ATYPICAL FORMS OF OCULAR TOXOPLASMOSIS IN CHILDHOOD. A CASE REPORT

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Dedicated to the memory of Professor Josef Janků – the world-renowned ophthalmologist and histologist who discovered ocular toxoplasmosis, when 100 years have passed since the discovery of this world-priority observation, which was published a year later.

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SUMMARY

Aim: To present an outline of acquired atypical forms of ocular toxoplasmosis (OT) in childhood, with reference to the 100th anniversary of the discovery of this etiology by Professor Janků from Czechoslovakia, who was first to describe the clinical congenital picture of OT characterised by macular scar.
Material and Methods: Symptoms of intraocular bilateral neuritis appeared in a 6-year-old girl, with visual acuity (VA) bilaterally 0.1. Toxoplasmic etiology was demonstrated in laboratory tests, and the patient was immunocompetent. Following treatment with macrolide antibiotic and parabulbar application of corticosteroid, the condition was normalised stably at VA 1.0 in both eyes. Bilateral retinal vasculitis was determined in an 8-year-old boy, with VA of 0.25 in the right eye and 0.25 in the left, with a medical history of strabismus detected after suffering from varicella. The examination for toxoplasmosis was negative, but pronounced general hypogammaglobulinaemia classes IgG, IgM and IgA was detected. Immunosuppressive and immunomodulatory therapy did not produce the desired effect, and the condition progressed to retinochoroiditis. Due to blindness and dolorous glaucoma, enucleation of the right eye was performed at the age of 15 years. Histologically toxoplasmic cysts with bradyzoites were detected, a subsequent laboratory test demonstrated toxoplasmic etiology upon a background of persistent regressing hypogammaglobulinaemia. General anti-toxoplasma and subsequent immunosuppressive treatment did not produce the desired effect, and at the age of 22 years the patient lost his sight also in the left eye.
Conclusion: Atypical form of OT intraocular neuritis in an immunocompetent patient had a favourable course, whereas retinal vasculitis with retinochoroiditis in a temporarily immunocompromised patient ended in bilateral blindness.
Key words: toxoplasmosis, Professor Janků, hypogammaglobulinaemia, intraocular neuritis, retinal vasculitis, retinochoroiditis, varicella

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INTRODUCTION

Toxoplasma gondii (intracellular parasite) triggers granulomatous inflammation characterised by necrotising retinitis, with concurrent affliction of the choroid and pronounced opacity of the retina (toxoplasmic retinochoroiditis). There are three vegetative forms of this parasite: tachyzoite-trophozoite (invasive form), bradyzoite (encysted form) and sporozoite (oocyst). In addition to the classic form of retinochoroiditis there are also further atypical forms with secondary manifestations: papillitis, vasculitis, anterior uveitis (spill-over) etc. Transmission of the infection to humans is possible via a number of paths: orally (poor thermal processing of meat with oocytes or

insufficient hygiene of hands or vegetables also contaminated by oocytes), penetration of tachyzoites through injured skin and finally transplacental transmission [1], which triggers the congenital form in newborns.

One hundred years ago (1922) Dr. Josef Janků, then an ocular consultant at the Královské Vinohrady hospital in Prague, detected sporocytes on histological preparations, specifically a parasitic basis of intraocular inflammation. He observed a three-month-old infant with an ocular finding and progressively developing enormous hydrocephalus up to the age of three years, when the child died. Doctor Janků then also participated in the autopsy of the child. At the time cicatricial foci were evident on the retina in the region of the yellow spot, which were then known as "coloboma maculae lutae congenitale".

Professor Josef Janků (Figure 1. – right) was born in Chrastavec u Svitavy in 1886. After completing his studies at grammar school in Litomyšl, he studied at the Faculty of Medicine of Charles University in Prague, and after graduated he commenced work at the Eye Clinic of Professor Deyl. During the First World War he worked as a military doctor. In 1919 he started in a post as an assistant at the Czech Eye Clinic in Prague, and qualified in 1923. He also began working as an ocular consultant at the hospital in the Vinohrady district of Prague. He was present at the establishment of the eye department at the hospital in 1930, where he worked as head physician after the Second World War. In 1953 he established the Department of Ophthalmology at the Královské Vinohrady University Hospital within the framework of the newly conceived Faculty of Hygiene, becoming the head of department until 1957. In 1955 he was awarded the title of professor, and in 1956 received the Jan Evangelista Purkyně gold medal. He retired in 1959 and died in 1963 [2,3]. In 2008 a commemorative plaque to Professor Janků was unveiled in his native village [2].

In 1923 he published the above observation from 1922, with colour sketched documentation [4]. It had not been possible to determine a parasite until that time, as documented by his meeting with the professor of microbiology Dr. Levanditi in Paris in 1924. Dr. Levanditi examined the preparations and congratulated Dr. Janků on being the first to discover a finding of a parasite in the human eye. The discovery remained unnoticed due to its Czech publication [2]. It was not until after the Second World War that this groundbreaking discovery reached the awareness of the international literature [5] and was later termed "Morbus Janku" or "Janku's disease". It is a sad fact that an understanding and acknowledgement of the importance of this discovery remained unrecognised in Czech scientific circles, and as Professor Janků recalled, this was accompanied by a great deal of bitterness [2]. In basic ophthalmology textbooks and monographs his name is remembered only in the books by the academic

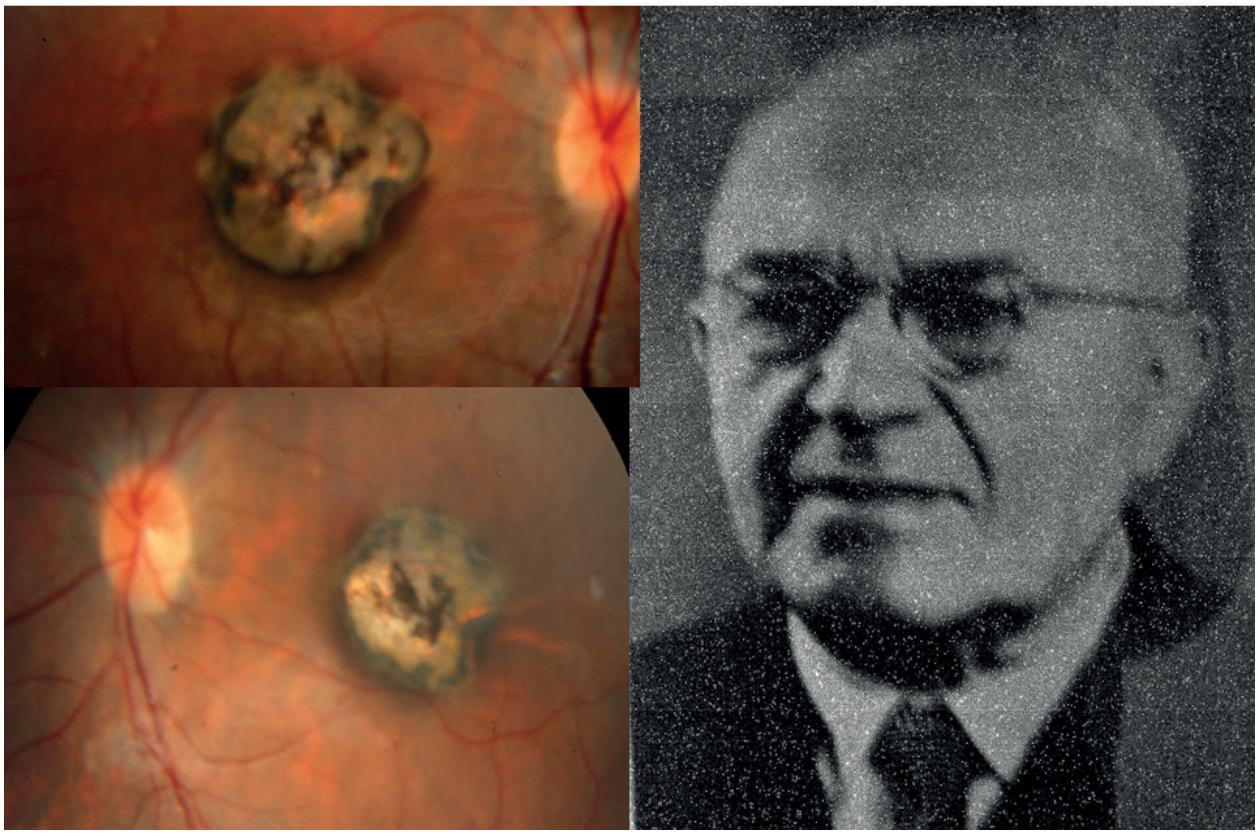

Figure 1. Congenital form of ocular toxoplasmosis in form of bilateral macular scar – left. Professor Josef Janků (1886-1963) – right

