Medical Dermatology Practice Gaps (and Clinical Pearls): Insights from Mayo Clinic

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Forum F033: Practice Gaps in Adult and Pediatric Dermatology: Illustrative Cases
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Disclosure

• I have no conflicts of interest
Overview

• Discuss 3 clinical insights from medical dermatology based on Mayo Clinic patients and research that address practice gaps

• Take home messages/clinical pearls
Can an unexplained skin eruption provide insights into evolving systemic disease?
Case Presentation

• 71 year-old man with widespread, mildly pruritic cutaneous eruption of 2 years’ duration
  • Started on hands → upper arms, face, trunk, lower extremities

• Outside biopsies showed “granulomatous” inflammation
  • Clinical diagnoses ranged from granuloma annulare to cutaneous sarcoidosis

• Prior unsuccessful treatments:
  • Clobetasol 0.05% cream
  • Intramuscular triamcinolone acetonide
  • Hydroxychloroquine 200 mg twice/d X 4 months
Case

• At the time of presentation to our institution:

  • 80% body surface involvement of cutaneous eruption

  • 60 pounds of unintentional weight loss during preceding year
Erythematous patches and widespread papules coalescing into plaques on the trunk, upper extremities, and lower extremities *Arch Dermatol*. 2011;147(3):331-335 [Figure 1]
Close-up images highlighting the cutaneous morphological features

Arch Dermatol. 2011;147(3):331-335 [Figure 1]
Interstitial dermal granulomatous inflammation with many multinucleated giant cells

*GMS and AFB stains – negative (tissue culture also negative)
*Immunoperoxidase studies – reactive T-cell infiltrate

Arch Dermatol. 2011;147(3):331-335 [Figure 2]
Laboratory testing

**Note markedly increased monocyte count in peripheral blood**

**Normal or negative:** ACE, calcium, CCP, immunoglobulins, MPO, PR3, dsDNA, ENA panel, SPEP, urinalysis, tuberculin skin test

**Peripheral flow cytometry:** No clonal B- or T-lymphocyte abnormality, no quantitative subset abnormality

**CT chest/abdomen/pelvis:** Mediastinal and abdominal adenopathy (without hilar or paratracheal adenopathy)
Because of:

(1) Generalized granulomatous skin findings
(2) Markedly increased monocyte count (42%)
(3) Weight loss
(4) Adenopathy on CT Scan

. . . Patient underwent bone marrow biopsy
Bone Marrow Biopsy

- Increased monocytes, promonocytes, and blast cells, consistent with myelodysplastic syndrome (MDS)
  - Cytogenetic studies – negative

- **Lenalidomide** started for treatment of skin findings AND myelodysplastic syndrome
Fading and flattening of cutaneous findings after 6 weeks of lenalidomide

Arch Dermatol. 2011;147(3):331-335 [Figure 3]
HOWEVER. . .

• Despite improvement in skin and decrease in monocyte count from 42% to 7%. . .
  • Leukocyte count increased from 6200/µL to 18,800/µL and contained 63% blast cells

• His MDS thus progressed to acute myeloid leukemia (AML)
  • Shortly thereafter he developed pneumonia and died
Myelodysplastic Syndrome Presenting as Generalized Granulomatous Dermatitis

Samuel J. Balin, David A. Wetter, MD; Paul J. Kartin, MD; Louis Letendre, MD; Mark R. Pittelkow, MD

**Background:** Granulomatous dermatitis has rarely been reported as a manifestation of leukemia or myelodysplastic syndrome (MDS). We describe a case of widespread granulomatous dermatitis that preceded the diagnosis of MDS by 2 years.

**Observations:** A 71-year-old man developed a generalized, mildly pruritic eruption that slowly progressed over a 2-year period. Punch biopsy specimens demonstrated interstitial dermal granulomatous inflammation. A complete blood cell count with differential showed marked monocytosis, and the findings of a subsequent biopsy of the bone marrow confirmed MDS. Lenalidomide therapy was initiated, and the patient's skin condition improved after 6 weeks of treatment; however, his MDS progressed to acute myeloid leukemia, and he died shortly thereafter.

