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Teaching Case

Marked Improvement of Anti-TIF1-γ Antibody-Positive Dermatomyositis After Chemoradiotherapy to Relevant Nasopharyngeal Cancer

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Introduction

It is well known that dermatomyositis (DM) sometimes presents as a paraneoplastic syndrome of malignant neoplasms.[1] Antitranscription intermediary factor 1 γ antibody (anti-TIF1-γ-Ab) was identified from sera of patients with DM in 2006 as an autoantibody directed against an immunoprecipitated doublet band of a 155-kDa protein.[2] Anti-TIF1-γ-Ab is established as a marker of associated cancer in patients with DM.[3] In anti-TIF1-γ-Ab-positive cancer-associated DM, TIF1-γ functions as a tumor autoantigen and induces DM.[4,5] However, its mechanism is not well understood. We report the first case of treatment of nasopharyngeal cancer (NPC) secondary to anti-TIF1-γ-Ab-positive DM using intensity modulated radiation therapy (IMRT) and concurrent chemotherapy.

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Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

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Case Report

Initial presentation and workup

Written informed consent was obtained from the patient for publication of this case report.

A 41-year-old man developed a rash on his face and papules over his fingers after a long period of exposure to sunlight. He also had weakness and pain in his upper arms and thighs. He presented to the department of rheumatology at our hospital. On physical examination, Gottron's papules on the knuckles, Gottron's sign on the knuckles and elbows, and erythematous or purpuric patches around the nails were observed. Laboratory tests revealed that creatinine kinase (1417 U/L; normal range, 59-248), erythrocyte sedimentation reaction (11 mm; normal limit, <7), and aldolase (15.0 U/L; normal limit, <6.0) were increased to abnormal levels. The blood cell count was normal and the chemistry panel included no other abnormalities. Needle electromyography suggested myositis and T2-weighted magnetic resonance imaging (MRI) of the femoral area detected a diffuse high-intensity area along the muscles (Fig 1). In addition, anti-TIF1-γ-Ab increased to an abnormal level of 115 (normal limit, < 32). According to the diagnostic criteria,[6] he received a diagnosis of anti-TIF1-γ-Ab-positive DM,

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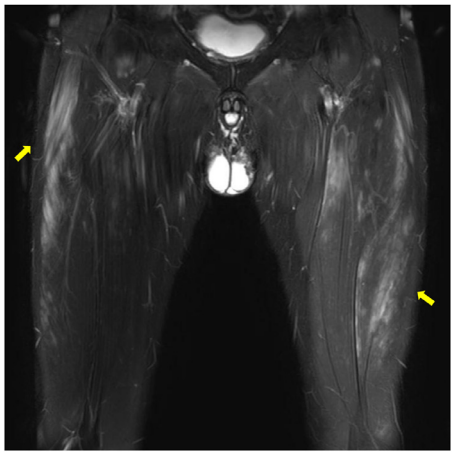

Figure 1 T2-weighted magnetic resonance imaging (MRI) of the femoral area.

which is highly associated with cancer. Whole-body computed tomography (CT) suggested a nasopharyngeal tumor (Fig 2A), which was confirmed by nasopharyngoscopy (Fig 2B) and MRI of the pharynx (Fig 2C). Tumor biopsy confirmed the diagnosis of undifferentiated carcinoma (ie, lymphoepithelioma). ^{18}F-fluorodeoxyglucose positron emission tomography/CT (PET-CT) detected bilateral retropharyngeal node metastases (Fig 2D). The patient had no evidence of metastasis to a distant organ on enhanced CT and PET-CT. Thus, he received a clinical diagnosis of T1N1M0 (stage II) NPC according to the eighth edition of the American Joint Committee on Cancer staging system, secondary to anti-TIF1-γ-Ab-positive DM. He had no notable medical history. During discussion of the treatment strategy, the multidisciplinary team decided that cancer management had priority over DM treatment because cancer was hypothesized to induce DM. Standard treatment of chemoradiotherapy (CRT) against NPC was selected. As DM symptoms, such as weakness and pain of extremities, progressively deteriorated just before CRT, prednisone at 30 mg daily was initiated concurrently with CRT.

