Myositis and cancer

Idiopathic inflammatory myopathies

- Primary idiopathic polymyositis
- Primary idiopathic dermatomyositis
- Juvenile poly/dermatomyositis
- Myositis associated with another CTD
- Myositis associated with malignancy – 8.5%
  - various statistics: 6-60% in DM and 0-28% in PM
  - Prague cohort: 16.5% DM and 6.3% PM. Overall 12%.

- Inclusion body myositis
  - malignancy very rare

Bohan A, Peter JB et al. N Engl J Med 1975; 292: 344–7, Medicine (Baltimore) 1977; 56: 255–86.

Questions about associations of malignacy and myositis

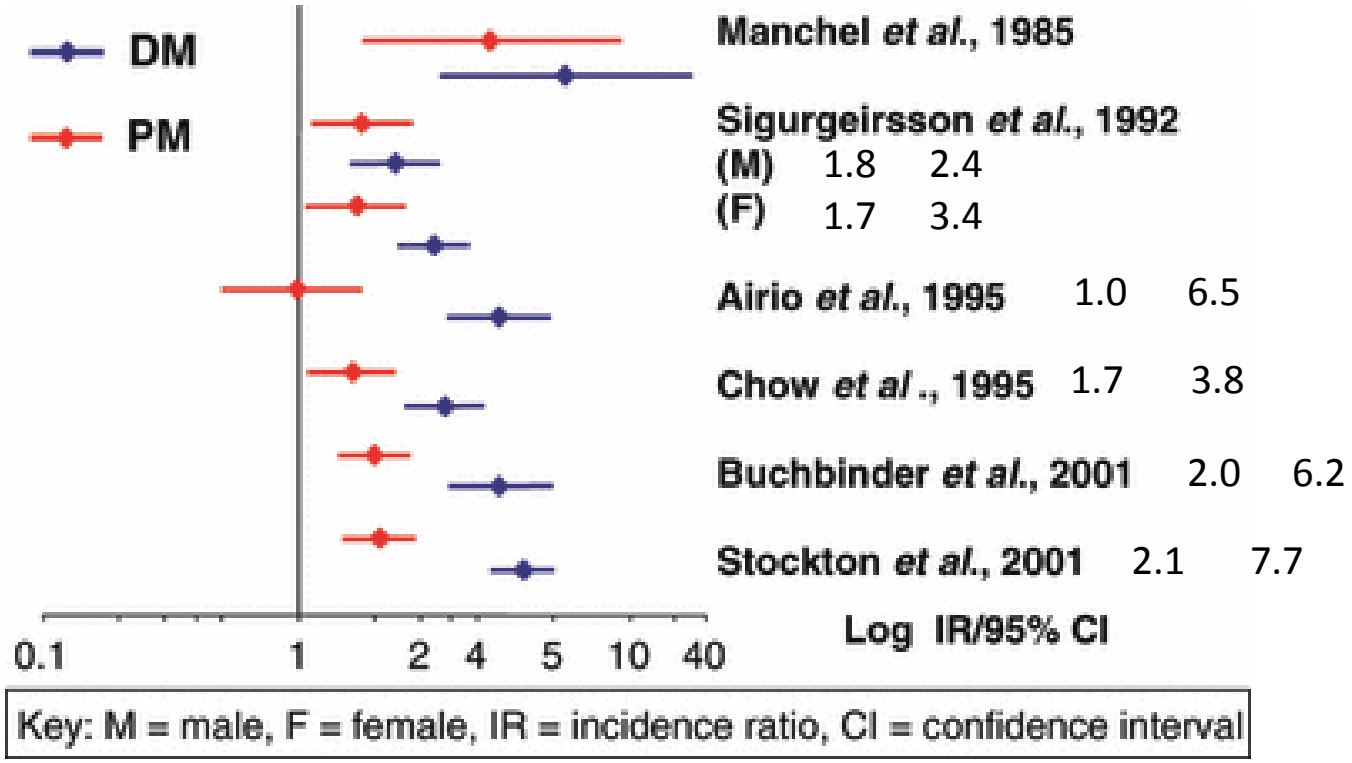
- Is there really an increased risk of cancer in patients with PM/DM?
- If such an association exists, what types of malignancies are increased and when?
- Are there clinical or laboratory findings that identify patients with myositis who are at risk for malignancy?
- Who should be screened and what is a reasonable screening evaluation for malignancy?
- What is the pathogenesis of malignancy-associated myositis?

