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Severe joint pain as a manifestation of paraneoplastic rheumatic syndrome in a patient with a malignant lymphoma: A case report and review of the literature

Rikke Asmussen Andreasen¹, Amir Emamifar¹, Jacob Christian Bang², Michael Boe Møller³, Inger Marie Jensen Hansen¹

¹Department of Rheumatology, Svendborg Hospital, Odense University Hospital, Valdemarsgade 53, DK-5700, Svendborg, Denmark
²Department of Radiology, Svendborg Hospital, Odense University Hospital, Valdemarsgade 53, DK-5700, Svendborg, Denmark
³Department of Pathology, Odense University Hospital Odense, J.B. Winsløwsvej 15, DK-5000, Odense, Denmark

Correspondence: Rikke Asmussen Andreasen
E-mail: Rikke.asmussen@rsyd.dk
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Background

Rheumatic diseases (RD) and malignancies may be connected to each other in different ways. It has previously been shown, that RD can be a primary manifestation of an underlying cancer as a paraneoplastic syndrome (PNS). RD are related with increased incidence of different malignancies due to the characteristic of the disease or as a result of drug therapy, for instance immunosuppressive agents and tumor necrosis factor inhibitors [1].

Paraneoplastic rheumatic syndromes (PRS) are rheumatologic diseases that are triggered by a malignant disease. Symptoms of PRS can not be explained by the anatomical location of the tumor or metastases, and they often remit following treatment of the underlying disease [2].

The pathogenesis of PRS is complex and not fully understood. Recent research has shown that certain tumors produce hormones, peptides or cytokines that can interact with the immune system and results in various clinical manifestations of the musculoskeletal system [3]. The PNS may be the patient's primary complaint and occurs up to two years before the underlying cancer is diagnosed. Non-Hodgkin's lymphoma is often associated with rheumatic disease [1, 4].

As a result of improvement in diagnostic and therapeutic technique the number of patients with cancer and probably the incidence of PRS will increase, which can affect the clinical course and management of the disease. Management of PRS consists of treatment of underlying malignancy and standard therapy of rheumatic syndrome [2].

The purpose of this case report is to emphasize the challenging elements in the differential diagnosis within rheumatology, and to describe a newly defined group of very aggressive lymphomas, so-called double-hit lymphoma (DHL), which are characterized by cytogenetic translocation of both MYC and BCL2. We report a case history of a 63-year-old woman with hip pain as a PRS.

Case report

A 63-year-old woman referred to the rheumatology outpatient clinic with a history of a persistent four weeks
right-sided hip pain. The pain was constant and severe. X-ray of the hip and pelvis were normal. Objectively, there was no sign of arthritis, except pain-related limitation of motion.

Laboratory work-up showed leukocytes: $10.4 \times 10^9$ / l, platelets: $110 \times 10^9$ / l, Hb: 5.6 mmol/l, C-reactive protein: 47 mg/l (normal range: <10 mg / l), ionized calcium: 1.22 mmol/l (normal range: 1.19-1.29mmol/l), Lactate dehydrogenase (LDH): 958 U/l (normal range: 105-205) and erythrocyte sedimentation rate: 17. Immunological test values including Immunoglobulin (Ig) M, IgG and IgA were within normal limits.

Four days later she was admitted to the local hospital with a preliminary diagnosis of cholecystitis. Ultrasound of abdomen identified supracapsular process on the right kidney upper pole. CT urography demonstrated 3 pathologically enlarged lymph nodes located centrally in the retroperitoneum. A biopsy of a subcutaneous nodule was performed. Pathology results revealed aggressive medium-sized B-cell lymphoma between diffuse large B-cell lymphoma and Burkitt lymphoma (Figure 1) with high mitotic activity (starry-sky appearance). Immunohistochemical staining of tumor cells were positive for CD20, CD10, PAX5, FOX P1, MUM1, lambda, MYC, BCL2 and Ki 67 (with 100% proliferation rate) and negative for CD21, BCL6, GCET1, TdT, EBER, CD3, CD5 and kappa. Flowcytometry analysis showed 59.4% B-cells with expression of CD20, CD22, CD79b, CD24, CD19 and lambda. In addition, these cells were weakly positive for CD10.

FISH technique detected translocation of MYC, BCL2, IGH and no translocation of the BCL6 gene. These findings are diagnostic of underlying double-hit lymphoma (DHL). Staging investigations showed widespread disease with involvement of several lymph node regions, bone marrow, subcutaneous tissue and myocardium equal to Ann Arbor staging 4B [5]. (Table 1). Intensive courses of chemotherapy with high doses of Methotrexate, Rituximab, Cyclophosphamide, Doxorubicin, Vincristine were started with supplemented high dose Prednisolone, and a month later hip pain disappeared. Patient achieved complete remission after chemotherapy, but the disease relapsed shortly after in central nervous system (Figure 2). The patient died after a total of 11 months disease.

**Discussion**

PNS is relatively rare and occurs in up to 8% of all cancer patients [2]. It is known that some rheumatological diseases are associated with increased incidence of cancer. In the literature there are underlying malignancies in 10-25% of cases with dermatomyositis, and up to 90% in hypertrophic osteoarthropathy (HOA). Therefore clinicians have to pay special attention to the symptoms of the above-mentioned diseases.

HOA is divided into primary/hereditary and secondary forms. The secondary form is commonly related with lung cancer, bone metastasis, nasopharyngeal carcinoma and rhabdomyosarcoma. Diagnosis of hypertrophic osteoarthropathy can be made by physical examination and radiographic evaluation. Subsequent treatment of the underlying cancer improves the condition [1, 2].

