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Biochemical analysis of aqueous humor in diabetic and non-diabetic patients with cataracts

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ABSTRACT

BACKGROUND: Although there are many factors stated in the etiology of cataract, the mechanisms which are formed during the formation of cataract are still not illuminated. The purpose of this study is to evaluate the biochemical analysis of aqueous humor in diabetic and non-diabetic patients with cataract in terms of the existence of pseudoexfoliation (PSX).

MATERIAL AND METHODS: Seventy-six patients who presented to our ophthalmology clinic with the complaint of cataract and who were planned to undergo phacoemulsification and IOL implementation were included in the study. The patients were classified into 4 groups as Group I: Cataracts with diabetes and without PSX, Group II: Cataracts without diabetes and PSX, Group III: Cataracts with diabetes and PSX, Group IV: Cataracts without diabetes and with PSX. The groups were compared statistically in terms of biochemical analysis of aqueous humor.

RESULTS: The mean age of the patients was 68.0 ± 8.5, and 51.3% of the patients were male. In Group II, Na value was significantly higher than in Group I and Group III. In Group IV, Na value was significantly higher than in Group I and Group III. Cl value in Group IV was significantly higher than in Group I-III-III. In Group IV, Ca value was significantly higher than in Group I-III-III. In Group I, P value was significantly higher than in Group II and Group III. Glucose levels in Group I were significantly higher than in Group II-III-IV. Glucose levels in Group III were significantly higher than in Group II-IV. Na value in the PSX (+) group was significantly lower than in the PSX (–) group. In the PSX (+) group, glucose value was significantly higher than in the PSX (–) group.

CONCLUSION: High glucose and low Na levels in the anterior chamber may play a role in the development of PSX and PSCC. High P level in the anterior chamber may be contributed to the development of cataract in diabetic non-PSX eyes. In non-diabetic PSX (+) group, high Ca and Cl levels may be contributed to developing cataracts.

KEY WORDS: cataract; biochemical analysis; aqueous humor; diabetes

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INTRODUCTION

Cataract is defined as a progressive loss of lens transparency. Some of the opacities are fixed and localized while others are progressive and widespread. Cataract is the most leading cause of curable blindness. Although there are many factors in the etiology, the exact mechanisms of cataract formation are not fully elucidated. Therefore, the prevention of cataract formation is not possible now and surgical treatment has emerged as the only option [1].

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Although there have been more than fifty years of basic and clinical research, there is no method to prevent age-related cataract and treat it without surgery. But there is a better understanding of this complexity; it is a multifactorial condition in which the occurrence and progression of this condition is modified by age, sex, radiation, oxidation, physical trauma, nutrition, diabetes, hypertension, smoking and drugs [2].

The mechanism in cataractogenesis has not been understood yet. Several risk factors have been identified in cataract development such as age, genetic predisposition, oxidative stress, and UV light exposure. It can be classified as congenital or secondary. Secondary cataract may also be due to reasons such as retinitis pigmentosa or uveitis, or systemic reasons such as diabetes or homocystinuria, or medications such as steroids [3].

The only source that meets the metabolic needs of the lens is the aqueous humor. Aqueous humor is not a simple ultrafiltrate of plasma. Changes in aqueous humor content are secondary to the active transport and dilutional changes of the vitreous due to hyaloid, iris blood vessels, lens and corneal endothelium [4–7].

Pseudoexfoliation (PSX) Syndrome is an age-related condition characterized by the production and accumulation of extracellular fibrillar materials in the anterior segment of the eye. Since the blood-aqueous barrier is affected, the protein content of the aqueous humor is changed in eyes with PSX compared to normal eyes.

The aim of this study is to evaluate the biochemical analysis of aqueous humor according to the presence of pseudoexfoliation in patients with diabetic and nondiabetic cataracts. In order to classify cataract types and to see the effect of changes in the anterior chamber, we included patients with PSX.

MATERIAL AND METHODS

The patients who were admitted to Adana Numune Training and Research Hospital, Department of Ophthalmology between May 2014 and November 2015 underwent phacoemulsification and IOL implantation for prospective investigation. The study was approved by the Ethics Committee of Adana Numune Training and Research Hospital in Adana in Turkey.

Seventy-six patients who underwent lensectomy and intraocular IOL implantation with phacoemulsification technique were included to the study. The same phacoemulsification equipment was used in all operations. These operations were made by the same two specialists.

Patients with glaucoma, glaucoma surgery, history of previous vitrectomy, corneal transplantation, and those with intravitreal injection history were excluded from the study. Those with systemic diseases other than diabetes and those with systemic steroid treatment for any reason were excluded.

The patients were grouped as followings:

- Group I: Cataracts with diabetes and without PSX;
- Group II: Cataracts without diabetes and PSX;
- Group III: Cataracts with diabetes and PSX;
- Group IV: Cataracts without diabetes and with PSX.

In all patients, the best corrected visual acuity (BCVA), eye pressure (To), biomicroscopic examination of anterior segment, and detailed fundus examination were performed preoperatively. BCVA was evaluated with Snellen chart. To was measured by an applanation tonometer. Cataract type was determined according to anatomic location. Fundus examination was performed with the 90D lens.

Approximately 10–15 IU of aqueous humor from the anterior chamber was taken with a 27-gauge insulin needle before the operation. Then, intraocular pressure was normalized by intraocular irrigation. Capsulorhexis + hydrodissection were performed. The nucleus was phacoemulsified. Cortex residues were aspirated by bimanual irrigation and aspiration (I/A). The collapsible acrylic hydrophilic intraocular lens (IOL) was implanted into the capsule bag. The anterior chamber was purged with I/A. 1 mg/0.01 ml cefuroxime axetil was given to the anterior chamber.

The samples were delivered to the biochemistry laboratory. Glucose, urea, creatinine (Cr), calcium (Ca), phosphate (P), magnesium (Mg) sodium (Na), potassium (K) were studied in the cobas 600 c-501 (Roche Diagnostics GmbH, Germany; Hitachi High-Technologies Corporation, Japan) autoanalyzer. Glucose was measured by hexokinase method, urea by urease-glutamate dehydrogenase enzymes by kinetic method, creatinine by Jaffe alkaline picrate method, calcium by NM-BAPTA, phosphate by ammonium molybdate, sodium and potassium by magnesium xylidil blue by photometric method.

STATISTICAL METHOD

In the descriptive statistics of the data, mean, standard deviation, median, lowest, highest, fre-

quency and ratio values were used. The distribution of the variables was measured by Kolmogorov-Smirnov test. ANOVA (Tukey test), Kruskal-Wallis, Mann-Whitney U test, and Independent Sample t-test were used to analyze the quantitative data. Chi-square test was used for the analysis of qualitative data and Fischer test was used since the Chi-square test conditions were not met. SPSS 22.0 program was used in the analysis.

RESULTS

The average age of the patients who were included into this study was 68.0 ± 8.5. 48.7% of the patients were female and 51.3% of them were male. The percentage of the patients who were smoking was 35.5% and the percentage of the patients who were not smoking was 64.5%. The mean examination findings were Vo: 0.11 ± 0.12 and To: 12.5 ± 2.4. The percentage of the posterior subcapsular cataract was 21.1%, nuclear cataract was 56.6%, and nuclear cataract + posterior subcapsular cataract was 22.4%. The mean values in the laboratory results were found as Na: 147.5 ± 3.8, K: 4.1 ± 0.2, Cl: 120.8 ± 4.2, Ca: 5.2 ± 1.2, P: 2.1 ± 0.5, Mg: 1.6 ± 0.1, Glucose: 102.0 ± 57.9, Urea: 34.4 ± 14.0, Cr: 0.2 ± 0.1 (Tab. 1)

The age of the patients in Group I was significantly lower than in Group II, Group III and Group IV ($p < 0.05$). In Group II, PSCC was significantly higher than in Group III and Group IV ($p < 0.05$) (Tab. 2).

In Group II, Na value was significantly higher than in Group I and Group III ($p < 0.05$). In Group IV, Na value was significantly higher than in Group I and Group III ($p < 0.05$). There was no significant difference ($p > 0.05$) between Group I and Group III for Na value. Cl value in Group IV was significantly higher than in Group I-III-III ($p < 0.05$). In Group I-II-III, there was no significant difference ($p > 0.05$) between Cl values. In Group IV, Ca value was significantly higher than in Group I-III-III ($p < 0.05$). In Group I-II-III, there was no significant difference for Ca value ($p > 0.05$). In Group I, P value was significantly higher than in Group II and Group III ($p < 0.05$). In Group I-IV,

Table 1. The demographic characteristics and examination findings of the patients

		Min–Max	Median	Mean ± SD/N	%
Age		51.0–86.0	65.5	68.0 ± 8.5	
Gender	Female			37	48.7%
	Male			39	51.3%
Smoking	Positive			27	35.5%
	Negative			49	64.5%
Va		0.01–0.50	0.05	0.11 ± 0.12	
Ip		2.0–21.0	12.5	12.5 ± 2.4	
Biomicroscope	PSCC			16	21.1%
	NC			43	56.6%
	NC + PSCC			17	22.4%
Fundus	Normal			19	25.0%
	Abnormal			57	75.0%
Na		141.0–162.0	147.5	147.5 ± 3.8	
K		3.5–4.6	4.1	4.1 ± 0.2	
Cl		114.2–136.0	120.0	120.8 ± 4.2	
Ca		2.3–7.1	5.6	5.2 ± 1.2	
P		1.4–5.3	2.0	2.1 ± 0.5	
Mg		1.2–2.9	1.6	1.6 ± 0.1	
Glucose		40.0–367.5	85.1	102.0 ± 57.9	
Urea		16.1–127.0	32.1	34.4 ± 14.0	
Cr		0.0–0.7	0.2	0.2 ± 0.1	

PSCC — posterior subcapsular cataract; NC — nuclear cataract; Va — vision acuity; Ip — intraocular pressure; Na — sodium; K — potassium; Cl — chlorine; Ca — calcium; P — phosphate; Mg — magnesium; Cr — creatine; SD — standard deviation

Table 2. The comparison of demographic characteristics and examination findings in groups I–IV

		Group I		Group II		Group III		Group IV		p
Age	Mean ± SD	62.8 ± 5,8		67.9 ± 9.0		71.7 ± 7.6		71.9 ± 8.2		**0.006**
	Median	62.0		65.0		70.5		72.0		
		N	%	N	%	N	%	N	%	
Gender	Female	12	70.6	16	45.7	4	33.3	5	41.7	0.190
	Male	5	29.4	19	54.3	8	66.7	7	58.3	
Smoking	Negative	10	58.8	23	65.7	8	66.7	8	66.7	0.958
	Positive	7	41.2	12	34.3	4	33.3	4	33.3	
Biomicroscope	PSCC	3	17.6	12	34.3	1	8.3	0	0.0	**0.043**
	NC	9	52.9	14	40.0	10	83.3	10	83.3	
	NC + PSCC	5	29.4	9	25.7	1	8.3	2	16.7	
Fundus	Normal	6	35.3	6	17.1	3	25.0	4	33.3	0.465
	Abnormal	11	64.7	29	82.9	9	75.0	8	66.7	
Va	Mean ± SD	0.11 + 0.11		0.11 + 0.12		0.11 + 0.11		0.13 + 0.13		0.718
	Median	0.10		0.05		0.05		0.08		
Ip	Mean ± SD	11.7 + 3.0		12.5 + 2.3		12.8 + 1.9		13.2 + 2.4		0.691
	Median	13.0		12.0		12.5		13.0		

PSCC — posterior subcapsular cataract; NC — nuclear cataract; Va — vision acuity; Ip — intraocular pressure; SD — standard deviation

P value was not significant ($p > 0.05$). There was no significant difference ($p > 0.05$) between Group II and Group III. Glucose levels in Group I were significantly higher than in Group II-III-IV ($p < 0.05$). Glucose levels in Group III were significantly higher than in group II-IV ($p < 0.05$). Glucose levels in Group II were significantly higher than in Group IV ($p < 0.05$). In Group I-II-III-IV, there was no significant difference ($p > 0.05$) for K, Mg, Urea and Cr (Tab. 3).

Patients with PSX (+) and PSX (–) were not significantly different in terms of age, sex distribution, and smoking rate ($p > 0.05$). Visual acuity, intraocular pressure, cataract distribution, and fun-

Table 3. The biochemical findings of aqueous humor in groups I–IV

Mineral	Mean/Median	Group I	Group II	Group III	Group IV	p
Na	Mean ± SD	146.2 ± 2.4	148.1 ± 3.7	145.1 ± 3.2	149.8 ± 4.8	0.007
	Median	145.0	148.0	144.0	150.0	
K	Mean ± SD	4.2 ± 0.2	4.1 ± 0.2	4.0 ± 0.2	4.1 ± 0.2	0.068
	Median	4.1	4.0	4.0	4.0	
Cl	Mean ± SD	119.2 ± 3.6	120.8 ± 3.9	119.9 ± 2.6	124.2 ± 5.6	0.011
	Median	118.2	120.3	120.0	124.4	
Ca	Mean ± SD	5.2 ± 0.9	4.8 ± 1.3	5.6 ± 0.7	6.0 ± 0.6	0.024
	Median	5.6	5.4	5.7	5.9	
P	Mean ± SD	2.2 ± 0.4	2.0 ± 0.3	1.8 ± 0.2	2.4 ± 1.0	0.018
	Median	2.2	2.0	1.8	2.1	
Mg	Mean ± SD	1.6 ± 0.2	1.6 ± 0.1	1.6 ± 0.1	1.6 ± 0.2	0.075
	Median	1.5	1.6	1.6	1.7	
Glucose	Mean ± SD	148.5 ± 6.95	92.7 ± 56.0	105.5 ± 21.5	60.0 ± 11.4	0.032
	Median	139.3	77.5	102.4	60.8	
Urea	Mean ± SD	33.0 ± 7.6	31.5 ± 8.7	38.5 ± 9.0	40.7 ± 29.2	0.084
	Median	33.1	30.8	34.2	31.9	
Cr	Mean ± SD	0.2 ± 0.1	0.2 ± 0.1	0.2 ± 0.1	0.3 ± 0.2	0.079
	Median	0.1	0.2	0.2	0.2	

PSCC — posterior subcapsular cataract; NC — nuclear cataract; Na — sodium; K — potassium; Cl — chlorine; Ca — calcium; P — phosphate; Mg — magnesium; Cr — creatine; SD — standard deviation

Table 4. The demographic characteristics and biochemical findings of PSX (+) and PSX (–) groups

		PSX (+)			PSX (–)			p
		Mean ± SD		Median	Mean ± SD		Median	
Age		66.5 ± 7.8		65.0	69.9 ± 8.9		68.0	0.214
		N	%		N	%		
Gender	Female	16	55.2		21	44.7		0.374
	Male	13	44.8		26	55.3		
Smoking	Negative	18	62.1		31	66.0		0.731
	Positive	11	37.9		16	34.0		
Va		0.1 ± 0.1		0.1	0.1 ± 0.1		0.1	0.948
Ip		12.2 ± 2.6		13.0	12.7 ± 2.4		12.0	0.672
Biomicroscope	PSCC	4	13.8		12	25.5		0.388
	NC	19	65.5		24	51.1		
	NC + PSCC	6	20.7		11	23.4		
Fundus	Normal	9	31.0		10	21.3		0.340
	Abnormal	20	69.0		37	78.7		
Na		145.7 ± 2.8		145.0	148.6 ± 4.0		149.0	0.001
K		4.1 ± 0.2		4.1	4.1 ± 0.2		4.0	0.477
Cl		119.5 ± 3.2		119.0	121.6 ± 4.6		120.8	0.053
Ca		5.3 ± 0.8		5.6	5.1 ± 1.3		5.6	0.638
P		2.1 ± 0.4		1.9	2.1 ± 0.6		2.0	0.894
Mg		1.6 ± 0.1		1.6	1.6 ± 0.1		1.6	0.392
Glucose		130.7 ± 58.4		114.8	84.4 ± 50.5		71.7	0.000
Urea		35.2 ± 8.5		33.1	33.8 ± 16.6		30.8	0.113
Cr		0.2 ± 0.1		0.2	0.2 ± 0.1		0.2	0.600

PSCC — posterior subcapsular cataract; NC — nuclear cataract; Va — vision acuity; Ip — intraocular pressure; Na — sodium; K — potassium; Cl — chlorine, Ca — calcium; P — phosphate; Mg — magnesium; Cr — creatine; PSX — pseudoexfoliation; SD — standard deviation

dus status did not differ significantly ($p > 0.05$) in patients with PSX (+) and PSX (-). Patients with PSX (+) and PSX (–) were not significantly different ($p > 0.05$) in terms of K, Cl, Ca, P, Mg, urea and Cr.

The Na value in the PSX (+) group was significantly lower than in the PSX (–) group ($p < 0.05$). In the PSX (+) group, glucose value was significantly higher than in the PSX (–) group ($p < 0.05$) (Tab. 4).

DISCUSSION

The incidence of cataract in patients with diabetes mellitus increases and cataract is considered to be a major cause of progression of visual impairment in diabetic patients. Many clinical studies have shown that cataract occurs more frequently and earlier in diabetic patients than in non-diabetic patients [8–10].

In our study, while other demographic factors showed similar characteristics in the diabetic group, it was found to cause cataract at the level that required surgery in younger patients. This finding supports that the presence of diabetes accelerates cataract formation in accordance with the literature. Increased glucose levels in the aqueous humor may induce glycation of lens proteins, may result in superoxide radicals (O_2) production, and may lead to a process leading to the formation of advanced glycation end products.

Glucose is taken from the aqueous humor by simple diffusion and facilitated diffusion. When the glucose increases in the body, the glycolysis is stopped by anaerobic glycolysis with the end products, glucose enters the sorbitol pathway and sorbitol is formed. Because the permeability of the lens to the sorbitol is high, sorbitol accumulates in the lens, water enters and opacity in the lens occurs [7]. In this study, in the aqueous humor analysis of the diabetic groups, glucose was found to be significantly higher. This finding supports the increasing effect of glucose on cataract formation in diabetic patients.

Studies that shed light on the pathophysiology of diabetic cataract have led to the development of anticataract therapies in diabetic patients. Two studies are presented below for this purpose:

— numerous experimental studies of anticataract therapy in diabetic patients support the role of ARI (Aldose-Reductase Inhibitors) in preventing diabetic cataract formation and progression. In an experimental diabetic rat model, animals were treated with AR inhibitor Renirestate [8];
— pyruvate, an endogenous antioxidant, has recently shown interest in the preventive effects of diabetic cataract formation on sorbitol formation and lipid peroxidation [9].

In epidemiological cross-sectional studies, the relationship between PSX and cataract has been established. Australian Blue Mountains Eye Study showed similar findings with our study. The PSX was associated with a significant nuclear cataract in accordance with the literature. The relationship between nuclear cataract and PSX has been established. Although the pathogenesis of PSX is not yet fully understood, it is probably a multifactorial condition associated with factors such as genetic and aging. In our study, biochemical analysis of the aqueous humor showed that in the presence of PSX a statistically significant level of glucose was found to be high and sodium was found to be low.

A significantly higher incidence of posterior subcapsular cataract in eyes with nondiabetic and nonexfoliative cataracts and a significantly higher Na concentration in this group suggest that there may be a relationship between aspirated cataract and aqueous humor Na concentration. Na is introduced into the lens according to the chemical concentration from the posterior capsule and then actively pumped from the epithelium with Na-K ATPase. According to this model, the K is found on the front of the lens, while the Na is more intense at the posterior of the lens [10–13].

Studies with calcium showed that calcium plays a special role in the development of cataract in humans. Calcium is associated with cataract level. It has been found that elevated calcium levels in human lenses play an important role in cortical cataracts.

In the present study, we performed biochemical analysis of aqueous humor in the presence of two diseases with the most common association with cataract. Diabetic patients had significantly higher amounts of glucose and lower calcium in the aqueous humor. Posterior subcapsular cataract was more frequent in diabetic patients. In diabetic non-PSX eyes, P value was significantly higher.

In PSX patients, glucose was found to be higher and sodium was lower than in the non-PSX group. This group was more frequently associated with cortical cataract. Ca and Cl ratio were significantly higher in nondiabetic PSX group.

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STATEMENT OF COMPETING INTERESTS

The authors report no competing interests.

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The prevalence of HBV, HCV, and HIV infections in patients with cataract in Turkey

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ABSTRACT

BACKGROUND: Hepatitis B (HBV), hepatitis C (HCV), and human immunodeficiency virus (HIV) cause common infections all around the world. The aim of this study is to determine the HBV, HCV, and HIV prevalence in cataract patients.

MATERIAL AND METHODS: This was a retrospective study and was carried out in the ophthalmology clinic of Adana Numune Research and Training Hospital (Adana, Turkey). One hundred and forty patients undergoing cataract surgery were included to the study. The clinical findings were extracted from the medical records of the patients. The serological analyzing was done by one step immunoassay-based rapid diagnostic card tests for hepatitis B surface antigen (HBsAg), anti-HCV, and anti-HIV antibodies. HBV and HCV confirmations were done by ELISA (enzyme-linked immunosorbent assay test)-based serological tests.

