

## 바터팽대부의 신경내분비종양 환자에서 발생한 피부근염

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### A Case of Dermatomyositis in a Patient with a Neuroendocrine Tumor at the Ampulla of Vater

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Dermatomyositis is an autoimmune disease characterized by chronic muscle inflammation that results in specific dermatological signs and decreased muscle strength. It is known to have a strong association with malignancy. Most neuroendocrine tumors arise from the gastrointestinal tract, with less than 1% of cases occurring at the ampulla of Vater. While cases of dermatomyositis associated with neuroendocrine tumors have been reported internationally, to date there have been no cases reported in Korea. This case report presents a 33-year-old male who had undergone pylorus-preserving pancreaticoduodenectomy for a neuroendocrine tumor located at the ampulla of Vater, and had been followed at the hospital after his procedure. Three years post-surgery, the patient developed serious muscle weakness in his upper-right and lower-left extremities, and was subsequently diagnosed with dermatomyositis. This paper presents the first domestic case of dermatomyositis developing in the context of a neuroendocrine tumor at the ampulla of Vater. A literature review on this subject follows in the discussion. (Korean J Med 2017;92:552-557)

**Keywords:** Dermatomyositis; Autoimmune diseases; Malignancy; Neuroendocrine tumor; Ampulla of Vater

#### INTRODUCTION

Dermatomyositis is an autoimmune disease of unclear etiology, characterized by unique dermatological findings as a result

of inflammatory cell invasion into muscle tissue. It has been reported to be associated with malignancy in approximately 7-34% of cases. Lung, ovary, breast, stomach, and colon malignancies are the most frequently associated malignancies, with cases of

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hepatoma, renal cell carcinoma, cholangiocarcinoma, and melanoma also reported in the literature. However, cases of neuroendocrine tumors in association with dermatomyositis are rare worldwide, and have not been described domestically. This paper describes the first domestic case of dermatomyositis in a patient with a history of a neuroendocrine tumor located at the ampulla of Vater, and reviews the background literature.

### CASE REPORT

A 33-year-old man presented with polyarthrititis of the wrist and shoulders, general weakness, fever, and pain in the distribution of his upper-right arm and left thigh. Despite treatment at his local hospital, the symptoms did not improve, and he was subsequently referred to the clinic. His medical history included pulmonary tuberculosis treated with full-course therapy and a stage III neuroendocrine tumor at the ampulla of Vater, which had been resected 3 years previously via a pylorus-preserving pancreaticoduodenectomy. He had frequent follow-up appointments, with no evidence of tumor recurrence.

On physical examination, he had difficulty raising his right arm above the level of his shoulder, as well as difficulty sitting or standing up. He complained of significant pain when climbing stairs and had multiple erythematous papules and pustules on his back (Fig. 1).

On neurological examination, normal sensory function of both the upper and lower extremities was noted; however, he had a IV/V decrease in function of his extensor and flexor compartments of his upper right arm and left thigh. His blood pressure was 110/60 mmHg, pulse was 95 beats/min, respiratory rate was 18 breaths/min, and body temperature was 38.6°C. Auscultation of the chest revealed no rales or wheeze, and his abdominal examination was normal.

He had a leukocytes count of 8,000/mm<sup>3</sup> (consisting of 86.0% neutrophils), a hematocrit level of 14.4 g/dL and a platelet count of 274,000/mm<sup>3</sup>: all were within normal range. His erythrocyte sedimentation rate and C-reactive protein level were elevated at 50 mm/h and 3.63 mg/dL, respectively. Additionally, elevated levels of creatinine kinase (2,341 IU/L), aldolase (39.7 U/L; reference range, 0-7.6), myoglobin (956.36 ng/mL), lactate de-



**Figure 1.** Skin lesions on the back. Multiple erythematous papules and pustules are present on the back.

hydrogenase (299 IU/L), aspartate aminotransaminase (90 IU/L), and alanine aminotransaminase (44 IU/L) were noted. His anti-nuclear antibody titer was 1:160, and in a speckled-type pattern. Antibodies against Jo-1 were positive, while those against rheumatoid factor, cyclic citrullinated peptides, double-strand DNA, and Sm were all negative. His hepatitis B surface antigen was negative, although he had positive hepatitis B surface antibodies. Antibodies against the hepatitis C virus were negative. Urinary tests for myoglobin were negative, with other urinalysis results being unremarkable.

