M2-Polarized Macrophages Compose Lupus Vulgaris Arising from a Bacillus Calmette-Guérin Vaccination Site

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Abstract
Since bacillus Calmette-Guérin (BCG) is an attenuated strain of \textit{Mycobacterium bovis}, lupus vulgaris (LV) is reported as one of the rare complications after BCG vaccination, correlating with immunosuppression in the lesional skin. In this report, we describe a case of LV arising from the BCG vaccination site 22 years after vaccination. Interestingly, in the present case, granuloma cells were composed of M2-polarized macrophages. Our case might explain the contribution of M2-polarized macrophages to the biology of LV arising from a BCG vaccination site.

Introduction
Bacillus Calmette-Guérin (BCG) is an attenuated strain of \textit{Mycobacterium bovis} [1, 2]. Since BCG is usually considered to be avirulent, it is used for vaccination against tuberculosis in Japan for infants. On the other hand, a previous report suggested that delayed granuloma formation could develop at the BCG vaccination site, though the granuloma-composing cells...
were still unknown [1–5]. In this report, we describe a case of lupus vulgaris (LV) arising from a BCG vaccination site 22 years after vaccination which was composed of M2-polarized macrophages.

**Case Report**

A 64-year-old Japanese man visited our outpatient clinic with a 30-year history of pruritic erythema on the left arm. His condition had been treated in a private clinic with topical steroids, and he consulted our hospital for metastatic skin cancer. He had been given BCG vaccination into the left arm when 12 years old. On his initial visit, physical examination revealed erosive, asymptomatic nodules developing from a well-defined erythematous plaque on the left arm (fig. 1a). A biopsy specimen showed non-caseating granulomas with epithelioid cells (fig. 1b, c). Cultures on 2% Ogawa medium detected the *Mycobacterium tuberculosis* complex, leading to identification of *M. bovis* BCG strain Tokyo 172. From the above finding, we diagnosed this patient as LV arising from the BCG vaccination site. We administered oral isoniazid 300 mg per day for 3 months. Consequently the nodule disappeared, leaving a scar. One year after stopping isoniazid, there was no sign of relapsing nodules.

Since *M. bovis* BCG has been reported to induce M1 macrophages [6] and, in contrast, M2-polarized macrophages have been reported to contribute to tissue remodeling [7], we employed immunohistochemical staining for CD68 (a common myeloid marker), iNOS (M1 marker), CD163 and CD206 (M2 markers), as well as periostin, which was previously reported to stimulate CD163+ macrophages to produce...
various functional factors such as chemokines and matrix metalloproteins [14]. As expected, the granuloma cells were mainly composed of CD68+ myeloid cells, CD163+ macrophages and CD206+ cells. In addition, periostin was prominent in the stroma of granulomas, suggesting that periostin might stimulate CD163+ macrophages to establish the granuloma by producing various chemokines [14]. Since this report presents only a single case, further analysis of the mechanisms underlying this phenomenon may provide fundamental insights into the biology of LV arising from a BCG vaccination site. Such issues will need to be clarified in future investigations.

Statement of Ethics

The patient gave written informed consent.

Disclosure Statement

The authors declare no conflict of interest.

References

Fig. 1. a Erosive, asymptomatic nodules developing from a well-defined erythematous plaque on the left arm. b, c Non-caseating granulomas with epithelioid cells were detected throughout the dermis. Original magnification: ×100 (b), ×400 (c).
Fig. 2. Paraffin-embedded tissue samples were deparaffinized and stained with anti-CD68 Ab (a), anti-iNOS Ab (b), anti-CD163 Ab (c), anti-CD206 Ab (d) and anti-periostin Ab (e, f). The sections were developed with liquid permanent red. Original magnification: ×100 (a–e), ×200 (f).