SINDROMI PARANEOPLASTICHE: IL PUNTO DI VISTA DEL REUMATOLOGO

Approcci interdisciplinari in reumatologia - 5° Edizione

Reumatologia e malattie neoplastiche

Torino, 13 ottobre 2017

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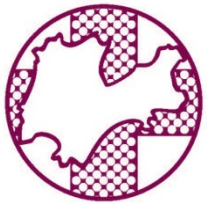

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Cancer and autoimmunity: Harnessing longitudinal cohorts to probe the link

Giordano Egiziano [a], Sasha Bernatsky [b, 1], Ami A. Shah [c, *]

Cancer risk in the autoimmune rheumatic diseases reported in recent meta-analyses.

Disease	Author (year)	Pooled SIR or RR for all cancers	Tumor types with increased risk
Rheumatoid arthritis	Simon (2015) [2]	1.09 (1.06, 1.13)	Lymphoma (Hodgkin, non-Hodgkin), lung, melanoma
Systemic lupus erythematosus	Bernatsky (2013) [3]	1.14 (1.05, 1.23)	Lymphoma (non-Hodgkin), lung, leukemia, thyroid
Systemic sclerosis	Onishi (2013) [4]	1.41 (1.18, 1.68)	Lung, liver, hematologic, bladder
Myositis	Yang (2015) [5]		
Polymyositis		1.62 (1.19, 2.04)	Lung, kidney, breast, lymphoma, bladder, endometrial, cervical, thyroid, brain
Dermatomyositis		5.50 (4.31, 6.70)	Ovary, breast, lung, colorectal, cervical, bladder, nasopharyngeal, esophagus, pancreas, kidney
Sjogren's syndrome	Liang (2014) [6]	1.53 (1.17, 1.88)	Non-Hodgkin's lymphoma, thyroid
ANCA-associated vasculitis	Shang (2015) [7]	1.74 (1.37, 2.21)	Nonmelanoma skin, l eukemia, bladder, lymphoma, liver, lung

Cancer and autoimmunity

Potential mechanisms linking cancer and the autoimmune rheumatic diseases.

Proposed mechanism	Example(s)
Cancer secondary to rheumatic disease	
Chronic inflammation and damage from rheumatic disease	1. Sjogren's: disease activity, severity, and duration predictive of non-Hodgkin's lymphoma risk 2. RA: elevated ESR and CRP associated with increased cancer risk; long-term corticosteroid therapy associated with lower lymphoma risk 3. SSc: pulmonary scar associated with lung cancer
Cytotoxic or biologic therapies	1. Cyclophosphamide: higher cumulative doses associated with an increased risk of lymphoproliferative and bladder cancers 2. Mycophenolate: Possible increase in nonmelanoma skin cancer and CNS lymphoma 3. TNF inhibitors: an increased risk of nonmelanoma and possibly melanoma skin cancer
Inability to clear oncogenic infections	SLE: risk higher for virus-associated cancers (e.g., cervical, vaginal/vulvar, and anal cancers associated with HPV)
Rheumatic disease secondary to cancer	
Cancer-induced autoimmunity	1. SSc: an increased risk of cancer at disease onset among patients with RNA polymerase III autoantibodies; genetic abnormalities of *POLR3A* in cancers associated with mutation-specific T cell immune responses and cross-reactive autoantibodies 2. Dermatomyositis: striking clustering of cancer diagnosis with disease onset; an increased risk of CAM in patients with unique autoantibodies (NXP-2 and TIF-1 gamma); clinical improvement in DM with cancer therapy
Immunotherapy or chemotherapy	1. IL-2 therapy or immune checkpoint inhibitors: inflammatory arthritis and other autoimmune phenomena have been reported 2. Bleomycin and gemcitabine: associated with skin sclerosis, development of exacerbation of Raynaud's and ischemic digits
Radiation therapy	Localized scleroderma may develop in radiation port
Shared etiology	
Common inciting exposure	Silica, solvents, organic chemicals, pesticides, smoking, infections, and hormonal state
Shared genetic susceptibility	Increased risks of Hodgkin's lymphoma in patients with a personal or family history of multiple autoimmune conditions

Best Practice & Research Clinical Rheumatology 30 (2016) 53–62

CONCISE REPORT

Rheumatoid arthritis and polymyalgia rheumatica occurring after immune checkpoint inhibitor treatment

Rakiba Belkhir,[1] Sébastien Le Burel,[2] Laetitia Dunogeant,[3] Aurélien Marabelle,[4] Antoine Hollebecque,[4] Benjamin Besse,[5] Alexandra Leary,[5] Anne-Laure Voisin,[6] Clémence Pontoizeau,[7] Laetitia Coutte,[8] Edouard Pertuiset,[9] Gaël Mouterde,[10] Olivier Fain,[11] Olivier Lambotte,[2,12] Xavier Mariette[1,13]

Conclusions This is the first description of RA occurring after ICI therapy for cancer. PMR can also occur after ICI, particularly after anti-PD-1 therapy. All cases responded to corticosteroids or with immunosuppressive therapy. Collaboration between rheumatologists and oncologists is crucial and could lead to better recognition and care of these patients.