Cancer in patients with myositis

- DM first decribed in 1887- 1891 (Wagner, Unverricht)
- First association with cancer 1916 (PM+ carcinoma of the stomach) (Sterz)
- Good description of 3 cases 1935 (Rudolf Bezecný)

Source: Oddis C, Medsger T in Rheumatology (Elsevier), Williams RC Ann Intern Med.

Risk of malignancy in patients with DM and PM based on data from epidemiological studies



Madan V et al. Clin Exp Dermatol 2009; 34: 451–455. Modified from Buchbinder R, et al. Curr Rheumatol Rep 2002; 4: 415–26.

SIR for cancer after diagnosis of DM or PM

Cancer type (ICD-7 code)	Dermatomyositis (n=618)		Polymyositis (n=914)	
	Number	SIR (95% CI)	Number	SIR (95% CI)
All (140–205)	115	3·0 (2·5–3·6)	95	1·3 (1·0–1·6)
Oesophagus (150)	1	2·9 (0·4–20·8)	1	1·3 (0·2–9·4)
Stomach (151)	7	3·5 (1·7–7·3)	1	0·3 (0·04–1·9)
Colorectal (153, 154)	12	2·5 (1·4–4·4)	10	1·1 (0·6–2·0)
Pancreas (157)	5	3·8 (1·6–9·0)	1	0·4 (0·1–2·7)
Lung, trachea, and bronchus (162)	19	5·9 (3·7–9·2)	20	2·8 (1·8–4·4)
Breast (170)	12	2·2 (1·2–3·9)	12	1·4 (0·8–2·5)
Cervix (171)	2	2·7 (0·7–10·8)	0	0 (0–2·9)
Ovary (175)	13	10·5 (6·1–18·1)	2	1·1 (0·3–4·2)
Prostate (177)	5	1·8 (0·8–4·4)	4	0·6 (0·2–1·6)
Kidney (180)	2	1·7 (0·4–6·7)	4	1·5 (0·6–3·9)
Bladder (181)	3	1·8 (0·6–5·6)	9	2·4 (1·3–4·7)
Non-Hodgkin lymphoma (200)	3	3·6 (1·2–11·1)	6	3·7 (1·7–8·2)
Hodgkin's lymphoma (201)	1	5·9 (0·8–42·0)	0	0 (0–11·1)
Myeloma (203)	1	1·5 (0·2–10·5)	2	2·1 (0·5–8·5)
Leukaemia (204)	2	2·6 (0·7–10·5)	2	1·4 (0·3–5·4)

Hill CL et al. Lancet 2001; 357: 96–100

Types of malignancies with increased incidence in PM/DM

- Dermatomyositis
  - Ovarian
  - Lung, trachea
  - Pancreas
  - Non-Hodgkin lymphoma
  - Stomach
  - Colon, rectum
  - Breast
- Polymyositis
  - Non-Hodgkin lymphoma
  - Lung, trachea
  - Bladder

