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Case Report: Targeted therapy for TIF1γ-positive dermatomyositis with possible macrophage activation syndrome, cardiac and gastrointestinal involvement: a case-based review

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Dermatomyositis (DM) is an autoimmune disorder characterized primarily by cutaneous and muscular inflammation. Although the TIF1γ antibody-positive variant frequently correlates with an underlying malignancy, instances of severe multisystem compromise lacking a neoplastic association remain exceptionally uncommon. Macrophage activation syndrome (MAS), a lethal cytokine storm, poses substantial diagnostic and therapeutic challenges in DM. Herein, we detail the case of a young man with TIF1γ-positive DM who initially presented with pyrexia, a characteristic exanthema, and myalgia, and then developed rare multisystem complications. Cardiac manifestations, including pericardial effusion and markedly elevated cardiac enzymes, and gastrointestinal complications, including pneumatosis intestinalis and abdominal wall subcutaneous emphysema, were followed by possible MAS, evidenced by sustained high fever and marked increases in inflammatory indices, specifically serum ferritin and interleukin-6 (IL-6). Recognizing the cytokine storm early, the clinical team used alternative diagnostic criteria rather than relying strictly on the HLH-2004 criteria and initiated immediate JAK/IL-6 blockade. Through dynamic surveillance of inflammatory markers, immunosuppressive regimens were meticulously titrated, culminating in successful disease control and a favorable outcome. This case underscores the rarity of simultaneous cardiac and gastrointestinal involvement in TIF1γ-positive DM in the absence of prior immune checkpoint inhibitor exposure. Furthermore, it emphasizes the need for clinical vigilance regarding MAS even when full diagnostic thresholds are not met. The case also highlights the need for vigilant tumor screening and proactive infection surveillance in anti-TIF1γ-positive DM.

KEYWORDS
cardiac involvement, gastrointestinal involvement, possible macrophage activation syndrome, targeted therapy, TIF1γ-positive dermatomyositis

Introduction

Dermatomyositis (DM) is an autoimmune disease affecting the skin, muscles, and internal organs and is diagnosed based on characteristic clinical manifestations (1). Anti-transcriptional intermediary factor 1γ (TIF1γ) antibodies, which recognize 140- and 155-kDa proteins, were first identified in Japan as serological markers of DM (2). Common complications include dysphagia; muscle weakness is usually mild, and interstitial lung disease is less frequent. Skin lesions appear as erythematous rashes with telangiectasia. This antibody is strongly linked to malignancies, making it a key indicator for cancer-associated DM (3, 4). Macrophage activation syndrome (MAS) is a rare hyperinflammatory syndrome in TIF1γ-positive patients (5). The patient presented with acute pyrexia, skin eruptions, and myalgia, followed by rapid deterioration and cytokine storm. This study aims to investigate the clinical features and targeted treatment strategies for TIF1γ-positive DM associated with possible MAS.

Case presentation

On 25 September 2025, a 22-year-old man with no prior medical history was admitted after 6 days of high fever (40 °C), worsening proximal muscle weakness, and a non-itchy red rash on the chest, shoulders, and arms, which persisted after the fever resolved. He had difficulty raising his arms, standing up from a lying position, and squatting. On admission, he had a temperature of 39 °C, a heart rate of 92, and a blood pressure of 131/81 mmHg. Throat examination showed redness and tonsil swelling (grade II) without discharge. Reduced breath sounds and crackles were noted on the lower left side. Muscle examination showed weakness (4/5) and generalized pain. Skin examination revealed erythematous macules and papules on shoulders, neck, chest, and abdomen, without excoriations (Figure 1.1). Blood tests showed a high white blood cell count (31.9 × 10^9/L, reference range 4.0–10.0 × 10^9/L), elevated C-reactive protein (CRP) (255.1 mg/L, reference range <3 mg/L), serum ferritin (SF) (16,279 ng/mL, reference range 30–400 ng/mL), serum amyloid A (SAA) (>288 mg/L, reference range <10 mg/L), IL-6 (258 pg/mL, reference range 0–6.4 pg/mL), and procalcitonin (PCT) (1.9 ng/mL, reference range 0–0.046 ng/mL), while other cytokines were normal. Clotting issues included high fibrinogen (11.64 g/L, reference range 1.8–3.5 g/L) and D-dimer (8.67 mg/L, reference range 0–0.55 mg/L), with cardiac injury (high-sensitivity troponin T [TnT] 346 ng/L, reference range <14 ng/L). Chest CT showed lung infiltrates, an enlarged heart, and fluid around the heart and lungs (Figure 1.3A). Electrocardiography showed sinus rhythm with T-wave inversions in leads I, V5, and V6. He was evaluated with a Myositis Disease Activity Assessment Tool (MYOACT) score of 0.67.

Despite broad-spectrum antibiotics (meropenem and moxifloxacin), the patient worsened rapidly with acute chest pain, abdominal distension, and respiratory distress. Cardiac biomarkers were elevated (high-sensitivity TnT at 501 ng/L; NT-proBNP at 4,169 pg/mL, reference range <300 pg/mL), and echocardiography showed a small pericardial effusion with a preserved ejection fraction (63%). Whole-abdominal CT (26 September 2025, Figure 1.2) revealed intestinal dilation, gas accumulation, and subcutaneous edema. Mesenteric artery computed tomography angiography (CTA) was normal, but pulmonary artery CTA showed widening of the trunk and uneven filling. The next morning, the patient developed respiratory distress and altered mental status. Autoimmune serology was positive for antinuclear antibodies (ANA) (titer 1:100, speckled), anti-PM-Scl, and TIF1γ antibodies. Pathogen screening for Epstein–Barr virus (EBV), cytomegalovirus (CMV), respiratory viruses, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and Brucella was negative, with positive IgG and negative IgM antibodies. Tumor markers,including carcinoembryonic antigen (CEA), alpha-fetoprotein (AFP), cancer antigen 15-3 (Ca15-3), carbohydrate antigen 19-9 (Ca19-9), and prostate-specific antigen (PSA),were negative. He was diagnosed with TIF1γ antibody-positive DM with myocardial and intestinal involvement and bilateral pneumonia, although nailfold capillaroscopy and MRI were not performed due to the patient's critical condition and serology precluding additional imaging. The patient was transferred to the respiratory ICU (APACHE II: 10). Treatment included methylprednisolone (80 mg/day), IVIG (20 g/day for 6 days), sivelestat, and antibiotics. A hematological workup excluded malignancy or primary marrow disease. Bone marrow aspiration showed granulocytic hyperplasia without leukemia, myelodysplastic syndromes, or hemophagocytosis. Cytogenetic and mutation tests were negative. PET-CT (9 October 2025) revealed diffuse marrow activity consistent with reactive hyperplasia (Figure 1.4). Over 2 weeks, despite high-dose methylprednisolone, fever persisted; leukocytes peaked at 77.5 × 10^9/L on 4 October, ferritin reached 63,716 ng/mL on 13 October, and helper T cells dropped to 211/μL on 9 October. Lung CT (9 October 2025) showed bilateral atelectasis and chronic inflammation, with reduced lesions from 25 September 2025 (Figure 1.3C). On 10 October, methylprednisolone was increased to 200 mg daily, and tacrolimus 1 mg twice daily was added.

