HSS

Grand Rounds from HSS

Management of Complex Cases

Rheumatology
March 2017 | Volume 6 Issue 3

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From the Editor

Mary K. Crow, MD

In this issue of Grand Rounds from HSS/Management of Complex Cases, we feature four patients with challenging or unusual presentations, and discussion of their evaluation and management.

Case 1, presented by **David R. Fernandez, MD, PhD,** and **Anne R. Bass, MD,** describes a patient with eosinophilic fasciitis associated with cancer immunotherapy who responded to steroid treatment.

Presented by **Bella Mehta, MD, Darius P. Melisaratos, MD,** and **Michael D. Lockshin, MD,** Case 2 depicts a woman with no significant past medical history who was referred for neck pain. Review of radiology scans confirmed a calcified intra- or extra-thecal mass at the transverse ligament of the atlas. She was treated with anti-inflammatory therapy. Hydroxyapatite deposition disease (HADD) is the most likely diagnosis based on the evolution and appearance of the deposits following therapy.

Arthur M. F. Yee, MD, PhD, discusses Case 3, in which a woman with a history of sarcoidosis was referred to HSS for a second opinion regarding chronic pain and swelling of the right wrist and acute loss of extension of the right small finger. The case draws attention to the potential for inflammatory synovitis and tenosynovitis to complicate sarcoidosis and discusses therapeutic approaches to maintain control of the disease.

Case 4 from **Nino Mikaberidze, MD,** and **Michael D. Lockshin, MD,** describes a patient with an acute presentation of cardiac and respiratory arrest in the setting of a history of asthma and recurrent sinusitis. Significant cardiac abnormalities along with a high eosinophil count supported a diagnosis of Churg-Strauss syndrome with cardiac involvement.

We hope you enjoy reading about the management of these challenging and interesting cases, and invite you to review archived issues at **hss.edu/complexcases**. where you can view enlarged images and find links to related articles. We welcome your feedback through **complexcases@hss.edu**.

Mary (Peggy) K. Crow, MD
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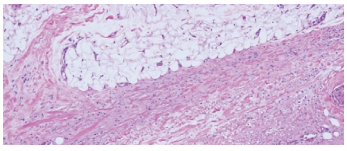
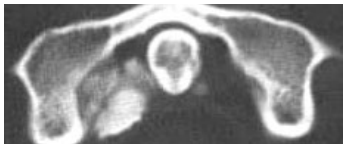
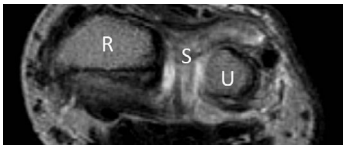
In This Issue



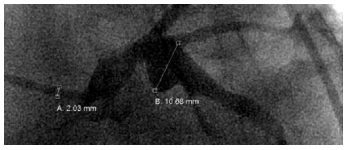
Case 1
Eosinophilic Fasciitis Associated with Cancer Immunotherapy



Case 2
Calcific Tendonitis: An Unusual Presentation of Neck Pain



Case 3
Inflammatory Erosive Arthritis and Tendon Rupture in Sarcoidosis



Case 4
Eosinophilic Granulomatosis with Polyangiitis with Cardiac Involvement

Case 1

Case presented by David R. Fernandez, MD, PhD, and Anne R. Bass, MD

Eosinophilic Fasciitis Associated with Cancer Immunotherapy

Case Report A 48-year-old man was referred for complaints of "stiffness" in his legs. One year prior to presentation he was diagnosed with stage IV lung adenocarcinoma (EGFR exon 19 deletion) with lung metastases. He was treated with nivolumab and erlotinib and experienced 50% tumor regression. Six months into treatment he began to note tightness and pain in his thigh and calf muscles, shoulders, ankles and wrists. He had trouble walking and rising from a chair. He also noted calf cramps and leg swelling. He denied Raynaud's phenomenon. Laboratory testing revealed CPK 933 and an absolute eosinophil count of 700. CPK normalized without intervention, but total eosinophils climbed to 3,500 over the next three months. Nivolumab was discontinued and the patient was referred to rheumatology. Examination revealed thickening of the fascia of the forearms and of the legs below the knees that limited mobility at the elbows, wrists, knees and ankles. The patient could barely pronate or supinate the right elbow. Extension of the right wrist was limited to 20° due to tightening of the fascia, and there were flexion contractures of both knees. A "groove sign" was noted over the left leg and right forearm (Figure 1). The superficial skin, nail fold capillaries and joints themselves were normal. The patient was treated with high-dose oral corticosteroids with moderate improvement. Deep skin biopsy was consistent with eosinophilic fasciitis (Figure 2). The patient continued treatment with high-dose corticosteroids and experienced gradual softening of the fascia and increased mobility of the arms, and to a lesser degree the legs. Methotrexate was added to his regimen to enable a rapid steroid taper prior to lobectomy for residual disease. The patient continued to require low doses of prednisone 10 months after the onset of his disease.

Discussion Eosinophilic fasciitis is a rare disease of unknown etiology, characterized by peripheral eosinophilia and induration of the deep fascia underlying the skin. [1] It is generally steroid-responsive but often requires prolonged therapy, and not all changes may be reversible. Eosinophilic fasciitis can be associated with trauma, drugs, infections, autoimmune conditions and cancer, but to our knowledge, this is the first case associated with cancer immunotherapy. [2] The timing of this patient's presentation suggests that the nivolumab and not the cancer itself was responsible.

