CASE REPORT

Anti-transcription intermediary factor 1 gamma (TIF1γ) antibody-positive dermatomyositis associated with ascending colon cancer: a case report and review of the literature

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Abstract

Background: Anti-transcriptional intermediary factor 1 gamma (TIF1γ) antibody is a marker for predicting cancer association in patients with dermatomyositis (DM). The overall survival rate in DM patients with cancer was reported to be considerably worse than that in DM patients without cancer. However, the treatment for cancer-associated DM remains controversial, because the treatment priority between surgical resection for the tumor and internal treatments, including glucocorticoids, immunosuppressive agents, and intravenous immune globulin, has not been established.

Case presentation: We report the case of a 57-year-old Japanese man diagnosed with anti-TIF1γ antibody-positive DM associated with ascending colon cancer. His clinical symptoms included facial and brachial edema, muscle weakness, dysphagia, myalgia, and rash. Physical examination revealed peri-orbital edema and Gottron's papules over his knuckles with brachial edema, and tenderness and weakness of the proximal limb muscles. The findings of hyper-intense muscles in T2-weighted sequences of brachial contrast-enhanced magnetic resonance imaging and the infiltration of lymphocytic cells and CD4-positive lymphocytes from muscle biopsy were compatible with the diagnostic criteria for dermatomyositis. Anti-TIF1γ antibody was positive by immunoprecipitation assay. He first started internal treatment including intravenous immunoglobulin, steroid pulse, prednisolone, and azathioprine, followed by surgical resection for the tumor because of the elevation of creatine kinase and progression of dysphagia. However, clinical symptoms did not improve, and the patient died 6 months later.

Conclusions: We faced difficulties in determining the treatment priority between surgical resection and internal treatment for our case; therefore, this case would be educational for readers. We searched PubMed to identify English-language case reports of anti-TIF1γ antibody-positive dermatomyositis with malignancy and found 21 reported cases. We herein review and summarize previously reported cases of anti-TIF1γ antibody-positive DM with malignancy. Cancer screening is essential in patients with anti-TIF1γ antibody-positive dermatomyositis because it is associated

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Background
Dermatomyositis (DM) is an inflammatory myopathy characterized by skin rash and progressive, symmetrical weakness of the proximal muscles [1, 2]. DM has been shown to be associated with malignant disease [3]. The overall survival rate in DM patients with cancer was found to be considerably worse than that in DM patients without cancer [4]. Recently, an anti-transcriptional intermediary factor 1 gamma (TIF1γ) antibody was reported as a marker for predicting cancer association in patients with DM, since TIF1γ, which regulates the tumor growth factor pathway, has been reported to be associated with tumor growth in some malignancies [5]. In a meta-analysis, Trallero-Araguas et al. reported that the pooled sensitivity of anti-TIF1γ antibody for diagnosing cancer-associated DM was 78%, whereas specificity was 89% [6]. The treatment for cancer-associated DM remains controversial, because the treatment priority between surgical resection for the tumor and internal treatments, including glucocorticoids, immunosuppressive agents, and intravenous immune globulin, has not been established. We searched PubMed to identify English-language case reports of anti-TIF1γ antibody-positive dermatomyositis with malignancy and found 21 reported cases [7–27]. Herein, we report a case of anti-TIF1γ antibody-positive dermatomyositis associated with ascending colon cancer; previously reported cases of anti-TIF1γ antibody-positive dermatomyositis with malignancy are reviewed and summarized. This case may provide a unique perspective for readers and illustrate the difficulties in determining treatment priority between surgical resection and internal treatment.