RESULTS: Of the 1040 patients included in the study, 462 (44.4%) were females and 578 (55.6%) were males. The mean age of the patients was 64.8 ± 13.7 years. HBsAg was positive in 39 (3.8%) patients and Anti-HCV was positive in 14 (1.3%) patients. None of the patients had HIV.

CONCLUSION: HBV is the most common infection among cataract patients and it is very important to apply infection prevention methods.

KEY WORDS: HBV; HCV; HIV; prevalence; cataract

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INTRODUCTION

Hepatitis B (HBV), hepatitis C (HCV), and human immunodeficiency virus (HIV) cause infections that are transmitted directly or indirectly by blood, blood products, and body fluids. They are very common in the population. According to the World Health Organization, HBV prevalence ranges from 0.7% to 6.2%, HCV from 0.5% to 2.3%, HIV from 0.4% to 3.1%. These infections are also quite important for health workers who are in high risk group. They may cause serious chronic liver and other organ diseases which needed to be prevented. Additionally, these infections can be transmitted from patient to patient easily [1].

Cataract is one of the most common eye diseases in the world. Surgery with local anesthesia is often used for the treatment of cataract. Local anesthesia is performed in the peribulbar or subtenon area in the form of injection. Since the injection process is too hard, the injector can be inserted into the hands of the surgeon or nurse. It has been estimated that a surgeon sustains 0.8 injuries/100 h of surgery time, resulting in a 6.9% lifetime risk of contracting hepatitis C and a 0.15% lifetime risk of HIV infection [1].

HBV, HCV, and HIV infections cause serious health problems around the world. There are approximately 350 million HBV and 210 mil-

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Table 1. The frequency of hepatitis surface antigen (HBsAg), hepatitis C antibody (anti-HCV), and human immunodeficiency virus antibody (anti-HIV) in patient with cataract

		Min–Max	Median	Mean ± SD/N%	
Age		3–97	66.0	64.8 ± 13.7	
Age		< 18		12	1.2%
		18–29		12	1.2%
		30–39		28	2.7%
		40–49		75	7.2%
		50–59		198	19.0%
		60–69		357	34.3%
		70–79		254	24.4%
		≥ 80		104	10.0%
Gender	Female			462	44.4%
	Male			578	55.6%
HBsAg	(–)			1001	96.3%
	(+)			39	3.8%
Anti-HCV	(–)			1026	98.7%
	(+)			14	1.3%
Anti-HIV	(–)			1040	100%
	(+)			0	0.0%

SD — standard deviation

lion HCV patients worldwide [2–4]. HBV, HCV, and HIV can be transmitted by percutaneous or perinatal route, contacts with the infected person, and sexual intercourse. The frequency of transmission of HBV and HCV is higher among health workers since HBV and HCV can remain on surgical tools such as scalpels or needles and in body fluids such as saliva or ejaculate. Therefore, the patients are screened by serological tests against these viral agents before invasive procedures such as surgery. Some studies have also showed the risk of transmission of HBV, HCV, and HIV during sequential phacoemulsification operation.

The aim of this study is to define the hospital-based prevalence of HBV, HCV, and HIV infections in 1040 patients undergoing cataract surgery and to investigate the possible risk factors for these infections.

MATERIAL AND METHODS

This study was carried out between September 2016 and September 2017 with 1040 patients who were hospitalized in the ophthalmology clinic of Adana Numune Research and Training Hospital because of cataract surgery and had serologic tests for HBV, HCV, and HIV before the operation. The cataract patients were subjected to detailed ocular examination and laboratory research. Tests were carried out by qualified and trained technicians under an experimental microbiologist.

Results were commentated as per the WHO and National AIDS Control Organization (NACO) guidelines for commendation of fast diagnostic card tests [5–8]. Reports of the tests were underwritten by microbiologists. The serological analysis was done by one step immunoassay-based rapid diagnostic card tests for HBsAg (hepatitis B surface antigen), anti-HCV, and anti-HIV antibodies. In addition, HBV and HCV confirmations were done by ELISA (Enzyme-Linked ImmunoSorbent Assay test)-based serological tests.

The files of all patients were retrospectively reviewed. The demographic details such as age, gender, and address were extracted from the medical records of the patients. Serological test results were noted as positive and negative.

STATISTICAL METHOD

Mean, standard deviation, median lowest, highest, frequency and ratio values were used in descriptive statistics of the data. SPSS 22.0 program was used in the analysis.

RESULTS

The demographic variables and frequencies of HBsAg, anti-HCV, and anti-HIV in patients with cataract are shown in Table 1. Of the 1040 patients

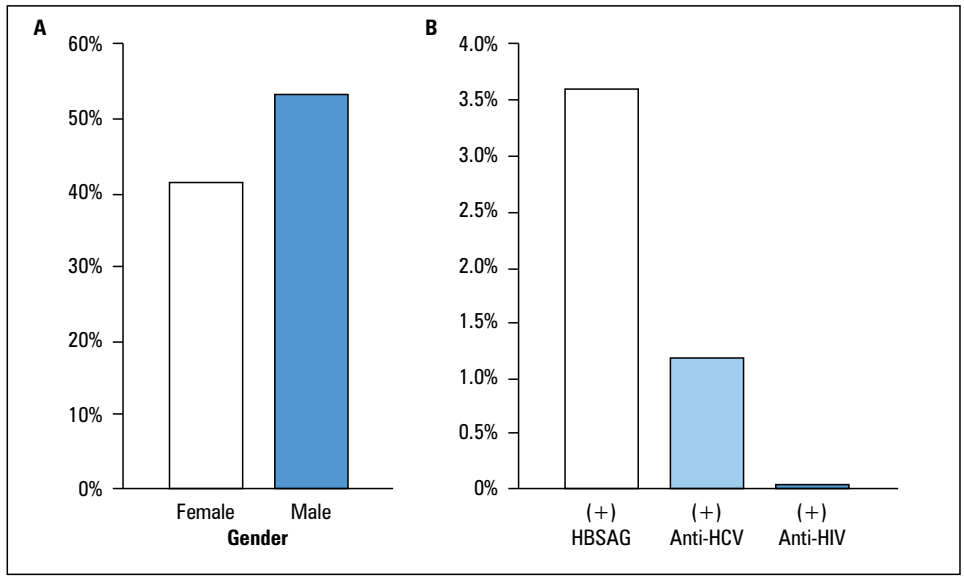

FIGURE 1. The demographic (**A**) and clinical (**B**) variables of the sample. HBsAg — hepatitis surface antigen; anti-HCV — hepatitis C antibody; anti-HIV — human immunodeficiency virus antibody

included in the study, 462 (44.4%) were female and 578 (55.6%) were male. The age range was 3–97. The mean age of the patients was 64.8 ± 13.7. HBsAg was positive in 39 (3.8%) patients and Anti-HCV positive in 14 (1.3%) patients. None of the patients had HIV. HBV was the most common viral infection among cataract patients.

DISCUSSION

Employees in the health sector have a higher risk of HBV, HCV, and HIV transmission since the risk of contact with blood and blood products is higher than that of normal people. In addition, there is the possibility that an anti-HCV positive healthcare personnel may transmit HCV to other patients and health care personnel. In our country, health personnel constitute the most important risk group for hepatitis and HIV. Employees such as physicians, nurses, or laboratory workers who carry the blood samples are in the risk group.

In our country, the incidence of HBV and HCV infection in health workers is at least 3–6 times higher than in people working in other occupations. Surgical physicians are 5.5 times more injured than other specialist physicians and exposed to contact with blood or other body fluids. In 12.2% of the operations, cutaneous injuries, and in 14.7% of the operations, blood and body fluid transmission are seen. In some studies, the risk of contamination of HBV and HCV because of a contaminated injector has been reported as 7–30% and 4–10%, respectively. The risk of transmission after a contact with mucosa was 0.36% for HCV and 0.09% for HIV, 0.5–4% and 0.1–0.3% after percutaneous injury [9, 10]. The probability of emergence of acute HCV infection following needle sticking to the healthcare personnel is 1.8% on average.

According to our study, the total prevalence of virus infection (HBV, HCV, and HIV) was 5.01% between cataract patients. In our study, HBsAg, anti-HCV, and anti-HIV positivity were found to be 3.8%, 1.3%, and 0%, respectively. Similar to our research, some studies from India and Pakistan showed that viral seroprevalence ranged between 4% and 16% [11, 12]. In a study of orthopedics and traumatology patients, HBsAg, anti-HCV, and anti-HIV seroprevalence were found to be 2.3%, 0.6%, and 0%, respectively [11]. In a study of patients scheduled for plastic and reconstructive surgery, HBsAg, anti-HCV, and anti-HIV were found to be 1.5%, 0.39% and 0%, respectively [12]. HBsAg, anti-HCV, and anti-HIV positivity were found to be 3.1%, 0.54%, and 0%, respectively, in a study of patients planned for urological surgery [8]. In a study conducted by cardiologists, HBsAg, anti-HCV, and anti-HIV positivity in patients undergoing angiography were 2.2%, 0.2% and 0%, respectively. In an ophthalmology study, it was found that 5.9% of patients undergoing cataract surgery were seropositive for HIV (0.09%), HBV (1.8%), or HCV (4.0%) [16]. Another ophthalmol-

ogy study from Nigeria showed that 0.2% of the patients were found to be HIV seropositive while 1.5% were HbsAg-positive [17]. In a donor cornea study, the seroprevalence of HIV, HBV, HCV, and *T. pallidum* in eye donors was 1.58%, 0.52%, 0.10%, and 0.21% respectively [18].

The use of materials like gloves to protect HBV, HCV, and HIV infections is very important for health personnel. It has been reported that the use of gloves reduces by 50% the amount of blood reaching the tissue as a result of needle sting, and the use of double gloves reduces this amount to 7% [15]. It is also recommended to use a mask for the face and surgical goggles for the eyes. Vaccination significantly reduced the incidence of acquired HBV infection. However, protection against HCV and HIV infection is not possible with a vaccine, so protection materials such as gloves, masks and goggles are very valuable for preventing these infections [13].

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STATEMENT OF COMPETING INTERESTS

The authors report no competing interests.

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ORIGINAL PAPER
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Hypertension and cerebrovascular diseases are related to corneal endothelial insufficiency — a retrospective study

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ABSTRACT

BACKGROUND: Corneal endothelium has an important role on the clarity of the cornea. Cataract surgery may cause corneal endothelial damages and serious vision problems. In this study, we aimed to investigate hypertension, cerebrovascular diseases, and trauma in patients who developed corneal endothelial insufficiency (CEI) after cataract surgery.

MATERIAL AND METHODS: The study was performed in the Department of Ophthalmology in Adana Ortadogu Hospital between October 2017 and October 2018. 24 patients who developed CEI after cataract surgery and 24 patients who did not develop CEI after cataract surgery were included to the study. Eye trauma, systemic hypertension, cerebrovascular diseases were investigated in the patients' own history. The findings were compared statistically.

RESULTS: The percent of cerebrovascular diseases was 54.2% in patients with CEI and 16.6% in patients without CEI. 58.3% of the patients with CEI had a systemic hypertension history. Hypertension was presented in 25% of the patients who did not develop CEI. The rate of trauma history in patients with CEI was 29.2% and 12.5% in those without CEI. The history of cerebrovascular disease and hypertension were significantly higher in patients with CEI.

CONCLUSION: Hypertension and cerebrovascular diseases appeared to be linked with CEI.

KEY WORDS: hypertension; cerebrovascular disease; trauma; cataract; corneal endothelial insufficiency

Ophthalmol J 2019; Vol. 4, 11–14

INTRODUCTION

Corneal endothelium is the most important layer of corneal transparency. Therefore, the protection of this layer during surgical procedures is very important. The endothelium maintains the corneal stroma in a steady state of hydration by maintaining the active fluid pump and barrier function. This has a direct effect on the clarity of the cornea. Cataract treatment with phacoemulsification is one of the most common surgical methods used today. It is known by everyone that corneal endothelium may be damaged during phacoemulsification operation [1]. The corneal endothelial cell layer has no ability to regenerate itself after trauma. The repair process is provided by the expansion of the remaining cells, amitotic nucleus division, migration, and the phenomenon of badge formation. As a result, the cellular density decreases, the average cell area grows proportionally, and the hexagonal cell pattern deteriorates [2, 3]. Endothelial cell count is also known to decrease with age [4]. Most people with phacoemulsification are older. The increase in life expectancy in these patients makes endothelial damage an important factor during surgery. The endothelial functions may decrease in various corneal diseases such as trauma, previous intraocular operation, inflammation, metabolic disorders (diabetes mellitus) or Fuch's distrophy, congenital hereditary

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endothelial dystrophy, and posterior polymorphic dystrophy. Thus, the endothelial cell function deteriorates and the transparency of cornea is impaired [5]. Corneal endothelial insufficiency (CEI) causes irreversible serious vision problems. Treatment of this condition is difficult and can only be possible surgically.

The aim of our study was to investigate hypertension, cerebrovascular factors, and trauma in patients who developed CEI after cataract surgery (Phacoemulsification + IOL implantation). Another aim is to determine whether systemic hypertension, cerebrovascular diseases, and trauma may be related to an endothelial insufficiency, or not.

MATERIAL AND METHODS

The study was performed in the Department of Ophthalmology in Adana Ortadogu Hospital between October 2017 and October 2018. The ethics committee approval was obtained from Adana City Hospital in Adana in Turkey. The nature and purpose of the study explained to all patients and informant consent was obtained from all patients.

24 patients who developed CEI after cataract surgery and 24 patients who did not develop CEI after cataract surgery were included to the study. 48 patients who underwent lensectomy and intraocular IOL implantation with phacoemulsification technique were included to the study. The same phacoemulsification equipment was used in all operations. These operations were made by the same specialist.

At the beginning of the operation, tropicamide 0.5% and phenylephrine HCL 2.5% were instilled 3 times 5 minutes apart to the planned eye. Each patient was operated 45 minutes after the last drop. Proparakain HCL 0.5% was instilled to both eyes before the operation. The planned eye and surrounding area were wiped out with a 10% batikon. Patient covered with a drape. Eyelash bottoms and ocular surface were washed with 5% batikon and waited for 3 minutes. Peribulbar anaesthesia was performed by administering 3 ml jetocaine to the subtenon area. The sideports were opened with a 20 Gauge knife. Viscoelastic substance (VEM) was administered to the anterior camera. A corneal tunnel was opened with a 2.8 knife. Capsulorhexis and + hydrodissection were performed. The nucleus was phacoemulsified. Cortex residues were aspirated by bimanual irrigation and aspiration (I/A). The collapsible acrylic hydrophilic intraocular lens (IOL) was implanted into the capsule bag. The anterior camera was purged with I/A. 1 cc of 5.45 mg moxifloxacin was given to the anterior camera of patients. All operations were finished without complications.

The files and records of patients with CEI were retrospectively reviewed. Eye trauma, systemic hypertension, and cerebrovascular diseases were investigated in the patients' own history. Patients with a positive history of these conditions were noted. Patients with glaucoma, glaucoma surgery, history of previous vitrectomy, corneal transplantation, and those with intravitreal injection history were excluded from the study. Those with systemic diseases other than hypertension and cerebrovascular diseases and those with systemic steroid treatment for any reason were excluded.

STATISTICAL METHOD

In the descriptive statistics of the data, mean, standard deviation, median lowest, highest, frequency and ratio values were used. The Chi-Square Test was used for the analysis of qualitative independent data. SPSS 21.0 program was used in the analysis.

RESULTS

The mean age of patients with corneal endothelial failure was 75.2 ± 5.71. The mean age of patients with no corneal endothelial failure was 76.1 ± 5.50. 54.2% (N = 13) of the patients with corneal endothelial failure were male and 50.0% (N = 12) of the patients with no corneal endothelial failure were male.

The percent of cerebrovascular diseases was 54.2% (N = 13) in patients with CEI and 16.6% (N = 4) in patients without CEI. When these two groups were compared statistically, p-value was found to be 0.007. The history of cerebrovascular disease was significantly higher in patients with CEI ($p < 0.05$).

Among the patients with CEI, 58.3% (N = 14) had a systemic hypertension history. Hypertension was presented in 25% (N = 6) of the patients who did not develop CEI. When the two groups were compared in terms of hypertension, p-value was determined as 0.019. The history of hypertension was significantly higher in patients with CEI ($p < 0.05$).

The rate of trauma history in patients with CEI was 29.2% (N = 7) and 12.5% (N = 3) in those without CEI. When the two groups were compared in terms of trauma, p-value was found to be

Table 1. Demographic variables and clinical characteristics of the patients

		Corneal endothelial failure		No corneal endothelial failure	
		Mean	SD	Mean	SD
Age		75.2	5.71	76.1	5.50
		N	**%**	**N**	**%**
Gender	Male	13	54.2	12	50.0
Eye side	Right	12	50.0	13	54.2
CVD		13	54.2	4	16.6
HT		14	58.3	6	25.0
Trauma		7	29.2	3	12.5

CVD — cerebrovascular diseases; HT — hypertension; SD — standard deviation

Table 2. The comparison of cerebrovascular diseases (CVD), hypertension (HT), and trauma between the groups

	Corneal endothelial failure N (%)	No corneal endothelial failure N (%)	p
CVD	13 (54.2)	4 (16.6)	0.007
HT	14 (58.3)	6 (25.0)	0.019
Trauma	7 (29.2)	3 (12.5)	0.155

0.155. Although the rate of trauma was higher in patients with CEI, this was not statistically significant ($p < 0.05$).

Demographic variables and clinical characteristics of the patients are shown in Table 1.

The comparison of cerebrovascular diseases (CVD), hypertension (HT), and trauma between the groups is presented in Table 2.

DISCUSSION

Cataract surgery is performed with various techniques such as conventional extracapsular cataract extraction, small incision cataract surgery, and phacoemulsification. Several studies have been conducted to examine the effects of all these surgical methods on the corneal endothelium. These studies showed dysfunctions and a decrease in the number of endothelial cells after surgery. However, the aetiology of these dysfunctions and a decrease in the number of corneal endothelial cells has not been fully elucidated. The cause of CEI is mostly due to endothelial damage during phacoemulsification surgery; the heat released by the phaco tip, micro-air bubbles and the formation of free radicals, surgical instruments and mechanical deformation of the cornea have been held responsible [6–8]. On the other hand, the operative risks of CEI were determined as the duration of operation time, inexperienced surgeon, ultrasonic vibrations, and heat. However, a limited number of studies were performed to determine the risk factors before the operation [8–11].

Lundberg B et al. investigated the causes of CEI in a study. In this study, postoperative corneal oedema was clinically demonstrated to be strongly associated with loss of corneal endothelial cells [9]. Pramod K. Sahu et al. reported that the patients with diabetes mellitus had significantly higher corneal endothelial density after phacoemulsification compared to non-diabetic patients. In addition, patients with diabetes showed a slower and weaker recovery response [12]. In one study, it was shown that the number of corneal endothelial cells decreased in smokers and in patients with diabetes mellitus [13].

There is limited literature about the relationship between corneal endothelial failure and vascular pathologies. A study conducted by Olsen reported that the frequency of cardiovascular disease was significantly higher in the group of Fuchs' endothelial dystrophy than in the control group [14]. In this study, it was reported that the corneal endothelial cells develop in intimate relationship with vascular mesenchymal cells and the corneal and vascular endothelium share biological properties. In this context, it was suggested that there might be a relationship between vascular pathologies and endothelial dystrophy. In the present study, we hypothesized

that hypertension and vascular diseases might be associated with corneal endothelial failure due to a decreased blood supply resulted in a decreased aqueous flow. A decreased aqueous flow might negatively affect the feeding of the cornea.

The above-mentioned studies evaluated the preoperative, perioperative, and postoperative possible causes of CEI after cataract surgery. However, there is no consensus about this subject. In this context, we thought that our study contributed significantly to the literature. In the present study, we showed that CEI after phacoemulsification surgery might be associated with systemic hypertension and cerebrovascular diseases. Future longitudinal studies with large samples are needed to clarify these findings.

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STATEMENT OF COMPETING INTERESTS

The authors report no competing interests.

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REVIEW ARTICLE
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Autosomal dominant neovascular inflammatory vitreoretinopathy — a review

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ABSTRACT

Autosomal dominant neovascular inflammatory vitreoretinopathy (ADNIV) is a hereditary autoimmune disorder of the eye caused by mutations in the CAPN5 gene. It is characterized by non-specific uveitis in the anterior chamber and vitreous leading to panuveitis, iris and retinal neovascularization, cystoid macular edema, abnormal retinal pigmentation, vitreous hemorrhage, intraocular fibrosis, membrane formation and tractional retinal detachment. ADNIV is a progressive disease leading to complete blindness despite of treatment. Confirmation is made by genetic analysis demonstrating mutations of the CAPN5 gene.

