Dermatology Practical & Conceptual

# M2 Polarization May Contribute to Formation of Granulomatous Dermatitis in Progression of Myelodysplastic Syndrome to Acute Myeloid Leukemia

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## Introduction

Myelodysplastic syndromes (MDS) are a group of clonal hematopoietic disorders which may convert into acute myeloid leukemia (AML). Cutaneous manifestations are uncommon but can be the first clinical sign of disease progression. Herein, we report a MDS patient who abruptly developed florid foreign body granulomas when progressing to AML.

## Case Presentation

A 73-year-old Asian male with MDS-excess blasts-2 (MDS-EB-2) presented with multiple scattered, painful erythematous to violaceous nodules over the face, chest, abdomen, and anterior aspect of limbs for 1 week (Figure 1, A and C). Associated symptoms included fever and malaise. Laboratory tests revealed progressing pancytopenia with increased blast cells. Gross examination of the skin biopsy specimen revealed black stone-like materials (Figure 1B). According to the patient, he had survived a mining accident 43 years ago, leaving multiple asymptomatic subcutaneous blue-gray papules over the face, trunk, and anterior aspect of extremities. Histopathological examination revealed foreign body granulomas with black substances in the deep dermis and subcutis infiltrated with multinucleated giant cells, histiocytes and lymphocytes (Figure 2A). No blasts or neoplastic cells were noted. Immunohistochemical staining was negative for CD34, lysozyme, CD117,

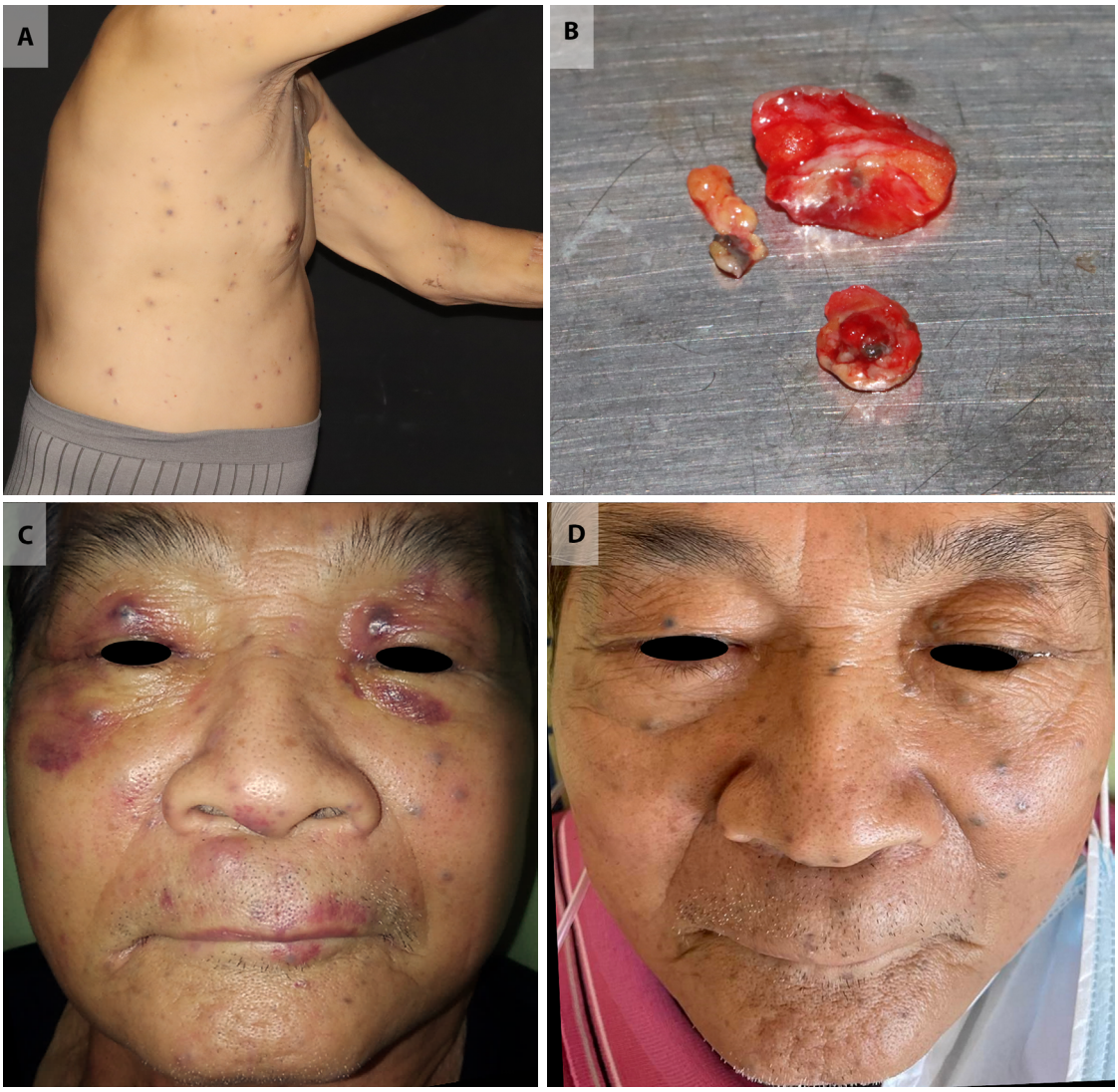


**Figure 1.** Clinical images of foreign bodies and treatment response of the patient. (A) Multiple scattered, erythematous, violaceous, and painful nodules over face, chest, abdomen, and anterior aspect of 4 limbs. (B) Black stone-like foreign bodies. (C) Cutaneous presentation before systemic corticosteroid treatment. (D) Lesions resolved after systemic corticosteroid treatment.

