SHORT COMMUNICATION

Nodal Marginal Zone Lymphoma with Eosinophilic Dermatosis of Haematologic Malignancy: A Case Report

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Eosinophilic dermatosis of haematologic malignancy (EDHM) is a rare cutaneous disorder associated with haematopoietic malignancies. It is characterized by non-specific skin lesions with a variety of manifestations, including erythema, papules, nodules, and occasionally vesicles and urticaria-like eruptions. The condition is commonly accompanied by intense pruritus and has a high recurrence rate (1). Among haematologic malignancies associated with EDHM, chronic lymphocytic leukaemia (CLL) is the most prevalent, followed by non-Hodgkin lymphoma, acute leukaemia, multiple myeloma, and myeloproliferative disorders (2). Its association with nodal marginal zone lymphoma (NMZL), a low-grade B-cell non-Hodgkin lymphoma, has been rarely documented. Two prior cases of NMZL-associated cutaneous eruptions were described as hypersensitivity to mosquito bites (HMB) (3, 4). Herein, we present the first well-characterized case of EDHM in association with NMZL, supported by clinical, histopathological, and therapeutic evidence.

CASE REPORT

A 67-year-old man presented with a 2-year history of progressive lymphadenopathy in the cervical and axillary regions, accompanied by generalized pruritic erythematous papules and vesiculopapular lesions. The patient denied systemic symptoms and had no significant medical or family history. Initial misdiagnosis as eczema led to an unsuccessful therapeutic response. Physical examination revealed multiple palpable masses in both sides of the neck, axillae, and groin. Dermatological examination showed erythematous papules, nodules with crusts, bullae, and non-blanching purpura on the extremities (**Fig. 1**).

Laboratory tests revealed marked eosinophilia (9.2%), and elevated levels of ferritin (537.00 ng/mL), interleukin-2 receptor (4929.0 u/mL), and erythrocyte sedimentation rate (56.0 mm/h). Autoimmune panels, BP-180, and EBV-DNA were negative. Histopathological examination of papules from the right forearm revealed multilocular intraepidermal and subepidermal blisters, dense lymphoid and eosinophilic infiltration around small blood vessels in the dermis and subcutis, and eosinophilic degranulation with flame figures. Some lymphocytes exhibited enlarged, darkly stained nuclei (Fig. S1A). Immunohistochemical analysis revealed that the infiltrating lymphoid cells expressed CD3, CD5, and CD7, with a CD4:CD8 ratio of approximately 5:1. Approximately 10% of the cells were CD30-positive. TIA-1, GrB, CD56, and CD20 were negative, while Ki-67 was expressed in approximately 20% of cells. *In situ* hybridization for EBER1/2 was negative (Fig. S1B). T-cell receptor (TCR) gamma gene rearrangement analysis did not detect a clonal T-cell population. Direct immunofluorescence showed linear deposition of IgM and C3. Lymph node biopsy

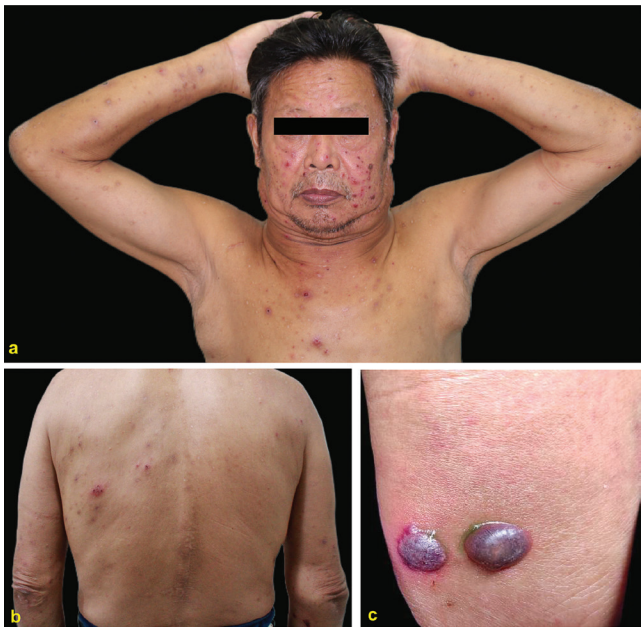

Fig. 1. Clinical photographs. (A) Multiple erythematous papules and nodules distributed across the face, neck, and upper extremities, with concurrent enlargement of cervical and axillary lymph nodes. (B) Widespread erythematous papules distributed across the back. (C) Haemorrhagic bullous lesions scattered on the left ankle.

