

Ultrasonographic Imaging of Salivary Glands: An Early Predictor of Sjogren's Syndrome in Patients with Rheumatoid Arthritis

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ABSTRACT

Background: Rheumatoid Arthritis is a slowly progressive systemic chronic inflammatory disease of the connective tissue which affects joints, often leading to permanent deformity, influencing other systems also. Sjogren's syndrome is a chronic autoimmune disorder of the exocrine glands with associated lymphocytic infiltrates. Dryness of mouth and eyes referred to as sicca syndrome results from involvement of the salivary and lacrimal glands. This exocrinopathy when occurs in the presence of another autoimmune disorder such as Rheumatoid Arthritis is termed as Secondary Sjogren's syndrome.

This paper is based on a combined radiological and fundamental study of salivary glands aimed to assess the ultrasonographic technique as a sensitive and an early predictor of Sjogren's syndrome in patients with Rheumatoid Arthritis. The patients were assessed for significant structural changes and salivary functions. Some of the ultrasonographic findings derived in the study of patients with Rheumatoid Arthritis were: Coarse and heterogeneous parenchymal echo pattern, a few level IB lymphadenopathy, increased or decreased vascularity, coarse honeycombed parenchymal appearance.

The suggested conclusion of this paper is that ultrasonography of salivary glands with Rheumatoid Arthritis compared with normal subjects is an effective method for diagnosing early changes and that patients with early onset and longstanding history of Rheumatoid Arthritis showed representative structural changes, suggestive of increased predisposition to secondary Sjogren's syndrome.

Keywords: Rheumatoid arthritis, Sjogren's syndrome, structural changes.

INTRODUCTION

Human body is a perfectly integrated system with inter linkages and inter reflections sometimes apparent and at times inherent and invisible to the eyes. Present day micro specialization has compartmentalized the entire system losing sight of inter linkages. The present study reveals one such connection between structural changes in salivary glands and Sjogren's syndrome in patients with Rheumatoid Arthritis. Such structural changes can be sensed in early stages by ultrasonography.^[1]

AIMS AND OBJECTIVES

A pilot study on 10 Indian Female patients to assess structural & functional changes of salivary glands were mapped radiographically to see if they can become early indicators of Sjogren's Syndrome in Rheumatoid arthritis.

- ❖ To assess for significant change in structure and function of salivary glands
- ❖ To compare oral sicca symptoms and USG findings with those of matched patients with

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Rheumatoid arthritis and oral sicca symptoms with those in healthy controls

Sjogren's syndrome (also referred to as Sicca Syndrome)

Sjogrens Syndrome is a chronic autoimmune disorder of the exocrine gland with associated lymphocytic infiltrate of the affected gland. The exocrinopathy can be encountered alone (primary Sjogren's Syndrome) or in the presence of another autoimmune disorder such as rheumatoid arthritis or systemic lupus erythematosus.

Criteria for Sjogren's Syndrome [2,3]

I. Ocular symptoms: a positive response to at least one of the three selected questions:

1. Have you had a daily feeling of dry mouth for more than 3 months?
2. Have you had recently or persistently swollen salivary glands as an adult?
3. Do you frequently drink liquids to aid in swallowing dry food?

II. Oral symptoms: a positive response to at least one of the three selected questions:

1. Have you have daily, persistent, troublesome dry eyes for more than 3 months?
2. Do you have a recurrent sensation of sand or gravel in the eyes?
3. Do you use tear substitutes more than three times a day?

III. Ocular signs: objective evidence of ocular involvement defined as a positive result in at least one of the following two tests:

1. Schirmer's I test (≤ 5 mm in 5 minutes)
2. Rose Bengal score (≥ 4 according to van Bijsterveld's scoring system)

IV. Histopathology: a focus score ≥ 1 in a minor salivary gland biopsy. (A focus is defined as an agglomerate of at least 50 mononuclear cells; the focus score is defined by the number of foci in 4 mm² of glandular tissue).

V. Salivary gland involvement: objective evidence of salivary gland involvement defined as a positive result in at least one of the following three diagnostic tests:

1. Salivary scintigraphy
2. Parotid sialography
3. Unstimulated salivary flow (≤ 1.5 mL in 15 minutes)

VI. Autoantibodies: to Ro(SS - A) or La(SS - B) antigens, or both

Rules for classification: In patients without any potentially associated disease, the presence of any four of the six items is indicative of SS.

In patients with a potentially associated disease (such as another connective tissue disease) item I or II plus any two from among items III, IV, V is indicative of secondary SS.

Exclusion criteria: pre-existing lymphoma, AIDS, Sarcoidosis, graft - versus - host disease, sialoadenosis and use of antidepressant and antihypertensive drugs, parasympatholytic drugs.

