tial effect, 3.0 (2.8) days (range, 1-7 days) for BT-B vs 14.3 (6.7) days (range, 7-20 days) for BT-A. Anhidrotic areas developed earlier in the BT-B side. Patients reported longer-lasting subjective benefit from BT-B than BT-A: 17.3 (7.4) weeks vs 12.9 (8.4) weeks.

All patients tolerated intradermally injected BT-A and BT-B well, although some experienced mild pain, especially during BT-B injections. No hematomas developed at the injection site, nor did any participant report systemic adverse effects.

Comment. In all patients, although both toxins improved axillary hyperhidrosis, BT-B proved more effective than BT-A in reducing sweat production and area. We therefore provide objective evidence that BT-B is safe and effective for treating bilateral axillary hyperhidrosis. When administered at the same dose ratio of 1:50 used for the motor system, BT-B blocks sweating better than BT-A. The subjective outcome measures, including the beginning and duration of benefit and treatment satisfaction scores, were also higher for BT-B than for BT-A treatment.

Our finding that BT-B effectively reduces axillary hyperhidrosis differs from other studies probably because the other studies used lower toxin ratios (1:40 or 1:20) and higher dilutions. Botulinum toxin type B might strongly reduce hyperhidrosis because it specifically targets the autonomic nervous system, as happens in botulism type B.

Botulinum toxin type B merits increasing use in palmar hyperhidrosis to guarantee long-lasting benefit without hand muscle weakening. Future research should compare how BT-A and BT-B affect the autonomic and motor nervous systems and how long their action on both systems lasts.

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Author Affiliations: Department of Neurology, Cittadella Hospital, Padua, Italy (Drs Frasson and Didone); and Department of Neurological Sciences and Vision, Section of Clinical Neurology, University of Verona, Verona, Italy (Drs Brigo, Acerl, Vicentini, and Bertolasi).

Correspondence: Dr Frasson, Department of Neurology, Cittadella Hospital, Via Casa di Ricovero 40, Padua 35013, Italy (e.frasson@uls15.pd.it).

Author Contributions: All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Frasson and Bertolasi. Acquisition of data: Frasson, Brigo, Acerl, and Vicentini. Analysis and interpretation of data: Frasson, Brigo, Acerl, and Didone. Drafting of the manuscript: Frasson, Brigo, Acerl, and Vicentini. Critical revision of the manuscript for important intellectual content: Frasson, Didone, and Bertolasi. Statistical analysis: Didone. Administrative, technical, and material support: Brigo, Acerl, and Vicentini. Study supervision: Frasson and Bertolasi.

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References

Neurogenic Rosacea: A Distinct Clinical Subtype Requiring a Modified Approach to Treatment

Rosacea is generally categorized into 4 distinct clinical subtypes: erythematotelangiectatic, papulopustular, phymatous, and ocular. 

Granulomatous rosacea, rosacea fulminans, and perioral dermatitis have been described as additional variants. Herein we describe 14 patients with rosacea and prominent neurologic symptoms, who represent another distinct subset of rosacea meriting a unique approach to management.

Methods. Patients with prominent neurologic symptoms in addition to classic features of rosacea were identified during routine appointments at a major teaching hospital. Details regarding medical history, disease symptoms and triggers, and response to treatments were obtained via clinic visits and telephone interviews. The study was approved by the institutional review board of the University of California, San Francisco.

