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CASE REPORT

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Observation of changes in the eye and joints due to the modification of therapy for ankylosing spondylitis and recurrent uveitis – a twenty-year follow-up study

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ABSTRACT

We present a twenty-year follow-up study of a patient and changes in his eyes and joints under various therapies for ankylosing spondylitis. Sulfasalazine, methotrexate, etanercept and adalimumab were used to treat the systemic disease. Ophthalmological treatment of recurrent uveitis occurring every 2 months included intravenous dexamethasone, oral prednisone and topical dexamethasone and 1% tropicamide. Long-term treatment with steroids resulted in complications such as cataracts and herpetic keratitis. Prior to treatment with adalimumab, treatment-resistant, recurrent uveitis and complications such as proliferative vitreoretinopathy and secondary retinal detachment resulted in irreversible lesions and blindness in the right eye. By switching the TNF-α inhibitor to adalimumab for rheumatological ailments, the patient achieved significant improvement in visual acuity in the left eye and a long-term absence of inflammatory symptoms in this eye, which confirms that in the case of spondyloarthropathy, the cooperation of a rheumatologist and an ophthalmologist is necessary.

KEY WORDS: ankylosing spondylitis, spondyloarthritis, biological treatment, non-infectious uveitis.

CASE REPORT

We present a twenty-year follow-up study of a patient and changes that developed in his eyes and joints as a result of the use of various treatments for ankylosing spondylitis (AS).

A diagnosis of the axio-peripheral form of AS was made in the patient at the age of 30 (1998), but the symptoms of the disease had appeared about eight years earlier. Sulfasalazine (2 g daily) was used to treat the underlying disease, followed by methotrexate (10 mg per week) due to the poor tolerance of sulfasalazine and non-steroidal anti-inflammatory drugs.

In the years 2008-2010, during treatment with methotrexate, the patient developed severe uveitis in the right eye (RE), recurring every 2 months, causing significant visual impairment to the level of counting fingers. Initially, the patient's ophthalmological treatment included orally administered prednisone (maintenance dose 10 mg), dexamethasone and 1% tropicamide administered in eye drops. In 2010, during the first period of hospitalization in the Department of Ophthalmology, due to severe bilateral uveitis, the patient received intravenous dexamethasone with an initial dose of 6 mg (in decreasing doses) followed by a 10 mg maintenance dose of prednisone. Best corrected visual acuity (BCVA) of the left eye (LE) was 1.0. In RE, vision improvement was not achieved and there was a complication – a steroid cataract. Three months after remission of inflammation, phacoemulsification of the cataract with an artificial lens was performed in RE. After this procedure vision of the RE improved slightly (BCVA RE = 0.02).

In February 2011, during the first period of hospitalization at the Department of Rheumatology, an increase in intensity of the underlying disease was documented (Bath Ankylosing Spondylitis Disease Activity Index [BASDAI] = 6.2). The patient was diagnosed with grade 4 radiographic changes in the spine and sacroiliac joints. Additionally, the presence

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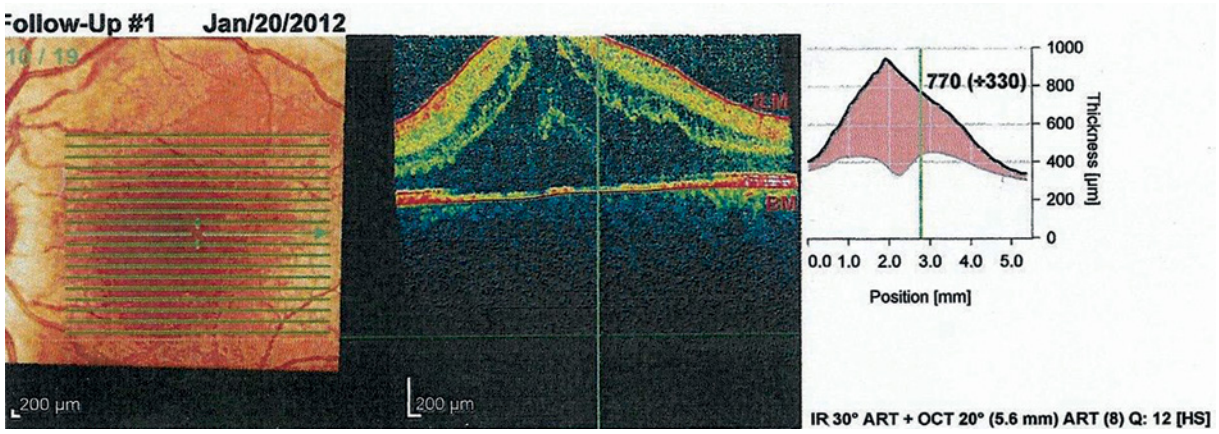

