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Interstitial lung disease with anti-melanoma differentiation-associated gene 5 antibody after allogeneic hematopoietic stem cell transplantation

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Anti-melanoma differentiation-associated gene 5 (MDA5) antibody is one of auto-immune antibodies which is associated with a rare subtype of dermatomyositis (DM), and MDA5-DM is well-characterized by rapid progressive interstitial lung disease (ILD) which in part resembles pulmonary complications after allogeneic hematopoietic cell transplantation (allo-HCT). However, previous studies about anti-MDA5 antibody after allo-HCT were extremely limited. Here, we present 4 cases of ILD with anti-MDA5 antibody after allo-HCT. All of the cases showed rapidly progressive clinical course and 3 of 4 cases died despite intensive immunosuppressive therapies which included prednisolone, cyclophosphamide and calcineurin inhibitor. Additionally, 3 of 4 cases had tested positive for anti-MDA5 antibody by using cryopreserved plasma which were collected about 2–3 months before the diagnosis of MDA5-DM-ILD. It suggests that an inflammatory condition due to MDA5-DM-ILD might have sub-clinically occurred before the development of respiratory failure. The current cases suggest that the clinical feature was relatively similar to classical MDA5-DM-ILD, although it is difficult to distinguish MDA5-DM-ILD from chronic GVHD and other pulmonary complications after allo-HCT. Since clinical courses of MDA5-DM-ILD is considerably aggressive, it is important to discriminate MDA5-DM-ILD from other complications after allo-HCT.

Bone Marrow Transplantation (2022) 57:1382–1388; <https://doi.org/10.1038/s41409-022-01730-6>

INTRODUCTION

Non-infectious pulmonary complications include various disease entities, leading to fatal diseases after allogeneic hematopoietic cell transplantation (allo-HCT) [1–6]. However, a distinct definition of these complications has not been clearly described, since the diagnosis of non-infectious pulmonary complications is mainly based on the exclusion of other diseases [7]. Bronchoscopy is a promising diagnostic procedure for distinguishing other pulmonary disease [5, 8, 9], but a considerable number of allo-HCT recipients are difficult to receive bronchoscopy due to their critically ill state. Therefore, clinically diagnosed pulmonary complications include heterogeneous manifestations and disease origins due to the limitation of diagnostic procedures.

Anti-melanoma differentiation-associated gene 5 (MDA5) antibody is one of auto-immune antibodies which is associated with a rare subtype of dermatomyositis (DM) [10–12]. MDA5-DM is well-characterized by mucocutaneous lesion, amyopathic or hypomyopathic muscle involvement and rapidly progressive interstitial lung disease (ILD) [13]. Prognosis of MDA5-DM is devastating and the 6-months survival rate was reported as 33–66% in the previous studies [14–17]. The symptoms of pulmonary complications after allo-HCT in part resemble MDA5-DM-related ILD. However, previous studies about anti-MDA5 antibody after allo-HCT were

extremely limited [18, 19]. Here, we present 4 cases of ILD with anti-MDA5 antibody after allo-HCT and analyzed the clinical courses in detail including the serial changes in anti-MDA5 antibody titers and possible association with Coronavirus disease 2019 (COVID-19) pandemic.

PATIENTS AND METHODS

Patients

We reviewed clinical charts of 504 patients who underwent allo-HCT at our center between June 2007 and December 2021. Among them, all the patients who diagnosed as MDA5-DM-ILD after the allo-HCT were included in this study. This study was approved by the Institutional Review Board of Jichi Medical University Saitama Medical Center and performed in accordance with the Declaration of Helsinki and its later amendments. Informed consent for using samples was obtained from each patient.