Radiographs of the upper and lower extremities as well as his chest showed normal findings.

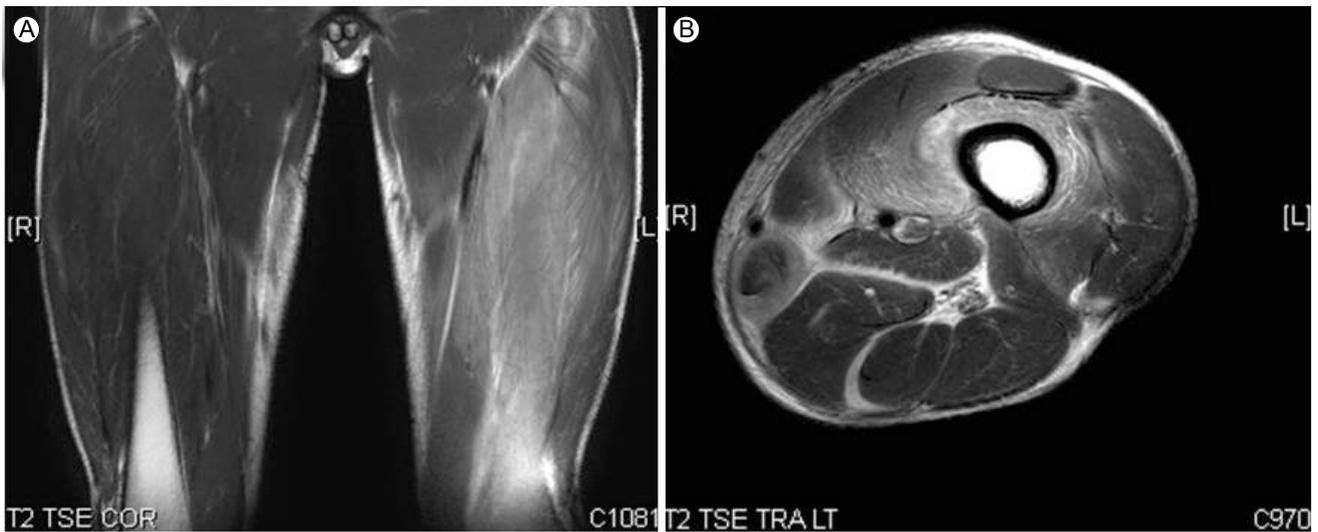
Electromyography did not demonstrate clear evidence of peripheral neuropathy or myopathy. However, magnetic resonance imaging of the left thigh (T2-weighted images) revealed multiple high-intensity signals at the vastus intermedius, vastus medialis, vastus lateralis, and rectus femoris. Inflammation of the intramuscular septa was also visible (Fig. 2). Based on his history of malignancy at the ampulla of Vater, a whole-body positron

emission tomography fused with computed tomography (PET-CT) scan was performed to search for potential malignancies, including recurrence of the neuroendocrine tumor. The PET-CT scan findings did not indicate malignancy; however, faint uptake of the tracer was noted bilaterally at the gracilis muscles located at the medial portion of the thigh.

