TJEM TURKISH JOURNAL OF ENDOCRINOLOGY AND METABOLISM

CASE REPORT
Turk J Endocrinol Metab. 2022;26(3):181-183

Urticarial Vasculitis After First Denosumab Injection in an Osteoporotic Woman Diagnosed with Cushing's Syndrome

ABSTRACT

Denosumab is a human-derived monoclonal immunoglobulin G2 antibody against the receptor activator of nuclear factor kappa B ligand, inhibiting the differentiation and function of osteoclast precursor cells by its antiosteoclastic action. Denosumab is approved for postmenopausal, glucocorti coid-induced, and male osteoporozis with high risk of fracture. The use of denosumab has increased in recent years. While new medications continue to be developed, the number of agents causing drug-induced vasculitis is expected to increase. It may be a good strategy to identify risk factors for vasculitis development and look for these factors before drug administration. Here, we present a rare complication of denosumab, urticarial vasculitis, after the first denosumab injection in an osteoporotic woman diagnosed with Cushing's syndrome.

Keywords: Denosumab, osteoporosis, urticarial, vasculitis

Introduction

Osteoporosis is common in patients with Cushing's syndrome. The prevalence of osteoporosis was reported in 40%-70% and osteopenia in 80%-85% of patients at the time of diagnosis with endogenous hypercortisolism.[1,2] Bone impairment could be partially but not completely reversed 2 years after cortisol levels are normalized.[3] Antiosteoclastic treatments with bisphosphonate or denosumab and teriparatide are recommended in osteoporotic patients with hypercortisolism.[4]

Denosumab is a human-derived monoclonal immunoglobulin G2 antibody against the receptor activator of the nuclear factor kappa B ligand that inhibits the differentiation and function of osteoclast progenitor cells by its antiosteoclastic action. Denosumab is approved for postmenopausal, glucocorticoid-induced, and male osteoporozis with high risk of fracture. An increased risk of urinary tract infections and eczema, as well as rare adverse events with severe infection and osteonecrosis of the jaw, has been reported in patients receiving denosumab therapy for osteoporosis.[5-8]

The most common adverse effects were back, limb, musculoskeletal pain; hypercholestero lemia; and cystitis.[9] Post-marketing reports showed severe bone, joint, and muscle pain from day 1 to several months after the administration of denosumab.[10]

A small proportion of women in the denosumab trials had a decrease in serum calcium levels to <8.5 mg/dL (1.7%).[9] The decrease was temporary, and there were no episodes of symptomatic hypocalcemia leading to the discontinuation of denosumab. Diseases such as chronic kidney disease, malabsorption syndromes, hypoparathyroidism, and symptomatic hypocalcemia may predispose to hypocalcemia. Osteonecrosis of the jaw and atypical fractures have been reported in patients who were under denosumab treatment for osteoporosis.[9,11-12]

Skin reactions to denosumab are rarely reported in the literature. Large clinical trials have shown significantly higher cutaneous adverse events called "eczema" than placebo.[5,13]

In addition, increased rates of infection and cellulitis have been reported in patients taking denosumab.[14-16] Cellulitis requiring hospitalization (0.3%) was also significantly more common in women who received denosumab than placebo in the FREEDOM study.[5] In addition, in 1 study, up to 10.8% of patients experienced an undesirable skin event (rash, itching, or eczema).[17]

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Received: April 13, 2022
Accepted: August 10, 2022

Cite this article as: İmre E, Şeker A, Gogas Yavuz D. Urticarial vasculitis after first denosumab injection in an osteoporotic woman diagnosed with Cushing's syndrome. *Turk J Endocrinol Metab.* 2022;26(3):181-183.

DOI: 10.5152/tjem.2022.22012

Here, we present a rare complication of denosumab, urticarial vasculitis, after the first denosumab injection in an osteoporotic woman diagnosed with Cushing's syndrome. Informed consent was obtained from the patient for publication of this case report.