Serological tests of the cases

The patients' plasma was prospectively cryopreserved on the day before the commencement of conditioning regimen, day 30, 60, 90, 120, 180, 270 and 360 after the allo-HCT. Additional cryopreservation was performed based on each physician's discretion. The plasma was used for measurement of anti-MDA5 antibody and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) IgG. Anti-MDA5 antibody was

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Received: 9 March 2022 Revised: 11 May 2022 Accepted: 26 May 2022

Published online: 4 June 2022

measured with ELISA and SARS-CoV-2 IgG was measured with CLEIA. The upper limit of the available value of anti-MDA5 antibody was 150. These tests were commercially performed by SRL, inc., Japan.

RESULTS

Clinical courses of the MDA5-DM-ILD cases

Among 504 patients, there were 60 ILD cases who had unidentifiable origin, and the cryopreserved plasma at the diagnosis of ILD was available from the 35 of 60 cases. Among the cases, we identified 4 cases of MDA5-DM-ILD during the study period. All of the cases were diagnosed during the clinical course, and any other MDA5-DM-ILD cases could not be found based on the review of cryopreserved samples. Median age at the onset of MDA5-DM-ILD was 45 years (34–61). Median duration between the onset of MDA5-DM-ILD and the latest allo-HCT was 234 days (134–469). One of the cases developed MDA5-DM-ILD after the second allo-HCT, and a duration between the onset and the first allo-HCT was 1410 days. Median follow-up duration was 90 days (49–291), and 3 of 4 cases died.

Case 1

A 60-year-old female was diagnosed as myelodysplastic syndrome with excess blast-2 (MDS-EB2). After 3 cycles of azacytidine, bone marrow aspiration revealed complete remission (CR), and she underwent allo-HCT from an HLA-matched unrelated donor. The summary of allo-HCT was shown in Table 1. She developed skin GVHD on day 28 and gut GVHD on day 58 of the allo-HCT. The maximum grade of acute GVHD was grade II. She was treated with prednisolone (PSL) from day 60. Acute GVHD gradually ameliorated, and the administration of PSL and cyclosporine was terminated 11 months from allo-HCT.

Six weeks after the end of immunosuppressive therapy, she developed lichen planus like skin, skin rash, nonspecific mucositis, arthritis and elevation of liver enzyme (gamma-glutamyl transpeptidase and alkaline phosphatase were predominant). She was clinically diagnosed as chronic GVHD without biopsy, and cyclosporine was restarted. However, she gradually suffered from dyspnea. She was emergently hospitalized after 2 weeks due to severe respiratory dysfunction, and was immediately intubated and transferred to intensive care unit (ICU). The images of lung computed tomography (CT) revealed diffuse bilateral ground glass opacity (GGO), suggesting immune-related pathogenesis (Fig. 1a). The day after admission, a steroid pulse therapy with methyl-PSL 1 g/day \times 3 days and a subsequent tapering phase was performed and her respiratory condition was slightly improved. One week after the admission, she revealed to test positive for anti-MDA5 antibody. Then, cyclophosphamide (CY) and tacrolimus were given with steroid 9 days after the admission. The dose of CY was 350 mg/m² on day 9, and 1000 mg/m² on 23 and 37 days after the admission. Since CY and tacrolimus could not improve her clinical status, tofacitinib 10 mg/day was additionally administered to the treatment. However, her respiratory condition rapidly deteriorated, and she died 49 days after the admission. The summary of the clinical course of MDA5-DM-ILD was shown in Table 2.

An autopsy revealed the diffuse alveolar damage with fibrosis and lymphocyte infiltration which were compatible with MDA5-DM-ILD. Dermis and pectoral muscle also showed slight lymphocyte infiltration which was consistent with DM.

Case 2

A 32-year-old female was diagnosed as acute myeloid leukemia (AML) with RUNX1-RUNX1T1 and was treated with idarubicin/cytarabine (Ara-C) as induction therapy followed by 3 cycles of high-dose Ara-C. However, she experienced AML relapse 4 months after the completion of chemotherapy. She was re-treated with induction chemotherapy including mitoxantrone, etoposide and Ara-C. She achieved CR state and underwent allo-HCT from an

Table 1. Summary of allo-HCT.