KEY WORDS: autosomal dominant neovascular inflammatory vitreoretinopathy; ADNIV; uveitis; neovascularization; proliferative vitreoretinopathy; cystoid macular edema; CAPN5; calpain-5

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INTRODUCTION

Autosomal dominant neovascular inflammatory vitreoretinopathy (ADNIV) is a very rare, autoimmune uveitis belonging to inherited vitreoretinal dystrophies [1]. The disease is caused by the mutations in the CAPN5 gene (calpain-5) [2, 3]. Genetic locus for ADNIV was mapped to chromosome 11q13 in 1992 by Stone et al. [4, 5]. This gene encodes a protein, calpain-5, which is an intracellular calcium-activated cysteine protease [2, 3, 6]. CAPN5 is the first nonsyndromic gene for autoimmune uveitis and among the very few Mendelian autoimmune diseases where the gene is identified [6]. There is significant phenotypic variance in ADNIV causes by different mutations in CAPN5 gene. Recent genetic tests have discovered two new mutations which were described in literature in 2017 [7].

The first scientific work describing ADNIV was published in 1990 by Steven Bennett and co-workers. The authors presented symptoms and causes of the illness illustrated with an example of large group of affected 28 of 61 members of a six generation family [8]. The ADNIV occurs with a frequency of approximately one in 1 000 000 births and has been found worldwide [9]. The pathophysiology and immunopathology are not yet well known. The first symptoms can occur at all ages [9]. The disease is very progressive despite the treatment and leading to complete blindness.

Loss of the b-wave amplitude on electroretinography (ERG) is a characteristic feature of ADNIV disease [8].

The pathophysiology of the illness has not been known well; therefore, the condition is given a descriptive name autosomal dominant neovascular inflammatory vitreoretinopathy.

DIAGNOSIS

The diagnosis of the disease is difficult due to several causes. Firstly, ADNIV is classified as a rare disease; secondly, the first signs can occur at any age and cannot be detected in childhood; therefore, unfortunately, the diagnosis is delayed in most cases. The symptoms of the disorder mimic several much more common eye diseases, including

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non-specific uveitis, retinitis pigmentosa, rod-cone dystrophy, proliferative diabetic retinopathy and proliferative vitreoretinopathy [8]. Because of its similarity to these disorders, ADNIV patients are often misdiagnosed. The very characteristic sign of the ADNIV is a lack of systemic features unlike in some of the disorders mentioned above [1]. It is important sign in differential diagnosis.

The family history is very important because helps to recognize hereditary nature of the disease and suggests a genetic etiology. If the patient lacks a family history of ADNIV and presents with vitreous inflammation, a thorough evaluation for infectious and inflammatory etiologies should be performed [10].

Key findings in correct diagnosis are molecular genetic examination and ERG testing. ADNIV is inherited in an autosomal dominant manner. It means that each child has a 50% chance of inheriting the condition from an affected parent. It is present in every generation of affected family. The disease is caused by the mutations in CAPN5 gene localized on chromosome 11q13.

Best's vitelliform dystrophy, another disease inherited in autosomal dominant manner, is caused by the gene mutation mapped also to chromosome 11q13 [11]. We do not know yet, whether there are any other common features with ADNIV disease.

Different molecular genetic testing is necessary to detect mutations. If there is no possibility to conduct comprehensive genetic testing, the diagnosis of ADNIV unfortunately is delayed.

Retinal degeneration in ADNIV patients can be detected by examining fundus autofluorescence (FAF) and infrared reflectance (IR) of the fundus. The fundus displays enhanced FAF observed during mid-to-late stage ADNIV and is associated with photoreceptor or RPE cell dysfunction. IR imaging of the retina shows pigmentary changes indicative of reactive retinal pigment epithelium cells and photoreceptor degeneration [12].

Another important examination confirming the diagnosis of the disease is ERG testing. The abnormality is detectable with electroretinography very early in the course of the disease despite the normal appearing of the retina. ERG signaling defects precedes the signs of photoreceptors degeneration [13]. In early stages, we observe a reduced b-wave on ERG, later it is selective loss of the b-wave in the scotopic bright flash [3]. This indicates dysfunction of signal transmission from photoreceptors to membranes of the inner retina such as bipolar cells due to localization of CAPN5 to the photoreceptor synapse [10]. With progression of the disease there is also a reduction of the a-wave and in the last stage the ERG is extinguished; it shows non-recordable cone and rod responses due to severe photoreceptor dysfunction [2, 3].

Genetic analysis or ERG testing is performed in patients who do not demonstrate classic features of ADNIV or those who are younger than 30 years of age [10].

SYMPTOMS

There are 5 stages in the course of ADNIV, each lasting approximately ten years.

The first stage begins in the second or third decade of life and is asymptomatic for the patient. In the first stage we observe inflammatory cells in the vitreous, minimal far peripheral arteriolar closure, pigmentation and mild peripheral ischemia. In this stage, ADNIV is clinically indistinguishable from an autoimmune, non-infectious uveitis.

The electroretinogram demonstrates early retinal and photoreceptor dysfunction. The most characterized feature is reduction of b-wave.

In the second stage, patients become symptomatic, the anterior chamber shows mild inflammatory cells and there is early development of cataract. The inflammatory cells are still observed in the vitreous. The posterior segment shows pigmentary retinal degeneration and some macular and optic nerve head edema.

Stage three of the disease usually develops during the third or fourth decades, but in some cases can start earlier [14]. There are moderate inflammatory cells, progressive cataract and iris synechiae. Sometimes peripheral iris stromal atrophy and thinning occur. Development of band keratopathy is sometimes seen in the patients. The posterior segment shows cystoid macula edema (Fig. 1AB), progressive vascular closure with neovascularization of the far peripheral retina or optic disc. With the development of inflammation in the vitreous, epiretinal and subretinal membranes start to develop (Fig. 2AB). There are extensive pigmentary and atrophic changes throughout the fundus. Optical coherence tomography reveals distortion of the retinal layers. There is a decline of peripheral vision with progressively constricted visual field, which indicates reduced retinal light sensitivity. In some cases despite of the significant disease progression, the limited central vision is observed [14].

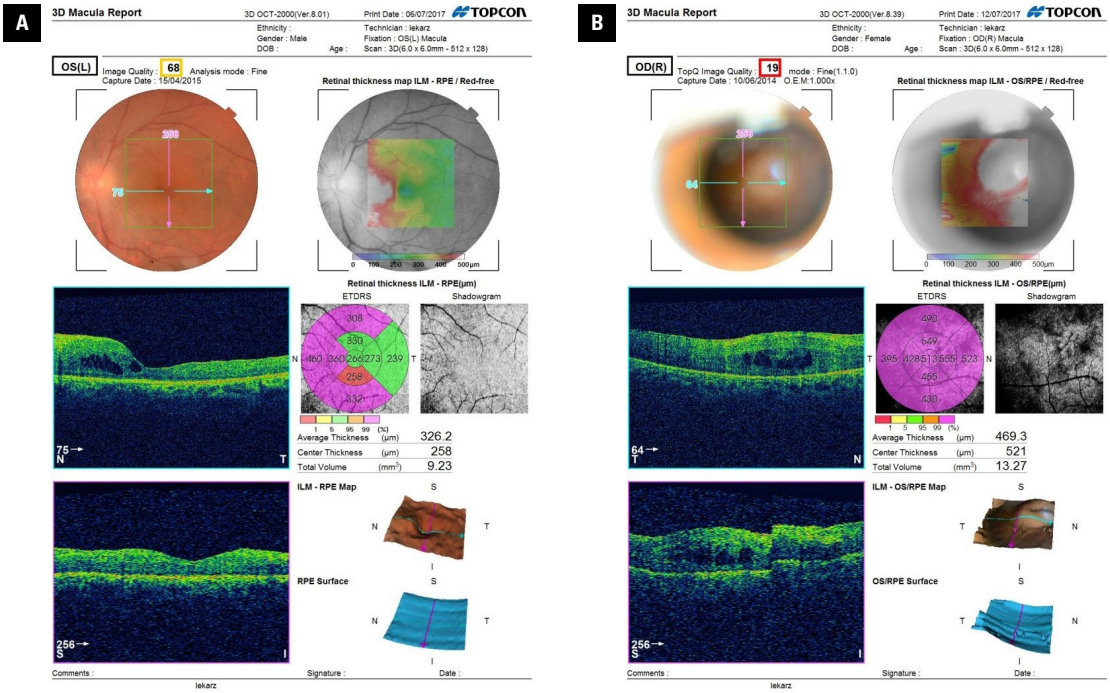

FIGURE 1AB. Optical coherence tomography (OCT) presenting cystoid macular edema (CME) in patients with autosomal dominant neovascular inflammatory vitreoretinopathy

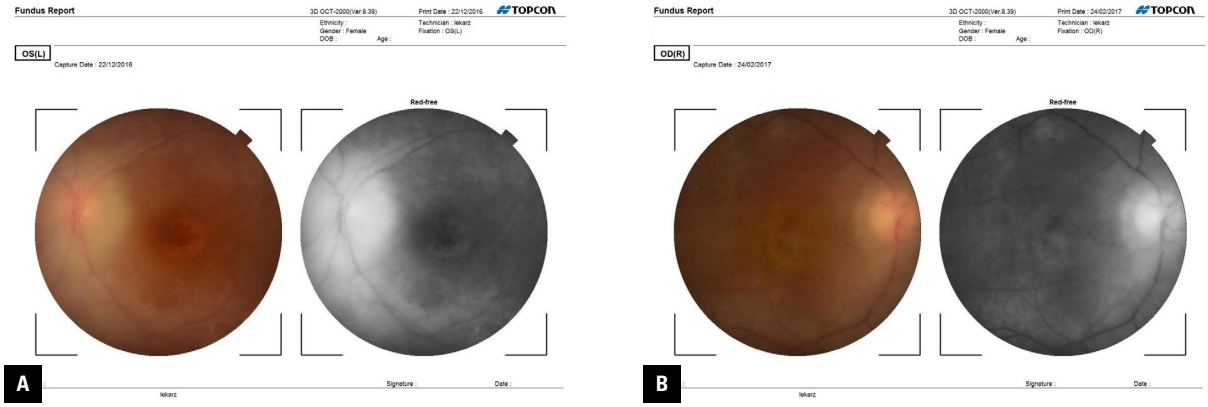

FIGURE 2AB. Fundus images showing vitritis in a patient with autosomal dominant neovascular inflammatory vitreoretinopathy

In stage four neovascular and angle closure glaucoma caused by inflammation in the anterior chamber is observed; next, epiretinal membranes formation and proliferative vitreoretinopathy starts. Profound visual loss is due to ongoing neovascularization of the retina that causes vitreous hemorrhage, tractional retinal detachment and neovascular glaucoma. In the last fifth stage, the eyes become hypotonous and subsequently phthisical, leading to complete blindness.

Patients with ADNIV have night blindness only as a very late manifestation of the disease. There is no evidence for systemic autoimmune or systemic inflammatory conditions in ADNIV patients.

The development of secondary glaucoma is observed in ADNIV patients. The IOP management is connected with uveitic glaucoma, steroid-response glaucoma, angle closure glaucoma and hypotony. The chronic uveitis can cause aqueous hyposecretion, due to inflammation of the ciliary body, but this IOP-lowering effect is usually overpowered by the increased resistance to trabecular drainage from inflammatory infiltrates and endothelial dysfunction [15]. Necessary steroids therapy is the result of

steroid-induced glaucoma. Furthermore, development of neovascularization in the anterior chamber causes angle closure glaucoma. In late stages, some ADNIV eyes become hypotonous [15]. Interestingly, some ADNIV patients do not develop elevated IOP or glaucoma despite decades of ADNIV and steroid therapy.

The rate of disease progression, specific features and vision loss vary between the affected members of a given family and is also asymmetrical between eyes. For example, some of the ADNIV patients develop blindness in one eye before the other, remaining partially sighted for years [16].

PATHOPHYSIOLOGY

Autosomal dominant neovascular inflammatory vitreoretinopathy is also an autoimmune disorder but pathophysiology and immunopathology is not well known. Immunohistological stain revealed T-cell infiltrated in ADNIV patients; hence, there is a suggestion that T-cell may play main role in immunopathology of the disease [17]. No specific antibodies were detected in ADNIV patients so far. It was noted that despite organ atrophy in the late stages of the disease, antigen reactions may still be active. The phthisis in the ADNIV eye seems to be immunologically different from that observed in eyes with phthisis from other conditions [17]. It is reported that cell-mediated rather than antibody-mediated autoimmunity may be the primary inflammatory mechanism [17]. Studies of human autopsy eyes indicated that ADNIV uveitis is primarily driven by cell-mediated immunity [12]. The vitreous biopsy revealed that interleukin-6 was elevated, suggesting a stimulated inflammatory or autoimmune response [12].

The physiologic role of calpain-5 is not well known. Calpain-5 was found to be located in the inner and outer segments of the photoreceptor cells and also within the outer plexiform layer [13]. The mutations alter its location inside the cells and probably its proteolytic activity or specificity. So CAPN5 could account for the various inflammatory degenerations, vascular and fibrotic phenotypes observed in ADNIV patients. Wert et al. report that the effect of the ADNIV mutation is to increase CAPN5 catalytic activity. This insight was next supported by physiologic testing of the CAPN5(R243) mutation in vivo [12]. Increased calpain activity is a feature of many eye-related pathologies including retinal degeneration, retinal hypoxia, retinitis pigmentosa, retinal detachment and glaucoma [18]. Retinal damage from these pathologies can be lessened by administering the calpain inhibitor SJA6017, but it is not known which isoform(s) exert(s) an inhibitory effect [18]. CAPN5 is widely expressed in the human body in the colon, kidney, liver, trachea, uterus, eye and brain, but the ADNIV is restricted just to the eye [13]. Retinal expression of CAPN5 may be sufficient to generate an autoimmune response. Study of CAPN5 mutations can provide insight into mechanisms of this disease and help us develop treatments for ADNIV and more common eye diseases with inflammation and neovascularization. Calpains have been implicated in the pathogenesis of different diseases including cancer, multiple sclerosis, Alzheimer's disease, cataract, diabetes and muscular dystrophy [3]. Several human neurological disorders have been associated with excess calpain activity. Wort et al. generated transgenic mice expressing human CAPN5(R243L) only in the retina and observed a clinical, histologic and molecular phenotype consistent with human ADNIV [12]. This mouse model can be used to explore protease mechanism, disease progression and possible therapies and have utility for other types of uveitis.

Uveitis in ADNIV is characterized by infiltrating CD3+ and CD4+ inflammatory cells in the vitreous, the uvea and the retina, suggesting a predominantly T-cell process [13, 6]. Mutation in calpain-5 causes both early CD3+, T-cell migration into the retina and reduction in ERG b-wave amplitudes and later photoreceptors degeneration.

The Mahajan et al. described enucleated eye of ADNIV patient due to phthisis and pain. Examination of the enucleated eye revealed a shrunken distorted phthisical globe. The intraocular contents were grossly disorganized. A segment of optic nerve was unremarkable. The cornea was depressed, brown and opaque, anterior chamber filled with hemorrhage. The posterior segment showed a vitreous filled with a red-brown material, a detached retina and subretinal hemorrhage. The optic nerve was atrophic with replacement of axons with collagenous bands. The iridocorneal angle was occluded by fibrous membranes. The retina showed extensive degeneration and retinal pigment epithelium significant cell loss [6].

Despite organ atrophy in the late stages of disease, antigens that instigate autoimmune reactions may still be active. The ADNIV autoimmune reac-

tion continues through end-stage disease when the eye becomes shrunken and blind [17].

The molecular mechanisms that initiate neuroinflammation are poorly understood.

Immunological mechanisms in the eye are also poorly understood.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis should include autoimmune uveitis, retinitis pigmentosa, rod-cone dystrophy, proliferative vitreoretinopathy and diabetic retinopathy [8, 13, 19, 20]. At different stages ADNIV mimics this diseases but most of them are characterized with systemic features otherwise then in ADNIV. Comparing neovascularization seen in proliferative diabetic retinopathy and ADNIV, significant capillary dropout or evidence of ischemia is absent in ADNIV. This suggests that a non-ischemic signaling pathway activates neovascularization. There is not a crisp demarcation line of vascular closure in the peripheral retina as can be seen in other peripheral retinal vascular diseases [8].

Retinal pigmentation in ADNIV begins in the area of vascular closure and becomes large deep round spots rather than the bone spicule pattern in the midperiphery seen in retinitis pigmentosa.

Another disease to be considered in the differential diagnosis is familial exudative vitreoretinopathy. In this condition, we observe abrupt termination of the retinal vessels at the equator. Vessels probably never develop normally. In contrast, ADNIV patients initially have normal vessels which gradually become occluded. Another difference is absence of vitreous cells and loss of the b-wave on ERG testing in patients with familial exudative vitreoretinopathy [8].

There are other conditions in which we observe a selective loss of the b-wave, including retinal vascular diseases such as central retinal artery or vein occlusions, quinine and methanol intoxication and siderosis. Inherited conditions in which the b-wave is affected include X-linked retinoschisis, myotonic dystrophy and forms of nonprogressive night blindness [8].

Autosomal dominant neovascular inflammatory vitreoretinopathy is a unique eye disease, because it shows pathological symptoms of several eye diseases that normally do not occur together. Recognition of familial nature of ADNIV is very helpful to diagnose properly.

The disorder is dominant, highly penetrant and displays severe and different phenotype. Phenotypic discordance may be due to epigenetic, postzygotic or environmental differences [16].

TREATMENT

Treatment of ADNIV patients is very difficult and many of them are refractory to it. One of the major reasons is a chronic, severe and non-specific autoimmune uveitis in the course of ADNIV. Another reason is iris and retina neovascularization leading to hemorrhage and fibrosis causing tractional retinal detachment and ongoing outer retinal degeneration.

Uveitis accounts for as much as 10–15% of blindness in the USA and is the fifth leading cause of vision loss in developed world. The management of uveitis is often ineffective especially in non-specific uveitis, like in ADNIV patients [14]. Immunohistopathological findings suggest that underlying ocular immune dysfunction is present. The treatment should be directed at major causes of profound vision loss such as photoreceptor degeneration, cataract, cystoid macular edema, vitreous hemorrhage, dense membrane formation leading to tractional retinal detachment, neovascular and steroid-responsive glaucoma.

Initial proceeding of ADNIV is directed to reduce active inflammation in anterior and posterior segment and prevent serious complication of ongoing inflammation and neovascularization. The therapy of ADNIV involves steroids including topical, periocular and intravitreal injections. Long term local and systemic therapies are limited because of the numerous side effects like cataracts, infections and glaucoma. Periocular and intravitreal steroids require injections at regular intervals in order to control inflammation and cystoid macula edema. Some authors report the benefit of the fluocinolone acetonide (FA) implant in the treatment of chronic uveitis in ADNIV patients [14]. It provides continuous release of intraocular corticosteroid for approximately 2.5 years. It is surgically implanted through the pars plana into the vitreous and sutured to the sclera. FA implant reduces inflammation, neovascularization and, which is important, the need for systemic or local therapy, but it does not stabilize long-term vision, retinal thickening and fibrosis [21]. The corticosteroid therapy in ADNIV is a non-specific therapy. Like some other uveitic conditions, AD-

NIV eventually becomes resistant to conventional steroid immunosuppression.

This nonspecific therapy might be optimized by medications directed at the specific mediators of ADNIV. One study suggests that therapeutic strategies targeting T cells may be more effective than nonspecific therapy. For example drugs such as cyclosporin A, FK06, anti-CD3 and rapamycin that target T cell activation and downstream T cell pathways might have greater effect than B cell drugs such as cyclosphamide and mycophenylate mofetil [17].

Treatment of ongoing iris and retinal neovascularization apart from steroids therapy includes also anti-VEGF medication. Some authors reported applying of bevacizumab for recurrent uveitis [15]. The laser photocoagulation of the peripheral retina is only partially effective. Likewise, vitrectomy surgery is related to recurrent membranes and detachments.

ADNIV patients could be candidates for retinal gene therapy, but if disease allele expression in the eye is not sufficient, therapies directed to cells outside the eye as calpain-5 expressing T-cells might be required [13].

There is no therapy for retinal degeneration and there are no specific therapies for calpains [13]. To develop specific treatment for ADNIV an animal model is needed [13].

The development of secondary glaucoma is associated with the need of applying antiglaucoma therapy. Management of glaucoma in ADNIV patients can be challenging. Antiglaucoma medications include topical medication, surgeries like trabeculectomy, Ahmed glaucoma valve surgery. Some authors report better results performing AGV concurrent with the FA implantation [15].

Maybe earlier therapy with T-cell immunomodulators will be more successful. Specific therapy may delay or reverse symptoms in ADNIV and also in related eye diseases.

Untreated or under-treated patients have very poor prognosis.

CONCLUSION

Autosomal dominant neovascular inflammatory vitreoretinopathy is a complex hereditary autoimmune disorder. The disease management poses several challenges like diagnosis, follow-up and in particular treatment. Recognition of the condition is important because it allows proper genetic counselling and prevents unnecessary diagnostic investigations. Despite the aggressive treatment the visual improvement is only transient — as the disease progresses patients progressively lose vision. ADNIV patients need careful, continuous long-term follow-up to address ongoing chronic inflammation, membrane formation, neovascularization and retinal degeneration.

To better understand ADNIV pathogenesis further investigations including immunology, physiology and genetic are necessary.

