CASE REPORT

Sjögren’s syndrome associated with chronic hepatitis C – the benefit of the antiviral treatment

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Abstract
Chronic hepatitis C virus infection (CHCV) has high prevalence of immunological abnormalities. Extrahepatic manifestations (EHM) have been reported in association with CHCV infection, whose heterogeneity makes difficult any correlation between the two disorders. Among extrahepatic symptoms of C virus hepatitis, sicca syndrome is also registered. Sjögren’s or sicca syndrome (SS) is a chronic, slowly progressive disease, with inflammatory-immune mediation characterized by lymphocytic infiltration of the lachrymal and salivary glands. A distinct primary form and a secondary one, occurring when presented in the context of an autoimmune or hepatic disease have been described. We present a case of SS in a patient with CHCV, commenting a possible link between primary SS and the CHCV, as well as the similarities and the distinctions among these conditions. Our conclusion is that CHCV can induce SS with some clinical particularities like presence of pericapillary and not pericanalicular lymphocytic infiltrate without destroying the salivary glands, in the absence of SS–A/SS–B antibodies. The favorable evolution of SS under IFN therapy is an argument for an authentic relation. Further studies are necessary to determine if CHCV is an etiological agent of SS or of it can induce a pseudo-sicca syndrome, characterized by a simple glandular inflammation consisting mainly in a simple lymphocytic adenitis.

Keywords: Sjögren’s syndrome, chronic hepatitis C, antiviral treatment.

Introduction
A high prevalence of immunological abnormalities occurs in patients with CHCV infection [1] while the high frequency of HCV infection with all its consequences for the liver makes it a major health problem among population. If hepatic alterations linked to HCV are well known, extra hepatic manifestations still requires further studies in order to clarify their correlation to HCV. Some of these are only suspected starting from clinical findings without virusologic or molecular biology evidence. Due to the very high prevalence in of CHCV in population, it is sometimes difficult to affirm the link with HCV infection and the reported EHM. Some of these disorders can be observed on patients in absence of treatment, while others can be linked to interferon or/and ribavirin. However, there are associations that cannot be longer considered as accidental. Current data [2] classifies the EHM in CHCV as follows:
• recognized associations: cryoglobulinemias, porphyria cutanea tarda, glomerulonephritis;
• probable associations: thyroiditis, autoimmune trombocytopenia, non-Hodgkin lymphomas, nodular poliarthritis, Mooren corneal ulcer;
• possible associations: Sjögren’s or sicca syndrome (SS), lichen planus, pulmonary fibrosis, progressive multiform leukoencephalitis, diabetes mellitus and more recently, disseminated granuloma annulare.

We are presenting a case of SS, a well-recognized autoimmune disease in a patient with CHCV, commenting the possible connection between the authentic SS and the syndrome associated to CHCV infection.

Patient and Methods
A 27-year-old woman patient was admitted for permanent, embarrassing sensation of dryness of the oral cavity impeaching phonation and mastication and inducing a state of thirst, associated with similar symptoms of eye dryness including burns, itching and sensation of foreign body. The patient also complained about blurry sight and photophobia. The ocular pain was more intense at the end of the day than in the morning. It has been setting slowly during almost a year. The patient also reported anorexia, nausea, fatigue and abdominal discomfort for over 6 months.

The patient history noticed acute viral hepatitis at
the age of 10, amigdalectomy five years ago and repeated dental treatments two years ago.

The clinical examination was completed with ophthalmologic and of the oral cavity examination. Besides the clinical examination, the ophthalmologic examination included:

- direct biomicroscopic examination of the anterior pole using colorants (1% Fluorescein), to show cornea alterations that do not appear all the time by biomicroscopy such as cornea diseptihelization, ulcers, dead and devitalized cells, etc.;
- Schirmer test using standardized filter paper placed in the inferior ocular bottom with the purpose of confirming the ocular dryness doing two successive examinations without using anesthetics or other ophthalmologic solutions prior to these findings;
- attentive examination of the eye ground.

