Adult-onset Satoyoshi Syndrome with Prominent Laterality of Clinical Features

Masaki Ishihara¹, Katsuhiko Ogawa¹, Yutaka Suzuki¹, Satoshi Kamei¹,
Toyoko Ochiai² and Masahiro Sonoo³

Abstract

We herein report the case of a patient with adult-onset Satoyoshi syndrome. Alopecia was detected on the patient's head, left leg and abdomen, with pigmentation on the left thigh and abdomen. Painful muscle spasms were also noted in the abdomen and left upper and lower extremities, and a sensory disturbance was present in the left thigh. A skin biopsy of this field showed lymphocyte infiltration, and the patient was found to be positive for antinuclear antibodies and rheumatoid factor. These clinical findings were atypical, as they were lateralized. This case is the first report of Satoyoshi syndrome associated with a sensory disturbance. The patient's histological findings and positivity for autoantibodies indicated the presence of immunological abnormalities in this case of Satoyoshi syndrome.

Key words: adult-onset Satoyoshi syndrome, prominent laterality, painful muscle spasms, sensory disturbance, lymphocyte infiltration

(Intern Med 53: 2811-2816, 2014)

(DOI: 10.2169/internalmedicine.53.2958)

Introduction

Satoyoshi syndrome is a childhood-onset progressive multisystem disorder characterized by the triad of progressive intermittent painful muscle spasms, alopecia, and diarrhea (1). Painful muscle spasms and alopecia are the most frequent features of Satoyoshi syndrome (1), usually followed by diarrhea (1). Patients who develop this syndrome before 12 years of age often exhibit skeletal abnormalities and growth retardation (2-4). Other clinical findings include low levels of serum protein and total cholesterol (2), and endocrine disturbances, such as amenorrhea with a tendency toward the development of a hypoplastic uterus and ovaries (1). Complications of autoimmune diseases, such as myasthenia gravis (5) as well as the presence of autoantibodies (auto-Abs) (2, 6-11) and responsiveness to treatment with corticosteroids (9, 11-13) and intravenous immunoglobulin (IVIG), have been reported in patients with Satoyoshi syndrome (7, 14), indicating that an autoimmune mechanism may play a role in the onset of this syndrome, although the

precise underlying mechanism remain unknown. The age of onset of Satoyoshi syndrome ranges from 5 to 19 years, with a mean age of 11 years (2, 15); however, adult-onset Satoyoshi syndrome is rare, having so far been reported in only a few patients (2, 7, 15-17). We herein report the case of a man with adult-onset Satoyoshi syndrome whose clinical features showed prominent laterality.

Case Report

A 45-year-old Japanese man was admitted to our hospital with complaints of painful muscle spasms in the upper and lower extremities on the left side and abdomen, with alopecia on the head and left thigh. The patient first noticed painful muscle spasms in the calf on the left side at 42 years of age, which gradually spread to the left thigh at 43 years of age, followed by the abdomen and left arm. Alopecia subsequently appeared on the head and left thigh at 44 years of age. The patient was ultimately admitted to a local hospital at 45 years of age, where he received etizolam and tizanidine, with unsatisfactory effects; therefore, he was referred

¹Division of Neurology, Department of Medicine, Nihon University School of Medicine, Japan, ²Department of Dermatology, Nihon University School of Medicine, Japan and ³Department of Neurology, Teikyo University School of Medicine, Japan

Received for publication March 26, 2014; Accepted for publication June 10, 2014

Correspondence to Dr. Katsuhiko Ogawa, ogawa.katsuhiko@nihon-u.ac.jp

Figure 1. Pictures of the head (A), abdomen (B), and thigh on the left side (C). Alopecia was noted on the head (white arrows) (A) and left side of the abdomen (B), as well as the thigh on the left side (C). Multiple magenta-pigmented spots were detected on the abdomen (black arrows) (B) and thigh (C) on the left side. Rt: right

to our hospital. His past history included hepatitis B at 26 years of age; however, his family history was unremarkable. In addition, diarrhea was absent at the time of onset.

On a physical examination, both anemia and jaundice were absent. The patient was 174.7 cm in height and weighed 66 kg. Alopecia was detected on his head as well as abdomen, thigh and lower leg on the left side (Fig. 1). Multiple magenta-pigmented spots were also noted on the abdomen and thigh on the left side (Fig. 1B, C). However, there were no joint deformities or skeletal abnormalities in the trunk or the four extremities. On a neurological examination, no abnormalities were noted in the patient's cranial nerves, muscle strength or muscle tone in the four extremities, deep tendon reflexes, coordination, standing, or gait. Babinski's sign was negative, and both muscle hypertrophy and atrophy were absent. The sensations of pinprick and light touch were moderately decreased in the lateral portion of the left thigh. The presence of abnormal sensations in this region was accompanied by alopecia and pigmentation. Vibrations and joint point sensations were normal. Painful muscle spasms occurred in the upper and lower extremities on the left side and the lateral portions of the abdomen on both sides 10 to 15 times a day. Painful spasms were also induced by muscle contractions in the left lower extremity.