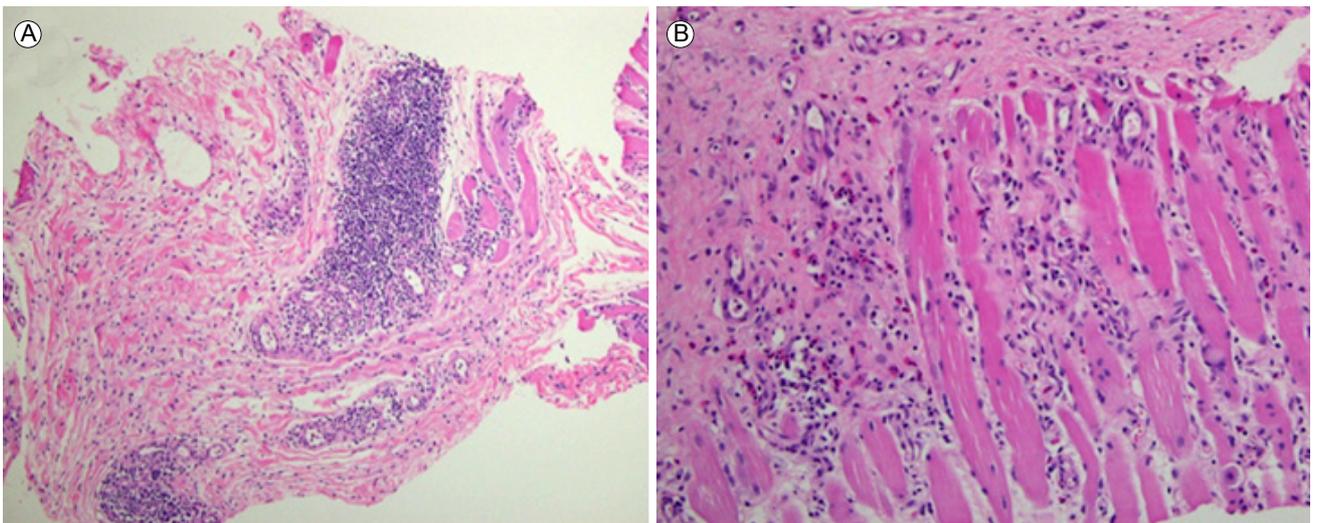
A muscle biopsy of the left thigh was performed, and infiltration of the endomysium and perimysium by inflammatory cells was noted (Fig. 3). These findings were all consistent with a di-

agnosis of dermatomyositis.

Treatment with high-dose oral steroids (1 mg/kg) was initiated, along with adjuvant methotrexate therapy. Despite one week of therapy, the patient's muscle pain and weakness persisted, and his serum muscle enzyme levels continued to increase. Therefore, intravenous immunoglobulin was administered for 5 days at a dose of 400 mg/kg. After administration of immunoglobulin, the patient's muscle weakness improved and his serum creatinine kinase level, lactate de-



**Figure 2.** Magnetic resonance imaging of the thigh. Edema of subcutaneous fat on the left thigh (A) and high-intensity signal and contrast-enhancement at the vastus intermedius, vastus medialis, vastus lateralis, and rectus femoris on T2-weighted images (B) are present.



**Figure 3.** Biopsy of the left thigh muscle. Invasion by inflammatory cells around the blood vessels are seen (A), with plasma cells, lymphocytes, and eosinophils are noted in the endomysium (B) (hematoxylin-eosin staining, A: ×100, B: ×200).

hydrogenase level, erythrocyte sedimentation rate, and C-reactive protein levels had all decreased. He was discharged on oral steroids and methotrexate (15 mg/week), which were tapered over several follow-up outpatient visits as his symptoms and serum creatinine kinase levels improved. He is currently not experiencing muscle weakness, and is being monitored at the clinic.

## DISCUSSION

Dermatomyositis is an idiopathic inflammatory disease of the muscles, in which inflammatory cells invade the skin and muscles. This leads to progressive muscle weakness at the proximal extremities, along with characteristic skin lesions.