Case	Disease	Disease status	Donor type	Donor source	HLA-DRB1	ABO	CMV serostatus	Conditioning	GVHD prophylaxis	Pre-transplantation PFT		Max severity of chronic GVHD (except for MDA5-DM-ILD)	
										%VC	FEV1%		%DLCO
Case 1	MDS	Marrow CR	MUD	BM	(04:06, 13:02)	Minor mismatch	D-/R+	FLU/BU4	CsA + sMTX (10-7-7-7)	116.0%	78.31%	157.2%	Moderate
Case 2 1 st allo-HCT	AML	CR	MRD	PB	(13:02, 15:02)	Major mismatch	D+/R+	BU/CY	CsA + sMTX (10-7-7-0)	113.0%	80.74%	170.4%	Severe
Case 2 2 nd allo-HCT	AML	CR	MUD	PB	(13:02, 15:02)	Major mismatch	D+/R+	FLU/MEL140	CsA + sMTX (10-7-7-7)	95.4%	56.93%	N/A	Moderate
Case 3	AML	CR	MRD	PB	(04:05, 13:02)	Match	D+/R+	BU/CY	CsA + sMTX (10-7-7-0)	99.5%	81.59%	87.0%	Mild
Case 4	AML	Non-CR	MUD	PB	(08:03, 15:02)	Major mismatch	D+/R+	BU/CY	CsA + sMTX (10-7-7-7)	99.7%	86.61%	143.2%	Mild

Severity of chronic GVHD was evaluated with National Institutes of Health consensus criteria (Biol Blood Marrow Transplant 2015; 21(3): 389-401). *allo-HCT* allogeneic hematopoietic stem cell transplantation, *HLA* human leukocyte antigen, *CMV* cytomegalovirus, *GVHD* graft-versus-host disease, *PFT* pulmonary function test, *%VC* percent vital capacity, *FEV1%* forced expiratory volume in 1 second, *%DLCO* percent diffusing capacity of the lung for carbon monoxide, *MDS* myelodysplastic syndrome, *AML* acute myeloid leukemia, *CR* complete remission, *MUD* matched unrelated donor, *MRD* matched related donor, *BM* bone marrow, *PB* peripheral blood, *FLU* fludarabine, *BU* busulfan, *CY* cyclophosphamide, *MEL* melphalan, *CsA* cyclosporin, *sMTX* short term methotrexate.

