

# A rare case of Sjögren's Syndrome associated with Intracranial Hemorrhage- case report and literature review

**Abstract:** Sjögren Syndrome (SS) is an autoimmune rheumatic disease, whose hallmark is ocular and mouth dryness secondary to autoimmune exocrinopathy. Rarely, SS can affect both peripheral nervous system (PNS) as well as central nervous system (CNS). When CNS is involved, SS is usually diagnosed after patients present with neurologic symptoms. Both ischemic and hemorrhagic stroke can present as first manifestation of primary SS. Stroke is described in literature as a rare entity associated with primary SS, and only few cases were reported. In some cases, CNS involvement was thought to be related to CNS vasculitis, but most of the times remains questionable. We present a rare case of intracranial hemorrhage as first manifestation of primary SS and a review of the pertinent literature.

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## Introduction

Sjögren Syndrome (SS) is an autoimmune rheumatic disease, whose hallmark is ocular and mouth dryness secondary to autoimmune exocrinopathy [1]. These symptoms are due to excessive lymphocyte infiltration. SS typically affects women after 40 years of age, but it has also been reported in young adults and adolescents. Serologic markers are positive Ro/SSA, La/SSB and antinuclear (ANA) antibodies. SS can also affect extra glandular systems such as neurologic system. While Peripheral Nervous System (PNS) involvement is often described, CNS manifestations are controversial and extremely rare [2]. The incidence of stroke in patients with primary SS is about 2% [3]. Based on a PubMed search, only 15 cases of stroke were described in primary SS since 1982. Out of these cases, five patients presented with subarachnoid hemorrhage and two patients with intracranial hemorrhage (ICH). Here we report a case of ICH as first manifestation of primary SS.

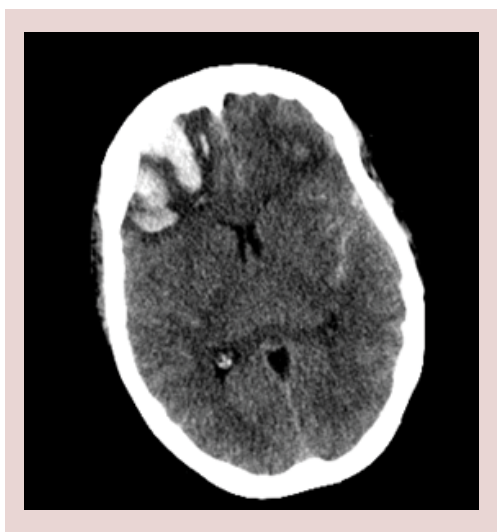
## Case presentation

A 61-year-old Caucasian female with a past medical history significant for Hashimoto thyroiditis, cervical cancer, osteoarthritis and migraines presented in the emergency room for worsening headaches. Patient was treated for one year with sumatriptan and topiramate for migraines. Within the previous year, she had both Computed Tomography (CT) head and magnetic resonance imaging MRI brain that were reportedly normal. Despite treatment, headaches worsened and interfered with her work as an accountant. On the day of admission,

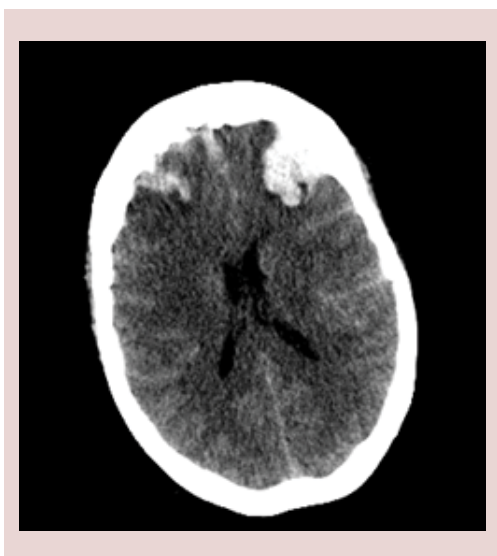
she also complained of dizziness, nausea and vomiting, photophobia. On examination, patient was confused, lethargic and requiring repeated stimulation to answer questions. Neurologic exam revealed 5/5 strength in all extremities, no pronator drift, no change in sensation, patellar deep tendon reflexes (DTR) 2+ bilaterally and negative bilateral Babinski. Electroencephalogram (EEG) was negative for acute seizures. CT head without contrast revealed subarachnoid hemorrhage (SAH) (Figures 1 and 2). Brain MRI was obtained and was consistent with SAH in left posterior fossa, bifrontal intracranial hemorrhage (ICH) and no evidence of midline shift (Figures 3-5). Neurosurgery was consulted, and cerebral angiogram was performed which revealed normal four vessel cerebral angiogram. MR Venogram of brain was negative for thrombosis. Neurosurgery performed right craniotomy and evacuation of the right frontal hematoma with cortical and dural biopsies. Following that, a detailed review of systems revealed long history of eye dryness (she had laser surgery and was applying lubricant drops in her eyes for many years), mouth dryness (using very frequent mint drops) and occasionally parotid gland swelling, along with multiple tooth decays, cavities, and halitosis. Over the past two to three months, the patient also noticed an unintentional 20-pound weight loss, decreased appetite, night sweats, jaw and axilla pain and short term memory loss.

