

## CASE REPORT

# Follicular lymphoma associated paraneoplastic myositis

Megan Melody<sup>1</sup>  | Ricardo Parrondo<sup>2</sup>  | Muhamad Alhaj Moustafa<sup>2</sup> | Kevin Wu<sup>3</sup> | David Menke<sup>3</sup> | Lynsey Seim<sup>1</sup> | Han W. Tun<sup>2</sup><sup>1</sup>Department of Internal Medicine, Mayo Clinic, Jacksonville, Florida, USA<sup>2</sup>Division of Hematology-Oncology, Mayo Clinic, Jacksonville, Florida, USA<sup>3</sup>Division of Laboratory Medicine and Pathology, Mayo Clinic, Jacksonville, Florida, USA**Correspondence**Han W. Tun, Mayo Clinic, 4500 San Pablo Rd S, Mangurian Building, 3rd Floor, Jacksonville, FL 32224.  
Email: Tun.Han@mayo.edu**Abstract**

This case illustrates an unusual presentation of paraneoplastic myositis in stage IV follicular lymphoma managed with high-dose steroids, a previously unreported entity in the literature.

**KEYWORDS**

cancer associated myositis, follicular lymphoma, Inflammatory myopathies, non-Hodgkin's lymphoma, paraneoplastic syndrome

## 1 | BACKGROUND

A patient with stage IV follicular lymphoma presented with high fevers and bilateral leg pain. Infectious workup was negative, and MRI suggested inflammatory myopathy, confirmed by muscle biopsy. He was diagnosed with paraneoplastic myositis and treated with high-dose steroids with rapid clinical improvement.

Follicular lymphoma (FL) is a non-Hodgkin lymphoma of germinal center B-cell origin and is the third most common lymphoma.<sup>1</sup> It is rarely associated with autoimmune manifestations or paraneoplastic syndromes. We report a very unusual case of steroid-responsive paraneoplastic myositis, involving distal musculature of the bilateral lower extremities, in the setting of relapsed/refractory FL. Cancer associated inflammatory myopathies, including dermatomyositis (DM) and polymyositis (PM), associated with lymphomas are rather rare and typically precede or are concurrently diagnosed with lymphoma.<sup>2-4</sup> They preferentially involve proximal musculature, and in the case of DM, pathognomonic cutaneous manifestations are seen.<sup>2,4,5</sup> The disease course of cancer associated inflammatory myopathies usually parallels that of the malignancy, achieving remission or progressing simultaneously.<sup>2,4,6</sup> Therefore, treatment of these inflammatory

myopathies usually consists of cytotoxic therapy targeted exclusively at the malignancy.<sup>2,4</sup> We identified two case reports of FL and DM diagnosed concurrently in the literature that were successfully treated with lymphoma-directed chemotherapy.<sup>2,3</sup> Here, we present a patient with relapsed/refractory stage IV follicular lymphoma with paraneoplastic myopathy, who was unable to tolerate additional cycles of chemotherapy and was accordingly managed with high-dose corticosteroids with rapid clinical improvement.

## 2 | CASE

Our patient is a 77-year-old man who was initially diagnosed with stage IV FL, WHO grade 2, 12 years previously, and had received eight lines of systemic therapy. Previous therapies included rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP); two years of maintenance rituximab; ibritumomab tiuxeten (Zevalin); lenalidomide; and four clinical trial treatments (EDO-S101, a novel PI3 kinase inhibitor, a novel IRAK-4 inhibitor, and combination of a novel BTK inhibitor and everolimus). His latest relapse was noted during schedule follow-up, while enrolled in a phase I clinical trial of a novel BTK inhibitor and everolimus,

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

© 2020 The Authors. *Clinical Case Reports* published by John Wiley & Sons Ltd.

and presented with 40% bone marrow involvement and significant lymphadenopathy in the abdomen, pelvis, and groin (Figure 1A and B). He was treated with obinutuzumab with stable disease on computed tomography (CT) scan. Two days after restaging imaging was obtained, he was admitted to the hospital at our institution with high fevers, chills, generalized weakness, and bilateral leg pain.