Immunohistopathological findings suggest that an underlying ocular immune dysfunction is present in ADNIV patients. The creation of a pre-clinical model of ADNIV could be used to study mechanisms of ADNIV disease progression and therapy.

Further study of mechanisms of ADNIV will provide important new insight into some of the most important causes of irreversible human blindness, such as autoimmune uveitis, retinitis pigmentosa, proliferative vitreoretinopathy and diabetic retinopathy. In-depth investigation of this disorder will hopefully lead to better understanding of its pathogenesis and ultimately result in effective treatment.

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CASE REPORT
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Bilateral exudative retinal detachment in a patient with end-stage renal disease — a case report

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ABSTRACT

End-stage renal disease (ESRD) is one of the most severe chronic kidney diseases occurring with a frequency of 0.1% in the general population. Patients with ESRD are more at risk of ocular complications, therefore cooperation between a nephrologist and an ophthalmologist is recommended. The most common complaints associated with the eye include the conjunctival chemosis, keratopathy, macular edema, optic neuropathy, elevated intraocular pressure and exudative retinal detachment.

In this article, a case report of bilateral exudative retinal detachment in patients with the end-stage renal disease is presented.

KEY WORDS: end-stage renal disease; exudative retinal detachment

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INTRODUCTION

End-stage renal disease (ESRD) is the most severe among chronic kidney diseases requiring treatment with dialysis or kidney transplantation. The prevalence of ESRD in the general population is 0.1% [1, 2]. In 1836, Richard Wright first described the relationship between kidney disease and blindness [3]. The period of organogenesis for the eyes and kidneys covers the period from the fourth to the sixth week of pregnancy. Disorders in embryogenesis during this period may cause anatomical anomalies and functionalities of both organs [4]. Some inborn renal disorders can lead to ESRD. Patients with end-stage renal disease are more at risk of eye complications. The most common complaints associated with eye include conjunctivitis, keratopathy, macular edema, ischemic optic neuropathy, elevated intraocular pressure, retinal detachment and retinal hemorrhage [5].

In this article, we present a case report of exudative retinal detachment in a patient with end-stage renal disease.

CASE PRESENTATION

A 31-year-old female reported to the Nephrology Department of Hospital in Zamość due to end-stage renal disease caused by glomerulonephritis. Her medical history informed that she had been treated for chronic glomerulonephritis for 9 years. Moreover, hypertension and diabetes type 2 was diagnosed, she had also had a NSTEMI infarction and caesarean section due to preeclampsia in the past. The laboratory results were as follows: creatinine 10.6 mg/dL, urea 165 mg/dL, erythrocytes 2.61 million/uL, hemoglobin 7.98 g/dL, electrolytes were Na 140.6 mmol/L and K 5.30 mmol/L, D-dimers 15371 ng/mL, 4.8 mg% glycated hemo-

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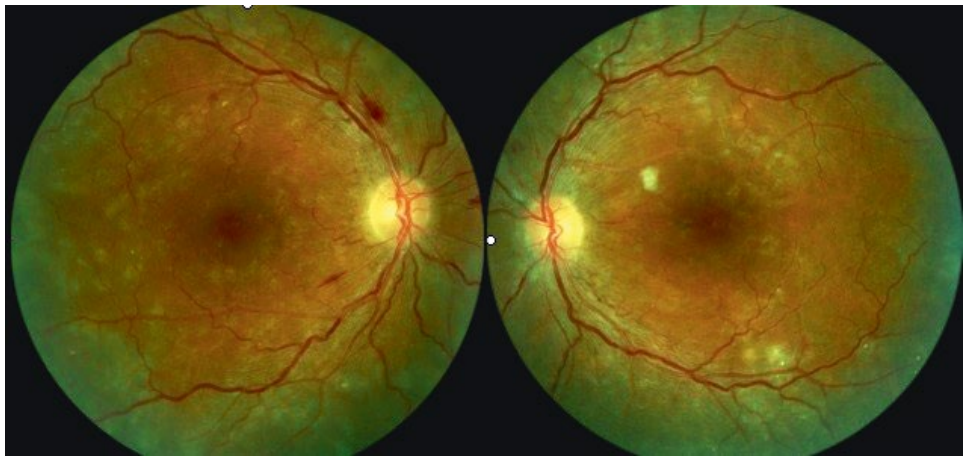

FIGURE 1. The fundus examination of both eyes showing hyperemic discs and multiple pockets of subretinal fluid in the posterior pole of both eyes

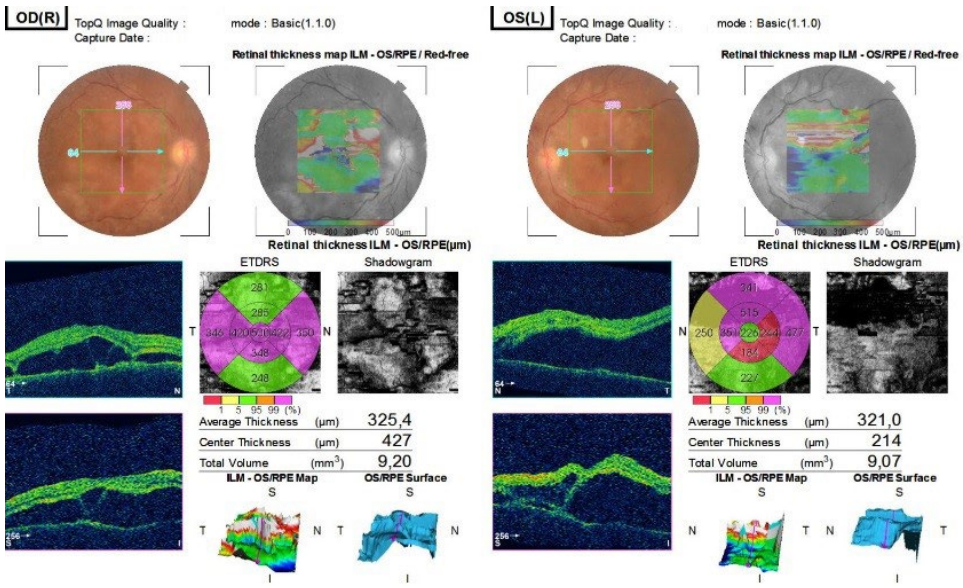

FIGURE 2. OCT scans showing fluid under the sensory retina in the macular region of both eyes

globin and diurnal urine collection showed proteinuria. Her blood pressure was 180/100 mm Hg. The patient was selected for dialysis. The patient showed hypoproteinemia in the blood (5.96 g/dl) and hypoalbumienemia (2.90 g/dl) after 3 dialyses. The patient was consulted ophthalmologically due to a sudden bilateral deterioration of vision. The best-corrected visual acuity (BCVA) was 0.075 in the right eye and "hand motions" the left eye. The intraocular pressure was 10 mm Hg in both eyes. Ophthalmological examination showed normal anterior segment, normal optic disc, retinal detachment with macular involvement, retinal hemorrhages and hard and cotton ball exudates, winding venous vessels and arteriovenous crossings (Fig. 1). The examination optical coherence tomography (OCT) and B scan of ultrasound examination confirmed the presence of retinal detachment (Fig. 2, 3). The patient was advised to continue dialysis and received prednisone 30 mg orally. The patient was disqualified from fluorescein angiography due to a general health condition. Thus, OCT-angio examination was performed and showed abnormal microvasculature of the retina (Fig. 4). The patient underwent 13 dialyses during a 17-days of hospital follow-up. The BCVA was 0.5 in the right and 0.3 in the left eye on the day of discharge. The intraocular pressure was 7 mm Hg in the right and 5 mm Hg

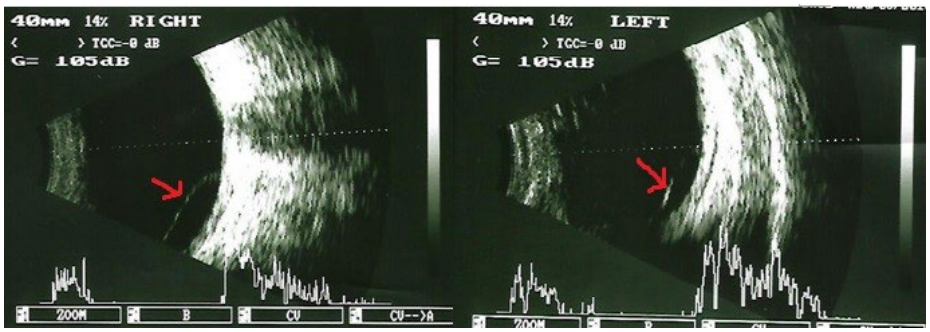

FIGURE 3. B-scan of ultrasound examination showing the retinal detachment in both eyes

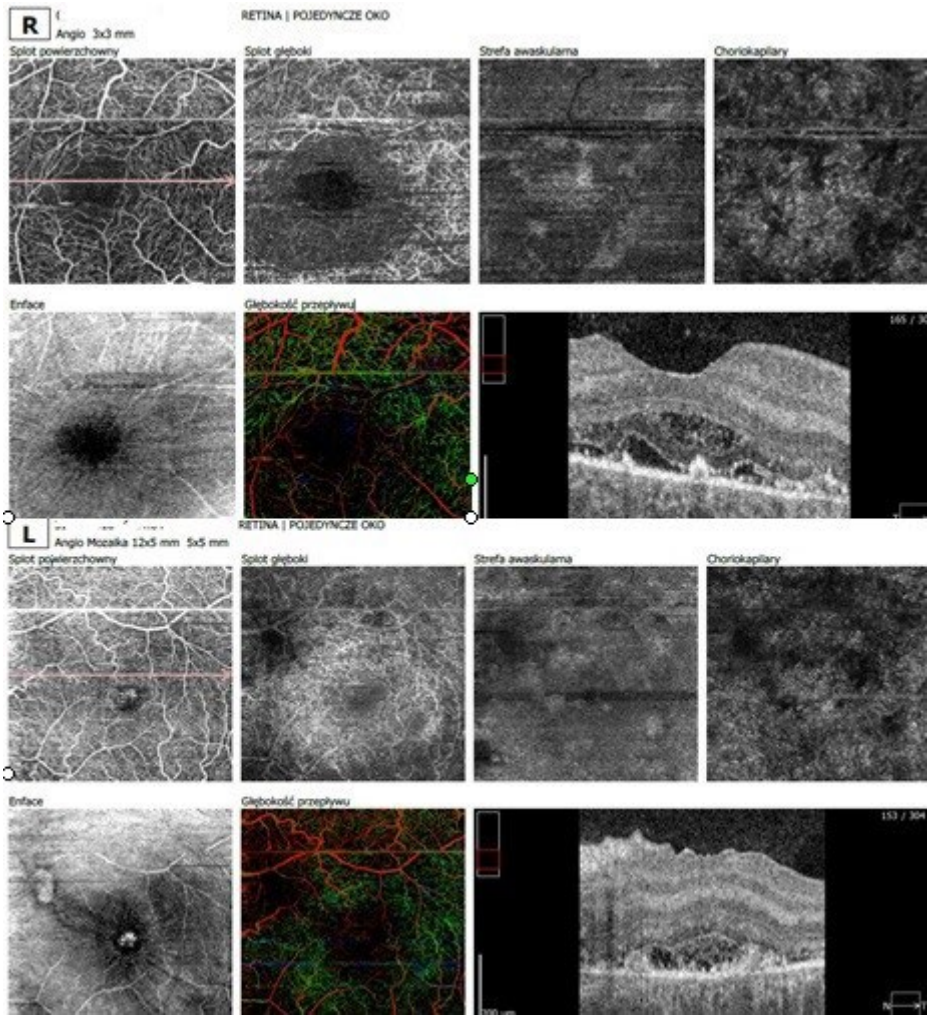

FIGURE 4. OCT-A scans showing abnormal retinal microvasculature of both eyes

in the left eye. The fundus examination of both eyes showed positive Gunn symptom, haemorrhages and retinal vascular tortuosity, retinal detachment in the lower quadrants of the retina. We observed partial resorption of subretinal fluid in the OCT. The patient was discharged on 15 mg prednisone from the hospital. The BCVA was 0.4 cc and 0.4 cc in both eyes after one month. The fundus examination of both eyes showed venous and arteries hardened and winding, positive Gunn symptom, an increase of haemorrhages in the retina and partial resorption of subretinal fluid in lower quadrants (Fig. 5). OCT

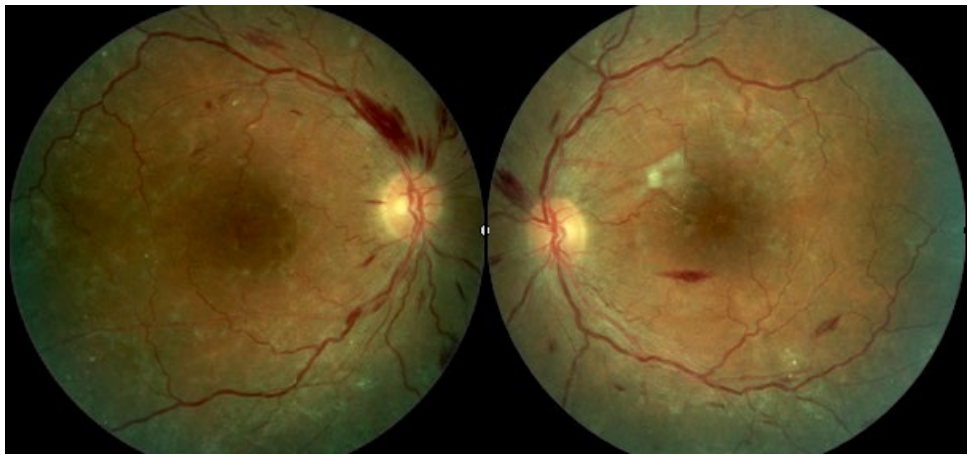

FIGURE 5. The fundus examination after one month showing hyperemic discs, intraretinal hemorrhages, hard and soft exudations, yellowish placoid lesions and narrowed arterial and venous blood vessels of both eyes

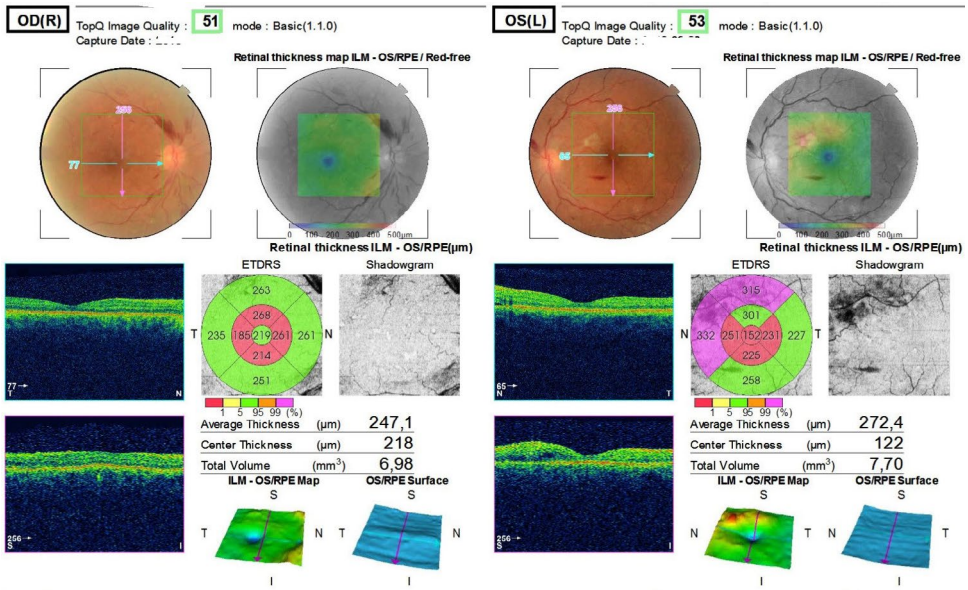

FIGURE 6. OCT scans after one month showing adhesion of the retina in the macular region of both eyes

showed an adhesion of the retina in the macular area (Fig. 6). A slight elevation of neurosensory retina occurred in the lower quadrants of the retina, which was confirmed by B-scan ultrasound (Fig. 7). The patient is still under strict ophthalmological and nephrological control.

DISCUSSION

End-stage retinal disease (ESRD) is associated with the potential risk of ocular complications, among others exudative retinal detachment (ERD). ERD occurs when the neurosensory retina separates from the retinal pigment epithelium leading to the visual impairment. The cause of the exudate is often not unequivocal, it may be present due to increased permeability and perfusion of the choroidal vessels, disorders of retinal pigment epithelium retention or changes in osmolarity and in a consequence fluid shift between different spaces. The potential causes of ERD should consider idiopathic, vascular, neoplastic, postsurgical, uveitis, systemic inflammatory diseases and infectious diseases [5, 6]. It is important to find the reason of differentiation, whether exudation is caused by primary ocular pathology or secondary in the course of the systemic disease. Ocular causes include intraocular tumours and posterior scleritis [7].

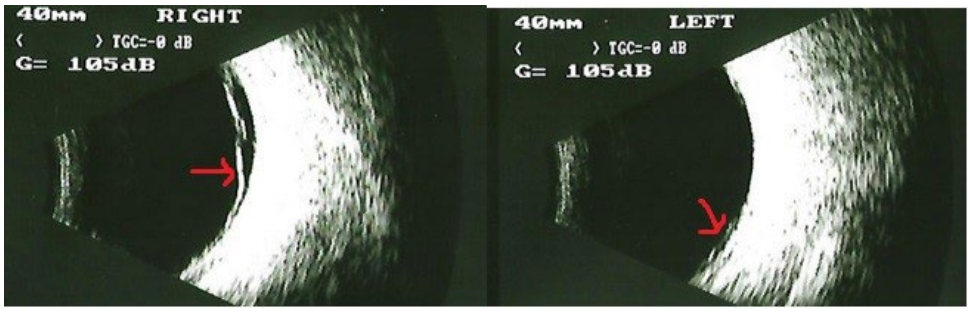

FIGURE 7. B-scan of ultrasound examination after one month showing the retinal detachment in the lower hemisphere of the retina of both eyes

Vogt-Koyanagi-Harada syndrome (VKH) should also be considered in the differential diagnosis of ERD. VKH is systemic inflammation with ophthalmic, neurological and skin lesions caused by an immune response to melanocytic cell antigens [8]. It usually affects young women. Its characteristic feature is a presence of bilateral serous retinal detachment including a macula and an increase degrees of vitreous cells. Zalts et al. described two cases of VKH syndrome development in long-term IgA nephropathy. The authors suggest a similar autoimmune mechanism of both diseases [9].

The literature also includes several reports on the relationship between bilateral exudative retinal detachment secondary to preeclampsia during pregnancy [10].

The bilateral retinal detachment may also be associated with a secondary factor in kidney disease, for example, hypertensive chorioretinopathy [11, 12]. A sudden increase in blood pressure may lead to vasoconstriction and ischemia of the retinal pigment epithelium (Elschnig spots) and consequently allow leakage into the subretinal space contributing to the ERD. Villalba-Pinto et al. reported the case of a 26-year-old man with bilateral massive serous retinal detachment on the background of high blood pressure associated with chronic IV renal failure. The subretinal fluid was resorbed as a result of a dialysis treatment with oral antihypertensive drugs [13, 14]. In our case, we observed changes characteristic for hypertensive retinopathy as a retina haemorrhages, soft and hard exudates, enlarged and twisted vessels and positive Gunn symptom. Pino et al. demonstrated on animal studies that hypoalbuminaemia causes a decreases osmotic pressure which affects a passage of fluid into the subretinal space [15]. The literature also describes cases of bilateral retinal detachment secondary to hypoalbuminemia [16, 17]. Wong et al. presented a description of three cases of exudative retinal detachment because of hypoalbuminemia [18].

CONCLUSION

In this paper author reported the case of a young woman with bilateral exudative retinal detachment secondary to end-stage renal disease. The cause of ERD is often complex and multifactorial. Patients with ESRD require close cooperation between a nephrologist and an ophthalmologist due to the risk of potential ocular complications.

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CASE REPORT
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Eales' disease

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ABSTRACT

This is a case report of a patient diagnosed with Eales' disease. Characteristics, etiology and symptoms will be described in this study. Moreover, we will present case of a 61-year-old woman and discuss the clinical features, treatment plan and its outcome in our patient.

KEY WORDS: Eales' disease; vitreous haemorrhage; floaters

Ophthalmol J 2019; Vol. 4, 28–30

INTRODUCTION

Eales' disease was first described by the British ophthalmologist in 1880 by Henry Eales, who thought that it is a non-inflammatory condition. The definition and etiology of Eales' disease are not adequately established [1]. In recent years, clinical and basic research, have provided significant clues to the understanding of the clinical features and etiology of Eales' disease [2]. It is an idiopathic peripheral retinal vasculopathy characterized by three overlapping stages of venus inflammation (vasculitis), occlusion and retinal features [2]. Other features of the disease are phlebitis, dilated aneurismal changes, shunt vessels and even macular edema [3]. Patients may present with decreased vision, photopsia and floaters unilaterally or bilaterally. Its etiology appears to be multifactorial [5]. It is claimed that hypertensive patients are prone to have this disease. The management depends on the stage of the disease and consists of medical treatment with oral corticosteroids in the active inflammatory stage and laser photocoagulation in the advanced retinal ischemia and neovascularization stages [5].

