CASE REPORT

Ophthalmological implications of the chronic infections with the hepatitis C Virus

Alexa Anisia-Iuliana*, Cantermir Alina**, Ciuntu Roxana Elena*, Chiselliţă Dorin* ***
*Ophthalmology Department, Emergency Hospital “Saint Spiridon” Iasi, Romania
**Oftaprof Clinic, Iasi, Romania
***Ophthalmology Department, „Gr. T. Popa” University of Medicine and Pharmacy, Iasi, Romania

Correspondence to: Alina Cantermir, MD
Oftaprof Clinic, Iasi, Romania
54 Stejar Street, Iasi, Romania
Mobile phone: +40722 143 186, +40746 933 617, E-mail: alina.cantemir@gmail.com

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Abstract

Objectives. Report of a clinical case reuniting the dry eye syndrome in a severe form, the Mooren's ulcer and necrotizing anterior scleritis with inflammation, with bilateral affection in the context of chronic infection with the hepatitis C virus.

Methods. A female patient aged 66 diagnosed with chronic hepatitis with HCV, with ophthalmological antecedents of Mooren's ulcer and severe form of dry eye syndrome in both eyes, comes to the emergency unit with hypopyon corneal ulcer in the right eye, shortly afterwards developing necrotizing anterior scleritis with inflammation. The patient is administered treatment for chronic hepatitis C, following which the ARN-HCV viremia decreases without ocular exacerbations. When the viremia level increases again, two lesions indicating necrotizing anterior scleritis are observed in the left eye. The evolution is favourable with topical and systemic treatment with corticosteroids. Complicated cataract is surgically treated in the right eye and vitreous humour is collected during surgery.

Results. Visual acuity increases in the right eye after the surgery, while antibodies-HCV are identified in the vitreous humour.

Conclusions. Chronic infection with hepatitis C virus displays multiple extra-hepatic manifestations and the ophthalmological ones require a multidisciplinary approach from both the chronic diseases practitioner and the ophthalmologist.

Keywords: Mooren's ulcer, necrotizing anterior scleritis, dry eye syndrome, hepatitis C virus

Introduction

Although the hepatitis C virus (HCV) was identified in 1980, the first scientific data was published in 1989, and only two decades later the first reports were published regarding the evolution and consequences of this viral infection [1]. At a global level there is no accurate estimation of the number of people infected with HCV, the most recent data being quoted by the World Health Organization, according to which the number of infected people is over 120 million [2]. The liver is the main target of the HCV, but it has a major impact on other organs, as well, that are infected through immunological mechanisms [3, 4].
At the ocular level there was no indication of pathognomonic signs or symptoms of the chronic infection with HCV, yet the literature in the field signalled series of cases of association between chronic viral infection and a range of affections, both at the anterior pole (lachrymal hyposecretion, Mooren’s ulcer, scleritis, trichomegaly) and the posterior pole (central retinal vein thrombosis, cystoid macular edema, non-arteritic anterior ischemic optic neuropathy or Vogt-Koyanagi-Harada [5]. Up to the present date there have been no studies to establish the correlations between the viremia level and the ocular manifestations.

Materials and methods

The present study describes the case of a 66 years old female patient diagnosed with chronic HCV hepatitis nine years before, with Mooren’s ulcer antecedents in both and severe form of dry eye syndrome who comes at the emergency unit in 2011 with a red, painful right eye with blepharospasm. The decrease of the visual acuity is observed at the right eye (0.02 without correction; it does not correct) as well as the presence of a peripheral ulcerative lesion in the temporal sector of approximately two mm, with an exudate adherent to the ulcerative lesion and the hypopyon, posterior iris synechiae on 360° and opacity of the crystalline; cornea is peripherally thinned with deep and superficial neo-vessels. The visual acuity in the left eye is 0.8 with correction; thinning of the peripheral cornea and the presence of neovascularization are observed in the supero-temporal sector, with a 2 mm Schirmer 1 test and a two-second lachrymal film breaking time. The hypopyon corneal ulcer is treated with moxifloxacin, autologous serum, corneal and mydriatic cicatrizants with slow favourable evolution, an epithelial defect still persisting. For the severe form of dry eye syndrome the patient was recommended long term artificial tears for both eyes.