Josef Kurtz: Basics of Ocular Medicine (1957), by Professor Jan Kolín: Ophthalmology for the General Practitioner (1994) and by Professor Pavel Kuchynka: Ocular Medicine (2002). Profesor Gary Holland, one of the chief authors of a fundamental monograph on the theme of uveitis worldwide, lists his name in first place in a historical overview of the diagnosis of toxoplasmosis: "Although some scholars cite the work of Dr. Janků in the 1950s, the details of the original Czech language publication remained unknown to the medical community outside of Czechoslovakia to a large extent until the work appeared in a German translation in 1959" [6]. The congenital form of ocular toxoplasmosis (OT) may afflict only the macular area in the form of a circular scar, which is richly pigmented and of varying diameter (first described by Professor Janků). The finding may also be bilateral (Figure 1. – left). This finding always means blindness in the afflicted eye, although there is no further exacerbation of the inflammation, and thus it constitutes the independent clinical unit of OT. Another possibility is the recurrent form of retinochoroiditis, also upon a background of intrauterine infection in the central region of the retina. The clinical picture has the form of rounded whitish cicatricial lesions smaller than 1 papillary diameter (PD), with possible pigmented bordering. A new lesion with necrotising retinitis appears on the edge of the old lesion, and the process may repeat several times, forming satellite foci (Figure 2.A). This mostly concerns a unilateral process. A frequent accompanying component is inflammatory vitreous reaction, which after pacification leads to an accentuation of the cicatricial process in the lesion (Figure 2. B, C). Patients are induced to visit an ophthalmologist by a sudden deterioration of visual acuity (VA), in which the scope is determined by the localisation of the new satellite focus or progressing blurring of the image due to the vitreous process. The problem consists in the time factor of exacerbation, since it may appear in both pre-school age and in adulthood. An OT lesion may have juxtapapillary localisation with the possibility of papillitis, in which case this concerns an image of "Jensen's form" (Figure 2D). It takes the form of variously extensive whitish-yellow lesions in the shape of an irregular triangle, overlying the disc of optic nerve with minimal pigment reaction. The source of these lesions is again intrauterine infection. Edema of the optic nerve and lesions together with affliction of the vitreous body is often an image of exacerbation, accompanied with deterioration of VA in this recurrent form. All of these aforementioned clinical pictures of OT represent

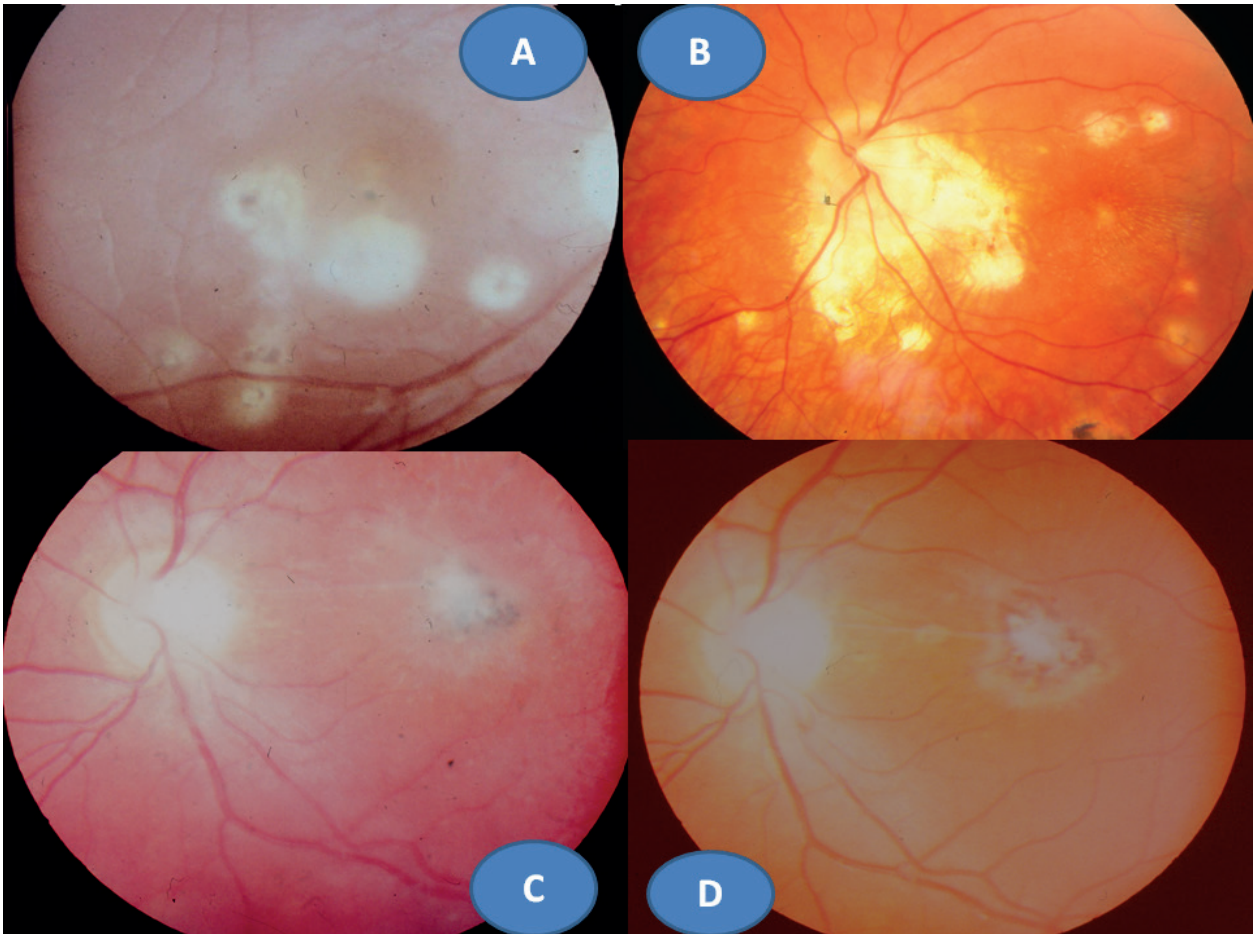

Figure 2. Recurrent retinochoroiditis with multiple satellite foci (acute and cicatricial) with CME (**A**). Jensen's form of recurrent retinochoroiditis with satellite foci (**B**). Exacerbation of retinochoroiditis with vitritis (**C**). Pacification of inflammation with atrophy of focus (**D**)

the most common manifestations of this parasitic infection, since acquired forms are rare, especially in childhood age. The two case reports presented below deal precisely with these rare observations.

CASE REPORT 1

A 6-year-old girl was bitten on the arm by a mouse in a field. The injury was treated in surgery. It was only after an interval of six weeks that she began to suffer from torpidity, fever and back pain. Due to the winter season the finding was assessed as influenza, and the girl was treated accordingly with antipyretic drugs. After a further two weeks a deterioration of VA was manifested. Upon an ocular examination, seepage of both discs of optic nerve was determined, with distended capillaries (Figure 3A, B), while the retina including the central region was without any lesion changes. VA of right eye (RE) = VA of left eye (LE) 0.1 naturally, not improved by correction. We concluded the finding as bilateral intraocular neuritis. A comprehensive laboratory examination was conducted, including zoonoses. A neurologist was consulted and stated that the neurological finding was now within the norm. The blood count showed slight leukocytosis with 2 % eosinophilia, sedimentation was 20 per hour. A surprising finding was the presence of positive antibodies for toxoplasmosis. Complement Fixation Reaction (CFR) 1:512 and Indirect Immunofluorescence Assay (IFA) IgG 1:2048, IgM 1:32. Oral treatment was commenced with Rovamycine (spiramycin) 4 x 250 mg per os for a period of 14 days, which was supplemented with a single parabulbar administration of Kenalog (triamcinolone) 1 ml bilaterally. After three months VA was normalised at 1.0 naturally in both the right and left eyes. The discs of optic nerve were bordered and atrophied (Figure 3.C, D). The laboratory values of the blood count and sedimentation were normalised. CFR decreased to 1:32 and IFA to IgG 1:512 and IgM was now negative. After one year the ocular finding was unchanged, while the laboratory values of toxoplasma antibodies continued to decline: CFR KFR 1:8 and IFA IgG 1:64.

