Rheumatic disorders as paraneoplastic syndromes

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Abstract

The long-established observation that some rheumatologic disorders (RDs) are associated with – or precede – the clinical manifestations of a variety of solid and hematological tumors represents an important clue for the early diagnosis and effective treatment of the cancers. Inflammatory myopathies, seronegative rheumatoid arthritis and some atypical vasculitides are the most frequently reported paraneoplastic RDs, although paraneoplastic scleroderma- and lupus-like syndromes, erythema nodosum, and Raynaud’s syndrome have also been observed. Generally, the clinical course of a paraneoplastic RD parallels that of the cancer, and surgical removal of the tumor or its medical treatment usually results in a marked regression of the clinical manifestations of the RD. Most paraneoplastic RDs are difficultly distinguishable from idiopathic RDs. Even so, some atypical features of the clinical presentation raise the suspicion of an underlying tumor. This review summarizes current hypotheses for the pathogenesis that leads a tumor to present as an RD and discusses the clinical features that help distinguish paraneoplastic from idiopathic RDs.

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Keywords: Autoimmune diseases; Cancer; Paraneoplastic rheumatic syndromes

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1. Introduction

The association between cancer and rheumatic disorders (RDs) is a matter of discussion in view of their intriguing relations [1–3]. Patients with both cancer and an RD are distinguished into three main classes. In the first class, an RD is directly triggered by a tumor or its metastases. An example of this first group is arthritis due to synovial infiltration by leukemic cells. The second class refers to patients with an established idiopathic RD who develop cancer within a temporal interval of up to 20 years. Sjögren’s syndrome can be such a tumor-associated RD, because it places patients at high risk of developing lymphoma. It is currently unknown whether the higher incidence of cancer in patients with idiopathic RDs is due to the disease itself, the long-term immunosuppressive treatment these patients receive, or both [3]. The third group includes patients with clinical manifestations of an RD, which is actually the expression of an occult cancer that becomes clinically evident within months or years. These apparently idiopathic RDs that precede cancer are called paraneoplastic RDs.

This review focuses on the third group of patients, i.e. those with paraneoplastic RDs. It summarizes current hypotheses for the pathogenetic mechanisms that lead a tumor to present as an RD and discusses the clinical features that help distinguish paraneoplastic from idiopathic RDs.

2. Pathogenetic hypotheses

The main distinguishing feature between tumor-associated and paraneoplastic RDs is the fact that surgical removal or pharmacological treatment of the cancer in the first case has no influence on rheumatic symptoms, whereas it almost always results in the disappearance of symptoms in paraneoplastic diseases (reviewed in [4]). These observations have prompted oncologists and rheumatologists to investigate the pathogenetic mechanisms of the rheumatic manifestations of cancer, leading to three distinct working hypotheses: a) both the malignancy and the paraneoplastic RD are independent effects of a common causal factor, such as a viral infection or exposure to drugs or particular physical stimuli (e.g. UV radiation); b) paraneoplastic RDs are a direct effect of toxins produced by tumors cells, which trigger inflammation in the tissues where RDs manifest; c) paraneoplastic RDs are mediated by a hypersensitivity reaction due either to tumoral expression of antigens shared by the cells targeted by the autoimmune disease or to the release of intracellular antigens, including nucleic acid-associated proteins, from apoptotic tumor cells [5]. Supporting this third hypothesis is the demonstration of auto-antibodies to nuclear proteins and to double-stranded DNA as well as antibodies to a wide array of tissue-associated antigens in the sera of patients with paraneoplastic RDs [5–8]. The specificities of these antibodies are known [6,7,9], but their roles as mediators of the clinical manifestations of RDs remain to be established.

3. Clinical features

That an apparently idiopathic RD can be an early manifestation of cancer has been known since the first case report published in 1916 (reviewed in [10]). Since then, several different types of paraneoplastic RDs have been described. Clinical presentations may resemble, for example, connective tissue disease, polymyalgia rheumatica or vasculitis. These diseases are almost indistinguishable from idiopathic RDs. Even so, certain clinical and laboratory findings can raise the suspicion of an underlying malignancy (Table 1).

3.1. Inflammatory myopathies

Estimates for the incidence of cancer in persons with an established autoimmune myopathy, namely polymyositis and dermatopolymyositis, range from 6% to 60% [26]. In contrast, the incidence of inflammatory myopathies that are really the expression of an occult cancer is undefined. Paraneoplastic inflammatory myopathies have been observed more often as the early clinical manifestations of ovarian [10], renal [11], lung [11] and colorectal carcinomas (unpublished observations) [11] and melanoma [12]. Following removal of the
cancer, the clinical and biological abnormalities usually resolve until the cancer relapses.