Ten days after discharge the patient returns to the emergency unit with a significant episcleral and conjunctival congestion in the right eye, as well as a nodular scleral lesion in the temporal sector at approximately 1.5 mm of the sclerocorneal limbus. During her second hospital stay, to the patient is administered the previously recommended topical treatment and systemically she is given prednisone 60 mg/day and 150 mg ranitidine twice a day to protect the stomach. The discharge diagnosis is necrotizing anterior scleritis of the right eye with inflammation, corneal ulcer sequelae – persistant epithelial defect, complicated cataract in evolution and Mooren’s ulcer sequelae and severe dry eye syndrome in both eyes. The scleral lesion is completely cured within four weeks of treatment.

As recommended by the infectious diseases doctor, treatment is initiated for the active chronic hepatitis with HCV with interferon α 2b 180 µg/week and ribavirin 1.2 g/day, for 16 weeks, the HCV ARN decreasing from the initial value of 5 233 874 UI/ml to an undetectable value.

After three years during which the patient comes regularly for ophthalmological check-ups, and the aspect remains stationary, the patient comes back with an intense painful sensation in the right eye, blepharospasms and red eye aspect. The presence of an approximately 2 mm nodular lesion is observed in the temporal sector on the 2 o’clock meridian. The patient is committed into hospital for further investigations in order to determine the aetiology of the necrotizing anterior scleritis in the right eye. Normal values are recorded for the complete blood cell count, biochemistry (ionogram, urea, creatinine blood test), erythrocyte sedimentation rate, uric acid, angiotensin conversion enzyme, the rheumatoid factor, neutrophil polynuclear anti-cytoplasmic antibodies, human lymphocyte antigen B-27 (HLA-B 27), antinuclear antibodies, cryoglobulinemia, RPR (Rapid Plasma Reagin test) and tuberculin intradermal test. The thorax x-ray, the sinus x-ray and the sacroiliac articulations x-ray are of a normal aspect. The rheumatologic clinical examination did not reveal any sort of rheumatologic issue. Increased transaminases values were observed, antibodies-HCV are present in the blood and the ARN-HCV viremy was of 1 754 237 UI/ml.

The right eye is topically treated with dexamethasone and indometacinum and systemically with methylprednisolone 32 mg/day. After three weeks of treatment a new scleritis lesion appears in the right eye in the
temporal sector on the 5 o'clock meridian at 3 mm from the limbus (Fig. 1). The methylprednisolone dose is increased to 48 mg/day for one month, and consequently lesions go into remission and the dose is progressively decreased. The topical treatment with dexamethasone was administered in decreasing quantities for four months, an increase of intraocular pressure (IOP) of 30 mmHg being recorded in the left eye. When the topical treatment with dexamethasone is interrupted IOP remains high in the left eye; a fixed combination treatment with timolol and dorzolamide, IOP values going back to normal consequently.

Alter a year when no particular events were recorded, the patient's visual acuity is counting fingers at 30 cm in the right eye and 0.4 in the left eye (without correction; it does not correct). A general prevention treatment with methylprednisolone 16 mg is initiated and two days later surgery is performed for the cataract in the right eye with clear cornea incisions, synechiolysis on 360°, phacoemulsification and posterior chamber pseudophakia (Fig. 2). Vitreous humour was extracted during the surgery in order to establish the presence or absence of antibodies-HCV.

Results

Six weeks after surgery the visual acuity is 0.4 without correction, the visual acuity being also affected by the corneal leukomas, while IOP has normal values and no other exacerbations of the inflammatory phenomena are observed. In the left eye, the visual acuity is 0.3 and the patient is scheduled for cataract surgery. Both in the vitreous humour extracted from the right eye and in the blood, the tests indicated the presence of antibodies-HCV.

