HSS

# Grand Rounds from HSS

## Management of Complex Cases

Rheumatology

October 2018 | Volume 7 Issue 3

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Mary K. Crow, MD
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In this issue, we feature four complex cases demonstrating the varied diagnostic and treatment challenges that rheumatologic disorders can present.

In Case 1, **Jonathan T.L. Cheah, MBBS,** and **Theodore R. Fields, MD, FACP,** discuss a woman in whom hypergammaglobulinemic purpura of Waldenström was diagnosed based on a recurrent rash, a history of hypergammaglobulinemia, and positive results for several autoantibodies.

In Case 2, **Kimberly Showalter, MD,** and **Anne R. Bass, MD,** present the case of a man who developed immune-related adverse events—inflammation involving the prostate, parotid, and lacrimal glands, the liver, and the joints—after receiving immunotherapy as treatment for metastatic renal cell carcinoma.

In Case 3, **Sarah B. Lieber, MD,** and **Michael D. Lockshin, MD,** describe the dangers to both mother and fetus of escalating hypertension during pregnancy. They discuss a 21-year-old pregnant woman with systemic lupus erythematosus who in her 23rd week of gestation developed preeclampsia.

In Case 4, **Sebastian E. Sattui Cortes, MD,** and **Steven K. Magid, MD,** describe a patient with finger swelling and a persistent lower-extremity rash. He was eventually diagnosed with pancreatitis, panniculitis, and polyarthritis (PPP) syndrome, a rare condition that can accompany pancreatic cancer.

All volumes of *Grand Rounds from HSS: Management of Complex Cases* are available at **hss.edu/complexcases**, where you can view enlarged images and find links to related articles. We welcome your comments at **complexcases@hss.edu**.

**Mary K. Crow, MD**
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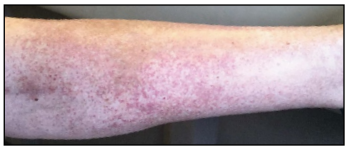
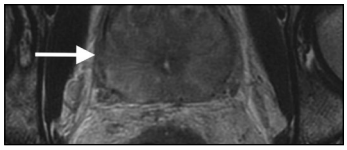
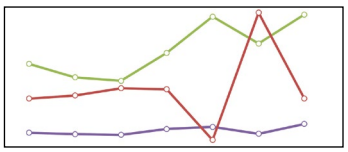
## In This Issue



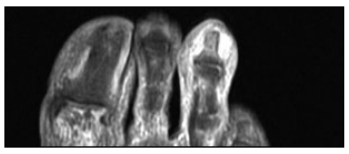
### Case 1
**Hypergammaglobulinemic Purpura of Waldenström**



### Case 2
**Polyglandular Inflammation Following Immunotherapy for Metastatic Renal Cell Carcinoma**



### Case 3
**Systemic Lupus Erythematosus and Severe Preeclampsia in Pregnancy**



### Case 4
**Pancreatic Disease, Panniculitis, and Polyarthritis Syndrome: Initial Manifestation of Acinar Cell Carcinoma**

# Case 1

Case presented by Jonathan T.L. Cheah, MBBS, and Theodore R. Fields, MD, FACP

## Hypergammaglobulinemic Purpura of Waldenström

**Case Report** A 53-year-old woman presented with a rash that had recurred intermittently on the lower extremities over 2 years. She reported that it was never itchy or palpable and would resolve spontaneously. Her medical history included renal tubular acidosis, polyclonal hypergammaglobulinemia (immunoglobulin [Ig] G, 4080 mg/dL), and multiple positive autoimmune serologies (anti-nuclear antibodies [ANA], 1:1280, speckled; anti-Ro and anti-La antibodies, both > 100 EU/mL; rheumatoid factor [RF], 89 IU/mL), as well as an intermittently elevated erythrocyte sedimentation rate (ESR) to 146 mm/hr and low complements (C4, 7.5 mg/dL). Review of symptoms was negative for dry eyes or mouth, arthritis, parotid hypertrophy, or lymphadenopathy.

Examination revealed non-palpable bilateral lower-extremity petechiae, with surrounding erythema and areas of post-inflammatory changes (Fig. 1). Laboratory testing was negative for cryoglobulins and antiphospholipid antibodies. Skin biopsy revealed both superficial and deep dermal neutrophilic infiltrate with erythrocyte extravasation. Immunofluorescence demonstrated significant complement deposition. Based on the clinical and pathological appearance of the rash, the presence of high inflammatory markers, and the patient's history of hypergammaglobulinemia, she was diagnosed with hypergammaglobulinemic purpura of Waldenström (HGPW).

Hydroxychloroquine (HCQ) was started at 200 mg twice daily for the petechiae, but after 2 months with no noticeable effect it was stopped in favor of dapsone 25 mg twice daily, with significant improvement (Fig. 2).