**Conclusions:** There is a paucity of literature documenting the occurrence of granulomatous dermatitis as a manifestation of an underlying hematologic disorder. This case illustrates a striking example of widespread granulomatous dermatitis heralding the onset of MDS. It is imperative that the dermatologic community recognize the rare association of granulomatous dermatitis with myelodysplasia, because the cutaneous manifestations may be the presenting finding and can precede the development of leukemia by several years.

*Arch Dermatol. 2011;147(3):331-335*
Cutaneous Signs of Hematologic Malignancies

“Doctor, Is There Something Wrong With My Blood?”


GA AND GA-LIKE CONDITIONS AS A PARANEoplast ic PHENOMENON ASSOCIATED WITH HEMATOLOGIC MALIGNANCIES

New and Callen¹ and Balin et al² raise important questions: Are GA and GA-like lesions associated with malignant disease? Are they associated with hematologic neoplasms in particular? Although in a recent report Li et al¹⁷ could not find a relationship between GA and malignant disease, the nexus between GA and malignant neoplasms remains to be fully elucidated. There are many reports of patients with cutaneous lesions of GA or interstitial granulomatous dermatitis who presented with a variety of neoplasms. These included Hodgkin and non-Hodgkin lymphoma, leukemia (acute myelogenous leukemia, chronic lymphocytic leukemia, myelomonoeytic leukemia, large granular lymphocytic leukemia), myelodysplastic syndromes, and solid tumors (breast, cervical, colon, lung, prostate, testicular, and thyroid cancers).¹⁸,¹⁰

In summary, the 2 observations published in this issue of the Archives demonstrate the value of dermatologists—and of medical dermatologists in particular—as physicians who can diagnose internal conditions based on the evaluation of the clinical and pathologic findings presenting in the skin of their patients.¹⁰ Knowledge of the cutaneous lesions associated with internal diseases will help to select which patients should be screened in order to rule out an underlying hematologic malignancy, and really know when there is something wrong with their blood.

Jose M. Mascaro Jr, MD
*Non-infectious granulomatous dermatitides*: skin diseases with predominantly dermal infiltrate composed largely of histiocytes

*Examples include: sarcoidosis, granuloma annulare, necrobiosis lipoidica, cutaneous Crohn’s disease, rheumatoid nodule, interstitial granulomatous dermatitis (IGD), palisaded neutrophilic and granulomatous dermatitis (PNGD)

*IGD/PNGD*: Can be associated with connective tissue disease (RA, SLE), systemic vasculitis, and drugs (e.g. TNF inhibitors)

*Non-infectious cutaneous granulomas also reported with lymphoid malignancies (e.g. CLL) and hereditary (e.g. CVID) and acquired (e.g. AIDS) immunodeficiencies*
Reactive Granulomatous Dermatitis

A Review of Palisaded Neutrophilic and Granulomatous Dermatitis, Interstitial Granulomatous Dermatitis, Interstitial Granulomatous Drug Reaction, and a Proposed Reclassification

Misha Rosenbach, MD, PhD, Joseph C. Engin III, MD

Reactive Granulomatous Dermatitis

Concept that “ties together” IGD, PNGD, and IGDR

KEY POINTS

- Palisaded neutrophilic and granulomatous dermatitis, interstitial granulomatous dermatitis, and interstitial granulomatous drug reaction represent cutaneous reaction patterns that occur in the setting of a systemic trigger.
- Systemic triggers include connective tissue diseases (lupus, vasculitis, rheumatoid arthritis, other inflammatory and reactive arthritis), malignancy (hematologic more often than solid organ), and medications.
- We suggest the unifying term “reactive granulomatous dermatitis” to encompass these entities, guide clinical management, and coordinate scientific literature regarding this group of reactive skin diseases.

