Kristen Randolph, PGY-2

Dermatology Journal Club

July 2023 (8/3/2023)

JID: IL-17 Signaling in Keratinocytes Orchestrates the Defense against *Staphylococcus aureus* Skin Infection

- *What is the general condition, procedure or disease under study?*
  - Regulation of the skin microbiome, particularly the effect on staph aureus infections
  - Consideration for IL-17 inhibiting biologics and increased susceptibility to skin infections
- *What was/were the research question(s)?*
  - What is the role and regulatory mechanism of IL-17 in keratinocyte defense against staph aureus?
- *Was the question answered to your satisfaction – validity? Do you trust the conclusions and recommendations?*
  - IL-17 has been found to be critical to T cell defense against S. aureus
  - IL-17 A/F double knockout (KO) and IL-17RA-deficient mice (del) had inflammatory lesions in facial/cervical regions. S. aureus was found in all mice with skin lesions in both IL-17 signaling-deficient strains as well as 38% of IL-17RA(del) and 24% IL-17AF(KO) w/o lesions (presymptomatic colonization).
  - Prior studies showed TH17 cells were expanded in mice globally lacking IL-17RA. TH17 populations were evaluated in cervical LN, peripheral LN, and mesenteric LN in IL-17RA(del) mice. TH17 cells were strongly expanded in cervical LN and peripheral LN (both skin draining), none in mesenteric LN. Overall, indicates skin infection is responsible for expansion of TH17 cells. Also noted to have <u>increased</u> serum IL-17A.
  - Previously proposed direct feedback mechanism where IL-17A inhibits population size of TH17 cells—though with above findings this does not fit. Created mice lacking IL-17RA specifically in aB T cells and observed no TH17 expansion in these mice, contrary to expectation for a direct negative feedback mechanism—conclude no auto-inhibitory mechanism. Note mice lacking IL-17 signaling in T cells did not develop spontaneous skin lesions or obvious signs of infection→microbiome dysbiosis causing T cell expansion in IL-17AF(KO) and IL-17RA(del)?
  - Created mice lacking IL-17RA specifically in keratinocytes [IL-17RA(K14)]. Bacterial invasion of the skin was 10-fold higher 7 days after infection in IL-17RA(K14) mice than controls w/ expansion of IL-17-prodcuing T cells. Supports decreased ability to clear S.aureus in acute skin infection.
  - IL-17RA(K14) mice resemble full-body IL-17RA(del) in skin phenotype, LN findings→conclude IL-17 signaling on keratinocytes responsible for the phenotypes observed in IL-17RA(del) and IL-17AF(KO).
  - Data show that response of keratinocytes to IL-17 is critical for host response to S.aureus and lack of this signaling leads to bacterial overgrowth resulting in both skin lesions and expansion of T cells.

    - Clinical relevance for patients treated with long term IL-17 pathway-targeting drugs might develop expansions of IL-17 producing T cells, greater susceptibility to S.aureus and candida infections if not treated promptly
- *Does this study prompt or inspire a different and better study?*
    - Rate of cutaneous candida or S. aureus infections in patients on IL-17 inhibitors.

JAAD: Rapid and sustained improvements in Generalized Pustular Psoriasis Physician Global Assessment scores with spesolimab for treatment of generalized pustular psoriasis flares in the randomized placebo-controlled Effisayil 1 study

