

A case of adult-onset Satoyoshi syndrome with gastric ulceration and eosinophilic enteritis

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SUMMARY

Background The patient was misdiagnosed as having Sjögren's syndrome (on the basis of a lower-limb rash and dry eyes and mouth) in 1999, and then as having systemic lupus erythematosus (on the basis of hair loss and a high antinuclear antibody titer) in 2005. Total alopecia, muscular spasms and diarrhea developed over the following 2 years, and the patient experienced gastric ulceration in 2006. A rheumatologic opinion was sought in 2007.

Investigations Physical examination, CBC, glucose tolerance test, iron studies, HLA typing, immunological investigations and complete gastrointestinal investigations, including gastroscopy, colonoscopy and small bowel biopsy.

Diagnosis Satoyoshi syndrome with autoimmune features (high levels of antinuclear antibody and antibodies to thyroid tissue) and malabsorption due to eosinophilic enteritis. This patient is only the fifth adult in the world reported to have Satoyoshi syndrome, and the first-reported adult case from South Africa.

Management The patient had only a transitory response to glucocorticoid treatment. Complete amelioration of symptoms resulted on two occasions when treated with intravenous immunoglobulin; however, the remissions only lasted for 6–8 weeks. More-intensive immunosuppression with azathioprine is currently being attempted.

KEYWORDS adult-onset Satoyoshi syndrome, antinuclear antibodies, eosinophilic enteritis, Hashimoto's thyroiditis, intravenous immunoglobulin

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Learning objectives

Upon completion of this activity, participants should be able to:

- 1 Describe clinical features of Satoyoshi syndrome.
- 2 Describe the most common profile of patients with Satoyoshi syndrome.
- 3 Describe clinical features of stiff-person syndrome.
- 4 Identify gastrointestinal problems most likely to be associated with Satoyoshi syndrome.
- 5 List treatment strategies for patients with Satoyoshi syndrome.

Competing interests

The authors, the Associate Publisher R Ashton and the CME questions author D Lie declared no competing interests.

THE CASE

The female patient, who is of Indian origin, developed a rash on her lower limbs in 1999, at the age of 46 years. The patient subsequently developed dry eyes and mouth, and was diagnosed with Sjögren's syndrome. Oral steroids (prednisone) were administered at a dose of 60 mg/day, which was slowly tapered over a 6-week period. The rash gradually subsided with the steroid treatment.

In 2005, the patient was hospitalized and diagnosed with systemic lupus erythematosus (SLE). Although there were no clinical indicators of SLE, the condition was suspected because the patient had experienced hair loss and had an antinuclear antibody (ANA) titer of 1:1,280. No other definitive serological tests for SLE were included in the patient's medical

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Figure 1 Patient with Satoyoshi syndrome showing alopecia totalis involving hair and eyebrows.

records from this time; however, the hair loss continued to total alopecia over the subsequent 2 years (Figure 1). The patient was referred to a neurologist because of abnormal movements, which were initially, and incorrectly, diagnosed as chorea. They were, in fact, painful muscular spasms that affected her arms, legs and abdominal musculature. The spasms occurred very frequently (every 1–3 min), lasted for ~5 min, and were associated with abnormal posturing of the limbs. The patient's husband resorted to massaging the affected muscles while the disabling spasms were occurring. MRI was normal. The patient was given clonazepam (up to 40 mg every 6 h, taken orally) and biperiden (up to 4 g three times a day, taken orally) in an attempt to control the abnormal movements, but no beneficial effects were observed.

In 2006, the patient developed a gastric ulcer. At this time, the painful muscular spasms were still occurring. She received three intravenous methylprednisolone (1 g) infusions and experienced a temporary improvement in her muscle spasms. Unfortunately, they recurred 2–3 weeks later.

Diarrhea commenced in early 2007, with episodes occurring 4–5 times per day. The patient underwent foregut and hindgut endoscopy, but no significant abnormalities were detected. The diarrhea and the spasms continued.