**Discussion** HGPW, first described in 1943, involves a combination of recurrent lower-extremity petechiae/purpura, elevated ESR, and polyclonal gammopathy [6]. Episodes of purpura may be triggered by increased hydrostatic forces in the lower extremity such as tight clothing or exercise and preceded by mild burning, itching, or pain. The purpura fades over days but can result in residual hyperpigmentation, and the frequency of attacks can range from days to months. Primary HGPW affects young women and can be associated with anti-Ro antibodies, leading to pregnancy complications such as intrauterine growth restriction and neonatal heart block [4]. Secondary HGPW affects older adults and is associated with Sjögren's syndrome (SS), systemic lupus erythematosus, rheumatoid arthritis, infection, and malignancy. Laboratory findings include mild anemia, elevated ESR, positive RF, polyclonal hypergammaglobulinemia (usually elevated IgG but at times also IgA and IgM), positive ANA, and anti-Ro antibodies [1].

It is thought that the pathogenesis relates to the polyclonal gammopathy, with RF-containing immune complex formation and deposition in blood vessels. Histopathology findings can include erythrocyte extravasation, perivascular lymphocytic infiltrates, and leukocytoclastic vasculitis, while immunofluorescence reveals immune complexes in the vessel wall.

Although generally benign and asymptomatic and therefore left to resolve spontaneously, HPGW can be managed by compression stockings, systemic glucocorticoids for severe cases, and indomethacin or HCQ for milder cases [5]. Despite no published studies supporting dapsone use in HGPW, it was chosen in this case because it is used in cutaneous vasculitis, such as leukocytoclas-tic vasculitis, which, as it was in this case, is often neutrophil mediated [2]. Our patient demonstrated many of the above features, including the presence of anti-Ro and anti-La antibodies, raising suspicion for SS. Although dry eyes or mouth were not present, the patient had a history of distal renal tubular acidosis, which has been described in up to 14% of SS patients [3], suggesting this case may represent a forme fruste of SS. ■

## Case 1 References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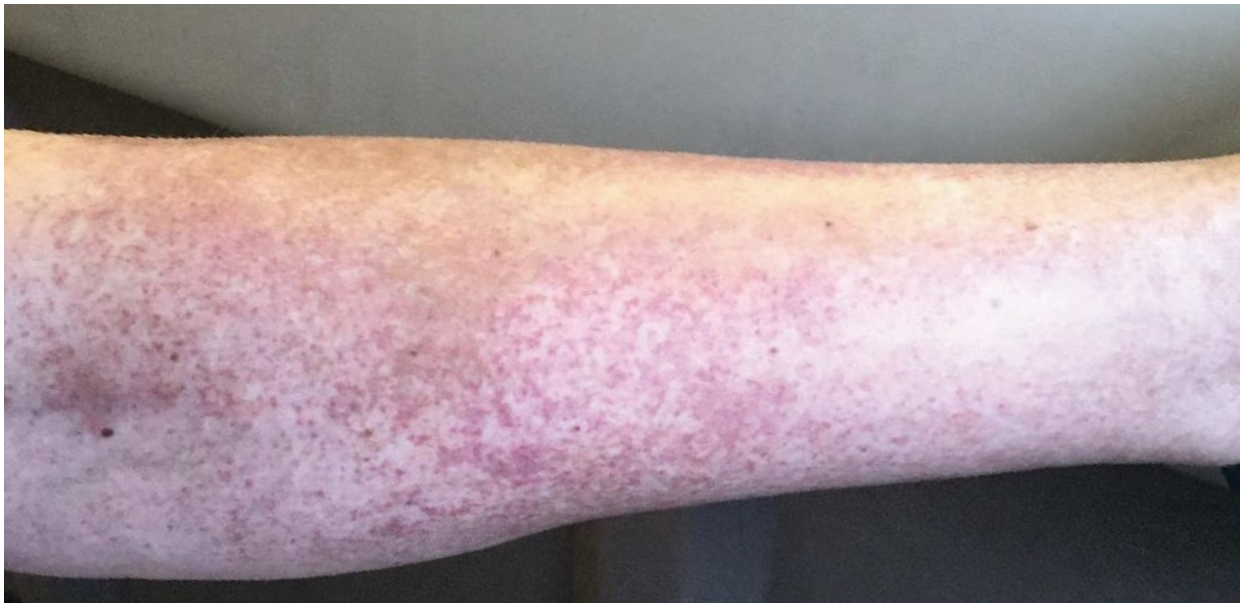
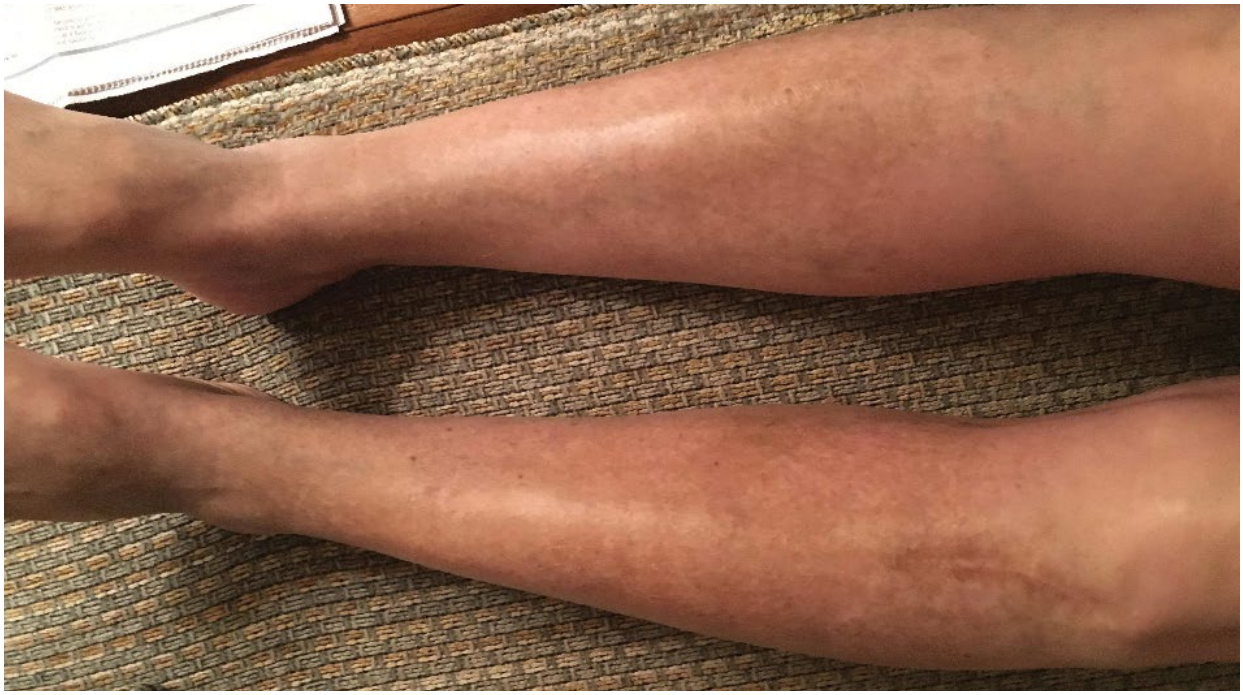
## Figure 1