The findings of a chest X-ray were normal, and an abdominal X-ray showed no abnormal gas in the intestinal tract. The patient's blood cell count was normal, as were the results of blood chemistry tests, with the exception of mildly increased levels of total cholesterol (222 mg/dL, normal; 159-219 mg/dL) and triglycerides (189 mg/dL, normal; 50-149 mg/dL). Meanwhile, the levels of creatinine phosphokinase, myoglobin, aldolase, vitamin B1, vitamin B2, folic acid, lactate, and pyruvate in the serum were normal. The immunoglobulin G (IgG) titer was also normal (1,547 mg/dL, normal; 870-1,700 mg/dL); however, antinuclear antibodies (ANA) were positive, with a titer of 1:640 (speckled pattern). In addition, the level of double-stranded DNA was

within the normal range (1.9 IU/mL; normal <12 IU/mL), whereas rheumatoid factor (RF) was positive (171 IU/mL, normal; <10 IU/mL). Furthermore, the CH50 level was normal (39.8 IU/mL, normal; 25.0-48.0 IU/mL), while antiglutamic acid decarboxylase antibodies were negative. The levels of free T3, free T4, thyroid-stimulating hormone, and adrenocorticotrophic hormone were also normal, and anti-thyroglobulin antibodies (ATGA) and anti-thyroid microsomal antibodies (ATMA) were negative. A cerebrospinal fluid analysis disclosed neither pleocytosis nor elevation of total proteins. The MRI findings of the head and total spinal cord were normal. On surface electromyography (sEMG) (Fig. 2), continuous muscle discharges were noted in the quadriceps femoris and tibialis anterior muscles on the left side and in the abdomen after the muscles in the left lower extremity contracted. The continuous muscle discharges in these four areas gradually receded after the patient was instructed to relax his muscles. Meanwhile, painful muscle spasms were clinically observed in these four areas while continuous muscle discharges appeared on sEMG. Continual muscle discharges were also detected in the rectus abdominis muscle on the left side after the patient was instructed to relax (Fig. 2). Needle electromyography (nEMG) of the gastrocnemius muscle on the left side showed continuous discharges at the time of spasms in this muscle (Fig. 3). In contrast, spontaneous and myotonic discharges were negative at rest on nEMG. The histological findings of the skin on the lateral portion of the left thigh showed lymphocyte infiltration in the papillary and reticular layers of the dermis and a remaining sebaceous gland (Fig. 4). In addition, an immunohistochemical study of the skin using antibodies to CD3 (monoclonal antibody, Novacastra™, Leica Biosystems, Newcastle, UK, 1:100) and CD20 (monoclonal antibody, Anti-Human CD20cy, DAKO, Glostrup, Denmark, 1:1,600) demonstrated CD3-positive lymphocytes in the dermis (Fig. 5). No CD20-positive lymphocytes, i.e., B-cell, were detected.

Figure 2. Surface electromyography performed during the muscle spasms showed continuous muscle discharges in the left quadriceps femoris and left tibialis anterior muscles, and lateral portions of the abdomen on both sides, following muscle contractions in the left extremity. The muscle discharges continued and then gradually receded after the patient was instructed to relax his muscles. Continual muscle discharges were also detected in the left rectus abdominis muscle. rt: right, lt: left

Figure 3. Needle electromyography of the gastrocnemius muscle on the left side showed continuous muscle discharges during the muscle spasms. This finding was consistent with the cramping discharges. msec: millisecond

Figure 5. The immunohistochemical findings of the skin showed the presence of CD3-positive lymphocytes in the dermis (arrows).

Dantrolene sodium was prescribed at a daily dose of 75 mg/day, and the patient's painful muscle spasms gradually disappeared, although the alopecia and sensory disturbance remained unchanged.

Figure 4. The histological findings of the skin on the left thigh showed lymphocyte infiltration spreading from the papillary layer (black single arrow) to the reticular layer (black double arrows). A remaining sebaceous gland is also shown (white single arrow) (Hematoxylin and Eosin staining).