The clinical features and laboratory findings of paraneoplastic inflammatory myopathies are generally similar to those of the idiopathic conditions, although onset in patients older than 50 years and a poor response to immunosuppressive treatment should prompt investigation into a possible underlying malignancy [10]. Laboratory tests showing occult blood in stool, sideropenic anemia, thrombocytopenia and hypergammaglobulinaemia should also raise the suspicion of an occult neoplasm. Biomarkers are of limited utility in screening for tumors and their sensitivity for an early diagnosis is low [5]. Data collected in these patients support the hypothesis that circulating auto-antibodies reactive with tissue proteins are involved in the pathogenesis of tissue damage [9].

Much less is known about the association of other types of inflammatory myopathies (e.g. inclusion body myositis, dermatomyositis sine myositis, necrotizing myopathy, localized nodular myositis, and myopathies with modest increase of muscle enzyme) and an underlying malignancy; the numbers of patients with each type of cancer are too small for a specific association to be defined or for specific conclusions to be drawn [1].

### 3.2. Rheumatoid arthritis-like syndrome

An increased occurrence of malignancies in patients with established rheumatoid arthritis (RA) has been found by several studies [2,3]. In most cases, the higher rate of cancer is linked to the use of immunosuppressive therapy, and the tumor generally takes several years to develop. However, a rapid-onset arthritis mimicking RA may be the early manifestation of an occult malignancy.

Patients with paraneoplastic RDs generally exhibit a form of asymmetric polyarthritis that may be confused with seronegative RA or spondyloarthropathy. The clinical features include: late and acute onset characterized by symmetric or asymmetric disease mostly affecting the lower extremities and usually sparing the small joints of the hands; non-specific synovitis with apparently normal joint radiographs; and frequent lack of rheumatoid factor. In this setting, disproportionate pain, marked weight loss, hepatosplenomegaly,
lymphadenomegaly, poor response to steroids and disease-modifying antirheumatic drugs (DMARDs), particularly if unexplained anemia or constitutional symptoms persist after treatment, should prompt further investigation [2].

The clinical course of an RA-like syndrome generally parallels that of the cancer. The symptoms often do not respond to antirheumatic therapy, whereas radical treatment of the primary neoplasm usually results in regression of a paraneoplastic RA [4]. RA-like syndromes have been associated with malignancies of the lung, colon, breast, ovary, stomach and oropharynx and with hematopoietic cancers. Often, the RA-like syndrome precedes the development of cancer by 8–12 months.

3.3. Raynaud's phenomenon and scleroderma-like syndrome

Both Raynaud’s phenomenon and scleroderma-like syndrome may occasionally be a paraneoplastic RD [1,4]. Idiopathic Raynaud’s phenomenon or Raynauld’s phenomenon associated with systemic sclerosis has been observed as the expression of an underlying tumor. When Raynaud’s phenomenon is observed as an isolated symptom, suspicion of an underlying malignancy should be raised if the age at onset exceeds 50 years, if asymmetric involvement of the fingers rapidly evolves to necrosis, and if there is a poor response to vasodilator therapy and sympathectomy [4,11]. As observed for other paraneoplastic RDs, once the tumor has been identified and removed, the digital vasospastic complications markedly resolve. Raynaud’s phenomenon has been diagnosed as the presenting symptom of carcinomas of the liver, ovary, testis, kidney and of melanoma, lymphoma, and multiple myeloma.

While several studies (reviewed in [27]) have demonstrated an increased frequency of lung, esophageal and breast cancer in patients with scleroderma, there are only a few observations of scleroderma-like syndrome preceding the manifestation of cancer. The main atypical clinical features that help differentiate these forms from idiopathic conditions are: age at onset over 50 years, sclerodactyly, progressive skin sclerosis extending to the neck and trunk, and acute onset of Raynaud’s phenomenon. By contrast, the absence of Raynaud’s phenomenon with a normal capillaroscopy pattern can be another distinguishing feature of cancer-induced systemic sclerosis. Rarely, high serum titers of antinuclear antibodies and anti-topoisomerase type 1 antibodies can be present in the absence of autoimmune disease symptoms. Single case reports of paraneoplastic scleroderma-like syndrome have been described in association with stomach [15], lung [16], skin [17] and breast cancer [18] and T-cell lymphoma [13]. Skin changes resembling scleroderma may also occur in patients with osteosclerotic myeloma may also occur in patients with osteosclerotic myeloma (POEMS syndrome) as the early manifestation of cancer [14].

