Serologic and Pathologic Correlation in Idiopathic Inflammatory Myopathies

Gloria Ortiz-Guerrero MD, Mazen M. Dimachkie MD,
Mamatha Pasnoor MD, Richard J. Barohn MD, Omar Jawdat MD,
Constantine Farmakidis MD, Jeffrey Statland MD, Melanie Glenn MD,
Duaa Jabari MD

Carrell-Krusen Neuromuscular Symposium
February 22, 2019

BACKGROUND

- Idiopathic inflammatory myopathies (IIMs) are a heterogeneous group of autoimmune disorders characterized by muscle weakness and inflammation
- According to Amato and colleagues and based on clinical features, creatinine kinase (CK) level, histopathologic findings, and other laboratory criteria, IIMs can be classified as:

- Dermatomyositis (DM)
- Necrotizing myopathy (NM)
- Non-specific myositis (NSM)
- Polymyositis (PM)

- Myositis-specific and associated antibodies may correlate with the phenotype of IIM patients
- There is limited knowledge regarding the correlation among serologic, pathologic, and clinical features

KU MEDICAL CENTER
The University of Kansas

Slide 2

DJ1 and based on
Duaa Jabari, 01/21/2019

DJ2 use either autoantibodies for both or antibodies for both
Duaa Jabari, 01/21/2019

gog1 ok
gloria ortiz guerrero, 01/21/2019

DJ20 You misunderstood: I meat use either antibody or autoantibody. Dont use both terms in the same sentence. Stay consistent
Duaa Jabari, 01/27/2019

gog15 I got your point. I did not see my mistake before. I thought both of them were refered as antibodies... corrected
gloria ortiz guerrero, 01/27/2019

DJ3 can you please share this reference with me again? Thanks
Duaa Jabari, 01/21/2019

gog5 119th ENMC international workshop:
Trial design in adult idiopathic inflammatory myopathies,
with the exception of inclusion body myositis,
10–12 October 2003, Naarden, The Netherlands
gloria ortiz guerrero, 01/23/2019

OBJECTIVE

To describe the correlation between serologic and histopathologic features along with clinical and laboratory aspects in IIMs

KU MEDICAL CENTER
The University of Kansas

METHODS

A retrospective review of electronic medical records of patients diagnosed with IIMs seen at The University of Kansas Medical Center between January 2005 and March 2018

IIM patients were identified via Healthcare Enterprise Repository for Ontological Narration (HERON), the research informatics platform for our electronic medical records at KUMC

KU MEDICAL CENTER
The University of Kansas

DEFINITIONS	
DERMATOMYOSITIS	• Proximal Muscle Weakness with typical rash for DM • **Muscle Biopsy:** Perifascicular atrophy or perivascular/perimysial inflammatory cell infiltrates
POLYMYOSITIS	• Proximal Muscle Weakness without rash • **Muscle Biopsy:** Endomysial inflammatory cell infiltrates invading non-necrotic muscle fibers
NON-SPECIFIC MYOSITIS	• "Non-specific perimysial/perivascular infiltrates or scattered endomysial infiltrate that does not clearly surround or invade muscle fibers without features diagnostic of PM or DM"[1]
IMMUNE-MEDIATED NECROTIZING MYOPATHY	• Proximal Muscle Weakness without rash • **Muscle Biopsy:** Necrotic Fibers as the predominant histological feature
ANTISYNTHETASE SYNDROME	• Presence of antisynthetase antibodies (JO-1, PL7, EJ, PL12, OJ)[2] MAJOR CRITERIA: 1. Interstitial Lung Disease 2. Myositis MINOR CRITERIA 1. Arthritis 2. Raynaud's phenomenon 3. Mechanic's Hands

1. Hoogendijk JE, Amato AA, Lecky BR, et al. 119th ENMC international workshop: Trial design in adult idiopathic inflammatory myopathies, with the exception of inclusion body myositis, 10–12 October 2003, Naarden, The Netherlands. Neuromuscular Disorders 14 (2004) 337–345
2. Salomon J, Swigris J, Brown KK. Myositis-related interstitial lung disease and antisynthetase syndrome. J Bras Penumol 2011, 37 (1) 100-109

RESULTS

- Screened patients: 242
- Excluded patients: 148 (insufficient information, diagnosis did not match with IIM, or Inclusion Body Myositis)
- Final Cohort: 94