Case Presentation

A 45-year-old postmenopausal woman with no chronic disease or drug history was admitted to our endocrinology outpatient clinic with complaints of muscle weakness, difficulty standing up, swelling of the legs and face, weight gain, and quickly gained bruises on the body for 3-4 years. The patient's physical examination revealed central obesity, prominent facial capillaries, and supraclavicular fullness suspected of Cushing's syndrome. Laboratory evaluation indicates hypercortisolism of adrenal origin. Serum cortisol level was 18.52 µg/dL after 1 mg suppression test and 18.5 µg/dl after 2 mg suppression. A 24-hour urine free cortisol level was found to be 453 µg and serum adrenocorticotropic hormone (ACTH) was <5 (0-46) pg/mL.

Magnetic resonance imaging evaluation revealed bilateral adrenal adenoma (38 × 29 mm in the right adrenal, 14 × 10 mm, and 18 × 9 mm in the left adrenal gland). Urine vanillylmandelic acid, metanephrine, and normetanephrine levels were within normal range. The patient has been diagnosed with ACTH-independent Cushing's syndrome due to adrenal adenoma after right adrenalectomy was performed, steroid replacement was administered due to adrenal insufficiency.

After surgery, bone mineral density evaluated using dual-energy x-ray absorptiometry (DEXA) reported osteoporosis. T score was −3.4 at L1-L4 and −2.4 in the femoral neck area. In the vertebral, an x-ray revealed multiple grades of 2 fractures. Denosumab 60 mg was administered subcutaneously for the treatment of osteoporosis 17 days after surgery. One day after the injection of denosumab, an itchy erythematous lesion was honored at the injection site. Widespread itchy lesions appeared on the back and lower extremities within 2 days (Figure 1). The history of the patient did not include symptoms or diagnoses of atopy or rheumatological disease. A dermatological evaluation revealed palpable purpura of urticarial vasculitis.

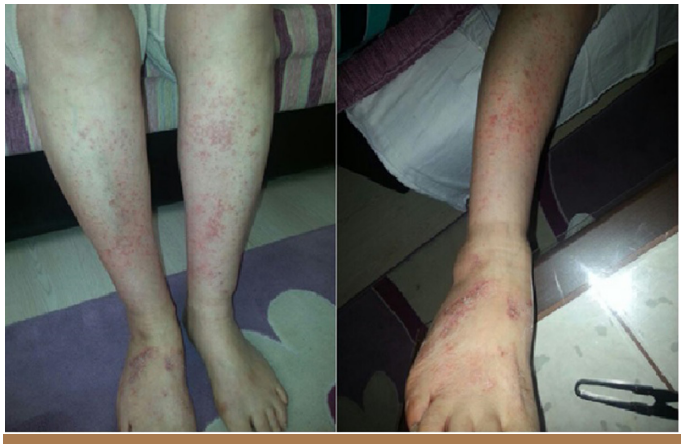

Figure 1. Widespread itchy lesions appeared on lower extremities after injection of denosumab and were thought to be palpable purpura of urticarial vasculitis.

The biochemical examination was performed in the laboratory examination to rule out infection and mixed cryoglobulinemia. Cryoglobin was negative; complete blood count showed white blood cells of 6.9×10^9/L, neutrophil (NEU) of 3.3×10^9/L, hemoglobin of 12.6, and platelet of 502×10^9/L. Sedimentation rate was 79 mm/h, creatinine: 0.9 mg/dL, complement c3: 1.73 g/L (0.75-1.4), and complement c4: 0.5 g/L (0.1-0.34). Serum analysis revealed the granular pattern's antinuclear antibody (ANA) positivity at 1/320 dilution. Antinuclear antibody was positive in 1/320 in the granular pattern. The patient was not tested for anti-neutrophil cytoplasmic antibody (ANCA) positivity, but it was not offered by the dermatology department and it was not needed because of ANA positivity and the clinical properties of the patient. Anti-histamines and topical steroid treatments were administered to the patients who received prednisolone 10 mg per day due to adrenal insufficiency. The lesions regressed within 2 weeks under treatment.

