lesions (n/n)	MH (n/n)	ILD (n/n)	Arthritis (n/n)	RP (n/n)	Fever (n/n)
Detected or confirmed by RNA and/or protein IP									
Targoff et al. (US, 1993, [12])	IIM	9	8/9	3/9	NA	8/9	6/9	1/9	NA
Friedman et al. (US, 1996, [31])	CTD/ILD	2	1/2	0/2	NA	2/2	1/2	0/2	0/2
Gelpi et al.[a] (US, 1996, [15])	ASS	1	1/1	0/1	NA	1/1	1/1	0/1	1/1
Ohosone et al. (Japan, 1998, [43])	PM-RA	1	1/1	0/1	NA	1/1	1/1	1/1	0/1
Sato et al.[b] (Japan, 2007, [44])	IIM/ILD	7	4/7	0/7	NA	7/7	4/7	0/7	NA
Koreeda et al. (Japan, 2010, [29])	ILD	1	0/1	1/1	NA	1/1	1/1	1/1	0/1
Noda et al. (Japan, 2011, [45])	DM	1	1/1	1/1	1/1	1/1	0/1	0/1	0/1
Kunimasa et al. (Japan, 2012, [30])	IIM-ILD	2	2/2	0/2	1/2	2/2	0/2	0/2	1/2
Hamaguchi et al.[b] (Japan, 2013, [35])	ASS	8	2/8	1/8	3/8	8/8	1/8	1/8	NA
Johnson et al. (US, 2014, [46])	ILD	2	1/2	0/2	0/2	2/2	NA	NA	0/2
Hamada et al. (Japan, 2017, [37])	JPM	1	1/1	0/1	0/1	0/1	1/1	1/1	1/1
Noguchi et al.[b] (Japan, 2017, [1])	IIM[c]	14	14/14[c]	8/14	NA	12/14	4/14	0/14	7/14
Pauling et al. (GB, 2017, [47])	SSc	1	1/1	0/1	NA	NA	1/1	1/1	NA
Kapoor et al. (US, 2018, [48])	ASS	1	1/1	1/1	NA	0/1	1/1	0/1	0/1
Total (n/n, %)		51	38/51 (75%)	15/51 (29%)	5/14 (36%)	45/50 (90%)	15/49 (31%)	6/49 (12%)	10/26 (38%)
Detected by IB									
Hervier et al. (France, 2011, [36])	ASS	1	1/1	0/1	0/1	1/1	0/1	1/1	NA

Incomplete data.
ASS = antisynthetase syndrome, CTD = connective tissue disease, DM = dermatomyositis, GB = Great Britain, IB = immunoblot (in both studies Euroimmun Myositis Profile, Lübeck, Germany), IIM = idiopathic inflammatory myopathy, ILD = interstitial lung disease, IP = immunoprecipitation, JPM = juvenile polymyositis, MH = mechanic's hands, NA = data not available or absence not explicitly stated, OM = overlap myositis, PM = polymyositis, RA = rheumatoid arthritis, SSc = systemic sclerosis. USA = United States of America. Myositis was defined as one or more of the following: clinically apparent muscle weakness, elevation of CK levels or findings compatible with myositis on muscle biopsy. ILD was defined by one or more of the following: clinical diagnosis of ILD, ILD pattern on CT chest, restrictive pattern on lung function testing or findings compatible with ILD on open lung or transbronchial biopsy.

[a] Coexistence of anti-Jo-1 autoantibodies.

[b] Overlap of patients could not be excluded.

[c] Presence of muscle involvement was an inclusion criterion for this study.

glucocorticoid therapy with improvement of ILD and/or myositis. The dose of oral prednisolone used in literature varied between 20 and 60 mg or 0.5–1 mg/kg daily. More intensive regimens described include pulse doses of glucocorticoids (1 g methylprednisolone) and cyclophosphamide [30,36,44,48]. Intravenous immunoglobulins have been used for cases refractory to glucocorticoid therapy [1]. As corticosteroid-sparing agents, azathioprine and cyclosporine were used [30,44,48]. The response to immunosuppressive drugs in the majority of patients underlines the importance of detection of anti-OJ in ILD patients.

7. Conclusion

Anti-OJ is a rare but frequently missed myositis-specific autoantibody. The precise target of anti-OJ remains elusive, but the epitope might be dependent on quaternary interactions in the MSC. IP remains the preferred detection method but is difficult to implement in daily practice for many hospitals. The need for practical and reliable immunoassays for detection of anti-OJ is high as the detection of this antibody is relevant for diagnosis and treatment. The performance of available immunoassays, such as LIA or DBA, should improve and the role of novel detection methods, such as PMAT, further explored. Anti-OJ is associated with ASS, with ILD often being the sole manifestation. Myositis, if present, seems to be more severe than in patients with other anti-ARSs. Overlap with or classification as other connective tissue-diseases are possible. While awaiting a widely available and reliable assay, clinicians need to consider anti-OJ in their workup of patients with ILD, be it isolated or combined with severe muscle involvement.

Take home messages

- Detection of anti-OJ autoantibodies lacks standardization due to the miss-understanding of the antigenic target.
- The reactivity of anti-OJ autoantibodies is heterogeneous and targets several components of the MSC.
- Clinically, anti-OJ autoantibody-positive patients have features of ASS, but further studies are required to further define the precise clinical phenotype.

Declaration of interest

XB has been a consultant for Inova Diagnostics. MM and KM are employees of Inova Diagnostics, a company commercializing autoimmune assays.

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