Key location(s): Frontoparietal scalp **CASE 1**

Presented by Vidya Shivakumar, MD and Warren Piette, MD

History of Present Illness

An 81-year-old female was admitted for work-up of "burning scalp". This sensation was present for two weeks, and began one week after application of a new hair dye. While she did not experience headaches or visual disturbances during admission, she did have a history of uncontrolled hypertension that resulted in a retinal vein branch occlusion with resultant macular edema of her right eye. This condition had improved with regular intraocular steroid injections. Additionally, she complained of perioral pain after prolonged mastication. One month prior to presentation, her primary care physician initiated prednisone for treatment of dysphagia.

Past Medical History

Hypertension, atrial fibrillation

Medications

Amiodarone, enalapril, hydralazine, warfarin, acetaminophen

Allergies

Penicillin

Social History

No history of alcohol or illicit drug use
Remote smoker

Review of Systems

Negative for fever, chills, headache, nausea, vomiting, diarrhea, vision changes, dizziness, chest pain, dyspnea, or abdominal pain

Physical Exam

Bilateral frontoparietal scalp: large, irregularly shaped ulcers with overlying eschar

Laboratory Data

The following labs were remarkable/abnormal:

Hb/Hct	10.8 g/dL	[12.9 – 16.8 g/dL]
WBC	9.6 k/μL	[4.4 – 10.6 k/μL]
Eosinophil #	1.0 k/μL	[0.0 – 0.4 k/μL]
Sedimentation Rate	48 mm/hr	[0 – 45 mm/hr]
CRP	11.40 mg/dL	[0 – 0.5 mg/dL]

Histopathology
Right temple skin, punch biopsy:
Granulomatous vasculitis in subcutaneous tissue with fat necrosis

Right temporal artery biopsy:
Granulomatous vasculitis consisting of multinucleated giant cells. There is vessel wall destruction and luminal narrowing. Elastin stain highlights a discontinuous and fragmented internal elastic membrane.

Diagnosis
Giant Cell Arteritis

Treatment and Course
High-dose prednisone therapy resulted in complete resolution of scalp ulcers and improvement of TMJ tenderness at her two month follow-up. She was transferred to an acute-care facility, but died five months later at an outside hospital. The cause of death was unknown.

Discussion
Giant cell arteritis (GCA) is a vasculitis involving medium and large-sized vessels in patients older than 50 years. Potential complications include vision loss and aortic rupture if left untreated. The American College of Rheumatology has formulated a classification criteria in order to differentiate GCA from other forms of vasculitis for the purpose of research studies. These include:

- Age greater than or equal to 50 years at time of disease onset
- Localized headache of new onset
- Tenderness or decreased pulse of the temporal artery
- Erythrocyte sedimentation rate (ESR) greater than 50mm/hour
- Biopsy revealing a necrotizing arteritis with a predominance of mononuclear cells or a granulomatous process with multinucleated giant cells

The presence of three of these five criteria is associated with 94% sensitivity and 91% specificity for the diagnosis of GCA. In addition to the aforementioned criteria, jaw claudication, abrupt onset of visual disturbances, unexplained fever, or anemia are manifestations of GCA. These clinical findings are a direct result of ischemia caused by diseased cranial vasculature originating from the aortic arch, particularly extracranial branches of the carotid artery. While symptoms vary for each patient, vision loss has been reported to occur in 15-20% of patients in most series. The gold standard for diagnosis is temporal artery biopsy.

Scalp necrosis is a rare and late presentation of GCA and portends a poor prognosis. Necrosis is considered to be the result of vascular occlusion of four arteries supplying the temporal region of the scalp: temporal, frontal, retroauricular, and occipital arteries. On average, there is a delay in diagnosis by one month compared to patients who do not have scalp necrosis. Therefore, these patients are more likely to have other severe sequelae, such as tongue necrosis and vision loss (35% vs. 20%). In addition, while one study found that the long-term survival of 205 patients with GCA was the same as that for the general population, patients with scalp necrosis were estimated to have a high mortality rate (standard mortality ratio of 4.2).

