厚生労働科学研究費補助金（難治性疾患克服研究事業）
分担研究報告書

小眼球症例のCT画像による眼窩内の形態評価に関する研究

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研究要旨：小眼球症例では，眼球の発育不良の影響で眼窩骨の発育も障害を受ける．さらには，外眼筋をはじめとする眼球付属器の発育にも影響が及ぶ可能性がある．このため，小眼球症例の眼球，眼窩骨，眼球付属器などの形態評価には，CTによる断層画像が有用と考える．本研究では小眼球症例の画像評価のために，眼窩CT撮影の最適条件と，その後の画像再構成の最適条件を検討した．

A．研究目的

小眼球症例では，眼球の形態的な発育障害により視機能障害をともなうことが多い．そして，眼球の形態的な発育障害は，眼窩骨の発育にも影響を及ぼす．さらには，眼球周囲の眼窩組織の発育にも影響を及ぼす可能性がある．このため，小眼球は視機能とともに整容面でも臨床上の問題が生じる．小眼球の形態異常の評価は，従来眼軸長測定によってなされてきた．しかし，小眼球の眼軸長測定は一次元的評価であり，眼球の二，三次元的評価も必要となる．また，小眼球に伴う眼球周囲と眼窩骨の形態的発育異常の二，三次元的評価も重要である．このため，小眼球とその周囲の眼窩組織，眼窩骨の形態的評価には，MRIやCTなどの眼窩断層画像が有用である．MRIは眼球，外眼筋，視神経など眼窩軟部組織の描出能に優れている半面，小眼球症例の中でも，とりわけ小児では，狭いガントリー内で長い検査時間，撮像中の大きな作動音が生じるMRI装置内での検査の実施は困難である．一方，検査時間が短く，検査時の頭部周囲が開放的であるCTは小児でも検査が可能である．しかも，現在のCTはヘリカルスキャン方式が主流で，本スキャン方式により画像データを三次元的に連続したボリュームデータとして得られるため，撮影後に画像再構成処理を行うと任意のスライス断面画像が選択できる．本研究では，小眼球症例の眼球，眼窩組織，眼窩骨の二次元および三次元的形態評価を行うためのヘリカルCT撮影の最適条件と，その後の画像再構成の最適条件を検討した．

B．研究方法

正常成人1名を被検者として，眼窩CTを条件別に撮影した．装置はヘリカルCTスキャナーであるPHILIPS社製 Brilliance 64を用いた．

1．CT撮影の条件の検討

CT撮影時の検討条件として，スライス厚，ピッチ幅とした．スライス厚は0.67 mm，1.0 mm，ピッチ幅は0.27 mm，0.48 mm，0.70 mmの各条件で眼窩CT撮影を行った．

2．再構成画像の条件の検討

画像再構成時の検討条件では，スライス厚として，スライス厚は1 mm，2 mm，3 mm，5 mmとした．

（倫理面への配慮）

正常成人の被検者は分担研究者自らとし，許容被爆線量内で撮影を実施した．

C．研究結果

1．CT撮影の条件

スライス厚0.67 mm，1.0 mmとも眼球，外眼筋，視神経などの眼窩組織が描出された．各ピッチ幅による撮影時間は0.27 mmで12.7秒，0.48 mmで7.1秒，0.70 mmで5.1秒であった．

2．再構成画像の条件

スライス厚1.0 mmでは外眼筋が10スライスに亘って描出され，スライス厚2.0mmでは5スライス，スライス厚3.0 mmでは3スライス，スライス厚5.0 mmでは2スライスに亘ってそれぞれ外眼筋が描出された．しかし，多数のスライスで眼窩組織が描出されたスライス厚1.0 mmではsignal / noise比（S/N比）の低い画像となった．

D．考察

本研究対象となる小眼球症例は小児である場合が多いため，検査中の静止や放射線被爆の観点から，スキャン時間の短縮が必要となる．そして，スキャン時間の短縮と放射線被爆量の軽減のためには，ピッチ幅を長く設定する必要がある．一方，詳細な形態評価の面では，眼窩組織画像の空間分解能の確保が必要で，そのためには上記とは逆にピッチ幅の短縮と薄切スライスが必要なる．

今回の検討で，被爆，撮影時間，空間分解能を考慮したCT撮影の条件として，ピッチ幅0.48mm，スライス厚0.67mmが適切であると考えた．また，本設定による撮影時間は7.1秒のため，小児例の撮影にも可能な条件と考えた．

再構成画像の条件として，スライス厚1.0mmの画像ではpartial volume effect が少ないため，外眼筋に代表される微小な眼窩内組織が多数の連続スライスに亘って描出されるが，薄切スライスのためにS/N 比が低く，眼窩組織の計測には支障をきたすことが予想される．一方，スライス厚5.0mmの画像では，partial volime effect が大きいため，外眼筋はわずか2枚のスライスでの描出となり，詳細な形態評価には困難が予想される．S/N 比とpartial volume effect を考慮すると再構成画像のスライス厚は2.0-3.0mmが適切と考えた．

E．結論

CTでの画像検査により，小児の小眼球症例でも，眼球，眼窩組織，眼窩骨の画像による形態評価が可能と考える．

F．健康危険情報

該当する危険なし

G．研究発表

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H．知的財産権の出願・登録状況

1. 特許取得
なし

2. 実用新案登録
なし

3. その他
なし

厚生労働科学研究費補助金（難治性疾患克服研究事業）
分担研究報告書

安全な小眼球症の白内障手術治療の開発に関する研究

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研究要旨：小眼球症への白内障手術の頻度、手術の問題点などを調べる目的で、岩手医科大学眼科にて平成 19 年 1 月 1 日から平成 21 年 12 月 31 日までに眼内レンズを挿入した白内障手術例 3729 眼から 28D 以上の眼内レンズを挿入した症例 29 例 33 眼を選び解析を行なった。このうち、角膜屈折力などが原因でなく眼軸長が短いために 28D 以上のレンズが挿入されたのは、20 例 24 眼（0.64%）で、小児、閉塞隅角緑内障、脈絡膜欠損(コロボーマ)を伴った症例が多く、視力予後も 0.3 以下が 8/17 眼（47.1%）と高く通常の白内障例に比して不良であった。術式で、PEA+IOL のみで対応できたものは 13/20 眼（65%）であったが、チン小帯の脆弱例が多く、前房内の安定性を高め、眼内圧を抑えた状態での手術法の開発が必要と思われた。