In conclusion, patients with cancer treated with immunotherapy and who develop autoimmune or other reactions should be managed by multidisciplinary care units (MCU). Cancer immunotherapy is very promising and the number of available treatments is raising; thus, an implementation of MCU could be of great value for patients with cancer.

Belkhir R, *et al*. *Ann Rheum Dis* 2017;**0**:1–4. doi:10.1136/annrheumdis-2017-211216

Sindromi paraneoplastiche - Definizione

malattie o sintomi ***non causati direttamente dal tumore o da metastasi****, ma da ormoni e citochine prodotti dal tumore o da meccanismi immunitari diretti contro il tumore stesso*

necessità di un ***principio di causalità*** tra tumore e sindrome paraneoplastica

Menger & Schett. Nature Reviews, Rheumatology, 2014

Rheumatic manifestations of neoplasia

Anthony C. Schwarzer, MB, BS, FRACP, and Leslie Schrieber, MD, FRACP

Royal North Shore Hospital, St. Leonards, Australia

Current Opinion in Rheumatology 1989, 1:545–550

Table 1. Direct associations between rheumatologic syndromes and neoplasia

Primary neoplasia
Synovium
Tenosynóvial sarcoma
Bone (juxta-articular)
Malignant
Osteogenic sarcoma
Chondrosarcoma
Fibrosarcoma
Benign
Osteoid osteoma
Secondary neoplasia
Hematologic
Leukemias
Lymphomas
Nonhematologic (to bone, synovium, or both)

Giuseppe Paolazzi, Trento

Rheumatologic Manifestations of Cancer

*David Stewart Caldwell, M.D.,**
and Rex Monroe McCallum, M.D.†

Table 4. *Indirect Associations Between Rheumatologic Syndromes and Cancer: Paraneoplastic Syndromes**

Myopathy (dermatomyositis/polymyositis)
Arthropathies
Hypertrophic osteoarthropathy
Amyloidosis
Secondary gout
Carcinoma polyarthritis
Miscellaneous presentations
Lupus-like syndrome
Necrotizing vasculitis
Cryoproteins
Immune-complex disease
Reflex sympathetic dystrophy syndrome
Scleroderma
Polyarteritis
Polymyalgia rheumatica
Panniculitis
Polychondritis
Lupus antibody syndrome
Pyogenic arthritis
Osteomalacia

**From* Caldwell, D. S.: Musculoskeletal syndromes associated with malignancy. *In* Kelley, W. N., Harris, E. D., Jr., Ruddy, S., et al. (eds.): Textbook of Rheumatology. Edition 2. Philadelphia, W. B. Saunders Co., 1985; with permission.

Malattie reumatiche e neoplasie

malattie reumatiche ⟷ **neoplasie**

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- maggior rischio di malignità legato alla patologia reumatica e ai potenziali effetti avversi delle terapie immunosoppressive
- manifestazione di neoplasie maligne, antecedendo spesso la comparsa di queste ultime

Malattie reumatiche e neoplasie

malattie reumatiche ⟷ **neoplasie**

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⇩

sindromi paraneoplastiche

Bradford Hill Criteria

- Strength of an association
- Consistency of findings by different researchers
- Specificity of a phenomenon
- Temporality or appropriate temporal sequence
- Biological gradient or dose-response effects
- Plausibility or pathophysiologic rationale
- Coherence with what is already known
- Experimental induction or abrogation of an effect
- Evidence from analogous conditions

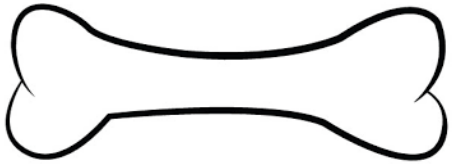
Menger & Schett. Nature Reviews, Rheumatology, 2014