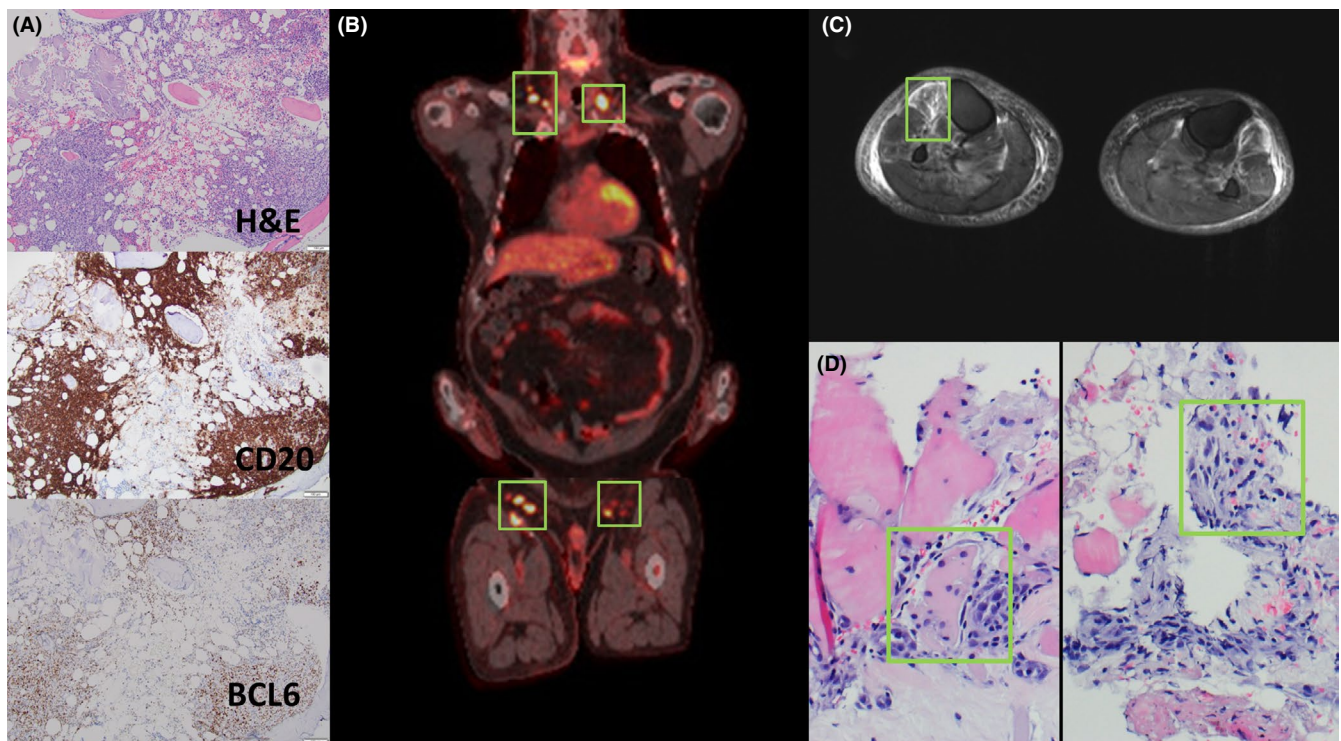
Patient's medical history was significant for chemotherapy induced cardiomyopathy; lower extremity edema, managed with spironolactone and furosemide; and hyperlipidemia, managed with simvastatin. Surgical history included resection of basal cell carcinoma on both shoulders and excision of melanoma on the scalp, ten years prior to presentation. Patient quit pipe smoking 40 years previously and endorsed consuming 1-2 shots of liquor per night.

