CLINICAL PROBLEM-SOLVING

Caren G. Solomon, M.D., M.P.H., *Editor*

Eye of the Beholder

Lindsey MacFarlane, M.D., Nora Osman, M.D., Susan Ritter, M.D., Ph.D., Amy L. Miller, M.D., Ph.D., and Joseph Loscalzo, M.D., Ph.D.

In this Journal *feature, information about a real patient is presented in stages (boldface type) to an expert clinician, who responds to the information, sharing his or her reasoning with the reader (regular type). The authors' commentary follows.*

From the Department of Medicine, Brigham and Women's Hospital, and Harvard Medical School — both in Boston. Address reprint requests to Dr. Miller at 75 Francis St., Boston, MA 02115, or at almiller@partners.org.

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A 47-year-old man with a history of hypertension presented to an urgent care ambulatory clinic with a 3-day history of swelling around his left eye and a sensation of tightness in his throat. He reported no pruritus, photophobia, diplopia, headache, changes in visual acuity, or pain. He was hoarse but did not have wheezing or shortness of breath. During the 3 days before presentation, it had become difficult for him to swallow solids, and he felt as if food was sticking in his throat. He reported no fevers, fatigue, gastrointestinal symptoms, or recent illness.

In a patient presenting with periorbital edema and oropharyngeal symptoms, angioedema should be considered to be present until proved otherwise, given the risk of airway compromise if the angioedema is not treated appropriately. The asymmetric distribution of angioedema is common. Isolated angioedema without pruritus or urticaria is often the result of increased levels of bradykinin, which increases vascular permeability and dilatation, leading to angioedema. Typical mediators of bradykinin-induced angioedema include angiotensin-converting–enzyme inhibitors, which decrease bradykinin degradation, and acquired or inherited C1 inhibitor deficiencies, which increase bradykinin production. In contrast, angioedema with urticaria is typically mediated by mast cells and IgE in response to interaction with an allergen, causing the release of chemokines and cytokines that leads to inflammation. Mast-cell–mediated reactions generally last for 12 to 36 hours, whereas bradykinin-induced reactions may persist for 2 to 4 days. Although hypothyroidism can cause eyelid edema and vocal hoarseness owing to fluid accumulation in the vocal cords, swelling usually occurs in both eyelids and is associated with generalized myxedema and other findings suggestive of hypothyroidism (e.g., bradycardia, fatigue, sensitivity to cold temperatures, and dry skin). Although orbital cellulitis and trichinella also cause periorbital swelling, these conditions are typically associated with pain and fever and not with oropharyngeal symptoms.

The patient was allergic to shellfish but had no known recent exposure. He took no prescription medications and had not used any new over-the-counter medications in the preceding month. He worked in real estate development and lived alone in Boston. He had traveled to China, Japan, and Mexico in the preceding 3 years but had not left the Boston area in the preceding 6 months. The patient had no pets, reported no exposures to new environments or foods, and had not had recent contact with sick persons. He did not smoke tobacco or consume alcohol. His family history was noteworthy for breast cancer in his mother.

A thorough history of possible exposures, including oral (e.g., food), inhaled (e.g., pollen, fumes, or solvents), and topical (e.g., creams or plants), is important in the elucidation of possible triggers for any patient in whom an allergic reaction or angioedema may be likely. Such triggers are often difficult to identify. A family history could be informative, since angioedema can be familial.

On examination, the patient's temperature was 37.3°C, his heart rate 95 beats per minute, blood pressure 130/80 mm Hg, and respiratory rate 18 breaths per minute. His oxygen saturation was 100% while he was breathing ambient air. He appeared to be comfortable and was speaking in full sentences with a hoarse, muffled voice. Edema surrounded the entire left eye, and there was faint erythema (Fig. 1). No ptosis was observed. Extraocular movements were intact, and pupils were equal in size, round, and reactive to light and accommodation. Mucous membranes had neither ulcerations nor lesions. The tongue appeared mildly and diffusely enlarged. Lungs were clear to auscultation. There was no stridor. The remainder of the examination of the skin was normal. The cranial nerves were intact, and muscle strength was 5/5 throughout (i.e., normal, as represented by active motion against full resistance). There was no peripheral edema.