Discussion

Satoyoshi syndrome is a disorder with multisystem involvement (1). Progressive alopecia, diarrhea, and intermittent painful muscle spasms throughout the body are the three cardinal symptoms of this disease (18). Other clinical findings include secondary skeletal abnormalities and endocrinopathy (1). The typical age of onset is before 15 years of age (18). Muscle spasms are the initial symptom in nearly all patients with Satoyoshi syndrome (15) and usually begin between 4 and 19 years of age (1). In general, the severity of alopecia is in proportion to that of the muscle spasms (15). The present patient was diagnosed with Sa-

Table. Previously Reported Patients with Adult-onset Satoyoshi Syndrome

Reference	age/sex	age of onset	painful muscle spasms	alopecia	skin pigmentation	diarrhea	sensory disturbance	auto-Ab	beneficial treatment	menstrual irregularity	complications
2	65/F	31	+ (whole body)	+ (frontal/occipital head, eyebrows, axilla, FE, pubic region)	–	+	–	+ (ANA, ATMA, ATGA)	dantrolene sodium, PSL	+ (amenorrhea)	Hashimoto T
7	54/F	52	+ (bil UE and LE / abdomen)	+ (whole body)	–	+	–	+ (ANA, ATMA, ATGA)	mPSL, IVIG, CP, diazepam	–	Hashimoto T, GU, EE
15	25/M	22	+ (rt side of the body)	+ (rt side of the body)	+ (rt side of the body)	–	–	–	dantrolene sodium	–	–
16	45/M	36	+ (whole body)	+ (whole body)	–	+	–	–	dantrolene sodium, botulinum toxin	–	–
17	39/F	36	+ (whole body)	+ (trunk, temporal head)	–	+	–	–	dantrolene sodium	+	–
Our patient	45/M	42	+ (lt arm and leg / bil lateral abdomen)	+ (head, lt leg / lt abdomen)	+ (lt thigh / lt abdomen)	–	+ (lt lateral thigh)	+ (ANA, RF)	dantrolene sodium	–	–

Abbreviation: ANA: anti-nuclear antibody, ATGA: anti-thyroglobulin antibody, ATMA: anti-thyroid microsome antibody, auto-Ab: auto-antibody, bil: bilateral, CP: cyclophosphamide, EE: eosinophilic esophagitis, F: female, FE: four extremities, GU: gastric ulcer, Hashimoto T: Hashimoto's thyroiditis, IVIG: intravenous immunoglobulin, LE: lower extremities, lt: left, M: male, mPSL: methyl prednisolone, PSL: prednisolone, RF: rheumatoid factor, rt: right, UE: upper extremities

toyoshi syndrome, based on the presence of progressive painful muscle spasms and alopecia; however, the adult onset of the initial symptoms, prominent laterality of the clinical features, absence of diarrhea, and presence of sensory disturbances observed in this case were atypical compared to the features of the usual form of this disease. In particular, sensory disturbances have not been noted in previously reported patients with Satoyoshi syndrome. The sensory disturbance detected in our patient was considered to be related to the pathogenesis of Satoyoshi syndrome, as disturbances were noted in the regions with pigmentation and alopecia. Most patients with childhood-onset Satoyoshi syndrome present with skeletal abnormalities and subsequent growth retardation due to the muscle spasms (2-4). However, our patient did not show any evidence of skeletal abnormalities or growth retardation. Meanwhile, nEMG demonstrated continuous muscle discharges during the painful muscle spasms, consistent with the cramping discharges, and sEMG showed continuous muscle discharges in the affected muscles. The appearance of continuous muscle discharges on both nEMG and sEMG reflected abnormalities in the function of the muscles affected by spasms in our patient. Skin biopsies were performed in two previously reported patients with childhood-onset Satoyoshi syndrome (9, 11). The histological findings of the skin were normal in one patient (9), while the other patient exhibited lymphocyte infiltration in the peribulbar area of the deep dermis (11). In contrast, the lymphocyte infiltration had spread to the papillary layer from the reticular layer in the dermis of the pigmented skin in our patient. CD3 is closely associated with the T lymphocyte antigen receptor (19). Therefore, the CD3-positive lymphocytes detected in our patient's skin were T lymphocytes (Fig. 5). The sites of termination of sensory peripheral nerves are called free nerve endings (FNEs) (20), and are distributed throughout the body. FNEs in the skin detect temperature, mechanical stimuli (touch, pressure, stretch), and pain (20). It is possible that impairment of FNEs due to the infiltration of T lymphocytes induced the sensory disturbance observed in our patient.

