Paraneoplastic rheumatic disorders: a narrative review

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SUMMARY
Paraneoplastic syndromes (PS) are a heterogeneous group of diseases related to a neoplasm, indirectly dependent on it. Diagnosis and the treatment are often a challenge for clinicians, not least because the pathogenetic mechanisms are highly complex and not entirely known. Nonetheless, in most cases, PS precede the diagnosis of malignancies, thus their identification is particularly important in addressing physicians’ diagnostic work-up with regard to early cancer diagnosis. Among paraneoplastic syndromes, those of rheumatologic interest represent a large component. In this paper, we review the main rheumatic PS.

Key words: Paraneoplastic syndromes; Rheumatic diseases; Tumors.

INTRODUCTION

The term paraneoplastic syndrome (PS) defines a group of pathological conditions characterized by various clinical expressions (rheumatological, endocrinological, neurological, etc.) observed in the presence of a neoplasm, but not dependent on the tumor itself or its metastases. The causative link between several neoplasms and PS is essentially supported by the fact that the surgical excision or other successful treatment of the tumor leads to improvement/resolution of the syndrome (1, 2).

PS encompasses many clinical-pathogenetic disorders, the nosologic classification of which is often hard because of the high heterogeneity of clinical presentation, with different and often unknown pathogenetic paths (1, 2). Several active substances (hormones, cytokines, enzymes) secreted by tumoral cells may trigger inflammatory processes involving a number of organs, including joints and muscles. In other cases, the immune reaction destroying neoplastic cells leads to cross-reactions against physiological antigens (3, 4).

In most cases, PS clinical signs can precede those directly dependent on the neoplasm; in other cases, manifestations may be simultaneous or subsequent (5). The PS of rheumatological pertinence represent the prevalent subgroup of these disorders (6). Besides the rheumatic-related PS (RPS), we underline that several autoimmune disorders constitute the favoring substrate to neoplasm development (e.g. lymphomas in rheumatoid arthritis, systemic lupus erythematosus, Sjögren’s syndrome, lung cancer in scleroderma, etc.) (6).

In this narrative review, based on a selection from about 500 scientific papers, we illustrate the main RPS, considering the pathological conditions that were referred to the rheumatologist at their clinical presentation (Table I and Figure 1).

HYPERTROPHIC OSTEOARTHROPATHY

Hypertrophic osteoarthropathy (HOA) represents the prototype of RPS. The mean clinical features are:
- Hippocratic fingers (drumstick finger; watch-crystal nail) associated with skin
thickening, which determines a *spatula* aspect of the hands and *elephant foot* at the lower extremities;
– Bone pain (not articular) worsened by movements and alleviated by rest;
– Joint involvement (arthralgias or arthritis), especially at wrists, knees and ankles;
– Vascular alterations caused by peripheral vasodilation, producing skin hyperthermia, cyanosis, and sweating of the extremities.

Primary HOA (pachydermoperiostosis) is infrequent, while the secondary form can complicate several pathological conditions, including tumors, especially bronchogenic carcinoma. In the form secondary to malignancies, regression of the syndrome can be obtained by tumor excision or chemoradiotherapy (7).

X-ray examination shows diaphyseal subperiosteal proliferation, especially of tibia, fibula, ulna, metacarpal and metatarsal...

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**Table I** - Summary of the main *rheumatic* paraneoplastic syndromes.

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**Figure 1** - Schematic representation of the rheumatologist’s role in the diagnosis of paraneoplastic syndrome (PS).

Interruption or chronic articular/periarticular inflammation, skin vasculitis, panniculitis, increased acute phase reactants without infective causes, presence of autoantibodies, rheumatoid factor or cryoglobulins are clinical features that induce the suspicion of PS of rheumatic pertinence.

