Sicca Syndrome and Dementia in a Patient with Hepatitis C Infection: A Case Report with Unusual Bifocal Extrahepatic Manifestations

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Abstract

Introduction Hepatitis C virus (HCV) infections are associated with extrahepatic manifestations in 40–75 % of cases. Sialitis and secondary Sjögren syndrome are well characterized complications of chronic HCV infections but the mechanisms (primary or secondary) leading to xerostomia are not understood. Similarly, brain lesions due to HCV can be primary or secondary but the pathology of primary HCV-related brain lesions is not well described. **Case report** We report the postmortem case of a 60-year old patient initially presenting with sicca syndrome and dementia. HCV was identified in the brain but not in the salivary glands using transcription-mediated amplification (TMA). Focal sialitis was found in submandibular glands. Neuropathological examination revealed the presence of multiple dot-sized demyelination foci.

Conclusion Sicca syndrome is a common concern in chronic HCV infections and may be due to secondary immune mechanisms (we could not isolate HCV in salivary gland tissues). TMA had never been applied to the detection of viruses in salivary glands and neural tissues and proves to be a promising technique. Neuropathological reports in HCV infections are rare and the lesions we report may be the first characterization of the direct effect of HCV on brain cells. More cases are needed to define the full spectrum of lesions potentially caused by the direct action of the HCV on salivary glands and neural tissues.

Keywords Hepatitis C · Sicca syndrome · Sjögren syndrome · Encephalitis · Oligodendrocyte · Transcription-mediated amplification

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Case Report

A 60-year old man developed slowly progressive amnesia and frontal behavioral problems associated with xerostomia. These symptoms were evolving for the last 2 years according to his family. After a fit of delirium and acute confusion, he was referred to a neurology department for further investigations. Clinical examination disclosed bilateral Babinski sign, frontal syndrome with Lhermitte behaviour and short-term and long-term memory alterations associated with encoding anomalies. Severe xerostomia was found using standard dry-mouth questions [1]. Schirmer's test was negative. EEG showed diffuse slowing. Brain MRI revealed bilateral hemispheric white matter lesions (Fig. 1). ESR (14 mm), white cell count, coagulation, ACE, alpha-fetoprotein, thyroid function and liver enzymes were normal. Screenings for HIV, Lyme's disease, syphilis, cryptococcosis, brucellosis, amoebiasis,

Fig. 1 Flair MRI revealing bilateral hemispheric white matter lesions predominating in the posterior parietal subcortical regions

cysticercosis, trypanosomiasis and listeriosis were negative. Anti-HBs and anti-HCV antibodies were positive. HBs antigen was negative. Cryoglobulins were positive (0.12 g/l), consistent with a mixed type II cryoglobulinemia. Waaler-Rose was positive 1/640. Serum immunoglobulins were raised (IgG 27.6 g/l, IgM 1.5 g/l). Antinuclear antibodies were positive 1/40, anti-DNA antibodies were positive (ELISA 165 UI/ml). Anti-Ro and anti-La antibodies were negative. Immune complexes were at 4.4 mg/l. CH50 was lowered (26 UH50/ml), but C3 (0.75 g/l), C4 (0.19 g/l) and B (0.15 g/l) were normal. HLA type was A2 B15 B35 BW6. CSF examination showed: 6 cells, 1.84 g/l of proteins, normal glucose and 2 peaks of gammaglobulins (18 and 5 %). Jejunal biopsy and myelogram were normal. Liver biopsy showed active chronic hepatitis without granuloma. Muscle biopsy did not reveal any vasculitis. Minor salivary gland biopsy showed focal inflammatory infiltration, predominantly formed by lymphocytes [2]. During the course of the screening, the patient died of massive pulmonary embolism. Consent had been obtained for postmortem investigations.

Postmortem visceral examination disclosed active hepatitis without fibrosis. Cervical lymph nodes had non-specific adenitis. Hematoxylin-eosin stains were performed on 5 µm thick sections from selected blocks of brain, cervical lymph nodes and submandibular gland tissue. Bodian-silver staining was performed on brain tissue. Immunostaining was performed on cerebral and salivary gland tissue against B-cells (CD20, Dako, 0.25 %), T-cells (CD3, Dako, 1 %), macrophages (CD68, Dako, 1 %) and on brain

tissue against JC-virus (papova, courtesy of Dr. DL Walker, University of Wisconsin, 0.2 %). Immunofluorescence was performed on brain tissue against human IgA, IgG and IgM (rabbit anti-human IgA, IgG and IgM, Dako, 2.5 %).

Focal pericanalar CD20-positive non-destructive inflammatory infiltrates were found in the salivary glands (Fig. 2). The brain white matter contained multiple disseminated, well-delimited, millimeter-sized demyelination foci containing macrophages filled with luxophile material, sparing the axons (Fig. 3). Moderate meningeal and perivascular non-destructive T cell infiltrates were reported. Demyelinating lesions were not co-localized with inflammatory blood vessels. The grey matter was not affected. Brain stem and spinal chord were free of lesions.

