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Acute phase reaction with zoledronic acid infusion mimicking COVID-19

Zoledronik asit infüzyonu sonrası COVİD-19'u taklit eden akut faz reaksiyonu

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ABSTRACT

During the pandemic, symptoms of many diseases that can be confused with the symptoms of COVID-19 have been detected and reported. In this case report, we reported a patient who showed flu-like symptoms and sudden lymphopenia within two days of zoledronic acid infusion. A 40-year-old female patient with a COVID-19 history was admitted to our hospital with abdominal pain. Hypercalcemia due to parathyroid adenoma was detected. Zoledronic acid (5 mg) was given intravenously for the treatment of hypercalcemia. Following the infusion; fever, C-Reactive Protein (CRP) increase and lymphopenia were detected in the patient. There were no apparent causes to explain these symptoms. The side effects we detected in the patient were confusingly similar to the symptoms of COVID-19. Repeated PCR tests and CT results indicated that the patient did not have COVID-19. A week later, the patient's symptoms improved and the laboratory findings along with the physical examination returned to normal. The patient's condition was considered to be due to zoledronic acid infusion. We would like to draw attention to the acute phase reaction after zoledronic acid infusion in the COVID-19 era in which the clinical situation could be confusing.

Keywords: Zoledronic acid, COVID-19, flu-like symptoms, lymphopenia.

ÖZ

Pandemi süresince, COVID-19 semptomlarıyla karıştırılan birçok hastalık tespit edilmiş ve bildirilmiştir. Bu vaka sunumunda, zoledronik asit infüzyonundan sonraki iki gün içerisinde grip benzeri semptomlar ve akut lenfopeni gösteren bir hastayı sunduk. Geçirilmiş COVID-19 öyküsü olan, 40 yaş kadın hasta, abdominal ağrıyla tarafımıza başvurdu. Paratiroid adenomuna bağlı hiperkalsemi saptandı. Hiperkalsemi tedavisi için IV Zoledronik asit (5mg) verildi. İnfüzyonu takiben hastada ateş, C Reaktif Protein yüksekliğinde artış ve lenfopeni tespit edildi. Hastada bu bulguları açıklayabilecek herhangi bir sebep bulunamamıştır. Hastada tespit ettiğimiz yan etkiler, kafa karıştırıcı bir şekilde COVID-19 semptomlarına benzemekteydi. Tekrarlanan PCR testleri ve BT sonuçları hastanın COVID-19 olmadığını göstermiştir. Bir hafta sonra ise hastanın semptomları gerilemiş ve laboratuvar bulguları, fizik muayene bulgularıyla birlikte normale dönmüştür. Hastanın bu durumunun zoledronik asit infüzyonuna bağlı olduğu düşünüldü.

Klinik durumun kafa karıştırıcı olabileceği COVID-19 döneminde zoledronik asit infüzyonu sonrası akut faz reaksiyonuna dikkat çekmek istiyoruz.

Anahtar Sözcükler: *Zoledronik asit, COVID-19, grip benzeri semptomlar, lenfopeni.*

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INTRODUCTION

Primary hyperparathyroidism caused by parathyroid adenoma is treated by parathyroid surgery. But, in most cases, because of high calcium levels, there is a need for the preoperative control of calcium levels in which operation can be managed safely. Sometimes, anti-resorptive medication such as bisphosphonates are used to provide lower levels of calcium before the operation (1). In this case report, we reported a patient who showed flu-like symptoms and sudden lymphopenia within two days of zoledronic acid infusion.

Written informed consent was obtained from the patient (or from his/her legal custodian) for publishing the individual medical records.

Case

Forty-year-old female patient with a known parathyroid adenoma presented to the emergency department with abdominal pain; her test results were as calcium 15.4mg/dL (8.6-10.2), phosphate 1.71 mg/dL (2.3-4.5), alkaline phosphatase 464 IU/L (35-104), and albumin 45.9g/L (35-52). For the past year, the patient has complained of occasional fatigue, headache, polydipsia, polyuria, nocturia, and pronounced myalgia below her knees. She has no chronic illnesses in her past medical history but about one and half months ago, the patient was hospitalized for nine days due to Coronavirus infectious disease-19 (COVID-19). The patient stated that she hadn't been using any alcohol or had no smoking habits. In addition, no allergies were known to exist.

There have been occasional episodes of abdominal pain and hospital admissions due to these episodes during the last four years. She applied to our hospital with abdominal pain. During our evaluation of the patient hypercalcemia was detected. The parathyroid hormone (PTH) levels were increased on occasional measurements which were 1028 ng/L (15-65ng/L). On physical examination, a nodule measured as 1x1 cm on the right side of the thyroid was palpable. During the auscultation, rough lung voices were noticed at the inferior right zone of the lung. The rest of the physical examination was normal. Hypercalcemia due to primary hyperparathyroidism was diagnosed. Neck ultrasonography revealed a parathyroid adenoma leading to hypercalcemia. The patient was given furosemide intravenously and hydrated with %0.9 NaCl (200cc/h). The calcium level decreased from 15.5 mg/dL to 13.4mg/dL. Zoledronic acid (5 mg) was given intravenously in addition to the previous treatment to provide normocalcemia on day three. After zoledronic acid infusion, C - reactive protein (CRP) (0-5 mg/L) increased from 3.49 mg/dL to 13.68 mg/dL in 24 hours (Figure-1A-B).

