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A Case of Dermatomyositis Along with Esophageal Cancer and Screening of Serum Transcriptional Intermediary Factor 1 Gamma Antibodies in Various Cancer Patients

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Patient: Male, 70-year-old
Final Diagnosis: Esophageal cancer
Symptoms: Muscle pain • weaknes of lower limbs
Medication: —
Clinical Procedure: Biopsy of the skin
Specialty: Rheumatology

Objective: Unknown ethiology

Background: Dermatomyositis (DM) is occasionally associated with malignancy, which is so-called cancer-associated myositis. The cancer screening in patients with dermatomyositis is an important clinical issue. That is because malignant disease underlying dermatomyositis is potentially life-threatening. Transcriptional intermediary factor 1γ (TIF1γ) antibodies (anti-TIF1γ Abs) are one of the myositis-specific autoantibodies, which are investigated as potential predictors of malignancy in patients with dermatomyositis. However, the etiology of anti-TIF1γ Abs generations in various cancer patients is not known.

Case Report: A 70-year-old male patient was admitted for muscle pain and weakness in both legs. Erythematous on the face, eruption, and a V sign were also observed. Laboratory tests showed the elevation of creatine kinase, myoglobin, and aldolase. He was diagnosed as dermatomyositis. Cancer screening was performed, and esophageal cancer was detected in the lower esophagus. Despite the symptoms of dermatomyositis were improved with steroid, methotrexate, and radical esophagectomy, he died with esophageal cancer 3 years after the onset of dermatomyositis. TIF1γ is frequently overexpressed in cancer tissues. Therefore, some cancer patients without dermatomyositis could be positive for anti-TIF1γ Abs. We retrospectively analyzed anti-TIF1γ Abs in cancer patients (n=131). However, the screening of anti-TIF1γ Abs in cancer patients without dermatomyositis (n=130) showed there were no seropositive patients. Only this cancer-associated myositis patient was positive for anti-TIF1γ Abs.

Conclusions: Our result suggested the generation of anti-TIF1γ Abs is specific for cancer associated myositis, not for tumorigenesis.

MeSH Keywords: Autoantibodies • Dermatomyositis • Gastrointestinal Neoplasms

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/922004

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Background

The association of malignancy with dermatomyositis, which is termed cancer-associated myositis, has been well evaluated. The risk of cancer increases during the first 3 to 5 years after the onset of dermatomyositis, with reported rates, are up to 32% [1]. Thus, cancer screening in these patients is a challenging clinical problem. Serum transcriptional intermediary factor 1γ (TIF1γ) antibodies (anti-TIF1γ Abs) have been used for diagnosing cancer-associated myositis and guiding disease management. In a meta-analysis of 6 cohort studies, the pooled sensitivity of anti-TIF1γ Abs for diagnosing cancer association in myositis patients was 78%, and the specificity was 89% [2].

Humoral immune response against intracellular antigens which are accumulated in cancer cells are sometimes detected in cancer patient's serum. For example, autoantibodies against mutated TP53 are widely observed in various cancer patient's serum and are clinically used as cancer diagnostic biomarkers [3]. TIF1γ, which is a transcription accessory factor that plays crucial roles in some biological functions and has oncosuppressive roles as it promotes chromosomal stability, is also frequently overexpressed in cancer tissues [4]. Although TIF1γ overexpression in cancers could theoretically induce anti-TIF1γ Abs, there have been only a few reports evaluating anti-TIF1γ Abs in cancer patients without dermatomyositis. Our reports aim to describe a case of cancer-associated myositis and to discuss the etiology for the generation of anti-TIF1γ Abs.