CASE REPORT

A 61-year-old woman complaining about floaters. Floaters caused by the mild vitreous haemorrhage. Her best corrected visual acuity (BCVA) was 20/20 in both eyes. The image we got through the OCT (Spectralis HRA+OCT, Heidelberg Engineering, Germany), revealed a preretinal haemorrhage in her left eye at her lower vascular arcade (Fig. 1).

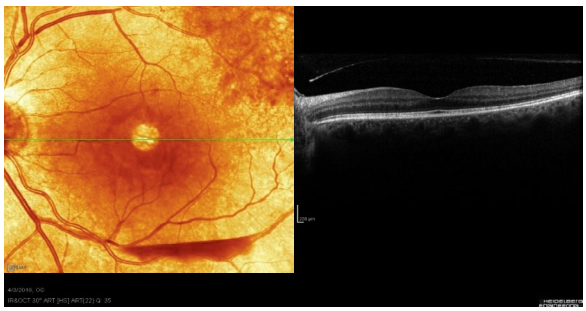

FIGURE 1. Left eye macula's image through the OCT imaging

The patient informed about her personal case history with hypertension and hereditary glaucoma coming from her father's side. Dr. Mallias decided that a multicolor imaging and a fluorescein angiography were essential in order to fully diagnose the case (Fig. 2).

The fluorescein angiography demonstrated abnormal staining in areas of vascular sheathing [6]. At the early stage of the examination, an area of hypo-fluorescence at the lower vascular arcade was found, which was attributed (Fig. 3) to a preretinal haemorrhage. Moreover, supertemporal to the macula an area of extended retinal ischemia was ob-

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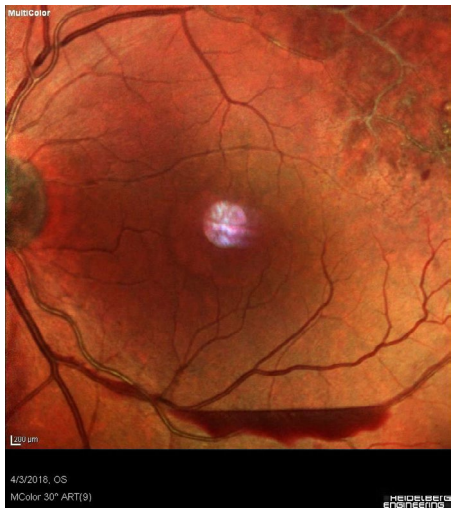

FIGURE 2. Left eye's image through the multicolor imaging

served, as well as the existence of multiple collateral vessels, in which small areas of focal hyper-fluorescence were found, being attributed to minor aneurisms. At the late stage of the examination, leakage of the fluorescence dye substance was observed which was attributed to retinal neovascularization. In addition, there was a leakage of the dye substance through the inner side of the veins of the retina. We performed a tuberculin test which turned out to be negative.

Argon laser photocoagulation was performed solely on the ischemic part of the retina. Three months later, we proceeded to a new fluorescein angiography where we observed that there was no retinal neovascularization. Furthermore, we noticed an improvement in the condition of the vessels and no vitreous haemorrhage occurred ever since.

DISCUSSION

The findings are compatible with Eales' disease, which is found at the late stage of retinal

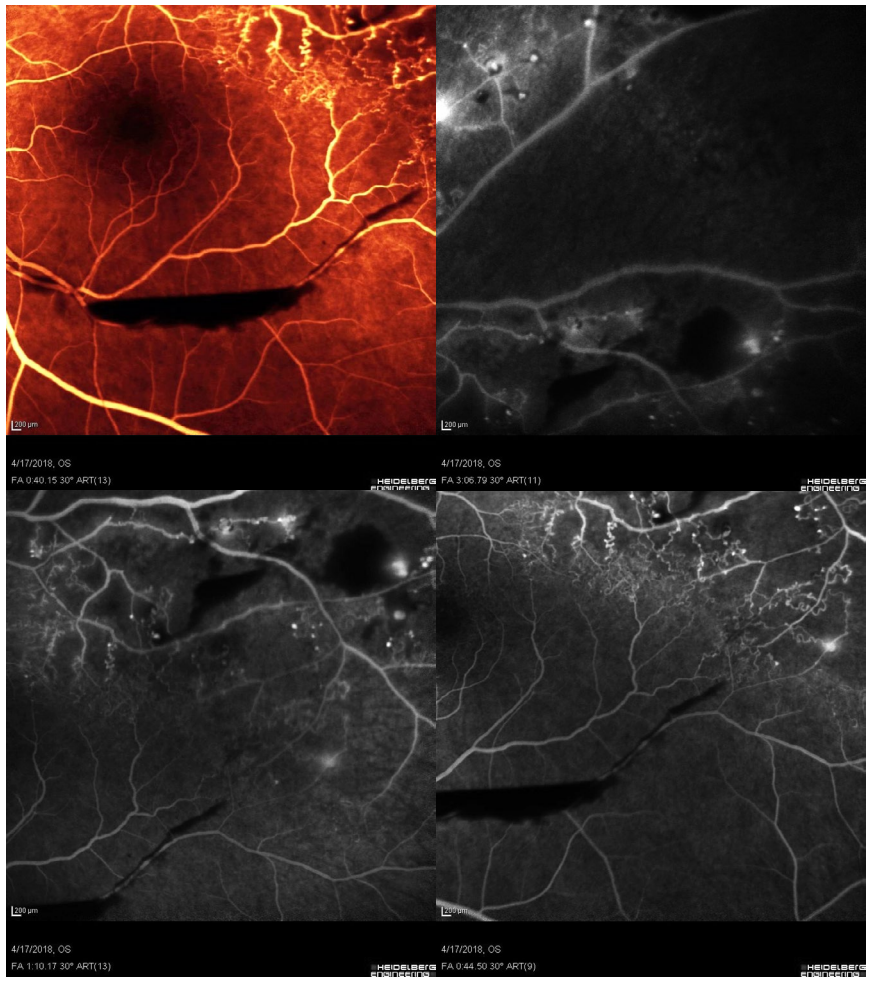

FIGURE 3. Left eye's image through the fluorescein angiography

ischemia accompanied by retinal neovascularization. The application of Argon Laser photocoagulation solely on the affected by ischemia area of the retina is recommended. With vascular non-perfusion and retinal neovascularization, intravitreal anti-VEGF therapy may be successful, however, its effects may cause vitreoretinal contraction [7]. In patients with exposure to tuberculosis, anti-tubercular therapy can be given for 9 months, but this is reserved for patients with massive infiltration, nodule formation, and venous obliteration. For non-resolving vitreous haemorrhage and/or retinal detachment (whether tractional, rhegmatogenous or combined), pars plana vitrectomy is necessary, with or without other vitreoretinal surgical procedures [8]. Endolaser treatment may be applied at the time of surgery. Vitrectomy for non-resolving vitreous haemorrhage should be performed no later than 6 months following onset of haemorrhage [9].

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CASE REPORT
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Autosomal dominant neovascular inflammatory vitreoretinopathy — a case series

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ABSTRACT

The objective of our study was to report the course of the disease in a family affected with autosomal dominant neovascular inflammatory vitreoretinopathy (ADNIV, OMIM#193235). ADNIV is a very rare inherited blinding disease due to mutations in CAPN5 gene.

We assembled a retrospective observational case series of ADNIV patients. We noticed first symptoms in different ages, similar course of the disease and its progression leading in most cases to complete blindness despite treatment.

KEY WORDS: autosomal dominant neovascular inflammatory vitreoretinopathy; ADNIV; uveitis; neovascularization; proliferative vitreoretinopathy; cystoid macular edema; CAPN5; calpain-5

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INTRODUCTION

Autosomal dominant neovascular inflammatory vitreoretinopathy (ADNIV) is an autoimmune uveitis belonging to inherited vitreoretinal dystrophies [1]. It is caused by the mutations in CAPN5 gene (calpain-5) located on chromosome 11q13 [2, 3]. The first scientific work describing ADNIV was published in 1990 by Steven Bennett and co-workers [4]. Autosomal dominant neovascular inflammatory vitreoretinopathy occurs with a frequency of approximately one in 1 000 000 births and has been found worldwide [5].

The first symptoms can appear at all ages [5]. Autosomal dominant neovascular inflammatory vitreoretinopathy is characterized by non-specific uveitis in the anterior chamber and vitreous leading to panuveitis, iris and retinal neovascularization, cystoid macular edema, abnormal retinal pigmentation, vitreous hemorrhage, intraocular fibrosis with membrane formation and tractional retinal detachment. Sometimes we observe the development of secondary glaucoma. It is due to uveitic glaucoma, steroid-induced glaucoma or angle closure glaucoma. The hypotony is also observed in ADNIV patients [6].

Unfortunately, despite treatment the disease is very progressive and often leads to complete blindness and, subsequently, phthisis. Another characteristic sign of ADNIV is loss of the b-wave amplitude and photoreceptors' degeneration on electroretinography (ERG) recordings [3, 7].

CASE REPORT

A retrospective case series was assembled from the medical reports of ADNIV patients from 1988 to present (2019). We reviewed the course of illness in 7 of 20 members of a four-generation family affected by ADNIV disease — 2 sisters (Patient 1 — P1, Patient 2 — P2), their father (Patient 3 — P3), father's two sisters (Patient 4 — P4, Patient 5 — P5), Patient's 5 daughter (Patient 6 — P6) and father's brother (Patient 7 — P7) (Fig. 1). All patients provided informed consent for taking part in this retrospective study. They were referred to our Department due to the suspicious of family vitreoretinopathy. Initially the diagnosis was based just on a typical clinical history and plotted pedigree by geneticist. The patients underwent a complete

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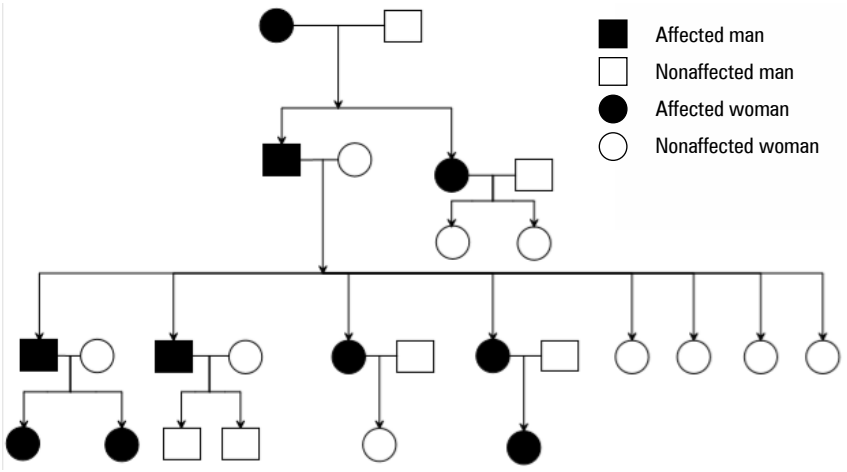

FIGURE 1. Family tree — affected and nonaffected members of the family

ophthalmological evaluation. Visual acuity assessment, slit lamp biomicroscopy and fundoscopy were performed. The image of macula was observed using the optical coherence tomography (OCT) and angioOCT. The fundus photographs were recorded. The patients were diagnosed using ERG testing (P1, P2) and were referred for genetic evaluation (P1, P2). The mutations in exon 6 of the CAPN5 gene were not found but this does not exclude the presence of ADNIV, because there are other not examined fragments of CAPN5 gene.

PATIENT 1

A 20-year-old woman with ADNIV has been followed up in our outpatient clinic since 2008. She was referred due to previous uveitis and gradual deterioration of visual acuity which started when she was 9. On examination, her best corrected visual acuity (BCVA) was 0.4 in the right eye (OD — *oculus dextra*) and 0.6 in the left eye (OS — *oculus sinistra*). Her anterior segment examination was normal in both eyes. We noticed inflammatory cells in the vitreous in both eyes. The posterior segment examination showed normal picture of optic discs and narrowing of the arteries. With progression of the disease, inflammatory cells in the anterior segment and vitreous increased. Her uveitis was managed with topical steroids. Because of the central macula edema (CME) in both eyes the subtenon triamcinolone acetate injections were performed 2 times in her OS (2010, 2014) and once in her OD (2010) (Fig. 2, 3AB). The cataract started to develop in both eyes. She was referred for ERG examination where progressive damage to the function of rods and cones was determined. On the following examinations we noticed chronic uveitis in the vitreous and intraocular fibrosis which obscured the view of her fundus.

Genetic examination performed in 2016 raised suspicion of autosomal neovascular inflammatory vitreoretinopathy. ERG testing in 2017 confirmed the diagnosis with reduced b-wave amplitudes and photoreceptors degenerations.

On the examination performed recently, her BCVA was 0.063 in OD and 0.08 in OS. Mild anterior segment uveitis was present. On fundus examination, we observed paler optic discs, narrowing of the arteries and veins, chronic CME and intraocular fibrosis.

She has been also treated due to hyperthyroidism for 3 years.

PATIENT 2

A 15-year-old girl was referred to our outpatient clinic for ophthalmological evaluation in 2006. Her three years older sister (Patient 1) was treated because of uveitis of unknown etiology and deterioration of visual acuity. On the first examination when she was 4 years old her visual acuity, the anterior and posteriori segments were normal. After 2 years of follow up, her BCVA decreased to 0.7 OD and 0.9 OS. As the disease progressed, inflammatory cells in the anterior segment and vitreous were noticed. It resulted in mild media opacity.

She was referred for genetic evaluation in 2016 where autosomal dominant neovascular inflammatory vitreoretinopathy was suspected. ERG testing in 2017 confirmed the diagnosis of ADNIV. It showed reduced b-wave amplitudes and photoreceptors degenerations.

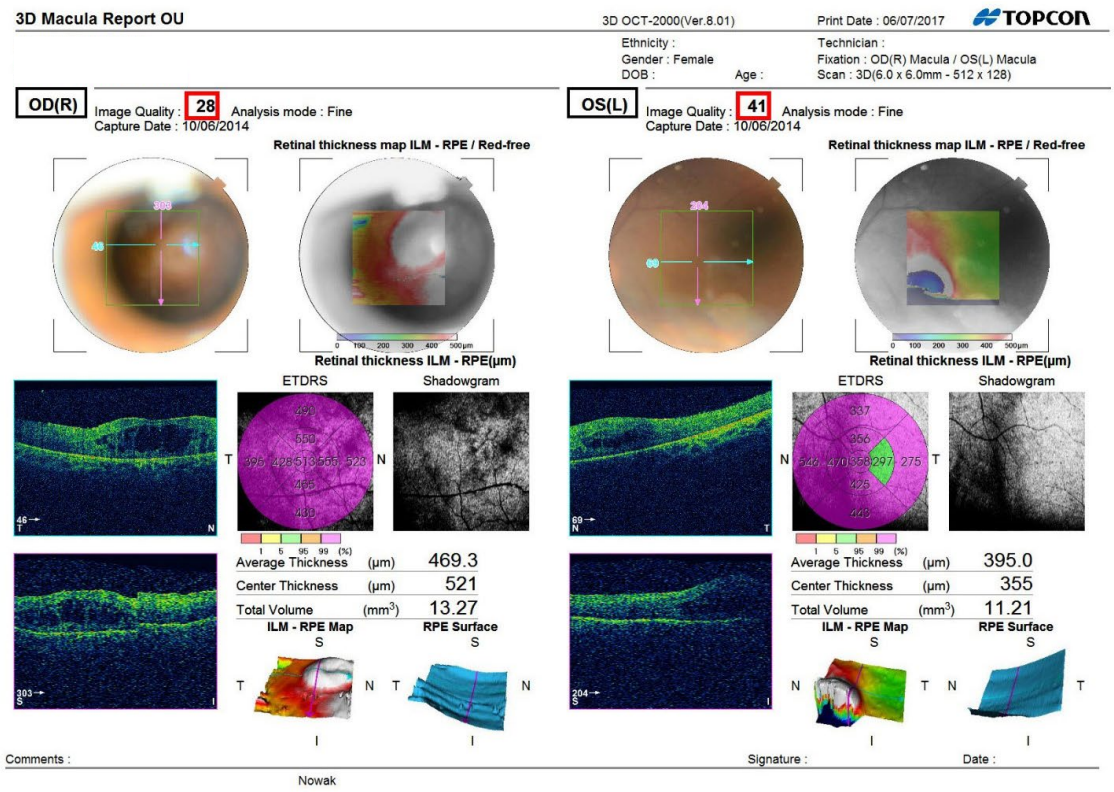

FIGURE 2. Patient 1 — cystoid macular edema in optical coherence tomography in 2014

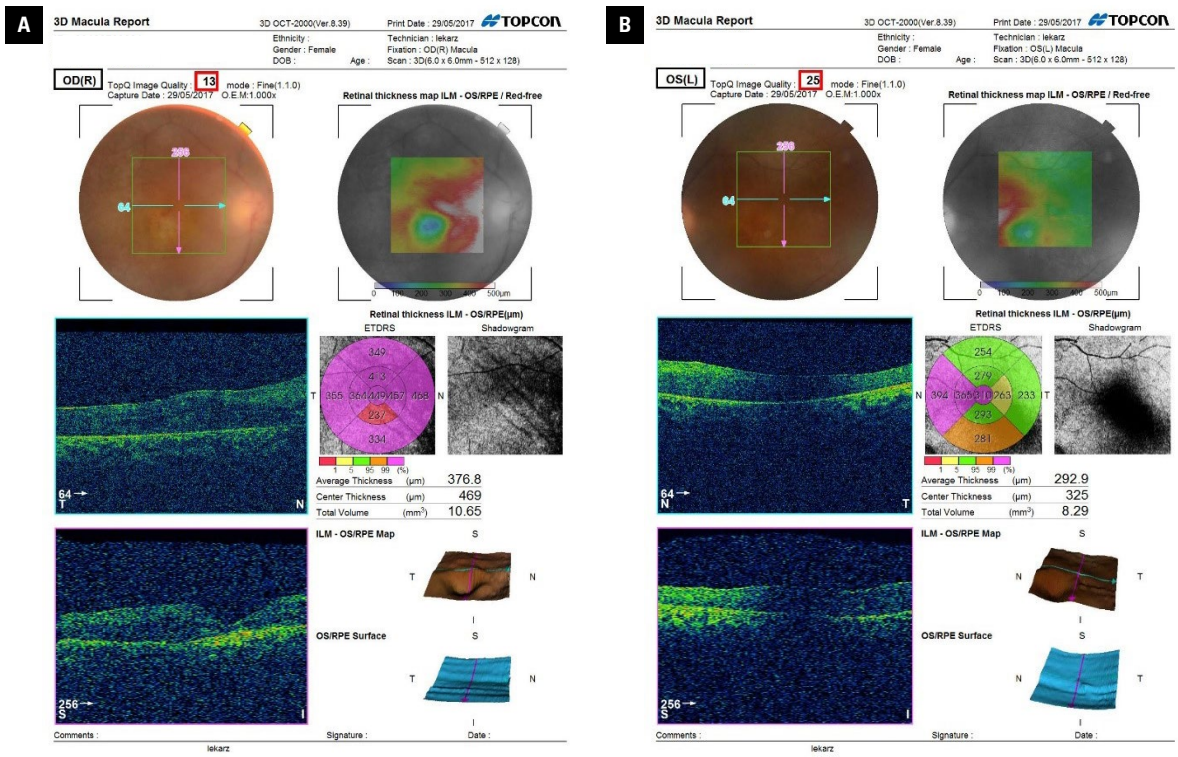

FIGURE 3AB. Patient 1 — cystoid macular edema in optical coherence tomography in the right eye (OD) and diminished central macula edema (CME) in the left eye (OS) in 2017