Two previous reports have documented the role of functional abnormalities of the neurons in the spinal cord in the pathogenesis of Satoyoshi syndrome (16, 21). For example, Merello et al. (16) reported that the muscle spasms observed in their study were caused by the interruption of the inhibitory effects of Renshaw cells on motor neurons, based on the findings of an nEMG examination. Similarly, Drost et al. (21) reported that deregulation of alpha motor neurons leads to muscle spasms, based on the results of an sEMG study. We therefore consider that the dysfunction of motor neurons in the spinal cord occurred predominantly on the lateral side in this case, thus resulting in the prominent laterality of the patient's muscle spasms.

Reports of adult-onset Satoyoshi syndrome are rare (2, 7, 15-17), with only five patients with adult-onset Satoyoshi syndrome having been reported (Table) (2, 7, 15-17). The most common age at onset was in

the 30s in three patients (2, 16, 17). In addition, painful muscle spasms developed on both sides in four patients (2, 7, 16, 17) and unilaterally side in two patients (15), including our patient. In contrast, alopecia occurred in all six patients (2, 7, 15-17), while pigmentation of the skin was observed in only two patients (15), including our patient. Meanwhile, four patients presented with diarrhea (2, 7, 16, 17), although this symptom was absent in this case. Importantly, sensory disturbances were detected in our patient alone. A unilateral presentation of clinical features was noted in two patients (15), including our patient, both of whom also exhibited skin pigmentation (15). Furthermore, auto-Abs were detected in three patients, including our patient (2, 7); ANA were detected in these three patients in common (2, 7), whereas both ATGA and ATMA were positive in the two reported patients with Hashimoto's thyroiditis (2, 7). RF was also detected in our patient, although complicating autoimmune diseases, such as rheumatoid arthritis, were absent in this case. A skin biopsy was performed in our patient alone among those with adult-onset Satoyoshi syndrome. An autoimmune mechanism has recently been considered in the pathogenesis of Satoyoshi syndrome. The lymphocyte infiltration in the skin and presence of auto-Abs noted in the current case support the role of an autoimmune mechanism in the pathogenesis of Satoyoshi syndrome, although it is difficult to explain the prominent laterality of clinical features observed in our patient, based on the effect of an autoimmune mechanism. Moreover, immunosuppressive therapy was administered in the two patients with Hashimoto's thyroiditis (2, 7) as well as prednisolone (2, 7), while IVIG and cyclophosphamide were administered in only one (7) of these patients, with satisfactory results (2, 7). In addition to immunosuppressants, the use of dantrolene sodium (22), botulinum toxin (16) and antiepileptic drugs, such as carbamazepine (23, 24) has been reported in cases of Satoyoshi syndrome in order to suppress the painful muscle spasms associated with this disease. Dantrolene sodium was most frequently prescribed (five patients) and found to be beneficial among previously reported cases (2, 7, 15-17), including our patient.

We herein reported the case of a patient with atypical adult-onset Satoyoshi syndrome who displayed prominent laterality of clinical features and sensory disturbances. This case is the first report of Satoyoshi syndrome to involve a sensory disturbance. Electrophysiological examinations detected functional abnormalities in the muscles affected by spasms, and characteristic lymphocyte infiltration was confirmed in the regions with sensory disturbances and pigmentation in this case. The confirmation of lymphocyte infiltration in the skin and presence of auto-Abs in our patient suggests the role of immunological abnormalities in the pathogenesis of Satoyoshi syndrome.

The authors state that they have no Conflict of Interest (COI).

