Case Report

Angiocentric T Cell Lymphoma of the Central Nervous System in a Patient with Sjögren's Syndrome

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ABSTRACT. Patients with Sjögren's syndrome (SS) have an increased risk of developing lymphoproliferative disorders, mainly non-Hodgkin's lymphoma and pseudolymphoma. We describe a young Caucasian woman with a 7 year history of SS, who presented with meningeal signs and symptoms and was found to have non-Hodgkin's lymphoma of the central nervous system. (J Rheumatol 2002;29:1548–50)

Key Indexing Terms:
SJÖGREN'S SYNDROME
CENTRAL NERVOUS SYSTEM
NON-HODGKIN'S LYMPHOMA
VASCULITIS

Patients with Sjögren's syndrome (SS) have an increased risk of developing lymphoproliferative disorders, primarily non-Hodgkin's lymphoma and pseudolymphoma[1]. Although lymphocytic infiltrates in exocrine glands are typical in patients with SS, lymphocytic proliferation may also occur in extraglandular tissues. We describe a young Caucasian woman with a 7 year history of primary SS who presented with meningeal signs and symptoms and was found to have an angiocentric T cell lymphoma of the central nervous system (CNS).

CASE REPORT

A 27-year-old Caucasian woman presented 7 years earlier with dry mouth, dry eyes, and bilateral parotid swelling. A minor salivary gland biopsy revealed lymphocytic replacement of the salivary epithelium and the presence of epimyoepithelial islands composed of keratin-containing epithelial cells. A diagnosis of primary SS was made. The patient had a benign course and was managed with supplemental artificial tears for her dry eyes. She worked as an agricultural inspector for the US Government and smoked 5–10 cigarettes a day. Six months prior to admission, she discontinued her oral contraceptives in an attempt to become pregnant. Within a few weeks, she subsequently developed swelling and pain in her hands and wrists as well as myalgias. The patient conceived but had a spontaneous first trimester abortion, after which the new symptoms resolved.

Two months prior to admission at the UCLA Medical Center, she developed an upper respiratory infection, followed by abdominal pain with vomiting. A diagnosis of pelvic inflammatory disease was made and the patient was admitted to a local hospital for intravenous antibiotics. During the hospitalization, she developed headaches, photophobia with meningeal signs, and a lumbar puncture was performed (Table 1). Magnetic resonance imaging (MRI) with gadolinium of the brain revealed 5 enhancing white matter lesions in the lateral periventricular region measuring up to 15 mm in diameter. A diagnosis of SS flare was considered and she was discharged taking prednisone 30 mg per day. She was readmitted one month later with severe headaches, photophobia, and vomiting. Another MRI with gadolinium showed that the number of enhancing lesions had increased to 20 and were now located in both the white matter and the cortex. She was transferred to UCLA Medical Center for further management.

On examination, she was alert and oriented with normal vital signs. She

Table 1. Laboratory tests.

	2 mo Prior to Admission	On Admission	Reference Values
Antinuclear antibody	> 1:2560	> 1:1280	< 1:40
SSA/SSB antibody	Positive	Positive	Negative
Anti-DsDNA		< 1:10	< 1:10
Hepatitis C antibody		Negative	Negative
Rheumatoid factor, IU/ml	579	150	< 25
HIV		Non-reactive	Non-reactive
ESR, mm/h		35	0–20
Lumbar puncture			
RBC, /mm^3	24	30	0–10
WBC, /mm^3	280	335	0–5
% Neutrophils	2	2	
% Lymphocytes	98	98	
Glucose, mg/dl	47	48	43-73
Protein, mg/dl	85	104	15–45
VDRL		Non-reactive	Non-reactive
Culture and stain	Negative	Negative	Negative
Oligoclonal bands		Positive	Negative
Cytology		Reactive and atypical lymphocytes	

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had a stiff neck and positive Kernig's sign, but no parotid gland enlargement, lymphadenopathy, or synovitis was noted. A lumbar puncture was repeated (Table 1). Another MRI of the brain with gadolinium confirmed the previously noted enhancing lesions in the white matter and cortex (Figure 1). Her complete blood count, serum chemistry panel, and urinalysis were normal. Serological studies were done (Table 1). Serum titers for *Cysticercus*, *Toxocara*, *Histoplasma*, coccidioidomycosis, and cytomegalovirus were negative. Antibody titers were also negative for viruses known to cause meningoencephalitis. High resolution computerized tomography of the chest was negative for any significant lymphadenopathy or interstitial lung disease, and an angiotensin converting enzyme level was 13 µl (reference values 10-60 µl). She was treated with intravenous methylprednisone 30 mg twice a day. Six days after admission, a left occipital leptomeningeal brain biopsy was obtained to establish the diagnosis. The parenchyma was essentially normal but the meninges showed chronic lymphoplasmacytoid infiltrates. The initial frozen section was suggestive of septate hyphal elements, and amphotericin B lysosomal complex (5 mg/kg/day) was initiated and methylprednisone was tapered to 30 mg/day. Permanent paraffin stains for fungus and acid-fast bacilli, however, were negative, as were all cerebrospinal fluid cultures. The patient developed a new left 6th and 7th peripheral nerve palsy and a repeat MRI of the brain did not show any new lesions. She continued to deteriorate, with subsequent cranial nerve palsies of the brainstem. In the absence of a clear diagnosis, an expanded surgical re-exploration of the initial leptomeningeal biopsy site was performed. Immunohistochemical stains revealed a prominent inflammatory reaction consisting of histiocytes and neutrophils (CD15 positive cells) in this second biopsy. Multiple angiocentric atypical T cell populations within the CNS parenchyma were composed primarily of a mixture of CD4 and CD8 cells without loss of CD7. The plasma cells appeared to be polyclonal, strongly suggestive of an angiocentric T cell lymphoma (Figure 2). Extensive reactive change was noted in the surrounding brain parenchyma including astrocytic gliosis. The patient was immediately treated with cisplatin, Ara-C, and high dose dexamethasone. Despite the intense chemotherapy, the patient became obtunded secondary to expanding brain lesions and hydrocephalus. She died on the 25th day of hospitalization.