2010 ACR/EULAR Diagnostic criteria for RA

Categories	Score
Patients who need to be investigated: (1) At least one joint involved with definite clinical synovitis (2) Patients presenting with synovitis not explained by any other disease	
Classification criteria for RA (add scores of categories A-D; definite RA = a score of $\geq 6/10$)	
A) Joint involvement	
• 1 large joint	0
• 2-10 large joints	1
• 1-3 small joints (with or without large joint involvement)	2
• ≥ 4 -10 small joints (with or without large joint involvement)	3
• >10 joints (with at least 1 small joint involved)	5
B) Serology (at least 1 test result is needed for classification)	
• Negative RF and negative ACPA	0
• Low positive RF or low positive ACPA	2
• High positive RF or high positive ACPA	3
C) Acute-phase reactant (at least 1 test result is needed for classification)	
• Normal CRP and normal ESR	0
• Abnormal CRP or abnormal ESR	1
D) Duration of symptoms	
• <6 weeks	0
• ≥ 6 weeks	1
Abbreviations: ACPA: Anti-citrullinated protein antibody; CRP: C reactive protein; ESR: Erythrocyte sedimentation rate; RA: Rheumatoid arthritis; RF: Rheumatoid factor	

METHODS AND METHODOLOGY

I. Study subjects

A study was conducted on 10 patients with positive oral sicca symptoms.

The subjects were divided into two groups

Group 1 – Study group

– Diagnosed with Rheumatoid arthritis with history of + 2 years

Group 2 – Control group

– Positive oral sicca symptoms, absence of Rheumatoid arthritis or any other autoimmune disease

Criteria used to select the subjects for the study

1) Inclusion Criteria –

- Subjects after a questionnaire based case history, clinical examination (lipstick and tongue blade sign) and assessment of whole unstimulated salivary flow rate for positive oral sicca symptoms were selected.^[4,5]
- 2 patients underwent biopsy of parotid and were reported with chronic lymphocytic infiltrate.

2) Exclusion Criteria –

- Subjects with history of any other autoimmune disorder other than Rheumatoid arthritis
- Subjects with medical history of systemic diseases or medication leading to xerostomia or sialorrhoea

II. Tools

1. Fox et al questionnaire for suggestive diagnosis of oral sicca symptoms
1. Graduated saliva collection container
2. Real time ultrasonographic unit with color doppler using 6 – 17 MHz high resolution linear probe

III. Methodology

1. Fox et al questionnaire was given to each of the study subjects.

Questionnaire:

1. Does your mouth feel dry at night or on awakening?
2. Does your mouth feel dry at other times of the day?
3. Do you keep a glass of water by your bed side?

4. Do you sip liquids to aid in swallowing dry foods?
5. Does your mouth feel dry when eating a meal?
6. Do you have difficulty in swallowing any food?
7. Do you chew gum daily to relieve oral dryness?
8. Do you use candies or mints daily to relieve oral dryness?

2. Collection of unstimulated whole saliva^[6,7,8]

- The collection of unstimulated whole saliva was performed under resting conditions between 8.30 am to 10.30 am, to avoid diurnal variation.
- The saliva was collected one hour after eating, following the standard procedure.
- Patient was asked to sit for 10 minutes, passively.
- Patient was asked to expectorate into a pre-weighted plastic graduated container for 5 minutes as the saliva accumulates in the floor of the mouth
- Volume was determined gravimetrically, the weight of each saliva sample (gm) was equated to volume (ml) since the specific gravity of saliva is 1.0
- The unstimulated whole salivary flow rate was expressed in ml/minute

Out of the sample size of 10 patients, 5 were found not to suffer from Rheumatoid Arthritis. The remaining 5 patients were clinically tested and ultrasonically mapped. Their major clinical parameters and complaints are tabulated below.

