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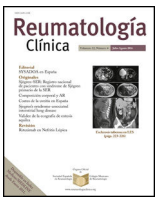

Brief Report

Rheumatic syndromes and occult tumor: 10-Year experience in a teaching hospital☆

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ABSTRACT

Objective: To describe the different clinical characteristics of patients admitted to the Rheumatology Department due to rheumatic manifestations as the first expression of an unknown malignant process.
Patients and methods: Retrospective and descriptive observational study involving the review of the medical records of those admitted to rheumatology in the University Hospital of Ciudad Real between January 2007 and August 2017 for initial rheumatic manifestations with a suspicion at discharge of an unknown tumor.
Results: In all, 64 patients were identified from more than 500 admissions. The most common rheumatic manifestations were inflammatory low back pain, polyarthralgia, hip pain, thoracic spine pain, cervical pain, polyarthritis and polymyalgia rheumatica. Forty-four percent had low haemoglobin, 70% had elevation of acute-phase reactants, 62% had abnormal tumor markers, 76% had metastatic lesions. In 20% the primary tumor was of pulmonary origin and only 26.56% received palliative treatment; 64% died.
Discussion: It is important to consider the possibility of an underlying malignant process in the differential diagnosis since its early identification can be determinant for prognosis.

Síndromes reumáticos y tumor oculto, experiencia de 10 años en un hospital universitario

Palabras clave:
Manifestaciones reumáticas
Tumor oculto
Diagnóstico diferencial
Pronóstico

RESUMEN

Objetivo: Describir las diferentes características clínicas de los pacientes ingresados en el Servicio de Reumatología por manifestaciones reumáticas como primera expresión de un proceso tumoral no conocido.
Pacientes y métodos: Estudio observacional retrospectivo y descriptivo protocolizado por la revisión de las historias clínicas de los ingresados en Reumatología del Hospital Universitario de Ciudad Real desde enero de 2007 hasta agosto de 2017 por manifestaciones iniciales reumáticas, con sospecha al alta de un tumor no conocido.
Resultados: De más de 500 ingresos, se obtuvieron 64 casos. Las manifestaciones reumáticas más frecuentes fueron lumbalgia inflamatoria, poliartralgias, síndrome de cadera, dorsalgia, cervicalgia, poliartritis y polimialgia reumática. Un 44% presentaban anemia, un 70% elevación de los reactantes de fase aguda, un 62% alteración en los marcadores tumorales y un 76% lesiones metastásicas. En el 20%, el tumor primario fue de origen pulmonar y solo el 26,56% recibió tratamiento paliativo. El 64% fallecieron.
Discusión: Es importante plantearse en el diagnóstico diferencial la posibilidad de un proceso tumoral subyacente, dado que su diagnóstico temprano puede ser determinante para el pronóstico.

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Introduction

A great variety of rheumatic manifestations have been associated with malignant processes.[1] This association between autoimmunity and malignancy is complex, since immune dysregulation and immunosuppressive treatments for rheumatic diseases (rheumatoid arthritis, Sjögren's syndrome, systemic lupus erythematosus, systemic sclerosis, eosinophilic fasciitis, spondyloarthropathies, dermatomyositis, polymyalgia rheumatica with atypical features) could facilitate onset of tumor processes, and anti-cancer therapy could also trigger onset of rheumatic processes.[2]

There are more than 30 rheumatic processes associated with neoplastic processes, often with metastatic involvement. The pathophysiological mechanisms of onset can be grouped as follows[3]:

1. Distant effects mediated by humoral factors (paraneoplastic syndromes): hypertrophic osteoarthropathy, carcinomatous polyarthritis, dermatomyositis, vasculitis and others. The features of these forms of polyarthritis are sudden onset at late age, oligoarticular distribution or asymmetrical polyarticular distribution, predominance in joints of the lower limbs, sparing the wrists and small joints of the hands, and the absence of erosions, deformities, rheumatoid factor and rheumatoid nodules. Their clinical course usually runs parallel to that of the tumor. Therefore, cure of the cancer normally results in cure of the rheumatic process.
2. Direct tumor invasion to bones, joints, muscles and soft tissues.
3. Metastatic involvement: they present in up to 70% of prostate and breast cancer patients, and in up to 30% of patients with lung, bladder or thyroid cancer. The main complications associated with bone spread are acute pain, spinal cord compression and pathological fractures.[4,5]

The objective of this study was to describe the different clinical features of patients admitted with rheumatic symptoms as a first manifestation of an unknown tumor process.