The rheumatologist should collect all anamnestic, clinical, laboratoristic, and instrumental data; moreover, consultations with other specialists are usually needed, especially in the cases with comorbidities and of difficult interpretation. Possible red flags for PS can be: atypical clinical features, anamnestic data indicative of an increased risk of cancer, lacking or reduced therapeutic response. On suspicion of PS, specific laboratory and instrumental examinations should be prescribed, in order to verify the presence of occult neoplasm.
bones. Bone scintigraphy provides early diagnostic images, showing linear periosteal uptake in the long bones. Both in primary and secondary HOA, serum levels of the vascular endothelial growth factor (VEGF) secreted by megakaryocytes and platelets (8) are higher than in healthy controls (9), suggesting a pathogenic role of this factor. Moreover, VEGF serum levels in secondary HOA were found to be higher than in primary HOA; therefore, its increase could be due also to the tumoral cells, besides megakaryocytes and platelets (9).

Supporting the hypothesis that VEGF is involved in the pathogenesis of HOA is the fact that osteogenesis is strictly dependent on angiogenesis (10); furthermore, VEGF in vitro is a strong promoter of osteoblast differentiation (11). Extra-articular HOA features, too, suggest the pathogenetic role of VEGF, since this cytokine induces neoangiogenesis, leading to the accumulation of extracellular matrix and typical edema of the skin in HOA patients (9). Finally, HOA signs may be reduced by treatment with octreotide, a VEGF inhibitor (12).

**RELAPSING POLYCHONDritis**

Relapsing polychondritis (RP) is a rare autoimmune disease characterized by recurrent inflammation of the cartilaginous tissues, particularly in the nose, ears, larynx, and trachea. Its etiology is still unclear; the presence of antibodies directed against II type collagen was proposed (13-16). Diagnosis is based on the presence of ascertained inflammatory episodes in at least two of the three chondral sites (ear, nose, larynx/trachea), associated with two or more manifestations among ocular inflammation, hearing loss, vestibular dysfunction and seronegative arthritis (17). Articular involvement may be represented by arthralgias, episodic, migrant, asymmetrical and non-erosive polyarthritis, sometimes with the characteristics of rheumatoid arthritis. The joints of the hands, knees and ankles are most frequently involved (18). Some cases of RP were reported in relation to hematological malignancies (leukemia, lymphoma), myelodysplasia (19-22) and, more rarely, solid tumors (breast, colon, lung, pancreas and others) (17, 23, 24).

**LAMBERT-EATON SYNDROME**

The Lambert-Eaton myasthenic syndrome is an autoimmune disease characterized by defective acetylcholine release in the neuro-muscular junctions, caused by autoantibodies against the voltage-gate calcium channels, onto the presynaptic terminals of the autonomic neurons. The cardinal clinical features are myalgia, muscle weakness, especially of the lower limbs, associated with abnormal sweating, orthostatic hypotension and sexual impotence (25). Diplopia, drooping of eyelids, and dysphagia are often reported (26).

This syndrome can precede or present simultaneously to a malignancy, mainly a small cell lung carcinoma or other tumors (lymphoproliferative disorders, carcinoma of breast, colon, stomach, kidney, bladder, pancreas and prostate) (27-29) or autoimmune diseases [e.g. thyroiditis, systemic lupus erythematosus (SLE), Sjögren’s syndrome, scleroderma, coeliac disease] (26).

**SECONDARY GOUT**

An increased cell nucleic acid degradation in patients affected by myelo-lymphoproliferative disorders or solid tumors treated with radiation or antiblastic therapy may induce hyperuricemia, responsible for secondary gout (30-34). Secondary gout differs from the primary form, since it presents later in life, is not present in relatives and affects both sexes; moreover, it is associated with high uric acid blood levels (more than 12 mg/dL). Finally, it more frequently involves the large joints such as the shoulders and the knees (30).

