

Sjögren syndrome successfully treated with oxygen-ozone auto-hemotherapy (O₂-O₃-AHT): a case report

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Abstract. – OBJECTIVE: Sjögren syndrome (SS) is an autoimmune disorder, affecting about 16,000 individuals in Italy, yet lacking a standardized therapy protocol and a plain inclusion in the reimbursed healthcare services. This raises many controversial issues about how managing the SS patient, to relief pain and discomfort and improve patients' health and social life. The ozone therapy resulted successful in previous reports, and therefore, it was used in this case report.

CASE PRESENTATION: A 69-years old female outpatient, showing positivity to Schirmer's test, was previously diagnosed as a primary Sjögren syndrome, who later developed an autoimmune thyroiditis and showed the presence of rheumatoid factors. The patient suffered from a marked ocular dryness, subsequently to a purported endothelitis, alongside with fatigue and pain. Laboratory tests showed a positive ANA 1:320 in a speckled pattern with negative anti-SSA and anti-SSB tests. From December 2020 to January 2021 she underwent 2 routes of three sessions of oxygen-ozone autohemotherapy (O₂-O₃ AHT), as described below and improved, with only 2 sessions, her symptomatology and clinical outcome, as ocular dryness, fatigue and pain, rapidly disappeared.

CONCLUSIONS: The use of ozone in the therapy of SS is a straightforward, affordable and feasible approach to treat primary Sjögren syndrome without significant side effects.

Key Words:

Sjögren syndrome, Ozone, Ozone therapy, Clinics, PI-NRS, Case report.

Introduction

Sjögren syndrome (SS) is a complex autoimmune disease, whose etiology is particularly burdensome to elucidate, so that many experts are still expanding a fundamental debate in the community, updating the knowledge of this pathology with novel evidence and biomarkers¹⁻³. Despite the scientific research on SS pathology is ongoing, SS therapy is still a matter of concern. Actually, such topics regarding its complex pathogenesis, described as a self-perpetuating loss of exocrine function due to immune mechanisms and causing a glandular hypo-functionality, are particularly stressed in the current literature elsewhere¹, whereas the therapy approach and protocols to treat SS are discussed in a lesser extent, probably because of the paucity in consensus committees and guidelines on SS therapy⁴⁻⁷.

A first concern is that SS diagnosis should be properly performed, for example, by separating SS from a "sicca" syndrome⁸ and diagnosing a primary Sjögren syndrome (pSS) in the complete absence of other primary rheumatic disorders, despite the terms primary and secondary may be considered misleading^{9,10}.

The pSS can be considered, briefly speaking, a chronic autoimmune epithelitis. This pathology should involve mainly women showing various clinical manifestations, such as a long-lasting inflammatory phenotype, leading to an accelerated apoptosis of epithelial tissues, impaired gland structure and function, and the production

of pro-inflammatory cytokines and chemokines, such as B-cell activating factor (BAF), IL-6, IFN- γ , CXCL13, CXCL12, TNF- α , also in the submandibular glands¹¹. The global prevalence calculated for pSS is 61 individuals for 100000 inhabitants, with the highest prevalence encountered in Europe¹².

Women (F) develop Sjögren syndrome more frequently than men (M), and actually the SS incidence range, as referred to the sex F/M difference, is between 9:1 and 19:1⁸. The mean age at time of first diagnosis of pSS is 56 years, with another peak occurring between 20 and 40 years^{13,14}.

Primary Sjögren syndrome can be distinguished from secondary Sjögren syndrome (sSS) as generally occurring as a part of other rheumatic diseases. sSS coexists especially with systemic lupus erythematosus (15-36%), rheumatoid arthritis (20-32%), limited and progressive systemic sclerosis (11-24%), yet less frequently with multiple sclerosis and autoimmune hepatitis and thyroiditis¹⁵. Cases of pSS with autoimmune thyroiditis as a secondary illness were also reported¹⁶.

Anti-Ro and/or anti-La (ENA) antibodies were reported in approximately 70% of pSS patients, generally with ANA positivity, therefore, some kind of pSS can be anti-ENA negative. Hyper-gammaglobulinemia and neutropenia are also commonly present in pSS¹⁷.