Sindromi paraneoplastiche in reumatologia

- Rare (2-3% dei tumori maligni)
- Difficile definizione fisiopatologica
- Scarsità di materiale in letteratura
- Relazione temporale malattia reumatica - neoplasia (2 aa ?)
- Patologie connettivitiche, miopatiche, artritiche
- Interessamento di tumori solidi ed ematologici
- Andamento clinico spesso «parallelo» a quello oncologico

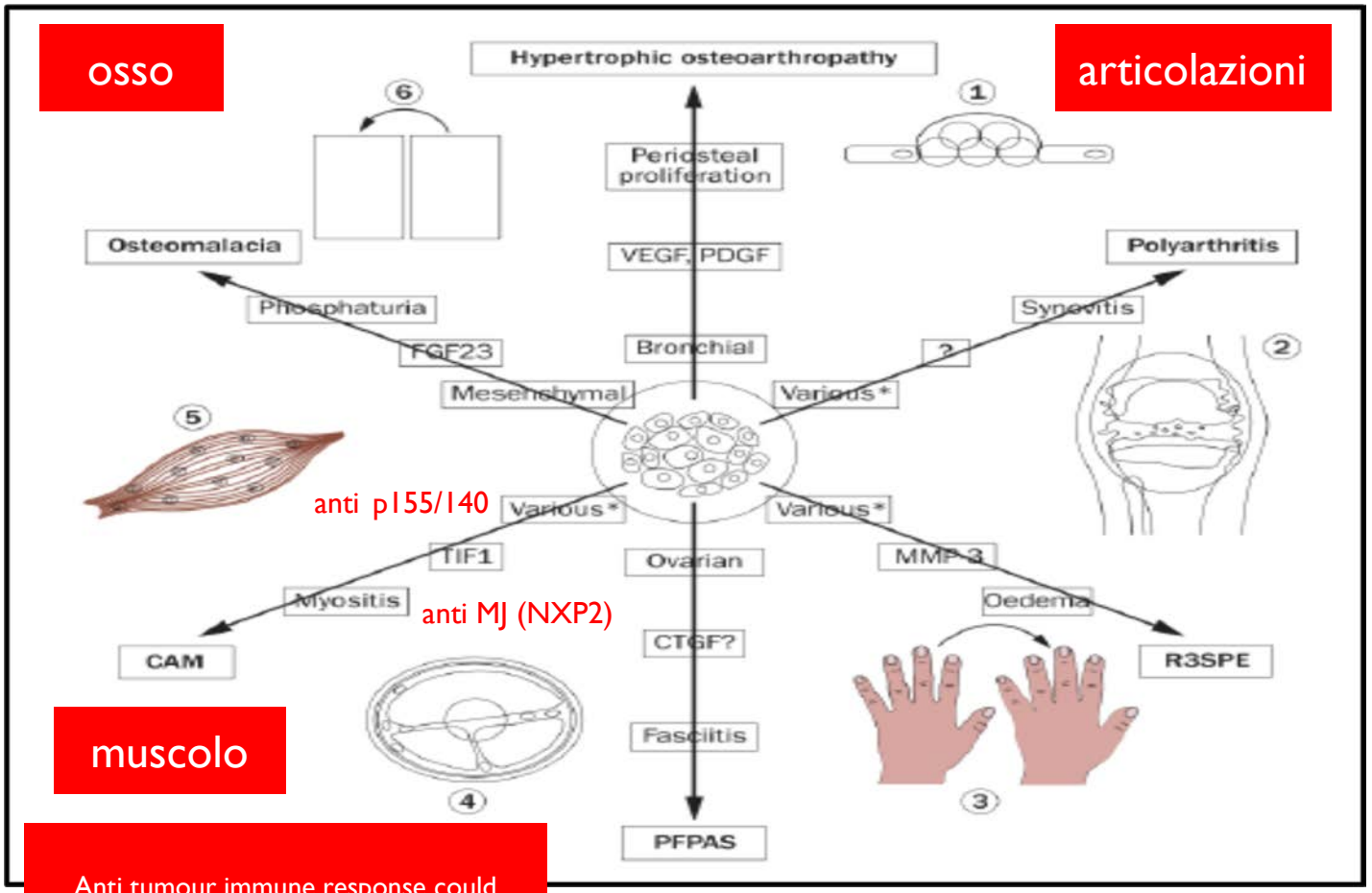
  (regressione dopo trattamento della neoplasia)
- Difficoltà nell'identificare caratteristiche cliniche sospette

Rugienè et al.. Clin Rheumatology, 2011



sindromi paraneoplastiche in reumatologia

Patogenesi e manifestazioni cliniche



Anti tumour immune response could induce anti TIFab by crossreactivity of immune response against tumour with regenerating muscle tissue

