Differentiating Polymyositis from IBM – Clues for the Clinician

Stefen Brady

Disclosures

DAVID

IBM an IIM but not really

- Classed as an idiopathic inflammatory myopathy (IIM)
- Clinically rather more differences than similarities between IBM and other IIM
  - Early involvement of finger flexors and quadriceps muscles
  - Weakness is often asymmetric
  - Clinical course is one of slow progression
  - Lack of response to immunosuppression

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  - Early involvement of finger flexors and quadriceps muscles
  - Weakness is often asymmetric
  - Clinical course is one of slow progression
  - Lack of response to immunosuppression
- Delay to diagnosis 60 months and frequent misdiagnosis

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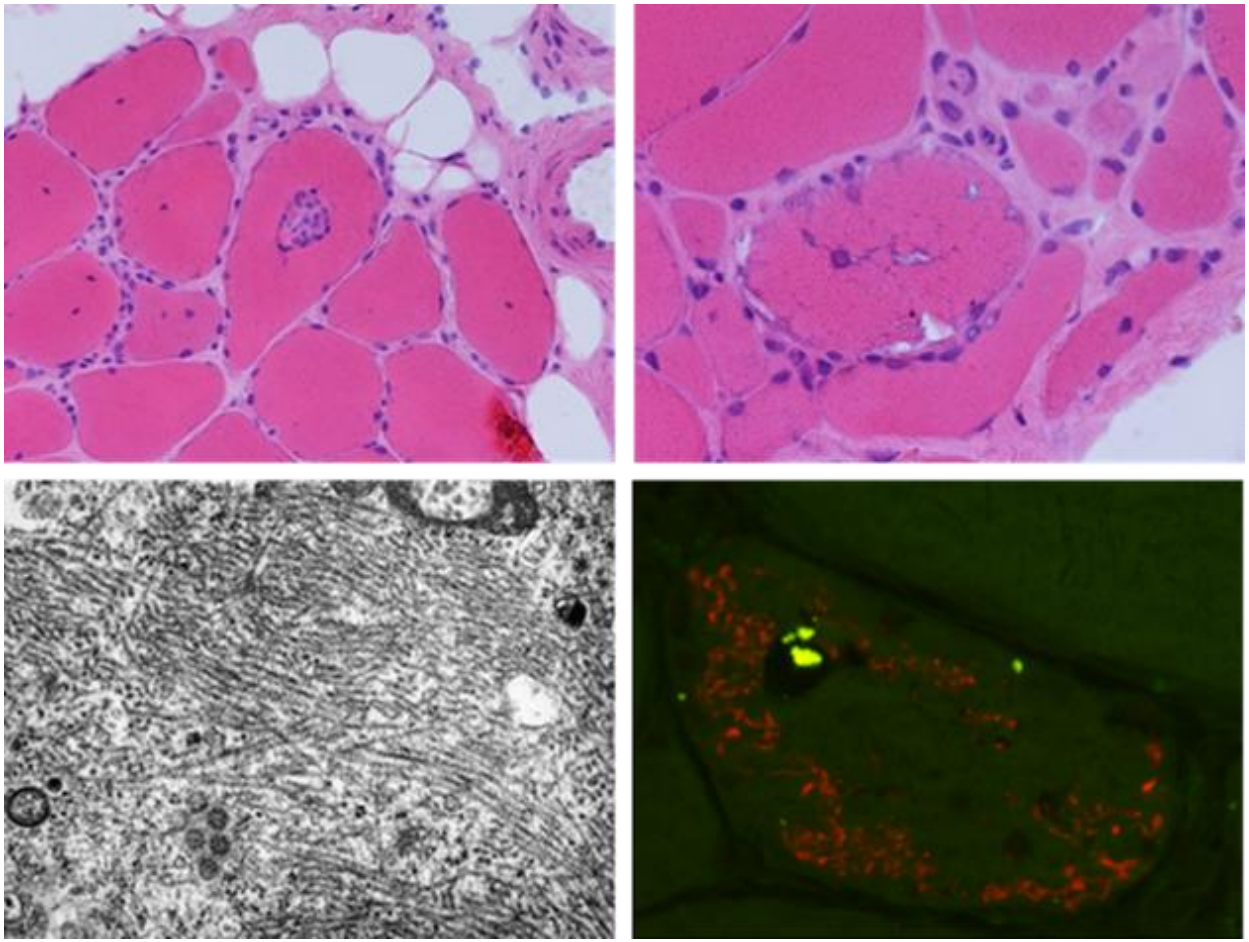
Development of diagnostic criteria

- 1967 Tubulofilamentous inclusions on muscle biopsy in a man with chronic polymyositis
- 1971 Eosinophilic inclusions and tubulofilaments in a patient and labelled the condition IBM
- 1987 Calabrese *et al.*
- 1989 Lotz *et al*.
- 1995 Griggs *et al.* ‘Griggs criteria’

Griggs Criteria



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Problems with the diagnostic criteria?

- Widespread acceptance of the rather strict Griggs (pathological) criteria

- Two main problems
  - Access to EM and amyloid staining
  - Sensitivity - patients with clinical IBM but pathological PM

- Reports of patients with clinically typical IBM lacking the pathological features started to appear in the literature
  Amato 1996, Blume 1997, van der Meulen 1998, Badrising 2000

Clinical IBM but pathological PM

- Publications examining cases of clinical typical IBM lacking examination findings

