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PARANEOPALSTIC SYNDROMES IN RHEUMATOLOGY: ANOTHER PIECE OF THE PUZZLE

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OUTLINE

1. The many faces of neoplasia in rheumatology

2. Clinical aspects of rheumatic paraneoplastic syndromes

3. Screening for malignancy

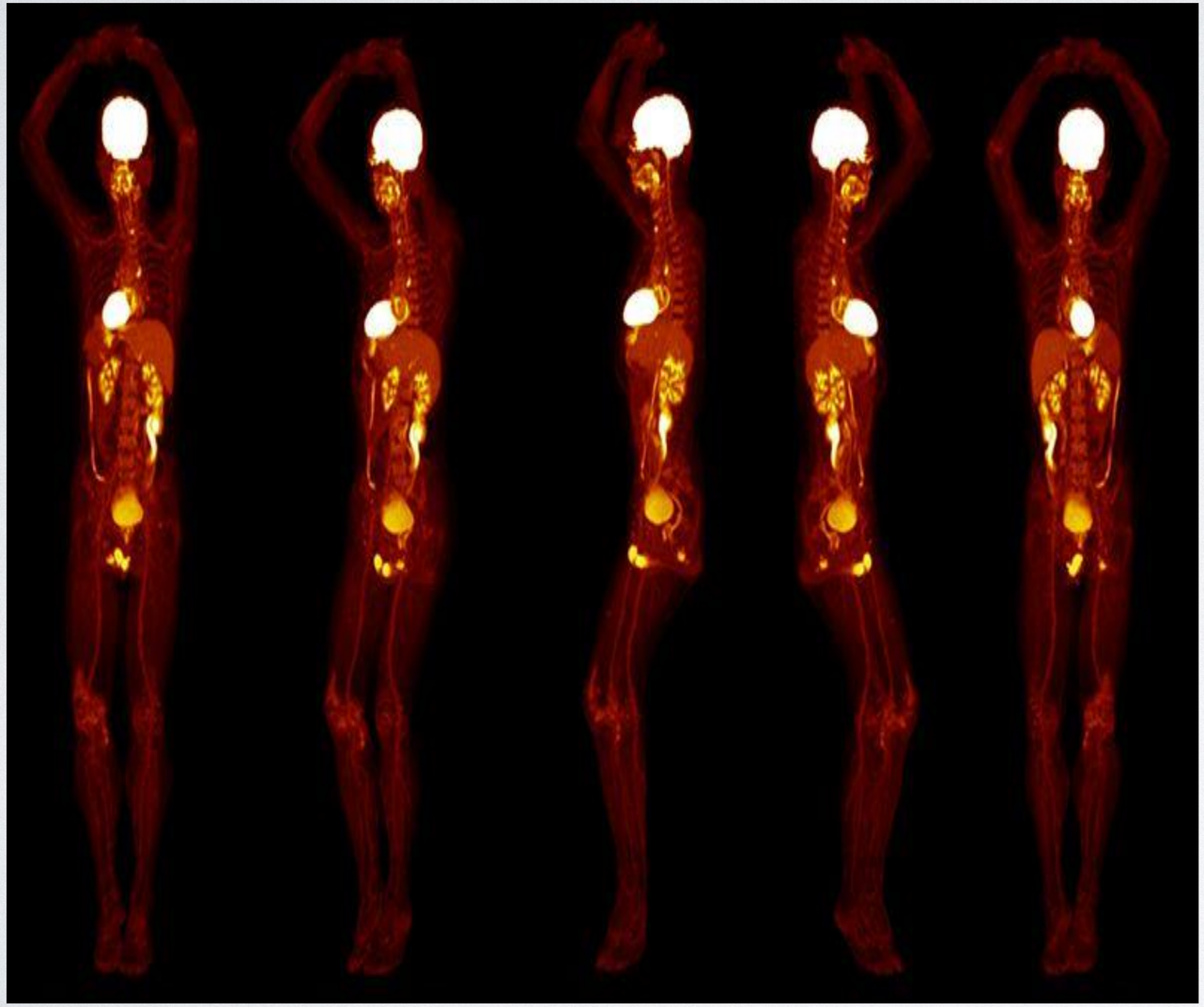
4. Take-home messages

CANCER RISK IS NOTHING NEW IN AUTOIMMUNITY

- Systemic sclerosis has a higher oncological risk compared to general population and POL3 antibodies well represent autoimmunity induced by cancer;
- An increased incidence of hematologic malignancies has been observed among patients with **rheumatoid arthritis**;
- **Systemic lupus erythematosus** is associated with a lower risk of all cancers compared with rheumatoid arthritis and systemic sclerosis, but an increased risk for non-Hodgkin's lymphoma compared with the general population (not to mention treatment-related cancer)
- Neurological autoimmune disease is the best studied example of cancer-induced tolerance breakdown (anti-HuD **encephalitis** in SCLC)

Abu-Shakra M, et al. Arthritis and Rheumatism, 1993.
Olesen AB, et al. The British J of Dermatology, 2010.
Chen YJ, et al. Arthritis Research and Therapy, 2010
Matteson EL, et al. J Rheumatology, 1991
Abu-Shakra M, et al. Arthritis Rheum, 1996.

Paraneoplastic syndromes



Symptoms that are not caused directly by the tumor or its metastases

- Occur in 10-15% of people affected by cancer
- Mediated by soluble factors or humoral and cellular immune mechanisms directed against tumor cells
- Symptoms can coincide, precede (up to 2 years), or follow the diagnosis of cancer or herald its recurrence
- The most commonly associated malignancies include SCLC, breast cancer, gynecologic and hematologic neoplasms

