Annals of Case Reports and Clinical Studies
Case Report (ISSN: 2834-5673)

Causal Relationship: Association Between Atrial Fibrillation and Zoledronic Acid in the Setting of Humoral Hypercalcemia of Malignancy

Juan Vargas, Kunal Deora, and Muftah Mahmud*

Midwestern University Internal Medicine Program, Verde Valley Medical Center, Cottonwood, Arizon

Citation: *Juan Vargas, Kunal Deora, and Muftah Mahmud. Causal Relationship: Association Between Atrial Fibrillation and Zoledronic Acid in the Setting of Humoral Hypercalcemia of Malignancy. Ann Case Rep Clin Stud. 2024;3(2):1-7.*

Received Date: 23 April, 2024; **Accepted Date:** 29 April, 2024; **Published Date:** 01 May, 2024

***Corresponding author:** Muftah Mahmud, Midwestern University Internal Medicine Program, Verde Valley Medical Center, Cottonwood, Arizona

INTRODUCTION

Atrial Fibrillation (AF) is the most common sustained arrhythmia, and its incidence and prevalence are increasing both in the United States and globally [1,2]. The prevalence of AF in the United States was estimated to be 5.2 million in 2010, with an expected rise to 12.1 million by 2030 [1]. Corresponding estimates for the incidence of AF in the U.S. were 1.2 million cases in 2010, projected to increase to 2.6 million cases by 2030 [1]. The rate of AF diagnosis varies according to factors such as education, income [3], clinical presentation [4,5], and genetic predisposition [4]. AF is associated with a 1.5- to 2-fold increased risk of mortality [6,7]; studies suggest that this risk may be higher in women than in men [6]. Meta-analyses have also shown that AF is linked to an increased risk of several adverse outcomes, including a 2.4-fold risk of stroke [7], a 1.5-fold risk of cognitive impairment or dementia [8], a 1.5-fold risk of Myocardial Infarction (MI) [9], a 2-fold risk of sudden cardiac death [10], a 5-fold risk of Heart Failure (HF) [7], a 1.6-fold risk of Chronic Kidney Disease (CKD) [7], and a 1.3-fold risk of Peripheral Artery Disease (PAD) [7].

Risk factors for AF include advancing age, smoking [9] and initiation of smoking [10], a sedentary lifestyle [11], participation in elite/extreme activities [12], alcohol consumption and its dose-response relationship, as well as genetically predicted heavy alcohol consumption (>35 U/week for women and >50 U/week for men) [10], obesity [9], increasing height [13], hypertension [9], use of blood pressure medications [14], and high systolic blood pressure [14]. Other risk factors include diabetes and pre-diabetes [15], heart failure [1], MI [1], history of MI [14], or genetically predicted Coronary Artery Disease (CAD) [16], significant heart murmur (any diastolic murmur and grade >/-3/6 systolic murmur), Coronary Artery Bypass Grafting (CABG) [17], chronic kidney disease [18], obstructive sleep apnea [19], hyperthyroidism [20], severe sepsis [21], increased PR interval [22] or Electrocardiographic Left Ventricular Hypertrophy (ECG LVH) [1], biomarkers such as BNP [23], CRP/IL-6, and TNF-alpha [24], as well as left atrial size or function parameters such as increased anterior-posterior dimension [25] and end-diastolic volume [26], increased left ventricular posterior wall thickness [25], and family history [26]. Certain medications can cause or contribute to the development of AF, including adenosine [27,28], and other medications capable of increasing vagal tone [29], drugs that enhance vagal tone such as digitalis. While bisphosphonates in general have not been associated with atrial arrhythmias, in the HORIZON

Pivotal Fracture Trial (which studied the effect of zoledronic acid given once per year for the treatment of osteoporosis in postmenopausal women), the number of patients who experienced arrhythmias, including serious AF, was greater in the zoledronic acid group compared to the placebo group (1.3% *versus* 0.5%) [30]. Zoledronic acid is a widely used bisphosphonate for the treatment of osteoporosis, hypercalcemia of malignancy and/or Paget disease. In a study by D'Silva et al, zoledronic acid has been found to be associated with a 25% high relative risk or an absolute risk difference of 3.69 events per 1000 person years of incident atrial fibrillation within the first year of treatment and patient is treated for osteoporosis [31]. An open-label pharmacokinetic and pharmacodynamic study of zoledronic acid was performed in 19 cancer patients with bone metastases and known, varying levels of renal function. Mean area under the plasma concentration versus time curve and mean concentration immediately after cessation of drug infusion were lower, and mean amounts excreted in urine over 24 hours from start of infusion were higher in normal subjects than in those with impaired renal function (36% *vs.* 28% of excreted dose [32]. Zoledronic acid has a terminal elimination half-life of 146 hours [33].

