Chapter 9
A 63-Year-Old Woman with Debilitating Muscle Pain

Lan Zhou

History

A 63-year-old Caucasian woman presented with debilitating muscle pain. She developed a rapid onset of severe soreness in the muscles of buttocks and thighs with fatigue. Over the course of 3 weeks, the symptoms progressed to involve her upper arms. She had difficulty climbing stairs and washing her hair because of the pain. She had no spine pain, shooting limb pain, or numbness. She had no fever, weight loss, appetite loss, joint pain, skin rash, or urinary symptoms. She went to a local hospital emergency department, and was discharged with pain medications. Due to the progressive symptoms, she went to the local hospital emergency department again, and was admitted for evaluation. Her serum creatine kinase (CK) level, thyroid stimulating hormone, free T4, ANA, ENA, and rheumatoid factor were unremarkable. Cervical and lumbosacral spine MRIs with and without contrast showed mild multi-level degenerative changes. She was discharged without a clear diagnosis. One week later, she presented to our emergency department for the progressive symptoms that significantly affected her function. She could not walk long distance or function as a physician due to the severe pain and fatigue in her proximal limb muscles. She was admitted to our neurology service for evaluation and treatment. She had a past medical history of hypothyroidism and poliomyelitis with mild residual left foot weakness. She took levothyroxine for hypothyroidism. Her family history was positive for hypertension and thyroid dysfunction. She did not smoke cigarettes, drink alcohol, or use illicit drugs.

L. Zhou (✉)
Departments of Neurology and Pathology, Boston University Medical Center, Boston, MA, USA
e-mail: lanzhou@bu.edu

L. Zhou et al. (eds.), *A Case-Based Guide to Neuromuscular Pathology*,
https://doi.org/10.1007/978-3-030-25682-1_9

Physical Examination

Her vital signs were normal. She was distressed by the muscle pain. General examination was otherwise unremarkable. Neurological examination showed normal mental status, cranial nerve functions, sensation, and coordination. There was severe tenderness to palpation in the bilateral deltoid, biceps, gluteal, and quadriceps muscles. Strength was intact except for her known mild residual weakness in the left foot and toes from prior polio infection. Deep tendon reflexes were absent at the ankles and normal elsewhere. Her gait was antalgic and slow; she fatigued very quickly, requiring frequent rest.

Investigations

Blood tests showed mildly elevated CK level at 367 IU/L (normal 25–175) and aldolase level at 9.1 U/L (normal 1.5–8.1). C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were markedly elevated at 124 mg/L (normal 0–5.0) and 79 mm/hr (normal 0–20), respectively. Antineutrophil cytoplasmic antibody (ANCA) titer was elevated at 1:160 (normal <1:20), and myeloperoxidase (MPO) antibody was positive at 186 U/mL (normal 0–19). Antibodies to proteinase 3 (PR3) and Jo-1 were negative. Urinalysis showed microscopic hematuria and proteinuria. Chest CT showed a very small lung nodule. Nerve conduction study (NCS) was normal. Electromyography (EMG) showed no abnormal spontaneous activity but subtle early recruitment of a few small motor unit potentials in the biceps and deltoid muscles, suggestive of a subtle non-irritable myopathy. A left deltoid muscle biopsy was performed for further evaluation.

Muscle Biopsy Findings

The muscle biopsy showed acute necrotizing vasculitis with transmural inflammation and fibrinoid necrosis of blood vessel walls involving several small- and medium-sized perimysial blood vessels (Fig. 9.1). There was no myopathic change or endomysial inflammation.