There is an association between ovarian, lung, breast, gastrointestinal system, non-Hodgkin lymphomas, prostate
Table 2. Different paraneoplastic rheumatic syndromes and their association with underlying cancer

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Associated cancers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertrophy osteoarthropathy</td>
<td>Lung cancer, metastasis to bone, nasopharyngeal carcinoma, rhabdomyosarcoma</td>
</tr>
<tr>
<td>Dermato-/polymyositis</td>
<td>Ovarian, lung, breast, gastrointestinal system, non-Hodgkin lymphomas, prostate and nasopharynx (Asian population)</td>
</tr>
<tr>
<td>Vasculitis</td>
<td>Lymphoproliferative and myeloproliferative disorders</td>
</tr>
<tr>
<td>Carcinomatous polyarthritis</td>
<td>Breast, colon and lung ovarian lymphoproliferative disorders</td>
</tr>
<tr>
<td>Palmar fasciitis</td>
<td>Ovarian (most common), stomach, pancreas, lung and colon</td>
</tr>
<tr>
<td>Reflex-sympathetic dystrophy</td>
<td>Pancoast tumor of the lung, malignancies that infiltrates the stellate ganglion or brachial plexus type II</td>
</tr>
<tr>
<td>syndrome (chronic regional pain syndrome)</td>
<td></td>
</tr>
<tr>
<td>Erythromelalgia</td>
<td>Myeloproliferative disorders especially Polycythemia Vera and essential trombocytosis</td>
</tr>
<tr>
<td>Polymyalgia Rheumatica (PMR)</td>
<td>Kidney, lung, colon cancer and multiple myeloma</td>
</tr>
<tr>
<td>Amyloidosis</td>
<td>Multiple myeloma, lymphomas and carcinomas</td>
</tr>
<tr>
<td>Digital necrosis - Raynaud’s</td>
<td>Solid tumors (most frequent stomach, lung, ovarian) and lymphoproliferative disorders.</td>
</tr>
<tr>
<td>syndrome</td>
<td></td>
</tr>
<tr>
<td>Remitting seronegative symmetric</td>
<td>Lymphoma, myelodysplastic syndrome, adenocarcinoma</td>
</tr>
<tr>
<td>synovitis with pitting edema</td>
<td></td>
</tr>
<tr>
<td>(RS3PE)</td>
<td></td>
</tr>
<tr>
<td>Multicentric reticulohistiocytosis</td>
<td>Carcinoma of the lung, stomach, breast, cervix, colon and ovary</td>
</tr>
<tr>
<td>Panniculitis</td>
<td>Hematologic malignancies or pancreatic cancer</td>
</tr>
<tr>
<td>Lupus-like syndromes</td>
<td>Ovarian carcinoma, hairy-cell leukemia and breast carcinoma</td>
</tr>
<tr>
<td>Scleroderma-like syndrome</td>
<td>Adenocarcinoma and carcinoid tumor</td>
</tr>
<tr>
<td>Sjögren’s syndrome</td>
<td>Lymphoproliferative disorders(non-Hodgkin’s lymphoma, lymphoma of mucosal-associated lymphoid tissue (MALT), Waldenström’s macroglobulinemia, chronic lymphocytic leukemia and multiple myeloma</td>
</tr>
<tr>
<td>Rheumatoid arthritis (RA)</td>
<td>Lymphoproliferative disorders, lung cancer</td>
</tr>
<tr>
<td>Systemic lupus erythematosus (SLE)</td>
<td>Lymphoproliferative disorders, gynecologic malignancies</td>
</tr>
<tr>
<td>Systemic sclerosis</td>
<td>Lung, breast, esophagus and skin</td>
</tr>
<tr>
<td>Paget’s disease of bone</td>
<td>Osteosarcoma (under 1%)</td>
</tr>
</tbody>
</table>

Figure 2. T1-weighted coronal sequence after Gd-contrast shows a 17x12x12 mm contrast enhancing tumor in the right temporal lobe.

to determine the underlying cancer in specific cases. Paraneoplastic dermatomyositis responds poorly to corticosteroid treatment. Treatment of the primary cancer is a mainstay and can cause symptom regression [1, 6, 7].

Vasculitis can occur as PRS especially in association with haematological cancers, but the prevalence is not exactly known (approximately 3-8%) [8]. Leukocytoclastic vasculitis is the most frequent finding in histopathological exam, which is responsible for 30-40% of all paraneoplastic vasculitis cases [8]. The etiology of paraneoplastic vasculitis is not clear. Paraneoplastic vasculitis responds poorly to conventional treatment. Other paraneoplastic rheumatic syndromes such as Raynaud’s phenomenon, erythema nodosum and non-specific symptom as arthralgia, are reported less frequently in a few case reports. (Table 2) [1-4, 8].

In recent years DHL has been identified as a group of extremely aggressive B-lymphomas with often poor treatment response and consequently short survival. Patients almost always present with advanced disease with involvement of extranodal sites. Poor prognostic factor associated with double hit lymphoma include increased LDH level, involvement of central nervous system/ bone marrow and a high international prognostic index score which primarily present in most of the cases. This case report illustrates a fulminant clinical course, which is characteristic of this type of lymphoma [9-10].
In rheumatologic studies it may be difficult for the clinicians to differentiate between underlying malignancy and primary rheumatologic disease, because the clinical manifestations are identical. But attention should be given when there are sudden occurrence of symptoms, unusual joint involvement, atypical age at disease onset and lack of response to therapy \[4, \]\[11\].

There is no consensus on when a patient with rheumatological symptoms should be screened for possible underlying cancer. It is not economically justifiable to start performing a comprehensive examination for occult cancer, where it could be PRS in every case, but it should be part of the differential diagnosis in patients showing an atypical course, since early diagnosis of PRS will increase the patient's quality of life and chance of survival.

References