The physical examination is consistent with angioedema, which often affects the larynx and tongue, as well as the lips and uvula, which do not appear to be involved in this patient. The mild erythema noted in the periorbital region is also observed in angioedema, although erythema may not be apparent in some patients, particularly those with darker skin. In the absence of a clear cause or trigger, I would evaluate levels of inflammatory markers and C4, since elevations in the former can suggest an underlying infectious or inflammatory cause, and abnormalities in the latter would suggest a hereditary or acquired deficiency in C1 inhibitor. Empirical treatment with glucocorticoids and an antihistamine for possible allergic angioedema could be considered, although the duration of symptoms and the absence of associated urticaria suggest that his symptoms are not related to an allergic reaction.

Empirical treatment for allergic angioedema was initiated with hydroxyzine and 40 mg of prednisone for 3 days, after which the dose of glucocorticoids was tapered. Nonetheless, the symptoms progressed, with worsening dysphonia, an increased sensation of throat swelling, nasal regurgitation of liquids, pain in the shoulders and hips, and loss of the ability to jump while playing basketball. These developments prompted the patient

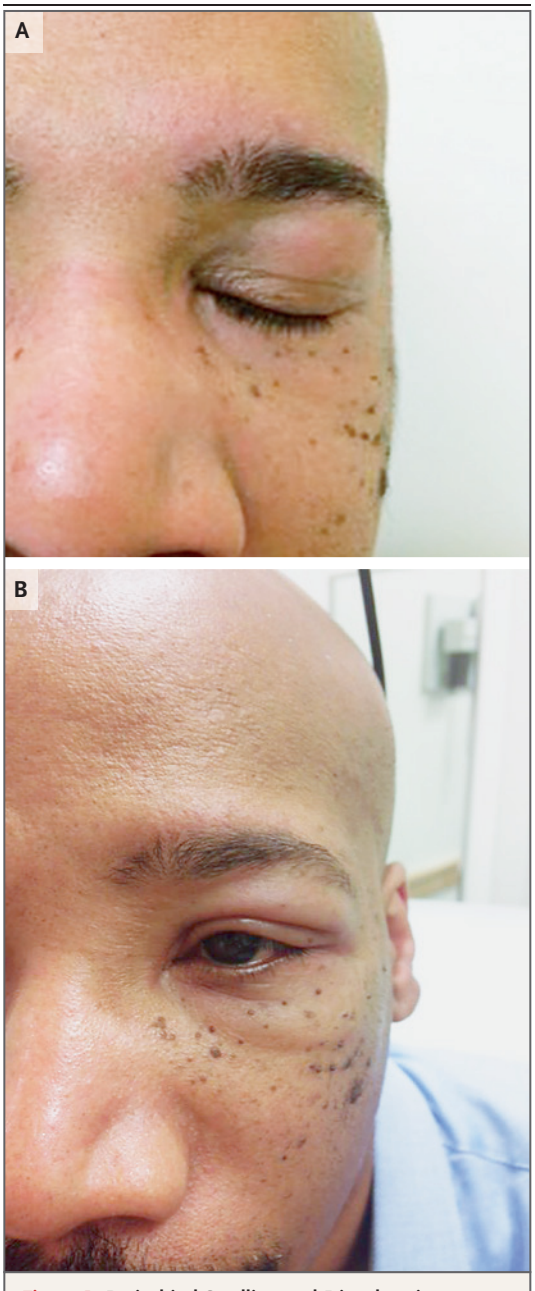

Figure 1. Periorbital Swelling and Discoloration.
Violaceous discoloration (Panel A) and swelling (Panel B) can be seen in the left periorbital region.

