

# Myelodysplastic Syndrome and Sweet's Syndrome Are Associated with a Mutation in Isocitrate Dehydrogenase 1

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**Abstract.** *Background: Sweet's syndrome (SS) is a febrile neutrophilic dermatosis that has been clinically linked to hematological malignancies, particularly myelodysplastic syndrome (MDS), in a number of case series. Many epigenetic changes underlying MDS have been identified, such as a mutation in the isocitrate dehydrogenase 1 (IDH1) gene, which causes DNA hypermethylation and alteration of a number of genes that lead to leukemogenesis. However, the pathogenesis of malignancy-associated SS is unknown. Case Report: We present two patients who were diagnosed with SS and concomitant IDH1-mutated MDS. Immunohistochemical staining of their skin lesions showed neutrophils diffusely positive for the IDH1 mutation. Conclusion: These cases demonstrate that IDH1 mutation may be implicated in the pathogenesis of malignancy-associated SS. Future investigation to elucidate this pathway is warranted. Establishing this molecular link can provide an earlier identification of patients with SS who are also at increased risk for developing MDS.*

Sweet's syndrome (SS) was first described in 1964 as an acute febrile neutrophilic dermatosis. It presents clinically with tender nodules that consist histopathologically of a heavy neutrophilic infiltrate in the subcutis as well as dermis (1). A variant of this condition called histiocytoid SS has a similar clinical presentation and includes infiltration of immature myeloid cells that morphologically resemble histiocytes and stain positively for myeloperoxidase (2). SS has been

clinically associated with myeloid malignancies including acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS) (3-8). The pathophysiology of malignancy-associated SS is largely unknown and there are no established guidelines regarding the treatment of this condition (9). Typically, SS responds to treatment with corticosteroids and treatment of the underlying myeloid malignancy.

MDS is a heterogeneous group of hematological disorders that are characterized by cytopenia due to ineffective hematopoiesis and confer an increased risk of development of AML. Isocitrate dehydrogenase (IDH) proteins are homodimeric enzymes that are involved in important cellular processes of histone and DNA modification as well as the cellular response to hypoxia (10). Recurring *IDH1* gene mutations have been detected in 20% of adults with AML and 5% of adults with MDS (11, 12). The *IDH1* and *IDH2* enzymes, under normal circumstances, catalyze the oxidative decarboxylation of isocitrate to  $\alpha$ -ketoglutarate ( $\alpha$ -KG). Mutant IDH enzymes however, catalyze the reduction of  $\alpha$ -KG to the onco-metabolite D-2-hydroxy-glutarate (D-2HG), resulting in numerous epigenetic aberrations that include DNA hypermethylation and altered expression of many important genes, leading to leukemogenesis (11, 13).

A clinical association between SS and MDS has been described in a number of reports. However, the molecular pathogenesis underlying this presentation has not yet been elucidated (7, 14). Here we present two patients with SS and underlying *IDH1*-mutated MDS whose skin biopsies stained positively for *IDH1*-mutant neutrophils. We discuss *IDH1* mutation as a possible molecular link between these two syndromes that can be treated by targeted therapy such as the IDH inhibitors.

## Case Reports

**Case 1:** A 50-year-old man presented with multiple subcutaneous nodules on his chest, upper and lower extremities

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**Key Words:** Sweet's syndrome, myelodysplastic syndrome, *IDH1* mutation.

