

BIBLIOGRAPHIC INFORMATION SYSTEM

Journal Full Title: [Journal of Biomedical Research & Environmental Sciences](#)

Journal NLM Abbreviation: J Biomed Res Environ Sci

Journal Website Link: <https://www.jelsciences.com>

Journal ISSN: 2766-2276

Category: Multidisciplinary

Subject Areas: [Medicine Group](#), [Biology Group](#), [General](#), [Environmental Sciences](#)

Topics Summation: 133

Issue Regularity: [Monthly](#)

Review Process: [Double Blind](#)

Time to Publication: 21 Days

Indexing catalog: [IndexCopernicus ICV 2022: 88.03](#) | [GoogleScholar](#) | [View more](#)

Publication fee catalog: [Visit here](#)

DOI: 10.37871 ([CrossRef](#))

Plagiarism detection software: [iThenticate](#)

Managing entity: USA

Language: English

Research work collecting capability: Worldwide

Organized by: [SciRes Literature LLC](#)

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**IndexCopernicus
ICV 2022:
83.03**

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CASE REPORT

Non-Specific Interstitial Pneumonia in a Woman with Osteoporosis Treated with Denosumab

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Abstract

Denosumab is an antiresorptive monoclonal antibody widely used in the treatment of osteoporosis.

A rare and potentially life-threatening adverse reaction likely associated with denosumab treatment is described, presenting as the first case report in the English literature of non-specific interstitial pneumonia (NSIP), to the best of our knowledge. The importance of clinically recognising drug-induced manifestations is evidenced in this case, where early withdrawal of the drug is usually associated with a clinical-prognostic improvement.

Introduction

Denosumab is an antiresorptive monoclonal antibody used in the treatment of osteoporosis. An exceptional case of Non-Specific Interstitial Pneumonia (NSIP) attributed to denosumab is described.

Case Description

A 68-year-old woman, with no history of exposure or consumption of toxic substances, was referred to the Pneumology Department due to progressive moderate exertional dyspnea, dry cough and intermittent vespertine fever since January 2023.

Her medical history includes osteoporosis and several vertebral crushes under follow-up by Rheumatology since 2011, which prescribed treatment with denosumab (60 mg, semiannual) in October 2022. Concurrently, three months after starting this treatment, she developed recurrent cystitis, dry oral and esophageal mucosa, gastric discomfort, asthenia and generalized pain.

Auscultation showed high-pitched bibasilar inspiratory crackles. There was no alteration of gas exchange while breathing room air at rest.

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DOI: 10.37871/jbres2062

Submitted: 15 December 2024

Accepted: 31 January 2025

Published: 31 January 2025

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OPEN ACCESS

Keywords

- Non-Specific Interstitial Pneumonia (NSIP)
- Denosumab
- Osteoporosis

MEDICINE GROUP

PULMONOLOGY

ORTHOPEDICS

VOLUME: 6 ISSUE: 1 - JANUARY, 2025



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How to cite this article: Prieto Maillo EC, Salazar Palacios AG, Martin Varillas AM, Fernandez Sanchez JL, Menendez SC, Sanchez Serrano AR. Non-Specific Interstitial Pneumonia in a Woman with Osteoporosis Treated with Denosumab. J Biomed Res Environ Sci. 2025 Jan 31; 6(1): 117-119. doi: 10.37871/jbres2062, Article ID: JBRES2062, Available at: <https://www.jelsciences.com/articles/jbres2062.pdf>

The chest radiograph revealed diffuse reticular-nodular pattern, predominantly in the lung bases. Pulmonary function tests showed a decrease in DLCO (diffusion capacity of carbon monoxide corrected by hemoglobin) of 3.14 mmol/min/kPa (58%). A chest high-resolution CT (computed tomography) scan displayed areas of increased density in symmetrical and central peribronchovascular 'ground glass' with reticular opacities and bronchiolectasis, findings compatible with interstitial lung diseases suggestive of NSIP (non-specific interstitial pneumonia) (Figure 1).

Serological and auto-immune panel were negative. The patient declined invasive diagnostic tests.

Given that the patient reported a symptomatic spectrum compatible and temporally framed with the start of treatment with denosumab, a severe adverse reaction with symptoms limiting daily life was assumed, so the drug was discontinued, and corticosteroid treatment was started, to evaluate the response.

After three months the patient showed clinical (of the various symptoms) and functional, improvement with a significant increase in DLCOc 5.04 mmol/min/kPa (87.7%). The CT scan showed an evident decreased 'ground glass' opacities (Figure 2).