Temiz *et al.* 2008	PM.Mito
Chahin and Engel 2008	PM/IBM

- Clinical features are specific enough to diagnose IBM

2008 IBM Workshop, London

Hilton-Jones *et al.* 2010

2009 IBM Workshop, Paris

Benveniste and Hilton-Jones 2010

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Clinical features	Classification	Histopathological features
Duration of weakness >12 months	Clinicopathologically defined IBM	All of the following:
Creatine kinase ≤15x ULN		Endomysial inflammatory infiltrate
Age at onset >45 years		Up-regulation of MHC Class I
Finger flexion weakness > shoulder abduction weakness		Rimmed vacuoles
AND/OR		Protein accumulation* or 15-18 nm filaments
Knee extension weakness ≥ hip flexor weakness		
Duration of weakness >12 months	Clinically defined IBM	One or more, but not all, of:
Creatine kinase ≤15x ULN		Endomysial inflammatory infiltrate
Age at onset >45 years		Up-regulation of MHC Class I
Finger flexion weakness > shoulder abduction weakness		Rimmed vacuoles
AND		Protein accumulation* or 15-18 nm filaments
Knee extension weakness ≥ hip flexor weakness		
Duration of weakness >12 months	Probable IBM	One or more, but not all, of:
Creatine kinase ≤15x ULN		Endomysial inflammatory infiltrate
Age at onset >45 years		Up-regulation of MHC Class I
Finger flexion weakness > shoulder abduction weakness		Rimmed vacuoles
OR		Protein accumulation* or 15-18 nm filaments
Knee extension weakness ≥ hip flexor weakness		

Oxford IBM study

Characteristic	IBM	IBM+RV	IBM/PM	p-value
No. of patients	67	29	38	-
Gender, M:F	46:21	20:9	26:12	0.96
Age at onset (IQR), years	62 (55-70)	63 (57-72)	61 (52-68)	0.19
Age at biopsy (IQR), years	67 (61-75)	73 (64-76)	66 (59-74)	0.04
Delay to diagnosis (IQR), months	62 (34-90)	58 (33-106)	63 (35-89)	0.44
Alternative diagnosis	26 (39)	8 (28)	18 (47)	0.10

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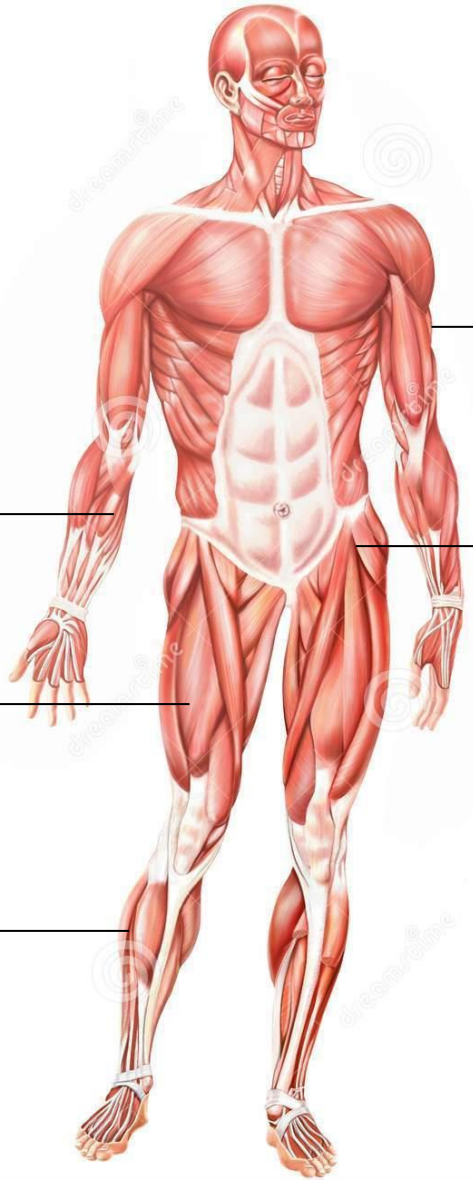
Presentation

Characteristic	IBM	IBM+RV	IBM/PM	p-value
No. of patients	67	29	38	-
Onset, n (%)				
Lower limbs	55 (82)	24 (83)	31 (82)	0.90
Upper limbs	5 (8)	1 (3)	4 (12)	0.38
Bulbar weakness	1 (1)	1 (3)	0 (0)	0.43
Lower and upper limbs	4 (6)	1 (3)	3 (8)	0.63
Bulbar and lower limbs	2 (3)	2 (7)	0 (0)	0.18