3.4. Lupus-like syndrome

The association between systemic lupus erythematosus and neoplastic diseases is rare and the relation between these two pathologies is uncertain [1]. A lupus-like syndrome has been described as the presenting symptom of ovarian and breast cancer and hairy cell leukemia [2,21]; it is characterized by polyserositis, Raynaud’s phenomenon and antinuclear antibodies in adult patients. An increased risk of lymphoma has also been reported [2]. Cases of subacute cutaneous lupus erythematosus associated with meningioma [28] and head–neck cancer [21] have been reported. The presence of antinuclear antibodies without clinical signs of rheumatic disease is not predictive of occult malignancy [29].

3.5. Polymyalgia rheumatica

Polymyalgia rheumatica, a relatively common disease in the elderly, is characterized by discomfort and stiffness of the shoulders and girdle, fatigue, anemia of chronic disease, and elevated erythrocyte sedimentation rate. While the relationship between polymyalgia rheumatica and giant cell arteritis is well recognized, its association with cancer is controversial. For example, a prospective study [30] of patients with classic polymyalgia rheumatica found that they do not have an increased risk of developing cancer, as do patients with inflammatory myopathies. Moreover, many diseases, including other RDs and systemic infections, can mimic polymyalgia rheumatica. Nonetheless, Naschitz [4] identified the following atypical features of polymyalgia rheumatica that can be the expression of an underlying malignancy: age <50 years, limited or asymmetric involvement of typical sites, an erythrocyte sedimentation rate less than 40 or higher than 100 mm/h, poor or incomplete response to low doses of corticosteroids, and long-lasting symptoms. All the seven patients examined by Naschitz and coworkers were found to have metastatic tumors.

Myelodysplastic syndromes and myeloproliferative syndromes are the malignancies most frequently associated with polymyalgia rheumatica [22]. Single associations with breast [24], colon [25], kidney and prostate cancer [23] have also been reported [1,4].
Recently, a benign cavernous hepatic hemangioma has been observed in a 59-year-old patient with polymyalgia rheumatica refractory to conventional therapy; resection of the lesion resulted in complete resolution of the RD [2].

3.6. Vasculitides

A number of vasculitic syndromes are occasionally associated with malignancies (Table 2). The incidence of malignancies in patients with vasculitides has been estimated to be 8% [1]. Cutaneous leukocytoclastic vasculitides are the most frequent paraneoplastic types and, importantly, clinical manifestations of skin involvement usually appear before or concurrent with the diagnosis or relapse of a tumor [31]. The most frequent types of cancer that develop in patients with vasculitis are lymphoproliferative disorders and myelodysplastic syndromes; solid neoplasms are less common [31,32].

The signs and symptoms of paraneoplastic vasculitides are similar to those in patients who do not have an underlying cancer. Nevertheless, the age at diagnosis, an unclear correlation with previous infections or systemic autoimmune diseases, a chronic-relapsing course, and lack of response to conventional treatment are the most suspicious findings suggestive of a hidden malignancy, besides weight loss and a decline in general health. Increased erythrocyte sedimentation rate, anemia and leukopenia are additional factors that should strengthen the suspicion of a coexistent tumor. Auto-antibodies, immune complexes and complement consumption are typically absent.

Erythema nodosum is a form of panniculitis frequently seen in clinical practice. It may be idiopathic or secondary to numerous causes, including exposure to drugs, infection, systemic diseases, and malignancies. The appearance, histological nature, and distribution of the skin lesions in paraneoplastic erythema nodosum are indistinguishable from those in the idiopathic condition and in secondary forms due to non-cancer causes. However, paraneoplastic erythema nodosum is distinguished by its poor response to conventional treatment. Patients with relapsing or treatment-resistant erythema nodosum that lasts 6–12 months or more should be

<table>
<thead>
<tr>
<th>Atypical vasculitis</th>
<th>Atypical presentation</th>
<th>Interval from onset to malignancy</th>
<th>Underlying malignancy</th>
<th>Solid tumors</th>
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<tbody>
<tr>
<td>Cutaneous leukocytoclastic vasculitis</td>
<td>&gt;50 Chronic relapsing course</td>
<td>Months to 3 years</td>
<td>Lymphomas, myelodysplastic syndromes [31]</td>
<td>Hepatocarcinoma, kidney, colon, head/neck and endometrial [32]</td>
</tr>
<tr>
<td>Polyarteritis nodosa</td>
<td>&gt;60 Skin involvement (100%)</td>
<td>Months to 2 years</td>
<td>Multiple myeloma, non-Hodgkin’s lymphoma [33]</td>
<td>Gastric, lung angiomatoid fibrous histiocytoma [34].</td>
</tr>
<tr>
<td>Henoch–Schönlein purpura</td>
<td>&gt;40 Severe renal involvement and arthralgias</td>
<td>1 year</td>
<td>Multiple myeloma [31]</td>
<td>NSCLC, prostate, breast, kidney [31].</td>
</tr>
<tr>
<td>Chronic erythema nodosum</td>
<td>&gt;60 Relapsing course</td>
<td>Months</td>
<td>Lymphomas, myelodysplastic syndromes [35]</td>
<td>–</td>
</tr>
<tr>
<td>ANCA-associated vasculitis</td>
<td>&gt;40 –</td>
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<td>–</td>
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<td>&gt;60 –</td>
<td>Years</td>
<td>Lymphomas, leukemia [40]</td>
<td>Bladder, breast, uterus, thyroid and stomach [40].</td>
</tr>
</tbody>
</table>