Patients' Parameters

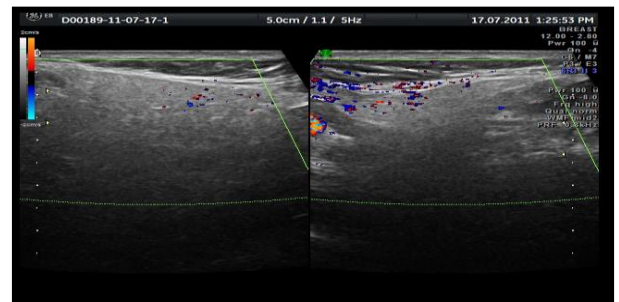
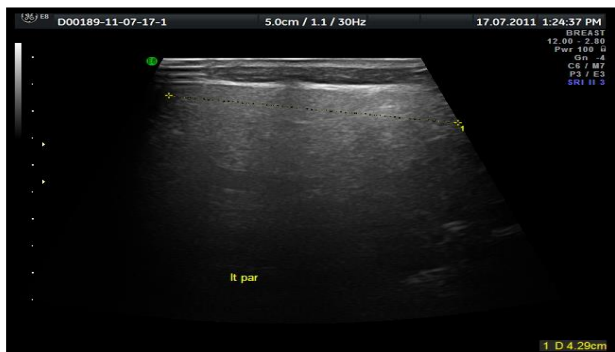
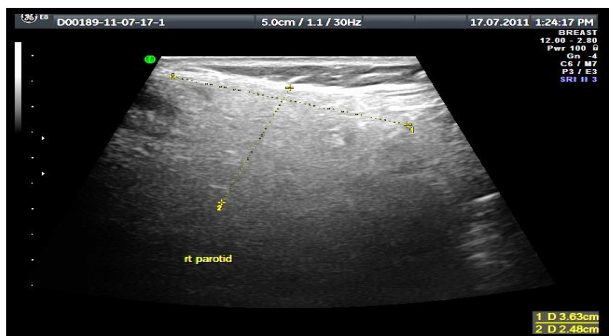
No	Name	Age (yrs)	History of arthritis (yrs)	Unstimulated whole salivary flow rate (ml/min)	Rheumatoid factor (RA) test +ve, (IU/ml)	Complaints
1	Ambika Dhuri	51	4	0.2	1.00	Multiple joint pain, Erythema, pain & swelling over the region of metacarpophalangeal joint, Morning stiffness
2	Aparna Raikar	54	3	0.1	1.00	-do-
3	Pratim	24	6	0.1	1.45	-do-

	a Tripat hi					
4	Vaysha li Thaku r	32	4	0.3	1.32	-do-
5	Arshia Ahmad	45	2	0.3	1.00	-do-

3. USG of neck Real time ultrasonography with color doppler of the neck for right and left sided parotid and submandibular salivary glands was performed using 6 – 17 MHz high resolution linear probe.

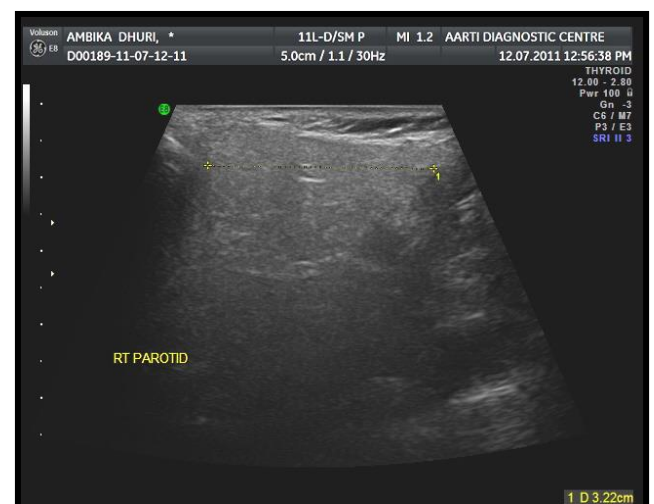
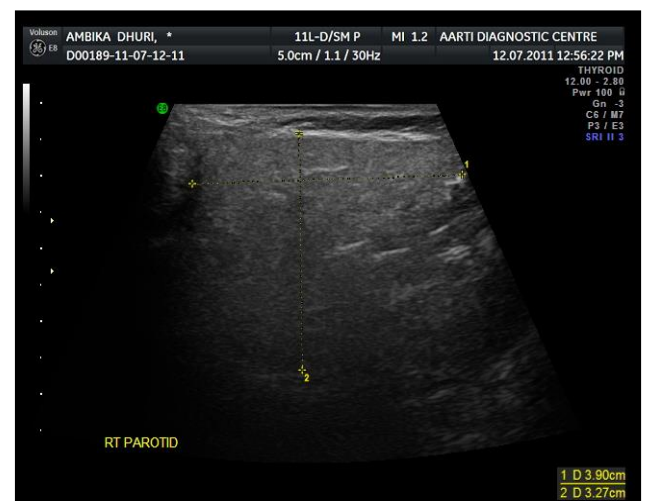
RESULTS

Ultrasonographic appearance of parotid and submandibular salivary glands in patients without rheumatoid arthritis.



