

Rheumatic manifestations of lymphoproliferative disorders

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Abstract

Objective

The association between musculoskeletal features and lymphoproliferative disorders as well as the association of rheumatic diseases with an increased risk of malignancies is well-known.

Methods

This paper describes three patients with inflammatory joint diseases treated with disease modifying antirheumatic drugs who developed lymphoproliferative disorders either of an abnormal type or with unusual clinical features.

Results

The difficulty in differentiating the musculoskeletal symptoms of an underlying lymphoproliferative disease from the features of the rheumatic disease itself with special regard to treatment with disease-modifying antirheumatic drugs including biologics is emphasised on the example of patient 1. Patient 2 presented with a rare type of lymphoma and had been mistakenly diagnosed as having seronegative RA. The last patient with oligoarthritis represents an example of the sarcoidosis-lymphoma syndrome.

Conclusion

This article addresses several of the problems rheumatologists may experience with the various rheumatologic manifestations of lymphoproliferative disorders. Until more definitive data are available, patients who develop unexpected arthritis should be considered for histologic biopsy to rule out coexistent neoplasia.

Key words

Rheumatoid arthritis, spondyloarthritis, disease modifying antirheumatic drugs, tumor necrosis factor blockers, lymphoma, sarcoidosis.

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Abbreviations:

AIL:	angioimmunoblastic lymphadenopathy;
AS:	ankylosing spondylitis;
DMARD:	disease-modifying antirheumatic drug;
NHL:	non-Hodgkin lymphoma;
NSAID:	nonsteroid antiinflammatory drug
RA:	rheumatoid arthritis;
SpA:	spondyloarthritis;
TNF:	tumor necrosis factor.

Introduction

The association between rheumatic symptoms and conditions and lymphoproliferative disorders has been well recognized (1). Recently there has been an increased interest in this association due to the introduction of potent anti-rheumatic therapies (2). Basically this association can be of three different kinds:

1. an underlying lymphoproliferative disease or other malignancy may manifest with musculoskeletal symptoms
2. a rheumatic disease may be associated with malignancy
3. anti-rheumatic therapy may induce or trigger malignancy.

Rheumatic manifestations in patients with lymphoproliferative disorders include a wide spectrum of osteoarticular, muscular and systemic features. Patients with these disorders usually complain about rheumatic symptoms rather late in the course of the disease. However, one should be aware that rheumatic symptoms may be the first indication of the presence of a lymphoproliferative disorder. Overall, a wide range of lymphoproliferative disorders may be associated with rheumatic features. Skeletal involvement by lymphoma (3) or leukemia (4) is generally well recognized, while polyarticular joint manifestations as the predominant symptom of lymphoproliferative disorder are quite uncommon (5). Because of the overall reduced prognosis of these conditions early recognition is important. However, at the time of the initial presentation lymphadenopathy and hepatosplenomegaly are often absent (6). This may obscure the diagnosis, as was the case in one of the patients described below.

Secondly, many rheumatic diseases, especially those with autoimmune phenomena, are associated with an increased risk for malignancy. In patients with primary Sjögren's syndrome and systemic lupus erythematosus there is a well documented risk of developing lymphoproliferative disorders while patients with dermatomyositis or polymyositis may develop other malignant diseases (7). In patients with rheumatoid arthritis (RA) an increased risk of

developing lymphoma has been reported in all recent studies (8-10).

Finally, patients with rheumatic disease who are unresponsive to standard disease-modifying antirheumatic drugs (DMARDs) are now increasingly being treated with tumor necrosis factor (TNF) blockers. There is a theoretical possibility that these agents may be associated with an increased risk of lymphoproliferative disorders or malignancy (11). Although several reports of lymphoma in patients exposed to anti-TNF- α treatment have been published (12) there is no current epidemiological evidence supporting an increased risk. We see > 5000 patients in our hospital every year and since have accumulated quite some experience with anti-TNF agents over recent years (13), and thus can present three interesting cases of patients with lymphoproliferative disorders who first presented to the rheumatologist (Table I), and discuss the recent literature with special regard to lymphoproliferative disorder and rheumatic disease.

