

An unusual case of musculoskeletal graft-versus-host disease mimicking dermatomyopathies

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ABSTRACT

Background. Musculoskeletal manifestations of graft-versus-host disease (GVHD) are rare but often result in mobility impairments, reducing the patient's quality of life. Typically, such diagnoses are made based on clinical findings without the need for performing a muscle biopsy.

Case Presentation. A 12-year-old boy diagnosed with acute myeloblastic leukemia (M2 subtype) underwent allogeneic hematopoietic stem cell transplantation (HSCT) due to a molecular relapse before his last chemotherapy cycle. Cyclosporine prophylaxis was stopped three months after transplantation, but the patient developed ocular, cutaneous, and oral chronic GVHD at four, five, and seven months after transplantation, respectively, for which intermittent steroid treatment and mycophenolate mofetil were given. All signs of GVHD resolved by one year after transplant, and immunosuppressive treatment was stopped; however, three months later, he experienced muscular weakness in bilateral upper and lower extremities. Subsequently, immunosuppressive treatment was restarted following a muscle biopsy.

Conclusion. Diagnosing musculoskeletal GVHD is challenging due to the lack of reliable parameters for histopathological diagnosis, and initial clinical findings can be mistaken for steroid-induced myopathy or inflammatory dermatomyopathies. We applied methylprednisolone, mycophenolate mofetil and extracorporeal photopheresis for treatment, and the clinical findings completely improved with these treatments.

Key words: graft-versus-host disease, allogeneic bone marrow transplantation, musculoskeletal symptoms, inflammatory dermatomyopathy.

Graft-versus-host disease (GVHD) is an immune-mediated condition often encountered after allogeneic bone marrow transplantation when the donor's immunocompetent T-cells deem the recipient's antigens, known as human leukocyte antigen, as foreign. GVHD represents a significant issue for patients undergoing allogeneic hematopoietic stem cell transplantation (HSCT). Typically, acute GVHD (aGVHD) commonly affects the skin, liver, and gastrointestinal tract, while

chronic GVHD (cGVHD) can affect nearly any organ system, with the gastrointestinal tract, oropharynx, skin, eyes, urogenital tract, lungs, and lymphohematopoietic system being the most frequently involved.¹

Musculoskeletal GVHD is a rare manifestation of cGVHD with an incidence rate of 0.6% (49 cases per 1,000,000,000 people/year).¹ It is extremely rare in children, with no prevalence data available, and only a few pediatric cases have been reported so far.² However, the

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condition can be potentially life-threatening and causes significant disability, impairment, and a severe decline in the patient's quality of life.²⁻¹¹ This case report describes the histopathological findings of musculoskeletal GVHD in a pediatric patient with acute myeloblastic leukemia (M2 subtype; AML-M2).

Case presentation

A 12-year-old boy presented with eye swelling and pancytopenia. Bone marrow aspiration cytology showed 40% myeloblastic cells, and flow cytometry revealed CD13, CD33, CD117, and myeloperoxidase positivity. Further bone marrow genetic analysis revealed trisomy-8 and t(8;21) (AML-ETO-1) positivity on polymerase chain reaction (PCR) testing, confirming the diagnosis of AML-M2. Accordingly, the AML Berlin-Frankfurt-Münster (BFM) 2019 chemotherapy protocol was initiated. After induction treatment, initially, the AML-ETO-1 PCR turned negative but eventually returned to positive before the fifth and final chemotherapy cycles. Consequently, he was transferred to a stem cell transplantation unit. As no suitable donor was found within the family, HSCT was performed from a 10/10 matched unrelated donor following the FLAG-IDA (fludarabine, cytarabine, granulocyte colony stimulating factor - idarubicin) protocol. The following myeloablative conditioning regimen was included – busulfan (3.8 mg/kg/day, days -7 to -4; cyclophosphamide 60 mg/kg/day, days -3 to -2; and melphalan 140 mg/m²/day, last day before HSCT). Additionally, cyclosporine and methotrexate were used for GVHD prophylaxis.