**AMYLOID ARTHROPATHY**

Amyloidosis is characterized by insoluble low-molecular-weight protein deposition, called amyloid, in the extracellular com-
partment of many organs; this compromises the organ functions, with subsequent different pathologic conditions. The polyarthropathy dependent on amyloid storage in the synovial membrane and periarticular tissues typically involves the shoulders, the knees and the wrists (31). Arthritis, often asymmetrical and not so painful (35), may be associated with multiple myeloma (36) and, less frequently, with Waldenstrom’s macroglobulinemia (31, 37-39).

**REMITTING SERONEGATIVE SYMMETRICAL SYNOVITIS WITH PITTING EDEMA**

Remitting seronegative symmetrical synovitis with pitting edema (RS3PE) is a disorder which can manifest as a primary syndrome or associated with different diseases, including malignancies (40-42). RS3PE, more frequently described in elderly men, is characterized by asymmetric arthritis, mainly involving metacarpophalangeal and proximal interphalangeal joints, wrists, shoulders and extensor tendons, with edema of both hands (boxing glove hands) (40, 43, 44); the inflammation may be easily documented by means of ultrasounds or magnetic resonance (42, 44).

In most cases, a marked increase of acute-phase reactants is observed, while the rheumatoid factor is negative (44). RS3PE was described in association with different solid tumors (stomach, colon, prostate, ovary and endometrium) (40, 45), as well as with malignant homeopathies (leukemia, non-Hodgkin lymphomas, myelodysplasia) (40, 43, 45-47).

**ADULT ONSET STILL’S DISEASE**

Adult onset Still’s disease is a rare disease very similar to the juvenile form. It is characterized by high persistent or intermittent fever >39°C, evanescent macular or maculopapular skin rash of the trunk and extremities, arthralgias or arthritis, possibly associated with pharyngitis, lymphadenopathies, hepatosplenomegaly, anemia, neutrophilic lymphocytosis and liver dysfunction (48, 49).

Some cases of association with solid tumors, like pharyngeal epidermoid cancer (50), cancer of the lung (51), breast (52), thyroid (53), esophagus (54) and malignant hemopathies (leukemia, angioimmunoblastic lymphadenopathy and myeloproliferative syndrome) (50, 55) are reported.

**VASCULITIS**

Vasculitides are a heterogeneous group of autoimmune diseases defined by an inflammatory and necrotic process involving the vessel walls of arteries or veins of various sizes, throughout the body. This large group of diseases encompasses primary and secondary forms; the latter include diseases in which the vessel damage depends on malignancies (56). The most frequent vasculitides found in the course of cancers are leukocytoclastic vasculitis and polyarteritis nodosa (42, 57). The former involves the small caliber vessels and is characterized by skin lesions (palpable purpura), mainly localized at the lower limbs (including ankles and feet); systemic symptoms (fever, myalgias, arthralgias) may be associated, without visceral vasculitic involvement (58).

Regarding the pathogenesis, some authors suggest the involvement of tumoral antigens in the context of circulating immune-complexes, which deposit in the vessel walls, activating the complement cascade, thus triggering the inflammatory process (59). Articular involvement can be characterized by mere arthralgias; in other cases, knee and ankles arthritis are described, but all joints can be involved (60).

Leukocytoclastic vasculitis was reported in association with lymphoproliferative disorders, including acute and chronic leukemias (61-68), lymphomas (69-71), myelodysplasias (67, 72, 73), as well as solid tumors (74-77). Polyarteritis nodosa (PN) is a necrotizing vasculitis of small and medium vessels of multiple organs, especially the kidneys; clinically, signs and symptoms are variable. In the early stages, fatigue, weight
loss, arthralgias or arthritis (hands, knees), skin vasculitis (palpable purpura), up to ulcers were noticed; moreover, peripheral neuropathy (asymmetric, sensitive and motor), necrotizing glomerulonephritis leading to hypertension, gastrointestinal ischemia (mesenteric vessel infarction) may develop (78-90).

Paraneoplastic PN was described in association with different solid neoplasms of the liver (76), colon (77), bladder (79), lung (80), hypopharynx (81) and hematologic diseases, namely leukemia (4, 65, 82, 83, 85, 86) and myelodysplasia (65, 87).

