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CASE REPORT

Tomohiko Shibata · Hidehiro Yamada · Nobuaki Hama
Jun Akaogi · Mitsubumi Abe · Emiko Yamasaki
Masako Mizoguchi · Shoichi Ozaki

A case of concurrent vitiligo vulgaris and polymyositis

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Abstract We present a rare case of simultaneous muscle weakness and cutaneous depigmentation. Muscle and skin biopsies confirmed the diagnosis of polymyositis and generalized vitiligo vulgaris. All symptoms improved after steroid therapy. Immunohistochemical analyses revealed predominant CD8-positive T cell infiltration in both muscular and cutaneous lesions. This case suggests that a common autoimmune mechanism mediated by cytotoxic T lymphocytes underlies the pathogeneses of these two diseases.

Key words CD8-positive T cell · Cytotoxic T lymphocyte · Polymyositis · Steroid therapy · Vitiligo

Introduction

The association of vitiligo vulgaris with autoimmune diseases such as autoimmune thyroiditis has been frequently reported.[1,2] An association of vitiligo and polymyositis, however, is so rare that it seems to have been reported only once, by Linthoudt et al. in 1989.[3] Recently we examined a rare case who presented with vitiligo vulgaris and polymyositis simultaneously. We found that CD8-positive T cells represented the predominant population among inflammatory cells infiltrating both dermal and muscular lesions. We believe that this finding may be of relevance to the pathogenesis of these two diseases.

T. Shibata (✉) · H. Yamada · N. Hama · J. Akaogi · S. Ozaki
Division of Rheumatology and Allergy, Department of Internal Medicine, St. Marianna University School of Medicine, 2-16-1 Sugao, Miyamae-ku, Kawasaki 216-8511, Japan
Tel. +81-44-977-8111; Fax +81-44-976-7112
e-mail: shibata@marianna-u.ac.jp

M. Abe
Department of Pathology, St. Marianna University School of Medicine, Kawasaki, Japan

E. Yamasaki · M. Mizoguchi
Department of Dermatology, St. Marianna University School of Medicine, Kawasaki, Japan

Case report

A 70-year-old man was admitted to hospital because of proximal muscle weakness and skin depigmentation. In 1992, he was diagnosed as having idiopathic thrombocytopenic purpura (ITP) by a local doctor, and underwent steroid therapy. Thereafter, the dose of steroids was gradually reduced to a final maintenance dose of 5 mg prednisolone (PSL) daily. Because *Mycobacterium tuberculosis* (*M. tuberculosis*) was detected in sputum cultures for tuberculosis on January 5, 2000, combination chemotherapy with isoniazid (INH), rifampicin (RFP), and ethambutol (EB) was started on January 21. The chemotherapy was stopped within 1 month because the patient developed fever and experienced general malaise accompanied by cutaneous depigmentation, thigh muscle weakness, and an elevation of the serum creatine kinase (CK) level (621 IU/l). Even after the cessation of treatment with antituberculosis agents, his cutaneous and muscular symptoms gradually progressed for the next 5 months. He was therefore referred to our hospital and admitted for further examination and treatment on July 3, 2000. There was no history of Raynaud's phenomenon, cold-intolerance, polyarthralgia, dry eye and dry mouth, or parotitis.

The patient was 165.9 cm tall and weighed 68.8 kg. His body temperature was 36.8°C, his blood pressure was 134/82 mmHg, and his pulse was regular at 68/min. The skin depigmentation was distributed diffusely over the face, bilateral forearms and fingers (Fig. 1), and on the bilateral lower legs. No heliotropic rash, Gottron's sign, or scleroderma were noted. There was no sign of either anemia or keratoconjunctivitis sicca. His lymph nodes and salivary glands were not swollen. Struma was not palpable. Fine crackles were audible in the right lung. No heart murmur was audible. The abdomen was flat and soft without tenderness. Liver and spleen were not palpable. The lower extremities were not edematous. Weakness was found bilaterally in the triceps, trapezius, and quadriceps muscles (4/5 in manual muscle tests). Laboratory data at the time of admission were as follows: erythrocyte sedimentation rate

