Grand Rounds from HSS
Management of Complex Cases
Rheumatology
October 2019 | Volume 8 Issue 3

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Diagnostic and Treatment Challenges in Rheumatology
Mary K. Crow, MD
Editor

This issue features descriptions of several fascinating and challenging patients successfully managed by our Hospital for Special Surgery rheumatologists. The cases highlight examples of the diagnostic and treatment challenges that our physicians address every day.

Case 1, presented by Halide Ozge Basaran, MD, Samir K. Trehan, MD, and Sarah F. Taber, MD, highlights the diagnosis of a 15-year-old boy with pachydermodactyly, a rare form of fibromatosis that can result from minor mechanical trauma to the fingers.

In Case 2, Nilasha Ghosh, MD, and Anne R. Bass, MD, describe the successful treatment of an 83-year-old woman who had checkpoint inhibitor–associated myositis and myocarditis, the result of her prior immunotherapy with nivolumab.

In Case 3, Pantelis P. Pavlakis, MD, PhD, and David R. Fernandez, MD, PhD, discuss a 56-year-old man whose neuropathy associated with trisulfated heparin disaccharide responded well to IV immunoglobulin treatment.

Case 4, presented by Kimberly Showalter, MD, Xiaoping Wu, MD, MS, and Jessica K. Gordon, MD, MS, features a previously healthy 36-year-old man with progressive shortness of breath and dry cough ultimately diagnosed with antisynthetase syndrome responsive to monthly IV cyclophosphamide for 6 months.

Find enlarged images and links to related articles for this and every issue of Grand Rounds from HSS: Management of Complex Cases at hss.edu/complexcases. We welcome your comments at complexcases@hss.edu.

Mary K. Crow, MD
Physician-in-Chief
Chair, Division of Rheumatology
Case 1
Case presented by Halide Ozge Basaran, MD, Samir K. Trehan, MD, and Sarah F. Taber, MD

Pachydermodactyly, a Rare and Benign Digital Fibromatosis, Diagnosed in a 15-Year-Old Boy

Case Report  A 15-year-old boy presented with a 5-year history of bilateral swelling of the proximal interphalangeal (PIP) joints. The swelling had occurred gradually, until he had visible deformity of both hands. He denied pain or stiffness in his fingers and could write and play sports without limitation. He had no other symptoms, including pain or swelling in his other joints, morning stiffness, fever, or rash. He denied any activity causing repetitive trauma to his fingers, although he did admit to the habit of cracking his knuckles multiple times a day. He had no significant medical or family history. He had previously seen 3 hand surgeons and a pediatric rheumatologist, with no diagnosis.

Clinical examination revealed bilateral periarticular swelling of the PIP joints of the second through fifth digits, with no joint tenderness or decreased range of motion. He had areas of thickened skin on the fingers of both hands (Fig. 1). There were no other joint findings, and his physical examination was otherwise normal. Laboratory investigations, including complete blood count, C-reactive protein, erythrocyte sedimentation rate, antinuclear antibody testing, rheumatoid factor, anti-cyclic citrullinated peptide antibodies, and human leukocyte antigen B27 were all normal. X-ray showed soft-tissue swelling around the PIP joints, with normal joint spaces, articular surfaces, and bone morphology (Fig. 2). Magnetic resonance imaging showed soft-tissue prominence, including collateral ligament thickening with infiltration of subcutaneous fat, but no effusions or erosions. In the absence of clinical, laboratory, and radiological findings suggestive of an inflammatory arthropathy, a diagnosis of pachydermodactyly (PDD) was made. The patient and his family were educated on the nature of this disease, and he was encouraged to refrain from repetitive mechanical trauma to his fingers, including knuckle cracking.

Discussion  PDD is a rare, benign, acquired digital fibromatosis marked by painless, progressive swelling of the periarticular soft tissues of the fingers, without joint involvement. Adolescent males are most commonly affected [1]. Although the precise etiology remains unknown, the disorder is thought to be related to repetitive minor mechanical trauma, including frequent cracking of the finger joints [2]. Patients present with progressive, painless swelling around the PIP joints, often with thickening of the overlying skin. PDD is diagnosed in patients with typical examination features and the absence of findings consistent with inflammatory arthropathy on imaging and laboratory tests. [1]. Although biopsy is not routinely necessary for diagnosis, histopathology shows hyperkeratosis, acanthosis, and dermal thickening, with increased collagen bundles and fibroblasts [3]. The prognosis is benign, and treatment is not required unless patients are disturbed by the appearance of the fingers. Intralesional corticosteroid injection and surgical excision have been used with benefit in some cases; avoidance of mechanical trauma is recommended [4].

PDD can mimic the appearance of an inflammatory arthropathy, such as psoriatic arthritis, rheumatoid arthritis, or juvenile idiopathic arthritis. Patients with PDD are often misdiagnosed, leading to unnecessary concern and treatments. Careful attention to the physical exam, history, and imaging is crucial in order to make the correct diagnosis. Awareness of this clinical entity allows physicians to provide reassurance to their patients and to avoid prescribing unwarranted antiinflammatory or immunosuppressive treatment.