Case presentation
A 57-year-old Japanese man presented with a 1-month history of progressive symptoms of facial and brachial edema, muscle weakness, dysphagia, myalgia, and a symmetrical widespread rash on his limbs and hands. He denied recent common cold symptoms. He was also noted to have unintentional weight loss (3 kg over 1 month). His medical and family histories were unremarkable. He was diagnosed with type 2 diabetes mellitus 8 years ago, but he did not go to the hospital until this visit. Vital signs showed that the patient was afebrile, with a heart rate of 90 beats per minute, blood pressure of 120/78 mmHg, normal respiratory rate, and oxygen saturation of 99% on room air. Physical examination revealed periorbital edema (Fig. 1a) and Gottron's papules over his knuckles (Fig. 1b) with brachial edema, and tenderness and weakness of the proximal limb muscles. Laboratory evaluation revealed elevated levels of creatine kinase (5002 U/L; reference range 30–175 U/L), aspartate transaminase (120 U/L; reference range, 12–35 U/L), alanine aminotransferase (46 U/L; reference range 6–40 U/L), lactate dehydrogenase (440 U/L; reference range 119–229 U/L), D-dimer (9.1 μg/mL; reference range <1.0 μg/mL), and hemoglobin A1c (9.2%; reference range 4.6–6.2 %); however, white blood count, C-reactive protein, hemoglobin, electrolytes, lipid profile, and renal function were normal. Hepatitis B and C, and HIV serologies were all negative. Chest radiography showed no consolidation. Respiratory function tests, electrocardiogram, and echocardiogram were unremarkable. Because of the history and significantly elevated muscle injury biomarkers, we suspected inflammatory myositis. The patient underwent further evaluation to investigate the probable diagnosis.

Additional laboratory data demonstrated that antinuclear antibody was positive at 1:40 with a speckled pattern and a high prevalence of malignancies. Our review revealed that initial surgical treatment should be recommended for better prognosis if the general condition allows.

Keywords: Dermatomyositis, Anti-transcription intermediary factor 1 gamma, Anti-TIF1γ antibody, Cancer, Malignancy

Fig. 1 Physical examination revealed periorbital edema (a) and Gottron's papules over his knuckles (b)
pattern. In addition, anti-TIF1γ antibody was positive by immunoprecipitation assay, although other markers including anti-aminocyl-tRNA synthetase, anti-melanoma differentiation-associated gene 5 antibody, and anti-Mi2 antibody were negative. Brachial contrast-enhanced magnetic resonance imaging (MRI) demonstrated hyperintense muscles in T2-weighted sequences (Fig. 2). A biopsy from the biceps brachii muscle was performed, and the infiltration of lymphocytic cells and CD4-positive lymphocytes was confirmed (Fig. 3). These findings were compatible with dermatomyositis. Since anti-TIF1γ antibody has been associated with malignancies in dermatomyositis patients, we performed a whole contrast computed tomography scan and endoscopy. Contrast computed tomography showed a tumor mass in the ascending colon with no other notable metastases (Fig. 4a). Colonoscopy revealed an ascending colon tumor (Fig. 4b). The histopathological findings of the biopsy from the ascending colon showed well-differentiated tubular adenocarcinoma (Fig. 5). A diagnosis of anti-TIF1γ antibody-positive dermatomyositis with ascending colon cancer (cT4aN2M0, clinical stage IIIb) was made.

The clinical course is shown in Fig. 6. He was initially scheduled to undergo surgical resection for the ascending colon cancer after the definitive diagnosis; however, elevation of creatine kinase (15,667 U/L) and progression of dysphagia were noted before the operation. Thus, we decided that medical treatment should be performed first. Subsequently, intravenous immunoglobulin (IVIG) and 1 mg/kg of prednisolone with slow tapering of the dose was started from day 40, and the level of creatine kinase decreased significantly. However, his dysphagia did not improve, and creatine kinase was elevated again on day 57. Thus, 1 g/day of methylprednisolone (mPSL) for three consecutive days was administered from day 58. After the second cycle of IVIG (on day 75) and steroid pulse therapy (on day 81), 50 mg/day of azathioprine was started on day 97 because creatine kinase was decreased but the dysphagia persisted. As the patient’s condition had deteriorated, manual muscle testing of his limb was

Fig. 2  Brachial contrast-enhanced magnetic resonance imaging demonstrated hyperintense muscles in T2-weighted sequences.

