First flare of seropositive inflammatory arthritis following denosumab: A case report

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June 1, 2023

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Key Clinical Message

We report a case of new-onset seropositive inflammatory arthritis following denosumab use in an elderly patient. This highlights the need to consider this rare adverse effect in patients who develop severe arthralgia and myalgia after denosumab.

Introduction

Denosumab is a fully human monoclonal antibody against the receptor activator of nuclear factor kappa B ligand (RANKL), commonly used to treat osteoporosis in males and postmenopausal females.[1] Rare but serious adverse effects include hypersensitivity reactions, atypical femoral fractures, severe infections and hypocalcaemia.[1,2] Relatively common side effects include mild infections, arthralgia and musculoskeletal pain–with a reported incidence of 7.7% in the FREEDOM trial.[2,3]

Denosumab-induced arthralgia and musculoskeletal pain is typically transient and mild, and not associated with an acute phase response.[4] In contrast, an acute phase response manifesting as a flu-like syndrome is a relatively common adverse effect of bisphosphonates.[5] In a Phase III denosumab study,[6] 2% of patients had a flare of underlying polymyalgia rheumatica (PMR)–an inflammatory disorder typically presenting with shoulder and pelvic girdle musculoskeletal pain.[7] However, there are no previous reports of new-onset PMR or other inflammatory arthritis following denosumab use. Furthermore, denosumab has also been studied in patients with rheumatoid arthritis (RA)–a systemic autoimmune disease characterised by synovitis and localised joint destruction–with no reports of flares secondary to denosumab.[8-10]

We present a case of an elderly patient who developed a flare of previously undiagnosed seropositive inflammatory arthritis with overlapping features of PMR and RA, after treatment with denosumab.

Case presentation

An 80-year-old gentleman independent from home presented to hospital on the 18th April 2023 with a one-week history of acute onset, progressively worsening large joint arthralgia and musculoskeletal pain following his first dose of denosumab. This 60 mg subcutaneous injection was prescribed by his general practitioner for osteoporosis. He was previously well with no prior arthralgia or musculoskeletal pain, infective symptoms, or history of falls or trauma. There was no immediate reaction. However, approximately five hours after denosumab administration, he began developing arthralgia and cramping musculoskeletal pain of fluctuating severity, with involvement of his bilateral knees, hips, thighs and shoulders. His symptoms were severe enough to limit range of motion and function of affected joints and did not respond to self-administered paracetamol and codeine treatment. The symptoms progressively worsened over the course of one week, at which point he also developed pain in his left wrist, which prompted him to seek medical attention.

On presentation, he had persistent bilateral joint pain involving the shoulders, knees and left wrist. He also had persistent musculoskeletal pain involving the right arm and bilateral thighs. Arthralgia, pain and joint stiffness were noted to be worse in the morning and eased through the day. He did not have any localising infective symptoms, fevers or constitutional symptoms apart from some fatigue associated with the arthralgia and musculoskeletal pain. He did not have any temporal headaches, visual disturbance or jaw claudication. He did not have significant small joint arthralgia, sicca symptoms, ocular inflammation, abnormal rash or symptoms of mononeuritis multiplex.

His medical history included osteoarthritis with a left total knee replacement three years prior, and a right reverse shoulder joint replacement ten years ago following a rotator cuff injury. He had chronic obstructive pulmonary disease, hypothyroidism, ischaemic heart disease and heart failure with reduced ejection fraction, all of which were stable. He also had a T7 spinal compression fracture diagnosed five months prior, with a dual x-ray absorptiometry (DEXA) scan confirming osteoporosis.

His regular medications included aspirin 100 mg once daily, rosuvastatin 20 mg at night, sacubitril 24.3 mg + valsartan 25.7 mg twice daily, furosemide 40 mg once daily, levothyroxine 100 μg once daily, nebivolol 5 mg once daily and spironolactone 12.5 mg once daily. He did not start any of these medications recently. He did not have any drug allergies.

The patient was a retired salesman who lived at home with his wife and was previously fully independent with his activities of daily living and mobility–regularly walking unaided for several kilometres a day. He ceased smoking 20 years ago following a 30 pack-year history, and did not drink alcohol.

