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Focal sialadenitis in patients with early synovitis

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ABSTRACT

Objective

To investigate the frequency of sialadenitis on lip biopsy in patients with synovitis of recent onset (ES), and see how sialadenitis relates to clinical and laboratory findings of ES.

Methods

Joint involvement, laboratory measures and biopsies of the minor salivary glands were evaluated in 10 ES patients. Diagnosis at a one-year follow-up exam was noted.

Results

Six ES patients (60%) had a positive lip biopsy (mononuclear cell focus score greater than 1). ES patients with a positive lip biopsy presented with oligoarthritis, while ES patients with a negative lip biopsy had a more polyarticular presentation. No differences in laboratory measures between patients with a positive and negative lip biopsy were present. Seven ES patients had a diagnosis of rheumatoid arthritis and three had undifferentiated arthritis at the end of one year.

Conclusion

ES patients had a higher than expected frequency of focal sialadenitis.

Introduction

Synovitis of recent onset (ES) is characterized by arthritic symptoms of less than one year's duration (1). Past studies have estimated the 20-56% of ES patients will develop chronic RA (2) and approximately 1/3 of RA patients will develop secondary SS (3). It is generally accepted that manifestations of secondary SS in chronic RA progress slowly (4); thus the presence of focal sialadenitis should be an uncommon finding in ES patients.

Focal sialadenitis is an important diagnostic feature of primary and secondary Sjögren's syndrome (SS). The pathological role and triggers for the characteristic periductal lymphocytic infiltrate seen in the salivary and lacrimal glands of SS patients are not well understood. In addition to primary and secondary SS, focal sialadenitis may occur in the absence of manifestations of SS. Numerous inflammatory disorders, normal aging processes, and autoimmune conditions with no other signs of SS have demonstrated glandular lymphocytic infiltrates (5-7). A salivary post mortem study demonstrated 16% of subjects without any known antecedent disease showed focal infiltrates of the minor salivary glands (8).

In the present study, we investigated the frequency of focal sialadenitis in lip biopsies of early synovitis patients. Past studies have not investigated this characteristic finding of SS in a group of ES patients. We hypothesized that a minor salivary gland lymphocytic infiltrate similar to that seen in SS would be uncommon in ES patients. We also investigated if serological or joint measures could predict the presence of a lymphocytic infiltrate in the glands.

Patients and methods

Patients. Ten patients with symptoms of synovitis for less than a year were evaluated. Patients were initially seen at the Early Arthritis Clinic at the NIH, Bethesda, MD. All patients had complaints of painful and/or swollen joints and had not been treated with corticosteroids or with disease-modifying antirheumatic drugs (DMARDs) such as azathioprine, methotrexate or cyclophosphamide. Information collected included past medical history, physical examination, measures of joint involvement, and serologic data. Patients were followed for one year, at the end of which time a diagnosis was recorded.

Consent was obtained for all procedures and this study was approved by a National Institutes of Health Institutional Review Board.

Articular involvement. A total of 60 joints were evaluated for tenderness and 58 joints for swelling (9). The joint tenderness or swollen joint count indicated the number of joints involved.

Lip biopsy measures. Patients were approached regarding a minor salivary gland biopsy evaluation at the Salivary Gland Dysfunction Clinic at the NIH, Bethesda, MD. Each patient underwent a labial salivary gland biopsy (LSGB). Lymphocytic infiltrate was measured by Tarpley class (10), Greenspan grade (11) and focus score (12). A focus score of 1 represented an aggregate of 50 lymphocytes in a 4 mm^2 area.

Statistics. Group comparisons utilized

the Wilcoxon rank-sum, ANOVA or Chi-square with continuity correction when appropriate.

Results

A total of 10 patients (mean age 37.9 ± 13.3 S.D. years, 6 females and 4 males) were evaluated. Six patients had a positive LSGB with a focus score >1 and 4 had minimal lymphocytic aggregates (i.e. ≤ 1) (12). Patients were divided into either a positive (+) LSGB or a negative (-) LSGB for further analysis.

The joint scores and laboratory results of patients with a (+) LSGB compared to (-) LSGB are listed in Table I. No significant differences were noted between the 2 groups for any the laboratory results. However, significant differences were noted when comparing joint involvement in early synovitis patients with a (+) LSGB or a (-) LSGB. ES patients with a (+) LSGB had less joint involvement, while patients with a (-) LSGB had polyarticular involvement.

By the one-year follow-up exam in the Early Synovitis Clinic, 7 of the 10 ES patients fulfilled the ACR criteria for RA. The remaining 3 ES patients had oligoarthritis without an evident infectious trigger as in reactive arthritis and were diagnosed as undifferentiated arthritis. A total of 4/4 ES patients with a (-) LSGB and 3/6 (+) LSGB patients were eventually diagnosed with RA. The remaining 3 patients with a (+) LSGB were diagnosed as having undifferentiated arthritis.

Discussion

The present study provided a unique opportunity to examine a series of early synovitis patients for focal sialadenitis. Unexpectedly, focal sialadenitis of the minor salivary glands was present in 60% of ES patients and was in fact most common in non-RA subjects. This finding questions if the lymphocytic infiltrate in ES patients is in fact the beginning of SS, which will evolve later or has some different mechanism especially in the oligoarthritis patients.

If SS is a later disease manifestation of RA, we would not expect to find evidence of focal sialadenitis in this population of patients with recent onset of synovitis. The finding of 60% of ES patients with focal sialadenitis is much higher than would be expected in the normal population.