Final Diagnosis

ANCA-Associated Vasculitis

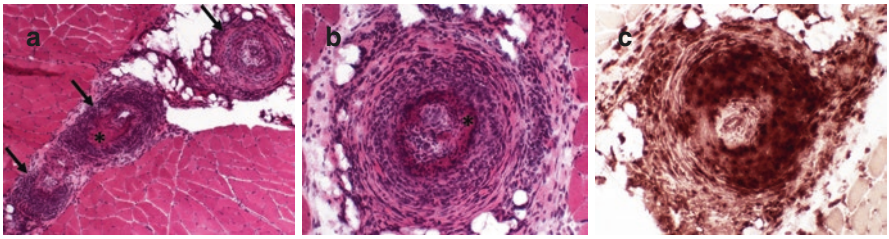

Fig. 9.1 H&E stain (**a** and **b**) shows transmural inflammation involving several perimysial blood vessels (arrows), destruction of blood vessel walls with deposition of fibrinoid material (asterisks), and occlusion of blood vessel lumen. Acid phosphatase stain (**c**) shows that some of the mononuclear inflammatory cells are acid phosphatase-positive macrophages

Patient Follow-up

The patient was treated with intravenous (IV) infusion of methylprednisolone 1 gram/day for 5 days. She showed marked improvement of her symptoms. After completing the course of IV steroids treatment, her muscle pain largely resolved and she was able to walk fast without fatigue. Due to the abnormalities revealed by urinalysis, she underwent a renal biopsy which showed crescentic glomerulonephritis. She was discharged on oral Prednisone and started on Rituximab by rheumatology. She was subsequently followed by rheumatology.

Discussion

ANCA are autoantibodies to neutrophilic granules and monocytic lysosomes [1]. There are two major types of ANCA, perinuclear ANCA (p-ANCA) and cytoplasmic ANCA (c-ANCA). The major antigens targeted by p-ANCA and c-ANCA are MPO and PR3, respectively. ANCA have been associated with three distinct vasculitides which involve inflammation of small-sized blood vessels: microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA, previously known as Wegener granulomatosis), and eosinophilic granulomatosis with polyangiitis (EGPA; previously known as Churg-Strauss Syndrome) [2–6]. The majority of patients with MPA are positive for MPO antibody, patients with GPA are usually positive for PR3 antibody, and about 50% of patients with EGPA are positive for MPO antibody [4]. Our patient had MPA.

ANCA-associated vasculitis (AAV) affects both genders equally; most of the patients are Caucasians and Hispanics. MPA is the most common AAV in Asians with a similar annual incidence in Japan and United Kingdom [7]. The estimated prevalence of AAV is 46–184 per million [8]. AAV is a multisystem disease, mostly affecting kidney, lung, skin and nerve. Nervous system is frequently involved in AAV with peripheral neuropathy predominated in each type of AAV (9). Common

presentations of peripheral nervous system involvement include mononeuritis multiplex, distal sensorimotor axonal polyneuropathy, and isolated cranial mononeuropathies [9, 10]. Muscle involvement is not as common as the nerve involvement. Patients with MPA are usually older with more severe renal disease along with skin rash and neuropathy [3]. Although myalgia is not uncommon in AAV, which have been reported in 48.2% patients with MPA [11], myalgia or muscle weakness as the predominant presentation without other systemic symptoms or neuropathies is exceedingly rare [12–14]. The clinical diagnosis can be delayed as seen in our case because of this rare entity. Our patient did not have objective weakness, CK was mildly elevated, and the EMG findings were very subtle. But the muscle biopsy showed fulminant necrotizing vasculitis. The severe myalgia is most likely due to muscle ischemia.

The diagnosis of AAV is established by findings of vasculitis on tissue biopsy and positive ANCA in serum. Muscle biopsy plays an important role in diagnosing AAV when muscle symptoms are prominent [12–14], and it may spare the need for a more invasive biopsy of an internal organ [15]. Tissue biopsy in MPA typically shows necrotizing vasculitis but no granulomatous inflammation as seen in GPA or EGPA. On muscle biopsy, the vasculitis mainly affects small- and medium-sized perimysial arterioles [12, 14, 16]. The pathological features of necrotizing vasculitis include transmural inflammation and fibrinoid necrosis of blood vessel walls. This frequently results in the occlusion of blood vessel lumen, causing tissue ischemia.

