Con il Patrocinio di

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Città della Salute e della Scienza di Torino

S.C. Reumatologia AO Città della Salute e della Scienza di Torino

Le sindromi paraneoplastiche in Reumatologia

Enrico Fusaro

Definition

Paraneoplastic syndromes involve symptoms mediated by

a) hormones and cytokines from a tumor

b) the consequence of humoral or cellular immune mechanisms directed against tumor cells

c) direct invasion by the tumor or metastases does not occur

Rheumatic manifestations of neoplasia

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

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

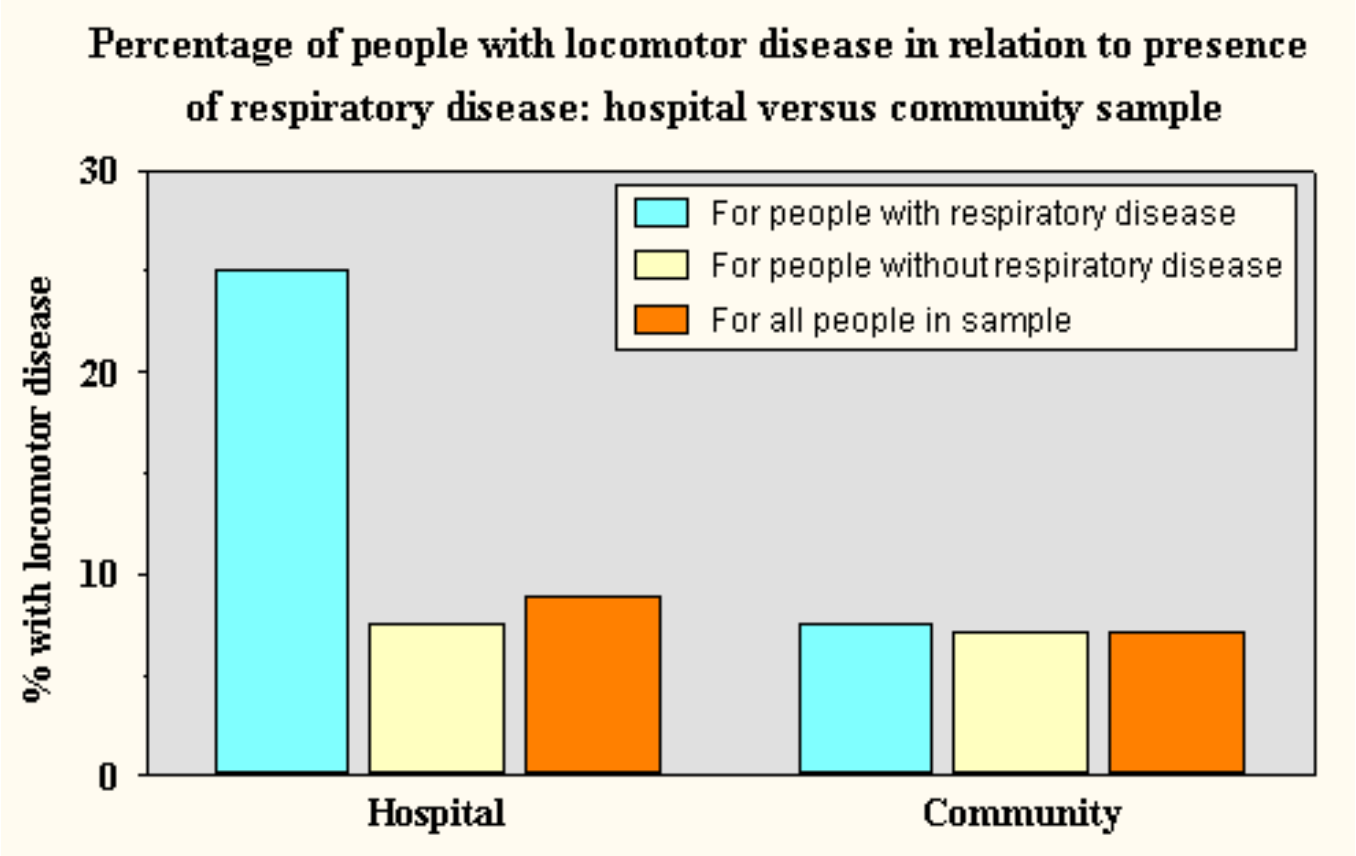
- *Myopathy* (dermatomyositis/polymyositis)
- *Arthropathies*
  - Hypertrophic osteoarthropathy
  - Amyloidosis
  - Secondary gout
  - Carcinoma polyarthritis
- *Miscellaneous presentations*
  - Lupus-like syndrome
  - Necrotizing vasculitis
  - Cryoproteins
  - Immune-complex disease
  - Reflex sympathetic 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.

Paraneoplastic syndromes timing

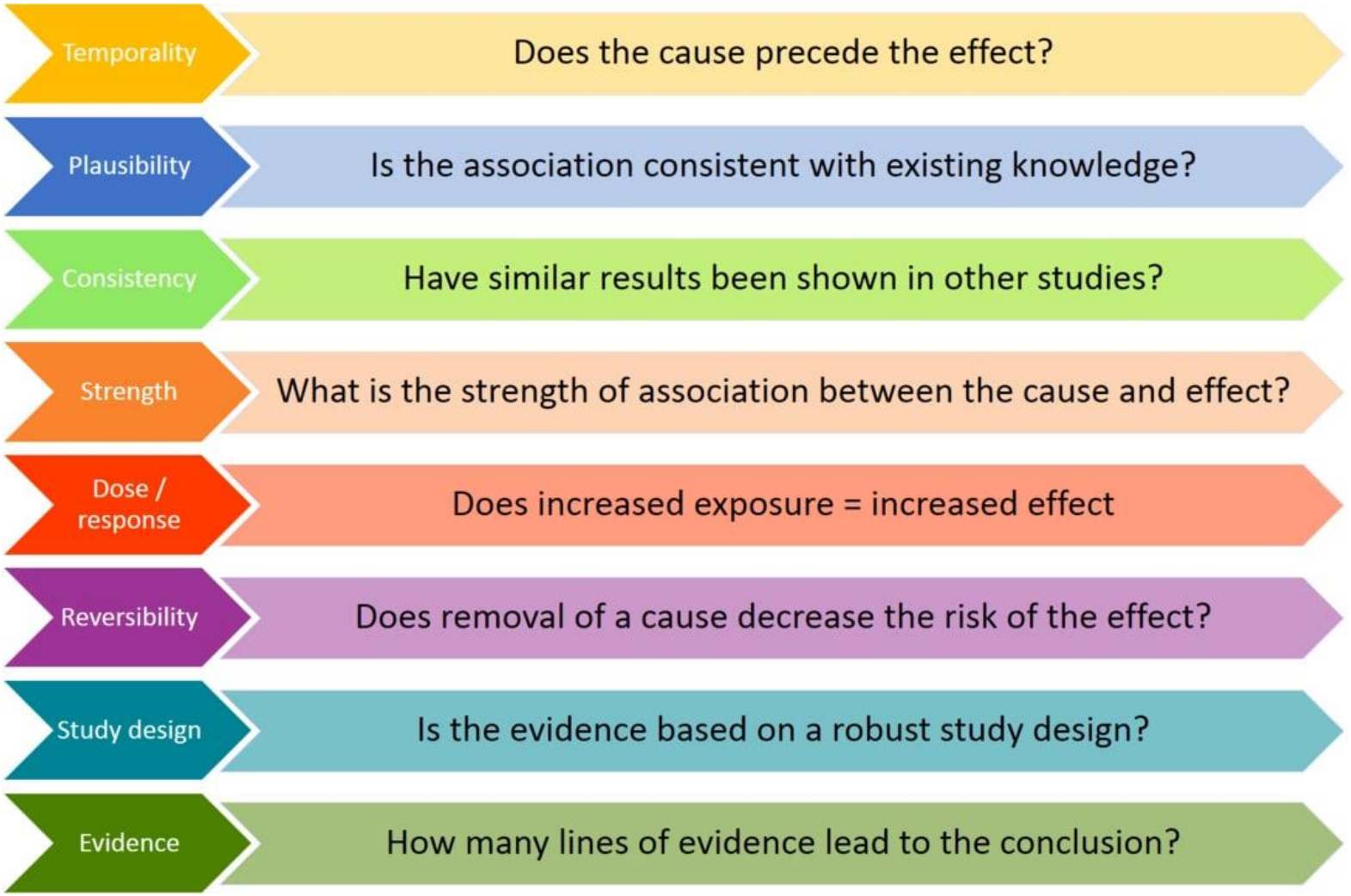
In the case of paraneoplastic rheumatic syndromes, rheumatic symptoms can **coincide, precede, or follow** the diagnosis of cancer or herald its recurrence, generally at no longer than 2 years before the diagnosis of associated cancer.

