Case Report

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Methotrexate Induced Accelerated Rheumatoid Nodulosis

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Abbreviations: RA: Rheumatoid Arthritis; DMARD: Disease-Modifying Antirheumatic Drugs; MTX: Methotrexate; MIARN: Methotrexate-Induced Accelerated Rheumatoid Nodulosis; AICAR: 5-Aminoimidazole-4-Carboxamide-Ribonucleotide

ABSTRACT

Rheumatoid arthritis is common systemic autoimmune disease prevalent in European and American populations with a female predominance. Recent analysis of disease epidemiology suggests lifetime risk of 3.6% and 1.7% in females and males respectively. Methotrexate is a commonly used disease-modifying antirheumatic drug in the treatment of rheumatoid arthritis. A possible adverse effect of methotrexate therapy is the development of methotrexate induced accelerated rheumatoid nodulosis. We present the case of a 54-year-old female with seropositive rheumatoid arthritis who developed methotrexate induced accelerated rheumatoid nodulosis one year after initiating methotrexate therapy. Disease-modifying therapy was changed with subsequent cessation of further nodule development. The mechanism is likely secondary to methotrexate inducing adenosine accumulation and adenosine 1 receptor activation. The rarity of this manifestation suggests certain population susceptibility through retention of the HLA-DRB1*0401 allele. The rheumatoid nodule and the methotrexate induced nodule are difficult to distinguish through histopathology. Currently, treatment research is limited and often medication change is recommended with other disease-modifying medications to treat Rheumatoid Arthritis.

Keywords: Rheumatoid Nodulosis; Rheumatoid Arthritis; Methotrexate

Introduction

Rheumatoid arthritis (RA) is a common systemic autoimmune disease prevalent in European and American populations with female predominance. Recent analysis of disease epidemiology suggests lifetime risk of 3.6% and 1.7% in females and males respectively [1]. Overall, North American and Northern European populations have an incidence of 1% [2]. While the characteristic feature of RA is polyarticular erosive inflammatory arthritis, it is associated with several extra-articular and systemic manifestations. The most common cutaneous manifestation of RA is rheumatoid nodules, which have been reported in upto 35% of patients [3] and can be present at the initial presentation [4]. Several Disease-Modifying Antirheumatic Drugs (DMARDs) are currently available and approved for management of RA, with extensive evidence supporting prevention of radiographic progression of RA by early initiation of DMARD therapy [5]. Methotrexate (MTX) is considered the first-line conventional DMARD in the treatment of RA and is used as monotherapy as well as combination therapy. MTX is usually well tolerated; however, several adverse effects are often described with MTX therapy with reports describing up to 20% of patients discontinuing MTX secondary to adverse effects6. Amongst other adverse effects, several cutaneous manifestations have been reported in the literature [6,7]. A well described cutaneous manifestation includes induction of nodulosis after MTX administrationcalled Methotrexate-Induced Accelerated Rheumatoid Nodulosis (MIARN). MIARN is a rare dermatologic manifestation [8] and warrants investigation of the literature for understanding, pathophysiology, treatments, and described prognosis.

Case Presentation

We present the case of a 54-year-old female who was diagnosed with seropositive (rheumatoid factor and anti-cyclic citrullinated peptide positive) RA three years ago. She was initially treated with corticosteroids and MTX. Corticosteroids were tapered off within one month of diagnosis. She was then maintained on MTX 25 mg weekly resulting in low RA disease activity. One year after starting the MTX, the patient started developing nodules on her hands. These nodules were soft, non-tender and present on the palmar and dorsal aspect of bilateral hands on the proximal and distal interphalangeal joints. Due to concerns of MIARN, her MTX was discontinued, and she was started on leflunomide. Unfortunately, leflunomide therapy could not be tolerated secondary to gastrointestinal adverse effects. She was then started on certolizumab pegol. Re-evaluation in the clinic 6 months after discontinuation of methotrexate and initiation of certolizumab pegol assured that her RA still had low disease activity. The nodules on her hands diminished in size but did not completely disappear. The patient did report that new nodules no longer developed after medication change.

Discussion

MTX-induced accelerated nodulosis is a phenomenon in RA patients that is rare but described in the literature. Rare individual cases of MTX-induced nodulosis have been reported in other diseases including psoriatic arthritis [9] and juvenile idiopathic arthritis [10,11] although most of the existing literature is in patients with RA. Current evidence suggests that certain individuals with RA are predisposed to developing this manifestation. Patients carrying certain alleles of HLA-DRB1 directly linked them to increased risk of MIARN. More specifically,the HLA-DRB1*0401 allele has been associated a significantly higher risk of accelerated nodulosis [12] with up to 71% of patients with MIARN carrying this allele which was seen in only 17% to 18% of control RA patients and healthy populations.

