# Overlap Syndrome

## A demonstrative case of the systemic autoimmune rheumatic disease

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# Autoimmune Connective Tissue Diseases

| | incidence |
|---|---|
| 1. Systemic lupus erythematosus | 15-50/100 000 |
| 2. Scleroderma | <10/100 000 |
| 3. Polymyositis | <10/100 000 |
| 4. Dermatomyositis | <10/100 000 |
| 5. Rheumatoid arthritis | <10/100 000 |
| 6. Sjogren’s syndrome | 0.5 to 3.6% |

# Relevance

- As many as 25% of connective tissue disease patients present with features of systemic lupus erythematosus, systemic sclerosis, polymyositis, or dermatomyositis, with rheumatoid arthritis and Sjögren's syndrome evolving concurrently or consecutively during the course of the disease
- Frequently these circumstances make the diagnosis of a specific rheumatic disease difficult
- It is still contentious whether or not overlap syndromes represent the coexistence of separate diseases, the broad clinical expression of the one rheumatic disease, or distinct clinical entities with distinctive aetiology and pathogenesis

# Definition

- "Overlap syndromes" refers to a diverse group of conditions that have clinical features of, and meet classification criteria for, more than 1 well-characterized rheumatic disease
- The pattern of organ involvement reflects the characteristic features of the well-defined rheumatic diseases occurring together

https://online.epocrates.com/diseases/101821/Overlap-syndromes/Definition

# Clinical classification

- Mixed connective tissue disease = high titer of U1-RNP autoantibodies + SLE + scleroderma + myositis + rheumatoid arthritis
- Antisynthetase syndrome = aminoacyl-tRNA synthetase enzymes + myositis + arthritis + interstitial lung disease
- Polymyositis/scleroderma syndrome = PM/Scl antibody + scleroderma + polymyositis, + Raynaud phenomenon + tendon inflammation + interstitial lung disease

*Experts are increasingly realizing that overlap syndromes of scleroderma and myositis are more common than the “pure” forms of the disease

# Incidence and Prevalence

- There are no epidemiology studies of overlap syndromes, apart from Japan, where the reported prevalence of mixed connective tissue disease (MCTD) is 2.7 per 100,000
- Antisynthetase antibodies (including anti-Jo-1 or antihistidyl-tRNA) are found in 5% to 20% of patients with polymyositis or dermatomyositis

# Patient A

# 71 yr old caucasian female

# Presenting Complaint

MAIN

- Dyspnoea during minor physical exertion ( up to 50m of quite walking on ground level), no at rest
- Dry cough
- Intermittent wheezing, sensation of obstructed expiration during physical exertion, as well as at rest or at night
- Chest tightness
- Lower extremities edema in the evening, after night it abates

# Presenting Complaint

ADDITIONAL

- Mouth dryness, difficulty swallowing
- Pain and sandy sensation in the eyes
- Dryness of skin
- Numbness and tingling of the lower limbs, especially distal parts, and the lateral aspects of the face
- Muscle weakness, especially during raising the hands up
- Intermittent joint pain in the knees, shoulders, wrist, ankles
- Subfebrile fever (up to 37.4°C)
- Fatigue
- Photosensitivity

# History of Presenting Complaint

Over 7 years (since 2011) patient suffers from dryness of eyes and mouth, intermittent pain in parotid salivary gland.

She was surveyed and treated by rheumatologist about

***Sjögren Syndrome, moderate level of activity***

Symptomatic treatment: • life style modification
• artificial tears liberally

During last year patient noticed numbness and tingling of the lower limbs and face, muscle weakness, rash on eyelids, fatigue, fever, photosensitivity

Rheumatologist diagnosed dermatomyositis

Manaement: • glucocorticoids 12 mg daily
• methotrexate 7.5 mg per week

Recent month occurred worsening, developed severe progressive dyspnea, dry cough

# Past Medical History

- Frequent flu
- Appendicitis complicated by peritonitis in youth

# Drug History

- Artificial tears liberally
- Topical NSAIDs for joint pain

# Allergies and Reactions

- No

# Social History

- Retired
- Worked as a programmer
- Has a daughter
- Live in a flat
- No history of smoking
- No history of alcohol
- No history of illicit drug use

# Family History

- Her mother suffered from musculoskeletal pain; she was not surveyed and had not precise diagnosis; she used NSAIDs and troxerutin gel locally to relieve her symptoms
- Her brother suffered from skin disease with hyperkeratosis, presumably seborrhea
- No family history  of hypertension,  diabetes mellitus

# VITAL SIGNS

- T 37,1°C
- PS 70 bpm
- BP 140/80 mm Hg
- RR 16 tpm
- Height 160 cm
- Weight 68 kg
- BMI 27

# Examination

Elderly female is well oriented to space and time

The posture is active,

Central type of obesity (waist circumference 112 cm)