Discussions

The exclusion of other aetiologies and the presence of antibodies-HCV in the vitreous humour support the hypothesis according to which the ocular condition (the dry eye syndrome, the Mooren's ulcer and the necrotizing scleritis) was the result of an autoimmune mechanism as a reaction to the HCV chronic infection. Another argument is the fact that over a 3 year period in which the blood viremia was maintained at undetectable levels, there were no exacerbations of the autoimmune ocular conditions, becoming thus obvious that there was a correlation between the increase in viremia and transaminases and the occurrence of ocular lesions.

Most data reported in literature about ocular conditions of patients diagnosed with HCV chronic hepatitis make reference to the dry eye syndrome. There are studies proving the fact that parameters such as decrease of the lachrymal film breaking time, increase of the ocular surface colouring with Lissamine green and lower scores in OSDI questionnaire (Ocular Surface Disease Index) are directly proportional with the hepatic fibrosis degree [6, 7]. A more severe lachrymal hyposecretion was reported in younger patients [3]. An indicator of hyposecretion is the lactoferrin level in the lachrymal film; its decrease in patients diagnosed with HCV chronic infection represent both an argument for the dry eye syndrome diagnosis and a proof of acinar cells dysfunction in the context of the viral infection [8]. The goblet cells density, the first parameter affected in the keratoconjunctivitis sicca, significantly
decreases in these patients as opposed to other healthy subjects [3, 9].

The pathophysiological mechanism of the dry eye syndrome consists of the fact that viruses trigger autoimmune reactions by inducing the expression of neoantigens of the host which are similar to the viral antigens, which determine the production of auto-antibodies and cells directed against the host’s cells [10, 11]. In the HCV infection context the presence of certain periductal and perivascular infiltrates was observed at the lachrymal gland level, made of B and T CD4 lymphocytes that release pro-inflammatory cytokines which produce the apoptosis of glandular epithelial cells with the exhibition of certain epitopes which auto-reactivate the lymphocytes. This vicious circle is responsible for the progressive destruction of the glandular parenchyma and the lachrymal secretion decrease [3, 12].

The treatment of the HCV infection with interferon α2b and ribavirinum may further affect the lachrymal film dynamics and ca induce the occurrence of squamous metaplasia, which might persist for as long as six months after treatment is ceased [13].

In the case of our patient one can notice the constant presence of the conjunctiva congestion and corneal pannus. There are studies describing the high frequency of these signs in HCV patients, which is explained based on immunological mechanisms, as well [4]. At the conjunctiva level there are numerous microphages and Langerhans cells which in contact with the HCV antigen act as antigen presenting cells and trigger the inflammation [3].

The conjunctiva, the lachrymal glands and the cornea form a functional unit, and consequently when one of them is affected, a generalized imbalance occurs. The cornea may be involved both indirectly, because of the effect upon the lachrymal glands and the conjunctiva, and directly, as there exist pathogenic associations between the Mooren’s ulcer, recurrent keratitis and chronic HCV infections [14].

The first cases of Mooren’s ulcer in patients diagnosed with hepatitis C were reported in literature in 1994, when a progressive decrease of symptoms and an improvement of the clinical aspect were noticed as soon as interferon α2b was initiated and the plasma viremia began to decrease [15]. A year later a similar case was reported, namely Mooren’s ulcer with initially static evolution which became favourable when the patient received treatment destined for chronic hepatitis C and the corneal ulcerous lesion resolution was correlated with the improvement of the hepatic functional parameters [16].

The peripheral cornea is affected because of the presence, at this level, of a high number of immunoglobulin M with a high molecular weight, macrophages, Langerhans cells and the C1 fraction of the complement. The antigen-antibody complexes formed at the cornea level, at the limbus vessels level or brought by the level of tears and vitreous humour trigger a chain of inflammatory reactions especially in the peripheral cornea, while the circulating immune complexes will be deposited at the limbus vessels causing immune vasculitis [3].