Case 1

A 35 year-old woman with a background of 12 years of lower back pain developed a symmetrical polyarthritis in July 2003. MRI showed symmetrical sacroiliitis. A diagnosis of HLA-B27-negative ankylosing spondylitis (AS) was made and she responded well to non-steroidal anti-inflammatory drugs (NSAIDs). She was treated with different DMARDs: methotrexate (09/03 until 12/03), infliximab (12/03 until 08/04), etanercept (09/04 until 12/04) and adalimumab (12/04 until 02/05). Methotrexate was ineffective for swollen joints and pain. Infliximab was initially effective but had to be stopped after 8 months due to allergy. Subsequently she was switched to etanercept which was ineffective, and then adalimumab was started. Nevertheless, joint swelling, pain and morning stiffness recurred. In addition, the patient frequently complained of fatigue since December 2004.

Under suspicion of a particularly severe case of spondyloarthritis, the patient was referred to our institution in March 2005 with low back pain and radicular

Table I. Patients' characteristics.

	Age	Sex	Rheumatic disease	Onset	Laboratory	Tumor diagnosis	Diagnosis
			Diagnosis			Symptoms	
Pat. 1	35	F	AS with peripheral joint involvement	2003	HLA-B27 negative	Radicular pain	B-cell NHL
Pat. 2	36	M	Polyarthritis	2004	RF negative ANA neg.	Pruritic rash Hepatopathy	Cutaneous T-cell NHL
Pat. 3	68	M	Monoarthritis Sarcoidosis	2004	RF negative	Bilateral hilar adenopathy	Hodgkin's disease

pain in the left leg. Physical examination revealed a swollen left wrist, and multiple enlarged lymph nodes were palpable. Laboratory testing showed an increased ESR of 42 mm (normal: 6–11) and an elevated level of LDH of 461 U/l (normal: 134–215). X-rays revealed a mass at the left hilus approximately 11 x 8 cm and bilateral pleural effusions. A chest and abdominal CT scan revealed splenomegaly and lymphadenopathy. MRI showed neoplastic infiltration of the entire spine with pathological fractures of L3 and L4. Excisional biopsy revealed a diffuse large B-cell non-Hodgkin's lymphoma (NHL). The patient was thus classified as stage IV B.

From March until July 2005 she underwent 8 cycles of R-CHOEP 14 chemotherapy (rituximab 375 mg/m, cyclophosphamide 750 mg/m, doxorubicin 50 mg/m, vincristine 2 mg, etoposidophosphat 114 mg/m and prednisone 100 mg). To date, she is on continuous chemotherapy, and mediastinal and lumbar irradiation are planned.

Case 2

A 36 year-old man presented with a 4-week history of polyarthritis. The patient had an increased ESR of 23 mm and CRP of 3.4 mg/dl (normal: < 0.5). He was tested negative for RF and ANA. X-rays showed swollen joints without erosions in the hands. In the synovial fluid taken from the knees the total white blood cell count was 5.4 x 10⁶/l (neutrophils 95%, lymphocytes 5%). The patient was diagnosed as having seronegative rheumatoid arthritis and started on diclofenac (100 mg/d), sulfasalazine (2g/d), and prednisolone (10 mg/d) which needed to be gradually increased up to 40 mg/day due to ongoing symptoms. Chemical synovectomy

(CSO, morrhuate sodium injection) of both knees was undertaken for resistant symptoms, once a week for three weeks. One day after completing the CSO regimen, the patient developed fever up to 38.8°C and a mildly pruritic rash involving mainly the trunk, in combination with an hepatic icterus (elevated total bilirubin 2.36 mg/dl (normal: < 1.1), direct bilirubin 1.88 mg/dl (normal: < 0.25)). Initially, diclofenac and sulfasalazine were withdrawn with a presumptive diagnosis of drug interactions and/or side effects. Elevation of liver function tests peaked after two weeks with a maximum ALT of 2873 U/l (normal: 9–51) and AST of 1293 U/l (normal: 9–51). At this time the patient developed multiple enlarged lymph nodes up to 4 cm in diameter. The histological appearance of the left axillary lymph node was consistent with a cutaneous T cell NHL. Based on these examinations the patient was staged as IV BE disease. He received six courses of a monthly chemotherapy regimen consisting of ifosfamid (3 mg/d), etoposid (400 mg/d), vincristine (2.0 mg/d) and dexamethasone. To date, he remains in clinical remission without any signs of arthritis.