In March 2007, the patient was hospitalized again (for 2 weeks) and examined by a rheumatologist for the first time, as the spasms

had become very obvious and involved her arms, hands, legs, feet and abdominal muscles. A second neurological opinion was sought and two possible diagnoses—stiff person syndrome (SPS) and adverse effects of the clonazepam—were considered. Clonazepam was, therefore, discontinued. Levels of antiglutamic acid-decarboxylase (anti-GAD) autoantibodies were measured to test for the suspected diagnosis of SPS syndrome; however, results were negative (<0.1 IU/ml). The patient was anemic, and iron studies confirmed an iron-deficiency anemia (Table 1). Serum folate levels were lower than normal (5.6 nmol/l; normal value >12.19 nmol/l), probably indicative of malabsorption. Serum B₁₂ levels were normal, as were markers for hepatic function. The patient's C-reactive protein level was normal. Tests for rheumatoid factor and antibodies against phospholipids, double-stranded DNA and extractable nuclear antigens were all negative. The patient, however, was again positive for ANA at a titer of 1:640 (speckled pattern). The patient also tested positive for antibodies to thyroid microsomes and antithyroglobulin antibodies, which is indicative of Hashimoto's thyroiditis. Thyroid function was normal. Serum immunoglobulin levels were normal. Results from a full glucose tolerance test were flat (fasting = 5.4 mmol/l [97.3 mg/dl], 30 min = 6.4 mmol/l [115.3 mg/dl], 60 min = 4.4 mmol/l [79.3 mg/dl], 90 min = 5.3 mmol/l [95.5 mg/dl], 120 min = 5.5 mmol/l [99.1 mg/dl]). Serum cholesterol and triglyceride levels were normal, as were creatine kinase levels (not measured during acute spasms). Hypoparathyroidism was excluded by normal calcium and parathyroid hormone levels. HLA studies revealed that the patient was A1, A3, B13, B35, C14, DR14, DR15, DQ5. Results from the serological tests performed in 2007 are shown in Table 1. Electromyography was performed in July 2007, the results of which were normal.

The patient was readmitted to hospital in August 2007 for 5 days of intravenous immunoglobulin (IVIG) (28 g/day) administered with diazepam (5 mg three times a day and 10 mg nightly). The patient experienced an immediate cessation of all spasms. A repeat upper endoscopic study of the esophagus, stomach and duodenum was performed, and infiltration of the duodenum was clearly visible (Figure 2A). Biopsy of the infiltrated area was compatible with eosinophilic enteritis (Figure 2B): abundant

Table 1 Results from serological tests performed in 2007.

Serological marker	Patient's results	Normal result or range
Hemoglobin	9.8 g/dl	12.4–16.7 g/dl
Serum iron	1.8 µmol/l	9.0–30.4 µmol/l
Serum ferritin	7 ng/ml	20–300 ng/ml
Serum B ₁₂	519 pmol/l	139–651 pmol/l
Serum folate	5.6 nmol/l	>12.19 nmol/l
C-reactive protein	9.5 mg/l	0–8 mg/l
Hepatic function markers		
Alkaline phosphatase	52 IU/l	51–117 IU/l
Gamma-glutamyl transferase	8 IU/l	0–44 IU/l
Alanine transaminase	13 IU/l	<35 IU/l
Aspartate transaminase	21 IU/l	13–35 IU/l
Autoantibodies		
GAD	Negative (<0.1 IU/ml)	0.0–10.0 IU/ml
Phospholipid	Negative	Negative
Rheumatoid factor	Negative	Negative
Double-stranded DNA	Negative	Negative
Extricable nuclear antigens	Negative	Negative
ANA	1:640 (speckled pattern)	Negative
Thyroid microsomes	39.51 IU/ml	0.16–5.61 IU/ml
Thyroglobulin	15.32 IU/ml	0.31–4.11 IU/ml
Thyroid function markers		
Thyroid-stimulating hormone	0.97 µIU/ml	0.35–4.94 µIU/ml
Thyroxine (also known as T ₄)	11.7 pmol/l (0.91 ng/dl)	9–19 pmol/l (0.70–1.47 ng/dl)
Serum immunoglobulins	76 IU/l	29–103 IU/l
Serum cholesterol	3.5 mmol/l (135.1 mg/dl)	<3.5 mmol/l (<135.1 mg/dl)
Serum triglycerides	1.3 mmol/l	<1.7 mmol/l
Creatine kinase	40 IU/l	26–140 IU/l
Calcium (total)	2.38 mmol/l (9.52 mg/dl)	2.15–2.65 mmol/l (8.60–10.60 mg/dl)
Calcium (corrected)	2.41 mmol/l (9.64 mg/dl)	2.15–2.65 mmol/l (8.60–10.60 mg/dl)
Parathyroid hormone	26 pg/l	12.6–87.0 pg/l

