RUSH UNIVERSITY MEDICAL CENTER

Rush University Medical Center
Section of Dermatology
May 18, 2022

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CHICAGO DERMATOLOGICAL SOCIETY

CASE 1

Presented by Katie Emerson, MD, Anas Alabkaa, MD, and Kyle Amber, MD
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HISTORY OF PRESENT ILLNESS

A 45-year-old male presented with a ten-month history of a pruritic rash. He initially noticed the rash on his lower extremities, and it progressed to involve his groin, chest, back, and face. He had completed a course of permethrin for suspected scabies, as well as a course of an unknown antibiotic and antifungal without improvement prescribed by primary care. He was referred to a community dermatologist who performed a skin biopsy that, according to the patient, showed "psoriasiform dermatitis." He was prescribed several courses of prednisone and stated the rash seemed to improve with oral steroids. He described a burning sensation on his tongue and an 80 pound unintentional weight loss over the past eight months. He denied diarrhea, abdominal pain, or blood in his stool.

PAST MEDICAL & SURGICAL HISTORY

None

FAMILY HISTORY

Ulcerative colitis in father
SLE in maternal grandmother and aunts

SOCIAL HISTORY

Non-smoker

MEDICATIONS

None

ALLERGIES

NKDA

PHYSICAL EXAMINATION

Erythematous to hyperpigmented annular and serpiginous patches with a scaly, crusted borders involving the central chest, axilla, antecubital fossa, neck, and back. Erosive plaques on the distal lower extremities and inguinal folds.

LABORATORY RESULTS

Normal:

Aldolase
ANA screen
B2, B3, folic acid, and B12
CK
LDH
Pemphigus and IgA pemphigus panels

Zinc

LABORATORY RESULTS (cont.)
Abnormal:
CBC – slight leukocytosis and normocytic anemia
CMP – hypoalbuminemia
Glucagon level – 6990
Urinalysis – proteinuria and glucosuria

IMAGING STUDIES
CT chest/abdomen/pelvis: Findings highly concerning for primary pancreatic malignancy with hepatic metastases. Ill-defined mass in the pancreatic body with marked atrophy and ductal dilation of the distal body and tail. Numerous hypodense hepatic lesions highly concerning for metastases.

DERMATOPATHOLOGY
Shave biopsy of the right upper back revealed subcorneal ballooning degeneration, psoriasiform hyperplasia, and mild dermal inflammation.

DIAGNOSIS
Necrolytic Migratory Erythema in the setting of Glucagonoma Syndrome

CLINICAL COURSE
Following consultation with dermatology, the patient was seen by gastroenterology. Their evaluation included: CT chest/abdomen/pelvis that demonstrated a pancreatic mass and hepatic lesions concerning for metastases and endoscopic gastroduodenoscopy(EGD)/ultrasound (EUS) with biopsy that was consistent with a well differentiated neuroendocrine tumor with positive peripancreatic lymph node involvement. The patient was referred to hematology/oncology for management of his glucagonoma, and plans were made to start treatment with lanreotide, a somatostatin inhibitor.

DISCUSSION
Necrolytic migratory erythema (NME) was first coined in 1942 by Becker and colleagues in a patient with an alpha cell tumor of the pancreas, along with elevated serum glucagon levels and hypoaminoacidemia. [1] It is characterized by a waxing and waning eruption of scaly, erosive, annular to serpiginous erythematous plaques with pustule and vesicle formation. The clinical differential diagnosis is broad and includes pemphigoid, pemphigus, acrodermatits enteropathica, psoriasis, seborrheic dermatitis, fatty acid deficiencies, annular chronic lupus, drug reactions, and various vitamin deficiencies.[2,3,4]

In patients with a glucagon secreting tumor of the pancreas, NME is present about 70% of the time, and is the most common cutaneous manifestation. [2,3] When NME is present in the absence of a pancreatic tumor, such as in the setting of hepatic disease, inflammatory bowel disease, pancreatitis, malabsorption disorders, or other malignancies, it is referred to as pseudoglucagonoma syndrome. Interestingly, glucagon levels in these patients are often elevated, although not to the extent as in glucagonoma syndrome.[5]

"Glucagonoma syndrome" was described in 1974 to encompass a series of 9 patients with NME, weight loss, and increased glucagon levels in the setting of an alpha cell tumor of the pancreas.[6]

Glucagonomas are typically sporadic, although infrequently they can be inherited in patients with multiple endocrine neoplasia type 1 (MEN 1) or von Hippel-Lindau syndrome.[7] They tend to occur equally in males and females, with an average age of diagnosis of 53 years. The tumor grows slowly, and metastasis occurs late in the disease course – affecting the liver most commonly, but also the regional lymph nodes or bones. It can take a median of 39 months from onset of symptoms to diagnosis, and NME is often the initial clinical manifestation.[8] Elevated glucagon levels can also lead to weight loss, diarrhea, stomatitis, cheilitis, diabetes mellitus, normocytic anemia, and thromboembolic events.

The lesions of NME tend to relapse and remit over a time course of one to two weeks and favor intertriginous areas but can also be present on perioral skin, the perineum, and distal extremities.[5] They can be both painful and pruritic, have a propensity to become secondarily infected, and have been known to koebnerize. Lesions resolve with hyperpigmentation and peripheral collarettes of scale, and they may appear on eczematous or psoriasiform as they evolve.[5]

On pathology, NME shows confluent parakeratosis, vacuolar degeneration of superficial epidermal keratinocytes and necrolysis in the upper 1/3 of the epidermis.[3,4] A neutrophilic infiltrate and occasionally lymphocytic perivascular inflammation can also be seen. The histopathologic differential diagnosis includes acrodermatitis enteropathica and other nutritional deficiencies such as pellagra.

Various theories have been proposed regarding the pathogenesis of NME. One theory favors glucagon as the etiologic agent for inducing skin changes, supported by the finding that when the tumor is removed or the hormone suppressed with a glucagon antagonist, the skin lesions resolve.[4,5] Another theory suggests that amino acid deficiencies, caused by the presence of high serum glucagon levels and resulting gluconeogenesis, lead to epidermal protein depletion and subsequent necrolysis.[4,5] Treatment with intravenous amino acids can improve NME in patients with low total protein levels or selective amino acid deficiencies.[9,10] Furthermore, specific amino acid deficiencies such as histidine and tryptophan can produce similar appearing cutaneous eruptions. Zinc deficiency may also play a role since there are cases of both glucagonoma syndrome and pseudoglucagonoma syndrome with NME improving with zinc supplementation.[11] The pathogenesis is likely multifactorial and related to a combination of the above factors, as well as a deficiency in essential fatty acids (caused by increased lipolysis in the setting of excess glucagon). There is also a potential role for inflammatory mediators, including arachidonic acid and its metabolites – prostaglandins and leukotrienes – which may be increased in the epidermis in the setting of elevated glucagon levels.[15] Local trauma to the skin may lead to the release of these inflammatory mediators, leading to the erosive skin lesions. Furthermore, low albumin levels are associated with increased release of fatty acids from tissue membranes where they can be degraded by prostaglandins into pro-inflammatory metabolites.

With regards to diagnosis, major criteria have been suggested including the presence of a pancreatic tumor on imaging, elevated glucagon levels (1000 or above), NME, or a personal history of MEN I, and meeting any one of these criteria should prompt a further workup for a

glucagonoma. [5] Fasting glucagon levels greater than 500 are specific for glucagonoma diagnosis,[12] but it is important to keep in mind that a mild increase in glucagon levels can also be seen in the setting of cirrhosis, renal failure, sepsis, pancreatitis, Cushing's syndrome, trauma, and diabetic ketoacidosis, to name a few.

Treatment of a glucagonoma can be accomplished by surgical removal, but given the high rates of metastatic disease at time of diagnosis, this method of treatment is not always feasible or definitive. Other options include chemotherapy, tyrosine kinase inhibitors such as sunitinib, mTOR inhibitors such as everolimus, and interferon. Somatostatin inhibitors such as octreotide, pasireotide, and lanreotide are particularly efficacious in treating NME, as well as decreasing the size of the tumor and the serum glucagon concentrations.[13,14] NME may also improve with supplementation of amino acids, zinc, and essential fatty acids.[9,10,11] The rash tends to be minimally responsive to glucocorticoids and antibiotics.

Overall, the prognosis for patients with glucagonoma syndrome is poor, with mean life expectancy between three to seven years after diagnosis.[5] Furthermore, the diagnosis is typically delayed – attributed to the rarity of the condition, under-recognition of NME, and lack of pathognomonic histopathology. [4,5] It is important to be aware of the clinical manifestations of this syndrome and the appropriate diagnostic work up for these patients in order to achieve a timely diagnosis and expedite care.