Here, we report a case of a 76-year-old male who developed Atrial Fibrillation with Rapid Ventricular Response within 24 hours of receiving a zoledronic acid infusion during hospitalization for the treatment of humoral hypercalcemia of malignancy secondary to Multiple Myeloma. There was no evidence of cardiac ischemia or structural heart disease on Transthoracic Echocardiogram, and there were no above-mentioned risk factors, except for age and Acute kidney injury on chronic kidney disease secondary to Multiple Myeloma. Possible confounding factors include acute illness caused by hypercalcemia of multiple myeloma, manifested by symptoms such as confusion.

CASE PRESENTATION

This is a 76-year-old male with a medical history of asthma and hypothyroidism that presented to the emergency room with complaints of severe back pain, rib pain, and shoulder pains for approximately 1 week associated with worsening confusion and severe fatigue. Initial investigations revealed a calcium level of 14.9 mg/dL, phosphorus of 4.0 mg/dL, magnesium level 1.6 mg/dL. A recent whole-body Positron Emission Tomography (PET) scan done for the mentioned pains revealed increased radio-tracer uptake in the left posterior 11th rib suspicious for malignancy. The patient was admitted with a diagnosis of severe symptomatic hypercalcemia of malignancy. Initial management included aggressive IV fluid resuscitation with crystalloids along with the utilization of the loop diuretic furosemide to aid in calcium diuresis, and continuous cardiac telemetry monitoring. Due to a poor response to improvement in his calcium levels, the patient received a single dose of zoledronic acid 3.28 mg (adjustments made on basis of creatinine clearance). Within 24 hours of administration of zoledronic acid, the patient's cardiac rhythm was noted to convert from normal sinus rhythm to atrial fibrillation at a rate of 108 bpm (Figure 1) with no evidence of ischemia based on troponin or symptoms, he remained hemodynamically stable during this period of atrial fibrillation with rapid ventricular response. During this episode, his potassium level was 3.9 mg/dL and magnesium level was 2.0 mg/dL, Thyroid Stimulating Hormone (TSH) level 2.26 uIU/mL (within normal limits). The patient received 2 g of magnesium sulfate intravenously and an additional 50 milliequivalent of oral potassium bicarbonate. He subsequently underwent spontaneous conversion into normal sinus rhythm (Figure 2) without any further pharmacologic interventions. There was no recurrence of atrial fibrillation during hospitalization. The patient's calcium level during this episode was 13.1, with a urea level of 13 mg/dL and a creatinine of 1.6 mg/dL (baseline creatinine was

estimated to be around 1.2 mg/dL). There was a very low suspicion for pulmonary embolism due to lack of symptoms, and a high sensitivity troponin was obtained within normal limits. A transthoracic echocardiogram revealed no hemodynamically significant valvular disease, left ventricular ejection fraction estimated 60% to 65%, left atrium normal in size, right atrium normal in size, and normal estimated pulmonary arterial systolic pressure. Given his elevated risk of stroke based on age, systemic anticoagulation was started with apixaban for cardioembolic stroke prevention. The patient's serum calcium concentration normalized with iv fluid resuscitation with crystalloids and Zaledronic acid infusion along with resolution symptoms. He was subsequently discharged with instructions to follow up with the oncology and cardiology service for further monitoring.