Distribution of weakness



Elbow flexion 63%

Finger flexion 79%

Hip flexion 63%

Knee extension 87%

Ankle dorsiflexion 66%

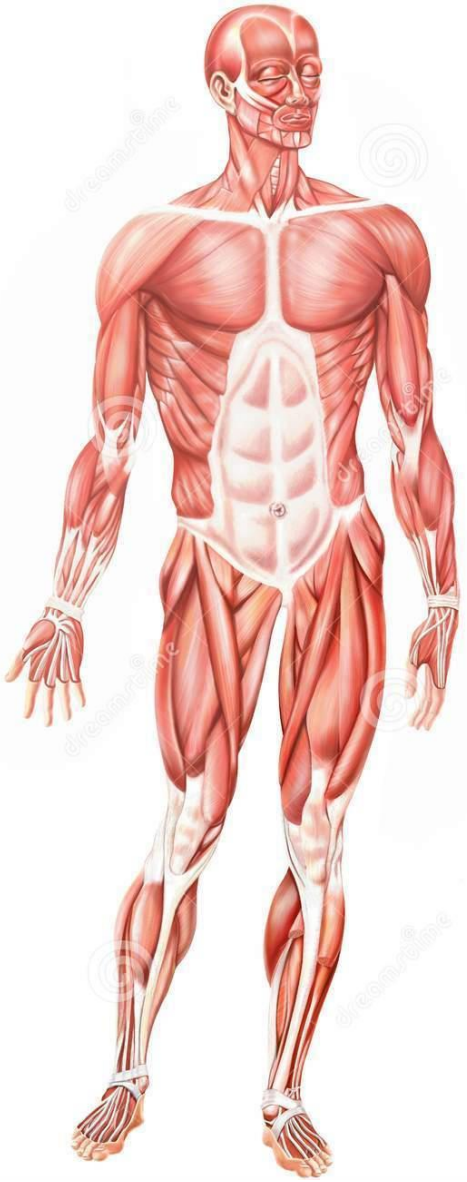
Distribution of weakness

96%

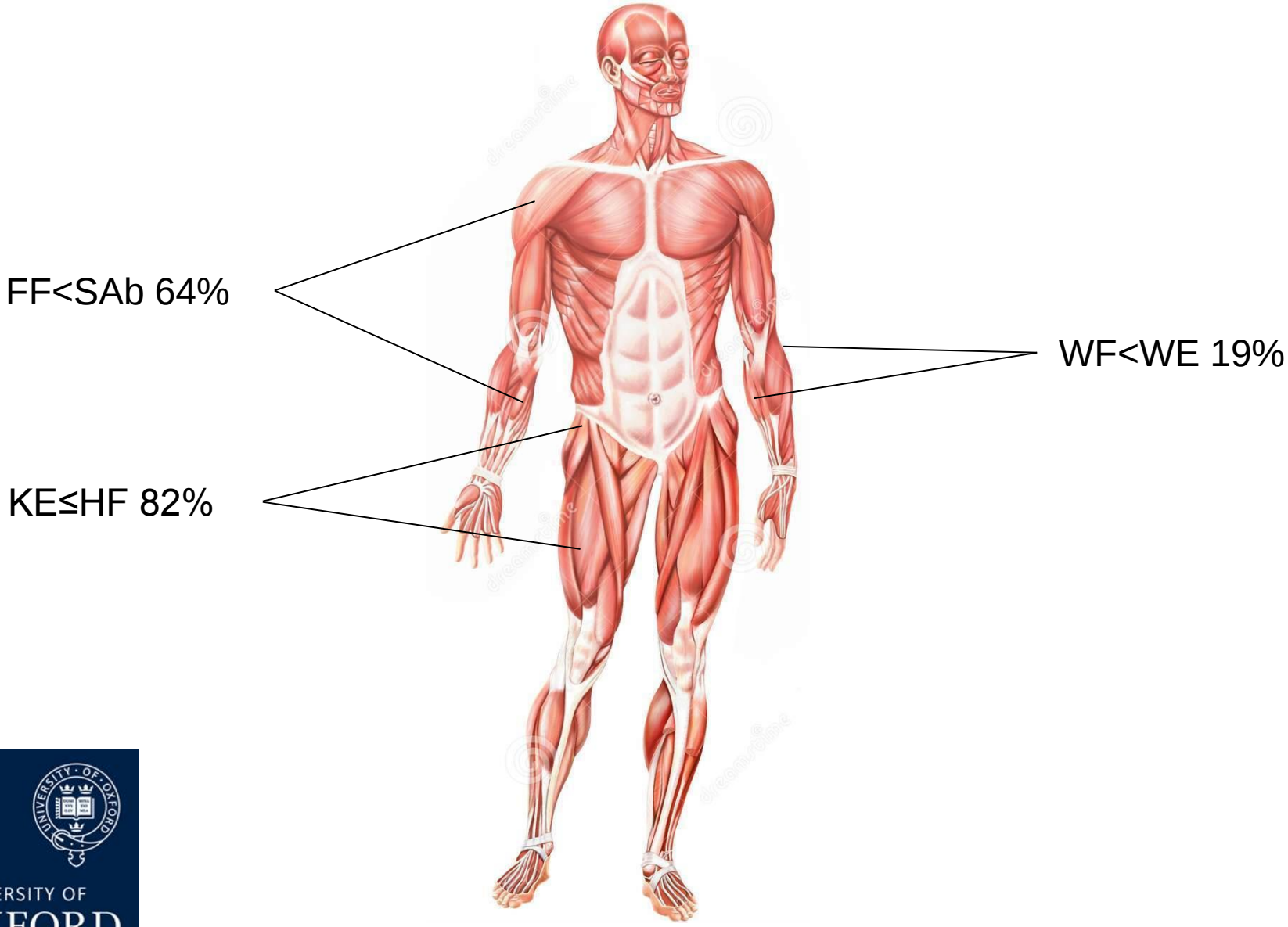
Finger flexion

OR

Knee extension



Patterns of weakness

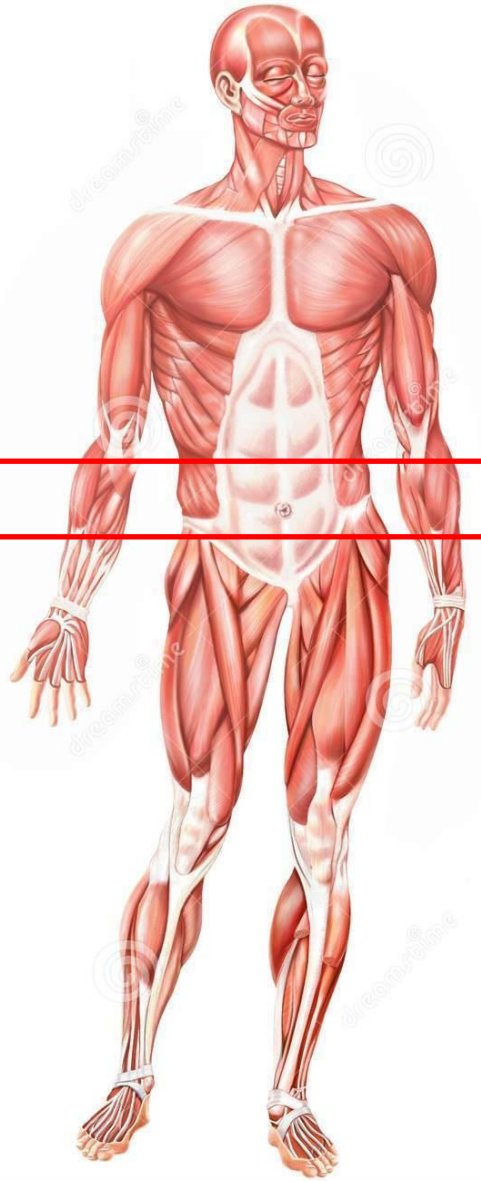


Patterns of weakness

FF<SAb

>50%

KE≤HF



>80%

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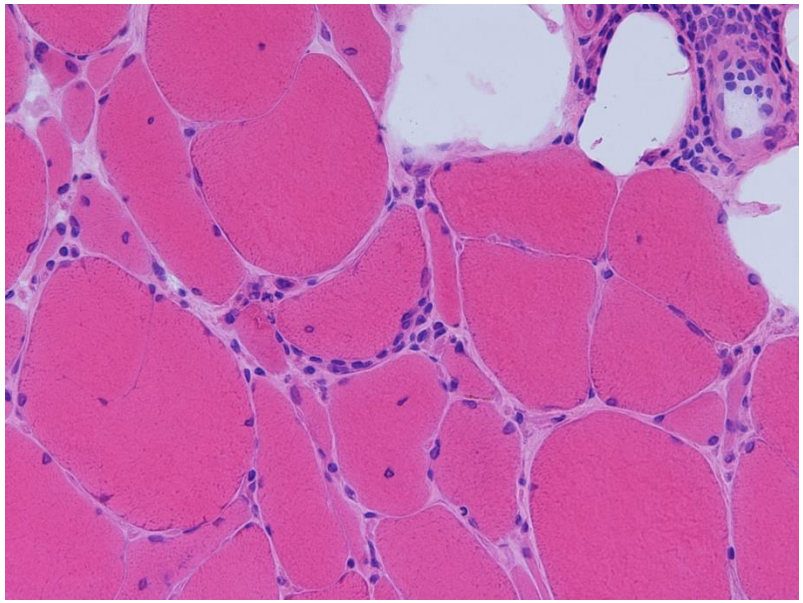
Investigations

Investigations	IBM	IBM+RV	IBM/PM	*p*-value
CK, IU/L	587 (286-1036)	521 (201-1025)	608 (328-1048)	0.40
Muscle biopsy, n (%)				