REFERENCES

1. Tierney, E. P., & Badger, J. (2004). Etiology and pathogenesis of necrolytic migratory erythema: review of the literature. *MedGenMed: Medscape general medicine*, *6*(3), 4.
2. Liu, Qian, Y.-T., & Ma, D.-L. (2019). Necrolytic Migratory Erythema. *JAMA Dermatology.*, *155*(10).
3. Lee, & Jang, Y. H. (2019). Necrolytic migratory erythema. *Canadian Medical Association Journal.*, *191*(10).
4. Tolliver, Graham, J., & Kaffenberger, B. H. (2018). A review of cutaneous manifestations within glucagonoma syndrome: necrolytic migratory erythema. *International Journal of Dermatology.*, *57*(6), 642–645.
5. John, & Schwartz, R. A. (2016). Glucagonoma syndrome: a review and update on treatment. *Journal of the European Academy of Dermatology and Venereology : JEADV.*, *30*(12), 2016–2022.
6. Mallinson CN, Bloom SR, Warin AP, Salmon PR, Cox B. A glucagonoma syndrome. *Lancet* 1974.
7. Castro PG, de Leon AM, Trancon JG et al. Glucagonoma syndrome: a case report. *J Med Case Rep* 2011.
8. Makis W, McCann K, Riauka TA, McEwan AJ. Glucagonoma pancreatic neuroendocrine tumor treated with 177Lu DOTATATE induction and maintenance peptide receptor radionuclide therapy. *Clin Nucl Med* 2016; 41: 50–52.
9. Thomaidou E, Nahmias A, Gilead L, Zlotogorski A, Ramot Y. Rapid Clearance of Necrolytic Migratory Erythema Following Intravenous Administration of Amino Acids. *JAMA Dermatol*. 2016 Mar;152(3):345-6.

10. Alexander EK, Robinson M, Staniec M, Dluhy RG. Peripheral amino acid and fatty acid infusion for the treatment of necrolytic migratory erythema in the glucagonoma syndrome. *Clin Endocrinol (Oxf).* 2002 Dec;57(6):827-31.
11. Lakdawala N, Babalola O 3rd, Fedeles F et al. The role of nutrition in dermatologic diseases: facts and controversies. *Clin Dermatol* 2013; 31: 677–700.
12. Kanakis G, Kaltsas G. Biochemical markers for gastroenteropancreatic neuroendocrine tumours (GEP-NETs). *Best Pract Res Clin Gastroenterol* 2012.
13. Kimbara S, Fujiwara Y, Toyoda M et al. Rapid improvement of glucagonoma-related necrolytic migratory erythema with octreotide. *Clin J Gastroenterol* 2014;
14. Caplin ME, Pavel M, Ćwikła JB, Phan AT, Raderer M, Sedláčková E, Cadiot G, Wolin EM, Capdevila J, Wall L, Rindi G, Langley A, Martinez S, Blumberg J, Ruszniewski P; CLARINET Investigators. Lanreotide in metastatic enteropancreatic neuroendocrine tumors. *N Engl J Med*. 2014 Jul 17;371(3):224-33.
15. Peterson LL, Shaw JC, Acott KM, Mueggler PA, Parker F. Glucagonoma syndrome: in vitro evidence that glucagon increases epidermal arachidonic acid. *J Am Acad Dermato*l 1984; 11: 468–473.

CHICAGO DERMATOLOGICAL SOCIETY

CASE 2

Presented by Ryan Kelm, MD, Warren Piette, MD, Aadil Ahmed, MD.
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HISTORY OF PRESENT ILLNESS

A 46-year-old male presented with a 1-to-2-year history of a slowly progressive infiltrated rash on his suprapubic region and in his left axilla. The areas were asymptomatic. The patient denied fever, chills, night sweats, weight loss, and fatigue. Additional review of symptoms was negative. He had been evaluated by another dermatologist who had not initiated any treatments. Of note, patient stated he was 11 years old, living in Belarus during the Chernobyl explosion, and was at risk for radiation fallout.

PAST MEDICAL & SURGICAL HISTORY

Type II diabetes mellitus, hypercholesterolemia

FAMILY HISTORY

Noncontributory

SOCIAL HISTORY

Light tobacco smoker

MEDICATIONS

Rosuvastatin, semaglutide, metformin

ALLERGIES

NKDA

PHYSICAL EXAMINATION

Large erythematous-to-violaceous indurated, edematous plaque with faint scale, encompassing the mons pubis area, extending down the penile shaft. In addition, the axilla had a poorly demarcated faint red-brown patch with mild wrinkling.

LABORATORY RESULTS

CBC, CMP, LDH – unremarkable

IMAGING STUDIES

CT chest, abdomen, pelvis: Mildly enlarged hilar, retroperitoneal and left inguinal lymph nodes and focal skin thickening in the pre-pubic area soft tissues was appreciated.

SPECIAL STUDIES

Peripheral blood T-cell receptor gene rearrangement analysis was equivocal.
Blood flow cytometry did not demonstrate any abnormalities.

DERMATOPATHOLOGY

Initial histopathologic analysis was read with expert consultative review, which demonstrated unremarkable epidermis with superficial interstitial band-like infiltrate with some reticular fibroplasia. Small to intermediate hyperconvoluted lymphocytes were seen without significant epidermotropism. Folliculotropic and granulomatous components were identified. Elastic Von Gieson stain did not demonstrate elastophagocytosis. Large cell transformation was not identified.

Repeat biopsy at Rush demonstrated similar findings with small to intermediate, irregular lymphoid cells with scattered giant cells with multinucleation and admixed eosinophils. In addition, focal epidermotropism, Pautrier's microabscesses, and tagging along the dermoepidermal junction was noted. Verhoeff Van Gieson's stain demonstrated complete loss of elastin throughout the entire dermis.

Immunohistochemical studies demonstrated tumor cells positive for CD3, CD4, and BF1, and negative for CD5, CD7, CD8, and TIA1.

DIAGNOSIS

Early evolving granulomatous slack skin syndrome vs. granulomatous MF

CLINICAL COURSE

The patient was started on bexarotene 300 mg daily and levothyroxine 75 mcg daily. At the 1-month follow-up, the patient demonstrated some clinical improvement with a decrease in size of the infiltrated plaque and remains on the same therapeutic regimen.

DISCUSSION

Mycosis Fungoides (MF) is the most common cutaneous T-cell lymphoma (CTCL) with different clinical or histologic subtypes including: erythrodermic, hypopigmented, papular, and granulomatous MF (GMF). In addition, MF has 3 recognized distinct variants by the World Health Organization-European Organization for Research and Treatment of Cancer (WHO-EORTC) that are: folliculotropic MF, pagetoid reticulosis, and granulomatous slack skin (GSS).

Approximately 2% of cutaneous lymphomas exhibit granulomatous features.[1] With respect to MF, it is important to differentiate GMF from GSS as these two entities may have different prognoses.

Granulomatous MF is a rare histopathologic variant characterized by a prominent granulomatous infiltrate. There is a slight male predominance, with a median age of diagnosis at 48 years, but the age range is broad, between 20 and 72 years old.[2] Incidence rates range from 0.6%-6.3% of CTCL cases.[3-4] Clinically, no distinct patterns suggest a granulomatous infiltrate as clinical manifestations typically resemble classic MF with patches and plaques; however, dermatofibroma-like lesions to lesions resembling other granulomatous disorders, such as granuloma annulare, may be appreciated.