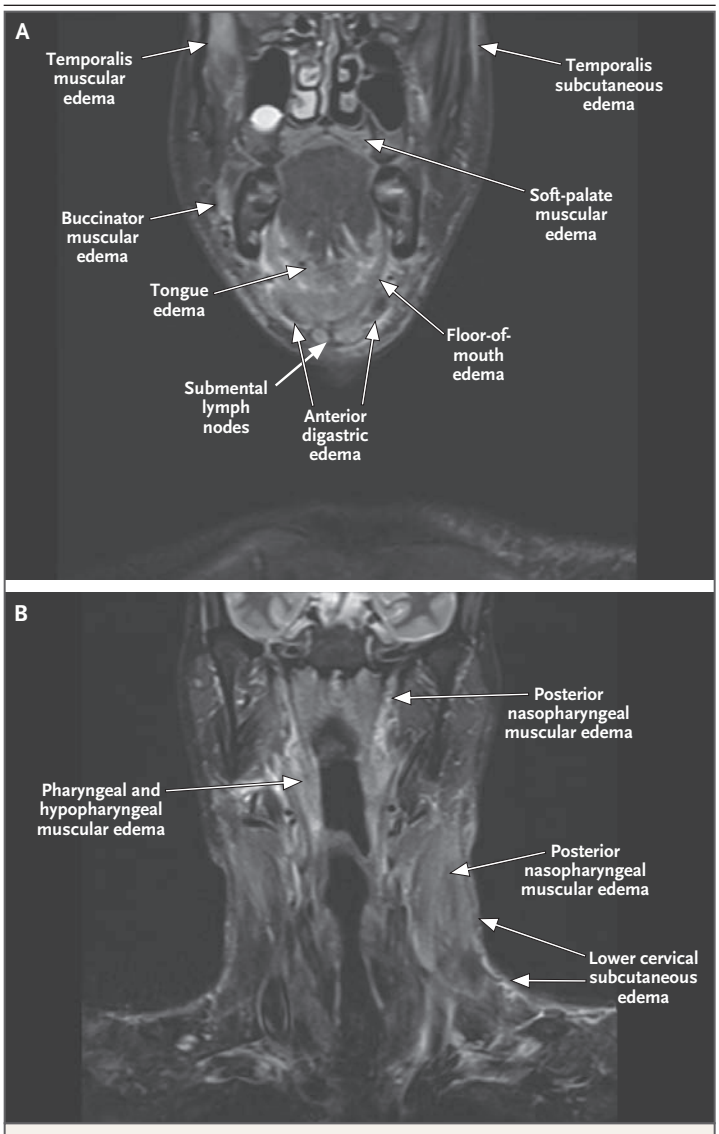

Figure 2. MRI of the Head and Neck.

Transverse images of the head (Panel A) and coronal images of the neck (Panel B) reveal increased focal signaling that is consistent with edema in multiple muscles.

to go to the emergency department 2 weeks after his initial presentation.

The evolution of the patient's symptoms is worrisome and points to a process that is causing proximal weakness as well as edema of the face and oropharynx, with possible myopathic involvement. Careful examination of the nervous and musculoskeletal systems is indicated to better define the distribution of disease throughout the body.

New findings on examination included tenderness to palpation over the anterior and lateral neck musculature and subcutaneous edema in both upper arms. Arm strength was 5/5 in both the upper and lower arms. Strength in hip flexion, extension, and abduction was 4/5, and strength in the lower legs was 5/5. Rising from a seated position was difficult and caused pain in the hips and thighs. No ptosis was observed. Sensation to light touch, pinprick, and vibration was intact. Deep-tendon reflexes were 2+ in the biceps, triceps, and patellas. Magnetic resonance imaging (MRI) of the head and neck revealed muscle edema of the left orbit, facial muscles, tongue, and neck musculature (Fig. 2).