Cyclosporine prophylaxis was stopped three months after transplantation. In the fourth month, there were signs of ocular GVHD, and at five months post-transplant, the patient developed grade III skin GVHD. Accordingly, mycophenolate mofetil and steroids were added to his regimen. At this time, he had 100% chimerism, and the bone marrow was in molecular remission. Although his skin and eye symptoms resolved, he developed oral grade II

GVHD in the seventh month during the steroid tapering phase, necessitating an increase in the steroid dose.

By the end of the first year, the GVHD had resolved, and immunosuppressive therapies had been discontinued; muscle, joint, and neurological examinations remained normal during this period. However, three months after immunosuppressive therapy cessation, he exhibited muscular weakness in all four limbs, primarily in the lower limbs. Biochemical tests and blood counts, including creatine kinase (CK: 34 IU/L), were normal, and he tested negative for Epstein-Barr virus and cytomegalovirus PCR, Lyme disease serology, rheumatoid factor, antinuclear antibody, anti-dsDNA, anti-cardiolipin antibodies immunoglobulin G, and immunoglobulin M. The patient was uncooperative; hence, an electromyography (EMG) could not be performed, but nerve conduction tests were within normal limits. A muscle biopsy confirmed muscle involvement in cGVHD. Eventually, extracorporeal photopheresis was planned, and steroid (2 mg/kg/day) and mycophenolate mofetil (1500 mg/m²) were reintroduced. During the treatment, he developed a cough, which was diagnosed as pulmonary GVHD based on pulmonary function tests and thoracic computed tomography. All symptoms resolved after receiving two months of extracorporeal photopheresis.

Histopathological findings

Microscopic examination of the muscle biopsy specimen showed distortions in the diameter and shape of the muscle fibers. Scattered atrophic fiber structures were seen in the periphery of the fiber bundles, with no fiber grouping. However, the internal architecture of the muscle fibers exhibited normal nuclear retraction (< 3%), with no evidence of vacuoles or accumulations. There was no increase in the endomysial fibrous tissue, while the perimysial connective tissue appeared edematous and degenerated (Fig. 1). An inflammatory cellular reaction, comprising of macrophages, lymphocytes, and a few

plasma cells, was predominant in the perimysial area and noticeable in the endomysial area, particularly around the capillary vessels (Fig. 2). Histochemical and enzyme staining revealed that the distribution and ratio of type I and type II fibers were preserved, and no abnormal glycogen or fat accumulation was detected. Cytochrome *c* oxidase (COX) and succinate dehydrogenase enzyme staining displayed no loss of enzymatic activity or mitochondrial aggregates. Immunohistochemical staining revealed sarcolemmal upregulation of major histocompatibility complex (MHC)-

1, which was slightly more pronounced in the perifascicular fibers. Acid phosphatase and C5b9 staining exhibited characteristic features of inflammatory myopathy, with positive staining in macrophages and capillary structures (Fig. 3 and Fig. 4). Finally, staining of the cluster of differentiation 3 (CD3), CD4, CD8, CD20, and CD68 cells showed a cellular reaction rich in CD8-positive T cells and macrophages. When combined with the patient's history, the histopathological findings were consistent with muscle involvement in cGVHD.

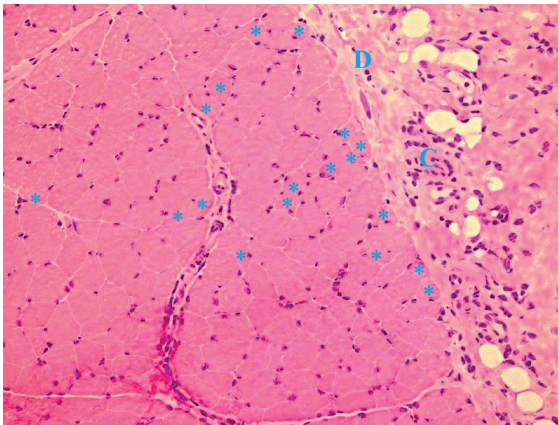


Fig. 1. In the striated muscle tissue sample, diameter and shape difference in the fibers, scattered atrophic fibers (*), as well as degeneration (D) and cellular reaction (C) in the perimysial connective tissue are observed (H&E, original magnification x200).