Granulomatous slack skin (GSS) is a very rare form of MF with less than 60 documented cases. It is more common in men and typically presents between the 3rd and 4th decades of life. There continues to be debate where exactly granulomatous slack skin fits within the spectrum of lymphoproliferative disorders, either as a variant of MF or as a lymphoproliferative cutaneous syndrome which may be associated with other lymphomas, especially Hodgkin disease. Clinically, GSS presents as infiltrated, poikilodermatous, well-demarcated, patches and plaques with overlying skin laxity and wrinkles which may become pendulous and bulky. GSS is predominately found in intertriginous areas such as the groin and axilla. Interestingly, some suggest the clinical manifestations may be a location-related phenomenon.[2]

Histologically, GMF and GSS share many overlapping features, which makes it difficult to differentiate these two entities. In general, for GSS and GMF, lymphocytes are small-to-medium and may have atypia. The lymphocytic infiltrate can be diffuse, perivascular, periadnexal, nodular, and can extend throughout the entire dermis into the subcutis. Granulomatous infiltrates with multinucleated wreath-like giant cells are common. Sarcoid granuloma is the most common pattern; however, other patterns have been reported.[2,4] Eosinophils may be present. Unlike classic MF, epidermotropism was only present in about half of the cases and may be subtle.[2] Early reports suggested that GMF can be differentiated from GSS with preserved elastin; however, studies have shown that this is not a reliable differentiator.[2] Both GMF and GSS demonstrate elastin loss and elastophagocytosis. To differentiate histologically, a more nuanced approach has been suggested. GMF typically presents with more superficial epithelioid granulomas, with giant cells harboring fewer nuclei, more focal elastin loss, and less lymphophagocytosis and elastophagocytosis.[5]

Immunohistochemical and T-cell gene rearrangement studies are similar for GMF and GSS. Early in the disease course, monoclonality may not be demonstrated, or may show a monoclonal amplification with a polyclonal background, to then subsequently develop monoclonality as the disease progresses. Lymphoid tumor cells depict a T-helper cell phenotype in GMF and GSS, expressing CD3+, CD4+, CD8-, in 75-80% of cases, and expressing CD3+, CD4-, CD8+ in 20-25% of cases, with loss of CD5 and CD7.[2] Monoclonality for TCR gamma and/or beta genes were seen in 87% of cases in GMF and 95% in GSS.[2,5]

Treatment of GMF and GSS is difficult with multiple treatment modalities documented in the literature without consistent efficacy.[2,4-6] Options include interferon alpha, mechlorethamine, retinoids, carumustin, UVA phototherapy, methotrexate, bexarotene, gemcitabine, doxorubicin, and brentuximab with varying response rates. Treatment often results in stable disease, MTX seemed to have best results in 8 patients with GSS.[6]

It is important to differentiate GMF from GSS because it has been suggested that GMF portends a worse prognosis and that GSS is an indolent lymphoproliferative disease. A study demonstrated that 44% of patients with GMF had a second malignancy compared to 22% of patients with classic MF.[4] The second malignancy can occur before, during, or after the diagnosis of GMF, which included Hodgkin lymphoma, CLL, diffuse large B-cell lymphoma, lymphomatoid papulosis, nodal CD30+ anaplastic large-cell lymphoma, and myeloid

leukemia.[2,4] Extracutaneous spread was seen in 33% of patients, involving the liver, lymph nodes, and bone marrow and CNS compared to 5% in classic MF.[2,4,7]

Forty percent of GMF patients died, including 100% of patients with CD30+ large cell transformation.[7-8] Disease specific 5-year survival was 66%.[2] However, a larger study with 26 GMF patients and 52 classic MF patients found that 5- and 10-year overall survival was not statistically different between GMF and classic MF, but did find that the progression-free survival at 5 and 10 years was significantly worse in the GMF group vs. the classic MF group.[4]

Prognosis for GSS seems to be better than that of GMF. A study with 4 patients demonstrated that GSS is a slowly progressive disease, without extracutaneous spread and 100% survival at 17-year follow-up.[2] In addition, the WHO-EORTC estimate the 5-year survival is 100%.[9] Extracutaneous spread is rare, and may involve lymph nodes; however, a study found that regional lymph node involvement did not portend worse survival.[2,10] Although disease-specific survival has been estimated to be around 100%, up to 48% of patients had a second lymphoid neoplasia, which may occur years or decades from GSS diagnosis.[2,10] In addition, some have suggested that the high rate of second lymphoid neoplasia may be overestimated from misinterpretation of large-cell transformation for the development of a second anaplastic large-cell lymphoma, which may be unrelated to GSS.[2] In contrast to previous survival reports, a recent 2021 study examined 8 patients with GSS.[6] Two patients had lymph node involvement and 2 patients had histology confirmed visceral involvement, liver and pharynx, stage IVb disease, and ultimately died from their disease 7 and 15 years after diagnosis, and a third patient died from hemophagocytic lymphohistiocytosis.

In summary, there are no pathognomonic histologic, immunohistochemical, or TCR rearrangement features that allows differentiation between GMF and GSS; however, slight subtle differences may favor one diagnosis over the other. The diagnosis of GSS vs. GMF should be made based on the clinical exam. Treatment of these entities is difficult and often requires a longer duration of treatment, with lower response rates relative to classic MF. Prognosis of GMF may not have a worse overall survival; however, it does seem to have a higher rate of progression. GSS may not be as indolent as previously reported. Lifelong follow-up is required as GMF and GSS are both associated with higher rates of large cell transformation and second malignancies.

REFERENCES

1. Jawed SI, Myskowski PL, Horwitz S, Moskowitz A, Querfeld C. Primary cutaneous T-cell lymphoma (mycosis fungoides and Sézary syndrome): part I. Diagnosis: clinical and histopathologic features and new molecular and biologic markers. *J Am Acad Dermatol.* 2014 Feb;70(2):205.e1-16; quiz 221-2. doi: 10.1016/j.jaad.2013.07.049. PMID: 24438969.
2. Kempf W, Ostheeren-Michaelis S, Paulli M, Lucioni M, Wechsler J, Audring H, Assaf C, Rüdiger T, Willemze R, Meijer CJ, Berti E, Cerroni L, Santucci M, Hallermann C, Berneburg M, Chimenti S, Robson A, Marschalko M, Kazakov DV, Petrella T, Fraitag S, Carlotti A, Courville P, Laeng H, Knobler R, Golling P, Dummer R, Burg G; Cutaneous Lymphoma Histopathology Task Force Group of the European Organization for Research and Treatment of Cancer. Granulomatous mycosis fungoides and granulomatous slack

skin: a multicenter study of the Cutaneous Lymphoma Histopathology Task Force Group of the European Organization For Research and Treatment of Cancer (EORTC). *Arch Dermatol*. 2008 Dec;144(12):1609-17.

3. Miyashiro D, Sanches JA. Characteristics and outcomes of 727 patients with mycosis fungoides and Sézary syndrome from a Brazilian cohort. *Int J Dermatol*. 2022 Apr;61(4):442-454. doi: 10.1111/ijd.15865. Epub 2021 Aug 26. PMID: 34435672.
4. Li JY, Pulitzer MP, Myskowski PL, Dusza SW, Horwitz S, Moskowitz A, Querfeld C. A case-control study of clinicopathologic features, prognosis, and therapeutic responses in patients with granulomatous mycosis fungoides. *J Am Acad Dermatol*. 2013 Sep;69(3):366-74. doi: 10.1016/j.jaad.2013.03.036. Epub 2013 May 16. PMID: 23685027.
5. Shah A, Safaya A. Granulomatous slack skin disease: a review, in comparison with mycosis fungoides. *J Eur Acad Dermatol Venereol*. 2012 Dec;26(12):1472-8. doi: 10.1111/j.1468-3083.2012.04513.x. Epub 2012 Mar 22. PMID: 22435618.
6. Battesti G, Ram-Wolff C, Dobos G, Aubin F, Algros MP, Guenova E, Joly P, Courville P, Mourah S, Cayuela JM, Moins-Tesserenc H, Battistella M, Vignon-Pennamen MD, Rivet J, Bagot M, de Masson A. Granulomatous slack skin: clinical retrospective study of 8 cases of the Cutaneous Lymphoma French Study Group. *Eur J Cancer*. 2021 Oct;156 Suppl 1:S35-S36. doi: 10.1016/S0959-8049(21)00690-0. PMID: 34649654.
7. Sidiropoulou P, Tsaoutou K, Constantinou A, Marinos L, Voudouri D, Iliakis T, Kanellis G, Pouliou E, Stratigos A, Nikolaou V. New insights into granulomatous mycosis fungoides (GMF): a single-center experience. *Eur J Cancer*. 2021 Oct;156 Suppl 1:S69-S70. doi: 10.1016/S0959-8049(21)00757-7. PMID: 34649669; PMCID: PMC8504787.
8. Chen KR, Tanaka M, Miyakawa S. Granulomatous mycosis fungoides with small intestinal involvement and a fatal outcome. *Br J Dermatol*. 1998;138(3):522-525.
9. Willemze R, Cerroni L, Kempf W, Berti E, Facchetti F, Swerdlow SH, Jaffe ES. The 2018 update of the WHO-EORTC classification for primary cutaneous lymphomas. *Blood*. 2019 Apr 18;133(16):1703-1714. doi: 10.1182/blood-2018-11-881268. Epub 2019 Jan 11. Erratum in: *Blood*. 2019 Sep 26;134(13):1112. PMID: 30635287; PMCID: PMC6473500.
10. Gadzia J, Kestenbaum T. Granulomatous slack skin without evidence of a clonal T-cell proliferation. *J Am Acad Dermatol*. 2004 Feb;50(2 Suppl):S4-8. doi: 10.1016/s0190-9622(03)01557-3. PMID: 14726855.