Skin - is pale and dry

- face and neck erythema – *V-sign*

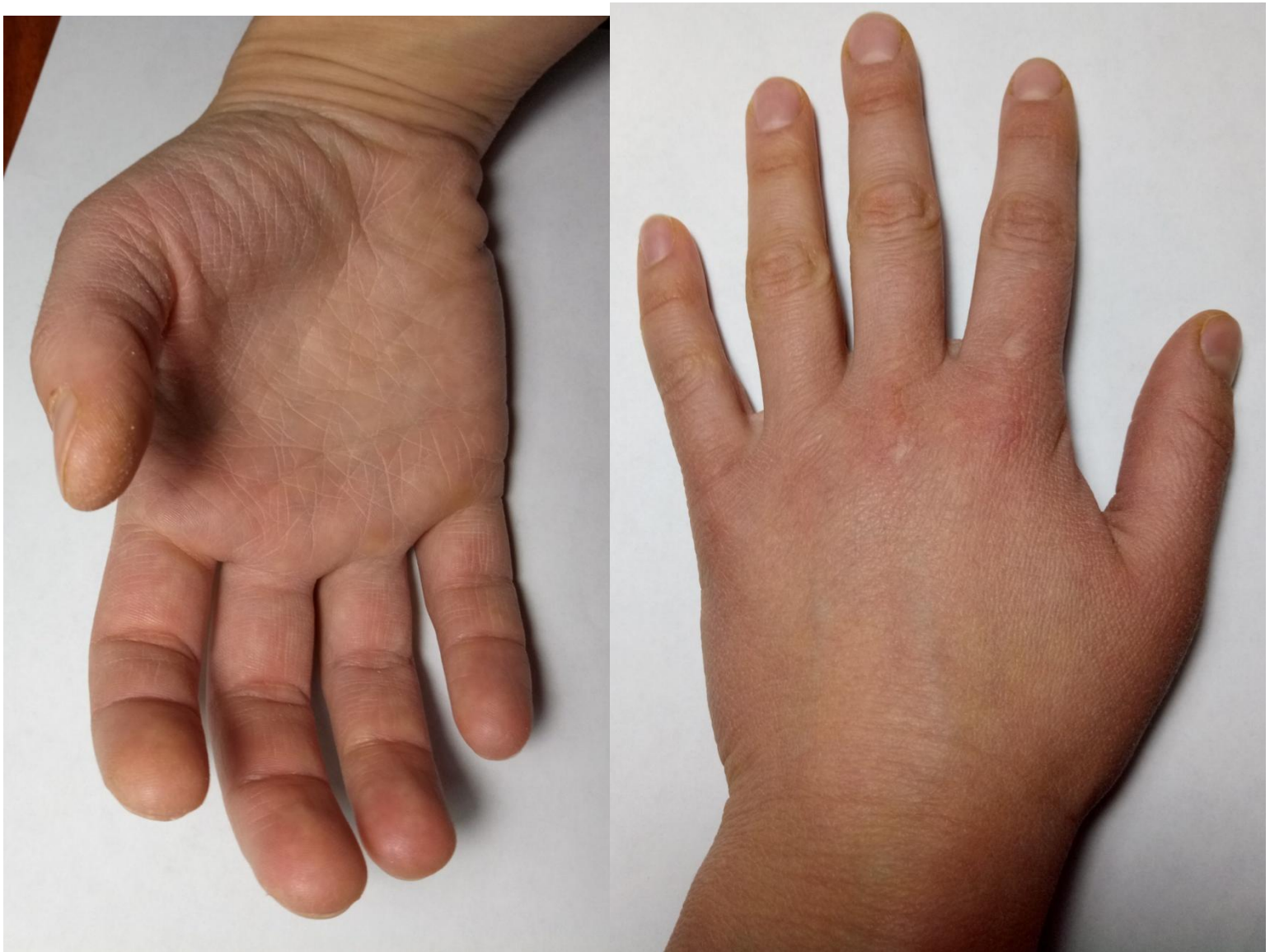
- eyes are puffy, periorbital violaceous erythema – *heliotropic rash*

- *hand puffiness*

- skin of the fingers is dry, rough, with a signs of hyperkeratosis and small fissures, no focal thickening were detected - *Mechanic's hand*

# Heliotropic Rash, V-sign

# Mechanic’s hand



# Examination

Conjunctiva is dry, hyperemic, but without fibrin threads and erosions/ulcers, yellowish crusts at the eyelids

Dryness of mucous membranes of the mouth, single erosions

Tongue is dry and bright pink, multiple fissures are present

Parotid and submandibular salivary glands are tender to palpation

# Examination

During lung percussion resonant sound is detected, borders are not changed

Bronchial breathing in lungs to auscultation, on basal parts of both lung occur fine crackles

Peripheral pulse is full and regular

JVP + 2cm

Apex beat is in $5^{th}$ intercostal space 1 cm to the left of the left midclavicular line, has diminished force

Soft S1 and S2 heart sounds to auscultation, diffuse systolic murmur (grade II) at all points of auscultation

Abdomen is increased in size, participate in breathing actively, old scar after median laparotomy is present; during palpation is soft and non tender, hyperpneumatosis occur, no visceromegaly

# Examination

Joints during examination are not changed, passive and active movement is painless

Peripheral muscles are atrophic, tender and dense to palpation, strength of shoulder girdle muscles is diminished, distal muscle strength is preserved

Peripheral oedema is absent at the time of examination

Stool is daily

Urination is decreased (no more than 1000 ml/24h)

Unstimulated  salivary flow during 15 minutes equals <1 mL

# Preliminary Diagnosis

Sjögren Syndrome

Dermatomyositis?

Overlap syndrome?

Paraneoplastic syndrome?