Patients and methods

An observational, retrospective and descriptive study was performed, protocolised by review of the clinical histories of patients admitted to the rheumatology department of the General University Hospital of Ciudad Real between January 2007 and August 2017 with initial rheumatic manifestations that contributed towards a diagnosis on discharge of an unknown malignant neoplasm.

The clinical data were collected (age, sex, duration of disease), laboratory and imaging tests, histological data and treatment received, and progression since discharge from hospital. A database was created on Excel 2007 with the data obtained, with subsequent statistical analysis of frequencies, means, standard deviation and relative risk using SPSS 21.

Results

Of a total of 500 admissions to the rheumatology department during the study period, a total of 64 cases were obtained, of which 34 were males (53%), and 30 females (47%), with a mean age of 66.75 years (±11.93). The average time from onset of symptoms to diagnosis of a neoplastic process was around 3 months (±2.35).

The most common rheumatic manifestations were 25 cases of inflammatory low back pain (39%), 13 cases of polyarthralgia (20.3%), 9 cases of inflammatory neck and pack pain (14%), 8 cases of hip pain (12.5%), and 2 cases of polyarthritis in patients with suspected inflammatory myopathy (3.1%). The characteristics of these polyarthritides were sudden onset at late age, oligoarticular or asymmetric polyarticular distribution, and predominance in the joints of the lower limbs. As associated extra-articular manifestations, 2 cases were observed of pulmonary dyspnoea (3.1%). The presence of constitutional syndrome (RR: 1.44; CI 95%: 1.00–2.06; $P = .058$) was noted in 42.1% of the patients.

Normocytic normochromic anaemia (Hb < 12 g/dl) was present in 28 patients (43.75%). CRP and ESR, acute phase reactants, were determined, and these were elevated (CRP > 1 mg/dl and ESR > 25 mm/h) in 41/64 (67.21%), in 42/64 (71.11%) patients respectively. Similarly, 40 patients (62.5%) had increased levels of a tumor marker (RR: 1.78; 95%CI: 1.08–2.92; $P = .0064$) on admission, principally CEA, Ca 125 and Ca 19.9 in 85% of these patients. The smoking rate calculated using the formula of number of packs/year (number of cigarettes/day divided by 20 and multiplied by the number of years that the patient had been smoking) was 40.21, with a standard deviation of ±21.35.

Radiography proved to be the basic imaging test for detecting lesions suggestive of malignancy, for tumor site, opacity, margins, transition zone, periosteal reaction, mineralisation, size and number of lesions, soft tissue component and fracture. Lesions suggestive of tumor disease were observed in 40%, and pathological fractures in 11.11%. Bone scans were pathological in 83.33% (35/42), tomography in 96.22% (51/53), magnetic resonance imaging in 90.90% (30/33), and PET-CT in 95.65% (22/23).

The primary focus was determined by histopathological study in 60 patients: 13 lung, 5 breast, 5 prostate, 4 colon, 2 kidney and pancreatic tumors, one brainstem glioma, and one typical meningioma. Haematological malignancies were found in 9 patients; these were 7 multiple myelomas, and 2 high-grade non-Hodgkin's lymphomas; 4 patients either did not have a had no histological diagnosis or it was inconclusive. Forty-nine patients had metastatic lesions at the time of diagnosis (RR: 1.78; 95%CI: .93–3.40; $P = .0264$).

In terms of treatment received, 73.44% received specific treatment (37.5% chemotherapy, 15.62% surgery, 12.5% chemotherapy + radiotherapy and 7.81% chemotherapy + surgery). While 26.56% received palliative treatment alone.