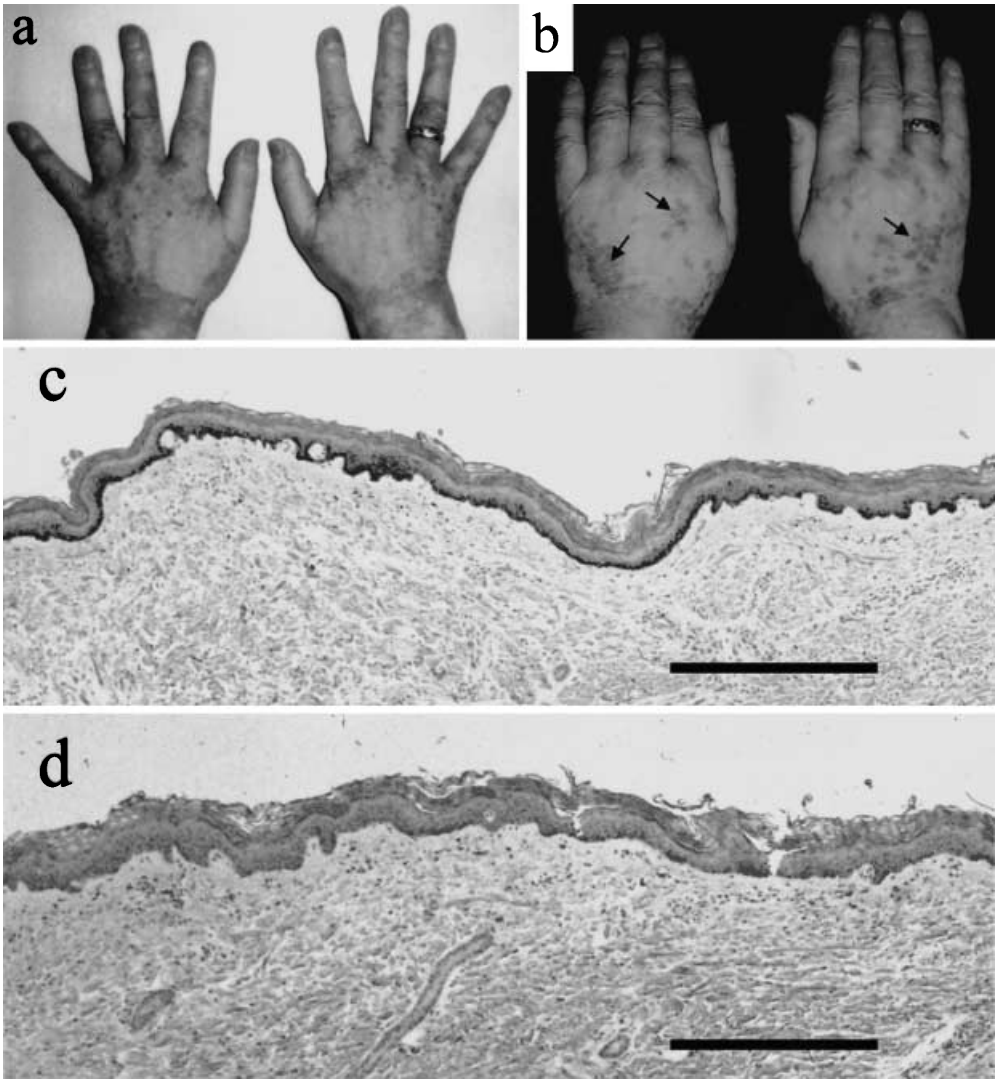

Fig. 1. **a** Cutaneous lesions (both hands) at the time of admission. Vitiliginous areas were found bilaterally on the fingers and the hands. **b** Vitiliginous areas after steroid therapy (both hands). Local repigmentation was noted 10 months after steroid therapy, as indicated by the *arrows*. Micrographs of biopsy material from a normal area of the skin (**c**) and from a vitiliginous lesion (**d**) (Fontana–Masson staining). A decrease and gradual disappearance of melanin-containing melanocytes can be seen in **d**. *Bar* 200 μm