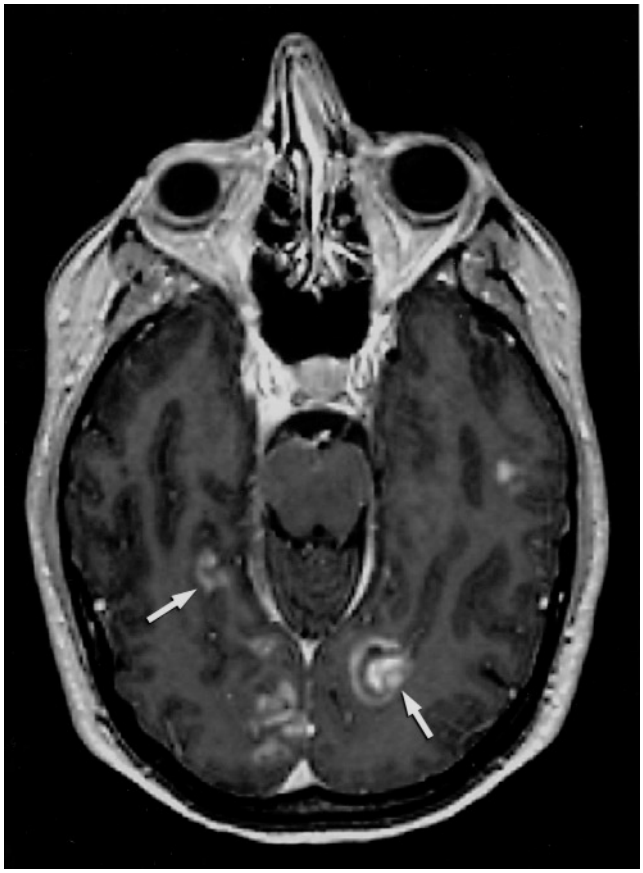

Figure 1. Axial T1 weighted magnetic resonance image (MRI) with gadolinium showing multiple enhancing lesions (arrows).

DISCUSSION

This is the first case report of an angiocentric T cell lymphoma of the CNS associated with primary SS. The occurrence of B cell non-Hodgkin's lymphomas (NHL) (low grade variant) has been described[1-3]. There have also been case reports of diffuse large B cell lymphomas[5] and T cell-rich histiocytic B cell lymphoma of the parotid gland[6] associated with primary SS. These lymphomas were considered to be blastic transformation of a low grade mucosa associated lymphoid tissue-type lymphoma[4].

The risk of developing NHL, which is equivalent for both primary and secondary SS, is estimated to be 44 times greater than that observed in a comparable normal population[2]. The various reported sites associated with B cell NHL have been parotid, lacrimal gland, buccal mucosa, skin, lymph node, and stomach[4]. The evolution from benign lymphocytic infiltration characteristic of SS to malignant NHL is probably a multistep process, the underlying molecular events of which are unknown[7]. Our patient developed a T cell lymphoma in contrast to the usual B cell lymphomas seen with SS. There has been one case reported of an angiocentric pulmonary T cell lymphoma with SS[7].

Angiocentric T cell lymphomas exhibit many similarities, both clinically and pathologically, to lymphomatoid granulomatosis (LG)[8]. Until recently, they were considered to be part of the same disease spectrum. However, recent data indicate that LG is an Epstein-Barr virus positive B cell proliferation associated with an exuberant T cell reaction[9]. Most primary CNS lymphomas (usually of B cell phenotype) are prominently angiocentric. Angiocentric T cell lymphomas (not necessarily involving the CNS) are also a subtype of peripheral T cell lymphomas[10]. This group of disorders is characterized by extreme morphologic diversity that renders a reproducible classification of them highly problematic. LG, as classically described, includes a component of angiodestruction, usually characterized by fibrinoid necrosis of all or a portion of a vessel wall around which the atypical inflammatory infiltrate is found[8]. Our patient's biopsy manifested no evidence of fibrinoid necrosis, a finding consistent with the T cell lymphoma diagnosis.