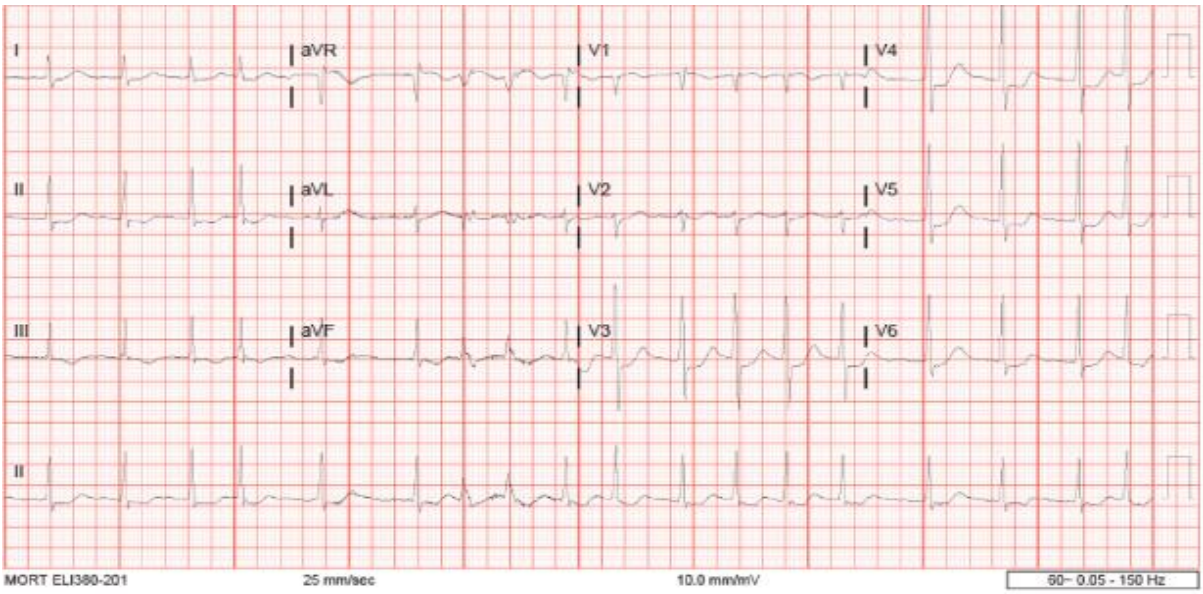

Figure 1: Initial EKG demonstrating atrial fibrillation at a rate of 108 beats per minute within 24 hours of zoledronic acid administration.

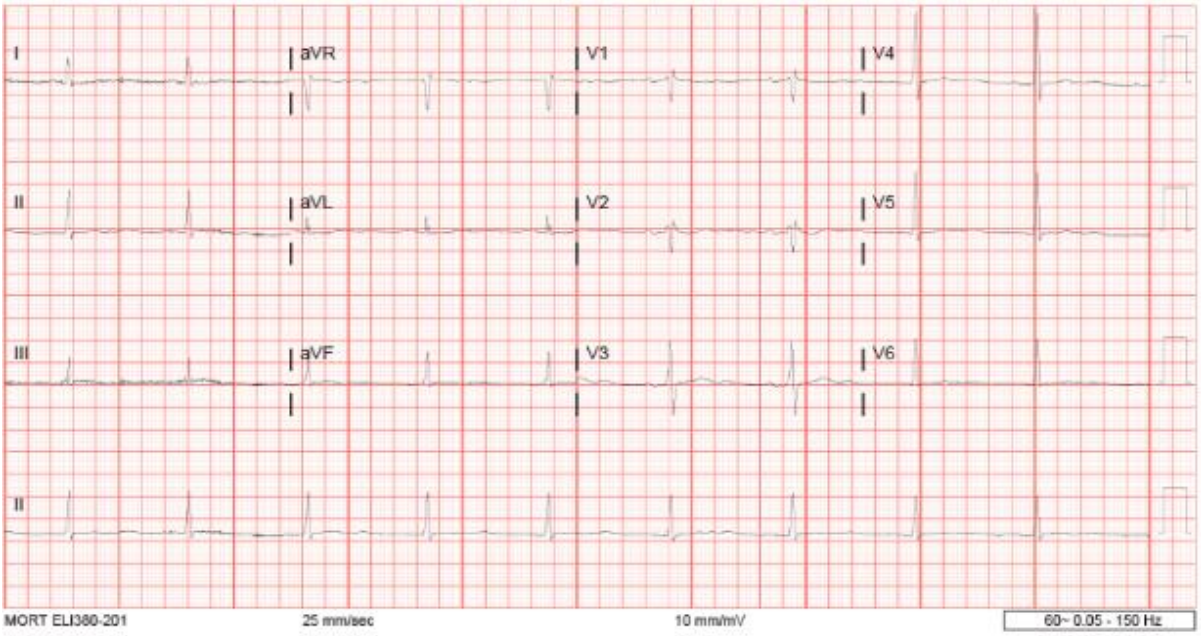

Figure 2: Follow up EKG demonstrating spontaneous conversion to normal sinus rhythm.

