A Rare Case of Aromatase Inhibitor-Associated Temporomandibular Joint Degeneration in a Breast Cancer Patient

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ABSTRACT

Introduction: Aromatase inhibitors (AIs) are essential components of adjuvant therapy for hormone receptor-positive breast cancer. Although AI-associated musculoskeletal syndrome commonly affects peripheral joints, temporomandibular joint (TMJ) involvement remains exceptionally rare and may represent an underrecognized complication.

Case: A 59-year-old female with a history of hormone receptor-positive breast carcinoma treated with modified radical mastectomy, chemotherapy, radiotherapy and prolonged AI therapy presented with left TMJ pain and progressive limitation of mouth opening. Clinical examination demonstrated restricted mandibular movements with deviation toward the affected side. Laboratory investigations, including antinuclear antibody and rheumatoid factor, were negative and bone mineral density was within normal limits, reducing the likelihood of common inflammatory and metabolic causes. Panoramic radiography and cone beam computed tomography revealed marked degenerative changes, including condylar flattening, cortical erosion, reduced condylar height, joint space narrowing and intra-articular loose bodies suggestive of advanced degenerative joint disease with possible early ankylosis. In view of the prolonged AI exposure and exclusion of alternative aetiologies, a possible association with AI-induced TMJ degeneration was considered. The patient showed symptomatic improvement following conservative management.

Conclusion: This report highlights a rare presentation of possible aromatase inhibitor-associated TMJ degeneration and emphasizes the importance of obtaining a comprehensive medication history in patients presenting with unexplained TMJ symptoms. Increased awareness among oncologists, dentists, and radiologists may facilitate earlier diagnosis, appropriate management and continued adherence to essential endocrine therapy.

Keywords: Aromatase inhibitors, Breast cancer, Cone beam computed tomography, Degenerative joint disease, Temporomandibular joint.

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INTRODUCTION

Hormone receptor-positive breast cancer is the most common subtype of breast carcinoma and a major cause of cancer-related morbidity in women. Estrogen plays a critical role in tumour proliferation, making endocrine therapy a key component of treatment. Aromatase inhibitors (AIs) are widely used as adjuvant therapy in postmenopausal women, where they reduce recurrence risk by inhibiting aromatase, the cytochrome P450 enzyme responsible for peripheral conversion of androgens to estrogens, thereby markedly suppressing circulating estrogen levels.[1–3]

Despite their proven oncologic benefit, AIs are associated with musculoskeletal adverse effects. Estrogen depletion can lead to AI-associated bone loss with reduced bone mineral density, osteoporosis, and increased fracture risk. In addition, many patients develop aromatase inhibitor-associated musculoskeletal syndrome (AIMSS), characterized by arthralgia, stiffness, myalgia, and tendon disorders that may impair daily function and compromise treatment adherence.[1,4]

While generalized skeletal complications of AI therapy are well documented, involvement of specific joints is less clearly described. Reports linking aromatase inhibitor therapy to temporomandibular joint (TMJ) degeneration are extremely rare. Recognition of this potential association is clinically important because early identification of drug-related joint changes may facilitate appropriate management while allowing continuation of oncologic therapy.

The temporomandibular joint is a complex load-bearing synovial joint whose structural integrity depends on balanced cartilage metabolism and subchondral bone remodelling. Therefore, alterations in systemic hormonal

regulation, particularly estrogen deficiency, may influence TMJ homeostasis and contribute to degenerative changes.[5,6] This report describes a rare case of temporomandibular joint degeneration in a patient receiving aromatase inhibitor therapy for hormone receptor-positive breast cancer and highlights the need for multidisciplinary awareness among oncologists, radiologists, and dental specialists.

CASE

A 59-year-old female presented to the Department of Oral Medicine and Radiology with a chief complaint of pain in the left temporomandibular joint (TMJ) region associated with restricted mouth opening for the past month. The patient had a medical history of right breast carcinoma and had undergone a modified radical mastectomy in November 2018. Histopathological staging revealed a stage pT2N2aM0 tumour that was positive for estrogen and progesterone receptors and negative for human epidermal growth factor receptor 2 (HER2). The patient subsequently received eight cycles of chemotherapy followed by radiotherapy in June 2019 and was maintained on long-term endocrine therapy with letrozole. The patient had no history of diabetes mellitus or hypertension.

Considering the prolonged duration of aromatase inhibitor therapy and the development of musculoskeletal symptoms, the treating oncologist had advised discontinuation of letrozole and initiation of exemestane along with supportive medication prior to the patient's presentation. The patient had no history of trauma to the maxillofacial region.