# Workup

- Complete blood count
- Urine analisis
- Biochemical blood profile
- Infectious profile
- Rheumatologic profile
- Immunologic profile
- Thyroid function tests
- ECG
- Pulmonary function tests
- Chest CT-scan
- Upper GIT endoscopy
- Double-contrast barium enema examination (Irrigoscopy)
- Echocardiography
- Abdomen ultrasound
- Thyroid ultrasound

# Complete Blood Count

| | Results | Reference range |
|---|---|---|
| RBC | $4.56\times10^{12/L}$ | $3.7\text{-}4.7\times10^{12}/L$ |
| Hb | 141 g/L | 120-140 g/L |
| WBC | $7.0\times10^{9}/L$ | $4.0\text{-}9.0\times10^{9}/L$ |
| Neutrophils | 59% | 47,0-72% |
| Bands | 3% | 1-6% |
| Eosinophils | 1% | 0,5-5,0% |
| Basophils | 0.2% | 0,0-1,0% |
| Lymphocytes | 33% | 19,0-37,0% |
| Monocytes | 4% | 3,0-10,0% |
| Thrombocytes | $201\times10^{9}/L$ | $180\text{-}320\times10^{9}/L$ |

***Normal values***

# Urine Analysis

| | Results | Reference range |
|---|---|---|
| Colour | Light yellow | |
| Specific gravity | 1.017 | 1.001-1.040 |
| pH | 5.6 | 5.0-7.0 |
| Protein | -- | -- |
| Glucose | -- | -- |
| Leucocytes | 1-2/hpf | 6-8/hpf |
| Erithrocytes | 2-4/hpf | single |
| Transitional epithelium | single | single |
| Casts | -- | -- |
| Crystals | -- | -- |

***Normal values***

# Biochemical Blood Profile

| | Results | Reference range |
|---|---|---|
| Glucose (capillar) | 4.53 mmol/L | 3.3-5.5 mmol/L |
| AlAT | 83 U/L | <33.0 U/L |
| AsAT | 45 U/L | <32.0 U/L |
| Bilirubin total<br>direct<br>indirect | 19.0 mkmol/L<br>4.1 mkmol/L<br>14.9 mkmol/L | 17-21 mkmol/L<br><5.0 mkmol/L |
| AP | 75 U/L | 35-104 U/L |
| LDH | 296.53 U/L | 135.0-214.0 U/L |
| α-amylase (serum) | 58.5 U/L | 28.0-100.0 U/L |
| Creatine kinase | 261 U/L | 26.0-140.0 U/L |
| Creatinine | 87 mkmol/L | 53.0-97.2 mkmol/L |
| Urea | 3.0 mmol/L | 2.76-8.07mmol/L |

***Rise of transaminases AlAT, AsAT, LDH and CK indicates presence of miositis***

# Biochemical Blood Profile

| | Results | Reference range |
|---|---|---|
| Potassium | 3.0 mmol/L | 3.5-5.1mmol/L |
| Sodium | 145.3 mmol/L | 136.0-145.0 mmol/L |
| Chloride | 82.3 mmol/L | 98.0-107.0 mmol/L |
| Phosphorus | 0.82 mmol/L | 0.81-1.45 mmol/L |
| Calcium | 2.13 mmol/L | 2.2 -2.55 mmol/L |

***Hypokaliemia***
***Hypochloremia***
***Hypocalcemia***

# Biochemical Blood Profile

- CA-19-9  29.0 U/mL

***Oncomarker to colonic, pancreatic, gallbladder cancers is negative***

# Infectious Profile

| | Results | Reference range |
|---|---|---|
| HBsAg | Negative | Negative |
| HCV | Negative | Negative |
| Human herpes virus 6 Ig G | 6,49 U positive | < 0.9 – negative<br>0.9-1.1 – suspicious<br>1.1 – positive |
| Human herpes virus 5 Cytomegalovirus Ig M | 0.1 negative | |
| Human herpes virus 5 Cytomegalovirus Ig G | 11.4 U positive | |
| Human herpes virus 3 Varicella Zoster Ig M | <0.1 Negative | |
| Human herpes virus 3 Varicella Zoster Ig G | 6,49 U positive | |
| HTLV type1 | Negative | Negative |
| HIV | Negative | Negative |

***Chronic herpes virus infection 6, 5, 3***

# Rheumatologic Profile

| | Results | Reference range |
|---|---|---|
| ESR | 35 mm/h | <30mm/h |
| C-RP | 3.6 mg/L | < 5.0 mg/L |
| RF | 37.0 IU/mL | < 14 IU/mL |
| Sialic acids | 1.9 mkmol/L | 2.0-2.33 mkmol/L |
| Seromucoids | 4.5 U/L | 0.13-0.2 U/L |
| LE cells | Negative | Negative |

***ESR, RF may rise at various rheumatic and nonrheumatic pathologies***

# Immunologic Profile

| | Results | Reference range |
|---|---|---|
| ANA | 1:3200 | < 1:100 – negative |
| Anti-dsDNA, IgG | >300 AI | <1.0 Negative<br>≥1.0 Positive |
| Nucleosome, Chromatin Ab, IgG | 0.8 AI | |
| Anti-Rib-P, Ig G | 0.2 AI | |
| Anti-SS-A, IgG | >8 AI | |
| Anti-SS-B IgG | >8 AI | |
| Anti-SmI gG | 0.7 AI | |
| Anti-Sm/RNP IgG | 0.3 AI | |
| Anti-RNP IgG | <0.2 AI | |
| Anti-Scl-70 IgG | <0.2 AI | |
| Anti-JO-1 IgG | >8 AI | |
| Anti-Centromere B, IgG | <0.2 AI | |