Menger & Schett. Nature Reviews, Rheumatology, 2014

Miopatie Infiammatorie (IMs)

Curr Rheumatol Rep (2011) 13:208–215
DOI 10.1007/s11926-011-0169-7

Malignancy in Myositis

Zaki Abou Zahr · Alan N. Baer

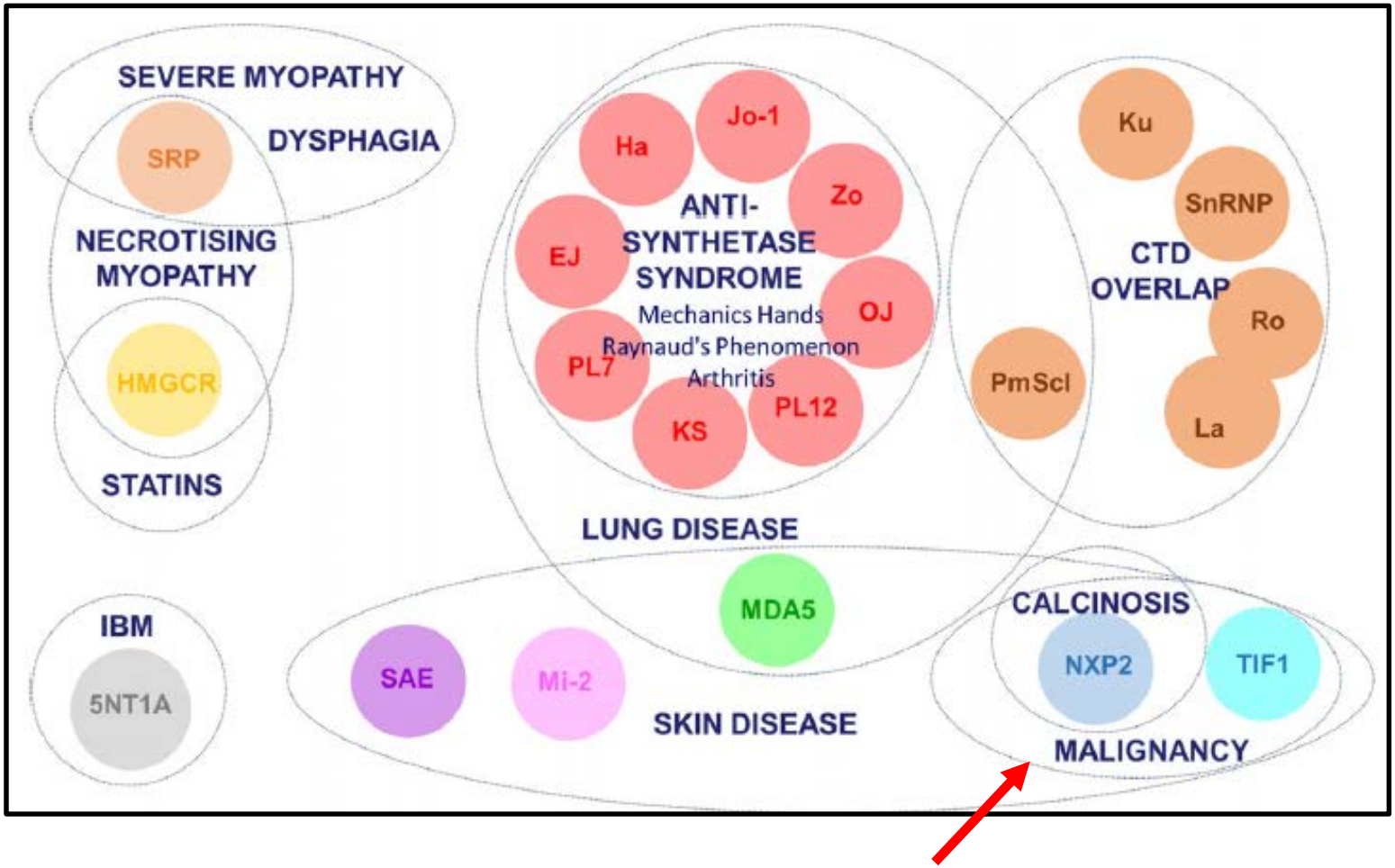
Metanalisi di 6 studi retrospettivi

Dermatomiosite: 2439 pz tot., 574 pz con neoplasia associata (**24%**)

Polimiosite: 947 pz tot., 97 pz con neoplasia associata (**10.7%**)