Literature reports cases of Mooren’s ulcer patients who had a favourable evolution after interferon α2b topical treatment used as a unique therapeutic agent [17]. This could be regarded as a treatment alternative, yet more ample studies are required to confirm the long term efficiency and the safety of the topical administration of α2b interferon.

The necrotizing scleritis with inflammation that the patient displayed bilaterally is the rarest type of anterior scleritis but also the most severe form; it actually threatens the integrity of the ocular globe; scleral necrosis can evolve from small areas of scleral thinning to extended necrosis areas. The characteristic sign is the presence of capillaries closure areas that frequently involve capillary plexus. In over 50% of the patients necrotizing anterior scleritis is associated with cornea conditions and systemic pathologies [18].

The HCV infection can induce secondary vasculitis because of cryoglobulinemia [19] and/or circulating immune complexes containing antibodies-HCV [20, 21]. Scleritis is characterized by the storage of circulating immune cells at this level and the induction of a vascular inflammation with infiltrates of the inflammatory cells and oedema of the sclera and episclera [22]. Histological sections of the episcleral or conjunctival biopsies indicate the presence of chronic diffuse of the inflammatory cells (lymphocytes and monocytes) [18]. An
immune-histochemical study performed on enucleated ocular globes, concluded, due to some severe forms of necrotizing scleritis, that the majority of the inflammatory cells involved is represented by B lymphocytes and macrophages [23]. The cytokines produced by these inflammatory cells stimulate in turn the excessive production of proteolytic enzymes (matrix metalloproteinase) which destroy the scleral tissue [24]. The loss of scleral collagen during the scleritis leaves areas of scleral thinning which have a blue-green coloration due to the visualisation through transparency of the choroid [25].

The patient had a favourable evolution under systemic and topical treatment with corticosteroids, yet in the left eye IOP increases were noted. Intraocular hypertension or cataract can occur as complications of scleritis or of long term treatment with corticosteroids [18, 26]. Complicated cataract had an incidence of 17% in a study following the evolution of scleritis patients for a period of 11 years [27].

Cataract surgery in patients with scleritis antecedents must be performed with further caution, since surgery in itself represents a risk factor. Scleritis occurs generally six months after surgery, most often after scleral incisions for cataract surgery [18] or in the case of the limbus incision for the extracapsular extraction [28]. In patients with scleritis antecedents the cataract surgery is recommended at least three months after the complete remission of the scleritis, the recommended techniques being clear cornea incisions and phacoemulsification [28]. These recommendations were thoroughly obeyed in the present clinical case, and the post-surgery result for the right eye is encouraging and supports the recommendation for cataract surgery in the left eye, as well.

The ophthalmological prognosis is favourable yet long term regular checks and periodical ophthalmological consultations are required. At the infectious diseases doctor the patient will continue with a second interferon α2b and ribavirinum treatment, which requires thorough monitoring, since ophthalmological complications of the interferon treatment should be also considered, such as ischemic retinopathy [29]. The vital prognosis is reserved because of the active chronic infection with HCV; in necrotizing scleritis patients mortality is 54% at 10 years because of the general vascular condition [22]. The particularity of the case is given by the bilateral effect upon the ocular surface in the context of HCV infection, exacerbations being correlated with the increase of viremia and transaminases.

Up to the present date there is no in vitro model of cells derived from ocular tissues infected with HCV. However, the design of such a model could explain more accurately the pathophysiological mechanisms of the ocular disease [30].

To conclude, the chronic HCV infection has multiple extra-hepatic manifestations, among which ophthalmological ones require a careful monitoring of the patients and an interdisciplinary approach of both the infectious diseases practitioner and the ophthalmologist, in order to improve the vital and ophthalmological prognosis and to increase patients’ quality of life.

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References

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