***Elevated ANA, anti-DNA antibodies present in variety autoimmune and rheumatic diseses***
***High titers of SS-A IgG + SS-B IgG indicates presence of Sjögren's syndrome***
***Anti-JO-1 antibodies are associated with antisynthetase syndrome***

# Immunologic Profile

| | Results | Reference range |
|---|---|---|
| MPO | <0.2 AI | <1.0 Negative<br>≥1.0 Positive |
| Serine Protease 3 Ab, IgG | <0.2 AI | |
| Anti-GMB, Ig G | <0.2 AI | |

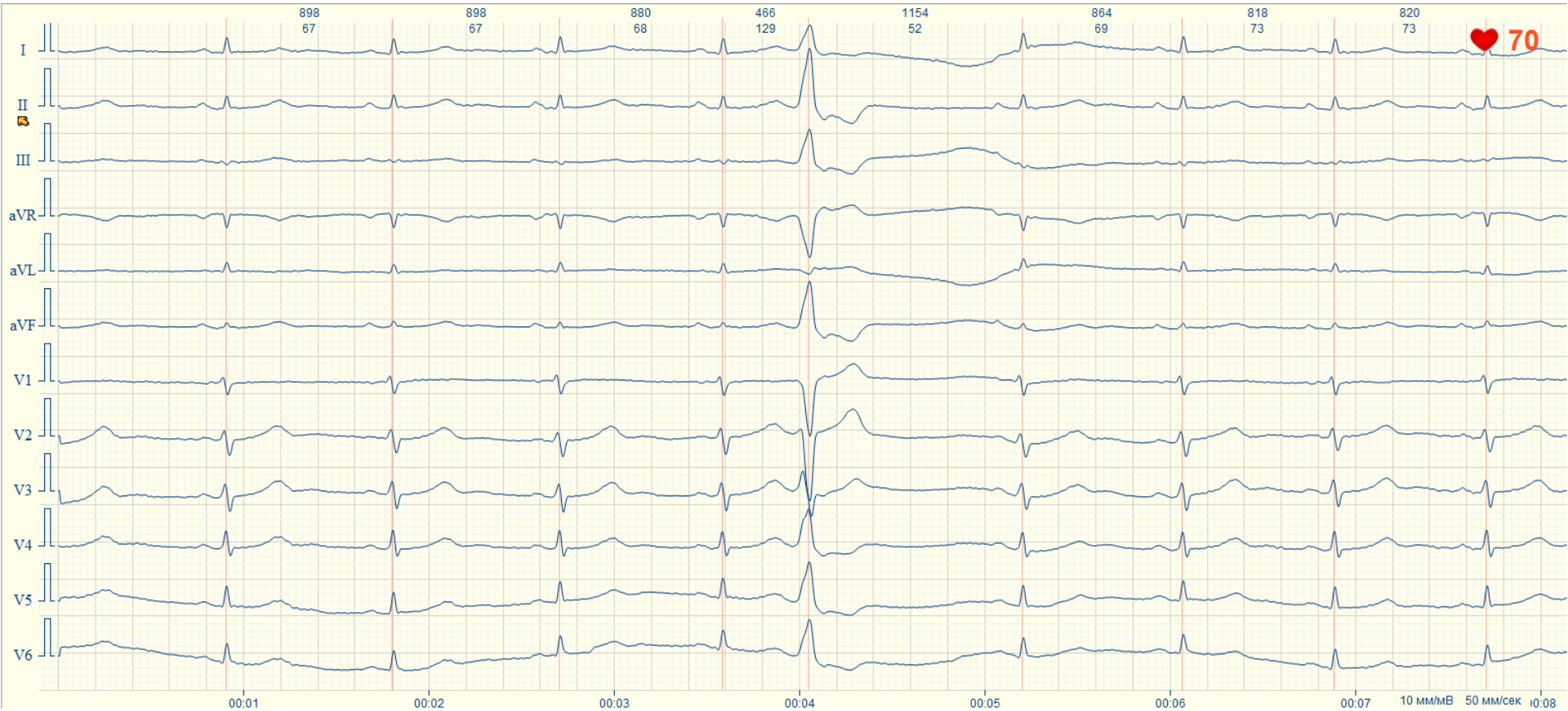
***There is no evidence of systemic vasculitis***

# Thyroid Function Tests

| | Results | Reference range |
|---|---|---|
| TSH | 13.38 µU/mL | 0.27-4.2 µU/mL |
| T4 free | 0.88 ng/dL | 0.93-1.7 ng/dL |
| TPO | 31.7 IU/mL | <34 IU/mL |

***Hypothyroidism***

# ECG




Low voltage ECG, sinus rhythm, 70 bpm, normal heart axis, ventricular premature contraction, right atrial enlargment (II,III), violation of repolarization in V5-V6

# Echocardiography

- Aorta: moderate consolidation of the wall
- Left and right atria are not enlarged
- Left ventricle

| | Norma | Result |
|---|---|---|
| LV EDD | 46–57 mm | 41.8 mm |
| LV ESD | 31–43 mm | 22.1 mm |
| LVPW | 7–11 mm | 12.2 mm |
| VST | 7-11mm | 12.9 mm |
| EF | 55-78 % | 78 % |
| SV | 60-100ml | 61.3 ml |

