WHAT'S YOUR DIAGNOSIS?

Persistent Flu-Like Symptoms in a Patient With Glaucoma and Osteoporosis

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A 62-year-old man presented to the emergency department (ED) with 3 days of chills, myalgias, and nausea. The patient's oral temperature at home ranged from 99.9 to 100.1 °F. He came to the ED after multiple phone discussions with primary care nursing over 3 days. His medical history included posttraumatic stress disorder, enlarged prostate, osteoporosis, gastroesophageal reflux, glaucoma, and left eye central retinal vein occlusion. Medications included fluoxetine 20 mg twice daily, omeprazole 20 mg twice daily, rosuvastatin 10 mg once daily, tamsulosin 0.4 mg nightly, and zolpidem 10 mg nightly. The patient's glaucoma had been treated with a dexamethasone intraocular implant about 90 days earlier. The patient started on intravenous (IV) zoledronic acid for osteoporosis, with the first infusion 5 days prior to presentation.

In the ED, the patient's temperature was 98.2 °F, blood pressure was 156/76 mm Hg, pulse was 94 bpm, respiratory rate was 16 breaths per minute, and 98% oxygen saturation on room air. He was in no acute distress, with an unremarkable physical examination reporting no abnormal respiratory sounds, no arrhythmia, normal gait, and no focal neurologic deficits. A comprehensive metabolic panel was unremarkable, creatine phosphokinase was 155 U/L (reference range, 30-240 U/L), and the complete blood count was notable only for an elevated white blood count of 15.3 × 10^9/L (reference range, 4.0-11.0 × 10^9/L), with 73.4% neutrophils, 16.2% lymphocytes, 9.1% monocytes, 0.5% eosinophils, and 0.4% basophils. The patient's urinalysis was unremarkable.

- What is your diagnosis?
- How would you treat this patient?

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DISCUSSION

The ED physician considered viral infection and tested for both influenza and COVID-19. Laboratory results eliminated urinary tract infection and rhabdomyolysis as possible diagnoses. An acute phase reaction to zoledronic acid was determined to be the most likely cause. The patient was treated with IV saline in the ED, and acetaminophen both in the ED and at home.

Although initial nursing triage notes document consideration of acute phase reaction to zoledronic acid, the endocrinology service, which had recommended and arranged the zoledronic acid infusion, was not immediately notified of the reaction. It does not appear any treatment (eg, acetaminophen) was suggested, only that the patient was given advice this may resolve over 3 to 4 days. When he was seen 2 months later for an endocrinology follow-up appointment, he reported that all symptoms (chills, myalgias, and nausea) resolved gradually over 1 week. Since then, he has felt as well as he did before taking zoledronic acid. However, the patient was wary of further zoledronic acid, opting to defer deciding on a second dose until a future appointment.

Prior to starting zoledronic acid therapy, the patient was being treated for vitamin D deficiency. Four months prior to infusion, his 25-hydroxyvitamin D level was 12.0 ng/mL (reference range, 30 to 80 ng/mL). He then started taking cholecalciferol 100 mcg (4000 IU) daily. Eight days prior to infusion his 25-hydroxyvitamin D level was 29.5 ng/mL.

Federal health care practitioners, especially those working in the Veterans Health Administration (VHA), will commonly encounter patients similar to this case.

Osteoporosisis is common in the United States with > 10 million diagnoses (including > 2 million men) and in VHA primary care populations.[1,2] Zoledronic acid is a frequently prescribed treatment, appearing in guidelines for osteoporosis management.[3-5]

The acute phase reaction is a common adverse effect of both oral and IV bisphosphonates, although it's substantially more common with IV bisphosphonates such as zoledronic acid. This reaction is characterized by flu-like symptoms of fever, myalgia, and arthralgia that occur within the first few days following bisphosphonate administration, and tends to be rated mild to moderate by patients.[6] Clinical trial data from > 7000 women with postmenopausal osteoporosis found that 42% experienced ≥ 1 acute phase symptom following the first infusion (fever was most common, followed by musculoskeletal symptoms and gastrointestinal symptoms), compared with 12% for placebo. Incidence decreases with each subsequent infusion.[7] Risk factors for reactions include low 25-hydroxyvitamin D levels,[8,9] no prior bisphosphonate exposure,[9] younger age (aged 64-67 years vs 78-89 years),[7] lower body mass index,[10] and higher lymphocyte levels at baseline.[11] While most cases are mild and self-limited, severe consequences have been noted, such as precipitation of adrenal crisis.[12,13] Additionally, more prolonged bone pain, sometimes quite severe, has been rarely reported with bisphosphonate use. However, it's unclear whether this represents a separate adverse effect or a more severe acute phase reaction.[6]

The acute phase reaction is a transient inflammatory state marked by increases in proinflammatory cytokines such as C-reactive protein, interleukin-6, and tumor necrosis factor-α. Proposed mechanisms include: (1) inhibition of farnesyl pyrophosphate synthase, an enzyme of the mevalonate pathway, resulting inactivation of γδ T cells and increased production of proinflammatory cytokines; (2) inhibition of the suppressor of cytokine signalling-3 in the macrophages, resulting in cessation of the suppression in cytokine signaling; or (3) negative regulation of γδ T-cell expansion and interferon-c production by low serum 25-hydroxyvitamin D concentrations.[11]

Prevention

Can an acute phase reaction to zoledronic acid be prevented? Bourke and colleagues reported that baseline calcium and/or vitamin D intake do not appear to affect rates of acute phase reaction in data pooled from 2 trials of zoledronic acid in postmenopausal women.[14] However, patients receiving zoledronic acid had 25-hydroxyvitamin D values > 20 ng/mL 86% of the time, and values > 30 ng/mL 36% of the time. Bourke and colleagues suggest that "coadministration of calcium and vitamin D with zoledronate may not be necessary for individuals not at risk of marked vitamin D deficiency."[14] However, they did not prospectively test this hypothesis.

