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Letter to Editor

Skin erythema with leukocytoclastic vasculitis and elastophagocytosis as the presenting features of an underlying myelodysplastic syndrome

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Myelodysplastic syndrome (MDS) is a clonal hematopoietic stem cell disease characterized by cytopenia, dysplasia in one or more of the major myeloid cell lines, ineffective hematopoiesis, and increased risk of development of acute myeloid leukemia [1]. The majority of patients with MDS present with symptoms related to cytopenia [1]. However, cutaneous manifestations have also been reported in patients with MDS [2, 3]. Different skin lesions have been documented, and are divided into specific and non-specific [2, 3]. Specific lesions are uncommon and characterized by the presence of neoplastic cells in the skin, which are referred to as leukemia cutis and indicate blastic transformation from MDS [4]. Non-specific lesions are common and include drug eruption and immunological impairment, such as infection or autoimmune diseases [2]. The most common skin lesions associated with MDS are Sweet's syndrome and leukocytoclastic vasculitis [2, 3, 5].

Elastophagocytosis, characterized by the presence of phagocytosis of dermal elastic material by histiocytes, is a non-specific finding, and is observed in various skin conditions, such as actinic granuloma, granuloma annulare, sarcoidosis, lichen sclerosus, and granulomatous mycosis fungoides [6-10]. Although only a few cases of granulomatous dermatitis as the presenting features of underlying hematological malignancies have been reported [11], the presence of elastophagocytosis associated with an underlying MDS has not been documented. Herein, we report the first documented case of skin erythema with leukocytoclastic vasculitis and elastophagocytosis as presenting features of an underlying MDS and review the literature.

A 67-year-old Japanese female with past history of angina pectoris and osteoarthritis of the knee joint presented with erythema in the bilateral forearms and elbows. She had experienced fatigue and loss of appetite for 3 months before her visit to our hospital. Physical examination revealed a relatively well-circumscribed annular erythema in the bilateral forearms and elbows. Biopsy was performed from the annular erythema of the elbow, and bone marrow aspiration was added according to the results of laboratory test of the peripheral blood.

Laboratory test revealed anemia, thrombocytopenia (red blood cells 2.83 x 10^{12}/L (range 3.8-4.8), hemoglobin 8.6 g/L (11.3-15.0), white blood cells 10.3 x 10^{9}/L (3.0-8.0), platelet 37 x 10^{9}/L (150-400)) and elevated C-reactive protein (16.21 mg/dL (<0.3)). Moreover, blastic cells were detected in the peripheral blood (3.3%). Autoantibodies, such as anti-double-strand DNA, SS-A, SS-B, Sm, and RNP, were negative.

Histopathological study of the biopsy specimen revealed leukocytoclastic vasculitis (**Figure 1A**, **1B**). Infiltrating lymphocytes and neutrophils were observed around the small vessels of the superficial dermis (**Figure 1A**). There was nucle-