Abbreviations: ANA, antinuclear antibody; GAD, glutamic acid decarboxylase.

lamina propria eosinophils (>10 per high-power field) with focal exocytosis between the intestinal crypt epithelium was observed. Tests for antiendomysin antibodies (IgA) and antibodies to gluten (IgG and IgA) gave negative results, which excluded the possibility of celiac disease. As the patient's hemoglobin level had fallen to 7 g/dl with a low serum iron level, four pints of packed cells were administered. The patient was prescribed diazepam (5 mg three times a day and 10 mg nightly) and discharged from hospital.

The effects of the IVIG lasted for 6–8 weeks. The patient was then readmitted and a further 5-day course of IVIG was administered, again with a 6–8 week improvement.

In December 2007, a further admission was necessary. The patient was still experiencing diarrhea, had recurrent episodes of abdominal pain and nausea that had prevented her from eating, and had lost ~20 kg in weight. Stool cultures were positive for *Clostridium difficile* and 5 days of antibiotic therapy resulted in cessation

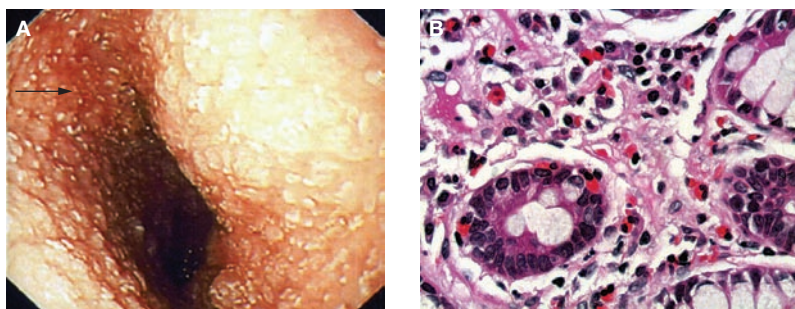


Figure 2 Analysis of the patient's esophagus, stomach and duodenum revealed signs of eosinophilic enteritis. (A) Endoscopy showing nodular infiltration in the duodenum (arrow). (B) Hematoxylin and eosin staining of a biopsy specimen of the patient's eosinophilic duodenitis revealed abundant lamina propria eosinophils (>10 per high-power field) with focal exocytosis between the intestinal crypt epithelium.

of her symptoms. As her medical insurance company was unwilling to pay for additional IVIG, intravenous cyclophosphamide (1 g) and increased doses of diazepam (15 mg three times a day and 30 mg nightly) were administered in an attempt to control the recurring spasms. Two further infusions of cyclophosphamide were administered at 3-week intervals. Intravenous steroids (methylprednisolone, 1,000 mg/day for 3 days) were also administered prior to the first cyclophosphamide infusion. The spasms, though diminished in frequency, returned after ~2 weeks; therefore, intravenous steroid administration was not continued. In early February 2008, the patient started azathioprine therapy (50 mg twice a day) whilst continuing to take the previously prescribed diazepam.