Case 1 References

Images on the next page
Case 1: Pachydermodactyly, a Rare and Benign Digital Fibromatosis, Diagnosed in a 15-Year-Old Boy

**Case Images**

**Figure 1**

Figure 1: Bilateral swelling of the PIP joints, with thickening of the overlying skin.

**Figure 2**

Figure 2: X-ray showing soft-tissue swelling around the PIP joints, without joint space narrowing, erosions, or other bony abnormalities.
Case 2 References


Images on the next page
Figure 1: Hematoxylin and eosin staining of right ventricle endomyocardial biopsy showing myocarditis with lymphohistiocytic infiltration.
Neuropathy Associated with Trisulfated Heparin Disaccharide Antibodies Responsive to IV Immunoglobulin Treatment

Case Report
A 56-year-old man with a history of gout and meralgia paresthetica presented with progressive, painful paresthesia since age 53, following a flu-like illness. The paresthesia initially affected his lower legs and then spread to his hands; he described the sensation as burning or crawling in nature. Initial assessment was consistent on nerve conduction studies with a sensorimotor polyneuropathy. Laboratory testing revealed a mildly positive rheumatoid factor and a 0.3 g/dL serum immunoglobulin G-κ(IgG-κ) monoclonal gammopathy of undetermined significance (MGUS), though urine immunofixation, vitamin B1, vitamin B12, and thyroid studies were normal, while Lyme antibody testing and transthyretin deoxyribonucleic acid (DNA) testing were negative. An abdominal fat pad biopsy was negative for amyloid deposition. Symptomatic management was attempted with trials of nonsteroidal anti-inflammatory drugs, amitriptyline, gabapentin, pregabalin, and duloxetine, but these were unsuccessful, and he soon required large doses of long-acting and short-acting opioids for pain control.

On evaluation at Hospital for Special Surgery, he described ongoing painful paresthesia, associated with erythema and edema of his legs. These symptoms remained severe despite his intensive opioid regimen, with clear worsening upon heat exposure. He also experienced new-onset photosensitivity, associated with petechial rash (Fig. 1). Neurologic examination showed normal strength and reflexes, with decreased pain, temperature, and vibration sensation in the distal arms and legs. Electrodiagnostic studies showed normal motor and sensory-evoked responses in the arms and legs, except for mild median neuropathy at the left wrist, and no abnormal spontaneous activity on needle electromyography. Magnetic resonance imaging showed only mild lumbar spine degenerative changes and normal lumbosacral plexus. Skin biopsy showed decreased intraepidermal nerve fiber density at the left calf (2.72 fibers/mm; normal, >3.3) and at the left distal forearm (2.79 fibers/mm; normal, >3). Laboratory testing for antinuclear antibodies, extractable nuclear antibodies, ganglioside, and paraneoplastic antibodies were negative. Immunoglobulin M (IgM) antibodies against IdoA2S-GlcNS-6S, a trisulfated heparin disaccharide (TS-HDS), were then tested and found to be positive (42,000; normal, <10,000).

Partial improvement in symptoms was seen with a trial of moderate-dose corticosteroid therapy. Given the evidence of immune-mediated neuropathy, this was followed by intravenous immune globulin (IVIG), 2g/kg over 4 days, followed by 0.4g/kg every 2 weeks. After starting IVIG therapy, the patient’s symptoms rapidly improved, with less pain and less sensitivity to heat and light. Remarkably, within weeks he no longer required long-acting opioids and could steadily taper the short-acting opioids over 9 months.

Discussion
We report a case of IVIG-responsive, predominantly small-fiber neuropathy associated with IgG-κ MGUS and TS-HDS antibodies. TS-HDS antibodies have previously been associated with immunoglobulin M-κ (IgMκ) MGUS and predominantly small fiber or sensory axonal neuropathy, both in adults [1, 2] and children [3]. As in prior studies, our patient had pure sensory, predominant small-fiber neuropathy. A majority of patients have IgM-κ MGUS; however, our patient had IgG-κ MGUS. Further, the degree of heat sensitivity and the appearance of a petechial rash with sun exposure has not been emphasized previously. Although this is an uncontrolled case study, our patient’s marked decrease in opioid requirement after IVIG therapy began provides a marker of treatment response, along with the decreased rash and photosensitivity. This indicates that IVIG may be a valuable agent in the treatment of this rare condition. Larger-scale, placebo-controlled studies are needed to further validate this observation in other patients.