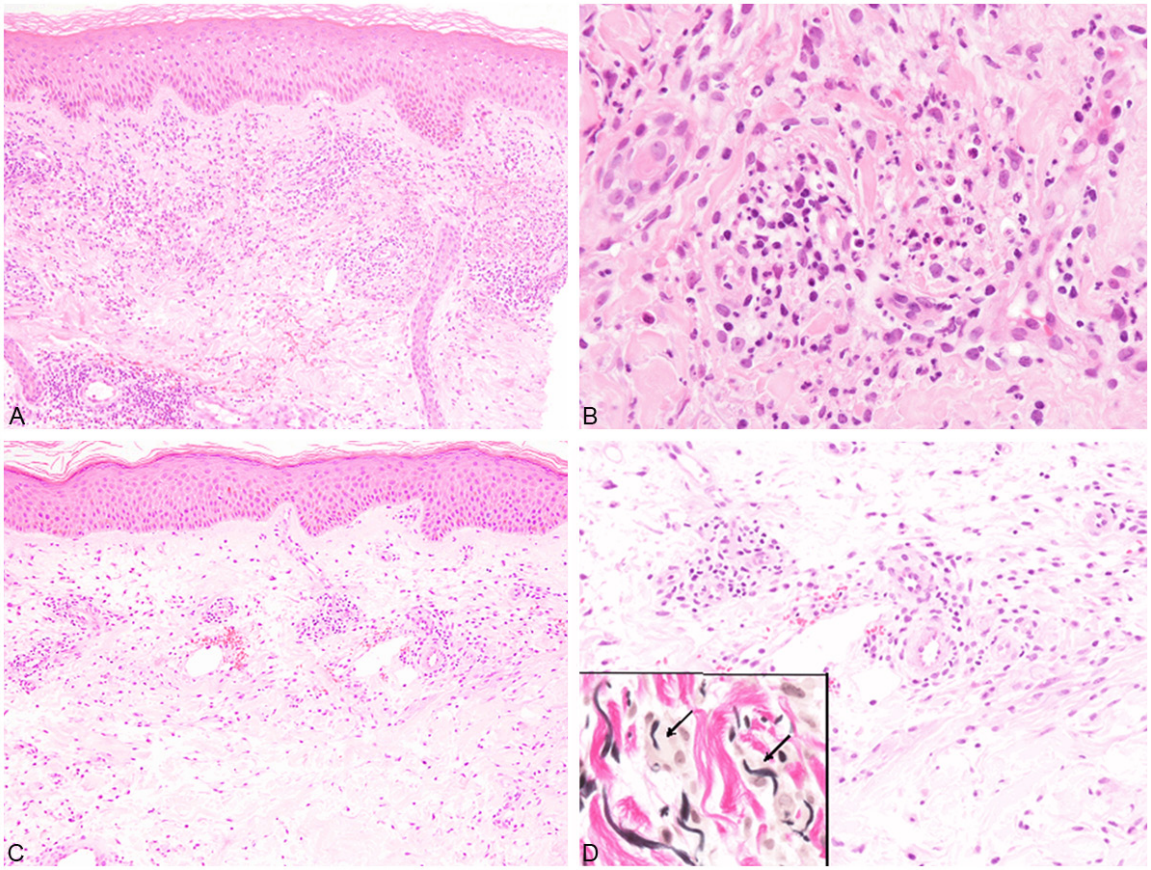

Figure 1. Histopathological features of the knee showing leukocytoclastic vasculitis and elastophagocytosis. A: Lymphocytes and neutrophils have infiltrated around the vessels of the superficial dermis. HE, x 100. B: Nuclear dust and fibrinoid necrosis of the vessels are observed. HE, x 400. C: Superficial perivascular lymphocytic infiltration and interstitial histiocytic infiltration. HE, x 100. D: Histiocytic infiltration into the superficial dermis. HE, x 400. Elastica van Gieson staining clearly showing elastophagocytosis (inset, x 400).

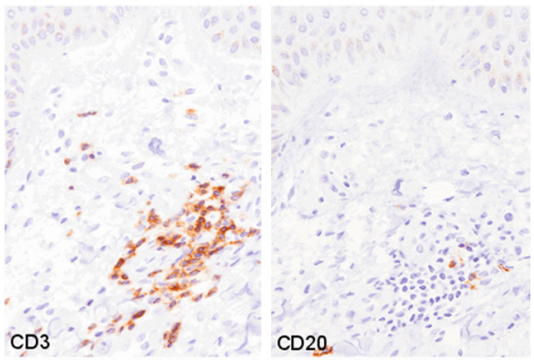

Figure 2. Immunohistochemical findings of the knee. CD3-positive lymphocytes are predominant, and a few infiltrating CD20-positive T-cells are observed, x 400.

ar dust around the small vessels, and fibrinoid necrosis of the small vessels was also noted (**Figure 1B**). In addition to the above-mentioned features of leukocytoclastic vasculitis, histiocyte infiltration was found around the small vessels and interstitially in the superficial dermis (**Figure 1C**, **1D**). Elastica van Gieson staining clearly demonstrated phagocytosis of elastic fibers by histiocytes (**Figure 1D**, inset). No infiltration of immature granulocytes or blastic cells was present in the skin.

Immunohistochemical studies were performed using an autostainer (Ventana) by the same method as previously reported [12-16]. Most of the infiltrating lymphocytes were CD3-positive, and only a few CD20-positive cells had infiltrated (**Figure 2**). No CD34- and c-kit-positive immature myeloid cells were observed in the skin.

The bone marrow aspiration specimen demonstrated hypercellularity with an increase of immature myeloid cells and decrease of normal

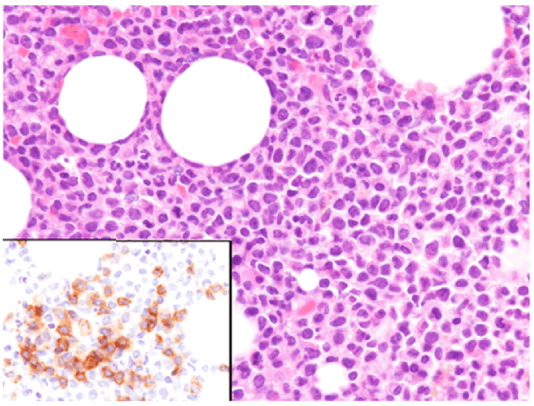

Figure 3. Histopathological and immunohistochemical features of the bone marrow. Hypercellular bone marrow with increase of blastic cells. HE, x 400. Most of the blastic cells are positive for c-kit. x 400.

hematopoietic cells (**Figure 3**). Blasts were increased (22.2%), and dysplastic changes were observed in both the myeloid series and megakaryocytes. Immunohistochemically, these blastic cells were positive for myeloperoxidase and c-kit (**Figure 3**, inset), but negative for CD34.