Table 5
Summary of initial evaluation and management of patients with reactive granulomatous dermatitis (RGD; includes PNGD, IGD, IGDR)

<table>
<thead>
<tr>
<th>Evaluation for drug-induced disease</th>
<th>Review of medications</th>
<th>Involving supplements, diet, herbal medications</th>
<th>Involving medications present for weeks to months</th>
<th>Focus on CCBs, BBs, ACE inhibitors, statins</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evaluate for systemic disease</td>
<td>Connective tissue disease</td>
<td>ANA</td>
<td>ANCA</td>
<td>Additional testing dictated by systemic symptomatology</td>
</tr>
<tr>
<td>Arthritis</td>
<td>RF/CCP</td>
<td>Rheumatology evaluation</td>
<td>Consider imaging</td>
<td></td>
</tr>
<tr>
<td>Malignancy</td>
<td>Age appropriate malignancy screen</td>
<td>CBC with differential</td>
<td>SBEV/UEP with IFE</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>Chest radiography</td>
<td>Ocult infections (endocarditis, hepatitis, pulmonary fungal infection)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Management</td>
<td>General</td>
<td>Skin biopsy</td>
<td>Medication cessation trial when indicated</td>
<td>Control underlying systemic disease</td>
</tr>
<tr>
<td>RGD specific</td>
<td>Wathful waiting</td>
<td>Topical or intranasal corticosteroids</td>
<td>NSAIDs</td>
<td>Dapsone</td>
</tr>
</tbody>
</table>

Table 6
Spectrum of reactive granulomatous dermatitis (RGD)

<table>
<thead>
<tr>
<th>Type</th>
<th>Predominant Clinical Presentation</th>
<th>Predominant Histopathologic Findings</th>
<th>Predominant Disease Associations</th>
</tr>
</thead>
<tbody>
<tr>
<td>RGD, PNGD type</td>
<td>Erythematous papules around the elbows</td>
<td>Intense neutrophilic inflammation, degenerated collagen, palisading granulomas, with or without leukocytoclastic vasculitis; minimal mucin</td>
<td>Connective tissue disease, Arthritis, Other (hematologic, solid organ)</td>
</tr>
<tr>
<td>RGD, IGD type</td>
<td>Erythematous cords on the trunk</td>
<td>Annular erythematous-to-violaceous plaques on proximal limbs and trunk</td>
<td>Intense neutrophilic vasculitis, eschar, absent vasculitis and no mucin</td>
</tr>
<tr>
<td>RGD, drug induced</td>
<td>Annular erythematous-to-violaceous plaques on proximal limbs and trunk</td>
<td>Spares interstitial histiocytes, rosettes of degenerated collagen, “floating” sign, absent vasculitis and no mucin</td>
<td>Arthritis, Connective tissue disease, Other (infection, drug)</td>
</tr>
<tr>
<td>RGD, polycyclic diffuse type</td>
<td>Polycyclic annular, erythematous-to-violaceous plaques with indurated border</td>
<td>Red-brown diffuse mildly infiltrated erythroderma</td>
<td>Spares interstitial histiocytes, rosettes of degenerated collagen surrounded by predominantly histiocytes, relatively scant neutrophils, rare eosinophils, absent vasculitis and nitro-scant mucin</td>
</tr>
</tbody>
</table>

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General points to consider:

(1) Skin involvement can be the first sign of an occult underlying malignancy

   * Variety of cutaneous presentations

(2) Granulomatous dermatitis has rarely been reported as the presenting feature of an underlying hematologic malignancy
<table>
<thead>
<tr>
<th>Source, y</th>
<th>Patient No./ Sex/Age, y</th>
<th>Underlying Disorder</th>
<th>Cutaneous Findings</th>
<th>Histologic Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Horiuchi et al., 11 1992</td>
<td>1/M/69</td>
<td>CMML</td>
<td>Pruritic nodules</td>
<td>Granuloma annulare</td>
</tr>
<tr>
<td>Vestey et al., 13 1993</td>
<td>2/M/66</td>
<td>MDS → AML</td>
<td>Diffuse papular eruption</td>
<td>Granuloma annulare</td>
</tr>
<tr>
<td>3/M/71</td>
<td></td>
<td>MDS</td>
<td>Diffuse papular eruption</td>
<td>Cutaneous sarcoidosis</td>
</tr>
<tr>
<td>Katz, 7 2003</td>
<td>4/F/66</td>
<td>MDS → AML</td>
<td>Numerous well-demarcated, nontender, eryhematos nodules</td>
<td>Granulomatous eruption</td>
</tr>
<tr>
<td>Anan et al., 5 2004</td>
<td>5/F/65</td>
<td>AML</td>
<td>Tender reddish eruption</td>
<td>Erythema nodosum and granulomatous lesions</td>
</tr>
<tr>
<td>Garg et al., 13 2006</td>
<td>6/M/57</td>
<td>AML</td>
<td>Multiple reddish brown pruritic papules coalescing into plaques</td>
<td>Annular elastolytic giant cell granuloma</td>
</tr>
<tr>
<td>Hinckley et al., 6 2009</td>
<td>7/M/76</td>
<td>CMML</td>
<td>Indurated dermal papules and plaques</td>
<td>Granuloma annulare</td>
</tr>
<tr>
<td>8/M/56</td>
<td></td>
<td>CMML</td>
<td>Hypopigmented indurated papules on extensor extremities with scleromyxedematous appearance</td>
<td>Granuloma annulare</td>
</tr>
<tr>
<td>Kawakami et al., 14 2009</td>
<td>9/M/70</td>
<td>Acute adult T-cell lymphoma</td>
<td>Erythematos grouped papules forming plaques</td>
<td>Granuloma annulare–like process</td>
</tr>
<tr>
<td>Present study</td>
<td>10/M/71</td>
<td>MDS → AML</td>
<td>Diffuse eryhematos patches and widespread papules</td>
<td>Granulomatous dermatitis (interstitial dermal granulomatous inflammation)</td>
</tr>
</tbody>
</table>

Abbreviations: AML, acute myeloid leukemia; CMML, chronic myelomonocytic leukemia; MDS, myelodysplastic syndrome; MDS → AML, MDS progressing to AML.

*Cases of necrobiotic xanthogranuloma were not included in the table; the occurrence of necrobiotic xanthogranuloma with underlying hematologic malignancies, including multiple myeloma, has been well documented elsewhere.¹

Arch Dermatol. 2011;147(3):331-335
Interstitial Granulomatous Dermatitis as the Initial Manifestation of Myeloma

Interstitial granulomatous dermatitis (IGD) has been associated with pharmacotherapy, various autoimmune conditions, and hematologic malignant conditions. Herein, we report a patient in whom IGD was the initial manifestation of a previously undiagnosed myeloma.

Report of a Case | A man in his 50s presented with a 1-year history of an asymptomatic symmetric eruption involving his upper back, arms, forearms, and hands. His medical history was significant for arthritis, diabetes mellitus, hypertension, and a retroperitoneal schwannoma that was excised with nega-
Take Home Messages (Part 1)

• Numerous causes of non-infectious cutaneous granulomatous eruptions

• Granulomatous dermatitis may rarely be the first sign of underlying myelodysplasia

• **PRACTICE GAP/CLINICAL PEARL**: In patients with generalized granulomatous eruptions of indeterminate cause: consider evaluation for underlying hematologic malignancy (in addition to evaluation for underlying rheumatologic disease and review of medications)
Worsening skin eruptions (despite appropriate immunosuppressive treatments) in (two) patients with underlying autoimmune connective tissue disease or vasculitis: Should immunosuppressive therapies be increased? . .
Case 1