i) Endomysial inflammation	62 (93)	29 (100)	33 (87)	0.06
ii) Partial invasion	56 (84)	26 (90)	30 (77)	0.33
iii) Rimmed vacuoles	29 (43)	29 (100)	0 (0)	-
All of i-iii	26 (39)	26 (90)	0 (0)	-
Mitochondrial	41 (73)	15 (65)	26 (79)	0.36
MHC Class I	46 (92)	17 (89)	29 (94)	0.63

Re-biopsy or not to re-biopsy?

- 10 cases had further sections cut and 9 had a further muscle biopsy



Re-biopsy or not to re-biopsy?

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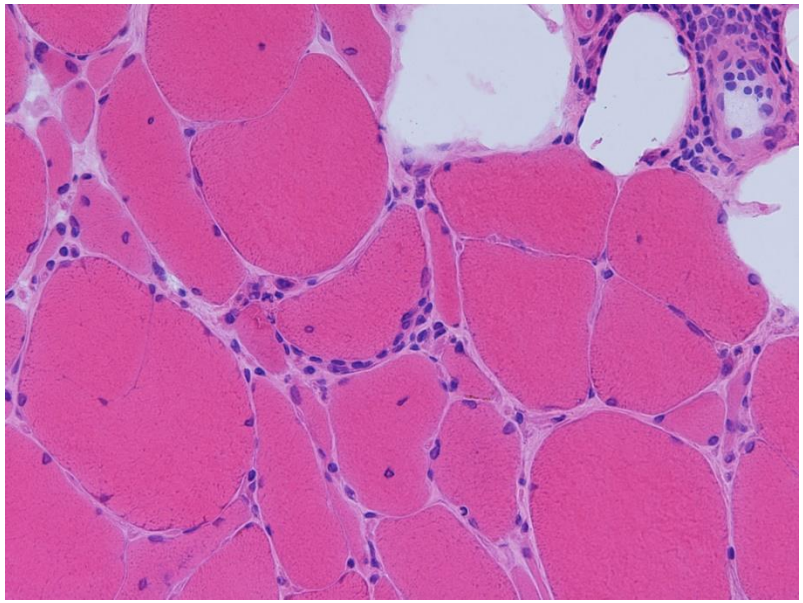
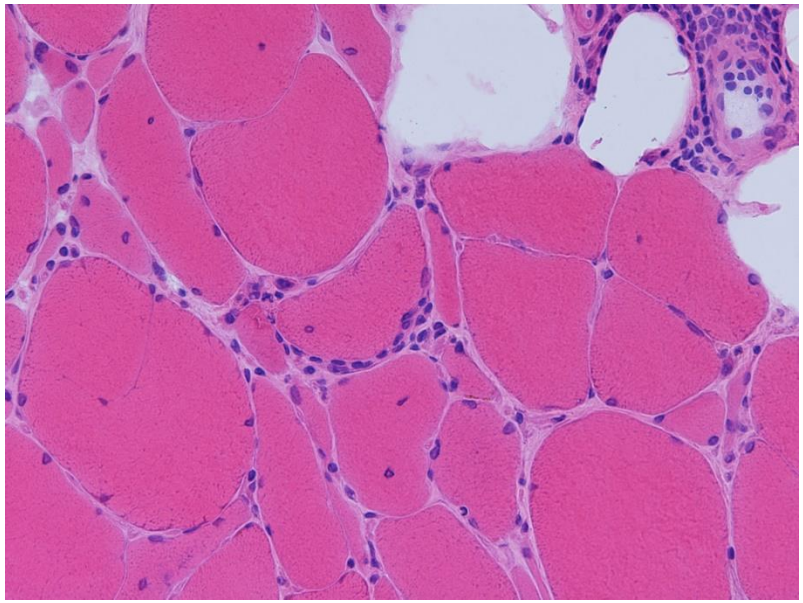
- 1 out of 10 revealed diagnostic changes



Re-biopsy or not to re-biopsy?