Systemic features may also occur in some patients with pSS, in particular some forms of arthritis. A positive rheumatoid factor (RF) is often observed and, in this perspective, if patients exhibit arthritis, dryness and a positive RF, a diagnosis of pSS should be considered as a possible alternative to rheumatoid arthritis (RA)¹⁸⁻²¹. Further common symptoms in patients with pSS are: fatigue (present in about 80% of patients), vaginal dryness, interstitial cystitis. Up to 40% of patients with SS have neurological symptoms that precede sicca manifestations, and a recent study²² on 184 patients with SS, showed that 93% of them were diagnosed after the appearance of neurological symptoms. Patients with pSS are susceptible to lymphomas in a wider extent than other autoimmune diseases²³. Moreover, those patients with SS suffering from cognitive dysfunction or “brain fog”, may be susceptible to interstitial lung disease and interstitial nephritis.

Regarding SS therapy, we should raise the concern that currently no sound cure, except for biological therapies, is available⁷. A good therapy approach should be tailored individually for each

patient to reduce symptoms, avoid complications, and improve quality of life²³.

Overall, the prognosis of the primary Sjögren syndrome (pSS) is yet favorable. The life expectancy of pSS patients is comparable to that of the general population²³. However, patients' quality of life is reduced by the diverse manifestations of the disease.

The best therapy of pSS is still a matter of debate^{24,25}. In the topical treatment of the so-called “sicca” (i.e., dry) keratoconjunctivitis, the patient must take artificial tears and eye drops based on methylcellulose or polyvinyl alcohol, therefore, the sensation of sand in the eyes, burning and dry eyes are easily relieved.

The number of applications depends on the degree of dryness. However, there are no specific medications for the treatment of the “sicca” pattern of manifestations in pSS, with the exception of medicines used to compensate for the lack in glandular secretion. In addition, anti-inflammatory drugs and immunosuppressants can be used to relieve inflammation and reduce the autoimmune reaction that characterizes this syndrome.

Therapies commonly prescribed are mostly targeted to only symptoms and pain relief, therefore, aiming at simply reducing the symptoms impact on the patients' quality of life. A therapy able to achieve both pain relief and a long-lasting disappearance of the pSS pathological signs, is highly preferable and commendable.

Case Presentation

A female outpatient (69 years old) turned to this healthcare center, because previously diagnosed as having a pSS and further counselled to be treated with our therapy protocol. The patient reported pain in the small and medium joints of the upper limbs and a bothersome ocular dryness since many years. After a counselling interview, the patient accepted to be included in the therapy scheduling, signed an informed consent for this study, according to the Declaration of Helsinki, and entered the therapy panel and the research investigation.

During childhood and in early youth, the patient exhibited an allergic diathesis with anaphylactic episodes. Hypersensitivity events increased with menarche and during the first pregnancy. In 1990 she suffered for fatigue for about six months and also for low-grade fever, associated with “brain fog”, difficulty in mental concentration and