Berkson's Bias



Sackett, D.L. (1979). Bias in analytic research. Journal of Chronic Diseases 32, 51-63.

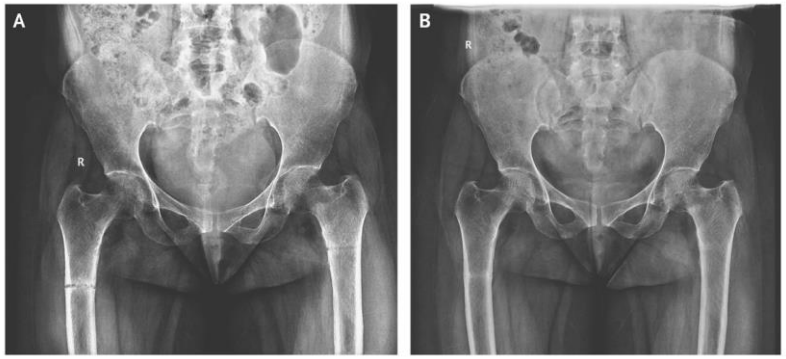
Brandford Hill Criteria

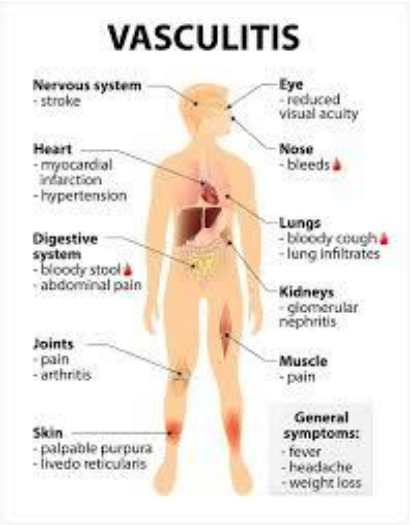


Hill AB. The environment and disease: association or causation? Proc R Soc Med. 1965;58(5):293–300.

Malignancies and rheumatic manifestations

- Malignancies are associated with a wide variety of paraneoplastic rheumatic manifestations, which may arise in joints, fasciae, muscles, vessels or bone





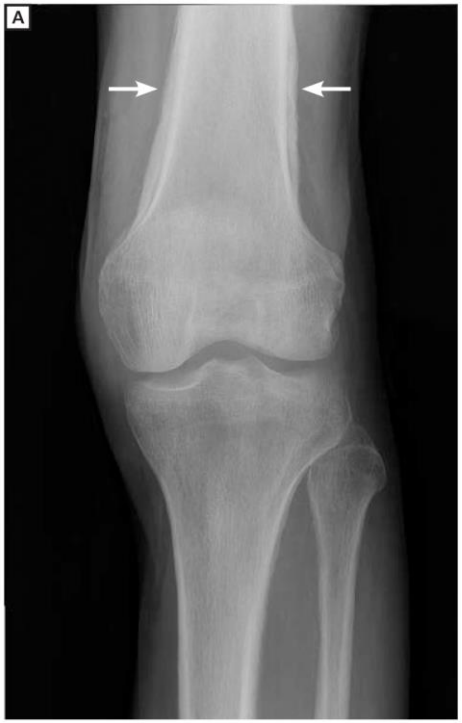
Clinical syndromes

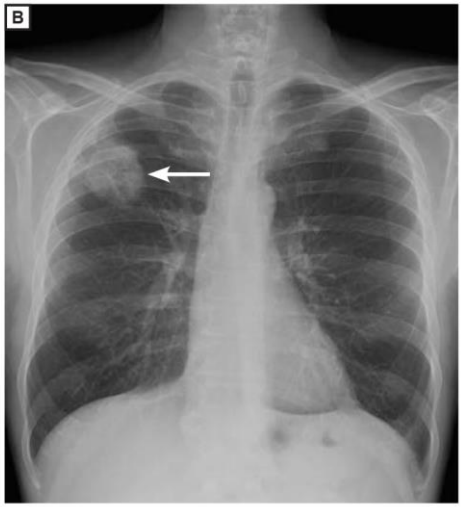
- Hypertrophic osteoarthropathy
- Paraneoplastic polyarthritis
- Remitting seronegative symmetrical synovitis with pitting oedema (RS3PE)
- Palmar fasciitis and polyarthritis
- Cancer-associated myositis
- Tumour-induced osteomalacia
- Paraneoplastic vasculitis

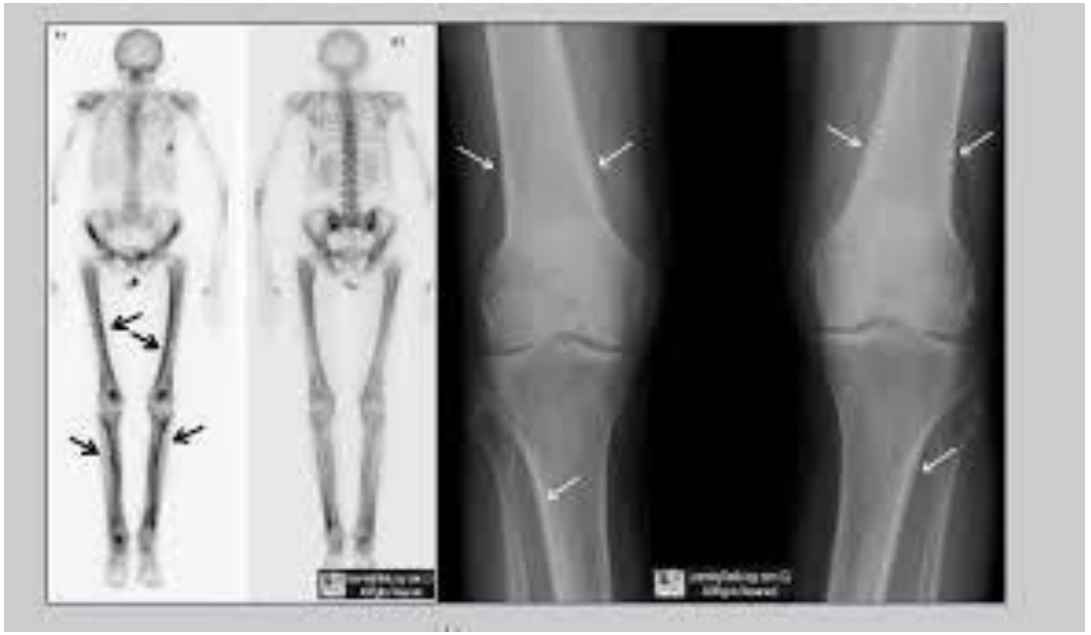
Hypertrophic osteoarthropathy

- **Periosteal osseous proliferations** can be detected by conventional radiography and the formation of new osseous tissue leads to increased tracer uptake in scintigraphic bone scans.
- **Tibial and femoral bone pain** is the typical musculoskeletal symptom associated with HOA, and arthralgia or synovitis of adjacent joints is common.
- The highly inflammatory character of periostitis also generates a strong signal that can be detected by **positron emission tomography.**