A. 研究目的

昨年度の研究により、小眼球症での白内障手術では、小児、閉塞隅角緑内障、脈絡膜欠損(コロボーマ)を伴った症例が多く、PEA+IOL のみで対応できたものは約 7 割であり、チン小帯の脆弱例が多く、前房内の安定性を高め、眼内圧を抑えた状態での手術法の開発が必要と思われた。そこで眼内圧の変動の少ない術式を開発すべく基礎データを集めることを目的とした。

B. 研究方法

PEA 装置はアルコン社のインフィニティ®，45°Kelman 型ミニフレアチップ，ウルトラスリーブを使用した。ボトル高を 60，75，90，100cm に設定し，1 分間連続灌流させ，その BSS をビーカーに溜めて重さを測定し灌流量(ml/分）とした。

BSS の創口やサイドポートからのリークの量を測定するため，豚眼に 2.4mm，3.0mm のスリットナイフを用いて角膜切開創を作成し，20G のスタイレットでサイドポートを作成した。連続灌流モードで BSS を眼内へ連続灌流させ創口から漏れた BSS をトレイに溜めリーク量を測定した。

リーク量が US チップから吸引をかけた際に変化が生じるか否かを確かめるため，切開幅 2.75mm の豚眼を用い，吸引（15ml/分, 30ml/分,45ml/分）をかけ創口とサイドポートからのリーク量を測定した。

C. 研究成果

US スリーブ（ウルトラスリーブ）からの単位時間当たりの平均灌流量はボトルの高さに比例して増加した。

吸引をかけていない状態での創口からとサイドポートからのリーク量を測定した結果を図 1 に示す。切開幅 2.4mm ではボトル高 60cm～100cm のいずれの設定でも平均 0.09ml/分で漏れはほとんどなかったが，切開幅 2.75mm と 3.0mm ではボトルを高くする程リーク量は増加した。サイドポートからのリーク量も同様にボトルが高い程増加した。

吸引を掛けた状態でのリーク量を図 2 に示す。同じ切開幅・ボトル高でも吸引流量が少ない程リーク量は多かった。

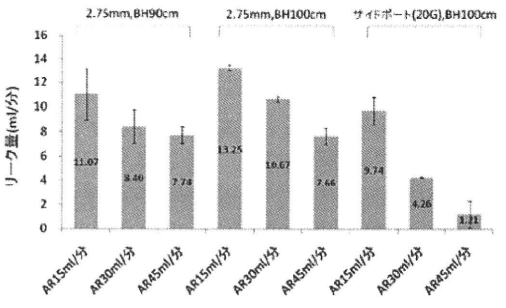

図2 リーク量（吸引あり）(n=3)
同じボトル高（BH）でも、吸引流量（AR）が少ない程漏れは多くなった。

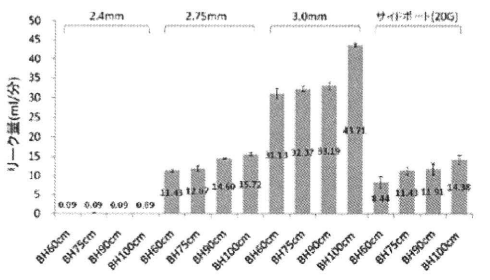

図1リーク量（吸引なし）(n=3)
創口からの漏れはボトル高（BH）が高いほど多く、また切開幅が大きいほど多かった。
サイドポートからの漏れも同様にBHが高いほど多かった。

D. 考按

前房を深く保つ方法としては大きく２つ挙げられる。ボトルの高さを上げて単位時間あたりの流入量を増やす方法と，吸引流量を減らして単位時間あたりの流出量を減らす方法である。ただ，前者ではボトルの高さを上げるとそれに比例して灌流量は増すため，前房は維持される方向に働くがリーク量も増す。従って、リーク量の分，前房を深くする効果は減弱してしまう。

また，吸引流量を減らして単位時間あたりの流出量を減らす状況では、吸引流量が少ないほうが，前房は安定する。ただ，吸引流量 30ml/分で吸引している状態は，リーク量が 10.67ml/分で吸引流量：リーク量が約 3：1 の割合であるが，吸引流量 15ml/分では，約 1：1 となり，核片の追従性が悪化し，乱流を生じる原因になると思われる。前房を深く保とうとするほど，ボトルを高くしても，吸引流量を減らしても，核片を捕える効率は低下してしまう。

一方，切開幅が 2.4ｍｍでは，ほとんど創口からのリーク量が認められなかった。リークが無い状況では，ボトルを高くしても，吸引流量を減らしても，創口からのリーク量が増加して前房を深く保つ効果が減弱されるということはない。創口への BSS の流れも生じないため，核片の追従性が損なわれることもなくなる。さらにサイドポートが閉鎖している場合には，サイドポートによる影響もなくなり，最も前房が深く保たれやすくなるとともに，核の追従性も保たれると思われた。ただし，リークが無い分，ボトル高による眼内圧の影響は直接的になり，同じボトル高でも，眼内圧が高くなることに注意が必要である。

E. 結論

術者は切開創に適応した US スリーブとチップを選択して創口からの BSS の漏れを減らすこと、サイドポートの使用を最小限にすることによって，効率的に前房の安定性が得られる可能性が考えられた。

F. 健康危険情報

該当する危険なし

G. 研究発表

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H. 知的財産権の出願・登録状況

なし

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Risk Factors for Recurrent Fibrovascular Proliferation in Aggressive Posterior Retinopathy of Prematurity After Early Vitreous Surgery

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• PURPOSE: To analyze risk factors for postoperative recurrence of fibrovascular tissue in eyes with aggressive posterior retinopathy of prematurity (AP ROP) treated with early vitreous surgery.