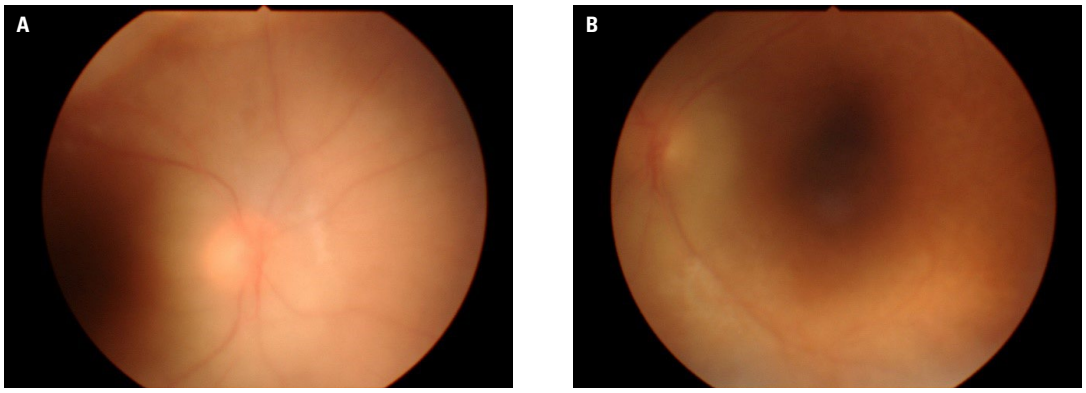

FIGURE 4AB. Patient 2 — obscured view of the fundus

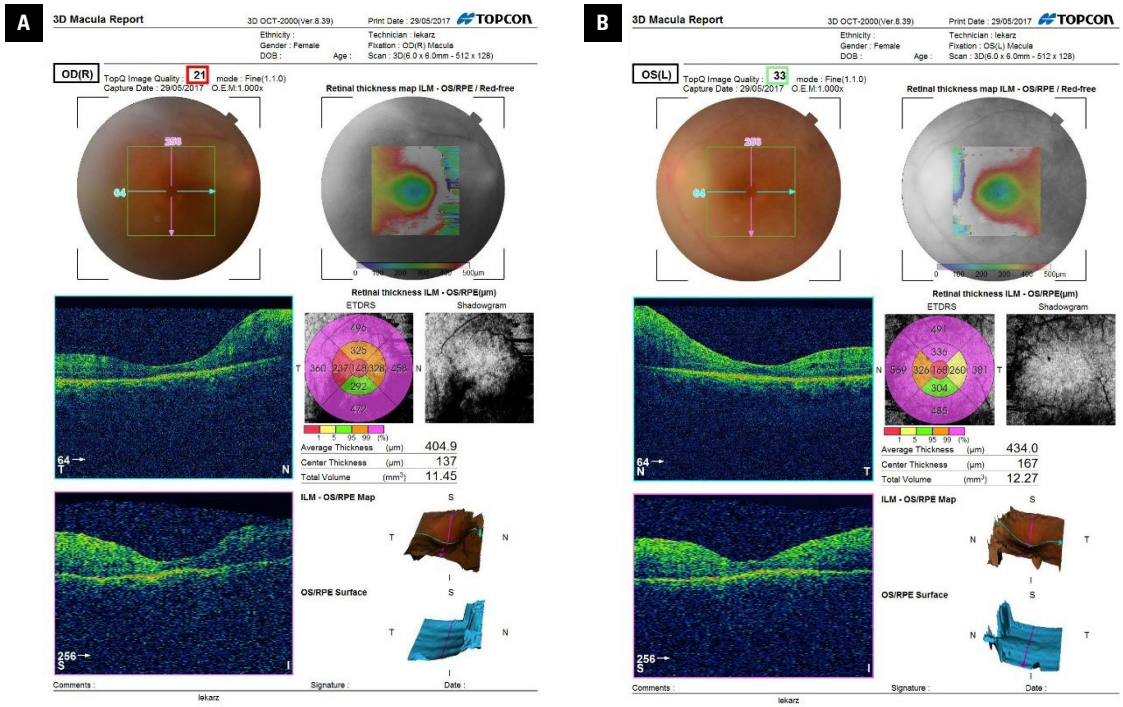

FIGURE 5AB. Patient 2 — thinning in the macula in optical coherence tomography in the right eye (OD) and the left eye (OS)

On the last examination, her BCVA was 0.7 in both eyes, the anterior segment was normal and significant uveitis in the vitreous was noticed. On her fundus examination, her optic discs were normal, whereas arteries and veins were narrowed (Fig. 4AB). The OCT examination revealed significant macular thinning in both eyes (Fig. 5AB).

She has been also treated for autoimmunological thyroiditis since 2014.

PATIENT 3

A 43-year-old man, a father of Patient 1 and 2. His first examination in our outpatient clinic was carried out in 2017. His visual acuity started to decrease when he was about 7 years old. Now he is blind. His OD vision is light perception and OS vision — no light perception. He is after cataract extraction with IOL implantation in his OD and mature cataract in his OS. The iridodonesis is visible due to subluxated lenses in both eyes. His pupils are distorted because of the posterior synechiae. Previously, he was treated due to glaucoma of both eyes. Now his eye pressure measurement was normal: 11 mm Hg in OD and 16 mm Hg in OS. The fundus examination was very limited because of the significant media opacity especially in OD

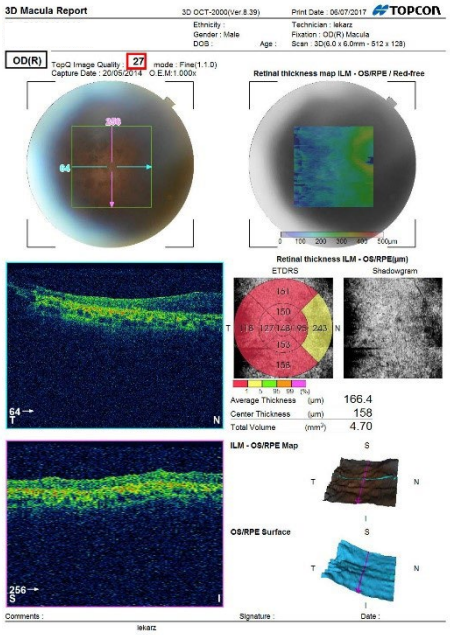

FIGURE 6. Patient 3 — thinning in the macula in optical coherence tomography

where the picture of the fundus was grey. In the OS, the optic disc was pale; very narrow arteries and veins and numerous pigment degenerations were visible (Fig. 6). Ultrabiomicroscopy B examination revealed vitreous tractions in OD (Fig. 7AB).

He was referred for genetic examination in 2005 together with his two sisters (Patient 4 and 5). The diagnosis of the familial inflammatory neurovitreoretinochoroidopathy was suspected.

He has been also treated for thrombocytopenia and splenomegaly.

PATIENT 4

A 45-year-old woman, a sister of Patient 3, was examined in our outpatient clinic in 2017. She is also blind, like her younger brother (Patient 3). Her visual acuity started to deteriorate when she was about 6 years old. In 1988, when she was 14 years old, she was diagnosed with hereditary neuropathy in both eyes. Her visual acuity was 0.1 in both eyes. It was treated frequently with intravenous steroids injections and oral steroids. Both eyes cataract was noticed in 2002. The familial neurovitreoretinochoroidopathy was suspected during genetic examination in 2005 (which she underwent together with her brother, Patient 3, and her sister, Patient 5).

Presently her visual acuity is no light perception in OD and light perception in OS. On the anterior segment examination we noticed iridodonesis due to subluxated cataract in both eyes. Grey picture of the fundus was caused by significant media opacity. Ultrabiomicrocopy B revealed intraocular fibrosis in both eyes.

She has been also treated for hypothyroidism since 2016. She underwent partially mastectomy in 2017.

PATIENT 5

A 32-year-old woman, a sister of Patient 3 and 4, was referred to our outpatient clinic in 2014 for ophthalmological examination. Her vision started to deteriorate when she was about 5 years old. In 2001, optic discs edema and uveitis in both eyes was determined. Her BCVA was 0.8 in both eyes. Her uveitis and papillitis was treated with intravenous and oral steroids. The toxoplasmosis [IgM (–), IgG (237)] was also diagnosed and treated in this year.

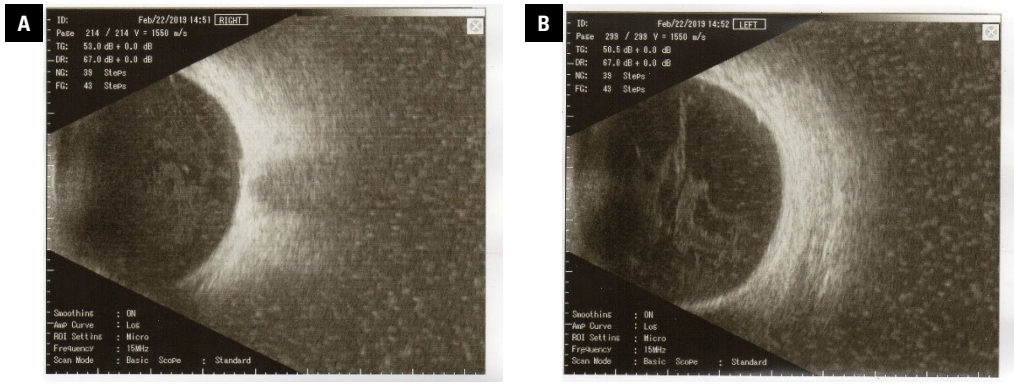

FIGURE 7AB. Patient 3 — increased density in the vitreous in the right eye (OD) and intraocular fibrosis in the left eye (OS) in ultrabiomicroscopy

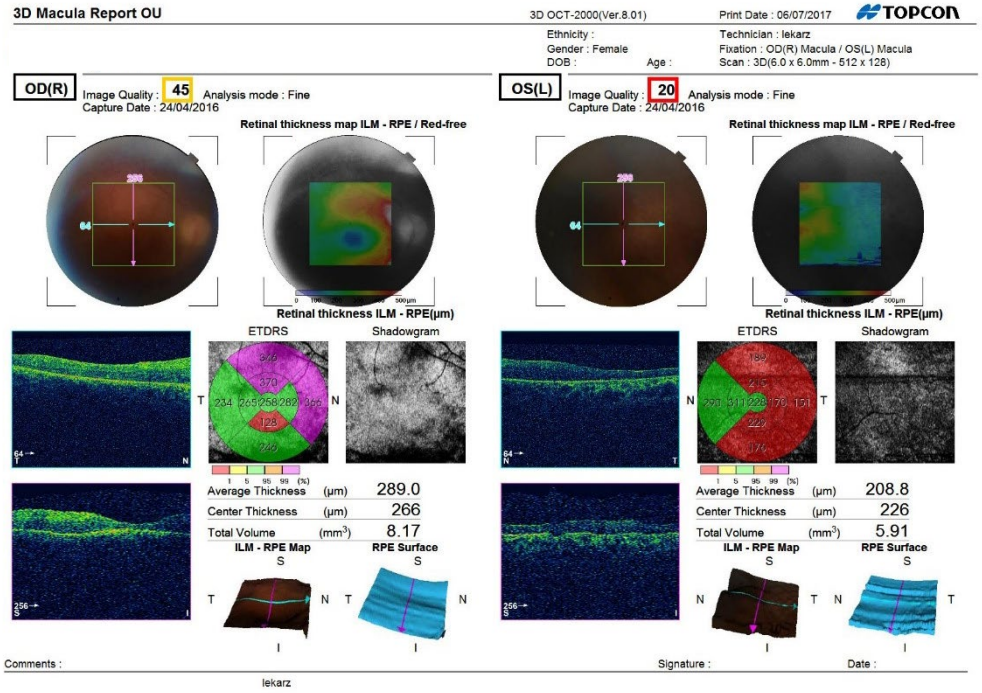

FIGURE 8. Patient 5 — diminishing of cystoid macular edema in optical coherence tomography in OU

She was referred for genetic examination with her brother (Patient 3) and her sister (Patient 4) and inflammatory neurovitreoretinochoroidopathy was suspected. OCT revealed CME in both eyes. It was treated with intravitreous triamcinolone acetate injections in OS (2009) and in OD (2010). The cataracts extractions were performed in both eyes in 2012 OD and in 2013 OS. No improvement in visual acuity was obtained. With progression of the disease, reduction in cystoid macular edema was observed (Fig. 8).

On the last examination in 2017, her visual acuity in OD was counting fingers from 30 cm and OS was just fingers movement before eye. On the anterior segment examination, we observed iridodonesis and on fundus examination — pale optic discs and very narrow arteries and veins. Numerous inflammatory cells were detected in the vitreous in both eyes.

PATIENT 6

A 13-year-old girl, a daughter of Patient 4, was examined in 2010 because of blurred vision in one eye. Her BCVA in OD was 1.0 and in OS was 0.6. The anterior segment examination was normal but posterior segment revealed CME in OCT exam. It was treated with topical non-steroidal anti-inflammatory eye drops and oral acetazolamide.

It was her first and last ophthalmological examination. Unfortunately, she died in car accident when she was 14 years old.

PATIENT 7

A 37-year-old man, a brother of Patient 3, Patient 4 and 5 Patient 5, was referred to our outpatient clinic in 2009 due to a decrease in his visual acuity in both eyes. His vision started to deteriorate at the end of the third decade of life. On the first visit the vitreoretinitis and CME in both eyes were diagnosed. He was treated with intravenous and oral steroids. His visual acuity was 0.3 in OD and 0.2 in OS. There was no improvement despite applied treatment. Next triamcinolone acetate injections in OS (2009) and in OD (2012) and subtenon steroid injection in OS (2010) were made. In 2012, the vitrectomy with ILM peeling in his OS was performed. Despite the treatment, the cystoid macular edema was present in OS and normal macula in OD was observed in 2015. Two years later swelling in the macula was detected in both eyes (Fig. 9AB, 10AB). The measurement of his intraocular pressure in OD was higher (28 mm Hg) in 2012. It was managed with topical antiglaucoma drops.

On the last examination his BCVA was 0.1 in both eyes. Anterior segment examination was normal. There was mild inflammation in the vitreous

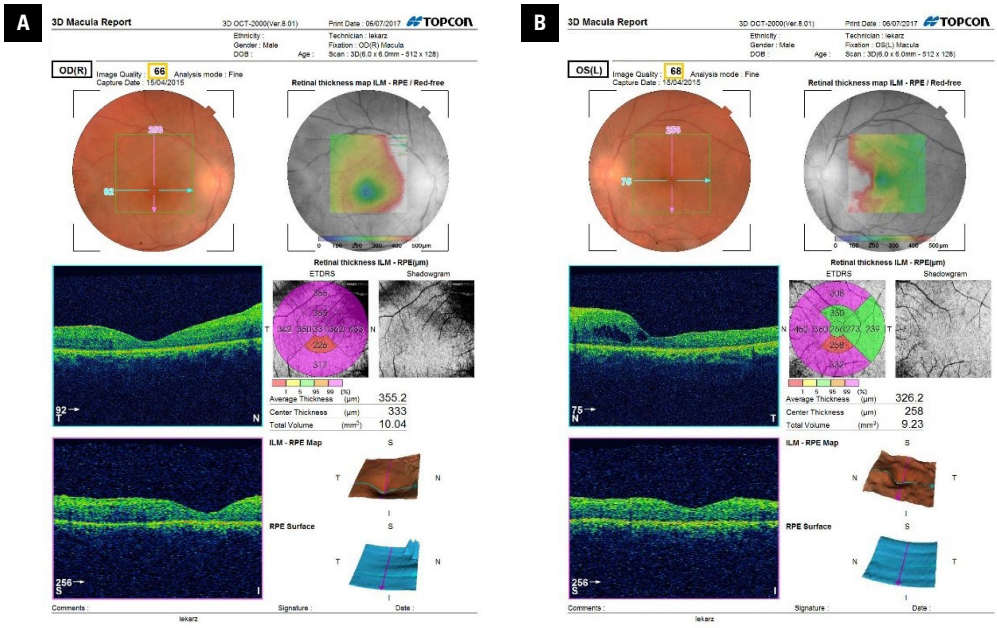

FIGURE 9AB. Patient 7 — normal macula in the right eye (OD) and cystoid macular edema in the left eye (OS) in optical coherence tomography in 2015

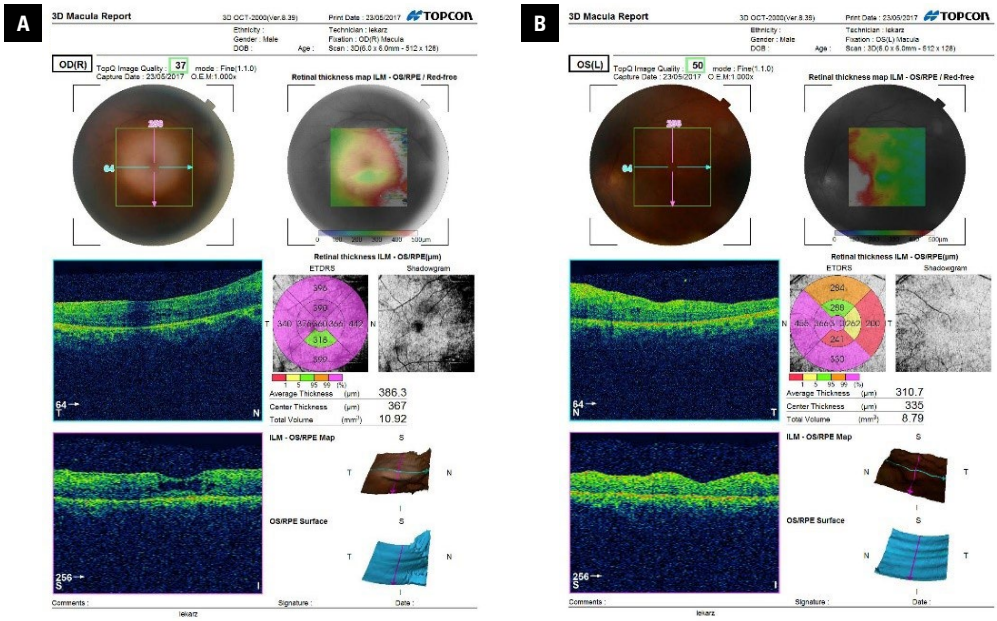

FIGURE 10AB. Patient 7 — swelling in the macula in the right eye (OD) and in the left eye (OS) in optical coherence tomography in 2017

in both eyes. In OCT exam we noticed significant thinning in the macula in both eyes. Additionally he smokes cigarettes and abuses alcohol.

DISCUSSION

Autosomal dominant neovascular inflammatory vitreoretinopathy (ADNIV) is a very serious disease leading to loss of vision. It is classified as a rare disease. The diagnosis of the illness is very difficult because its symptoms mimic much more common eye conditions like uveitis, retinitis pigmentosa, rod-cone dystrophy, proliferative vitreoretinopathy and diabetic retinopathy [4, 7–9]. A very characteristic sign of ADNIV is lack of systemic features [1].

The symptoms of the disease are divided into 5 stages, each lasting approximately ten years [10] The affected members of the family showed clinical signs of ADNIV disease previously reported by other authors [2, 11, 12], including non-infectious uveitis in the anterior segment and vitreous, cystoid macular edema, epiretinal membrane formation, proliferative vitreoretinopathy, cataract, neovascular glaucoma and, ultimately, blindness. Like other authors, we observed asymmetric disease progression between the eyes of affected patient and also between affected members of the family. The clinical severity of the disease was indistinguishable among affected males and females.

The first symptoms can start at all ages [5]. In our series, first symptoms occurred in the first decade of life in all patients except Patient 7. His visual acuity started to decrease at the end of the third decade of life. We observed significant deterioration of visual acuity with age in all patients (Tab. 1). Over the years, with disease progression there were different but characteristic symptoms of ADNIV in each patient. We noticed recurrent uveitis in the anterior segment in the majority of patients and inflammation in the vitreous in all patients. The cataract formation was also observed in all patients, even in the youngest ones (Patient 1 and 2). The papilledema was noticed in three patients: Patient 3, 4 and 5. OCT detected CME in Patient 1, 6, and 7; preretinal membrane in Patient 2 and thinning in the macula in Patient 2 and 7. We also observed raised intraocular pressure in Patient 3, 4 and 7. The examination of the anterior segment revealed the presence of iridodonesis in patients with cataract (Patient 4) and after extraction of cataract (Patient 3 and 5). All patients had more or less significant media opacity due to ongoing inflammation in the vitreous and intraocular fibrosis which especially obscured view of the fundus. Disease progression was observed in all patients. They showed the signs of stage II/III (Patient 1, 2, 6 and 7) and stage IV (Patient 3, 4 and 5) ADNIV.

On electroretinography loss of the b-wave was recorded.

In our genetic analysis (Patient 1and 2), the mutations in exon 6 of the CAPN5 gene were not detected but this does not exclude the presence of ADNIV disease because other fragments of the gene was not examined. Exon 6 of the CAPN5 gene was subjected to genetic testing because other authors [3] reported mutations in this exon.

Treatment of ADNIV poses many challenges. The pathophysiology and immunopathology are still unknown and for this reason the treatment is symptomatic rather than specific. The management of chronic immune-mediated uveitis is often very difficult and ineffective [13]. The patients received repeated injections of immunosuppressive medications to control cystoid macular edema and intraocular inflammation, but in all of them the disease progressed despite treatment. Long-term local and systemic steroid therapies are limited because of the numerous side effects. Some authors report the benefit of the fluocinolone acetonide (FA) implant in the treatment of chronic uveitis in ADNIV patients [13].

In our series we observed deterioration of visual acuity despite recommended continuous treatment.

CONCLUSION

Autosomal dominant neovascular inflammatory vitreoretinopathy is a very serious progressive disease. Medical therapy for ADNIV has limited efficacy. Despite the aggressive treatment, we observed deterioration of visual acuity due to severe complications of the disease. The patients with ADNIV require constant ophthalmological care. Further investigations including immunology, physiology and genetics are necessary to better understand ADNIV pathogenesis.

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CASE REPORT
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Therapeutic penetrating keratoplasty for the treatment of microbial keratitis due to *Staphylococcus MRSA*

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ABSTRACT

This is a case report of one patient who was diagnosed with microbial keratitis caused by staphylococcus MRSA. Its characteristics, etiology and symptoms will be described below. Moreover, we will discuss the clinical features, treatment plan and treatment outcome on our patient.