- *What is the general condition, procedure or disease under study?*
    - Generalized Pustular Psoriasis
    - Effisayil 1 randomized, placebo-controlled study demonstrated efficacy of Spesolimab, an IL-36R monoclonal antibody, in treating GPP flares
- *What was/were the research question(s)?*
    - Are benefits seen 1 week after treatment sustained at 12 weeks?
- *Was the question answered to your satisfaction – validity? Do you trust the conclusions and recommendations?*
    - Built off the data from randomized controlled trial; randomized 2:1 to spesolimab 900mg IV vs placebo on day 1. Optional open-label spesolimab offered for persistent flare symptoms to both arms of the study on day 8 and additionally for a new flare after achieving clinical response prior to 12 weeks. Followed intention to treat (ITT) analysis.
    - GPPGA total score and subscores in: pustulation, eryhtma, scaling were assessed days 1-7 and weeks 1-4, 8, and 12. Minimal clinically important differences (MCID) were defined as >/=2 point change in pustulation subscore and >/= 1 point change in total score.
    - Primary endpoint = GPPGA pustulation score of 0 (no visible pustules) at 1 week
    - Secondary endpoint = GPPGA total score of 0 or 1 at 1 week
    - 23/35 (65.7%) of spesolimab group achieved primary endpoint (0 pustule) or MCID at 1 week vs 4/18 (22.2%) placebo
    - 25/35 of spesolimab group achieved secondary endpoint (total score 0 or 1) or MCID at week 1 vs 7/18 (38.9%) placebo
    - 15/18 participants randomized to placebo received the OL spesolimab on day 8, and 2 participants after day 9 for a new flare. Pustule score of 0 improved from 1/18 (5.6%) at week 1 to 15/18 (83.6%) at week 2 [1 week after receiving spesolimab]
    - Spesolimab group: Pustule subscore 23/34 (67.6%) [1]→31/32 (96.9%) [12]; Total score 35/34 (73.5%) [1] → 32/32 (100%) [12]
    - Placebo group: pustule score 4/18 (22.2%) [1]→ 16/18 (88.9%) [2]→15/15 (100%) [12]; Total score 7/18 (38.9%) [1]→16/18 (88.9%) [2]→15/15 (100%) [12]
    - <u>Improvement was rapid in most cases—within 24-48hrs. Improvements observed at 1 week were sustained through week 12. Participants initially randomized to placebo that received OL spesolimab at day 8 showed equally rapid and sustained clearance as the experimental group.</u>
    - Limitations:

        - Because participants who were randomized into placebo group were given the option to receive spesolimab on Day 8, there was not a proper control group to compare against spesolimab at 12 weeks.
        - Unable to identify factors that may indicate responders/who might require additional dosing.
- *Does this study prompt or inspire a different and better study?*
    - Randomized, placebo portion demonstrates efficacy of spesolimab. Sustainability and dosing would benefit from further investigation.

A SEASONED APPROACH TO TREATING THE "SALT AND PEPPER" DYSPIGMENTATION OF SYSTEMIC SCLEROSIS

Dermatology World Insights and Inquiries

By Warren R. Heymann, MD, FAAD
Feb. 1, 2023
Vol. 5, No. 5

It only takes a nanosecond for a dermatologist to recognize the “salt and pepper” dyspigmentation (SPD) of systemic sclerosis (SSc), but a lifetime to understand and manage it. Of all the cutaneous signs of SSc (sclerodactyly, telangiectasias, calcinosis, digital ulcerations), SPD may be among the most emotionally disconcerting for the patient.

SSc is an autoimmune multisystem disorder whereby inflammation may lead to microvascular endothelial changes and progressive vascular dysfunction resulting in fibrosis of the skin and internal organs. It is sub-classified by the degree of skin involvement into diffuse cutaneous (dcSSc), limited cutaneous (lcSSc), SSc sine scleroderma, and scleroderma overlap syndrome (SOS). The dcSSc variant is associated with higher morbidity and mortality.

According to Solanki et al, “Onset is more rapid in dcSSc, and is often accompanied by early organ involvement (within the first 3 years) and an increased propensity for constitutional, lung, renal and cardiovascular manifestations. The window of

opportunity for intervention usually occurs relatively early in this subset. Early distinction between limited and diffuse disease may help to decide on the timing of further investigations, potential disease-modifying treatment and follow-up." (1)

In his treatise "On diffuse scleroderma," Sir William Osler thoroughly described 8 patients with the disorder. In my reading, case 8 was likely the first patient described with SPD, He was a 39-year-old man, whose skin of the hands "was a deep mahogany brown. The patch of leukoderma has in it many spots of pigmentation." Other sites were reported as "mottled." (2) There are predominantly 3 patterns of dyspigmentation in SSc: 1) generalized hyperpigmentation; 2) focal pigmentary changes; and 3) SPD. (3)