DISCUSSION

Our patient did not have risk factors associated with A-fib, including smoking, sedentary lifestyle, participation in elite/extreme activities, alcohol use, obesity, hypertension, diabetes or pre-diabetes, heart failure, coronary artery disease, hypothyroidism, severe sepsis, EKG changes such as increased PR interval or ECG LVH, increased left atrial size or increased AP dimension and end-diastolic volume, increased left ventricular posterior wall thickness, family history, or outpatient medications predisposing to A-fib. Although our patient was given doses of Lasix to cause urine calcium excretion, which could lead to hypomagnesemia or other electrolyte abnormalities that could cause A-fib, continuous monitoring of electrolytes eliminated this risk factor. He was given continuous IV crystalloid infusion, which could have led to fluid overload predisposing to arrhythmias; however, the patient never got fluid overloaded. Zoledronic acid has a high terminal elimination half-life of 146 hours and our patient had acute kidney injury with creatinine of 1.6, theoretically the mean area under the plasma concentration versus time And mean concentration immediately after cessation of drug infusion would be high and mean amount excreted in the urine over 24 hours from the start of infusion would be lower in our patient because of impaired renal function, but our patient was given the drug's dose corresponding to creatinine clearance as per FDA recommendations.

It is well known in the literature that an acute phase response is commonly seen shortly after intravenous administration of bisphosphonates. This is characterized by fevers, rigors, fatigue and arthralgia within 3 days of infusion. This is known to be mediated by inflammatory cytokines that include interleukin 6, Tumor Necrosis Factor (TNF)-alpha, and other inflammatory cytokines released after bisphosphonate administration [34]. There is a strong link between atrial fibrillation and acute phase reactants, and the abundance of data surrounds those acute phase reactants Interleukin (IL)-6 and TNF-alpha. The mechanisms by which acute phase reactants cause atrial fibrillation are believed to be prolongation of the ventricular action potential duration caused by membrane ion channels modulation, impairment of intracellular Calcium handling, gap junction dysfunction, via changes in connexins, and, promotion of cardiac fibrosis [35]. This association was further strengthened by the findings of Wu, et al. [24]. It is also the possibility that the underlying malignancy of this patient predisposed to higher levels of inflammatory markers at baseline hence increasing the likelihood of new atrial fibrillation after bisphosphonate infusion via this mechanism. Unfortunately, we did not measure levels of inflammatory markers due to hospitalization cost concerns.

CONCLUSION

In the presence of risk and confounding factors such as age, dehydration and other symptoms of hypercalcemia of malignancy, the plausibility of zoledronic acid's association with atrial fibrillation emerges, although establishing a causal relationship remains challenging. To better understand this potential link, we advocate for comprehensive meta-analyses or systematic reviews to synthesize and evaluate the weight of evidence regarding zoledronic acid or other bisphosphonates' impact on atrial fibrillation. In the interim, it is prudent to exercise caution and closely monitor patients with multiple risk factors for atrial fibrillation or a history of paroxysmal, persistent, or longstanding persistent A-fib when administering bisphosphonates. This proactive approach can help mitigate potential adverse events and optimize patient safety. Furthermore, ongoing research efforts are warranted to unravel the underlying mechanisms and identify specific risk factors contributing to zoledronic

acid-induced atrial fibrillation. By advancing our understanding in this area, we can enhance clinical decision-making and elevate the standard of care for patients receiving bisphosphonate therapy.