Long-term corticosteroid treatment is well established as first line therapy for GCA, and delay in therapy is detrimental. New onset vision loss after commencement with corticosteroid therapy is rare. Corticosteroid-sparing agents such as methotrexate and cyclophosphamide have been used. Uncomplicated GCA typically runs a self-limited course over months to years, and only in a few is chronic steroid therapy necessary after one year.

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Key location: Upper legs **CASE 5A**

Presented by Christina Kranc, MD, Jerry Feldman, MD, and David Reid, MD

History of Present Illness

A 39-year-old man with a history of type I diabetes mellitus presented with four asymptomatic nodules on his upper legs, in areas of previous insulin injection. He first noticed the lesions nine months prior to presentation. He subsequently switched his injection site to the abdomen, without development of new nodules. Despite being compliant with his insulin regimen, he had a long history of irregular glucose control, including frequent hypoglycemic episodes.

Past Medical History

Diabetes mellitus (type I), diabetic neuropathy, hyperlipidemia

Medications

Insulin (initially regular and NPH; 3 months prior to visit, switched to long-acting glargine and short-acting lispro), enalapril, lovastatin

Allergies

Penicillin

Social History

No alcohol, tobacco, or illicit drug use
Occupation: limousine dispatcher and real estate agent

Physical Exam

Lateral thighs: each with two soft, nontender, exophytic nodules with surrounding hyperpigmented and hyperkeratotic collarette
Nodule size ranged from 2.0-3.5cm in diameter and 0.5-0.7 cm in height

Laboratory Data

The following labs were remarkable:

Glucose	207 mg/dL	[65-110 mg/dL]
Glycohemoglobin	8.8%	[4.4-6.7 %]
Serum protein electrophoresis	Normal	
Immunofixation	Normal	

Histopathology

Right upper lateral thigh (representative report for all lesions):
Diffuse dermal amyloidosis (nodular type) associated with prominent papillomatosis, hyperkeratosis, hypergranulosis, acanthosis, focal melanin pigment deposition, and minimal superficial perivascular lymphocytic infiltrate. Congo red and trichrome stains supportive for the above interpretation. Liquid chromatography tandem mass spectrometry consistent with deposition of AIns amyloid, a protein precursor of insulin.

Diagnosis

Localized cutaneous AIns (insulin-derived) amyloidosis

Treatment and Course

Due to the size and persistent nature of the lesions, the nodules were removed by tangential excision. In addition, he was advised to continue rotating injection sites frequently. The patient's blood glucose levels are now well controlled, and he has not developed new nodules.

Key location: Lower abdomen **CASE 5B**

Presented by Christina Kranc, MD, Jerry Feldman, MD, and David Reid, MD

History of Present Illness

A 53-year-old woman with a history of type II diabetes mellitus presented with painful subcutaneous nodules on the lower abdomen. The nodules developed approximately one month after she began injecting insulin subcutaneously to these areas and were slowly enlarging over the past year. She switched injection sites shortly after noticing the lesions, but the nodules persisted. The patient had a long history of poor glucose control with chronically elevated glycohemoglobin and blood glucose levels, attributable to poor diet and non-compliance with medications.

Past Medical History

Hypertension, asthma, diabetes mellitus (type II)

Past Surgical History

C-section, hysterectomy, uterine fibroid excision, umbilical hernia repair

Medications

Insulin (regular), albuterol inhaler, enalapril, hydrochlorothiazide

Allergies

NKDA

Social History

No alcohol, tobacco, or illicit drug use

Physical Exam

Left lower abdomen: 5.5cm x 3.5cm hyperpigmented, exophytic, smooth nodule with similar adjacent nodule measuring 1.7cm
Right lower abdomen: 2.5cm hyperpigmented, exophytic, smooth nodule

Laboratory Data

The following labs were abnormal:

Glucose	197 mg/dL	[65-110 mg/dL]
Glycohemoglobin	9.3%	[4.4-6.7 %]

Histopathology

Left lower abdomen, punch biopsy:
Diffuse dermal amyloidosis (nodular type) associated with prominent hyperkeratosis, hypergranulosis, acanthosis, and focal melanin deposition in the papillary dermis. Congo red stain supportive of above interpretation.