Nivolumab is one of a new class of medications directed at enhancing anti-tumor immunity by inhibiting normal checkpoints on immune cell function. Immune checkpoint blockade has revolutionized the treatment of many cancers, sometimes resulting in complete and sustained remissions, but coming at the expense of frequent immune-mediated side effects. [3] The programmed cell death-1 (PD-1) receptor is an immune checkpoint molecule expressed on activated T cells which transmits inhibitory signals to T cells and enhances the generation of regulatory T cells. High expression of PD-1 on T cells can be seen in the setting of chronic infections and is associated with a phenomenon called "exhaustion", associated with poor T cell function and high expression of inhibitory molecules on T cells. [4]

Normally, cells in the peripheral organs can increase expression of programmed cell death ligand 1 (PD-L1) in certain settings, and this is one important mechanism to protect against autoimmunity. However, cancer cells also frequently express PD-L1, leading to diminished T cell-directed immune responses against tumors. Nivolumab blocks PD-1 signaling, leading to enhanced anti-tumor immunity, but has important side effects related to induction of autoimmunity, such as rash, hepatitis, pneumonitis, and thyroiditis. Interestingly, the autoimmune manifestations associated with immunotherapy can be short-lived when treated with steroids or tumor necrosis factor-α inhibitors, and generally lack the characteristic autoantibodies associated with spontaneous-onset rheumatologic diseases. [5]

This case implies a potential role for PD-1 signaling as a key tolerance mechanism preventing development of eosinophilic fasciitis in susceptible individuals. ■

Case 1 References

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2. Pinal-Fernandez I, Selva-O' Callaghan a., Grau JM. Diagnosis and classification of eosinophilic fasciitis. *Autoimmun Rev* 2014;13(4-5):379—82.
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Authors Disclosures

Dr. David R. Fernandez does not have a financial interest or relationship with the manufacturers of products or services.

Dr. Anne R. Bass does not have a financial interest or relationship with the manufacturers of products or services.

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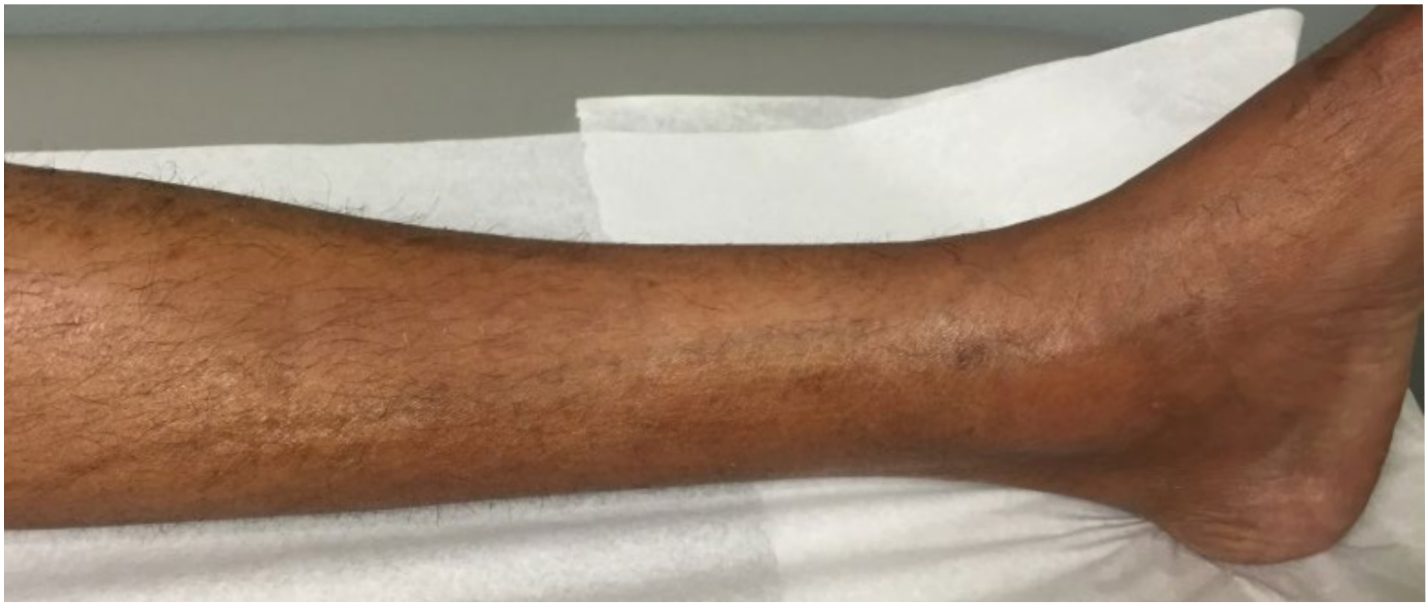
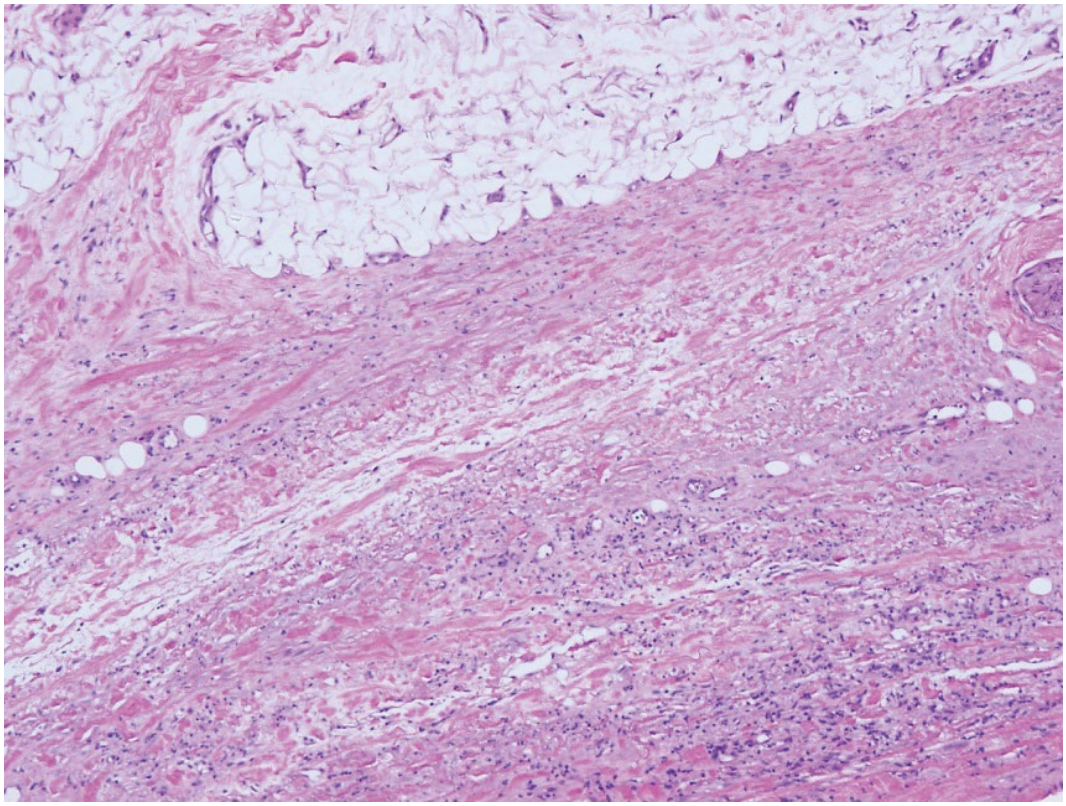
Figure 1



Photograph of the left leg demonstrating a “groove sign” along the path of a superficial vein.