In the emergency department, patient was febrile to 39.5°C, tachycardiac with a heart rate of 113, hypotensive with a blood pressure of 94/59, and was saturating at 99% on room air. Physical examination revealed a port-a-cath on the anterior right chest wall, without erythema, exudate, or tenderness. Lungs were clear to auscultation bilaterally. Cardiac examination was consistent with sinus tachycardia without murmur or lower extremity edema, and the abdomen was soft, nontender, and nondistended. The remainder of the physical examination was without abnormal findings. Initial

laboratories were significant for a white blood cell count (WBC) of 2.0 (normal 3.4-9.6  $\times 10^9/L$ ), platelet count (plt) of 26 (135-317  $\times 10^9/L$ ), and hemoglobin (Hgb) of 9.3 g/dL (13.2-16.6 g/dL). His lactate, renal function, transaminases, and procalcitonin were within normal limits. Chest X-ray was normal. Blood and urine cultures had no growth after five days of incubation.

The initial diagnostic impression was neutropenic sepsis, and he was started on IV meropenem and vancomycin. However, extensive infectious disease workup came back negative, and his fevers persisted with a highest temperature of 103.1°F despite antimicrobial therapy and neutrophil count responding to granulocyte colony-stimulating factor (G-CSF). CT scan of the chest/abdomen/pelvis was negative for a source of infection. Polymerase chain reactions for enterovirus, parvovirus, Epstein-Barr virus, and cytomegalovirus were negative. Transthoracic echocardiogram was negative for endocarditis.

Pain in the calf muscles progressively worsened, associated with significant swelling and inability to walk. Ultrasound examination was negative for deep vein thrombosis. Magnetic resonance imaging (MRI) of the lower extremities showed symmetric, multifocal muscle, and fascial edema consistent with inflammatory myopathy (Figure 1C). CT-guided muscle biopsy revealed inflammatory exudate



**FIGURE 1** Imaging and pathology A, Bone marrow biopsy, at 400 $\times$  magnification showing nodular marrow infiltration by follicular lymphoma, WHO Grade II (40% marrow involvement). B, PET-CT showing hypermetabolic cervical, supraclavicular, inguinal, and pelvic lymphadenopathy, consistent with relapsed disease. C, T2-weighted MRI image showing muscle edema, perifascial fluid, and focal enhancement on the right in the flexor hallucis muscle indicative of inflammatory myositis. D, Left: Area of regenerating skeletal muscle fibers and necrotic fibers (lower right) replaced by macrophages. Right: Focal area of inflammatory infiltrate within muscle. H/E stain, 20 $\times$

and necrotic fibers replaced by macrophages and regenerating muscle fibers consistent with active myositis (Figure 1D). No evidence of lymphoma was seen in the biopsy. Laboratory rheumatologic workup was negative (Table 1), and creatine kinase was normal at 75U/L (39-308 U/L). In the absence of definitive etiology such as infection, rheumatologic disorder, and direct involvement by lymphoma, the diagnosis of paraneoplastic myositis was made. He was initiated on 1 mg/kg of IV methylprednisone daily with rapid clinical improvement. Fevers subsided 4 days later with significant improvement in pain and swelling. He was discharged home on an oral prednisone taper.

The outpatient follow-up 2 weeks later showed complete resolution of myositis symptoms; however, the patient had pancytopenia with a Hgb of 6.3 g/dL, plt of  $8 \times 10^9/L$ , and WBC of  $0.9 \times 10^9/L$ . The decision was made to hold on additional therapy until bone marrow recovery. He was continued on a steroid taper and supported with blood transfusions as needed. Two weeks later, the patient presented to the emergency department for generalized weakness and fevers. Laboratories were significant for a WBC of  $0.6 \times 10^9/L$  with 18% blasts. Repeat bone marrow biopsy showed hypocellular bone marrow, with decreased hematopoiesis, and 5%-10% blast, concerning for treatment related myelodysplastic syndrome/acute myeloid leukemia. Given the limited treatment options and poor overall prognosis, patient elected to enroll with home hospice care and passed away three days later.

