

# Fatal Myocarditis Following Administration of Zoledronic Acid: A Case Report

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## Abstract

Myocarditis is a potentially life-threatening condition which occurs due to inflammation of the cardiac muscle. It has a multitude of causes including certain medications. Zoledronic acid is a bisphosphonate given as an intravenous preparation for bone-related diseases. Medical literature provides details about only very few cases of Zoledronic acid-induced myocarditis and all of them were non-fatal. We report a fatal case of myocarditis due to the administration of intravenous Zoledronic acid. A 40-year-old male with a history of multiple joint pain and swelling for one week and right knee joint swelling for three months was administered intravenous Zoledronic acid. One day after the administration of Zoledronic acid patient developed dizziness and eventually became drowsy. His ECG revealed ST depressions in leads I, II, and aVF, as well as leads V3 to V5. Highly sensitive Troponin I was elevated to 2195.3 pg/ml (normal:<26.5 pg/ml) and Echocardiogram showed an ejection fraction of 30% with hypokinetic wall segments and regional wall motion abnormalities. He went into cardiogenic shock and was pronounced dead. At the autopsy, the macroscopic examination did not reveal any noticeable fatal pathology. However histological examination of the myocardium revealed diffuse infiltration of mononuclear cells with myocyte necrosis. Although life-threatening adverse effects of Zoledronic acid such as severe systemic inflammatory response syndrome and myopericarditis have been previously reported, fatalities due to Zoledronic acid-induced myocarditis, like in this case, has not been reported. This case highlights the importance of being vigilant in using this drug.

**Keywords:** Myocarditis, Zoledronic acid, Bisphosphonate, Drug-induced

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## Introduction

Myocarditis is a potentially life-threatening condition which occurs due to inflammation of the cardiac muscle. It has a multitude of causes including infections, medications, and systemic diseases. Zoledronic acid is a bisphosphonate given as an intravenous preparation which is used for the treatment of osteoporosis, Paget's disease, malignant hypercalcaemia, and multiple myeloma.[1] Theoretically, any medication used in medical practice can cause myocarditis, however, the commonest medications are Tricyclic anti-depressants, clozapine, cyclophosphamide, phenothiazines etc.[2] Here we present a rare case of medication-induced fatal myocarditis due to Zoledronic acid.

## Case report

A 40-year-old male with a history of dyspeptic symptoms presented to a teaching hospital with multiple joint pain and swelling for one week and

right knee joint swelling for three months. He also had a loss of appetite and loss of weight. Blood investigations showed leukocytosis and thrombocytosis. The Erythrocyte sedimentation rate was 22mm in the first hour (normal:<8mm). His serum calcium level was 1.47mmol/L (normal range:1.1-1.32mmol/L). His previous contrast-enhanced computed tomography of the abdomen had been inconclusive, and he was awaiting a bone marrow biopsy.

He was treated with tramadol, prednisolone, and, on the second day of admission with one dose of IV Zoledronic acid (4 milligrams).

On the third day of admission, he developed dizziness, nausea and later became drowsy. His ECG revealed ST depressions in leads I, II, aVF, as well as leads V3 to V5. High-sensitive Troponin I was elevated to 2195.3 pg/ml (normal:<26.5 pg/ml). While being managed as a non-ST elevation

myocardial infarction, he developed cardiogenic shock and was given intravenous fluids, noradrenaline, and ephedrine. He was admitted to the intensive care unit. An Echocardiogram showed an ejection fraction of 30% with hypokinetic wall segments and regional wall motion abnormalities. He went into cardiac arrest the same day and died despite multiple attempts at resuscitation.

The post-mortem examination revealed a 60ml straw-coloured pericardial effusion. The left anterior descending artery showed a 45% eccentric atheroma and had myocardial bridging of 3mm in length and 3mm in-depth, but the rest of the coronary vessels were unremarkable. The Myocardium did not show any macroscopic abnormalities.

Histological examination of the myocardium showed focal areas of infiltrations with predominantly mononuclear cells with some myocyte necrosis (Fig. 1 & 2).

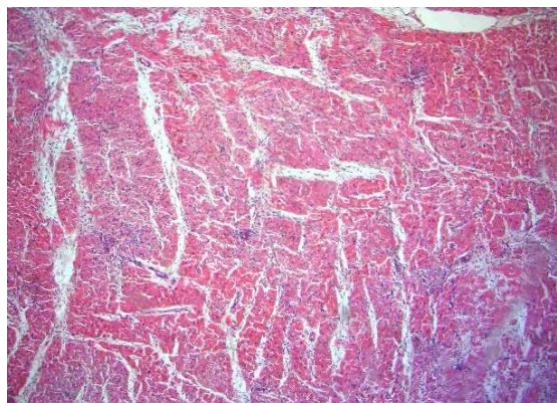


Figure 01. Photomicrograph of the myocardium – H & E staining x 04 – Show diffuse mononuclear cell infiltration in the myocardium