Due to concern of CNS vasculitis process, an autoimmune work up was performed and revealed positive ANA (titer 1: 160, speckled

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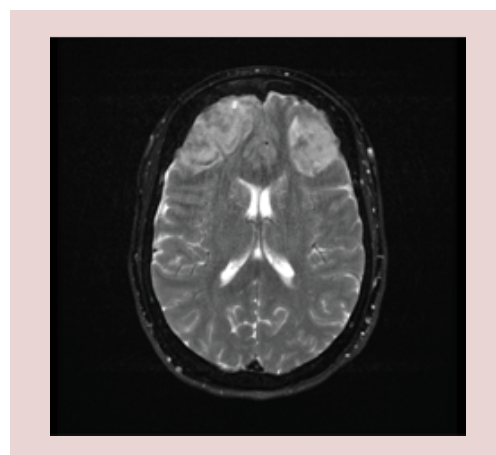
**Figure 1. CT head without contrast.**



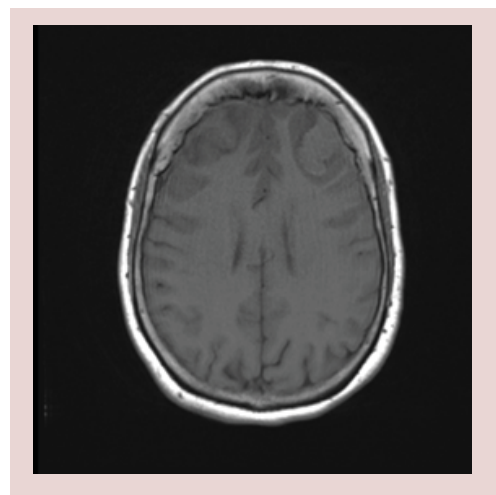
**Figure 2. CT head without contrast.**

pattern) and SSA. All other autoantibodies were negative (Table 1). Complement levels were normal. Both Erythrocyte Sedimentation Rate (ESR) and C-Reactive Protein (CRP) were elevated. Salivary gland biopsy confirmed lymphocytic infiltration consistent with a diagnosis of primary SS (Figure 6). Given the sudden onset of intracranial hemorrhage and newly diagnosed primary SS, the suspicion of associated CNS vasculitis persisted. Further work up with brain and leptomeningeal biopsy was negative for vasculitis, amyloid deposition or neoplasia.

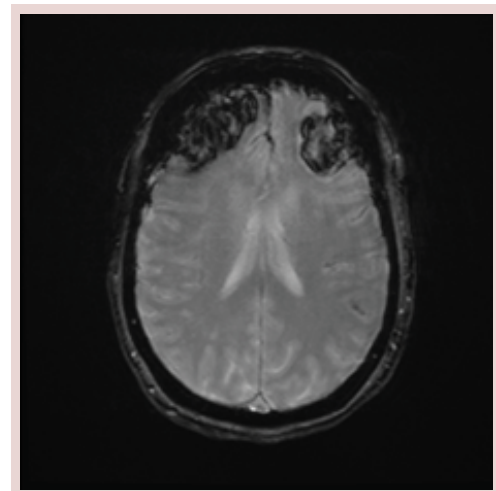
During this time, patient was started on high dose IV methylprednisolone for three days, followed prednisone 60 mg daily. Within the first week, the patient mentation improved significantly. She was discharged to acute rehabilitation on prednisone taper, levetiracetam and all previous