Case Report

A 70-year-old Japanese male was admitted to our hospital for muscle pain and weakness in both legs. He was a heavy smoker and drank an average of 400 mL of distilled spirits daily. He also complained of an erythematous rash on the face, erythematous eruptions on the back of the hands and finger joints, and he had a V sign (Figure 1A, 1B). Manual muscle testing resulted in grade 3 or 4 for the upper and lower limb muscles. Laboratory tests showed the following: creatine kinase at 6727 IU/L; myoglobin at 1474 ng/mL; and aldolase at 35.3 U/mL. The results for anti-nuclear antibodies were positive (1: 40, speckled). The anti-TIF1γ Abs index was positive at 130, but that of anti-Jo-1 antibodies was negative. Computed tomography revealed no evidence of interstitial pneumonia. Fat-suppressed T2-weighted magnetic resonance imaging (MRI) showed signal hyperintensities in the quadriceps femoris muscles. Electromyography of the biceps brachii, deltoid, and iliopsoas muscles showed a myopathic pattern. The pathological findings from a cutaneous biopsy of the left hand showed interface dermatitis with basal vacuolar degeneration at the dermal–epidermal junction and mucin deposition, which were compatible with inflammatory dermatomyositis (Figure 2A, 2B). Dermatomyositis was diagnosed based on the criteria of Bohan and Peter [5]. After upper digestive endoscopy for cancer screening, an esophageal cancer of the lower esophagus was detected (Figure 3). The patient was administered intravenous immunoglobulin before undergoing open esophagectomy with 2-field lymph node dissection, and the pathological finding was basaloid squamous carcinoma, pT3N2 M0 stage IIIB (Figure 4A, 4B). Eighty milligrams of methylprednisolone were prescribed after surgery. Then, the patient was given prednisolone at 60 mg/day with methotrexate 6 mg/week. The symptoms of cutaneous manifestations and muscle weakness, as well as the laboratory data, all gradually improved. After that, the patient was transferred to another hospital for rehabilitation. However, he died because of cancer recurrence 3 years after surgery.

Retrospective study of anti-TIF1γ Abs in cancer patients

Patients

A total of 131 patients with primary esophageal cancer (n=26), gastric cancer (n=44), colorectal cancer (n=31), and breast cancer (n=30) were enrolled. They were all surgically treated without any neoadjuvant therapy at the Toho University Hospital between January 2010 and December 2014. Pathological lesions were classified using the TNM staging based on the American Joint Committee on Cancer – Union for International Cancer Control – TNM staging system, 8th edition [6]. Serum samples were obtained preoperatively and stored at –80°C until assayed. Signed informed consent forms were obtained from all patients. The ethics committee of Toho University Omori Medical Center approved this protocol (#26-256). Patient characteristics are shown in Table 1. The patients' average age was 67 years (ranging from 39–89 years), and there were 54 (41%) men and 77 (59%) women. Cancer classification yielded a total of 33 (25%) patients with stage I disease, 46 (35%) with stage II, 31 (23%) with stage III, and 21 (16%) with stage IV.

Assay of serum TIF1γ autoantibodies

Anti-TIF1γ Abs were analyzed with commercially available a highly specific, quantitative enzyme-linked immunosorbent assay kit (MESACUP anti-TIF1γ test; Medical & Biological Laboratories, Nagoya, Japan). The protocol detecting anti-TIF1γ Abs titer was followed by the manual. The dynamic range of Ab Index was 5 to 150.

Serum titers of anti-TIF1γ Abs in cancer patients

One esophageal cancer patient who had preoperatively diagnosed dermatomyositis detected high titer (Index 130). Additionally, one stage II gastric cancer patient (Index 21) and one stage II colorectal cancer patient (Index 7) showed low