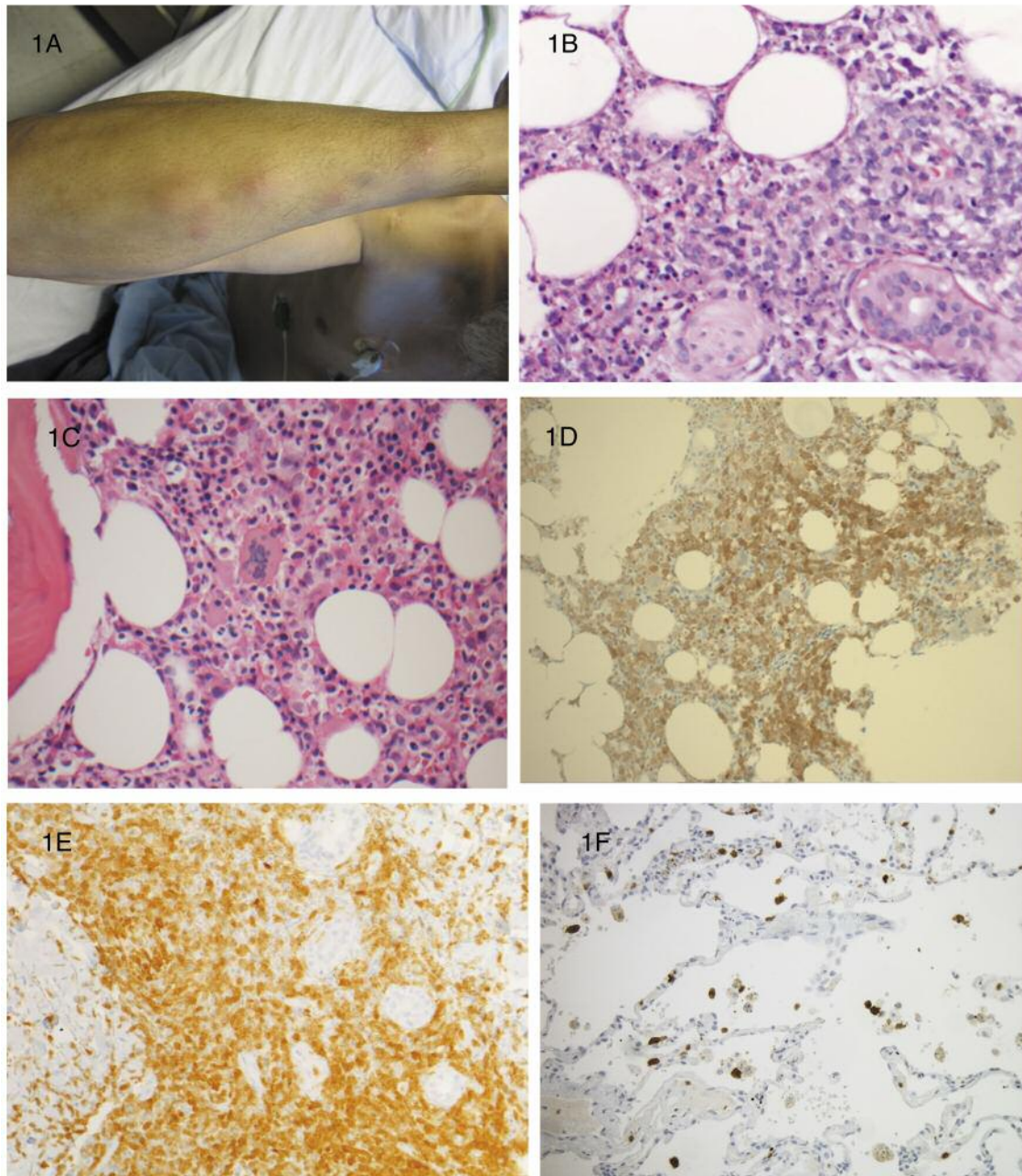


Figure 1. Biopsy findings in case 1. A: Tender, erythematous and edematous subcutaneous nodules on the dorsum of patient 1 arm. These nodules were present on his chest, upper and lower extremities. B: Skin nodule biopsy showing an infiltrate composed of many neutrophils, including immature neutrophils resembling histiocytes, which was confirmed by myeloperoxidase and CD68 stains (not shown). Hematoxylin and Eosin, magnification 40 $\times$ . C: Bone marrow biopsy showing slightly hypercellular marrow and with a dysplastic megakaryocyte. D: Immunohistochemical (IHC) staining for the isocitrate dehydrogenase 1 (IDH1) mutation of the bone marrow showing positive staining in myelomonocytic cells and megakaryocytes. Magnification 20 $\times$ . E: IHC staining for the IDH1 mutation on the skin biopsy showing neutrophilic infiltrate diffusely positive for the IDH1 mutation. F: IHC staining for the IDH1 mutation of the lung parenchyma showing positive staining in macrophages.

that were erythematous, edematous and mildly tender to palpation (Figure 1A). His medical record showed a history of development of unexplained febrile neutropenia and similar skin findings during the year prior to this admission. Punch biopsy

of a skin lesion on the right arm was performed and showed subcutaneous histiocytoid SS (Figure 1B). Within weeks of this presentation, he was found to have neutropenia and macrocytic anemia on routine blood tests. His complete blood count