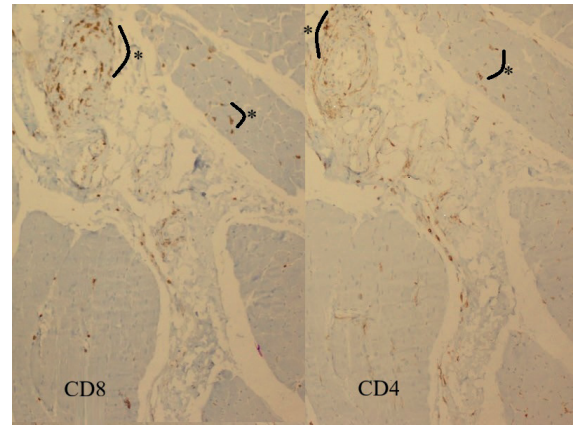


Fig. 2. T cell reaction (*) is observed via CD8 (left) and CD4 (right) staining in the perimysial connective tissue and around the endomysial capillaries (original magnification x200).

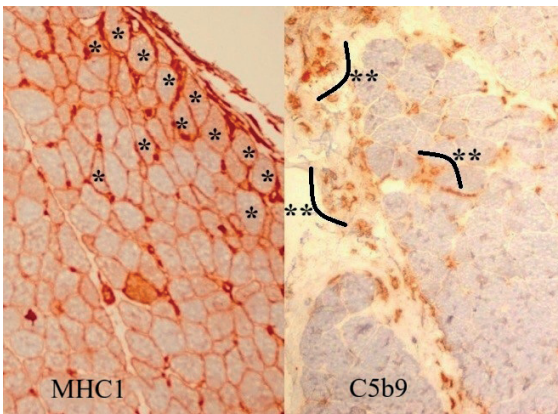


Fig. 3. Left: In MHC-1 staining, a positive sarcolemmal reaction (*) is observed in the fibers. Right: In C5b9 staining, a positive reaction is observed in macrophages (**) and around the capillary (original magnification x200).

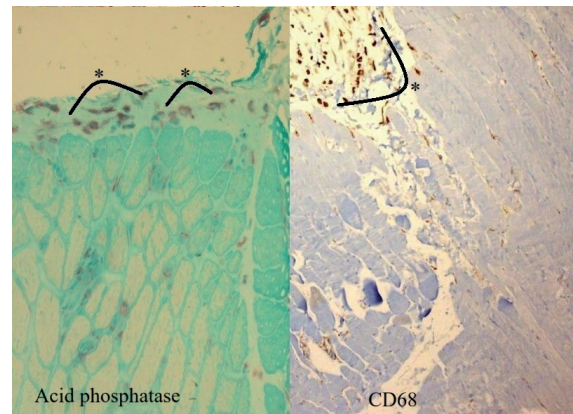


Fig. 4. In the striated muscle tissue sample, a positive reaction is observed in macrophages (*) in acid phosphatase and CD68 staining (original magnification x200).

Informed consent was obtained from the patient's parents, who agreed to the publication of the case findings.

Discussion

This case report underscores the importance of recognizing rare manifestations of cGVHD, particularly in pediatric patients. The existing literature affirms that musculoskeletal involvement in cGVHD implies a unique pathological process. In the present case, positive MHC-1 and C5b9 staining supported the diagnosis of inflammatory myopathy associated with cGVHD, highlighting the need for careful interpretation of the diagnostic findings in such cases.