KEY WORDS: microbial keratitis; penetrating keratoplasty; staph MRSA

Ophthalmol J 2019; Vol. 4, 40–43

INTRODUCTION

Methicillin-resistant *Staphylococcus aureus* (MRSA) is a form of contagious bacterial infection that is resistant to numerous antibiotics including methicillin, amoxicillin, penicillin, and oxacillin. This resistance makes it challenging to treat [1]. Methicillin is an antibiotic related to penicillin; it was once effective against *staphylococci* (staph), a type of bacteria. Staph bacteria have since developed a resistance to penicillin-related antibiotics, including methicillin. These resistant bacteria are called methicillin-resistant staphylococcus aureus, or MRSA. If staph MRSA is diagnosed, its treatment will vary depending on a lot of factors, such as the type of infection, the location of infection, the severity of symptoms and the antibiotics to which the strain of MRSA responds [2]. Medication options for MRSA skin and soft tissue infections may include clindamycin, doxycycline, minocycline, trimethoprim and sulfamethoxazole; rifampin and linezolid are treatment options for MRSA skin and soft tissue infections. *Staphylococcus* aureus (MRSA) may severely infect the eye including the cornea, the anterior chamber and the vitreous body. Microbial keratitis and endophthalmitis due to staph MRSA are vision-threatening infections and if not treated properly may result in severe loss of visual acuity or even blindness [3]. A case series of catastrophic eye infections caused by MRSA has been reported recently in patients after Lasik and cataract surgery [4–7]. Microbial keratitis if not treated appropriately may lead to cornea perforation and endophthalmitis.

CASE REPORT

A 72-year-old patient, who was functionally one-eyed, contacted us reporting redness and foreign body sensation in his left eye. As he lives on an island far away from our clinic, it was highly unlikely that he would come to the clinic soon enough. Thus, with the view to assisting him in the best possible way we prescribed moxifloxacin and urged him to contact an ophthalmologist on his island. The patient did not trust the local ophthalmologist's diagnosis; therefore, he preferred to come and be examined in our clinic.

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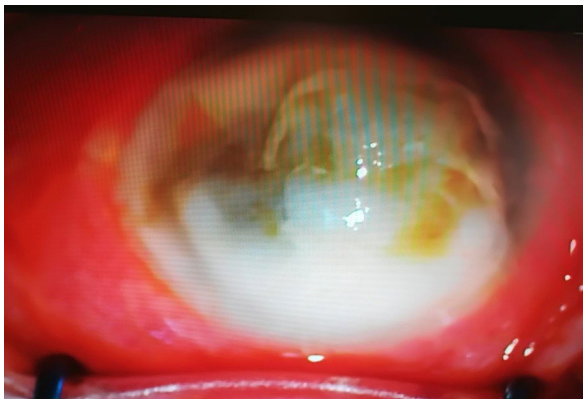

FIGURE 1. The photograph of the eye we took just before the surgery of penetrating keratoplasty

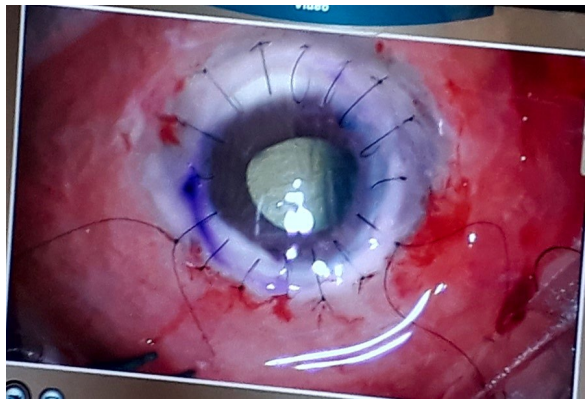

FIGURE 2. The image we took after the surgery of penetrating keratoplasty was over

The case-history of this patient was that he had lost vision in his right eye in the past due to an unsuccessful surgery for the detachment of the retina. As he also suffered from type 2 diabetes, he had an inflammation in macula in his left eye. Thus, we administered injections with anti-VEGF factors on a regular basis. Moreover, he used a lens in his left eye, as the eye was aphakic after endocapsular cataract surgery many years ago. His visual acuity was NLP for the right eye and 20/40 for his left eye. In the past month, the patient had been treated with Simbrinza, Duotrav and Acetazolamide pills, as he had also developed increased eye pressure. The examination was indeed conducted four days later. The examination led to an urgent penetrating keratoplasty due to an extensive infection in the cornea. The patient was prescribed moxifloxacin to be used every hour one day before the surgery (Fig. 1). The next day penetrating keratoplasty was performed. During the surgery a terphination of 8.5 mm was used because the patient was aphakic. During the surgery, wash out of the anterior chamber was performed combined with limited anterior vitrectomy. Intraoperatively, we saw a grey mash on the posterior segment of the eye (Fig. 2) which was due to choroidal detachment caused by severe inflammation. The host cornea was sent to microbiology lab. During the first post-operating days, the patient was administered antibiotics that covered both gram positive (moxifloxacin) and gram negative bacteria (amikacin fortified drops) as well as fungi (voriconazole drops and orally). The results of the microbiological lab tests were negative, so we decided to send the lens and the lenses' case he had used for

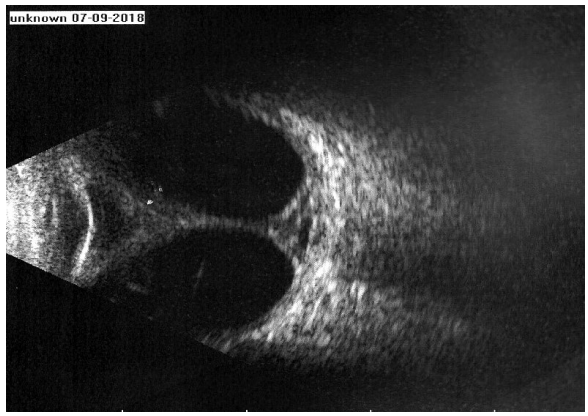

FIGURE 3. Choroidal detachment (Kissing choroidals)

the correction of aphakia for PCR. The surgery of the penetrating keratoplasty was successful. The patient was treated with both moxifloxacin and amikacin fortified drops, as we did not know what had originally caused the inflammation. We stopped this particular treatment when the microbiological laboratory where we had sent the lens informed us that they had found staphylococcus MRSA. His visual acuity for the next month was LP. One week after the surgery, the intraocular pressure was still under 10 mm Hg, and after a B-scanning we noticed that the inflammation had infected the pars plana, as the patient had a choroidal detachment due to severe inflammatory reaction to microbial keratitis (Fig. 3).

We decided to increase the dose of methylprednisolone we had already prescribed and to examine our patient once a week. One month later, the visual acuity of his left eye was 1/20. Through a B-scanning examination, we saw that the serous choroidal detachment had already been cured (Fig. 4).

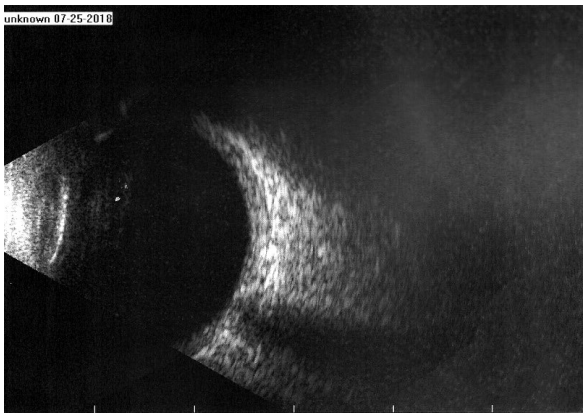

FIGURE 4. B-scanning image a month after the surgery. The choroid is totally cured

It has been six months since the operation was performed. Now, the patient has a visual acuity 1/20 on his left eye and he is only using moxifloxacin on a regular basis.

DISCUSSION

When the microbiological tests on the graft came as negative on account of moxifloxacin, we went on to send the lenses' case for PCR, which turned out to be positive for MRSA. Staphylococcus MRSA may bring on severe microbial keratitis. It's remarkable that during the first attempt to detect which microbe had caused the inflammation, the answers did not include Staphylococcus MRSA. Prior to the operation, there was no B-scan in order to detect the choroidal detachment. The choroidal detachment was cured after the increased dose of corticosteroids and moxifloxacin [8–10]. We treated these symptoms with Medrol in advance, and they were cured within twenty-five days. As a result, we have come to the conclusion that, regarding the choroidal detachment, it is preferable to insist on the administration of cortisone before we proceed to an operation. [11] There was resistance of the Staphylococcus MRSA to moxifloxacin or vancomycin.

Community-associated MRSA (CA-MRSA) is becoming increasingly prevalent, and ophthalmologists will see more ophthalmic MRSA infections. Although ophthalmic CA-MRSA commonly presents as preseptal lid infection and conjunctivitis, sight-threatening infections also occur. Ophthalmologists must identify MRSA patients, adjust empirical treatment regimens where MRSA is endemic, and take steps to control emergence of resistant organisms in both inpatient and outpatient practices [12, 13]. Three of the five patients with MRSA keratitis had nosocomial infection. In all but one, effective antibiotic coverage was initiated empirically. That patient had atopic dermatitis with a history of shield ulcers bilaterally and was administered ciprofloxacin ophthalmic drops as therapy initiation. The isolate proved resistant to both levofloxacin and ciprofloxacin. Of the other patients, two had a history of cocaine use (one with definite crack keratopathy), one had preceding herpes zoster ophthalmicus after decompressive craniotomy for intraparenchymal hematoma due to motor vehicle collision, and one suffered trauma to the eye when a container of medical waste exploded. The latter patient was considered to have nosocomial infection, and the MRSA isolate had reduced susceptibility to levofloxacin and resistance to tetracycline [14–16].

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CASE REPORT
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Holmes-Adie syndrome

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ABSTRACT

Holmes-Adie syndrome (HAS) is a rare neuro-ophthalmological disorder, which mostly presents in young females as a unilateral dilated pupil. We present a case of a 12-year-old girl with bilateral tonic pupils. She had vermiform movement of the iris with segmental palsy, as well as loss of ankle jerks. The diagnosis was confirmed with pilocarpine 0.125% test, and she was symptomatically treated with the same drops.

KEY WORDS: Holmes-Adie syndrome; tonic pupils; light-near dissociation

Ophthalmol J 2019; Vol. 4, 44–45

INTRODUCTION

Holmes-Adie syndrome (HAS), as described by Adie in 1932, is a unilateral dilated pupil that is unresponsive to light, in association with lower limb hyporeflexia [1]. It is a rare neuro-ophthalmological disorder, more common in females, and it mostly presents unilaterally [1, 2].

CASE REPORT

A 12-year-old girl was referred to the eye clinic by her neurologist for the evaluation of bilateral dilated, non-reactive pupils. The patient had gone to a neurology clinic with complaint of headache. She had undergone complete neurological workup with MRI of the head, which was unremarkable.

Her past medical/surgical history was unremarkable and there were no ocular complaints. There was no history of drug use or trauma. She had no history of neurological deficits.

On ocular examination, the best-corrected visual acuity was 6/6 in the right eye and 6/7.5 in the left eye. There was no ptosis with full extra-ocular movements bilaterally. Her pupils were mid-dilated with a diameter of 4.2 mm in the right eye and 5 mm in the left eye. The pupils were non-reactive to light but were reactive to accommodation.

On careful examination of her iris, we found that she had vermiform movement of the iris bilaterally, left more than right. There was sectoral iris palsy in the left eye at three o'clock. The rest of the anterior and posterior segment examination was unremarkable.

The right and left pupils showed significant response to 0.125% pilocarpine test with remarkable reduction of size to about 3 mm bilaterally in 20 minutes. On neurological examination, she had reduced ankle jerks bilaterally.

The diagnosis of HAS was made. The patient was sent home on pilocarpine 2% twice daily, and her headache improved on subsequent follow-up a week later.

DISCUSSION

Holmes-Adie syndrome refers to idiopathic tonic pupils with absent or decreased deep tendon reflexes. It is more common in females and presents unilaterally in 80% of cases, with a 4% chance of bilaterality each year [1–4]. Our patient had bilateral HAS with anisocoria.

Bilateral HAS has been discussed in the literature [5]. And in such cases it is important to differentiate it from generalised peripheral neuropathy,

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i.e. diabetic autonomic neuropathy [5]. Apart from hypersensitivity to diluted pilocarpine eye drops, vermiform iris movement, and reduced/absent tendon reflexes in HAS, there should be sectoral palsy and anisocoria > 1 mm [5]. A detailed medication history is important to rule out any use of mydriatic agents in a patient with bilateral dilated pupils. Also, Argyll Robertson pupil needs to be ruled out in bilateral cases of tonic pupils with light-near dissociation [6].

The first six cases of tonic pupils were reported by Adie in 1931, showing the relationship between deep tendon reflexes and tonic pupils [1]. Gordon Holmes in 1931 reported 54 cases of tonic pupils, 19 of which had diminished or absent tendon reflexes [4].

Holmes-Adie syndrome is further classified into complete and incomplete forms. In complete form, tonic pupil is associated with reduced or absent deep tendon reflexes in the lower limbs. In incomplete form, there is only tonic pupil or atypical phases of tonic pupil [1]. Our patient was an example of complete HAS.

The postulated pathophysiology in HAS is parasympathetic pathway defect due to viral neuropathy [2–5, 7, 8]. Ciliary muscle denervation and sphincter pupillae denervation lead to diminished accommodation and mydriasis, respectively [4]. Light-near dissociation of pupils occurs due to aberrant degeneration. Achilles reflexes are the most frequently affected reflexes and are thought to be due to spinal ganglion defect [4].

Patients with HAS generally present with blurring of near vision as a main complaint [4, 7, 8]. They also have poor light response, slow response to near vision with light-near dissociation, hypersensitivity to cholinergic eye drops, and decreased tendon reflexes [9]. Sectoral palsy of the iris along with vermiform movement can occur in HAS [6, 7]. Tonic pupil may become miotic with the passage of time, known as "little old Adie pupil".

In the literature another very rare entity of HAS has been described, known as Ross syndrome. It is defined as HAS with segmental anhidrosis or hyperhidrosis [9].

Holmes-Adie syndrome has been suggested to be associated with Sjögren's disease, temporal arteritis, and rheumatoid arthritis, and it can also present as a paraneoplastic syndrome in association with lung and breast malignancies [10]. Holmes-Adie syndrome is also believed to occur in association with autoimmune hepatitis and coeliac disease [11]. Once the diagnosis of HAS has been established, the patients mostly need reassurance with short-term pilocarpine eye drops.

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CASE REPORT
DOI: 10.5603/OJ.2019.0005

Refractory macular edema in X-linked juvenile retinoschisis

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ABSTRACT

X-linked juvenile retinoschisis (XLRS) is one of the most common X-linked inherited, bilateral vitreoretinal dystrophies affecting males in the first two decades of life. In this article, we present a case report of a young man who presented with gradual decrease in visual acuity in both eyes that was attributed to macular edema and foveal schisis in the inner retinal layers. He was investigated by appropriate ocular images which were consistent with a diagnosis of XLRS. He was treated by anti-vascular endothelial growth factor (anti-VEGF) intravitreal injection, dorzolamide eye drops and intravitreal steroids injection without improvement.

KEY WORDS: retinoschisis; macular edema; juvenile; carbonic anhydrase inhibitors; vascular endothelial growth factor

Ophthalmol J 2019; Vol. 4, 46–48

INTRODUCTION

X-linked juvenile retinoschisis (XLRS) is a relatively common early-onset retinal degenerative disease that affects males early in life [1]. Characteristic features include mild to severe loss in central vision, splitting of inner retinal layers in the fovea and in peripheral retina, and a reduction in b-wave amplitude in Electroretinogram (ERG) [2]. Currently, there is no approved treatment for XLRS and management involves treating complications, which commonly include vitreous hemorrhage and retinal detachments [3].

CASE REPORT

Twenty-year-old male patient presented complaining of bilateral gradual painless decrease in vision during the last few months. He denied any nyctalopia. The patient visited another doctor who has diagnosed him with macular edema and treated him previously with bilateral anti-VEGF (ranibizumab 0.5 mg/0.05 cc). On examination, the patient's best corrected visual acuity of the right eye was 0.2 and of the left eye was 0.3. Anterior segments of both eyes were within normal limits and intraocular pressure was 12 mm Hg in each eye. Fundus examination (Fig. 1) in both eyes revealed blunted foveal reflex, peripheral inferiotemporal oval retinoschisis in the form of oval defects and retinal veils. Ocular coherent tomography (OCT) was done (Fig. 2) which revealed bilateral asymmetrical foveal cystic spaces and schisis in the inner retinal layer. Fundus Fluorescein Angiography (FFA) was done (Fig. 3) and showed bilateral dry macula and peripheral hypofluorescence in the area of retinal veils. ERG test showed selective decreased b-wave response. All of these findings are consistent with XLRS. Because the patient received the injection of anti-VEGF 2 months ago without any improvement (as demonstrated by comparing the OCT before and after the injection), a decision was made to start the patient on topical dorzolamide eye drop (2%) 3 times a day for 1 month. The patient came back with no improvement. A trial

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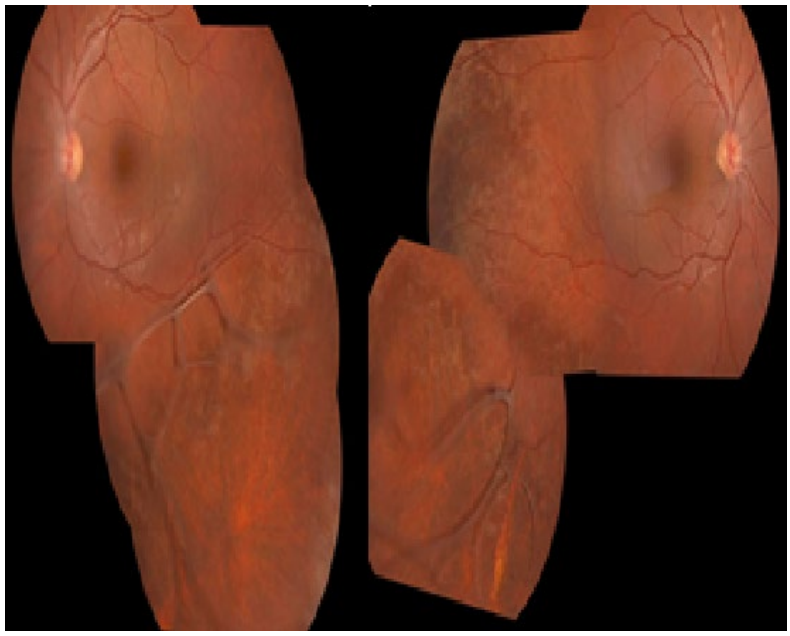

FIGURE 1. Color fundus photograph of both eyes showing the peripheral veils (left: left eye, right: right eye)

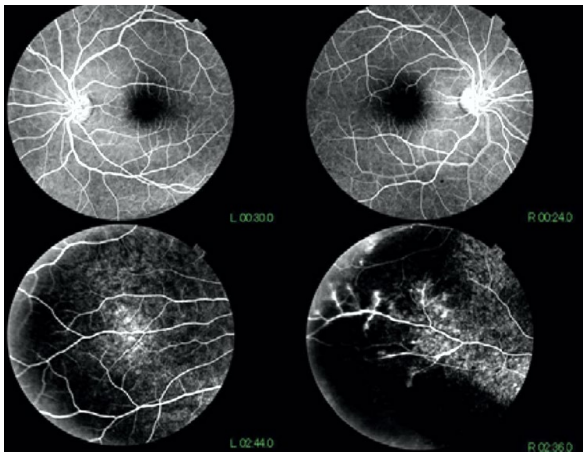

FIGURE 2. OCT of both eyes showing foveal inner layer schisis (left column: left eye, right column: right eye)

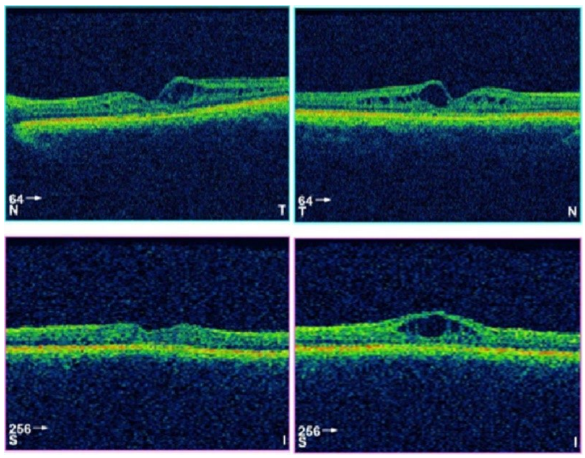

FIGURE 3. FFA for both eyes showing absence of leakage in the macula (left column: left eye, right column: right eye)

of intravitreal injection of preservative free triamcinolone (4mg/0.1 cc) was given and the patient was followed up for 2 months. The patient came back with no improvement also. So a decision was made just to follow up the patient.