Mrs. Ambika Dhuri

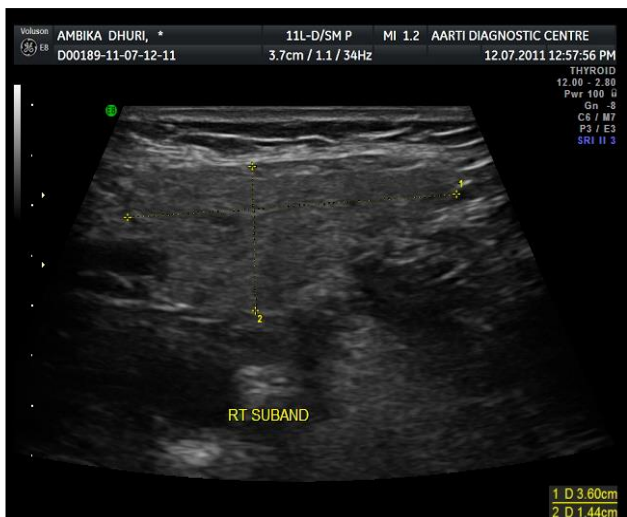
- History of Rheumatoid arthritis since 4 years
- Age – 51 years
- Complaints of multiple joint pain, erythema, pain and swelling over the region of metacarpophalangeal joint, morning stiffness
- Positive oral sicca symptoms
- Rheumatoid factor (RA) test +ve, 1.0 IU/ml
- Unstimulated whole salivary flow rate – 0.2ml/min
- Histopathology report-lymphocytic infiltrate





IMPRESSION

There is normal glandular vascularity

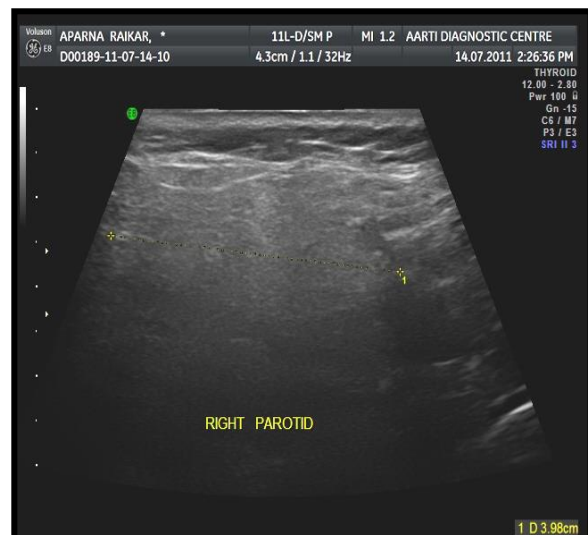


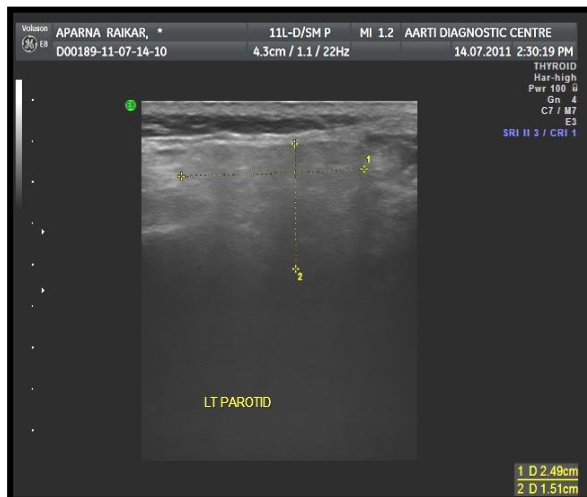
IMPRESSION

The submandibular gland are normal in size, shape and echopattern

Mrs. Aparna Raikar

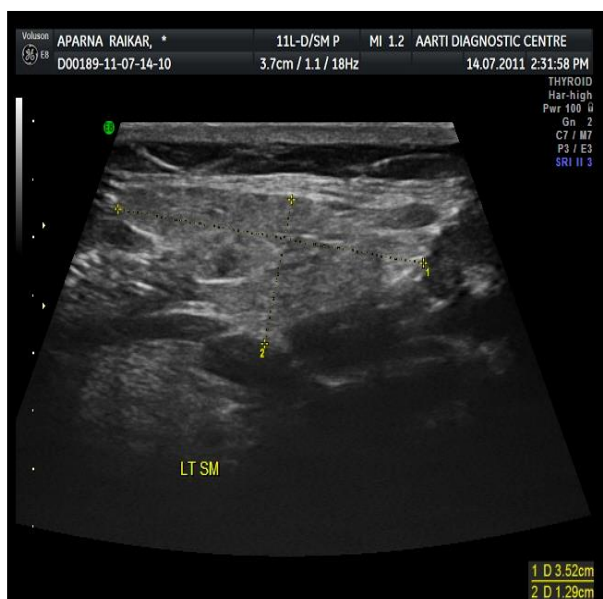
- History of Rheumatoid arthritis since 3 years
- Age – 54 years
- Complaints of multiple joint pain, erythema, pain and swelling over the region of metacarpophalangeal joint, morning stiffness
- Positive oral sicca symptoms
- Rheumatoid factor (RA) test +ve, 1.0 IU/ml
- Unstimulated whole salivary flow rate – 0.1ml/min





IMPRESSION

The parenchymal echopattern of the parotid glands bilaterally is mildly coarse and heterogenous.



