Sjogren's – More Than Just Dry Eyes and Dry Mouth
Case Presentation

ID: 45 y/o Vietnamese female presenting for unexplained ascites

HPI: Beginning 10/15, started developing abdominal pain and ascites. Had IUD removed and treated with Protonix without relief. Late 10/15, had CT Abdomen showed moderate ascites only. In mid 11/15, given ascites ongoing, tumor markers ordered and CA 125 elevated. Paracentesis done and no malignant cells seen, consistent with exudative process. Later in 11/15, admitted for ex-lap that was negative. During hospitalization, developed large pleural effusion consistent with transudative process. ECHO normal. Extensive labs sent for showing elevated ESR of 85 and positive ANA 1:320 speckled. Rheumatology consulted.

On further questioning during initial consult, no SLE symptoms revealed.
Case Presentation

PMH: negative
Family Hx: negative
Surgical Hx: negative
Social Hx: negative
Meds:
Dexilant, Lasix, Spironolactone
Case Presentation

Physical Exam:

Vital Signs: T: 36.4, HR: 90, RR: 18, BP 112/68

General: female, NAD, A&Ox4, pleasant

Lungs: CTAB, no rales, rhonchi, wheezes

Cards: RRR, S1, S2, no murmurs, rubs, clicks

Abdomen: distended with abdominal wall edema and pitting edema in buttocks and back

Extremities: 3-4+ pitting edema in LE an 2+ pitting edema in UE

MSK: no joint effusions noted

Skin: No rashes noted
Case Presentation

Labs and Imaging:
TBill: 0.3
AST: 18
ALT: 17
WBC: 8.4
Hgb: 12.5
Plt: 288
Total Protein: 5.2
Albumin: 2.2
Spot urine protein: 14
Spot urine creatinine: 86
CT Chest and Abdomen: Large pleural effusions and ascites
Case Presentation

Hospital Course: Now concern for protein losing enteropathy as no other clear etiology for low protein. Pt's clinical course worsened with rapidly recurring pleural effusions and ascites following paracenteses and thoracenteses. Albumin at one point < 1.5. Minimally responsive to Albumin infusions. Eventually needed to be intubated, which occurred multiple times due to respiratory failure.

ANA subset testing revealed SSA and SSB positivity, reviewed history again and learned that pt had developed dry eyes and dry mouth symptoms months before onset of symptoms.

As extensive malignancy and infectious work-up negative, eventually concluded that she might have Sjogren's Protein Losing Enteropathy.
Case Presentation

Hospital Course: Based on case reports documenting similar cases, decided to start on IV steroids, Rituxan and then Cytoxan given Rituxan takes longer to have efficacy. Within 6 weeks or so, patient started to slowly improve with decreasing pleural effusions, ascites, and edema. Her protein levels very slowly started to rise and her CA 125 levels started to decrease.

Eventually able to be discharged and in recent follow-up, almost one year after being seen, pt has had complete resolution of these signs and symptoms, with normal protein and albumin levels.

She remains on Rituxan infusions and Cellcept, having tapered off Prednisone.
Board question

Patients with Sjogren's are at highest risk of developing:

1) Pancreatitis
2) Pancreatic Cancer
3) B-cell Lymphoma
4) Amyloidosis
5) MALT Lymphoma
A 37 year old female with a history of primary Sjogren's syndrome and no other medical history complains of a progressive severely painful burning sensation within her hands and feet ongoing for the last 6 months. Other than having dysesthesias on exam, there are no motor deficits. A nerve conduction study was negative. What would be the next best step that would likely confirm the diagnosis?

1. Obtain a skin biopsy
2. Obtain a sural nerve biopsy
3. Obtain ANCA testing for suspicion for vasculitis neuropathy
4. Obtain cryoglobulin testing for suspicion for vasculitis neuropathy
What is Sjogren's Disease?

A chronic autoimmune inflammatory disorder characterized by diminished lacrimal and salivary gland function with resultant dryness of eyes and mouth

1) Dry eyes
2) Dry mouth
3) Autoimmune disease
Primary vs Secondary Sjogren's

- Primary Sjogren's: occurs by itself as an autoimmune disease with exocrine gland dysfunction.