Figure 1.1 displays patchy erythematous rashes on the bilateral shoulders, hands, anterior neck, chest, and abdomen. CT in Figure 1.2 (26 September 2025) reveals intestinal dilation, gas accumulation, and subcutaneous edema with gas in the left abdominal wall. Figure 1.3A demonstrates serial chest CT findings: on 25 September 2025, bilateral pneumonia, cardiomegaly with pericardial effusion, and minimal pleural effusions; on 28 September 2025, progressive atelectasis and pneumonia with larger pleural effusions (Panel B); on 9 October 2025, regressed lesions with chronic inflammation and minimal pleural effusions (Panel C). Figure 1.4 PET-CT (9 October 2025) demonstrates diffuse bone marrow hypermetabolism, mild cardiomegaly with minimal pericardial effusion, and subcutaneous gas in the left lower abdominal wall.

By 13 October, specialists noted 23 days of fever above 39.5°C and ferritin over 60,000 μg/L, with no infection identified. Bone marrow biopsy and PET-CT ruled out hematological diseases. The patient had a cytokine storm with possible MAS (HScore 180, 70% probability, seen in Figure 2). A cutoff HScore of 169 has been shown to identify hemophagocytic lymphohistiocytosis (HLH) with 93% sensitivity and 86% specificity, and a score of 169 or greater is considered diagnostic of HLH in people with a high pretest

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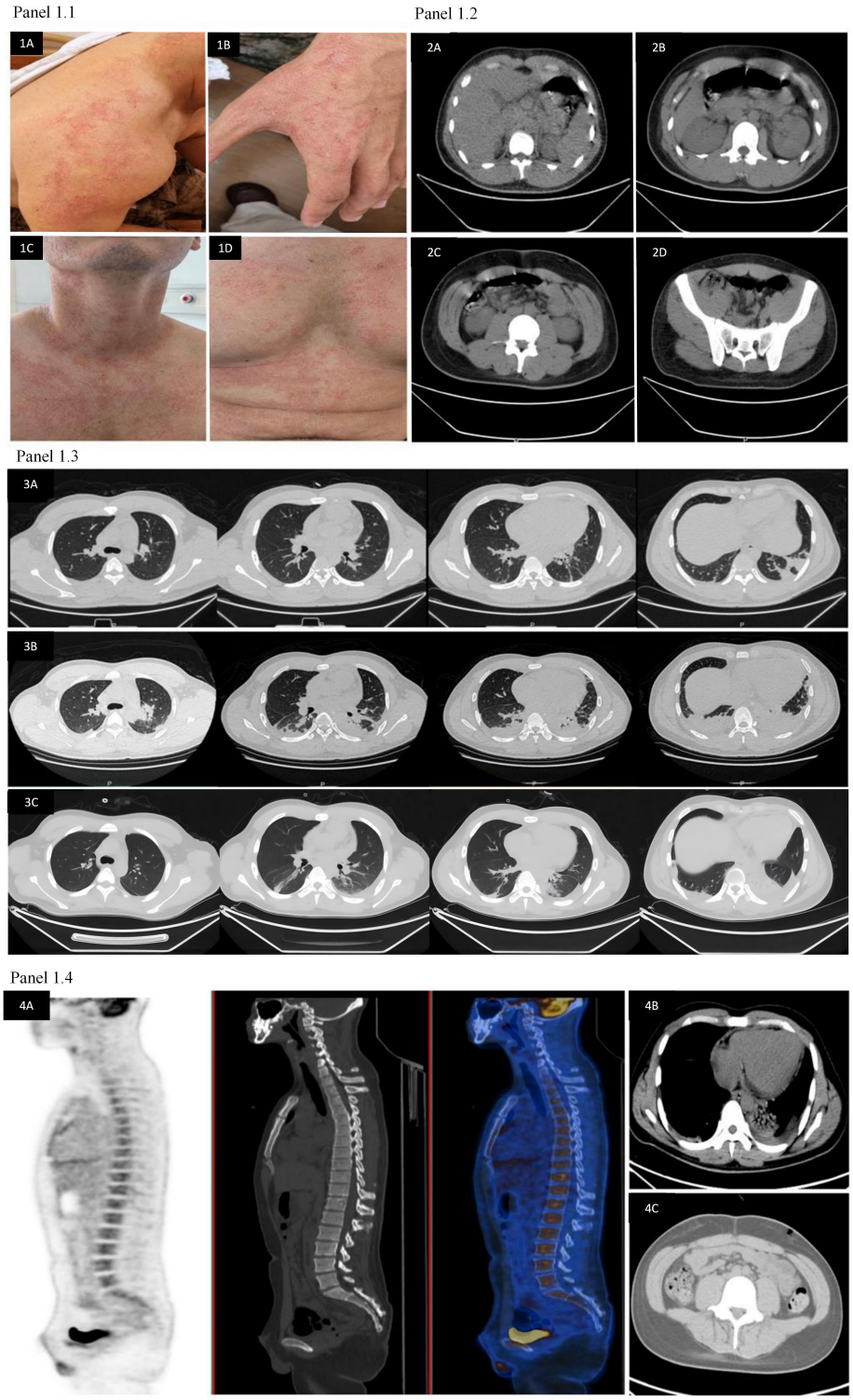


FIGURE 1
Clinical and radiological findings. **(1)** Patchy erythematous rashes on the bilateral shoulders, hands, anterior neck, chest, and abdomen, without excoriations. **(2A–2D)** Abdominal CT (26 September 2025) showing intestinal dilation, gas accumulation, and subcutaneous edema with gas in the left abdominal wall. **(3A)** Chest CT (25 September 2025) showing bilateral pneumonia, cardiomegaly with pericardial effusion, and minimal pleural effusions. **(3B)** Chest CT (28 September 2025) showing progressive atelectasis and pneumonia with larger pleural effusions. **(3C)** Chest CT (9 October 2025) showing regressed lesions with chronic inflammation and minimal pleural effusions. **(4A)** PET-CT (9 October 2025) whole-body and sagittal views demonstrating diffuse bone marrow hypermetabolism. **(4B, 4C)** Axial CT images through the thorax and abdomen showing mild cardiomegaly with minimal pericardial effusion **(4B)** and subcutaneous gas in the left lower abdominal wall **(4C)**.