Discussion

Denosumab is a human monoclonal antibody used in the treatment of osteoporosis to inhibit the growth

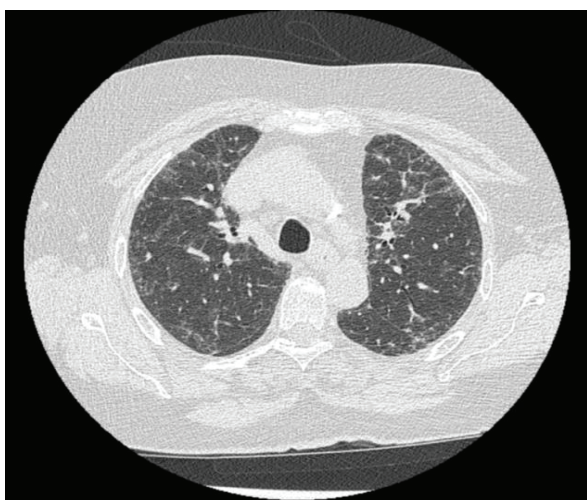


Figure 1 Chest high-resolution CT image, axial reconstruction, shows areas of increased density peribronchovascular and symmetrical and bronchiolectasis, findings compatible Non-Specific Interstitial Pneumonia (NSIP).

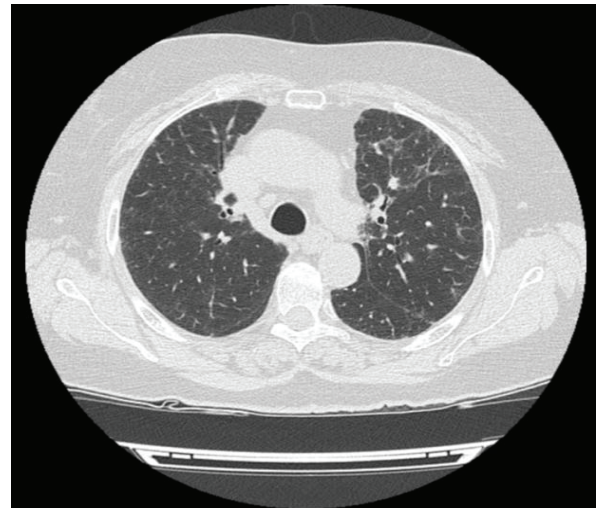


Figure 2 Chest high-resolution CT image, axial reconstruction, after withdrawal of denosumab, shows radiological improvement with decreasing areas of 'ground glass'.

and function of osteoclasts. It binds to the Receptor Activator of Nuclear Factor Kappa-B Ligand (RANKL) and prevents binding to the receptor activator of nuclear factor kappa-B (RANK). Both are expressed in the lung, allowing degradation of the extracellular matrix [1,2].

Drug-induced Interstitial Lung Disease (ILD) is complex to diagnose due to the long list of drugs involved, and diagnosis is usually by exclusion [3].

In susceptible subjects, the most common adverse effects of denosumab are back, flank and extremity pain, myalgia, hypercholesterolaemia, diarrhoea, gastro-esophageal reflux and epigastric pain, cystitis and recurrent urinary and respiratory infections, stomatitis/mucositis, dry skin and mucous membranes, asthenia and dyspnea, some of which were also reported by the patient. Interstitial lung disease associated to denosumab is an exceptional adverse reaction. The Pneumotox website (www.pneumotox.com) incorporate denosumab as a causative agent of ILD, describing only one case of hypersensitivity pneumonitis and other one case of organised pneumonia secondary to this treatment, in two women [4,5]. However, no cases of non-specific interstitial pneumonia have been reported.

In a study published in 2018 [6], the time-to-onset of drug-induced interstitial lung disease after administration of monoclonal antibodies was analysed, being more than 2 months the median time-to-onset of ILD for denosumab, consistent with the time sequence of our case.



The history of drug exposure, the absence of more likely alternative diagnoses and the clinical-radiological improvement after withdrawal of denosumab, as well as the good response to corticosteroid therapy, reinforce the hypothesis of a causal relationship. In addition, a score of 6 on the Naranjo probability scale determines as probable the relationship of this adverse effect (NSIP) with this specific drug.

Denosumab, by inhibiting the interaction between RANKL and its receptor RANK on alveolar macrophages, could plausibly decrease extracellular matrix degradation. We hypothesize that this mechanism, along with the patient's age [3] and a possible individual susceptibility (family history of a maternal aunt who died from supposed Idiopathic Pulmonary Fibrosis (IPF)), could contribute to the development of ILD.

In the clinical practice, these findings highlight the importance of exhaustive medical history, reviewing concomitant treatments and the temporal evolution of symptoms. This allows the search for a causal agent of the interstitial lung disease, whose control will enhance both the clinical and prognosis.

In conclusion, diffuse interstitial lung disease encompasses a heterogeneous group of pathologies that, in general, present a progressive clinical and functional evolution, as well as a poor prognosis. The described adverse effects of monoclonal antibodies such as denosumab should be taken into account, assessing the risk-benefit of their indication in each patient. This case highlights the importance of clinically recognising drug-induced manifestations,

since early withdrawal of the drug is usually associated with a clinical-prognostic improvement.

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How to cite this article: Prieto Maillo EC, Salazar Palacios AG, Martin Varillas AM, Fernandez Sanchez JL, Menendez SC, Sanchez Serrano AR. Non-Specific Interstitial Pneumonia in a Woman with Osteoporosis Treated with Denosumab. *J Biomed Res Environ Sci.* 2025 Jan 31; 6(1): 117-119. doi: 10.37871/jbres2062, Article ID: JBRES2062, Available at: <https://www.jelsciences.com/articles/jbres2062.pdf>