Hypertrophic osteoarthropathy

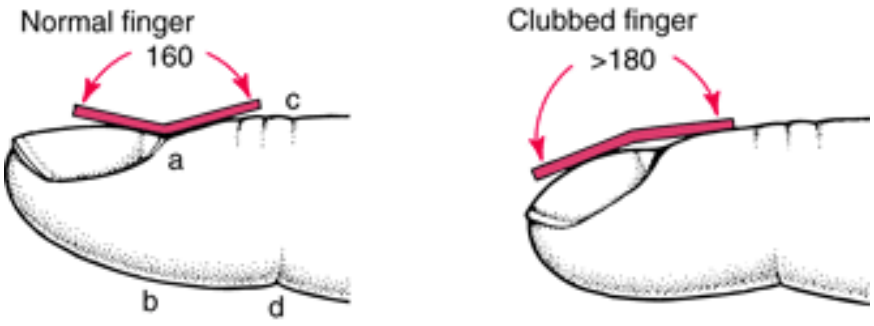


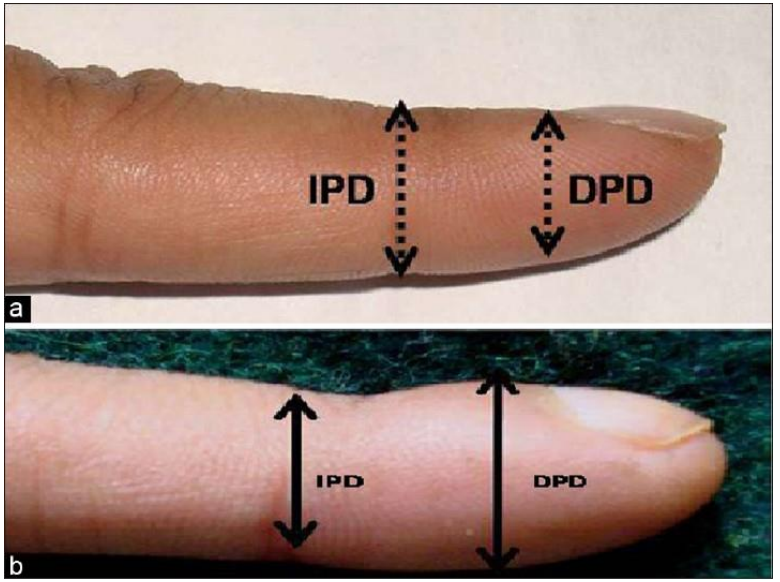




Hypertrophic osteoarthropathy

- Another characteristic finding is **clubbing** of fingers and/or toes.
- This clinical sign, first described by Hippocrates, is characterized by an **increase in the angle of the hyponychium** to over 180°, periungual oedema and softening of the nail bed.





Digital clubbing

- In an analysis of over 1,200 bone scans from patients with lung cancer increased linear femoral or tibial tracer uptake was found in 4.5% of patients, but only 0.8% displayed the full clinical picture of HOA, with digital clubbing and arthralgias.

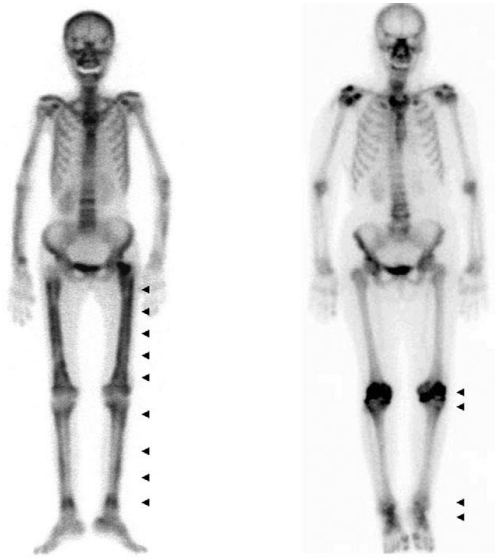
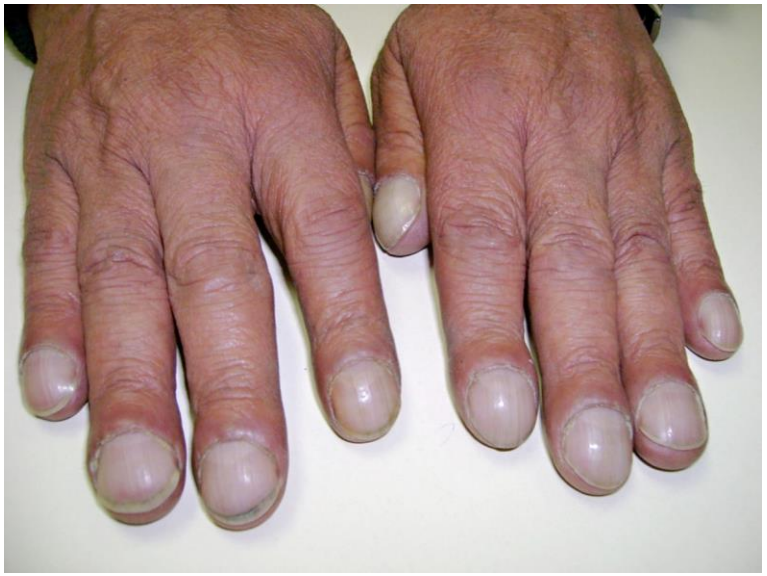
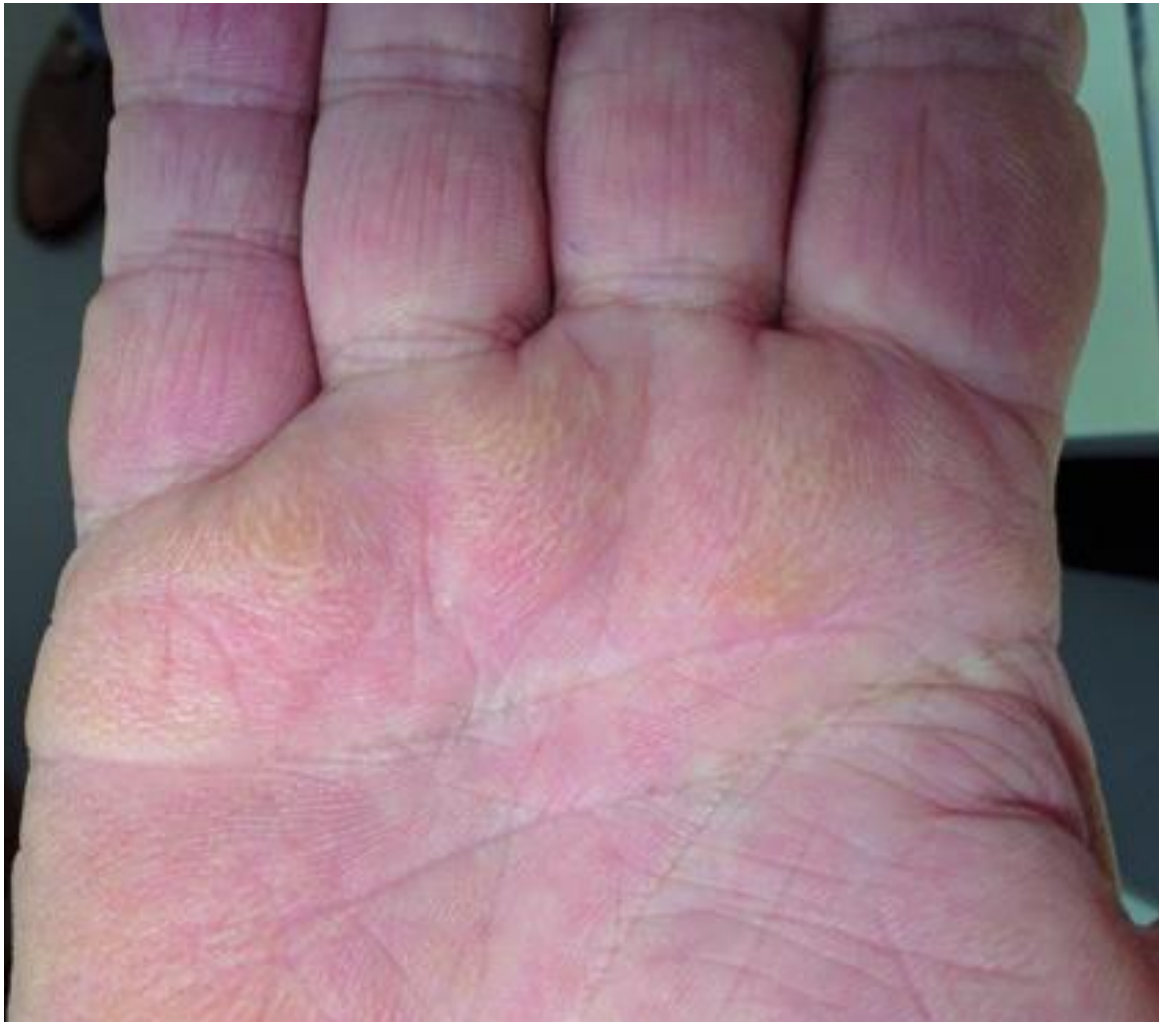


Figure 1 Left: pattern of uptake of ^{99m}Tc-hydroxymethylene diphosphonate in the long bones on bone scintigraphy. Abnormally high uptake is visible bilaterally in the tibias and femurs (arrows). Right: pattern of uptake of ^{99m}Tc-hydroxymethylene diphosphonate in the joints on bone scintigraphy. Abnormally high uptake is visible predominantly bilaterally in the knees and ankles (arrows).