IIM SUBTYPES (n=94)	
Dermatomyositis (DM)	42 (45%)
Non-specific Myositis (NSM)	22 (23%)
Necrotizing Myopathy (NM)	21 (22%)
Polymyositis (PM)	9 (10%)

KU MEDICAL CENTER
The University of Kansas

Slide 6

DJ4 put the number "94"
Duaa Jabari, 01/21/2019

gog2 ok
gloria ortiz guerrero, 01/21/2019

DEMOGRAPHIC DATA

DEMOGRAPHIC AND CLINICAL FEATURES OF IIM PATIENTS (n=94)				
	DM (n=42)	**NSM (n=22)**	**NM (n=21)**	**PM (n=9)**
Gender (F/M)	35/7	19/3	13/8	5/4
Age	53 ± 17	55 ± 15	59 ± 11	57 ± 13
Proximal muscle weakness n (%)	42 (100%)	22 (100%)	21 (100%)	9 (100%)
CK level – median (IQR)	457 IU/L (145-1,0[illegible])	1,181 IU/L (300-3,830)	2,117 IU/L (1,239-3,606)	2,406 IU/L (1,500-3,823)
Myositis-specific antibodies (n=28, 30%)	10 (24%)	6 (27%)	10 (48%)	2 (22%)
Myositis-associated antibodies (n=21, 22%)	8 (19%)	8 (36%)	2 (10%)	3 (33%)
Irritative myopathy on EMG n (%)	40 (95%)	22 (100%)	20 (95%)	9 (100%)

Slide 7

DJ5 put the number for each subtype
Duaa Jabari, 01/21/2019

DJ6 SD
Duaa Jabari, 01/21/2019

DJ7 How can you have SD larger than the mean for CK value?
Duaa Jabari, 01/21/2019

gog6 Because the CK level among them is wide. For example. in PM patients, CK levels range from 600 to 9000.... I double checked and the results are consistent between the spreadsheet and tables...
gloria ortiz guerrero, 01/23/2019

gog12 median instead of mean
gloria ortiz guerrero, 01/24/2019

DJ19 I removed +/-
Duaa Jabari, 01/27/2019

DJ8 We need to look at this patient who had NM without irritative myopathy on EMG
Duaa Jabari, 01/21/2019

gog7 NM patient without irritative myopathy: Diagnosis of myositis was in 2008: statin associated necrotizing myopathy. EMG done outside/ 2008: "She had an EMG which shows some median and ulnar sensory neuropathy and a noninflammatory myopathy". EMG at KUMC in 2013 also negative (looking at large fiber neuropathy).
gloria ortiz guerrero, 01/23/2019

SEROLOGIC PROFILE – Myositis-specific Antibodies

MYOSITIS-SPECIFIC ANTIBODIES				
	DM (n=42)	NSM (n=22)	NM (n=21)	PM (n=9)
Jo-1	3/41 (8%)	3/21 (14%)	0/20	1/9 (11%)
PL-7	0/34	3/17 (18%)	1/17 (6%)	0/9
PL-12	1/34 (3%)	0/16	0/17	0/9
EJ	0/34	1/16 (6%)	1/17 (6%)	0/9
OJ	0/34	0/16	0/17	0/9
Mi-2	2/32 (6%)	0/16	2/17 (12%)	0/9
MDA-5	0/12	1/7 (14%)	1/6 (17%)	0/3
TiF1-y	2/13 (15%)	0/9	0/5	1/4 (25%)
NXP-2	4/14 (28%)	0/7	0/6	0/3
SRP	0/32	0/18	2/15 (13%)	0/9
HMGCR	0/1	0/1	4/9 (44%)	0/1

KU MEDICAL CENTER
The University of Kansas

Slide 8

DJ9 again, put the number
Duaa Jabari, 01/21/2019

gog8 ok
gloria ortiz guerrero, 01/23/2019

SEROLOGIC PROFILE – Myositis-associated Antibodies

MYOSITIS-ASSOCIATED ANTIBODIES				
	DM (n=42)	**NSM (n=22)**	**NM (n=21)**	**PM (n=9)**
Anti-SSA	4/28 (14%)	5/12 (41%)	1/41 (2%)	3/6 (50%)
U1-RNP	2/15 (13%)	2/10 (20%)	1/41 (2.4%)	0/4
U2-RNP	1/35 (2.8%)	1/15 (6%)	1/11 (9%)	0/5
U3-RNP	0/11	0/9	0/6	0/4
Pm-scl	3/23 (13%)	0/15	0/12	0/15
KU	0/31	2/19 (10%)	0/15	0/8