Appearance of rash prior to therapy.

## Figure 2



Appearance of rash after initiation of dapsone.

# Case 2

Case presented by Kimberly Showalter, MD, and Anne R. Bass, MD

## Polyglandular Inflammation Following Immunotherapy for Metastatic Renal Cell Carcinoma

**Case Report** A 59-year-old man was referred for periorbital edema and prostatitis following immunotherapy for metastatic renal cell carcinoma diagnosed 1 year prior. The patient received combination ipilimumab/nivolumab followed by nivolumab monotherapy, with partial tumor response. Two months after immunotherapy initiation, he developed thyroiditis. Five months later, he was hospitalized for prostatitis, confirmed by magnetic resonance imaging (MRI) (Fig. 1), that was unresponsive to antibiotics but improved with corticosteroids. The prostatitis was thought to be related to immunotherapy, which was discontinued.

While the corticosteroids were tapered, the patient developed bilateral parotid gland pain and swelling, lacrimal gland swelling with periorbital edema, and unilateral knee arthritis. Arthrocentesis revealed 25,000 white blood cells/μL (95% polymorphonuclear leukocytes), absent crystals, and negative cultures. An MRI of the orbits demonstrated bilateral dacryoadenitis (Fig. 2). His symptoms worsened when prednisone was tapered to 40 mg daily. Mycophenolate mofetil was initiated. Subsequently, the patient developed transaminitis (aspartate aminotransferase, 306; alanine aminotransferase, 1100). Liver biopsy revealed mixed inflammatory infiltrate. Testing was unremarkable for rheumatoid factor, complement, and immunoglobulin G subclasses, as well as anti-cyclic citrullinated peptide, anti-smooth muscle, anti-mitochondrial, liver-kidney microsome type 1, antinuclear, and extractable nuclear antigen antibodies. His liver injury responded to steroids (methylprednisolone 180 mg daily) and mycophenolate up-titration (3 g daily).

As steroids were tapered, hydroxychloroquine was added for worsening eye dryness, hand stiffness, and shoulder pain. His symptoms subsequently improved, although hydroxychloroquine was held 6 months later due to diarrhea. After 1 year, mycophenolate was discontinued due to minimal remaining symptoms on methylprednisolone 2 mg daily. The patient developed adrenal insufficiency from immunotherapy vs. chronic steroid use, and hydrocortisone replaced methylprednisolone. Three years after cancer diagnosis, the patient is asymptomatic on hydrocortisone and in longstanding partial remission.