Case 3

A 68 year-old man had pain and swelling in both ankles of one year's duration. He had been diagnosed with sarcoidosis on the basis of the presence of erythema nodosum and bilateral hilar adenopathy eight months ago. Therapy consisted mainly of prednisone at an average dose of 10 mg/d. Since his joint symptoms showed a poor response to NSAIDs and corticosteroids, he had been treated with azathioprine for the last two months. At the initial presentation to our hospital, he was on azathioprine

(150mg/d) and prednisolone (7.5 mg/d). On physical examination the patient was noted to have synovitis in both ankles. Both ESR (120 mm) and CRP (24 mg/dl) were raised, and RF was negative. An x-ray of the chest disclosed an infiltration of the right lung. The patient was started on antibiotics with a presumptive diagnosis of pneumonia. Chest CT scan was remarkable for multiple enlarged lymph nodes in the right paratracheal, mediastinal and paraaortic groups. Because no histological confirmation was done eight months ago, cervical and mediastinal exploration with lymph node excision was performed revealing Hodgkin's disease (HD) with mixed cellularity. He was staged as IV B disease and received 6 courses of ABVD combination chemotherapy (adriamycin (57 mg), bleomycin (23 U), Velban (14 mg), and DTIC (848 mg)) with a partial remission of his lymphoma. His arthritis symptoms completely resolved.

Discussion

This article addresses several of the problems rheumatologists may experience with the various rheumatologic manifestations of lymphoproliferative disorders. The association of rheumatic symptoms and lymphoma can include a variety of conditions, most of which have no specific features distinguishing them from idiopathic rheumatic disorders. We have described 3 patients with malignant diseases who initially presented with rheumatic musculoskeletal symptoms. All cases are of interest because of the difficulty to differentiate between rheumatic and lymphoproliferative disease. In addition, in case 1 there is a possible influence of anti-TNF agents and in case 2 there is the potential impact of treatment with sul-

fasalazine, whereas there was no specific drug history in case 3.

The patient presented as case 2 had been mistakenly diagnosed as having seronegative RA and treated as such by a rheumatologist based on progressive symmetrical polyarticular symptoms. In retrospect, our patient's clinical picture showed some features that were quite atypical for RA. He had denied any morning stiffness and showed poor response to even a relatively high dose of prednisolone. Features including severe joint pain disproportionate to physical findings, a poor response to conventional antirheumatic treatment, and early significant osteopenia or lytic lesions have been reported as distinctive for paraneoplastic arthritis in adult patients with leukaemia (14).

In case 1, the first question is whether the initial sacroiliitis was due to spondyloarthritis (SpA) or already the initial manifestation of lymphoma, as has been described (15, 16). The patient had inflammatory back pain and radiographic changes in the sacroiliac joints and, thus, fulfilled the classification criteria for a diagnosis of AS (17). No definitive diagnosis can be made but the fact she initially responded well to NSAIDs and infliximab suggests that indeed SpA was being treated at this point in time. The second question is whether one, two or all three anti-TNF agents given may have influenced the development of lymphoma. Theoretically there are several possibilities: a. no influence of anti-TNF therapy, b. triggering or induction of lymphoma by one or more anti-TNF agents, and c. catalysing a pre-existing lymphoma by one or more anti-TNF agents. Again here, it seems difficult to determine a causal relationship especially given the fact that the initial diagnosis can not be considered as firmly established.