• 45 year-old woman with skin eruption and proximal muscle weakness
Violaceous erythema of the upper chest with focal erosions of the upper breast
Violaceous and lichenoid patches of the dorsal forearms and hands with focally-eroded papules over the interphalangeal joints and nail capillary fold changes
Violaceous erythema of the proximal upper extremities and lateral hips
Case 1: Classic Dermatomyositis

- **Skin involvement** consistent with dermatomyositis
  - Skin biopsy showed consistent findings (including vacuolar interface dermatitis)

- **Muscle involvement** based on proximal muscle weakness and elevated muscle enzymes

- **Negative malignancy workup** (including computed tomography of chest/abdomen/pelvis; transvaginal ultrasound; CA-125; and other screening)

- **Normal pulmonary function tests**
  - No evidence of interstitial lung disease

- **Negative autoantibody** (MyoMarker 3) panel (including anti-MDA5, TIF1-gamma, NXP-2)
Case 1 (continued)

• At the time of photographs (previous slides), patient was receiving prednisone 60 mg daily and mycophenolate mofetil 3 grams daily

• Intravenous immunoglobulin (IVIg) (2 grams per kilogram [divided over 2 days], given every month) was initiated:
  • Skin and muscles were “a million times better” after 3 cycles
  • Prednisone was tapered to 5 mg daily

• However, one month after starting IVIg, patient developed histoplasmosis tenosynovitis of left wrist and initiated itraconazole
Before and after surgical debridement, 3 months after starting IVIg
Case 1 (continued)

• 3 months later (despite her skin and muscle being under excellent control), she had persistent ulcerations on her left hand. Prednisone and mycophenolate mofetil were discontinued.

• One month later dermatology was asked to urgently see her due to progressive hand lesions and whether they could be due to dermatomyositis or another inflammatory condition such as pyoderma gangrenosum.
Ulcerated papules and nodules of the left dorsal hand.

Other hand was normal and remainder of skin showed no findings of dermatomyositis.
Skin biopsy showed findings consistent with cutaneous histoplasmosis

- Continued on systemic antifungals
- Repeat surgical debridement (photo depicts 3 weeks later)
Case 2: Persistent leg nodules in setting of Cogan syndrome

- 63 year-old man with longstanding Cogan syndrome (variable vessel vasculitis involving eye and inner ear)
  - Currently treated with prednisone, methotrexate, and adalimumab

- **Persistent right leg nodules** of 6 months’ duration that developed after trauma from a “steel pipe” while working in his yard

- Referred to dermatology due to concern of cutaneous vasculitis and possible need for modification of immunosuppressive therapy
Erythematous-to-hyperpigmented deep dermal nodules on the right calf and shin (also healing surgical site on posterior lower leg)
Multilobulated dermal nodule of the right medial ankle
Skin biopsy and tissue cultures consistent with atypical mycobacterial infection (*Mycobacterium chelonae*)

Patient started treatment with azithromycin and tigecycline
LEARNING POINT: In both case 1 and case 2, the *unilateral distribution of the skin lesions in the setting of immunosuppression* should alert the clinician to the possibility of infection.

Infection and infection prevention in patients treated with immunosuppressive medications for autoimmune bullous disorders.

Lehman JS¹, Murrell DF, Camilleri MJ, Kalaaji AN.

Author information

Abstract

Infection contributes to considerable morbidity and mortality in patients treated for autoimmune bullous disorders because of the impaired cutaneous barrier, alteration of the protective normal flora, and host immunosuppression (inherent and iatrogenic). Prevention of cutaneous impetigoization and infection starts with excellent wound care. In patients to be started on immunosuppressive medications, consideration should be given to vaccination status and possible need for pneumocystis pneumonia prevention. Patients should be educated on the signs and symptoms of early infection and the need to seek early medical intervention as needed.
Anticipating and preventing infection in patients treated with immunosuppressive medications for dermatologic indications: A dermatologist’s checklist

Julia S. Lehman, MD, David A. Wetter, MD, Mark D. P. Davis, MD, Rokca A. el-Azhary, MD, PhD, Lawrence E. Gibson, MD, and Amer N. Kalaaji, MD