Diagnosis

Localized cutaneous AIns (insulin-derived) amyloidosis

Treatment and Course

The patient began injecting away from the amyloid nodules without the development of lesions at new injection sites. The original nodules have persisted, and surgical excision is planned.

Discussion

Amyloidosis consists of approximately 30 protein-folding disorders sharing the common feature of abnormal extracellular amyloid deposition. In each type of amyloidosis, a specific soluble precursor protein aggregates to form the insoluble fibrils of amyloid, characterized by the beta-pleated sheet structure.

Amyloidosis occurs as either a systemic or localized process. Insulin-derived amyloidosis, a localized process occurring at injection sites, was first reported in 1983. Until recently, there were less than 20 reported cases. In 2014, there were 57 additional cases reported from just two institutions, indicating that insulin-induced amyloidosis may be more common than previously thought. Despite the increasing prevalence of diabetes mellitus and insulin use, there is a paucity of published cases and a lack of awareness of the condition among both dermatologists and general practitioners.

The exact pathogenesis of insulin-induced amyloidosis is unknown, but insulin is the suspected precursor protein. The fibril protein that is derived from insulin in these tumors is now identified as insulin-type amyloid (AIns). It is hypothesized that insulin accumulates locally and, by an unknown mechanism, is converted to amyloid. Other potential contributory factors include chronic inflammation and foreign body reactions seen around amyloid deposits, as well as repeated trauma from injections into a single site. It appears that lesions may derive from a wide range of insulin types and occur after variable time periods.

A majority of iatrogenic amyloid cases describe a single firm subcutaneous mass at injection site, commonly misdiagnosed as lipomas or lipohypertrophy. To our knowledge, none of the reported cases resembled the multiple discrete exophytic nodules seen in our two patients. The surrounding hyperkeratosis noted in patient A is another uncommon feature of AIns. Only three cases describe acanthosis-like changes, and only one of these provides a clinical image.

All AIns cases describe histopathological findings consistent with homogenous, eosinophilic amyloid deposition, and positive Congo-red staining with green birefringence by polarization. Immunohistological staining of the amyloid deposit with insulin antibody can confirm diagnosis. Mass spectrometry was performed on patient A's specimen, and peptide profiles were consistent with insulin-type amyloid. Mass spectrometry results are currently pending for patient B. However, the history of insulin injection in areas of confirmed amyloid deposition strongly supports the diagnosis of AIns in this case.

Recent literature suggests that the deposition of amyloid at insulin injection sites has the potential to interfere with insulin absorption, leading to poor glucose control. Hence, injection site rotation is a crucial aspect of AIns treatment and prevention. Nagase et al. compared serum insulin levels after injection into insulin-derived amyloidosis sites to injection into normal skin in four patients, and found that insulin absorption at amyloid sites was 34% of that at normal sites ($p=0.030$). Patients should be instructed to inject away from the amyloid deposit once it is identified. Glucose levels should be monitored closely when patients first inject away from the amyloid mass, as injection of the same dosage to an area of normal skin can lead to increased insulin absorption and hypoglycemia. It is possible that patient A's frequent hypoglycemic episodes were due to increased insulin sensitivity after switching to injection sites away from amyloid lesions.

Our patients demonstrate unique presentations of localized cutaneous amyloidosis at

repeated insulin injection sites. We report these cases to complement the current data of iatrogenic amyloidosis and provide insight into this likely under-reported phenomenon.

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Key locations: Lower extremities **Case 9**

Presented by Donna Hart, MD, Nicole Joy, MD, and Warren Piette, MD

History of Present Illness
A 65-year-old man with past medical history of hypertension, diabetes mellitus, and granulomatosis with polyangiitis (Wegener's granulomatosis) was admitted for acute kidney injury and an asymptomatic purpuric rash of unknown duration. He was diagnosed with granulomatosis with polyangiitis (c-ANCA and PR-3 positive vasculitis) more than two years prior to presentation. His symptoms at that time included nasal crusting and alveolar hemorrhage. He had been previously treated with cyclophosphamide, rituximab, and oral steroids. However, he had not required immunosuppressant medications for the past eight months. He did not recall having a similar rash in past. The patient endorsed polyarticular joint pain but no joint swelling.