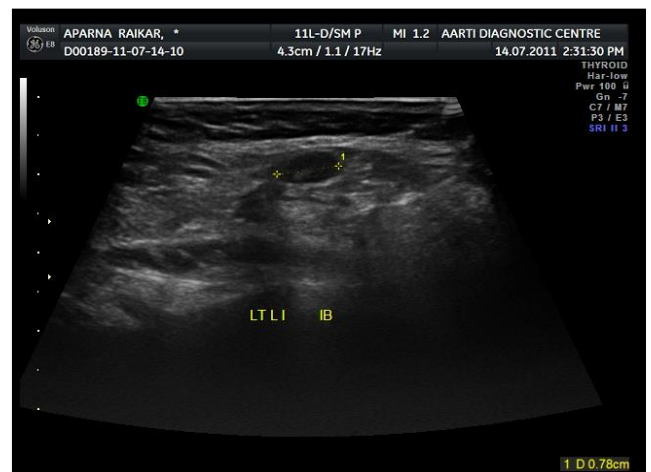
IMPRESSION

The submandibular glands are normal in size but show a coarse parenchymal echopattern, bilaterally



IMPRESSION

The submandibular glands show an increased vascularity, bilaterally



IMPRESSION

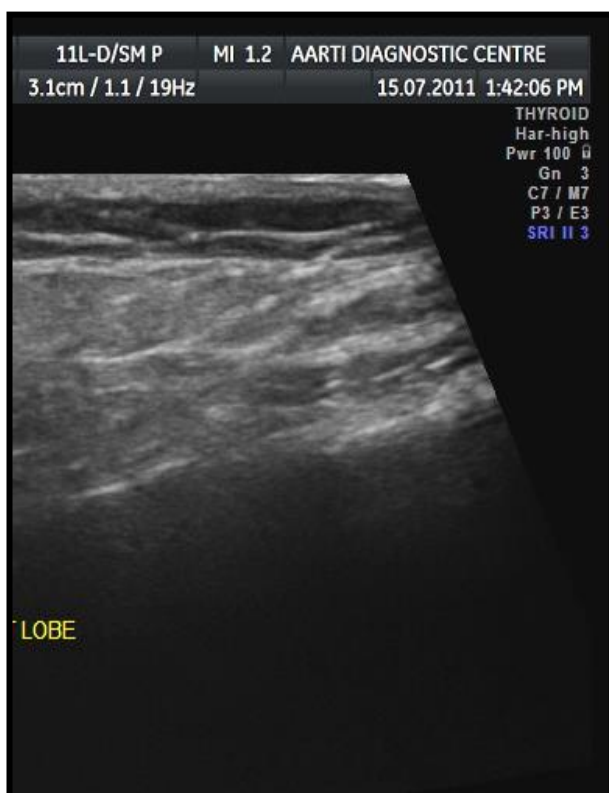
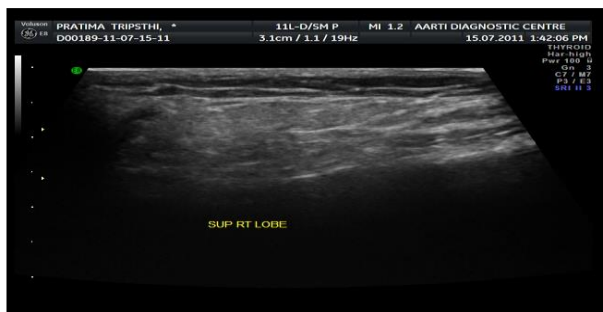
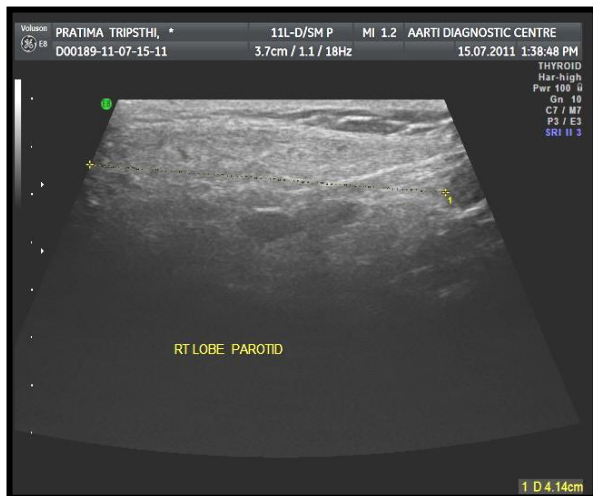
Level 1 B lymphadenopathy

There are few enlarged level 1 B nodes, oval in shape and show hilar fat and vascularity

Mrs. Pratima Tripathi

- History of Rheumatoid arthritis since 6 years
- Age – 24 years
- Complaints of multiple joint pain, erythema, pain and swelling over the region of metacarpophalangeal joint, morning stiffness
- Positive oral sicca symptoms