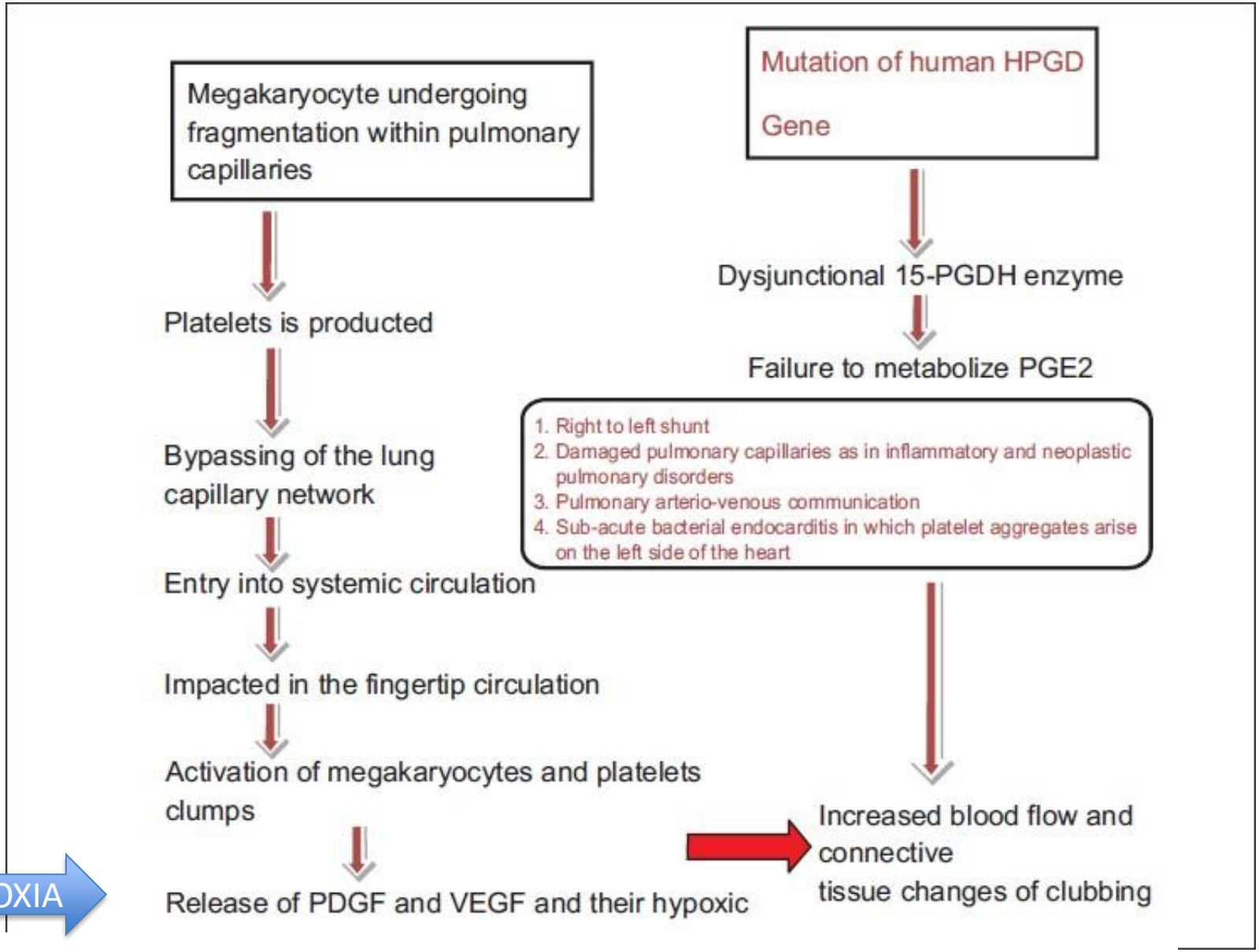
Nakanishi, Y. Incidence of hypertrophic pulmonary osteoarthropathy associated with primary lung cancer. Respirology 15, 809–812 (2010).

Acanthosis palmaris



Acanthosis palmaris or tripe palms in a patient with **lung cancer** who had also developed marked clubbing of the terminal phalanges of all fingers.

Pathogenesis of HOA



Malay Sarkar M, Digital Clubbing. Lung India. 2012; 29:354-362

Prognosis and therapy of HOA

- In the event of **complete remission of the underlying malignancy** achieved by resection, radio- or chemotherapy, clubbing and HOA can also completely diminish.
- Periostitis and bone pain usually respond well to prostaglandin inhibition by **NSAIDs**, which is consistent with the detection of mutations in enzymes of prostaglandin metabolism accompanied by high levels of circulating PGE2 in primary HOA, as outlined above.
- In cases when NSAIDs cannot sufficiently control the symptoms of HOA, **zoledronic acid** has been used successfully. In addition to directly suppressing bone turnover, zoledronic acid has also been shown to reduce VEGF levels in patients with metastatic tumours.
- Another therapeutic alternative is the somatostatin analogue **octreotide**, which is presumably effective through its ability to inhibit VEGF production.

Paraneoplastic polyarthritis

- **Cancer and polyarthritis are both common conditions in the general population**, so their coexistence in one patient does not necessarily establish a causal relationship between the two conditions.
- Only when there is a close temporal relationship between the onset of polyarthritis and the detection of a malignant process, or when successful tumour therapy leads to the remission of joint symptoms, does a paraneoplastic process seem likely.

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.*	3	1:2	63.3	0:3	2:1	67	3.0
Alvarez Lario *et al.*	5	2:3	65.4	0:5	4:5	40	4.2
Pfitzenmeyer *et al*	12	7:5	61.2	0:12	12:0	42	3.3
Stummvoll *et al.*	2	2:0	59.5	0:2	2:0	0	8.0
Morel *et al.*	26	16:10	57.5	6:20	22:4	31	4.4
Hakkou *et a*	3	2:1	34.3	3:0	3:0	0	4.3
Yamashita *et al*	5	3:2	65.8	5:0	4:1	20	19.2
Kisacik *et al.*	65	43:22	50.2	26:39	2:31 (12 with monoarthritis)	23	5.1

Malignancy dominated with rheumatic manifestations: A retrospective single-center analysis

Jian Wen[1], Han Ouyang[2], Ru Yang[1], Lin Bo[1], Yi Zhang[1], Mei Tang[1] & Zhichun Liu[1]

Autoantibody	All patients N = 21	Arthritis N = 7	Vasculitis N = 4	Other CTDs N = 10
ANA	38%	14%	25%	60%
Anti-dsDNA	0	0	0	0
Anti-nucleosome	0	0	0	0
Anti-nonhistone	0	0	0	0
Anti-Sm	0	0	0	0
Anti-U1RNP	0	0	0	0
Anti-Ribosomes-P protein	0	0	0	0
Anti-SSA	0	0	0	0
Ro-52	0	0	0	0
Anti-SSB	0	0	0	0
Anticentromere	0	0	0	0
Anti-Scl70	0	0	0	0
Anti-Jo-1	0	0	0	0
RF	43%	57%	25%	40%
anti-CCP	10%	29%	0	0
ANCA	10%	0	50%	0

Pathogenesis

- No convincing pathogenetic hypothesis for paraneoplastic arthritis has so far been proposed.
- Earlier claims that circulating immune complexes were involved could not be substantiated.
- In one patient with renal- cell carcinoma and oligoarthritis, a **clone with identical T-cell-receptor γ gene rearrangement** was isolated from synovial tissue as well as from tumour-infiltrating cells, suggesting that lymphocytes directed against the tumour can **crossreact** with synovial antigens to trigger paraneoplastic synovitis.

