A Case of Sweet Syndrome Associated With Human Granulocytic Anaplasmosis

Charles L. G. Halasz, MD; G. William Niedt, MD; Caroline P. Kurtz, MD; Diana G. Scorpio, DVM, MPH; Johan S. Bakken, MD, PhD; J. Stephen Dumler, MD

Background: Acute febrile neutrophilic dermatosis, or Sweet syndrome (SS), is a condition that is presumed to be triggered by infectious disease agents. We report a case of SS associated with human granulocytic anaplasmosis (HGA), which is of interest because *Anaplasma phagocytophilum* infects, multiplies in, and disrupts the function of neutrophils, the key infiltrating cell in SS.

Observations: A patient with initial dermatologic manifestations of SS who did not respond to standard SS treatment was suspected to have concurrent HGA with the demonstration of leukopenia, thrombocytopenia, and elevated hepatic transaminase levels. The HGA diagnosis was established when morulae in neutrophils were observed on a peripheral blood smear, a finding confirmed by both serologic examination and polymerase chain reaction on the skin biopsy specimen used to establish the SS diagnosis.

Conclusion: The significant involvement of neutrophils with both SS and HGA warrants a broader search for additional cases that may further define whether pathogenetic linkages could exist.

Arch Dermatol. 2005;141:887-889

A CUTE FEBRILE NEUTROPHILIC dermatosis, or Sweet syndrome (SS), was first described in 1964. The 4 cardinal features in the original report by Sweet were (1) fever; (2) neutrophilic leukocytosis; (3) painful plaques on the limbs, face, and neck; and (4) dense dermal neutrophilic infiltration on skin biopsy specimen. Since then, numerous disease associations have been reported, including inflammatory diseases and syndromes such as Behçet disease, Crohn disease, ulcerative colitis, lupus erythematosus, and Sjögren syndrome; hemoproliferative disorders and solid tumors; and infectious agents such as *Yersinia*, *Salmonella*, *Toxoplasma*, *Histoplasma*, *Mycobacterium*, cytomegalovirus, and human immunodeficiency virus, among many others. In the following case report, we describe a new infectious association with SS, namely the tickborne infectious agent of human granulocytic anaplasmosis (HGA; formerly human granulocytic ehrlichiosis), *Anaplasma phagocytophilum*. The association is of particular interest because *A. phagocytophilum* is an obligate intracellular bacterium that infects, propagates within, and alters the function of host neutrophils.

On June 5, 2002, a 59-year-old white woman was referred by her allergist for dermatologic consultation. She had a 3-day history of a painful rash on the knees, ankles, and wrists. Her temperature was 101.3°F (38.5°C). Erythematous papules, plaques, and nodules were noted on the thighs, knees, ankles, heels, forearms, wrists, and hands (Figure A). Skin biopsy specimens for hematoxylin-eosin staining were taken from each thigh (Figure, B) and revealed a dense dermal neutrophilic infiltration on skin biopsy specimen. Since then, numerous disease associations have been reported, including inflammatory diseases and syndromes such as Behçet disease, Crohn disease, ulcerative colitis, lupus erythematosus, and Sjögren syndrome; hemoproliferative disorders and solid tumors; and infectious agents such as *Yersinia*, *Salmonella*, *Toxoplasma*, *Histoplasma*, *Mycobacterium*, cytomegalovirus, and human immunodeficiency virus, among many others. In the following case report, we describe a new infectious association with SS, namely the tick-borne infectious agent of human granulocytic anaplasmosis (HGA; formerly human granulocytic ehrlichiosis), *Anaplasma phagocytophilum*. The association is of particular interest because *A. phagocytophilum* is an obligate intracellular bacterium that infects, propagates within, and alters the function of host neutrophils.

See also pages 834, 881, and 893
Anaplasma phagocytophilum infection was present during the initial SS presentation was sought. For this, sections from the paraffin-embedded skin biopsy specimen were obtained for detection of A phagocytophilum by electron microscopy, immunohistochemical analysis, and polymerase chain reaction targeting the multicopy msp2 gene.

Neither electron microscopic nor immunohistochemical analysis revealed any organisms; however, a 550–base pair band was noted after polymerase chain reaction and was not present in the negative control (Figure, D).