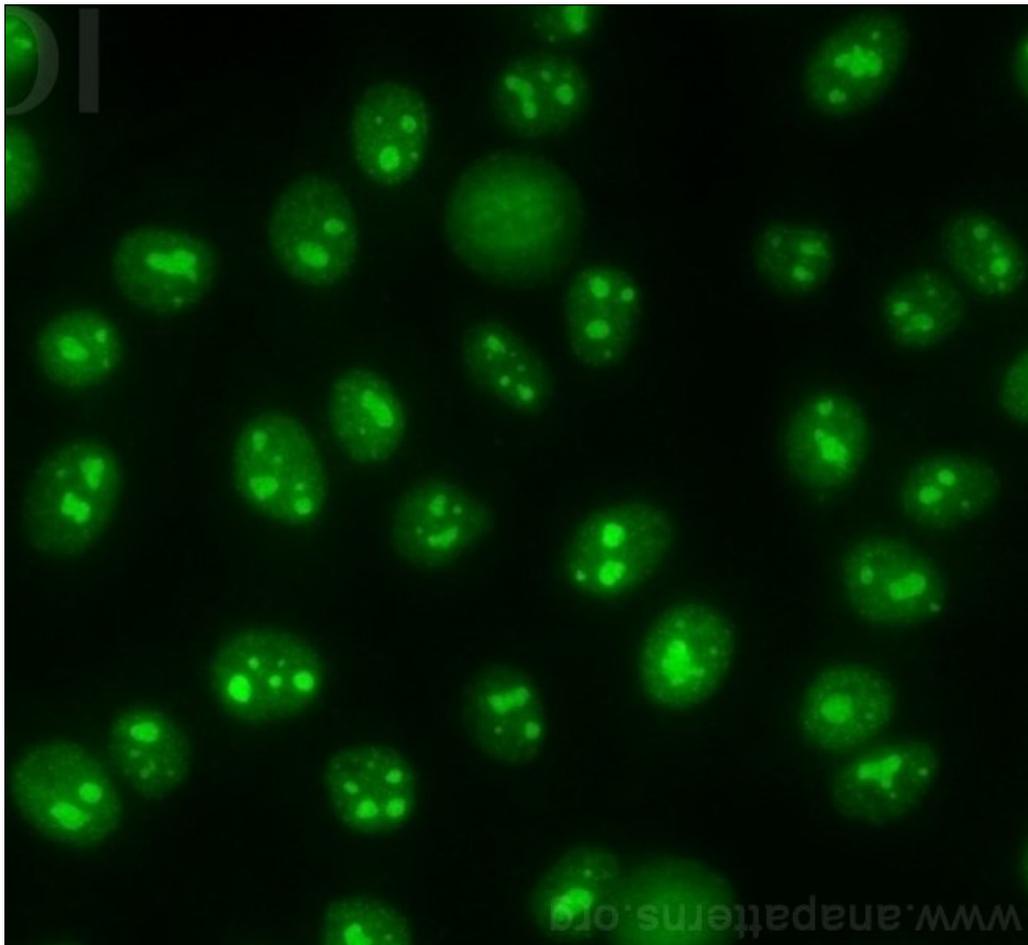


Figure 1. ANA test in the patient before O₂-O₃-AHT treatment (ANA by IFA, Labcorp Mcleansville NC, USA, speckled pattern), 1:320 [magnification 400X (40x10)].

mild cognition impairments, which disappeared spontaneously. In 1999 she was diagnosed with Hashimoto's thyroiditis with positivity to anti-thyroid antibodies [i.e., anti-thyroglobulin (anti-Tg) antibodies and anti-thyroid peroxidase (anti-TPO) antibodies] and an evident hypothyroidism, for which she was treated with levothyroxine. The pathology was associated with ventricular ectopic beats requiring therapy with propafenone.

In 2010, she had dry eyes (xerophthalmia) associated with eyes pain and paresthesia in the upper limbs. The physical examination revealed the presence of soft and mobile axillary lymph nodes. Subsequently, dry mouth (xerostomia) and dryness of the nasal cavities occurred. Ultrasound examination of the salivary glands revealed hypertrophy of the parotids and glandular structural inhomogeneity. Laboratory analysis revealed positivity to Schirmer's test, a positive anti-nuclear antibody test (ANA, 1:320, Figure 1) in a speck-

led pattern with negative anti-SSA and anti-SSB, leukopenia and neutropenia (WBC 3,900/ μ l, neutrophils = 47%) and hypergammaglobulinemia (IgG = 20.5%), erythro-sedimentation rate (ESR) = 22 mm/h and C-reactive protein (CRP) = 0.52 mg/L. Subsequently, she had a marked worsening of the sicca syndrome and of arthralgia.

As no successful therapy fulfilled the patient's need to feel better, an attempt with ozone therapy was agreed. From December 2020 to January 2021 she underwent 2 routes of three sessions of oxygen-ozone autohemotherapy (O₂-O₃ AHT), as described below and improved within only 2 sessions her symptomatology and clinical outcome.