Image from reference 8.SPD is one of the earliest cutaneous findings in SSc and may be the sole dermatologic manifestation, although it may be found in sclerotic skin. (4) SPD appears as vitiligo-like depigmentation with relative sparing of the perifollicular areas. In a study of 22 patients with SSc, of which 20 had diffuse SSC, the most common sites were the chest, followed by the back, forearm, scalp, perioral region, hand, and eyebrows. All patients had sparing of the perifollicular areas, 9 (40.9%) demonstrated sparing of the skin folds and creases within the depigmented areas, and 2 (9%) displayed sparing over superficial veins. (3) Pigment preservation over veins has been attributed to a temperature differential, with skin being warmer overlying the vessels. (5) In their retrospective review of 15 patients with SSc (14 with diffuse SSc) and SPD, 5 patients demonstrated SPD at the time of diagnosis. As in other studies, SPD was mainly observed in patients with dark phototypes (60% Fitzpatrick IV, 40% Fitzpatrick III). (6) In their cohort of 59 patients with SSc, SPD was found in 16 (24.6%). Of these, 11 (68.75) had diffuse SSc and 6 (31.25%) had localized SSc. (1) In a study of 566 Thais with SSc, 220 (38.9%) demonstrated SPD; in localized SSc, 27/155 (17.4%) and 193/411 (47%) with diffuse SSc displayed the dyspigmentation. (7) These 2 studies confirm the observation that SPD is more commonly observed in diffuse disease.

Although the exact pathogenesis of SPD is unknown, it is reasonable to compare it to vitiligo, due to autoimmune T-cell-mediated melanocyte injury. Theoretically, with that analogy, this disturbing dyspigmentation should be at least partially responsive to therapeutic measures. Despite the lack of defined protocols for treating SPD, there are reports of success. Freiman et al report the case of a 40-year-old woman with scleroderma who experienced "auto"-repigmentation of the lesions on the left arm, which was exposed to natural sunlight as she was driving with the car window down. The authors suggested that phototherapy might be an appropriate treatment for SPD. (8) To date, a PubMed review of phototherapy and SPD was nonrevealing; regardless, I would have no qualms offering this option to patients (assuming no other contraindications).

SPD has been the subject of 2 “Images in Clinical Medicine” in the *New England Journal of Medicine*. A 31-year-man with SPD had a partial response to mycophenolate mofetil and prednisone. (9) “Immunosuppressive therapy,” which was not defined, led to partial regression of the SPD in a 68-year-old man with diffuse SSc. (10) Min et al reported at least 75% improvement in 3 patients (all African American; a man and a woman with SS and a woman with mixed connective tissue disease) with mycophenolate mofetil. According to the authors, mycophenolate mofetil “is thought to have antisclerosing effects by inhibiting transforming growth factor *β,* fibroblast proliferation, and collagen deposition…Because salt-and-pepper dyspigmentation occurs in areas of cutaneous sclerosis, treating underlying sclerosis would hypothetically improve overlying salt-and-pepper dyspigmentation.” (11)

The current darlings of dermatological therapy are the JAK inhibitors. There is increasing evidence that tofacitinib could be a therapeutic option for treating the musculoskeletal and cutaneous features of SSc. (12) Topical ruxolitinib has been approved for vitiligo. We can anticipate imminent reports on the use of oral and topical JAK inhibitors for SPD.

In conclusion, it is important to recognize SPD early and to be aware that this distressing feature may be improved with a variety of immunosuppressive therapeutic maneuvers, akin to treating vitiligo. I applaud those researching these treatments, so it is appropriate to end with lyrics from *Beauty and the Beat* by the hip-hop group Salt-N-Pepa:

Clap your hands now people clap hard
Clap your hands now people clap your hands
Clap your hands now people stomp your feet
Clap your hands now people clap with me

Point to Remember: “Salt and Pepper” dyspigmentation may present early in the course of systemic sclerosis. Although its pathogenesis is incompletely understood, immunomodulatory therapies may improve this distressing condition.

