Mogamulizumab-induced bone granuloma: a multicenter nationwide case series

Dear Editor, Mogamulizumab, a humanized monoclonal antibody directed against C-C chemokine receptor 4 (CCR4), has been approved by the Food and Drug Administration for treatment of relapsed or refractory Mycosis Fungoides (MF) and Sézary syndrome (SS). Although granulomatous skin rash is a common adverse event, this inflammation pattern has not been reported in other organs to date. We hereby provide the first case series of mogamulizumab-induced bone granulomatous infiltrates.

A nationwide survey was carried out by the Cutaneous Lymphoma French Study Group about patients developing bone granulomas during mogamulizumab treatment since the drug was marketed in 2018. Three cases were identified, two patients with SS and one with MF. Median age was 78 years (range 77 - 78). The median interval between mogamulizumab initiation and granulomatous lesion diagnosis was 18 months (range 15 - 25). All three patients displayed a complete disease response at the time of the adverse event.

Case 1 was a 78-year-old man with stage IVB SS diagnosed in 2017. He was successively treated with extracorporeal photopheresis, methotrexate and liposomal doxorubicin. He started mogamulizumab in October 2019, which allowed a complete response of the disease after six months. In November 2021, he experienced back pain and progressive paraplegia. Spinal MRI showed suspicious bone lesions from T3 to T5 with spinal cord compression and epidural infiltration (Fig. 1a). Spinal decompression surgery with laminectomy from T1 to T5 along with multiple bone and epidural biopsies were carried out and histopathological examination revealed a polymorphic lymphocytic and eosinophilic infiltrate with epithelioid and giant cells noncaseating granulomas (Fig. 1b,c). Case 2 was a 77-year-old woman with stage IVB SS diagnosed in 2020, treated with methotrexate then bexarotene. Mogamulizumab was initiated in January 2021 and allowed complete response in November 2021. In July 2022, a 18F-FDG PET-scan performed for follow-up showed multiple asymptomatic bone fixations of sternum, skull, cervical-dorsal spine, costal grill, and pelvis with SUVmax ranging from 4.0 to 7.9 (Fig. 1d). A sternal biopsy showed an inflammatory, partially granulomatous and follicular lesion with no evidence of tumoral infiltrate. Case 3 was a 78-year-old woman with stage IIIA MF diagnosed in...
2019, treated with methotrexate and UVB-phototherapy. She started mogamulizumab in June 2020 and reached complete response one year after. On October 2021, she presented with lower back pain lasting for several months. Spinal MRI revealed a bone infiltration on L4 with a histopathological pattern of epithelioid and giant cell granulomatous histiocytic infiltrate.

In all three cases, an exhaustive work-up ruled out infectious, tumoral and inflammatory differential diagnoses of granulomatous lesions. The bone histological pattern was strikingly similar in all cases and the search for a dominant T-cell clone by molecular biology (PCR-based assays) in granulomatous lesions was negative in cases 1 and 3 and not performed in case 2, thus virtually excluding localized progression of the underlying lymphoma. Cases 1 and 3 discontinued mogamulizumab while infusions were maintained in Case 2 every four weeks instead of two. Complete or almost complete spontaneous regression of bone lesions, without any additional medical treatment, was observed in all three cases within 3 to 6 months but case 1 suffered from neurological sequelae despite normalization of MRI and PET scan. To date, all three patients remain in complete response after a median follow-up time of 12 months even though cases 1 and 3 are still off treatment.

Mogamulizumab depletes both CCR4+ tumor cells and CCR4+ regulatory T-cells (Tregs), thus stimulating cytotoxic T-cell anti-tumor immunity but may consequently elicit autoimmune adverse events. Granulomatous skin rashes may occur in 20-30% of patients, mostly associated with complete and protracted responses. The underlying immunological mechanism of mogamulizumab-induced granuloma is not fully elucidated yet but might be related to direct CD163+ macrophage activation.

In some autoinflammatory setting such as sarcoidosis, granuloma formation and maintenance requires an activation of CD163+ macrophages and an inhibition of Tregs, both being induced by mogamulizumab. On another hand, bone and bone marrow are known to harbor a high density of resident CD163+ macrophages promoting bone repair and possibly participating in hematopoietic stem cell niches regulation. These data might be the conceptual basis of bone possibly being the second main location of mogamulizumab-induced granulomas after skin. Conversely, the rarity of bone or bone marrow involvement in MF and SS rules out the hypothesis of an immune reaction against tumor cells, although this cannot be formally excluded.
Although our experience is limited to the three reported patients, we suggest that bone lesions similar to those hereby described and identified in patients treated by mogamulizumab should be managed as follows: 1- Perform a bone biopsy to assess the presence of noncaseating granulomas and to rule out differential diagnoses of bone involvement (i.e. underlying lymphoma progression, metastasis, mycobacterial infection); 2- Perform a complete workup to eliminate other causes of granulomatosis, including sarcoidosis, tuberculosis and other infectious diseases (Treponemic Test, Tropheryma whippelii PCR, Coxiella burnetii serology); 3- In case of asymptomatic bone involvement, discuss mere monitoring as granulomas may regress spontaneously. In case of symptoms, systemic corticosteroid therapy seems to be the most appropriate treatment. In our case 1, surgery was primarily carried out but a prior knowledge of this new adverse event might have resulted in corticosteroids been considered as a first choice.

Our case series reports a new immune related adverse event and provides three important facts that need highlighting. First, granulomatous reactions do not only occur in the skin but can also affect bones. Second, although possibly transient and spontaneously regressive, such lesions may result in protracted functional disabilities owing to their location and the interest of systemic steroids in this setting remains to be established. Finally, they should not be mistaken with an unfavorable evolution of the underlying disease and seem instead to be associated with protracted responses.

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References


Figure Legends

**Figure 1. Histological and radiological features of the bone granulomas.** (a) Sagittal Short TI Inversion Recovery (STIR) and axial fat-suppressed T1 after gadolinium injection showing osseous involvement of T3-T4-T5 with epiduritis and cord compression (Case 1); (b, c) HES staining x5 (b) x20 (c) showing polymorphic lymphocytic and eosinophilic infiltrate with epithelioid noncaseating granulomas and giant cells, without lymphoid tumoral infiltration. Mycobacterial culture and *Mycobacterium tuberculosis* PCR were negative (Case 1, similar findings for Cases 2 and 3); (d) 18F-FDG PET-scan showing multiple bone fixations of the sternum, skull, cervical-dorsal spine, costal grill, and pelvis with SUVmax ranging from 4.0 to 7.9 (Case 2)
Figure 1
160x174 mm (x DPI)
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