• DESIGN: Retrospective, consecutive, observational case series.

• METHODS: Thirty-one patients (50 eyes) with AP ROP who underwent early vitreous surgery between March 2005 and April 2008 participated. Eyes with stage 4A or 4B disease in which fibrovascular tissue was not attached to the vitreous base were included; those in which fibrovascular tissue was attached extensively to vitreous base or those without dense photocoagulation to the nonvascularized retina were excluded. Eligible eyes were divided into 2 groups based on postoperative recurrence or no recurrence of fibrovascular tissue. Data on gender, gestational age, birth weight, Apgar score, intubation duration, severe systemic complications, preoperative ROP stage, zone, fibrovascular tissue and vitreous base adhesion, clock hours of fibrovascular tissue, postmenstrual age at the initial application of dense photocoagulation, dense photocoagulation to both vascularized and nonvascularized retina, postmenstrual age at vitrectomy, and intraoperative hemorrhage were collected and analyzed.

• RESULTS: Fifty eyes of 31 patients underwent early vitrectomy. Seven (14%) eyes were excluded and 43 eyes (86%) were included. Eight (18%) of 43 eyes had a recurrence of fibrovascular tissue. Both univariate and multivariate analysis indicated application of dense photocoagulation to both the vascularized and nonvascularized retina was a significant factor in the decreased recurrence of fibrovascular tissue ($P = .002$ and $P = .008$, respectively).

• CONCLUSIONS: Application of preoperative dense photocoagulation to vascularized and nonvascularized retina may be important for lowering the recurrence of fibrovascular tissue in eyes with AP ROP. (Am J Ophthalmol 2010;150:10–15. © 2010 by Elsevier Inc. All rights reserved.)

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AGGRESSIVE POSTERIOR RETINOPATHY OF PREMATURITY (AP ROP) is characterized by posterior retinopathy usually in zone I, substantial dilatation and tortuosity of the vessels at the posterior pole, a flat network of neovascularization on the retinal surface, circumferential fibrovascular tissue extending for 12 clock hours, and rapid progression to stage 5 without the classic course that includes stages 1 through 3.[1] Previous randomized trials have reported that application of photocoagulation to the nonvascularized retina prevents retinal detachment in classic ROP, but that photocoagulation often cannot prevent progression in eyes with AP ROP.[2]

Because the visual prognosis is poor after vitrectomy performed when AP ROP progresses to stage 5,[3,4] several early surgical interventions have been tried to prevent stage 5 retinal detachment. Scleral buckling that reduces the traction between the fibrovascular tissue and the retina is ineffective for AP ROP that is characterized by fibrovascular tissue nearly 360 degrees circumferentially in the posterior retina.[5–8] Lens-sparing vitrectomy usually is successful if performed for tractional retinal detachment in eyes with classic ROP, but the surgery is unsuccessful for AP ROP.[9] Although it is controversial whether lensectomy is necessary during vitrectomy to treat retinal detachment in eyes with AP ROP,[10,11] wide-field vitrectomy with lensectomy may be required to treat retinal detachment in eyes with AP ROP, which always is characterized by high disease activity despite the disadvantages of lens removal.

Eyes with AP ROP that have undergone early vitrectomy often have a retinal reattachment;[9] however, among these eyes, we recently identified eyes in which proliferation of fibrovascular tissue recurred after surgery. Because a very low birth weight, young gestational age, or long-term high oxygen therapy are risk factors for severe ROP,[12–14] we analyzed the correlation between recurrent fibrovascular tissue proliferation after early vitrectomy and the associated risk factors.

METHODS

THE MEDICAL RECORDS OF ALL EYES THAT UNDERWENT early vitrectomy with lensectomy[9] for stage 4 ROP associated with AP ROP were reviewed retrospectively at the Department of Ophthalmology, National Center for Child

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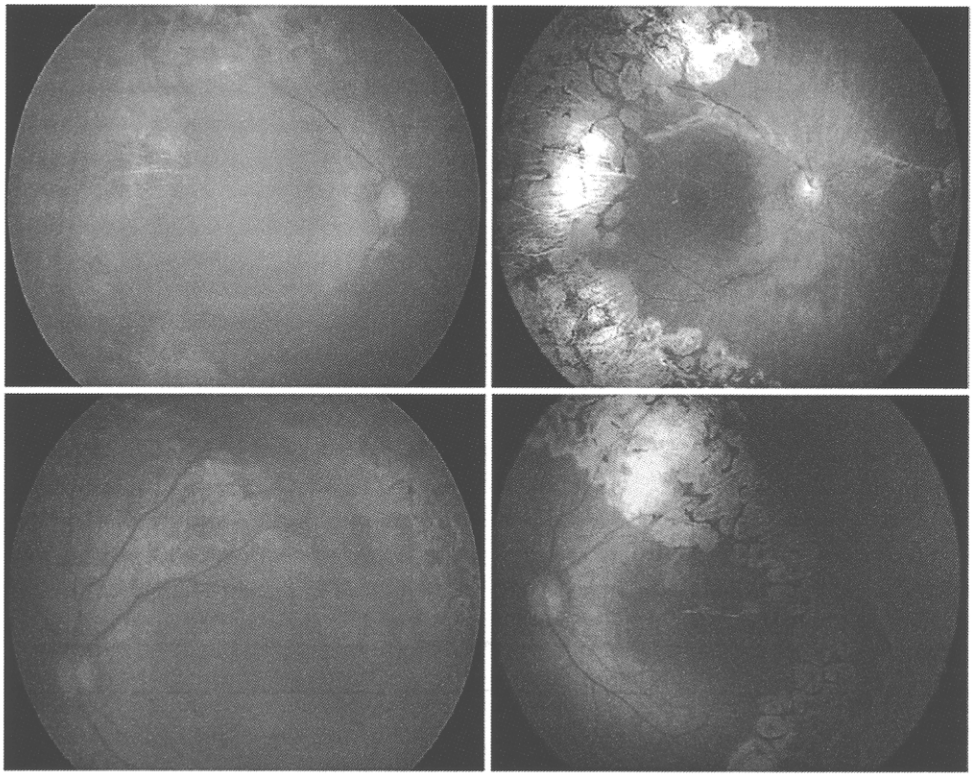

FIGURE 1. Fundus photographs of aggressive posterior retinopathy of prematurity in eyes of patients who underwent early vitreous surgery and preoperative photocoagulation to both the vascularized and nonvascularized retina. (Top left and Bottom left) Fundus photographs obtained before surgery showing densely applied photocoagulation in both the nonvascularized retina and the vascularized retina 3 to 4 spots posterior to the junction. Fibrovascular tissue and a focal tractional retinal detachment are seen at the junction. (Top right and Bottom right) Fundus photographs obtained 4 months after surgery showing that the retinopathy has been treated successfully without recurrence of fibrovascular tissue.