probability (6). TIF1γ antibody-positive DM with possible MAS was diagnosed. Further tests for soluble CD25 and NK activity were needed. Etoposide was postponed. On 14 October, treatment was switched to dexamethasone 10 mg every 12 hours and ruxolitinib 10 mg twice daily; tacrolimus was stopped. Fever persisted for 3 more days. On 16 October, soluble CD25 was 11,428 ng/L (reference range <6,400 ng/L), and natural killer (NK) cell activity was 10.43% (reference range 15.11%–26.91%), supporting possible MAS because he met only 4 of 8 HLH-2004 criteria (7) and 2 Essential criteria and 1 Supplementary criterion under the 2016 Paediatric Rheumatology International Trials Organisation (PRINTO) MAS criteria (8), as shown in Figure 2. The patient received 560 mg of intravenous (IV) tocilizumab, reducing the fever. Neurological function improved, with muscle strength of 5⁻/5 and restoration of walking ability, although left-sided chest pain persisted. Inflammatory markers normalized, and Th rose to 699/μL. IL-6 increased to 518.92 pg/mL on 20 October.

Virological surveillance and antiviral intervention

Notably, the patient's immunological profile on 9 October revealed profound immunosuppression, with an absolute CD4+ T-cell count of 211/μL and an inverted CD4/CD8 ratio of 0.92. On 17 October, plasma HCMV-DNA and EBV-DNA levels measured by quantitative PCR (qPCR) were both below the detection limit ($<4.0 \times 10^2$ copies/mL), while herpes simplex virus (HSV)-1/2 IgG was 34.9 AU/mL (consistent with prior exposure). On 21 October 2025, plasma metagenomic next-generation sequencing (mNGS) detected high-abundance HHV-6A (72,209 reads) and CMV (3,459 reads). The discrepancy between the \ qPCR-negative result from 17 October and the mNGS-positive result from 21 October is attributable to the higher sensitivity of mNGS and the intermittent nature of viral release during immunosuppression. Given the temporal precedence of immunosuppression and the absence of IgM seroconversion to CMV/EBV at baseline (26 September: CMV-IgM 0.4 AU/mL negative, CMV-IgG 3.5 AU/mL positive; EBV VCA-IgM 0.4 AU/mL negative), we interpreted the detected HHV-6A and CMV as secondary reactivations of latent herpesviruses following intense immunosuppression rather than as primary triggers of the possible MAS hyperinflammatory syndrome. A 5-day course of ganciclovir was administered accordingly. Ruxolitinib was discontinued on 28 October. Subsequent sera showed negative IgM for herpesvirus, EBV, and CMV. On 31 October, tofacitinib 5 mg twice daily was initiated, and tacrolimus was up-titrated to 1.5 mg twice daily. A mild fever and elevated CRP on 3 November 2025 resolved after tocilizumab; tofacitinib was discontinued. The patient was discharged on 9 November 2025, with methylprednisolone (56 mg daily) and tacrolimus (1.5 mg twice daily), and a MYOACT score of 0.15, as shown in Figure 3A.

Follow-up and outcomes: Follow-up showed gradual methylprednisolone reduction by 10% every 10 days and improvement in markers (shown in Figure 3B); muscle strength returned to normal, and the left-sided chest pain disappeared 4 months after discharge. By May 2026, after adjustment to methylprednisolone (5 mg daily) and tacrolimus (1 mg twice daily), mild symptoms of an upper respiratory infection developed, including fever (37.6 °C), sore throat, chest pain, and joint pain. Labs showed leukocytosis (17.5×10^9/L) and high CRP (138 mg/L). Methylprednisolone was increased to 20 mg daily intravenously and then reduced to 8 mg orally, with the addition of tofacitinib (5 mg twice daily) and continued tacrolimus (1 mg twice daily). Remission was achieved within a week. Cancer screening (CT of the chest, abdomen, and pelvis, tumor markers, and gastroenteroscopy) was negative.

Patient's perspective

A previously healthy 22-year-old man rapidly developed high fever, proximal muscle weakness, rash, chest pain, abdominal distension, dyspnea, and altered mental status within days, losing basic self-care ability and enduring a prolonged 23-day high fever. He felt significant physical and psychological distress during critical illness. After tocilizumab treatment, his symptoms improved significantly; his muscle strength was restored, and he regained the ability to walk independently. He experienced a mild relapse in May 2026 but achieved quick remission following treatment adjustment. Despite invasive examinations and complex long-term therapy, he actively cooperated throughout the treatment course. He hopes his case can remind clinicians to recognize severe anti-TIF1γ-positive dermatomyositis complicated by possible MAS early. Written informed consent was obtained from the patient for publication of this case report and accompanying images.

Discussion

This case report describes a young man with TIF1γ antibody-positive DM presenting with fever, skin lesions, and muscle pain, who rapidly developed severe multisystem complications culminating in possible MAS. Despite failure of high-dose glucocorticoids, he improved with a targeted strategy combining dexamethasone, ruxolitinib (JAK inhibitor), tocilizumab (IL-6 inhibitor), and ganciclovir for HHV-6A/CMV viremia. This case highlights diagnostic challenges and the efficacy of early multimodal therapy.

Clinical features and immune characteristics of DM with associated MAS

MAS is a life-threatening complication of IIM, characterized by fever, cytopenia, coagulopathy, multi-organ dysfunction, and elevated ferritin and sCD25 (9). Diagnosis relies on the HLH-2004 or PRINTO/ACR criteria, which emphasize fever, hyperferritinemia, and thrombocytopenia (10). In DM, fever and hepatic dysfunction are often mistaken for disease flares or drug toxicity, delaying MAS recognition (11, 12). Clinicians should maintain a low threshold for MAS in DM patients with unexplained fever, cytopenia, or rising ferritin levels (13).