ANCA-associated vasculitis has also been related to neoplastic diseases (78). Lastly, Horton arteritis, giant cell vasculitis primarily involving the branches of the aorta, especially extracranial vessels (particularly the temporal arteries), can be associated with solid tumors or malignant hemopathies (e.g. myelodysplasia) as a PNS (89-93).

CARCINOMATOUS POLYARTHRITIS

Carcinomatous polyarthritis (CP) is a rare acute paraneoplastic disorder of the elderly, commonly characterized by asymmetric arthritis of the large joints of the lower limbs (42, 94). Moreover, general malaise and fever are experienced. Serological inflammation indexes are increased; anemia is common, while RF and anti-CCP are negative (40, 95). Histologic examination of synovial biopsy reveals nonspecific synovitis. The differential diagnosis includes late-onset rheumatoid arthritis. CP has been reported with several solid tumors of the stomach (96), colon (97), lung (97), pancreas (98), breast (99), larynx (100), ovaries (101), as well as lymphoproliferative disorders, such as leukemia (102, 103). In any case, in the presence of an elderly patient with the above clinical features, especially if not responding to conventional treatments, an underlying malignancy should be suspected.

EOSINOPHILIC FASCIITIS

Eosinophilic fasciitis (EF) is a rare disease characterized by scleroderma-like lesions mainly involving the limbs. Fibrosis and inflammatory injury involving the deep subcutaneous tissue and the fascia are characteristic (104, 105). The clinical picture is represented by pain, swelling and reduced function of the limbs, due to thickened skin limbs lesions, which spare the extremities. In the involved areas, the skin is inelastic and thickened, evolving into dimpling or peau d’orange appearance. Some patients experience arthritis, sometimes with erosive evolution, tenosynovitis, and periostitis of the long bones (106-109). The most relevant laboratory findings are hyper-eosinophilia, hypergammaglobulinemia, and increased erythrocyte sedimentation rate. EF can be classified as PNS when associated with malignant diseases, especially hematologic (myeloproliferative disorders, leukemia) (108, 110-112).

JACCoud’s ARTHROPATHY

Jaccoud’s disease is a deforming, not erosive, arthritis, which mainly involves the joints of the hands. We generally observe ulnar deviation with bilateral flexion deformities at the MCP joints, hyperextension at PIP and muscle wasting (swan neck finger deformities) (56, 113). Firstly described in the course of rheumatic fever or systemic lupus erythematosus, it has also been reported with lung mesothelioma (114, 115). Unlike carcinomatous polyarthritis, it presents an insidious onset, absence of pain and joint swelling, symmetrical involvement and predilection of the joints of the hands and prominent deformities of the fingers (57).

CRYOGLOBULINEMIA

Cryoglobulins are immunoglobulins which precipitate in the serum at a temperature below 37°C and return into solution with rewarming. Three types of cryoglobulins have been identified (115, 116): type I is characterized by a single monoclonal Ig (IgM, IgG, IgA) or, more rarely, by a single light chain; type II (mixed cryoglobulinemia) is characterized by monoclonal IgM and polyclonal or oligoclonal IgG; type III
occurs where the cryoprecipitate is represented by polyclonal IgG, IgA and IgM. Cryoglobulins may induce organ damage in two main ways: blood hyperviscosity (especially in type I); type II-III immune-mediated reactions (117).

Monoclonal cryoglobulinemia is mostly associated with hemopathies, such as Waldenstrom’s granulomatosis, multiple myeloma or chronic lymphatic leukemia and is frequently asymptomatic (118, 119). Mixed cryoglobulinemia (MC) is determined by the deposition of circulating immune complexes (cryoglobulins and complement) in the small and medium size vessels (120). MC, which recognizes HCV as the main etiological factor, is clinically characterized by the classic trio of purpura, asthenia, arthralgias and by the involvement of one or more organs (cutis, liver, kidney, peripheral nerves, joints); it should be noted that MC presents high risk of developing non-Hodgkin lymphoma (121).