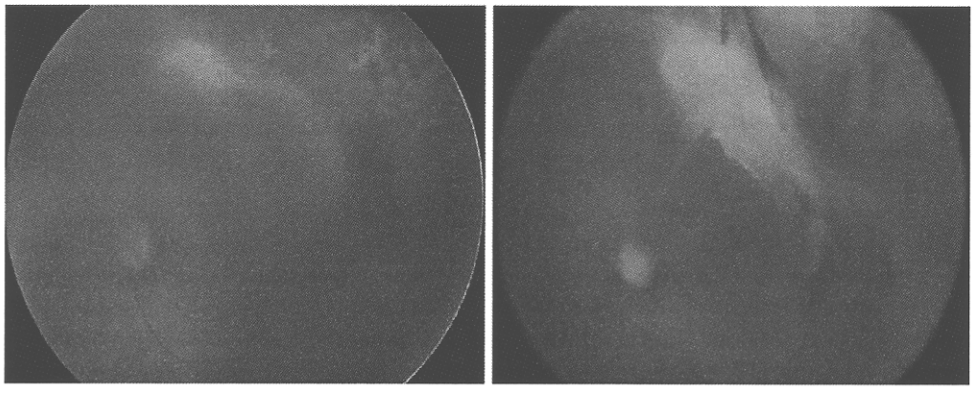

FIGURE 2. Fundus photographs of aggressive posterior retinopathy of prematurity in the left eye of a patient who underwent early vitreous surgery and preoperative photocoagulation to the nonvascularized retina. (Left) Fundus photograph obtained before surgery showing that photocoagulation was applied to the nonvascularized retina. Reddish fibrovascular tissue and a tractional retinal detachment are observed at the junction. (Right) Fundus photograph obtained 1 month after surgery showing recurrence of fibrovascular tissue in the posterior vascularized retina with a traction retinal detachment.

Health and Development, Tokyo, Japan, from March 2005 through April 2008. All eyes with AP ROP were diagnosed at the referring hospital or our institution based on the description published in 2005.[1] Eyes with stage 4A or stage 4B ROP in which fibrovascular tissue did not reach the vitreous base[9] were included; eyes with fibrovascular tissue attached extensively to the vitreous base or eyes without dense and early application of photocoagulation even to the nonvascularized retina were excluded, because those eyes usually have a stage 5 retinal detachment, and rigorous evaluation of

TABLE. Univariate Analysis between Baseline Demographics and Recurrence in the Eyes with Aggressive Posterior Retinopathy of Prematureity after Early Vitreous Surgery

	Total (n = 43)	Recurrence after Early Vitreous Surgery		*P* Value (2-Tailed)
		Yes (n = 8; 19%)	No (n = 35; 81%)	
Baseline characteristics				
No. eyes/patients	43/29	8/6	35/25	
Male, no (%)	13 (30.2)	5 (62.5)	8 (22.9)	.042[a]
Gestational age (wks), mean ± SD	25.1 ± 2.3	24.8 ± 2.0	25.2 ± 2.4	.703[b]
Birth weight (g) mean ± SD	808.7 ± 369.6	789.5 ± 302.2	813.0 ± 387.0	.873[b]
Apgar score at 5 min, median (range)	6 (1 to 10)	6 (2 to 10)	5 (1 to 10)	.311[c]
Intubation duration (wks), mean ± SD	57.0 ± 40.6	60.9 ± 49.2	56.1 ± 39.2	.767[b]
Severe systemic complication, no. (%)	12 (27.9)	2 (25.0)	10 (28.6)	>.99[a]
Follow-up (mos), mean ± SD	23.8 ± 10.7	22.6 ± 7.8	24.1 ± 11.3	>.99[b]
ROP findings				
Zone, no. (%)				.404[a]
1	29 (67.4)	4 (50.0)	25 (71.4)	
2	14 (32.6)	4 (50.0)	10 (28.6)	
Stage, no. (%)				.067[a]
4A	37 (86.0)	5 (62.5)	32 (91.4)	
4B	6 (14.0)	3 (37.5)	3 (8.6)	
Fibrovascular tissue and vitreous base adhesion, no. (%)	5 (11.6)	3 (37.5)	2 (5.7)	.037[a]
Clock hours of fibrovascular tissue, median (range)	5 (2 to 12)	9 (2 to 12)	5 (2 to 12)	.344[c]
PMA (wks) at initial PHC, mean ± SD	32.9 ± 1.8	32.1 ± 0.8	33.1 ± 1.9	.180[b]
Interval between initial PHC and virectomy (wks), mean ± SD	6.9 ± 3.2	7.0 ± 2.6	6.3 ± 3.3	.892[b]
PMA (wks) at vitrectomy, mean ± SD	39.7 ± 3.1	39.1 ± 2.9	39.2 ± 3.9	.536[b]
Intraoperative hemorrhage, no. (%)	13 (30.0)	3 (37.5)	10 (28.6)	>.99[a]
PHC to both vascularized and nonvascularized retina, no. (%)	27 (62.8)	1 (12.5)	26 (74.3)	.002[a]

mos = months; PHC = photocoagulation; PMA = postmenstrual age; ROP = retinopathy of prematmity; SD = standard deviation; wks = weeks.
[a]Fisher exact test.
[b]*t* test.
[c]Mann–Whitney *U* test.

recurrence of fibrovascular tissue is almost impossible. The follow-up period after vitrectomy exceeded 6 months in all eyes in the analysis. All surgeries were performed by 1 surgeon (N.A.).