- Secondary Sjogren's: occurs in association with other autoimmune diseases (i.e. SLE, RA).

- Dry eyes and mouth tend to be worse in the primary disease.
Who get's Sjogren's?

- 400,000 to 3.1 million adults have Sjögren's in U.S. – estimated to be 2nd most common Rheumatological d/o in U.S.!
- Can affect people of any age but peak is around ages 45-55
- 9:1 female to male predominance
- 50 percent have primary Sjogren's
- 50 percent have secondary Sjogren's
Pathogenesis:

- Lymphocytic infiltration into glands interferes with production of tears and saliva

- Mostly CD-4 T-cells (70 percent) and also B-cells (20 percent)

- Increased levels of B-cell activating factor (BAFF) or B-lymphocyte stimulator leads to B-cell survival
Diagnosis - dry eye symptoms

- Dry mouth questions:
  - Do you constantly have to drink water throughout the day?
  - Do you wake up at night to drink water due to dry mouth?
  - Do you have to drink a lot of fluids just to swallow?
  - Have you had any persistently swollen salivary glands?
  - Have you had issues with getting more and more cavities recently?
Diagnosis – dry eye symptoms

- Dry eye questions:
  - Do you have a sensation of sand or gravel in your eyes?
  - Do you have any burning or irritating sensation within your eyes?
Diagnosis – other common complaints

- As saliva protects against bacteria, can get increase in dental decay and gingivitis
- can complain of dryness of other mucous membranes
  - Nasal passages
  - Throat
  - Vagina – yeast infections
- Increased risk for eye infections and damage to cornea
Diagnosis – exam findings

- Enlarged salivary glands with in submandibular area or parotid glands
- Decreased salivary pool
- Red tongue
- Red eyes
Diagnosis – ACR 2012 criteria

If 2 of following 3 criteria are met:

1) Positive SSA and or SSB OR positive RF and ANA > 1:320
2) Labial salivary gland biopsy exhibiting focal lymphocytic sialadenitis with focus score > 1 focus/4 mm
3) Keratoconjunctivitis sicca with ocular staining score > 3
Diagnosis – ACR/EULAR 2016

If score greater than or equal to 4:

1) Labial salivary gland with focal lymphocytic sialadenitis and focus score > 1 foci /4 mm ---------3
2) SSA positive ---------------------------------------------3
3) Ocular Staining Score > 5 in one eye ---------------------1
4) Schirmer's test < 5 mm/5 minutes in one eye --------------1
5) Unstimulated whole saliva flow rate < 0.1 ml/min ----1
Diagnosis - lab testing

- Autoantibodies:
  - RF - 50-60 percent (ANA with RF meets criteria)
  - ANA - speckled pattern - 85-90 percent
  - SSA - 50-70 percent (higher in primary disease)
  - SSB - 33-50 percent (higher in primary disease)

- Other labs tests:
  - Hypergammaglobulinemia - 80 percent
  - Hypocomplementemia
  - Elevated ESR - 85-90 percent
  - Anemia of chronic disease - 25 percent
  - Leukopenia - 10 percent
  - Thrombocytopenia - rare
Diagnostic tests – Schirmer's

Measures tear production:
- place folded test strip of filter paper over margin of each eyelid (between middle and lateral thirds)
- measure extent of wetting over 5 minutes

Interpretation:
- <5 mm is consistent with decreased function
- 15 mm if seen in healthy individuals
Diagnostic tests – Ocular surface staining

Certain dyes can stain areas of devitalized tissue in cornea and conjunctiva:

1) Rose Bengal dye – original
2) Fluorescein and lissamine green combo getting more popular as less painful

Interpretation:
- Scoring systems used for each method to determine positivity
Diagnostic tests – Tear break-up time (TBUT)

Measures tear stability: how well they wet and protect eye surface
- stain tear film with one drop of fluorescein dye
- measure time in seconds for dry spot to appear (disruption in tear film)

Interpretation: TBUT < 10 seconds is abnormal and indicates deficiency or abnormal quality of outermost mucous layer of tear film
Diagnostic tests - Quantifying salivary hypofunction (mostly for research)