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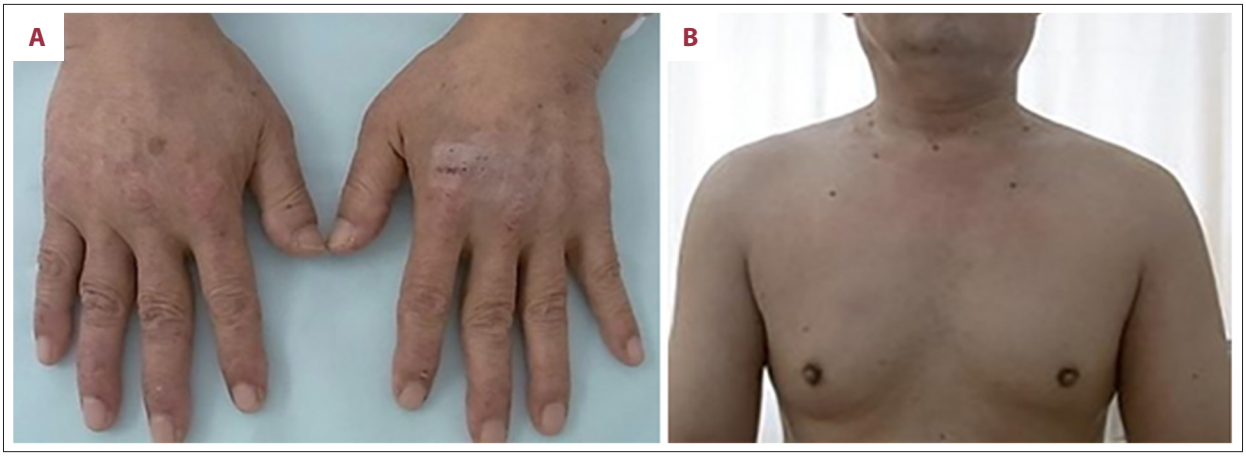

Figure 1. (**A**) Erythematous eruptions on back of the hand and finger joints. (**B**) V sign (macular exanthema on the front site of chest).

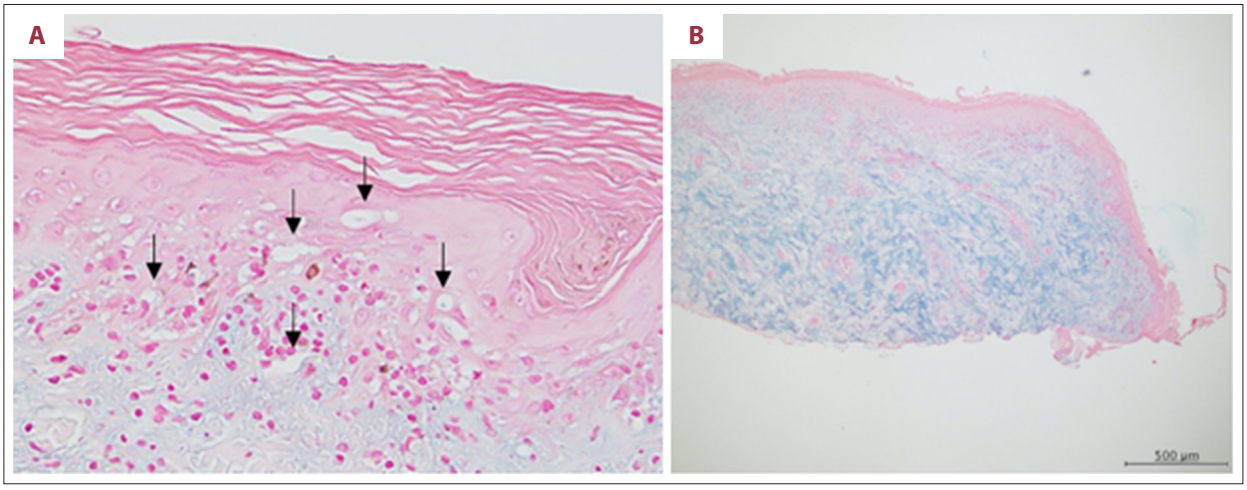

Figure 2. (**A**) Immunohistochemistry (IHC) staining in skin biopsy of the left hand, showing vacuolar degeneration at the dermal-epidermal junction (arrow). (**B**) Alcian blue staining, showing mucin deposition.