Zahr & Baer, Curr Rheumatology Rep, 2011

Miopatie Infiammatorie (IMs)



Betteridge & McHugh, Journal of Internal Medicine, 2016

Dermatomiosite

Rischio di forma paraneoplastica

Aumento

- Sesso M
- Età avanzata
- Severo interessamento cutaneo e/o muscolare
- Marcato rialzo degli indici flogistici
- Calo C4

Riduzione

- Ab anti sintetasi / positività ANA
- Interstitial Lung Disease
- Fenomeno di Raynaud

Zahr & Baer, Curr Rheumatology Rep, 2011

Dermatomiosite

Associazione con K:

- nasofaringe (Sud Est Asia, Cina, Nord Africa)
- ovaio
- stomaco
- colon

Esito

- Ottima risposta allo steroide e al trattamento oncologico

- Rischio di recidiva anche in assenza di recidiva tumorale:

(feed-forward mechanism?)

- Sopravvivenza minore rispetto a forme non paraneoplastiche

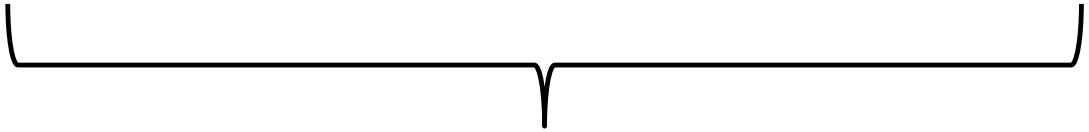
Menger & Schett. Nature Reviews, Rheumatology, 2014

Polimialgia reumatica

associazione con neoplasie: studi di non univoco risultato

Red flags :

- Età < 60 aa
- Scarsa rigidità muscolare
- Indici di flogosi nella norma o estremamente elevati
- Interessamento prettamente pelvico
- Interessamento artritico (RS3PE syndrome)



«forme atipiche»

Polimialgia reumatica

Guidelines

BSR The British Society for Rheumatology

BHPR British Health Professionals in Rheumatology

BSR and BHPR guidelines for the management of polymyalgia rheumatica

(ii) Core exclusion criteria:

- Active infection
- Active cancer
- Active GCA (see part iii)

(4) We recommend early specialist referral in the following circumstances (C).

Atypical features or features that increase likelihood of a non-PMR diagnosis:

- Age <60 years
- Chronic onset (>2 months)
- Lack of shoulder involvement
- Lack of inflammatory stiffness
- Prominent systemic features, weight loss, night pain, neurological signs
- Features of other rheumatic disease
- Normal or extremely high acute-phase response

Dasgupta et al. Rheumatology, 2010

RS3PE syndrome

Remitting Seronegative Symmetrical Synovitis Pitting Edema

- Forma idiopatiche e paraneoplastiche (24 % dei casi)
- Correlazione maggiore con K colon e mammella (= pop. gen.)
- Ottima risposta a steroide
- Buona prognosi: remissione con trattamento della neoplasia
- Patogenesi: VEGF con aumento permeabilità vascolare ; MMP3 sierico marker per forma paraneoplastica

Menger & Schett. Semin Arthritis Rheum, 2014
Li et al. Curr Rheumatol Rep, 2015

Artrite paraneoplastica

fondamentale stabilire il ***rapporto temporale*** tra artrite e tumore per definire l' artrite «paraneoplastica», data la frequenza di entrambe le malattie nella popolazione generale.

- Poliartrite associata K polmone, mammella o linfoma
- Frequentemente sieronegativa (20 % FR+, 10 % ACPA +)
- Importante flogosi sistemica
- Scarsa risposta a FANS/steroide/DMARDs
- Remissione con il trattamento del tumore
- Scarsa possibilità di recidiva al recidivare della neoplasia

Menger & Schett. Nature Reviews, Rheumatology, 2014

Paraneoplastic syndromes in rheumatology

Bernhard Manger and Georg Schett

Table 1 | Demographic and clinical characteristics of patients with paraneoplastic arthritis*

Study	Number of patients	Males:females	Mean age (years)	Tumour type (haematologic: solid)	Arthritis type (polyarthritis: oligoarthritis)	RF-positivity (%)	Time between onset of arthritis and tumour diagnosis (months)
Pines *et al.*[38]	3	1:2	63.3	0:3	2:1	67	3.0
Alvarez Lario *et al.*[39]	5	2:3	65.4	0:5	4:5	40	4.2
Pfitzenmeyer *et al.*[40]	12	7:5	61.2	0:12	12:0	42	3.3
Stummvoll *et al.*[41]	2	2:0	59.5	0:2	2:0	0	8.0
Morel *et al.*[42]	26	16:10	57.5	6:20	22:4	31	4.4
Hakkou *et al.*[43]	3	2:1	34.3	3:0	3:0	0	4.3
Yamashita *et al.*[44]	5	3:2	65.8	5:0	4:1	20	19.2
Kisacik *et al.*[45]	65	43:22	50.2	26:39	22:31 (12 with monoarthritis)	23	5.1

*Published in case series since 1984. Abbreviation: RF, rheumatoid factor.

