Osteoblastic flare phenomenon in a patient treated for disseminated non-tuberculous mycobacterial infection

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A previously healthy 64-year-old woman presented with a 2-month history of anterior chest pain. Physical examination disclosed a 3.5×6.0 cm tender mass protruding from her mid-sternum and crusted herpes zoster lesions on her left arm. CT revealed a 3.8×4.2×6.2 cm sternal mass with osteolytic destruction, mild bronchiectasis in the lingula of the left upper lobe and multiple osteolytic lesions over vertebrae and ribs (figure 1A–C). Bone scintigraphy revealed increased tracer uptake at skull, sternum, ribs, vertebrae and pelvic bones (figure 2A). Pathological findings of the sternal tumour biopsy were necrotising granuloma and the presence of acid-fast bacilli (figure 1D–E). The specimen and sputum were culture-positive for Mycobacterium avium complex. The patient was tested negative for HIV but positive for high-titre neutralising anti-interferon-γ (IFN-γ) autoantibodies, suggesting IFN-γ autoantibody-related disseminated non-tuberculous mycobacterial (NTM) infection.

The patient was treated with parenteral amikacin, oral azithromycin, rifampicin and levofloxacin but without ethambutol due to poor visual acuity. Despite treatment for 2 months, her chest pain persisted and occipital headache worsened. Brain MRI confirmed osteomyelitis at skull base and first and second cervical vertebra (figure 1F–G). She received single-dose rituximab as adjunct therapy 2 weeks later. Three months after antibiotic initiation, her symptoms improved but follow-up bone scintigraphy demonstrated increased intensity in existing lesions (figure 2B). Given the evidence of new bone formation (figure 1H) and clinical improvement, osteoblastic changes were attributed to the ‘osteoblastic flare phenomenon’ during effective treatment. Thus, she continued combined oral antibiotics. After 6-month antimicrobial therapy, the sternal mass disappeared and a bone scintigraphy revealed decreased uptake in the lesions (figure 2C).

The osteoblastic flare phenomenon, referring to increased osteoblastic activity in bone lesions after effective therapy, is known in patients with lung, breast and prostate cancer with bone metastasis.
Increased intensity in bone scintigraphy reflects the healing response to chemotherapy or hormone therapy. In patients with bone infectious diseases, although abnormalities on bone scintigraphy may persist even after resolution of infection as a result of ongoing remodelling in bone healing, such a dramatic flare phenomenon has not been reported.

Patients with IFN-γ autoantibody, mostly middle-aged East and Southeast Asian women, are susceptible to disseminated NTM and other opportunistic infections, such as herpes zoster. More than half of cases with IFN-γ autoantibody-related NTM infection had bony and articular involvement. In our case, the increased uptake may reflect bone repair in response to antimicrobial treatment. Of note, she also received rituximab, a chimeric monoclonal antibody directed against human CD20 on mature B cells and plasmablasts, which causes circulating B cell depletion to reduce autoantibody titers and improve IFN-γ signalling for infection control. Interestingly, IFN-γ plays an important role in bone homeostasis: promotes osteoblasts as well as inhibits osteoclasts. Therefore, the enhanced IFN-γ signalling following rituximab use may also have contributed to the paradoxical osteoblastic flare phenomenon.

In patients with disseminated NTM infection with bony involvement, the osteoblastic flare phenomenon should be considered during treatment. Serial images and clinical assessment can help clinician differentiate bone healing from disease progression.

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**REFERENCES**