Summary: The transmission of infection cannot be traced retrospectively, possibilities include geophagia or the penetration of oocysts through injured skin. The initial manifestations may have been neurological symptoms. General treatment of acute toxoplasmosis, above all with atypical ocular symptoms, using macrolide antibiotics, was highly effective. No recurrence of inflammation appeared in this immunocompetent patient throughout the entire observation period.

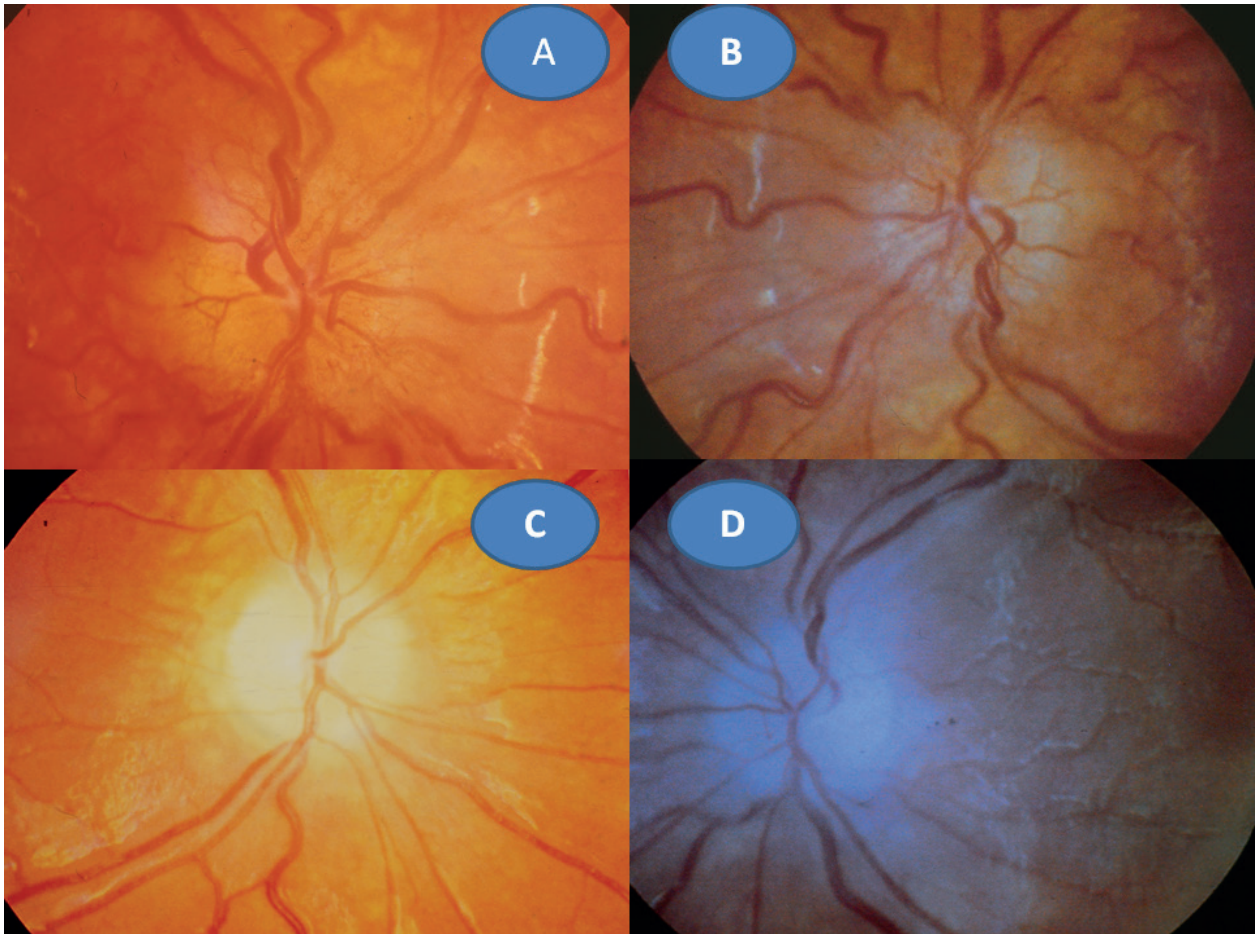

Figure 3. Toxoplasmic neuritis on right (**A**) and left (**B**). Post-inflammatory atrophy of right optic nerve papilla (**C**) and left (**D**)

CASE REPORT 2

This 8-year-old male patient was from the mother's fourth pregnancy, which was successfully delivered. The two previous pregnancies had ended with one spontaneous miscarriage and one death of the child at the age of 14 days from campomelic dysplasia. As a result of this history, the parents were examined in detail before the 4th pregnancy; they had a normal immunological finding and neither toxoplasmosis nor any other infection was detected serologically. Their HLA loci were determined, both had HLA B5. The child's development following his physiological birth within a regular term was without problems. He did not suffer from any serious complaints, but only underwent a tonsillectomy before starting school due to repeated tonsillitis. It was not until the boy reached the age of 7 years, one month after suffering from varicella with a febrile course, that his parents noticed convergent strabismus in the right eye, accompanied by a deterioration of vision. Upon a detailed examination on the finding on the anterior segment of both eyes was without inflammatory or degenerative manifestations bilaterally. In the right eye there was manifest deformation of the disc of optic nerve with constriction of the vascular bundle slightly temporally (Figure 4.A), opacity of the vitreous body above the disc of optic nerve and in the periphery, mainly temporally inferior vitreoretinal cystic and proliferative changes as a consequence of vasculitis, in places reminiscent of an image of retinoschisis (Figure 4C). VA RE 6/24 and near VA Jaeger (J) no. 4 naturally. In the left eye the finding in the central region was physiological (Figure 4.C), with bridging bands of vasculitis in the periphery above the capillaries. VA LE 6/6, patient read Jaeger no. 1 naturally. Conclusion: vasculitis retinae bilaterally, more in the right eye with vitritis in the right eye. A detailed serological examination including toxoplasmosis was negative. Hypogammaglobulinaemia IgG and IgA was detected with borderline values of IgM (Table 1). Erythrocyte rosettes (examination used for verifying cell immunity before 1990) were within the norm. With regard to the finding of vasculitis and HLA B5 as the patient's main locus, a detailed examination of the kidneys and liver was performed, with a negative result. Immunosuppressive therapy was commenced with prednisone (synthetic glucocorticoid) 2mg/kg/day for a period of 14 days, with gradual discontinuation. Despite immunosuppressive maintenance treatment with 10 mg prednisone every other day, the finding progressed. After less

