CORRESPONDENCE

Occurrence of cholangiocarcinoma three years after negative seroconversion of anti-TIF1γ antibody in a dermatomyositis patient

Short title: Anti-TIF1γ-positive DM complicated with cancer

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Editor

It is widely known that anti-TIF1γ antibody-positive dermatomyositis (DM) often occurs in association with internal malignancies; therefore, thorough screening for underlying malignancies is performed for anti-TIF1γ antibody-positive adult patients upon DM diagnosis. However, it is unclear how long we should continue cancer screening after the diagnosis if no malignancy is found.

Here, we report a 73-year-old anti-TIF1γ antibody-positive Japanese man with DM in whom no malignancy was found at the time of DM diagnosis. Cancer screening had been continued annually while the DM was inactive, with the negative seroconversion of anti-TIF1γ antibody. Unfortunately, a malignant tumor was found 4 years after the diagnosis of DM. We reported the detailed clinical features at onset and during the initial therapy, including intramuscular hemorrhage, in the present patient in this journal [1]. He presented with a 3-month history of skin erythema including heliotrope rash and Gottron's sign, and symmetric muscle weakness. Serum levels of creatine kinase (CK) and aldolase were elevated and anti-TIF1γ antibody was positive with an index of 70 (cutoff value: 32) (MBL, Nagoya, Japan). We performed various examinations, including CT imaging, endoscopies, and serum biomarker tests, but no malignancy was noted. He received two courses of steroid pulse therapy (methylprednisolone 500 mg/day for 3 days),

and then oral prednisolone 25 mg/day and azathioprine 50 mg/day. About 6 months after the diagnosis, the anti-TIF1γ antibody became negative (index value: 26), the serum levels of CK normalized, and the DM symptoms disappeared. Since he showed no elevated anti-TIF1γ antibody titers, no other blood test abnormalities including elevated serum CK levels, and no relapse of DM symptoms, the oral prednisone dose was further reduced. Finally, his disease activity was well controlled with prednisolone at 1 mg/day and azathioprine at 100 mg/day (Fig. 1A).

However, approximately 4 years after the diagnosis of DM, liver enzymes were suddenly elevated, and cholangiocarcinoma with peritoneal dissemination was discovered. No elevation of anti-TIF1γ antibody (index value: 20) nor relapse of DM symptoms was observed before the elevation of liver enzymes; however, after the malignancy was noted, the anti-TIF1γ antibody titer did increase to become positive (index value: 73). Even so, the DM symptoms did not relapse even up to death. The cholangiocarcinoma was treated with a combination of cisplatin and gemcitabine, but the treatment was ineffective, and the patient died 6 years after the diagnosis of DM (Fig. 1B). TIF1γ expression was not elevated in the cancer tissue as determined by immunohistochemistry (data not shown).

Two previous meta-analyses reported several risk factors for malignancy in DM patients: age >45 years, male, skin necrosis, anti-TIF1γ positivity, dysphagia, and elevated erythrocyte sedimentation rate [2, 3]. Other reports suggested the following risk factors associated with malignancy: age >52 years at diagnosis, skin necrosis, periungual erythema, hypocomplementemia, and the rapid onset of cutaneous and muscular symptoms [4]. Our patient had plural risk factors for cancer complications. As for the timing of malignancy discovery, we reported that the majority of patients with anti-TIF1γ antibody-positive DM develop visceral malignancies within 2 years before and after the diagnosis of DM [5]. Another report revealed that no malignancies occurred from 2.5 to 7.5 years after the diagnosis of anti-TIF1γ antibody-positive DM [6]. However, in our patient, cholangiocarcinoma was discovered approximately 4 years after the diagnosis of DM, suggesting that this case is atypical. A recent study [7] showed the following trends in titer changes of anti-TIF1γ antibodies in DM: i) anti-TIF1γ antibodies became negative with treatment of both malignancy and DM, ii) patients with advanced cancer who had no treatment option never demonstrated negative seroconversion. Our patient had no cancer complications at the time of DM diagnosis and the anti-TIF1γ antibody became negative after the DM was treated. Since he had had no recurrence of DM symptoms nor re-elevation of the antibody titers for more than 3 years, we did not perform any imaging

tests, such as CT scans, during that period. No previous reports have shown the elevation of anti-TIF1γ antibodies associated with malignancy but without DM eruptions.

Anti-TIF1γ antibodies are not always useful biomarkers for the early detection of malignancy in DM and that tumor screening should be performed with great caution even several years after DM diagnosis, especially in high-risk cases.

Disclosure

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Conflicts of interest: None.

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Figure 1.