**Discussion** Immunotherapy augments anti-tumor immune response by inhibiting checkpoints that would otherwise downregulate immune system activity. Ipilimumab targets cytotoxic T-lymphocyte antigen 4 (CTLA-4), and nivolumab targets programmed cell death 1 (PD-1) [3]. Immunotherapy use can improve cancer survival but also cause an array of immune-related adverse events weeks to months after immunotherapy initiation or discontinuation. These may include colitis, pneumonitis, hypophysitis, uveitis, hepatitis, adrenal insufficiency, nephritis, arthritis, and rash [3].

Following immunotherapy our patient developed polyglandular inflammation involving the prostate, parotid, and lacrimal glands, hepatitis, and arthritis that responded to immunosuppression. Cappelli et al. report 13 patients who received ipilimumab/nivolumab; 4 developed sicca syndrome, 1 with Sjögren's antibodies [1]. Prostatitis caused by immunotherapy is uncommon. Kwon et al. conducted a randomized, double-blind trial in which 799 men with metastatic prostate cancer received radiotherapy followed by ipilimumab or placebo [2]. Patients receiving ipilimumab vs. placebo experienced more adverse events (75% vs. 45%), most of them immune related. No patient developed prostatitis, and studies using combination immunotherapy for prostate cancer are ongoing.

Immunosuppression is the cornerstone of managing immune-related adverse events, and treatment strategies follow algorithms derived from expert experience. Corticosteroids are commonly used. Other agents are added based upon organ system involvement. For example, colitis is treated with infliximab, a medication used for inflammatory bowel disease [3]. Inflammatory arthritis has been successfully managed with corticosteroid monotherapy or steroid-sparing agents including hydroxychloroquine, methotrexate, and infliximab [4]. ■

## Case 2 References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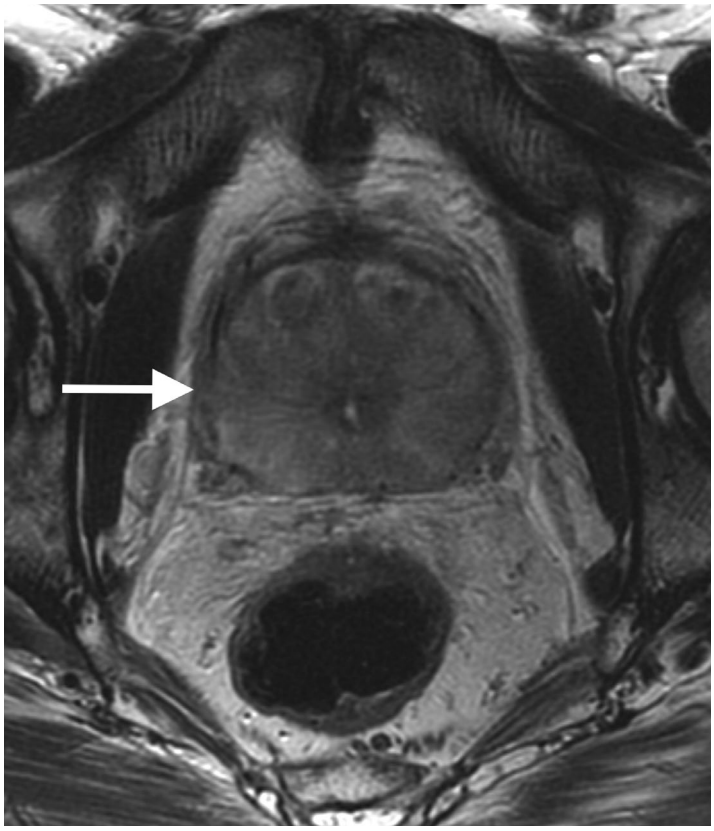
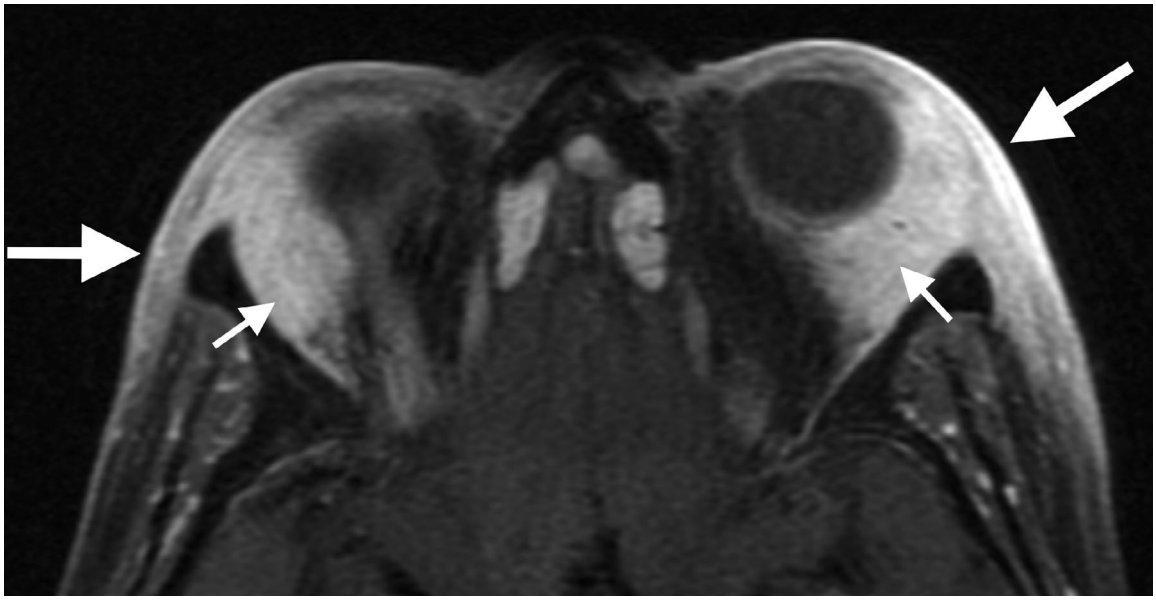
## Figure 1