Upon extraoral examination, restricted mouth opening and limited mandibular movements were observed. Tenderness was present over the left preauricular region. Intraorally, deviation of the mandible toward the affected side was appreciated. Based on the clinical findings, a provisional diagnosis of left TMJ disc displacement without reduction was considered. Differential diagnosis included TMJ ankylosis, left condylar hypoplasia, and degenerative joint disease. Vital parameters were stable. Laboratory investigations revealed an antinuclear antibody (ANA) level of 0.22 AU/mL (negative) and a rheumatoid factor level of 9.69 IU/mL (within normal limits), thereby reducing the likelihood of systemic autoimmune or inflammatory arthropathies. Bone mineral density assessment using dual-energy X-ray absorptiometry (DEXA) revealed a T-score of −0.5, consistent with normal bone mineral density according to the World Health Organization classification.

Panoramic radiography demonstrated morphological alterations involving the left temporomandibular joint, characterized by flattening of the condylar head, reduction in condylar height and irregularity of the cortical outline, findings consistent with degenerative joint disease [Fig.1].

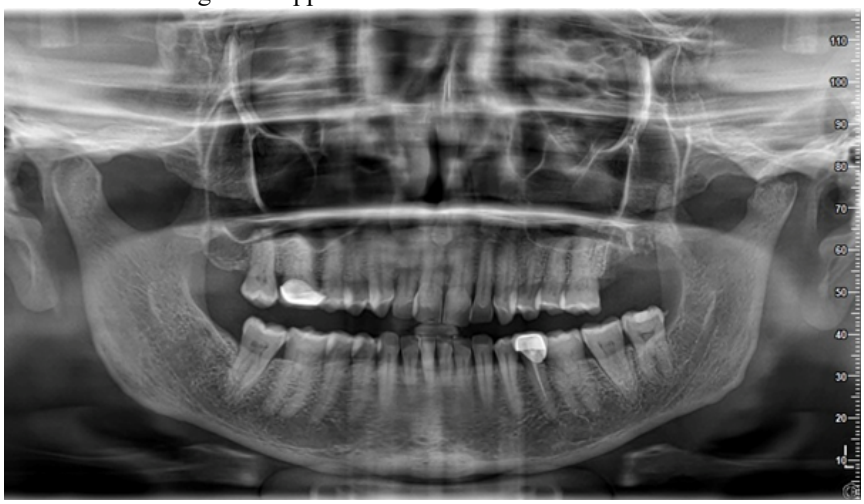


Figure 1: OPG shows flattening of the left condylar head with reduced condylar height and cortical irregularity is noted, consistent with degenerative joint disease.

Cone beam computed tomography (CBCT) demonstrated marked deformity of the left condylar head, characterized by cortical erosion, reduction in condylar height, and multiple intra-articular loose bodies (joint mice). The glenoid fossa demonstrated significant remodelling with joint space narrowing. Medial approximation of the condyle and glenoid fossa with loss of normal joint architecture was observed, suggesting advanced degenerative joint disease with possible early bony ankylosis [Fig.2].

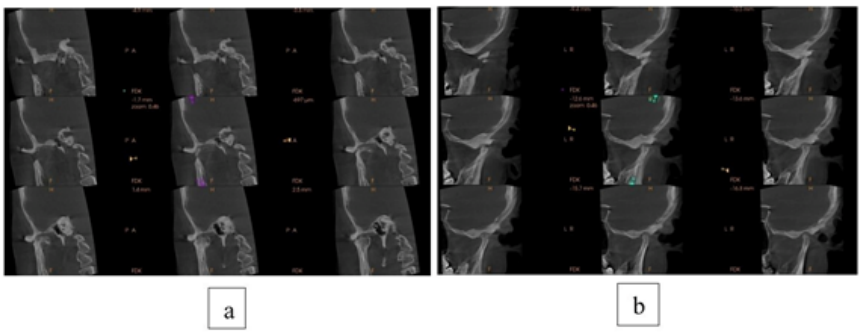


Figure 2. CBCT image of Left TMJ. (a) Coronal sections demonstrating joint space narrowing and intra-articular loose bodies, suggestive of advanced degenerative joint disease with possible early ankylosis on the lateral aspect of condyle

(b) Sagittal sections showing condylar flattening, cortical erosion, and reduced height with irregular cortical surface of the articular eminence.