(ESR) was slightly increased (39 mm/h); the results of urinalysis were negative; WBC was 6000/μl with normal differentiation, red blood count (RBC) was 403×10^4/μl, platelets were 14.0×10^4/μl. His Hb level was 13.2 g/dl and his Hct value was 39.9%. On biochemical examination of the serum, the levels of aspartate aminotransferase (AST) (64 IU/l), alanine aminotransferase (ALT) (91 IU/l), and lactate dehydrogenase (LDH) (774 IU/l) were found to be slightly elevated. The amylase level (165 IU/l) was in the normal range. The CK level (1473 IU/l) was elevated. Proportions of MM and MB types of CK were 87% and 13%, respectively. The level of C-reactive protein (CRP) was in the normal range (0.3 mg/dl). On immunological examination of the serum, the results from the RA test (182 U/ml) and the titer of antinuclear antibodies (×2560) were found to be elevated. The serum was negative for anti-Jo-1 and anti-RNP antibodies. The serum titers of anti-SSA and anti-SSB antibodies were positive at ×64 and ×4, respectively. The gum test (10.5 ml/10 min), Schirmer's test (right, 8 mm/5 min; left, 9 mm/5 min), and rose bengal test were all negative. This patient did not fulfil the San Diego criteria for Sjögren's syndrome.[4] Thyroid function was found to be normal. Serum anti-TSH receptor antibodies (3.1%), antithyroid peroxidase antibodies (less than 0.2 U/ml), and antithyroglobulin antibodies (less than 0.5 U/ml) were all negative. A chest X-ray showed a region of pleural thickening and a nodular shadow in the right pulmonary apex. The tuberculin skin test was positive. *M. tuberculosis* was detected in sputum cultures incubated for 4 weeks. Electromyographic examination showed no abnormalities. T2-intensified magnetic resonance images of the thigh revealed scattered areas with high intensity in bilateral quadriceps muscle and femoral rectus muscles. Biopsy specimens of the left femoral rectus muscle were taken on July 14. Histopathological examination of these specimens revealed myogenic muscle fiber atrophy and degeneration, as well as the infiltration of inflammatory cells into the spaces between muscle fibers (Fig. 2). Immunohistochemical staining showed that CD8-positive T cells predominated in the inflammatory infiltrate in the spaces between the muscle

fibers (Fig. 3). HE staining of biopsy specimens obtained from lesional skin showed moderate inflammatory cell infiltration in the superficial layer of the dermis, the infiltrating cells mainly consisting of lymphocytes. Fontana–Masson staining showed a decrease and disappearance of melanocytes (see Fig. 1). Immunohistochemically, most of lymphocytes in the superficial layer of the dermis were found to be CD8-positive T cells (see Fig. 3).

Based on the histopathological findings, the patient was diagnosed as having vitiligo vulgaris together with polymyositis. Because vitiligo was found on the face and extremities, it was identified as a generalized type. Because symptoms of these two diseases appeared immediately after starting antituberculosis chemotherapy, we suspected the occurrence of allergic reactions to these drugs, but the possibility was less likely because the symptoms of the two diseases slowly progressed even after the drugs were stopped. Furthermore, direct lymphocyte stimulation testing for INH, RFP, and EB reactivities were all negative. While administering streptomycin, paraaminosalicylate, and pyrazinamide for active pulmonary tuberculosis, we began giving 30 mg PSL daily as a treatment for the polymyositis. Thereafter, the affected muscles began to recover their strength and the serum CK level decreased. In addition, the vitiligo began to improve 10 months after the start of the treatment with PSL, as reflected by repigmentation of vitiliginous areas (see Fig. 1).

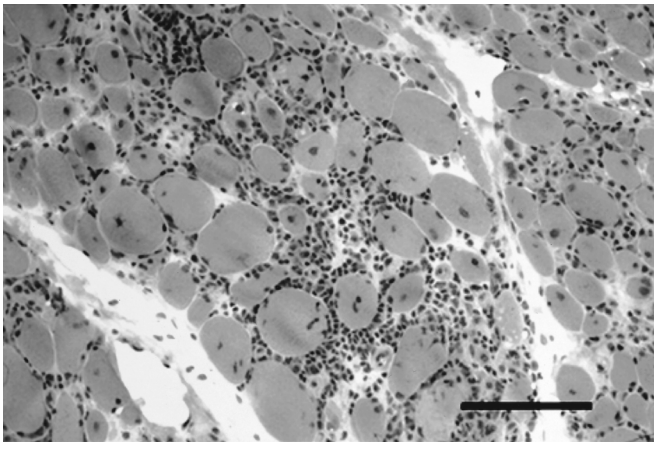

Fig. 2. Micrograph of biopsy material from the left femoral rectus muscle (HE staining). Myogenic muscle fiber atrophy and degeneration is visible, with the infiltration of inflammatory cells into the space between muscle fibers. *Bar* 200 μm