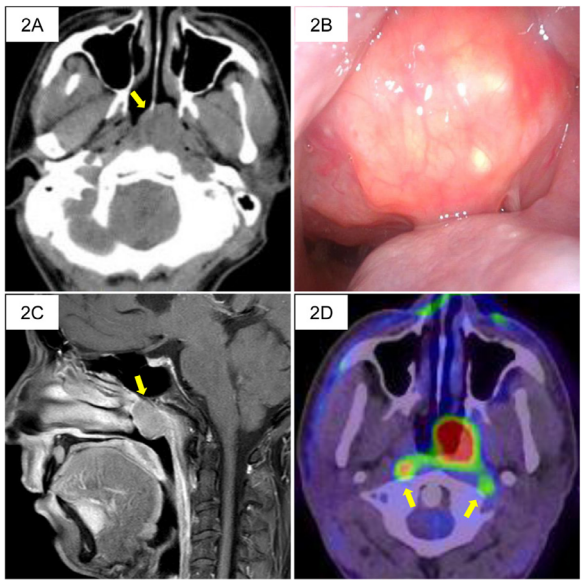

Figure 2 (A) Nasopharyngeal tumor on computed tomography (CT), (B) nasopharyngeal tumor on nasopharyngoscopy, (C) nasopharyngeal tumor on the sagittal image of enhanced magnetic resonance imaging (MRI), and (D) ^{18}F-fluorodeoxyglucose uptake in the nasopharyngeal tumor and bilateral retropharyngeal node on positron emission tomography/CT (PET-CT).

Treatment planning

The patient was treated by adaptive 2-step IMRT[7] using helical tomotherapy. He was immobilized in the supine position with a thermoplastic mask covering the head to shoulders and was simulated twice by CT with a 2.5-mm slice for the initial and boost plans. All target volumes and the organs at risk were delineated according to the reference[8] on the RayStation treatment planning system (RaySearch Medical Laboratories AB, Stockholm, Sweden). The primary clinical target volume (CTV) on the initial plan included the primary gross tumor volume (GTV) with an appropriate margin and the extent of microscopic extension. The entire nasopharynx and one-third posterior part of the nasal cavity were included to the primary CTV as microscopic extension. The CTV of the boost plan included only the primary GTV with an appropriate margin. The CTV of the node on the initial plan included the GTV of the node with an appropriate margin and prophylactic nodes (ie, bilateral retropharyngeal nodes, levels II, III, IV, and Va). The CTV of the boost plan included only the GTV of the node with an appropriate margin and bilateral level II small nodes, which were unable to be excluded as metastases on MRI and PET-CT. The planning target volume was defined as CTV with 5-mm margins for the initial and boost plans. The dose distributions for the initial (A) and boost (B) plans are shown in Figure 3. The TomoProvider planning system (Accuray, Sunnyvale, USA) was used with the superposition algorithm for the planned calculation. The plan was optimized to achieve a target coverage of 50% of the planning target volume receiving 100% of each prescription dose and to minimize the dose to the organs at risk using dose-volume histogram constraints. Tomotherapy plans were generated using 6-MV x-ray beams of TomoHD (Accuray). The prescription doses for the initial and boost plans were 46 and 20 Gy, respectively, in 2-Gy fractions. The total dose was 66 Gy in 33 fractions over 48 days. Megavoltage CT was acquired for daily set-up verification. Three courses of triweekly cisplatin at 100 mg/m^2 were administered concurrently with IMRT.