**Figure 3. MRI without contrast, T2.**

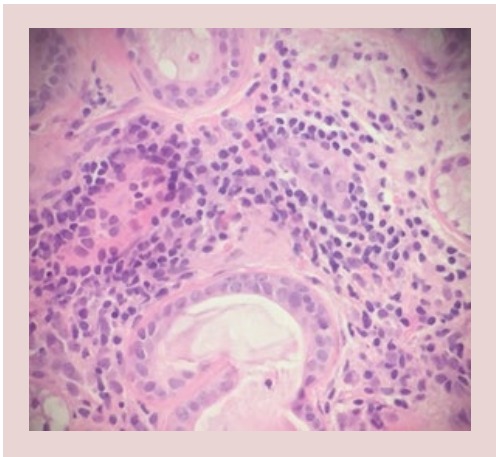


**Figure 4. MRI without contrast, T1.**



**Figure 5. MRI without contrast, GRE.**

home medications. Repeat cerebral angiogram was performed in one month after discharge from the hospital and was also normal with no evidence for primary CNS vasculitis.



**Figure 6. Salivary gland biopsy.**

**Discussion**

Neurologic and psychiatric involvement in primary SS varies between 0%-70% according to reports and depends on their clinics, but generally affects 20% of the patients [1]. PNS involvement can manifest as axonal polyneuropathies, sensory ganglioneuropathy, motor neuropathy, small-fiber neuropathy, multiple mononeuritis, trigeminal and other cranial neuropathies, autonomic neuropathies, or demyelinating polyradiculoneuropathy [1].

CNS involvement can be divided into focal (seizures, movement disorders, cerebellar syndrome, optic neuropathy, etc.), multifocal (cognitive impairment, encephalopathy, dementia, aseptic meningoencephalitis), spinal

cord dysfunctions, MS-like syndrome and CNS vasculitis [1].

CNS involvement occurs mostly in women, with a mean age of 40-50-years-old. It usually manifests after 10-11 years of disease. The focal manifestation is the most common CNS manifestation [1]. The initial work-up that should be done when neurologic primary SS is suspected consists of autoimmune serologies. Anti-Ro antibodies are associated with severity of disease as well as abnormal findings suggestive of small vessel angiitis seen on cerebral angiography [4].

Lumbar puncture may be considered, however is nonspecific. Cerebrospinal fluid (CSF) analysis may show increased lymphocytosis, oligoclonal bands number and increased IgG index [5-7].

EEG has limited value and is more useful in detecting subclinical abnormalities that precede the development of clinical primary SS with CNS manifestations [5].

In terms of imaging studies, MRI is more sensitive than CT scan. MRI findings include anatomical abnormalities, increased signal intensity (T2) predominantly in subcortical and periventricular white matter, cerebral venous thrombosis or transverse myelitis.

MRI is also useful for detecting focal CNS involvement, more than diffuse CNS disease [5,8,9]. Cerebral angiography is helpful to exclude other causes of CNS disease however only about 45% of patients with primary SS and CNS disease have findings suggestive of small

**Table 1. Autoimmune work up.**

Lab	Result	Reference Value
CRP	34	3-24 mg/L
ESR	54	0-30 mm/h
ANA	Positive, titers 1: 160 homogenous	Negative
Anti SSA/Ro antibody	73	0-40 AU/mL
Anti SSB/La antibody	2	0-40 AU/mL
Anti dsDNA antibody	Negative	Negative
Anti-Smith antibody	0	0-40 AU/mL
Rheumatoid factor	<20	<20 IU/mL
Anti CCP antibody	14	0-19U
Anti Scl antibody	2	0-40 AU/mL
Anti-centromere antibody	1	0-40 AU/mL
Ant phospholipid antibodies	negative	negative
Anti RNP antibody	1	0-40 AU/mL
ANCA	<1: 20	<1: 20
Complement C3	93	79-152 mg/dL
Complement C4	18	16-38 mg/dL

CRP= C-reactive protein; ESR=erythrocyte sedimentation rate, ANA=antinuclear antibody, dsDNA= double stranded DNA, CCP=cyclic citrullinated peptide, RNP= ribonucleic protein, ANCA= antineutrophilic cytoplasmic antibodies

**Table 2. Complete blood count with differential.**

Lab	Result	Reference Value
WBC	15.8	3.60-10.50 thou/mcL
RBC	4.32	3.80-5.20 thou/mcL
Hemoglobin	12.8	12.0-15.2 g/dL
Hematocrit	38	36%-46%
MCV	88	82-97 fL
Platelet	273	140-375 thou/mcL
Absolute neutrophil count	14.60	1.80-7.70 thou/mcL
Absolute lymphocyte count	0.90	1.00-4.00 thou/mcL
Absolute monocyte count	0.40	0.20-0.90 thou/mcL
Absolute eosinophil count	0.00	0.03-0.45 thou/mcL
Absolute basophil count	0.00	0.00-0.20 thou/mcL