An MRI scan of the prostate shows diffuse inflammatory changes consistent with prostatitis (infiltration of fat around prostate gland indicated by arrow).

## Figure 2



An MRI scan of the orbits shows extensive inflammation involving enlarged lacrimal glands (small arrows) and soft tissues (large arrows), consistent with bilateral dacryoadenitis.

# Case 3

Case presented by Sarah B. Lieber, MD, and Michael D. Lockshin, MD

## Systemic Lupus Erythematosus and Severe Preeclampsia in Pregnancy

**Case Report** A 21-year-old woman was hospitalized at 23 weeks and 5 days of pregnancy because of epigastric pain and nausea lasting 3 days.

She had had systemic lupus erythematosus (SLE) for 4 years and proteinuria and microscopic hematuria for 6 months; renal biopsy showed class IV and class V lupus glomerulonephritis without chronicity. Shortly after the biopsy, she had learned she was pregnant. After discussion of treatment options and potential risks, she opted to continue her pregnancy on high-dose corticosteroids, tacrolimus, azathioprine, hydroxychloroquine, and low-dose aspirin, the latter added to reduce risk of preeclampsia. Proteinuria improved, but hypertension worsened, requiring initiation and dose escalation of nifedipine.

On admission, her blood pressure was 210s/120s. She had mild periorbital edema but no stigmata of active lupus. Aspartate aminotransferase and alanine amino-transferase levels were 120 and 65 U/L, respectively; uric acid was 7.5 mL/dL, and platelet count was 163 × 103/μL, down from 363 × 103/μL 6 weeks earlier. Haptoglobin was low, lactate dehydrogenase high, anti-double-stranded DNA antibody positive but unchanging, C3 improving to normal, and C4 mildly depressed but improving. Urinary protein increased to 7.7 g/day (Fig. 1). Lupus anticoagulant and anticardiolipin antibody were absent. Abdominal ultra-sound showed only mildly heterogeneous hepatic echotexture.

She was treated with antihypertensive agents, intravenous magnesium, and betamethasone for fetal lung protection. Serial fetal growth ultrasound scans showed fetal weight decreasing to less than 1% of predicted for 24 weeks' gestational age. With anasarca and respiratory distress, the patient was transferred to intensive care, where she consented to induction of labor. The fetus was not viable. Following delivery, her respiratory status and blood pressure rapidly improved; tacrolimus was discontinued in favor of mycophenolate mofetil prior to discharge.

**Discussion** Lupus nephritis is associated with adverse pregnancy outcomes, including preeclampsia and prematurity [4]. While deferral (or termination) is safer for women with active lupus nephritis, some patients choose to proceed with pregnancy.

Preeclampsia is defined either by hypertension beginning after 20 weeks' gestation plus proteinuria or, in the absence of proteinuria, by hypertension plus thrombocytopenia, elevated serum creatinine, transaminitis, pulmonary edema, or cerebral or visual symptoms [1], and it can be difficult to distinguish from active lupus nephritis. Hyperuricemia and hypoalbuminemia are included in international guidelines [2]. These features can appear in both preeclampsia and lupus nephritis; rising anti-double-stranded DNA antibody, falling complement levels, and clinical evidence of active SLE such as rash or arthritis suggest lupus nephritis, which may require escalation of immunosuppressive therapy, including corticosteroids. In preeclampsia, prudent use of corticosteroids is indicated. In this case, stable DNA antibody and normal or near normal complement levels pointed to preeclampsia.