1) Salivary gland scintigraphy
   - provides dynamic picture of function of salivary glands
   - low uptake of radionuclide is highly specific for Sjogren's but not sensitive
Diagnostic tests – Quantifying salivary hypofunction (mostly for research)

1) Whole sialometry
   - measures rate of saliva production from glands
   - pt expectorates once and collects into pre-weighed container
   - after 5-15 minutes, collection vial reweighed and volume of saliva calculated using specific gravity for water

Interpretation: collection < 0.1 ml/min considered positive
Imaging Tests - Ultrasound

- Reveals abnormalities in structure of gland parenchyma
- Will see multiple hypoechoic areas
- Has been shown to be comparable to scintigraphy or biopsy!
- Needs to be performed by specialized/well-trained examiners
Imaging tests – MRI

- Positive imaging shows heterogeneous parenchyma on T1 and T2 weighted images, with hypo and hyper intense areas.

- Good because non-invasive.
Imaging Tests – Parotid Sialogram

- Dye placed into salivary gland
- X-rays show movement of dye through gland
- If seeing cherry blossom appearance, this is consistent with inflammation seen in Sjogren's
Minor Salivary Gland Biopsy

- From lip vermillion border
- Obtain for those with SSA absent, SSA weakly positive, or only have isolated SSB
- Focal collection of lymphocytes termed focal lymphocytic sialadenitis
  - Need 1 or more of these foci per 4 mm surface area
- If just see atrophy and scattered lymphocytes, this is due to aging changes
Differential Diagnosis

- Atrophy due to aging – most common
- Medications (such as anti-cholinergics, diuretics, etc)
- Sarcoidosis
- IgG4 disease
- Hepatitis C infection
- HIV causing DILs (diffuse infiltrative lymphocytosis)
So is it just dry eyes and dry mouth?

Common Extra-glandular symptoms:

- Fatigue (70 percent)

- Arthralgias/Arthritis (45-60 percent)

- Myalgia (20-30 percent)
What other organs are involved?

- Autoimmune thyroiditis (14-33 percent)
- Lung involvement (10-20 percent)
- Peripheral neuropathy (10-33 percent)
- Renal involvement (10-15 percent)
- Skin rash (SCLE) (5-10 percent)
- Vasculitis (5-10 percent)
- Lymphoma (4-8 percent)
- CNS disease (1-2 percent)
Arthritis/Arthralgias

- Inflammatory in nature
- Symmetric and similar to RA in distribution
- Unlike RA however, NON-EROSIVE
- Tends to be milder than RA as well
Muscles

- Can develop myalgias

- Can develop mild myositis with insidious onset of proximal muscle weakness (like polymyositis)

- Has been found to be associated with IBM as well

- Also commonly can develop fibromyalgia
Lung Involvement

- Can involve parenchyma causing ILD (NSIP most common)
- Can involve airways causing bronchiolitis
- Should think about Sjogren's if have pt with + ANA, ILD, and no other clear etiology
- If suspecting, obtain imaging with HRCT and PFTs
Vasculitis

- Vasculitis mostly involves just skin rather than multiple organs (rare)
- Therefore, palpable purpura can occur in Sjogren's vasculitis
- Also can involve medium sized vessels causing PAN like picture
- Can even cause mononeuritis multiplex
- Can develop:
  1) SCLE
  2) Sweet's like rash
  3) Erythematous papular eruption

- NONE are scarring
- Can occur in face, neck, but also on chest, arms
SCLE

- Photosensitive rash in people with strong association with SSA antibodies (80% have it)

- Small, erythematous scaly papules --> psoriiform plaques or annular plaues

- 50 percent of patients have SLE but don't always

- Due to UV-induced DNA damage, exposing SSA antigen, leading to inflammatory response against
1) Renal tubular acidosis – 10 percent
   - Mild metabolic acidosis
   - Low potassium
2) Interstitial nephritis – <5 percent
   - leads to atrophy and interstitial fibrosis
3) Glomerulonephritis – rare, in association with secondary cryoglobulinemia, type II
Peripheral neuropathy – occurs in 10-35 percent