SIR of cancer by year after diagnosis of myositis

Type of cancer	0-1 year follow-up		2-5 years follow-up		>5 years follow-up	
	Number	SIR (95% CI)	Number	SIR (95% CI)	Number	SIR (95% CI)
Dermatomyositis						
All	55	13·5 (10·4–17·6)	30	2·5 (1·7–3·5)	30	1·4 (1·0–2·0)
Stomach	6	27·5 (12·4–61·3)	0	0 (0–4·7)	1	1·9 (0·3–13·3)
Colorectal	4	8·6 (3·2–22·8)	2	1·2 (0·3–5·0)	6	2·3 (1·03–5·1)
Pancreas	1	7·1 (1·0–50·4)	2	4·1 (1·03–16·5)	3	4·1 (1·3–12·6)
Lung	10	28·3 (15·2–52·5)	5	4·7 (2·0–11·4)	4	2·2 (0·8–5·9)
Non-Hodgkin lymphoma	3	42·3 (13·6–131·0)	0	0 (0–12·3)	0	0 (0–6·2)
Breast	5	9·9 (4·1–23·8)	4	2·4 (0·9–6·3)	4	1·3 (0·5–3·4)
Ovary	9	72·0 (37·5–138·4)	3	7·3 (2·4–22·6)	1	1·5 (0·2–10·6)
Prostate	3	9·6 (3·1–29·7)	0	0 (0–3·2)	2	1·4 (0·4–5·6)
Polymyositis						
All	19	2·6 (1·6–4·0)	40	1·5 (1·1–2·1)	36	0·9 (0·6–1·3)
Colorectal	0	0 (0–3·3)	6	1·8 (0·8–4·1)	4	0·8 (0·3–2·2)
Pancreas	2	7·5 (1·9–30·1)	0	0 (0–3·2)	0	0 (0–2·2)
Bladder	1	2·7 (0·4–18·8)	5	3·8 (1·6–9·0)	1	0·5 (0·1–3·7)
Lung	2	2·3 (0·6–9·3)	10	3·4 (1·8–6·4)	6	1·4 (0·7–3·2)
Non-Hodgkin lymphoma	2	12·6 (3·2–50·3)	1	1·8 (0·3–12·7)	2	2·2 (0·6–8·8)
Breast	1	1·3 (0·2–8·9)	5	1·7 (0·7–4·0)	6	1·3 (0·6–2·8)

Hill CL et al. Lancet 2001; 357: 96–100

Summary

- Risk is increased, more for DM
- Some malignancies are more frequent although many can occur
- The risk is highest around the diagnosis of myositis
- For some tumors risk is increased even after several years of disease duration.

Factors associated with increased risk of malignancy in idiopathic inflammatory myositis

Risk-enhancing features	References
Older age at myositis diagnosis	Sigurgeirsson *et al.*, Marie *et al.*, Fudman *et al.*
Atypical, extensive and severe cutaneous symptoms	Ponyi *et al.*
Refractory disease	Ponyi *et al.*
Rapidly progressing severe muscle weakness	Ponyi *et al.*
Cutaneous necrosis	Ponyi *et al.*, Basset-Seguin *et al.*, Gallais *et al.*
Cutaneous vasculitis	Feldman *et al.*, Hunger *et al.*
Capillary damage evident on muscle biopsy	Urbano-Márquez A *et al.*
Use of immunosuppressive medications	Kamel *et al.*
Persistently raised erythroctye sedimentation rate	Basset-Seguin *et al.*
Absence of interstitial lung disease	Chen *et al.*

Madan V et al. Clinical and Experimental Dermatology, 2009; 34: 451–455.

Risk of malignancy in inflammatory myositis

Parameter	OR (95%CI)	p Value
Age at diagnosis >45	9.10 (2.03-40.74)	0.004
Male vs. female	4.06 (1.06-15.57)	0.04
Interstitial lung disease	0.04 (0.01-0.21)	<0.001
CPK >160 U/L	4.80 (0.85-27.23)	0.08
DM	4.83 (0.84-27.66)	0.08

Chen Y-J et al. Br J Dermatol 2001;144:825-831.

Serological frequencies in patients with and without CAM

Autoantibody status	Non-CAM	CAM
Myositis-specific antibodies		
Jo-1	57 (21.6)	0
PL-7	1 (0.4)	0
PL-12	1 (0.4)	0
EJ	1 (0.4)	0
OJ	3 (1.1)	0
KS	1 (0.4)	1 (6.2)*
Mi-2	16 (6.1)	2 (12.5)
SRP	7 (2.7)	0
p155/140	11 (4.1)	8 (50.0)
Myositis-associated antibodies		
U1-RNP	32 (12.1)	1 (6.2)*
U3-RNP	4 (1.5)	0
Ku	5 (1.9)	0
PM-Scl	29 (10.9)	0
None of the above auto-antibodies	106 (39.8)	5 (31.2)