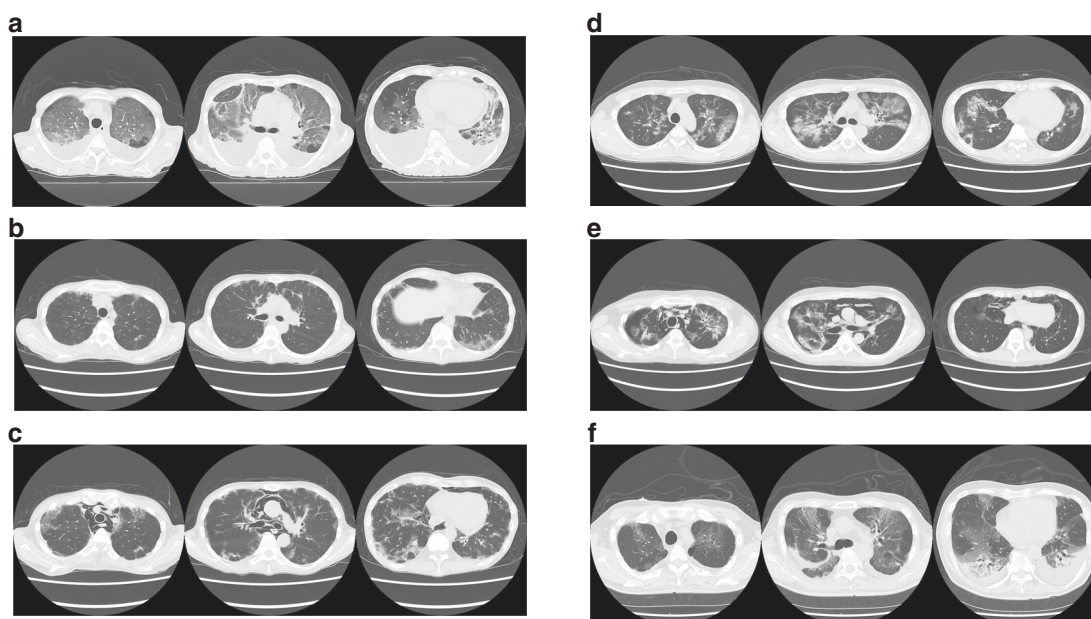


Fig. 1 Lung CT images. **a** Case 1 at the onset of MDA5-DM-ILD. **b** Case 2 at the onset of MDA5-DM-ILD. **c** Case 2 at the development of pneumothorax and pneumomediastinum. **d** Case 3 at the onset of MDA5-DM-ILD. **e** Case 3 at the development of pneumothorax and pneumomediastinum. **f** Case 4 at the onset of MDA5-DM-ILD.

HLA-matched related donor (Table 1). Three months later, she was complicated with moderate bronchiolitis obliterans, and was given a treatment with inhaled corticosteroid, long-acting beta agonist and long-acting muscarinic antagonist. Since a copy number of RUNX1-RUNX1T1 was increased 22 months after allo-HCT, she received 3 times of donor lymphocyte infusion. However, she developed extramedullary mass of AML in front of chest and the right upper lobe of lung 3 years after allo-HCT. She was treated with radiotherapy, 1 cycle of high-dose Ara-C and 1 cycle of a combination therapy with Ara-C, aclarubicin and gemtuzumab ozogamicin. She achieved CR state and underwent the second allo-HCT from an HLA-matched unrelated donor (Table 1).

She developed hepatic and mucosal chronic GVHD 6 months after the second allo-HCT, while a copy number of RUNX1-RUNX1T1 increased 7 months after the second allo-HCT. Eight months later from the second allo-HCT, she suffered from cough and skin rashes of fingers and face, and respiratory dysfunction with 1–2 L/min of oxygen demand. Lung CT showed bilateral sporadic GGO and she tested positive for anti-MDA5 antibody, resulting in the start of 10 mg/day of PSL (Fig. 1b). At the same time, she was hospitalized at our center due to the regrowth of extramedullary mass of AML in a lumbar spine. A treatment for AML preceded an intervention for MDA5-DM-ILD, and she received radiotherapy for extramedullary mass. After the completion of radiotherapy, a treatment for ILD was commenced. Due to a concern of AML recurrence, an intensive immunosuppressive therapy was avoided. On the day 24 of the admission, an intervention by 1 mg/kg of PSL and cyclosporine was commenced, and her respiratory condition was slightly improved. However, she developed pressing feeling in chest 49 days after the admission, and lung CT on the day 53 revealed pneumothorax on the right chest and pneumomediastinum (PNM) (Fig. 1c). Her respiratory condition gradually deteriorated and CT scan on the day 71 after the admission showed exacerbation of the pneumothorax. She was treated with CY with 500 mg/m² on the day 75 and with 750 mg/m² on the day 89 after the admission, but her respiratory condition had not been improved. Although she received surgical drainage of mediastinum for reducing mass effect of PNM on the day 92 of the admission, her respiratory condition became worse, leading to intubation and transfer to ICU. Her respiratory condition

was further exacerbated and veno-venous extracorporeal membrane oxygenation was initiated. An additional dose of 1000 mg/m² of CY was administrated 103 and 117 days after the admission. However, her respiratory condition was not improved and she died on the day 131 after the admission (Table 2).