Pelosof et al Mayo Clin Proc. 2010 Sep; 85(9): 838–85

Systemic Syndromes

Fatigue

Cachexia

Fever

Orthostatic Hypotensions

Nonbacterial Thrombotic Endocarditis

Systemic Lupus Erythematosus

Neurological Syndromes

Cerebellar Syndrome

Mono Neuritis Multiplex

Lambert-Eaton Myasthenic Syndrome

Cerebral Encephalopathy

Visual loss

Visceral neuropathy

Necrotising myelopathy

Stiff Person Syndrome

Endocrine Syndromes

SIADH

Hypercalcaemia

Cushing's Syndrome

Hyperglycaemia

Hypertension

Acromegaly

Hyperthyroidism

Hypercalcitoninemia

Gynaecomastia

Galactorrhea

Carcinoid Syndrome

Hypoglycaemia

Hypophosphatemia

Lactic acidosis

Hypouricaemia

Haematologic Syndromes

Anaemia

Leukocytosis

Thrombocytosis

Hypercoagulability

Trousseau's syndrome

Polycythaemia

Thrombocytopenic Purpura

Dysproteinaemia

Leukoerythroblastic

Eosinophilia

Rarer Other Syndromes

Hypertrophic Osteoarthropathy

Dermatomyositis

Rheumatologic

Ophthalmological

Glomerulopathy

Acquired Hypertrichosis Lanuginosa

Acrokeratosis

Erythema Gyratum Repens

Exfoliative Dermatitis

Tripe Palms

Acanthosis Nigricans

Acquired Ichthyosis

Acquired Palmoplanter Keratoderma

Erythema Annulare Centrifugum

Florid Cutaneous Papillomatosis

Pemphigus Vulgaris

Pitriasis Rotunda

Pruritus

Leser-Trelat sign

Sweet's Syndrome

Vasculitis

John White Transl Lung Cancer Res 2016;5(3):227-2

A diagnostic nightmare

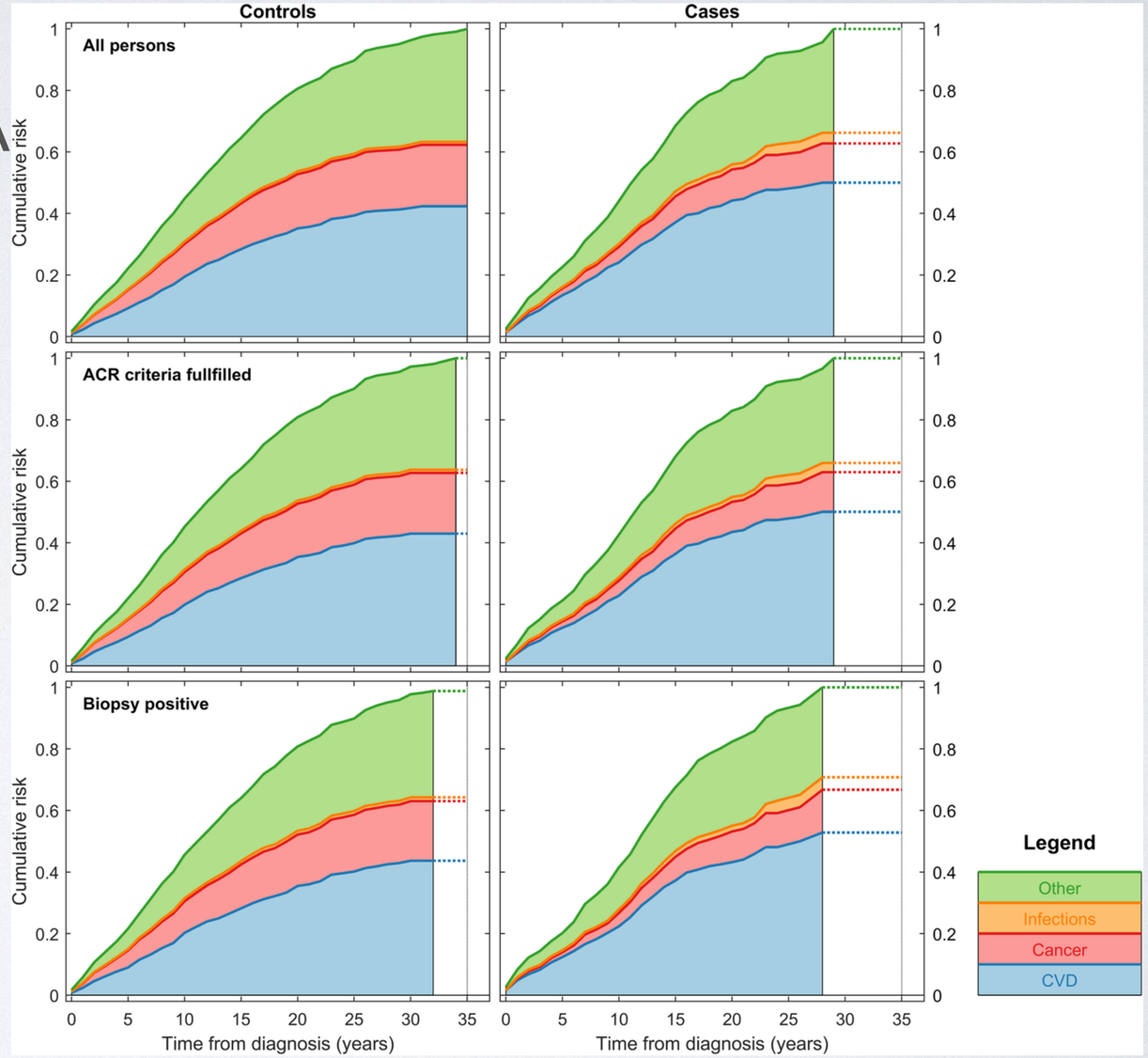
Table 50-2. Preexisting Connective Tissue Disease Associated With Malignancy

DISEASE	MALIGNANCY	CLINICAL RISKS
Rheumatoid arthritis	Lymphoproliferative disorders (2 to 3 times increased risk) Lung cancer (2 times risk) Melanoma and other skin cancers	Longer disease duration, immunosuppression, Felty's syndrome, paraproteinemia
Systemic lupus erythematosus	Lymphoproliferative disorders (2 to 4 times increased risk) Cervical cancer	Adenopathy, splenomegaly
Discoid lupus	Squamous cell epithelioma	HPV-related, in plaques > 20 years
Sjögren's syndrome	Lymphoproliferative disorders, hematologic malignancies (4% to 10% lifetime risk)	Palpable purpura, cutaneous ulcers, cryoglobulinemia, adenopathy, splenomegaly, MALT lymphoma
Systemic sclerosis	Alveolar cell carcinoma, nonmelanoma skin cancer, adenocarcinoma of esophagus lymphoproliferative disorders	Pulmonary fibrosis, areas of skin fibrosis, Barrett's metaplasia
Dermatomyositis	Adenocarcinoma, melanoma, lymphoproliferative disorders, nasopharyngeal tumors (Asians)	Older age, ulcerative skin lesions, anti-p155/p140
Polymyositis	Adenocarcinoma	Polymyositis < dermatomyositis
Paget's disease	Osteogenic sarcoma	Occurs in 1% of lesions
Eosinophilic fasciitis	Lymphoproliferative disorders	Aplastic anemia, thrombocytopenia

- Paraneoplastic rheumatic syndromes are difficult to distinguish from their classical forms.
- A number of major rheumatic disorders are associated with an increased risk for various malignancies
- Immunosuppressive or cytotoxic therapy used to treat the disease, can result in an increased risk of the development of malignancy

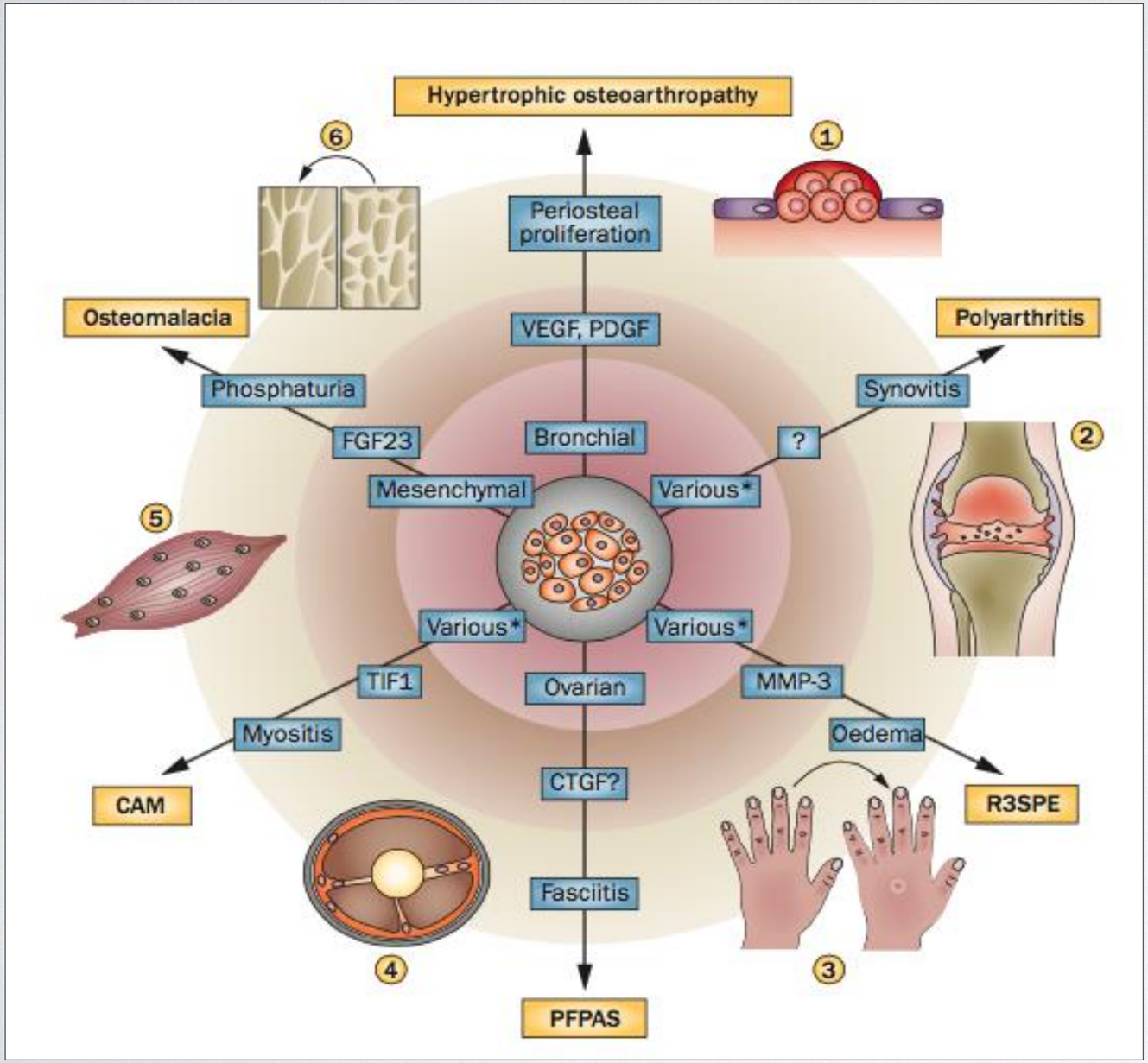
Disorders with virtually no paraneoplastic etiology