References

1. Schnabel RB, Yin X, Gona P, Larson MG, Beiser SA, McManus DD, et al. 50-year trends in atrial fibrillation prevalence, incidence, risk factors, and mortality in the Framingham Heart Study: a cohort study. Lancet. 2015;386(9989):154-62.
2. Tsao CW, Aday AW, Almarzooq ZI, Anderson AMC, Arora P, Avery CL, et al. Heart disease and stroke statistics-2023 update: a report from the American Heart Association. Circulation. 2023;147(8):e93-621.
3. Mou L, Norby FL, Chen LY, O'Neal WT, Lewis TT, Loehr LR, et al. Lifetime risk of atrial fibrillation by race and socioeconomic status: ARIC study (Atherosclerosis Risk in Communities). Circ Arrhythm Electrophysiol. 2018;11(7):e006350.
4. Weng LC, Preis SR, Hulme OL, Larson MG, Choi SH, Wang B, et al. Genetic predisposition, clinical risk factor burden, and lifetime risk of atrial fibrillation. Circulation. 2018;137(10):1027-38.
5. Staerk L, Wang B, Preis SR, Larson MG, Lubitz SA, Ellinor PT, et al. Lifetime risk of atrial fibrillation according to optimal, borderline, or elevated levels of risk factors: cohort study based on longitudinal data from the Framingham Heart Study. BMJ. 2018;361:k1453.
6. Emdin CA, Wong CX, Hsiao AJ, Altman DG, Ae Peters S, Woodward M, et al. Atrial fibrillation as a risk factor for cardiovascular disease and death in women compared with men: systematic review and meta-analysis of cohort studies. BMJ. 2016;532:h7013.
7. Odutayo A, Wong CX, Hsiao AJ, Hopewell S, Altman DG, Emdin CA. Atrial fibrillation and risks of cardiovascular disease, renal disease, and death: systematic review and meta-analysis. BMJ. 2016;354:i4482.
8. Papanastasiou CA, Theochari CA, Zareifopoulos N, Arfaras-Melainis A, Giannakoulas G, Karamitsos TD, et al. Atrial fibrillation is associated with cognitive impairment, all-cause dementia, vascular dementia, and Alzheimer's disease: a systematic review and meta-analysis. J Gen Intern Med. 2021;36(10):3122-35.
9. Huxley RR, Lopez FL, Folsom AR, Agarwal SK, Loehr LR, Soliman EZ, et al. Absolute and attributable risks of atrial fibrillation in relation to optimal and borderline risk factors: the Atherosclerosis Risk in Communities (ARIC) study. Circulation. 2011;123(14):1501-8.
10. Lu Y, Guo Y, Lin H, Wang Z, Zheng L. Genetically determined tobacco and alcohol use and risk of atrial fibrillation. BMC Med Genomics. 2021;14(1):73.
11. Mohanty S, Mohanty P, Tamaki M, Natale V, Gianni C, Trivedi C, et al. Differential association of exercise intensity with the risk of atrial fibrillation in men and women: evidence from a meta-analysis. J Cardiovasc Electrophysiol. 2016;27(9):1021-9.
12. Newman W, Parry-Williams G, Wiles J, Edwards J, Hulbert S, Kipourou K, et al. Risk of atrial fibrillation in athletes: a systematic review and meta-analysis. Br J Sports Med. 2021;55(21):1233-8.
13. Allan V, Honarbakhsh S, Casas JP, Wallace J, Hunter R, Schilling R, et al. Are cardiovascular risk factors also associated with the incidence of atrial fibrillation? A systematic review and field synopsis

of 23 factors in 32 population-based cohorts of 20 million participants. Thromb Haemost. 2017;117(5):837-50.