- Right ventricle

| | Norma | Result |
|---|---|---|
| RV EDD | 46–20.5 mm | 22 mm |
| RVW | 31–43 mm | 6 mm |

Increase total contractility of the left ventricle

Increase diastolic stiffness of both ventricles

- Pericardial effusion, max thickness 7 mm in LV PW

***Aortic sclerosis***

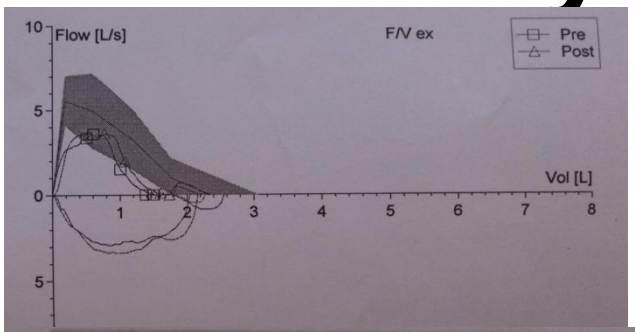
***LV and RV hypertrophy***

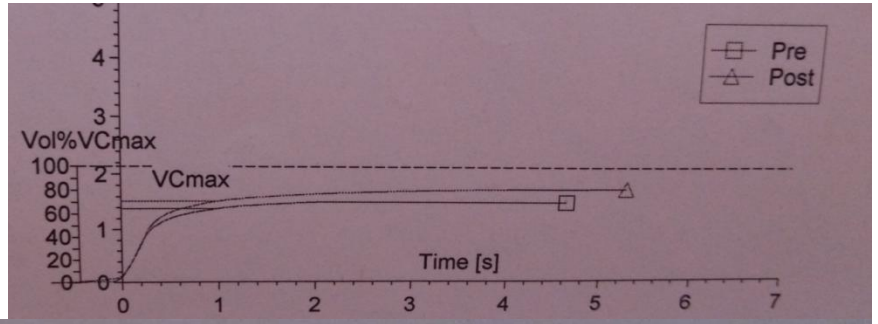
***Diastolic dyfunction***

***Signs of pulmonary hypertension***

***Mild pericardial effusion***

# Pulmonary Function Tests

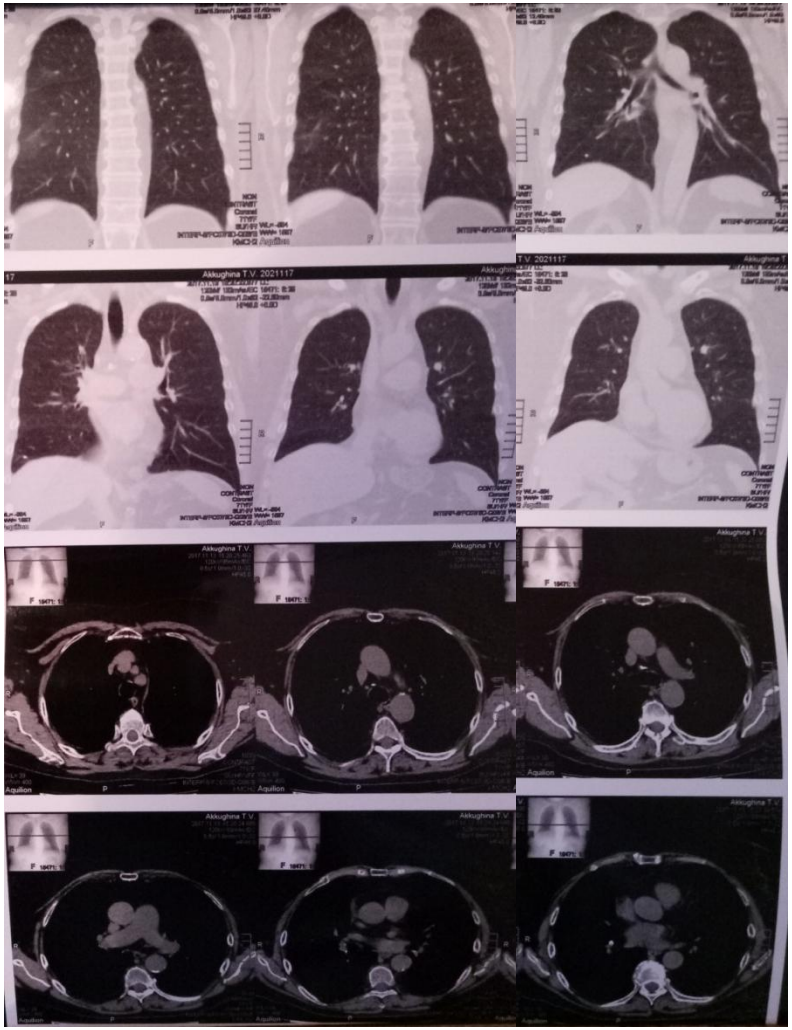


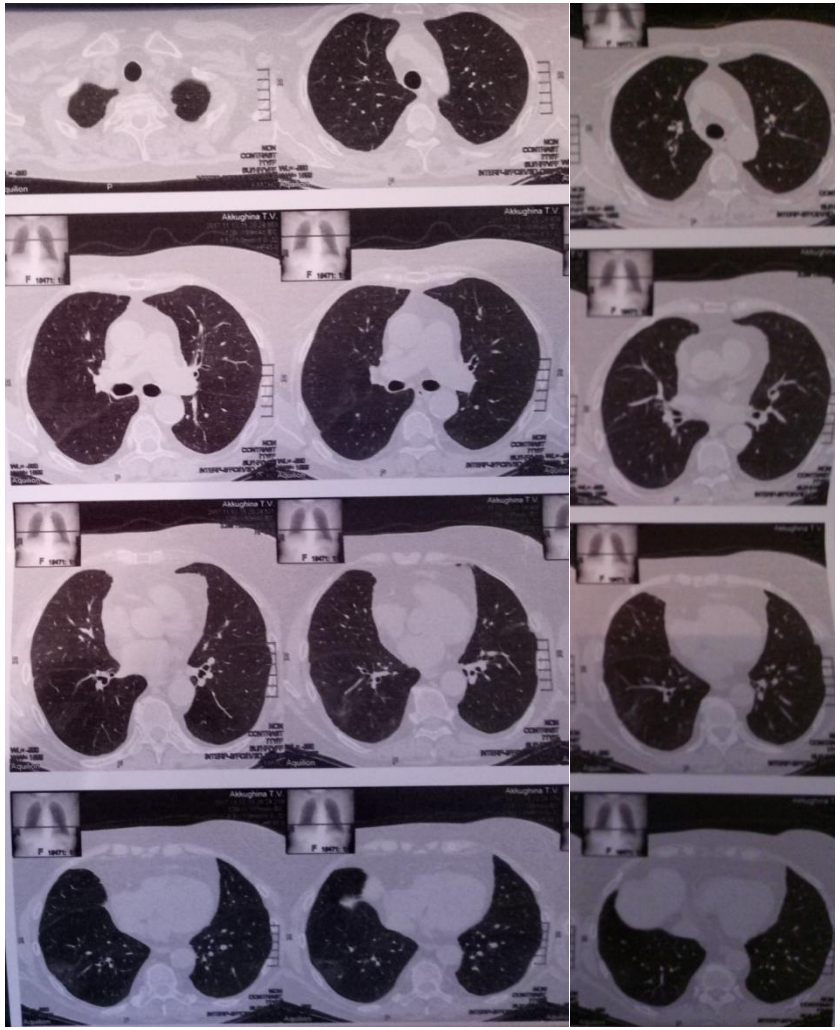




| | | Pred | Pre | %(Pre/Pred) | Post | %(Post/Pred) | %(Post/Pre) |
|---|---|---|---|---|---|---|---|
| VC MAX | L | 2.47 | 2.00 | 81 | 2.14 | 86 | 107 |
| VC IN | L | 2.47 | 2.00 | 81 | 2.14 | 86 | 107 |
| IC forced | L | 1.85 | 2.33 | 126 | 2.09 | 113 | 90 |
| IRV | L | | | | | | |
| ERV forced | L | 0.62 | « | -135 | « | -57 | 42 |
| VT forced | L | 0.46 | 0.54 | 116 | 0.34 | 73 | 63 |
| BF forced | 1/min | 20.00 | 23.64 | 118 | 25.37 | 127 | 107 |
| FVC | L | 2.35 | 1.49 | 63 | 1.73 | 74 | 116 |
| FEV 1 | L | 1.94 | 1.38 | 71 | 1.51 | 78 | 110 |
| FEV 6 | L | | | | | | |
| FEV 1 % VC MAX | % | 75.61 | 68.82 | 91 | 70.69 | 93 | 103 |