The physical examination revealed proximal weakness and edema. The newly detected weakness makes angioedema much less likely. Hypothyroidism can cause weakness, but myopathy would be unexpected in an adult. Trichinella can cause unilateral periorbital swelling and dysphagia in addition to myopathy, but the patient's travel history, the absence of ocular pain or visual disturbance preceding gastrointestinal symptoms, and the absence of fever are less consistent with this diagnosis. Although neurologic conditions such as myasthenia gravis should be considered in a patient with weakness and bulbar symptoms (dysphagia and dysphonia), these conditions are not associated with muscle edema. A more likely explanation would be an inflammatory myopathy, such as dermatomyositis, polymyositis, or necrotizing autoimmune myopathy, all of which cause proximal muscle weakness. Inclusion-body myositis, another inflammatory myopathy, is unlikely, since it typically affects older patients, has a more indolent onset than that observed in this patient, and often spares the deltoids, preferentially affecting the lower arms. Clinically, dermatomyositis is distinguished from polymyositis and necrotizing autoimmune myopathy by its distinctive dermal findings, including Gottron's papules (violaceous papules on the dorsum of the metacarpophalangeal and interphalangeal joints), Gottron's sign (nonpalpable macules over the extensor surfaces of joints), heliotrope rash (a violaceous rash involving the periorbital skin), V sign (also known as shawl sign), in which there are macular erythematous lesions over the anterior chest and back, and holster sign, in which these lesions appear over the upper lateral thighs. This patient's peri-

orbital discoloration is consistent with a mild heliotrope rash, although the asymmetric periorbital edema is atypical. Diffuse edema is rare in patients with dermatomyositis, but it can herald more aggressive disease. In both dermatomyositis and polymyositis, oropharyngeal or esophageal weakness can lead to dysphagia and nasal regurgitation. Histologic analysis of muscle tissue is useful in confirming the diagnosis.

The thyrotropin level was 0.708 mIU per liter (normal range, 0.5 to 5.7), alanine aminotransferase level 298 U per liter (normal range, 10 to 50), aspartate aminotransferase level 857 U per liter (normal range, 10 to 50), and alkaline phosphatase level 49 U per liter (normal range, 43 to 130). The creatine kinase level was 33,950 U per liter (normal range, 39 to 308). The erythrocyte sedimentation rate was 16 mm per hour (normal range, 0 to 12 mm), and the C-reactive protein level was 24.1 mg per liter (normal range, 0.0 to 3.0). The C4 level was 44 mg per deciliter (normal range, 10 to 40 mg). Antinuclear antibody titers were positive at 1:160; the myositis-specific antibody panel, including the anti–Jo-1 antibody, was negative. A muscle-biopsy specimen taken from the left deltoid showed mild variability in fiber size without perifascicular atrophy. Frozen sections stained with hematoxylin and eosin showed an inflammatory infiltrate present, predominantly around epimysial blood vessels. Staining for major histocompatibility complex (MHC) class I was positive and had a patchy distribution on nonnecrotic fibers. A stain that was specific for membrane attack complex (MAC) showed positivity surrounding scattered capillaries (Fig. 3).

Patients with inflammatory myopathies frequently have elevated levels of creatine kinase and liver enzymes. Although many patients also have antinuclear or anticytoplasmic antibodies and elevated levels of inflammatory markers, such findings are neither sensitive nor specific. The pathologic findings (including inflammation surrounding the vascular structures, MHC class I positivity on analysis of muscle fibers, and MAC deposition on endothelial cells) together with the clinical presentation support a diagnosis of dermatomyositis. I would initiate high-dose systemic glucocorticoids and recommend a low threshold for the addition of a glucocorticoid-sparing agent, such as methotrexate or azathioprine. Given the association of dermatomyositis with an increased risk of cancer, age-appropriate cancer screening should be performed if screening is not up to date. In this case, I would perform a careful physical examination (including testicular examination); some experts recommend imaging to rule out cancer, but the benefit is uncertain.