DISCUSSION OF DIAGNOSIS

The combination of painful recurrent muscle spasms, alopecia and malabsorption in our patient made for a diagnosis of Satoyoshi syndrome. Satoyoshi and Yamada first described this unusual disorder in 1967,¹ when it was called generalized *komura-gaeri* disease (*komura* meaning *calf* and *gaeri* meaning *spasm*). The disorder is characterized by progressive, painful muscular spasm of the whole body, alopecia universalis, diarrhea due to malabsorption, endocrinopathy, secondary skeletal abnormalities (in prepubertal and pubertal cases), and, in some cases, immunological disturbances.² By 2007, 52 cases of Satoyoshi syndrome had been described. Two-thirds of reported patients are Japanese, but single cases have been reported from other countries. The usual age of onset for

Satoyoshi syndrome is 5–19 years, with a mean of 10.9 years, and females are twice as likely to be affected as males. Ikeda *et al.*³ documented and reviewed the three adult cases of this syndrome reported up to 1998. Heger *et al.*⁴ reported a fourth adult case (a 19-year-old German woman) in 2006.

We report a unique case of Satoyoshi syndrome in a middle-aged female. She is only the fifth adult in the world to be reported to have Satoyoshi syndrome, and the first-reported adult case from South Africa. The patient demonstrated positivity for ANA as well as antibodies to thyroid microsomes, indicating Hashimoto's thyroiditis, and exhibited an excellent initial response to intravenous steroids; however, this response was short-lived. The long positive response to administration of IVIG suggests an immunological pathogenesis of this extremely rare condition. In 1998, Ikeda *et al.*³ reported a 65-year-old female who also had low ANA positivity and antibodies to thyroid microsomes. Other associated autoimmune diseases, such as idiopathic thrombocytopenia, nephritis and myasthenia gravis, have also been reported.⁵

In younger patients, there might be associated endocrine abnormalities, such as primary amenorrhea and menstrual abnormalities with hypoplasia of the uterus and ovaries, suggesting hypothalamic dysfunction. Abnormal estrogen, gonadotropin or gonadotropin stress tests have been reported in a few cases.¹ As our patient was postmenopausal and had restrictions placed by her medical insurance company, tests for these hormones could not be performed.

Skeletal abnormalities, such as joint deformities, growth retardation, epiphyseal separation, fatigue fractures, osteolytic lesions, slippage of multiple epiphyses, bone fragmentation, early osteoarthritis and unique bone lesions known as multiple metaphyseal lesions, are but some of the musculoskeletal problems that might be evident in patients with Satoyoshi syndrome. Repeated traumatic physical injuries to the growth plates, epiphyses and tendon attachments might be responsible for some of the skeletal problems encountered.⁶ Growth retardation and joint deformities that affect the knees, wrists or ankles are not seen if the symptoms commence when patients are older than 13 years of age. Endocrine and musculoskeletal problems are mostly seen in pubertal and prepubertal patients.

Painful muscle spasms usually commence at 6–15 years of age. Drost *et al.*⁷ posed the question

of whether the painful muscle contractions had a peripheral (i.e. cramp) or central (i.e. spasm) origin. Cramps are limited to a single muscle. These authors hypothesized that the mass activity found on their electromyography studies of a single patient provided evidence against the muscle contractions being cramps and that, as Satoyoshi had thought,² an abnormal discharge from anterior horn cells was responsible for this massive hyperactivity or discharge at the alpha motor neuron level.