Discussion

Vitiligo vulgaris is an intractable, acquired disorder of cutaneous pigmentation characterized by depigmentation. It affects approximately 1% of the population irrespective of race or sex.[5] In general, oval depigmented lesions appear in the initial stage, and these become confluent to form an irregular topographical arrangement. The main pathological feature of vitiligo is the decrease and disappearance of melanocytes. Although its pathogenesis remains largely unknown, several theories have been proposed, and autoimmune mechanisms for vitiligo are considered to be important by many authors.[6–9] Clinically, vitiligo is classified into three types according to the distribution of the depigmented areas: first, the generalized type in which lesions are observed over the whole body; second, the localized type in which one lesion exists in isolation; third, the dermatomic type in which lesions are distributed according to the dermatomal rule.[2] Koga and Tango[6] classified vitiligo

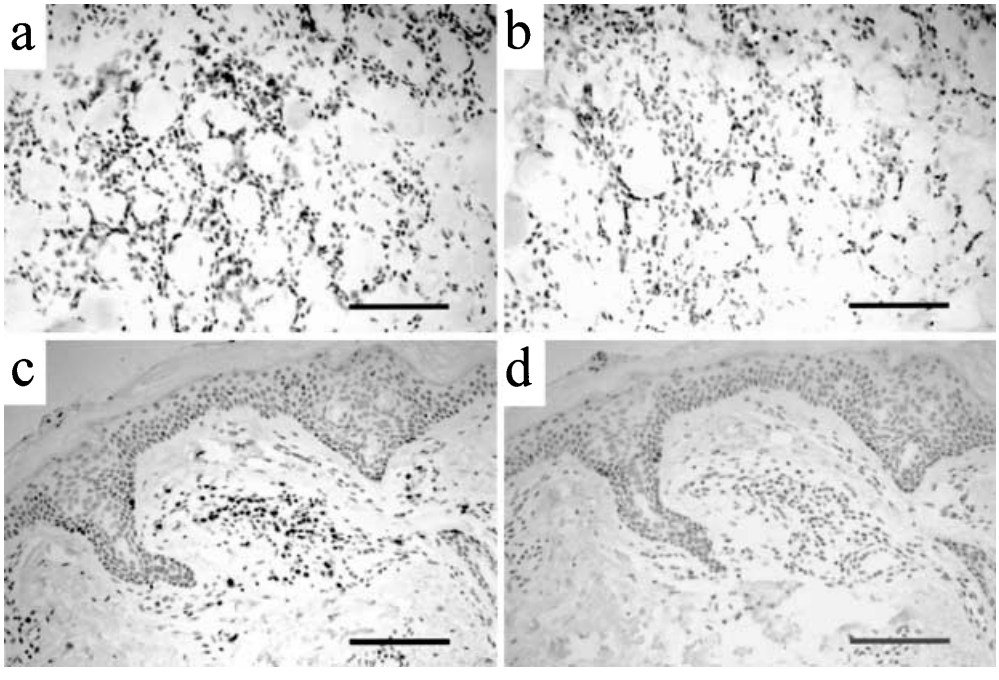

Fig. 3. Immunohistological staining of muscle (**a**, **b**) and skin (**c**, **d**). Biopsy specimens were stained with anti-CD8 (**a**, **c**) and anti-CD4 (**b**, **d**) monoclonal antibodies. CD8-positive T cells predominated in inflammatory infiltrates in the space between muscle fibers and in the superficial layer of the dermis. *Bar* 50 μm

into two types: type A or the non-segmental type, including the generalized type; type B or the segmental type, which is identical to the dermatomic type described above. Type A is characterized by (a) being commonly accompanied by autoimmune diseases, (b) associating with Halo naevus or Köbner's phenomenon, (c) having titers of autoantibodies elevated in the serum, and (d) infiltrations of CD8-positive T cells around melanocytes in the basement membrane on histopathology.[2,6–11] Therefore, it has been suggested that an autoimmune mechanism might contribute to the pathogenesis of type A.[6] Type B is characterized by (a) lesions that are distributed according to the dermatomal rule and disorders that are found in peripheral nerve terminals on electron microscopy, and (b) its association with disorders of perspiration in the affected areas. These characteristics suggest that certain nerve-derived factors contribute to the pathogenesis of type B.[2,6] From the clinical and laboratory findings, this patient was diagnosed as having generalized (type A) vitiligo.