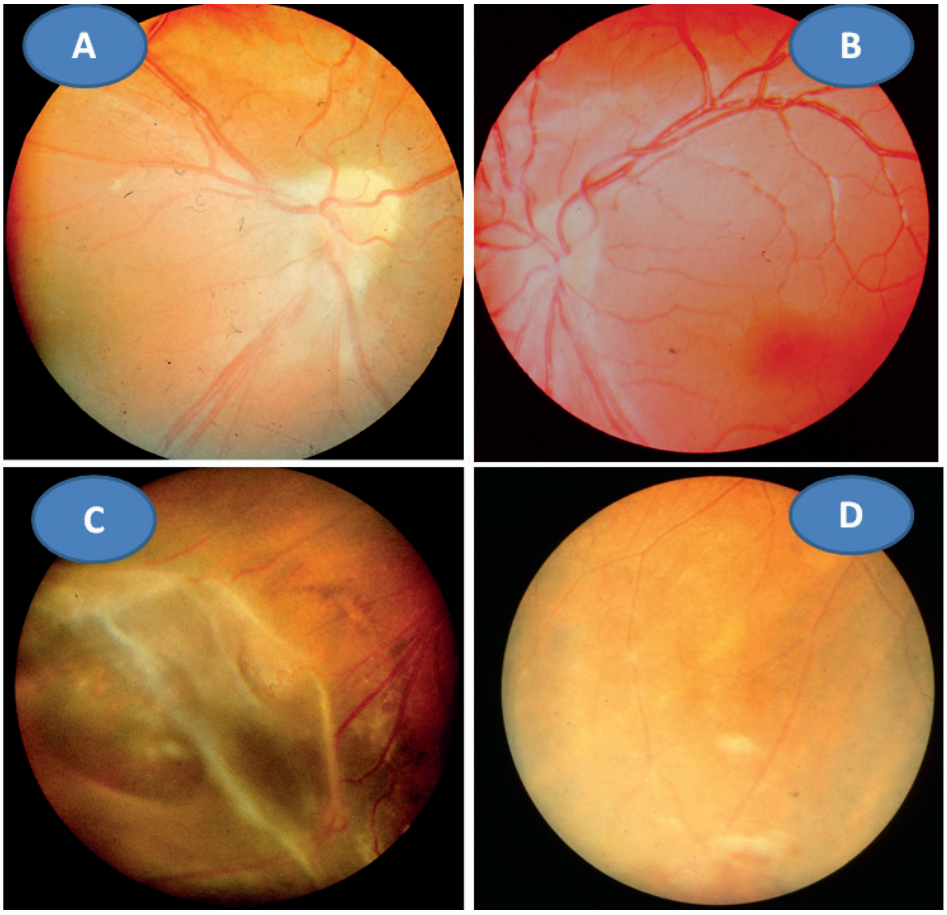

Figure 4. Summary image of papillomacular bundle on right (**A**). Physiological image of central macular landscape on left (**B**). Vitreoretinal cystic and proliferative changes in peripheral vasculitis on right (**C**), only bridging right peripheral bands of vasculitis on left (**D**) at the age of 8 years

than one year there was present hypogammaglobulinaemia IgA with borderline values of IgG and IgM (the borderline value of IgG was relative according to the norms, since for the age of 6–7 years it would mean a pathologically reduced value). Further immunosuppressive treatment with prednisone followed, supplemented with a substitution of immunoglobulins by repeated infusions of fresh plasma from the same group 20 ml/kg. Despite the subsequent immunosuppressive maintenance therapy, the ocular finding progressed bilaterally, although the levels of immunoglobulins gradually normalised. At the age of fifteen years, a finding of panuveitis in the right eye with complicated cataract and secondary dolorous glaucoma (Figure 5.A) led to the decision to perform enucleation of the eye, also due to demonstrated total retinal detachment on an ultrasound (US) examination and with VA of doubtful light perception. In the left eye a finding of retinitis was added, which was accompanied

Table 1. Immunoglobulins IgG, IgA, IgM in relation to age: reduced value (yellow), borderline value (green)

Age (years)	IgG	Standard	IgA	Standard	IgM	Standard
	g/l					
8	5,4	6,0–13,0	0,65	0,7–2,3	0,38	0,4–1,5
9	6,1		0,65		0,41	
10	6,7	7,0–14,0	0,68	0,7–2,5	0,48	
15	7,9	7,0–16,0	0,75	0,7–4,0	0,81	0,4–2,3
18	7,76		1,43		0,61	
19	8,14		0,92		0,87	
20	6,3		1,19		0,8	
22	6,99		0,89		0,9	
24	7,95		1,43		0,61	
26	8,5		1,27		0,88	

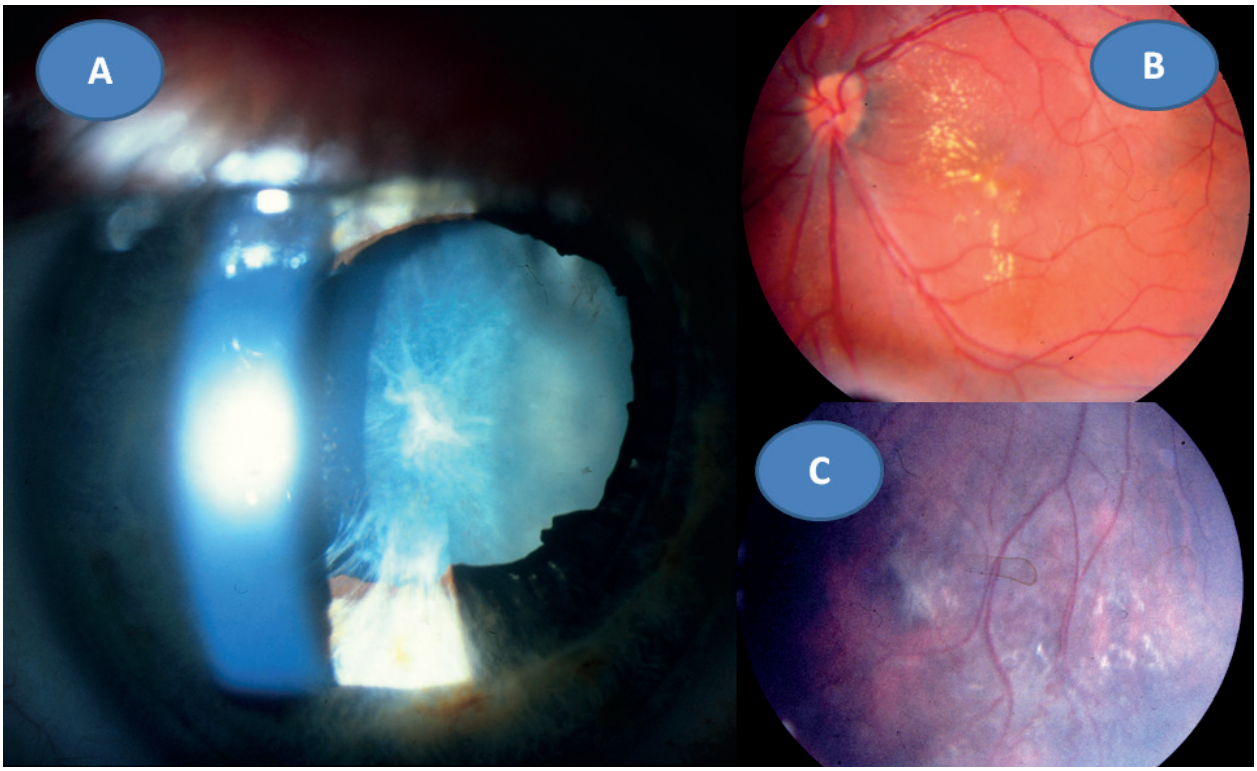

Figure 5. Panuveitis with cataract and secondary glaucoma on right at age of 8 years (**A**) and image of star figure in macular edema (**B**). Progression of vasculitis and vitritis in left periphery (**C**) at time of enucleation