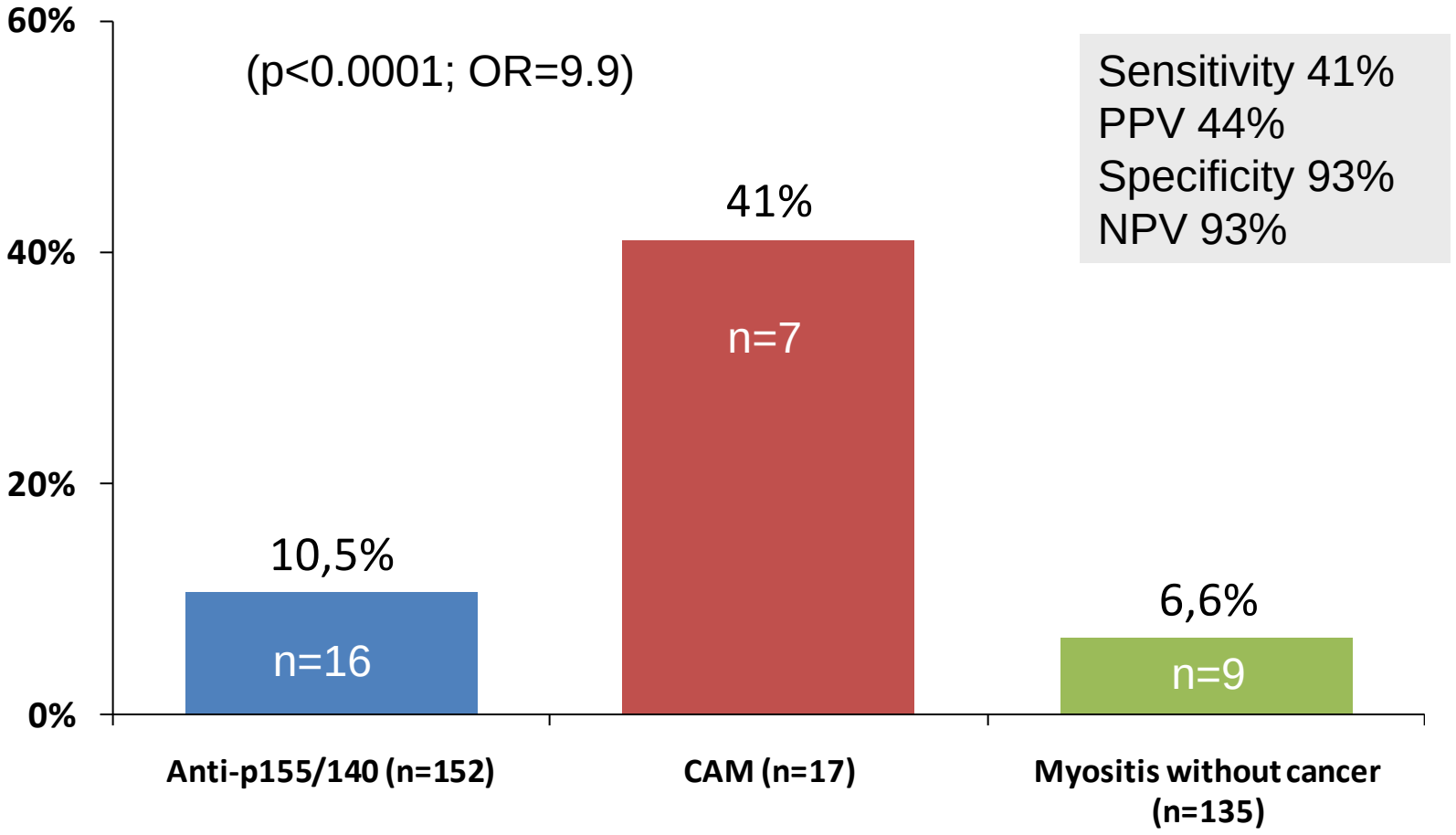
Chinoy H et al. Ann Rheum Dis 2007;66;1345-1349;