KU MEDICAL CENTER
The University of Kansas

Slide 9

DJ10 put the number
Duaa Jabari, 01/21/2019

gog9 ok
gloria ortiz guerrero, 01/23/2019

CONDITIONS RELATED TO IIM

1) Antisynthetase Syndrome
2) Interstitial Lung Disease
3) Cancer

KU MEDICAL CENTER
The University of Kansas

ANTISYNTHETASE SYNDROME

- Fourteen patients (14.8%) were positive for anti-aminoacyl-tRNA synthetases (anti-ARS) antibodies. However, just eleven of them fulfilled clinical criteria for antisynthetase syndrome
- The pathology of the 3 cases that did not fulfill clinical criteria was NSM, NM, and PM

ANTISYNTHETASE SYNDROME (n=11)		
Antibodies	**Prevalence n (%)**	**Pathologic Findings**
Jo-1	5 (45%)	NSM (n=3) DM (n=2)
PL-7*	4 (36%)	NSM (n=3) NM (n=1)
EJ	1 (9%)	NM (n=1)
PL-12*	1 (9%)	DM (n=1)

*These antibodies found only in antisynthetase syndrome in our cohort

KU MEDICAL CENTER
The University of Kansas

Slide 11

DJ11 Was any antobody specific for antisenthetase?
Duaa Jabari, 01/21/2019

gog4 ok
gloria ortiz guerrero, 01/21/2019

gog14 I included the symbol * in the specific antibodies for ASS
gloria ortiz guerrero, 01/24/2019

INTERSTITIAL LUNG DISEASE (ILD)

- Sixteen out of ninety-four patients (17%) ha[illegible]D
- Detected antibodies were non-specific for IL[illegible]

IIM SUBTYPE	ILD	MSAs/MAAs
DM (n=42)	5 (12%)	Jo-1 (n=1) SSA/Jo-1 (n=2) No AB (n=2)
NSM (n=22)	7 (32%)	SSA/Jo-1 (n=2) SSA/U1RNP (n=1) SSA/PL-7 (n=1) Jo-1/EJ (n=1) No AB (n=2)
NM (n=21)	2 (10%)	Mi-2 (n=1) No AB (n=1)
PM (n=9)	2 (22%)	SSA (n=1) SSA/TIF1-γ (n=1)

KU MEDICAL CENTER
The University of Kansas

Slide 12

DJ12 Was any antibody specific for ILD?
Duaa Jabari, 01/21/2019

gog10 ok
gloria ortiz guerrero, 01/23/2019

gog13 There were not specific antibodies
gloria ortiz guerrero, 01/24/2019

DJ21 ok
Duaa Jabari, 01/27/2019

CANCER

- Fourteen out of ninety-four patients (15%) had cancer within the 3 years after the IIM diagnosis

IIM SUBTYPE	Cancer Type	Antibodies
DM (n=7, 17%)	Breast (n=3) Colon (n=1) Non-Hodgkin L. (n=1) Melanoma (n=1) Prostate (n=1)	TIF1-γ (n=1) ----- ----- ----- -----
NSM (n=3, 14%)	Breast (n=2) Lymphoma (n=1)	MDA-5/KU (n=1) KU (n=1)
NM (n=3, 14%)	Melanoma (n=2) Bladder (n=1)	Mi-2 (n=1) MDA-5/HMGCR (n=1)
PM (n=1, 11%)	L. granulomatosis (n=1)	-----

KU MEDICAL CENTER
The University of Kansas

DISCUSSION

- In our cohort, DM was the most prevalent IIM subtype
  - Just one metanalysis[1], which gathered all the epidemiologic information of IIM up to 2015, was found:
    - There is not precise epidemiologic information due to the lack of uniformity in diagnosis and classification criteria
    - The incidence of DM in the northern hemisphere was higher over the other subtypes suggesting a latitudinal gradient

KU MEDICAL CENTER
The University of Kansas

Slide 14

gog11 It was difficult to find something precise about the epidemiology of IIM. The literature is very broad and inconsistent. I just found a metanalaysis about the IIM epidemiology....
gloria ortiz guerrero, 01/23/2019