WBC= white blood cell count, RBC= red blood cell count, MCV=mean corpuscular volume

**Table 3. Basic Metabolic Panel.**

Lab	Result	Reference Value
Sodium	134	135-145 mEq/L
Potassium	3.7	3.6-5.1 mEq/L
Chloride	101	101-111 mEq/L
CO <sub>2</sub>	22	24-36 mEq/L
BUN	9	8-26 mg/dL
Creatinine	0.78	0.44-1.03 mg/dL
Glucose	167	70-99 mg/dL
Calcium	9.2	8.5-10.5 mg/dL

**Table 4. Additional Work Up.**

Lab	Result	Reference Value
UPEP	Negative	Negative
SPEP	Negative	Negative
Homocysteine	7.4	<11 mcmol/L
Cold agglutinins	<1:32	<1: 32

**Table 5. List of case reports.**

Year and Author Name	Patient demographics	Type of CNS involvement
1982, Alexander	37, F	SAH
1994, Bragoni	44, F	Ischemic stroke
1994, Urban	41, F	Venous sinus thrombosis
1995, Giordano	55, F	SAH
1996, Nagahiro	17, F	Ischemic stroke
2002, Koh	50, F	Ischemic stroke
2009, Klingler	46, F	SAH
2010, Hayashi	54, F	SAH
2012, Asai	52, F	Thalamic hemorrhage
2012, Ishizaka	66, F	SAH
2013, Wang	39, F	ICH
2013, Mercurio	43, F	Venous sinus thrombosis
2013, Mercurio	44, F	Venous sinus thrombosis
2016, Ho TH	50, F	Venous sinus thrombosis
2018, present patient	61, F	ICH

vessel vasculitis.

Stroke is an extremely rare manifestation of primary SS. It can be ischemic or hemorrhagic. Since 1982, fifteen cases have been reported including ours [3,10-21]. Out of these, six patients presented with SAH, three patients with

cerebral infarction, four patients with venous sinus thrombosis, two patients with ICH and one of them with thalamic hemorrhage [3]. In all these reported cases, patients were females (Tables 2-5).

One of the causes of ischemic stroke is internal

carotid atherosclerosis. There have been several studies showing a strong connection between systemic rheumatic disease and early atherosclerosis [22]. A non-randomized study done by Ciccone et al. evaluated the differences in carotid intima-media thickness (C-IMT) in patients affected by autoimmune diseases [23]. A comparison between systemic Scleroderma (SSc) patients versus other connective tissue disease patients (such as systemic lupus erythematosus, polymyositis/dermatomyositis, antiphospholipid syndrome, mixed connective tissue disease, Sjogren's syndrome) versus control patients showed no differences of incidence in terms of atheromatous plaques in both SSc and other connective tissue diseases with higher number of plaques than control group. These investigators demonstrated the abnormal function of the endothelial layer in SSc group predisposes to macrovascular changes such as increased C-IMT (which can lead to ischemic events) and microvascular changes (which can lead to Raynaud's phenomenon). Thus, patients with systemic rheumatic disease are at risk for ischemic events by the increased number of atheromatous plaques compared to general population but not by increased thickness of the carotid intima-media.

Our patient was a middle age female with new onset of cognitive issues and headaches that developed ICH with secondary SAH. Although the cerebral angiogram and brain and leptomeningeal biopsies were negative for CNS vasculitis, this could not be excluded since this patient had no risk factors that could cause the ICH (such as diabetes, hypertension, cerebral aneurism or vessel spasm, exposure to NSAIDs), Bifrontal lobe involvement was also unusual. Previous reports regarding small CNS vessel vasculitis reported a sensitivity of only 75% for leptomeningeal biopsy [24].

Currently there is no standard of care for SS with CNS involvement; previous reports described the use of immunosuppressive therapy involving high dose pulse steroids, Rituximab or Cyclophosphamide [24]. Our patient did receive methylprednisolone 1 g for 3 consecutive days, followed by oral prednisone 1 mg/ kg that was tapered down over the course of 4 months. The patient's mentation improved in one week and the confusion resolved. She remains without any neurological deficits.

### Conclusion

Our case emphasizes the importance of a taking a detailed history in ICH cases, which may detect an autoimmune etiology. Although extremely rare, ICH can be seen in patients with primary

SS and CNS involvement. Increasing awareness about the neurologic manifestations of SS may lead to prompt treatment and better prognosis of these patients.

### Conflicts of interest'

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