Data collected from each case record included gender, gestational age, birth weight, the Apgar score at 5 minutes, the duration of intubation, and the presence of severe systemic complications (i.e., hydrocephalus, patent ductus arteriosus, or necrotizing enterocolitis requiring surgery). We included the duration of intubation as an indicator of the degree of oxygen exposure. ROP findings included the preoperative ROP stage, zone, fibrovascular tissue and vitreous base adhesion, clock hours of fibrovascular tissue, postmenstrual age at the initial application of photocoagulation, photocoagulation to both vascularized and nonvascularized retina (Figure 1) or only to nonvascularized retina (Figure 2), postmenstrual age at vitrectomy, and intraoperative hemorrhage. Although the area of photocoagulation generally is limited to the nonvascularized retina, because the importance of photocoagulation to the vascularized retina has been suggested in eyes with severe ROP,[15,16] we included eyes treated with photocoagulation applied to both the vascularized and nonvascularized retina. ROP findings were recorded by detailed retinal drawings and RetCam (Massie Research Laboratories, Inc, Pleasanton, California, USA). The eyes that fulfilled the inclusion criteria were divided into 2 groups based on the recurrence or absence of recurrence of fibrovascular tissue after surgery. The factors listed previously were compared between the 2 groups.

Statistical analyses were performed using statistical software (StatLab, SPSS for Windows, version 16.0; SPSS, Inc, Chicago, Illinois, USA). Univariate analyses to determine the association between risk factors and recurrence after early vitrectomy were performed using the Mann–Whitney *U* test, the *t* test, and the Fisher exact test as appropriate. A multivariate logistic regression model was constructed with recurrence as the dependent variable and with the factors that differed at the significance level of $P < .2$ in univariate analyses, including the gestational age, preoperative ROP stage, fibrovascular tissue and vitreous base adhesion, the postmenstrual age at the initial application of photocoagulation, and photocoagulation to both the vascularized and nonvascularized retina as independent variables. $P < .01$ was considered significant.

RESULTS

A TOTAL OF 50 EYES OF 31 PATIENTS (19 GIRLS, 12 BOYS) underwent early vitrectomy. Among them, 5 (10%) eyes that had not received sufficient photocoagulation even to the nonvascularized retina and 2 (4%) eyes that had extensive fibrovascular tissue adhesion to the vitreous base were excluded. Forty-three eyes (86%) of 29 patients were included. Of the 29 patients, 19 were girls and 10 were boys, with a mean gestational age of 25.2 ± 2.3 weeks and a mean follow-up of 23.8 ± 10.7 months.

Eight (18.0%) of 43 eyes had a recurrence of fibrovascular tissue after surgery (Figure 2), and the others did not have a recurrence and the retina reattached (Figure 1). The recurrences, which began 2 to 8 weeks after surgery and progressed gradually, were characterized by proliferation that developed mainly toward the vascularized posterior retina probably via the residual vitreous framework, where fibrous strands often formed between the disc and the fibrovascular tissue with an irregular tractional retinal detachment (Figure 2). Three of the 8 eyes underwent a second vitrectomy 1 to 2 months after surgery because of severe recurrent fibrovascular tissue with a total retinal detachment. Because recurrent fibrovascular tissue adhered strongly to the retina where the tissue was not removed completely, retinal reattachment was obtained in only 1 eye. Four of 8 eyes had a recurrence of fibrovascular tissue that was less severe with a partial retinal attachment after primary surgery, and 1 eye had early progression to phthisis bulbi, and a second vitrectomy was not performed.

The data and statistics are summarized in the Table. There were more boys in the recurrence group than in the nonrecurrence group, but the difference was not significant ($P = .042$). There were no significant differences in the other baseline characteristics between the 2 groups. Before surgery, the incidences of both stage 4B and fibrovascular tissue adhesion to the vitreous base were slightly higher in the recurrence group, but these did not reach significance ($P = .067$ and $P = .037$, respectively). Photocoagulation was applied more often to both vascularized and nonvascularized retina in the group in which there was no recurrence of fibrovascular tissue compared with the group in which there was recurrence (74.3% vs 12.5%); the difference between the two was significant ($P = .002$). There was no difference in the ROP findings between the 2 groups. Multivariate analyses using a stepwise logistic regression model also showed that only photocoagulation to both the vascularized and nonvascularized retina (odds ratio, 0.049; 95% confidence interval, 0.005 to 0.459; $P = .008$) was associated with postoperative recurrence of fibrovascular tissue, and the other factors were not significantly associated with recurrence.

DISCUSSION

THE RECURRENT FIBROVASCULAR TISSUE DEVELOPED mainly toward the posterior retina in 8 eyes. The main purpose of early vitrectomy to treat AP ROP is to remove the vitreous framework through which fibrovascular tissue aggressively and rapidly grows to reach the posterior lens surface and the ciliary body or vitreous base, which has condensed vitreous.[9] Thus, almost all vitreous gel, especially in the vitreous base and around the fibrovascular tissue, needs to be resected during vitrectomy; however, some vitreous gel remains on the surface of the posterior retina because of tight adherence to the retina[17] that prevents creation of a posterior vitreous detachment. In addition, vitreous on the avascular retina that is anterior to the fibrovascular tissue is liquefied partially by dense photocoagulation,[18] in contrast to vitreous on the vascularized posterior retina. Consequently, recurrent fibrovascular tissue can develop easily on the posterior retina via the residual vitreous when the disease activity is not controlled before surgery.

Three of 8 eyes with recurrent fibrovascular tissue underwent a second vitrectomy. Because vitreous attachment to the retina in neonates is very strong where the dense collagen fibers of the vitreous are connected to the retina,[17] tight adhesion develops between the recurring fibrovascular tissue and the retina. Thus, once the tissue forms, total removal of the tissue to release the traction is almost impossible, and attention must be paid to developing prophylactic measures to prevent recurrence of the fibrovascular tissue.