Rochester, Minnesota

CLINICAL CHALLENGE

Infections are an important source of morbidity and mortality in patients treated with immunosuppressive medications for dermatologic indications, such as autoimmune bullous dermatoses, psoriasis, and connective tissue disease. By the very nature of these conditions, the integrity of the mucocutaneous barrier—the body’s primary defense against potential pathogens—is compromised. Moreover, the medications used to treat many of these conditions often further suppress the patient’s immune system. In some patients, systemic immunosuppression may lead to a more complicated course of a routine infection (e.g., urosepsis after a lower urinary tract infection). In other patients, latent infectious diseases (e.g., tuberculosis, hepatitis B and C, strongyloidiasis, deep fungal infections, or HIV) may reactivate, leading to adverse patient outcomes.

SOLUTION

Fortunately, several common or serious localized and systemic infections in this population can be anticipated and prevented. Based on our clinical experiences and our reading of the literature, we have developed a checklist for dermatologists to use when caring for patients with immune-mediated dermatoses that require iatrogenic immunosuppression (Table 1). In particular, patients may benefit from being educated about the importance of general hygiene (including regular hand washing) and about the signs and symptoms of early infection. Consideration should be given to screening for certain latent infectious diseases, vaccine administration, and pneumocystis pneumonia prophylaxis, based on individual patient risk factors. We advise dermatologists to have a low threshold to screen for and aggressively treat bacterial impetiginization, fungal colonization, and the presence of herpes simplex virus or varicella zoster virus, especially in patients with recalcitrant erosive mucocutaneous disease. We advocate future investigations to validate these recommendations.

Cognitive heuristics (mental shortcuts/quick problem-solving methods) can lead to diagnostic error – anchoring heuristic could lead to overlooking diagnosis of infection in cases 1 and 2.
"Metacognitive" strategies to improve diagnosis

Some of these likely could have been employed to more quickly render the diagnosis of infection in cases 1 and 2 (rather than attributing the lesions as a manifestation of the underlying condition [dermatomyositis and vasculitis, respectively])
Take Home Messages (Part 2)

- **PRACTICE GAP/CLINICAL PEARL**: Consider infectious causes of worsening or unusual skin eruptions in patients with underlying autoimmune or inflammatory dermatoses being treated with immunosuppressive therapy.

- Be aware of common cognitive heuristics that may lead to misdiagnosis (and cognitive strategies to overcome them).
Are there any non-immunosuppressive systemic treatment options for patients with morphea? (And can Mayo Clinic research help us find an answer?)
TABLE 36.1 Approach to the treatment of morphea.

Treatment is most effective in active, inflammatory lesions. Topical monotherapy should not be used if any of the following are present: progressing functional impairment, joint contractures or involvement across joints, linear facial involvement.

<table>
<thead>
<tr>
<th>Morphea Variant</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Circumscribed morphea</td>
<td>First line:</td>
</tr>
<tr>
<td></td>
<td>• Topical class I or intralesional CS</td>
</tr>
<tr>
<td></td>
<td>• Topical tacrolimus</td>
</tr>
<tr>
<td></td>
<td>Second line:</td>
</tr>
<tr>
<td></td>
<td>• Lesion limited phototherapy** or</td>
</tr>
<tr>
<td></td>
<td>• Topical imiquimod or</td>
</tr>
<tr>
<td></td>
<td>• Topical vitamin D analog under occlusion ± class I treated CS</td>
</tr>
<tr>
<td>Generalized morphea</td>
<td>(Without joint contractures)</td>
</tr>
<tr>
<td></td>
<td>First line:</td>
</tr>
<tr>
<td></td>
<td>• Phototherapy** (Fig. 36.11)</td>
</tr>
<tr>
<td></td>
<td>Second line:</td>
</tr>
<tr>
<td></td>
<td>• Weekly methotrexate ± systemic CS</td>
</tr>
<tr>
<td>Linear morphea</td>
<td>(Involving face or crossing joints)</td>
</tr>
<tr>
<td></td>
<td>First line:</td>
</tr>
<tr>
<td></td>
<td>• Weekly methotrexate ± systemic CS</td>
</tr>
<tr>
<td></td>
<td>Second line:</td>
</tr>
<tr>
<td></td>
<td>• Phototherapy** or</td>
</tr>
<tr>
<td></td>
<td>• CS-sparing agents</td>
</tr>
<tr>
<td>Pansclerotic morphea</td>
<td>(Often poor response to treatment attempts)</td>
</tr>
<tr>
<td></td>
<td>First line:</td>
</tr>
<tr>
<td></td>
<td>• Weekly methotrexate ± systemic CS</td>
</tr>
<tr>
<td>Mixed morphea</td>
<td>Treatment as above, depending on variants</td>
</tr>
</tbody>
</table>