| FEV 1 % FVC | % | 82.70 | 92.53 | 112 | 87.13 | 105 | 94 |
| FEV 1 % FEV 6 | % | | | | | | |
| PEF | L/s | 5.56 | 3.58 | 64 | 3.63 | 65 | 101 |
| FEF 75 | L/s | 1.02 | 0.99 | 97 | 0.73 | 72 | 74 |
| FEF 50 | L/s | 3.30 | 3.55 | 108 | 3.53 | 107 | 99 |
| FEF 25 | L/s | 4.98 | 2.95 | 59 | 3.51 | 71 | 119 |
| MMEF 75/25 | L/s | 2.51 | | | 0.74 | 29 | |
| Substance | | | | | Salbutamol | | |
| Dose | | | | | 400мкг | | |

***Moderate violation of lung ventilation, mixed (obstructive & restrictive) type, salbutamol test: +10% FEV1***

# Chest CT-Scan





***Moderate apical pneumofibrosis***
***In the lower lobe of both lungs detected areas of decreased pneumatisation with indistinct borders – ground glass pattern, up to 45x30 mmØ***

# Haemostasis

| | | Reference range |
|---|---|---|
| Prothrombin time | 11.9 s | 9.9-11.8 s |
| INR | 1.09 | <1.0 |
| APTT | 22.6 s | 22.7-31.8 s |
| Thrombin time | 17.7 s | 14.0-21.0 s |
| Fibrinogen | 3.141 g/L | 1.8-3.5 g/L |

| | | |
|---|---|---|
| D-dimer | 8.1 µFEU/mL | <0.5 µFEU/mL |

***Evidence of thrombosis***

# CT Pulmonary Angiography

- Signs of multiple segmental thromboembolism of the pulmonary artery branches (segmental arteries of 4,5,8,9 segments of the left lung and 4,6,9,10 segments of the right lung)