Case 3

A 33-year-old male was diagnosed as AML with KMT2A-MLL1 and was treated with idarubicin/Ara-C followed by 3 cycles of high-dose Ara-C. After the chemotherapy, he achieved CR state, and underwent allo-HCT from an HLA-matched related donor (Table 1). Although he developed skin acute GVHD 25 days after allo-HCT, GVHD was rapidly improved with topical steroid. He developed infectious pneumonia 6 months after allo-HCT, and was treated with antibiotics for 2 weeks. Since he was also complicated with organizing pneumonia and lung CT showed patchy GGO, 0.5 mg/kg of PSL was also added and subsequently tapered gradually.

He suffered from dyspnea 7 months after allo-HCT, and lung CT after 8 months revealed an exacerbation of bilateral GGO (Fig. 1d). He showed mild respiratory dysfunction with peripheral capillary hemoglobin oxygen saturation 94–95% at room air, and needed 2–4 L/min of oxygen supplementation. At the same time, he revealed to test positive for anti-MDA5 antibody, and cyclosporine was increased from 10 mg/day to 150 mg/day. He did not experience skin rash lesion. One week later, he was hospitalized at our center for the treatment of MDA5-DM-ILD with steroid pulse therapy. After the completion of steroid pulse, he was treated with 7 doses of CY as following: 500 mg/m² on day 7, 750 mg/m² on day 23, 1000 mg/m² on days 37 and 51, 500 mg/m² on days 76, 92 and 134 of the admission. Due to nausea and liver enzyme elevation, the dose of 5–7th CY was reduced. Although his respiratory condition was gradually improved after the second administration of CY, CT scan revealed PNM on day 15 and pneumothorax on the right chest on day 49 of the admission. Since he developed right chest pain and exacerbation of dyspnea and pneumothorax (Fig. 1e), he received surgical drainage of the right chest on the day 58 of the admission. After the operation, his respiratory condition was improved, although he needed oxygen supplementation of 1 L/min at a rest and 1–2 L/min at an effort. He initiated home oxygen therapy and discharged at the day 136 of

Table 2. Summary of MDA5-DM-ILD.

	Onset	Preceding event	CT findings	Respiratory condition at the onset	Treatment	Outcome
Case 1	15 months from allo-HCT	Exacerbation of chronic GVHD	Bilateral GGO	SpO2 57% (RA), RR 21/min, immediately intubated.	PSL/CY/TAC/TOF	Died
Case 2	8 months from 2nd allo-HCT	Exacerbation of chronic GVHD and AML relapse	Bilateral GGO, pneumothorax and PNM	SpO2 91% (RA), RR 24/min	PSL/CY/CsA	Died
Case 3	8 months from allo-HCT	Pneumonia	Bilateral GGO, pneumothorax and PNM	SpO2 92% (RA), RR 30/min	PSL/CY/CsA	Alive
Case 4	4 months from allo-HCT	Termination of CsA	Bilateral GGO	SpO2 92% (RA), RR 20/min	PSL/CY/CsA	Died

MDA5-DM-ILD melanoma differentiation-associated gene 5 dermatomyositis interstitial lung disease, allo-HCT allogeneic hematopoietic stem cell transplantation, GVHD graft-versus-host disease, AML acute myeloid leukemia, CT computed tomography, GGO ground glass opacity, PNM pneumomediastinum, SpO2 peripheral capillary hemoglobin oxygen saturation, RA room air, RR respiratory ratio, PSL prednisolone, CY cyclophosphamide, TAC tacrolimus, TOF tofacitinib, CsA cyclosporin A.

the admission. However, two months after the discharge, he re-suffered from dyspnea and was admitted to our center. His respiratory condition gradually deteriorated. He is now planned to undergo lung transplantation (Table 2).

