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Bullous hemorrhagic Sweet syndrome with cryptococoid neutrophils in patients positive for antineutrophil cytoplasmic antibody without primary vasculitis



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INTRODUCTION

Sweet syndrome (SS) is a febrile neutrophilic dermatosis characterized by pyrexia, peripheral leukocytosis, and an abrupt onset of painful erythematous plaques and nodules.^{1,2} Lesions are typically found in an asymmetric distribution on the face, neck, and upper extremities and are often associated with an underlying malignancy, a systemic inflammatory condition, or a preceding infection.^{1,2} Histopathologic examination reveals a dense neutrophilic infiltrate with papillary dermal edema, and serum laboratory tests show leukocytosis, an elevated erythrocyte sedimentation rate, or both.^{1,2} Atypical bullous or hemorrhagic presentations have been described in the literature, with the majority in a setting of hematologic malignancy.³⁻⁷ Twenty percent of patients with SS have an underlying malignancy that can manifest with atypical bullae.⁸

Herein, we describe 3 patients with hemorrhagic SS and cryptococoid-appearing neutrophils on histopathologic examination, all of whom were found to be positive for antineutrophil cytoplasmic antibodies (ANCA) and negative for malignancy. This constellation of findings has rarely been described in the literature and raises new diagnostic and prognostic considerations for SS patients presenting with a hemorrhagic or bullous morphology.

Abbreviations used:

ANCA: antineutrophil cytoplasmic antibody
SS: Sweet syndrome

CASE DESCRIPTIONS

Case 1

A 70-year-old Caucasian woman with end-stage renal disease, diabetes, and chronic obstructive pulmonary disease presented to an outside hospital with fever, nausea, vomiting, and abdominal pain. Head computed tomography demonstrated a soft tissue swelling of the subcutaneous layer along the right parotid and submandibular glands, consistent with a subcutaneous infection, while chest X-ray revealed bilateral infiltrates. A culture of bronchial washings was positive for *Pseudomonas*. She was diagnosed with bilateral pneumonia complicated by septic shock and an infection of the parotid and submandibular glands before the development of hemorrhagic bullae on her face and arms. Subsequently, respiratory distress requiring intubation developed, and she was transferred to our hospital. She received multiple antibiotics, including vancomycin, cefepime, doxycycline, cephalexin, cefazolin, and piperacillin/tazobactam, prior to the transfer. Physical examination showed erythematous to violaceous tense hemorrhagic bullae on her face, neck, upper portion of

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Fig 1. SS with erythematous to violaceous tense hemorrhagic bullae in the right antecubital fossa of patient 1. SS, Sweet syndrome.



Fig 2. SS with violaceous tense bullae and focal erosions on the dorsal surface of the left hand of patient 1. SS, Sweet syndrome.

the chest, both arms, dorsal surface of the hands, and lateral aspect of the fingers (Figs 1 and 2). The differential diagnosis included atypical SS versus bullous small-to-medium-vessel vasculitis. A biopsy of the upper portion of the right arm showed a dense neutrophilic infiltrate in the mid-dermal layer with papillary dermal edema (Figs 3 and 4). The blood

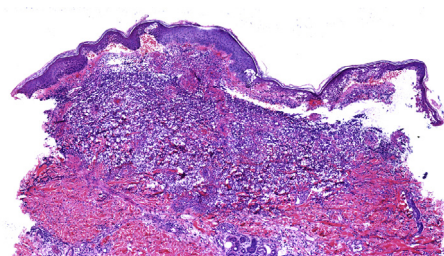


Fig 3. SS punch specimen from the right antecubital fossa showing a dense mixed-cell infiltrate in the superficial dermis. (Hematoxylin-eosin stain; original magnification: $\times 10$). SS, Sweet syndrome.