# Upper GIT Endoscopy

- Esophagus is accessible to pass; mucosa is pink; III degree (total) lower esophageal sphincter opening
- Stomach contain large amount of fluid with bile admixture; antrum is hyperemic and edematous
- Pylorus and duodenum are not changed

***Lower esophageal sphincter failure, GERD 0 stage***
***Duodenogastral reflux***
***Erythematous reflux gastritis***

# Double-Contrast Barium Enema Examination (Irrigoscopy)

All parts of the colon are filled by contrast and air. There is no narrowing. Gaustration is pronounced in all parts, unremarkable. Emptying of the colon is delayed. Mucosa of the descending colon has thickened folds. Lesions are not determined.

***Descending colitis***

***Organic changes of the colon are not determined***

# Abdomen Ultrasound

- Kidneys' echogenicity is increased, single cysts (22, 26, 28, and 34 mm Ø)
- Liver normal sized, echogenicity is increased
- Galbladder, pancreas, spleen are not changed

***Diffuse pathology of the liver and kidneys, multiple kidneys' cysts***

# Thyroid Ultrasound

- Thyroid gland is normal sized
- In the left lobe visualized cyst 15×13mm, anechogenic growth 9×7mm
- Thyroid isthmus anechogenic growth with colloid 4-5mm

***Thyroid nodules***

***Goiter I degree***

# Consultations Gastroenterologist

Moderate GERD. Chronic refluxgastritis. Duodenogastral reflux.

# Consultations Endocrinologist

Autoimmune thyroiditis. Goiter I degree. Hypothyroidism.

# Consultations Ophthalmologist

Dry eye syndrome. Angiopathy of retina of both eyes

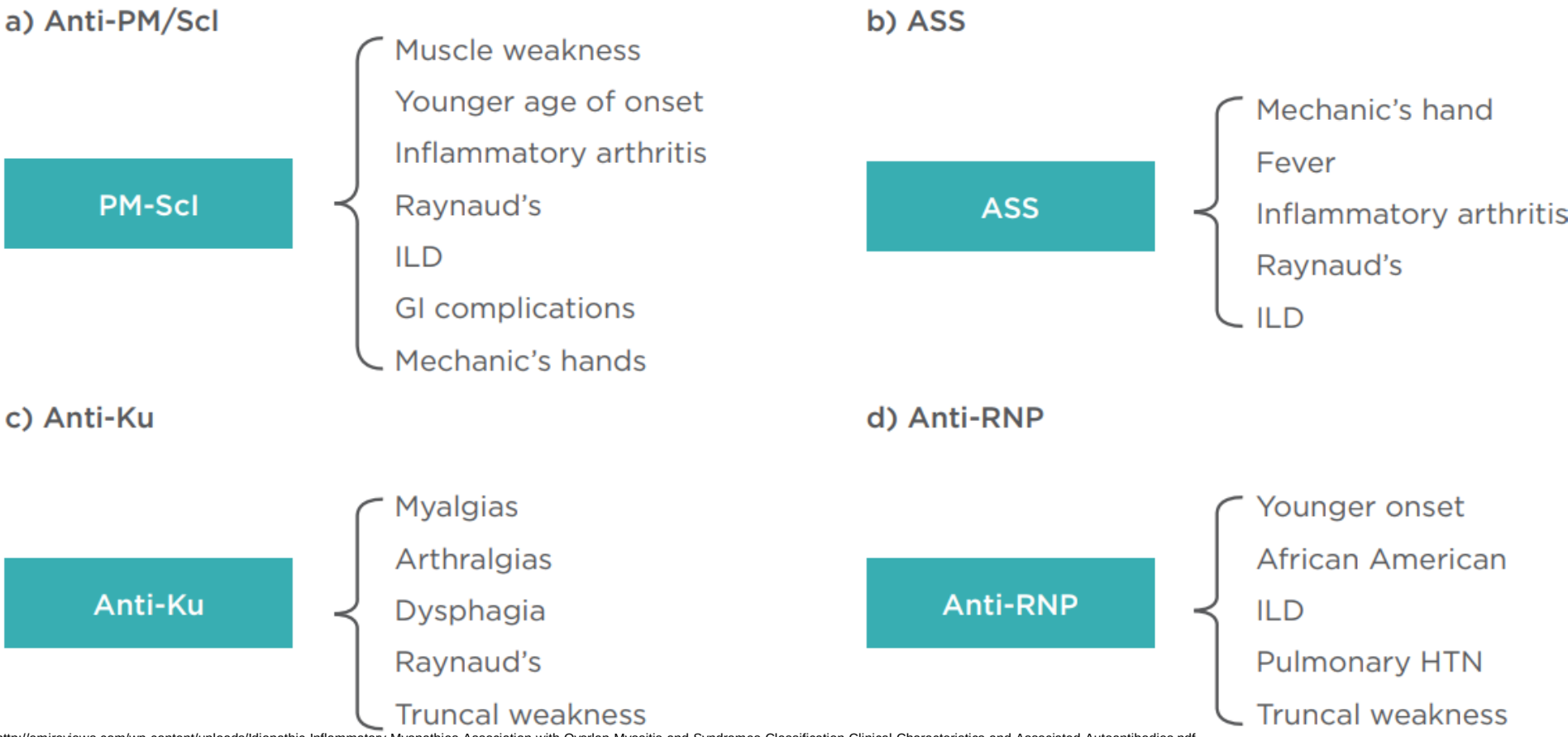
# Consultations Gynecologist

Pathology was not detected. Involutive changes of uterus. Inspection of mammal glands are unremarkable.