Manger, B. & Schett, G. *Nat. Rev. Rheumatol.* **10**, 662–670 (2014)

Rheumatologic Manifestations of Cancer

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Table 7. *Features of Carcinoma Polyarthritis**

Close temporal relationship (10 months) between onset of arthritis and malignancy
Late onset of arthritis
Asymmetric joint involvement
Explosive onset
Predominant lower-extremity involvement, with sparing of wrists and small joints of hands
Absence of rheumatoid nodules
Absence of rheumatoid factor
Negative family history for rheumatoid disease
Nonspecific histiopathology of synovial lining

**From* Caldwell, D. S.: Musculoskeletal syndromes associated with malignancy. *In* Kelley, W. N., Harris, E. D., Jr., Ruddy, S., et al. (eds.): Textbook of Rheumatology. Edition 2. Philadelphia, W. B. Saunders Co., 1985; with permission.

K polmone

Review

Autoimmune paraneoplastic syndromes associated to lung cancer: A systematic review of the literature

Valérie Durieux[a], Michelle Coureau[b], Anne-Pascale Meert[b], Thierry Berghmans[b], Jean-Paul Sculier[b,*]

Out of 506 references, 13 articles [49–61] were deemed eligible. Two more articles [62,63] were retrieved from the bibliography of the selected publications. Most of them were single case reports, only one article included 3 cases [52].

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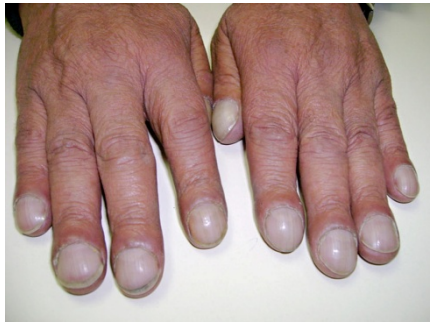
12 casi di poliartrite

3 casi di polimialgia reumatica

Durieux et al.. Lung Cancer 106 (2017)

Osteoartropatia ipertrofica

- Inspessimento corticale ossea delle ossa lunghe AAII
- Periostite
- Artrite delle articolazioni adiacenti
- Clubbing digitale
- Acanthosis palmaris



secondaria **primaria**

↓

carcinoma polmonare: (0.8 % clinica **+**, 4.5 % PET **+**)

Izumì et al.. Respirology, 2010

Osteoartropatia ipertrofica

- **Patogenesi**: - Platelet Derived Growth Factor (PDGF)
  - Vascular Endotelial Growth Factor (VEGF)

↓

aumento permeabilità vascolare
crescita cellule mesenchimali e fibroblasti
differenziazione osteoblastica

- **Terapia**: - trattamento K polmone ⇐
  - Acido zoledronico
  - FANS

Fascite palmare e poliartrite (PFPAS)

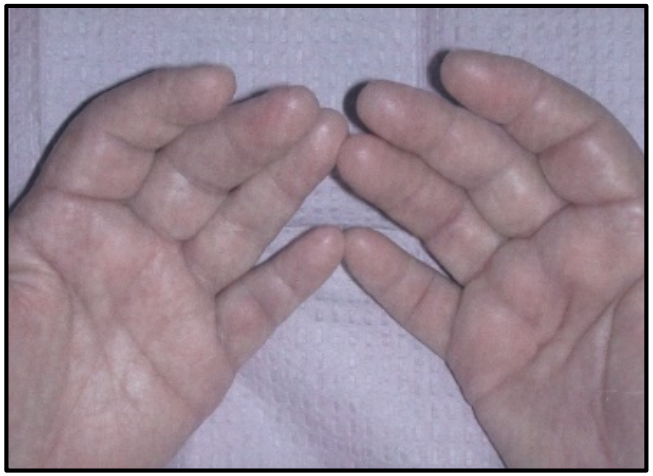
Infiammazione fascia palmare e/o artrite MCF/IFP

Proliferazione fibroblastica

Marcato inspessimento nodulare («*woody hands*»)