BB-UVA, broadband ultraviolet A light phototherapy; UVA1, narrowband ultraviolet A light phototherapy; NB-UVB, narrowband ultraviolet B light phototherapy; PUVA, psoralens plus ultraviolet A light phototherapy.

Are there any non-immunosuppressive systemic treatment options for this patient with generalized morphea who did not experience improvement with phototherapy?
At Mayo Clinic, my faculty teachers during residency taught me that hydroxychloroquine was an effective treatment for morphea.

But where did this recommendation come from? Whenever I looked up the literature, I could not find anything supporting this teaching.
Hydroxychloroquine is not included in this algorithm

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Objective. Juvenile localized scleroderma (LS) is a chronic inflammatory skin disorder associated with substantial morbidity and disability. Although a wide range of therapeutic strategies has been reported in the literature, a lack of agreement on treatment specifics and accepted methods for clinical assessment has made it difficult to compare approaches and identify optimal therapy. Our objective was to develop standardized treatment plans, clinical assessments, and response criteria for active, moderate to high severity juvenile LS.

Methods. A core group of pediatric rheumatologists, dermatologists, and a lay advisor was engaged by the Childhood Arthritis and Rheumatology Research Alliance (CARRA) to develop standardized treatment plans and assessment parameters for juvenile LS using consensus methods/non-statistical group techniques. Recommendations were validated in 2 face-to-face conferences with a larger group of practitioners with expertise in juvenile LS. The final recommendations agreed to utilize these consensus plans to treat patients referred to CARRA centers. Using consensus methodology, we have developed standardized treatment plans for juvenile LS. The high level of support among pediatric rheumatologists will support studies and enable the development of evidence-based guidelines for the treatment of LS.

Target population. The initial intent of the juvenile LS Core Workgroup was to develop separate CTPs for high and moderate severity patients. As severity levels for juvenile LS have not been defined previously, the juvenile LS Core Workgroup developed provisional definitions for use in developing CTPs (see Supplementary Table 1, available in the online version of this article at http://onlinelibrary.wiley.com/doi/10.1002/jrhe.201511-4658). Briefly, high severity was defined as presentation with generalized or panarteral sclerosis, craniofacial linear scleroderma (en coup de sabre), or other subtype with evidence of high morbidity (e.g., central nervous system involvement, extremity shortening, joint contracture). Moderate severity was defined as circumscribed deep morphea or linear scleroderma of the trunk or extremity without evidence of high morbidity. Patients with low severity juvenile LS, typically those with superficial circumscribed morphea (plaque lesions), are not routinely referred to pediatric rheumatologists but are managed primarily by dermatologists (15). Based on the juvenile LS CARRA survey:

- In moderate-to-severe pediatric morphea: methotrexate +/- systemic corticosteroids recommended
- Hydroxychloroquine not recommended
Table 44.2 Treatment of morphea and lichen sclerosus. Trials of ultrapotent topical corticosteroids have been performed primarily in women with vulvar lichen sclerosus. +++ , Highly effective; ++, effective; +, moderately effective; 0, low efficacy or ineffective. Key to evidence-based support: (1) prospective controlled trial; (2) retrospective study or large case series; (3) small case series or individual case reports.