- 10 cases had further sections cut and 9 had a further muscle biopsy
- 1 out of 10 revealed diagnostic changes
- 4 out of the 9 were diagnostic after repeat biopsy



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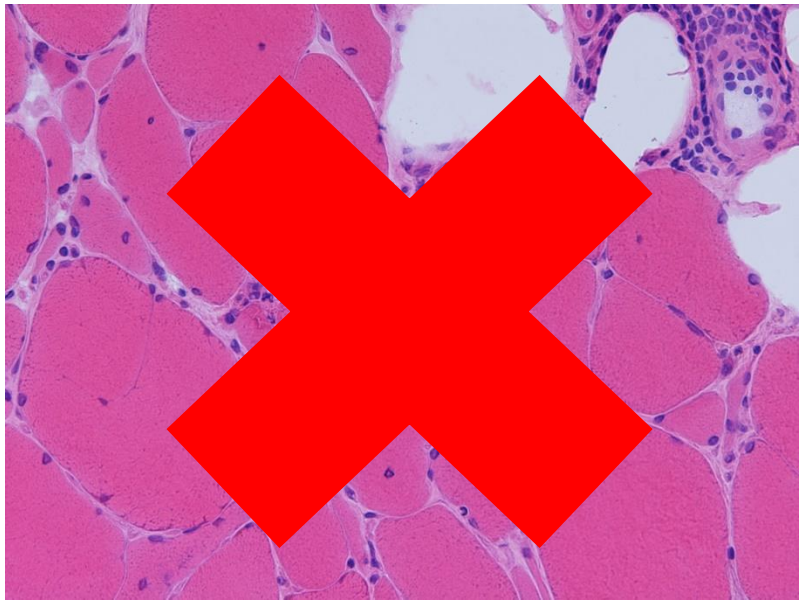
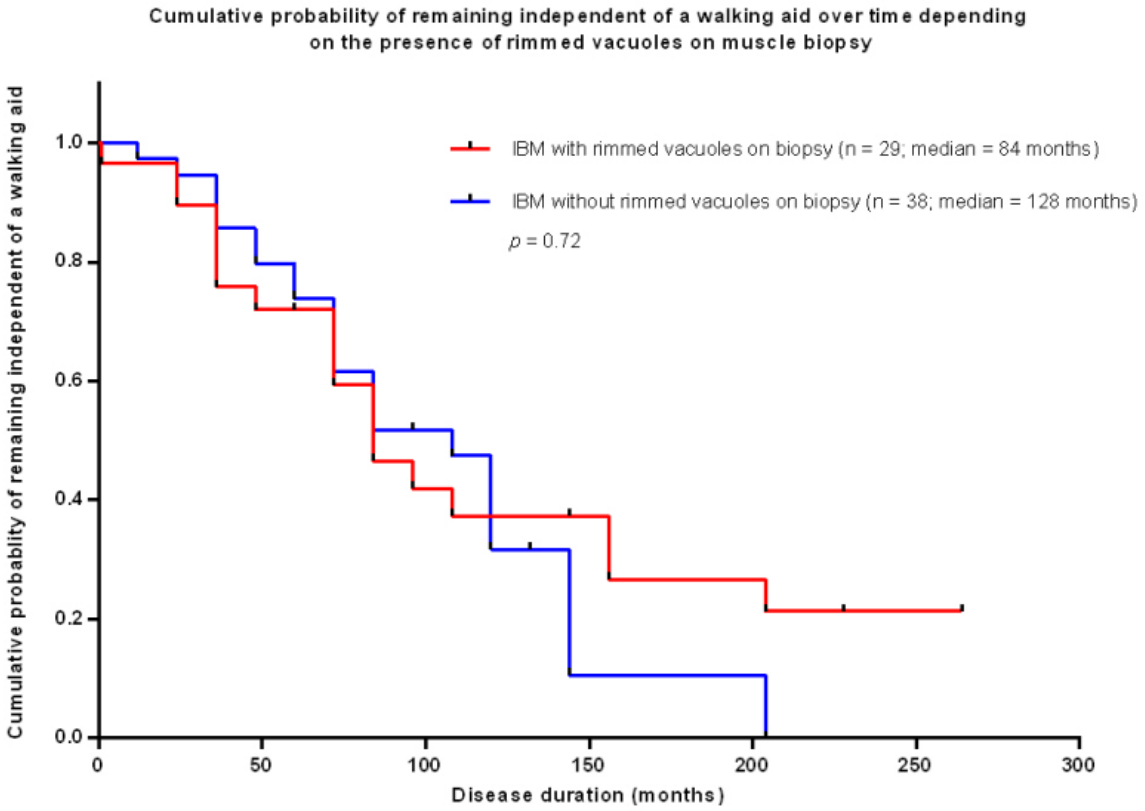


Disease progression



Research criteria at presentation

Criteria	*N* (%)
ENMC 2011	59 (88)
Clinicopathologically defined	11 (16)
Clinically defined	26 (39)
Probable	22 (33)
Griggs 1995	18 (27)
ENMC 1997	51 (76)

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IBM compared with SRIM (and PAM)

Characteristic	IBM	SRIM	*p*-value
Age at onset (IQR), years	62 (55-70)	52 (43-62)	0.007
Delay to diagnosis (IQR), months	62 (34-90)	15 (6-31)	< 0.0001
Onset, *n* (%)			
Lower limbs	55 (82)	3 (20)	< 0.0001
Upper limbs	5 (8)	1 (7)	1.00
Bulbar weakness	1 (1)	0 (0)	1.00
Lower and upper limbs	4 (6)	10 (67)	< 0.0001
Pain	0 (0)	3 (20)	0.005
Bulbar and lower limbs	2 (3)	1 (7)	0.46
CK, IU/L	587	2000	< 0.0001

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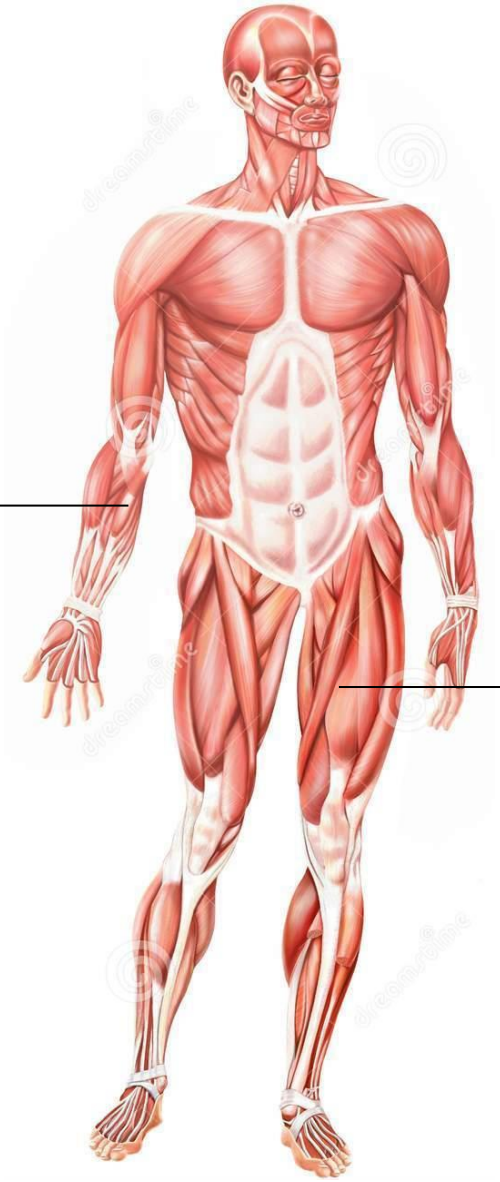
IBM compared with SRIM