Anti-p155/140 antibodies in IIM patients

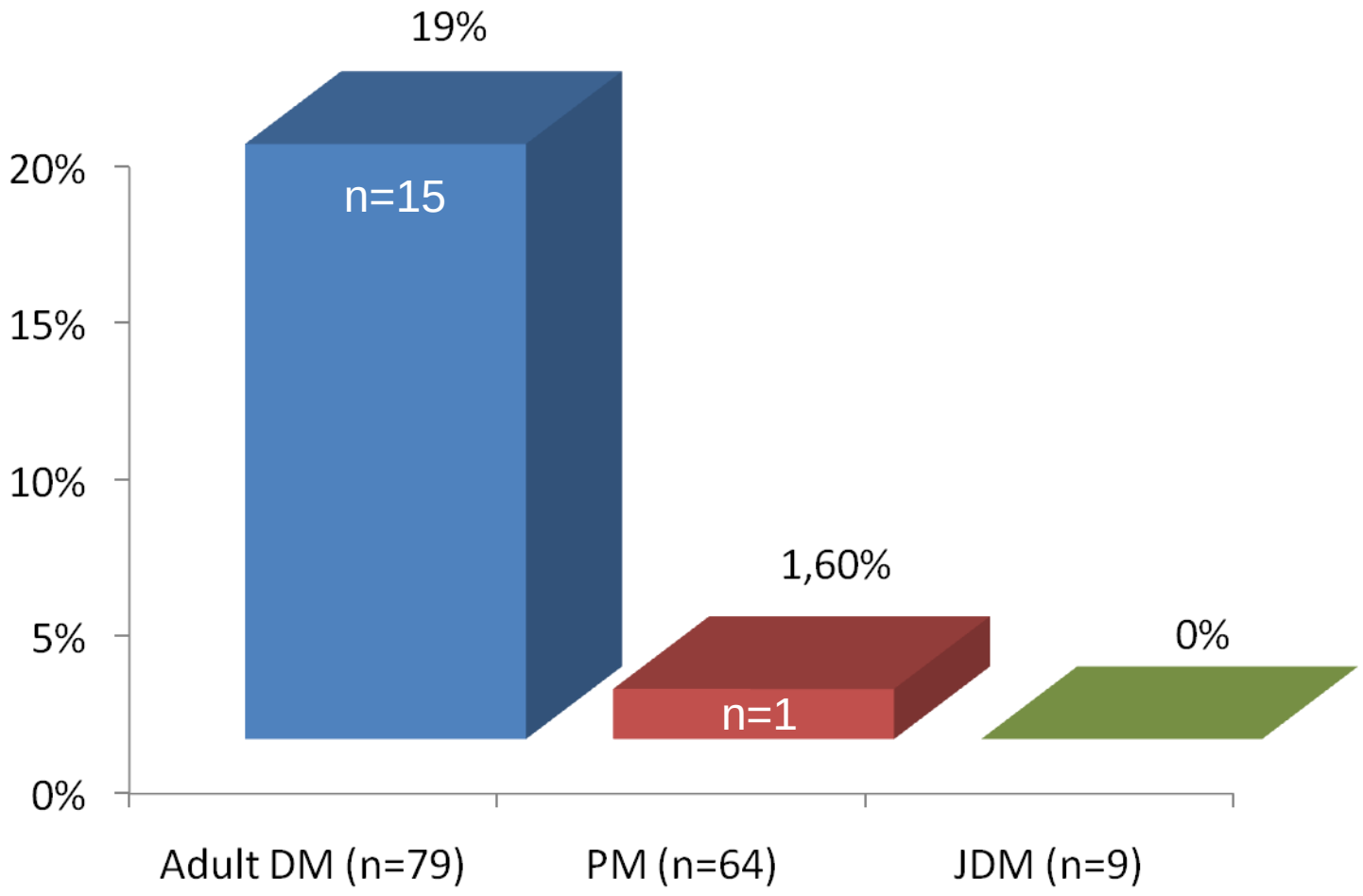
Author	All IIM	JDM	DM	PM	CAM	Anti-p155/140+ no CAM
Targoff	21%	29%	21%	0	75%	n=2
Kaji			13%		71%	
Gunawardena		23%	30%	0	100%	
Chinoy			18.4%		50%	n=11
Trallero-Araguás	19%		23%	5%	62.5%	n=6
Vencovský	10.5%	0	19%	1.6%	41%	n=9 (6.6%)

Targoff IN et al . Arthritis Rheum 2006;54:3682-9. Kaji K et al. Rheumatology 2007;46:25-8. Gunawardena H et al. Rheumatology (Oxford). 2008 ;47:324-8. Chinoy H et al. Ann Rheum Dis 2007;66:1345-9. Trallero-Araguás E. et al. Medicine (Baltimore). 2010 ;89(1):47-52. Vencovsky J. et al. ACR Meeting 2009.