Treatment with O₂-O₃ AHT was performed using a dosage of 45 μ g/ml O₃ in 200 ml (final volume included the gas mixture) of autologous peripheral blood, mixed in a SANO3 certified sterile bag and reinjected into the host. ANA were reduced to 1:160 (Figure 2). A volume of 100 ml of blood was

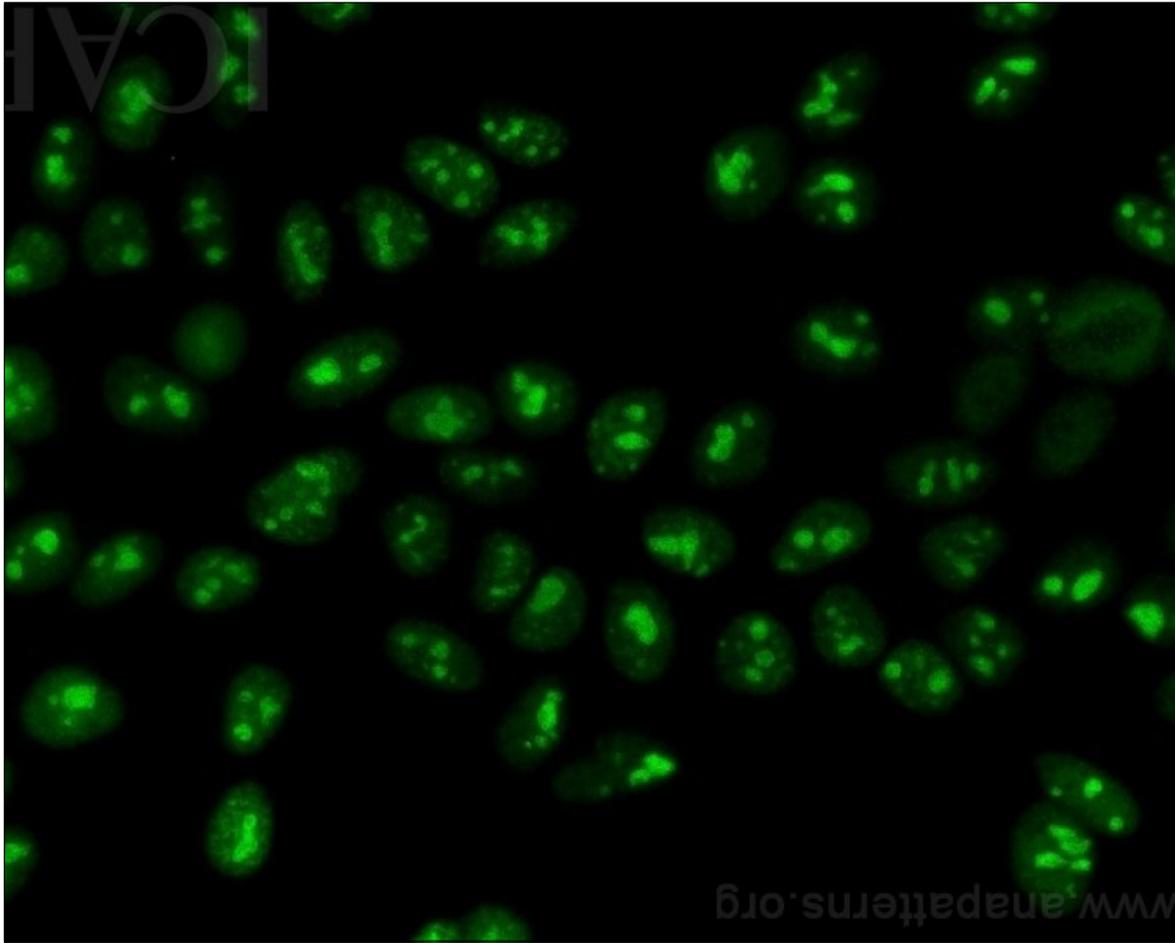


Figure 2. ANA test following 1 year of O₂-O₃-AHT treatment (ANA by IFA, Labcorp Mcleansville NC, USA, speckled pattern), 1:160 [magnification 400X (40x10)].