The prevalence and outcomes of DM-associated MAS are increasingly defined. Liang et al. reported an HLH prevalence of 4.2% among 424 idiopathic inflammatory myopathy (IIM) patients, with a short-term mortality of 77.8%; risk factors included high

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Score

Parameter	No. of points (criteria for scoring)
Known underlying immunosuppression*	0 (no) or 18 (yes)
Temperature (°C)	0 (<38.4), 33 (38.4–39.4), or 49 (>39.4)
Organomegaly	0 (no), 23 (hepatomegaly or splenomegaly), or 38 (hepatomegaly and splenomegaly)
No. of cytopenias†	0 (1 lineage), 24 (2 lineages), or 34 (3 lineages)
Ferritin (ng/ml)	0 (<2,000), 35 (2,000–6,000), or 50 (>6,000)
Triglyceride (mmoles/liter)	0 (<1.5), 44 (1.5–4), or 64 (>4)
Fibrinogen (gm/liter)	0 (>2.5) or 30 (≤2.5)
Serum glutamic oxaloacetic transaminase (IU/liter)	0 (<30) or 19 (≥30)
Hemophagocytosis features on bone marrow aspirate	0 (no) or 35 (yes)
HScore	180

HScore	Probability of hemophagocytic syndrome, %
90	<1
100	1
110	3
120	5
130	9
140	16
150	25
160	40
170	54
180	70
190	80
200	88
210	93
220	96
230	98
240	99
250	>99

- *Score issued from the manuscript "Development and validation of the HScore, a score for the diagnosis of reactive hemophagocytic syndrome". Fardet L, Galicier L, Lambotte O, et al. Arthritis Rheumatol. 2014*

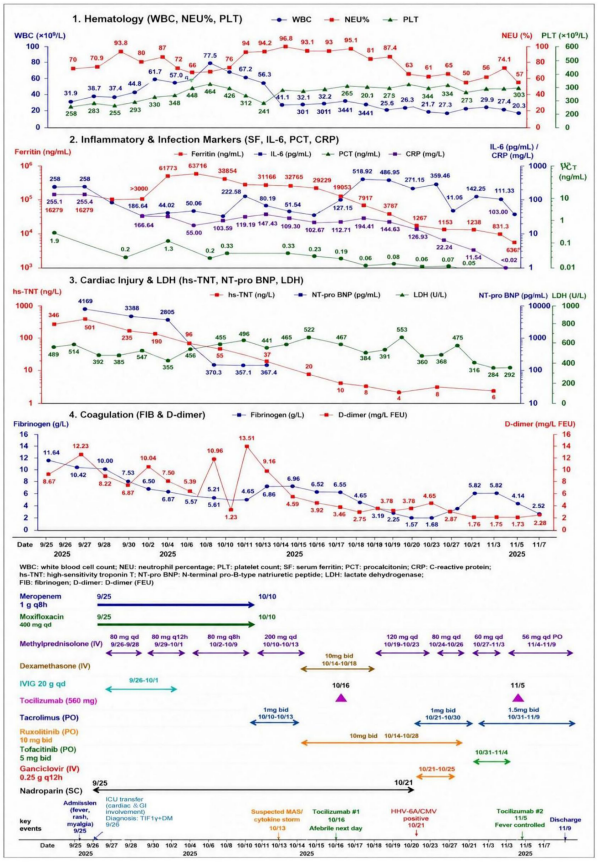
HLH-2004 Criteria (for HLH) The diagnosis HLH can be established if one of either 1 or 2 below is fulfilled	2016 MAS Classification (PRINTO Criteria) Requires all 2 and ≥2 of 4 supplementary criteria
(1) A molecular diagnosis consistent with HLH (2) Diagnostic criteria for HLH fulfilled (5 out of the 8 criteria below) • Fever >38.5°C more than 7days √ • Splenomegaly • Cytopenias ≥2 lineages (Hb<90g/L, PLT <100×10⁹/L, N1.0×10⁹/L) • Hypertriglyceridemia>3mmol/L and/or Hypofibrinogenemia ≤ 1.5 g/L • Hemophagocytosis in bone marrow, spleen, or lymph nodes, • Low or absent NK cell activity √ • Feritin ≥ 500 μg/L √ • sCD25 (sokuble IL-2Ra)≥2400 U/mL √	**Essential criteria (all 2):** √ Fever >38.5°C more than 7days √ √ Ferritin>684 ng/mL √ **Supplementary criteria (≥2):** • Platelet counts ≤181×10%/L • Elevated AST(>48U/L)√ • Triglycerides>156mg/dl (1.76mmol/L) • Fibrinogen ≤360 mg/dl (3.6g/L)

FIGURE 2
HScore and HLH/MAS diagnostic criteria assessment. Total score range: 0–337 points. A score ≥169 suggests a high probability of HLH (sensitivity 93%, specificity 86%). Scores <90 correspond to <1% probability, while scores >250 correspond to >99% probability.

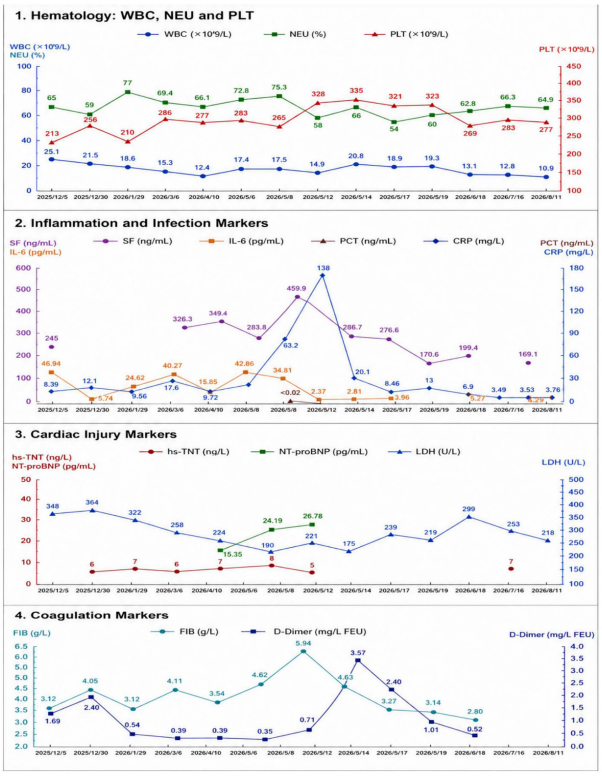
disease activity, exacerbation of interstitial lung disease (ILD), and infection (11). A recent cohort of 201 DM patients reported a MAS prevalence of 10.9% and a 90-day survival rate of 18.2%, with cardiac injury observed in half of the rapidly progressive ILD (RP-ILD)/MAS cases (14). Among five DM-MAS patients, Xing et al. noted that four of five had ILD and two of five had MAS; despite aggressive treatment, four of five survived, with one death attributable to pulmonary failure (12). Collectively, these data underscore the high lethality of DM-MAS.