Results. Twelve of the 14 patients were women, and 12 were white. Mean age at disease onset was 38 years. Prominent symptoms included burning or stinging pain (100% [14 of 14]), erythema (100% [14 of 14]), and flushing (93% [13 of 14]), sometimes accompanied by facial edema (50% [7 of 14]), telangiectasias (50% [7 of 14]), pruritus (43% [6 of 14]), and papules (36% [5 of 14]). Important symptom triggers included heat (93% [13 of 14]), sunlight (93%[13 of 14]), hot showers (79%[11 of 14]), stress (71%[10 of 14]), exercise (64% [9 of 14]), and alcohol consumption (57% [8 of 14]). Use of makeup (50% [7 of 14]), eating spicy foods (43% [6 of 14]), touching skin (36% [5 of 14]), drinking hot beverages (29% [4 of 14]), cold weather (21% [3 of 13]), and humidity (14% [2 of 13]) were less reliable triggers. Notably, 71% of patients experienced relief from cooling via fans or cold compresses or ice applied to the face or held in the mouth (10 of 14). Figure 1 depicts typical examination findings in these patients.

A notably high percentage of patients had neurologic symptoms (100% [14 of 14]) or neuropsychiatric conditions, including complex regional pain syndrome, es-
tributions from dysfunctional cutaneous vasculature and likely multifactorial, with significant proposed con-
tection of these patients and aid the practicing dermatolo-
subgroup, we hope to increase awareness and recogni-
rogenic rosacea underrecognized subgroup of rosacea that we term
strikingly prominent neurologic symptoms represents an
Comment. We propose that this group of patients with
sentential tremor, depression, and obsessive-compulsive dis-
order. Neurovascular disorders, including headaches (71% [10 of 12 were helped), topical steroids (1 of 8), and oral antibiotics, usually tetracyclines (4 of 8). Most patients benefitted from neurologically focused treatments (9 of 12), including gabapentin (5 of 11), duloxetine (4 of 6), pregabalin (1 of 4), tricyclic antidepressants (2 of 3), and memantine (2 of 2). Topically formulated neuroleptic agents, including doxepin, glycopyrrolate, amitriptyline, capsai-
neurologically focused treatments (9 of 12), including gabapentin (5 of 11), duloxetine (4 of 6), pregabalin (1 of 4), tricyclic antidepressants (2 of 3), and memantine (2 of 2). Topically formulated neuroleptic agents, including doxepin, glycopyrrolate, amitriptyline, capsai-
cin, and ketamine, were occasionally effective (3 of 7). Hydroxychloroquine (3 of 5), an antimalarial agent with neuromodulatory effects, and vasoactive agents including β-blockers and alpha-1 adrenergic receptors (2 of 5) were each effective in a subset of patients. Comorbid-
ties, demographic data, and individual treatment re-
sponses are summarized in the Table.

Figure 1. Facial erythema is seen in most patients at baseline and uniformly during flares. Inflammatory papules and pustules and rhinophymatous change are unusual in this subset of patients.

Figure 2. Facial pruritus, flushing, and dysesthesias are unusual in this subset of patients.

The cause of rosacea is complex, poorly understood, and likely multifactorial, with significant proposed con-
tributions from dysfunctional cutaneous vasculature and
innate immunity. We believe neuronal dysregulation is
equally integral to rosacea pathogenesis. It may contrib-
ute to disease via various mechanisms, such as vaso-
motor instability, release of proinflammatory neuro-
peptides, and neuronal injury leading to perceived
dysesthesias. In an individual patient, the relative im-
portance of each of the mechanisms may differ, influ-
encing both the spectrum of clinical symptoms and the
optimal treatment strategy.

We propose the diagnostic and treatment algorithm
illustrated in Figure 2 as a guide for clinicians in man-
aging a patient with suspected neurogenic rosacea. Pa-
tients with prominent vasomotor symptoms, defined clini-
cally by flushing and telangiectasias, may respond to
vasoactive medications, including β-blockers, alpha-1 ad-
renergic blockers, and calcium channel blockers. In ad-
dition, laser- and light-based therapies seem to be more
effective in this subset of patients.

Patients with inflammatory features such as papules,
pustules, or edema may respond, if symptoms are mild,
to traditional topical therapies such as metronidazole,
azelaic acid, or sulfur. Systemic antibiotics and antima-
larial agents used for their anti-inflammatory effect may
be useful for nonresponders.