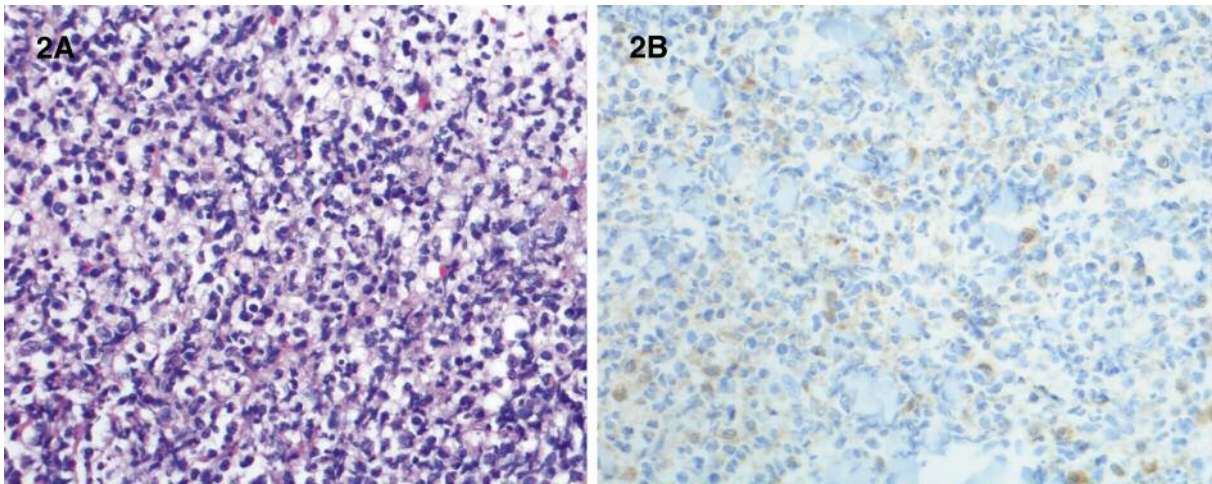


Figure 2. Biopsy findings in case 2. A: Skin nodule biopsy showing a dense neutrophilic infiltrate. Hematoxylin and Eosin, 40×. B: Immunohistochemical staining for the isocitrate dehydrogenase 1 (*IDH1*) mutation on the skin biopsy showing neutrophilic infiltrate positive for the *IDH1* mutation. Magnification 40×.

demonstrated a hemoglobin of 9.2 g/dl, hematocrit of 31.3, white blood cell count of  $2.5 \times 10^9/l$ , platelets of  $252 \times 10^9/l$ , and a mean corpuscular volume (MCV) of 100 fl. Subsequently, the patient underwent a bone marrow biopsy for pancytopenia, which revealed a diagnosis of intermediate-risk MDS by the International Prognostic Scoring System criteria (15) (Figure 1C). Molecular profiling of the bone marrow aspirate with a 44-myeloid gene mutational panel showed somatic mutations in the *IDH1* gene (c.395G>A; p.R132H) with an allelic frequency of 35%. It also showed a somatic mutation in the splicing factor Zinc finger CCCH-type, RNA binding motif and serine/arginine rich 2 (*ZRSR2*) gene (c.263\_266delTAAA; frameshift). Immunohistochemical staining (IHC) of the bone marrow biopsy was positive for the *IDH1* mutation in myelomonocytic cells and megakaryocytes (Figure 1D). IHC of a lesion of the right upper extremity demonstrated the majority of infiltrating neutrophilic cells also to be positive for the *IDH1* (R132H) mutation (Figure 1E). A serum sample from the patient was analyzed for D-2HG level, which was found to be significantly elevated at 1438 ng/ml (reference range: 18-263 ng/ml).

The patient was treated with 40 mg of oral prednisone for SS. He experienced rapid improvement of his skin lesions and resolution of fever. The skin lesion recurred and the patient underwent seven cycles of treatment with a hypomethylating agent, azacitidine, which is the first-line therapy for higher risk MDS. Treatment with azacitidine resulted in improvement of anemia. The skin lesions only partially improved and the patient required numerous cycles of prednisone, with temporary resolution. The patient subsequently developed *IDH1*-mutated neutrophilic infiltration in the lungs (Figure 1F), and after multiple prolonged hospitalizations was transferred to hospice care with multi-organ failure.

**Case 2:** A 73-year-old male was referred to the hematology clinic for persistent leukopenia and anemia. He had a history of SS diagnosed 4 years prior based on skin biopsy (Figure 2A). He experienced intermittent relapse of SS characterized by painful erythematous and edematous nodules on his hands, usually treated with prednisone. Recurrence was often associated with fever, leukocytosis, and myalgia. At the time of presentation to the hematology clinic, his complete blood count demonstrated: hemoglobin 10 g/dl, hematocrit 32.4, white blood cell count  $3.4 \times 10^9/l$ , platelets  $148 \times 10^9/l$ , with MCV of 95.3 fl.