DISCUSSION

- Overall, only four antibodies were specific to certain IIM subtypes in our cohort[2]:
- Anti-HMGCR and anti-SRP in NM
- Anti-PL-12 and anti-NXP2 in DM

- Consistent with the literature, Jo-1 was the most common antibody in antisynthetase syndrome (45%), followed by PL-7 (36%) and PL-12 (9%)[3]

- In our cohort, Jo-1 antibody was non-specific for antisynthetase syndrome unlike Yoshida and Targoff's studies[4,5] which found anti-Jo-1 specifically associated with it. PL-7 and PL-12 antibodies were the only ones specific in this syndrome in our study

DJ22

KU MEDICAL CENTER
The University of Kansas

Slide 15

DJ22 Please do literature search to find out how specific they were in other studies

Duaa Jabari, 01/27/2019

DISCUSSION

- Patients with KU antibody (NSM=2) and MDA5 (NM=1/NSM=1) had cancer in our cohort:
  - Different authors have found a correlation between KU antibody and breast cancer[6,7]
  - However, Liu and colleagues[8] found a high risk of malignancy in DM patients who tested negative for MDA-5; similar to Sato and colleagues[9], who found a low risk of cancer in MDA-5 patients

- Irritative myopathy on EMG was highly sensitive for IIM (96.8%), consistent with Bligham's study which also showed a high sensitivity (87%) for irritative myopathy in IIM patients[10]

DJ23

KU MEDICAL CENTER
The University of Kansas

Slide 16

DJ23 Should you delete the "4]."?
Duaa Jabari, 01/27/2019

CONCLUSIONS

DJ24

- Few MSAs were specific to one type of IIM in our cohort
- Anti-KU and anti-MDA5 were associated with cancer in our study

KU MEDICAL CENTER
The University of Kansas

Slide 17

DJ24 I recommend you search the literature to find out how specific these 4 antibodies were in other studies. I think the HMGCR might be specific but not the others!

Duaa Jabari, 01/27/2019

THANKS…

???

KU MEDICAL CENTER
The University of Kansas

REFERENCES

1) Meyer A, Meyer N, Schaeffer M, et al. Incidence and Prevalence of inflammatory myopathies: a systematic review. Rheumatology (Oxford). 2015; 54(1):50-63

2) Satoh, M., Tanaka, S., Ceribelli, A. et al. A Comprehensive Overview on Myositis-Specific Antibodies: New and Old Biomarkers in Idiopathic Inflammatory Myopathy. Clinic Rev Allerg Immunol. 2017; 52: 1

3) Chatterjee S, Prayson R, Farver C. Antisynthetase syndrome: not just an inflammatory myopathy.. Cleve Clin J Med. 2013; 80 (10): 655-66

4) Yoshida S, Akizuki M, Mimori T, Yamagata H, Inada S, Homma M. The precipitating antibody to an acidic nuclear protein antigen, the Jo-1, in connective tissue diseases. Arthritis Rheum. 1983; 26:604–611

5) Targoff IN. Update on myositis-specific and myositis-associated autoantibodies. Curr Opin Rheumatol. 2000; 12:475–481

6) Hoa S, Hudson M, Troyanov Y, et al. Single-specificity anti-Ku antibodies in an international cohort of 2140 systemic sclerosis subjects: clinical associations. Medicine (Baltimore). 2016; 95(35): e4713

7) Madrid FF, Maroun MC. Serologic Laboratory Findings in Malignancy. Rheum Dis Clin North Am. 2011 Nov;37(4):507-25

8) Liu Y, Xu L, Wu H, et al. Characteristics and predictors of malignancy in dermatomyositis: Analysis of 239 patients from northern China. Oncol Lett. 2018; 16(5): 5960–5968

9) Sato S, Kurabayashi T, Sasaki S, Koyama Y, Nogi S, Chinen N, Yamada C, Suzuki Y. Risk of Malignancy in Dermatomyositis with Anti-CADM-140/ Melanoma Differentiation- Associated Gene 5 Autoantibody [abstract]. *Arthritis Rheumatol.* 2015; 67 (suppl 10)

10) Blijham PJ, Hengstman GJD, Hama-Amin AD. Needle Electromyographic Findings in 98 Patients with Myositis. Eur Neurol. 2006;55(4):183-8

KU MEDICAL CENTER
The University of Kansas