Fig. 3  a Hematoxylin and eosin stain (x40 magnification) of the muscle showing the infiltration of lymphocytic cells. b CD4 antibody staining (x100 magnification) and c CD8 antibody staining (x100 magnification) confirmed the predominant presence of CD4-positive lymphocytes.
grade 2 out of 5, and medical treatment was considered ineffective, PSL was increased from 15 to 20 mg per day and surgery including right hemicolectomy, gastrostomy, and tracheostomy was performed on day 124.

After surgery, the patient was almost bedridden due to disuse syndrome despite continuous rehabilitation. Fever was noted on day 146, and broad-spectrum antibiotic therapy was not effective. Further investigation revealed positive serum cytomegalovirus antigen levels. Administration of ganciclovir 300 mg/day was initiated, but further complication of melena was noted. Gastroscopy was performed and showed cytomegalovirus esophagitis (Fig. 7). The patient died 6 months later (204 days) after hospitalization due to the progression of uncontrollable infection.

**Discussion**

The prevalence of malignancy in patients with dermatomyositis is estimated at approximately 20–30% [28]. An anti-TIF1γ antibody associated with malignancy has been identified in dermatomyositis [7]. This antibody is confirmed in approximately 20% of adult patients with dermatomyositis, and 60% to 90% of these patients have malignant disease [6, 28]. The treatment order for cancer-associated DM has not been established, especially whether internal treatment or surgical resection should occur first. To our knowledge, this is the first reported case of anti-TIF1γ antibody-positive dermatomyositis associated with colon cancer.

The major clinical features of the 21 previously reported cases of anti-TIF1γ antibody-positive dermatomyositis associated with cancer and our case are summarized in Table 1 [7–27]. We also investigated the relationship between outcome and treatment, since we faced difficulties in determining the treatment priority between surgical resection and internal treatment. The mean age (± standard deviation) of the population was 63.7 ± 13.7 years (range, 22–83 years), of whom 12 were male and 10 were female. The most common presenting symptom was rash (86%), followed by muscle weakness (50%), dysphagia (45%), facial edema (14%), and myalgia (14%). Although all cases were associated with concurrent DM and cancer, initial diagnosis of DM (68%) was more prevalent than that of cancer (32%). Most of the cases were single cancer; however, two cases of double...
cancer and one case of triple cancer were noted. The types of cancer included lung ($n=7$), breast ($n=5$), gastric ($n=5$), colon ($n=1$), esophageal ($n=1$), urothelial ($n=1$), pancreatic ($n=1$), thyroid ($n=1$), thymic ($n=1$), ovarian ($n=1$ case), extragonadal germ cell tumor ($n=1$), and myelodysplastic syndrome ($n=1$). Creatine kinase values differed widely. Our case reported the maximum value of creatine kinase (15,667 U/L) among all cases in the literature. The option for treatment showed surgical treatment to internal treatment in five cases, whereas the opposite was true in seven cases. Internal treatment only was performed in nine cases, and surgical treatment only was performed in one case. Regarding response to internal treatment, “partial response” was defined as temporary remission of the symptoms and creatine kinase level only to worsen later. “No response” was defined as progressive symptoms over time. Remission was noted in five cases and partial response was observed in eight cases, while seven cases showed no response to the internal treatment.