drawn either with a G19 or G21 (G = gauge) needle and supplemented with 11 ml of 3.8% Na-citrate, then, 100 ml of the O₂-O₃ mixture was added, with O₃ adjusted to 45 µg/ml *via* a photometric device applied to the machinery. A total ozone dosage of 4.5 mg was calculated in the single session, accounting on one session/week, for a total of six discontinued weeks into two routes, with 10 days lag. Just at the end of the second O₂-O₃ session, the patient obtained complete regression of orbital erythema, arthralgia and dryness syndrome (Figure 3). The patient then continued the O₂-O₃ AHT sessions with good symptoms control.

Figure 3 shows the previously ill patient before the treatment (Figure 3A) and the ocular outcome following one month from starting the O₂-O₃ AHT (Figure 3B). A skin endothelitis of the peri-palpebral region with palpable purpura and eyes pain occurred before (Figure 3A) and then disappeared (Figure 3B).

The patient still had this normal appearance so far. Moreover, a 16-item Patient-Reported Arthralgia Inventory (PRAI)²⁶, reported that the arthralgia was reduced from 135 to 91 ($p = 0.00000147$) and fatigue, in the 9-item Fatigue Severity Scale (FSS)²⁷, reduced by 75% ($p = 0.0000213$).

Discussion

The use of ozone therapy in the Sjögren syndrome (SS) was pioneered by some authors in recent years, showing amelioration in a 51-yr old female patient following three months of 20 µg/ml of 300 ml rectal ozone²⁸. The case report herein described is the first evidence reporting a clear amelioration in the dryness symptomatology of a diagnosed pSS, involving an improvement also in pain and fatigue relief, due to oxygen-ozone autohemotherapy (O₂-O₃-AHT). At the best of our knowl-