Frequency of anti-p155/140 (anti-TIF1γ) in patients with PM/DM and in those with or without associated malignancy

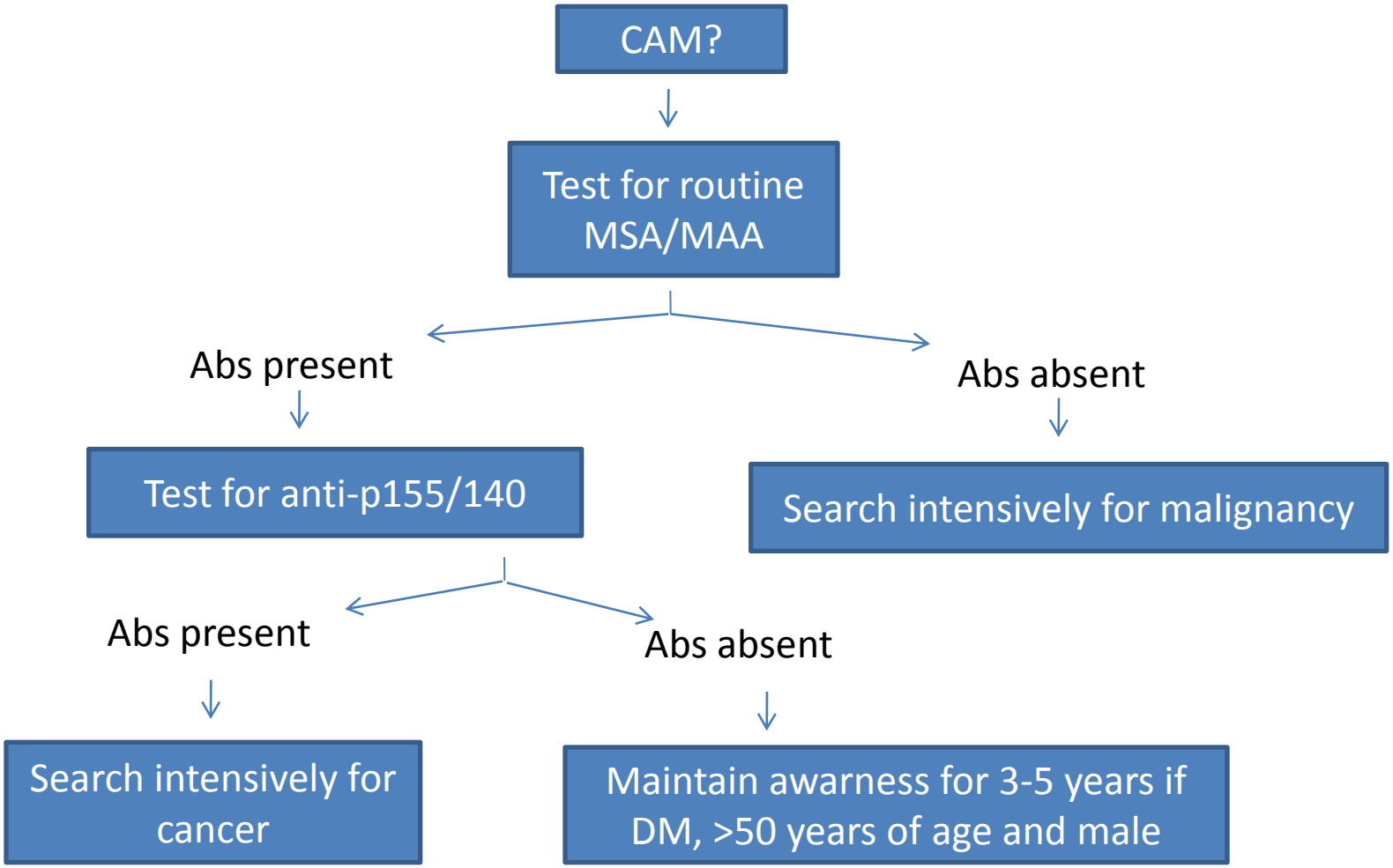


Frequency of anti-p155/140 antibodies in IIM subgroups



OR=12.95 p=0.002

Possible strategy for cancer search in cancer-associated patients with myositis.