The patient was treated with 1000 mg of intravenous methylprednisolone daily for 3 days, followed by oral prednisone at a dose of 60 mg daily. There was initial amelioration of his periorbital rash and dysphonia and reduction in creatine kinase levels, but his proximal strength improved only partially, and he continued to have difficulties performing the activities of daily living owing to weakness. Dysphagia, resulting in weight loss, also continued. Given the severity of his disease, he was started on subcutaneous injections of methotrexate at a dose of 20 mg weekly. Substantial improvement in his strength followed, the dysphagia and weight loss resolved, and creatine kinase levels returned to normal. Pulmonary-function tests and computed tomography of the chest showed no respiratory involvement. Six months after the resolution of symptoms and laboratory abnormalities, after the prednisone dose had been tapered to 15 mg per day, a disease flare developed, which was manifested by proximal muscle weakness, elevated levels of creatine kinase, and Gottron's papules, which had not been present previously. He was subsequently started on monthly intravenous infusions of immune globulin and a higher dose of metho-

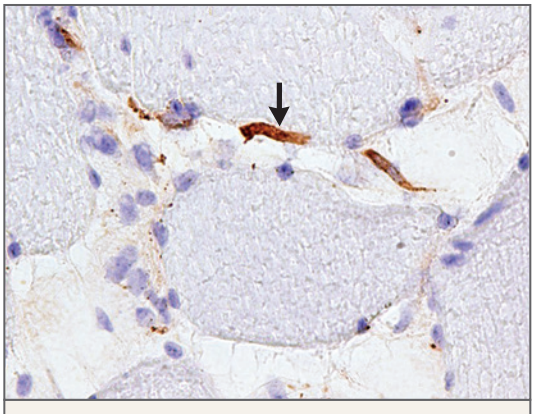

Figure 3. Biopsy Specimen of Muscle Tissue.
Staining with immunoperoxidase revealed the deposition of membrane-attack complex (MAC) on the endothelium of capillaries (arrow). MAC deposition results from activation of the complement cascade.

trexate — 25 mg weekly — after which his symptoms abated. No cancer has been detected.

COMMENTARY

This case represents a rare clinical challenge — an atypical presentation of a rare disorder. In this patient, the evolution of symptoms (from initial unilateral periorbital swelling to muscle tenderness and weakness) led to a shift in the differential diagnosis and identification of the correct diagnosis.

The inflammatory myopathies are rare, with an annual incidence of 1 in 100,000.[1] Dermatomyositis is slightly more common among adults than among children,[1,2] and the other inflammatory myopathies are substantially more common among adults. Dermatomyositis is also singular in its association with skin manifestations (for examples, see the interactive graphic, available with the full text of this article at NEJM.org), including heliotrope erythema, Gottron's papules, Gottron's sign, shawl sign, and holster sign, which may precede or occur concurrently with proximal muscle weakness.[3] Patients may have dilated nailfold capillaries (which can be visualized with a dermatoscope) and ragged or thickened cuticles. Proximal weakness is often progressive, with patients reporting difficulty in raising their arms above their head, climbing stairs, or standing from a seated position. In rare instances, the characteristic cutaneous features of dermatomyositis develop without muscle involvement, in a condition that is designated amyopathic dermatomyositis or dermatomyositis sine myositis.[4]

An interactive graphic is available at NEJM.org

Elevation in creatine kinase levels is characteristic of all the inflammatory myopathies, with levels rising up to 50 times as high as the upper limit of the normal range in patients with dermatomyositis.[1] Myositis-specific antibodies are often measured, since findings can have prognostic significance. The most common such antibody is anti–Jo-1, which is present in up to 20% of patients with polymyositis or dermatomyositis.[4] The anti–Jo-1 antibody is associated with the antisynthetase syndrome, a constellation of arthritis, Raynaud's phenomenon, mechanic's hands (in which there is cracking along the distal tip and edges of the fingers), and interstitial lung disease, which is associated with a poorer prognosis in patients with an inflammatory myopathy.