As for treatment for DM, systemic steroid therapy is considered the gold standard. Oral prednisolone at an initial dose of 0.5–1 mg/kg/day followed by a slow progressive dose reduction is recommended. In patients with severe disease, steroid pulse of intravenous mPSL 1000 mg for three consecutive days is also an option for treatment. In addition, the introduction of IVIG or immunosuppressive medications such as methotrexate, azathioprine, cyclophosphamide, or ciclosporin is another option if the patient does not respond to steroid therapy or suffers adverse side effects [9, 29]. Although these internal treatments are essential for the control of DM, the risk of surgical treatment will increase due to the immunocompromised effect. Since tapering of the prednisolone dose takes a relatively long time, the timing of surgery before or after internal treatment is important. In our case, surgical treatment was delayed due to uncontrollable dysphagia and long-term use of steroid therapy. The treatment for cancer in the case reports included surgical resection and chemoradiotherapy. Immune checkpoint inhibitors such as nivolumab and ipilimumab were reported in three cases [22, 23, 26]. One report noted that only surgical removal of the tumor resulted in the disappearance of the skin rash of DM [15].
| Case | Reference/Year | Author | Age (years) | Sex | Chief complaint | Initial diagnosis | Cancer type | Initial CK (U/L) | Order for treatment | Treatment | Response to internal treatment | Outcome from the diagnosis of DM |
|------|----------------|--------|-------------|-----|-----------------|-----------------|-------------|----------------|------------------|-----------|-------------------------------|----------------------------------|
| 1    | [7], 2013      | Ito    | 59          | M   | Rash            | DM              | Gastric cancer IgG4-positive pulmonary inflammatory pseudotumor | 97              | Surgical to internal treatment | Surgical resection (stomach resection and right lower lobectomy) Prednisolone | Remission | Alive but no detailed described |
| 2    | [8], 2016      | Ogawa  | 63          | F   | Facial edema    | Cancer          | Breast cancer | 2326            | Surgical to internal treatment | Surgical resection (partial excision of left breast) Chemoradiotherapy Tacrolimus Prednisolone | ND       | Alive at 11 months             |
| 3    | [9], 2016      | Kubecek| 43          | M   | Fever Fatigue Myalgia Dysphagia Rash | DM              | Breast cancer | 1574            | Internal treatment | Steroid pulse Prednisolone Chemoradiotherapy | No response | ND                              |
| 4    | [10], 2016     | Taki   | 22          | M   | Rash            | DM              | Extragonadal germ cell tumor | Normal         | Internal to surgical treatment | Prednisolone Chemoradiotherapy Surgical resection (tumor resection, left orchectomy and retroperitoneal lymph node dissection) | Partial response | Alive at 7 months               |
| 5    | [11], 2016     | Murase | 73          | M   | Rash Muscle weakness Dysphagia | DM              | Gastric cancer | 1266            | Internal treatment | Prednisolone chemotherapy | No response | Dead after 95 days              |
| 6    | [12], 2017     | Matsushita | 66      | F   | Dysphagia Muscle weakness Rash | Cancer          | Breast cancer | 864             | Internal to surgical treatment | Prednisolone | No response | Dead after few months          |
Table 1 (continued)

| Case | Reference/Year | Author | Age (years) | Sex | Chief complaint | Initial diagnosis | Cancer type | Initial CK (U/L) (Maximum value if noted) | Order for treatment | Treatment | Response to internal treatment | Outcome from the diagnosis of DM |
|------|----------------|--------|-------------|-----|----------------|------------------|-------------|------------------------------------------|---------------------|-----------|-------------------------------|--------------------------------|
| 7    | [13], 2017     | Palterer | 78          | F   | Muscle weakness | DM               | Myelodysplastic syndrome | 56          | Internal treatment               | Steroid pulse, IVIG, Methotrexate, Prednisolone | Partial response | Dead after 1 year              |
| 8    | [14], 2017     | Kikuchi  | 69          | F   | Rash            | DM               | Papillary thyroid cancer, Breast cancer, Gastric cancer | 536         | Internal to surgical treatment   | Prednisolone, Surgical resection (Thyroid gland, cervical lymph node, left breast, total stomach and gallbladder resection) | Partial response | Dead after 18 months           |
| 9    | [15], 2017     | Schiffmann | 64           | F   | Rash            | Cancer           | Gastric cancer | Normal                                   | Surgical resection (stomach resection) | NA         | Alive at least 2 months later  |
| 10   | [16], 2018     | Karino   | 72          | M   | Rash            | DM               | Thymic carcinoma | 1576         | Surgical to internal treatment      | Surgical resection (thymus resection), Prednisolone | Remission   | Alive at least 1 year later    |
### Table 1 (continued)