CHICAGO DERMATOLOGICAL SOCIETY

CASE 3

Presented by Luke S. Wallis MD, Sarah Ibrahim MD, David C. Reid MD
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HISTORY OF PRESENT ILLNESS

A 77-year-old female presented for evaluation of intensely pruritic lesions on her anterior trunk. The lesions first began one year prior to presentation and were gradually increasing in size. She was initially treated by her primary care provider with selenium sulfide shampoo, topical terbinafine, and hydroxyzine for a presumed fungal infection, but the lesions did not improve, and the pruritus persisted. She denied other symptoms.

The patient had a remote history of infiltrating ductal breast carcinoma, diagnosed in 2007. At that time, she was treated with a bilateral mastectomy and a course of tamoxifen, but she was lost to follow-up with oncology.

PAST MEDICAL & SURGICAL HISTORY

Infiltrating ductal breast carcinoma, s/p bilateral mastectomy – 2007

MEDICATIONS

Selenium sulfide shampoo, terbinafine cream, hydroxyzine 10-20 mg nightly as needed

SOCIAL HISTORY

Denied tobacco, alcohol, or drug use

REVIEW OF SYSTEMS

Positive for severe itching. Negative for pain.

PHYSICAL EXAM

Chest: bilateral mastectomy scars without reconstruction.

Anterior trunk and upper abdomen: sclerodermoid-like, indurated, hyperpigmented plaques studded with pink papules and overlying scale.

HISTOPATHOLOGY

Punch biopsy, chest: deep dermal interstitial and periadnexal infiltration of relatively bland-appearing cells with atypical nuclei. Immunohistochemical staining strongly positive for cytokeratin AE1/AE3, estrogen receptor, and progesterone receptor.

IMAGING STUDIES

Nuclear medicine bone scan, staging PET-CT: unremarkable

DIAGNOSIS

Carcinoma en cuirasse secondary to recurrent breast cancer

TREATMENT AND COURSE

After diagnosis, the patient was referred to oncology. Staging imaging, including a PET-CT, showed no clear evidence of distant metastases. After thorough discussion with the patient, a palliative treatment plan was initiated, and the patient was started on letrozole.
Discussion Carcinoma en cuirasse is an exceedingly rare form of metastatic cutaneous carcinoma. Although most cases are associated with primary breast cancers, carcinoma en cuirasse has been documented with primary lung, kidney, and gastrointestinal cancers.1,2 Clinically, lesions first present as erythematous papules or nodules. As the metastatic cells begin to invade the superficial lymphatic vessels, the lesions evolve to develop a sclerotic, morphea-like, and fibrotic appearance.3 Rarely, it can present as a keloid-like lesion.2 The lesions can be associated with bleeding, pruritus, or foul-smelling discharge.4

While carcinoma en cuirasse can be the presenting sign of a new breast cancer, it much more commonly presents a period of time after prior treatment of breast cancer, such as after mastectomy, chemotherapy, or radiation therapy.1 Although there is limited data on the chronology between initial breast cancer diagnosis and later presentation of carcinoma en cuirasse, most documented cases have occurred within three years of initial cancer treatment.1 A case of carcinoma en cuirasse presenting after more than ten years of initial breast cancer diagnosis, such as our case, has not been previously reported in the English language medical literature.

Histopathology of carcinoma en cuirasse typically reveals tumor cells organized in single file lines.2 The surrounding tissue is densely fibrotic, with decreased vascularity. The decreased vascularity of the tissue makes treatment of carcinoma en cuirasse challenging, and there is no gold standard therapy.1,2,4 Current accepted strategies include hormonal interventions, chemotherapy, local irradiation, and skin grafting.2,4

REFERENCES

1. Alani A, Roberts G, Kerr O. Carcinoma en cuirasse. BMJ Case Reports. Published online December 2, 2017:bcr-2017-222121. doi:10.1136/bcr-2017-222121.
2. Mullinax K, Cohen JB. Carcinoma En Cuirasse Presenting as Keloids of the Chest. Dermatol Surg. 2004;30(2):226-228. doi:10.1111/j.1524-4725.2004.30071.x.
3. Waldman RA, Finch J, Grant-Kels JM, Stevenson C, Whitaker-Worth D. Skin diseases of the breast and nipple. Journal of the American Academy of Dermatology 2019;80(6):1467-1481. doi:10.1016/j.jaad.2018.08.066.
4. Siddiqui MA, Zaman MN. PRIMARY CARCINOMA EN CUIRASSE. Journal of the American Geriatrics Society. 1996;44(2):221-222. doi:10.1111/j.1532-5415.1996.tb02455.x.

CHICAGO DERMATOLOGICAL SOCIETY

CASE 4

Presented by Julie Bittar, MD, Anas Alabkaa, MD, Warren Piette, MD.
Division of Dermatology, RUSH University Medical Center

HISTORY OF PRESENT ILLNESS

A 29-year-old male with no pertinent past medical history presented to his primary care physician with a three week history of swollen, tender nodules of his right upper extremity and chest. He denied any drainage, arm swelling, trauma, or involvement of any other body site. He also denied fever, chills, nausea, vomiting, unexpected weight loss, and night sweats. His primary care physician was concerned for thrombosis of the cephalic vein versus lymphadenopathy and ordered a duplex ultrasound which showed patent veins of the right upper extremity and no evidence of thromboses. He was referred to general surgery who appreciated significant lymphadenopathy and performed an excisional biopsy of one of the lesions of the right anterior chest wall.

PAST MEDICAL & SURGICAL HISTORY

Congenital heart disease (repaired immediately after birth)

FAMILY HISTORY

No known family history of cutaneous disease, myeloproliferative syndromes, or autoimmune conditions.

SOCIAL HISTORY

3.75 pack year smoking history, rare alcohol consumption, no history of recreational drug use.

MEDICATIONS

None

ALLERGIES

Penicillin (anaphylaxis)

PHYSICAL EXAMINATION

Right chest, right upper arm, left chest: several firm, indurated subcutaneous nodules

LABORATORY RESULTS

CBC with differential- slight leukopenia and neutropenia (WBC 3.91, ANC 1.56) otherwise normal
CMP- normal
LDH- normal (208)
Uric acid- normal (6.4)
Immunoelectrophoresis- normal
Quantitative Immunoglobulins- normal IgG, IgA, IgM
Autoimmune panel- elevated CRP (10.8), +ANA (<1:40), +Anti RNP and+ Anti-Sm (5.3)
Iron panel- normal
Ferritin- elevated (424)

IMAGING STUDIES

PET CT- Multiple FDG avid nodular soft tissue densities/subcutaneous fat stranding in the chest, abdomen, bilateral upper limbs, and posterior right thigh. Multiple hypermetabolic supradiaphragmatic lymph nodes. Diffuse FDG avidity in soft tissue density in superior mediastinum.

PATHOLOGY

Excisional biopsy of the right anterior chest wall nodule showed a dense cellular infiltrate in the fat, consisting of lymphocytes of small to medium size with areas of necrosis and clustered apoptotic cells. The cells showed mild to moderate cytologic atypia resembling activated lymphocytes. Scattered plasma cells were present. Immunostaining showed: no loss of pan T cell markers: CD2, CD5, CD7, CD3; CD4 and CD8 were of equal frequency of staining cells however CD8+ cells were rimming the adipocytes. CD163 highlighted scattered macrophages and were negative for S100 and CD1a. CD56, EBER were negative.

Bone marrow biopsy- Normocellular

DIAGNOSIS

Subcutaneous Panniculitis-like T-Cell Lymphoma

CLINICAL COURSE

The patient was referred to multidisciplinary CTCL clinic for further evaluation. The patient had a challenging disease that proved refractory to multiple therapies. He started on corticosteroid and hydroxychloroquine for four months (discontinued due to progressive disease), transitioned to methotrexate for four months (no response to therapy), then to pralatrexate (no response), then 1 dose of gemcitabine (positive response/skin breakdown, discontinued due to patient request), bexarotene (discontinued due to high fevers and hospitalization), repeat gemcitabine for 1 dose (discontinued again upon patient request) and resumed bexarotene. After two months on bexarotene the patient's course was complicated by the development of Hemophagocytic Lymphohistiocytosis (HLH). The HLH94 protocol (dexamethasone, etoposide, and intrathecal methotrexate) was initiated. The patient continued to follow in clinic for his SPTCL and various metabolic derangements (hyponatremia, hypothyroidism, and hypertriglyceridemia) which were thought to be multifactorial due to HLH, bexarotene and noncompliance. A week later, he presented to the ED with altered mental status and admitted to the MICU for IV insulin to treat his hypertriglyceridemia. His triglyceride levels improved and he was transferred to the medical floors under the hematology service where he continued HLH treatment. Two days after receiving the etoposide, the patient developed recurrent altered mental status and subsequently had a witnessed seizure. He was intubated for airway protection and transferred back to the MICU where Neurology was consulted and attributed the seizure to his HLH. Two days later, he was extubated and transferred back to the floors where he had progressive decreased responsiveness. Psychiatry was consulted and diagnosed him with catatonia vs malignant catatonia. He started scheduled Ativan which ultimately improved his mentation and remained hospitalized for the next 3 weeks. By the end of his hospitalization, his mental status returned to baseline. He had experienced significant muscle atrophy and was wheel chair bound upon

discharge. After a few weeks, he showed significant improvement in his clinical status and was re-initiated on bexarotene therapy. He is currently on etoposide, alternating with dexamethasone, as well as bexarotene and continues to improve, his skin lesions are healing, and he is now walking without assistance.