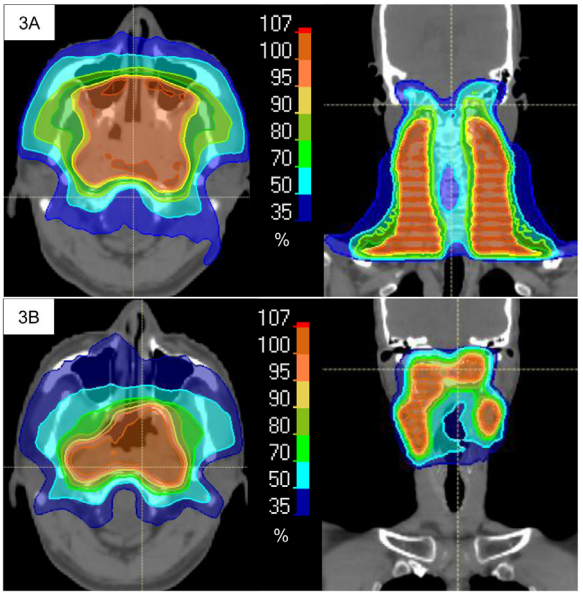

Figure 3 Dose distribution for (A) the initial (46 Gy in 23 fractions) and (B) boost (20 Gy in 10 fractions) plans.

Treatment course and follow-up

The rash on his face and papules over his fingers disappeared less than 2 weeks after the start of CRT. The weakness and pain in his upper arms and thighs also improved gradually during CRT. As marked improvement in DM symptoms was noted during CRT, the dose of prednisone was reduced rapidly and regularly, and was 12.5 mg at the end of IMRT (Fig 4). IMRT and concurrent chemotherapy were performed with minimal acute complications and no prolonged radiation therapy (RT) period. He developed grade 2 radiation dermatitis, grade 2 alopecia, grade 1 dysgeusia, and grade 1 xerostomia during CRT. The patient was followed closely without anticancer adjuvant therapy. He achieved a complete response on enhanced MRI and PET-CT at 1 month after IMRT. The anti-TIF1-γ-Ab decreased gradually to a normal level: 115 before CRT; 83 during CRT; 38 at 1 month after CRT; and 32 at 4 months after CRT (Fig 4). Of note, the adverse events due to CRT slowly became significant despite acute minimal complications. He developed grade 2 dysgeusia and grade 2 xerostomia at 1 month after CRT. Slight numbness in his feet, suspected to be grade 2 peripheral sensory neuropathy due to cisplatin, developed at 2 months after CRT. He also developed sclerosis of the muscle of the neck (grade 2 neck pain). His DM and NPC remain controlled at 6 months after CRT.

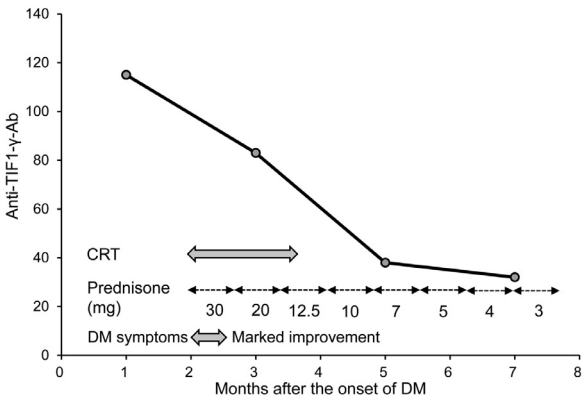

Figure 4 Change in the serum antitranscription intermediary factor 1 γ antibody (anti-TIF1-γ-Ab) level after the onset of dermatomyositis (DM).