References

1. Satoyoshi E. A syndrome of progressive muscle spasm, alopecia, and diarrhea. *Neurology* **28**: 458-471, 1978.
2. Ikeda K, Satoyoshi E, Kinoshita M, Wataka N, Iwasaki Y. Satoyoshi's syndrome in an adult: a review of the literature of adult onset cases. *Intern Med* **37**: 784-787, 1998.
3. Ehlayel MS, Lasassie Y. Satoyoshi syndrome: an unusual postnatal multisystemic disorder. *Am J Med Genet* **57**: 620-625, 1995.
4. Haymon ML, Willis RB, Ehlayel MS, Lasassie Y. Radiological and orthopedic abnormalities in Satoyoshi syndrome. *Pediatr Radiol* **27**: 415-418, 1997.
5. Satoh A, Tsujihata M, Yoshimura T, Mori T, Nagataki S. Myasthenia gravis associated with Satoyoshi syndrome: muscle cramps, alopecia, and diarrhea. *Neurology* **33**: 1209-1211, 1983.
6. Matsuura E, Matsuyama W, Sameshima T, Arimura K. Satoyoshi syndrome has antibody against brain and gastrointestinal tissue. *Muscle Nerve* **36**: 400-403, 2007.
7. Asherson RA, Giampaolo D, Strimling M. A case of adult-onset Satoyoshi syndrome with gastric ulceration and eosinophilic enteritis. *Nat Clin Pract Rheumatol* **4**: 439-444, 2008.
8. Kamat D, Petry L, Berry S. A case of Satoyoshi syndrome: a multisystem disorder. *Clin Pediatr* **42**: 745-748, 2003.
9. Yamagata T, Miyao M, Momoi M, Matsumoto S, Yanagisawa M. A case of generalized komuragaeri disease (Satoyoshi disease) treated with glucocorticoid. *Rinsho Shinkeigaku (Clin Neurol)* **31**: 79-83, 1991 (in Japanese, Abstract in English).
10. Drost G, Yerrips A, Hooijkaas H, Zwarts M. Glutamic acid decarboxylase antibodies in Satoyoshi syndrome. *Ann Neurol* **55**: 450-451, 2004.
11. Oyama M. Satoyoshi syndrome. *Arch Dermatol* **135**: 91-92, 1999.
12. Cecchin CR, Félix TM, Magalhães RB, Furlanetto TW. Satoyoshi syndrome in a Caucasian girl improved with glucocorticoids--a clinical report. *Am J Med Genet A* **118**: 52-54, 2003.
13. Kuru S, Riku S, Nakayabu M, Kobayashi Y, Ieda T. A case of "syndrome of progressive muscle spasm, alopecia, and diarrhea (Satoyoshi)" treated with steroid pulse therapy. *Rinsho Shinkeigaku (Clin Neurol)* **32**: 612-615, 1992 (in Japanese, Abstract in English).
14. Arita J, Hamano S, Nara T, Maekawa K. Intravenous gammaglobulin therapy of Satoyoshi syndrome. *Brain Dev* **18**: 409-411, 1996.
15. Salah Uddin ABM, Walters AS, Ali A, Brannan T. A unilateral presentation of 'Satoyoshi syndrome'. *Parkinsonism Relat Disord* **8**: 211-213, 2002.
16. Merello M, García H, Nogués M, Leigurrda R. Masticatory muscle spasm in a non-japanese patient with Satoyoshi syndrome successfully treated with botulinum toxin. *Mov Disord* **9**: 104-105, 1994.
17. Tajima Y, Tashiro K, Gotoh Y. Satoyoshi disease (generalized komuragaeri disease) associated with bilateral gastrocnemius hypertrophy. *Shinkeinaika (Neurol Med)* **41**: 93-94, 1994 (in Japanese, Abstract in English).
18. Venegas-Vega CA, Rivera-Vega MR, Cuevas-Covarrubias S, Orozco J, Kofman-Alfaro S. Satoyoshi syndrome with unusual skeletal abnormalities and parental consanguinity. *Am J Med Part A* **149A**: 2448-2451, 2009.
19. Steward M, Bishop R, Piggott NH, Milton ID, Angus B, Horne CH. Production and characterization of a new monoclonal antibody effective in recognizing the CD3 T-cell associated antigen in formalin-fixed embedded tissue. *Histopathology* **30**: 16-22, 1997.
20. Malkoc E, Ates F, Tekeli H, Kurt B, Turker T, Basel S. Free nerve ending on skin extracted by circumcision and its relation to premature ejaculation. *J Androl* **33**: 1263-1267, 2012.
21. Drost G, Verrips A, van Engelen BG, Stegeman DF, Zwarts MJ. Involuntary painful muscle contractions in Satoyoshi syndrome: a

- surface electromyographic study. *Mov Disord* **21**: 2015-2018, 2006.
- 22.** Matsuura T, Yokoe M, Shinno S. A case of Satoyoshi syndrome complicating marginal gingivitis of the mandible and dislocation of the temporomandibular joint. *Rinsho Shinkeigaku (Clin Neurol)* **42**: 889-891, 2002 (in Japanese, Abstract in English).
- 23.** Heger S, Kuester RM, Volk R, Stephani U, Sippell WG. Satoyoshi syndrome: a rare mutisystemic disorder requiring systemic and symptomatic treatment. *Brain Dev* **28**: 300-304, 2006.
- 24.** Castiglioni C, Díaz A, Moënné K, Mericq V, Salvador F, Hernández C. Satoyoshi syndrome: report of one case. *Rev Med Chil* **137**: 542-546, 2009.

© 2014 The Japanese Society of Internal Medicine
<http://www.naika.or.jp/imonline/index.html>