- Polymyalgia rheumatica / GCA
- Raynaud phenomenon
- ANCA - associated vasculitis



Brekke LK et al. Arthr Res Ther 2019

Rheumatic disorders with a well-documented paraneoplastic etiology



- Hypertrophic osteoarthropathy
- Cancer-associated myositis
- Remitting seronegative symmetrical synovitis with pitting edema (RS3PE)
- Tumor-induced Osteomalacia
- Palmar fascitis and polyarthritis
- Paraneoplastic polyarthritis
- Leukocytoclastic vasculitis

Bernhard Manger & Georg Schett Nature Reviews Rheumatology volume10, pages662–

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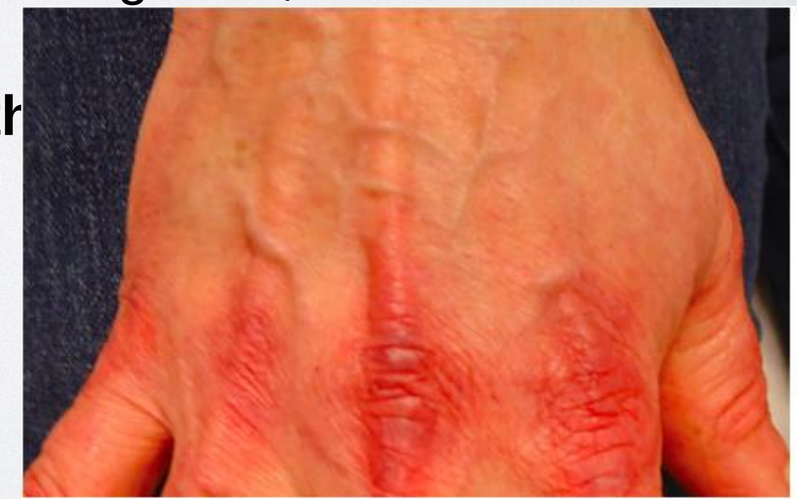
ISOLA-II:
HR for developing cancer over 15 years for ANA-positive subjects

ANA at any titer	HR	95%CI	*p* value
Crude analysis	1.03	0.75-1.43	0.54

Selmi et al. Autoimmun Rev 2016

Cancer-Associated Myositis

- Up to 30% of DM cases
- Cancer can develop before, after or simultaneously to autoimmune diseases
- Usually there is a close temporal relationship between cancer and autoimmune diseases
- The risk of malignancy is usually highest in the first year of diagnosis;
- **In dermatomyositis cancer is generally diagnosed with**



Hill CL, et al. Lancet 2001.

CANCER RISK IN POLYMYOSITIS AND DERMATOMYOSITIS

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)

Table 1: **Standardised incidence ratios (SIR) and 95% CIs for cancer after diagnosis of dermatomyositis or polymyositis**

Hill CL, et al. Lancet 2001.

Autoantibody	Frequency in dermatomyositis (%)	Clinical association
Antisynthetase antibodies		
All antisynthetases	30–40	Antisynthetase syndrome
Anti-Jo1	15–20	
Anti-PL12	<5	
Anti-PL7	<5	
Anti-EJ	<5	
Anti-OJ	<5	
Anti-KS	<5	
Anti-Ha	<1	
Anti-Zo	<1	
Other MSAs		
Anti-Mi2	<10	Hallmark cutaneous features, milder myopathy, low risk of ILD, good response to treatment
Anti-SRP	5–10	Necrotizing myopathy
Novel myositis autoantibodies		
Anti-p155 (anti-TIF1-γ)	13–21	Malignancy
Anti-CADM140 (anti-MDA5)	50–73 (Asian cohorts; not found in Caucasian individuals)	CADM and rapidly progressive ILD
Anti-SAE	<5	Initial CADM, later myositis with systemic features, low risk of ILD
Anti-p140 (anti-NXP2)	<5	ILD and hallmark cutaneous features

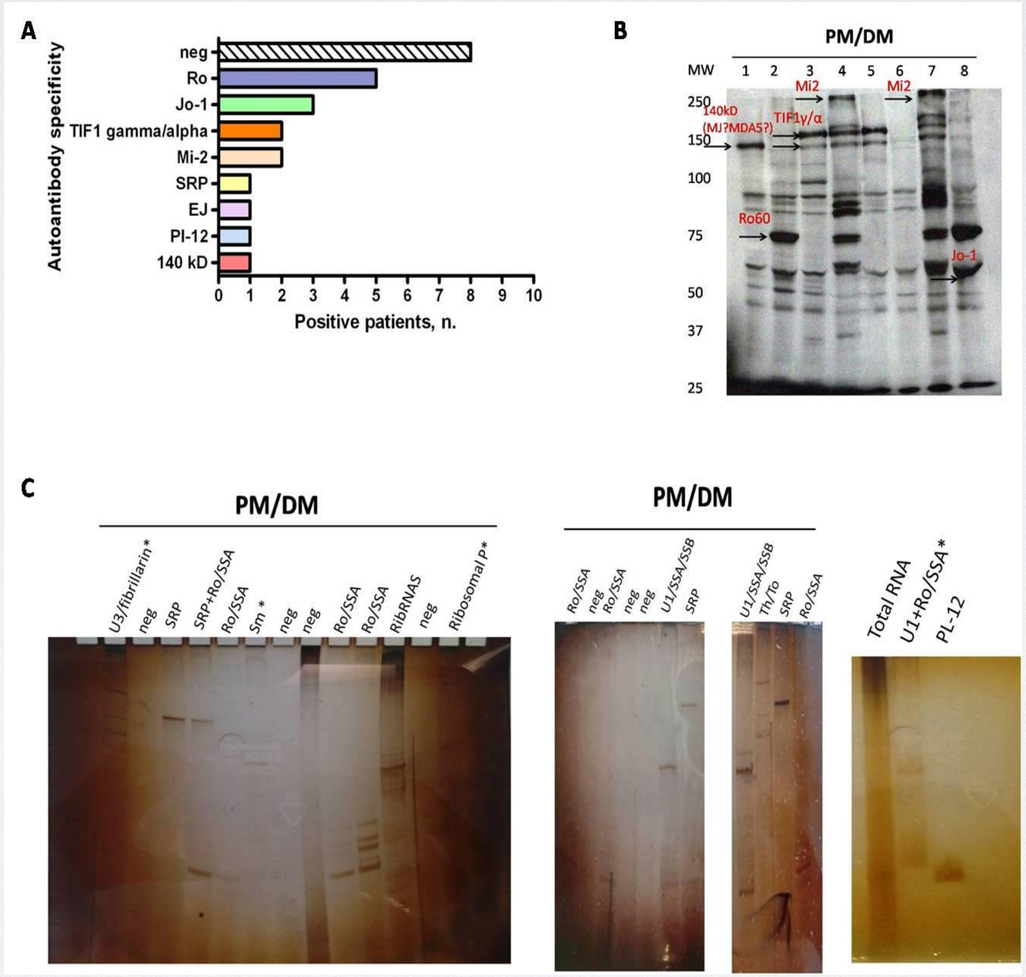
CADM: Clinically amyopathic dermatomyositis; ILD: Interstitial lung disease; MSA: Myositis-specific antibody; SRP: Signal recognition particle.