Case 4

A 51-year-old male was diagnosed as AML with RUNX1-RUNX1T1 and treated with idarubicin/Ara-C as induction therapy followed by 3 cycles of high-dose Ara-C. However, AML recurred 6 months after the completion of chemotherapy. Although he had been treated with 1 cycle of high-dose Ara-C and 1 cycle of combination therapy with Ara-C and gemtuzumab ozogamicin, he did not achieve CR state after these treatments. He was additionally treated with a standard-dose of AraC as a cyto-reductive therapy and subsequently received a conditioning regimen including BU and CY, followed by allo-HCT from an HLA-matched unrelated donor (Table 1). A bone marrow aspiration on day 27 revealed that he achieved molecular CR. Although he was complicated with skin acute GVHD on 28 days after allo-HCT, GVHD was gradually improved with topical steroid. His cyclosporine was discontinued on the day 113.

He suffered from dyspnea 4 months after allo-HCT, and lung CT revealed an exacerbation of bilateral GGO (Fig. 1f). He showed mild to moderate respiratory dysfunction with 92% of peripheral capillary hemoglobin oxygen saturation at room air. He did not demonstrate definite skin rash lesions. Although he was given a treatment with a broad-spectrum antibiotic, his respiratory condition was not improved. Therefore, PSL 1 mg/kg was administered from the day 3 of the admission. On the day 6, he revealed to test positive for anti-MDA5 antibody. Based on the detection, a combination therapy of steroid, cyclosporine and CY was commenced immediately. CY was administered as following: 500 mg/m² on day 7, 1000 mg/m² on day 15, and 500 mg/m² on days 29 and 43 of the admission. Since his respiratory state deteriorated drastically, steroid pulse therapy (methyl-PSL 1 g/day for 3 days) was also added on day 16 and day 29. Despite the combination therapy, his respiratory condition deteriorated, leading to an intubation and transfer to ICU on day 29. He died on day 51 of the admission.

Serological findings of the MDA5-DM-ILD cases

We additionally measured anti-MDA5 antibody with cryopreserved plasma of the 4 cases at several time points during the clinical courses (Fig. 2). The higher titers of anti-MDA5 antibody than the upper limit was detected in Cases 1 and 2. Anti-MDA5 antibody had been detected 43–99 days before the diagnosis of their ILD in all of the cases except Case 4. After the commencement of treatment, the titer of anti-MDA5 antibody had declined in Case 3 and Case 4. Although the titers of anti-MDA5 antibody might have declined also in Case 1 and Case 2, the tendency was not evaluated due to the considerably high titers of the 2 cases.

In addition, we experienced 3 cases of MDA5-DM-ILD in 2021, whereas there was only 1 case before 2020 at our center. Considering about the reason about the incidence, COVID-19 pandemic is one of differences between the periods before and after 2020. Therefore, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) IgG was also measured using cryopreserved plasma at the diagnosis of MDA5-DM-ILD for the purpose of exploring the association between the detection of anti-MDA5 antibody and the viral pandemic. Case 4 showed a positive result of SARS-CoV-2 IgG, while the other two cases tested negative. Case 4 had not developed any definite symptoms related to COVID-19 during the whole clinical course.

DISCUSSION

MDA5-DM is one of rare but distinct subtype of clinically amyopathic DM which is predominantly observed in east Asia