Case 3 References

Images on the next page
Case 3: Neuropathy Associated with Trisulfated Heparin Disaccharide Antibodies Responsive to IV Immunoglobulin Treatment

Case Images

Figure 1

Figure 1: Patient’s petechial rash, which emerged after sun exposure.
Case Report  A 36-year-old previously healthy man presented with progressive shortness of breath and dry cough for 3 months and intermittent fevers for 2 weeks. He had no Raynaud’s phenomenon, joint pain, muscle weakness, or skin changes. A chest radiograph demonstrated bilateral basilar infiltrates. Computed tomography (CT) angiography showed bilateral basilar ground-glass opacities, traction bronchiectasis, and a dilated thickened esophagus without pulmonary embolism. He was treated with antibiotics without improvement. A bronchoscopy with biopsy was performed, and pathology from the small sample was read initially as organizing pneumonia. Prednisone 60 mg daily was started. His cough and fevers resolved; however, he subsequently experienced worsening dyspnea, 15-lb. weight loss, dysphagia, and proximal muscle weakness. On the 6-minute-walk-test (6MWT), he desaturated to 90%, with a Borg dyspnea score of 4 (“somewhat severe”). Repeat CT demonstrated worsening ground-glass opacification (Fig. 1).

The patient was readmitted for pulmonary disease progression despite high-dose steroids. Bacterial cultures and tests for respiratory viruses, aspergillus, Pneumocystis jiroveci pneumonia, HIV, and tuberculosis were negative. Antinuclear antibody titer was 1:80 (speckled). Other serologic tests were negative including rheumatoid factor and autoantibodies against cyclic citrullinated peptide, Ro (SSA), La (SSB), double-stranded DNA, ribonucleoprotein (RNP), myeloperoxidase, proteinase-3, Jo-1, Scl-70, anticientromere, RNA polymerase III, and anti–glomerular basement membrane. With steroid therapy, creatine phosphokinase level was normal, and aldolase level was mildly elevated (9.2 U/L; upper limit: 8.1). The patient had an isolated urinary bladder hemorrhia that resolved on repeat study. On re-evaluation of the small initial biopsy sample, there was concern for capillaritis. Repeat lung biopsy was pursued given diagnostic uncertainty and showed mixed cellular and early fibrotic non-specific interstitial pneumonia (NSIP) (Fig. 2). Cyclophosphamide was given by IV, and eventually a myositis-specific serologic panel was positive for anti-PL-12 (alanyl-tRNA synthetase) antibody.

The patient was diagnosed with antisyntethase syndrome and received monthly IV cyclophosphamide for 6 months, with an excellent response, evidenced by clinically significant improvement in 6MWT distance (92 m) and Borg dyspnea score (2-unit improvement). Steroids were tapered, and mycophenolate was initiated for maintenance. Eight-month CT imaging improved significantly (Fig. 1). After 12 months of treatment, forced vital capacity was 94% predicted (from 89% 3 months post-treatment), and diffusing capacity for carbon monoxide was 62% predicted (from 57% 3 months post-treatment). Eighteen months after diagnosis, the patient had no pulmonary, musculoskeletal, or gastrointestinal symptoms.

**Discussion** Clinical features of antisyntethase syndrome include myositis, interstitial lung disease (ILD), arthritis, fever, and Raynaud’s phenomenon [1]. The most common radiographic ILD patterns are NSIP and organizing pneumonia [1]. Autoantibodies in antisyntethase syndrome include anti-Jo-1 (most common), anti-PL-7, anti-PL-12, anti-EJ, anti-OJ, anti-KS, anti-Zo, anti-SC, anti-JS, and anti-YRS [1]. Differences in disease features by antisyntethase antibody have been observed. Specifically, anti-PL-12 positivity is associated with amyopathic dermatomyositis and isolated ILD [2], and patients with anti-PL-12 antibody (vs. anti-Jo-1 antibody) have more severe ILD and worse prognosis [1]. Accordingly, among 202 patients with antisyntethase syndrome, 5-year survival was better in patients with than those without anti-Jo-1 antibody (90% vs. 75%, respectively; p < 0.005) [3].

Randomized controlled trials testing therapies in antisyntethase syndrome are lacking. Steroids are considered first-line treatment; however, steroid monotherapy is associated with frequent disease flares. Other immunosuppressive agents used off-label include azathioprine, mycophenolate, tacrolimus, rituximab, and cyclophosphamide [1]. In a systematic review, data was pooled from 12 nonrandomized studies that included 141 patients with idiopathic inflammatory myopathy–associated ILD treated with cyclophosphamide [4]. Cyclophosphamide was associated with forced vital capacity and diffusing capacity for carbon monoxide improvement in 58% and 64% of patients, respectively [4]. Our case illustrates symptomatic and radiographic improvement of antisyntethase syndrome treated with cyclophosphamide with durable response at 18 months on mycophenolate maintenance therapy.

**Case 4 References**


**Images on the next page**
Case 4: Progressive Dyspnea and Cough in a Healthy, Young Man

Case Images

Figure 1A

Figure 1B

Figure 1: (A) Initial CT scan of the lungs demonstrates bilateral ground-glass opacities and peribronchovascular consolidation. (B) Follow-up CT scan, 8 months later, demonstrates significant improvement in the areas of ground-glass and consolidation with persistent mid-to lower-lobe traction bronchiectasis consistent with fibrotic non-specific interstitial pneumonia without progression.
Case 4: Progressive Dyspnea and Cough in a Healthy, Young Man

Figure 2: Right lower lobe lung biopsy demonstrates mixed cellular and early fibrotic non-specific interstitial pneumonia (image courtesy of Alain Borczuk, MD).
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