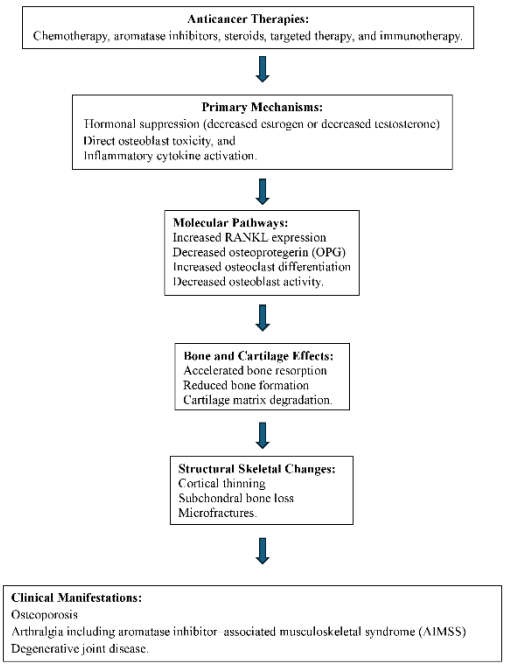
Considering the patient's prolonged history of aromatase inhibitor therapy, characteristic radiological findings, and the absence of other identifiable etiological factors, a possible association between aromatase inhibitor therapy and TMJ degeneration was considered. The patient was managed conservatively with indomethacin (NSAID), resulting in symptomatic improvement.

DISCUSSION

Aromatase inhibitors (AIs) are widely used as adjuvant endocrine therapy for hormone receptor-positive breast cancer because they suppress estrogen synthesis through inhibition of the aromatase enzyme. Although these agents significantly improve oncologic outcomes, estrogen depletion produces systemic skeletal effects that may adversely affect bone and joint physiology. Estrogen plays an essential role in skeletal homeostasis by regulating osteoclast and osteoblast activity; therefore, estrogen suppression can accelerate bone turnover and resorptive processes.[2,7] In addition to its skeletal role, estrogen contributes to joint integrity by maintaining the cartilage extracellular matrix and exerting anti-inflammatory effects through suppression of cytokines such as tumor necrosis factor-α and interleukin-1β.[2] These mechanisms explain why states of estrogen deficiency may predispose to degenerative joint changes.

Musculoskeletal complications associated with AI therapy are collectively described as aromatase inhibitor-associated musculoskeletal syndrome (AIMSS), which is a common adverse effect and an important cause of discontinuation of treatment. Approximately half of patients receiving AI therapy report new or worsening joint pain within the first year of treatment. Although the pathophysiology of AIMSS remains incompletely understood, estrogen deprivation is considered a major contributing factor. Estrogen receptors are present in articular cartilage, and experimental studies have shown that estrogen deficiency accelerates cartilage erosion and subchondral bone loss, whereas estrogen supplementation suppresses cartilage degeneration.[3]

Imaging studies of patients with AI-associated arthralgia have demonstrated structural abnormalities, including intra-articular fluid accumulation, tendon sheath thickening, and joint effusions, suggesting that these symptoms may reflect underlying structural joint pathology rather than representing merely subjective pain perception.[1] The mechanisms underlying anticancer drug-induced bone resorption are summarized in Flowchart 1.



Several medications are known to increase bone resorption and reduce bone mineral density by disrupting normal bone remodelling pathways (Table 1).

Author(s)	Year	Drugs Discussed	Key Finding
Teissonnière M. et al.[6]	2025	Glucocorticoids (dexamethasone, prednisone, prednisolone), hormone therapies, tyrosine kinase inhibitors, proteasome inhibitors	Anticancer therapies alter osteoblast and osteoclast activity leading to bone fragility and increased fracture risk.
Castañeda S. et al.[7]	2022	Aromatase inhibitors (anastrozole, letrozole, exemestane), chemotherapy agents, GnRH agonists, antiandrogens	Cancer treatments including endocrine therapy and chemotherapy increase risk of osteoporosis and bone loss.
Dhabhar B.[8]	2022	Aromatase inhibitors, GnRH agonists, chemotherapy agents (cyclophosphamide, methotrexate, 5-fluorouracil), radiotherapy	Endocrine therapy and chemotherapy increase osteoclastic activity and reduce bone mineral density.
Ottewell P.D. et al.[9]	2009	Doxorubicin, Zoledronic acid	Sequential administration influences bone microenvironment and osteoclast activity in cancer models.
Wilson K.L. et al.[10]	2024	Aromatase inhibitors (anastrozole, letrozole)	Aromatase inhibitors used in breast cancer therapy frequently cause musculoskeletal symptoms and bone loss due to estrogen depletion.
Kwon M. et al.[11]	2025	Aromatase inhibitors, tamoxifen, chemotherapy agents, anti-HER2 therapy	Aromatase inhibitors are associated with the highest risk of osteoporosis in breast cancer survivors.
Taxel P. et al.[12]	2018	Chemotherapy agents, aromatase inhibitors, androgen deprivation therapy, GnRH agonists, radiation therapy	Cancer treatments accelerate bone loss through hypogonadism and disruption of bone remodelling pathways.