Medscape

- CAM is currently thought to be caused by the immunological cross-reaction because of the similarity between tumour antigen and injured or regenerating muscular tissue

- **The lack of reactivity demonstarted by the routine antibody panel (Jo-1, PM-Scl, U1-RNP, U3-RNP and Ku) has positive predictive value for malignancy**

OUR RESEARCH ACTIVITY ON MYOSITIS ASSOCIATED ANTIBODIES



Ceribelli A et al, Clin Rheumatol 2017

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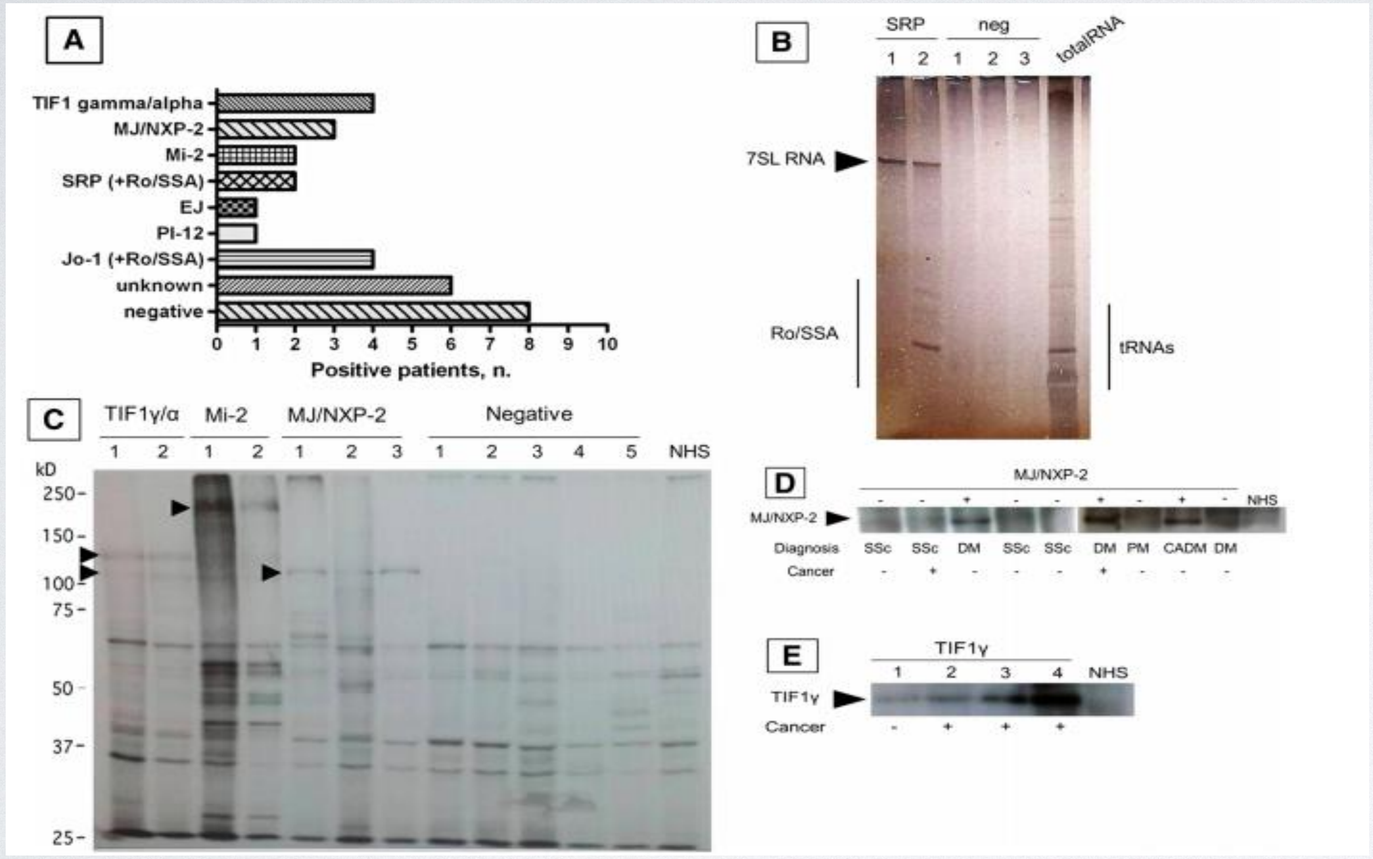
CANCER-ASSOCIATED AUTOANTIBODIES IN MYOSITIS

- TIF1-gamma (DM)
- NXP2 (DM)
- HMGCR (necrotizing myositis)
- MDA-5 (DM)
- MI-2 (DM, negative association?)

Myositis-specific autoantibodies and their association with malignancy in italian patients with polymyositis and dermatomyositis

Angela Ceribelli, Natasa Isailovic, Maria De Santis, Elena Generali, Micaela Fredi, Ilaria Cavazzana, Franco Franceschini, Luca Cantarini, Minoru Satoh, Carlo Selmi



We calculated the positive predictive value (75%), negative predictive value (79%), sensitivity (50%), specificity (92%), and area under the ROC curve (0.7083) for the **risk of paraneoplastic DM in anti-TIF1γ/α (+)**”