Hyperthyroidism, pernicious anemia, and systemic sclerosis have been reported to be associated with an increased incidence of vitiligo vulgaris.[1,12–14] On the other hand, an association of polymyositis with vitiligo vulgaris has been reported only once.[3] In that case, proximal muscle weakness and dysphagia occurred suddenly 20 years after the onset of vitiligo vulgaris, and a diagnosis of polymyositis was made. As with our present patient, that case belonged to the generalized type (type A) and was negative for autoantibodies. The symptoms of polymyositis rapidly improved during a course of 80 mg PSL administered daily. At the beginning of the treatment there was a partial and limited repigmentation of the skin lesions around the hair follicles. This improvement persisted, but did not progress further after the first few weeks.[3] In our case, the vitiligo was classified clinically as type A, occurred simultaneously with polymyositis, and tended to resolve during steroid treatment. It is conceivable, therefore, that an autoimmune mechanism is contributing to the pathogenesis.

Cytotoxic T cells (CTLs) specific to muscle tissues and melanocytes are believed to contribute to the pathogenesis of polymyositis and vitiligo vulgaris, respectively.[15,16] This hypothesis is supported by the finding that sites of inflammation are infiltrated by leucocytes, predominantly CD8-positive T cells. It has been reported that CTLs which recognize melanocyte-specific antigens are found in the peripheral blood of patients with vitiligo vulgaris,[17] as well as those with melanoma,[18] and that these CTLs express the skin-homing receptor, cutaneous-associated leukocyte antigen (CLA),[19] which facilitates their infiltration of cutaneous tissues. Furthermore, vitiligo vulgaris was reported to occur in 26% of patients with melanoma which resolved after the activation of melanoma-specific CTLs by immunotherapy.[20] This report suggests that such CTLs destroy melanocytes, thereby inducing vitiligo. In contrast, autoantigens recognized by CTLs have not been identified in polymyositis.

There are several possible mechanisms by which these two diseases occurred simultaneously in the present case. First, specific CTLs recognized an unknown antigen which was common to melanocytes and muscle tissues. Second, CTLs specific for melanocytes cross-reacted with an antigen in muscle tissues. Third, different CTLs specific for muscle tissues and melanocytes were activated simultaneously by unknown triggers and migrated to the muscle and skin, respectively. Because no target antigens have been identified in polymyositis, evidence supporting the first and second possibilities is lacking. In addition, we believe that the expression of tissue-specific receptors such as CLA is essential for the infiltration of CTLs into a target tissue. Therefore, the first and second possibilities seem improbable. The present patient had had ITP in the past and was positive for anti-SSA/SSB antibodies at the time of admission to the hospital, which suggests the possibility that various autoimmune abnormalities existed, although they were not clinically evident. Consequently, we hypothesize that any triggering factors activated organ-specific autoreactive CTLs, resulting in the development of polymyositis and vitiligo vulgaris in this case.

Another possibility which needs to be considered is that the antituberculosis drugs were a factor triggering the autoimmune disease. There have been no reports that antituberculosis drugs (INH, RFP, EB) induce vitiligo and polymyositis. However, it is possible that the administration of RFP triggered the development of polymyositis and vitiligo which had been suppressed by the daily administration of 5 mg PSL, since RFP is known to facilitate the metabolism of PSL.[21]

Vitiligo can escape the notice of physicians because it is sometimes of a localized type and apparently without clinical significance. This may be one reason why cases of vitiligo concurrent with polymyositis are rarely reported. We therefore suggest that there are probably unreported cases which are similar to the present patient. To clarify the pathogenesis of the two diseases, it seems necessary to identify more cases of vitiligo associated with polymyositis from careful clinical observations, and to accumulate more information about these diseases.

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