Prognosis and therapy

- A characteristic feature of paraneoplastic arthritis is a **rather poor response to NSAIDs and steroid therapy** in comparison with other forms of early arthritis.
- Remission is usually not achieved by immunosuppression, but successful surgical removal or chemotherapy of the underlying malignancy frequently leads to the complete resolution of all rheumatic symptoms.
- **In most cases, however, a tumour relapse is not accompanied by the recurrence of arthritis.**

Table 2 Characteristics of musculoskeletal IRAEs, laboratory and imaging results

Patient	Pattern of arthritis	PMR-like disease	Other MS IRAEs	Latency MS IRAE after ICI start (days)						
1	Oligo	+ve	–ve	174						
2	Mono	–ve	–ve	121						
3	Mono	+ve	Sicca	289						
4	Poly	+ve	–ve	1			–ve			
5	Poly	+ve	–ve	48	38.6	–ve /–ve	1:3200/ –ve	–ve	ND	1
6	Oligo	–ve	–ve	143	38.2	–ve /–ve	1:1600/ –ve	ND	ND	1
7	Oligo	–ve	Sicca	43	71.3	–ve /–ve	–ve / ND	–ve	2600	1
8	Mono	–ve	–ve	31	21.2	–ve /–ve	1:800/ –ve	–ve	ND	2
9	Mono	–ve	–ve	716	≤5.0	–ve/–ve	1:200/ –ve	–ve	ND	2, 3, 4
10	Mono	–ve	–ve	253	≤5.0	+ve/ ve	1:100/ ND	ND	ND	1, 4
11	Oligo	–ve	Myositis	76	≤5.0	–ve/–ve	–ve / ND	–ve	20 000	1, 2, 3
12	Mono	–ve	–ve	139	6.8	+ve/–ve	1:400/ –ve	–ve	ND	4
13	Oligo	–ve	–ve	116	48	+ve/–ve	1:12800/ SSA	–ve	6000	1, 2, 3
14	Mono	+ve	–ve	394	114	+ve/–ve	–ve / –ve	–ve	ND	1
	7 M 5 O 2 P	**5 +**		**1-715**	**4 – 10 +**	**FR 5 APCA 2**	**3 +**			

Autoimmunity

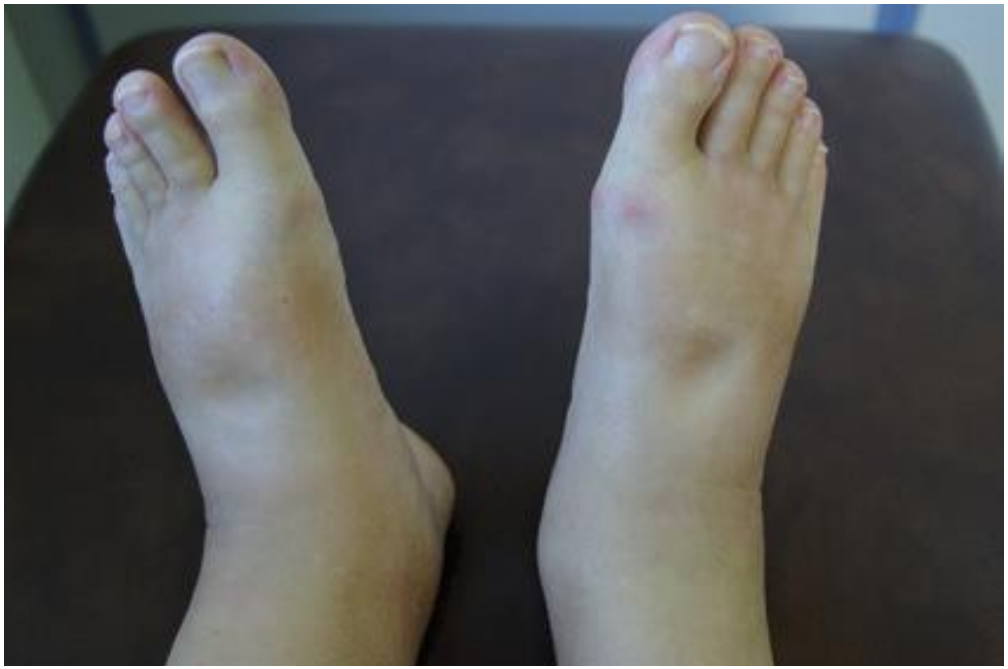
RMD Open
Rheumatic & Musculoskeletal Diseases

CLINICAL CASE

Characteristics and treatment of new-onset arthritis after checkpoint inhibitor therapy

Jan Leipe,[1] Lisa A Christ,[1] Andreas P Arnoldi,[2] Erik Mille,[3] Frank Berger,[2] Markus Heppt,[4] Ilana Goldscheider,[4] Diego Kauffmann-Guerrero,[5] Rudolf M Huber,[5] Claudia Dechant,[1] Carola Berking,[4] Hendrik Schulze-Koops,[1] Alla Skapenko[1]

RS3PE



Remitting seronegative symmetricall synovitis with pitting oedema (RS3PE) is characterized by the symmetrical involvement of small joints and marked pitting oedema on the dorsum of the hands and feet, a sudden inflammatory onset, rheumatoid factor negativity and an overall excellent prognosis.

Remitting seronegative symmetrical synovitis with pitting oedema in a patient with non-Hodgkin lymphoma.

RS3PE

- Increasing numbers of cases were reported, with a neoplastic process being diagnosed immediately after the first symptoms of RS3PE or during follow-up.
- In five small case series of a total of 89 patients with RS3PE, a malignancy was reported in 22 patients (24.7%), in five cases of haematopoietic origin.
- No significant demographic or clinical differences were observed between idiopathic and paraneoplastic cases of RS3PE.

Pathogenesis RS3PE

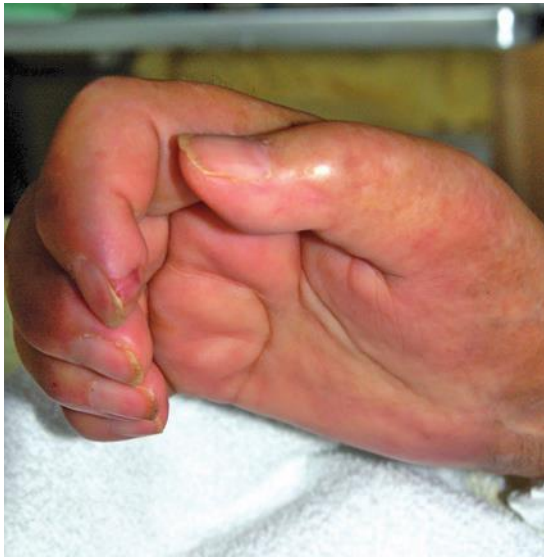
- **VEGF has been proposed to be important in the pathogenesis of RS3PE in both idiopathic and paraneoplastic cases**, with elevated serum levels in comparison with other autoimmune rheumatic diseases reported for idiopathic RS3PE as well as for cases associated with sarcoidosis or angioimmunoblastic T-cell lymphoma.
- Since VEGF is a potent angiogenic and vasoactive molecule, it could **facilitate both synovial hypervascularity (synovitis) and increased vascular permeability (sub- cutaneous oedema) in RS3PE**.

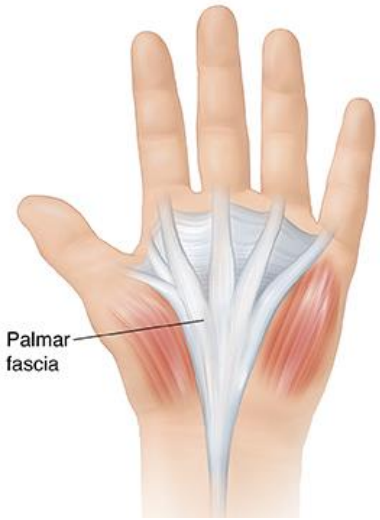
Pathogenesis RS3PE

- So far, the only marker specific for **paraneoplastic RS3PE is matrix metallo- proteinase (MMP)-3**, the levels of which are significantly elevated in the serum.
- The pathogenetic relevance of this finding remains unclear, but MMPs have been shown to be involved in the invasion or progression of solid tumours as well as in the pathologic destruction of joint tissues in arthritides.

Palmar fasciitis and polyarthritis

- Palmar fasciitis and polyarthritis syndrome (PFPAS) is a **rare** paraneoplastic disorder first described as a separate entity in 1982 by Medsger *et al.*, who reported the sudden onset of **stiffness and diffuse painful swelling of both hands together with polyarthritis** in six postmenopausal women with malignant **ovarian** tumours.





Palmar fasciitis and polyarthritis

- The hallmark of PFAPS is inflammation of the **palmar fascia**, which leads to flexion contractures with nodular thickening similar to, but more severe than, that occurring in Dupuytren's contracture .
- The palpatory sensation of the marked **induration** of subcutaneous tissues has led to the descriptive term **'woody hands'.**
- The **polyarthritis** aspect involves metocarpophalangeal and proximal interphalangeal joints and wrists, while arthritides of other joints are frequent but usually milder.
- **Carpal tunnel syndrome** can be present.