Finally, on the date of the last assessment it was observed that 64.06% of the patients had died, 10.93% had suffered a complication, either due to the disease itself or the treatment received, and 25% of the patients had progressed favourably after diagnosis up until the date that this study ended. The variables studied during the period of hospitalisation that were most associated with a fatal outcome over time were: abnormal tumor markers (RR: 1.78; 95%CI: 1.08–2.92; $P = .0064$), constitutional syndrome (RR: 1.44; 95% CI: 1.00–2.06; $P = .058$), and the presence of metastases at time of diagnosis (RR: 1.78; 95%CI: .93–3.40; $P = .0264$).

Discussion

Interest in the rheumatic manifestations of occult tumor has increased in recent years, stimulated by practical considerations that include prompt diagnosis of cancer, which could be enabled if the rheumatic syndromes associated with it are known.[2,3] Furthermore, rheumatic symptoms could flag up potentially resectable localised neoplasms, and chemotherapy could be beneficial for some types of cancer, even if they have already metastasised.[6,7]

A major group in the spectrum of rheumatic manifestations associated with neoplastic processes comprises those caused by metastatic bone lesions. The risk factors most associated are age, a history of cancer, and harmful habits or drugs.[2,4,5] In our series lower back pain, with inflammatory features and of metastatic origin, was the most frequent aetiology. It is striking that there were

only 2 cases in patients with inflammatory myopathy, and with initial symptoms of polyarthritis, who were diagnosed with high-grade non-Hodgkin's lymphoma. Since these are very common symptoms in the general population, if correctly assessed we will be able to discount other aetiologies that entail different treatment and prognosis.[8,9]

Metastatic vertebral involvement generally causes continuous pain with flare-ups that can lead to functional impairment. It is difficult to distinguish it clinically from pain caused by other degenerative bone conditions, therefore a thorough clinical history and physical examination will help guide diagnostic suspicion and complementary tests.[10] Plain x-ray is the first imaging test in the initial approach, which will help to determine the features of bone lesions, levels of involvement, and the location of the lesion in the vertebral body. However, in most cases these findings tend to be non-specific, therefore the use of other complementary imaging tests such as bone scintigraphy, magnetic resonance and PET-CT will greatly help in determining the cause of the vertebral involvement.[11] With these tests it is just about possible to identify the primary tumor, in up to 86% of cases according to some series that highlight cancer of the lung, prostate and breast, however the cancer site could not be determined in 13.4%.[12]

Of the analytical variables determining progression, abnormal tumor markers, the presence of constitutional syndrome and of metastases at time of diagnosis were associated with torpid progression and fatal outcome. The anaemia, ESR and CRP variables had no statistically significant association with progression.

In our patients with malignant neoplasms, for those whose osteoarticular lesions were caused by local infiltration, it was essential to take biopsies of the metastatic lesions to establish the diagnosis, which was confirmed by biopsy of the primary lesions.

Some published studies describe smokers (with chronic diseases and new-onset polyarthritis), and mention lung adenocarcinoma as the most common tumor, who achieved a good median survival as a result of early diagnosis.[13] A systematic review,[14] through Medline, observed that the rheumatic manifestations associated with certain clinical findings and complementary tests (laboratory, imaging) can justify searching for and making a differential and suspected diagnosis of an occult cancer. Therefore, it is important to identify atypical rheumatic manifestations to avoid delaying the diagnosis of a possible occult cancer.

Given all of the above, we can conclude that, although an extensive search for occult cancer as part of the initial assessment of a patient with rheumatic manifestations is not considered cost-efficient, we recommend that it should be undertaken for cases with an atypical presentation, warning sign or specific finding on initial complementary tests that would suggest a malignancy. Similarly, we believe it important to highlight the importance of considering the possibility of an underlying tumor in the differential diagnosis, since its early diagnosis can determine prognosis.

Conflict of interests

The authors have no conflict of interests to declare.

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