ANTI-TIF1 ANTIBODIES AND CANCER AT DIFFERENT AGES

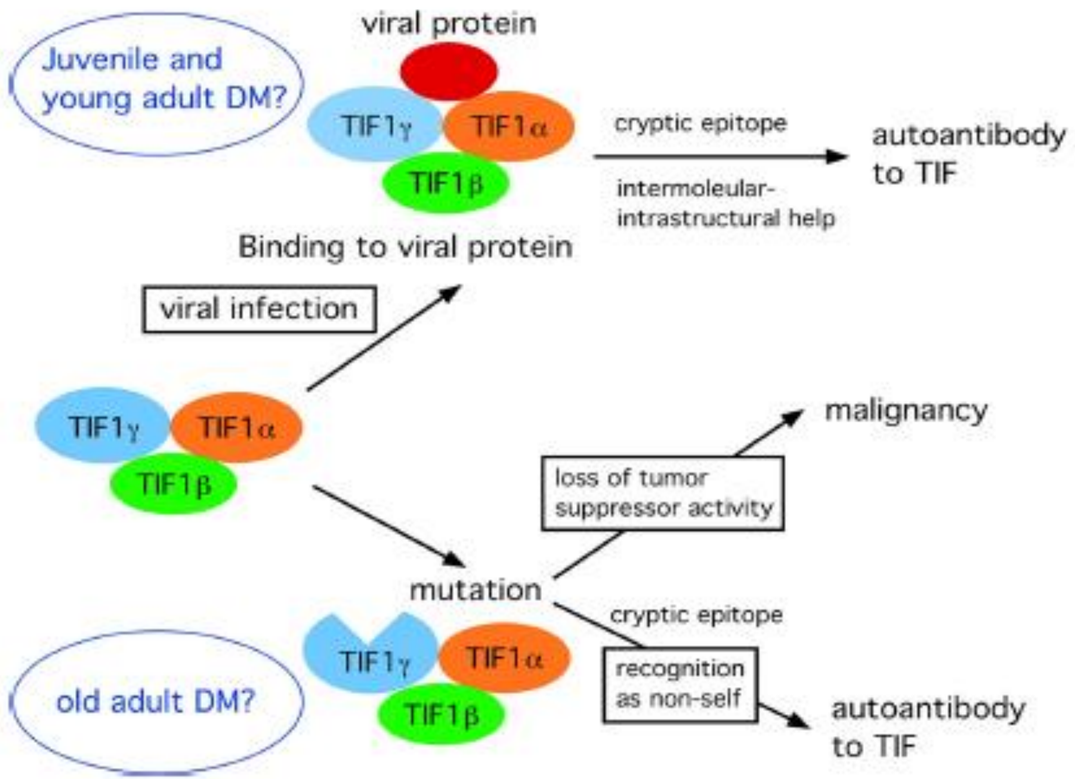


Fig. 6 Hypothesis on the production of anti-TIF1γ/α antibodies based on mutation of TIF1γ or interaction of viral proteins with TIF1. In old adult DM patients with malignancy, TIF1γ mutation may allow development of malignancy while the mutated protein may also trigger autoimmune response to TIF1γ. In JDM or young adult DM patients, interaction of viral proteins with TIF1 proteins may create cryptic epitopes, leading to the autoimmune response

Satoh M et al, Clin Rev Allergy Immunol 2015

ANTI-NXP2 (ALSO KNOWN AS MJ) ANTIBODIES

First report

	Oddis 1997 (abstract)
Patients n.	80
Race-country	n/a-USA and Argentina
Patients' age	Pediatric
Anti-MJ+, (%)	17.5%
Anti-MJ (+) in PM:DM	0:13
% of PM in anti-MJ(+)	0
% of DM in anti-MJ(+)	93%
% of overlap syndromes in anti-MJ(+)	7%
Clinical features	Severe and refractory DM with arthritis, joint contractures, severe calcinosis, dysphagia, gastrointestinal vasculitis

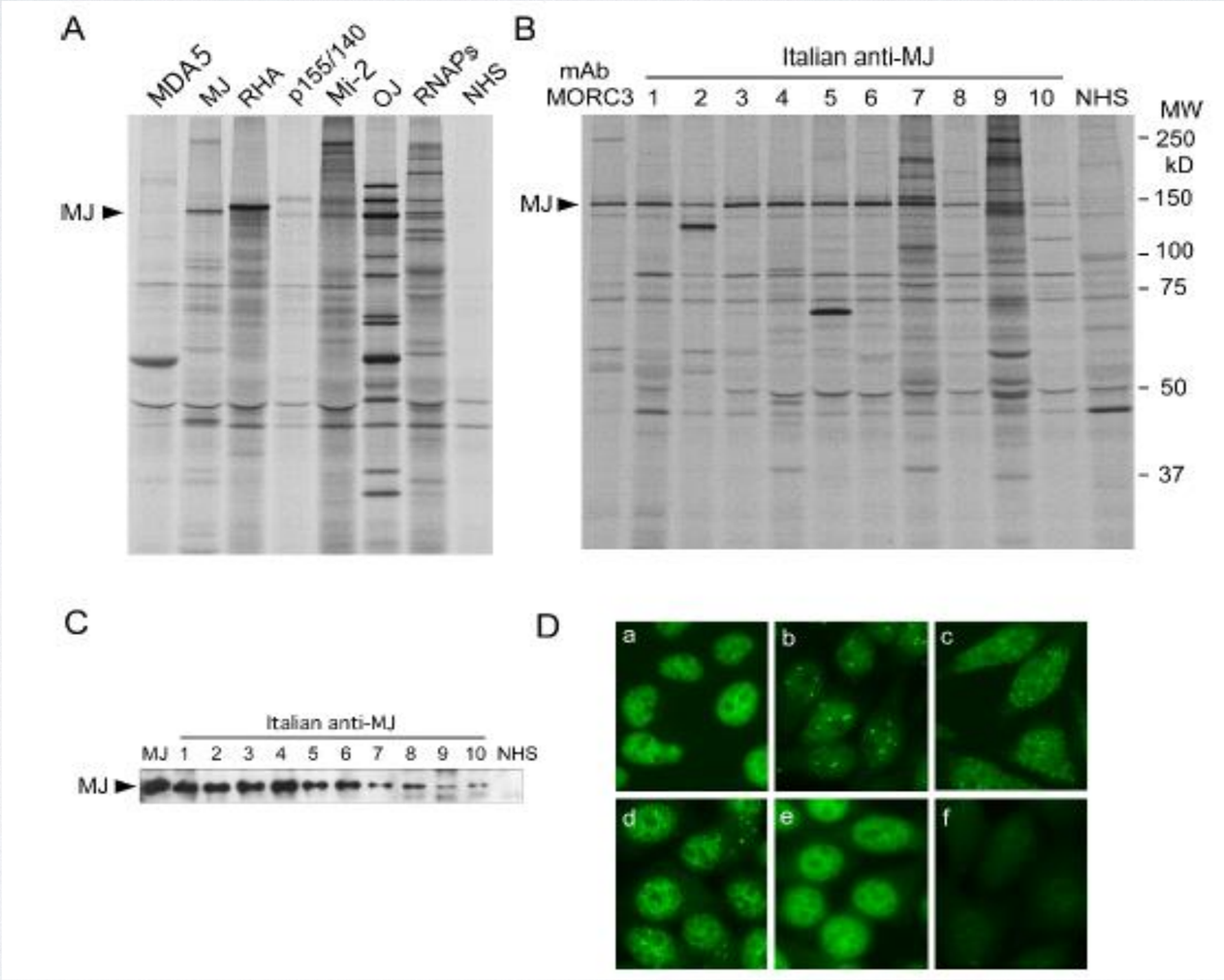
Cancer was detected in 24-37.5% of adults
No distinct type of tumor was associated

Clinical features:

- Mild skin involvement, frequency of calcinosis
- Myalgia, mild to severe weakness, muscle atrophy, frequent dysphagia mild to severe
- Peripheral edema

Oddis CV et al, Arthritis Rheum 1997 (abstract)
Aussy et al, Frontiers in Immunology 2017