DISCUSSION

Subcutaneous Panniculitis-like T-Cell Lymphoma (SPTCL) is a rare, primary T-cell lymphoma.[1] It is characterized by infiltration of subcutaneous tissue by cytotoxic T cells mimicking panniculitis. It was first described in 1991 by Gonzalez et al.[2] and ultimately defined by the World Health Organization (WHO) in 2001.[3] Diagnosis of SPTCL is dependent on a combination of clinical presentation, imaging (PET/CT), and histopathologic findings. Patients typically present with multiple painless subcutaneous nodules and plaques on the trunk and extremities.[4]

Historically, SPTCL was comprised of two subtypes depending on whether the tumor was composed of alpha/beta or gamma/delta T cells. However, because each form carries a distinct clinical, pathological and prognostic course, the World Health Organization reclassified these two subtypes as distinct diseases in their 2008 revision. SPTCL now refers specifically to the alpha/beta subtype whereas the gamma/delta form is classified under "cutaneous gamma/delta T cell lymphoma".[5]

SPTCL is typically in younger patients (median age 36), +/- B symptoms, commonly associated with autoimmune disease (20%) and has an indolent course. The prognosis is excellent, with an 82% five-year survival rate. Meanwhile, gamma/delta CTCL affects older patients (median age 59 years old), B symptoms and lab abnormalities are common and severe, and patients tend to undergo rapid clinical deterioration. HLH is relatively common with an incidence of approximately 45%. Prognosis is poor regardless of whether patients develop HLH with an estimated five-year survival rate of 11%.

Histologically, SPTCL shows predominant infiltration of subcutaneous tissue by medium to large lymphocytes with mild pleomorphism and minimal tumor invasion in the superficial dermis with mild to moderate apoptosis and patchy necrosis. The more aggressive gamma/delta CTCL shows large blast-like lymphocytes with significant pleomorphism, is commonly angio-invasive and shows extensive apoptosis with massive necrosis. Immunophenotype of the SPTCL typically shows CD4-, CD8+, CD56- while gamma/delta CTCL often shows CD4-, CD8-, CD56+/-.

Our patient was unusual in that he had SPTCL complicated by HLH. HLH is a hyperinflammatory condition, due to dysregulation of the innate immune system that results in multi-organ failure. HLH is either primary or secondary. Primary HLH presents in early childhood and is the result of an underlying genetic mutation that affects the interactions between NK cells, CD8+ T cells, and antigen presenting cells. Secondary HLH presents in adults and typically due to an acute illness trigger, most commonly: infection, malignancy, or autoimmune disease.[6] The incidence of HLH in SPTCL alpha/beta subtype is uncommon, with an estimated incidence of 17%. Meanwhile, the incidence of HLH in the gamma/delta is approximately 45%. The treatment of HLH is immunosuppression. The implementation of the HLH-94 protocol, which uses a combination of immunosuppressive and cytotoxic therapy, considerably improved

outcomes for patients with HLH, increasing 5-year survival rates from a reported 4%[7] to 54% ± 6%.[8] No consensus guidelines exist for treatment of SPTCL however immunosuppression is the mainstay of therapy (with corticosteroids, methotrexate or cyclosporine). Bexarotene has been increasingly reported in the literature as a favorable treatment option. Chemotherapy is reserved for SPTCL cases that are more aggressive or complicated by HLH.[9,10]

Key points:

- SPTCL is a rare primary T cell lymphoma that mimics panniculitis
- Historically SPTCL had two subtypes however now refers to the alpha/beta group which generally has a good prognosis
- Autoimmune disease in 20% of cases
- HLH is a potential complication that portends a worse prognosis
- Treatment depends on severity

REFERENCES

1. Alsomali DY, Bakshi N, Kharfan-Dabaja M, El Fakih R, Aljurf M. Diagnosis and treatment of subcutaneous panniculitis-like T-cell lymphoma: A systematic literature review. *Hematology/Oncology and Stem Cell Therapy.* 2021.
2. Gonzalez CL, Medeiros LJ, Braziel RM, Jaffe ES. T-cell lymphoma involving subcutaneous tissue. A clinicopathologic entity commonly associated with hemophagocytic syndrome. *Am J Surg Pathol.* 1991;15(1):17-27.
3. Jaffe ES HN, Stein H, Vardiman JW, eds. *Pathology and Genetics of Tumours of Haematopoietic and Lymphoid Tissues.* IARC Press; 2001.
4. Parveen Z, Thompson K. Subcutaneous panniculitis-like T-cell lymphoma: redefinition of diagnostic criteria in the recent World Health Organization-European Organization for Research and Treatment of Cancer classification for cutaneous lymphomas. *Arch Pathol Lab Med.* 2009;133(2):303-308.
5. Willemze R, Jansen PM, Cerroni L, et al. Subcutaneous panniculitis-like T-cell lymphoma: definition, classification, and prognostic factors: an EORTC Cutaneous Lymphoma Group Study of 83 cases. *Blood.* 2008;111(2):838-845.
6. Al-Samkari H, Berliner N. Hemophagocytic Lymphohistiocytosis. *Annu Rev Pathol.* 2018;13:27-49.
7. Janka GE. Familial hemophagocytic lymphohistiocytosis. *Eur J Pediatr.* 1983;140(3):221-230.
8. Trottestam H, Horne A, Aricò M, et al. Chemoimmunotherapy for hemophagocytic lymphohistiocytosis: long-term results of the HLH-94 treatment protocol. *Blood.* 2011;118(17):4577-4584.
9. Go RS, Wester SM. Immunophenotypic and molecular features, clinical outcomes, treatments, and prognostic factors associated with subcutaneous panniculitis-like T-cell lymphoma: a systematic analysis of 156 patients reported in the literature. *Cancer.* 2004;101(6):1404-1413.
10. Fujii K. New Therapies and Immunological Findings in Cutaneous T-Cell Lymphoma. *Front Oncol.* 2018;8:198.

CHICAGO DERMATOLOGICAL SOCIETY

CASE 5

Presented by Megha Trivedi, MD, Anas Alabkaa, MD, Kyle Amber, MD
Division of Dermatology, RUSH University Medical Center

HISTORY OF PRESENT ILLNESS

A 76-year old Caucasian male with a history of papillary thyroid carcinoma s/p thyroidectomy, hypertension, and hyperlipidemia presented with discrete erythematous papules on the left lower leg. The lesions appeared one year ago and had been progressing in number and size.

The patient endorsed mild tenderness to palpation of the lesions but denied any itching. There was no history of any preceding trauma and no recent travel history. Prior to presentation, the patient was prescribed a trial of an unknown oral antibiotic at an outside hospital with no improvement. He denied any history of diabetes. Additionally, review of systems was negative for recent unintentional weight loss, fatigue, fevers, or chills.

PAST MEDICAL & SURGICAL HISTORY

Papillary Thyroid Carcinoma, Hypertension, and Hyperlipidemia

FAMILY HISTORY

No known family history of cutaneous disease or autoimmune conditions.

SOCIAL HISTORY

Never Smoker. Consumes alcohol occasionally in social settings. No reported history of recreational drug use.

MEDICATION

Irbesartan, metoprolol, amlodipine, simvastatin, aspirin, liothyronine

ALLERGIES

NKDA

PHYSICAL EXAMINATION

Examination revealed multiple atrophic pink to red papules and plaques on the left ankle and extending up the left lower leg. 1+ pitting edema of the left lower leg

LABORATORY RESULTS

Tissue culture (aerobic, anaerobic, fungal) negative for microorganisms
PAS and Fite stains- negative

DERMATOPATHOLOGY

Histopathologic analysis of a punch biopsy taken from a lesion on the left lower leg demonstrated a dermis containing layers of palisading granulomas with necrobiotic altered collagen and surrounding lymphocytic infiltrates. The epidermis and dermo-epidermal junction were intact.

