Elderly Onset Rheumatoid Arthritis in a 97-year-old Man

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Rheumatoid arthritis (RA) is an autoimmune chronic inflammatory disease characterized by synovitis leading to polyarthritis. It affects 1% of the population [1]. Genetic and environmental factors are linked to the development of RA and include the presence of HLA-DR4 and shared epitope, and smoking is the primary representative of the negative environmental factor [1].

However, RA mainly affects middle age. Late-onset RA that initiates after 60 years is sometimes named elderly onset rheumatoid arthritis (EORA) [2]. This disease's prevalence varied from 2.03% to 2.34% in a large study in the United States. EORA affects more women than men [1]. However, to the best of our knowledge, no patient description of RA initiated at 97 years of age has been described.

PATIENT DESCRIPTION

A 97-year-old male with a past medical history of systemic arterial hypertension and a past history of heavy smoking (50 pack-year) presented to our clinic. Smoking stopped 40 years earlier. In June 2018, he presented with polyarthralgia and morning stiffness followed by rapid developmental polyarthritis a few weeks later. He was referred to acupuncture but did not notice improvement. His physical examination showed polyarthritis of all metacarpophalangeal and interphalangeal, wrists, elbows, and knee joints bilaterally. Laboratory tests showed rheumatoid factor of 107 U/ml (normal range [nr] < 15 U/ml), C-reactive protein (CRP) of 182 mg/L (nr < 5 mg/L), erythrocyte sedimentation rate (ESR) of 120 mm first hour (nr < 20 mm/first hour), hemoglobin 9.6 g/dl (nr 13–18 g/dl), ferritin 1072 ng/ml (nr 23–336 ng/ml), albumin 2.8 g/dl (nr 3.9–5.3 g/dl), gamma globulin 1.8 g/dl (nr 0.6–1.6 g/dl), and no evidence of monoclonal gammopathy on the serum electrophoresis. Screening for neoplasms was negative and included abdominal ultrasound, thorax X-ray, and fecal occult blood test. Antinuclear antibodies and anti-cyclic citrullinated peptide antibodies were negative. An X-ray of the hands and knees was suggestive of osteoarthritis, with no erosions. An EORA diagnosis was determined [5], and methotrexate 10 mg/week plus folic acid 5 mg/week and vitamin D3 10,000 IU/day and one single dose betamethasone was initiated. After one month, his clinical picture improved. ESR reduced to 66 mm/first hour and CRP to 91.1 mg/L. Vitamin D increased to 60 ng/ml. An increase of methotrexate to 20 mg/week was initiated and creatine 20 g/day for 4 days, 5 g/day for low muscle mass was added. After 3 months, he noted marked improvement of clinical features, no arthritis was observed on his physical examination, CRP was 16.77 mg/L, and ESR 67 mm/first hour. After 2 years of treatment, he was still asymptomatic, CRP of 3 mg/L and ESR 19 mm/first hour, under methotrexate 25 mg/week plus folic acid and creatine 5 g/day.

The authors followed the World Medical Association Declaration of Helsinki in this study. Informed consent was obtained from the patient for publication of his case. No image of him is used.

COMMENT

A neurological study evaluated 421 patients over 90 years old with dementia after an autopsy study showed 9 patients had RA. No data regarding the age of RA onset in these patients is available [3].

RA in the elderly has peculiar clinical and pathophysiological characteristics [2]. Contrary to the insidious evolution that younger individuals show, in elderly individuals, the appearance of symptomatic manifestations can be abrupt. In the older age group, the critical differential diagnosis is with neoplasms and polymyalgia rheumatica. A link between RA and increased risk of developing lymphoma and other cancers is known. This association can be explained by cellular immune aging, greater exposure to chronic inflammation, and repair of defective DNA, which occurs in immunosenescence, which may predispose lymphoma occurrence [4]. RA and lung cancer share similar risk factors, such as smoking. Another factor to be considered is the association between the use of biological disease-modifying anti-rheumatic drugs used in the treatment of RA and malignancy, but this relationship is still controversial. Although the relationship

between RA and malignancies has been proven, our patient obtained negative screening for neoplasms.

In older individuals, systemic manifestations are more frequent, such as fatigue, weight loss, and malnutrition, the evidence of inflammatory activity is substantial at the beginning of the disease. The frequency of positive rheumatoid factor (RF) in older individuals is lower when compared to younger patients, which may be related to pathophysiological changes related to immunosenescence [5]. Elderly individuals also have a worse clinical outcome, and this cause is multifactorial. There is a higher incidence of co-morbidities, more significant functional limitation and severity of joint damage, and cellular senescence [5]. Immune cell senescence is related to the aging process [5]. With advancing age, there is a significant decrease in T cells, the primary cells involved in the RA pathophysiological process [5]. There is a continuous and exacerbated proliferation of peripheral T cells resulting in exhaustion and immunosenescence and forming negative CD8 + T cells [5]. However, despite being a physiological phenomenon in healthy people, these senescent T cells are characterized by a shorter telomere with each replication, becoming more susceptible to DNA defects; therefore, they are dysfunctional cells, which predispose to autoimmunity, malignancies, infections, and inflammation. This situation includes the exacerbated expression of proinflammatory cytokines such as tumor necrosis factor-α and interleukin-6 and a marked increase in CRP [1], as observed in our patient.

Smoking is also a vital element to be considered since it is an established risk factor for RA onset. It is believed that smoking was a significant risk factor for the development of RA by our patient since he presented a prolonged exposure to smoking for 50 pack-years.

Thus, knowing this population group's singularities, therapeutic management is a challenge because despite studies showing safety and efficacy in the elderly, co-morbidities and old age require a less aggressive approach, with lower drug doses and decreased drug change frequency [2]. Therefore, according to the presence of co-morbidities, polypharmacy, and cognitive dysfunction, elderly patients with RA can be divided into high-risk and low-risk groups, in which the recommend for the latter group include treat-to-target. With high-risk patients, treatment should be individualized [2]. The first-line drug is methotrexate, started at a low dose and titrated gradually. The second treatment line is monotherapy with biological agents. A gradual reduction in glucocorticoids is recommended, as their adverse effects associated with chronic use are relevant, especially in this age group.

A single dose of deposit corticoid was chosen in our patient, as it has high efficacy and limited duration, maximum 2 to 3 weeks, thus limiting possible adverse effects of corticosteroid therapy, as observed in our patient.

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The world is changed by your example, not your opinion.
Paulo Coelho (born 1947), Brazilian lyricist and novelist

Capsule

T cell metabolic fitness

Organelle cross talk plays a fundamental role in cell biology, but how this cross talk controls tumor-infiltrating CD8⁺ T cells (TILs) is not understood. **Yang** et al. investigated the role of the protein mitofusin-2 (MFN2) in CD8⁺ TILs, finding that mitochondrial interaction with the endoplasmic reticulum is required for metabolic fitness and antitumor activity. MFN2 expression was associated with better survival in patients with cancer. Promoting MFN2 expression in CD8⁺ T cells improved response to immune checkpoint blockade in mice. Together, these findings identify a critical role for MFN2 in regulating the metabolism, function, and survival of CD8⁺ T cells and suggest that boosting MFN2 expression is an attractive avenue for improving immunotherapy.

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