The clinical phenotype of DM-MAS varies according to myositis-specific autoantibody (MSA) specificity. Anti-MDA5-positive DM-MAS often presents as a pulmonary-predominant catastrophe, with mortality reaching 50% in one study, where older age further amplified risk (15). Brown et al. reported a case of necrotizing autoimmune myopathy with anti-Jo-1 positivity that triggered MAS/HLH and required etoposide and anakinra (16). Both that case and our anti-TIF1γ-positive DM case demonstrate that MAS can complicate diverse IIM phenotypes and that conventional therapies may fail in severe IL-6-dominant cytokine storms. The response of our patient to JAK inhibition and IL-6 receptor blockade suggests that early cytokine-targeted immunotherapy may represent a safer alternative. Anti-TIF1γ-positive DM typically involves severe cutaneous and muscular disease, systemic inflammation, and a high malignancy risk. Our patient's presentation—, a ferritin level of

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A.



B.

FIGURE 3
(A) Inflammatory markers, cardiac injury indicators, and coagulation markers varied over time and with the major drug treatment timeline.
(B) Inflammatory markers, cardiac injury indicators, and coagulation markers fluctuated over time during post-discharge follow-up after the first hospitalization.

63,716 ng/mL, and an HScore of 180—represents a high-risk phenotype in which these organ injuries are underrecognized.

The immune basis of anti-TIF1γ-positive DM helps explain this vulnerability. Affected patients cluster into cytokine-defined groups, with a hyperinflammatory subset exhibiting elevated CXCL10, CCL2, galectin-9, IL-18, TNF-α, and TNFR1, which correlate with severe muscle weakness and high malignancy risk (17). VEGF-A, TNF-α, CCL2, IL-6, and IFN-γ predict malignancy with an area under the curve (AUC) of ≥0.8, outperforming anti-TIF1γ alone (17). These cytokines correlate with muscle enzyme levels, suggesting that TIF1γ antibodies may link tumor immunity and myositis by activating dendritic cells and macrophages (18–21). In our patient, elevated IL-6 (258 pg/mL at admission, rising to 518.92 pg/mL after tocilizumab administration) identifies IL-6 as a key pathogenic node.

Timeline and pathogenic role of detected HHV-6A and CMV

The central question is whether HHV-6A and CMV viremia triggered MAS or were secondary reactivations from immunosuppression. Based on longitudinal data, we favor the latter. Immunosuppression preceded high-level viral detection, with a CD4 + count of 211/μL and an inverted CD4/CD8 ratio on 9 October, 12 days before mNGS detected HHV-6A and CMV. Serology confirmed latent infection, with positive CMV and EBV IgG and negative IgM. A mild CMV-IgG rise did not meet the 4-fold increase consistent with primary infection (22). In immunocompromised hosts, CMV IgM is unreliable, and diagnosis relies on quantitative PCR. The qPCR result from 17 October was below the detection limit ($<4.0 \times 10^2$ copies/mL), but high mNGS read counts on 21 October reflect its ability to capture low-level viral replication (23). The dominance of IL-6 and sCD25 over IFN-γ in the cytokine profile argues against a primary viral etiology, as classical virus-triggered HLH is driven by excessive IFN-γ (24). In this patient, IL-6 dominated, and sCD25 was elevated, while NK activity dropped, a pattern more congruent with an autoantibody-driven, TIF1γ-mediated cytokine storm. Literature precedent in immunosuppressed cohorts shows that severe immunosuppression drives HHV-6 and CMV reactivation, and high mNGS read counts of HHV-6A/CMV likely reflect and amplify existing immune dysregulation rather than initiating it (25, 26).

This case of fulminant MAS aligns with autoantibody-driven immune priming and active anti-TIF1γ-positive DM, where HHV-6A/CMV reactivation indicates immune collapse and requires antiviral therapy alongside immunosuppression. However, without serial mNGS or droplet digital polymerase chain reaction (ddPCR) sampling before MAS onset, we cannot rule out earlier low-level herpesvirus replication that may have triggered the hyperinflammatory cascade, a limitation for future prospective studies.

Cardiac and gastrointestinal involvement in TIF1γ antibody-positive dermatomyositis

Cardiac involvement in DM is rare but serious. Prior studies have noted frequent electrocardiographic abnormalities in DM and polymyositis (PM) cohorts (27, 28). In immune checkpoint inhibitor (ICI)-induced myositis, anti-TIF1γ positivity does not correlate with myocarditis (29). In the present case, the patient developed pericardial effusion and elevated myocardial enzymes without prior ICI exposure. After malignancy had been reasonably excluded, these findings suggested an inherent cardiotoxic potential of anti-TIF1γ-positive DM.

Gastrointestinal involvement, presenting as pneumatosis intestinalis and subcutaneous emphysema, is even rarer and likely reflects systemic immune activation with microvascular injury or intestinal vasculitis (30). Anti-TIF1γ antibodies have been reported as an independent risk factor for dysphagia in IIM (31), but gastrointestinal complications of this severity are seldom documented. This case emphasizes that unexplained abdominal symptoms in anti-TIF1γ-positive DM warrant prompt imaging and interdisciplinary care (30).

The presence of anti-PM-Scl antibodies in our patient, without clinical features of scleroderma (no skin thickening, telangiectasia, or calcinosis), was considered a secondary autoantibody arising in the context of profound immune dysregulation. Anti-TIF1γ remained the dominant pathogenic driver, as evidenced by the clinical phenotype of severe cutaneous involvement, systemic inflammation, and the absence of overlapping myositis–scleroderma features. Anti-PM-Scl positivity in this setting likely reflects epitope spreading or polyclonal B-cell activation during the cytokine storm, rather than a distinct overlap syndrome.

Malignancy risk, immunological implications, and cancer surveillance in anti-TIF1γ-positive DM

Anti-TIF1γ-positive DM is a rare autoimmune disease characterized by immune dysregulation and tumor associations. Anti-TIF1γ antibodies are specific DM markers that are strongly linked to malignancy. The MYONET study found that anti-TIF1γ had the highest malignancy rate (33%) among DM antibody subtypes (32). TIF1γ (also known as TRIM33) participates in transcription, DNA repair, and differentiation, inhibiting tumors through the TGF-β/Smad and Wnt/β-catenin pathways (33). Immunohistochemistry has demonstrated elevated TIF1γ expression in DM muscle tissues (42.1% versus 0%), which was associated with anti-TIF1γ positivity ($P = 0.042$), suggesting a local autoantibody source (34). This connects the autoimmune response to neoplastic risk.