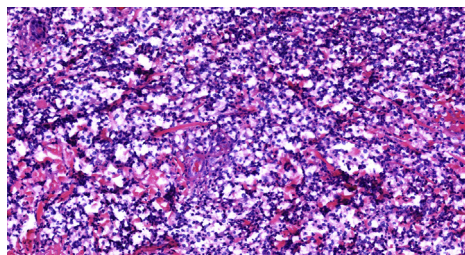


Fig 4. SS punch specimen from the right antecubital fossa showing many nuclei with prominent cleared-out space having an encapsulated appearance. (Hematoxylin-eosin stain; original magnification: $\times 40$). SS, Sweet syndrome.

vessels appeared to be intact. The neutrophils in the dermis exhibited prominent vacuolated cytoplasm. Gram, Grocott methenamine silver, and periodic acid-Schiff stains were negative for micro-organisms. Direct immunofluorescence test result was negative for IgG, IgM, IgA, and C3. ANCA test result was positive for perinuclear antineutrophil cytoplasmic antibody (p-ANCA), with titers elevated at $>1:640$. Proteinase 3 antibodies were also elevated at 123.4 (normal range, 0-20). Based on these findings, she was diagnosed with SS. Rheumatology and hematology/oncology workups failed to reveal the underlying cause. She was started on dapsone and a slow prednisone taper, with eventual clearance of her skin lesions.

Case 2

A 68-year-old Caucasian woman with chronic anemia, hypertension, and hypercholesterolemia, was admitted and intubated for a retropharyngeal abscess and respiratory distress as well as hemorrhagic papules and plaques on her face, arms, hands, legs, and eyelids. The patient was successfully extubated, with the resolution of her retropharyngeal abscess following the administration of intravenous antibiotics. Biopsies of the left arm and hand demonstrated dense neutrophilic infiltrates with leukocytoclasia and fibrin deposition, suggesting vasculitis. The differential diagnosis included neutrophilic



Fig 5. SS showing a crusted, hemorrhagic granulation tissue and violaceous plaque on the right ear of patient 3. SS, Sweet syndrome.

dermatosis with secondary vasculitis, primary small-vessel vasculitis, or a pustular drug eruption. Periodic acid–Schiff stain, acid-fast bacilli test, Gram stain, and tissue cultures were negative for infectious organisms, while direct immunofluorescence test failed to reveal vasculitis. The patient was positive for p-ANCA and negative for cytoplasmic antineutrophil cytoplasmic antibody (c-ANCA). Myeloperoxidase antibodies were elevated at 6.0 (negative < 0.4). Proteinase 3 antibodies were equivocal at 0.7 (negative < 0.4, equivocal 0.4-0.9). Hematology/oncology, rheumatology, and infectious disease workups were negative. Based on the negative direct immunofluorescence test result, p-ANCA positivity, and histologic neutrophilic infiltrate, the patient was diagnosed with SS with secondary vasculitis. She was treated with prednisone, mycophenolate mofetil, and dapson, but she ultimately died due to urosepsis and multiorgan failure.

Case 3

A 70-year-old Caucasian woman with end-stage renal disease, diabetes, and recent cardiac catheterization was admitted for respiratory syncytial virus pneumonia. She was found to have painful ulcerations of varying durations on her head, upper extremities, and tongue. She denied having fevers, chills, changes in vision, weight loss, or cocaine use. Examination showed a crusted, hemorrhagic granulation tissue on the bilateral triangular fossae (Fig 5). The posterior part of the left forearm, plantar

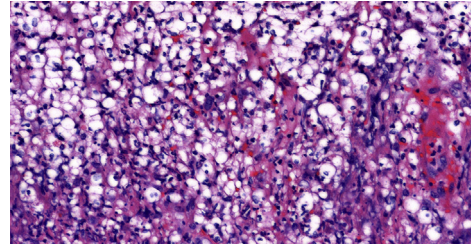


Fig 6. SS punch specimen from the right ear showing a dense infiltrate consisting of neutrophils and their nuclear dust and lymphocytes. (Hematoxylin-eosin stain; original magnification: $\times 39$). SS, Sweet syndrome.

surface of the index fingers, and the left side of the tongue showed deeply erythematous to violaceous exudative plaques and papules with hemorrhage. The differential diagnosis included calciphylaxis, cholesterol emboli, and neutrophilic dermatoses. Without intervention, she reported a progression in the number of lesions, with new painful, purpuric papules on her hands and elbows and worsening of the existing lesions.

A biopsy of the upper part of the left ear showed a dense neutrophilic infiltrate, without the evidence of vasculitis or fungal infection. A biopsy of the right ear later showed a dense neutrophilic infiltrate with cryptococoid-appearing bodies, which was further described as a dense neutrophilic infiltrate (Fig 6). Gram stain and tissue culture for acid-fast bacilli and fungi failed to reveal an infectious cause. Myeloperoxidase antibody titers were elevated at >0.8 (negative < 0.4). Antinuclear antibody titers were 1:320 in a homogeneous pattern. Antihistone antibody titers were elevated at 2.6 (negative < 1.0). Extractable nuclear antigen ribonucleoprotein IgG antibody titers were elevated at >8.0 (negative < 1.0). Proteinase 3 antibody titers were negative at <0.2 (negative < 0.4). The patient was diagnosed with SS, and she improved following the initiation of prednisone, dapson, and mycophenolate mofetil.