Past Medical History
Hypertension, diabetes mellitus, hyperlipidemia, granulomatous with polyangiitis, aortic valve replacement, benign prostatic hyperplasia, degenerative joint disease

Medications/ Allergies
Ergocalciferol, calcium carbonate, famotidine, gabapentin, metoprolol, simvastatin, tamsulosin

No known drug allergies

Social History
No tobacco, alcohol, or illicit drug use

Review of Systems
He denied fever, chills, dyspnea, weight loss, malaise, night sweats, cough, hemoptysis, dysuria, or hematuria.

Physical Exam
Inguinal folds and lower extremities with scattered round purpura, some minimally palpable. Several lesions arranged in a linear koebnerized array and few early retiform purpura.

Laboratory Data

The following labs were abnormal:

Hemoglobin	8.8 g/dL	[12.9 – 16.8 g/dL]
Hematocrit	26.2%	[38.1 - 49%]
WBC	16.8 k/μL	[4.4 – 10.6 k/μL]
Creatinine	5.3 mg/mL	[0.6 – 1.4 mg/dl]
BUN	114 mg/dL	[8 – 20 mg/dL]
Rheumatoid Factor	71 IU/mL	[normal <20 IU/mL]
c-ANCA (titer)	Positive (1:320)	
PR3 (ANCA)	>800	[normal< 1.0]

Urinalysis: Blood large, protein 30 mg/dL, leukocyte esterase moderate, red blood cell casts and dysmorphic RBCs present.

The following labs were within normal limits:
ANA/Complements, p-ANCA, cryoglobulins

Histopathology

Right lower leg skin, punch biopsy:
Leukocytoclastic vasculitis with vascular and perivascular infiltration of polymorphonuclear leukocytes and nuclear dust, extravasation of erythrocytes, and fibrinoid necrosis of the vessel walls.
Direct immunofluorescence: There was granular IgM, C3, C5b-9 and fibrinogen deposition in and around superficial (and at least mid-dermal) small blood vessels. Weaker granular IgA and IgG deposition was also noted in vascular areas.

Renal, needle biopsy:
Pauci-immune focal crescentic necrotizing glomerulonephritis with acute tubular necrosis.
Fluorescence microscopy: Two glomeruli contain necrosis that stains for fibrin (3+), on a scale of 0-3+. The glomeruli contain segmental mesangial staining for IgA (2+), IgM (1+), kappa and lambda light chains (2+), and C3 (trace).

Radiology

Renal Ultrasound: Bilateral calculi, moderate hydronephrosis left kidney

Diagnosis

Granulomatosis with polyangiitis and immune-complex vasculitis

Treatment and Course

Immunosuppression therapy was implemented with rituximab and prednisone for his flare of granulomatosis with polyangiitis. The skin lesions have since resolved.

Discussion

Granulomatosis with polyangiitis (GPA—formerly known as Wegener granulomatosis) is a multisystem autoimmune disorder characterized by necrotizing granulomatous inflammation, pauci-immune small- and medium-sized vessel vasculitis, and focal necrotizing glomerulonephritis. GPA most classically involves the upper and lower respiratory tract and the kidneys, but can affect any organ system. Therefore, a spectrum of clinical symptoms may be seen. Disease onset may be insidious with recurrent respiratory infections and nonspecific constitutional symptoms (fevers, night sweats, fatigue, and loss of appetite) or more acute with multiple organ involvement. Clinical sequelae may involve the respiratory tract (hemorrhage, lung nodules, cavities), peripheral nervous system (mononeuritis multiplex), kidneys (glomerulonephritis), and skin (palpable purpura, friable gingiva, painful subcutaneous nodules, papulonecrotic lesions).