ANTI-MJ IN ITALIAN DM/PM PATIENTS

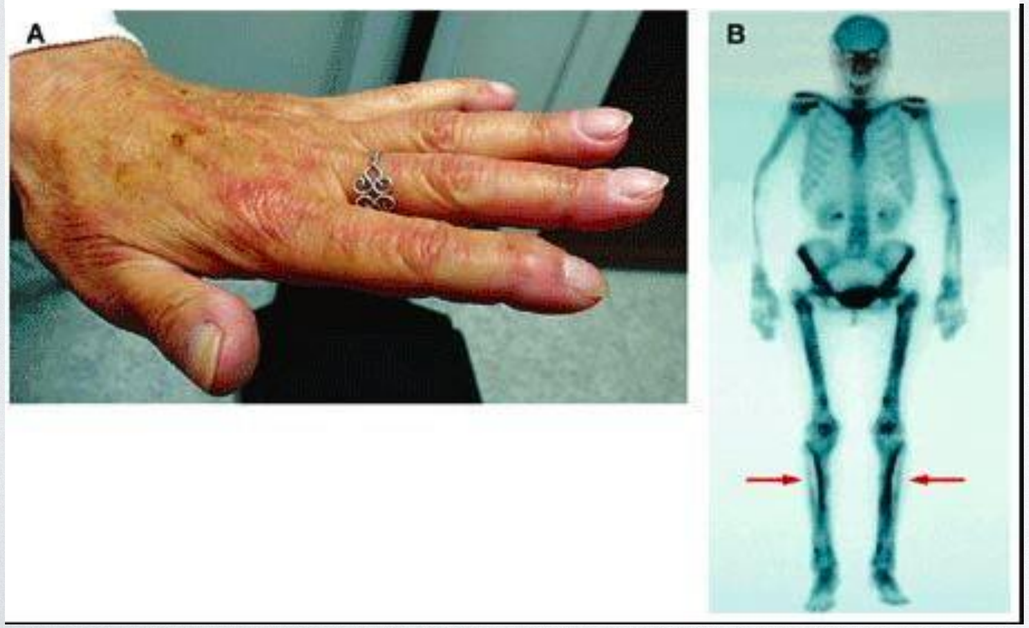


Ceribelli A et al, Arthritis Res Ther 2012

Hypertrophic Osteoarthropathy

Abstract

Background A 65-year-old woman presented with weakness, 9 kg weight loss, dysphagia, facial and bilateral upper-extremity swelling, and debilitating, bilateral lower-extremity pain. The patient had undergone a right upper lobectomy for a 5 mm, poorly differentiated adenocarcinoma of the lung 4 years previously. Medical history included chronic obstructive pulmonary disease (emphysema), hypertension, cerebrovascular disease and multinodular goiter. Surgical history included a right carotid endarterectomy. The patient's history was remarkable for 50+ pack-years of smoking.

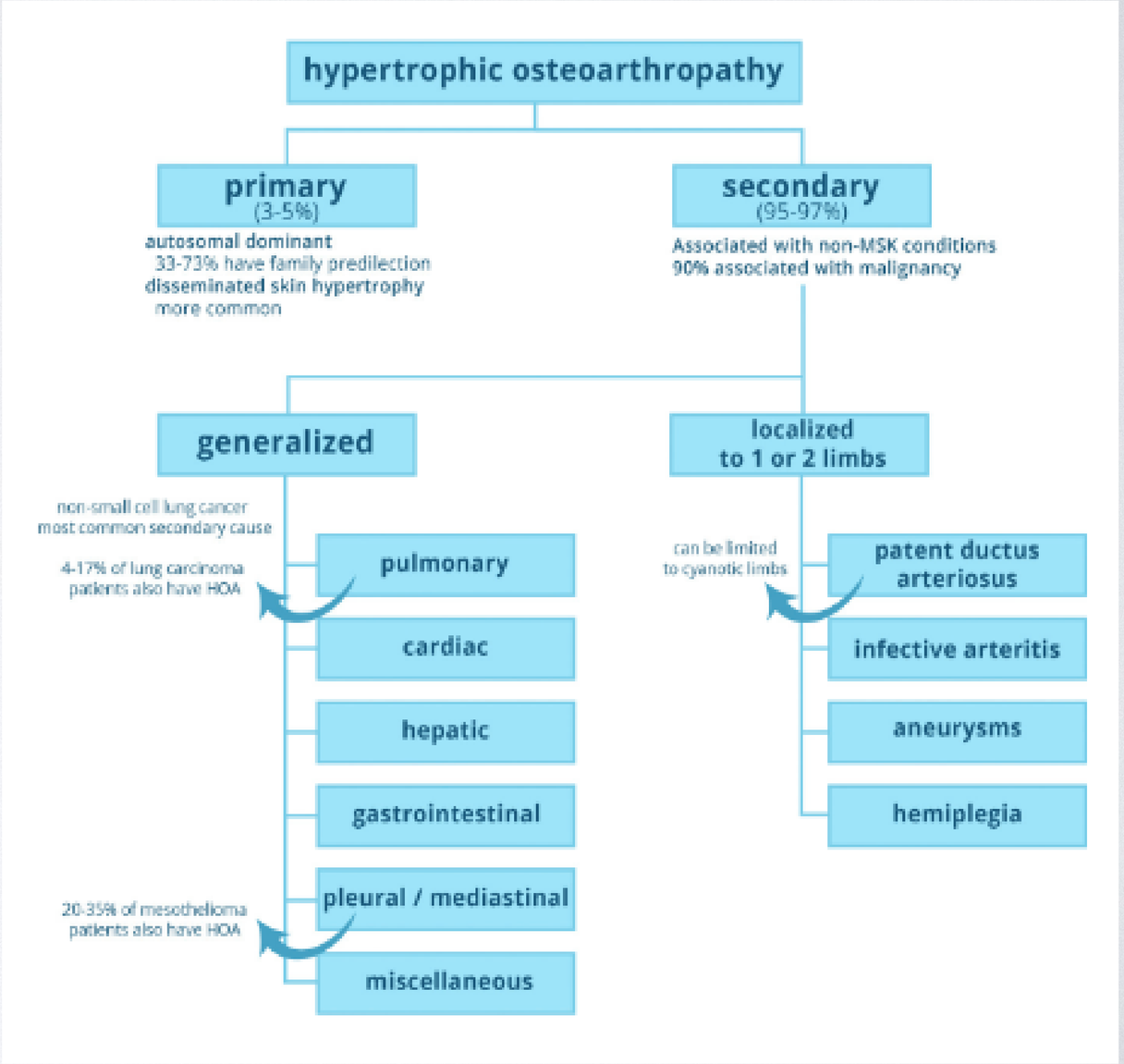


- Clinically, HOA presents with a triad **of periostitis, digital clubbing and painful arthropathy of the large joints**.
- Tibial and femoral pain is the typical symptom; arthralgia or synovitis (with noninflammatory effusions) of adjacent joints are common.
- Periosteal proliferations can be detected by conventional radiography, bone scintigraphy or PET
- Management includes treatment of the underlying condition, bisphosphonates, nsaids and palliative radiation

Bernhard Manger & Georg Schett Nature Reviews Rheumatology volume10, pages662–670 (2014