Differential diagnosis in this patient included SPS. Classical SPS is a disease characterized by rigidity, lumbar hyperlordosis and painful spasms.⁸ Increased anti-GAD autoantibody titers (>20 nmol/l), needle electromyography with continuous motor unit activity in at least one axial muscle, normal MRI and normal cerebrospinal fluid studies characterize the condition. Episodic spasms involve the axial and limb musculature. Variants of SPS include those with focal limb dysfunction (stiff limb syndrome), encephalomyelitis (SPS plus), and cases associated with paraneoplastic autoantibodies.⁹ An autoimmune etiology for SPS is proposed, based on its association with autoantibodies and other autoimmune diseases, as well as its response to immunomodulatory therapy. Anti-GAD autoantibodies have been demonstrated in 65% of patients with SPS. A young patient with Satoyoshi syndrome positive for anti-GAD antibodies was documented by Drost and colleagues.¹⁰ Our patient did not demonstrate the anti-GAD antibodies or lumbar lordosis that are common in SPS.

Gastrointestinal problems can also be associated with Satoyoshi syndrome. Malabsorption accompanied by steatorrhea or diarrhea occurs in 50% of patients, and intestinal polyps are another abnormality that has been reported. Hypochromic microcytic anemia, low cholesterol levels and a flat glucose tolerance curve are indicative of malabsorption. Our patient demonstrated an iron deficiency anemia, a flat glucose tolerance curve and a low folate level, the latter also in keeping with a diagnosis of malabsorption.

The patient also demonstrated eosinophilic enteritis, a group of disorders that selectively affect the gastrointestinal tract with eosinophil-rich inflammation in the absence of known causes of eosinophilia.¹¹ This disorder has been described in association with rheumatoid arthritis¹² and SLE.¹³ Primary eosinophilic

gastrointestinal disorders, including esophagitis, gastritis, enteritis and colitis, are being encountered with increasing frequency, but our patient seems to be the first case of this disorder occurring with Satoyoshi syndrome and autoimmune dysfunction (positivity for ANA, Hashimoto's thyroiditis). Clinically, patients with eosinophilic enteritis present with episodes of nausea, vomiting, diarrhea and abdominal pain. Treatment with steroids has resulted in amelioration of symptoms in reported patients. In our patient, one of these episodes was due to *C. difficile* infection, which responded to the appropriate antibiotic therapy (vancomycin).

The first endoscopy performed in our patient revealed the presence of a gastric ulcer, which was also present in a case report of a 13-year-old girl.¹⁴ An interesting 17-year-old patient with Satoyoshi syndrome and chronic diarrhea was described by Matsuura *et al.* in 2007.¹⁵ Multiple ulcer scars were seen, and histological analysis showed small white granules in the duodenum, indicating infiltration of inflammatory cells. Matsuura *et al.*¹⁵ reported the presence of a ~90 kDa antibody on western blot analysis of the sera from two patients with Satoyoshi syndrome against both brain and stomach tissue, implying a common autoimmune pathogenesis.

TREATMENT AND MANGEMENT

Treatment of patients with Satoyoshi syndrome consists of symptomatic care with benzodiazepines and/or baclofen, as well as other neuromodulators, such as antiepileptic medications and muscle relaxants. Immunomodulation and immunosuppression (e.g. with oral and/or intravenous steroids,^{15–17} botulinum toxin¹⁸ and gamma globulins¹⁹) have also been used. Methotrexate has only been successful in alleviating symptoms in some patients. A therapeutic regimen of tacrolimus and glucocorticoids has been successful in one patient.¹⁴

CONCLUSIONS

The prognosis in the current patient is poor, and she is clearly severely depressed by the spasms that only temporarily responded to administration of steroids and IVIG. More-intensive immunosuppression was attempted using cyclophosphamide and is currently being attempted using azathioprine. The combination of Satoyoshi syndrome, gastric ulceration and eosinophilic enteritis is unique in the global medical literature.

Acknowledgments

With regret, we announce that RA Asherson passed away before the publication of this article. Dr Asherson proposed and wrote this article before his passing. Désirée Lie, University of California, Irvine, CA, is the author of and is solely responsible for the content of the learning objectives, questions and answers of the Medscape-accredited continuing medical education activity associated with this article.

Competing interests

The authors declared no competing interests.

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