confirmed a diagnosis of NMZL, characterized by small B-cell proliferation expressing CD20, CD23, and CD43, and light chain restriction. Molecular testing showed IGH and IGK gene rearrangements without MYD88 or BRAF mutations. EBV *in situ* hybridization was also negative.

The patient's skin lesions demonstrated minimal clinical improvement with antihistamines and topical corticosteroids. Subsequently, he received systemic treatment for NMZL using the R–B protocol (rituximab and bendamustine). At the 1-year follow-up, his skin lesions and lymphadenopathy in the cervical and axillary regions had almost resolved (**Fig. 2**).

DISCUSSION

In 1965, Weed first described severe skin reactions in patients with CLL, attributing them to an exaggerated hypersensitivity reaction to insect bites (5). However, subsequent studies showed that most patients lacked a confirmed history of insect exposure, and the lesion morphology, seasonal variation, and histopathological features were inconsistent with true insect bite reactions (6). Consequently, more descriptive and neutral terminology such as "insect bite-like reaction" (IBLR) was adop-

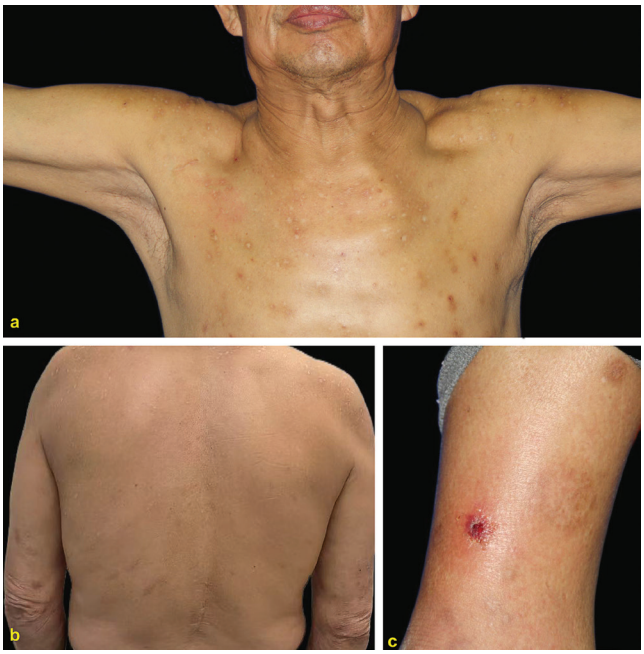

Fig. 2. Follow-up clinical photographs. After treatment, the skin lesions of the (A) face, neck, and upper extremities, cervical and axillary lymph nodes, (B) back, and (C) lower limbs were significantly improved.