DIAGNOSIS

Papular Necrobiosis Lipoidica

CLINICAL COURSE

The patient was started on hydroxychloroquine 200 mg twice daily with follow up at eight weeks. On follow-up, he noted no new lesions since last being seen and an improvement in symptoms of pain on palpation. He also noted that the existing lesions appeared slightly less erythematous compared to before.

DISCUSSION

Necrobiosis lipoidica (NL) is a rare, chronic granulomatous disorder with collagen degeneration and endothelial wall thickening.[1] It is classically characterized by the development of well-circumscribed yellow to red-brown telangiectatic atrophic plaques affecting the anterior shins bilaterally with frequent ulceration.[2] However, involvement of the abdomen, upper extremities, genital region, and scalp has also been described with varied morphologic patterns. The prevalence of diabetes is greater than fifty percent in patients with NL, but only 0.3-1.2% of diabetic patients develop NL. There seems to be a stronger association in diabetics who are insulin-dependent[2,3]. Other systemic associations include inflammatory bowel disease, thyroid disorders, sarcoidosis, and rheumatoid arthritis[4]. Although the diagnosis is often made clinically, a biopsy may be obtained for definitive diagnosis, especially in atypical cases. In a recent review of the literature, plaque morphology was most common and found in 88% of cases, although several morphologic variants have been described[5]. Here we present a case of papular NL, an uncommon presentation of this condition.

While discrete papules are often present with initial onset, they usually develop within or in conjunction with larger plaques. Pure chronic papular morphology is rare with only two reported cases in current literature[6,7]. The pathophysiologic characteristics of the condition are not well understood but the leading hypothesis suggests microangiopathic changes from glycoprotein deposition and reduced tissue oxygenation. However, this concept is debated by several sources.[4]

Three distinct histologic patterns have been described including palisading, tuberculoid and intermediate. The palisading pattern is more commonly seen in patients with diabetes mellitus, whereas the tuberculoid in patients with non-diabetic NL[8]. Once diagnosed, the clinical course is often unpredictable and varies widely between patients. Some patients continue to have a chronic form and others experience spontaneous resolution, with non-diabetic patients more frequently comprising the latter group.[4]

Treatment proves to be challenging due to a lack of randomized control trials and various agents described in published case reports/series.[4] Patients are counseled to minimize trauma due to potential koebnerization and ulceration which has been described in several cases. Although an association with diabetes has been discussed above, there is not enough evidence to refute or support glycemic control for treatment of NL.[4]

The most effective treatment based on case series include topical calcineurin inhibitors, intralesional steroids, antimalarials, cyclosporine, intralesional infliximab, and PUVA.

Hyperbaric oxygen, PDT, CO2 laser, pioglitazone, cellcept, clofazimine, colchicine, niacinamide, pentoxifylline, and aspirin have all been tried with less long-term success.[4]

This case illustrates a rare presentation of NL and the importance of considering NL in the differential of atrophic lesions on the lower legs despite lack of classic morphology. Tissue culture should be obtained when there is suspicion for an infectious process and biopsy can help differentiate between other histiocytic disorders and ulcerative etiologies. While the clinical course is unpredictable, early detection and treatment can impact prognosis and prevention of spread/ulceration.

REFERENCES

1. Sibbald C, Reid S, Alavi A. Necrobiosis lipoidica. *Dermatol Clin*. 2015;33(3):343-360.
2. Hashemi DA, Brown-Joel ZO, Tkachenko E, et al. Clinical features and comorbidities of patients with necrobiosis lipoidica with or without diabetes. *JAMA Dermatol*. 2019;155(4):455-459.
3. Lowitt MH, Dover JS. Necrobiosis lipoidica. *J Am Acad Dermatol*. 1991;25(5):735-748. doi:10.1016/S0190-9622(08)80961-9.
4. Reid SD, Ladizinski B, Lee K, Baibergenova A, Alavi A. Update on necrobiosis lipoidica: A review of etiology, diagnosis, and treatment options. *J Am Acad Dermatol*. 2013;69(5):783-791. doi:10.1016/j.jaad.2013.05.034.
5. Severson KJ, Costello CM, Brumfiel CM, et al. Clinical and morphological features of necrobiosis lipoidica. *J Am Acad Dermatol*. 2022;86(5):1133-1135. doi:10.1016/j.jaad.2021.04.034.
6. Matas-Nadal C, Fernández-Armenteros JM, Casanova Seuma JM, Vilardell F, Baradad M, Aguayo-Ortiz RS. Papular spreading necrobiosis lipoidica: a rare clinical presentation of this pathology. *Clin Exp Dermatol*. 2019;44(4):e159-e160. doi:10.1111/ced.13947.
7. Hashemi DA, Nelson CA, Elenitsas R, Rosenbach M. An atypical case of papular necrobiosis lipoidica masquerading as sarcoidosis. *JAAD Case Rep*. 2018;4(8):802-804. doi:10.1016/j.jdcr.2018.07.011.
8. Muller SA. Necrobiosis Lipoidica Diabeticorum: Histopathologic Study of 98 Cases. *Arch Dermatol*. 1966;94(1):1. doi:10.1001/archderm.1966.01600250007001.

CHICAGO DERMATOLOGICAL SOCIETY

CASE 6

Presented by Julie Bittar, MD, Anas Alabkaa, MD, Faiyaaz Kalimullah, MD.
Division of Dermatology, RUSH University Medical Center

HISTORY OF PRESENT ILLNESS

A 49-year-old female with a history of lap sleeve gastrectomy and nephrolithiasis presented with tender, flesh-colored papules coalescing into ill-defined plaques distributed along the right medial cheek, right upper and lower eyelids and bilateral medial canthi present for the past 2 years. She was evaluated by a dermatologist at another institution who performed a skin biopsy of the right cheek (lymphohistiocytic infiltrate with multinucleated giant cells and focal xanthomatous infiltrate) and was diagnosed with rosacea. She completed a 30-day course of doxycycline with no improvement and sought out a consultation with an ophthalmologist who diagnosed her with xanthelasma and referred to oculoplastics for surgical evaluation. The oculoplastic surgeon felt that the patient's presentation was more consistent with syringomata and that surgical intervention was not a reasonable option. She was referred to dermatology for possible nonsurgical therapies.

PAST MEDICAL & SURGICAL HISTORY

Lap sleeve gastrectomy, nephrolithiasis, anxiety

FAMILY HISTORY

No known family history of cutaneous disease, myeloproliferative syndromes, or autoimmune conditions.

SOCIAL HISTORY

No reported history of smoking, alcohol, or recreational drug use.

MEDICATIONS

Alprazolam, ferrous gluconate, thiamine, ibuprofen

ALLERGIES

Tamsulosin, tetracycline

PHYSICAL EXAMINATION

Right medial cheek and medial canthus with skin colored papules coalescing into ill-defined thick plaque. Nasolabial folds (right greater than left) with skin colored, coalescent papules.

LABORATORY RESULTS

CBC- normal
CMP- albumin (3) otherwise normal
Lipid profile demonstrated elevated LDL (129) and low HDL (HDL) total cholesterol and triglycerides were normal
SPEP/UPEP/IFE- elevated gamma-SPE-QT (2.6); elevated kappa (7.51); lambda (2.88) and elevated kappa/lambda ratio (2.61).

LABORATORY RESULTS (cont)
Paraprotein (M-spike) was detected as monoclonal IgG kappa and the quantitation yielded a level of 1.4 gm/dL.
Quantitative Immunoglobulins- elevated IgG (2,775), normal IgA and IgM

IMAGING STUDIES
Normal findings: CXR, MRI Brain/Spine (Cervical, Thoracic, Lumbar, Pelvis), CT Abdomen/Pelvis, PET-CT Skull base-Mid thigh

PATHOLOGY
Histopathologic analysis of two separate shave biopsies taken from the right lower eyelid and right nasolabial fold demonstrated xanthogranulomatous infiltration consisting of epithelioid and foamy histiocytes in addition to Touton giant cells, through the reticular dermis. No necrobiosis was appreciated.
Bone marrow biopsy showed normocellular marrow.