14. Alonso A, Krijthe BP, Aspelund T, Stepas KA, Pencina MJ, Moser CB, et al. A simple risk model predicts the incidence of atrial fibrillation in a racially and geographically diverse population: the CHARGE-AF consortium. J Am Heart Assoc. 2013;2(2):e000102.
15. Aune D, Feng T, Schlesinger S, Janszky I, Norat T, Riboli E. Diabetes mellitus, blood glucose, and the risk of atrial fibrillation: a systematic review and meta-analysis of cohort studies. J Diabetes Complications. 2018;32(5):501-11.
16. Wang Q, Richardson TG, Sanderson E, Tudball MJ, Ala-Korpela M, Smith GD, et al. A phenome-wide bidirectional Mendelian randomization analysis of atrial fibrillation. Int J Epidemiol. 2022;51(4):1153-66.
17. Mathew JP, Fontes ML, Tudor IC, Ramsay J, Duke P, Mazer DC, et al. A multicenter risk index for atrial fibrillation after cardiac surgery. JAMA. 2004;291(14):1720-9.
18. Shang W, Li L, Huang S, Zeng R, Huang L, Ge S, et al. Chronic kidney disease and the risk of new-onset atrial fibrillation: a meta-analysis of prospective cohort studies. PLoS One. 2016;11(5):e0155581.
19. Zhang D, Ma Y, Xu J, Yi F. Association between obstructive sleep apnea (OSA) and atrial fibrillation (AF): a dose-response meta-analysis. Medicine (Baltimore). 2022;101(30):e29443.
20. Huang M, Yang S, Ge G, Zhi H, Wang L. Effects of thyroid dysfunction and the thyroid-stimulating hormone levels on the risk of atrial fibrillation: a systematic review and dose-response meta-analysis from cohort studies. Endocr Pract. 2022;28(8):822-31.
21. Walkey AJ, Wiener RS, Ghobrial JM, Curtis LH, Benjamin EJ. Incident stroke and mortality associated with new-onset atrial fibrillation in patients hospitalized with severe sepsis. JAMA. 2011;306(20):2248-54.
22. Kwok CS, Rashid M, Beynon R, Barker D, Patwala A, Morley-Davies A, et al. Prolonged PR interval, first-degree heart block, and adverse cardiovascular outcomes: a systematic review and meta-analysis. Heart. 2016;102(9):672-80.
23. Sinner MF, Stepas KA, Moser CB, Krijthe BP, Aspelund T, Sotoodehnia N, et al. B-type natriuretic peptide and C-reactive protein in the prediction of atrial fibrillation risk: the CHARGE-AF Consortium of community-based cohort studies. Europace. 2014;16(10):1426-33.
24. Wu N, Xu B, Xiang Y, Wu L, Zhang Y, Ma X, et al. Association of inflammatory factors with occurrence and recurrence of atrial fibrillation: A meta-analysis. Int J Cardiol. 2013;169(1):62-72.
25. Vaziri SM, Larson MG, Benjamin EJ, Levy D. Echocardiographic predictors of non-rheumatic atrial fibrillation. The Framingham Heart Study. Circulation. 1994;89(2):724-30.
26. Olsen FJ, Mogelvang R, Jensen GB, Jensen SJ, Biering-Sørensen T. Relationship between left atrial functional measures and the incident atrial fibrillation in the general population: the Copenhagen City Heart Study. J Am Coll Cardiol Img. 2019;12(6):981-9.
27. Varriale P, Ramaprasad S. Aminophylline-induced atrial fibrillation. Pacing Clin Electrophysiol. 1993;16(10):1953-5.
28. Strickberger SA, Man KC, Daoud EG, Goyal R, Brinkman K, Knight BP, et al. Adenosine-induced atrial arrhythmia: a prospective analysis. Ann Intern Med. 1997;127(6):417-22.

29. Coumel P. Autonomic influences in atrial tachyarrhythmias. J Cardiovasc Electrophysiol. 1996;7(10):999-1007.
30. Black DM, Delmas PD, Eastell R, Reid IR, Boonen S, Cauley JA, et al. Once-yearly zoledronic acid for the treatment of postmenopausal osteoporosis. N Engl J Med. 2007;356(18):1809-22.
31. D'Silva KM, Cromer SJ, Yu EW, Fischer M, Kim SC. Risk of incident atrial fibrillation with zoledronic acid versus denosumab: a propensity score-matched cohort study. J Bone Miner Res. 2021;36(1):52-60.
32. Skerjanec A, Berenson J, Hsu C, Major P, Miller WH, Ravera C, Schran H, et al. The pharmacokinetics and pharmacodynamics of zoledronic acid in cancer patients with varying degrees of renal function. J Clin Pharmacol. 2003;43(2):154-62.
33. FDA approved drug products: Zometa zoledronic acid intravenous injection.
34. Papapetrou P. Bisphosphonate-associated adverse events. Hormones (Athens). 2009;8(2):96-110.
35. Lazzerini PE, Abbate A, Boutjdir M, Capecchi PL. Fir(e)ing the rhythm: Inflammatory cytokines and cardiac arrhythmias. JACC Basic Transl Sci. 2023;8(6):728-50.