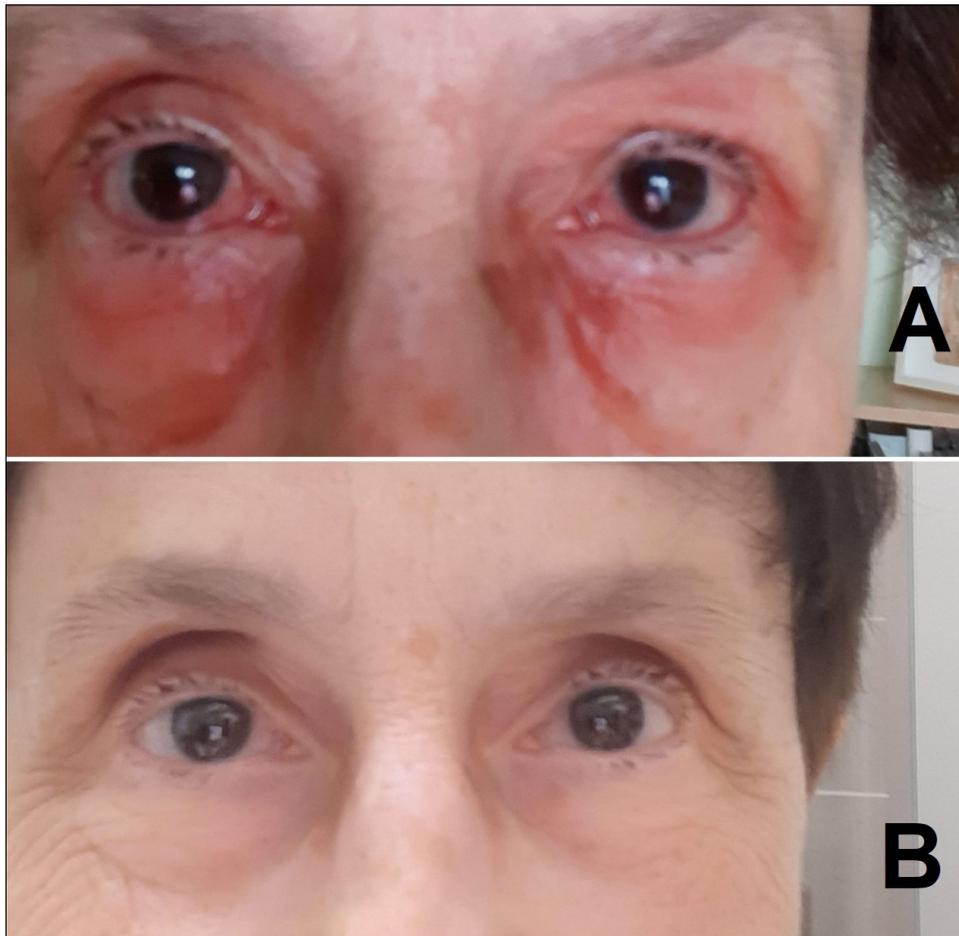


Figure 3. Patient ocular visage before (A) and after (B) 3 sessions of O₂-O₃-AHT.

edge, no further evidence was reported so far in the literature or elsewhere regarding the ability of medical ozone to relieve pSS symptoms and heal ocular dryness (the so-called “sicca manifestations”). The patient feels better even to date and did not need O₂-O₃-AHT sessions anymore. Therefore, we can forward the consideration that O₂-O₃-AHT established a long-lasting immune functionality, able to greatly reduce patient’s pain and discomfort.

A possible hypothesis to explain the evidence here reported may involve mitochondria function, as they rule the mito-hormetic mechanisms by which ozone can act as a beneficial molecule^{29,30}. Mitochondria dysfunction has been reported to be a possible causative factor in the etiopathogenesis of the Sjögren syndrome³¹. Dysfunctional mitochondria can release myokines and mitochondria-derived products of damage, such as cardiolipin, mitochondria-derived formylated peptides and mitochondrial DNA, all factors that can act as damage-associated molecular patterns (DAMPs)³¹. As

it is well known, DAMPs induce inflammation *via* pattern recognition receptors (PRR), such as the inflammasome NLRP3, TLR9, ZBP1 and cGAS/STING, causing the chronic inflamed phenotype typical of the Sjögren syndrome³¹.

Ozone can modulate mitochondria biogenesis and lifespan, acting on the ability of mitochondria to be regulated by small amounts of ozone-induced ROS, so re-establishing the correct mitochondria functionality, PGC-1 α activity and many survival pathways in the cell, reducing cell apoptosis and also necrotic phenomena^{29,30}.

The possibility to feel better from a pSS is a rare event, yet the application of at least three sessions of O₂-O₃-AHT, with one-week interval each other, restored the patient’s optimal health, most probably by re-balancing the correct Th17/Treg homeostasis in the immune system. However, further insights are needed to elucidate the causative elements of the evidence reported, a research item that we are going to deepen in next forthcoming investigations.

Limitations

This is a case report study. Further investigations have to be performed before assessing the undisputable effectiveness of O₂-O₃-AHT on pSS. This is a target we are going to fulfil in next research studies and plans, alongside with SIO-OT, by increasing the number of patients recruited and optimizing the methodology and devices used so far.

Conclusions

Oxygen-ozone auto-hemotherapy (O₂-O₃-AHT) resulted efficacious in reducing sicca symptomatology, fatigue and arthralgia in a patient with primary Sjögren syndrome, suggesting therefore a possible therapeutic solution for pSS in alternative to pharmaceutical drugs with possible adverse effects, able to improve greatly the quality of life in these patients.

Consent to Participate

The patient signed an informed consent for sharing her data for research studies.

Consent for Publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Corresponding Author at complete disposal of the Editor-in-Chief of this journal.

Availability of Data and Materials

Each raw data can be requested to Dr. Edoardo Rossi or to Dr. Salvatore Chirumbolo (Corresponding Author).

Conflict of Interest

The Authors do not have any conflict of interest.

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None.

Authors' Contributions

Conceptualization: ER, LV, SC; Data collection: ER, LV, SC. Manuscript writing: SC; Validation: ER, MTC, RS, DB, VS. Scientific supervision: LV, SP, SC; Management: LV, ER, MF. Data elaboration: SP, LV. Submission: SC.

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