DIAGNOSIS
Multiple Eruptive Periorbital and Facial Xanthogranulomas with Smoldering Myeloma

CLINICAL COURSE
After the patient's histopathologic diagnosis of xanthogranuloma, an extensive workup was initiated to assess for underlying plasma cell dyscrasia/monoclonal gammopathy. Since her SPEP was abnormal she was referred to hematology/oncology who performed a bone marrow biopsy. She was diagnosed with smoldering myeloma and underwent, PET-CT, and MRI of the brain/spine for staging. She remained interested in aesthetic treatment options for her xanthogranulomas. Options including dermabrasion, laser resurfacing, and isotretinoin were discussed along with risks and benefits of each. She elected a trial of isotretinoin that was coordinated with her primary care and hematology/oncology. The patient was initiated on low dose isotretinoin 20mg and slowly titrated up to maximum of 80mg. After completing 8 months of therapy without significant clinical response she developed COVID pneumonia, and the isotretinoin was discontinued. She noted significant improvement in her xanthogranulomas (thinner and lighter in color) after completing a methylprednisolone dose pack for her pneumonia. Afterwards, other steroid-sparing therapeutic options including methotrexate were discussed with the patient however she declined due to concern for side effects and satisfaction with the improvement of facial lesions after her short course of steroids. Three months after discontinuation of isotretinoin, patient's xanthogranulomas appeared to worsen. She subsequently had a PET/CT scan for myeloma restaging which showed interval size increase in a now FDG avid left lower lobe lung nodule concerning for malignancy and metastasis. Hematology/oncology is planning to sample her lung nodule and initiate myeloma directed therapy pending tissue pathology.

DISCUSSION
Adult Xanthogranulomatous Disease of the Orbit (AXDO) is a group of non-Langerhan cell histiocytoses that can be further divided into four subtypes. AXDO includes Adult-onset Orbital

Xanthogranuloma (AOX), Adult-onset Asthma and Peiriocular Xanthogranuloma (AAPOX), Necrobiotic Xanthogranuloma (NXG), and Erdheim-Chester Disease (ECD).[1]

Key differentiating factors between AXDOs and other xanthomatous orbital lesions is that these lesions are typically infiltrated to the touch clinically and have a granulomatous infiltrate on histology.[2] The subtypes can present in a similar manner both clinically and histologically (all forms show the presence of foamy histiocytes and Touton giant cells) however there are some nuanced differences. While most cases could be classified as one of the four AXDO syndromes, some cases fall in between.[1]

AOX is thought to be the adult-variant of juvenile xanthogranuloma (JXG). JXGs that arise in children tend to involute spontaneously while adult onset lesions are more persistent.[3] AOX is typically limited to the anterior orbit and presents solely with eyelid lesions although few case reports demonstrate multiple generalized AOXs.[4] Histologically, these lesions show foamy CD68+ S100- histiocytes, and no other findings.[5] There are no standardized guidelines for treatment however case reports have shown improvement with surgical debulking, CO2 laser,[6] isotretinoin, [4] and corticosteroids.[7-9]

AAPOX is a systemic disorder characterized by adult-onset asthma, lymphadenopathy and periocular xanthogranulomas disease. Clinically, a triad of periorbital swelling, asthma and chronic rhinosinusitis should raise suspicion for this disease.[10] Asthma tends to appear at the same time of the periocular lesions. Histologically, the tissue appears similar to AOX but can also demonstrate lymphoid aggregates with germinal centers.[5] Corticosteroids are the mainstay of therapy to decrease periorbital swelling.[11]

NXG manifests as discrete, slowly developing yellow to red periorbital nodules and plaques with a tendency to ulcerate and become fibrotic.[12] On histology, necrobiosis with pallisading epithelioid histiocytes is typically seen.[5] There is a well-established relationship between NXG and paraproteinemia and therefore workup for hematologic malignancy is key. Although no standardized treatment guidelines exist, a recent systematic review showed corticosteroids (local and systemic) and immunosuppression as the most common modes of therapy.[13]

ECD is a rare disease characterized by diffuse histiocytic infiltration of organs and bones. ECD usually presents clinically with bone pain and periocular xanthogranulomas.[10] Histology demonstrates marked interstitial fibrosis and imaging studies often show sclerotic destruction of long bones. Retroperitoneal fibrosis, pericardial effusion and thickening, infiltration of the aorta and pulmonary arteries are all possible manifestations of ECD which contribute to its poor prognosis. Treatment is centered around corticosteroids and immunosuppressants.[11]

Taken together, AXDOs are rare and can be challenging to differentiate. They are discerned based on their occasional histologic differences but more so by their associated systemic manifestations.

Key Points

- Keep xanthogranulomas on periocular disease differential
- Four types of adult xanthogranulomas disease of the orbit

- History and physical are key
- Workup for underlying systemic disease
- Treatment and prognosis depend on subtype

REFERENCES

1. Sivak-Callcott JA, Rootman J, Rasmussen SL, et al. Adult xanthogranulomatous disease of the orbit and ocular adnexa: new immunohistochemical findings and clinical review. *Br J Ophthalmol.* 2006;90(5):602-608.
2. Ortiz Salvador JM, Subiabre Ferrer D, Pérez Ferriols A. Adult Xanthogranulomatous Disease of the Orbit: Clinical Presentations, Evaluation, and Management. *Actas Dermosifiliogr.* 2017;108(5):400-406.
3. Cohen BA, Hood A. Xanthogranuloma: report on clinical and histologic findings in 64 patients. *Pediatr Dermatol.* 1989;6(4):262-266.
4. Achar A, Naskar B, Mondal PC, Pal M. Multiple generalized xanthogranuloma in adult: case report and treatment. *Indian J Dermatol.* 2011;56(2):197-199.
5. Guo J, Wang J. Adult orbital xanthogranulomatous disease: review of the literature. *Arch Pathol Lab Med.* 2009;133(12):1994-1997.
6. Almeida RDC, Tellechea Ó, Pereira MP, Mascarenhas RCC. Multiple adult xanthogranuloma. *An Bras Dermatol.* 2020;95(1):113-115.
7. Elner VM, Mintz R, Demirci H, Hassan AS. Local corticosteroid treatment of eyelid and orbital xanthogranuloma. *Ophthalmic Plast Reconstr Surg.* 2006;22(1):36-40.
8. Elner VM, Mintz R, Demirci H, Hassan AS. Local corticosteroid treatment of eyelid and orbital xanthogranuloma. *Trans Am Ophthalmol Soc.* 2005;103:69-73; discussion 73-64.
9. Burris CKH, Rodriguez ME, Raven ML, Burkat CN, Albert DM. Adult-Onset Asthma and Periocular Xanthogranulomas Associated with Systemic IgG4-Related Disease. *Am J Ophthalmol Case Rep.* 2016;1:34-37.
10. Cavallazzi R, Hirani A, Vasu TS, et al. Clinical manifestations and treatment of adult-onset asthma and periocular xanthogranuloma. *Can Respir J.* 2009;16(5):159-162.
11. Kerstetter J, Wang J. Adult Orbital Xanthogranulomatous Disease: A Review with Emphasis on Etiology, Systemic Associations, Diagnostic Tools, and Treatment. *Dermatol Clin.* 2015;33(3):457-463.
12. Finan MC, Winkelmann RK. Necrobiotic xanthogranuloma with paraproteinemia. A review of 22 cases. *Medicine (Baltimore).* 1986;65(6):376-388.
13. Miguel D, Lukacs J, Illing T, Elsner P. Treatment of necrobiotic xanthogranuloma - a systematic review. *J Eur Acad Dermatol Venereol.* 2017;31(2):221-235.

CHICAGO DERMATOLOGICAL SOCIETY

CASE 7

Presented by Morgan M. Ellis, MD, MS, David C. Reid, MD
Division of Dermatology, RUSH University Medical Center

HISTORY OF PRESENT ILLNESS

A 72-year-old male with a history of end stage renal disease on hemodialysis presented to the hospital for evaluation of left upper extremity redness and swelling. The rash began on the hand and distal forearm two days prior and had progressed proximally. The patient endorsed associated pain and pruritus, but he had no preceding trauma, recent travel, contact with fish/shellfish, glove use, new jewelry, or chemical exposures.

The patient was admitted due to concern for arteriovenous (AV) fistula dysfunction or infection and empirically treated for cellulitis with cefepime and vancomycin. His swelling and erythema progressed over the next two days, and antibiotics were broadened to vancomycin, piperacillin-tazobactam, and clindamycin. Orthopedic surgery was consulted to rule out necrotizing fasciitis, and dermatology was consulted for further evaluation.