The examination of the oral cavity consisted in observations of the aspect of the oral mucosa and the anatomicopathologic examination of the accessory salivary glands by labial biopsy, formalin-fixed, paraffin-embedded and stained with Hematoxylin–Eosin. The purpose of the examination was to establish the diagnosis of SS and to evaluate other conditions that could lead to xerostomia such as sarcoidosis, amiloidosis, hemochromatosis and others.

Abdominal ultrasound examination and liver biopsy were also performed.

Results

The overall clinical examination showed discrete pallor. The liver has the superior edge in the V space intercostal right and the inferior one to 2 cm below the costal arch with tendency of thickness and moderate increased consistency. The spleen was palpable at 2 cm below the costal arch, and the abdomen was slightly sensitive to palpation in the right superior side.

The ophthalmologic examination noticed a pale and dry aspect of the cornea setting Fluorescein in line with the palpebral slit (Figure 1) and numerous isolate or conglomerate, punctiform diseptihelizations fixing Fluorescein, in the superior and inferior area of the cornea. All these elements sustained the diagnosis of superficial punctured keratitis.

The examination of the oral cavity presented a dry-reddish, mucosa, dry tongue, with smooth erosions and splits at both labial ends.

Abdominal ultrasound examination showed liver with antero-posterior diameter of the left lobe of 9 cm and prerenal diameter of the right lobe of 14 cm, hyper-echogeneous, homogenous, portal vein 11 mm, homogenous spleen, 13 cm long axis, no venous dilatations in the splenic hill, the rest of the organs within normal limits.

Histopathologic examinations included hepatic biopsy and inferior labial biopsy. The liver biopsy examined by coloration with HE and van Gieson showed a prominent inflammatory infiltration of the portal tracts. This infiltrate consisted primarily of lymphocytes with variable plasma cells and macrophages and occasionally a few neutrophils or eosinophils. The lymphocytes were organized into lymphoid follicles, sometimes with germinal centers. Most portal tracts were involved to some extent, but the intensity of involvement ranged from a sparse collection to a dense crowding of the portal tract; some portal tracts were spared (Figures 2–5).

Bile duct proliferation was also noted, generally of mild degree, with damaged interlobular bile as manifest by epithelial swelling, vacuolation, and inflammatory infiltration.

The examination of the inferior labial mucous after HE coloration showed mixed minor salivary gland (Figures 6 and 7) with mixed acines and excretory vials with integral morphology but with inflammatory infiltrated lymphoplasmocytary perivascularly chronically disposed (Figures 8 and 9).

The current laboratory analysis have shown a moderate anemia of inflammatory type, high speed of sedimentation of hematies, presence of reactive C protein, hepatic cytolysis at medium values, without cholestasis phenomena.

Immunologically, it is discovered a polyclonal hyper-gamaglobulinemia, presence of antinuclear antibodies with stained aspect, anti-VHC antibodies – VHC with viral ARN over 100.000 copies/mL, anti-extractable nuclear antigen (ENA) as well as circulant immune complexes and cryoglobulines. A diminished serous complement is also shown and the absence of anti-La (SS–B) and anti-Ro (SS–A) antibodies is to be retained.

It was not possible to investigate the viral genome or the human leukocyte antigen class II DQB1*02 that was highly significantly associated with viral persistence and was significantly associated with the development of sicca syndrome.

The diagnosis set following the clinical and paraclinical examination of the respective case was of viral C chronic hepatitis associated with sicca syndrome.

Therapeutically, the main objective was to combat infection viral with HCV. We used classical therapeutics scheme with PEG–IFN alpha 2a 180 mg/week + RBV 800 mg/day. Hematological secondary effects of the antiviral treatment did not require the reduction of the doses or the interruption of therapy.