Palmar fasciitis and polyarthritis

- The most frequent tumour type in patients with para- neoplastic PFPAS is **ovarian** adenocarcinoma (present in 37% of cases), which, together with **breast** cancer and other malignancies involving female reproductive organs, is responsible for more than half of all published cases of paraneoplastic PFPAS.
- For this reason, PFPAS is over four times more prevalent in **females** than in males.
- In patients with PFPAS, inflammation markers show a great range of variability, rheumatoid factor is negative or only weakly positive, and ACPAs have not been detected.

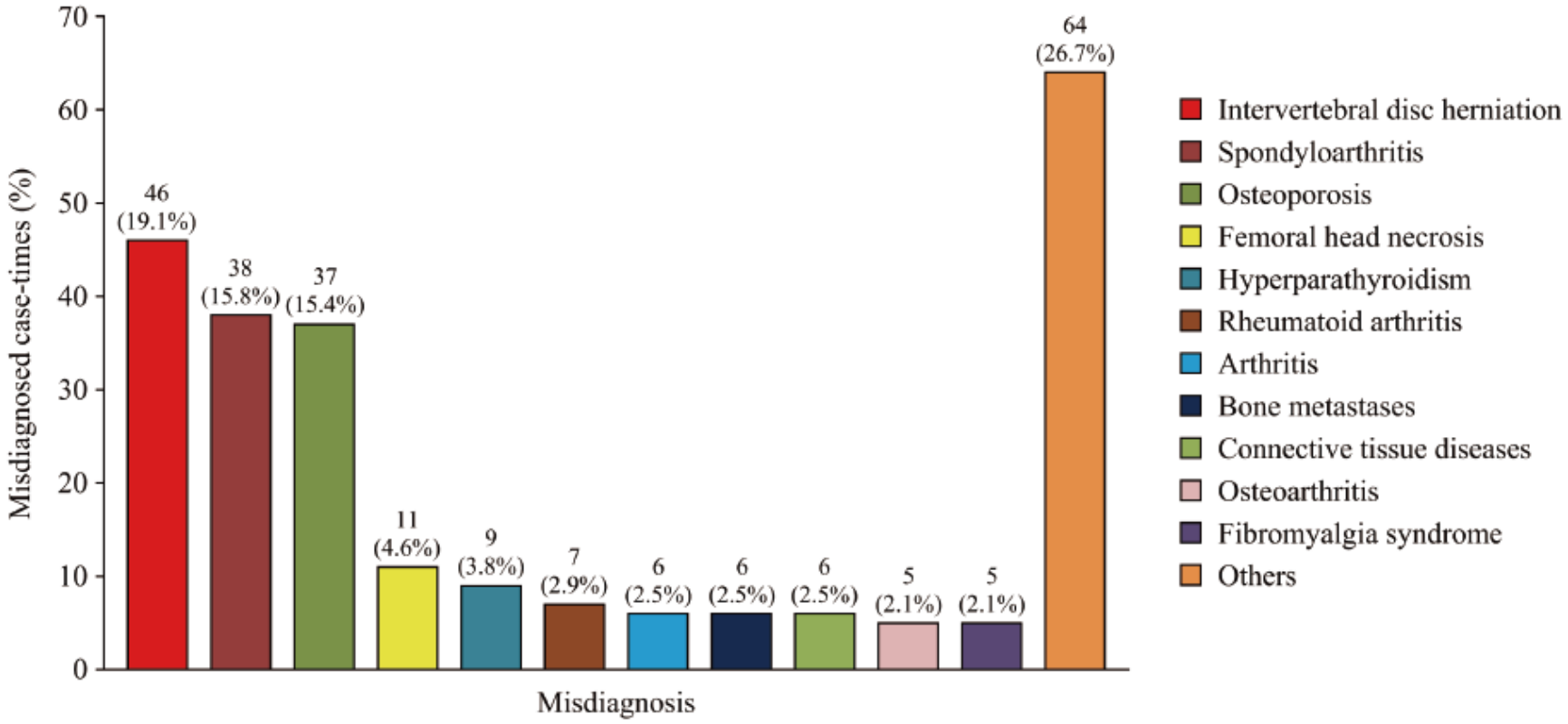
Tumour-induced osteomalacia

- More than 300 similar cases have been reported in the literature, and the syndrome has been named **tumour-induced osteomalacia (TIO) or oncogenic osteomalacia.**
- It is characterized by pathologic fractures, muscle weakness, height loss, **hypophosphataemia, hyperphosphaturia**, and normal or low levels of 1,25-dihydroxyvitamin D.
- Other causes of genetic and acquired hypophosphataemia must be excluded in the diagnostic work-up and, in most cases, it often takes a long time to identify and locate the underlying tumour.

FGF23

- tumours secrete the endocrine **fibroblast growth factor 23 (FGF23**; also known as phosphatonin), a member of the fibroblast growth factor superfamily, which binds to proximal tubule cells of the kidney and thereby induces a marked increase in phosphate excretion.
- The typical type of neoplasm associated with TIO and the production of FGF23 is a **phosphaturic mesenchymal tumour** (mixed connective tissue variant), but other histologic diagnoses, such as haemangiopericytoma, osteosarcoma, giant cell tumour and other mesenchymal tumours

Diagnosi errate in 144 casi di Osteomalacia Oncogenica



Feng J et al. *Endocrine Journal* 2017

Tumori correlati

“*strange tumors in strange places*”

>10%	<1%
Hemangiopericytoma	Benign Connective Tissue tumor
	Brown tumor
5-10%	Degenerated Osteoid
	Diffuse Giant Cell tumor
Mesenchymal Tumor	Extraskeletal Chondroma
Nonossifying Fibroma	Mesenchymal Chondrosarcoma
Prostatic Carcinoma	Atypical chondroma
	Giant Cell Fibrous malignat Histiocytoma
1-5%	Hemangiofibroma
	Mesenchymal Spindle Cell Tumor
Angiolipoma	Mesenchymoma
Epidermal Nevi	Mixed Mesenchymal tumor
Malignant Chondroblastoma	Vascular Mesenchymoma
Giant Cell Chondroma	Myelomatosis
Giant Cell Granuloma	Neurinoma
Giant Cell tumor	Neuroma
Hemangioma	Malignant Neuroma
Hemangioendothelioma	Oat Cell Carcinoma
Cavernous Hemangioma	Odontogenic Fibroma
Ossifying mesenchymal tumor	Fibrosarcoma
Ossifying Fibroma	Low Grade Fibrosarcoma
Fibroangioma	Fibrous Xanthoma
Osteoblastoma	Osteochondroblastoma
Benign Osteoblastoma	Osteosarcoma
Polyostotic Fibrous Dysplasia	Paraganglioma
Primary Bone tumor	Sarcoma
Sebaceous Naevi	Small Cell Carcinoma
Sclerosing Hemangioma	Transitional Cell Carcinoma
Synovial tumors	Vascular Tumor

Prognosis and therapy

- The prognosis for TIO is excellent following complete resection of the occult neoplasm, which leads to the rapid and complete reversal of all symptoms.
- A return of serum FGF23 levels to normal indicates the successful removal of the entire tumour.
- If the tumour cannot be found or its removal is not possible, medical therapy using phosphate supplementation and active vitamin D compounds is necessary.

Paraneoplastic Vasculitis in Patients with Solid Tumors: Report of 15 Cases

ROSER SOLANS-LAQUÉ, JOSEP ANGEL BOSCH-GIL, CARMEN PÉREZ-BOCANEGRA, ALBERT SELVA-O'CALLAGHAN, CARMEN P. SIMEÓN-AZNAR, and MIQUEL VILARDELL-TARRES

Characteristics of patients with vasculitis and solid tumors.