The classification method proposed by Bohan and Peter [1] has been widely used to subtype and diagnose dermatomyositis. The diagnosis of 'definite' dermatomyositis is made when 3 or more of the following criteria are met in addition to the presence of characteristic skin lesions: 1) symmetric weakness of proximal muscles, 2) characteristic findings on muscle biopsy, elevated serum muscle enzyme levels, and 3) abnormal electromyogram findings. The diagnosis of 'probable' dermatomyositis is made when muscle biopsy shows findings that indicate dermatomyositis in the absence of skin lesions. Typical skin lesions suggestive of dermatomyositis include a heliotrope rash (violaceous eruption on the upper eyelids), Gottron's papules (scaly, erythematous papules at the extensor side of the proximal interphalangeal joint), and the Shawl or V-sign (widespread red colored area on the upper back, shoulders, and anterior chest). Gerami et al. [2] reported that these skin lesions might precede muscle weakness by several months or years, as well as occur simultaneously with, or after the development of muscle weakness. This patient exhibited muscle weakness of the upper and lower extremities, elevated serum creatinine kinase, elevated lactate dehydrogenase, and elevated aldolase level, as well as findings indicative of dermatomyositis on muscle biopsy. These taken together would indicate a diagnosis of 'probable' dermatomyositis. However, the classification scheme suggested by Bohan and Peter [1] distinguishes dermatomyositis from polymyositis solely on the presence or absence of skin lesions, so

findings consistent with dermatomyositis on muscle biopsy may be misdiagnosed as polymyositis when there is an absence of skin lesions. Polymyositis is characterized by invasion of CD8<sup>+</sup> cells into muscle fibers, whereas dermatomyositis is characterized by perimyofascial and perivascular invasion by B and CD4<sup>+</sup> cells. Based on these findings, the European Neuromuscular Center workshop [3] has attempted to revise the traditional classification scheme and reclassify primary myositis on the basis of specific pathological findings in the presence of precise clinical symptoms. However, the clinical adoption of immunohistochemistry in myositis is currently limited, and further advancements in immunopathology are required for reclassification of various myositis syndromes. Immunohistochemistry of muscle tissue was not performed in this case, but the invasion of inflammatory cells into the endomysium and perimyofascial layer, in addition to hypertrophy of capillaries, are characteristics that point toward a diagnosis of dermatomyositis. While a detailed history was not taken, the patient may have developed skin lesions prior to muscle weakness. Muscle weakness may also precede skin lesions, and would require closer follow-up. Investigation with electromyography may show normal findings in the early phase of myositis. Furthermore, Kim et al. [4] reported that in a series of 100 Korean patients with dermatomyositis, 12 out of 95 patients who underwent electromyography had normal findings. This may explain the absence of abnormalities suggestive of myopathy on electromyography in our patient. Fluorodeoxyglucose uptake in the muscle on a PET-CT scan, in addition to high-intensity signal at the same anatomical site on T2-weighted magnetic resonance imaging images, suggested that there were inflammatory changes in the muscle.

The association between dermatomyositis and malignancy has been well documented. The exact mechanism behind this association remains unclear, but several authors have suggested that it is caused by the formation of autoantibodies as a result of immunological dysfunction. Others have suggested that dermatomyositis may be a paraneoplastic syndrome associated with malignancy.

Many reports of dermatomyositis associated with malignancies have been presented worldwide, including Korea. A retrospective cohort study on 151 Korean patients [5] found that

23 of 98 patients (23.5%) diagnosed with dermatomyositis had malignancy. Lung cancer was the most frequent malignancy associated with dermatomyositis, followed by malignancies in the stomach, breast, biliary tract, nasopharynx, thyroid, and pancreas.