DISCUSSION

We present a case series linking rare findings that have not been previously reported together in SS. Three elderly Caucasian women presented with bullous hemorrhagic lesions that were temporally related to infections. Further investigation revealed that each patient was positive for ANCA, with vacuolated basophilic bodies on the biopsy and the histologic evidence supporting vasculitis. While these findings have been reported independently, this is the first time, to our knowledge, that all 3 have been reported in a similar population. We predict

that these atypical findings are associated and have a causal relationship.

The bullous variant of SS presents with hemorrhagic bullae and splitting of the dermoepidermal junction.³⁻⁵ The marked activation of the neutrophils and subsequent tissue destruction may be related to the expression of CD3, CD163, tumor necrosis factor- α , interleukin (IL) 8, IL-17, matrix metalloproteinase-9, and myeloperoxidase.⁴ This extensive destruction by the neutrophils may be compounded in patients positive for ANCA. Both c-ANCA and p-ANCA have been seen in SS.^{4,5}

The absence of vasculitis has been a hallmark of SS. However, a study by Malone et al investigating the association between vasculitis and SS found that 21% of patients in the study met the diagnostic criteria for vasculitis, not including patients with signs of vessel damage without fibrinoid necrosis.⁹ The study proposed that vasculitic changes could be secondary to neutrophil activation and degranulation, not immune complex deposition.⁹

SS may induce secondary vasculitis.¹⁰ A case report of neutrophilic dermatosis of the dorsal surface of the hands found the patient to be positive for p-ANCA, with a decrease in the level of p-ANCA corresponding to the “clinical activity of the dermatoses,” suggesting a correlation between neutrophilic dermatosis and ANCA.¹⁰

The presence of ANCA without autoimmune vasculitis has been noted in the literature. In a retrospective analysis of patients positive for ANCA, 60.2% of the 113 patients positive for c-ANCA or p-ANCA had no evidence of ANCA-associated vasculitis.¹¹ There are several etiologies associated with ANCA positivity without vasculitis, including infectious diseases.¹¹

Another report of a patient with SS suggested that the patient, initially negative for ANCA, became positive for ANCA because of abnormal neutrophil fragmentation and degradation, allowing the normally sequestered intracellular contents of the neutrophils to be exposed to the immune system, leading to ANCA generation.¹² Other studies have hypothesized that fragmented neutrophils and the release of neutrophilic antigens may be responsible for the development of ANCA in patients with SS.¹³

While SS can be a harbinger of vasculitis positive for ANCA-positive vasculitis, the detection of circulating ANCA more likely results from the intense neutrophil degradation in the setting of SS triggered by an infectious etiology, as demonstrated by this case series. The lack of small-to-medium-vessel involvement in other organ systems and improvement of ANCA titers corresponding to the resolution

of SS can be helpful indicators against a diagnosis of primary ANCA vasculitis.

A histologic variant of SS exists when the neutrophilic dermal infiltrate surrounds vacuolated spaces with basophilic bodies, mimicking the encapsulated appearance of cryptococcal infections.^{6,7,14,15} These acellular, cryptococoid bodies are thought to be due to degenerating neutrophils within the neutrophilic infiltrate.^{6,14,15} Their basophilic component stains similar to the nuclei of the surrounding neutrophils, with negative fungal stains.⁶

Our hypothesis states that there are likely varying degrees of SS, and the infections that each of our patients experienced led to an acute, exuberant stimulation of the neutrophils. We believe that the vacuolated spaces or cryptococoid appearance seen on the biopsy represented rapidly degenerating neutrophils that led to abundant neutrophilic antigens and the resultant production of ANCA without true autoimmune vasculitis. The cryptococoid-appearing neutrophils and ANCA positivity may portend a more clinically aggressive presentation of SS. In the absence of other risk factors or laboratory abnormalities, providers should consider these findings as a representation of infection-induced hemorrhagic SS rather than pursuing an aggressive workup for an underlying malignancy. Further studies are needed to fully understand the relationships among these rare findings.

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