Figure 2



Deep skin biopsy demonstrating broad, hyalinized collagen bundles within the fascia with deposition of mucin and a lymphocytic and plasma cell infiltrate.

Case 2

Case presented by Bella Mehta, MD, Darius P. Melisaratos, MD, and Michael D. Lockshin, MD

Calcific Tendonitis: An Unusual Presentation of Neck Pain

Case Report A 44-year-old woman with no significant past medical history was referred for neck pain. Two weeks prior to presentation she developed a "crick" in her neck, attributed to a sleeping position; within 2 days the pain intensified from 5/10 to 8–9/10 at night and radiated to her head, interfering with sleep. She had markedly decreased range of movement and became hypersensitive to sounds. She went repeat-edly to a local emergency room, where she was given corticosteroids, diazepam, and NSAIDs for torticollis, with minimal relief. C-reactive protein was slightly elevated. A computerized tomography (CT) scan showed a calcified mass posterior to the odontoid process, which was the reason for referral. She complained of new pain in the right eye, ear, and jaw. She did not have arm pain, weakness, gait abnormality, dysphagia, odynophagia, bowel or bladder involvement, fevers, nausea, vomiting, diarrhea, weight loss, rash, lymphadenopathy, tingling, numbness, or syncope. Neck range of motion was markedly limited. Neurologic examination was normal, including normal strength, deep tendon reflexes and Babinski.

Discussion Review of the CT scan and a new magnetic resonance imaging (MRI) scan suggested a calcified intra- or extra-thecal mass, possibly hemangioma, meningioma, or other tumor at the transverse ligament of the atlas, but hydroxyapatite (HA, calcific tendonitis) or calcium pyrophosphate (CPPD, pseudogout), both rare in this location, were other possibilities. The location and size of the calcification raised concern for spinal cord compression. Emergent consensus review by neurosurgery, radiology, and rheumatology concluded that the mass was not malignant and that there was no immediate neurological threat or indication for surgery. Suggestion of dissolution of part of the mass most suggested HA deposition disease (HADD), an hypothesis supported by the acute nature of pain symptoms, similar to that of calcific tendonitis occurring in other sites. Given the inaccessibility of the site and the absence of neurological compromise we opted for a conservative course of anti-inflammatory therapy. A follow-up CT scan of the neck two months later, at which time the patient was asymptomatic, showed decrease in mineralization along the transverse ligament and more dissolution with no associated canal encroachment (Figure 1 and 2).

The clinical presentation, radiographic appearance, and evolution make HADD the most likely diagnosis. Earlier case reports have described cervical HADD anterior to the cervical vertebrae; this may be the first case of HADD inside the spinal canal. The location of the mass in a tendon area and its gradual dissolution support the identification of the deposit as HA rather than CPPD, since CPPD deposits in cartilage and does not dissipate. CPPD at the odontoid process has been called crowned dens syndrome. Though crystal identification was not accomplished, in such cases CPPD was assumed from its presence elsewhere in the body, [1] as in the intervertebral disc, the ligamentum flavum, and apophyseal joints. The cases reported by Bouvet may be HA, though not identified as such. [2]

HADD occurs most commonly in adults between 30 and 60 years of age of either sex. The etiology of the deposition is unclear, but repetitive trauma, recent injury, tissue necrosis, or ischemia may play a role. Inflammatory markers, which may be slightly elevated, are nonspecific. We did not recognize an inciting event in the current case. Though we do not have crystal confirmation, we believe the serial changes in radiographic appearance support our conclusion that this is HADD and not pseudogout. ■

Case 2 References

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Authors Disclosures

Dr. Bella Mehta does not have a financial interest or relation-ship with the manufacturers of products or services.

Dr. Darius P. Melisaratos does not have a financial interest or relationship with the manufacturers of products or services.

Dr. Michael D. Lockshin does not have a financial interest or relationship with the manufacturers of products or services.

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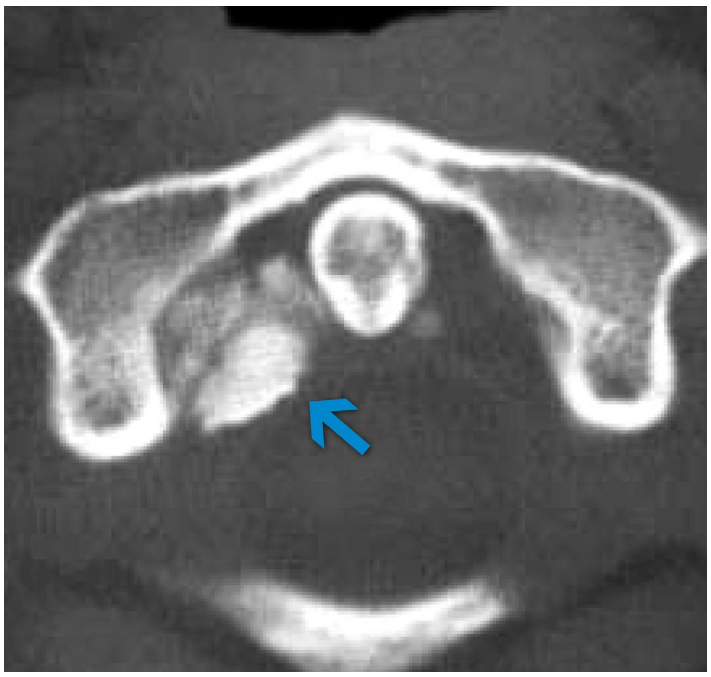
Figure 1A