- painful sensory neuropathy -usually small fiber so NCS could be negative – skin bx needed!
- axonal sensorimotor polyneuropathy – sensory issues with mild distal muscle weakness, NCS usually positive
- can develop sensory ataxic neuropathy – loss of proprioception with ataxia, difficulty finding Limbs in space
- can get autonomic neuropathies as well
Nervous system - Central

CNS - focal lesions can be present in cerebral white matter and in spinal cord

- can present with multifocal recurrent episodes with disease free intervals and slow progression can mimic multiple sclerosis
- can also present with stroke and cranial neuropathic
1) Liver involvement
   - can be just abnormal biochemical tests
     In both hepatocellular or cholestatic pattern
   - can cause PBC or autoimmune hepatitis
2) Atrophic chronic gastritis
3) GERD - saliva acts as buffer for gastric acid
4) Protein Losing Enteropathy
   - can involve stomach/small intestine, causing
to excessive loss of protein into GI tract
   - leads to severe hypoproteinemia, leading to
diffuse edema, pleural/pericardial effusions

Figure 1
Tc-99m albumin scintigraphy showing leakage of the radiotracer in the right lower abdominal quadrant (4-hour static images), which increased in subsequent images.
- Seems to be a link between thyroid disorders and Sjogren's – likely due to both having HLA-DR3 gene association

- Up to 10-70 percent of primary SS pts had evidence of thyroid disease based on multiple studies

- Autoimmune thyroiditis is the most common
B-cell Non-Hodgkin Lymphoma

Non-Hodgkin Lymphoma is a severe complication:
- risk 13-44 times healthy population
- affects about 5 percent of SS patients
- occurs typically in salivary glands and other mucosa associated lymphoid tissue

Can also get MALT cancers
Risks associated with developing lymphoma

- Persistently enlarged parotid glands
- High focus score on biopsy > 3
- Splenomegaly
- Lymphadenopathy
- Low C4
- Reversal of lab tests: Loss of positive RF, poly to monoclonal gammopathy, hyper to hypogammaglobulinemia
Treatment - symptomatic

Dry eyes:
- Artificial tears
- Restasis (cyclosporine) eye drops – reduce inflammation
- Punctual plugs in eye ducts
- Fish Oil supplementation
- Should follow ophthalmologist for signs of cornea damage
Treatment - symptomatic

Dry mouth:
- Lemon drops
- Biotene products - toothpaste, mouthwash, gum
- Sialogogues: increase salivary production
  - Pilocarpine (Salagen) - first muscarinic agonist agent FDA approved - 20 mg/day in divided doses (5 mg tablets)
  - Cevelimine (Evoxac) - 30 mg tablets taken TID
Treatment - symptomatic

Dry mouth medications:

Used with some success:
- Plaquenil
- Methotrexate
- Cyclosporin

All patients need regular dental care to prevent cavities and tooth loss
Treatment - Arthritis

- NSAIDs
- Prednisone
- Chloroquine or Hydroxychloroquine – not consensus
- MTX if not responsive to Hydroxychloroquine
Treatment – Nervous system

Peripheral Neuropathy –
- Gabapentin to start with
- Steroids and IVIG – usually reserved for more severe cases

CNS –
- IV steroids + Cytoxan
Treatment – Skin

- Skin – antimalarials, MTX, topical steroids or tacrolimus

- Skin vasculitis – immunosuppressive therapy
Treatment – various extra-glandular manifestations

- Protein losing enteropathy – Rituxan and Cytoxan
- RTA – sodium bicarbonate
- PBC – bile salt chelators such as Actigall
- GERD – PPI
- ILD – steroids and Cytoxan
Therapies currently being studied

Rituxan – anti-CD20 antibody
  - RCTs yet to strongly support but open label studies have shown promise
Benlysta – BAFF inhibitor
Abatacept – costimulation inhibitor
Epratuzumab – anti-CD22 antibody which doesn't deplete B-cells but modulates activity
Board question

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ANSWER: B-cell Lymphoma
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ANSWER: Obtain a skin biopsy
Major Take Home Points

- Sjogren's patients are at increased risk for B-cell lymphoma
- There is an association with autoimmune thyroiditis
- Can cause RTA and interstitial nephritis
- Can cause ILD
- Commonly has peripheral neuropathy
- Strongly associated with SCLE
Happy Halloween!!!