OBSERVATION

A Case of Sweet Syndrome Associated With Human Granulocytic Anaplasmosis

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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.

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Report of a Case

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
phase serologic titer for HGA was less than 64, but sub-
disease and blood cultures were negative. The acute-
eral blood smears revealed scattered morulae in neutro-
examination of Wright-stained buffy-coat and periph-
mg twice daily, was initiated for presumptive HGA. An
range [RR, 20-125 U/L]), an alanine aminotransferase level
of 60 U/L (RR, 2-40 U/L), a $\gamma$-glutamyltransferase level
of 167 U/L (RR, 2-60 U/L), an elevated erythrocyte sedi-
ment rate of 76 mm/h (RR, 0-30 mm/h), negative find-
ings from an antinuclear antibody test, and a rheu-
matoid factor titer of 16 (RR, <14).

The patient responded immediately to treatment with
40-mg prednisone, and 14 days later after the predni-
sone was tapered to 20 mg, the fever and clinical signs
returned. Her WBC and platelet counts dropped to as low
as 2500/µL and $23 \times 10^3/µL$, respectively. Based on fall-
ing WBC and platelet counts, doxycycline hyclate, 100
mg twice daily, was initiated for presumptive HGA. An
examination of Wright-stained buffy-coat and periph-
eral blood smears revealed scattered morulae in neutro-
 phils consistent with human granulocytic anaplasmosis
(HGA) (Figure, C). Serum IgG and IgM titers for Lyme
disease and blood cultures were negative. The acute-
phase serologic titer for HGA was less than 64, but sub-
sequent convalescent titers rose to 2048. Elevated titers
were confirmed by a second laboratory.

After doxycycline treatment, fever and malaise re-
 solved promptly, and the WBC and platelet counts began
to normalize over the next 2 days. The patient was main-
tained on doxycycline therapy for an additional 2 weeks
and was healthy on follow-up. Because of the co-
ocurrence of 2 unique and infrequent diseases, evidence
that A phagocytophilum infection was present during the
initial SS presentation was sought. For this, sections from
the paraffin-embedded skin biopsy specimen were ob-
tained for detection of A phagocytophilum by electron mi-
scopy, immunohistochemical analysis, and polymer-
ase chain reaction targeting the multicopy msp2 gene.3,4
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 Liu5 and revised by Von den Dreisch.3 The 2 major
criteria, abrupt onset of tender red plaques or nodules
and a neutrophilic infiltration of the dermis without leu-
kocytoclastic 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 cor-
ticosteroid administration. Subsequently, HGA was di-
agnosed, based largely on worsening systemic symp-
toms associated with falling WBC and platelet counts.

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 $\times4$; inset, hematoxylin-eosin,
original magnification $\times40$). 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 $\times400$). 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.

The Anaplasmataceae family consists of obligate intra-
cellular, gram-negative bacteria that are causes of tick-
borne zoonoses. In 1994, human granulocytotropic ehrli-
chiosis was described.5 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 2001.7

Confirmation of the diagnosis of HGA in a patient with
clinically compatible illness requires 1 or more of the fol-
lowing: (1) 4-fold change in antibody titer by indirect
fluorescent antibody test, (2) a positive result on poly-
merase chain reaction targeting A phagocytophilum DNA,
(3) visualization of morulae in neutrophils and a single
positive serum antibody titer by indirect fluorescent anti-
tody, (4) immunohistochemical analysis of antigen in
a skin biopsy specimen or tissue sample, or (5) isolation
and culture from a clinical specimen.8 The case pre-
sented herein fulfills 3 separate HGA diagnostic criteria.

In general, descriptions of cutaneous eruptions in adults
with HGA are infrequent and brief, and along with hu-
mam monocytic ehrlichiosis, it has been referred to as “spot-
less” Rocky Mountain spotted fever.8,9 Although Wallace
et al10 mentioned rash in 10 (16%) of 62 patients, local tick
bite reactions were included, and only 2 patients had “ery-
thematosus” rashes. Similarly, in a large study by Bakken
et al,10 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-
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.

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**REFERENCES**