On examination, he was alert, orientated and comfortable at rest. Observations were within normal limits and he was afebrile. He had an average build. He had marked limitation of right shoulder abduction and range of motion to less than 30 degrees along with generalised tenderness on palpation of his shoulder girdle and deltoid muscle belly. There were no bony step deformities nor focal areas of particular tenderness. His left shoulder had similar tenderness but preserved range of motion. He had tenderness on palpation of his left wrist but no deforming polyarthropathy and no active tenosynovitis. There were no stigmata of scleroderma, endocarditis or dermatomyositis. He had limitation of hip flexion to less than 30 degrees bilaterally, along with palpation tenderness in his quadriceps. He had preserved range of motion in his knees without significant pain on anterior joint space palpation. His power and sensation was preserved in all limbs. His gait was slow and antalgic, but otherwise normal. He did not have significant spinal tenderness or limited range of motion. He had no rash or evidence of ocular inflammation. Cardiorespiratory and abdominal examination was unremarkable and he was clinically euvolaemic.

Investigations on presentation revealed elevated inflammatory markers with an erythrocyte sedimentation rate (ESR) of 140 mm/hr and C-reactive protein (CRP) of 163.8 mg/L (Table 1). CRP peaked at 235.2 mg/L on the following day. Ferritin was mildly elevated along with low transferrin saturation, in keeping with an inflammatory state.

He had a mild normocytic anaemia with a normal platelet count (Table 1). There was a mild monocytosis but otherwise normal white blood cell count and differential. Renal function, liver function and thyroid function tests were normal. There was mild hypocalcaemia with a corrected calcium of 2.08 mmol/L, and low-normal phosphate of 0.76 mmol/L in the setting of denosumab therapy. Parathyroid hormone was appropriately elevated. 25-hydroxy Vitamin D level was normal. Other serum electrolytes were unremarkable. Creatine kinase was normal at 108 U/L.

Autoimmune serology revealed an elevated rheumatoid factor (RF) and anti-cyclic citrullinated peptide antibodies (ACPA) (Table 1). Antinuclear antibodies were detected at a 1:320 titre with a homogenous and speckled pattern, but extractable nuclear antigen antibody screen and double-stranded DNA antibodies were negative. Complement factor 3 and 4 levels were normal.

Respiratory virus swab was negative for Influenza A/B, Adenovirus, Rhinovirus, Respiratory syncytial virus, Human parainfluenza virus 1-4 and Severe acute respiratory syndrome coronavirus 2 (SAR-CoV-2). Blood

and urine cultures were negative. Chest x-ray revealed expected emphysematous changes, but no consolidation or pleural effusions. Cervical spine x-ray revealed stable multilevel degenerative changes without fracture or malalignment. Bilateral shoulder x-ray revealed a previous right total shoulder replacement and narrowing of the left glenohumeral joint space inferiorly, but no fracture or heterotopic soft tissue ossification. Computerised tomography of the right shoulder did not show any evidence hardware migration, periprosthetic fracture or joint effusion. Ultrasound of the right shoulder revealed a supraspinatus tendon anterior portion partial-thickness tear (Figure 1a), and subscapularis insertional tendinosis with a partial thickness tear (Figure 1b). There was no significant subdeltoid subacromial bursitis (Figure 1c). Long head of biceps was surgically absent following shoulder replacement (Figure 1d).

Outcome and follow-up

Prior to the autoimmune serology results becoming available, a clinical diagnosis of PMR was made. This was based on the elevated inflammatory markers, typical joint involvement and symptoms, and patient demographic. The differential diagnoses included other autoimmune arthritis such as RA or seronegative spondyloarthropathy. The inflammatory arthritis was thought to be secondary to denosumab given the time course of symptom onset soon after the injection.

Early in the admission, the patient was started on celecoxib with minimal improvement. Given the suspicion for PMR, he was subsequently started on 10 mg prednisolone once daily. There was a remarkably good response the following day, with the patient returning to full range of motion in his right shoulder as well as noting significant reduction in musculoskeletal pain.