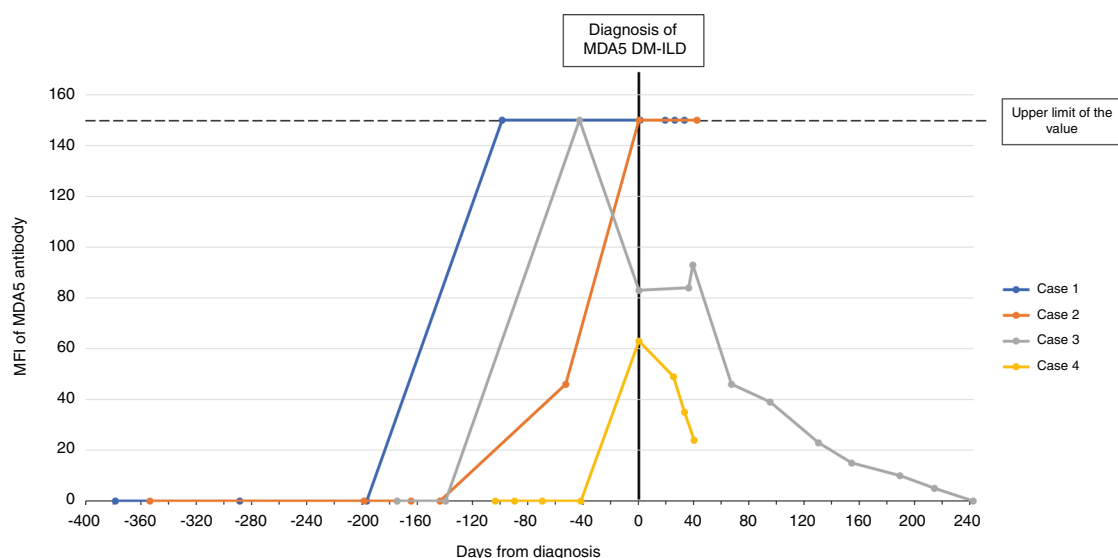


Fig. 2 Clinical course of anti-MDA5 antibody.

[13]. Clinical features of this disease entity include distinctive mucocutaneous lesion, ILD, arthritis, fever, hand swelling and PNM [20]. ILD due to MDA5-DM is generally rapidly progressive and the survival prognosis is unfavorable despite various intensive immunosuppressive therapies [14, 15, 21, 22]. Radiological findings of MDA5-DM-ILD have not been fully elucidated. One of previous studies reported that majority of MDA5-DM-ILD patients showed an unclassifiable pattern which was a mixture of consolidation and GGO [23], while another study reported that 74.2% of MDA5-DM-ILD showed an organizing pneumonia pattern [24]. PNM was also a unique radiological finding of MDA5-DM-ILD, and the prognosis of MDA5-DM-ILD with PNM was unfavorable (1y-OS 40%) [25]. Although an appropriate risk stratification and treatment are important to overcome the inferior prognosis, treatment strategies are mainly based on clinical experiences and expert opinions due to the paucity of clinical evidence [26]. In Japan, “triple therapy” is a widely accepted treatment for MDA5-DM-ILD which includes high-dose glucocorticoid, tacrolimus and cyclophosphamide [16]. The combination therapy showed significantly the higher 6-months survival rate than control group (89% vs 33%, $P < 0.001$).

All of the 4 cases in this study showed rapidly progressive clinical courses and 3 of them died within 5 months despite the intensive immunosuppressive therapy. Their main radiological findings were GGO and PNM. Two of 4 cases showed skin rashes, while no case developed typical mucocutaneous ulcer. Overlap of skin chronic GVHD might make it difficult to distinguish DM related skin lesion from GVHD. Since the current study was based on retrospective review of clinical charts, actual findings of skin lesions could not be confirmed. All of the 4 cases were treated with a combination treatment including high-dose corticosteroid, calcineurin inhibitor and cyclophosphamide based on the previous study [16]. In case 1, tofacitinib, a JAK inhibitor, was additionally administered due to refractoriness to the combination therapy [27]. Clinical features of MDA5-DM-ILD after allo-HCT in this study was relatively comparable with classical MDA5-DM-ILD except skin involvement and more rapid progression of ILD. Since a previous study of MDA5-DM after allo-HCT by dermatologists showed typical skin lesion such as pad inflammation, palmar violaceous papules and digital ulcerations [18], the lack of detail cutaneous examination might be a reason of discrepancy between the current and previous reports. The clinical course of MDA5-DM-ILD seems to be more aggressive than other pulmonary complications after allo-HCT. Moreover, MDA5-DM-ILD after

allo-HCT also seems to be more rapidly progressive than de novo MDA5-DM-ILD. Therefore, it is important to distinguish MDA5 DM-ILD from other complications.