**TABLE 1** Laboratory rheumatology workup

Antibody	Serum Level <0.2 (Negative)
SS-A/Ro	<0.2
SS-B/La	<0.2
Smith	<0.2
U1 RNP	<0.2
U2 SN RNP	<0.2
Scl 70	<0.2
Jo 1	<0.2
Antinuclear	<0.2
SRP	<0.2
PL 7	<0.2
PL 12	<0.2
EJ	<0.2
OJ	<0.2
MI 2	<0.2
TIF 1 Gamma	<0.2
MDA 5	<0.2
NXP 2	<0.2
PM/SCL	<0.2
KU	<0.2

### 3 | DISCUSSION

Cancer associated inflammatory myopathies are rare syndromes occurring in 10%-30% of all malignancies, with paraneoplastic myopathies accounting for only 15% of this unusual condition.<sup>4,7</sup> Inflammatory myopathies associated with hematological malignancies are even rarer entities, first defined in a retrospective analysis and literature review by Marie, et al in 2011. Lymphoma is the most common hematological malignancy associated with inflammatory myopathies, with B-cell lymphomas comprising 54%-62% of all cases.<sup>5</sup>

Due to the limited reporting in the literature of paraneoplastic myopathies, distinguishing features between DM/PM associated with malignancy and paraneoplastic inflammatory myopathies remain unclear. DM/PM associated with cancer usually predates the diagnosis of the malignancy; however, in the 15%-30% of patients in which hematological malignancy preceded the diagnosis of DM/PM, the inflammatory myopathy was typically diagnosed within the first two years following diagnosis, with <1.6% of cases occurring after 5 years.<sup>4,5,8</sup> The patient presented here was diagnosed with stage IV follicular lymphoma twelve years before presenting with symptoms consistent with myositis. The sequence and significant lapse of time between diagnosis of lymphoma and onset of myopathy suggests an alternative underlying pathology than that of a cancer associated DM or PM.

Patients with DM/PM usually report an insidious or subacute onset of mild muscle pain and bilateral, proximal muscle weakness, often preceded by cutaneous manifestations, in the case of DM.<sup>9,10</sup> Our patient's chief complaint on presentation was high fevers, chills, generalized weakness, and bilateral distal leg pain. Although primarily still affecting the proximal muscles, up to 30% of patients with DM/PM can present with a similar constellation of symptoms (acute disease onset, fever, weight loss, and myositis) called anti-synthetase syndrome.<sup>11</sup> However, patients affected with this syndrome have antibodies to aminoacyl-transfer ribonucleic acid (tRNA) synthetase enzymes such as anti-Jo 1, PL 12, OJ, EJ, PL 7, PL 12, KS, Zo.<sup>11</sup> Full rheumatologic workup of this patient was negative, as shown in Table 1.

Histologic features of muscle biopsies in DM/PM include perifascicular atrophy and fibrosis with macrophage and plasmacytoid dendritic cell infiltrate.<sup>12</sup> Muscle pathology more specific to PM also includes abnormal necrotic and regenerating muscle fibers scattered throughout the fascicle and varying muscle fiber size.<sup>12</sup> Our patient's muscle biopsy was histologically compatible with a diagnosis of inflammatory myopathy, demonstrating inflammatory exudate and necrotic fibers replaced by macrophages and regenerating muscle fibers.

This case describes a patient who developed a case of biopsy proven myositis twelve years after his initial diagnosis

of stage IV follicular lymphoma. Acuity of onset, symptomatology, and myopathy of the distal musculature was discordant with a diagnosis of DM or PM. Although a confirmatory paraneoplastic panel was not obtained, autoimmune and infectious workups were negative and patient's malignancy showed rapid progression within the following month, further suggesting a paraneoplastic mediated process.

## 4 | CONCLUSION

Our case illustrates an unusual presentation of paraneoplastic myositis in follicular lymphoma characterized by bilateral involvement of distal musculature in lower extremities, high fevers, and rapid response to high-dose steroids. The late onset twelve years after the initial FL diagnosis suggests a clonal evolution of lymphoma with the new clone provoking immune-mediated inflammation of the muscles. The characteristic findings in our case likely represent a previously unreported entity of lymphoma associated paraneoplastic myositis.