PAST MEDICAL & SURGICAL HISTORY

Paroxysmal atrial fibrillation on anticoagulation, coronary artery disease status post percutaneous intervention to left anterior descending and obtuse marginal arteries, type II diabetes mellitus, end-stage renal disease on hemodialysis, and myocardial infarction

MEDICATIONS

Aspirin, sevelamer, apixaban, furosemide, amiodarone, metoprolol, atorvastatin, metolazone

REVIEW OF SYSTEMS

Positive for intermittent fevers, generalized fatigue, left upper extremity pain, swelling

PHYSICAL EXAMINATION

A well-demarcated erythematous, edematous plaque with multiple intact and ruptured bullae and cigarette-paper-like skin extended circumferentially from left dorsal hand to mid-forearm. Involving the extensor aspect of the left upper extremity, there was a second well-demarcated, erythematous, edematous plaque featuring a large, eroded, heme-crusted bulla.
Brightly erythematous, edematous, non-scaly satellite papules were scattered along the left forearm and proximal upper extremity.

LABORATORY RESULTS

CBC with differential notable for neutrophilic-predominant leukocytosis (WBC 13.02, Neutrophil # 10.25, neutrophils % 78.7), normocytic anemia (Hgb 11.0, MCV 78.6, RDW 16.3), thrombocytopenia (PC 111)

CMP notable for hyponatremia (136), hyperkalemia (5.5), azotemia (BUN 79, Cr 12.28), hyperglycemia (136), hypoalbuminemia (3.3)

CRP elevated to 178.9. CK within normal limits.

IMAGING STUDIES

Duplex ultrasound, left upper extremity – patent AV fistula without deep venous thrombosis
X-ray, left hand and forearm – diffuse swelling without subcutaneous emphysema
CT with contrast, left forearm– diffuse subcutaneous swelling and skin thickening throughout forearm without abscess or osteomyelitis

DERMATOPATHOLOGY

Punch biopsy, left arm: mild papillary dermal edema and focal perivascular hemorrhage. Deep reticular dermis and subcutis with scattered foci of neutrophilic infiltrate and leukocytoclasia without evidence of vasculitis.

DIAGNOSIS

Necrotizing neutrophilic dermatosis

CLINICAL COURSE

The patient exhibited rapid improvement with prednisone 40 mg daily. As necrotizing neutrophilic dermatoses may be associated with malignancy, age-appropriate cancer screening was recommended and serum protein electrophoresis (SPEP) was obtained, which was significant for kappa and lambda biclonal gammopathy. The patient was referred to hematology/oncology for further evaluation and continued to follow with dermatology after discharge. The patient received a two-week course of prednisone 40 mg daily, which was tapered to 20 mg daily for an additional two weeks. He exhibited complete resolution of his necrotizing neutrophilic dermatosis at one-month follow-up.

DISCUSSION

Neutrophilic dermatoses constitute a heterogenous group of clinical phenotypes with shared histopathologic features of perivascular and diffuse neutrophilic infiltrates without the presence of an identifiable infectious agent. The term necrotizing neutrophilic dermatoses (NND) was proposed to describe variants of neutrophilic dermatoses that clinically resemble necrotizing fasciitis (NF).[1]

NF is a potentially fatal, rapidly progressing mono- or polymicrobial bacterial infection characterized by exuberant inflammation of the deep fascia resulting in necrosis of subcutaneous tissues. Disproportionately affecting immunocompromised hosts and those with underlying systemic disease, NF can occur without a clear portal of entry; however, a history of penetrating trauma and breaches in the skin barrier are commonly reported.[2] Clinically, NF presents as erythema and edema of the skin with pain disproportionate to physical findings. Despite antibiotic therapy, the edema progresses and may become associated with bullae, necrosis, ecchymoses, crepitus, and woody induration. Systemic symptoms, including fever, lethargy, hypotension, and tachycardia, frequently accompany the cutaneous manifestations. Early recognition of NF is difficult, and the diagnosis is often made on clinical grounds as immediate surgical debridement of infected and devitalized tissue is crucial for survival.[3] Delayed intervention results in extremely high mortality (~80 to 100%), and even with intervention mortality rates remain as high as 30 to 50%.[4]

Mimicking NF, NND has been described as a recently recognized, unusual variant of acute febrile neutrophilic dermatosis (Sweet syndrome). Clinically, Sweet syndrome (SS) presents with pyrexia, neutrophilia, and tender erythematous skin lesions (papules, nodules, and plaques) frequently involving the face, neck, and upper extremities. Papillary dermal edema and an underlying dense infiltrate composed of mature neutrophils are histopathologic characteristics of SS. Associated triggers include infections, malignancies (especially hematologic), myelodysplasia, inflammatory bowel disease, autoimmune disorders, drugs, and pregnancy.[5] Systemic corticosteroids are the therapeutic gold standard for SS, and treatment initiation is associated with dramatic improvement in cutaneous lesions and systemic symptoms.[6]

The NND variant presents with rapid progression of cutaneous disease and systemic symptoms that clinically resemble NF. Histologically, the neutrophilic infiltrate in NND is a deeper process than that seen in traditional SS and may be associated with leukocytoclasia, edema, and necrosis extending to fascia or skeletal muscle.[7] NND has been associated with comorbidities analogous to those implicated in classic SS and demonstrates a similar response to systemic corticosteroids.[8]

Several cases of NND misdiagnosed as NF have been reported in the literature, leading to inappropriate administration of antibiotics, unnecessary surgical debridement, and rarely, amputation.[1,8-11] Tissue biopsy specimens and cultures are critical in distinguishing NND from NF. Increasing awareness and recognition of NND may serve to reduce the significant morbidity associated with inappropriate diagnosis and treatment.

Key Points:

- Necrotizing neutrophilic dermatosis (NND) describes a variance of Sweet syndrome that clinicopathologically mimics necrotizing fasciitis
- Tissue stains, tissue cultures, and the differential response to antibiotics versus corticosteroids may aid in differentiating NND from NF
- Inappropriate diagnosis and management of NND as NF is associated with marked morbidity

REFERENCES

1. Kroshinsky D, Alloo A, Rothschild B, et al. Necrotizing Sweet syndrome: a new variant of neutrophilic dermatosis mimicking necrotizing fasciitis. *J Am Acad Dermatol*. 2012;67(5):945-954. doi:10.1016/j.jaad.2012.02.024.
2. Leiblein M, Marzi I, Sander AL, Barker JH, Ebert F, Frank J. Necrotizing fasciitis: treatment concepts and clinical results. *Eur J Trauma Emerg Surg*. 2018;44(2):279-290. doi:10.1007/s00068-017-0792-8.
3. Goh T, Goh LG, Ang CH, Wong CH. Early diagnosis of necrotizing fasciitis. *Br J Surg*. 2014;101(1):e119-e125. doi:10.1002/bjs.9371.
4. Bilton BD, Zibari GB, McMillan RW, Aultman DF, Dunn G, McDonald JC. Aggressive surgical management of necrotizing fasciitis serves to decrease mortality: a retrospective study. *Am Surg*. 1998;64(5):397-401.

5. Villarreal-Villarreal CD, Ocampo-Candiani J, Villarreal-Martínez A. Sweet syndrome: a review and update. *Actas Dermosifiliogr*. 2016;107(5):369-378. doi:10.1016/j.ad.2015.12.001.
6. Cohen PR. Sweet's syndrome--a comprehensive review of an acute febrile neutrophilic dermatosis. *Orphanet J Rare Dis*. 2007;2:34. Published 2007 Jul 26. doi:10.1186/1750-1172-2-34.
7. Chan MP. Neutrophilic panniculitis: algorithmic approach to a heterogeneous group of disorders. *Arch Pathol Lab Med*. 2014;138(10):1337-1343. doi:10.5858/arpa.2014-0270-CC.
8. Sanchez IM, Lowenstein S, Johnson KA, et al. Clinical features of neutrophilic dermatosis variants resembling necrotizing fasciitis. *JAMA Dermatol*. 2019;155(1):79-84. doi:10.1001/jamadermatol.2018.3890.
9. Gowda A, Christensen L, Polly S, Barlev D. Necrotizing neutrophilic dermatosis: a diagnostic challenge with a need for multi-disciplinary recognition, a case report. *Ann Med Surg (Lond)*. 2020;57:299-302. Published 2020 Jul 26. doi:10.1016/j.amsu.2020.07.037.
10. Lipof JS, Beck LA, Reddy SC, Southgate RD, Carney-Young K, Hammert WC. Necrotizing Sweet Syndrome of the upper extremity after elective hand surgery. *J Hand Surg Am*. 2018;43(4):389.e1-389.e6. doi:10.1016/j.jhsa.2017.08.019.
11. Anand A, Gentile T, Kato H, Wang Q. Recurrent soft tissue inflammation, necrotizing fascitis or Sweet syndrome, diagnostic dilemma. *Clin Case Rep*. 2019;7(12):2483-2487. Published 2019 Nov 13. doi:10.1002/ccr3.2445.