Case	Age/Sex	Type of Vasculitis	Presenting Features of Vasculitis	Type of Neoplasia	Occurrence of Vasculitis/Neoplasia
1	84 F	LCV	Purpura, arthritis, microhematuria	Urinary bladder transitional carcinoma	6 mo before
2	74 M	LCV	Purpura, arthritis, microhematuria	Urinary bladder carcinoma	3 mo before
3	83 F	LCV	Purpura, arthritis, microhematuria	Urinary bladder carcinoma	2 mo after
4	72 M	LCV	Purpura, arthritis, digital ischemia, limb ulcers	Prostate adenocarcinoma	4 mo before
5	69 M	LCV	Purpura, arthritis, weight loss	Prostate adenocarcinoma	2 mo after
6	80 M	LCV	Purpura	Lung squamous carcinoma	3 mo before
7	69 M	LCV	Purpura, digital ischemia	Lung adenocarcinoma	synchronous
8	67 M	LCV	Purpura, limb ulcers	Colon adenocarcinoma	synchronous
9	73 F	LCV	Purpura, arthritis, limb ulcers	Colon adenocarcinoma	synchronous
10	68 M	HSP	Purpura, arthritis, renal failure, pulmonary hemorrhage, abdominal pain, rectorrhage	Colon adenocarcinoma	synchronous
11	58 M	HSP	Purpura, arthritis, abdominal pain, renal failure	Lung adenocarcinoma	synchronous
12	69 M	PAN	Purpura, arthritis, chondritis, panniculitis, eyelid edema, myalgia, limb paresthesis	Colon adenocarcinoma	10 mo before
13	83 F	GCA	Cephalgia, scalp tenderness	Cholangiocarcinoma	6 mo before
14	61 F	GCA	Cephalgia, fever, polymyalgia rheumatica	Renal cell carcinoma	4 mo before
15	77 F	GCA	Scalp tenderness, monocular amaurosis, polymyalgia rheumatica	Breast carcinoma	synchronous

LCV: leukocytoclastic vasculitis; HSP: Henoch-Shönlein purpura; PAN: polyarteritis nodosa; GCA: giant cell arteritis.

J Rheumatol 2008;35:294–304)

Paraneoplastic Vasculitis in Patients with Solid Tumors: Report of 15 Cases

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Summary of the treatment and outcome of patients with vasculitis and solid organ tumors.

Case	Vasculitis	Malignancy AJCC Staging System	Vasculitis Therapy	Malignancy Therapy	Response to Treatment		Outcome (mo)
					Vasculitis	Malignancy	
1	LCV	Urinary bladder (T1, N0, M0)	PDN	Endoscopic resection	Remission*, 1R**	1 recurrence	Free of disease (36)
2	LCV	Urinary bladder (T3, N2, M0)	PDN	Surgical resection, chemotherapy, radiotherapy	Remission†	Resolution	Deceased (24)
3	LCV	Urinary bladder (T1, N0, M0)	PDN	Endoscopic resection	Remission*, 3R**	3 recurrences	Free of disease (48)
4	LCV	Prostate (T3, N1, M0)	PDN	Chemotherapy	Remission†, 1R**	Lung metastases	Deceased (18)
5	LCV	Prostate (T4, N1, M0)	PDN	Chemotherapy	Remission†, 3R	Bone metastases	Deceased (12)
6	LCV	Lung (T4, N3, M0)	PDN	Palliative therapy	Remission	Progression	Deceased (4)
7	LCV	Lung (T3, N2, M0)	PDN	Chemotherapy	Remission†, 1R**	Liver metastases	Deceased (8)
8	LCV	Lung (T3, N3, M1)	PDN	Palliative therapy	Partial remission	Cerebral metastases	Deceased (1)
9	LCV	Colon (T3, N0, M0)	PDN	Surgical resection	Remission*	Resolution	Free of disease (60)
10	HSP	Colon (T3, N1, M0)	PDN, CF, IGG, PE	Chemotherapy	No response	No response	Deceased (1)
11	HSP	Lung (T2, N2, M0)	PDN + IGG	Surgical resection	Remission*, 1R	Liver metastases	Deceased (8)
12	PAN	Colon (T2, N1, M0)	PDN + CF	Surgical resection	Remission*	Resolution	Deceased (18)
13	GCA	Biliary tract (T3, N1, M0)	PDN	Surgical resection	Remission*, 1R**	Liver metastases	Deceased (16)
14	GCA	Kidney (T1, N0, M0)	PDN, AZT	Surgical resection	Remission*	Resolution	Free of disease (36)
15	GCA	Breast (T1, N0, M0)	PDN	Surgical resection + tamoxifen	Remission*	Resolution	Free of disease (96)

AJCC: American Joint Committee on Cancer; LCV: leukocytoclastic vasculitis; HSP: Henoch-Shönlein purpura; PAN: polyarteritis nodosa; GCA: giant cell arteritis; PDN: prednisone; CF: cyclophosphamide; IGG: intravenous immunoglobulins; PE: plasma exchange. * Remission after cancer removal; † remission after cancer treatment and immunosuppressive therapy; R*: relapse of vasculitis heralding tumor recurrence or tumor progression.

J Rheumatol 2008;35:294–304)

Reported PAN and ANCA-vasculitis associated with solid organ tumors

Type of Vasculitis	n	Age/Sex	Neoplasia	Occurrence of Vasculitis in Relation to Tumor	Evolution of Vasculitis/Followup
PAN	1	63 M	Urinary bladder	Synchronous	Remission**/NA
	1	56 M	Urinary bladder	Synchronous	Remission*/alive at 7 yr
	1	83 M	Duodenum carcinoma	6 mo before	Remission*/death at 1.5 mo
	1	NA	Liver carcinoma	Synchronous	Remission*/NA
	1	62 M	Cholangiocarcinoma	6 mo before	Partial remission†/death 4 mo
	1	62 M	Gastric carcinoma	Synchronous	Resolution*/alive at 24 mo
	1	50 M	Gastric carcinoma	Synchronous	Death
	1	58 M	Colon carcinoma	3 mo before	Resolution**/NA
	1	75 F	Colon carcinoma	Synchronous	Resolution**/death at 11 mo
	1	62 F	Colon carcinoma	Synchronous	Remission†/NA
	1	65 M	Colon carcinoma	Synchronous	NA
	1	56 F	Colon carcinoma	Synchronous	Resolution**/alive at 4 mo
	1	NA M	Lung carcinoma*	25 mo before	Remission**/death
	1	37 M	Lung carcinoma*	17 mo before	Remission**/death at 22 mo
	1	49 M	Lung carcinoma*	Synchronous	No treatment/death
	1	65 M	Lung carcinoma*	9 mo before	Remission†/death at 11 mo
	1	58 M	Lung carcinoma*	7 mo before	Partial remission†/death 10 mo
	1	83 M	Lung carcinoma*	Before	Remission**/NA
	1	63 M	Prostate carcinoma + mesothelioma	9 mo after	Remission†/death at 13 mo
	1	66 M	Pharyngeal carcinoma	Synchronous	Resolution**/NA
	1	NA	CUO	NA	Resolution*/NA
	1	NA	CUO	NA	Death
MPA	1	NA	Lung carcinoma*	NA	Remission**/death
	1	62 F	Lung carcinoma*	Synchronous	Death
	1	68 M	Mediastinal carcinoma	4 mo before	Death at 2 mo
	1	NA	Prostate carcinoma	NA	Remission**/NA
	1	NA	Urinary bladder	NA	Remission**/NA
	1	69 F	Liver carcinoma	Synchronous	No treatment/death
	1	NA	Breast carcinoma	Synchronous	Remission**/NA
	1	NA	Colon carcinoma	Synchronous	Remission**/NA
	1	NA	Renal carcinoma	Synchronous	Remission**/NA
CSS	1	31 F	Melanoma	Synchronous R*	Death
WG	1	45 M	Renal carcinoma	7 mo before	Remission**/NA
	1	41 F	Renal carcinoma	Synchronous	Resolution**/alive at 2 yr
	1	45 M	Renal carcinoma	Synchronous	Partial resolution**/alive at 2 yr
	1	49 F	Renal carcinoma	Synchronous	Resolution**/VL relapse††
	1	54 M	Renal carcinoma	Synchronous	Partial remission**/death 12 mo
	1	62 F	Renal carcinoma	Synchronous	Partial remission**/alive at 2 yr
	1	58 M	Bladder carcinoma	Synchronous	NA/NA
	1	59 F	Thyroid carcinoma	Synchronous	Partial improvement**/death
	1	63 F	Thyroid carcinoma	Synchronous	NA/NA
	1	67 F	Gastric carcinoma	Synchronous	NA/NA
	1	64 M	Gastric carcinoma	Synchronous	Death
	1	62 M	Colon carcinoma	Synchronous	NA/NA
	1	46 F	Uterus carcinoma	Synchronous	NA/NA
	1	72 F	Breast carcinoma	Synchronous	NA/NA
	1	68 F	Breast carcinoma	Synchronous	Remission*/NA
	1	63 M	Lung carcinoma*	Synchronous	NA/NA
	1	55 F	Vocal cord carcinoma	Synchronous	NA/NA
	1	58 M	Urinary bladder	Synchronous	NA/NA
	1	81 M	Pancreatic carcinoma	Synchronous	Improvement/death 5 days