Figure 1. Optical coherence tomography (OCT) of the macula of the left eye (January 2012) – patient's own photo. Visible macular edema with subretinal fluid, 770 µm thick

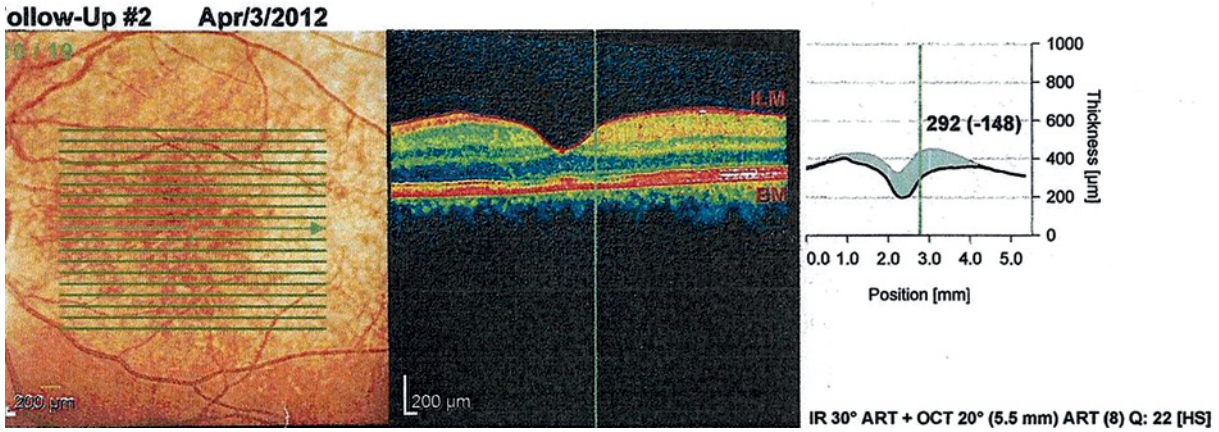

Figure 2. OCT of the macula of the left eye (April 2012) – patient's own photo. Visible fovea contour, no macular edema, after intravitreal injection of triamcinolone acetate

of HLA B27 was found in the blood serum. Due to the high activity of inflammation (BASDAI = 8.8) and recurrent uveitis, the patient was qualified for biological treatment, after prior chemoprophylaxis due to the positive result of the interferon test for latent infection with *Mycobacterium tuberculosis*.

In December 2011, biological therapy of AS with a tumour necrosis factor inhibitor was initiated and the patient was treated with 50 mg of etanercept (tumour necrosis factor α [TNF-α] receptor fusion protein) subcutaneously once a week. The treatment resulted in a good response from the musculoskeletal system but relapses of uveitis were still very common (on average every 3 months). After three months of treatment with etanercept, visual acuity of the LE deteriorated (BCVA LE = 0.4) due to the occurrence of cystoid macular oedema (CMO) and the coexistence of steroid cataract (Figure 1). Two intravitreal injections of triamcinolone acetate – in February 2012 and April 2013 – were administered, after which the macular oedema in the LE decreased (Figure 2). In April 2012, due to severe right uveitis with CMO, a pars plana vitrectomy was performed with the administration of silicone oil into the vitreous chamber (Figure 3). After six months, another pars plana vitrectomy was performed due to proliferative vitreoretinopathy and retinal traction detachment. Four months after revitrectomy vision of RE was at the level of hand movements (HM) due to the occurrence of CMO and coexistence of epiretinal membrane. The intraocular pressure was normal.