Madan V et al. Clin Exp Dermatol 2009; 34: 451–455.

Screening for malignancy in myositis

- Careful history, associated disease (no ILD), broad screening (CBC, ESR, urinary cytology, biochemistry, autoantibodies), fecal occult blood test, CXR, mammography, pelvic and other ultrasonography, gynecological examination.

- Tumor antigen markers.
- PET/CT.

- Endoscopic examinations, thoracoabdominal-pelvic computed tomography (CT), bone marrow biopsy, immunoelectrophoresis, FACS analysis, MRI…

Tumor antigen markers for the detection of solid cancers in inflammatory myopathies

- Not recommended as a screening test for many cancers in the general population
- Assessed in 102 patients (50 DM, 52 PM)
  - carcinoembryonic antigen (CEA)
  - carbohydrate antigen-125 (CA125)
  - carbohydrate antigen 19-9 (CA19-9)
  - carbohydrate antigen 15-3 (CA15-3)
- Median follow-up 59 months (2-208)
- 10 (9.8%) developed solid cancer

Amoura Z et al. Cancer Epidemiol Biomarkers Prev 2005;14(5):1279-1282.

Initial serum tumor markers in 10 DM/PM patients who subsequently developed a solid cancer

Pt.	G	Dg	Age	Time interval (mo)	Type of cancer	CEA (*n* < 5 ng/mL)	CA15-3 (*n* < 25 U/mL)	CA19-9 (*n* < 37 U/mL)	CA125 (*n* < 35 U/mL)
1	F	DM	62	4.3	Cholangiocarcinoma	1.6	**61**	**168**	**171**
2	F	DM	58	4.1	Peritoneal papillary	0.7	**529**	**723**	**4.360**
3	F	DM	46	90	Ovarian	0.5	15	10	**167**
4	F	DM	71	21	Lung large cell carcinoma	3.1	13	8	13
5	M	DM	58	10.3	Gastric adenocarcinoma	3	6	0.5	4
6	M	PM	44	165	Renal carcinoma	1	12	7	7
7	M	PM	36	10	Lung adenocarcinoma	1.6	14	**68**	**189**
8	M	PM	58	100	Lung adenocarcinoma	0.5	10	31	10
9	M	PM	78	0.7	Rectum adenocarcinoma	0.5	15	30	**41**
10	M	PM	56	1.2	Lung large cell carcinoma	2.7	4	1.8	11

Amoura Z et al. Cancer Epidemiol Biomarkers Prev 2005;14(5):1279-1282.

Diagnostic value of tumor markers in IIM

	Increased marker levels			P	Solid cancer OR (95%CI)	*P′*
	in all (*n* = 102)	with cancer (*n* = 10)	without cancer (*n* = 92)			
CEA	4	0	4	0.9	1 (0.05-18.6)	0.9
CA15-3	22	2	20	0.9	0.9 (0.17-4.5)	0.6
CA19-9	11	3	8	0.07	4.5 (1-18.7)	0.018
CA125	8	5	3	0.0001	29.7 (8.2-106.6)	<0.0001
CA19-9 + CA125	3	3	0	0.0007	86.3 (4.06-1,832)	<0.0001

Amoura Z et al. Cancer Epidemiol Biomarkers Prev 2005;14(5):1279-1282.

Value of whole-body [^{18}F] fluorodeoxyglucose PET/computed tomography

- Prospective, multicenter 3-year study
- 55 consecutive PM/DM
- Compared with conventional screening
  - (thoracoabdominal CT, Tumor markers, mammography, gynecologic examination, US)
- Similar overall predictive value 92.7%, equivalent sensitivity and specificity for occult malignancy
- FDG-PET/CT: PPV 85.7% and NPV 93.8%
- Conventional screening: PPV 77.8% and NPV 95.7%.

Selva-O'Callaghan A . et al. Am J Med. 2010;123(6):558-62.