MDA5 is a member of retinoic acid inducible gene I like receptors which is binding with viral RNAs. When a viral infection occurs, viral RNAs trigger MDA5. Activated MDA 5 interact with the adaptor mitochondrial antiviral signaling protein, leading to the transcription of the genes encoding type I interferons [28]. Since MDA5 acts as a receptor of viral RNAs, preceding infection might be one of the causes of MDA5-DM. Seasonal and residential clustering of the disease supports this hypothesis [29, 30]. Case 3 in this study developed pneumonia before MDA5-DM-ILD, and it might have affected the occurrence of MDA5-DM-ILD. Additionally, SARS-CoV-2 might be a trigger of MDA5-DM-ILD. SARS-CoV-2 is detected by MDA5 and induces subsequent interferon responses [31–33]. A similarity of clinical features between MDA5-DM-ILD and COVID-19 also suggests a relationship between these diseases [34–36]. Since Case 4 tested positive for SARS-CoV-2 IgG, asymptomatic SARS-CoV-2 infection might have affected the incidence of MDA5-DM-ILD in the case. Moreover, cellular RNAs also trigger MDA5 in several settings such as autoinflammatory diseases and cancer treatments [28]. Auto-/allo-immune pathogenesis of chronic GVHD might affect the occurrence of MDA5-DM after allo-HCT.

Human leukocyte antigen (HLA) is another factor which might be related with the incidence of MDA5-DM-ILD. In a Japanese cohort study, HLA-DRB1* 01:01 and DRB1* 04:05 were reported to be associated with susceptibility to MDA5-DM-ILD [37]. Since these HLA alleles are frequently observed in Japanese population, it might be a reason why MDA5-DM is often seen in East Asia. Case 3 in this study also had the allele of HLA-DRB1* 04:05, which might be associated with the occurrence of MDA5-DM-ILD.

In addition to the diagnosis, anti-MDA5 antibody might be utilized for monitoring MDA5-DM-ILD. Although titers of anti-MDA5 antibody at a diagnosis were not associated with severity of MDA5-DM-ILD [38], titers of the antibody after treatments were correlated with survival and relapse of ILD [39]. In our case series, 2 of 4 cases showed declining titers of anti-MDA5 antibody, and 1 case has still been alive despite the severe respiratory failure. Moreover, 3 of 4 cases had tested positive for anti-MDA5 antibody about 2–3 months before the diagnosis of MDA5-DM-ILD. Since Case 2 and 3 were complicated with bronchiolitis obliterans or infectious pneumonia, these pulmonary complications might have

made it difficult to distinguish MDA5-DM-ILD from other pulmonary diseases. However, Case 1 had not shown any definite pulmonary complications before the development of MDA5-DM-ILD. Therefore, it suggests that an inflammatory condition due to MDA5-DM-ILD might have sub-clinically occurred before the development of respiratory failure.

In conclusion, we experienced 4 cases of MDA5-DM-ILD. All cases showed rapidly progressive clinical course, and 3 of them died within very short duration despite the intensive immunosuppressive therapy. The clinical feature was relatively similar to classical MDA5-DM-ILD, although it is difficult to distinguish MDA5-DM-ILD from the other immune and infectious pulmonary complications after allo-HCT. Since clinical courses of MDA5-DM-ILD is considerably aggressive, it is important to discriminate MDA5-DM-ILD from other complications after allo-HCT.

DATA AVAILABILITY

Please contact the corresponding author or Masaharu Tamaki (Division of hematology, Jichi Medical University Saitama Medical Center. E-mail: m.tamaki.221@gmail.com).

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AUTHOR CONTRIBUTIONS

MT and SM conceived the original idea and collected the data. MT wrote the manuscript. HN and YK advised on methods and wrote the manuscript. YN, MK, S.Kawamura, JT, NY, YM, KY, AG, AT, YO, MK and KK collected the data. SIK and SKako collected the data and contributed to critical revision of the manuscript. All authors approved the final version of the manuscript.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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