Choi Y.J.[13]	**2024**	**Endocrine therapy, chemotherapy, radiotherapy, glucocorticoids, tyrosine kinase inhibitors, immune checkpoint inhibitors**	**Cancer therapies disrupt osteoblast and osteoclast activity leading to cancer treatment-induced bone loss.**
Mazziotti G. et al.[14]	**2010**	**Glucocorticoids, aromatase inhibitors, androgen deprivation therapy, thyroxine, anticoagulants**	**Multiple medications induce osteoporosis through impaired osteoblast function and increased bone resorption.**
Panday K. et al.[15]	**2014**	**Glucocorticoids, proton pump inhibitors, anticonvulsants, SSRIs, thiazolidinediones, aromatase inhibitors, androgen deprivation therapy**	**Many commonly prescribed medications alter bone remodeling and contribute to drug-induced osteoporosis.**
Zhu N. et al.[16]	**2024**	**Chemotherapy drugs (doxorubicin, epirubicin, cyclophosphamide, methotrexate, 5-fluorouracil, taxanes)**	**Chemotherapy can directly damage bone tissue or induce ovarian failure leading to estrogen deficiency and bone loss.**
Pfeilschifter J. & Diel I.J.[17]	**2000**	**Cancer treatments including chemotherapy, hormonal therapy and irradiation**	**Cancer treatment can lead to osteoporosis through direct bone toxicity and hormonal changes.**

Table 1: Studies Reporting Anticancer Drugs Associated with Bone Loss / Bone Resorption

The temporomandibular joint (TMJ) is a load-bearing synovial joint whose structural integrity depends on balanced bone remodelling and cartilage metabolism, which are strongly influenced by systemic sex steroid hormones, particularly estrogen. [3,7] Although musculoskeletal symptoms involving peripheral joints are well recognized in patients receiving aromatase inhibitors, involvement of craniofacial joints has rarely been described.

Previous reports of aromatase inhibitor-associated musculoskeletal syndrome have predominantly described involvement of peripheral joints, particularly hands, wrists, knees, shoulders, and hips, presenting mainly with arthralgia and stiffness.[1–4] In contrast, our patient developed unilateral temporomandibular joint degeneration characterized by condylar flattening, cortical erosion, reduced condylar height, joint space narrowing, and intra-articular loose bodies on CBCT following prolonged aromatase inhibitor therapy. This uncommon pattern of craniofacial joint involvement expands the spectrum of aromatase inhibitor associated musculoskeletal manifestations.

To date, published reports of aromatase inhibitor-associated TMJ degeneration remains extremely limited, making the present case unusual in demonstrating advanced structural TMJ changes on CBCT. Tomura et al. demonstrated the aromatase inhibition reduced 17β-estradiol levels, resulting in cartilage thinning, increased osteoclast activity, and accelerated degenerative changes of the TMJ in an animal model.[8]

In the present case, autoimmune causes were considered less likely based on negative serologic markers, and bone mineral density measured by DEXA scan was within normal limits, suggesting the absence of systemic osteoporosis and supporting a localized degenerative process. The onset of symptoms following prolonged AI therapy, together with the exclusion of other potential aetiologies, suggests a possible drug-related mechanism.

Although a definitive causal relationship cannot be established from a single case, the biological plausibility of estrogen-deficiency-mediated cartilage and bone changes, combined with clinical and imaging findings, supports a potential association between aromatase inhibitor therapy and TMJ degeneration. Recognition of this possible adverse effect is important because early identification may prevent misdiagnosis, facilitate appropriate management, and help maintain adherence to life-saving endocrine therapy.

CONCLUSION

This case highlights a rare possible association between long-term aromatase inhibitor therapy and temporomandibular joint degeneration. Clinicians should obtain a detailed medication history in patients presenting with unexplained TMJ symptoms. Early recognition may facilitate appropriate management while maintaining essential endocrine therapy. Further studies are required to establish a causal relationship.

Consent

Written informed consent was obtained from the patient for publication of this case report.

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