Ophtalmologically, a palliative treatment was chosen with artificial tears to prevent ocular complications due to diminished lachrymal secretion. The treatment aiming xerostomia included a high quantity of liquids and treatment of oral candidosis (a complication of dry mouth) with fluconasole.

Evolution under treatment

The supervision of the antiviral therapy showed an EVR (Earlier Viral Response) with an undetectable level of HCV–RNA in the twelfth week of treatment. The treatment was well tolerated, the six months biological control showed the negativation of HCV–RNA, absence of cryoglobulines, antinuclear antibodies and ENA. Besides, there was an almost total remission of the ocular and salivary symptomatology.
Figure 1 – Numerous isolate or conglomerate, punctiform disepithelizations fixing Fluorescein, in the superior and inferior area of the cornea – superficial punctured keratitis

Figure 2 – Portal fibrosis, large inflammatory lymphoplasmocytes infiltration, vacuolation (van Gieson stain, ob. ×10)

Figure 3 – Portal fibrosis, inflammatory lymphoplasmocytes infiltration, vacuolation (HE stain, ob. ×10)

Figure 4 – Portal fibrosis, chronic inflammatory infiltration of the portal tracts, micro and macrovacuolation (HE stain, ob. ×10)

Figure 5 – Portal fibrosis, micro and macrovacuolation (van Gieson stain, ob. ×10)

Figure 6 – Mixed minor salivary gland with mixed acines and excretory vias with integral morphology (HE stain, ob. ×4)

Figure 7 – Mixed salivary gland, mixed acines with inflammatory infiltrated lymphoplasmocytary perivascular (HE stain, ob. ×4)

Figure 8 – Mixed acines and excretory vias with integral morphology but with inflammatory infiltrated lymphoplasmocytary perivascularly chronically disposed (HE stain, ob. ×10)
**Discussion**

Sjögren’s syndrome or sicca syndrome is a chronic immune mediated inflammatory disorder characterized by lymphocytic infiltration of lachrymal and salivary glands associated with the clinical features of keratoconjunctivitis sicca and xerostomia [3].

In relation to the manner of presentation isolated or associated with other extra-glandular manifestations there are two clinical forms:

- primary form when clinical symptoms are dry keratoconjunctivitis and xerostomia with histological confirmation of the lymphocytary infiltration of the minor salivary glands (answers to four or many criteria of diagnosis (Table 1) [4];
- secondary form in which immunological alterations are represented exclusively by sicca complex (minor salivary glands associated with the clinical features of primary Sjögren’s syndrome, especially because the salivary glands (approximately 15%) [6], there was hypothesis that the presence of antibodies normally present in Sjögren’s syndrome to 57% of the patients infected with HCV in comparison to 5% of the control group, a xerostomia being accused only by 1/3, without xerophtalmia, but the prevalence was null in the HCV non-infected witness group, the cryoglobulinemia being present in 1/3 of the HCV infected patients [9].

Several studies have been effectuated in this direction. In one of them, the presence of a lymphocytic sialadenitis is observed similar to the one in Sjögren’s syndrome to 57% of the patients infected with HCV in comparison to 5% of the control group, a xerostomia being accused only by 1/3, without xerophtalmia, but with abnormal Schirmer test to three of six patients and in absence of antibodies normally present in Sjögren’s syndrome [8]. The authors do not specify if the cryoglobulines were present or not.

Aspects of sialadenitis are also obvious in a study to 14% of the patients with chronic HCV hepatitis, while the prevalence was null in the HCV non-infected witness group, the cryoglobulinemia being present in 1/3 of the HCV infected patients [9].

Jorgensen C et al. observed a high prevalence of HCV-infection in these patients with sicca syndrome. HCV-positive sicca syndrome patients had specific clinical characteristics and were seronegative for SS–A/SS–B antibodies. Moreover, HCV–RNA was present in the saliva of patients with HCV associated sicca syndrome [10].