Finger Flexion
Sensitivity 79%
Specificity 93%



Knee Extension
Sensitivity 87%
Specificity 87%

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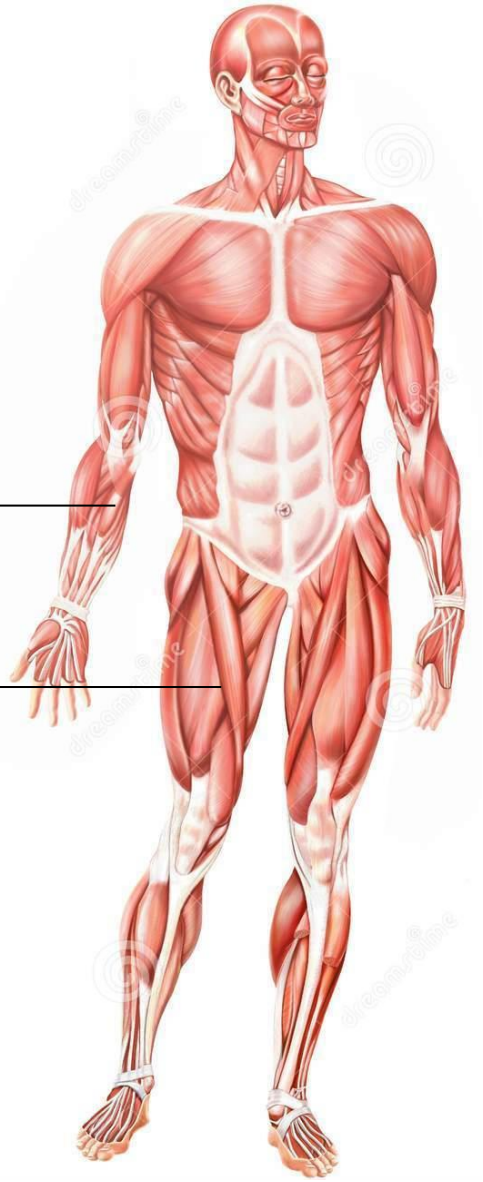
IBM compared with SRIM



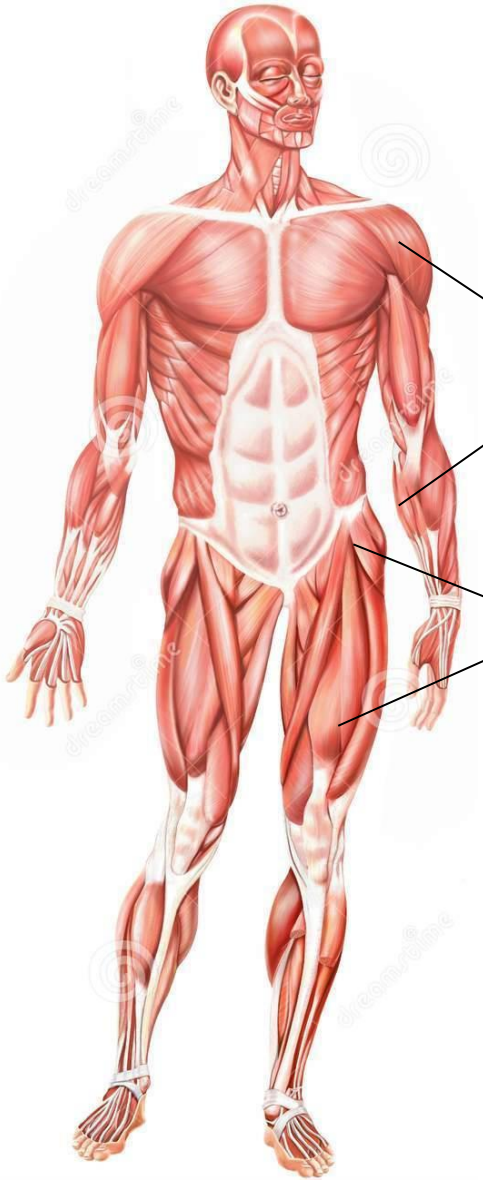
Finger Flexion

&

Knee Extension

Sensitivity 66%
Specificity 100%

IBM compared with SRIM



FF<SAB
Sensitivity 64%
Specificity 100%

KE≤HF
Sensitivity 82%
Specificity 87%

KE<HF
Sensitivity 48%
Specificity 100%

IBM is a clinical diagnosis supported by muscle biopsy findings

- IBM is associated with a characteristic pattern of weakness
- Patients with IBM who do not fulfil the pathological criteria are at least as common as those that do
- No difference between patients with clinically or pathologically diagnosed IBM
- The absence of both partial invasion and mitochondrial changes to be strong evidence against a diagnosis of IBM and a further muscle biopsy is unlikely to be diagnostic

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Muscle biopsy

- Muscle biopsy reveals both degenerative and inflammatory changes

- Over the past 2 decades many proteins (≈80) have been reported in IBM

  Neurodegenerative: β amyloid and hyperphosphorylated tau
  Newer neurodegenerative markers: p62 and TDP-43
  Myofibrillar proteins: myotilin and desmin

- A number of pathological changes (protein aggregates) have been suggested for diagnostic use