Contratture in flessione

> In adenocarcinoma ovarico, spesso avanzato



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Fascite palmare e poliartrite (PFPAS)

- Associazione con **K ovaio (37%) e mammella**
- Meccanismo ignoto, presumibilmente immunomediato
- Scarsa risposta a steroide e DMARDs
- Prognosi sfavorevole: K spesso metastatizzato alla diagnosi

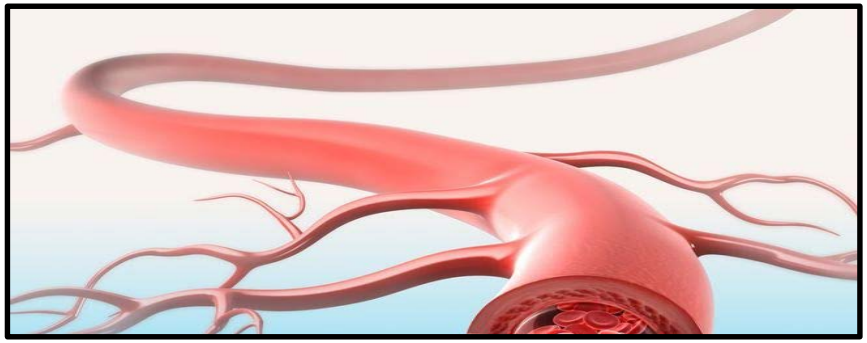
Menger & Schett. Semin Arthritis Rheum, 2014

Osteomalacia oncogenica

- FGF23 (fosfatonina): legame a cellule del tubulo prossimale con aumento escrezione fosfati
- Tumore: 40 % osseo (AAII), 60 % altre sedi
  spesso di minime dimensioni
- Clinica:
  - Fratture ossee
  - Debolezza muscolare
  - Iperfosfaturia con ipofosfatemia
  - Vitamina D nella norma o solo lievemente ridotta
- Ottima risposta a rimozione del tumore

Vasculiti

- Rara manifestazione paraneoplastica
- Correlazione con neoplasie ematologiche
- Patogeneticamente legata a immunocomplessi (?)
- Forme ANCA + e -
- Istologicamente spesso vasculiti leucocitoclastiche
- Scarsa risposta alla terapia convenzionale



Bojinca & Ianta. MedicA, 2012.

Intern Emerg Med
DOI 10.1007/s11739-017-1626-8

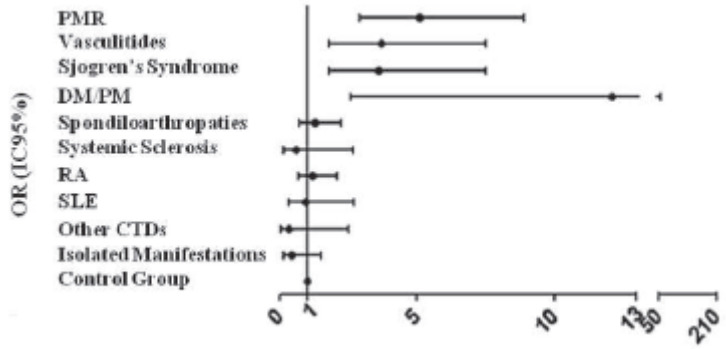
IM - ORIGINAL

Association between rheumatic diseases and cancer: results from a clinical practice cohort study

Mattia Bellan[1,2] · Enrico Boggio[1] · Daniele Sola[1,2] · Antonello Gibbin[1,2] · Alessandro Gualerzi[1,2] · Serena Favretto[1,2] · Giulia Guaschino[1,2] · Ramona Bonometti[1,2] · Roberta Pedrazzoli[2] · Mario Pirisi[1,2,3] · Pier Paolo Sainaghi[2,3]

08 February 2017

Sjogren/DM/PM/vasculiti



In conclusion, we confirm the strong association between rheumatic diseases such as Sjogren's syndrome, DM/PM and vasculitis with both haematologic and solid cancer. Also, we report the existence of an association with cancer for patients who received a recent diagnosis of PMR: among them, aged males with involvement of at least six joints seem to be at particularly high risk.