Abbreviations: ANA, antinuclear antibodies; ANCA, anti-neutrophil cytoplasmic antibodies; CA-125, cancer antigen 125; ESR, erythrocyte sedimentation rate; hyper-Ig, hypergammaglobulinemia; NSCLC, non-small cell lung cancer; RF, rheumatoid factor.
investigated for occult cancer [4]. In these patients, the skin lesions may antedate the symptoms of cancer by several months. Paraneoplastic erythema nodosum has been observed in patients with hematological malignancies (lymphoma, myelodysplastic syndromes) and only rarely in patients with solid tumors (reviewed in [11]).

Less commonly associated with tumors are systemic vasculitides such as polyarteritis nodosa, Henoch–Schönlein purpura, giant cell arteritis, Takayasu’s arteritis, Behçet’s syndrome and anti-neutrophil cytoplasmic antibody (ANCA)-positive vasculitis (Table 2).

4. Conclusions

There is increasing recognition that tumors may be associated with a wide range of rheumatic disorders (RDs). The etiology of paraneoplastic RDs is often unknown and the pathogenesis of this association remains to be determined. Paraneoplastic RDs generally precede the diagnosis of cancer, and thus are predictive of malignant disease. The clinical course usually parallels that of the primary tumor, and in most cases treatment of the tumor resolves the paraneoplastic symptoms.

It is important to recognize the clinical signs that suggest an underlying neoplasm and that help distinguish a paraneoplastic from an idiopathic RD. These signs include: rapid-onset of symptoms, atypical age at onset, poor response to corticosteroids or immunosuppressive therapy, atypical distribution of involved joints, and abnormal laboratory tests (e.g. persistent anemia, thrombocytopenia, occult blood in feces, hypergammaglobulinemia). Nevertheless, caution must be exercised in interpreting abnormal clinical and laboratory features, in that most evidence is from single case reports and small studies. The risk of not detecting cancer early, on one hand, and the risk of undertaking expensive, unfruitful diagnostic procedures in a patient with an atypical RD, on the other, should prompt the medical community to establish a consensus on diagnostic procedures and criteria. To this end, the establishment of reference centers, where data are collected in a homogeneous and consistent manner, could be instrumental. Greater understanding of the pathogenetic mechanisms and clear definition of the presenting features of paraneoplastic RDs are needed to help physicians understand when a search for a hidden cancer is appropriate.

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Take-home messages

- Several apparently idiopathic rheumatic diseases can be early manifestations of hidden cancer.
- Atypical clinical and laboratory features of these rheumatic diseases aid in the diagnosis.
- Recognition of a paraneoplastic rheumatic disease may permit early diagnosis and more effective treatment of the cancer.
- Current evidence is from single case reports and small studies; to improve the evidence base in this area, international reference centers that systematically collect data could be established.
- Diagnostic procedures and criteria should be developed to guide physicians considering the need for further, often expensive, investigations for a hidden cancer.

References

Fas (also known as Apo-1 and CD95) receptor has been suggested to control T cell expansion by triggering T cell-autonomous apoptosis. This paradigm is based on the extensive lymphoproliferation and systemic autoimmunity in mice and humans lacking Fas or its ligand. However, with systemic loss of Fas, it is unclear whether T cell-extrinsic mechanisms contribute to autoimmunity. In this study, Stranges PB et al. (Immunity 2007; 26: 629-41) found that tissue-specific deletion of Fas in mouse antigen-presenting cells (APCs) was sufficient to cause systemic autoimmunity, implying that normally APCs are destroyed during immune responses via a Fas-mediated mechanisms. Fas expression by APCs was increased by exposure to microbial stimuli. Analysis of mice with Fas loss restricted to T cells revealed that Fas indeed controls autoimmune T cells, but not T cells responding to strong antigenic stimulation. Thus, Fas-dependent elimination of APCs is a major regulatory mechanism curbing autoimmune responses and acts in concert with Fas-mediated regulation of chronically activated autoimmune T cells.

Elimination of antigen-presenting cells and autoreactive T cells by Fas contributes to prevention of autoimmunity