# Complementary Tests

- Right-heart catheterization with documentation of vasomotor responsiveness to vasodilators
- Electromyography
- Muscle MRI
- Skin and muscle biopsy
- anti-TPO and anti-Tg antibodies
- Glycemic profile
- OGTT

# Autoantibodies related to overlap myositis syndrome and associated clinical characteristics




http://emjreviews.com/wp-content/uploads/Idiopathic-Inflammatory-Myopathies-Association-with-Overlap-Myositis-and-Syndromes-Classification-Clinical-Characteristics-and-Associated-Autoantibodies.pdf

# AECG Diagnostic Criteria Sjögren's syndrome

**The presence of four out of the six items, including positive history or serology, or the presence of three of the four objective items**

*1. Ocular symptoms:* positive response to one of the following questions:

- have you had daily persistent trouble with dry eyes for more than 3 months?
- do you have a recurrent sensation of sand or gravel in the eyes?
- do you use tear substitutes more than three times per day?

*2. Oral symptoms:* positive response to one of the following questions:

- have you had a daily feeling of dry mouth for more than 3 months?
- have you had recurrent or persistent swollen salivary glands as an adult?
- do you frequently drink liquids to aid swallowing dry food?

*3. Ocular signs:* positive Schirmer's test performed without anesthesia (5 mm in 5 minutes) or positive rose bengal score (≥4)

4. *Histopathology:* focal lymphocytic sialadenitis with a focus score > one focus per 4 mm2 of minor salivary glandular tissue

*5. Salivary gland involvement:* a positive response for at least one of the following diagnostic testing:

- unstimulated whole salivary flow (<1.5 mL in 15 minutes) or parotid sialography showing the presence of diffuse sialectasis
- parotid gland sialography showing the presence of diffuse sialectasis without evidence of obstruction in the glands
- salivary scintigraphy showing delayed uptake, reduced concentration, and/or delayed excretion of tracer

6. Autoantibodies: presence of anti-SSA (Ro) or anti-SSB (La) or both

# Sjögren's International Collaborative Clinical Alliances Cohort

**At least two out of the three objective criteria needed for the diagnosis**

1. Positive anti-SSA (Ro) and/or Anti-SSB (La) or positive RF and ANA ≥1:320
2. Labial salivary gland biopsy with a focal lymphocytic sialadenitis with a focus score ≥ one focus per 4 $mm^2$
3. Keratoconjunctivitis sicca with an ocular staining score ≥3

# Final Diagnosis

**MAIN**

Primary Sjögren's syndrome, moderate.

Anti-Jo-1-antisynthetase syndrome. Interstitial lung disease. Non-massive pulmonary thromboembolism. Pulmonary hypertension. Respiratory failure type I

Chronic mild pericarditis associated with rheumatic disease. Heart failure with preserved EF (78%) II FC NYHA

**CONCOMITANT**

Autoimmune thyroiditis, hypothyroidism

Moderate GERD. Chronic refluxgastritis. Duodenogastral reflux. Descending colitis.

# Management

*Pulmonary embolism*

- Enoxaparin 60 mg bid #7
- Varfarin 5 mg controlled by INR 2-3

*Symptomatic treatment*

- Methylprednisolone 64 mg daily
- Mycophenolate mofetil 60 mg daily with following titration
- Omeprazole 20 mg in the morning

*Further treatment of pulmonary hypertension*

- Diltiazem-retard 90 mg bid
- Sildenafil 5 mg tid

*Herpes virus infection*

- Acyclovir 400 bid

# Prognosis

- Patients with antisynthetase syndrome are generally considered to have a poor prognosis, with mortality 3 times greater than that of myositis without antisynthetase syndrome
- The overall outlook is defined by the severity of organ involvement.
- The onset of pulmonary hypertension, cardiac involvement, or interstitial lung disease each portends a poorer prognosis, and they are indications for aggressive immunosuppressive therapy
- Pulmonary hypertension is the commonest disease-related cause of death in patients with antisynthetase syndrome

# Conclusion

- Connective tissue diseases are characterised by considerable clinical diversity and heterogeneity
- Characteristic clinical features and the detection of specific autoantibodies help to define these disorders and facilitate diagnosis and appropriate treatment

# Conclusion

- It should be noted that overlap between organ specific autoimmune syndromes, such as myasthenia gravis, Hashimoto's thyroiditis, and insulin dependent diabetes mellitus, is frequently seen

# Conclusion

- There are no FDA-approved therapies for the management of any of the overlap syndromes
- There is a paucity of data from controlled trials to support management strategies, in whom the clinical features and need for treatment are highly variable and tailored to the organ systems involved and the severity of involvement
- The overall goal of therapy is symptom control and, where possible, arrest of the underlying autoimmune disease process

# Unresolved Questions

- To determine the origin of chronic and persistent activation of immune system
- To elucidate the role of immunologic, immunogenetic and neuroendocrine factors in the pathogenesis of the disease
- To find a specific immune intervention to alleviate disease