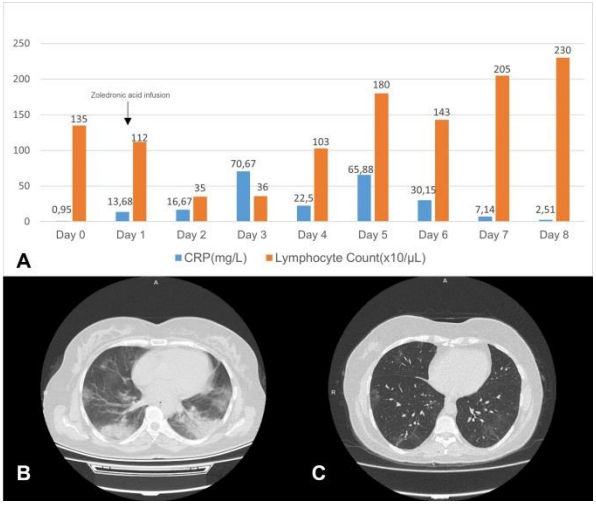

Figure-1 A. Changes in CRP and lymphocyte count before and after zoledronic acid infusion **1 B-C:** High Resolution Computer Tomography (HRCT) images of lungs at the time of COVID-19 and images of lung showing regression of ground glass opacities after COVID-19.

Tests conducted based on the suspicion of the infection were not able to explain CRP increase. After one day of the infusion, lymphopenia had occurred. Her lymphocyte level was $0.35x10^3$/µL ($1.01-3.38x10^3$). On evaluation, the patient's fever increased to 38.3°C. Because of fever and lymphopenia, the patient was isolated at the Respiratory Diseases Clinic with the suspicion of COVID-19. On High-resolution Computer Tomography (HRCT) taken on the same day, ground glass opacities were detected. In comparison with the CT taken during the hospitalization of the patient due to COVID-19 pneumonia, a significant regression was observed as far as the ground glass opacities were concerned (Figure-1C). The COVID PCR (Polymerase Chain Reaction) tests performed were negative. Any other tests regarding viral infections were not performed. After two days of the infusion leukocytopenia occurred in addition

to lymphopenia. Her white blood cell level was $2.92x10^3$/μL(4.5 - $11.0x10^3$), lymphocyte level was $0.36x10^3$/μL (1.01-$3.38x10^3$) and CRP level was 73.71 mg/dL (Figure-1A-B). After seven days of the infusion, CRP level was normal and the patient's lymphopenia had disappeared (Figure-1A-B). Thyroidectomy and parathyroidectomy have been performed and normocalcemia has been provided. After two days of the operation, the patient has been discharged.

DISCUSSION

The Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), formerly known as the 2019 novel Coronavirus (2019-nCoV) has emerged as a severe pandemic since December 2019 (2).

In the study of Rodriguez-Morales et al.(3), fever (88.7%, 95%Cl 84.5–92.9%), cough (57.6%, 95 %CI 40.8–74.4 %), and dyspnea (45.6 %, 95%CI 10.9–80.4 %) were the most common clinical symptoms. Hypoalbuminemia, as well as high inflammatory markers like CRP, Lactate Dehydrogenase (LDH), and Erythrocyte Sedimentation Rate (ESR) were among the most common laboratory abnormalities discovered. In addition, lymphopenia was shown to be prevalent in more than 40% of patients in eight trials including over 500 individuals (3). Furthermore, in another study lymphocytopenia occurred in 40% patients, partly due to T-cell apoptosis (4).

Bisphosphonates are most commonly used for the treatment of hypercalcemia of malignancy. Bisphosphonates inhibit farnesyl diphosphate synthase (FPPS) in the mevalonate pathway, ultimately causing osteoclast malfunction and apoptosis (5). One of the most reliable drugs among bisphosphonates is zoledronic acid. Although zoledronic acid is used very often, there are also common drug-related adverse events. In patients taking intravenous zoledronic acid, an initial systemic inflammatory response marked by fever, arthralgia, myalgia with or without nausea and edema is common. Although acute zoledronic acid responses are very common, the symptoms are usually predictable and have no long-term complications. The response usually appears within 48 hours of the initial treatment, is short-lived and self-limiting within a few days and is associated with less severe symptoms if detected with repeated medication (5). In one randomized study which is comparing a yearly infusion of 5 mg of zoledronic acid to a placebo; 16.1% fever, 9.5% myalgia, 7.8% influenza-like sickness, and 6.3% arthralgia were all reported by individuals who received zoledronic acid. All of these side effects were shown to be substantially more common than placebo (6, 7).

This increase in temperature was linked to a significant decrease in lymphocyte count, which fell to around 61% of starting levels, as well as a significant increase in serum CRP levels (8, 9). As with oral treatment, the temperature was related to temporary substantial decreases in lymphocyte count and rises in serum CRP levels (8, 9). In the research of Adami et al. (9), lymphopenia and an increase in serum CRP were all dose-dependent alterations. In the study of Cui et al. (10), lymphocytes decreased from day 1 to day 3 after zoledronic acid infusion. On the first day of zoledronic acid infusion significant decrease in the CD3+T cells and CD3+CD4+ T cell counts occurred. On the second day there was a significant decrease for CD3+ T cells and CD3+CD4+ T cells. The first zoledronic acid infusion caused a significant decrease of the CD16+CD56+ NK cell counts also. It was stated that the decrease in the CD3+CD4+ T cells and CD16+CD56+ NK lymphocytes found in this study might be explained by the immunomodulation properties of zoledronic acid (10).

CONCLUSION

In conclusion, our case has shown acute phase reaction after zoledronic acid infusion. This reaction including fever, myalgia, and increase in CRP level together with lymphopenia was mimicking COVID-19. So, we would like to draw attention to the acute phase reaction after zoledronic acid infusion in the COVID-19 era in which the clinical situation could be confusing.

Conflict of interest: Declare that they have no conflict of interest.

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