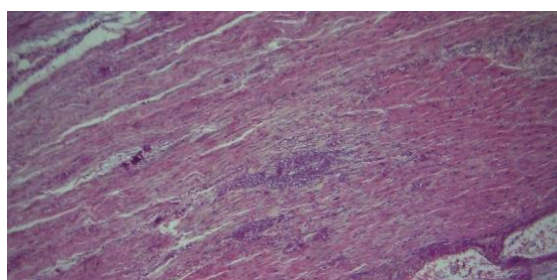


Figure 01. Photomicrograph of the myocardium – H & E staining x 10 Show diffuse mononuclear cell infiltration in the myocardium with patchy necrosis of myocytes where there is cellular infiltration

Few neutrophils were also noted. No significant fibrosis was noted and blood vessels in the myocardium showed deposition of darkly stained amorphous material. However, this amorphous material did not show the classical amyloid appearance with Congo-red staining. Pericardial tissue was normal. There were no features of

amyloid deposition in the myocardium or cardiomyopathy. The histopathology of other organs did not show any significant pathology. Bone marrow biopsy revealed a heavy infiltration of plasma cells suggestive of an underlying plasma cell neoplasm.

The cause of death was stated as drug-induced (Zoledronic acid) myocarditis.

### Discussion

Zoledronic acid is an intravenously administered nitrogen-containing bisphosphonate which selectively inhibits farnesyl pyrophosphate synthase (FPPS).[3] It has the advantage of having no gastrointestinal (GI) side effects as it bypasses the GI tract which improves compliance compared to oral bisphosphonates. Its common adverse effects are acute phase reaction (characterized by low-grade fever, fatigue, aches, and pains), arrhythmias (especially atrial fibrillation), and musculoskeletal pain.[3] A Literature search on PubMed revealed only one previous case report of Zoledronic acid causing myopericarditis which was in a patient who developed fever, chest pain, and elevated cardiac enzymes, 24 hours after IV administration of Zoledronic acid for Paget's disease in which the patient survived.[4] In one clinical trial, 3.4% of patients taking Zoledronic acid died from cardiovascular causes such as arrhythmias and strokes which, however, was less than those in the placebo group.[5] The risk of adverse events is typically higher following the first dose. A considerable literature survey did not yield previously reported fatalities due to myocarditis following the administration of Zoledronic acid, therefore this is possibly the first reported case.

Medication induced myocarditis can occur either due to direct toxicity or by inducing a hypersensitivity reaction. The clinical manifestations lie in a spectrum ranging from asymptomatic disease to congestive heart failure, arrhythmias, and occasionally sudden death. It is usually diagnosed once other causes of cardiac dysfunction are excluded. Investigations such as a 2D echocardiogram, cardiac MRI, and electrocardiogram are useful; however, an endomyocardial biopsy is required to confirm the diagnosis.[6]

Histologically myocarditis is evident by necrosis and/or degeneration and an infiltrate of inflammatory cells. The predominant type of inflammatory cells gives a clue to the aetiology. Other methods such as immunohistochemical or immunofluorescence staining and viral nucleic acid studies are also done but are of debatable use.[7] Although some other reported cases had pericarditis together with myocarditis after the administration of

Zoledronic acid, this case did not show the involvement of pericardium.[8]

In this case, the patient was suspected to have a plasma cell neoplasm which was later confirmed by the postmortem bone marrow biopsy. He was started on Zoledronic acid in order to control the hypercalcaemia; which resulted in the development of cardiovascular symptoms which were absent previously.

The histological diagnosis of myocarditis requires the presence of myocardial inflammation and myocyte injury. Even though several criteria have been presented for the histological diagnosis of myocarditis, their practical utility in postmortem specimens remains questionable.[8] The myocyte injury patterns consist of myocyte destruction by inflammation or patchy fibrosis associated with residual inflammation. The absence of myocyte injury distant from the sites of inflammation is a key feature in differentiating myocarditis from other pathologies such as ischaemic injury and neurocardiogenic injury.[8] The postmortem histological examination, in this case, was consistent with the above findings which confirmed the presence of myocarditis. Considering all the aspects and the absence of any other aetiology, it was reasonable to assume that this was a case of drug-induced myocarditis due to Zoledronic acid.

### Conclusions

Although life-threatening adverse effects of this drug have been previously reported, this is the first known death associated with myocarditis due to IV administration of the Zoledronic acid. Therefore, it is important for clinicians to consider this possibility and monitor patients carefully especially when administering the first dose.

### Disclosure statement

**Conflicts of interest:** The author declares that she has no conflicts of interest.

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