The malignancy burden is substantial across populations. A Greek cohort reported malignancy in 60% of antibody-positive patients versus 20.4% of antibody-negative patients (35), and a Japanese study reported 68% (36). Pooled analyses estimate cancer co-occurrence at 30%–40% (37, 38), reaching up to 54.5% in some series (39). Anti-TIF1γ antibody serves as an independent predictor of adult DM-associated malignancy, with 64.3% sensitivity and 92.7% specificity (40, 41); the IgG2 subclass has a near-100% predictive value for cancer and mortality (42). The tumor distribution includes lung (≈25%), colorectal (≈15%), and ovarian (≈10%) cancers (43, 44), with sex-specific patterns (35, 45). Malignancy typically emerges within a narrow window—from 13 months before to 4 months after DM onset (44, 45)—highlighting the importance of early surveillance.

Despite the strong antibody–cancer association, the immunological interplay is more complex than a simple linear relationship. While elevated TIF1γ expression may trigger immune responses, comparative studies show no significant difference between cancer-associated and non-cancer-associated DM patients (46), suggesting additional immunoregulatory factors orchestrate disease onset. The co-occurrence of anti-CCAR1 antibodies attenuates cancer risk (47), highlighting the nuanced role of autoantibody networks. In Chinese juvenile DM cohorts, anti-TIF1γ positivity is linked to earlier onset, prolonged duration, and lower alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), and ferritin levels (48), indicating ethnic and age-dependent modifiers. These findings suggest anti-TIF1γ production arises from failed immune surveillance and loss of self-tolerance, driving systemic inflammation and potentially fostering a permissive milieu for neoplastic evolution.

Systematic tumor surveillance is crucial for anti-TIF1γ-positive DM patients due to high malignancy risk. The 2023 International Myositis Assessment and Clinical Studies Group (IMACS) guideline recommends risk-stratified screening, including 18F-FDG PET-CT for patients aged >40 years with additional risk factors (49). However, the positive predictive value of PET-CT is suboptimal, highlighting the need for individualized protocols based on age, sex, cancer epidemiology, and prior results. In 2026, the multicenter Japanese MYKO cohort established a five-factor risk-stratification model for cancer-associated myositis (CAM) in IIM, incorporating anti-TIF1γ positivity, elevated CRP, DM subtype, older age at IIM onset, and family history of malignancy (50). Anti-TIF1γ positivity was identified as the strongest predictor in random forest analysis (model AUC 0.86), providing an evidence base for individualized screening strategies. For anti-TIF1γ-positive DM patients with concomitant MAS, high-dose immunosuppression and the catabolic state induced by MAS may mask early signs of malignancy; therefore, optimizing screening frequency and test combinations based on the risk-stratification model is essential to avoid missing occult tumors. We propose a structured regimen: repeat imaging at 6 months, then annually for 3 years (51, 52), with serial tumor markers and anti-TIF1γ antibody monitoring (48, 52). For male patients, vigilance for occult lesions is critical. Rigorous malignancy surveillance was maintained throughout the management of the present case, in line with this risk-stratification concept.

In our patient, baseline screening with chest and whole-abdominal CT, tumor markers, and PET-CT revealed no malignancy. At the six-month follow-up, repeat imaging, tumor markers, and gastroenterological endoscopy again identified no malignancy. This does not negate the need for continued vigilance, because many anti-TIF1γ-associated malignancies emerge beyond the initial period. This case highlights both the value of early surveillance and the limits of a single negative screen, underscoring that sustained follow-up remains essential for this high-risk phenotype.

Pathological mechanisms of cytokine storm: from sCD25 and JAK-STAT to the IL-6 pathway

sCD25, the cleaved extracellular domain of IL-2Rα, is a key biomarker for T-cell activation. In this case, sCD25 reached 11,428 pg/mL (reference value <1,000 pg/mL), indicating profound T-cell hyperactivation. Excessive IFN-γ, central to classical HLH (24), was not prominently elevated; instead, IL-6 dominated the cytokine profile. This pattern resembles infection-associated secondary HLH, but negative admission viral screens for primary infection (positive IgG and negative IgM for EBV/CMV on admission) and qPCR results for HCMV-DNA and EBV-DNA below the detection limit ($<4.0 \times 10^2$ copies/mL) on 17 October suggest an autoantibody-driven cytokine storm, with the subsequently detected HHV-6A/CMV viremia interpreted as reactivation under immunosuppression.

Ruxolitinib, a JAK1/2 inhibitor, was initiated to block common γ-chain cytokine signaling (53). Xu et al. described the use of ruxolitinib in anti-TIF1γ-positive DM (54), demonstrating its short-term efficacy in ameliorating refractory cutaneous and muscular manifestations, which is consistent with the JAK inhibitor strategy adopted in the present case. Kaewin S et al. (55) demonstrated sustained activation of the type I IFN signaling pathway in peripheral blood mononuclear cells from patients with anti-TIF1γ-positive DM. This pathway not only mediates cutaneous and muscular damage but also amplifies macrophage activation, creating a permissive environment for MAS onset. These findings provide a mechanistic rationale for targeting the JAK-STAT pathway in this patient population. Ruxolitinib normalized sCD25 and decreased ferritin, consistent with JAK-STAT pathway inhibition (56). Ruxolitinib may enhance glucocorticoid-induced apoptosis in activated CD8+ T cells (57). IL-6, a major mediator of MAS that activates the JAK/STAT3 pathway (58), was targeted with tocilizumab, resulting in rapid defervescence and normalization of inflammatory markers. The dynamic IL-6, sCD25, and ferritin trajectory provides a biological metric for therapeutic efficacy and supports dual-axis (JAK/IL-6) blockade in refractory DM-MAS, as shown in Figure 4.