and myeloperoxidase (Figure 2B). The infiltrated cells were composed of CD68-positive cells (Figure 2C) and numerous CD163-positive cells (Figure 2D). Tissue cultures were all negative. Intravenous methylprednisolone 80 mg/day was administered and the erythematous granulomatous nodules resolved within 1 week, reverting to its original blue grey appearance (Figure 1D). Unfortunately, the patient progressed into AML within 1 month and died shortly after.

## Conclusions

Granulomatous dermatitis, including cutaneous sarcoidosis, granuloma annulare and necrobiosis lipoidica have all been reported to herald the onset of MDS or precede MDS progression to AML [1-3]. We present a case of florid foreign body granulomatous reaction associated with MDS progression to AML. M2 macrophages play an important role in granuloma formation [4], which may be the link between the two phenomena. Immunohistochemical staining of the foreign body granulomas showed infiltration of $CD163^{+}$ M2 macrophages with elevated CD163/CD68 ratio. As for MDS transformation to AML, recent reports have shown the importance of M2-like tumor-associated macrophages (TAMs) with elevated CD163/CD68 ratio [5]. The macrophages in the bone marrow of high risk MDS patients were shown to polarize to M2 and not to M1 macrophages leading to insufficient antitumor effect [6]. Therefore, we hypothesized that the increased M2 macrophage population in the present

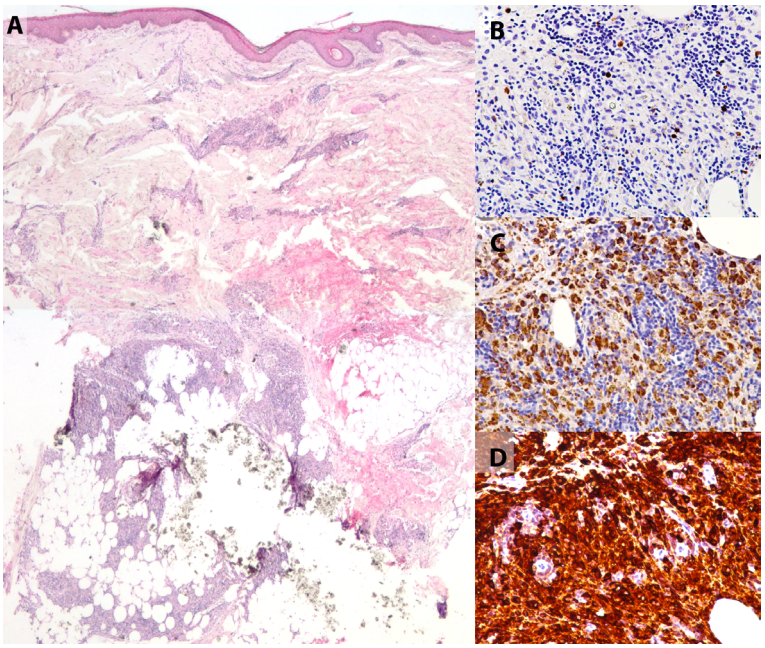


**Figure 2.** Histopathology and immunohistochemical staining of skin biopsy. (A) Histopathological examination revealed retained foreign bodies in the deep dermis and subcutis infiltrated with multinucleated giant cells, histiocytes and lymphocytes (hematoxylin and eosin, original magnification ×20). (B) Cells in foreign body granulomas showed negative for myeloperoxidase (immunohistochemistry for myeloperoxidase, original magnification ×200). (C) Multiple scattered $CD68^+$ macrophages in foreign body granuloma (immunohistochemistry for CD68, original magnification ×200). (D) A large number of $CD163^+$ macrophages in foreign body granuloma (immunohistochemistry for CD163, original magnification ×200).

case was due to M2 polarization in the bone marrow. These M2 macrophages were then attracted by the foreign body in the skin, thus leading to acute foreign body granulomatous reaction.

In summary, we present a case of a MDS patient with subsequent progression to AML associated with an abrupt appearance of diffuse foreign body granulomas. Predominant M2 macrophages in the foreign body granulomas may correlate to M2 polarization in the bone marrow of high risk MDS or AML patients. Therefore, it is important to recognize that the granulomatous dermatitis in MDS patients may associate with disease progression and poor prognosis.

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