The investigation of cryoglobulines in this study showed a higher frequency of these in positive HCV subjects (62% in comparison to 30%). On the contrary, other authors do not find a significant association [11–13].

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**Table 1 – Criteria for the classification of Sjögren’s syndrome (European Community Study Group) [4]**

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<tr>
<th>1. Ocular symptoms. A positive response to at least one of these questions:</th>
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<tr>
<td>a) Have you had daily, persistent, troublesome dry eyes for more than 3 months?</td>
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<tr>
<td>b) Do you have a recurrent sensation of dry mouth for more than three months?</td>
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<tr>
<td>c) Do you use tear substitutes more than three times a day?</td>
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<th>2. Oral symptoms. A positive response to at least one of these questions:</th>
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<tr>
<td>a) Have you had a daily feeling of dry mouth for more than three months?</td>
</tr>
<tr>
<td>b) Have you had recurrent or persistently swollen salivary glands as an adult?</td>
</tr>
<tr>
<td>c) Do you frequently drink liquids to aid in swallowing dry foods?</td>
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<th>3. Ocular signs: Objective evidence of ocular involvement, determined based on a positive result on at least one of the following tests:</th>
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<tr>
<td>a) Schirmer test (≤5 mm in 5 minutes);</td>
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<tr>
<td>b) Rose Bengal score (≥4 according to the van Bijsterveld scoring system).</td>
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| 4. Histopathologic features: Focus score of 1 or more on minor salivary gland biopsy (focus defined as an agglomeration of at least 50 mononuclear cells: focus score defined as the number of foci per 4 sq mm of glandular tissue). |

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<th>5. Salivary gland involvement. Objective evidence of salivary gland involvement, determined on the basis of a positive result on at least one of the following tests:</th>
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<tr>
<td>a) Salivary scintigraphy;</td>
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<tr>
<td>b) Parotid sialography;</td>
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<tr>
<td>c) Unstimulated salivary flow (≤5 mL in 15 minutes).</td>
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<th>6. Autoantibodies present of at least one of the following serum autoantibodies:</th>
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<tr>
<td>a) Antibodies to Ro (SS–A) or anti-La (SS–B) antigens;</td>
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<tr>
<td>b) Antinuclear antibodies;</td>
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<tr>
<td>c) Rheumatoid factor.</td>
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**Probable Sjögren syndrome:** Presence of three criteria.

**Certainly Sjögren syndrome:** Presence of four or many criteria.

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**Figure 9 – Detail of the previous figure (no. 8) (HE stain, ob. ×20)**
King PD et al., because of their research concerning 48 patients, conclude that patients with Sjögren’s syndrome, without cryoglobulinemia and with detectable SS–A/SS–B antibodies, do not have clinically apparent liver disease, hepatitis C viremia by polymerase chain reaction, or antibodies to hepatitis C virus by second generation testing using RIBA–2 [5].

This research suggests that the presence of cryoglobulinemia might have an important role in this association. At the same time, a cryoglobulinemia is found only in less than 2/3 of the HCV infected patients and with Sjögren’s syndrome [10].

Boscagli A et al. find a prevalence of HCV of 4.7% during the course of Sjögren’s syndrome without a significant difference in comparison to the witness population and without correlation with the presence of a circulating cryoglobulin [14].

All these data are not convincing enough to sustain the implication of hepatitis C virus in the pathogeny of Sjögren’s syndrome even if viral ARN was evidenced in saliva [15] or in situ at the level of the salivary glands accessories in patients with sicca syndrome, chronic hepatitis C and cryoglobulinemia [16], further research is necessary for these results to be confirmed.

At the same time, in HCV-infected patients, the Sjögren’s syndrome presents some histological, immunological and clinical differences from Sjögren’s syndrome without markers of HCV infection.

Histologically, the examination of the salivary glands in patients with lymphocytic sialadenitis HCV infection associated shows the presence of a lymphocytary pericapillary infiltrate and not pericanalicular and the absence of salivary glands destruction.