## ACKNOWLEDGMENTS

Published with written consent of the patient.

## CONFLICT OF INTEREST

Each named author has approved of the contents of this paper. Additionally, all of the named authors certify that they have no affiliations with/involvement in any organization/entity with any interest, financial or otherwise, in the subject matter or materials discussed in this manuscript.

## AUTHOR CONTRIBUTIONS

Megan Melody MS, MD: conceived presented idea and wrote the manuscript with support from coauthors. Ricardo Parrondo, MD: made substantial contributions to conception of idea and drafting of manuscript. Muhamad Alhaj Moustafa, MD: participated in drafting the article and revising it for important intellectual content. Kevin Wu, MD and David Menke, MD: provided interpretation of results and played a critical role in revision of final manuscript. Lynsey Seim MBA, MD: made substantial contributions to the conception of idea and helped to supervise the findings of this work. Han W. Tun, MD: encouraged primary author to investigate unique clinical presentation and supervised the

findings of this work. All authors provided critical feedback and contributed to the final manuscript.

## ORCID

Megan Melody  <https://orcid.org/0000-0002-1923-1410>

Ricardo Parrondo  <https://orcid.org/0000-0002-9314-9933>

## REFERENCES

1. Teras LR, DeSantis CE, Cerhan JR, Morton LM, Jemal A, Flowers CR. 2016 US lymphoid malignancy statistics by World Health Organization subtypes. *CA Cancer J Clin*. 2016;66(6):443-459.
2. Healy CM, Tobin AM, Kirby B, Flint SR. Oral lesions as an initial manifestation of dermatomyositis with occult malignancy. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2006;101(2):184-187.
3. Maldonado-Romero LV, Sifuentes Giraldo WA, Larena-Grijalba C, Bachiller-Corral J. Follicular non-Hodgkin lymphoma-associated dermatomyositis. *Rev Clin Esp (Barc)*. 2014;214(2):108-109.
4. Stubgen JP. Inflammatory myopathies and lymphoma. *J Neurol Sci*. 2016;369:377-389.
5. Burton E, Schafernak K, Morgan E, Samet J. Skeletal Muscle Involvement in B-Cell Lymphoma: Two Cases Illustrating the Contribution of Imaging to a Clinically Unsuspected Diagnosis. *Case Rep Radiol*. 2017;2017:2068957.
6. Marie I, Guillevin L, Menard JF, et al. Hematological malignancy associated with polymyositis and dermatomyositis. *Autoimmun Rev*. 2012;11(9):615-620.
7. Ponge A, Mussini JM, Ponge T, Maugars Y, Cottin S. Paraneoplastic dermatopolymyositis. *Rev Med Interne*. 1987;8(3):251-256.
8. Aggarwal R, Oddis CV. Paraneoplastic myalgias and myositis. *Rheum Dis Clin North Am*. 2011;37(4):607-621.
9. Bohan A, Peter JB, Bowman RL, Pearson CM. Computer-assisted analysis of 153 patients with polymyositis and dermatomyositis. *Medicine (Baltimore)*. 1977;56(4):255-286.
10. Tymms KE, Webb J. Dermatopolymyositis and other connective tissue diseases: a review of 105 cases. *J Rheumatol*. 1985;12(6):1140-1148.
11. Katzap E, Barilla-LaBarca ML, Marder G. Antisynthetase syndrome. *Curr Rheumatol Rep*. 2011;13(3):175-181.
12. Amato AA, Barohn RJ. Evaluation and treatment of inflammatory myopathies. *J Neurol Neurosurg Psychiatry*. 2009;80(10):1060-1068.

**How to cite this article:** Melody M, Parrondo R, Alhaj Moustafa M, et al. Follicular lymphoma associated paraneoplastic myositis. *Clin Case Rep*. 2020;8:2003–2006. <https://doi.org/10.1002/ccr3.3046>