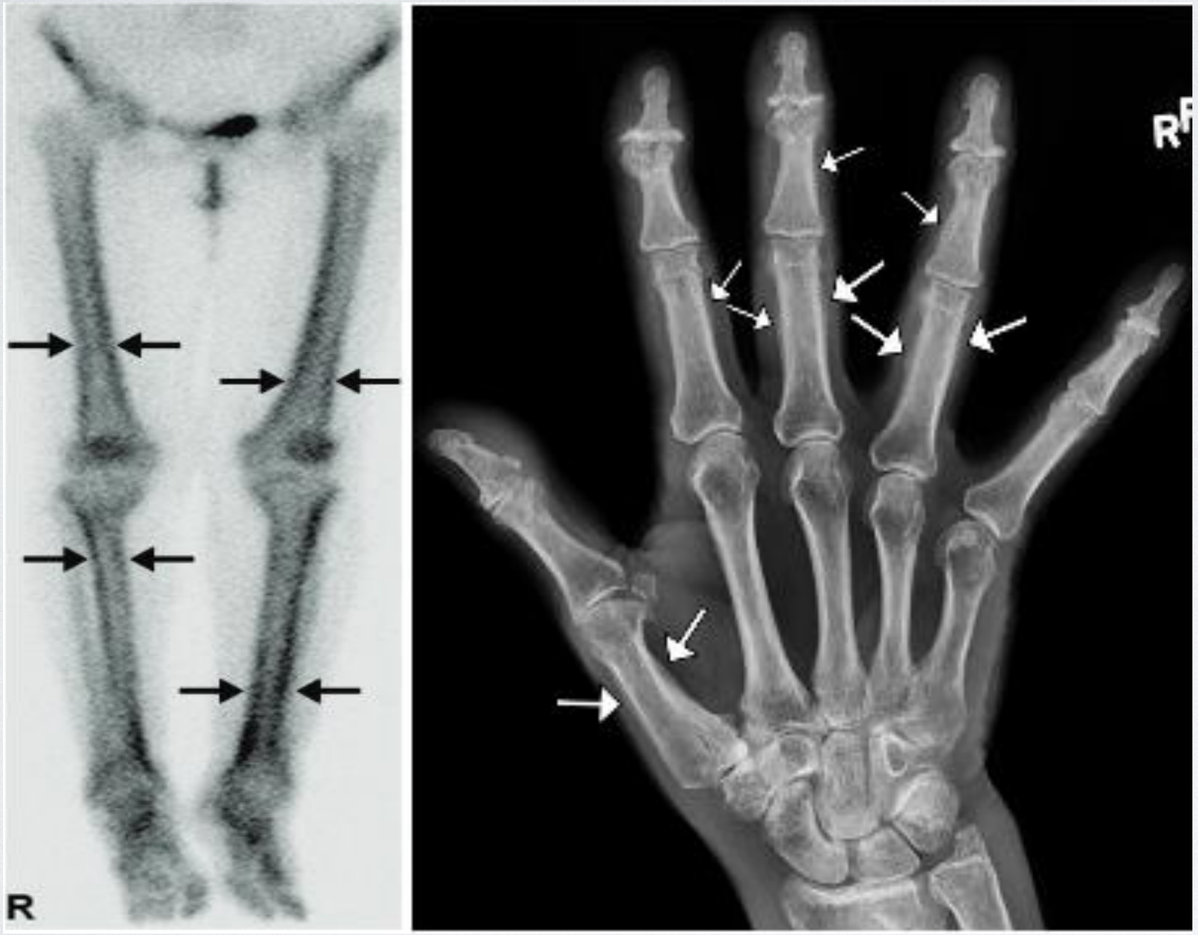
Hypertrophic Osteoarthropathy

- Syndrome marked by abnormal skin proliferation at the distal parts of the extremities, as well as periosteal proliferation of the long bones
- Majority of cases is associated with **pulmonary malignancies (90%)** and chronic inflammatory diseases of the lungs.
- Studies report prevalence of 0.8% in patients with lung cancer
- A primary form of the disease (autosomal dominant) accounts for a small percentage of cases.



Yap et al RadioGraphics 2017; 37:157–175

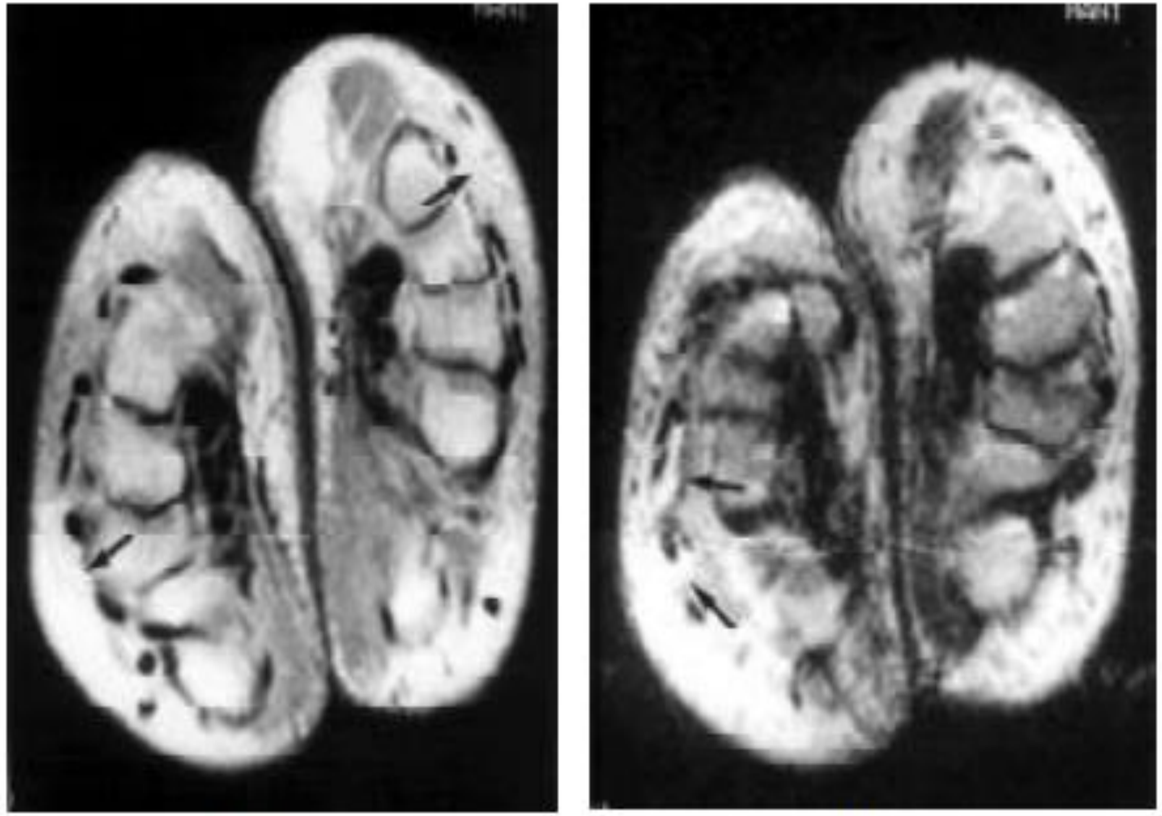
Hypertrophic Osteoarthropathy



- Plain radiographs of the extremites can demonstrate abnormalities even in asymptomatic patients
- Bone scintigraphy is the most sensitive test showing periosteal involvement.
- Characteristic findings on bone scans are bilateral symmetrical linear uptake of the tracer along the cortical margins of the long bones, which is also known as **tram line or double stripe sign**

Yap et al RadioGraphics 2017; 37:157–175

Remitting seronegative symmetrical synovitis with pitting edema (RS3PE)



(a) (b)

Fig. 2. Hand MRIs in patient 2. (**A**) Axial proton density section through the midpoint of the palm shows marked subcutaneous edema (**arrows**). (**B**) Axial T2 weighted section through the midpoint of the palm shows fluid collection in the extensor synovial sheaths (**arrows**).

- Symmetrical involvement of small joints and marked pitting oedema on the dorsum of the **hands** and feet
- The clinical picture may be observed in various rheumatic conditions: PMR, RA and SpA.
- Based on a case series of 89 patients, malignancy was found in 24%. Mostly adenocarcinomas and NHL.
- . No significant clinical differences were observed between paraneoplastic and benign cases.

Cantini et al Clinical and Experimental Rheumatology 1999; 17: 741-

Features distinguishing between benign and paraneoplastic forms of arthritis

Characteristic features proposed for the diagnosis of paraneoplastic arthritis
Men aged >50 years
Mean time between arthritis and neoplasia diagnosis<6 months
Polyarthritis (symmetric or asymmetric)
Degradation of general health status
Absence of rheumatoid nodule
Negative rheumatoid factor
High C-reactive protein level
Non-erosive joint on *x* ray
Regression of arthritis after specific anti-tumoural therapy

More et al Ann Rheum Dis 2008; 67 :244–247.

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Screening for tumours in paraneoplastic syndromes: report of an EFNS Tas' Force

M. J. Titulaer,a R. Soffietti, J. Dalmau,c N. E. Gilhus,d,e B. Giometto,f F. Graus,g W. Grisold,h J. Honnorat,i,j P. A. E. Sillevis Smitt,k R. Tanasescu,l C. A. Vedeler,d,e R. Voltz,m and J. J. G. M. Verschuurena

Good clinical practice points:

- For screening of the thoracic region, a CT-thorax is recommended
- if negative is follow-up with fluorodeoxyglucose-positron emission tomography (FDG-PET)
- For the pelvic region, ultrasound (US) is the investigation of first choice followed by CT
- Dermatomyositis patients should have CT-thorax/abdomen, US of the pelvic region and mammography in women
- If negative, repeat screening after 3–6 months and screen every 6 months up till 4 years

Antibodies – are neurologists beating us to it?