Although early vitreous surgery prevents progression of retinal detachment and dramatically improves the visual prognosis of AP ROP,[9] the current study showed that some eyes had postoperative recurrence of fibrovascular tissue and that photocoagulation applied to vascularized retina may be the most important factor to minimize the incidence of recurrence. In classic ROP, the retinal vasculature is completed in the vascularized posterior retina,[19] where photocoagulation to only nonvascularized retina is sufficient.[2] In contrast, a wide-field area of hypoperfusion has been detected in nonvascularized retina and in vascularized retina in AP ROP.[20] In these cases, application of photocoagulation to only the nonvascularized retina is insufficient, because angiogenic factor continues to be released from the hypoperfusion retina[21,22] that is already vascularized, although angiogenic factor in the vitreous cavity may be washed out transiently by vitrectomy.[23]

One report on eyes with AP ROP suggested the importance of additional application of photocoagulation to the nonvascularized retina beneath regressing flat neovascularization that is left untreated,[24] and several studies reported the necessity of applying photocoagulation to already vascularized retina posterior to the junction.[15,16] Our previous study[20] and the results of the current study strongly suggested that dense photocoagulation to both the

vascularized retina and nonvascularized retina in eyes with AP ROP is essential for a good prognosis because it prevents aggressive disease progression and inhibits postoperative recurrence of fibrovascular proliferation. However, extensively applied photocoagulation not only to nonvascularized retina but also to vascularized retina may have several side effects, including reduced night vision, insufficient dark adaptation, loss of peripheral vision, blind spots, a risk of cystoid macular edema, and neovascularization. However, preserving the posterior retina by extensive preoperative photocoagulation and early vitreous surgery may be more beneficial for visual prognosis in patients with AP ROP.

Although an anti-vascular endothelial growth factor drug that inhibits the process of neovascularization prevents progression of the severe form of ROP,[25–27] the drug also causes excessive scar formation in ROP.[26,28] A transforming growth factor beta antagonist and rho kinase inhibitor are candidates for preventing vitreoretinal proliferation.[29] A preoperative or postoperative enzymatic approach for vitreolysis may reduce recurrence by resolving the residual vitreous gel that is difficult to detach from the retina mechanically;[30] however, the effects of such drugs on ROP have not been studied, and the long-term systemic effects on neonates are unknown. In addition, because the activity of AP ROP is very high, their contribution to the treatment of AP ROP may be minimal. Meanwhile, photocoagulation to treat ROP is safe. Thus, preoperative photocoagulation that includes the vascularized posterior retina may be the most reasonable approach for obtaining good visual prognosis in eyes with AP ROP.

The limitations of the current study are its retrospective nature, the absence of a control group, and the nonstandardized protocols for both photocoagulation and vitrectomy in patients with AP ROP in some institutions. Nevertheless, the total sample size of 50 eyes and the follow-up periods ranging from 7 to 42 months seem adequate for analyzing a correlation between recurrence after early vitreous surgery and the associated risk factors. A randomized controlled trial is warranted.

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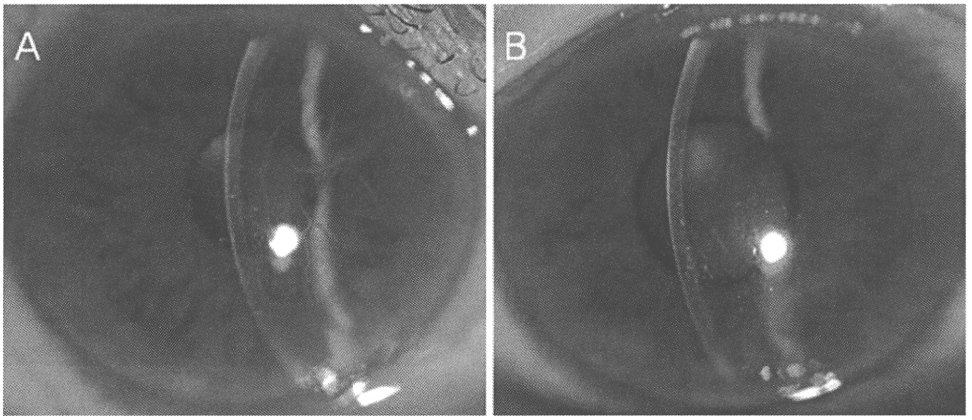

Figure 1A, B. Slit-lamp photographs demonstrating the corneal findings. **A** Several bifurcating, thick lattice lines in the superficial stroma are noted in the right eye. **B** Discrete and nodular opacities are noted in the deep stroma of the central cornea in the patient's left eye.

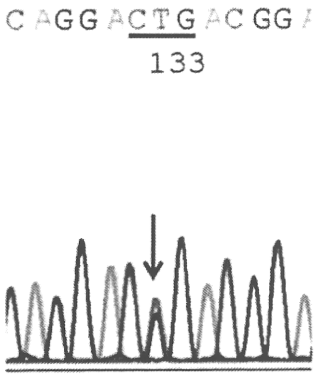

Figure 2. Results of the direct sequencing of exon 12 in the *TGFBI* gene. A heterozygous L527R mutation (CTG→CGG) is detected.

with the L527R mutation is unique in terms of its late onset, sporadic occurrence, and regional idiosyncrasy. It has been reported that the L527R mutation is descended from a founder mutation that occurred in a single Japanese ancestor.[5] Therefore, additional data are required to elucidate the clinical and genetic manifestations of lattice corneal dystrophy associated with the L527R mutation.

Keywords: lattice corneal dystrophy, L527R mutation, *TGFBI* gene

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Endogenous Candida Chorioretinitis in a Healthy Infant

Endogenous *Candida* endophthalmitis is often observed in patients with a history of recent major surgery, bacterial sepsis, use of systemic antibiotics, placement of central venous catheters, or a combination of these. Newborns, especially those born prematurely, do not have a sufficiently developed immune system against pathogens; however, they rarely develop endogenous fungal infections. Several infants with *Candida* chorioretinitis have been reported so far, all of whom had undergone surgery or total parenteral alimentation, received antibiotics, or were not full-term babies.[1] We report a case of a healthy infant with endogenous *Candida* chorioretinitis who had no risk factors for an opportunistic infection.