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Reported giant cell arteritis (GCA) associated with solid organ tumors.

n	Age/Sex	Neoplasia	Occurrence of GCA Related to Tumor Diagnosis	Followup Vasculitis/Malignancy
1	NA	Lung carcinoma	3 yr before	NA/died of cancer
1	45 F	Lung carcinoma	Synchronous	Remission*/alive and well (36 mo)
1	60 M	Lung carcinoma	1.5 yr before	Remission*/alive and well
1	60 M	Lung carcinoma	Synchronous	NA/died of cancer
1	77 M	Colon carcinoma	3 yr before	Remission*/died of cancer (36 mo)
1	72 M	Colon carcinoma	Synchronous	Died
1	87 F	Colon carcinoma	Synchronous	NA/died of stroke (6 mo)
1	78 F	Colon carcinoma	Synchronous	NA/died post-surgery (11 mo)
1	79 M	Colon carcinoma	Synchronous	Remission*/alive and well (76 mo)
1	82 F	Renal carcinoma	Synchronous	Remission*/NA
1	77 F	Renal cell carcinoma	Synchronous	Died
1	72 M	Bladder carcinoma	6 mo before	NA/NA
1	81 F	Bladder carcinoma	Synchronous	Remission*/alive and well (29 mo)
1	74 M	Prostate carcinoma	19 mo before	NA/died of cancer at 2 yr
1	64 M	Prostate carcinoma	Synchronous	Remssion*/died (153 mo)
1	72 F	Breast carcinoma	Synchronous	VL remission†
1	NA	Uterus carcinoma	4 yr before	Died
1	68 F	Uterus carcinoma	Synchronous	Remission*/NA
1	79 F	Uterus carcinoma	Synchronous	Remission*/lost followup (17 mo)
1	65 F	Thyroid carcinoma	Synchronous	Remission*/died of cancer (105 mo)
1	80 M	Gastric carcinoma	Synchronous	Remission*/died of cancer (19 mo)
1	80 M	Gastric carcinoma	Synchronous	Remission*/died of cancer (29 mo)
1	77 M	Brain tumor	Synchronous	NA/died of cancer (20 mo)
1	62 M	Brain tumor	11 mo before	Remission*/died of cancer (6 mo)
1	73 F	Mediastinum	Synchronous	NA/died of cancer (6 mo)
1	86 F	Neuroendocrine	Synchronous	NA/died of cancer (11 mo)
1	NA	Maxillar carcinoma	2 yr before	Remission*/died of cancer (24 mo)
1	70 F	CUO	2 yr before	Remission*/died of cancer (24 mo)
1	NA	CUO	4 yr before	No treatment/died of cancer
1	NA	CUO	4 yr before	No treatment/died of cancer

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Paraneoplastic syndromes and vasculitis

(1) malignancy may present initially with an acute vasculitis;

(2) 2.5 to 5% of patients with vasculitis have a related malignancy that may not be obvious at presentation

(3) chronic or persistent vasculitis with poor response to usually effective therapy, especially in elderly patients, should be evaluated bearing in mind the possibility of them being paraneoplastic;

(4) recurrence of a tumor might be suspected when vasculitis appears or relapses in patients diagnosed as having malignancy.

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PMR come sindrome paraneoplastica?

- Alcuni dati di associazione solo nel breve termine (6-12 mesi)
- Maggiore associazione con linfomi, tumori prostatici ed ematologici
- Associazione fenotipo PMR/neoplasia non chiara
- Attenzione forme atipiche *(assenza di rigidità mattutina prolungata, non risposta a GC, imaging non tipica..)*
- Attenzione età avanzata, sesso maschile, coinvolgimento esteso articolare

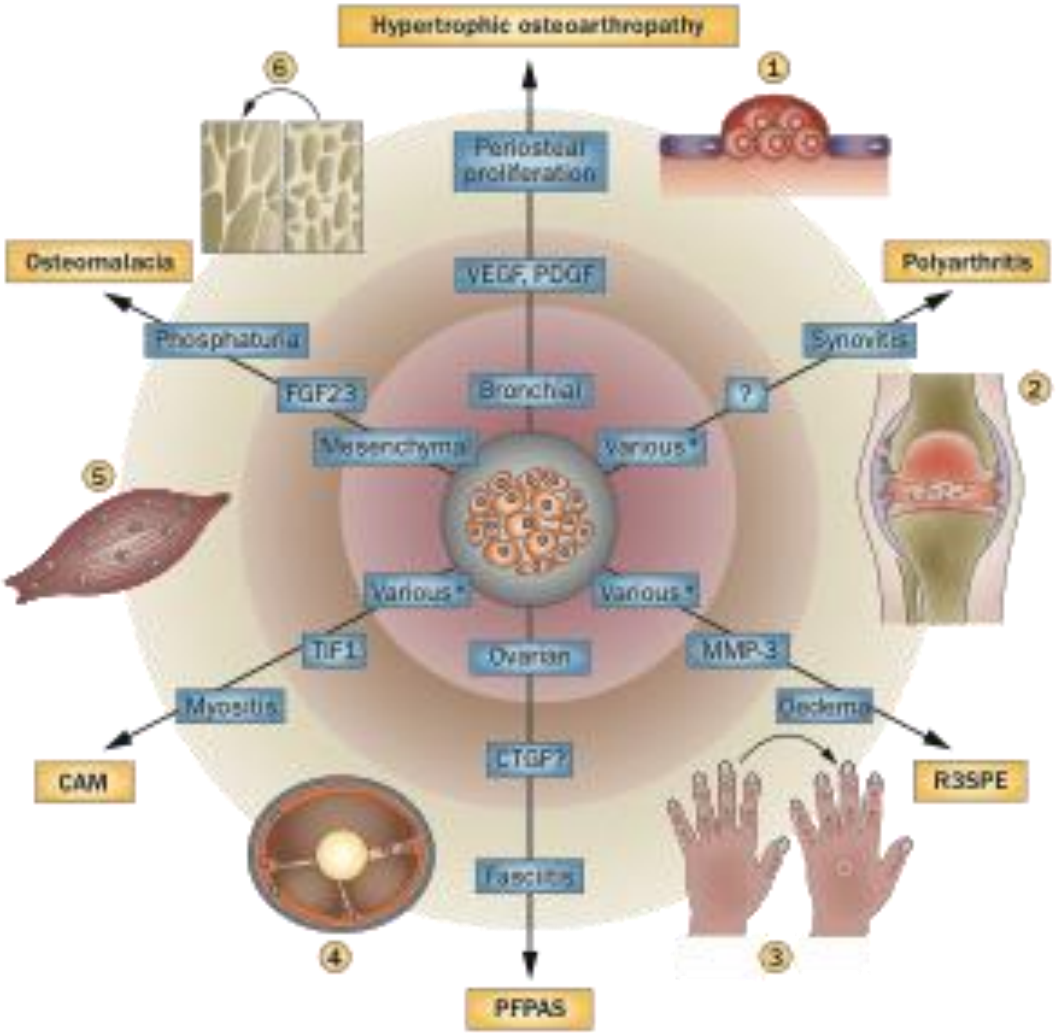
PMR non è forma paraneoplasica. Potenziale associazione da considerare anche nel follow up. Diagnosi rigorosa.

S. Muller et al., Reumatismo 2018;70(1) 25-37

Cancer-associated myositis

- A meta-analysis of six population-based cohort studies revealed the highest association for a close temporal relationship between tumours and dermatomyositis, with standard incidence ratios (SIRs) ranging from 3.8 to 7.7.80
- The association is much **weaker** for polymyositis (the SIR in five studies ranged from 1.7 to 2.15) or inclusion-body myositis

Pathophysiology and clinical signs of paraneoplastic rheumatic syndromes



Conclusions

- Paraneoplastic syndromes in rheumatology being **rare**, often precede other clinical manifestations of neoplasms and can facilitate the timely diagnosis and potential cure of a malignant disease.
- If the malignant cells can be successfully eliminated, the paraneoplastic symptoms usually subside,
- reappearance of musculoskeletal symptoms can indicate a relapse or metastatic spreading
- Paraneoplastic symptoms can also have a significant impact on the quality of life, morbidity and mortality of patients with tumours.
- Paraneoplasias provide an interesting link between the pathomechanisms of neoplastic and rheumatic disorders, which still hold a variety of unresolved questions.


A PENSARE MALE SI FA PECCATO
MA SPESSO CI SI AZZECCA