The pathogenesis of AAV is not entirely clear [5, 6]. MPO-ANCA has been shown to be pathogenic by the active transfer experiment in a murine model [17] and the passive transfer of the disease in a newborn from a mother with positive MPO-ANCA [18]. Evidence that supports a pathogenic role of PR3-ANCA is still lacking. Neutrophil priming, T cell disturbance, ANCA production, complement system activation, and high levels of circulating inflammatory cytokines have all been implicated in the pathogenesis of AAV, and they become the targets of therapy development [5].

Treatment of AAV consists of two phases: remission induction therapy and maintenance therapy [6]. The combination of corticosteroids and another immunosuppressive agent is used for inducing disease remission. Corticosteroids is the cornerstone of the therapy for AAV. The initial treatment can be oral prednisone 1 mg/kg/day or intravenous infusion of methylprednisolone 1 gram/day for 3–5 days followed by oral prednisone. The dose can be gradually tapered after 2–4 weeks of treatment to reduce the side effects. It can be used alone for mild AAV, but usually another immunosuppressive agent is needed especially for patients with GPA and severe MPA and EGPA. At present, cyclophosphamide and rituximab are two choices to combine with steroids for remission induction. Rituximab is as effective as and probably less toxic than cyclophosphamide with respect to the risks of infertility and late cancers [19–21]. It is a monoclonal anti-CD20 antibody depleting B cells with subsequent reduction of ANCA and B cell cytokines. It is used as 4 infusions of 375 mg/m^2 each given at 1-week intervals. Plasmapheresis may be used as a rescue treatment for severe cases of AAV [22–24]. Once clinical remission is achieved, maintenance therapy is critical to prevent disease relapses. The conventional immunosuppressive

agents used for this purpose include azathioprine and methotrexate, and they are equally effective and safe [25, 26]. Mycophenolate mofetil showed a higher relapse rate than azathioprine [27]. Rituximab is another option for the maintenance therapy especially in patients following a corticosteroids-rituximab-based induction. It can be given at the point of the B-lymphocyte reconstitution based on the CD19+ CD20+ lymphocyte count and/or ANCA reappearance or significant titer increase [28], or at regular intervals every 6–12 months independent of the B-cell count or ANCA status [29–33]. The efficacy of using rituximab every 4 months as maintenance therapy for AAV has been undergoing evaluation by a large-scale study [34].

Pearls

Clinical Pearls

1. Acute, severe, and progressive myalgia should raise a suspicion for vasculitis, especially in the presence of markedly elevated ESR and CRP and positive ANCA. The pain is most likely caused by muscle ischemia.
2. Acute, severe, and progressive myalgia can be a predominant initial presentation of AAV. Biopsy of a symptomatic muscle is essential to establish a tissue diagnosis to initiate prompt treatment.
3. Treatment of AAV consists of induction therapy to induce disease remission by using corticosteroids plus rituximab or cyclophosphamide, and maintenance therapy to prevent disease relapses by using azathioprine, methotrexate, or rituximab.

Pathology Pearls

1. The hallmark of acute vasculitis is transmural inflammation and destruction of blood vessel walls with deposition of fibrinoid material (fibrinoid necrosis). It can cause blood vessel lumen occlusion and subsequent tissue ischemia.
2. Necrotizing vasculitis revealed by a muscle biopsy usually affects small- and medium-sized arterioles in perimysium.

References

1. Davies DJ, Moran JE, Niall JF, Ryan GB. Segmental necrotising glomerulonephritis with antineutrophil antibody: possible arbovirus aetiology? Br Med J (Clin Res Ed). 1982;285(6342):606.
2. Kallenberg CG. The diagnosis and classification of microscopic polyangiitis. J Autoimmun. 2014;48–49:90–3.