Case Report

A 41-week-gestation female infant (body weight, 2910 g) was delivered by Caesarean section because of delayed labor. No problems occurred during the developmental and perinatal periods. At 6 months of age, she became transiently febrile with temperatures above 38°C despite a lack of other systemic symptoms and was hospitalized for administration of transvenous antibiotics (piperacillin for 3 days and panipenem/betamipron for 10 days). After 2 weeks, she became

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afebrile, and a prominent conjunctival injection developed bilaterally. Slit-lamp biomicroscopy identified posterior synechiae and nodules in the iris of the left eye. Ophthalmoscopy identified multiple white lesions along the retinal vessels bilaterally and an exudative total retinal detachment in the left eye (Fig. 1). Fluorescein angiography (FA) showed anastomosis of the vessels and an avascular area in the peripheral retina of the right eye (Fig. 1). Whole-body computed tomography and biochemical, immunological, and culture examinations of blood and cerebrospinal fluid failed to detect any abnormalities. Polymerase chain reaction (PCR) analysis detected *Candida* DNA in the cerebrospinal fluid (2.4×10^2 copies/ml) and vitreous (9.4×10^4 copies/ml) obtained by needle aspiration. Immunological and culture examinations of blood and vaginal secretion from the mother failed to identify any signs of *Candida* infection. After administration of fluconazole (intravenous injection of 100 mg for 3 weeks, then 50 mg orally for 3 months), the retina of the left eye reattached and the volume of white lesions decreased, resulting in residual retinal scars (Fig. 2).

Comment

Endogenous *Candida* endophthalmitis is commonly seen in compromised hosts. Only two adult cases of *Candida* endophthalmitis without severe systemic disease have been reported, one in a patient with a common cold and the other

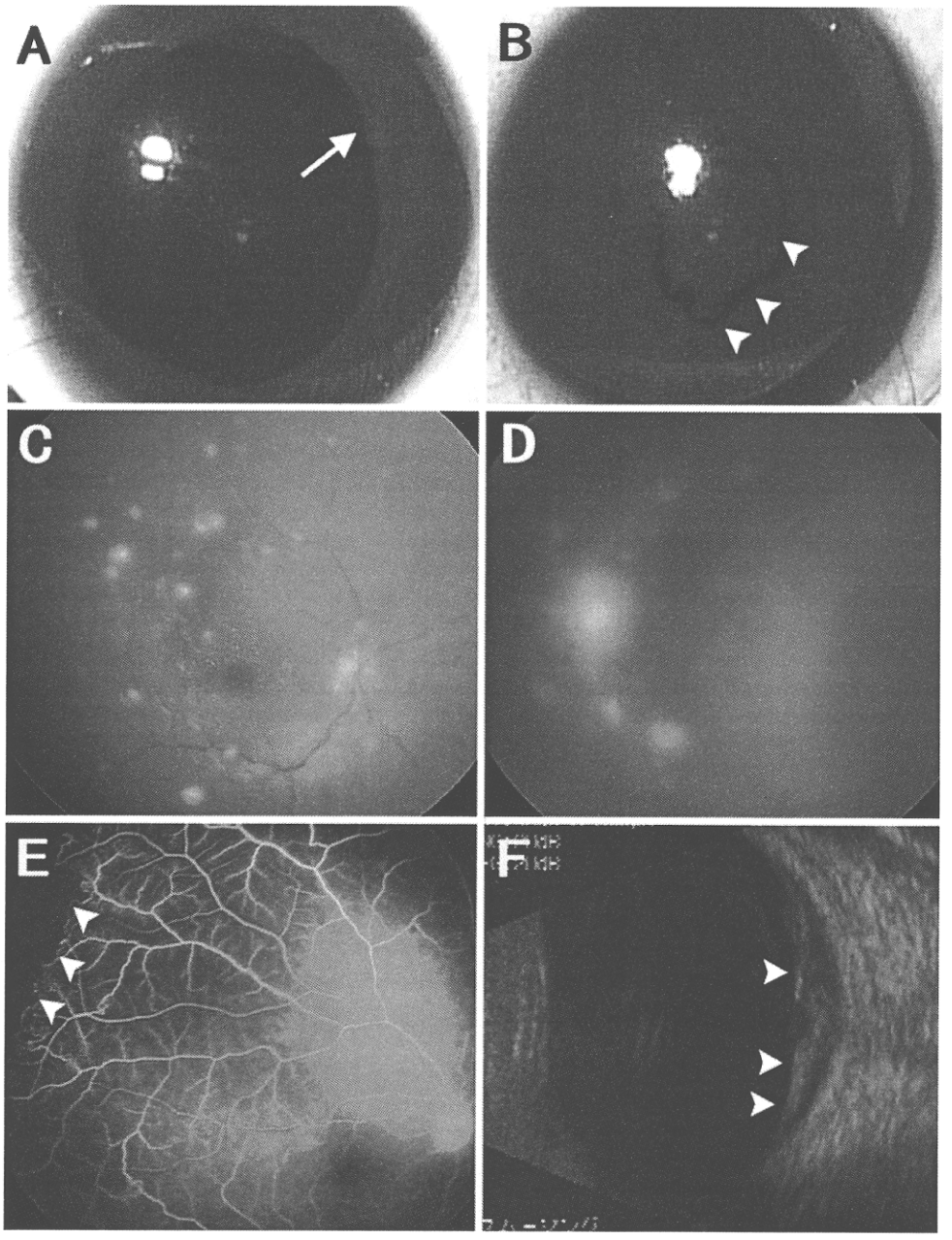

Figure 1A–F. Chorioretinitis before treatment. Photographs of the anterior segment (**A, B**) and fundus (**C, D**); fluorescein angiogram (**E**); and ultrasonogram (**F**). **A, C, E** Right eye; **B, D, F** left eye. **A** A slight posterior synechia of the iris margin (*arrow*) was observed. **B** An entire posterior synechia and nodules of the iris (*arrowheads*). **C** Multiple white lesions were seen along the retinal vessels. **D** Exudative retinal detachment and multiple white lesions were observed along the retinal vessels. **E** An avascular area in the peripheral retina (*arrowheads*) and anastomosis of vessels and leakage from retinal veins were observed, despite no staining of the white lesions. **F** Retinal detachment (*arrowheads*) was detected by ultrasonography.