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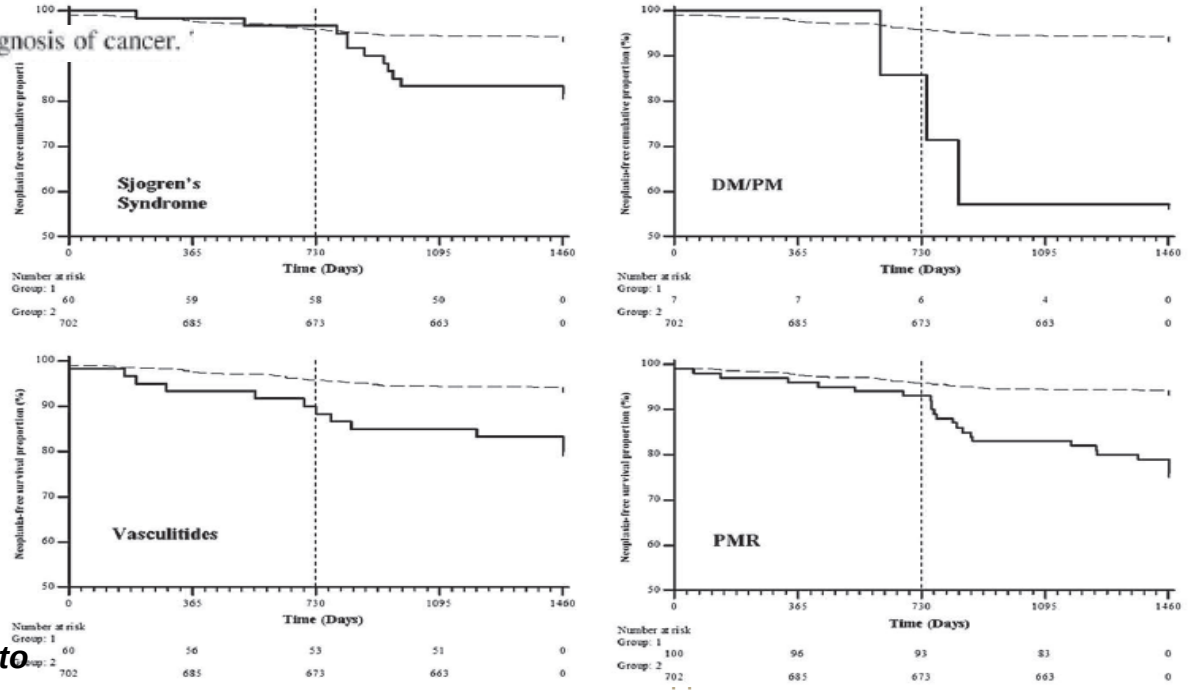
Table 2 Frequency distribution of neoplastic conditions in the population studied

Neoplastic disease	Number of patients	Percentage
Breast cancer	29	20.4
Colorectal adenocarcinoma	17	12.0
LH and LNH	17	12.0
Bladder cancer	11	7.8
Multiple myeloma	9	6.3
Chronic myeloproliferative and myelodysplastic syndromes	8	5.7
Lung cancer (SCLC e NSCLC)	7	4.9
Thyroid cancer	7	4.9
Endometrial cancer	6	4.2
Renal cancer	5	3.5
Prostatic adenocarcinoma	5	3.5
Other solid neoplasms	21	14.8
Total	142	100.0

"Other solid neoplasms" is a diagnostic category collecting all those syndromes diagnosed in less than

PMR > rischio se sesso maschile, recente diagnosi, impegno poliarticolare

Time-to-event analysis for a diagnosis of cancer.



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Take home messages

- Le sindromi paraneoplastiche **sono causate da fattori solubili** prodotti da cellule tumore **o sono conseguenza di reazioni immuni** contro le cellule tumorali stesse.

- La **scarsa risposta** di una forma reumatica ad una **terapia** impone un **approfondimento** alla ricerca di potenziali cause neoplastiche.

- **Artriti, miositi, periostiti, fascite, osteomalacia possono essere manifestazioni paraneoplatiche di neoplasie**.

Menger & Schett. Nature Reviews, Rheumatology, 2014.

Take home messages

- A causa delle proprietà di alcuni fattori solubili prodotti dalle cellule tumorali, **alcune** neoplasie mostrano un **caratteristico interessamento di specifici tessuti** muscoloscheletrici (es.VEGF inducing HOA or FGF23 inducing osteomalacia)

- Nonostante la loro rarità, è **fondamentale riconoscere elementi clinici** potenzialmente **sospetti** di una forma paraneoplastica.

- La scoperta dei meccanismi molecolari alla base di queste manifestazioni reumatiche rappresenterà uno step fondamentale nella conoscenza sia delle malattie reumatiche che di quelle neoplastiche.

Menger & Schett. Nature Reviews, Rheumatology, 2014.

Grazie!

Un particolare grazie al dott. Masen Abdel Jaber specializzando Reumatologia UNI VR