After 18 months of the use of etanercept, symptoms of hypersensitivity to the drug developed and the treatment was switched to adalimumab (human anti-TNF-α monoclonal antibody). From October 2013 to March 2017, the patient received 40 mg of adalimumab subcutaneously every other week together with methotrexate in a dose of 25 mg per week. As a result of switching the biological drug, the activity of AS was low, and a good ocular response was also observed. The number of uveitis relapses decreased significantly to once a year. In February 2014, due to a steroid cataract, an LE cataract phacoemulsification procedure with an artificial lens implantation was performed resulting in BCVA LE = 0.4. In August 2014, August 2015 and October 2016, the patient received three injections of triamcinolone acetate into the vitreous chamber of the LE and the macular oedema subsided. Two and a half years after the implantation of the artificial lens, cloudiness of the posterior capsule appeared in the LE. It was decided to perform Nd:YAG laser posterior capsulotomy. In December 2016, after the procedures mentioned above,

during treatment with adalimumab, LE achieved full visual acuity with no inflammatory symptoms (BCVA LE = 1.0). From February 2014, low intraocular pressure was maintained in the RE (2-6 mmHg). In July 2015, a vitrectomy was performed with the replacement of silicone oil, after which the intraocular pressure normalized to 16 mmHg. In October 2015 and a year later, RE herpetic keratitis occurred. Due to earlier complications, vision in the RE did not improve (BCVA RE = HM), and hypotension reappeared.

In March 2017, after achieving low disease activity, adalimumab was discontinued in accordance with drug programme guidelines. Treatment with methotrexate was continued at a dose of 25 mg per week. One month later, AS and arthritis exacerbation (BASDAI = 6.1) as well as severe bilateral uveitis occurred, which resulted in deterioration of vision of the LE (BCVA LE = 0.7). Adalimumab was reintroduced into treatment, with a very rapid improvement in the musculoskeletal system and slow improvement in ophthalmic symptoms. Within four months of reintroducing adalimumab, there were three relapses of uveitis, resulting in the significant worsening of the vision in the LE (BCVA LE = 0.2). This necessitated the treatment of oral prednisone for three months (maintenance dose 10 mg). In October 2017, an intravitreal injection of triamcinolone acetate was administered due to CMO of the LE. Within two months, LE achieved full visual acuity (BCVA LE = 1.0). In February 2018, uveitis of the LE occurred for the last time during our observation, causing deterioration of vision to BCVA LE = 0.7. The course of inflammation was mild; drip treatment with dexamethasone and 1% tropicamide was enough to control the inflammation. 10 months after the reintroduction of adalimumab, uveitis was in remission, with no macular oedema and full visual acuity of the LE (BCVA LE = 1.0) was achieved.

To this day, the patient continues adalimumab treatment together with methotrexate in a dose of 25 mg per week, after which the activity of AS is low. The patient does not require ophthalmic treatment with oral and topical glucocorticoids. For three years, there has been no recurrence of uveitis, and LE has full visual acuity (BCVA LE = 1.0) (Figure 4).

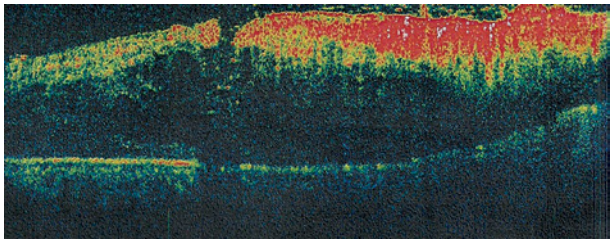

Figure 3. OCT of the macula of the right eye (March 2013) – patient's own photo. Visible diffuse macular edema, raised fovea contour, epiretinal membrane

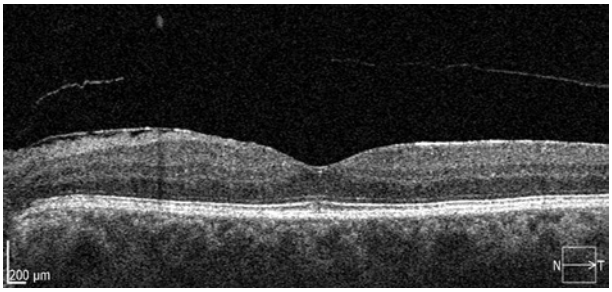

Figure 4. OCT of the macula of the left eye (December 2020). Visible fovea contour, no macular edema, epiretinal membrane