Our expert’s viewpoint

David A. Wetter, MD, FAAD
Professor of Dermatology

Mayo Clinic
Rochester, Minnesota

Cutaneous manifestations of autoimmune connective tissue diseases (ACTDs) are varied and oftentimes challenging to treat. Analogous to the Gilliam classification of skin disease associated with lupus erythematosus (LE) (14), ACTDs may exhibit "specific" lesions that demonstrate typical histopathology of ACTD or may manifest with "non-specific" skin conditions that do not display characteristic histopathology of ACTD and may be observed in other diseases. Although the SPD described in patients with SSc is a unique morphologic presentation of pigmentary changes, generally pigmentary changes in patients with ACTD are considered a "non-specific" manifestation of ACTD. As highlighted in Dr. Heymann's commentary, non-specific cutaneous manifestations of ACTDs suffer from a paucity of well-established treatment protocols and may severely impact patients' quality of life.

Denny Tuffanelli, MD (a 1961 graduate of our Mayo Clinic Dermatology residency) was renowned for his expertise in systemic sclerosis and received our department's Honored Alumnus award in 2012. Along with Richard Winkelmann, MD, he authored a seminal paper of 727 patients with "systemic scleroderma" (15); 222 patients (30.5%) had pigmentary changes, although it is unclear how many of these patients had SPD. Tuffanelli and Winkelmann wrote: "Most of the patients also had scattered, small areas of depigmentation or vitiligo." (15)

Two patients I cared for during the COVID-19 pandemic illustrate the importance of finding effective treatments for the "non-specific" cutaneous manifestations of ACTDs. The first patient had an overlap CTD with SSc, systemic LE, and Sjögren syndrome. Large areas of SPD of the trunk caused her great distress and we recommended phototherapy. (Unfortunately, we do not have follow-up information available to document how the SPD responded to treatment.) The second patient had SSc and received mycophenolate mofetil and ultraviolet A-1 (UVA-1) treatment for cutaneous sclerosis and pruritus. Given the persistence of pruritus despite a variety of other topical (amitriptyline-ketamine cream) and systemic (pregabalin) medications, low-dose naltrexone (4.5 milligrams daily) was prescribed, based upon a previously published case series of 3 patients (16). (Unfortunately, at follow-up 2 months later, the patient reported that he had not filled the prescription.)

Calcinosis cutis is another non-specific cutaneous manifestation of ACTDs that can have a devastating impact on patients. A previous study that assessed 35 patients with juvenile dermatomyositis (JDM) concluded that early and aggressive treatment of JDM can successfully minimize the development of sequelae such as calcinosis

cutis (17). We performed a retrospective review of 78 patients with calcinosis cutis occurring in association with ACTD and used a surrogate measure of ACTD severity (the number of treatments administered to treat the underlying ACTD and the number of body locations affected by calcinosis cutis). Our analyses did not show a statistically significant correlation between the severity of the underlying ACTD and the severity of calcinosis cutis. (18)

It heartens me to see new research of promising treatments for cutaneous sequelae of ACTDs such as SPD associated with SSc. I look forward to similar studies of other impactful conditions such as calcinosis cutis that torment our patients with ACTDs.