The use of low-dose aspirin reduces the incidence of preeclampsia in pregnant women at high risk and is recommended for patients with active lupus, including lupus nephritis [3]. Depending on the severity of preeclampsia, expectant management or consideration of preterm delivery may be appropriate, as in this case [1]. When preeclampsia occurs early in pregnancy, as is common in women with lupus, the benefits to the fetus of extending pregnancy must be weighed against the risks to the mother, which may be grave. ■

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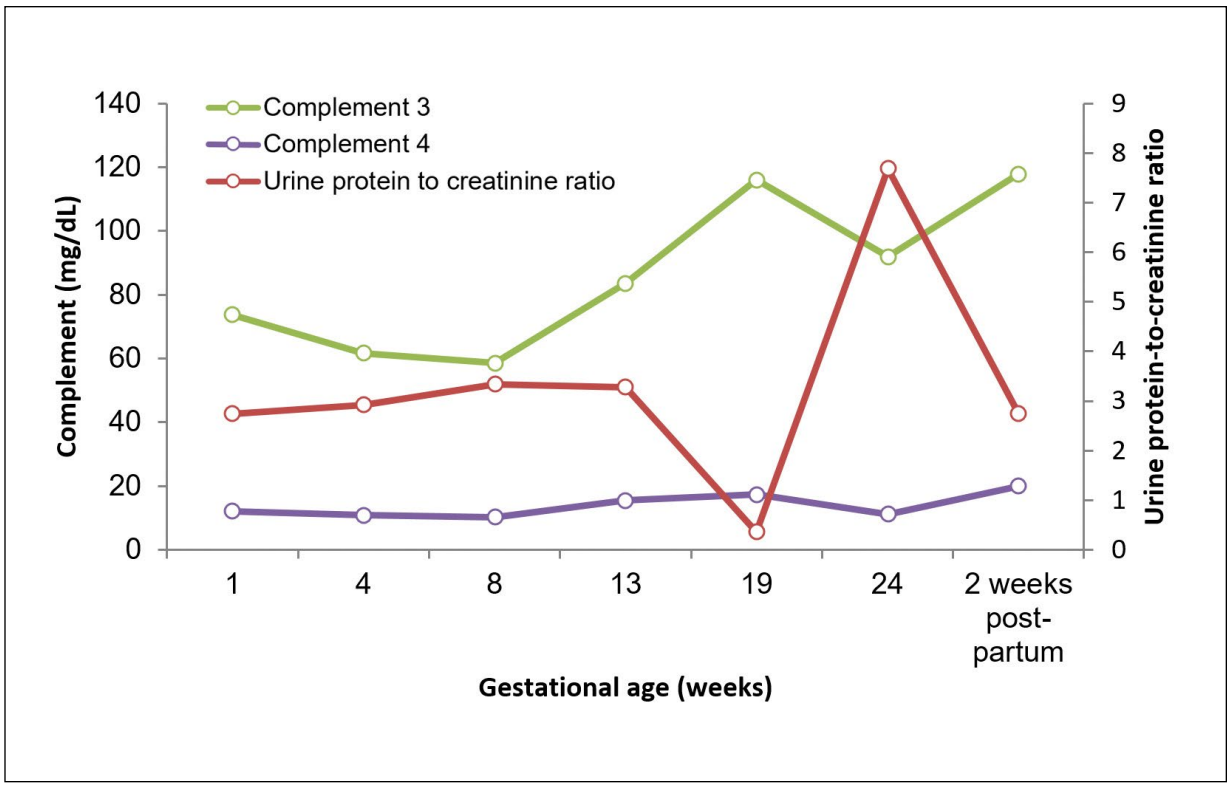
## Figure 1




Laboratory data trend.

# Case 4

Case presented by Sebastian E. Sattui Cortes, MD, and Steven K. Magid, MD

## Pancreatic Disease, Panniculitis, and Polyarthritis Syndrome: Initial Manifestation of Acinar Cell Carcinoma

**Case Report** A 76-year-old white man with a history of coronary disease and hypertension presented to the emergency department (ED) for the evaluation of an erythematous and edematous right middle finger. Six weeks prior, he had developed "red bumps and rash" on his right leg along with pain in his ankles and toes and had gone to his local ED when the joint pain worsened with left leg extension. He was discharged with steroids and antibiotics. Symptoms partially improved, until his finger swelling began.

On exam multiple small indurated and erythematous nodules were noted on the lateral aspect of both feet and shins. The diffusely swollen right middle finger was violaceous, with severe tenderness (Fig. 1). On further questioning, the patient disclosed a 20-lb weight loss in the prior 2 months. Laboratory analysis revealed a mild increase in total bilirubin, and abdominal ultrasound revealed a pancreatic mass and several hepatic masses. A diagnosis was made of pancreatitis, panniculitis, and polyarthritis (PPP) syndrome, with a presumed pancreatic malignancy. The patient's serum lipase level was more than 3500 U/L, with an elevated erythrocyte sedimentation rate (87 mm/hr) and C-reactive protein level (21.4 mg/L). Because infection was a concern, incision and drainage were performed on the right middle finger. All cultures sent were negative. Biopsy of the pancreatic and hepatic masses were positive for an acinar cell carcinoma. During initial treatment with chemotherapy, skin lesions and joint pain improved with the declining lipase levels.