Discussion

We report the first case of treatment of anti-TIF1-γ-Ab-positive DM associated with head and neck cancer by CRT, which resulted in the marked improvement in DM symptoms. In this case, DM presented as a paraneoplastic syndrome of NPC because anti-TIF1-γ-Ab, a marker of cancer association, increased to an abnormally high level. Approximately 20% of patients with DM have malignancies. As the primary sites of cancer have no particular types,[9] there were some papers regarding DM associated with various sites of head and neck cancer.[9,10] As these papers were original articles to examine the risk of cancer in patients with DM, they had insufficient information about the improvement in DM symptoms and RT-related adverse events.[9,10] A case series of DM associated with NPC was also reported in an Asian population,[11] but anti-TIF1-γ-Ab was not described and NPC is a common malignancy in Asians. There is only 1 case report of anti-TIF1-γ-Ab-positive DM associated with NPC.[12] However, the patient of the case report was not associated with DM at the diagnosis of NPC and seemed to develop anti-TIF1-γ-Ab-positive DM after the administration of an immune checkpoint inhibitor of nivolumab for recurrence of NPC.[12] CRT for head and neck cancer usually has a high rate of acute and late adverse effects such as xerostomia, pharyngeal mucositis, and dysgeusia.[13] DM has a potential risk of increasing these RT-related adverse events.[14] However, we recommended the standard treatment of CRT because tumor resection or anticancer therapy may result in the disappearance or remission of the paraneoplastic DM symptoms.[15] Indeed, the marked improvement of DM symptoms soon after starting CRT was of interest.

Anti–TIF1-γ-Ab was first identified from sera of patients with DM in 2006.[2] Two meta-analyses demonstrated that the sensitivity of anti-TIF1-γ-Ab for diagnosing cancer-associated myositis is 78%, with a specificity of 89%, and the presence of anti-TIF1-γ-Ab has a 9-fold greater risk of association with malignancy.[10,16] Thus, detection of anti-TIF1-γ-Ab is useful for both DM diagnosis and confirming cancer.[17] In addition, anti-TIF1-γ-Ab can decrease to a normal level after the cancer is cured along with improvement of DM symptoms.[18] However, its mechanism is not well understood. Anti-TIF1-γ-Ab-positive DM in adults has several clinical features: (1) severe typical rash, such as heliotrope rash and Gottron's papules; (2) rapid

muscle weakness; and (3) a lack of interstitial lung disease (ILD).[19,20] These were consistent with the clinical features in our current case.

There were 3 concerns regarding the implementation of CRT in our case: (1) the onset of ILD induced by irradiation of the lung; (2) an increase in RT-related adverse events due to DM; and (3) unknown adverse events in patients with DM who were administered prednisone. ILD occurs in approximately 40% of patients with DM, but is less common in cancer-associated DM, as mentioned previously.[19,20] However, as RT can exacerbate ILD, we were careful not to irradiate the apex area of the lung (Fig 3A). There is a potential risk of increased RT-related adverse events in patients with connective tissue diseases.[14,21] Our patient developed fewer acute adverse effects than patients without DM. This may have been due to the administration of prednisone concurrently with CRT. However, the adverse events due to CRT slowly became notable despite minimal acute complications after reduction of the prednisone dose.

The limitation in our present case was the administration of prednisone concurrently with CRT, which may have resulted in the improvement of DM symptoms. Oral prednisone at an initial dose of 0.5 to 1 mg/kg/d is usually administered as initial therapy, followed by slow progressive dose reduction not earlier than 6 weeks after the myositis has become inactive.[22] In our current case, the lowest dose of prednisone was used at an initial dose of 0.5 mg/kg/d, and the dose was reduced every 3 weeks. Thus, the clinical course of NPC, DM symptoms, and anti-TIF1-γ-Ab suggested that CRT itself resulted in the marked improvement in DM symptoms.

In conclusion, we reported the first case of CRT for anti-TIF1-γ-Ab-positive DM associated with NPC. There is a potential risk of increased RT-related adverse events in patients with connective tissue diseases, but only minimal adverse effects have been observed thus far. The marked improvement in DM symptoms soon after starting CRT is of great interest, and both DM and NPC remain controlled in the patient. Their mechanism is under investigation.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.adro.2021.100695.

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