Finally, patients with dysesthesia out of proportion
to flushing or inflammation can be difficult to treat and
require a unique approach first used to treat disorders
such as complex regional pain syndrome and neuro-
pathic itch. In our experience, neuroleptic agents (eg, gab-
apentin, pregabalin), tricyclic antidepressants, and pain-
modifying antidepressants (eg, duloxetine) are the most
effective. N-methyl-D-aspartic acid receptor antagonists
(eg, memantine), systemic antibiotics, and other topi-
cally formulated medications (eg, ketamine, glycopyr-
rolate, capsaicin) may be helpful in certain cases. Be-
cause of the associated heightened sensitivity to heat and
sunlight, laser- and light-based interventions should be
used with caution.

Because our understanding of this enigmatic sub-
class of rosacea is extremely limited, further research is
clearly needed to better describe the underlying path-
physiologic characteristics and to identify additional ef-
teptive treatment methods.

Tiffany C. Scharschmidt, MD
John M. Yost, MD, MPH
Sam V. Truong, MD
Martin Steinhoff, MD, PhD
Kevin C. Wang, MD, PhD
Timothy G. Berger, MD

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Author Affiliations: Department of Dermatology, Uni-
versity of California, San Francisco (Drs Scharschmidt,
Truong, Steinhoff, Wang, and Berger); School of Medi-
cine, University of Michigan, Ann Arbor (Dr Yost); Los
Angeles Medical Center, Kaiser Permanente, Los Ange-
les, California (Dr Truong); and Program in Epithelial
Biology, Stanford University School of Medicine, Stan-
ford, California (Dr Wang).

Correspondence: Dr Wang, Department of Dermatol-
ogy, Stanford Medicine Outpatient Center, 450 Broad-
Author Contributions: Drs Scharschmidt, Wang, and Berger had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Drs Scharschmidt and Yost contributed equally to this work.

Study concept and design: Scharschmidt, Yost, Wang, and Berger.

Acquisition of data: Scharschmidt, Yost, Truong, and Steinhoff.

Analysis and interpretation of data: Scharschmidt, Yost, Steinhoff, and Wang.

Drafting of the manuscript: Scharschmidt, Truong, and Steinhoff.

Critical revision of the manuscript for important intellectual content: Steinhoff, Wang, and Berger.

Statistical analysis: Yost.

Administrative, technical, and material support: Scharschmidt, Truong, and Steinhoff.

Study supervision: Scharschmidt, Steinhoff, Wang, and Berger.

Neural dysregulation

Vasomotor

Inflammatory

Neuropathic

Flushing, telangiectasia

Edema, papules, pustules

Dysesthesia, pruritus

β-Blockers, vascular lasers

Antibiotics, immune modulators

Dysesthesia, pruritus

Neuroleptics

β-Blockers, vascular lasers

Antibiotics, immune modulators

Figure 2. Proposed diagnostic and treatment algorithm for a patient with rosacea based on clinical-pathologic correlation. In any given patient, more than 1 pathway and treatment method might be important, but identifying individual components can help guide management.