Differential diagnoses: bacterial infection, viral infection, adult-onset Still's disease, and lymphoma

This patient had persistent high fever, extreme hyperferritinemia (>60,000 ng/mL), leukocytosis, elevated IL-6, and sCD25, requiring the exclusion of infection-triggered secondary HLH, AOSD, and occult lymphoma (59). Broad-spectrum antibiotics failed to halt disease progression, and microbial workup was negative. The cytokine profile, with high IL-6 and sCD25, rising ferritin, and suppressed NK activity, was inconsistent with bacterial sepsis (60). Baseline serology showed prior herpesvirus exposure, not acute infection. Plasma qPCR on 17 October detected no CMV or EBV DNA, while mNGS on 21 October found high HHV-6A and CMV sequences, which were interpreted as secondary reactivation after immunosuppression, not the cause of MAS (61). AOSD shares features with DM complicated by MAS, but the patient had persistent fixed erythema, proximal muscle weakness, and dermatomyositis lesions (62). Lymphoma-associated hemophagocytic syndrome (LAHS) requires exclusion of occult hematologic malignancy, especially T/NK-cell lymphoma, in unexplained cytokine storm (63). In this case, bone marrow aspiration ruled out leukemia, myelodysplastic syndromes, and hemophagocytosis. PET-CT showed diffuse reactive bone marrow hypermetabolism without focal FDG-avid lesions. Tumor markers were normal, and cancer

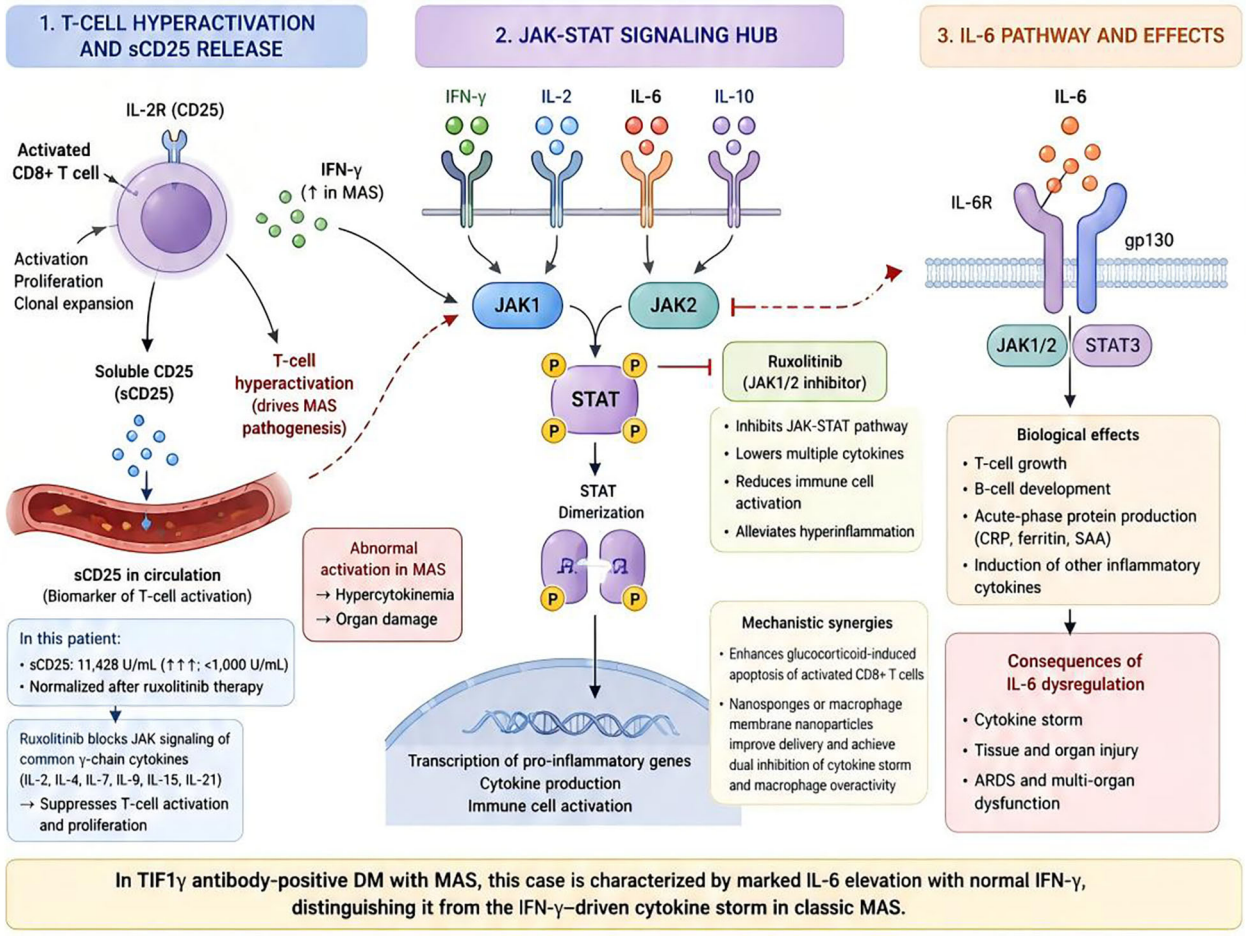


FIGURE 4
The pathological mechanisms of IL-6, sCD25, and the JAK-STAT pathway underlying the cytokine storm.

screening at six months remained negative. Although anti-TIF1γ-positive DM carries malignancy risk, LAHS was reasonably excluded in the acute phase. Long-term surveillance is warranted due to persistent cancer association.

Comprehensive clinical, serological, imaging, and bone marrow evaluations supported anti-TIF1γ-positive DM-associated possible MAS as the primary diagnosis. Secondary HHV-6A/CMV reactivation amplified immune dysregulation but was not the trigger. This framework emphasizes avoiding over-attribution of cytokine storm to viral reactivation, which may delay targeted immunomodulatory therapy.

Considerations in diagnostic criteria and treatment decisions

MAS diagnosis in autoimmune diseases is challenging. The HLH-2004 criteria were developed for primary HLH and may not capture all rheumatic MAS cases (7). Bone marrow hemophagocytosis is not essential, and splenomegaly may be masked by infections or drugs. Our patient met only four of eight HLH-2004 criteria but fulfilled 2 essential and 1 supplementary PRINTO criteria, with an HScore of 180 (68.35% probability), leading to a diagnosis of possible MAS. Initiating immunosuppressive therapy based on a holistic assessment —persistent fever, markedly elevated ferritin (typically >10,000 ng/mL), and multi-organ involvement—proved rational and imperative. This approach prioritizes immediate control of cytokine storm but requires stringent infection surveillance.

In our patient, plasma mNGS on 21 October captured HHV-6A and CMV viremia with extraordinarily high read counts. Crucially, the immunosuppression profile (CD4 + 211/μL, CD4/CD8 0.92) was already established on 9 October —before viral detection—and baseline serologies (26 September) confirmed latent infection rather than primary acquisition. These data collectively support the interpretation of the viremia as secondary reactivation rather than a primary MAS trigger. Targeted antiviral therapy with ganciclovir was therefore deployed as preemptive, not definitive, treatment.