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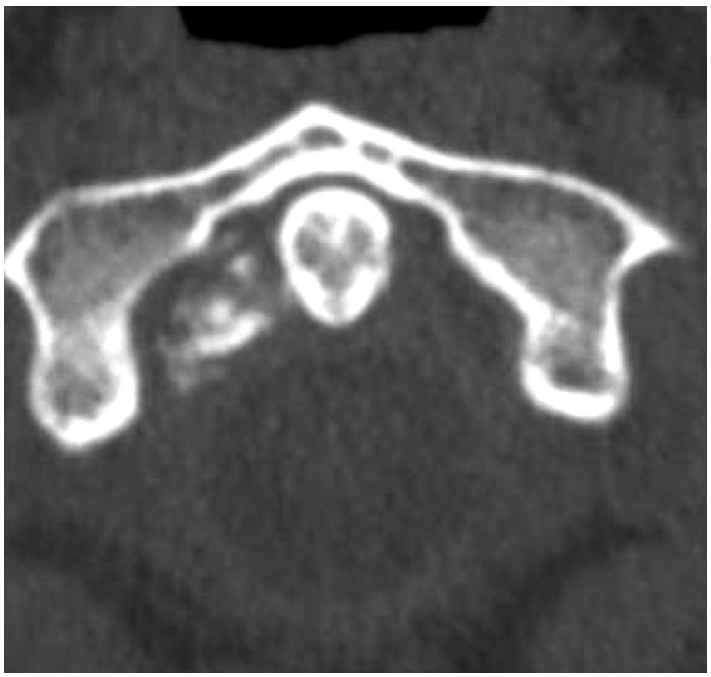

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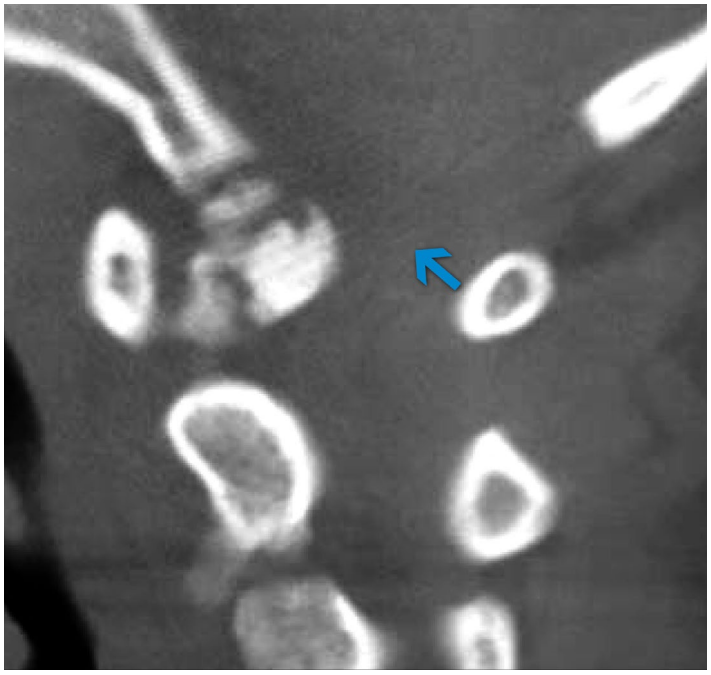
Figure 1: CT scan of cervical spine showing a calcified mass at the transverse ligament at baseline (A) and 2 months later (B).

Figure 2C



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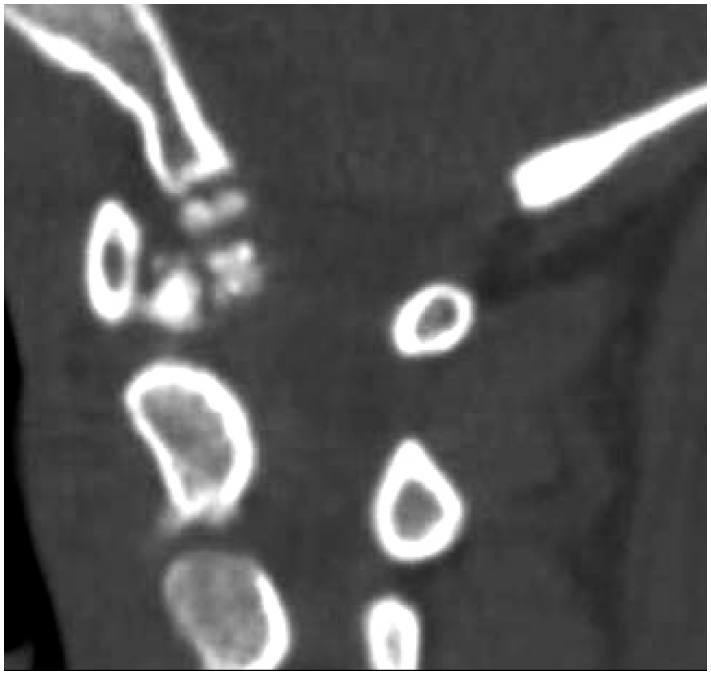

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Figure 2: Sagittal view at baseline (C) and 2 months later (D) showing fragmentation and partial dissolution of the mass.