This case was diagnosed initially by a dermatologist as SS and fulfilled the diagnostic criteria proposed by Su and Liu and revised by Von den Dreisch. The 2 major criteria, abrupt onset of tender red plaques or nodules and a neutrophilic infiltration of the dermis without leukocytoclastic vasculitis, were both met. There was also fever, malaise, an elevated erythrocyte sedimentation rate, a differential leukocyte count that revealed greater than 70% neutrophils in blood, and a response to systemic corticosteroid administration. Subsequently, HGA was diagnosed, based largely on worsening systemic symptoms associated with falling WBC and platelet counts.

The Anaplasmataceae family consists of obligate intracellular, gram-negative bacteria that are causes of tick-borne zoonoses. In 1994, human granulocytotropic ehrlichiosis was described. The causative organism was subsequently determined to be the same as Ehrlichia equi and Ehrlichia phagocytophila, and all were classified as a single species, A phagocytophilum, in 2001.

Confirmation of the diagnosis of HGA in a patient with clinically compatible illness requires 1 or more of the following: (1) 4-fold change in antibody titer by indirect fluorescent antibody test, (2) a positive result on polymerase chain reaction targeting A phagocytophilum DNA, (3) visualization of morulae in neutrophils and a single positive serum antibody titer by indirect fluorescent antibody, (4) immunohistochemical analysis of antigen in a skin biopsy specimen or tissue sample, or (5) isolation and culture from a clinical specimen. The case presented herein fulfills 3 separate HGA diagnostic criteria.

In general, descriptions of cutaneous eruptions in adults with HGA are infrequent and brief, and along with human monocytic ehrlichiosis, it has been referred to as “spotless” Rocky Mountain spotted fever.

Although Wallace et al mentioned rash in 10% of patients, local tick bite reactions were included, and only 2 patients had “erythematous” rashes. Similarly, in a large study by Bakken et al, only 1 patient (2%) was found to have a rash.

The case described herein raises the possibility that an additional cutaneous reaction, SS, may also be a mani-

**Figure.** Sweet syndrome (SS) in human granulocytic anaplasmosis (HGA). A, Pink plaques on extremities characteristic of SS. B, Confirmed in part by the presence of a neutrophilic infiltrate in the superficial dermis (hematoxylin-eosin, original magnification ×4; inset, hematoxylin-eosin, original magnification ×40). C, A morula (arrow) is noted within cytoplasm of a polymorphonuclear leukocyte in the patient’s peripheral blood 14 days after SS presentation and after prednisone tapering (Wright stain, original magnification ×400). D, A 550-base pair amplicon separated by agarose gel electrophoresis after polymerase chain reaction amplification of Anaplasma phagocytophilum msp2 DNA from a paraffin-embedded skin biopsy specimen obtained during SS presentation 14 days prior to the diagnosis of HGA by blood smear. mw Indicates molecular size ladder; lane 1, patient sample; lane 2, positive control; and lane 3, negative control.
festation of Ehrlichia or Anaplasma infections. The positive polymerase chain reaction result during the earliest phases of SS supports the hypothesis that neutrophils may have been activated by a small number of A phagocytophilum organisms.

Some superficial similarities exist between SS and HGA, including their self-limiting nature, seasonal occurrences, and responses to doxycycline. However, the broader geographic distribution of SS suggests that any connection between these entities may be as a result of activation and recruitment of neutrophils by cytokines and chemokines. Increasing evidence suggests that SS results from local or even systemic cytokine and chemokine recruitment and activation of neutrophils. Likewise, the pathogenesis of HGA is increasingly linked to aberrant neutrophil activation and deactivation by virtue of the intracellular infection, including local and systemic inflammation. Whether such pathogenetic linkages between HGA or other infectious agents and neutrophilic dermatoses such as SS exist will require more study.

Accepted for Publication: January 31, 2005.
Correspondence: J. Stephen Dumler, MD, Division of Medical Microbiology, Department of Pathology, The Johns Hopkins University School of Medicine, 720 Rutland Ave, Ross 624, Baltimore, MD 21205 (sdumler@jhmi.edu).
Funding/Support: This study was supported in part by grant R01 AI 44102 from the National Institutes of Allergy and Infectious Diseases, Bethesda, Md (Dr Dumler).

REFERENCES