Previous studies by Shono et al.⁴ contribute to the understanding of bone marrow GVHD, while Shulman et al.³ focus on the neurologic and cardiac complications associated with GVHD. Lehky et al.⁶ investigated the prevalence of neuropathy and muscle cramps in patients undergoing HSCT and found that 2.6–8.1% of patients exhibiting cGVHD symptoms may develop neuromuscular complications. Myositis was the most common neuromuscular disorder, followed by neuropathy and, less frequently, myasthenia gravis, and 55% of patients with neuromuscular symptoms experienced muscle cramps, while 65% demonstrated a muscle weakness phenotype.⁶

Kvinge et al.² conducted a comprehensive review of the literature on musculoskeletal manifestations of cGVHD and reported that cutaneous (52%) and oropharyngeal (37%) complications were the most common complications of cGVHD, while musculoskeletal complications (0.5%–3%) were among the rarer findings. They also emphasized that muscle pain is a grave and debilitating condition that should be considered in patients exhibiting muscle weakness, joint stiffness, and tissue inflammation.

Rørvik et al.⁷ provided an overview of different clinical presentations of cGVHD, categorizing

fasciitis and joint stiffness as musculoskeletal findings, and myositis and polymyositis as diagnostic indicators; notably, they described cardiac myositis and pericardial involvement as uncommon. Likewise, Tan et al.¹¹ reported a case of polymyositis following stem cell transplantation in a 6-year-old patient with thalassemia. The researchers underline that approximately 40 comparable cases have been acknowledged worldwide, the treatment of which is intricate. Moreover, Allen et al.¹² provided clinical, pathological, and molecular examination details of three patients with cGVHD who developed myopathy post-allogeneic HSCT. In each instance, Allen et al.¹² noticed perifascicular atrophy, a histological hallmark of dermatomyositis (DM).

There are no reliable benchmarks for the histopathological confirmation of muscle involvement in either aGVHD or cGVHD; however, excluding potential causative factors leading to similar morphological appearances may help determine a confirmed diagnosis. The upregulation of MHC-1 is a significant finding in inflammatory/immune-related myopathies; this is particularly noteworthy for dermatomyopathies, where it is more pronounced in perifascicular regions. However, our patient did not exhibit other typical features of dermatomyopathies, such as perifascicular atrophy, cell reactions with CD20-positive lymphocytes (especially pronounced in the perimysial region), COX deficiency in enzyme stains, and a serological increase in CK. Hence, inflammatory dermatomyopathy was not considered a potential diagnosis.

Other potential differential diagnoses of musculoskeletal manifestations of GVHD include hereditary myopathies (facioscapulohumeral muscular dystrophy [FSHMD], limb girdle muscular dystrophy [LGMD] 2A and 2B, hereditary inclusion body myopathy [HIBM]). In such cases, dystrophic findings from the distribution of cellular reactions in the biopsy specimen, combined with the patient's personal and family history, may facilitate differentiation.

Table I. Differential diagnosis in immune dermatomyopathy syndromes.¹⁴

Features		IM + perimysial pathology	Dermatomyositis + vascular pathology	Regional ischemic immune myopathy	DM: pauci-myopathic	cGVHD	Myositis + Mi-2 antibody	Systemic sclerosis
Clinical	Age at onset	Adult > child	Child or adult	Older adult	Adult	Adult	Child or adult	Adult
	Weakness	Proximal > distal	Proximal > distal	Proximal > distal	Uncommon	Proximal ± distal (50%)	Proximal (98%)	Proximal
	Myalgia	Common	Common	Common	None or Mild	Some		
	Skin pathology	Raynaud	Rash	Rash (70%)	Palmar: papules & ulcers	Sclerosis	Rash	Scleroderma
		Rash	Heliotrope		MxA + Keratinocytes	Dyskeratosis	Raynaud	Raynaud
		Mechanic's hands	Limbs: Extensor surface		Type I IFN			Capillary telangiectasia
		Psoriasisiform	Capillary Δ Tif1γ: Photosensitive		Alopecia			
	Interstitial lung disease	Eczematous	Palm hyperkeratosis					
		Dyskeratosis	NXP2: Edema					
		Common	Uncommon	No	Common	Common	Rare	Some
Serum	Neoplasm association	No	Adults	Common; 72% > 60 yrs.	No	Prior, hematologic	No	No
		Joints	Calcification; GI			GI; mucous membranes	Joints; GI	Esophagus, small bowel
	Myositis-associated antibody	Jo-1	TIF1γ	TIF1γ	MDA5	Varied	Mi-2	Calcinosis
		tRNA synthetase	NXP-2	NXP-2				HEp-2 IIF nuclear
		Some	Few	Most	No	No	Most	SMN
	CK > 1,000 U/L				No			Some