| Case | Reference/Year | Author | Age (years) | Sex | Chief complaint | Initial diagnosis | Cancer type | Initial CK (U/L) (Maximum value if noted) | Order for treatment | Treatment | Response to internal treatment | Outcome from the diagnosis of DM |
|------|----------------|--------|-------------|-----|-----------------|------------------|-------------|----------------------------------------|---------------------|-----------|---------------------------------|----------------------------------|
| 11   | [17], 2018     | Teraishi | 42          | F   | Rash, Muscle weakness | DM              | Breast cancer (1st) Ovarian cancer (2nd) | 500 (1st) 232 (2nd) | Surgical to internal treatment (1st) Internal to surgical treatment (2nd) | Chemotherapy | Prednisolone (1st) Chemotherapy | Remission (1st) Remission (2nd) | Alive at 8 years (1st) Alive at least 5 months later (2nd) |
| 12   | [18], 2019     | Aritomi | 63          | F   | Cough, Hoarseness | Cancer | Small cell lung cancer | 3272 | Internal treatment | Chemotherapy | Prednisolone (2nd) | No response | Dead after a few months |
| 13   | [19], 2019     | Kato    | 68          | F   | Rash             | DM              | Small cell lung cancer | 252 | Internal to surgical treatment | Chemotherapy | Prednisolone (2nd) | Partial response | ND |
| 14   | [20], 2019     | Saraya  | 58          | M   | Rash, Cough, Muscle weakness, Dysphagia | DM              | Lung adenocarcinoma | 7833 | Internal treatment | Prednisolone Chemoradiotherapy | No response | Dead after 6 months |
| Case | Reference/Year | Author | Age (years) | Sex | Chief complaint | Initial diagnosis | Cancer type | Initial CK (U/L) (Maximum value if noted) | Order for treatment | Treatment | Response to internal treatment | Outcome from the diagnosis of DM |
|------|----------------|--------|-------------|-----|-----------------|------------------|-------------|----------------------------------------|-------------------|----------|-------------------------------|--------------------------------|
| 15   | [21], 2019     | Varedi | 65          | F   | Myalgia, Dysphagia, Rash | DM | Pancreatic neuroendocrine tumor | Normal | Internal treatment | Mycophenolate mofetil, Hydroxychloroquine, Prednisolone, Methotrexate, Tacrolimus, ointment, Surgical resection (pancreas resection) | Remission | Alive at 2 months |
| 16   | [22], 2019     | Shibata| 71          | M   | Rash, Dysphagia | Cancer | Gastric cancer | 300 (>1000) | Internal treatment | Chemotherapy (Nivolumab, Prednisolone, Steroid pulse, MG), Tacrolimus, Surgical resection (cystoprostatectomy and right ureteronephrectomy) | No response | Dead after 142 days |
| 17   | [23], 2020     | Zarkavelis | 72 | M | Muscle weakness, Rash | Cancer | Urothelial carcinoma | 1025 | Surgical to internal treatment | Ipilimumab, Nivolumab, Prednisolone, MG, Tacrolimus, Surgical resection (cystoprostatectomy and right ureteronephrectomy) | Remission | Alive at least 5 months later |
| 18   | [24], 2020     | Nakanishi | 80 | F | Dyspnea, Dysphagia, Muscle weakness | DM | Lymphoepithelioma-like carcinoma | 268 | Internal treatment | Steroid pulse, Prednisolone, Radiotherapy | Partial response | Alive at least 6 months later |
| 19   | [25], 2020     | Kuczmarka-Haas | 83 | M | Rash, Muscle weakness, Dysphagia | DM | Small cell lung cancer | ND | Internal treatment | Prednisolone MG, Radiotherapy | Partial response | Alive at least 6 months later |
| Case | Reference/Year | Author | Age (years) | Sex | Chief complaint       | Initial diagnosis | Cancer type | Initial CK (U/L) (Maximum value if noted) | Order for treatment | Treatment | Treatment Response to internal treatment | Outcome from the diagnosis of DM |
|------|----------------|--------|-------------|-----|-----------------------|------------------|-------------|---------------------------------------|---------------------|-----------|----------------------------------------|----------------------------------|
| 20   | [26], 2020     | Osaki  | 64          | M   | Rash, Muscle weakness | Cancer           | Lung adenocarcinoma | 6381 | Internal treatment                     | Nivolumab Chemotherapy, Prednisolone MG | Prednisolone | No response                          | Dead after 6 months               |
| 21   | [27], 2020     | Sumazaki | 70          | M   | Muscle weakness, Myalgia, Rash | DM               | Esophageal cancer | 6727 | Internal to surgical treatment        | IVIG | Surgical resection (esophagectomy with 2-field lymph node dissection) Prednisolone | Partial response                     | Dead after 3 year               |
| 22   | 2020           | Ono    | 57          | M   | Facial edema, Brachial edema, Muscle weakness, Dysphagia, Myalgia, Rash | DM               | Ascending colon cancer | 5002 (15,667) | Internal to surgical treatment | MG Steroid pulse, Prednisolone Azathioprine Surgical resection (right hemicolectomy, gastrostomy, and tracheostomy) | Partial response | Dead after 6 months |