DISCUSSION

In the described case, severe axio-peripheral AS coexisted with severe, treatment-resistant uveitis. According to the current Assessment of SpondyloArthritis International Society/European League Against Rheumatism (ASAS-EULAR) recommendations, the treatment of spondyloarthritis should be individualized depending on the current symptoms of the disease, as well as comorbidities [1]. Biological treatment of AS (TNF-α, IL-17-inhibitors) is considered in the case of persistent high disease activity despite treatment with non-steroidal anti-inflammatory drugs, glucocorticoids, and traditional disease-modifying drugs. In non-infectious uveitis, biological treatment should be started in the case of inability to achieve an inactive stage of the disease despite treatment with glucocorticoids and immunomodulating drugs, first of all methotrexate, which is highly effective (59%) [2]. In 2016, adalimumab was approved by the FDA for non-infectious uveitis treatment, and since 2019 it has been reimbursed in Poland for the treatment of chronic, persistent or recurrent disease in adults as third-line therapy, and in severe cases, also as second-line therapy [3].

In retrospective research in patients with chronic uveitis, who had previously been resistant to infliximab or etanercept, inflammation was controlled in 35% of cases with the use of adalimumab [4]. In clinical trials, adalimumab significantly reduced the risk of treatment failure in patients with non-infectious intermediate as well as posterior uveitis, or panuveitis, with either active (VISUAL I) or inactive inflammatory processes. These patients were initially treated with oral glucocorticoids corresponding to a dose of ≥ 10 to ≤ 35 mg prednisone (VISUAL II) in comparison with the placebo [5]. Compared to the placebo, adalimumab increased the likelihood of quiescence of the inflammatory process in patients with active uveitis, and allowed for better visual acuity and a reduction in the dose of oral glucocorticoids. In the majority of patients with initially inactive inflammation, the use of adalimumab in comparison with the placebo, the drug allowed the inactive process to be maintained without the need to increase the dose of oral glucocorticoids (VISUAL III) [6].

In the described case, treatment with sulfasalazine or methotrexate had no effect on the activity of either AS or uveitis. Treatment with etanercept resulted in a good response from the musculoskeletal system without affecting the organ of vision. Eventually switching to adalimumab resulted in a reduction of inflammation within the musculoskeletal system and eyes.

After more than 20 years of inflammation, disease remission was achieved. During this period, serious and irreversible complications developed both in the musculoskeletal system and eyes. Changes in the organ of vision, such as cataract, herpetic keratitis, macular oedema, proliferative vitreoretinopathy and secondary retinal detachment were the result of inflammation as well as side effects caused by glucocorticotherapy.

Biological treatment of AS is recommended in the case of persistent high disease activity and extra- articular features despite conventional treatment. In the described case, late diagnosis of the disease (after 8 years of its duration), lack of response to conventional treatment and unavailability of biological treatment led to irreversible changes in the musculoskeletal system and eyes. It can also be assumed that a factor influencing the maintenance of high disease activity was the use of a low dose of methotrexate in the initial stage of the disease (10 mg per week with the recommended 25-30 mg per week). First-line treatment with etanercept rather than adalimumab also had an impact on the progression of ophthalmic disease. Discontinuation of adalimumab treatment after remission was another factor that influenced disease progression. According to the ASAS-EULAR recommendations, after disease remission, use of the biological agent should be maintained, or gradual dose reduction should be considered to prevent exacerbation of inflammation.

In conclusion, the initiation of biological treatment, regardless of the disease duration and irreversible changes, may lead to the inhibition of disease progression and a significant improvement in the quality of life. The treatment of spondyloarthritis should be individualized especially in patients with extra-articular manifestations. Since 2011, the treatment of the patient has been carried out in cooperation with rheumatologists and ophthalmologists. At the time of writing the case report, the patient is 52 years old; despite the disability, he works in his profession and is independent.

DISCLOSURE

The authors declare no conflict of interest.

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