The uptrending CRP began to decrease after starting prednisolone–the level was 235.2 mg/L the day prior to initiating therapy, and declined to 178.9 mg/L one day after the initial 10 mg dose. He was discharged after two days with a slow weaning dose of prednisolone and planned for rheumatology clinic follow-up. The patient was advised to switch to a different osteoporosis treatment.

The subsequently available results of an elevated RF and ACPA led to the revised diagnosis of denosumab-induced seropositive inflammatory arthritis with overlapping features of late-onset RA and PMR.

Discussion

Arthralgia and musculoskeletal pain associated with denosumab are usually mild and transient, and is not typically associated with a systemic inflammatory response.[4] Denosumab has been noted to cause flares of known PMR,[6] but has not been associated with causing new-onset PMR. Denosumab has been studied in populations with RA for treatment of steroid-induced osteoporosis, and has not been noted to worsen or cause new-onset inflammatory arthritis.[8-10]

We present a case of an elderly patient with new-onset seropositive inflammatory arthritis following denosumab therapy. Using the Naranjo scale,[11] this case scored five points, making this a probable association. A literature search using terms “denosumab”, “polymyalgia rheumatica”, “rheumatoid arthritis” and “inflammatory arthritis” on PubMed, Scopus and Google Scholar databases did not report any similar cases. Hence, this represents the first case report of newly-diagnosed seropositive inflammatory arthritis associated with denosumab.

The diagnosis of late-onset seropositive RA best encapsulates the presentation of inflammatory arthritis in the setting of elevated RF and ACPA. However, the patient presented with typical features of PMR including shoulder and hip girdle involvement, with relative sparing of small joints. The subscapularis and supraspinatus pathologies (Figure 1) in this patient are in keeping with ultrasound findings in PMR,[12] although subdeltoid subacromial bursitis and long head of biceps tendinopathy are typically seen.[12]There was no evidence of extra-articular manifestations of RA. The patient appeared to have exquisite response to low-dose prednisolone, which is characteristic of PMR[7].

We postulate that the patient had pre-existing RA autoantibodies and subclinical disease that was unmasked by denosumab therapy. The patient was an ex-smoker, and in genetically susceptible patients, smoking is

a well-recognised trigger for self-protein citrullination and autoantibody production–from which RA pathogenesis stems.[13] The patient also had osteoporosis, which is associated with RA.[13]

RF is an autoantibody against the crystallisable fraction portion of human immunoglobulin G (IgG) and plays a pathogenic role in RA.[14] In this case, we postulate that denosumab–a fully human IgG molecule[1]–may have acted as an antigen that was recognised by the patient's pre-existing autoreactive B-cell repertoire, which subsequently triggered aberrant RF autoantibody production and immune complex formation–resulting in the disease flare.[14] However, the precise mechanism of how denosumab would cause an inflammatory arthritis flare is unclear. Future research could involve observational studies looking for severe autoimmune adverse effects to denosumab, with further investigation of the underlying molecular mechanisms of this adverse reaction.

We cannot disprove that the administration of denosumab and arthritis flare were coincidental. However, we think this is very unlikely given the time course of the patient receiving denosumab on the same day prior to symptom onset, and being completely well prior to treatment. We believe this case represents a first flare of seropositive inflammatory arthritis secondary to denosumab, which exceeds the arthralgia and musculoskeletal pain adverse effects previously reported.[2,6]

Interestingly, despite denosumab being studied in RA populations, no flares have been reported.[8-10] We postulate that this is because in those studies, all patients already had RA diagnosed and were on at least low-dose prednisolone immunosuppressive therapy as part of inclusion criteria.[8-10] Thus, such therapy may have mitigated any potential flares induced by denosumab. This is supported by the exquisite response to low-dose prednisolone observed in our patient. Alternatively, denosumab-induced inflammatory arthritis flares may be a very rare event that was not observed in the studies.

In summary, we present a case of newly-diagnosed seropositive inflammatory arthritis flaring after initiating denosumab therapy. This case highlights the need to closely monitor for adverse effects in patients, and consider this rare adverse effect of seropositive inflammatory arthritis in patients who develop severe, progressive arthralgia and musculoskeletal pain after starting denosumab.

Ethics statement

Written informed consent was obtained from the patient for this case report.

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