by an image of central macular edema including a star figure (Figure 5.B), as well as worsening of vasculitis in the periphery and vitritis (Figure 5.C), VA LE 0.4, the patient read Jaeger no. 6 naturally, not improved by correction. At that time there was a stable process of gradual equilibration of the levels of immunoglobulins (Table 1). Histological verification produced a surprising result; this concerned severe necrotising granulomatous retinochoroiditis with basophile toxoplasmic cysts and retinal vasculitis with thromboses and microcalcifications in the granulomas (Figure 6.A, B, C, D). Acquired toxoplasma infection was subsequently confirmed serologically (CFR 1:16; IgG 0.576 g/l; IgA 0.7g/l; IgM 0.8 g/l and IgE 14.0 IU/l). The youth was transferred to the infection clinic for general therapy: 100 mg of Daraprim (pyrimethamine) together with 3g Sulfadiazine (pyrimidinylsulfanilamide) and two boluses of 2 x 500mg Solumedrol (methylprednisolone) with transition to Medrol (prednisolone) 64 mg per day for a period of one week, after which Medrol was reduced and subsequently discontinued after 6 weeks. Cicatricial progression continued on the ocular fungus, first of all macular jaundice appeared (Figure 7.A), the scope of vasculitis was heightened in the periphery (Figure 7.B), at the age of 18 years the patient was without more pronounced affliction of VA. The laboratory assessment of toxoplasmosis showed a reduction: CFR negative, IgG 0.505, IgA 0.3 and IgM 0.1, which was assessed only as anamnestic levels of IgG. At the age of 20 years proliferative changes also afflicted the centre (Fig. 7C), and the image of vasculitis in the periphery, which took on a granulomatous character, was accentuated (Figure 7.D). VA decreased to 0.1 naturally, but with optic system to 0.5, and the patient read Jaeger no. 10. A control examination continued to demonstrate a slight, only transitional decrease of hypogammaglobulinaemia IgG, but levels of IgA and IgM were now within the norm (Table 1). The values of the absolute quantity of T lymphocytes (CD3) and lymphocytes (CD20) were within the range of the lower limit of the norm upon a normal immunoregulatory index (ratio CD4/CD8), and a proliferation of NK (natural killer – CD3-CD56+) cells was demonstrated. An increase of CD56 and CD20 appeared. Immunosuppressive therapy was commenced, first of all with prednisone 2 mg/kg/day, with Azaprine (azathioprine) 1mg/kg/day initially for 14 days, with reduction. This combination of immunosuppressive treatment was replaced with Equoral (cyclosporine A) 2 mg/kg/day initially for one month, with a long-term maintenance dose. In the subsequent

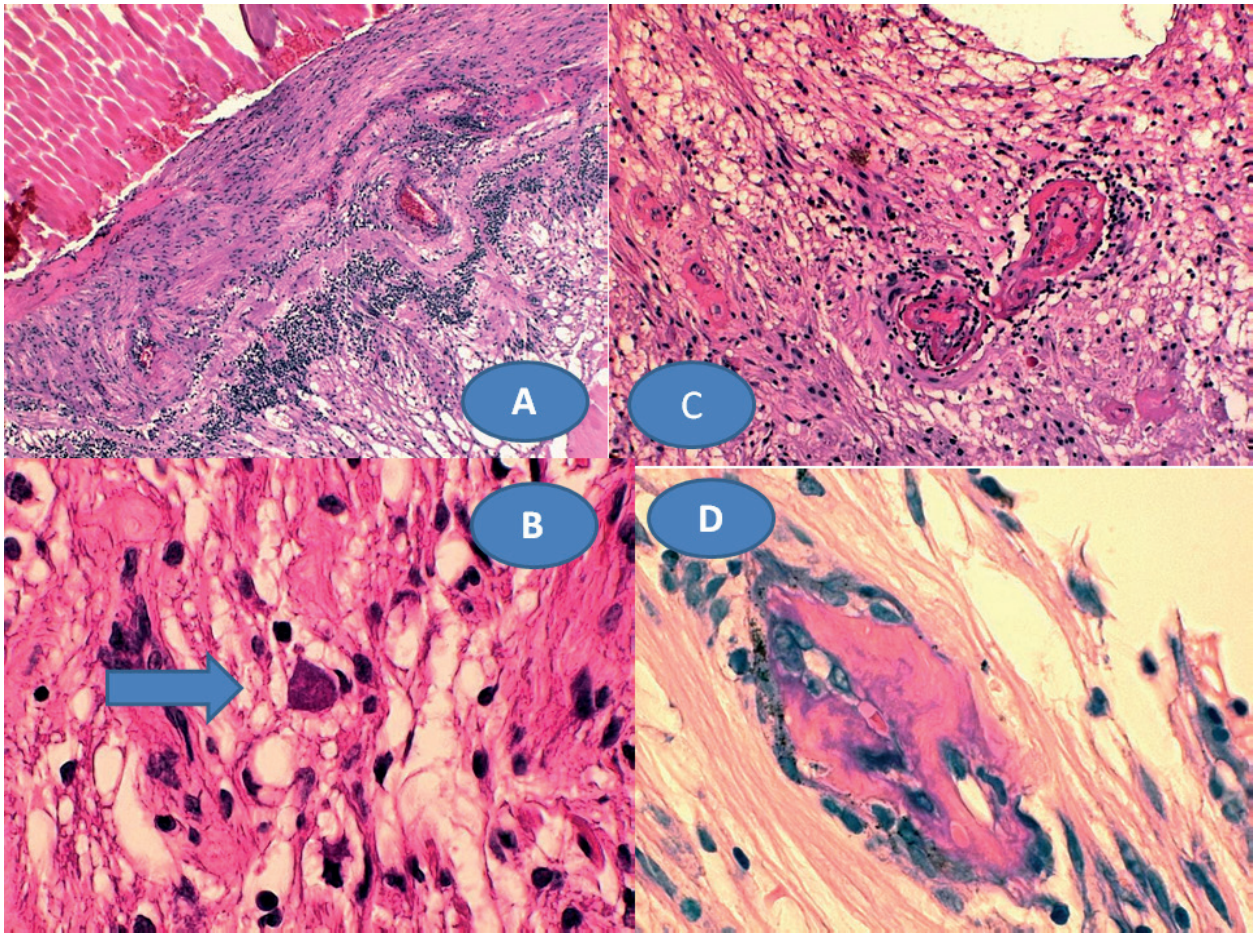

Figure 6. Chronic retinochoroiditis (**A**) magnification 50x, HE. Toxoplasmosis cyst with bradyzoites - arrow (**B**), magnification 500x, HE. Retinal vasculitis with thromboses (**C**), magnification 125x, HE. Microcalcifications identified in granulomas (**D**), magnification 500x, HE