ted. In 2012, Farber et al. introduced the term EDHM to emphasize its paraneoplastic nature and immunopathogenesis, given its strong correlation with haematologic malignancies and unique immunohistopathological characteristics (7). By 2020, over 200 EDHM cases had been reported, the majority of which were associated with CLL (77%) and other types of lymphoma (16.5%) (8). EDHM associated with NMZL is extremely rare. Two previously reported NMZL cases were documented as HMB rather than as EDHM (3, 4). Notably, HMB has been reclassified within the spectrum of EBV-positive T/NK-cell lymphoproliferative disorders (EBV-T/NK-LPD), in which EBER1/2 *in situ* hybridization is consistently positive, reflecting EBV-driven proliferation of cytotoxic T or NK cells (9). In contrast, EBER was negative in our patient, and the dermal infiltrate consisted predominantly of CD4-positive T cells rather than cytotoxic CD8-positive or NK cells, effectively excluding EBV-associated HMB or other EBV-T/NK-LPDs. Histopathological examination of our case revealed prominent flame figures – a feature not previously reported in NMZL-associated HMB cases – reflecting the deposition of eosinophil-derived major basic protein along collagen bundles. As highlighted by Leiferman and Peters (10), flame figures are not specific to a single disease; rather, they indicate intense eosinophil degranulation and tissue injury. The presence of flame figures in the absence of insect exposure supports an endogenous, immune-mediated mechanism characteristic of EDHM, rather than an exogenous hypersensitivity reaction. Moreover, the eruption was refractory to corticosteroids and antihistamines but responded fully to rituximab–bendamustine targeting the underlying lymphoma, thereby confirming its paraneoplastic nature. To date, EDHM has not been reported in association with other marginal zone lymphoma (MZL) subtypes, such as splenic or extranodal MZL. Therefore, our case probably represents the first well-documented instance of EDHM clearly associated with NMZL, expanding the clinicopathologic spectrum of this entity within the MZL family.

The patient's cutaneous manifestations and histopathology necessitated consideration of several differential diagnoses, including cutaneous T-cell lymphoma (CTCL), insect bite reaction, Wells syndrome, and autoimmune blistering disease. CTCL was excluded based on the absence of epidermotropism or Pautrier microabscesses – hallmark features of CTCL – together with retention of CD7 expression in the T-cell population and the lack of TCR gamma gene rearrangement. In addition, the mild cytologic atypia observed was considered reactive, likely reflecting lymphocytic activation secondary to intense inflammation rather than true neoplastic transformation. An insect bite reaction was considered unlikely due to the absence of insect exposure, seasonal recurrence, and the atypical distribution and chronicity of the lesions. Wells syndrome was considered given the presence of eosinophilic infiltrates and flame figures; however, the recurrent, widespread pruritic papulovesicular eruptions, together with large nodular lesions on the neck and axillae temporally associated with NMZL, favoured a diagnosis of EDHM. Given the patient's advanced age and the presence of vesicular and haemorrhagic vesicles, autoimmune blistering diseases such as bullous pemphigoid were initially considered. However, the coexistence of polymorphic lesions – including erythematous papules, crusted nodules, and non-blanching purpura – together with histopathological findings of dense eosinophil-rich inflammatory infiltrates extending throughout the full thickness of the dermis, are atypical for bullous pemphigoid. Direct immunofluorescence showed weak linear IgM and C3 deposition along the dermoepidermal junction; although such findings are uncommon in EDHM or HMB, the absence of IgG deposition suggests that the C3 accumulation likely represents secondary complement activation due to local tissue inflammation rather than a primary autoimmune process, consistent with a non-specific reactive phenomenon. Furthermore, BP-180 testing was negative, collectively excluding autoimmune blistering disease and supporting EDHM as the most plausible diagnosis.

Although the precise pathogenesis of EDHM remains unclear, current evidence suggests a Th2-skewed immune dysregulation, with elevated cytokines such as IL-4 and IL-5 that promote eosinophil proliferation and activation (11). EBV testing was negative, effectively excluding EBV involvement in this case. No standardized treatment for EDHM exists. Conventional therapies such as antihistamines and corticosteroids often provide limited

relief. Our patient showed marked improvement only after systemic treatment targeting the underlying lymphoma with rituximab and bendamustine, underscoring the role of EDHM as a paraneoplastic manifestation. Recent advances in the understanding of its immunopathogenesis have led to the use of biologic agents such as dupilumab (an IL-4 receptor antagonist) and omalizumab (an anti-IgE antibody) in refractory cases, which have demonstrated promising efficacy (12, 13).

In conclusion, this well-characterized case of NMZL-associated EDHM highlights the importance of recognizing EDHM as a distinct entity to distinguish it from insect bite hypersensitivity reactions. Raising awareness is crucial for facilitating early diagnosis and guiding appropriate management of the underlying hematologic malignancies, thereby potentially improving patient outcomes.

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