**PALMAR FASCIITIS**

This syndrome is represented by fibrosis of the palmar fascia, with a following progressive hand finger flexion (claw hands); upper limbs polyarthritis may be associated. The disease, which often rapidly progressive, has been described in patients affected by ovarian carcinoma (122) and subsequently in other malignancies (breast, uterus, prostate, lung, pancreas, stomach, etc.) (40, 123), along with other non-tumoral diseases (tuberculosis, thyroiditis and benign ovarian cysts) (94).

**ERYTHEMA NODOSUM**

Erythema nodosum is a localized vasculitis involving dermal and subcutaneous tissue vessels on the legs. The typical manifestations of this disease are multiple nodules which are painful and sometimes confluent. Frequently, arthralgias or arthritis of the knees and ankles can be associated. The vasculitic process can be observed in association with several disorders, including solid tumors and hematologic malignancies (78).

**POLYMYALGIA RHEUMATICA**

Polymyalgia rheumatica (PMR) is a typical disorder of the elderly, characterized by pain and stiffness of the shoulder and pelvic girdles, impairment of general conditions, increased serological acute phase reactants and prompt response to steroid therapy. Malignancies may clinically manifest as PMR (124, 125); significantly, PMR with one or more atypical features may represent the first clinical manifestation of a diffused cancer (94).

Atypical features of PMR are an onset age of <50 years, incomplete or asymmetrical involvement at the typical PMR sites, an erythrocyte sedimentation rate lower than 50 mm/1 h or greater than 100 mm/1 h, partial or delayed (after >48 hours) improvement with 10 mg/day of prednisone (94). An atypical PMR may appear 1 to 13 months before the diagnosis of cancer (126).

The association between typical PMR and malignancies is still discussed (42). The most frequent tumors observed in the course of PMR include cancer of the kidney, lung, colon and those related to hematopoietic system (25, 42, 127, 128).

In any case, since an atypical PMR may represent the first indirect manifestation of a cancer, a screening in order to look for a possible occult neoplasia should be considered (95).

**LOCALIZED NODULAR MYOSITIS**

Localized nodular myositis is a rare disorder characterized by a rapidly enlarging nodular inflammatory mass, usually affecting a single muscle (129-131). In a few cases, this disorder has been described as PNS (132-134).

**MULTICENTICRETICULOHISTOCYTOSIS**

Multicentric reticulohistiocytosis is a rare multisystemic disease, of unknown etiology, characterized by histiocytes and multinucleated giant cells tissue infiltration into the synovium or the skin (135). Clinically, papulonodular eruption at the ears, nose,
sculpt, back of the hands, forearms and elbows is present; in 50% of patients mucous papules at the lips, mouth, tongue, nose, pharynx and larynx are found (136). Joint involvement may occasionally show a destructive and mutilating aspect (137) at the IP of the hand fingers, wrists, shoulders, hips, knees, feet, spine and temporal-mandibular joints (138). Many other organs, such as bones, liver, salivary glands, lymph nodes, heart and lungs, may be affected (137-140). Multicentric reticuloendotheliosis may be associated with TB, hypothyroidism, diabetes, cancer of the lung (141), stomach (142), breast (143), cervix (144), colon (145), ovary (146), and malignant lymphoma (147-149).

**Paraneoplastic Raynaud’s phenomenon (Paraneoplastic Acral Vascular Syndrome)**

Paraneoplastic Raynaud’s phenomenon has been reported in literature, though rarely (150). The appearance of Raynaud’s phenomenon in a patient aged over 50, presenting an asymmetrical involvement of the fingers with digital necrosis, must induce the diagnostican to consider the presence of an underlying neoplasia, especially at the gastrointestinal system and the lung (42). The typical clinical manifestation of secondary Raynaud may be similar to the primary phenomenon, although an asymmetric pattern with a tendency towards gangrene suggest a PNS (151). Association with many carcinomas, sarcomas, lymphomas and leukemias has been reported (152). It can develop at any stage of the neoplastic disease and may represent the presenting symptom (152, 153); furthermore, it may be a surrogate activity marker of the disease, improving after the favorable treatment of the underlying malignant condition (154, 155).