3. Yates M, Watts R. ANCA-associated vasculitis. Clin Med (Lond). 2017;17(1):60–4.
4. Jennette JC, Falk RJ, Bacon PA, Basu N, Cid MC, Ferrario F, et al. 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. Arthritis Rheum. 2013;65(1):1–11.
5. Nakazawa D, Masuda S, Tomaru U, Ishizu A. Pathogenesis and therapeutic interventions for ANCA-associated vasculitis. Nat Rev Rheumatol. 2018.
6. Pagnoux C. Updates in ANCA-associated vasculitis. Eur J Rheumatol. 2016;3(3):122–33.
7. Fujimoto S, Watts RA, Kobayashi S, Suzuki K, Jayne DR, Scott DG, et al. Comparison of the epidemiology of anti-neutrophil cytoplasmic antibody-associated vasculitis between Japan and the U.K. Rheumatology (Oxford). 2011;50(10):1916–20.
8. Watts RA, Mahr A, Mohammad AJ, Gatenby P, Basu N, Flores-Suarez LF. Classification, epidemiology and clinical subgrouping of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis. Nephrol Dial Transplant. 2015;30(Suppl 1):i14–22.
9. Zhang W, Zhou G, Shi Q, Zhang X, Zeng XF, Zhang FC. Clinical analysis of nervous system involvement in ANCA-associated systemic vasculitides. Clin Exp Rheumatol. 2009;27(1 Suppl 52):S65–9.
10. Koike H, Sobue G. Clinicopathological features of neuropathy in anti-neutrophil cytoplasmic antibody-associated vasculitis. Clin Exp Nephrol. 2013;17(5):683–5.
11. Guillevin L, Durand-Gasselin B, Cevallos R, Gayraud M, Lhote F, Callard P, et al. Microscopic polyangiitis: clinical and laboratory findings in eighty-five patients. Arthritis Rheum. 1999;42(3):421–30.
12. Birnbaum J, Danoff S, Askin FB, Stone JH. Microscopic polyangiitis presenting as a "pulmonary-muscle" syndrome: is subclinical alveolar hemorrhage the mechanism of pulmonary fibrosis? Arthritis Rheum. 2007;56(6):2065–71.
13. Kim MY, Bae SY, Lee M, Chung H, Lee J, Ahn JK, et al. A case of ANCA-associated vasculitis presenting with calf claudication. Rheumatol Int. 2012;32(9):2909–12.
14. Oiwa H, Kurashige T. Muscle weakness as a presenting symptom in ANCA-associated vasculitis. Eur J Rheumatol. 2018;5(2):139–41.
15. Hervier B, Durant C, Masseau A, Ponge T, Hamidou M, Mussini JM. Use of muscle biopsies for diagnosis of systemic vasculitides. J Rheumatol. 2011;38(3):470–4.
16. Bahou E, Zhou L. ANCA-associated vasculitis predominantly presenting with severe myalgias. Neurol Neuroimmunol Neuroinflamm. 2017;4(4):e365.
17. Xiao H, Heeringa P, Hu P, Liu Z, Zhao M, Aratani Y, et al. Antineutrophil cytoplasmic autoantibodies specific for myeloperoxidase cause glomerulonephritis and vasculitis in mice. J Clin Invest. 2002;110(7):955–63.
18. Bansal PJ, Tobin MC. Neonatal microscopic polyangiitis secondary to transfer of maternal myeloperoxidase-antineutrophil cytoplasmic antibody resulting in neonatal pulmonary hemorrhage and renal involvement. Ann Allergy Asthma Immunol. 2004;93(4):398–401.
19. Jones RB, Tervaert JW, Hauser T, Luqmani R, Morgan MD, Peh CA, et al. Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis. N Engl J Med. 2010;363(3):211–20.
20. Specks U, Merkel PA, Seo P, Spiera R, Langford CA, Hoffman GS, et al. Efficacy of remission-induction regimens for ANCA-associated vasculitis. N Engl J Med. 2013;369(5):417–27.
21. Stone JH, Merkel PA, Spiera R, Seo P, Langford CA, Hoffman GS, et al. Rituximab versus cyclophosphamide for ANCA-associated vasculitis. N Engl J Med. 2010;363(3):221–32.
22. de Joode AA, Sanders JS, Smid WM, Stegeman CA. Plasmapheresis rescue therapy in progressive systemic ANCA-associated vasculitis: single-center results of stepwise escalation of immunosuppression. J Clin Apher. 2014;29(5):266–72.
23. Walsh M, Catapano F, Szpirt W, Thorlund K, Bruchfeld A, Guillevin L, et al. Plasma exchange for renal vasculitis and idiopathic rapidly progressive glomerulonephritis: a meta-analysis. Am J Kidney Dis. 2011;57(4):566–74.
24. Walsh M, Merkel PA, Peh CA, Szpirt W, Guillevin L, Pusey CD, et al. Plasma exchange and glucocorticoid dosing in the treatment of anti-neutrophil cytoplasm antibody associated vasculitis (PEXIVAS): protocol for a randomized controlled trial. Trials. 2013;14:73.