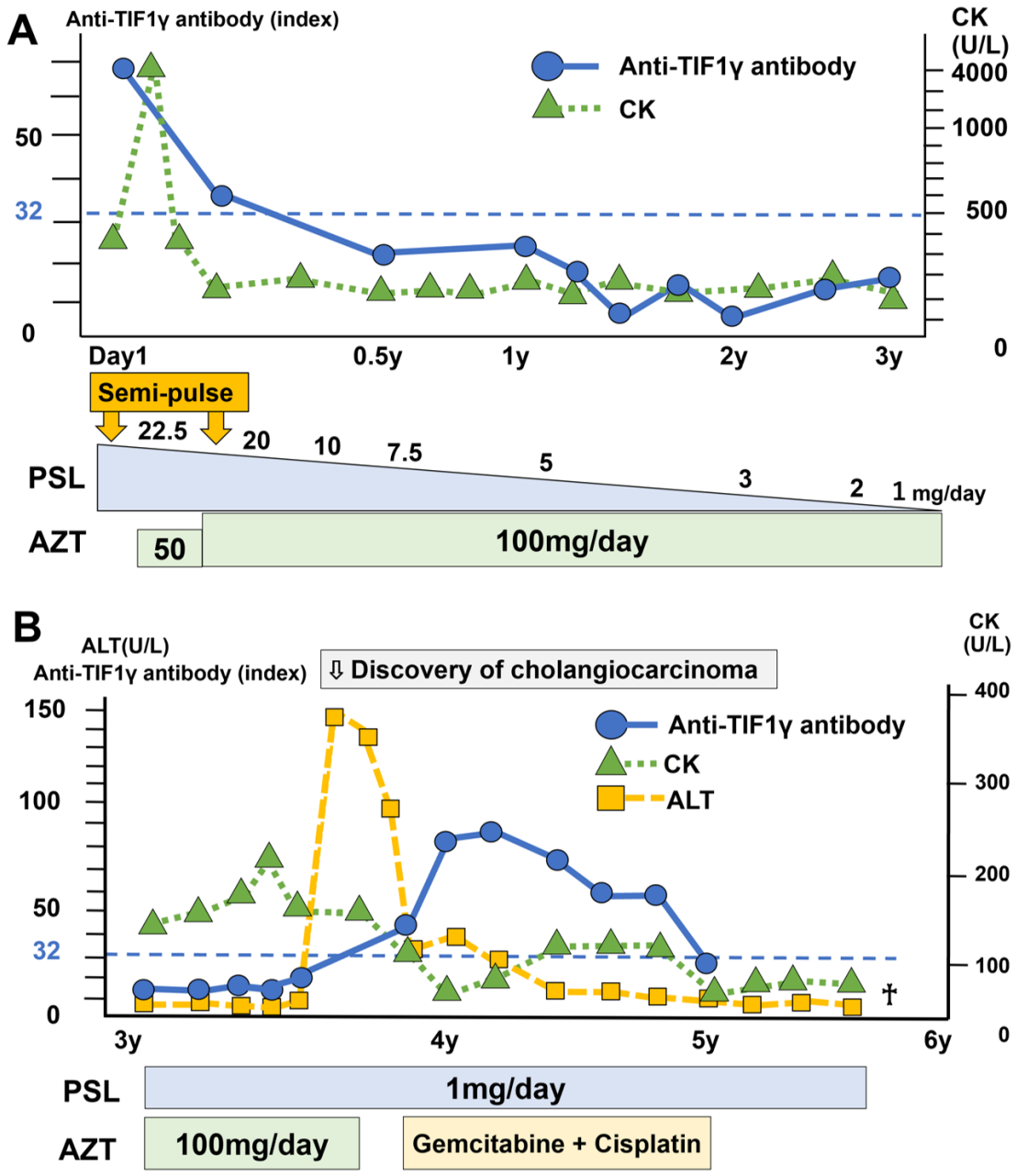
A
Anti-TIF1γ antibody (index)
CK (U/L)
Anti-TIF1γ antibody
CK
50
32
0
4000
1000
500
0
Day1
0.5y
1y
2y
3y
Semi-pulse
22.5
20
10
7.5
5
3
2
1 mg/day
PSL
AZT
50
100mg/day
B
ALT(U/L)
Anti-TIF1γ antibody (index)
⇩ Discovery of cholangiocarcinoma
CK (U/L)
Anti-TIF1γ antibody
CK
ALT
150
100
50
32
0
400
300
200
100
0
3y
4y
5y
6y
PSL
1mg/day
AZT
100mg/day
Gemcitabine + Cisplatin

Figure legend

Figure 1. Clinical course of the present DM patient complicated with cholangiocarcinoma. A) The 3-year period from the time of DM diagnosis (Day 1). B) The 3-year period from the diagnosis of DM to the patient's death. Elevated anti-TIF1γ antibodies were observed after cholangiocarcinoma diagnosis.

The broken lines at 32 denote a cutoff value of anti-TIF1γ antibody in ELISA.

AZT: azathioprine; CK: creatinine kinase; PSL: prednisolone.