**Autoimmune Diseases**

The activation of autoimmune mechanisms during a neoplastic disease may promote the development of a rheumatic syndrome, through the synthesis of antibodies directed against various self-antigens, including those expressed by tumor cells (156).

**Dematomyositis/Polymyositis**

Polymyositis (PM) and dermatomyositis (DM) are two connective tissue diseases characterized by muscle inflammation, with cutaneous lesions forming DM. Increased incidence of malignancies has been described in the course of PM/DM: squamous cell carcinomas (head, neck, esophagus and cervix); adenocarcinomas (stomach, colorectal, pancreas, thyroid, breast, ovary, uterus and prostate); hematopoietic and lymphoid malignancies (non-Hodgkin’s lymphoma, Hodgkin’s lymphoma, multiple myeloma and leukemia) (157). The relationship between cancer and myositis is not entirely known. However, in some patients we can find a close temporal correlation (about 1 year) between the occurrence of a DM and the discovery of a cancer, which suggests the presence of a paraneoplastic association (58, 158-161).

**Systemic Sclerosis**

Skin lesions similar to those present in systemic sclerosis (SSc) have been found in patients with malignant tumors and other diseases, defined by the terms pseudoscleroderma or pseudosclerosis (162, 163). Lung, breast and stomach cancer, plasmacytoma and carcinoids can be associated with this PNS (163-166). Regarding lung cancer, the release of biochemical mediators, such as hormones and growth factors, may represent the probable pathogenetic mechanism underlying skin sclerosis (167). In several cases it is necessary to differentiate SSc from a PNS (166); the latter is more probable in the case of history of cancer, exposure to carcinogens, onset of symptoms in elderly people, systemic symptoms (fever, fatigue, weight loss) (166). SSc itself, in some patients, shows a close temporal relationship with a diagnosis of cancer; in these cases, a common trigger and/or predisposing back-
ground for both SSc and the cancer might be suspected (57, 168).

**SYSTEMIC LUPUS ERYTHEMATOSUS**

An SLE-like syndrome has been described in association with malignancies. A syndrome characterized by non-deforming arthritis, polyserositis, glomerulonephritis and Raynaud’s phenomenon, has been related to breast, lung and ovary cancer, as well as leukemias and lymphomas (31, 40, 169-176). Positive ANA and anti-DNA or anti-phospholipid antibodies have been detected (40, 57).

**OSTEOMALACIA**

Osteomalacia may occur during cancer; several cases have been reported in literature of the syndrome named *tumor-induced osteomalacia* (TIO) or *organic osteomalacia* (177). It is characterized by hypophosphatemia, hyperphosphaturia, normal or low levels of 1,25-dihydroxy-vitamin D, pathologic fractures, muscle weakness, height loss (178). Phosphaturic mesenchymal tumor is the neoplasm most frequently associated with TIO, with production of the endocrine fibroblast growth factor 23 (FGF23, responsible for increased renal excretion in phosphate). Other tumors, such as hemangiopericytoma, osteosarcoma, giant cell tumor and other mesenchymal tumours have been described in association with TIO (177, 179).

**CONCLUSIONS**

A number of pathological conditions generally defined as for referral to rheumatology may actually be the consequence of occult cancer. These syndromes, named PNS, often share differences from the respective primary form, because of the presence of atypical features. Therefore, PNS should be suspected in elderly patients, whose clinical symptoms, laboratory/instrumental findings, or therapeutic response diverge from what is usually expected.

In any case, on suspicion of PNS, we suggest a deepened clinical-instrumental work-up and a close follow-up, in order to verify the diagnosis of suspected cancer.

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