Figure 2E

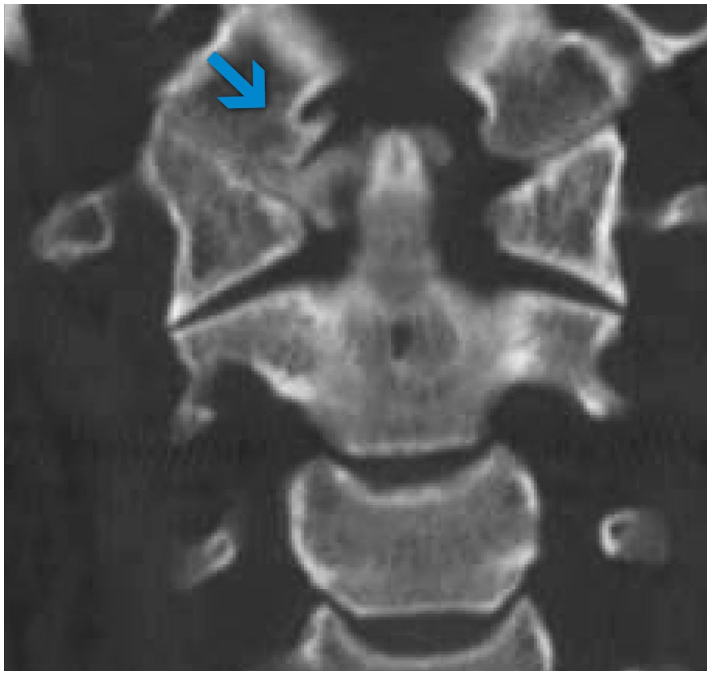

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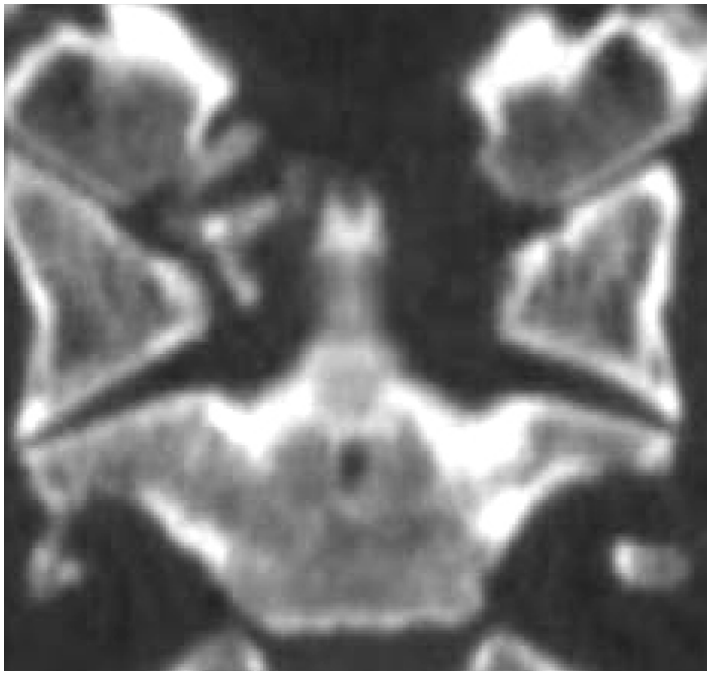
Figure 2F



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Coronal view at baseline (E) and 2 months later (F) showing fragmentation and partial dissolution of the mass.

Case 3

Case presented by Arthur M. F. Yee, MD, PhD

Inflammatory Erosive Arthritis and Tendon Rupture in Sarcoidosis

Case Report A 64-year-old woman was referred to the HSS Division of Rheumatology for a second opinion regarding chronic pain and swelling of the right wrist and acute loss of extension of the right small finger. The patient had a 20-year history of sarcoidosis initially presenting as right eye uveitis and retinal vasculitis and acute polyarthritis. Evaluation at the time revealed mediastinal lymphadenopathy, the biopsy of which led to the diagnosis of sarcoidosis. She was treated chronically for many years with varying dosages of prednisone before eventual addition of weekly methotrexate enabled subsequent withdrawal of all corticosteroid therapies. After several months of clinical remission, methotrexate was also discontinued. She remained symptom-free for several months before developing insidiously progressive chronic right wrist pain and swelling. MRI demonstrated extensive inflammatory arthritis and tenosynovitis with marked erosions in the distal radius and ulna and encroachment upon the extensor tendons (Figures 1 and 2). She was treated with non-steroidal anti-inflammatory drugs and periodic short courses of systemic corticosteroids with marginal responses. After two years of waxing and waning inflammatory right wrist arthritis, she developed an acutely dropped right small finger, prompting referral to HSS.

Physical examination was notable for moder-ate swelling, tenderness, and warmth of the right wrist; loss of extension of the right small finger; and baseline loss of visual acuity of the right eye without active inflammation. There was no evidence of active synovitis elsewhere. Complete blood count, metabolic panel, erythrocyte sedimentation rate, C-reactive protein, angiotensin-converting enzyme, rheumatoid factor, and anticyclic citrullinated protein antibodies were normal or negative. Large erosions of the distal right ulna and radius were evident on plain radiography (Figure 3).

An immediate consultation to the Hand and Upper Extremity Service was made, and the patient underwent prompt synovectomy and repair of the ruptured extensor tendons. Histopathology showed inflammatory synovitis and excluded infectious etiologies. After a brief uncomplicated postoperative period, oral methotrexate was initiated and was expeditiously titrated to 15 mg weekly, on which the patient has done well for five years without recurrence of inflammatory arthritis or uveitis.

Discussion Sarcoidosis is an enigmatic systemic inflammatory disorder characterized by non-caseating granulomatous inflammation of potentially any tissue. While non-specific arthralgias are common, frank inflammatory arthritis is infrequent and can be categorized as acute or chronic. In one recent long-term North American series, one tenth of all patients developed acute inflammatory arthritis/periarthritis, [1] typically oligoarticular or polyarticular, although prevalence may range widely depending on the population examined. The most stereotypical presenta-tion is Lofgren's syndrome (acute bilateral ankle periarthritis, erythema nodosum, and uveitis) which can be quite painful but fortunately self-limited and non-destructive. [2] In most cases, acute sarcoid arthritis is reminiscent of exacerbations of inflammatory arthritis seen in other systemic conditions, likely reflecting non-specific systemic inflammatory processes rather than direct granulomatous infiltration in the joint. In contrast, infiltrative chronic granulomatous synovitis, as seen in the presented case, is much less common, is sometimes quite resistant to medical therapy, and occasionally leads to local tissue injury. [3] A diverse array of clinical scenarios, such as bursitis, enthesopathies, sacroiliitis, and carpal tunnel syndrome, resulting from granulomatous inflammation have been reported. [4]

The challenges facing HSS physicians in this case were to first repair the ruptured fifth extensor mechanism and then to implement a medical regimen to prevent recurrence. Surgery entailed the successful transfer and attachment of the ruptured extensor digiti minimi tendon to the extensor digitorum of the ring finger. After adequate post-operative healing and rehabilitation, medical management was initiated.