“No experience” using hydroxychloroquine in the literature
Because of the discrepancy between our Mayo Clinic experience and the literature, we decided to pursue a retrospective study. . .
Treatment of morphea with hydroxychloroquine: A retrospective review of 84 patients at Mayo Clinic, 1996-2013

Anagha Bangalore Kumar, MBBS,Elizabeth K. Blixt, MD, Lisa A. Drage, MD, Rokea A. el-Azhary, MD, PhD, and David A. Wetter, MD
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Background: Few studies support treating morphea (localized scleroderma) with hydroxychloroquine.

Objective: To assess the efficacy of hydroxychloroquine treatment of morphea.

Methods: We conducted a retrospective study of 84 patients who had morphea and were treated with hydroxychloroquine monotherapy for at least 6 months at our institution from 1996 through 2013. The median times to initial and maximal responses were assessed.

Results: Of the 84 patients (median age at diagnosis, 29.5 years), 65 (77.4%) were female, 36 (42.9%) had a complete response to hydroxychloroquine, 32 (38.1%) had a partial response greater than 50%, 10 (11.9%) had a partial response less than or equal to 50%, and 6 (7.1%) had no response. The median time to initial response was 4 months, and the median time to maximal response was 12 months. Ten patients (11.9%) experienced adverse effects from hydroxychloroquine; the most common adverse effect was nausea (6 patients).

Limitations: Retrospective study.

Conclusions: Hydroxychloroquine is a valuable treatment for morphea because of its high response rate and low rate of adverse effects; however, prospective studies are needed to determine its true efficacy. (J Am Acad Dermatol 2019;80:1658-63.)
Mayo Clinic Study

• Retrospective study of 84 patients with morphea
  • Hydroxychloroquine (HCQ) monotherapy for at least 6 months (concomitant topical treatment was allowed)
• Follow-up for at least 6 months after initiation of HCQ
• EXCLUDED patients who had received systemic therapy or phototherapy (a) during HCQ treatment, or (b) within 3 months of initiation of HCQ
CR or PR >50%:

- 81% overall (68 of 84)
- Plaque morphea – 96.6% (28 of 29)
- Linear morphea – 72.4% (21 of 29)
- Generalized morphea – 64.3% (9 of 14)
- Deep morphea – 80% (8 of 10)
- Mixed morphea – 100% (2 of 2)
Median time to initial response: 4 months

Median time to maximal response: 12 months

Adverse effects were mild – occurred in 11.9% (10 of 84)

Relapse (greater than 1 year after CR) occurred in 11 of 36 (30.6%) patients with CR
  - Most occurred greater than 1 year after stopping HCQ
  - Few occurred on lower doses of HCQ
Take Home Messages from Mayo Clinic Study (Part 3)

**CAPSULE SUMMARY**

- Data on the efficacy of hydroxychloroquine as therapy for morphea are sparse. Of our 84 patients, 81% had a complete response or a partial response greater than 50% to hydroxychloroquine.
- Hydroxychloroquine should be considered a treatment option for morphea.

- Despite limitations of the study (see manuscript), **HCQ had a high response rate and few adverse effects; and therefore should be considered a treatment option for morphea**

- We hope this study leads to prospective studies to determine the true efficacy of HCQ for the treatment of morphea
**SUMMARY (TAKE HOME MESSAGES)**

• (1) Consider workup for underlying systemic disease in patients with generalized granulomatous eruptions of indeterminate cause
  • Hematologic malignancy
  • Rheumatologic conditions

• (2) Keep infection in the differential diagnosis of a worsening skin eruption in a patient treated with immunosuppressive medications for autoimmune or inflammatory dermatoses

• (3) Consider hydroxychloroquine as a potential treatment for morphea (based on new Mayo Clinic study)