

Revisiting rheumatic diseases and cancer

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Acta Reumatologica Portuguesa (ARP) had previously published a review paper on rheumatic diseases and malignancies by Jesus G et al¹ focusing on rheumatic syndromes most frequently associated with malignancy and characterizing features that could suggest the presence of a hidden neoplasm. Another focus of discussion in this field, as recently reviewed by Turesson C and Matteson E², is malignancy as a comorbidity condition in the context of rheumatic diseases. Patients with systemic autoimmune rheumatic diseases are at increased risk of developing malignancies. This risk is related to the disturbances of the immune system present in these conditions and to the immunosuppressive treatments. In this ARP issue a remarkable collection of papers highlighting the relationship between rheumatic diseases and cancer was published.

Raposo A et al³ bring us an interesting review on Monoclonal gammopathy of undetermined significance (MGUS), one of the most prevalent premalignant disorders among people aged 50 years or older and a very frequent dilemma in current rheumatology practice. Are we facing the cause of the rheumatic complains, in the context of the direct musculoskeletal symptoms induced by an emerging multiple myeloma (MM) or of a paraneoplastic syndrome driven by the MM or is this just a bystander in the process? Is this patient with a prediagnosed MGUS evolving now into a MM or is it just a smoldering MM (SMM), an asymptomatic form of MM? Is a patient carrying a MGUS a suitable candidate for an anti-TNF treatment? Recent medical knowledge on the spectrum of plasma cell disorders is reviewed by Raposo A et al³, helping decision making in this moving field. MGUS and SMM are found in association with Systemic Lupus Erythematosus (SLE), Sjogren Syndrome (SS), Rheumatoid Arthritis (RA) and spondylarthritis. This does not seem to be a simple co-

incidence and different mechanisms, like antigenic stimulation and cytogenetic abnormalities have been postulated. Importantly, the development of MM in this setting seems unusual. In addition, the effect of treatments for rheumatic diseases, including biologics and methotrexate, in patients with MGUS remains uncertain and no specific recommendations exist regarding which should be the preferred treatment option³.

RA patients have increased risk of lymphoma, which is higher in patients with severe, refractory, highly active forms of disease, suggesting that a high inflammatory state per se is the major risk factor. So far methotrexate (MTX) and biologics have not been found to be an independent risk factor for lymphoma. However, there are numerous reports that suggest that the risk of lymphoproliferative diseases may be increased with the use of MTX. In fact, a specific effect of MTX on malignancy risk may be difficult to sort out from an association with disease activity². Despite that, there are 50 descriptions of MTX associated B cell lymphomas that entered into spontaneous remission after MTX discontinuation, 4 of them positive for EBV⁴.

Terroso G et al contribute for this ongoing discussion by describing a case report of a MTX treated RA presenting a rare type of lymphoma (nasal NK/T lymphoma) with active EBV replication. However the lymphoma didn't regress after MTX withdrawal⁵.

In general, large observational studies have not shown an increased risk of malignancies associated with anti-TNF treatment for RA². Another crucial clinical question is whether patients with pre-existent cancers should be exposed to anti-TNF treatment. Patients with pre-existent malignancies are generally excluded from clinical trials, and, in clinical practice, clinicians are reluctant to treat such patients with anti-TNF therapy. Analyses from the British Biologics Register and the German Biologic Registry detected no increased risk of recurrent cancer in patients with pre-existing malignancy treated with anti-TNF agents. However, conclusions were limited by very few events in these ana-

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lyses². Giraldo WAS et al report us an interesting case of a Colonic perforation secondary to metastatic lung adenocarcinoma occurring in an 73 years-old ankylosing spondylitis smoking patient, suffering from diverticulosis, after 5 years on infliximab treatment⁶. This was a particularly complex patient as he had also chronic infection by Hepatitis B virus and was on antiviral treatment with lamivudine. This case reports highlights that events reported under the use of biologics have to be carefully screened for concomitant risk factors. Elderly, smoking males are clearly at high risk of lung cancer and colonic perforation occurs most frequently in patients with older age, history of diverticulosis and concomitant treatment with NSAIDs and corticoids, as was the case herein reported. The interaction of infliximab with the risk of cancer and of colonic perforation is very difficult to access here. Regardless of that, clinicians should be aware of risk factors for the occurrence of other medical conditions, such as cancer, bacterial infection or viral reactivation, and actively discuss that when offering biologic treatment to patients, keeping a high degree of awareness towards the appearance of new symptoms.

Musculoskeletal manifestations can be directly caused by tumours, particularly in the context of back pain or neurologic symptoms. As a good exemple of this, Pimenta R show us the impressive presentation of a large buttock lipoma that was detected in the investigation of sciatic pain⁷.

Occasionally, rheumatic diseases may emerge as paraneoplastic syndromes and this is particularly recognized in the case of polymyositis/dermatomyositis. In this ARP issue the rare occurrence of systemic sclerosis as a paraneoplastic condition is reported. This reports highlights the fact that most rheumatic diseases can be mimic by paraneoplastic syndromes. A concomitant malignant disease should be suspected whenever less typical disease features are present, refractoriness to treatment occurs, progression is rapid and late onset occurs⁸.

On the contrary, sometimes the workout of an initially apparent malignant disease reveals a rheumatic condition. Pardo-Cabello AJ et al⁹ describes a leukemoid reaction in the context of a fever of unknown ori-

gin that after extensive investigation revealed to be an Adult Still's Disease.

In summary, this issue of ARP remind us of the need of being aware of paraneoplastic syndromes expressing the typical features of some rheumatic diseases and the continuous surveillance that is needed on rheumatic patients for the early detection of cancers, mainly related to classic risk factors, but to which chronic immune dysfunction should be added.

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