In our patient, vitamin D deficiency had been identified and treated, nearly achieving 30 ng/mL. The 2020 guidelines for postmenopausal osteoporosis recommend maintaining serum 25-hydroxyvitamin D levels 30 to 50 ng/mL, advising to supplement with vitamin D_3 as needed.[5] The 2012 guidelines for osteoporosis in men from the Endocrine Society suggest that men with low vitamin D levels receive vitamin D supplements to raise the level > 30 ng/ml.[4]

Oral analgesics have been studied for the prevention of adverse effects related to zoledronic acid. Initiating 650 mg acetaminophen 45 minutes before zoledronic acid infusion and then every 6 hours over the next 3 days has been shown to significantly reduce symptoms.[15] Acetaminophen or ibuprofen given every 6 hours for 3 days (starting 4 hours after zoledronic acid infusion) has been shown to reduce fever and other symptoms.[16]

Statins have been shown in vitro to prevent bisphosphonate-induced γδ T cell activation.[17] This has led to studies with various statins, although none have yet shown benefit in vivo. A double-blind, randomized, placebo-controlled trial of postmenopausal women for fluvastatin (single dose of 40 mg or 3 doses of 40 mg, each 24 hours apart) did not prevent acute phase reaction symptoms, nor did it prevent zoledronic acid-induced cytokine release.[17] Rosuvastatin 10 mg daily starting 5 days before zoledronic acid treatment and taken for a total of 11 days did not show any difference in fever or pain.[18] A protocol for pravastatin has been disseminated,

but no study results have been published yet.[19]

Prophylactic dexamethasone has also been studied. A randomized double-blind, placebo-controlled trial of oral dexamethasone 4 mg at the time of first infusion of zoledronic acid found no significant difference in temperature change or symptom score over the following 3 days.[20] Chen and colleagues compared the efficacy of acetaminophen alone vs acetaminophen plus dexamethasone over several days.[21] Acetaminophen 500 mg was given on the day of infusion and 4 times daily for 3 to 7 days for both groups, while dexamethasone 4 mg was given for 3 to 7 days. The dexamethasone group reported substantially lower incidence of any acute phase reaction symptoms (34% vs 67%, $P = .003$). A more recent study by Murdoch and colleagues comparing dexamethasone (4 mg daily for 3 days with the first dose 90 minutes before zoledronic acid infusion) with placebo found that the dexamethasone group had a statistically significant lower mean temperature change and acute phase reaction symptom score.[22]

Adverse Effect Treatment

Treatment after development of acute phase reaction due to zoledronic acid infusion is generally limited to supportive care and/or nonsteroidal anti-inflammatory drugs (NSAIDs) acetaminophen or dexamethasone, largely based on extrapolation of the noted preventive trials and expert opinion.[3,6] Experiencing an acute phase reaction may portend better fracture risk reduction from zoledronic acid, although there is a potential association between acute phase reaction and mortality risk.[23,24]

Our case was typical for acute phase reaction to zoledronic acid. The patient was already taking rosuvastatin 10 mg daily for hypercholesterolemia as prescribed by his primary care physician. Rosuvastatin was not shown to prevent symptoms, although it was not studied in patients on long-term statin therapy at the time of zoledronic acid infusion.[18] The patient was also taking vitamin D_3 supplementation and was nearly in the reference range.[5] His ED treatment included IV fluids and acetaminophen. Pretreatment (prior to or at the time of zoledronic acid infusion) with acetaminophen or ibuprofen may have prevented his symptoms, or at least lessened them to the point that an ED visit would not have resulted. The endocrinologist who prescribed the zoledronic acid documented a detailed discussion of the adverse effects of zoledronic acid with the patient, and the initial nursing call documents consideration of acute phase reaction. It is unclear whether the persistence of symptoms or worsening of symptoms ultimately led to the ED visit. Because no treatment was offered, it is unknown whether earlier post-treatment with acetaminophen, ibuprofen, or dexamethasone might have prevented his ED visit.

CONCLUSIONS

Clinicians who treat patients with osteoporosis should be aware of several key points. First, acute phase reaction symptoms are common with bisphosphonates, especially zoledronic acid infusions. Second, the symptoms are nonspecific but should have a suggestive time course. Third, dexamethasone may be partially protective, but based on the various trials discussed, it likely needs to be given for multiple days (instead of a single dose on the day of infusion). Given that acetaminophen and NSAIDs also seem to be protective (when given for multiple days starting on the day of infusion), both have lower overall adverse effect profiles than dexamethasone, consideration may be given to using either of these prophylactically.[6] Dexamethasone could then be prescribed if symptoms are severe or persistent despite the use of acetaminophen or NSAIDs.

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Ethics and consent

Verbal and signed informed consent for publication was granted by the patient. A supporting letter from the Office

of Research and Development was also obtained. Both documents can be provided upon request.

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