The demonstration of myopathic motor potentials on electromyography can be useful in distinguishing the inflammatory myopathies from other diseases that affect the neuromuscular unit but cannot be used to distinguish among the various inflammatory myopathies.[3] MRI may show increased signaling on short-tau inversion recovery (STIR) sequences, indicating areas of muscle edema, which can be used to help select the site for muscle biopsy.[1,5] Muscle biopsy is the diagnostic standard, since the inflammatory myopathies can be differentiated on histologic analysis. The presence of MHC class I antigen on muscle sarcolemma is an early histologic marker of inflammatory myopathy that often persists throughout the disease course. Perifascicular atrophy is a typical finding in dermatomyositis, but it occurs later in the disease process and is identified in only 50% of biopsies obtained in the early stages of disease.[4] In dermatomyositis, the inflammatory infiltrate consists of macrophages, B cells, and CD4+ T cells, all of which often surround vascular structures, whereas in polymyositis and inclusion-body myositis, CD8+ T cells surround and invade nonnecrotic muscle fibers.[4]

A reported 15 to 25% of patients with dermatomyositis have had prior cancer or have concurrent cancer, or cancer will develop in them.[1] However, there does not appear to be a correlation between dermatomyositis and a particular type of cancer; in most patients, the diagnosis of dermatomyositis comes after the diagnosis of cancer.[6] There are no consensus guidelines for cancer screening in patients with inflammatory myositis. It is prudent to ensure age-appropriate cancer screening; some experts recommend chest, abdominal, and pelvic imaging for further assessment in patients without a known cancer, although data are lacking in regard to the associated cost-effectiveness and outcomes. Anti–transcriptional intermediary factor 1γ (also referred to as anti-p155) and anti–nuclear matrix protein 2 are associated with an increased risk of cancer in adults with dermatomyositis[3]; the former, which is included in the myositis-specific antibody panel at most laboratories, has been reported to have a positive predictive value of 78% and a specificity of 89%.[7]

Patients with inflammatory myopathies should be evaluated for pulmonary manifestations, including an assessment of forced vital capacity, since diaphragmatic or intercostal weakness can lead to hypercarbia as a result of hypoventila-

tion. Interstitial lung disease is reported in 10 to 40% of patients with inflammatory myopathies and approaches 70% in patients with anti–Jo-1 antibodies or anti–melanoma differentiation–associated protein-5 antibodies.[3]

Although there is a paucity of controlled trials on the treatment of dermatomyositis, glucocorticoids are the mainstay of treatment for dermatomyositis, polymyositis, and autoimmune necrotizing myositis — largely on the basis of clinical experience.[3] Oral prednisone is often started at a dose of 0.75 to 1 mg per kilogram of body weight, with intravenous glucocorticoids reserved for severe or progressive cases; doses are tapered gradually, primarily on the basis of the patient's symptoms.[3] Additional immunosuppressants are often added as glucocorticoid-sparing agents — most often methotrexate or azathioprine, although mycophenolate and cyclosporine have also been used.[3] Protection from and avoidance of the sun are recommended for patients with manifestations of dermatomyositis on the skin, such as Gottron's sign, shawl sign, and holster sign. These manifestations can be highly photosensitive.

Intravenous immune globulin was shown to be beneficial in the treatment of recalcitrant dermatomyositis in a randomized, controlled trial[8]; this treatment has the advantages of fairly rapid onset of effect without immunosuppression. Case reports have described improvements with rituximab therapy in the condition of patients with refractory cases, although it was not reported to be beneficial in one randomized trial involving patients with refractory dermatomyositis or polymyositis.[9] Tumor necrosis factor inhibitors are generally avoided in the treatment of inflammatory myopathies owing to reports indicating that these agents aggravate disease, but case reports have described improvement after treatment with the interleukin-6 inhibitor tocilizumab and the interleukin-1 inhibitor anakinra.[3,10,11] An open-label trial of cyclophosphamide involving patients with dermatomyositis and polymyositis suggested amelioration of interstitial lung disease.[12] Unlike the other inflammatory myopathies, inclusion-body myositis is refractory to immunosuppression, including treatment with glucocorticoids; physical rehabilitation and assistive devices are the mainstays of care.[3]

The current case highlights the fact that the manifestations of the inflammatory myopathies may be subtle and insidious. Awareness of these diagnoses and their associated features enables timely diagnosis and treatment.

No potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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