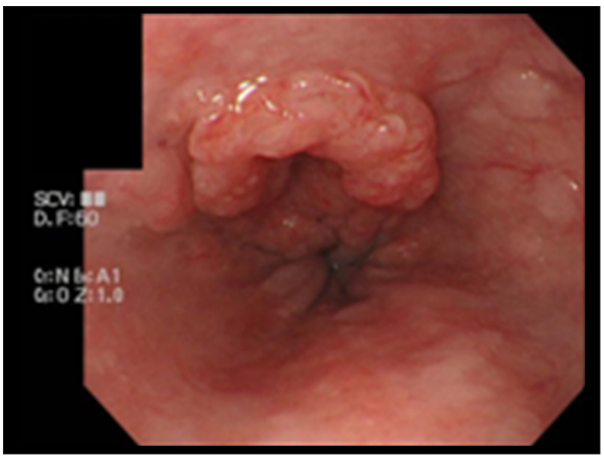

Figure 3. Upper digestive endoscopy finding, showing advanced carcinoma in the lower esophagus.

titer, which were lower than the cut off value for dermatomyositis diagnosis [7]. Except for only these 3 patients, all cancer patients showed lower titers than the lower limit of the assay, and there were no differences between cancer types (Figure 5).

Discussion

Here, we reported one cancer-associated dermatomyositis patient who was positive for anti-TIF1γ Abs, then retrospectively screened anti-TIF1γ Abs in patients with various types of cancer (131 patients in total). Some dermatomyositis is considered paraneoplastic syndromes that develop during the clinical course of malignancy [8]. However, such a disease state is rare. Our case was a cancer-associated myositis, and a result did not conflict with the idea that his cancer-associated myositis was a paraneoplastic phenomenon. Screening of anti-TIF1γ Abs in cancer patients was negative that most cancer

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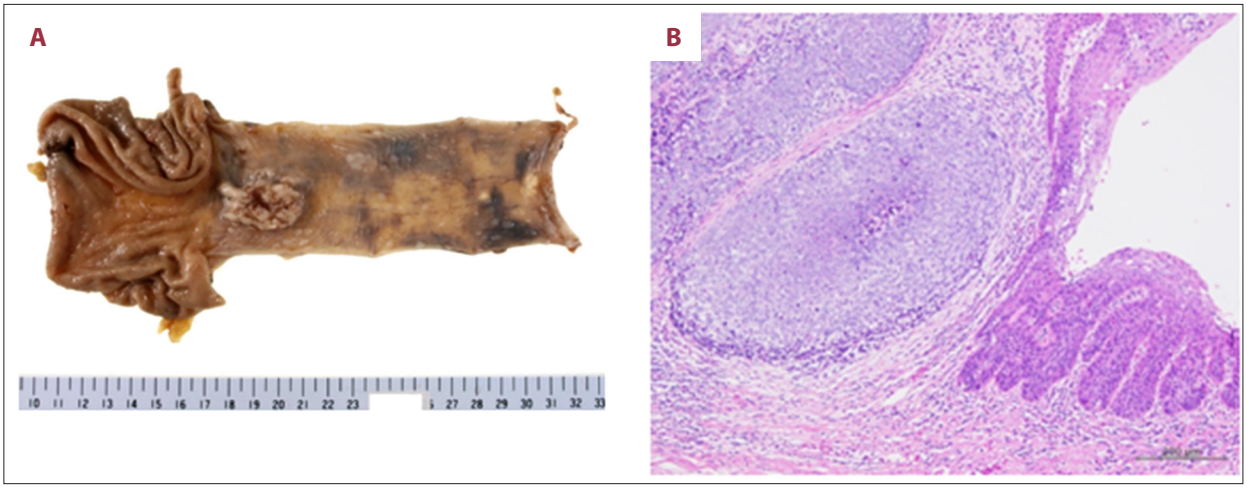

Figure 4. (**A**) Photography of the resected specimen. (**B**) Immunohistochemistry (IHC) staining of the resected specimen showing, basaloid squamous carcinoma.