The current case demonstrates the diverse and serious non-exocrine manifestations that can occur in SS. It also underlines the importance of aggressive diagnostic studies that may be needed, as in this instance, where 2 leptomeningeal brain biopsies were required. Although the

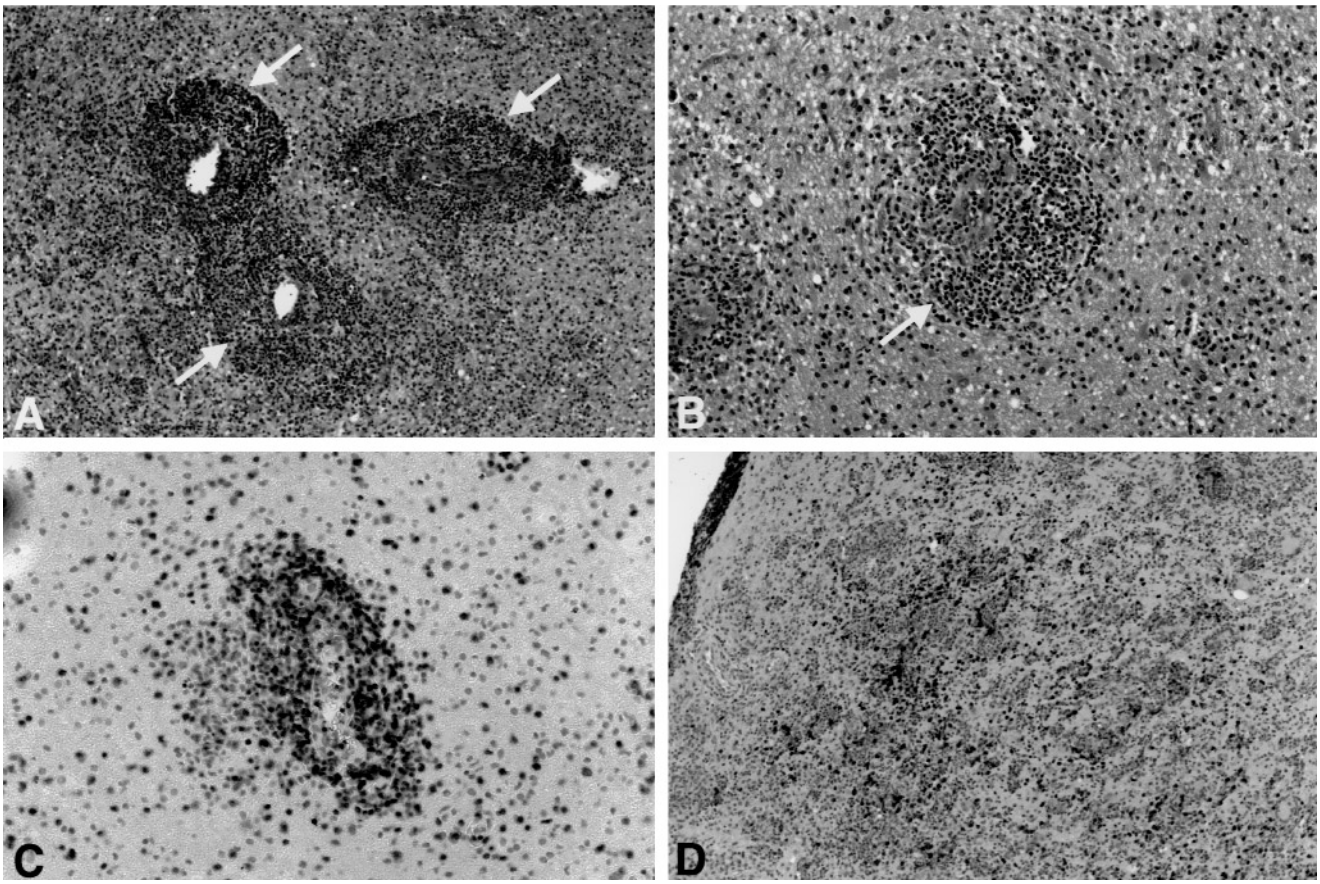

Figure 2. A. Biopsy sample (hematoxylin & eosin) shows 3 dense aggregates of atypical lymphoid cells (arrows) centered on blood vessels; lymphoid cells infiltrate surrounding brain parenchyma. B. Magnified view (hematoxylin & eosin) of a single angiocentric infiltrate (arrow), among which markedly atypical lymphoid cells are seen. Surrounding brain parenchyma shows scattered reactive astrocytes and less dense lymphoid cells. C. A section immunostained with antibodies to the T cell marker CD3 shows a predominately T cell infiltrate in the vessel wall, whereas Panel D (from a section immunostained with primary antibodies to the B cell marker CD20) shows only scattered immunoreactive cells. Notice that magnified views of angiocentric infiltrates (B, C) show no evidence of angionecrosis or vascular thrombi. (Original magnification: A ×90, B–D ×180.)

patient subsequently died, this report now adds angiocentric T cell lymphoma to the potential CNS events that occur in Sjögren's syndrome.

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