Chronic inflammation is associated with an increased risk for malignant lymphoma. Sarcoidosis as a granulomatous inflammatory disease may predispose to malignancy and the coexistence of sarcoidosis and malignancy has been recognized for nearly three decades, initially termed the "sarcoidosis-lymphoma syndrome" by Brincker in 1986 (18). In a retrospective study

Asking *et al.* found a doubled relative risk for NHL in sarcoidosis over the first decade of follow-up (19). Where sarcoidosis and lymphoma occur in association, lymphoma almost invariably develops subsequent to sarcoidosis after disease-free intervals of a number of years. The typical features of this syndrome are the development of Hodgkin's lymphoma in a patient with a preexisting diagnosis of sarcoidosis. Typically, the patient is older than average for the sarcoid population (median, 45 years of age) and has had chronically active pulmonary sarcoidosis for a period of several years (20). Patient 3 in this article represents an example of the sarcoidosis-lymphoma syndrome, but shows in contrast to the literature a disease duration of only 8 months. In sarcoidosis the alternative or additional diagnosis of lymphoma has to be considered, especially in those without histological confirmation.

Muskuloskeletal complaints in patients with lymphoma are not unusual, but peripheral joint involvement as a presenting feature is quite rare. These patients may present with monoarticular (21) or polyarticular arthritis (22, 23). It is estimated that 7–25% of patients develop skeletal lesions during the course of NHL (24). Direct synovial involvement by lymphoma cells is less common and could not be shown in all cases when synovial biopsy was performed (25).

On the other hand, patients with rheumatoid arthritis (26) and early inflammatory polyarthritis (27) have a two to threefold increased risk of developing lymphoproliferative disorder compared with the general population. The occurrence of malignancies or lymphoproliferative disorders in patients with RA seems to be associated with persistent inflammatory disease activity (28). The reason for an increased lymphoma risk in RA patients is still unclear, but available studies support the hypothesis of a link between RA disease activity and the risk of lymphoma, rather than increased risks associated with specific treatment regimes. Irrespective of the increased incidence of lymphoma in patients with RA, the incidence of NHL in the general population has also

increased dramatically over the last decades (29).

The change in treatment paradigms for RA towards the early use of more potent immunosuppressive therapy has caused a major concern about the possibility of treatment-related lymphoma risks. No specific DMARD has clearly been linked to an increased lymphoma risk. Reports of lymphoma in patients treated with TNF blocking agents have brought renewed interest in this issue (30). TNF has a documented tumor reducing capacity, and treatment with anti-TNF drugs might thus theoretically promote the formation of tumors (31). This raises a theoretical concern that agents blocking TNF- α may contribute to an increased risk of such lymphomas. Furthermore, these therapies are typically reserved for patients with the most severe disease, who may already be at increased risk of lymphoma development. Observation times for the TNF-blocking therapies are still short and current data are inconclusive but an enhanced risk of malignancy, particularly lymphoma, can not be excluded (32). In the largest currently available study there was no increased risk for lymphoma in RA patients treated with TNF-antagonists when compared to RA patients not treated with such compounds (33). However, the long-term risk following prolonged exposure with TNF-antagonists for many years remains to be adequately investigated.

There is now increasing evidence that anti-TNF therapy is efficacious not only for RA but also in patients with AS (34, 35). The side effect profile seems to be comparable with that reported previously for patients with RA (36). As confirmed in recent studies, lymphomas are increased in RA, but this might not be the case for AS. In general, no overall increase in cancer risk was found for haematopoietic malignancy (37). In particular, no increased lymphoma risk in patients with AS in the absence of TNF-antagonists could be observed (38).

Alongside TNF-antagonists, other DMARDs have to be considered when discussing carcinogenesis, for example side effects due to sulfasalazine. Our patient (patient 2) developed a periph-

eral T-cell lymphoma after 3 weeks of treatment with sulfasalazine, which needed to be differentiated from an angioimmunoblastic lymphadenopathy (AIL). Sulfasalazine has been reported to induce this specific form of an uncommon peripheral lymphoproliferative T cells disorder (39). As with our reported case, most of the patients with AIL have hepatosplenomegaly, but other features, such as musculoskeletal pain are observed to a lesser extent. In contrast to peripheral T-cell lymphoma, corticosteroids are very effective for the suppression of cutaneous symptoms in AIL. Because of similarities in clinical findings, histopathologic examination of lymph nodes is essential for establishing the correct diagnosis. Clinicians should be aware of the potential risk of malignancy in patients with rheumatic diseases. Until more definitive data are available, patients who develop unexpected arthritis should be considered for histologic biopsy to rule out coexistent neoplasia.

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