Table 1. Patient characteristics.

Cancer type	Esophageal (n=26)	Gastric (n=44)	Colorectal (n=31)	Breast (n=30)	Total (n=131)
Characteristics					
Gender					
Male	18	24	12	0	54 (41%)
Female	8	20	19	30	77 (59%)
Age					
Mean±SD (years)	70±9.9	68±11.3	65±10.6	63±12.8	69±10.6
Stage					
I	5	11	7	10	33 (25%)
II	9	14	10	13	46 (35%)
III	9	10	7	5	31 (23%)
IV	3	9	7	2	21 (16%)
Total	26	44	31	30	131 (100%)

SD – standard deviation.

patients without dermatomyositis were lower than the cut-off value of the assay.

There were several reports about the presence of anti-TIF1γ Abs in cancer patients without dermatomyositis. Research for lung cancer and breast cancer cohort also revealed that seropositive patients without dermatomyositis were rarely observed [9,10]. Venalis et al. also reported anti-TIF1γ Abs are rarely present in patients with solid cancers or paraneoplastic rheumatic syndromes [11]. Our study demonstrated that gastric cancer and colorectal cancer without dermatomyositis were negative for anti-TIF1γ Abs likewise. Overexpress of TIF1γ in cancer tissues is frequently observed, and anti-TIF1γ Abs were generally positive in cancer-associated myositis. However, previous reports and our study showed that cancer patients without dermatomyositis were mostly negative for anti-TIF1γ Abs; it may well be that the generation of autoantibodies against TIF1γ is highly specific for dermatomyositis, not for carcinogenesis. This specificity reflects the mechanism for production of autoantibodies in rheumatic disease, which is the principal mystery of the disease.

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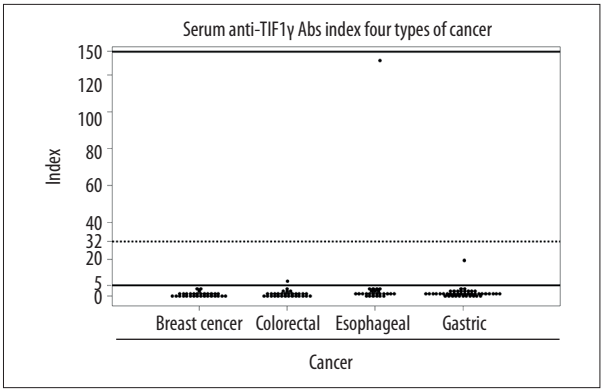

Figure 5. Serum anti-TIF1γ Ab Index in 4 types of cancer. Three patients could detect the titer. One seropositive patient was an esophageal cancer patient who was preoperatively diagnosed dermatomyositis and the other 2 patients were lower than the cutoff value for dermatomyositis. Broken line showed the cut off Index for dermatomyositis and between the solid lines showed the dynamic range of Ab Index. Samples within the dynamic range of the assay were painted in black.

Our study had a few limitations. At first, we did not measure TIF1γ expression in the cancer tissues. According to reports, we would have found cancer tissues expressing TIF1γ; overexpression of TIF1γ was observed in 33% of stage I and II colorectal cancer patients, in 66% of stage III colorectal cancer patients [12], and 35% of breast cancer patients [13]. Secondly, anti-TIF1γ Abs of a patient with dermatomyositis change after surgery was not confirmed because the patient transferred to a rehabilitation hospital. Future studies will consider measuring anti-TIF1γ Abs in patients with other cancer such as pancreas or liver cancer and change before and after surgery.

Conclusions

Although anti-TIF1γ Abs were absent in various cancer patients without dermatomyositis, anti-TIF1γ Abs may be useful to detect cancer in dermatomyositis patients.

Department and Institution where work was done

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Conflicts of interest

Kazutoshi Shibuya received research grants from Pfizer Inc. and Dainippon-Sumitomo Pharma, and received payments for lecture from Dainippon-Sumitomo Pharma.

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