**Discussion** PPP syndrome is rare, associated with both benign (e.g., pancreatitis or pseudocysts) and malignant pancreatic conditions. Acinar cell carcinoma has been reported as the most common malignancy associated with PPP [3]. The pathophysiology of the panniculitis and arthritis is related to hyperlipasemia, in which lipase and other proteases are released into the bloodstream, causing adipose tissue necrosis and skin lesions. In addition, synovial effusion, joint inflammation, and bone infarction can occur. Panniculitis can be the initial manifestation of both benign and malignant conditions, presenting with or without arthritis.

Arthritis symptoms can present in poly-, oligo-, and monoarticular manner (polyarticular being the most common), most often affecting the ankles, the small joints of the hands, and the knees, in that order [1]. Bone infarction, usually aseptic (as in this case), may be detected by magnetic resonance imaging (MRI) [2] (Fig. 2).

Subcutaneous nodules—painful or painless, edematous and violaceous—usually occur in the lower extremities. They sometimes ulcerate and drain a viscous, creamy discharge, which is sterile. Pathology shows a septal necrotizing panniculitis with neutrophil infiltration. After his initial visit, our patient had a biopsy of one of these nodules that was reported as "traumatic fat necrosis."

Treatment with nonsteroidal anti-inflammatory drugs, steroids, and high doses of intravenous octreotide, an octapeptide inhibitor of pancreatic hormones, has been reported, although it is usually ineffective [3]. Treatment of the underlying condition, with normalization of pancreatic enzymes, is the only effective approach. Usually, skin lesions regress completely, as they did in our patient, although arthritis symptoms can sometimes persist due to structural damage.

Patients with pancreatic malignancy and panniculitis (either with or without arthritis) seem to have a shorter median survival time than patients without this presentation [3]. Since PPP syndrome can be an initial presentation of this aggressive malignancy, prompt recognition and workup are vital. ■

### Case 4 References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## Figure 1A

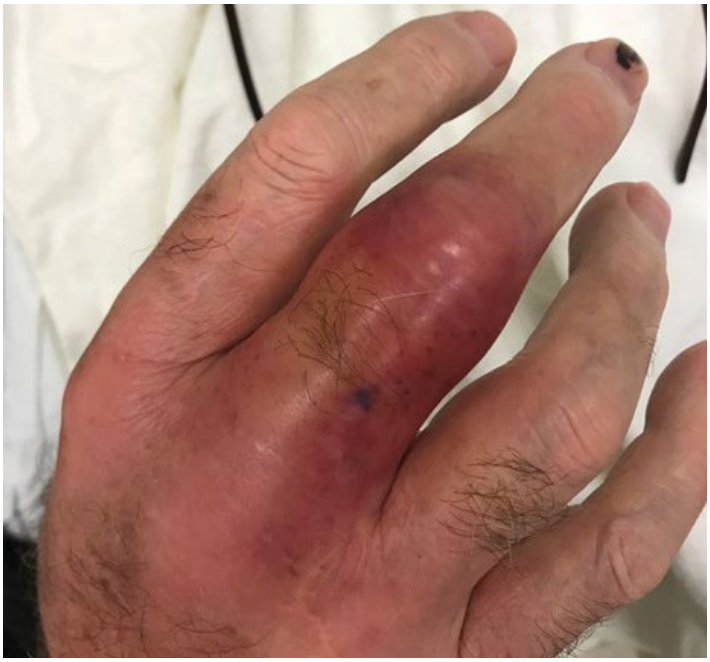
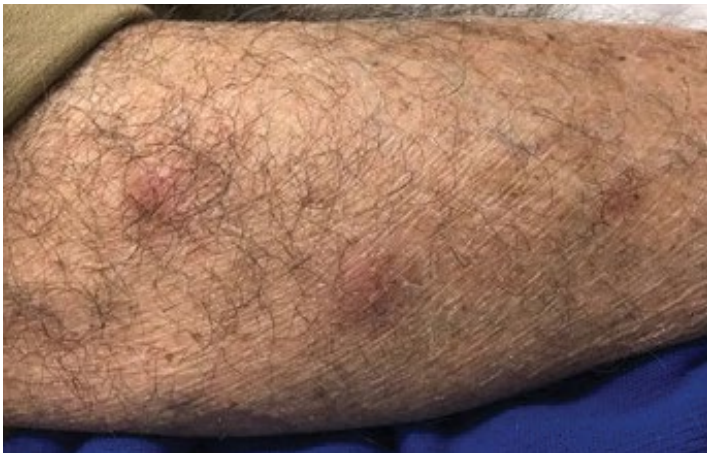
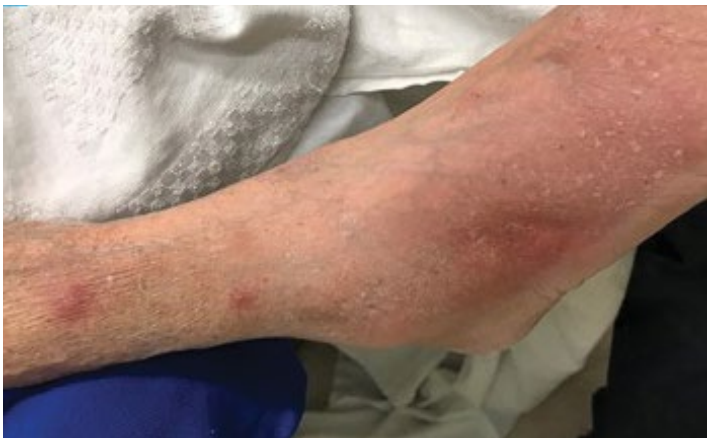