CK creatine kinase, DM dermatomyositis, F female, IgG4 immunoglobulin G4, IVIG intravenous immunoglobulin, M male, NA not applicable, ND not described
The outcomes revealed that half of the patients were alive while the others had died. We further investigated the relationship between outcome and dysphagia, initial treatment, and maximum creatine kinase values. Table 2 demonstrates this relationship. First, dysphagia is a major complication of DM because it leads to oral feeding difficulties and malnutrition [22]. Table 2 (a) shows the relationship between dysphagia and outcome; no significant difference \((P=0.12; \text{Pearson's chi-square test})\) was noted between them, although the presence of dysphagia tended to be associated with a worse outcome. Table 2 (b) shows the relationship between initial treatment and outcome. Of note, initial surgical treatment led to better outcomes \((P=0.0007; \text{Pearson's chi-square test})\). However, interpretation must consider potential bias, as patients who are able to undergo surgery may have better general condition. In fact, patients with early-stage disease could firstly undergo surgery according to the cancer stage in Table 1. Conversely, the patients with initial internal treatment include unresectable cancers, in which surgical resection itself is not applicable at the point of diagnosis \([9, 13, 20, 22, 24, 26]\). Table 2 (c) shows the relationship between the maximum creatine kinase level and outcome. In all four cases where the level was greater than 5000 U/L, the patients died \((P=0.033; \text{Pearson's chi-square test})\). Lastly, the relationship between response to internal treatment and outcome is shown in Table 2 (d). In five of the cases with remission, the patients were alive, and in the group with no response, six patients had died. Among those with partial response, three patients were alive and four had died. These results suggest that a response to internal treatment is needed for lifesaving results.

### Conclusions

In conclusion, we reviewed and summarized previously reported cases of anti-TIF1γ antibody-positive DM with malignancy. Cancer screening is essential in patients with anti-TIF1γ antibody-positive dermatomyositis because it is associated with a high prevalence of malignancies. Our review revealed that initial surgical treatment should be recommended for better prognosis if the general condition allows.

### Abbreviations

DM: Dermatomyositis; MG: Intravenous immunoglobulin; TIF1γ: Transcriptional intermediary factor 1 gamma; mPSL: Methylprednisolone; MRI: Magnetic resonance imaging.

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### Authors’ contributions

RO was a major contributor to the writing of the manuscript and patient management. TK, MI and MY contributed to patient management. TM and KI critically revised the report and approved the final report. All authors read and approved the final manuscript.

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### Availability of data and materials

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### Ethics approval and consent to participate

Not applicable.

### Consent for publication

Written informed consent was obtained from the patient’s next of kin for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

### Competing interests

The authors state that they have no conflicts of interest.

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### Table 2

|             | Dysphagia (+) | Dysphagia (−) |
|-------------|---------------|---------------|
| Alive       | 3             | 7             |
| Dead        | 7             | 4             |

| Initial treatment | Surgical | Internal |
|-------------------|----------|----------|
| Alive             | 6        | 4        |
| Dead              | 0        | 10       |

| Max creatine kinase (U/L) | <5000 | >5000 |
|---------------------------|-------|-------|
| Alive                     | 9     | 0     |
| Dead                      | 6     | 4     |

| Response to internal treatment | Remission | Partial | No response |
|-------------------------------|-----------|---------|-------------|
| Alive                         | 5         | 3       | 0           |
| Dead                          | 0         | 4       | 6           |
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