The patient underwent a bone marrow biopsy, which showed a hypercellular marrow (50-60%) with trilineal hematopoiesis, mild erythroid hyperplasia, mild dysplasia and no significant increase in blasts. Molecular profiling of the bone marrow aspirate showed somatic mutations in the *IDH1* gene (c.395G>A; p.R132H) with an allelic frequency of 45%. It also showed a somatic mutation in the serine and arginine rich splicing factor 2 (*SRSF2*) gene (c.284C>A;p.P95H) with an allelic frequency of 46%. A diagnosis of low-grade MDS was made. On immunohistochemical staining, the skin biopsy showed the neutrophilic infiltrate to be positive for the *IDH1* mutation (Figure 2B). The patient required close monitoring, but no acute intervention for MDS.

## Discussion

Sweet's syndrome and the histiocytoid variant have been associated with myeloid malignancies. Some reports have estimated the incidence of SS and concomitant hematological malignancy to be as high as 18% (16, 17). MDS, in particular, appears to have a unique association with SS, with the suggestion of a higher association of the histiocytoid variant



rather than conventional SS with MDS (18, 19). In one case series, 31.8% of patients with histiocytoid SS were diagnosed with MDS (19). A distinct chronic subset of SS has also been described that is often associated with fever and arthralgia. A number of reports have suggested that this atypical presentation of SS is closely associated with the later development of MDS (18, 20, 21). The time lag between development of skin findings and diagnosis of MDS in these cases was 0-7 years (18, 21). For both our patients, their skin manifestations and diagnosis of SS predated their diagnosis of MDS, and this fits the pattern as previously described in the literature. This presentation highlights the importance of working up a patient that presents with SS for an underlying hematologic malignancy. In cases where the skin findings are chronic and associated with constitutional symptoms, this may suggest a more specific association of SS and MDS.

Epigenetic mutations and genetic dysfunction are thought to play a significant role in the pathogenesis of MDS. Patients with mutant *IDH1/2* exhibit a global hypermethylation phenotype associated with significant suppression of gene expression compared to patients without IDH-mutated myeloid malignancies (10). The presence of *IDH1/2* mutation correlates well with elevated serum D-2HG in patients with AML (22). Mutant *IDH1/2* proteins catalyze the reduction of  $\alpha$ -KG to D-2HG, which is structurally similar to  $\alpha$ -KG and has been shown to competitively inhibit  $\alpha$ -KG-dependent enzymes. Important among these are the ten-eleven-translocation (TET) 2 enzyme and histone lysine demethylases. TET2 is thought to cause DNA demethylation by genome-wide, as well as locus-specific, hydroxymethylation. The histone demethylase enzymes are important for regulating the process of gene transcription by chromatin modifications (11). Compared to the significant amount of information available about mutant *IDH1/2* in MDS, almost nothing is known about the pathobiology of malignancy-associated SS. Recently, a presentation of SS and concomitant MDS was reported in association with a heterozygous mutation in the *MEFV* gene, associated with familial Mediterranean fever, with high fever and marked neutropenia (23). Another report noted an increase in interleukin-1 $\beta$  expression within the SS skin lesions (24). This leads us to speculate that alterations in immune signaling play a large role in the pathophysiology of SS. Future studies directed at the association of mutant *IDH1* and immune signaling in SS will help forward our understanding of this association. The presence of an elevated level of D-2HG as well as multi-organ involvement with *IDH1*-mutated immune cells in our first patient strongly suggests that *IDH1* mutations may dysregulate a myriad of cellular pathways and functions beyond its known effects that are causative of hematological malignancies. In summary, we strongly feel that *IDH1* mutations may predispose to a global dysfunction that extends beyond its known effects in dysregulated hematopoiesis.

## Conclusion

We presented two cases of *IDH1*-mutated MDS and SS. The *IDH1* mutation (R132H) was seen in virtually all of the infiltrating neutrophils in the skin lesions which preceded the development of cytopenia and MDS. Establishing a new molecular link such as the *IDH1* mutation between SS and MDS can provide an earlier identification of patients presenting with SS who are also at increased risk for developing myeloid malignancies, particularly MDS. It can also guide patients to molecularly targeted therapies such as IDH inhibitors that are specific to the biology of their disease (25-27).

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Received January 31, 2018  
 Revised February 26, 2018  
 Accepted February 27, 2018