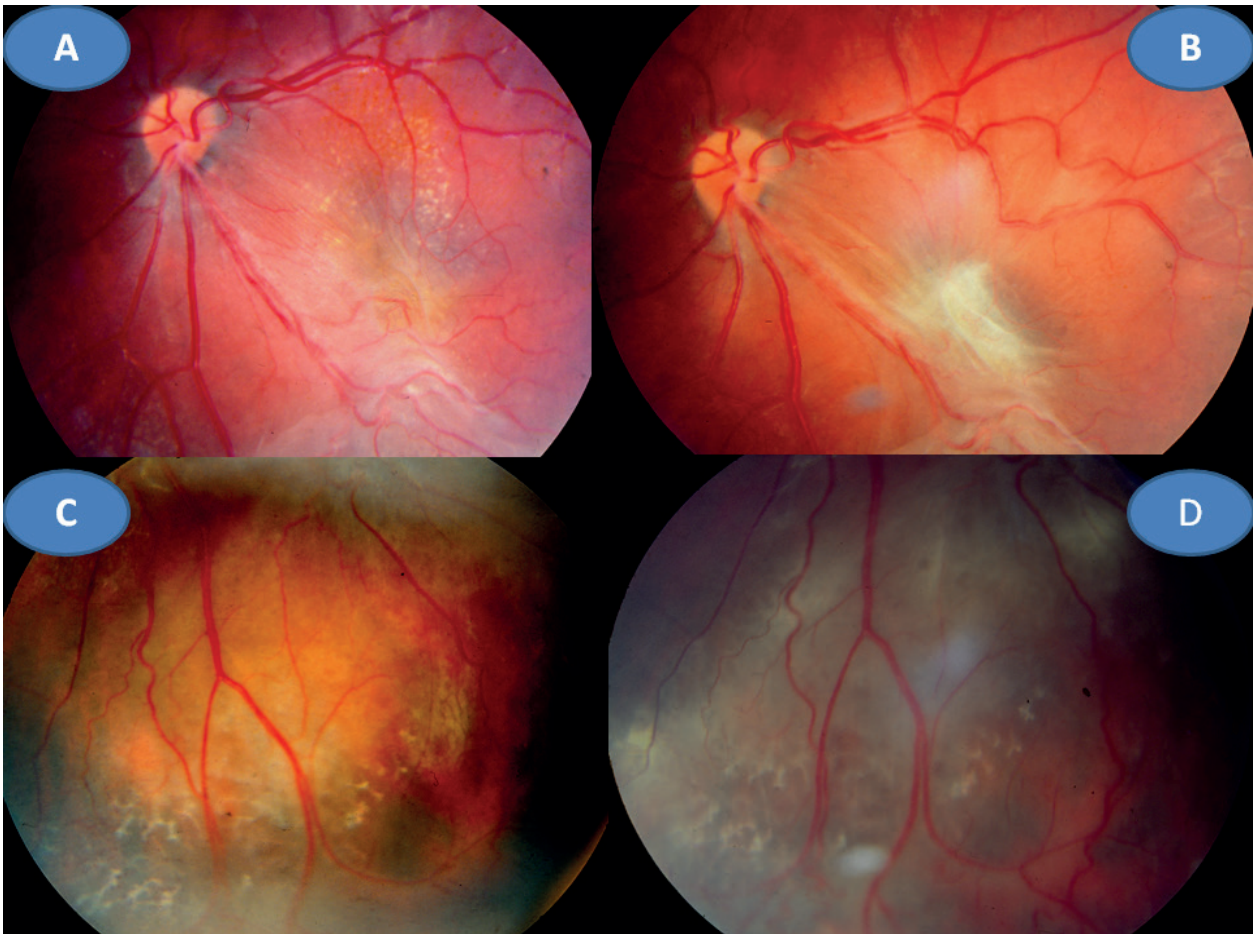

Figure 7. Cicatricial progression in centre left with highlighted ocular yellow (**A**) and accentuation of vasculitis in periphery at age of 18 years (**C**). Proliferative changes also in centre of retina (**B**). Vasculitis in periphery taking on a granulomatous character (**D**) at age of 20 years

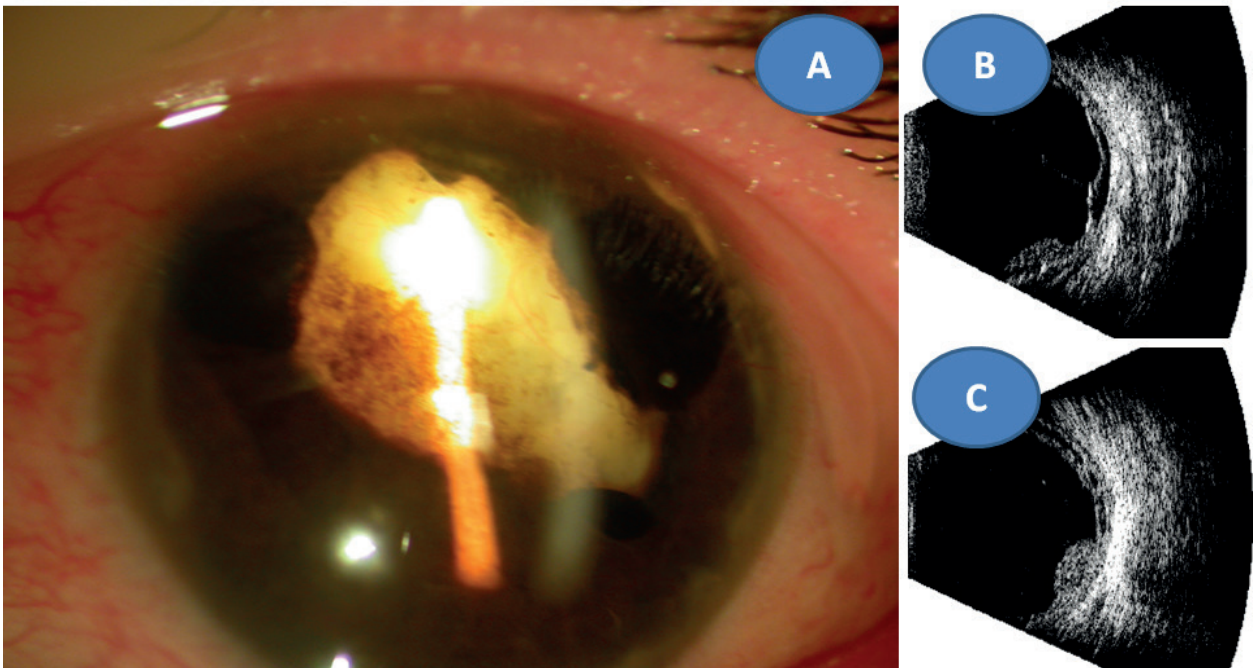

Figure 8. Reduced total cataract with pupil occlusion at age of 22 years (**A**). Ultrasound image of total retinal detachment (**B**) and retinal granuloma 2.9 x 9.6 mm (**C**)

course when the patient was aged 22 years, the condition was again complicated by cataract, which later spontaneously regressed (Figure 8.A), with continuing vitreoretinal scarring in the form of total detachment and severe granulomatous changes in the form of a granuloma 2.9 x 9.6 mm on ultrasound (US) (Figure 8.B, C), which were causes of blindness and a contraindication of a surgical solution. Secondary glaucoma appeared, which was sufficiently compensated for by conservative therapy. As a result, the immunosuppressive maintenance treatment with cyclosporine A 0.5 mg/kg/day was discontinued at the age of 23 years, at that time the levels of immunoglobulins in all classes were normalised and also cell immunity did not manifest any pathological changes. Immunoglobulins were last examined when the patient was aged 26 years.

Summary: Strabismus could have been triggered by a febrile condition causing irritation of the brain tissue. The changes on the papilla of the right eye were most probably of congenital origin, and retinal vasculitis with vitritis may have been linked with the fact that the patient had suffered from varicella, since it ranks among the rare complications of this pathology. However, it is not possible to assume that within such a short time varicella would by itself cause complex hypogammaglobulinaemia, which must have been a long-term condition. It is not possible to confirm retrospectively whether this was congenital. The patient inherited the locus HLA B5, which is related to vasculitis. No other organ affliction of this type was determined. Toxoplasmosis infection was of acquired origin during the course of ocular pathology, which was still while the patient was in an immunocompromised condition. This infection contributed to the destruction of the choroid and retina, even if the proportion of its contribution to this process cannot be precisely determined. Diagnosed immunodeficiency of the antibody type may have contributed to its manifestation, similarly to the impact of varicella on the retina. Combined long-term immunosuppressive therapy with a modulating component in one phase of the treatment may have aided the normalisation of immunoglobulin levels, but this cannot be assessed precisely. Even subsequent anti-toxoplasma treatment failed to produce any effect within the almost thirty-year course of observation.

DISCUSSION

Toxoplasmosis is one of several parasitic human pathologies, which markedly afflicts the functioning of the eyes according to the localisation of the inflammation. Affliction of the macular landscape and its surrounding area is of decisive significance, whereas peripheral lesions are frequently detected by chance within the framework of preventive examinations [6]. There is nevertheless a difference between VA and disorders of the visual field, which is affected more significantly in OT. Upon a decrease of VA in 41% of eyes there was a defect of the visual field in as many as 94% of eyes; there was therefore a statistically fundamental difference in retinochoroidal damage [7]. The classic division of OT states two basic groups in terms of affliction of the complex of the retina and choroid, as well as affliction of other ocular structures. This concerns the groups of recurrent retinochoroiditis and acquired retinochoroiditis [6]. The photographic documentation we present here is from a comprehensive photo archive compiled during the course of the last thirty years and relates to almost forty patients. In our region OT is indicated rather as chorioretinitis [8–10], which is condition by the historical view of central macular scarring from the times of Professor Janků. The difference