AP: Alkaline phosphatase, cGVHD: Chronic graft versus host disease, CK: Creatine kinase, COX: Cytochrome oxidase, C5b9: complement 5b-9, DM: Dermatomyositis, GI: Gastrointestinal, IM: Immune myopathies, MHC-1: Major Histocompatibility Complex class I, NOS: Nitric oxide synthase.

Table I. Continued.¹⁴

Features		IM + perimysial pathology	Dermatomyositis + vascular pathology	Regional ischemic immune myopathy	DM: pauci-myopathic	cGVHD	Myositis + Mi-2 antibody	Systemic sclerosis
Muscle pathology	Inflammation							
	Focal	Some	Yes (80%)	No	No	Uncommon	Yes (50%)	No
	Location	Perimysium	Perivascular				Perinysial & Endomysial	
	Type	Histiocytic	Lymphocyte (B-cell)				Lymphocyte	No
Perimysium pathology	Fragmentation	Common	Occasional	Necrotic regions	Some	Common		
	Immune cells	Histiocytic Scattered	Lymphocyte (B-cell) perivascular	Histiocytic	Histiocytic	Histiocytic	Histiocytic	
	AP	Some	Uncommon	Yes	Scattered	Some	Common	
Myofibril pathology	General							
	Perifascicular	Often	Yes	No	Mild or no	Glycosylation ↓		
	COX staining reduced	Never	Most patients		NOS2	No	Yes	MHC-1 upregulated
	Necrosis & regeneration	Common	Unusual		No			
	LC-3 aggregates	Rare	Common					
	Atrophy	Uncommon	Common				Common 60%	
	Necrosis			Regional	No	No	Perifascicular	
	Capillaries near myofiber	Normal	Reduced		Normal	Reduced	Normal	Thick walls
	C _{3b-9}	Normal	Large	Large				
	AP stain	Absent	Few	Common				
	Large vessel pathology	No	Artery + vein	Vein	No	No	No	No

AP: Alkaline phosphatase, cGVHD: Chronic graft versus host disease, CK: Creatine kinase, COX: Cytochrome oxidase, C5b9: complement 5b-9, DM: Dermatomyositis, GI: Gastrointestinal, IM: Immune myopathies, MHC-1: Major Histocompatibility Complex class I, NOS: Nitric oxide synthase.

On the other hand, in toxic and drug-induced myopathies, pathological findings attributed to the causative agent are crucial. Notably, steroids, commonly utilized in treating GVHD, can cause steroid-induced myopathy, which is characterized by painless proximal muscle weakness in the bilateral upper and lower extremities. The diagnosis is primarily clinical, with fatty alterations in proximal muscles seen on magnetic resonance imaging. Unlike other myopathies, steroid-induced myopathy is less likely to be detected via EMG⁵; muscle biopsy often reveals selective atrophy of type II muscle fibers.¹³ In cases of polymyositis and DM linked to connective tissue diseases, both clinical history and serologic findings play a significant role (Table I).¹⁴

In conclusion, this case report describes the features of a rare case of musculoskeletal GVHD with DM-like manifestations in a pediatric patient undergoing allogeneic HSCT for AML-M2. Through this unique case, we aim to enhance the understanding of atypical GVHD presentations and highlight the need for a comprehensive diagnostic approach for prompt and effective treatment.

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Ethical approval

Informed consent was obtained from the patient's parents. They also agreed to the publication of this case.

Author contribution

The authors confirm contribution to the paper as follows: Study conception and design: BE, ZCÖ; data collection: BE, Hİ; analysis and

interpretation of results: BE; draft manuscript preparation: BE, ZCÖ, ÖB. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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