HCV RNA was extracted from frozen samples from the frontal cortex, the subcortical frontal white matter and submandibular glands using the RNeasy Fibrous Kit (Qiagen, Courtaboeuf, France). Total RNA yield was determined by spectrophotometric measurement of the optimal density at 260 and 280 nm (GeneQuant III, Pharmacia Biotech, Fribourg, Germany). RNA was stored at −80 °C. We used the Transcription Mediated Amplification (TMA, Versant HCV RNA Qualitative assay, Siemens Medical Solution Diagnostics, Eragny, France) method for the detection of the extracted HCV RNA [3]. Extracted HCV RNA was quantified with VERSANT® HCV RNA 3.0 (bDNA) [4]. The results, in copies/ml, obtained automatically by the Quantiplex computerized program, were converted and corrected into copies/µg of total extracted tissue cellular RNA. TMA is an isothermal autocatalytic three-step target amplification method: (1) target capture, (2) target amplification and (3) specific detection of target amplicons. Target capture involves a 5' non-coding HCV sequence as a primer for amplification by a T7 RNA polymerase. This method has a detection limit smaller than 10 IU/ml and a quantification limit of 600 HCV RNA IU/ml [5]. We found presence of HCV RNA in the brain and lymph nodes (over the detection limit but below the quantification limit) but we could not detect HCV RNA in the submandibular glands.

The post-mortem diagnosis was chronic HCV infection with bifocal extrahepatic manifestations: sialitis and encephalitis. The cause of death (pulmonary embolism) was also confirmed.

Discussion

Sialitis in HCV Infection

The link between HCV infections and salivary gland disorders was initially reported in 1992 [6]. 10–35 % of

Fig. 2 **a** Submandibular gland postmortem histology: focal inflammatory infiltration without canalicule destruction. **b** B-cell (CD20) immunostaining showing high predominance of B-lymphocytes in the salivary gland infiltration

Fig. 3 **a** Postmortem liver histology: chronic hepatitis; inflammatory infiltration without fibrosis. **b** Brain vein in the frontal cortex: perivascular inflammatory infiltration without parietal lesions. **c** B-cell (CD20) immunostaining showing the presence of B-cells in the perivascular space of a vein, frontal cortex. **d** Demyelination focus without axonal destruction containing spumous macrophages, frontal

cortex. **e** Macrophage immunostaining (CD68) confirming the presence of macrophages in a demyelinating lesions of the frontal cortex. **f** Macrophages inside a demyelinating lesion of the frontal cortex: autofluorescence in favor of the presence of myelin destruction products

patients with HCV infections complain from xerostomia [2, 7] and Sjögren syndrome (SS) is the systemic autoimmune disease most strongly related to HCV: in the HISPAMEC registry, 18 % (151) of 858 SS patients had chronic HCV infection and SS accounted for 47 % of autoimmune disorders associated with chronic HCV infection [8, 9]. This association led to the concept of *SS secondary to hepatitis C* [10].

Nevertheless, despite the established link between salivary gland disorders and HCV infections, the presence of HCV in saliva and salivary glands is not correlated with the presence and severity of dry mouth [2, 11]: the mechanisms of sialitis in chronic HCV infections are not currently understood.

Our results are in line with the literature: we could not isolate HCV from the submandibular gland while the patient had severe xerostomia. Furthermore, anti-nuclear and anti-DNA antibodies were positive, CH50 was lowered and a mixed type II cryoglobulinaemia was found while anti-Ro and anti-La antibodies were negative: this predominance of cryoglobulin-related markers over SS-related markers is a reported characteristic of SS secondary to HCV as opposed to primary SS [8, 9].

Brain Lesions in HCV Infections

The brain demyelination we report does not resemble the brain lesions found in primary SS: neuropathological

lesions in SS are large perivascular demyelinated areas containing a massive lymphocytic infiltrate. Several secondary brain affections are associated with HCV. Cerebral HCV-associated panarteritis nodosa causes demyelinating lesions similar to what is found in primary SS. Cryoglobulinemia associated with HCV can induce demyelinating lesions [12] via an obstructive vasculitis by intraluminal deposition of protein aggregates but this condition does not induce diffuse demyelination foci.

Leukoencephalopathy in HCV encephalitis is reported [13–16] and HCV has already been detected in the brain without detailed neuropathological description [6, 13, 17, 18]. The unique lesions we describe are demyelination foci containing spumous macrophages and sparing axons, resembling the neuropathological aspect of multifocal progressive leukoencephalopathy due to JC-virus infection. Virus-induced demyelination can be direct or result from secondary immune or metabolic mechanisms [19]. HCV is a flavivirus and no flavivirus is known to induce demyelination in humans, so that straightforward mechanistic analogies are not available. Interestingly, immunohistochemical analyses have shown that HCV is found in astrocytes and seems to spare oligodendrocytes in HIV–HCV co-infected patients [20, 21]. The neuropathological aspect in the case we report suggests that oligodendrocytes are also targeted by the virus, possibly by an indirect immunological or metabolic mechanism if the virus is confirmed to localize in astrocytes rather than in oligodendrocytes. The same type of indirect immune mechanism could cause HCV-associated sialitis.

Clinical Consequences

From the prospect of the oral and maxillofacial surgeon, this case report underlines the importance of (1) HCV screening in the management of sicca syndrome and (2) regular intra-oral examination in the follow-up of patients with chronic HCV infections despite negative SS-related markers [8, 9]. This case also calls for further pathological investigations in extra-hepatic organs targeted by HCV in order to better understand the mechanisms of these manifestations.

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