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POLYARTHRITIS FOLLOWING INFUSION OF ZOLEDRONIC ACID: A CASE STUDY

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ABSTRACT – *Objective:* Osteoporosis is a skeletal disorder characterized by compromised bone strength which predisposes one to the development of fragility fractures. Bisphosphonates are the most commonly used medications for the treatment of osteoporosis. Zoledronic acid is a popular bisphosphonate due to its convenience and efficacy. The most common side effects of zoledronic acid include pyrexia, myalgia, arthralgia, headache, and flu-like symptoms. More severe side effects such as arthritis are rarely reported. The current case describes a patient with underlying osteoarthritis who experienced polyarthritis following an infusion with zoledronic acid.

Case presentation: A case of a 68-year-old female with osteoporosis on a background of osteoarthritis who experienced polyarthritis after receiving an intravenous zoledronate infusion is reported. Though this is a rare phenomenon, a review of the literature suggests that patients with pre-existing osteoarthritis may be more likely to develop arthritis after bisphosphonate exposure.

Conclusions: The current case, therefore, highlights the importance of discussions with patients around additional side effects of zoledronic acid, especially in those with underlying degenerative arthritis.

KEYWORDS: Zoledronate, Bisphosphonate, Polyarthritis.

LIST OF ABBREVIATIONS: Intravenous (IV), Gastroesophageal Reflux Disease (GERD), Bone Mineral Density (BMD), Proximal Interphalangeal (PIP)

INTRODUCTION

Osteoporosis is a skeletal disorder characterized by compromised bone strength, including bone mass and quality, which predisposes one to the development of fragility fractures[1]. In Canada, there are over 2.3 million people aged 40 and older living with a diagnosis of osteoporosis; approximately 80% of those are female[2]. Regarding treatment for osteoporosis, bisphosphonates are the most used medications[3]. Bisphosphonates bind to hydroxyapatite crystals in bone and are taken up by osteoclasts, resulting in reduced bone resorption[4]. Zoledronic acid is a popular bisphosphonate choice due to its intravenous (IV) route, convenience, and efficacy. It is delivered annually via intravenous infusion and is generally well-tolerated. The five most common side effects reported from the HORIZON Pivotal Fracture Trial were: pyrexia (16.1%), myalgia (9.5%), flu-like symptoms (7.8%), headache (7.2%) and arthralgia (6.3%). After the first infusion, 31.6% of patients reported at least one of the five most common post-infusion symptoms; this number diminished with future annual infusions (6.6% after the second infusion and 2.8% after the third infusion)[3]. These reactions are generally self-limiting with an average duration of three days and seldomly result in treatment discontinuation. Severe adverse effects such as cardiovascular events or renal events are rare[3].

The current study describes a case of a 68-year-old female with osteoporosis on a background of osteoarthritis who experienced polyarthritis after receiving an IV zoledronate infusion. She initially experienced the more common flu-like reaction, but then went on to develop swelling in multiple joints. A review of the literature suggests that patients with pre-existing osteoarthritis may be more likely to develop arthritis after bisphosphonate exposure. The current case, therefore, highlights the importance of discussions with patients around additional side effects of IV zoledronate, especially in those with underlying degenerative arthritis.

CASE REPORT

A 68-year-old female presented to clinic with low bone mass in the osteoporotic range. Menarche was at age 13. She stopped menstruating at age 40 after her hysterectomy. Her medical history included osteoarthritis, hemithyroidectomy due to papillary microcarcinoma, gastroesophageal reflux disease (GERD), irritable bowel syndrome, central serous retinopathy, hysterectomy, tonsillectomy, appendectomy, jaw surgery (age 19), colon polyp, calcific tendinosis, and sleep apnea. She had a history of a parental hip fracture. She denied fragility fractures or historical height loss. She was a lifelong non-smoker. Her alcohol intake was up to three drinks per week. She consumed one to two cups of decaffeinated coffee daily. She reported occasional dysphagia with liquids. She had no prescribed medications. She supplemented with 2000U of Vitamin D. She had stopped supplementing with calcium due to her calcific tendinosis. She had previously been treated with etidronate for 3 years approximately 9 years prior. Regarding exercise, she did Zumba, walked, and golfed seasonally. She had received intra-articular corticosteroid injections in the past but denied any recent or high dose glucocorticoid exposure.

Her investigations indicated normal calcium, albumin, estimated glomerular filtration rate, creatinine, alkaline phosphatase, phosphate, parathyroid hormone, and Vitamin D. Her bone mineral density (BMD) test from September 2020 indicated T-scores of -3.6 at the spine, -1.7 at the femoral neck, and -1.5 at the total hip. There had been a 14.1% loss in her spine density and 3.6% loss in her total hip density since her last BMD in 2018. Spinal imaging indicated degenerative changes with no compression fractures.

Due to her underlying GERD, occasional dysphagia, and irritable bowel syndrome, she requested IV zoledronate over an oral bisphosphonate. Within 24 hours of receiving the IV zoledronate, she reported a flu-like response. Ten days later, she noticed right wrist, right ankle and right fourth proximal interphalangeal (PIP) joint swelling. She was right-handed. She had not previously been diagnosed with an inflammatory arthritis. She did, however, have a history of osteoarthritis. Prior hand x-rays indicated degenerative changes at the PIP joints (Figure 1), one of the sites where she experienced post-infusion joint swelling. As her arthritis was mild, she was still able to complete all her activities of daily living.

