CORRESPONDENCE

Anti-TIF1-γ-positive young adult dermatomyositis with germ cell tumor

Etsuko Taki, M.D.[1], Makoto Shimizu, M.D., Ph.D.[1], Yuya Soeda, M.D.[2], Miyuki Shirai,M.D.[3] , Yoshinao Muro, M.D., Ph.D.[3]

[1]Department of Dermatology, National Hospital Organization Nagoya Medical Center

[2]Department of Urology, National Hospital Organization Nagoya Medical Center

[3]Department of Dermatology, Nagoya University Graduate School of Medicine

Corresponding author:

Yoshinao Muro, M.D., Ph.D.

Division of Connective Tissue Disease & Autoimmunity

Department of Dermatology

Nagoya University Graduate School of Medicine

65 Tsurumai-cho, Showa-ku, Nagoya, 466-8550 Japan

Tel: 81-52-744-2314 Fax: 81-52-744-2318

E-mail: ymuro@med.nagoya-u.ac.jp

Word count for the text: 681 words; 0 tables; 1 figure

Dermatomyositis (DM) is a systemic autoimmune disease characterized by inflammation in multiple organ systems, most commonly the skin and muscle. Many patients with DM have circulating autoantibodies, which are often associated with distinct clinical phenotypes [1]. Antibodies against transcriptional intermediary factor (TIF) 1-γ are associated with malignancy in adult DM [1,2] but are rarely found in young adults. Here, we describe a young adult with dermatomyositis who had anti-TIF1-γ antibodies and germ cell tumor.

A 22-year-old man noticed erythema on his face and hands 2 months before his initial visit to another hospital. A month later, physical examination at our hospital showed facial erythema, Gottron's sign, dilated capillary loops on the periungual area, and V-neck sign (Fig. 1A, 1B). He also had pruritic scratch dermatitis on the back and upper arms. He had no muscle pain or weakness. Histological examination of the erythema on the dorsum of his hand revealed vacuolar degeneration, dermal edema and lymphocytic infiltration in the upper dermis (Fig. 1C). Laboratory findings revealed anti-nuclear antibodies at a titer of 1:40 (speckled) and the normal level of creatine kinase. Serum anti-TIF1-γ antibodies were positive and anti-NXP2 antibodies were negative by ELISA using recombinant proteins produced by *in vitro* transcription and translation [3], and the diagnosis of clinically amyopathic DM was

made. Oral prednisolone (10mg/day) was initiated; however, the skin symptoms did not improved. Computed tomography (CT) images of his lung were normal. Three months later, he reported stomach pain, and upper and lower gastrointestinal endoscopy was performed. However, there were no abnormal findings. Two weeks later, he visited the emergency room because of back pain. Laboratory examinations showed elevated levels of lactate dehydrogenase (639 IU/L) and C-reactive protein (4.11 mg/dl). CT scans showed multiple nodules in the lung, and a mass and swelling of the lymph nodes in the retroperitoneum. Tests of tumor markers revealed human chorionic gonadotropin (hCG) at 2,454 mIU/ml (normal range: 0.0~0.5 mIU/ml) and α-fetoprotein (AFP) at 137 ng/ml (<20 ng/ml). He was diagnosed with extragonadal germ cell tumor and lung metastases. After four courses of chemotherapy with bleomycin hydrochloride, etoposide and cisplatin, the tumor became smaller and the serum levels of AFP and hCG normalized. He received residual tumor resection, left orchiectomy and retroperitoneal lymph node dissection. There was no malignancy in any of the resected specimens. With treatment of the tumor, anti-TIF1-γ levels decreased (Fig. 1D) and the skin symptoms improved. He was in complete clinical remission and remained disease-free during 7-month follow-up.