This distinction is clinically pivotal: it validates the decision to prioritize cytokine-directed immunotherapy (tocilizumab, ruxolitinib)

over etoposide-centric HLH protocols while maintaining vigilance for opportunistic viral replication.

The patient's experience highlights that anti-TIF1γ-positive DM with possible MAS can cause sudden disability in young adults. Multimodal immunotherapy successfully controlled the cytokine storm and restored daily function, emphasizing the necessity of early individualized treatment.

Stepwise targeted therapy strategy and dynamic adjustment

Methylprednisolone pulse therapy (up to 200 mg daily) failed to control the MAS-driven cytokine storm in this patient, with ferritin surging to 63,716 ng/mL. Persistent hyperpyrexia, elevated IL-6 and sCD25, and suppressed NK activity (10.43%) led to the addition of ruxolitinib, which reduced inflammatory markers; however, fever recurred, prompting the introduction of tocilizumab. The patient became afebrile, with gradual organ improvement.

Plasma mNGS on 21 October detected high-abundance HHV-6A (72,209 reads) and CMV (3,459 reads). Given the temporal sequence described above (immunosuppression preceding viral detection by 12 days), of ganciclovir was administered as preemptive antiviral therapy. This stepwise approach—glucocorticoids → JAK inhibition → IL-6 blockade → targeted antiviral therapy—demonstrates that multimodal immunomodulation can rescue severe anti-TIF1γ-positive DM-MAS even in the presence of comorbid viral reactivation. By day 12, ferritin dropped to 3,787.00 ng/mL, and CRP normalized. This stepwise approach—glucocorticoids → JAK inhibition → IL-6 blockade → targeted antiviral therapy—shows that multimodal immunomodulation coincided with severe anti-TIF1γ-positive DM-MAS. Partial response to ruxolitinib suggests TIF1γ antibody–mediated JAK-STAT and NF-κB pathway activation.

This is a single case observation; the temporal association between the introduction of tocilizumab/ruxolitinib and clinical improvement suggests a potential therapeutic effect, but causality cannot be established without controlled studies.

Controversies and limitations

Nailfold capillaroscopy and MRI were not performed due to the patient's critical condition, and serology precluded additional imaging. Genetic testing for familial HLH was not performed, and serial mNGS or ddPCR testing of herpesvirus load before MAS onset was not performed; consequently, we cannot definitively exclude the possibility that low-level viral replication participated in initiating or amplifying the hyperinflammatory cascade. Familial HLH (fHLH) was considered less likely given the patient's age and lack of family history. fHLH cannot be formally excluded, and long-term follow-up should include vigilance for recurrent HLH episodes. The absence of serial cytokine profiling (beyond IL-6, sCD25, and ferritin) and serial NK function assessment limited mechanistic conclusions regarding the relative contributions of viral versus autoantibody-driven pathways. Future prospective studies in DM-MAS should incorporate longitudinal plasma mNGS for herpesviruses to dissect this temporal relationship with higher precision.

Conclusion

This report details a rare case of anti-TIF1γ-positive DM with simultaneous cardiac and gastrointestinal involvement, progressing to possible MAS. It highlights that MAS should be recognized even when traditional diagnostic thresholds are not met and that such recognition may contribute to favorable outcomes in similar cases. The case also emphasizes the need for vigilant tumor screening and proactive infection surveillance in anti-TIF1γ-positive DM. Our longitudinal data indicate that HHV-6A/CMV viremia in this context most likely represents secondary reactivation under intense immunosuppression—a biomarker of immune collapse rather than a primary MAS trigger—yet one that complicates management and necessitates the integration of targeted antiviral therapy into the stepwise immunomodulatory strategy.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

Ethics statement

The requirement of ethical approval was waived by the Ethics Committee of the Northern Theater Command General Hospital for the studies involving humans. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

YDL: Project administration, Data curation, Writing – original draft, Writing – review & editing. YPL: Investigation, Writing – review & editing. PL: Funding acquisition, Writing – original draft, Writing – review & editing.

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Conflict of interest

The author(s) declared that this work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

The author(s) declared that generative AI was not used in the creation of this manuscript.

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Glossary

ACR	American College of Rheumatology
AFP	alpha-fetoprotein
ALT	alanine aminotransferase
ANA	antinuclear antibody
anti-MDA5	anti-melanoma differentiation-associated gene 5
anti-TIF1γ	anti-transcriptional intermediary factor 1γ
AOSD	adult-onset Still's disease
APACHE II	Acute Physiology and Chronic Health Evaluation II
AST	aspartate aminotransferase
AUC	area under the curve
Ca15-3	cancer antigen 15-3
Ca19-9	carbohydrate antigen 19-9
CCL2	C-C motif chemokine ligand 2
CEA	carcinoembryonic antigen
CMV	cytomegalovirus
CRP	C-reactive protein
CXCL10	C-X-C motif chemokine ligand 10
ddPCR	droplet digital polymerase chain reaction
DIC	disseminated intravascular coagulation
DM	dermatomyositis
EBNA	Epstein–Barr virus nuclear antigen
EBV	Epstein–Barr virus
FDG	fluorodeoxyglucose
HCT	hematopoietic cell transplantation
HHV-6A	human herpesvirus 6A
HLH	hemophagocytic lymphohistiocytosis
HScore	hemophagocytic syndrome score
ICI	immune checkpoint inhibitor
IFN-γ	interferon gamma
IgA	immunoglobulin A
IgG	immunoglobulin G
IgM	immunoglobulin M
IIM	idiopathic inflammatory myopathy
IL	interleukin
IL-6	interleukin-6
ILD	interstitial lung disease
IMACS	Internat ional Myositis Assessment and Clinical Studies Group
LAHS	lymphoma-associated hemophagocytic syndrome
LDH	lactate dehydrogenase
MAS	macrophage activation syndrome
mNGS	metagenomic next-generation sequencing
MSAs	myositis-specific antibodies
MYOACT	Myositis Disease Activity Assessment Tool
NK	natural killer
NT-proBNP	N-terminal pro-B-type natriuretic peptide
PM	polymyositis
PRINTO	Paediatric Rheumatology International Trials Organisation
PSA	prostate-specific antigen
qPCR	quantitative polymerase chain reaction
RP-ILD	rapidly progressive interstitial lung disease
SAA	serum amyloid A
sCD25	soluble CD25
TGF-b	transforming growth factor beta
TNF- α	tumor necrosis factor alpha
TNFR1	TNF receptor 1
TnT β	troponin T
VCA	viral capsid antigen
VEGF-A	vascular endothelial g