Discussion

Denosumab was given to treat osteoporosis, as the guidelines suggested. A rare complication of denosumab, vasculitis, was immediately observed on day 1 of injection. In this case, the patient had severe osteoporosis with vertebral compression fractures due to Cushing's syndrome.

Denosumab is a human-derived monoclonal IgG2 antibody against the receptor activator of the nuclear factor kappa B ligand that inhibits the differentiation and function of osteoclast progenitor cells.[18,19]

Various side effects are reported with increasing use. The most common adverse effects were back, limb, musculoskeletal pain; hyper cholesterolemia; and cystitis.[9] In post-marketing reports, severe bone, joint, and muscle pain were reported from day 1 to several months after the administration of denosumab.[20] It rarely causes atypical femoral fracture and osteonecrosis of the jaw.[11,12] In addition to some cases of cutaneous vasculitis, there is a case of cytoplasmic ANCA (c-ANCA) associated vasculitis, which has been officially published in the literature.[21]

Vasculitis is a vascular wall inflammation with bleeding and ischemic events. Drug-induced vasculitis is the most common form of vasculitis. Drug-induced cutaneous vasculitis affects a minority among all patients with drug-induced adverse cutaneous reactions. Studies have demonstrated an 8%-11% incidence in the inpatient setting.[22,23] The occurrence of cutaneous vasculitis typically occurs about 7-10 days after drug exposure, which is thought to correlate with the formation of immune complexes and their deposition into blood vessels. Cutaneous lesions are usually present on the lower extremities in the majority.[24] Unlike idiopathic vasculitis, drug-induced vasculitis usually has a milder course, with rapidly progressive glomerulonephritis being a less common manifestation.[25] While there is no definitive laboratory test or unique clinical finding that helps distinguish drug-induced vasculitis from other vasculitis or idiopathic autoimmune diseases, it may be difficult to make the diagnosis.

However, elevated acute-phase reactants such as erythrocyte sedimentation rate (ESR) or C-reactive protein are neither sensitive nor specific to diagnosis in patients with drug-induced vasculitis.[25] Other findings such as anemia and urine abnormalities (hematuria and proteinuria) should be investigated. A tissue biopsy (i.e., skin,

kidneys, or lungs) is primarily necessary for the definitive diagnosis of vasculitis.[25] As a result of findings such as persistence of plaques from urticaria for more than 24 hours, palpable purpura, and increased ESR, the diagnosis of urticarial vasculitis without biopsy was considered, and the clinical picture receded after appropriate treatment, confirming the diagnosis.

One case of c-ANCA vasculitis after the initiation of denosumab, which has been reported in the literature, had rapidly progressing glomerulonephritis, received high doses of pulsed intravenous steroids containing 500 mg of methylprednisolone, and then weaned to prednisone 40-60 mg daily.[21] The patient received plasmapheresis 3 times a week and rituximab weekly for a total of 3 weeks. Despite the treatment, the patient's condition worsened and end-stage kidney disease occurred. The patient, in this case, had a milder disease and a better course than the previously reported case.

There are cases of vasculitis due to denosumab, the use of which has increased in recent years. While new medications continue to be developed, the number of agents causing drug-induced vasculitis is expected to increase. Characteristics of patients with drug-induced vasculitis, the associated risks, and precautions will be better revealed by reporting new cases and conducting further studies. It may be a good strategy to identify risk factors for vasculitis development and look for these factors before drug administration.

Informed Consent: Written informed consent was obtained from the patient who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – E.İ., D.G.Y.; Design – D.G.Y.; Supervision – D.G.Y.; Data Collection and/or Processing – A.S.; Analysis and/or Interpretation – E.İ.; Literature Review – E.İ.; Writing – E.İ., D.G.Y.; Critical Review - D.G.Y.; Materials – E.İ., A.S.

Declaration of Interests: The authors have no conflict of interest to declare.

Funding: This study received no funding.

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