Anti-TIF1-γ-positive adult DM patients were found to have malignant

disease at a rate of 65% [4] and cancer prevalence increased with age, with an inflection point evident at ~60 years of age [5]. It is very infrequent in the second and third decade of life. Testicular cancer associated with DM seems rare. However, tumors of the testes affect young men with a peak incidence of 20 to 35 years [6]. Dourmishev *et al.* reviewed 10 cases of DM associated with testicular cancer and described his additional case [7]. According to our survey, we found other 3 DM cases with germ cell tumor [8-10] than cases mentioned by Dourmishev *et al.* Their average age is 31.4 years (range: 24-46 y.o.) and 6 of these cases had lung metastasis. In 9 patients, the DM preceded the onset of cancer. Our case is the youngest male DM patient known to be complicated with germ cell tumor and the first to be determined as anti-TIF1-γ-positive. We were unable to find any case reports of female young adult patients with DM complicated with malignant germ cell tumors. We suggest that it is necessary to screen for cancer, especially for testes tumors, in young adult male cases with DM. We should screen for cancer even in young adults, especially in those with anti-TIF1-γ. Interestingly, the anti-TIF1-γ level was diminished after the therapy targeted at the malignancy. Although Fujimoto et al. reported that anti-TIF1-γ levels decreased after therapy [4], few reports heave featured detailed longitudinal evaluations of this phenomenon. Future studies are needed to establish whether serum

anti-TIF1-γ antibody levels are a good indicator of response to therapy.

References

1. Satoh M, Tanaka S, Ceribelli A, *et al.* A comprehensive overview on myositis-specific antibodies: new and old biomarkers in idiopathic inflammatory myopathy. *Clin Rev Allergy Immunol* (in press).

2. Hoshino K, Muro Y, Sugiura K *et al.* Anti-MDA5 and anti-TIF1-γantibodies have clinical significance for patients with dermatomyositis. *Rheumatology.* 2010; **49**: 1726-33.

3. Muro Y, Sugiura K, Akiyama M. A new ELISA for dermatomyositis autoantibodies: rapid introduction of autoantigen cDNA to recombinant assays for autoantibody measurement. *Clin Dev Immunol* 2013; 2013: 856815.

4. Fujimoto M, Hamaguchi Y, Kaji K *et al.* Myositis-specific anti-155/140 autoantibodies target transcription intermediary factor 1 family proteins. *Arthritis and rheumatism* 2012; 64: 513-22.

5. David F. Fiorentino, Lorinda S Chung, Lisa Christopher-Stine *et al.* Most patients with cancer-associated dermatomyositis have antibodies to nuclear matrix protein NXP-2 or transcription intermediary factor 1γ. *Arthritis Rheum* 2013; 65: 2954-62.

6. Carver BS1, Sheinfeld J. Germ cell tumors of the testis. *Ann Surg Oncol* 2005; 12: 871-80.

7. Dourmishev LA, Popov JM, Rusinova D. Paraneoplastic dermatomyositis associated with testicular cancer: a case report and literature review. *Acta Dermatoven APA* 2010; 19: 39-43.

8. Vattemi G, Tonin P, Martignoni G, *et al.* Dermatomyositis and retroperitoneal germ cell cancer. *Eur Neurol* 2001; **45**: 52-3.

9. Tan E, Young D, McLaren B, Wright A. Early-stage testicular cancer: a rare association with dermatomyositis. *Australas J Dermatol* 2010; 51: 139-41.

10. Norrenberg S, Gangji V, Del Marmol V, Soyfoo MS. Diffuse muscular pain, skin tightening, and nodular regenerative hyperplasia revealing paraneoplastic amyopathic dermatomyositis due to testicular cancer. *Case Rep Rheumatol* 2012; 2012: 534236.

Acknowledgments

Financial Support: None.

Conflicts of Interest: None.

Figure legends

Figure 1. Clinical images, skin histopathology and longitudinal changes of anti-TIF1-γ antibody in sera and in the clinical course.

A. Facial erythema. **B.** Gottron's sign on the dorsum of the hands. **C.** Histological findings of the papule on the distal interphalangeal joint. The scale bar is 50μm. **D.** The clinical course is shown by the levels serum α-fetoprotein (AFP) and human chorionic gonadotropin (HCG). After treatment, the unit of anti-TIF1-γ antibody measured by ELISA was decreased (the cutoff is 7.3 U). PSL: prednisolone. BEP: bleomycin hydrochloride, etoposide and cisplatin.