Accordingly, an ultimate diagnosis of MDS (refractory anemia with excess blast with transformation (RAEB-t)) according to the FAB Classification (AML with maturation by WHO Classification) was made.

It has been recognized that the prevalence of skin lesions associated with MDS is approximately 10-20% [2, 3]. Dalamaga *et al*. studied a cohort of 84 newly diagnosed MDS patients to assess cutaneous manifestation present at the time of diagnosis and during 1 to 3 years of follow-up [3]. Twenty-one patients (25%) developed skin lesions; the most common lesions were leukocytoclastic vasculitis (6 cases) and photosensitivity not associated with autoimmune disease (6 cases). The development of cutaneous manifestation generally preceded or was concomitant with MDS diagnosis in their series. Moreover, they concluded that the presence of skin manifestation was a significant predictor of the high-risk MDS group [3]. Farah *et al*. also studied a cohort of 157 cases of primary MDS [2]. Fifteen patients (9.55%) experienced skin lesions; Sweet's syndrome was the most common skin manifestation (7 cases), followed by specific lesions (5 cases) and vasculitis (2 cases) [2]. Therefore, the skin lesion of the present case must be differentiated from Sweet's syndrome, which is one of the most common skin manifestations of MDS [2]. Sweet's syndrome, also referred to as acute febrile neutrophilic dermatosis, is a skin condition characterized by the following features: tender erythematous plaque, nodules, or papules; prodromal symptoms such as fever, malaise, or arthralgia; and diffuse infiltrate of neutrophils in the dermis [17]. Diagnostic criteria of this syndrome has been proposed, and the major criteria includes i) abrupt onset of tender or painful erythematous or violaceous plaques or nodules, and ii) predominantly neutrophilic infiltration in the dermis without leukocytoclastic vasculitis [17]. In the present case, the skin biopsy from the erythema clearly demonstrated leukocytoclastic vasculitis, therefore, this case can be differentiated from Sweet's syndrome. However, it has been well-recognized that Sweet's syndrome is associated with malignancy (27 of 77 cases were associated with malignancy in the case series reported by Rochet *et al*.) [17]. The most common malignancy in Sweet's syndrome is of hematologic origin, and moreover, MDS is the most common cause in malignancy-associated Sweet's syndrome. Therefore, it is important to evaluate the underlying malignancy in patients with Sweet's syndrome.

Leukocytoclastic vasculitis is a clinicopathological entity, characterized clinically by palpable purpura, and pathologically by acute necrotizing inflammation of the small vessels in the dermis [18]. This process is associated with many diseases or conditions, including connective tissue diseases, bacterial and viral infections, drugs, and malignancies, in approximately 50% of cases with leukocytoclastic vasculitis, no such associations are found [18]. Leukocytoclastic vasculitis can also occur in association with malignant disorders, especially hematopoietic malignancies [19-21]. Fain *et al*. analyzed 60 cases of malignancy-associated vasculitis [19]. The most common form of vasculitis was leukocytoclastic vasculitis, (45%) and one-third of them were associated with MDS, lymphoid malignancies, and solid tumors [19]. The pathogenic association between malignancy and leukocytoclastic vasculitis has not been resolved, however, immune dysregulation or dysfunction caused by malignancy has been assumed to play an important role. One hypothesis is that neoplastic cells may produce cytokines, leading to a massive inflammatory

state. Recent study demonstrated that interferon regulatory factor-1, one of the cytokine transcription factors, has been associated with the development of autoimmune manifestations in MDS [22].

Elastophagocytosis is a non-specific tissue reaction pattern associated with inflammatory process of the skin, and is observed in various skin conditions [6-10]. Although some hypotheses have been postulated, the mechanism for the occurrence of elastopahgocytosis is still unclear. Cell-mediated immune response to elastic fibers is thought to be associated with this condition [23]. It has been proposed that cytokines produced by lymphocytes may directly promote phagocytosis of elastic fibers [24]. Moreover, Loo *et al*. reported a case of Sweet's syndrome with elastopahgocytosis [25]. They speculated that elastase, collagenase and other potent mediators of inflammation released by neutrophils were responsible for the elastolysis in their case [25]. In the present case, both leukocytoclastic vasculitis and elastopahgocytosis may have occurred in the setting of immune dysregulation or dysfunction caused by an underlying MDS.

In conclusion, we report the first documented case of skin erythema with leukocytoclastic vasculitis and elastophagocytosis as the presenting features of an underlying MDS. It is well recognized that leukocytoclastic vasculitis and Sweet's syndrome are skin manifestations of MDS. This case clearly demonstrated that elastophagocytosis can be another skin manifestation of MDS, therefore, further investigations are required to establish a possible cause in cases with elastophagocytosis of unknown etiology.

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