As for other systemic inflammatory conditions, corticosteroids are often the mainstay therapy for initial control of inflammation. However, they are associated with well-known adverse effects and, as shown in this case, may not necessarily prevent injury to affected organs. Steroid-sparing agents are increasingly being used for the treatment of sarcoid-osis, but none are formally approved for use. Nonetheless, methotrexate has emerged as the preferred steroid-sparing agent. [5] Controlled clinical studies of methotrexate in the treatment of sarcoidosis have demonstrated efficacy in specific common phenotypes such as pulmonary disease, cardiomyopathy, and panuveitis, and there are ample case reports and series of use in other manifestations such as involvement of skin, bone, neuraxis, muscle, etc. [4]

The acknowledged efficacy of methotrexate has led to the development of proposed guidelines for its use in sarcoidosis. [5] Many recommendations echo those for the use of methotrexate in rheumatoid arthritis, but some reflect the personal practice and expert opinion of "sarcoidologists." It is very notable that the majority of experts recommended weekly methotrexate maintenance dosages of no more than 15 mg. This contrasts with common practice among rheumatologists in the treatment of rheumatoid arthritis and other conditions in which 15 mg is the bottom of the therapeutic window. Therefore, it is possible that methotrexate is underutilized in sarcoidosis. ■

Case 3 References

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2. Mana J, Gomez-Vaquero C, et al. Lofgren's syndrome revisited: a study of 186 patients. Am J Med 1999; 107: 240-5.

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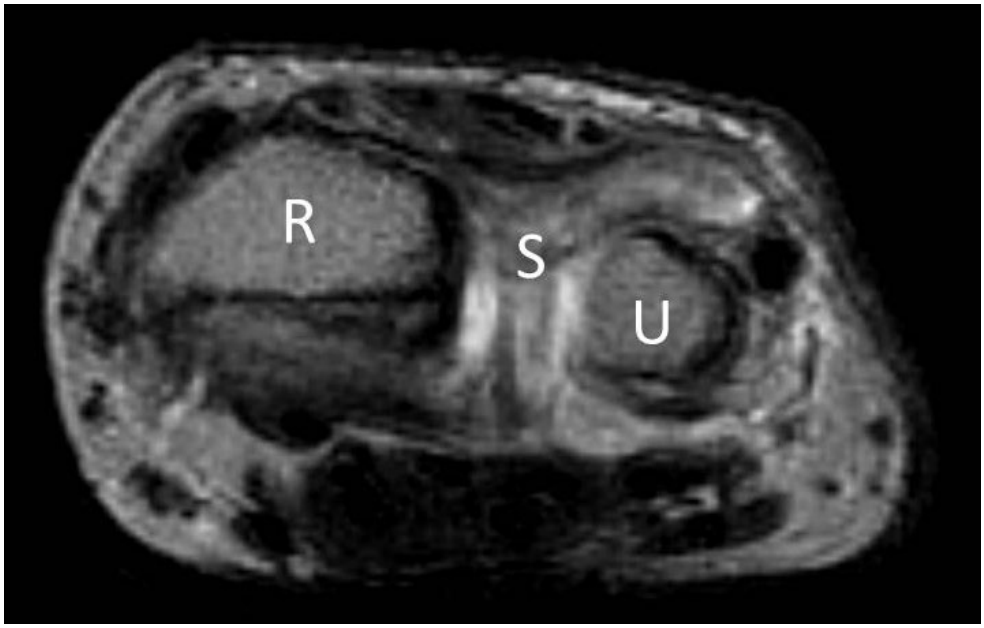
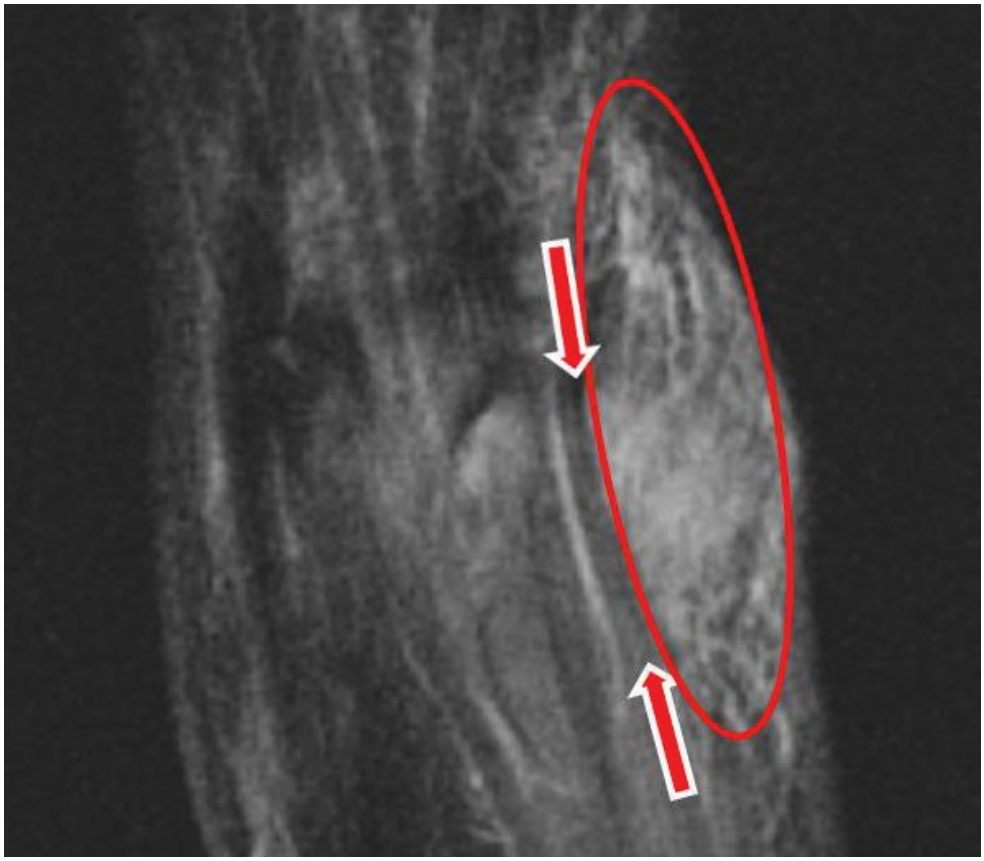
Figure 1