Although the majority of skin biopsy specimens show nonspecific histopathologic changes (e.g. perivascular lymphocytic infiltrates), up to 50% demonstrate leukocytoclastic vasculitis and/or granulomatous inflammation. Routine laboratory tests are not specific in GPA. Inflammatory markers may be elevated and rheumatoid factor is often positive with a low titer.

Cytoplasmic antineutrophil cytoplasmic antibody (c-ANCA) directed against proteinase 3 (PR3) is most specific for GPA and occurs in up to 90% of patients. However, some patients can express perinuclear-staining ANCA (p-ANCA) specific for myeloperoxidase (MPO). ANCAs are primarily directed against intracellular neutrophilic proteins, which translocate to the neutrophil's cell surface following primary activation by cytokines such as TNF-α. Binding to surface antigens on neutrophils results in enhanced adhesion of neutrophils to vascular endothelium with subsequent release of inflammatory mediators and vessel damage. ANCA associated vasculitides are classically characterized by a lack of immune complex deposition in and around vessel walls ("pauci-immune").

The presence of immune deposits in skin, lung, and renal biopsies of patients with GPA have been demonstrated in few case reports and small studies. Brons et al. conducted a retrospective review of patients with GPA who had undergone a skin biopsy during an active phase of the disease. The biopsies were tested for the presence of immune deposits using direct immunofluorescence. They found that 4 of 11 biopsies taken at initial presentation and 4 of 21 biopsies taken at the onset of a relapse of GPA showed granular IgG and/or IgA immune deposits in the subepidermal blood vessels. Additionally, Yu et al. found that 35% of patients with GPA had immune complexes present in their renal biopsies, mostly in a mesangial distribution.

Immune complex- versus ANCA-mediated vasculitides are currently thought to have distinct pathogeneses. The vessel damage in ANCA-positive vasculitides is directly mediated by neutrophils rather than by immune complexes; however, animal models of ANCA-associated glomerulonephritis have shown immune deposits along the glomerular capillary wall at early stages of lesion development. These deposits are then degraded rapidly, resulting in "pauci-immune" lesions.

Further studies are needed to fully understand whether GPA, in a subset of patients, may start as an immune complex-mediated vasculitis or whether these patients have two distinct processes: an ANCA-mediated vasculitis with an additional immune-complex vasculitis.

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Key location: Face **NOT YOUR USUAL SUSPECTS**

Presented by Christina Kranc, MD, and Warren Piette, MD

A 23-year-old man presented with a six-month history of multiple emergency department evaluations for presumed angioedema. Facial swelling always improved with prednisone but never completely resolved. He was persistently noncompliant with follow-up and required frequent hospitalizations for recurrence. Later in the course, dermatology consultation confirmed previous history and exam but noted a firm mass in the right temporomandibular area. Fine needle aspiration was non-diagnostic. Incisional biopsy was diagnostic of NK/T Cell lymphoma, nasal type. Our case demonstrates an angioedema-like presentation of this condition, a presentation rarely reported in the literature. The asymmetry and incomplete resolution in our patient's facial swelling are clues to correct diagnosis. NK/T Cell lymphoma should be considered in patients with unusual or recalcitrant angioedema.

Key locations: Ears, Right cheek, Thighs, Lower legs **NOT YOUR USUAL SUSPECTS**

Presented by Sangeetha Venkatarajan, MD, and Warren Piette, MD

A 25-year-old woman with a history of heroin use was admitted for altered mental status and a new rash. On examination, she had violaceous, well-defined, retiform patches and plaques on ear helices, earlobes, right cheek, lower legs, and thighs. Despite history, urine drug screen was positive for cocaine and biopsy revealed thrombotic leukocytoclastic vasculitis in the superficial and deep dermis. She was diagnosed with levamisole-induced purpura. Levamisole is used as a cutting agent in cocaine in North America. As of 2009, levamisole was found in 3% of heroin that was confiscated by the U.S. DEA and this percentage is thought to have increased significantly since 2009.