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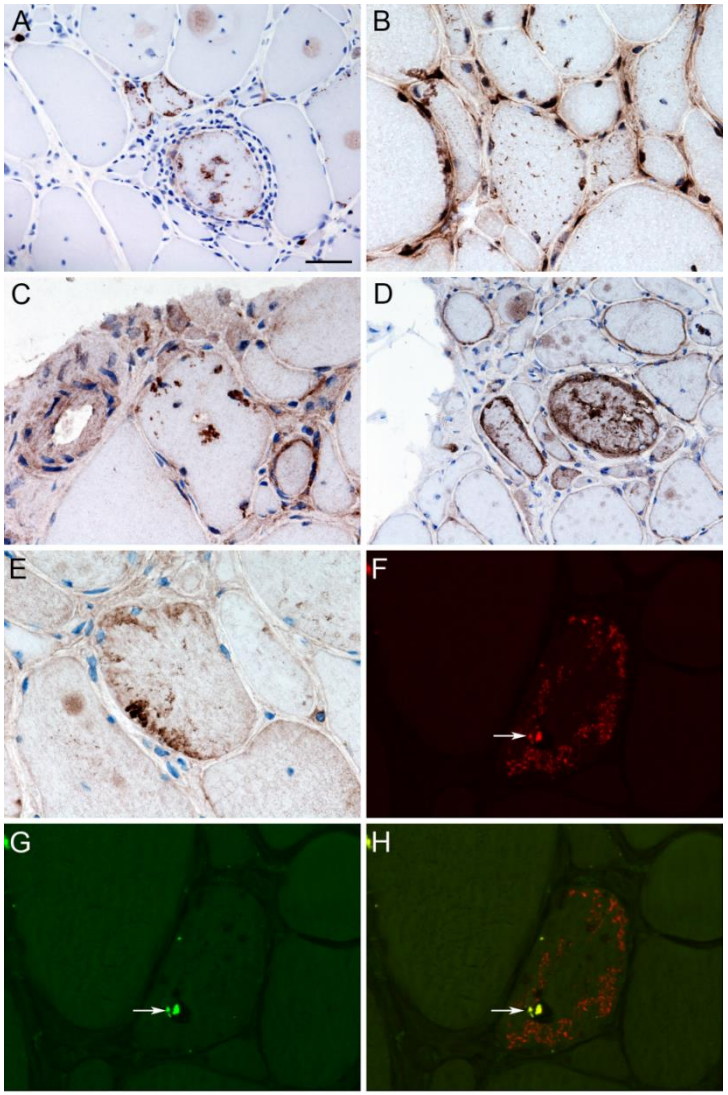
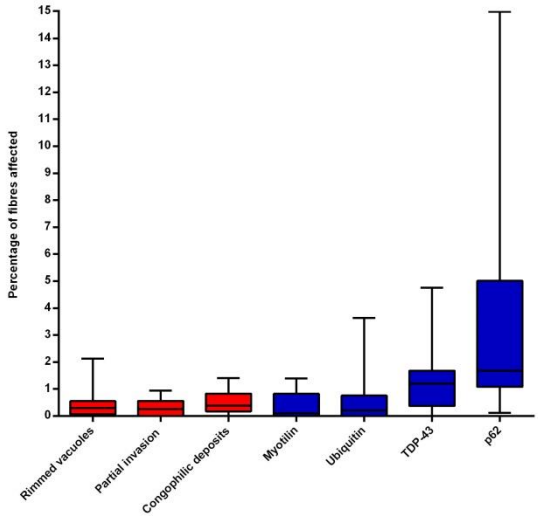
Muscle biopsy study

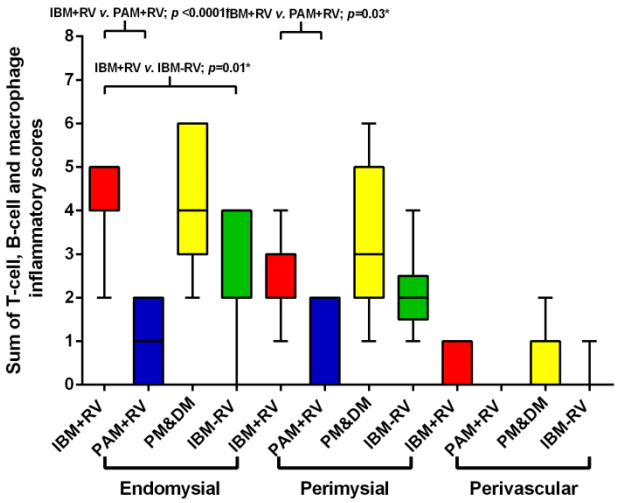
A. p62
B. TDP-43
C. Ubiquitin
D. α B-crystalline
E. Myotilin
F-H Amyloid

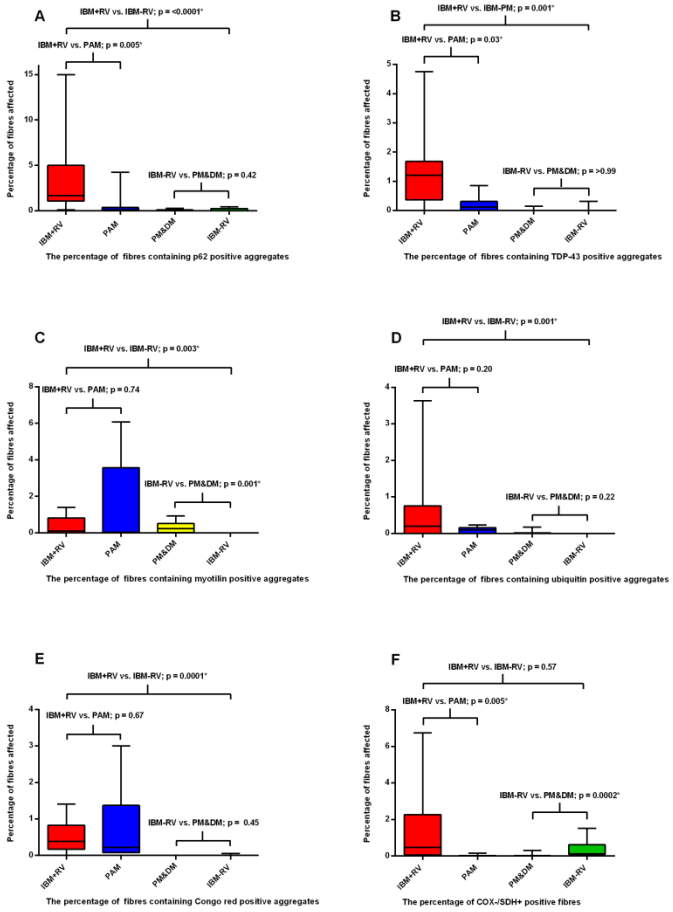




Muscle biopsy study part II

- Clinically relevant by comparing biopsies with rimmed vacuoles and inflammatory biopsies