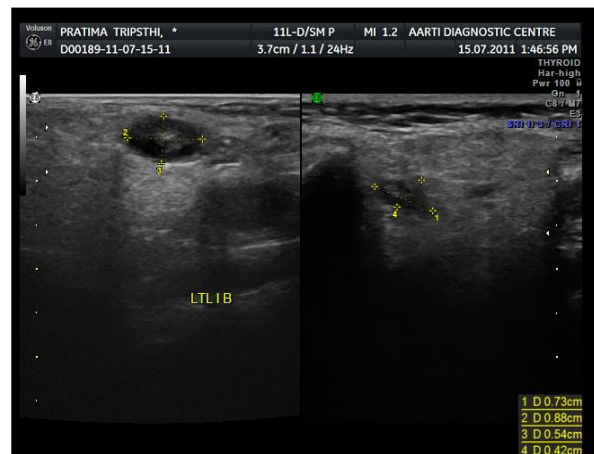
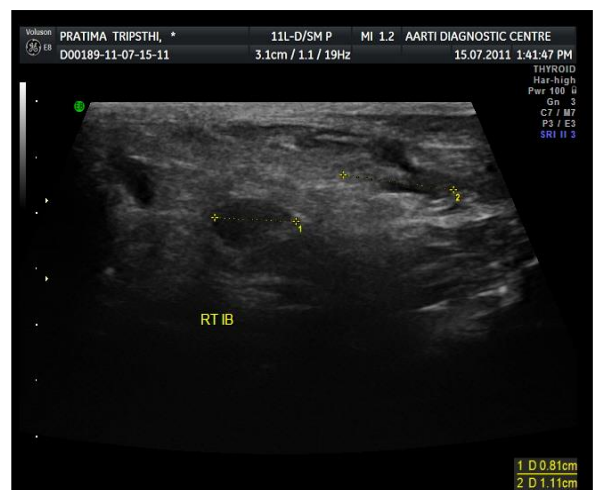
- Rheumatoid factor (RA) test +ve, 1.45 IU/ml
- Unstimulated whole salivary flow rate - 0.1ml/min



IMPRESSION

Coarse honeycombed parenchymal appearance of parotid salivary gland

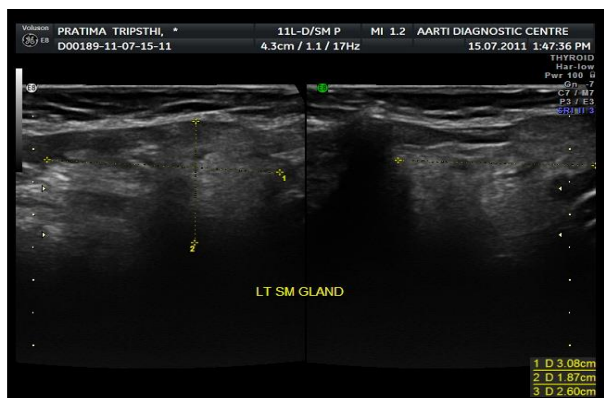
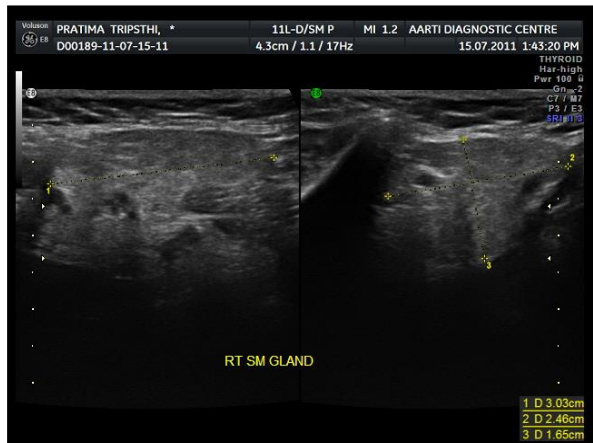
- The parenchymal echogenecity is coarse and heterogenous with honeycomb like changes
- The intraglandular septae are thickened and prominent
- Multiple tiny hypoechoic areas are seen
- Histopathology report- chronic lymphocytic infiltrate



IMPRESSION

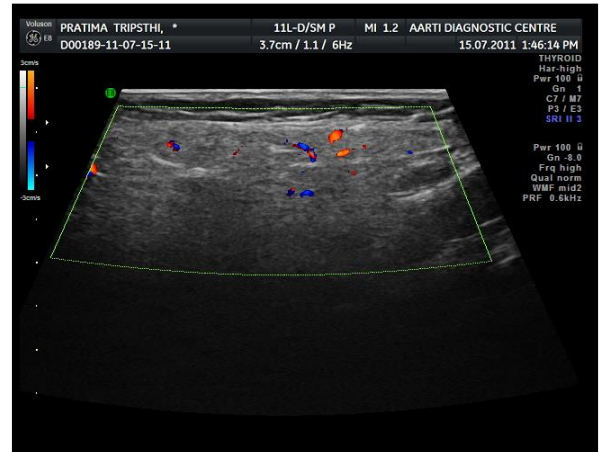
Level 1 B Lymphadenopathy

There are multiple (8 - 10 no.) enlarged intraparotid and submandibular nodes, irregular in shape and outline and shows hilar fat and vascularity



IMPRESSION

The submandibular glands are normal in size and shape with normal parenchymal echopattern .