1. Solanki KK, Hor C, Chang WSJ, Frampton C, White DHN. Clinical utility of hypo- and hyperpigmentation of skin in diffuse cutaneous systemic sclerosis. Int J Rheum Dis. 2017 Jun;20(6):767-773. doi: 10.1111/1756-185X.13049. Epub 2017 Mar 6. PMID: 28261995.
2. Osler WJ. On diffuse scleroderma, with special reference to diagnosis and to the use of thyroid gland extract. J Cutan Dis 1989;16:49
3. Ghosh SK, Mondal S. Sparing phenomenon in salt and pepper pigmentation of systemic sclerosis: an unusual observation. Clin Exp Dermatol. 2021 Dec 22. doi: 10.1111/ced.15073. Epub ahead of print. PMID: 34939220.
4. Sakamoto T, Kaburaki M, Shimizu T. Salt-and-pepper skin appearance and systemic sclerosis. QJM. 2021 Nov 5;114(8):599-600. doi: 10.1093/qjmed/hcab070. PMID: 33956977.
5. Jawitz JC, Albert MK, Nigra TP, Bunning RD. A new skin manifestation of progressive systemic sclerosis. J Am Acad Dermatol. 1984 Aug;11(2 Pt 1):265-8. doi: 10.1016/s0190-9622(84)70163-0. PMID: 6480928.
6. Ocampo-Candiani J, Suro-Santos Y, Villarreal-Martinez A, Herz-Ruelas ME, Galarza-Delgado DA, Hernandez-Galarza IJ, Villareal-Alarcon MA, Flores-Alvarado DE, Gomez-Flores M, Vazquez-Martinez OT, Chavez-Alvarez S. Systemic sclerosis in Hispanics: cutaneous salt and pepper lesions. Int J Dermatol. 2022 Mar;61(3):e94-e96. doi: 10.1111/ijd.15925. Epub 2021 Oct 2. PMID: 34599598.
7. Foocharoen C, Peansukwech U, Mahakkanukrauh A, Suwannaroj S, Pongkulkiat P, Khamphiw P, Nanagara R. Clinical characteristics and outcomes of 566 Thais with systemic sclerosis: A cohort study. Int J Rheum Dis. 2020 Jul;23(7):945-957. doi: 10.1111/1756-185X.13859. Epub 2020 May 18. PMID: 32420701.

8. Freiman A, Khanna M, Muhn CY, Billick RC. Ultraviolet autorepigmentation in scleroderma. J Am Acad Dermatol. 2003 Nov;49(5):960-1. doi: 10.1016/s0190-9622(03)00853-3. PMID: 14576693.
9. Giberson M, Brassard A. Salt-and-Pepper Skin Changes. N Engl J Med. 2017 Jul 13;377(2):173. doi: 10.1056/NEJMicm1610737. PMID: 28700851.
10. Colquhoun M, Penn H. Salt-and-Pepper Skin Changes in Systemic Sclerosis. N Engl J Med. 2021 Jul 22;385(4):357. doi: 10.1056/NEJMicm2103390. PMID: 34289279.
11. Min MS, Mazori DR, Kassamali B, Cobos G, Ho A, LaChance AH, Vleugels RA. Treatment With Mycophenolate Mofetil for Salt-and-Pepper Dyspigmentation Caused by Autoimmune Sclerosing Disease. JAMA Dermatol. 2022 Feb 9. doi: 10.1001/jamadermatol.2021.5848. Epub ahead of print. PMID: 35138336.
12. Karalilova RV, Batalov ZA, Sapundzhieva TL, Matucci-Cerinic M, Batalov AZ. Tofacitinib in the treatment of skin and musculoskeletal involvement in patients with systemic sclerosis, evaluated by ultrasound. Rheumatol Int. 2021 Oct;41(10):1743-1753. doi: 10.1007/s00296-021-04956-7. Epub 2021 Jul 27. PMID: 34313812; PMCID: PMC8390399.
13. Shalabi MMK, Garcia B, Coleman K, Siller A Jr, Miller AC, Tyring SK. Janus Kinase and Tyrosine Kinase Inhibitors in Dermatology: A Review of Their Utilization, Safety Profile and Future Applications. Skin Therapy Lett. 2022 Jan;27(1):4-9. PMID: 35081305.
14. Gilliam JN, Sontheimer RD. Distinctive cutaneous subsets in the spectrum of lupus erythematosus. *J Am Acad Dermatol*. 1981;4:471-5.
15. Tuffanelli DL, Winkelmann RK. Systemic scleroderma: A clinical study of 727 cases. *Arch Dermatol*. 1961;84:359-71.
16. Frech T, Novak K, Revelo MP et al. Low-dose naltrexone for pruritus in systemic sclerosis. *Int J Rheumatol*. 2011;2011:804296.
17. Fisler RE, Liang MG, Fuhlbrigge RC et al. Aggressive management of juvenile dermatomyositis results in improved outcome and decreased incidence of calcinosis. *J Am Acad Dermatol*. 2002;47:505-11.
18. Balin SJ, Wetter DA, Andersen LK, Davis MDP. Calcinosis cutis occurring in association with autoimmune connective tissue disease: The Mayo Clinic experience with 78 patients, 1996-2009. *Arch Dermatol*. 2012;148:455-62.