The pathophysiology of MIARN is multi-factorial which can attribute to the overall rarity of this manifestation. Inhibition of dihydrofolate reductase and thymidylate synthase leading to depletion of necessary precursors for nucleotide synthesis is a well-known mechanism of action of MTX, however, this action is thought to be responsible primarily for the anti-cancer properties of MTX [6]. Anti-inflammatory effects of MTX are primarily a result of inhibition of 5-aminoimidazole-4-carboxamide-ribonucleotide (AICAR) transformylase [13] leading to increased levels of AICAR. This subsequently inhibits Adenosine Monophosphate (AMP) deaminase, leading to an increase in levels of intracellular/extracellular adenosine and AMP [14]. Adenosine binds to the Adenosine A2a receptors on lymphocytes, monocytes, macrophages, natural killer cells, and neutrophils leading to dampening of inflammation by several downstream mechanisms [15]. Thus, the buildup of adenosine stimulates A2 receptors stimulating anti-inflammatory effects of MTX. Paradoxically, stimulation of A1receptors on monocytes may induce giant cell formation and subsequently nodulosis [16]. Furthermore, there are stark differences in the gene expression in nodule tissue against synovial tissue of RA patients. Genetic components of methylation reactions downstream from dihydrofolate reductase tend to be reduced in nodule tissue in comparison to the synovium. This may be partially responsible for the different reactions of MTX therapy causing therapeutic benefit for RA and co-concomitant accelerated nodulosis [17]. Of note, immunosuppression has been directly linked to nodulosis in several settings. Epstein-Barr virus (EBV) infection in a patient with prior history of RA treated with MTX has been directly implicated in further nodule development [18]. The combination of MTX-induced immunosuppression with additional EBV infection is suspect for inducing nodule formation. This became evident by characteristics of typical rheumatoid nodules with lymphocyte proliferation and EBV detection on histology [18]. In addition, TNF-alpha inhibitors have been associated with accelerated rheumatoid nodulosis [19-21]; however, the mechanism describing this phenomenon is not clear and may be different from MTX's supposed role [16]. The summation of the literature up to this point is ultimately conflicting, but it is certain that immunologic modification in a genetically susceptible population is the priming agent for MIARN.

Clinically and histopathologically, MIARN can be difficult to differentiate from rheumatoid nodules. Observational data suggests a high percentage of patients who develop MIARN are positive for rheumatoid factor [12,22], which is also the case with rheumatoid nodules [23]. Development of MIARN does not necessarily depend on the cumulative dose or duration of MTX therapy, with reports of MIARN development after exposure to MTX ranging from 3 months [24-26] to 144 months [27] and after a cumulative dose ranging from 60 mg26to 7200 mg [27]. MTX-induced nodules are smaller in comparison to rheumatoid nodules8 and tend to be present predominantly on the fingers [22]. Like rheumatoid nodules, they are usually non-tender and soft. Histopathologically, these nodules are indistinguishable from rheumatoid nodules, both showing palisading granuloma formation evident by central necrosis and surrounding granulation tissue. The central necrosis is the result of necrotic macrophages and endothelial cells and is surrounded by palisading macrophages and granulation tissue consisting of histiocytes and lymphocytes. Focal vasculitis can be a feature in more than 30% of rheumatoid nodules [28] but is usually not seen in MTX-induced nodules [29]. The cause is often difficult to prove due to the stark similarities between rheumatoid nodules and MIARN in patients with RA, and it is assessed primarily based on time-course of events.

Currently, there is no evidence of any therapeutic strategy effective for the management of MIARN. Common practice is the discontinuation of the offending agent, typically MTX, or the anti-TNF agent [30].Other medications with suggested effectiveness include hydroxychloroquine [31,32], colchicines [33,34],

sulfasalazine [35] and D-penicillamine [26]; however, the research is limited and dated [30]. Further, it is unclear if the regression in nodules is secondary to discontinuation of MTX, or the new therapy. Possible protective effects of hydroxychloroquine when co-administered with MTX in future development of nodules has also been proposed [12]. Surgical excision is rarely indicated and not usually recommended due to increased risk of post-surgical complications including infection and delayed healing. Ultimately, due to the paucity of treatment guidelines, further investigation of MIARN pathophysiology and randomized control trials of potential targets will help isolate appropriate therapeutics or interventions needed for the future.

Conflicts of Interest

The authors have no conflicts or interests to declare.

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