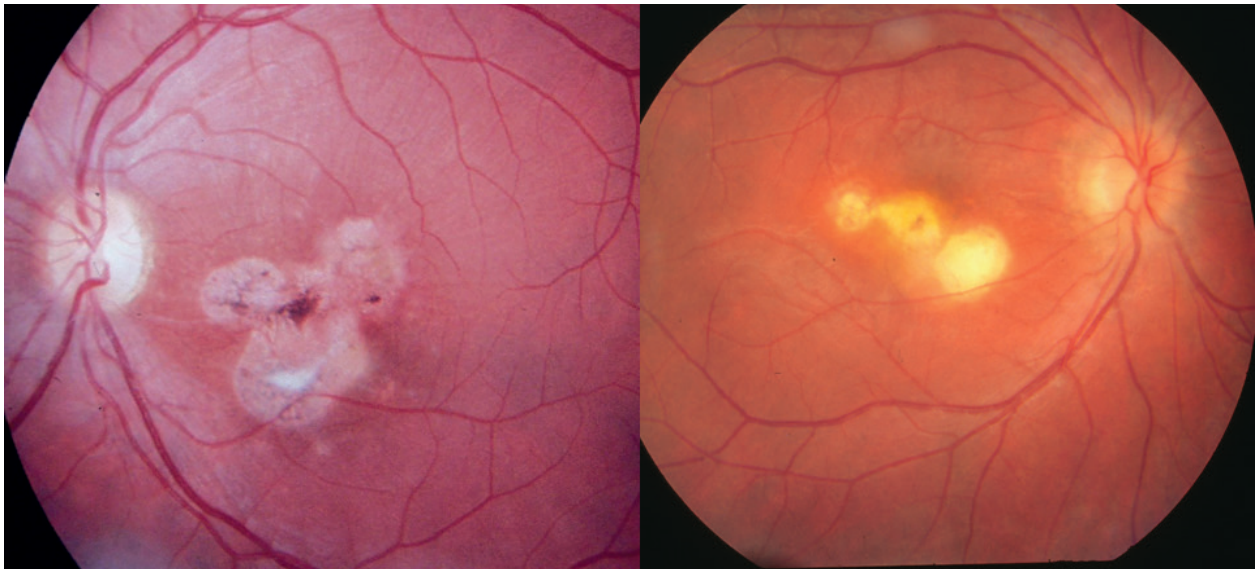

Figure 9. Condition after recurrent form of ocular toxoplasmosis in form of three satellite foci: in chorioretinitis – right, and in retinochoroiditis – left

between both designations of OT can be traced also from the ophthalmological view of cicatricial changes on the ocular fundus in satellite (subsidiary) foci, as is evident in photographic form (Figure 9.A, B). Recurrent inflammation mostly no longer has an intrinsic infectious basis but is rather an immunological response to a sequestrated antigen from the cysts of the parasite (see below), and may take on an image of a coloboma scar with loss of choroid and retina, reminiscent of a chorioretinal coloboma with a whitish sclera on the base of the defect. The retina is the primary location of toxoplasma infection in both of the aforementioned forms. They are mostly whitish, local lesions, frequently accompanied by vitreous inflammatory reaction. The choroid is affected only secondarily, because findings of lesions here do not occur without retinal etiology [6]. The development of this congenital inflammation has also been described in the contemporary Czech literature, also from the perspective of differential diagnostics in the case of general neurological affliction of a newborn [10]. The optic nerve or iris may also be affected primarily, mostly only in the case of immunocompromised patients. The second group of OT comprises inflammatory lesions without manifest acute ocular infection: neuroretinitis, retinal vasculitis in patients with recently acquired systemic toxoplasmosis. There are also ocular manifestations associated with old toxoplasmic retinochoroidal scars detected by chance beneath an image of recurrent iridocyclitis or persistent vitritis [6]. Both clinical pictures in our patients of acquired atypical form could be classified within the second group of OT affliction.

In the 20th century, two extensive comprehensive studies on paediatric uveitis and also dealing with the issue of OT were published in post-war Czechoslovakia [8,9]. Another study was published 45 years later, focusing on a case report of bilateral congenital form of OT from the perspective of a progressively developing diagnosis from primary hydrocephalus to ocular manifestations. The study presents an extensive overview of the medical procedure and development of ocular changes within the framework of therapy managed by an infectious disease specialist [10].

A detailed study conducted over a period of almost 6 years incorporating 1300 patients with uveitis demonstrated OT in 154 of the patients (12%). A primary retinal lesion was present in only 28% of patients, and the larger remaining group of OT represented a combination of an active lesion with concurrent retinochoroidal scarring [11]. Affliction of the optic nerve in OT ranks among its clinical manifestations; it was observed in three eyes (14.4%) out of 18 affected with juxtapapillary activation (70.5%). The effect of treatment was favourable depending on the localisation of the inflammation [12]. Retrospectively in children (mean age 9.5 years), the main ocular symptoms were as follows: strabismus in 32% and deterioration of VA in 23%. In the clinical picture inactive retinal scar dominated in 71.5% of cases, panuveitis in 14%, posterior uveitis in 12.5% and there was one case of neuroretinitis [13].

The pathogenesis of inflammation is associated with a reaction of lymphocytes secreting lymphokines, which destroy the toxoplasma parasite with the co-participation of macrophages. Recurrence of the inflammation is conditioned by hypersensitivity of the retinal antigen triggered following a rupture of toxoplasmosis cysts. Type 4 hypersensitivity contributes to the condition [14], which was demonstrated experimentally with the use of an extract from the retinal photoreceptors [15]. This was in accordance with the capacity of highly purified soluble S-antigens that can trigger a specific stimulus for lymphoblastic changes [16]. Iridocyclitis was also experimentally triggered within 48 hours following intravitreal inoculation of a soluble toxoplasma antigen, which confirmed a delayed hypersensitive cell reaction [13]. Exacerbation of inflammation then need not have its basis in the infectious agent of toxoplasmosis, but in a hypersensitive reaction, unless a rise in levels of antibodies is confirmed upon a new attack of the infection. In our immunocompromised patient the problem was more complex, since he had inherited the locus HLA B5, which pointed to the fact that this locus together with subtype B51 is 3–6 times higher in patients with Behcet's disease than in the healthy population [17]. Fortunately, laboratory tests within the framework of vasculitides did not confirm this. The contribution of toxoplasmosis infection to the destruction of the retinochoroidal complex was not determined but diagnosed immunodeficiency of the antibody type may have aided its manifestation, and this was very probably congenital [18]. At the age of seven years a serological examination of specific antibodies for toxoplasmosis may produce a false negative result. This is described in immunocompromised patients, and only rarely in immunocompetent individuals [19,20]. Clinically asymptomatic chronic toxoplasmosis was present in the boy. Varicella at the age of 7 years with a more severe, febrile course upon a background of evidently congenital hypogammaglobulinaemia may have activated chronic toxoplasmosis [21].

At the end of the 20th century, it was epidemiologically estimated that half a billion people worldwide were afflicted with toxoplasma infection, with the antibody background in approximately 70% in adulthood. In addition to the eyes, toxoplasma infection mainly affects the brain, but also the heart, liver, lungs and muscles. The prevalence of acquired form of toxoplasmosis in pregnancy at that time was stated at 1:750 to 1:8000, of which 10% was in the 1st trimester, 30% in the 2nd trimester and the remaining 60% coming within the 3rd trimester [6]. Miscarriage is triggered upon transplacental infection in the 1st trimester. Brain malformations are associated with infection in the 2nd trimester and trigger obstructive hydrocephalus and necrotising granulomatous inflammations, calcifications along the 3rd brain ventricle and aqueduct of Sylvius, and central affliction of the retina. In the 3rd trimester there is now a milder course of the affliction, with regard to ocular manifestations only retinochoroiditis, mostly outside the central landscape [22]. OT more frequently appears postnatally on the basis of contamination by oocysts in

insufficiently processed meat, unwashed vegetables or upon drinking contaminated water. OT lesions appear a number of years after toxoplasma infection [23]. The occurrence of ocular affliction is of fundamental significance. In children with neurological symptomatology, ocular manifestations are present in 95%, in disseminated form eyes are affected in 2/3, but in 10% OT may be without general symptoms. The prognosis of the pathology ensues from this situation. Whereas in adult immunocompetent patients the prognosis is universally good, in the congenital form mental and physical affliction may be manifested within the framework of a general impact of parasitic infection [6], and in addition the possibility of blindness, primarily bilateral, is statistically more significant [11].