The high percentage of ES patients with a lymphocytic focal infiltrate of the minor salivary glands was unexpected. To help understand this finding, we compared the laboratory and clinical parameters of the (+) LSGB with the (-) LSGB ES patients. No differences were present between the two LSGB groups with the laboratory studies examined. The best predictor for the LSGB outcome was the degree of joint involvement. ES patients with polyarticular symptoms were less likely to present with a (+) LSGB than ES patients with oligoarticular involvement. Perhaps lymphocyte traffic through minor salivary glands of ES patients presenting with oligoarticular involvement differs from that seen in polyarticular involvement.

Table I. Comparison of diagnostic tests of early synovitis patients with a (+) LSGB or a (-) LSGB

Diagnostic Test	(+) LSGB (n=6)	(-) LSGB (n=4)	p value
Anti-nuclear antibody (ANA)	1/6 positive	2/4 positive	NS
Erythrocyte sedimentation rate (ESR)	3/6 positive	2/4 positive	NS
Rheumatoid factor (RF)	3/6 positive	3/4 positive	NS
C-reactive protein (CRP)	3/6 positive	2/4 positive	NS
Swollen joint count (SJC)	3.2 ± 2.9	23.8 ± 13.2	F = 14.2, p = 0.005*
Tender joint count (TJC)	8.5 ± 6.8	31.5 ± 13.8	F = 12.7, p = 0.007*

*ANOVA

Note:Extractable nuclear antigens were negative in all ES patients (i.e.,anti-SSA,anti-SSB, anti-DNA, anti-RNP, anti-SM).

The main limitation of the present study is the small sample size. Cautious interpretation of the current findings must be stressed. Although all 4 ES patients with a (-) LSGB eventually developed RA while only 50% of ES patients with a (+) LSGB developed RA, the small number of patients limits the use of the LSGB as a predictive tool. In addition, incomplete diagnostic data for SS was available. Thus, it is unknown if the ES patients met the criteria for SS.

Past studies have shown that up to 50% of early synovitis patients will eventually progress to RA (2). Early synovitis patients with polyarticular involvement appear to be more likely to eventually develop RA. We would expect that ES polyarticular cases more likely represent an autoimmune phenomenon and more likely to present with focal sialadenitis; whereas ES with oligoarthritis would be more in keeping with a reactive arthritis. The findings from the present study demonstrated that, in fact, ES patients with oligoarthritis were more likely to present with focal sialadenitis. An oligoarthritis initial presentation, however, does not assure these patients will strictly have a disease with this level of articular involvement (e.g. Reiter's syndrome). An early arthritis patient with an initial oligoarthritis may eventually develop into a polyarthritis. Further study will be required to determine whether lymphocytic infiltrates in the glands of ES patients are a transient phenomenon, a usual feature of ES, or a herald of secondary SS associated with later RA, SLE or other autoimmune rheumatic diseases.

In conclusion, ES patients had a higher than expected frequency of focal sialadenitis which may represent a previously overlooked finding in ES. Future prospective studies could evaluate whether ES patients that present with focal sialadenitis represent a transient immune phenomenon or an early subclinical sign of SS.

References

1. EMERY P, SYMMONS DP: What is early rheumatoid arthritis ?: Definition and diagnosis. *Baillière's Clin Rheumatol* 1997; 11: 13-26.

2. HULSEMANN JL, ZEIDLER H: Undifferentiated arthritis in an early synovitis out-patient clinic. *Clin Exp Rheumatol* 1995; 13: 37-43.
3. ANDONOPOULOS AP, DROSOS AA, SKOPOULI FN, MOUTSOPOULOS HM: Sjögren's syndrome in rheumatoid arthritis and progressive systemic sclerosis. A comparative study. *Clin Exp Rheumatol* 1989; 7: 203-5.
4. TALAL N: Sjögren's syndrome and connective tissue diseases associated with other immunologic disorders. *In* MCCARTYDJ (Ed.): *Arthritis and Allied Conditions: A Textbook of Rheumatology*. Philadelphia, London, Lea and Febiger, 1989, pp 1197-213.
5. ATKINSON JC, FOX PC: Salivary gland dysfunction. *Clinics in Geriatric Medicine* 1992; 8: 499-511.
6. HOCHBERG MC,TIELSCH J, MUNOZ B, BANDEEN-ROCHE K, WEST SK, SCHEIN OD: Prevalence of symptoms of dry mouth and their relationship to saliva production in community dwelling elderly: The SEE project. Salisbury Eye Evaluation. *J Rheumatol* 1998; 25: 486-91.
7. COLL J, TOMAS S, COROMINAS JM: Autoimmune sialadenitis: A form of onset of Sjögren's syndrome ? *Ann Med Interne (Paris)* 1995; 146: 229-32.
8. TAKEDA Y, KOMORI A: Focal lymphocytic infiltration in the human labial salivary glands: A postmortem study. *J Oral Pathol* 1986; 15: 83-6.
9. COOPERATING CLINICS COMMITTEEOFTHE AMERICAN RHEUMATISM ASSOCIATION: A seven day variability study of 499 patients with peripheral rheumatoid arthritis. *Arthritis Rheum* 1965; 8: 302-34.
10. TARPLEY TM, ANDERSON LG, WHITE CL: Minor salivary gland involvement in Sjögren's syndrome. *Oral Surg* 1974; 37: 64-74.
11. GREENSPAN JS, DANIELS TE, TALAL N, SYLVESTER RA: The histopathology of Sjögren's syndrome in labial salivary gland biopsies. *Oral Surg* 1974; 37: 217-229.
12. DANIELS TE: Labial salivary gland biopsy in Sjögren's syndrome: Assessment as a diagnostic criterion in 362 suspected cases. *Arthritis Rheum* 1982; 27: 147-56.