Table. Patient Characteristics

<table>
<thead>
<tr>
<th>Patient No./Sex/ Age at Onset, y/ Symptom Duration, y</th>
<th>Pertinent Medical History</th>
<th>Previous Ineffective Therapies</th>
<th>Therapies With at Least Partial Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/F/38/9</td>
<td>Depression, chronic pain, cervical stenosis, fibromyalgia, migraines, essential tremor, Raynaud phenomenon</td>
<td>Topical steroids, topical clindamycin</td>
<td>Gabapentin, combination cream of ketamine, 15%/amitriptyline, 5%/clonidine, 0.2%/ketoprofen, 10%</td>
</tr>
<tr>
<td>2/F/45/15</td>
<td>Depression, migraines</td>
<td>Topical capsaicin, pregabalin, tramadol</td>
<td>Gabapentin, duloxetine</td>
</tr>
<tr>
<td>3/F/25/10</td>
<td>Acne vulgaris, migraines, allergic contact dermatitis</td>
<td>Oral tetracyclines, topical metronidazole, nadolol, gabapentin, amitriptyline</td>
<td>Amoxicillin, desonide for itch</td>
</tr>
<tr>
<td>4/F/50/10</td>
<td>Carpal tunnel syndrome, autoimmune thyroiditis, chronic pain, neurogenic itch, spondyloarthropathy</td>
<td>NA</td>
<td>Gabapentin, duloxetine</td>
</tr>
<tr>
<td>5/F/36/8</td>
<td>Complex regional pain syndrome, positive ANA without other known autoimmune disease</td>
<td>Oral antibiotics, topical steroids</td>
<td>Pregabalin, duloxetine</td>
</tr>
<tr>
<td>6/F/29/8</td>
<td>Mixed connective tissue disease, Raynaud phenomenon, depression, bulimia</td>
<td>Topical metronidazole, hydroxychloroquine</td>
<td>Gabapentin, minocycline</td>
</tr>
<tr>
<td>7/M/37/13</td>
<td>Scoliosis dysesthesia, psoriasis, C3-6 degenerative joint disease</td>
<td>Topical metronidazole</td>
<td>Minocycline, doxycycline</td>
</tr>
<tr>
<td>8/F/41/17</td>
<td>Rheumatoid arthritis</td>
<td>Topical metronidazole, topical steroids, oral antibiotics, β-blockers, gabapentin, hydroxychloroquine, amitriptyline</td>
<td>Nortriptyline</td>
</tr>
<tr>
<td>9/M/15/10</td>
<td>Psoriatic arthritis, irritable bowel syndrome, obsessive compulsive disorder</td>
<td>Topical metronidazole, topical steroids, gabapentin, topiramate, botulinum toxin type A, laser therapy, thoracic sympathectomy, clonidine, propranolol</td>
<td>Topical glycopyrrolate, 3%; prazosin, memantine NMDA-receptor antagonist</td>
</tr>
<tr>
<td>10/F/53/5</td>
<td>Oral lichen planus, headaches</td>
<td>Topical sulfa</td>
<td>Amoxicillin</td>
</tr>
<tr>
<td>11/F/32/12</td>
<td>Headaches</td>
<td>Topical metronidazole, topical steroids, gabapentin, pregabalin</td>
<td>Topical capsaicin, duloxetine</td>
</tr>
<tr>
<td>12/F/60/2</td>
<td>Complex regional pain syndrome, Raynaud phenomenon, depression, esophageal dysmotility, positive ANA without other known autoimmune disease</td>
<td>Topical metronidazole, topical steroids, topical doxepin</td>
<td>Gabapentin, hydroxychloroquine</td>
</tr>
<tr>
<td>13/F/37/8</td>
<td>Anxiety, depression, headaches, Raynaud phenomenon</td>
<td>Topical sulfasalazine, topical metronidazole, azelastine, doxycycline, gabapentin, intense pulsed light, topical amitriptyline, topical ketamine</td>
<td>Titanium dioxide, hydroxychloroquine, amitriptyline, propranolol</td>
</tr>
<tr>
<td>14/F/22/9</td>
<td>Systemic lupus erythematosus, Raynaud phenomenon</td>
<td>Topical metronidazole, oral tetracyclines, gabapentin, pregabalin, β-blockers, vascular laser therapy, topical doxepin, topical ketamine</td>
<td>Hydroxychloroquine, memantine</td>
</tr>
</tbody>
</table>

Abbreviations: ANA, antinuclear antibody; NA, not applicable; NMDA, N-methyl-d-aspartic acid.
Bullous Amyloidosis Complicated by Cellulitis and Sepsis: A Case Report

Report of a Case. A 78-year-old African American man was seen with a history of easy bruising for 1 year. Workup revealed free \( \lambda \) light chains in the serum and urine. After bone marrow biopsy, the patient was diagnosed as having multiple myeloma. He underwent chemotherapy with cyclophosphamide, bortezomib, and dexamethasone along with prophylaxis with sulfamethoxazole-trimethoprim, fluconazole, and acyclovir and began to show improvement.