Regarding her underlying osteoporosis, she experienced a significant benefit from the IV zoledronate. Her September 2022 BMD test indicated T-scores of -2.9 at the spine, -1.5 at the femoral neck, and -1.0 at the total hip. There was an increase of 11.4% at the spine and 6.8% at the hip. Her significant spinal improvement could in part be related to degenerative changes. Though subsequent reactions can diminish after repeated IV zoledronate doses, the patient expressed that she preferred to instead trial an alternate medication if required for future osteoporosis treatment.

DISCUSSION

Osteoporosis is a disease that affects millions of people worldwide and is associated with a high level of morbidity and mortality. Bisphosphonates are the most common medication used in the treatment of osteoporosis[3]. Unfortunately, approximately half of patients prescribed oral bisphosphonates do not adhere to the medication after one year. Therefore, IV zoledronate is a popular alternative. Side effects are generally rated as mild to moderate and resolve within 3 days on average.[3] Though arthralgia is one of the five most observed side effects, arthritis has rarely been reported.

This case describes a 68-year-old female with osteoporosis on a background of osteoarthritis who experienced polyarthritis after receiving an IV zoledronate infusion. She initially experienced the more common flu-like reaction, but then went on to develop swelling in multiple joints. Three other case studies mention the occurrence of arthritis following IV zoledronate administration[4-6]. Such reactions do not appear to be dose dependent[4]. There have also been cases reporting synovitis or arthritis in patients receiving the oral bisphosphonates alendronate and risedronate[7-9].

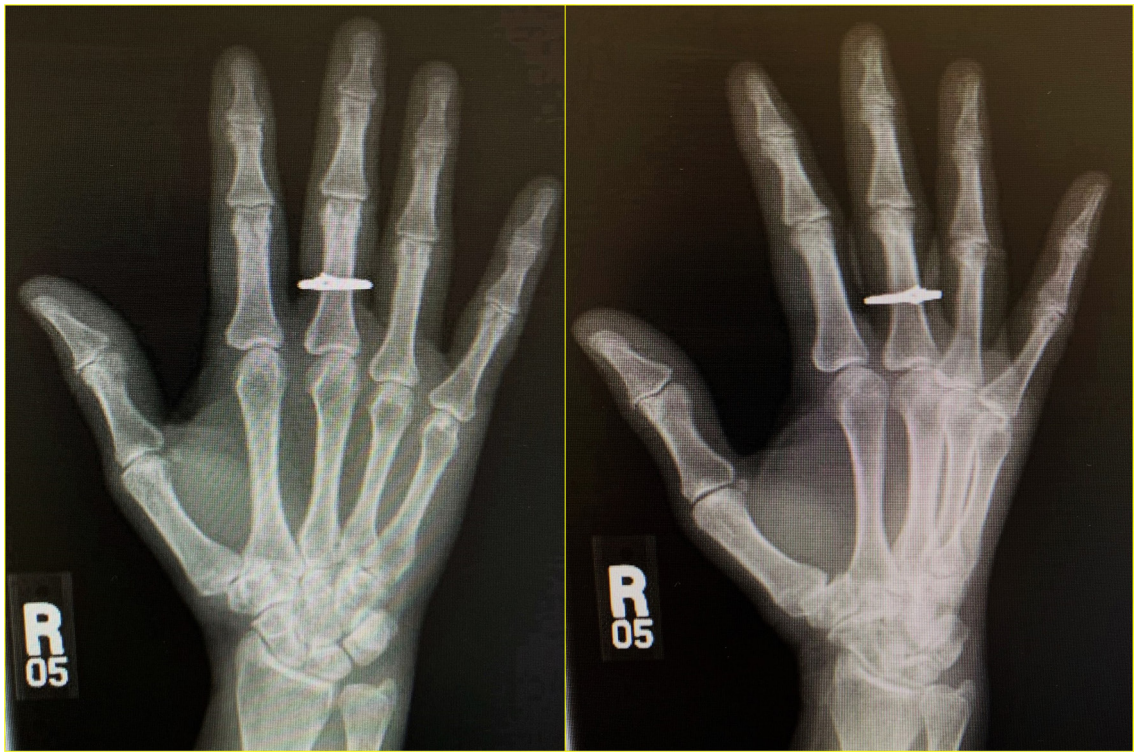

Figure 1. Right hand x-rays taken in 2010 indicate underlying proximal interphalangeal (PIP) osteoarthritis evident prior to receiving IV zoledronate.

Interestingly, similar to the 68-year-old female in the current case study, patients in two of the three IV zoledronate case reports had reported underlying osteoarthritis and experienced flares at involved sites[4,6]. My patient's reaction was not as severe as that noted in the case by White et al[4]. It had been postulated that age-associated frailty may reduce tolerance to even milder side effects. My patient was significantly less frail than the patient described by White et al[4]. She was not re-challenged with IV zoledronate, though reported side effects appear to decrease with future infusions[3]. She was not naive to bisphosphonates prior to her infusion, as she had previously taken etidronate approximately 9 years earlier. It is unclear if prior exposure to oral bisphosphonates reduces the occurrence of side effects in IV zoledronate[10,11].

CONCLUSIONS

This case study describes a patient who experienced a rare side effect of polyarthritis after receiving IV zoledronate. She was still able to perform all her activities of daily living and did not require hospitalization. However, she reported that she would prefer to consider alternative treatments in the future. A review of the literature suggests that patients with pre-existing osteoarthritis may be more likely to develop arthritis after bisphosphonate exposure. The current case, therefore, highlights the importance of discussions with patients around additional side effects of IV zoledronate, especially in those with underlying degenerative arthritis.

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