Table 2. Antineuronal-Antibody–Associated Paraneoplastic Disorders.*

Antibody	Neuronal Reactivity	Protein Antigens	Cloned Genes	Tumor	Paraneoplastic Symptoms	References
Anti-Hu (ANNA-1)	Nucleus more than cytoplasm (all neurons)	35–40 kD	*HuD, HuC, Hel-N1*	Small-cell lung cancer, neuroblastoma, prostate cancer	Paraneoplastic encephalomyelitis, paraneoplastic sensory neuronopathy, paraneoplastic cerebellar degeneration, autonomic dysfunction	Graus et al.,[22] Dalmau et al.,[44] Szabo et al.,[45] Levine et al.,[46] Sakai et al.[47]
Anti-Yo (PCA-1)	Cytoplasm, Purkinje cells	34 and 62 kD	*CDR34, CDR62*	Ovarian, breast, and lung cancers	Paraneoplastic cerebellar degeneration	Peterson et al.,[8] Fathallah-Shaykh et al.,[48] Darnell et al.[49]
Anti-Ri	Nucleus more than cytoplasm (central nervous system neurons)	55 and 80 kD	*Nova*	Breast, gynecologic, lung, and bladder cancers	Ataxia with or without opsoclonus–myoclonus	Jensen et al.,[50] Yang et al.,[51] Luque et al.,[52] Buckanovich et al.[53]
Anti-Tr	Cytoplasm, Purkinje cells	?	—	Hodgkin's lymphoma	Paraneoplastic cerebellar degeneration	Peltola et al.[54]
Anti-VGCC	Presynaptic neuromuscular junction	64 kD	P/Q type VGCC, *MysB*	Small-cell lung cancer	Lambert–Eaton myasthenic syndrome	Carpentier and Delattre[30]
Antiretinal	Photoreceptors, ganglion cells	23, 65, 145, and 205 kD	Recoverin	Small-cell lung cancer, melanoma, gynecologic cancers	Cancer-associated retinopathy, melanoma-associated retinopathy	Maeda et al.,[55] Polans et al.,[56] Thirkill et al.[57]
Anti-amphiphysin	Presynaptic nerve terminals	128 kD	Amphiphysin	Breast cancer, small-cell lung cancer	Stiff-person syndrome, paraneoplastic encephalomyelitis	Saiz et al.,[58] De Camilli et al.,[59] Folli et al.[60]
Anti-CRMP5 (Anti-CV2)	Oligodendrocytes, neurons, cytoplasm	66 kD	*CRMP5 (POP66)*	Small-cell lung cancer, thymoma	Encephalomyelitis, cerebellar degeneration, chorea, sensory neuropathy	Yu et al.[61]
Anti-PCA-2	Purkinje cytoplasm and other neurons	280 kD	—	Small-cell lung cancer	Encephalomyelitis, cerebellar degeneration, Lambert–Eaton myasthenic syndrome	Bataller et al.[30]
Anti-Ma1	Neurons (subnucleus)	40 kD	*Ma1*	Lung cancer, other cancers	Brain-stem encephalitis, cerebellar degeneration	Rosenfeld et al.[62]
Anti-Ma2	Neurons (subnucleus)	41.5 kD	*Ma2*	Testicular cancer	Limbic brain-stem encephalitis	Rosenfeld et al.[62]
ANNA-3	Nuclei, Purkinje cells	170 kD	—	Lung cancer	Sensory neuronopathy, encephalomyelitis	Chan et al.[63]
Anti-mGluR1	Purkinje cells, olfactory neurons, hippocampus	Metabotropic glutamate receptor	Glu receptor	Hodgkin's lymphoma	Paraneoplastic cerebellar degeneration	Smitt et al.[64]
Anti-VGKC	Peripheral nerve	VGKC	Potassium channels	Thymoma, small-cell lung cancer	Neuromyotonia	Vernino and Lennon,[65] Hart et al.[66]
Anti-MAG	Peripheral nerve	MAG	*MAG*	Waldenström's macroglobulinemia	Peripheral neuropathy	Vital[67]

Darnell et al N Engl J Med 2003; 349:1543-1554

OUR COHORT OF MYOSITIS

2 patients with breast cancer had anti-Mi-2, previously associated with non-CADM

Ceribelli A et al, Clin Rheumatol 2017

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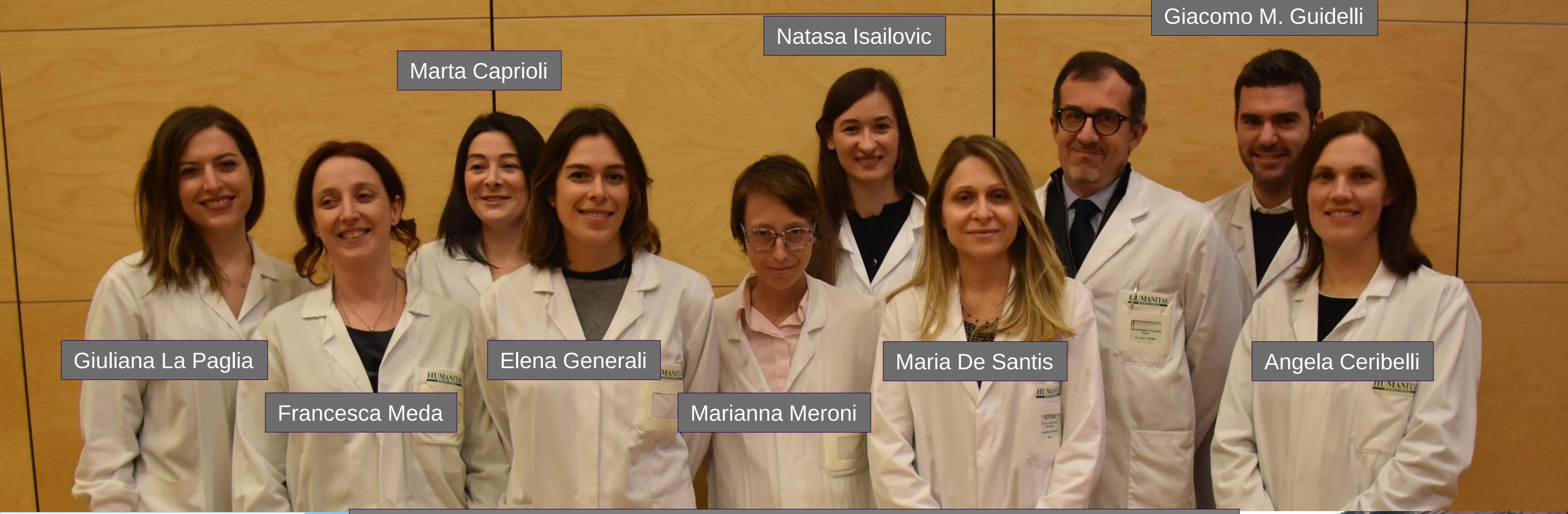
CONCLUSIONS

- Paraneoplastic syndromes can precede appearence of the malignancy – early diagnosis is key
- Rheumatic paraneoplastic syndromes are rare diseases with a broad range of manifestations, often difficult to differentiate from their benign forms;
- Not all associations between malignancy and rheumatological disorder are synonymous with a paraneoplastic syndrome;
- Better diagnostic modalities and algorhytms are essential for care of patients with paraneoplastic rheumatic syndromes



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Thanks for your attention