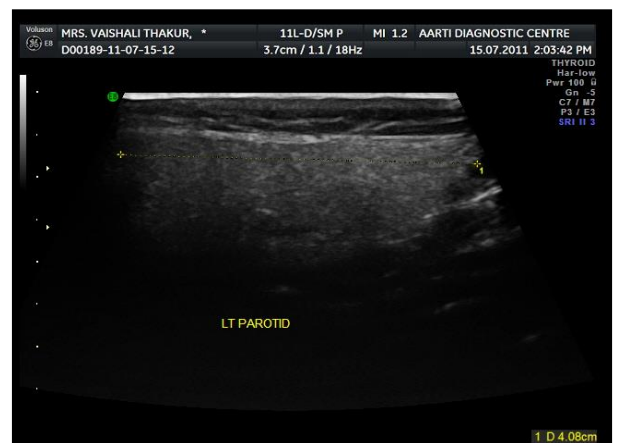


IMPRESSION

The glandular vascularity is normal

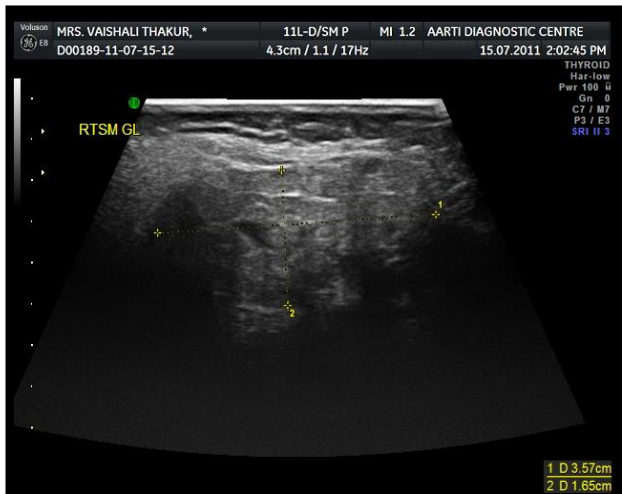
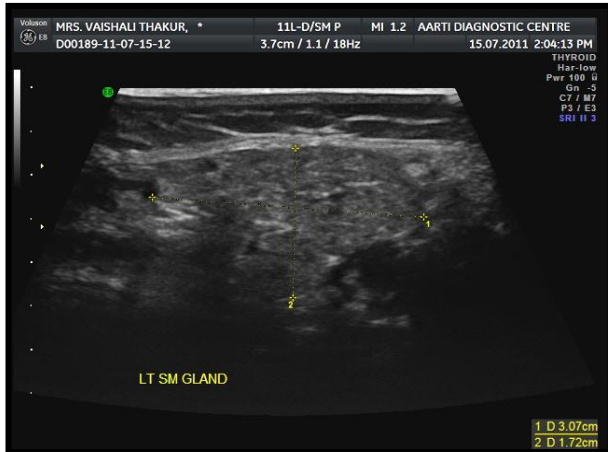
Mrs. Vaishali Thakur

- History of Rheumatoid arthritis since 4 years
- Age - 32 years
- Complaints of multiple joint pain, erythema, pain and swelling over the region of metacarpophalangeal joint, morning stiffness
- Positive oral sicca symptoms
- Rheumatoid factor (RA) test +ve, 1.32 IU/ml
- Unstimulated whole salivary flow rate - 0.3ml/min



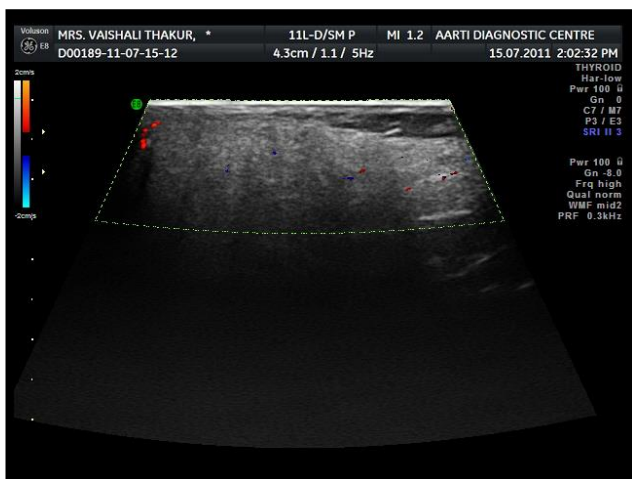
IMPRESSION

The parotid gland are normal in size, shape and parenchymal echogenecity.