However, 3 months into treatment, he was seen in the emergency department for septic shock. No source of infection was initially evident. Dermatology was consulted for evaluation of bullous skin lesions, which had been present for 2 weeks prior to admission. Although the patient had been seen by a physician during this time, no diagnostic studies or therapeutic measures to address his skin lesions were undertaken. His last chemotherapy treatment was 2 days prior to admission.

Dermatologic examination revealed tender, erythematous patches with hemorrhagic bullae and few erosions in an intertriginous distribution, with lesions in the axillae, groin including the penis, and medial thighs (Figure). Nikolsky and Asboe-Hansen signs were negative. One or 2 superficial erosions were present on the dorsal aspects of the hands and feet. Mucous membranes were clear. No macroglossia or lymphadenopathy was found.

A punch biopsy specimen from the medial thigh revealed hemorrhage and intradermal vesicle formation (cleavage plane in the papillary dermis). A fine granular eosinophilic material in the papillary dermis was confirmed to be amyloid by electron microscopy and Congo red stain with apple green birefringence on polarized microscopy. In addition, a moderate neutrophilic infiltrate was present throughout the dermis and superficial subcutis, suggestive of cellulitis. Direct immunofluorescence showed IgG and \( \lambda \) light chains in the papillary dermis but no IgA, IgM, \( \kappa \) light chains, or C3.

A diagnosis of bullous amyloidosis complicated by cellulitis was made. Blood cultures were positive for Escherichia coli. It was believed that the source of the patient’s bacteremia was cutaneous breakdown in the groin. The patient responded well to antibiotic therapy and was discharged after 1 week.

Comment. Amyloidosis typically occurs in the setting of multiple myeloma and occurs less commonly with Waldenstrom macroglobulinemia. Twenty-five percent of patients with amyloidosis exhibit cutaneous involvement, with lesions ranging from petechiae and ecchymoses to papules, plaques, nodules, alopecia, or sclerodermatous changes.1 Mucous membrane involvement rarely occurs.2 Bullous lesions are rare, with fewer than 40 cases reported.3 The eruption is often intertriginous, likely exacerbated by friction. Hemorrhage is likely secondary to fragility of vessel walls, which contain amyloid.4

Amyloidosis related to multiple myeloma is usually due to immunoglobulin light chain deposition. Few cases of heavy chain amyloidosis have been reported.4 Of interest, our case showed positive direct immunofluorescence findings for IgG and \( \lambda \) light chains in the papillary dermis where amyloid deposition was seen, indicating that this might be the first case of mixed heavy chain and light chain bullous amyloidosis reported in the literature.

Another interesting feature of this case was the development of septic shock. Our patient was immunocompromised due to his underlying malignant neoplasm as well as by recent chemotherapy, and he exhibited E coli sepsis. Bullous amyloidosis complicated by secondary infection and gram-negative rod septicemia (with E coli and Enterococcus faecalis) has only once been reported in the literature, to our knowledge.5 The predominantly intertriginous localization of bullous amyloid lesions is likely a contributing factor.

Kalpana Reddy, MD
Syed Hoda, MD
Adam Penstein, MD
Tarun Wasil, MD
Sheng Chen, MD, PhD

Author Affiliations: Department of Dermatology, State University of New York (SUNY) Downstate Medical Center, Brooklyn (Dr Reddy); and Departments of Pathology (Drs Hoda and Chen) and Medicine (Drs Penstein and Wasil), North Shore–LIJ Health System, New York, New York.

Correspondence: Dr Reddy, Department of Dermatology, SUNY Downstate Medical Center, 450 Clarkson Ave, Box 46, Brooklyn, NY 11203 (kalpanared@gmail.com).

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