Immunohistochemistry of minor salivary gland biopsy specimens for patients with Sjögren’s syndrome with and without hepatitis C virus infection, showed a predominance of CD4 over CD8 T-cells (2 : 1 ratio) in HCV and non-HCV-infected patients. The analysis of the lymphocytic focus showed that the HCV infected patients had a predominance of CD20 positive cells. Activation molecules (C 25 and HLA–DR) were expressed in HCV and non-HCV infected patients in lymphocytic and epithelial cells, however epithelial cell expression of CD25 was low in HCV-infected patients. As expected, a pronounced Th1 response was observed in the lymphocytic foci of HCV patients. These data suggest that HCV-infected patients may develop an autoimmune sialadenitis, similar to that described in primary Sjögren’s syndrome [17].

Immunologic, no significant difference in HLA type was observed. Human leukocyte antigen DQB1*02 was significantly associated with the development of sicca syndrome, P = 0.02 [1]. On the other hand, the prevalence of anti-ENA antibodies was significantly higher in patients with sicca syndrome and chronic HCV infection [18]. At the same time, is necessary to emphasize that HCV-positive sicca syndrome patients were seronegative for SS–A/SS–B antibodies [10].

Clinically, HCV-positive SS-patients exhibited a trend for more frequent chronic gastritis (50 vs. 22%), fibromyalgia (33 vs. 14%), peripheral neuropathy (33 vs. 18%), purpura vascularis (33 vs. 19%) and cryoglobulinemia (33 vs. 6%) [19].

The mechanism of lymphocyte infiltration that observed in the course of chronic hepatitis C is still unknown. It could be caused either of disimmunitary phenomena or by the direct action of HCV at the level of salivary glands, or by the infection of mono-nucleate cells [2]. The high prevalence of lymphocyte sialadenitis in other hepatopathies, for some authors pleads rather for systemic immune disorders induced by chronic viral infection or the hepatic disease [20]. It cannot be excluded the fact that, immune circulator complexes setting the complement and forming of HCV–RNA and anti–HCV antibodies, may alter the salivary and lachrymal glands during their elimination with the saliva and tears [2].

Thus, the development of immune disease in patients with chronic hepatitis C virus infection depends on the interaction of multiple factors, including viral persistence and human leukocyte antigen type of the patients [1].

Loustaud-Ratii V et al., as a result of a study concerning to prevalence and characteristics of Sjögren’s syndrome in hepatitis C virus infection, affirm that HCV infection appears to account for a subgroup of patients with sicca syndrome in which half the cases meet the definition for SS according to European and Manthorpe’s criteria. This subgroup is characterized by the constant finding of xerostomia, the absence of classical systemic manifestations observed in primary sicca syndrome, and the absence of anti–SS–A or anti–SS–B antibodies. Such characteristics delineate a distinctive, virus-associated entity that differs from primary sicca syndrome [21].

The case presented by us totally corresponds to the description of sicca syndrome in HCV-infected patients. However, it distinguished though in at least two aspects. First, the setting of sicca syndrome symptomatology prior to the hepatic one suggesting the effectuation of investigations with the purpose of decelating a potential HCV-infection and its confirmation. Second, something that is extremely important to us, the amelioration of salivary and ocular symptomatology following interferon and ribavirine therapy, which undoubtedly can sustain the implication of HCV viral infection in developing sicca syndrome.

\section*{Conclusions}

Our conclusion is that CHCV can induce SS with some clinical particularities like presence of pericapillary and not pericanalicular lymphocytic infiltrate without destroying the salivary glands, in the absence of SS–A/SS–B antibodies.

The favorable evolution of SS under IFN therapy is an argument for an authentic relation. Further studies are necessary to determine if CHCV is an etiological agent of SS or of it can induce a pseudo-sicca syndrome, characterized by a simple glandular inflammation consisting mainly in a simple lymphocytic adenitis.
References


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