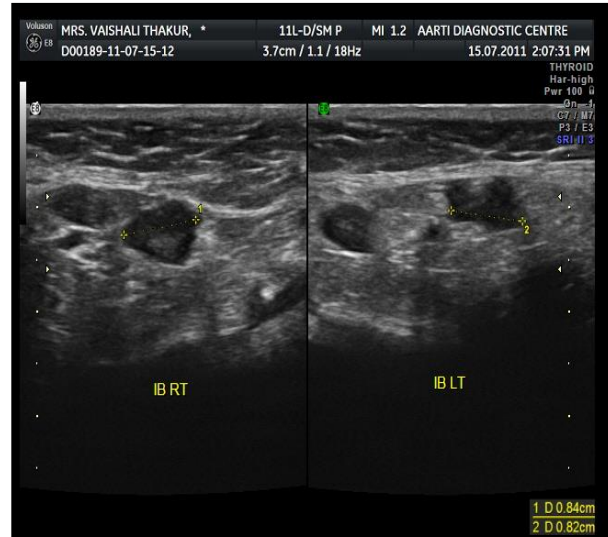
IMPRESSION

The submandibular glands show a coarse parenchymal echopattern



IMPRESSION

The submandibular gland show decreased vascularity.



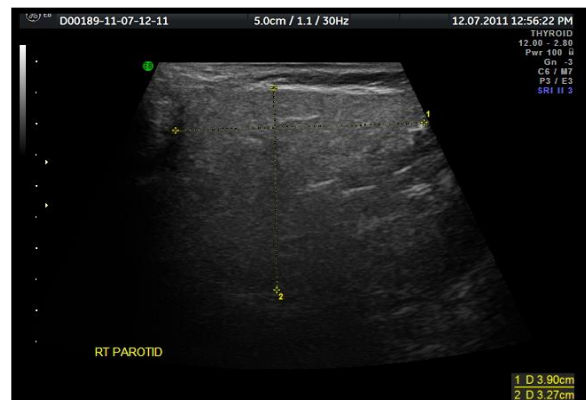
IMPRESSION

Level 1 B lymphadenopathy

There are few (3 – 4 no.) enlarged level 1 B nodes, round and irregular in shape and shows hilar fat and vascularity

Mrs. Arshia Ahmed

- History of Rheumatoid arthritis since 2 years
- Age – 45 years
- Complaints of multiple joint pain, erythema, pain and swelling over the region of metacarpophalangeal joint, morning stiffness
- Positive oral sicca symptoms
- Rheumatoid factor (RA) test +ve, 1.0 IU/ml
- Unstimulated whole salivary flow rate – 0.3ml/min





IMPRESSION

The parotid glands show a mildly coarse parenchymal echopattern

DISCUSSION^[9,10,11,12,13]

Ultrasonographic features of salivary gland changes in patients with Rheumatoid Arthritis, without Sjogren's Syndrome

Bilateral heterogenous, hypoechoic parotid and submandibular gland with multinodular or honeycomb like changes in the parenchyma

In more advanced stages, hyperechoic signals scattered through the affected glands

Multiple hypoechoic areas consistent with cystic changes (sonographic representation of lymphocytic infiltration)

Hypervascularity of the gland by color doppler sonography.

Lymphadenopathy

Drug therapy is very important for the progression of disease, so treatment of these patients was analysed. ^[14,15]

- 1st Group which lacked standard treatment for one month and
- 2nd Group which underwent standard treatment with corticosteroids.

There was no significant difference between the two groups

These drugs might influence the development of disease, but that can't be calculated accurately.

- The incidence of circulating autoantibodies directed against salivary ducts has been reported to be greater in patients with rheumatoid arthritis and sicca syndrome than in patients with sicca syndrome alone
- In a study conducted, 58% of patients showed abnormally reduced salivary flow rate indicating impaired salivary secretion occurring more frequently in rheumatoid arthritis than with patients with dry mouth alone.

CONCLUSION

Ultrasonography of salivary glands in patients with Rheumatoid Arthritis compared with normal reveals early reflection of Sjogren's Syndrome on the structure of salivary glands.

Patients with early onset and long standing history of Rheumatoid Arthritis showed remarkable structural differentials suggestive of increased predisposition to secondary

Sjogren's Syndrome.

1. Patients with progressive reduction in unstimulated whole salivary flow rate, correlated with progressive structural parenchymal changes in the salivary gland.
2. Ultrasonographic technique being non-ionizing, non-invasive and economical can be an effective screening tool for salivary gland involvement in patients with Rheumatoid Arthritis. This enables early diagnosis of Sjogren's syndrome setting in and, therefore, should be included as an important part of investigation protocol of Rheumatoid Arthritis.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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