DISCUSSION

X-linked juvenile retinoschisis is the leading cause of juvenile macular degeneration in males and leads to splitting within the inner retinal layers leading to visual deterioration [4]. Many missense and protein truncating mutations have been identified in the causative retinoschisis gene (RS1) which secrets retinal protein, retinoschisin, which is implicated in cell–cell interactions and cell adhesion. Mutations cause loss of retinoschisin and consequently loss of its function [5].

The name derives from an internal splitting of the retina mostly affecting the temporal periphery of the fundus which occurs in less than 50% of affected individuals, whereas foveal involvement is present in all affected patients, which is usually associated with moderate visual loss [1]. Nevertheless,

these figures vary according to the studied population and the mutated gene [6].

If the inner sheet of the schisis degenerates, the retinal vessels may remain running free through the vitreous cavity presenting as so called vitreous veils. If additional breaks occur in the outer sheet of the schisis, a retinal detachment may occur [1]. Vitreous hemorrhage is also a known complication resulting from the rupture of unsupported blood vessels or pre-retinal neovascularization [7].

Macular edema in this disease is peculiar because of the absence of leakage on FFA, which narrows the differential diagnosis to a few diseases, namely, some types of retinitis pigmentosa, X-linked retinoschisis, nicotinic acid maculopathy, and some cases of epiretinal membrane and vitreomacular traction syndrome [8].

One theoretical mechanism of macular edema involves intracytoplasmic edema of Muller cells, which may stem from an initial microvascular insult. This same process may occur in XLRS, where abnormal retinoschisin accumulation causes dysfunctional Muller cells [3]. Based on this theory, many attempts have been taken to treat the edema using anti-inflammatory medications; one such trial was taken successfully by injections of intravitreal triamcinolone acetate, dexamethasone implant, intravitreal fluocinolone acetonide implant [3], and even subteneon triamcinolone [9]. Others have tried carbonic anhydrase inhibitors, such as dorzolamide and acetazolamide [10–12]. In fact, carbonic anhydrase inhibitors are thought to enhance adhesion between retina and retinal pigment epithelium (RPE). XLRS patients with foveal cystic cavities unresponsive to or worsening on carbonic anhydrase inhibitors may benefit from discontinuation for up-to 6 months ("medication vacation") and later retreatment with the same agent. The ON/OFF medication regimen is believed to allow the RPE metabolic pump to partially recover and therefore facilitate the ability for a future response to treatment [13]. In our patient, both of these drugs were used without success.

Although anti-VEGF drugs may be an effective and safe way to prevent deterioration of XLRS with certain complications such as vitreous hemorrhage and exudative retinal detachment [6], it was used in this case to treat macular edema without any benefit.

So, we ended up with a case that is refractory to all known medications. We advocated observing the patient since then.

CONCLUSION

In conclusion, XLRS is a genetic disease with many ocular manifestations which in some patients were found to respond to pharmacotherapy. Patients with refractory edema may be observed closely.

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None.

CONFLICT OF INTERESTS

No competing interests.

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CASE REPORT
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Spontaneous closure of stage two idiopathic macular hole with persistent vitreous attachment

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ABSTRACT

The classical rule was so far to observe idiopathic macular holes of stage 1a and 1b because of the high probability of spontaneous closure of the hole, while in higher stages surgical treatment was recommended. However, a growing number of case reports are available nowadays that suggest that even a more advanced stage macular hole may occasionally close spontaneously. In this article, we present a case of a 71-year-old female patient who presented with gradual bilateral decrease of vision, which was attributed to a combination of cataract and macular holes in both eyes. The macular hole in one eye was stage 1A and the other eye was stage 2. Follow up over a period of 6 months revealed conversion of the stage 1A hole to lamellar hole and spontaneous closure of the stage 2 hole.

KEY WORDS: idiopathic macular hole; spontaneous closure; optical coherence tomography

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INTRODUCTION

A full-thickness macular hole is defined as complete loss of tissue from the foveal center; it can be traumatic or more commonly, idiopathic. It has been classically staged by Gass into four categories: in stage 1 a yellow spot or halo develops associated with loss of the normal anatomic foveal depression. No vitreous separation is present. This may resolve or progress to a small (less than 400 micron), early macular hole (stage 2). This hole gradually enlarges to a diameter more than 400 micron. The vitreous usually remains attached (stage 3). Some eyes have complete posterior vitreous separation (stage 4) [1]. The spontaneous closure of idiopathic macular hole is not new; it has been documented many years ago, even before the introduction of vitrectomy as a standard way of managing this entity. [2]

CASE REPORT

A 71-year-old female patient presented with gradual painless decrease of vision in both eyes for the past several months. On examination, best corrected visual acuity was 0.2 in the right eye and 0.1 in the left eye. Anterior segment examination showed cataract nuclear sclerosis of +3 in each eye. Optical coherence tomography (OCT) revealed stage 1A macular hole in the right eye and full-thickness macular hole stage 2 (290 microns of minimal hole width) with persistent vitreous attachment in the left eye (Fig. 1). Patient was given an appointment for combined cataract extraction and vitrectomy in the left eye after 6 months. When she came back for the surgery, she reported mild improvement of vision in the left eye. OCT was done again and revealed spontaneous closure of the macular hole in the left eye and conversion from

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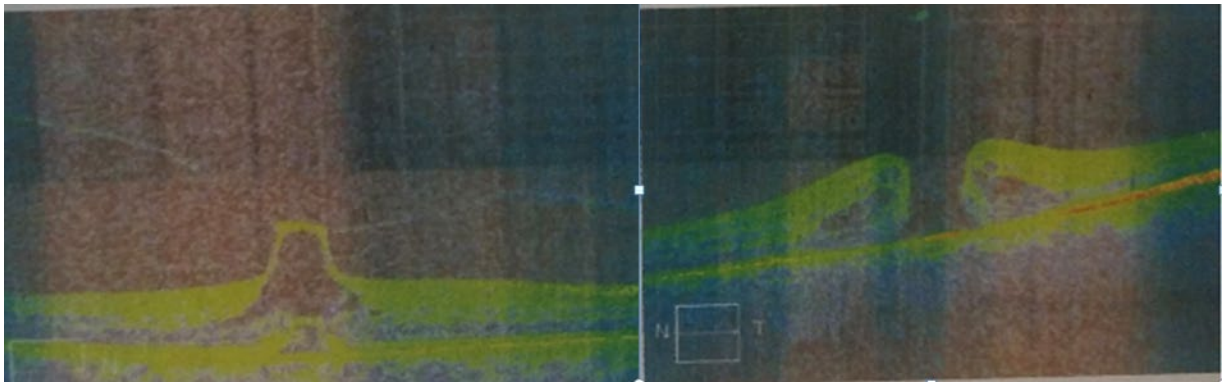

FIGURE 1. Optical coherence tomography of both eyes at presentation (left — right eye, stage 1A macular hole, right — left eye stage 2 macular hole)

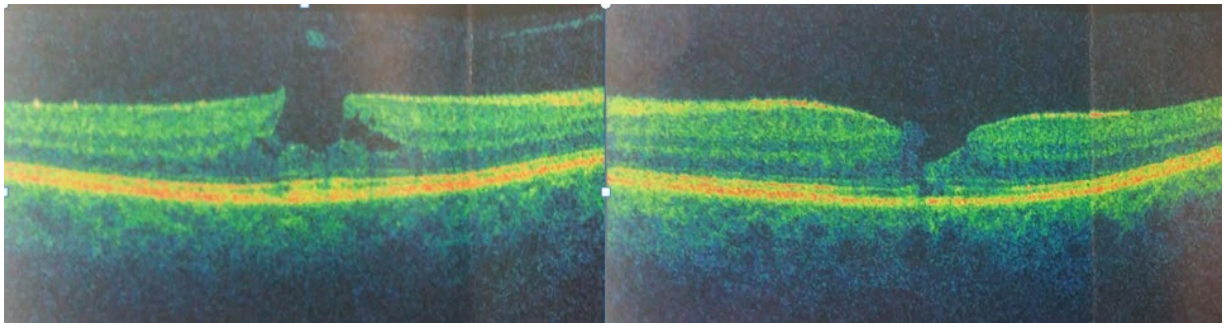

FIGURE 2. Optical coherence tomography of both eyes after 6 months (left — right eye, resolution into lamellar macular hole; right — left eye, closed macular hole)

1A macular hole to lamellar hole in the right eye (Fig. 2). The vision remained 0.2 in the right eye but improved to 0.3 in the left eye.

DISCUSSION

The proportion of spontaneous closure in idiopathic macular hole has been reported to be 2.7–6.2% [2–4]. However, relatively higher proportion (10.7% to 44.4%) of traumatic macular holes close spontaneously. Therefore, an observation for a period of up to four months may be a management of choice for traumatic macular hole [5].

The mechanism of macular hole closure or the predictive factors for possible spontaneous closure is not understood very well and most of our assumptions came from previous studies about traumatic macular holes; for example, a study was published by Haoyu Chen et al. identified two predictive factors associated with spontaneous closure of traumatic macular holes. The first factor is small minimum diameter of the macular hole at baseline, which may allow easy migration of glial cells. The other associated factor was absence of intraretinal cysts, which may be an indicator of internal limiting membrane traction, which may activate Müller cells and cause accumulation of extracellular fluid in the retina [6]. Further studies are needed to establish whether or not these assumptions can be extrapolated to idiopathic age-related holes.

Some explanations have been proposed for the spontaneous resolution of a macular hole. These include: complete detachment of the posterior hyaloid from the foveal area leading to a release of traction; cell proliferation at the base of the hole; formation of a contractile epiretinal membrane resulting in shrinkage and closure of the hole; and bridging of the retinal tissue across the hole [7].

Although these explanations may sound highly convincing, a number of case reports show contradictions to at least some of them – such as our case in which the vitreous is still attached as well as case reports by Kelkar et al. [8] and Sugiyama et al. [3].

Since OCT revealed the closure of the macular hole with the resolution of the cystic spaces and bridging of the inner retinal layers with or without

lamellar defects and without any posterior vitreous detachment or glial tissue proliferation, it is thought that the bridging of the retinal tissue allowed the resolution of the cystoid spaces by preventing the influx of vitreous fluid into intraretinal spaces and therefore leading to a spontaneous closure of the macular hole [8].

Hence, out of the 4 mechanisms mentioned above, posterior vitreous detachment and epiretinal membrane formation may or may not always be evident in patients with spontaneous closure of a macular hole, but the bridging of the sensory retina and the smaller size of the macular hole appear to be the most consistently reported findings for the spontaneous closure of macular holes [9].

As to the origin of the bridging of the retinal tissue, proliferation of the retinal post-mitotic neurosensory cells has been proposed, but could not be identified; proliferation of glial or retinal pigment epithelial cells has also been suggested. Since the concept of cell proliferation as a mechanism of macular hole closure is still speculative, the exact mechanism of how the spontaneous macular hole closure with maintained normal retinal structure occurs is still unclear [10].

CONCLUSIONS

Although spontaneous closure is well known in traumatic macular hole, this phenomenon is less well recognized in idiopathic age-related macular hole. The growing number of case reports of spontaneous closure may promote changing in our way to approach these cases; which means that a waiting period of few months before surgery may be warranted for selected cases.

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None.

CONFLICT OF INTERESTS

None.

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CASE REPORT
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Retinoma — the first identified case in Jordan

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ABSTRACT

Retinoma (or retinocytoma) is a rare benign intraocular tumor with characteristic features and can be diagnosed clinically. In this article, we present a case report and a review of literature about retinoma. The case is about an incidentally diagnosed retinoma in an asymptomatic young female who presented for vision checkup and was found to have an intraocular translucent-grey, elevated mass extending into the vitreous cavity from the retina with the characteristic features of retinoma. The main differential diagnosis included retinoblastoma and astrocytic hamartoma. The mass showed no growth over a period of 6 months of follow up with colored fundus photography and ultrasound. This case is, to the best of our knowledge, the first case of retinoma diagnosed in Jordan.

KEY WORDS: retinoma; retinocytoma; retinoblastoma; Jordan

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INTRODUCTION

Retinoma is a retinal tumor that is highly associated with retinoblastoma, but lacking malignant characteristics, that has been inaccurately initially considered as "spontaneous regression" of retinoblastoma [1]. However, clinical evidences do not support this hypothesis and suggest that retinoma rather represents a step towards retinoblastoma development [1–6]. Dimaras and colleagues demonstrated that retinomas display inactivation of both RB1 alleles, absence of proliferative markers, low level of genomic instability and high expression of the senescence-associated proteins; while retinoblastomas, on the other hand, show reduced expression of senescence-associated proteins and increased genomic changes, indicating progression from retinoma; which means that retinoma started from the beginning as retinoma, with the possibility to stay stable as retinoma, or rarely convert to retinoblastoma [7].

CASE REPORT

A 30-year-old female patient was referred to our center because of an intraocular retinal mass. The patient was asymptomatic and was incidentally found to have this lesion during a routine vision examination by another ophthalmologist. On examination, best corrected visual acuity was 6/6 in both eyes, anterior segment examination was within normal limits and intraocular pressure was 14 mm Hg in both eyes. Fundus examination of the left eye was normal while that of the right eye revealed an intraocular endophytic translucent retinal mass (Fig. 1) which was located in the superionasal quadrant protruding toward the vitreous cavity, surrounded by areas of chorioretinal atrophy and few spots of retinal pigment hyperplasia. The lesion has a cottage-cheese like appearance resembling post-radiation treated retinoblastoma. B-scan ultrasonography (Fig. 2) revealed hyperechoic lesion with high internal reflectivity and dense orbital shadowing consistent

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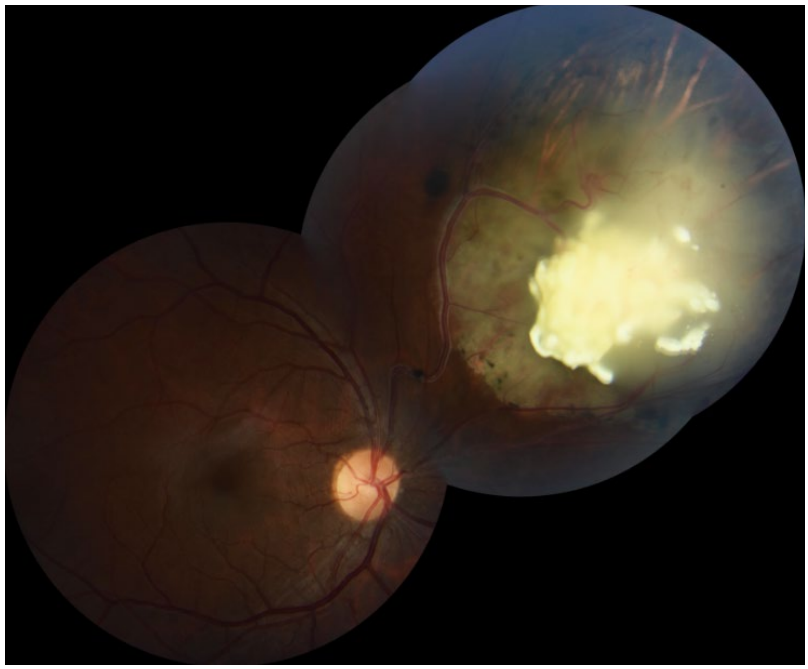

FIGURE 1. Color fundus photography of the right eye with retinoma

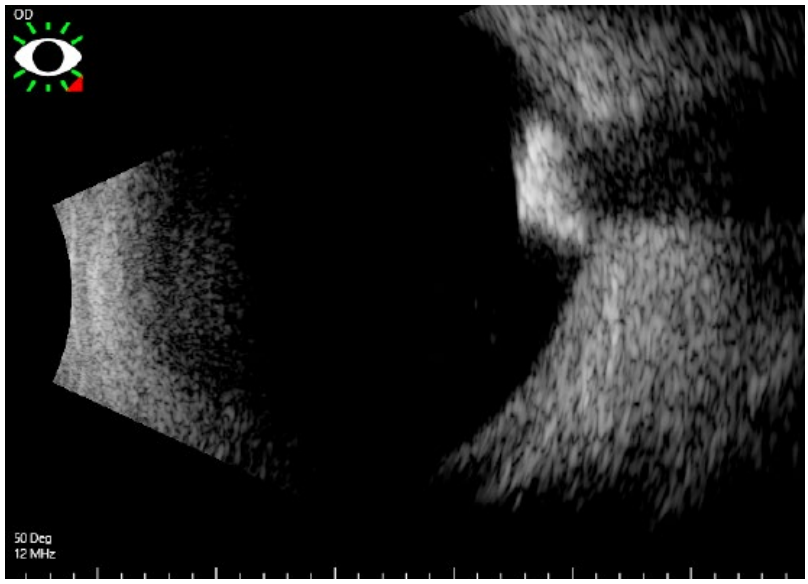

FIGURE 2. B-scan ultrasonography of the right eye with retinoma

with calcification inside the tumor. The patient was followed up over a period of 6 months by colored fundus photography and B-scan ultrasonography, which showed no growth and verified our diagnosis.

DISCUSSION

Retinoma is a rare benign tumor with incidence among retinoblastoma patients ranging between 1.8% and 15.6 % [5–7]. The disease is usually asymptomatic and may be diagnosed sporadically in a patient with retinoblastoma in the same eye, retinoblastoma in the other eye, or retinoblastoma in the family member [5, 6].

Margo et al. studied retinomas by light and electron microscopy and tested them with certain tissue markers and reported that these small placoid, noninvasive lesions were composed entirely of

benign-appearing cells with numerous fleurettes and showed no necrosis or mitotic activity. Ultrastructurally, they were composed predominantly of neuronal cells exhibiting photoreceptor differentiation [4].

Ophthalmoscopically, these tumors are characterized by translucent mass, calcification, chorioretinal atrophy, and retinal pigment epithelium changes [1, 6, 8]. Calcified vitreous deposits is a recently described feature of retinoma in addition to the four classical features [9]. It was noted that up to 4% of retinomas may undergo benign cystic enlargement, which might be associated with an aggressive tumor potential [10].

Despite the characteristic ophthalmoscopic features mentioned above, certain entities, such as retinoblastoma and astrocytic hamartoma, can closely resemble retinoma. Retinoblastoma is usually diagnosed before the age of 5 and retinoma is usually diagnosed in adults. Although calcification is seen in both tumors, areas of chorioretinal atrophy and associated retinal pigment epithelial changes are uncommon in untreated retinoblastoma. In addition, dilated, tortuous retinal feeder vessels are a feature of retinoblastoma rather than retinoma. Characteristically, retinoblastoma will show growth within 4–6 weeks, whereas retinoma will appear unchanged. Astrocytic hamartoma is a benign retinal tumor and can also closely resemble retinoma because both lesions may be calcified. Calcification, when present, can demonstrate subtle differences, as it tends to be dull and chalky white in retinoma, whereas in astrocytoma it is more glistening yellow, resembling fish eggs. Surrounding retinal pigment epithelium alterations, a common finding in retinoma, is typically absent in astrocytic hamartoma as they are situated superficially in the retina [11].

Malignant transformation into retinoblastoma is rare [3, 5], although a new study reported higher transformation rate that might reach up to 12% [10]. In the unfortunate event that malignant transformation occurs, systemic chemotherapy combined with consolidation focal therapy has become the standard treatment for retinoblastoma [12], with external beam radiation as a less favored treatment option [13]. The incidence of second malignant neoplasms in RB1 gene mutation carriers with retinocytoma is unknown, but well documented [10].

Retinoma is considered a rare phenotype of RB1 gene mutation and carries the same genetic implication as retinoblastoma [14]. The exact reason of why some patients develop retinoma rather than retinoblastoma is not yet known, but hypothetically it may arise if the second hit occurred in a later stage of cell maturation when the precursor cell has a limited mitotic capability and is unable to accumulate further mutations [15].

Studies aimed at clarifying retinoma/retinoblastoma relationship at molecular level are rarely performed. This is principally due to the fact that retinoma tissue is very difficult to obtain since patients are not treated and retinoma/retinoblastoma mixed tissues are rarely reported in enucleated eyes [2]. However, from the few reported cases, which have been dissected and analyzed, it turned out that from genetic point of view, retinoma should be considered as retinoblastoma with autosomal dominant inheritance pattern involving a mutation in the RB1 gene locus on chromosome 13q14 [1, 2]. The diagnosis of retinoma strongly suggests the presence of the retinoblastoma gene, necessitating genetic counseling and frequent observation of the retinas in the individual and his offspring [1, 2]. We suggest that the same mutations can cause either retinoma or retinoblastoma: benign hyperplastic nodules or retinoma when the mutations occur in relatively mature retinoblasts; and malignant retinoblastoma when the same mutations arise in immature retinoblasts [1].

Although retinoblastoma is a well-known tumor in Jordan and the reported epidemiological data indicates that the incidence of retinoblastoma in Jordan is similar to that reported in various countries of the world [16], this is the first case of retinoma diagnosed in Jordan.

CONCLUSIONS

It is of paramount importance to diagnose retinoma and differentiate it from retinoblastoma because the management plan for both is completely different; retinoblastoma necessitates urgent treatment while retinoma needs only observation. Nevertheless, these patients should be monitored for life because of the small risk of malignant transformation or associated second malignant neoplasms

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None.

CONFLICT OF INTERESTS

None.

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