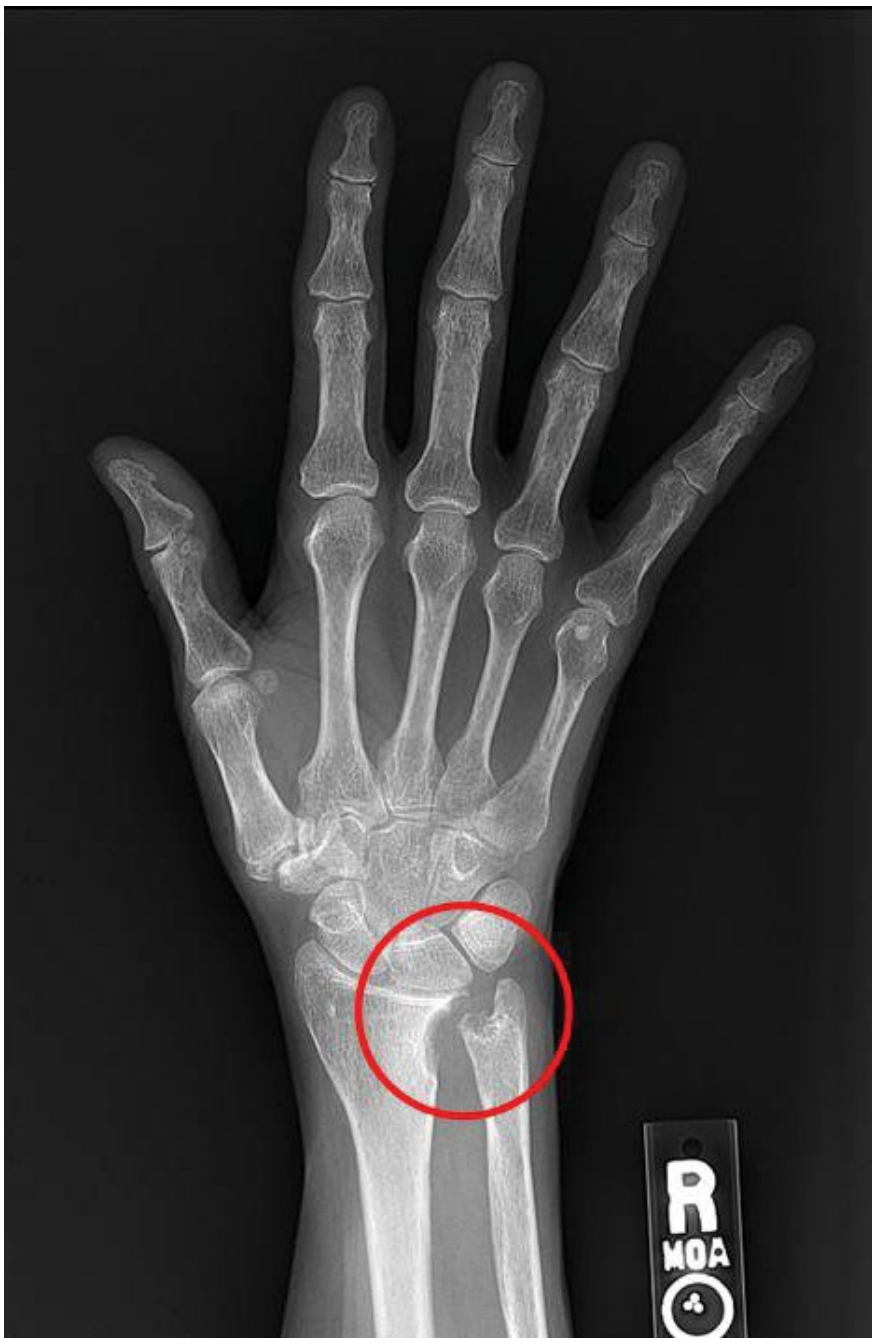
Proton density, fast spin echo MRI (axial view) of the right wrist. The distal radius (R) and ulna (U) have sustained erosive changes due to inflammatory synovitis (S).

Figure 2



Fat-suppressed MRI (coronal view) of the dorsum of the right wrist/hand. Bulky inflammatory synovitis (enclosed in red oval) impinges on the extensor digitorum longus tendon (arrows) to the small finger.

Figure 3



Frontal view of the right wrist/hand. Large erosions (encircled) are evident in the distal radius and ulna.

Authors Disclosures

Dr. Yee is on a Speaker's Bureau and has participated on Advisory Boards for Bristol-Myers Squibb and has stock shares in Abbvie and Pfizer.

Case 4

Case presented by Nino Mikaberidze, MD, and Michael D. Lockshin, MD

Eosinophilic Granulomatosis with Polyangiitis with Cardiac Involvement

Case Report A 66-year-old woman with a past medical history of hypertension, hyperlipidemia, osteoarthritis, asthma and recurrent sinusitis received frequent anti-bacterial treatment and was treated with an antifungal agent for possible aspergillus infection two months prior to presentation. She had experienced diarrhea, malaise, decreased oral intake and lethargy for one day. Forty-five minutes prior to arrival in the Emergency Department, her husband found her cold and clammy, with pulse but without respiration. He initiated, and emergency medical services continued, CPR. By the time of arrival the patient had received 45 mins CPR, six rounds of epinephrine, and defibrillation. She was unresponsive. Laboratory studies showed leukocytosis with 29% eosinophils, and EKG showed ST segment elevation and depres-sions. Chest x-ray showed diffuse consolidation; transthoracic echocardiogram revealed a severe hypokinetic inferolateral wall and moderate mid-anterolateral and anterior wall hypokinesis. Chest CT demonstrated diffuse bilateral lung consolidation, and bronchoscopy showed diffuse airway erythema and pink frothy secretions. Left heart catheterization revealed areas of aneurysmal dilation of coronary arteries, with a giant proximal left circumflex aneurysm measuring 1 centimeter involving the first obtuse marginal origin with severe ectasia (Figure 1), and an aneurysmal segment in the proximal first diagonal branch. The right coronary artery showed moderate ectasia.

Given the patient's history of recurrent sinusitis, asthma, eosinophilia, and coronary aneurysms, we diagnosed eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome, CSS) with cardiac involvement and recommended high-dose corticosteroid treatment. The patient remained critically ill on life support, then suffered uncal and transtentorial herniation, at which time her family requested withdrawal of life support. Autopsy revealed necrotizing vasculitis involving pericardial and intramyocardial vessels as well as eosinophilic and giant cell inflammation of the heart and lungs, supporting the diagnosis of CSS. The left circumflex coronary artery aneurysm was attributed to this diagnosis.