In the 1950s, synergism between pyrimethamine and sulfonamides was first used in the treatment of toxoplasmosis [24]. Pyrimethamine interferes with the conversion of folinic acid to folic acid by blocking the enzyme dihydrofolate reductase, and simultaneously sulfonamides interfere with the formation of folinic acid. The result is damage to cell division upon replication of the parasite [6]. Classic therapy therefore consists of a triple combination of pyrimethamine (Daraprim) + sulfonamide (Sulfodiazim) + corticosteroid, supplemented with folic acid. This type of therapy is respected and approved also in the Czech Republic by the Infectious Medicine Society of the Czech Medical Association of J. E. Purkyně [25], and is still considered the optimum procedure worldwide [26]. In our patient this triple combination was applied following confirmation of toxoplasma etiology, as a corticosteroid Solu-Medrol was applied intravenously, followed by Medrol orally in progressively reduced doses. In the treatment of toxoplasmosis, with regard to the toxicity of sulfonamides (gastrointestinal complaints, allergic skin reactions, up to Stevens-Johnson and Lyell's syndrome) and pyrimethamine (suppression of blood formation), antibiotics are also applied, primarily macrolides (clindamycin, clarithromycin, spiramycin) [6] and in the Czech Republic azithromycin [1]. In combination with corticosteroids this should be administered two days beforehand, since monotherapy with a corticosteroid alone could trigger a fulminant course of inflammation with fatal results for the eye [1], which applies also in the case of recurrent forms unless anti-parasitic treatment is applied, with resultant worsened VA [11]. It is more advisable to administer an antibiotic with corticosteroids than to wait for a potential rise in the levels of antibodies confirming reactivated infectious etiology. The aim of treatment in the case of lesions in the central region in the acute phase is faster healing and reduction of scarring, and thus also improvement of VA [1]. In our female patient we used spiramycin successfully. Of macrolide antibiotics Clindamycin appears to be the most effective, since it penetrates into ocular tissues and penetrates into the cysts of the parasite, thereby reducing their number [27]. Clindamycin was applied intravitreally in adult patients with severe acute forms with deteriorated VA, with oral corticosteroids [28], or generally with intravitreal application of dexamethasone [29], with regression of lesions and improvement of VA. This antibiotic was also used in combination with Cotrimoxazole (sulfamethoxazole), which belongs to the range of sulfonamides [30]. Overall, it is possible to conclude that the most appropriate therapeutic combination is pyrimethamine + clindamycin + corticosteroids, as is documented by the presented case of laboratory confirmed acquired OT. In the initial phase of treatment of a 28-year-old man, azithromycin, pyrimethamine and a local steroid were administered without any effect. There were associated neurological symptoms, and although the classic triple combination improved the patient's condition, due to vomitus sulfonamide was replaced by clindamycin, with general clinical and ocular improvement [31]. Exacerbation of OT is possible on average in 12–15% of cases in the first two years of affliction, and thereafter continues to decrease. General prophylaxis was tested by general administration of trimethoprim and sulfamethoxazole three times per week for a period of 12 months, with a sevenfold reduction of relapses over the course of three years [32]. Similar confirmation was demonstrated by the course of a 20-month randomised trial [33]. Clindamycin [27] or co-trimoxazole [31] are also appropriate for preventing exacerbation of inflammation. The median period without recurrence of inflammation was significantly extended following the use of systemic monotherapy with corticosteroids in comparison with the use of specific antibiotic therapy alone against toxoplasmosis [34].

Toxoplasmic retinochoroiditis may bring complications, namely subretinal neovascularisation, branch occlusion of arterioles and venules, and central macular edema [6]. Application of anti-VEGF (vascular endothelial growth factor) preparations can be used for treatment of the condition, primarily in the case of neovascularisation, specifically ranibizumab [35] or aflibercept [36].

The issue of diagnosis of toxoplasma etiology in an ocular process consists in assessing the dynamics of changes in the levels of antibodies for a clear determination of the diagnosis. Higher values of IgG and IgM can be confirmed only in the acute phase in the acquired form, whereas in the case of relapse of the congenital form IgG are low and IgM may be absent [6], when the infectiousness of the process cannot be confirmed by this means. Furthermore, positive levels of IgG may attest to the fact that the patient had come into contact with parasitic infection, and have only an anamnestic value [6], which confirms a high prevalence within the population. False positive results may be produced e.g. in the case of lupus erythomatodes [27] or in patients with antinuclear and rheumatoid factor [6]. Positivity of IgE in an acute or exacerbated process upon a background of infectious etiology is characteristic for childhood age [6]. In our female patient with neuritis the titre of these antibodies was not determined, and in our male patient with vasculitis they were not specific.

Chickenpox (varicella) and herpes zoster are triggered by the same virus, namely the varicella-zoster virus. Varicella itself is a typical illness for primoinfection, as a rule in

childhood age, manifested in fevers with characteristic skin exanthema, which appears after an incubation period of 14–16 days on average. Papillomatous seeding frequently progresses into boils and may also afflict the mucous membranes. Progressive varicella is manifested in immunodeficient children, patients with tumours and haematoblastoses, or in malnourished children of mothers who have not undergone a course of varicella. Even at the present time, this form has a mortality rate as high as 10%. General complications in otherwise healthy children are rare, consisting of interstitial pneumonia or encephalitis (0.05% of patients). Symptomatic treatment is both local (liquid powder) and general (paracetamol, or if applicable antihistamines in the case of pronounced itching). In the case of severe courses in immunocompromised children, treatment with acyclovir is appropriate. For children with low immunity, it is appropriate to administer specific immunoglobulin (Varitec) preventively, and classic immunoglobulin (Norga) is also effective, although within three days of exposure to infect, i.e. before the appearance of skin manifestations. Vaccines against chickenpox are available, which can also be used to actively immunise susceptible immunocompromised individuals [37]. In the case of our male patient his low immunity was not known in advance, furthermore immunisation within three days of exposure represents a technical problem, since the timeline is always difficult to determine.

Ocular manifestations also include lesions on the eyelids, with potential punctate scarring necroses. Conjunctivitis and dentritic interstitial keratitis may also be manifested, leading to neovascularisations [6]. Further affliction is now rare: anterior uveitis, chorioretinitis and neuritis of the optic nerve or extraocular pareses [38]. A case of unilateral chorioretinitis with yellowish-white exudates with periphlebitis and vitritis was recorded in a young man, when chorioretinitis was cicatrised [39]. Unilateral ischaemic retinal vasculitis with edema of the optic nerve and deterioration of VA to movement in front of the eye was also observed in an 18-year-old male patient with a two-week history of varicella. The patient was treated with acyclovir, the optic nerve atrophied, and the level of VA improved only to counting fingers in front of the eye [40]. A 10-year-old girl suffered from chickenpox one month before panuveitis with necrotising retinitis. Immediate antiviral therapy corrected the inflammatory symptoms [41]. Blurred vision and dilated pupils due to internal ophthalmoplegia appeared two months after varicella in a boy of the same age, anterior uveitis and interstitial keratitis were detected. Subsequent topical treatment with steroids suppressed the inflammatory symptoms, but internal ophthalmoplegia persisted [42]. Optic neuritis with macular retinitis was also reported in a three-year-old boy only three days after the discovery of chickenpox. VA was affected due to the aforementioned affliction [43]. Retinitis may appear in immunocompromised children after varicella, e.g. in the case of lymphoblastic leukaemia [44] or primary immunodeficiency [45]. All these rare observations illustrate that chickenpox also may have a fundamentally negative impact on the visual organ. It is for this reason that, in combination with toxoplasmosis, varicella devastated VA in both eyes to the level of blindness in our immunocompromised patient at the time of these inflammations, despite all therapeutic endeavours. This is also documented by a histological analysis, in which vasculitis was initially triggered by varicella, but the inflammatory intraocular process at that time could already have been influenced by possible hitherto covert toxoplasmosis. The acute phase of inflammation beneath an image of vasculitis was attested to by thromboses. The granulomatous form of retinochoroiditis was a chronic, "quiescent" phase, which applies rather in the case of toxoplasma infection with perceptible pseudomicrocysts and bradyzoites. The old lesion was then characterised by necrosis and calcifications [46].

CONCLUSION

The aim of this paper was to illustrate the issue and the diversity of images of OT, in which opinions may vary with regard to therapeutic procedures also because attempts at therapy are not always successful. Atypical form of OT intraocular neuritis in an immunocompetent female patient had a favourable course, resulting in normalisation of VA, whereas retinal vasculitis with retinal choroiditis in a temporarily immunocompromised male patient ended in bilateral blindness.

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