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Muscle biopsy study part II

- No single pathological feature could differentiate IBM and disease controls
- Significant differences between IBM+RV and IBM/PM
- Most useful pathological findings:

IBM/PM and SRIM = mitochondrial abnormalities and p62 aggregates

Muscle biopsy study part II

- No single pathological feature could differentiate IBM and disease controls
- Significant differences between IBM+RV and IBM/PM
- Most useful pathological findings:

IBM+RV and PAM = inflammatory changes* (CD3,4,8 and CD68 and MHC class I)

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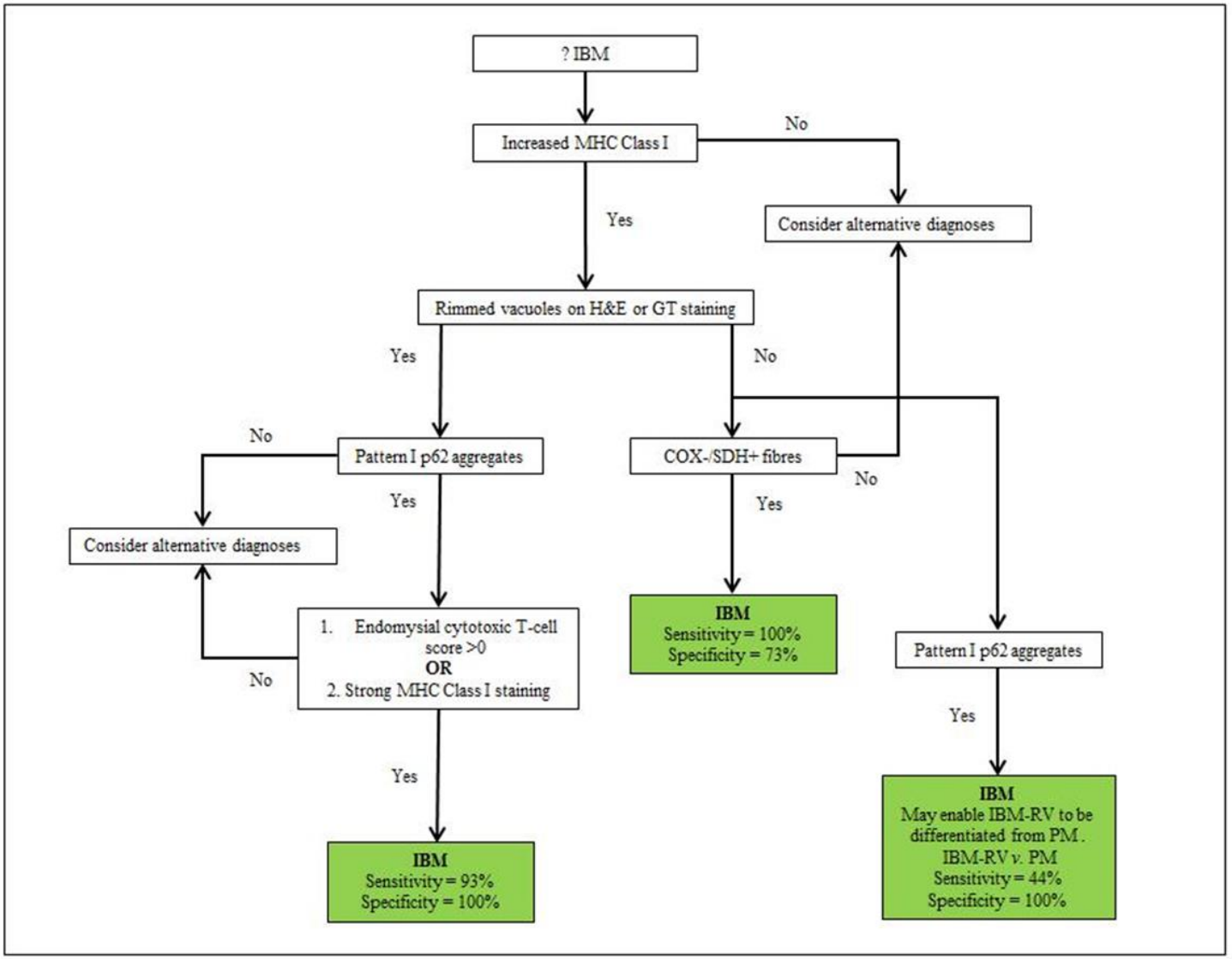
*Using JDM scoring tool

Muscle biopsy pathway



Cytosolic 5-nucleotidase antibodies (cN-1A)

- 5 studies examining its diagnostic utility

  Larman *et al.* 2013, Pluk *et al.* 2013, Greenberg, Herbert *et al.* 2015
  Lloyd *et al.* 2015

- Controls included: PM/DM, other autoimmune disorders, non-autoimmune neuromuscular disorders and healthy volunteers

- IBM 34-61%; PM/DM 4-15%, other AI disorders 14-36%, healthy volunteers 5%

Conclusions

- IBM has a **DIAGNOSTIC** clinical picture
- The diagnosis is **CLINICAL** with a supportive muscle biopsy
- The ENMC 2011 **(RESEARCH)** criteria have good sensitivity and specificity
- No pathological feature is diagnostic but include staining for **p62, MHC class I** and **COX/SDH**

Thank you
&
Acknowledgements

Dr David Hilton-Jones
Dr Waney Squier

Prof. Janice Holton
Prof. Caroline Sewry
Prof. Mike Hanna

Neuropathology Laboratory staff at the John Radcliffe Hospital, Oxford, UCL Institute of Neurology, London and Queen Square Brain Bank, London

Myositis Support Group and Muscular Dystrophy Campaign

Patterns of p62 staining