Discussion CSS is a rare form of systemic vasculitis characterized clinically by asthma, hypereosinophilia, and vasculitis and pathologically by extravascular granulomas and necrotizing vasculitis of small vessels. CSS typically consists of three distinct phases. The initial phase starts with asthma, allergic rhinitis, and nasal polyposis; the second is a period of peripheral and tissue eosino-philia associated with pulmonary infiltrates; and the third is characterized by systemic vasculitis. Involvement of the heart usually occurs in the third phase as vasculitic lesions in myocardium and the coronary vessels, causing (peri) myocarditis, heart failure, cardiac tamponade, myocardial infarction, or pericardial effusion, as in our patient. Myocardial damage is caused by vasculitis leading to coronary occlusion due to the release of toxic mediators by activated eosinophils causing direct myocardial damage, or by replacement of the myocardium with granulomas and scar tissue. [2] Eosinophil activation in CSS requires specific cytokine stimulation. This role is partly mediated by CSS patients' T cells, which predominantly exhibit an activated Th2 phenotype, resulting in the secretion of high levels of IL-4, IL-13, and IL-5. IL-5 is particularly essential for eosinophil activation, maturation, and survival. Possible cross-talk occurs between eosinophils and Th2-type lymphocytes in CSS, via the secretion of IL-25, a potent Th2-response enhancer, by the eosinophils themselves. This and other factors, for example eosinophil-apoptosis impairment through high levels of soluble CD95, might account for the persistent eosinophilia in active CSS. Eotaxin-3, a chemokine highly secreted by endothelial and inflammatory cells in CSS patients' damaged tissues, seems to directly target eosinophils toward affected tissues. Th1-type lymphocytes that secrete cytokines, such as interferon-gamma and soluble IL-2 receptor, are possible inducers of granuloma formation. [4]

Cardiac involvement in CSS is not rare. Depending on the report, its frequency varies between 16 and 92%. Heart involvement in CSS patients who are in clinical remission is very common and is characterized by fibrosis and by an active inflammatory process. [3]

Endomyocardial disease (Loeffler endocarditis) may represent the most severe form of cardiac involvement, similar to other hypereosinophilic disorders. High eosinophil counts and a negative ANCA test are associated with cardiac disease. [1] Cardiac involvement is also responsible for a dismal prognosis; it is the major cause of morbidity in CSS patients and the first cause of their mortality (48% of deaths). [4] ■

Case 4 References

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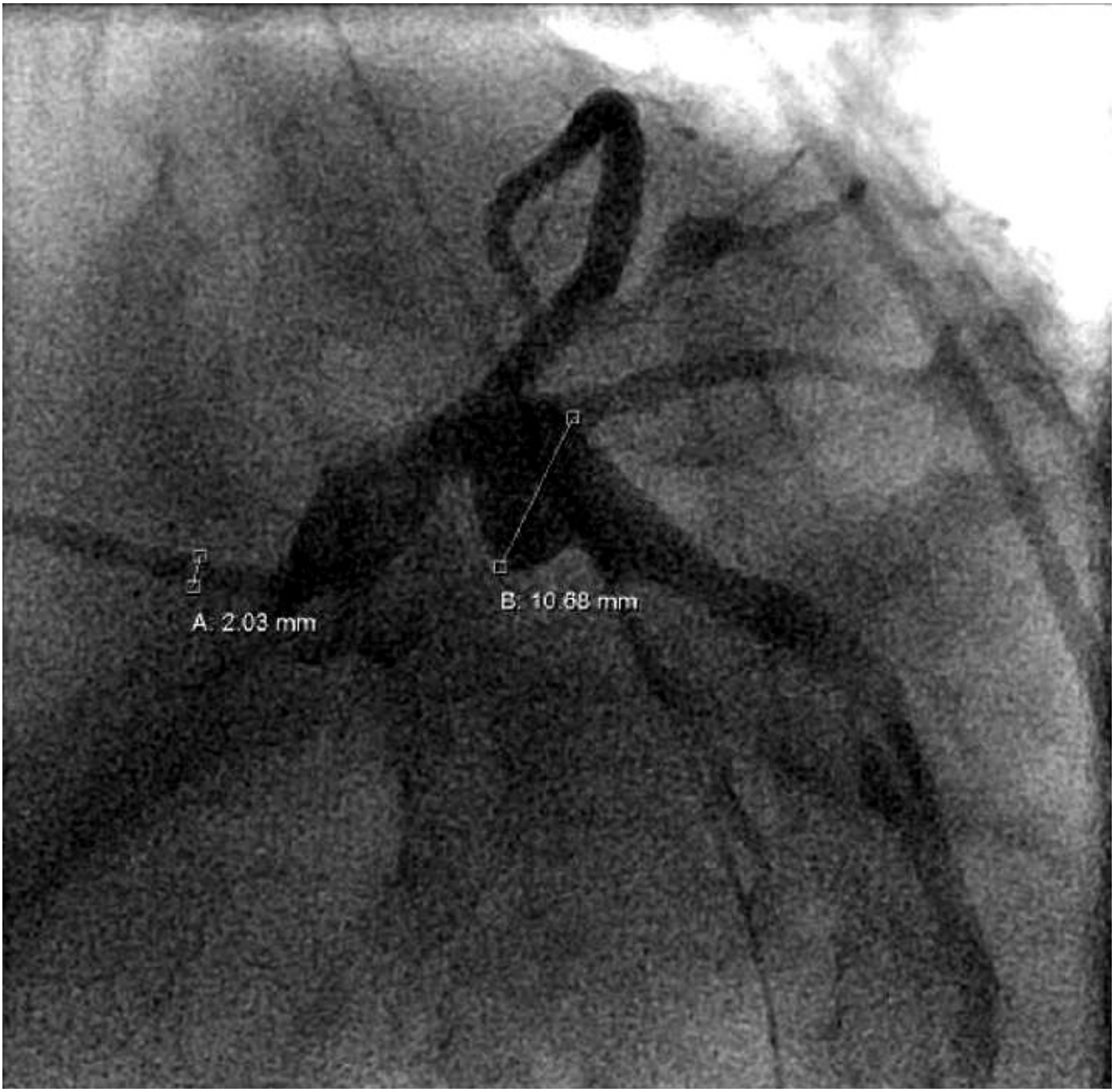
Images on the next page

Figure 1



Coronary angiography showing a giant proximal left circumflex aneurysm measuring 1 cm involving the first obtuse marginal origin.

Authors Disclosures

Dr. Michael D. Lockshin does not have a financial interest or relationship with the manufacturers of products or services.

Dr. Nino Mikaberidze does not have a financial interest or relationship with the manufacturers of products or services.

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