**Figure 1:** (A) Swollen and tender right middle finger. (B and C) Nodular panniculitis lesion in legs.

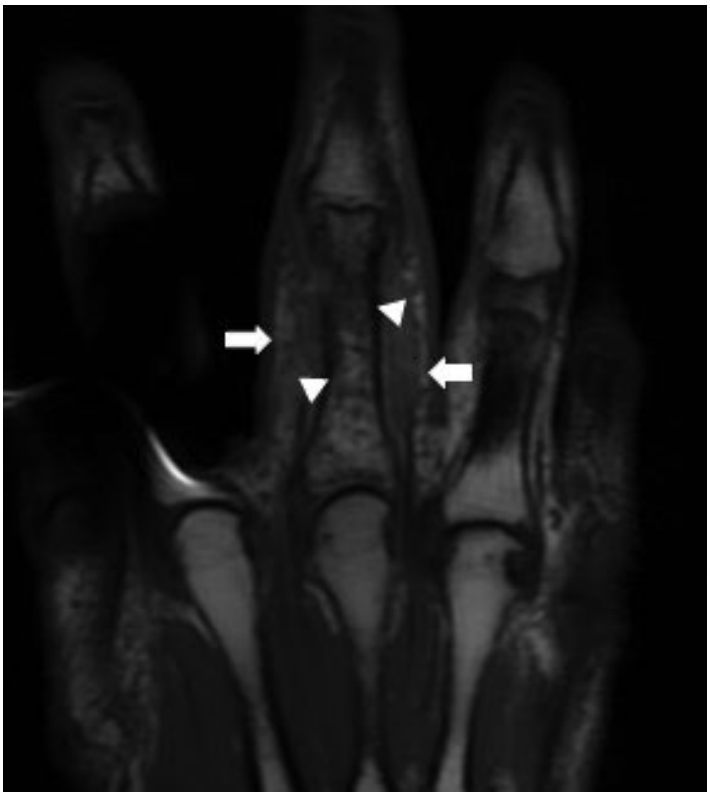
## Figure 1B



## Figure 1C



## Figure 2A



## Figure 2B

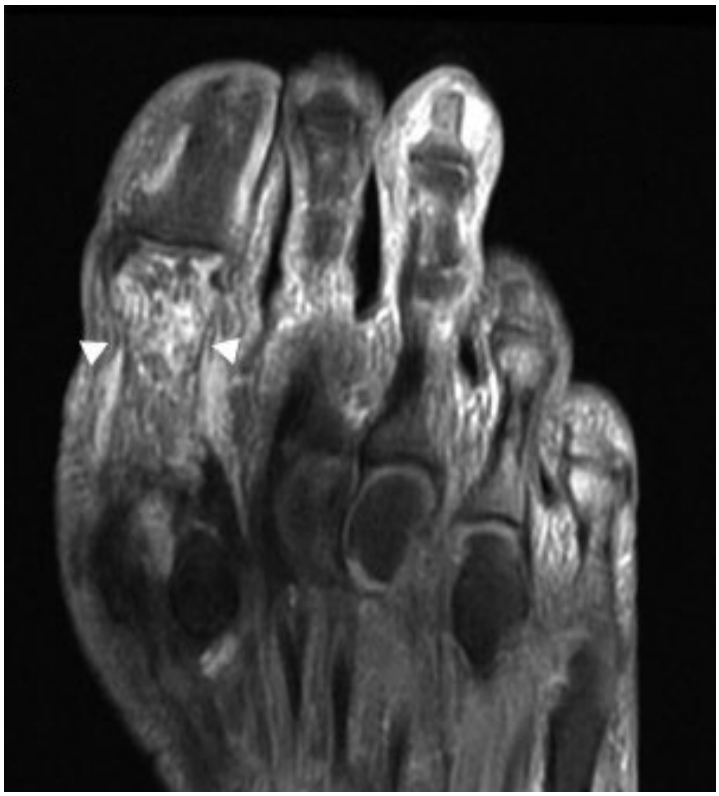


**Figure 2:** (A) Right hand MRI T1 coronal image showing patchy infiltration of the bone (arrowheads) and patchy infiltration of the fat (arrows). (B) Left foot MRI T1 weighted fat-suppressed image following intravenous contrast administration with enhancement with periosteal edema in first proximal phalanx (arrowheads).