Neuroendocrine tumors originate from neuroendocrine cells that produce hormones, and show specific neuroendocrine differentiation on histological, immunohistochemical, and biochemical evaluation. Most neuroendocrine tumors arise from the gastrointestinal tract, with less than 1% of these tumors occurring at the ampulla of Vater. According to a large-scale Surveillance, Epidemiology, and End Results program run by the National Cancer Institute [6], there were a total of 6,081 cases of ampulla of Vater malignancies and among these, only 139 were carcinoid or neuroendocrine carcinoma in origin (57 high-grade neuroendocrine carcinomas [0.94%], 82 carcinoids [1.3%]).

Reports of dermatomyositis accompanied by a neuroendocrine tumor are extremely rare worldwide. Tanabe et al. [7] reported a case of a Barrett's esophageal neuroendocrine tumor that presented with dermatomyositis, which was suspected due to symptoms of dysphagia and muscle weakness. Among these reports, none have described dermatomyositis in association with a neuroendocrine tumor occurring at the ampulla of Vater. Furthermore, there have been no reports of dermatomyositis associated with a neuroendocrine tumor in Korea. To our knowledge, this is the first report to present a neuroendocrine tumor of the ampulla of Vater in a patient previously diagnosed with dermatomyositis.

The time at which malignancy is diagnosed and when dermatomyositis is discovered varies widely. A cohort study performed by Buchbinder et al. [8] found that 74% of malignancies were diagnosed simultaneously or after the initial diagnosis of inflammatory myopathy. A review of malignancies identified prior to the diagnosis of dermatomyositis in Korea found a case report by Ha et al. [9], which identified a case of dermatomyositis occurring 2 years after remission of an ovarian cancer. Although a PET-CT scan in our patient demonstrated no evidence of recurrence of malignancy, future monitoring of cancer recurrence is suggested.

As mentioned above, dermatomyositis is strongly associated with malignancies in several organs, which include the stomach

and thyroid glands. Dermatomyositis is a complication that may develop in rare type malignancies, such as neuroendocrine tumors of the ampulla of Vater. Therefore, various tests, including esophagogastroduodenoscopy and colonoscopy, as well as laboratory and radiologic studies, are required for the detection of malignancy. When patients with known malignancy complain of muscle weakness, the possibility of dermatomyositis, in addition to chemotherapy-related side effects, should be considered. Serum muscle enzyme levels should be checked in these patients to rule out the possibility of dermatomyositis.

The primary treatment for dermatomyositis includes the administration of corticosteroids. Methotrexate or azathioprine may be used alone or in conjunction with corticosteroids if a case warrants them. In cases of dermatomyositis refractory to treatment with steroids and immunosuppressants, intravenous immunoglobulin administration should be considered. Our patient did not respond to high-dose steroid and methotrexate treatment, and required treatment with intravenous immunoglobulin.

Factors associated with malignancy in dermatomyositis include male sex, increasing age, dysphagia, dermal necrosis, and abscesses of interstitial lung disease [5]. A retrospective cohort study of 121 patients [10] found that male sex, older age at onset, rapid development of cutaneous or muscular symptoms, necrotic skin lesions, high creatinine phosphokinase (CPK) and antinuclear antibody levels, and low C4 and C3 levels were associated with dermatomyositis in the underlying malignancy. The patient in this case was male, had a rapid onset of muscular symptoms, had an elevated serum level of CPK, and had a high titer of anti-nuclear antibody. These factors indicate a predisposition to developing dermatomyositis. Therefore, elderly male patients with malignancy who have an acute onset of muscular symptoms in the presence of necrotic skin lesions should be considered to be at high risk for dermatomyositis. These patients should be closely monitored for the development of signs of dermatomyositis, and should be investigated when they develop muscle weakness or characteristic skin lesions.

Dermatomyositis is often accompanied by malignancies occurring in the lung, breast, and nasopharynx. This report described a rare case of dermatomyositis in a patient with a prior history of a neuroendocrine tumor at the ampulla of Vater, and

discusses this in the context of prior reports in the field.

**중심 단어:** 피부근육염; 자가면역 질환; 악성 종양; 신경내분비종양; 바터팽대부

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