25. Jayne D, Rasmussen N, Andrassy K, Bacon P, Tervaert JW, Dadoniene J, et al. A randomized trial of maintenance therapy for vasculitis associated with antineutrophil cytoplasmic autoantibodies. N Engl J Med. 2003;349(1):36–44.
26. Pagnoux C, Mahr A, Hamidou MA, Boffa JJ, Ruivard M, Ducroix JP, et al. Azathioprine or methotrexate maintenance for ANCA-associated vasculitis. N Engl J Med. 2008;359(26):2790–803.
27. Hiemstra TF, Walsh M, Mahr A, Savage CO, de Groot K, Harper L, et al. Mycophenolate mofetil vs azathioprine for remission maintenance in antineutrophil cytoplasmic antibody-associated vasculitis: a randomized controlled trial. JAMA. 2010;304(21):2381–8.
28. Cartin-Ceba R, Golbin JM, Keogh KA, Peikert T, Sanchez-Menendez M, Ytterberg SR, et al. Rituximab for remission induction and maintenance in refractory granulomatosis with polyangiitis (Wegener's): ten-year experience at a single center. Arthritis Rheum. 2012;64(11):3770–8.
29. Besada E, Koldingsnes W, Nossent JC. Long-term efficacy and safety of pre-emptive maintenance therapy with rituximab in granulomatosis with polyangiitis: results from a single centre. Rheumatology (Oxford). 2013;52(11):2041–7.
30. Charles P, Neel A, Tieulie N, Hot A, Pugnet G, Decaux O, et al. Rituximab for induction and maintenance treatment of ANCA-associated vasculitides: a multicentre retrospective study on 80 patients. Rheumatology (Oxford). 2014;53(3):532–9.
31. Jones RB, Ferraro AJ, Chaudhry AN, Brogan P, Salama AD, Smith KG, et al. A multicenter survey of rituximab therapy for refractory antineutrophil cytoplasmic antibody-associated vasculitis. Arthritis Rheum. 2009;60(7):2156–68.
32. Roubaud-Baudron C, Pagnoux C, Meaux-Ruault N, Grasland A, Zoulim A, LE Guen J, et al. Rituximab maintenance therapy for granulomatosis with polyangiitis and microscopic polyangiitis. J Rheumatol. 2012;39(1):125–30.
33. Smith RM, Jones RB, Guerry MJ, Laurino S, Catapano F, Chaudhry A, et al. Rituximab for remission maintenance in relapsing antineutrophil cytoplasmic antibody-associated vasculitis. Arthritis Rheum. 2012;64(11):3760–9.
34. Gopaluni S, Smith RM, Lewin M, McAlear CA, Mynard K, Jones RB, et al. Rituximab versus azathioprine as therapy for maintenance of remission for anti-neutrophil cytoplasm antibody-associated vasculitis (RITAZAREM): study protocol for a randomized controlled trial. Trials. 2017;18(1):112.