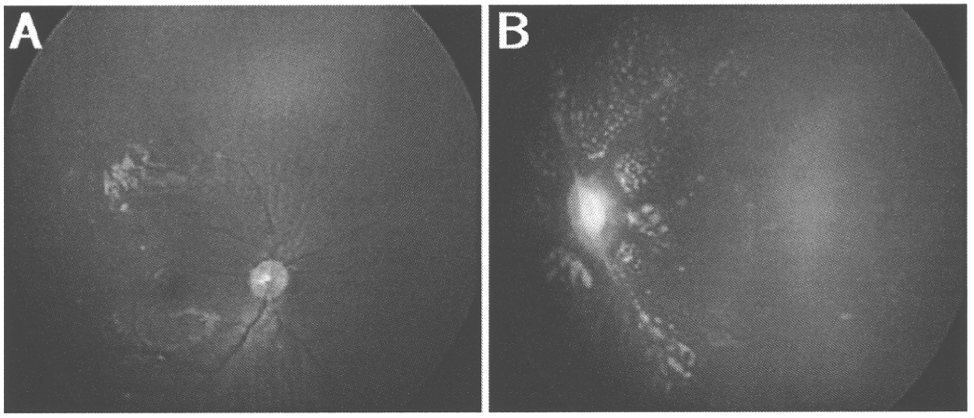

Figure 2A, B. Fundus photographs of the **A** right and **B** left eyes 1 month after administration of fluconazole. **A** The size of the white lesions had decreased significantly. **B** Retinal reattachment with hard exudates, white vessels, and optic disc pallor were observed.

in a patient with *Candida* vaginitis and onychomycosis; both patients were treated with antibiotics.[2,3] The current patient had no systemic abnormalities but evidently had endogenous *Candida* endophthalmitis because PCR analysis detected sufficient quantities of *Candida* DNA in the vitreous and the cerebrospinal fluid to diagnose the infection. FA findings of abnormal vasculature in the peripheral retina are usually seen in eyes with retinopathy of prematurity or familial exudative vitreoretinopathy, which prompted us to suspect that the *Candida* infection in the present case was congenital. Generally, a congenital *Candida* infection occurs by vertical transmission through the uterus or vagina and is associated with systemic involvement, including dermatitis, meningitis, anomaly of the brain, and oral mucositis.[4] However, the patient was delivered by Caesarean section, and no signs of *Candida* infection were detected in the mother. Thus, acquired *Candida* infection was the most likely diagnosis in the present case. Intravenous antibiotics delivered 2 weeks before the onset of bilateral endophthalmitis likely caused iatrogenic *Candida* infection because of inadvertent manipulation. Possible insufficient growth of the retinal vasculature might have facilitated the proliferation of *Candida* in the patient's retina.

To diagnose and treat such a difficult case, broad-range PCR for the 18S ribosomal RNA sequence is a good screening tool.[5] Moreover, real-time PCR can examine the quantity of the pathogen and determine its relation to the endophthalmitis. Early treatment of infectious endophthalmitis is essential in infants, in whom vision develops rapidly. Thus, a broad-range, real-time PCR system using ocular samples is useful when the patient has uveitis or endophthalmitis of unknown origin.

Keywords: *Candida* chorioretinitis, *Candida* infection, polymerase chain reaction

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Choroidal Neovascularization in a Child Following Laser Pointer-Induced Macular Injury

Laser pointer-induced macular injury is characterized by a decrease in visual acuity and metamorphopsia.[1] High-energy lasers can cause chorioretinal damage, which can lead to choroidal neovascularization (CNV) in animals.[2] Case reports of the development of a CNV following laser-induced macular injury have also been published.[3,4] We report the case of a child with a CNV that developed following a macular injury caused by repeated exposure to a green laser pointer. The prevalence of CNV in children is low, but it is still an important cause of visual impairment.[5] To the best of our knowledge, this is the first report of a child developing CNV following a macular injury caused by exposure to a green laser pointer.

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Case Report

An 11-year-old boy with decreased visual acuity in the right eye was referred to our hospital for consultation. The parents reported that the child stared directly at a commonly used green laser pointer. He did not understand the cautionary statement, and from the age of 2 to 3 years stared at it with his dominant right eye every day for more than 10 s at a time, as if it were a toy, at a distance of 30 cm. Although he had a congenital hearing loss and mental retardation, his visual functions developed normally up to the time of the injury. When he was 7 years old, his visual acuity was 1.0 OU, after correction of bilateral astigmatism, –4.0 diopters.

When he was 11 years old, his best-corrected visual acuity (BCVA) was 0.2 OD and 1.0 OS. No abnormalities were found in the anterior segment of either eye. Ophthalmoscopy identified a yellow exudate-like lesion or fibrous tissue surrounded by subretinal hemorrhage in the right macula (Fig. 1A). The left eye was completely normal. Two years later when he was 13 years of age, the fundus showed a yellow fibrous lesion in the right macula (Fig. 1B) that demonstrated leakage on fluorescein angiography (Fig. 1C, D). A STRATUS optical coherence tomography image showed a highly reflective mass that extended from the outer retinal layer through the retinal pigment epithelium and Bruch's membrane into the choroidal tissue of the right macula (Fig. 1E). The left eye was normal. Investigations for ocular infectious diseases did not reveal any disease.

We elected to follow the patient with careful observation and not to perform invasive therapy because of his age and mental condition. He is now 14 years old, and his BCVA and the appearance of the fibrous tissue are unchanged.

Comment

By the results of the ophthalmological examinations and the history of events, we diagnosed the patient as having laser pointer-induced macular injury. An accurate diagnosis of laser pointer-induced macular injury did not come easily, because it was difficult to interpret the complaints of the

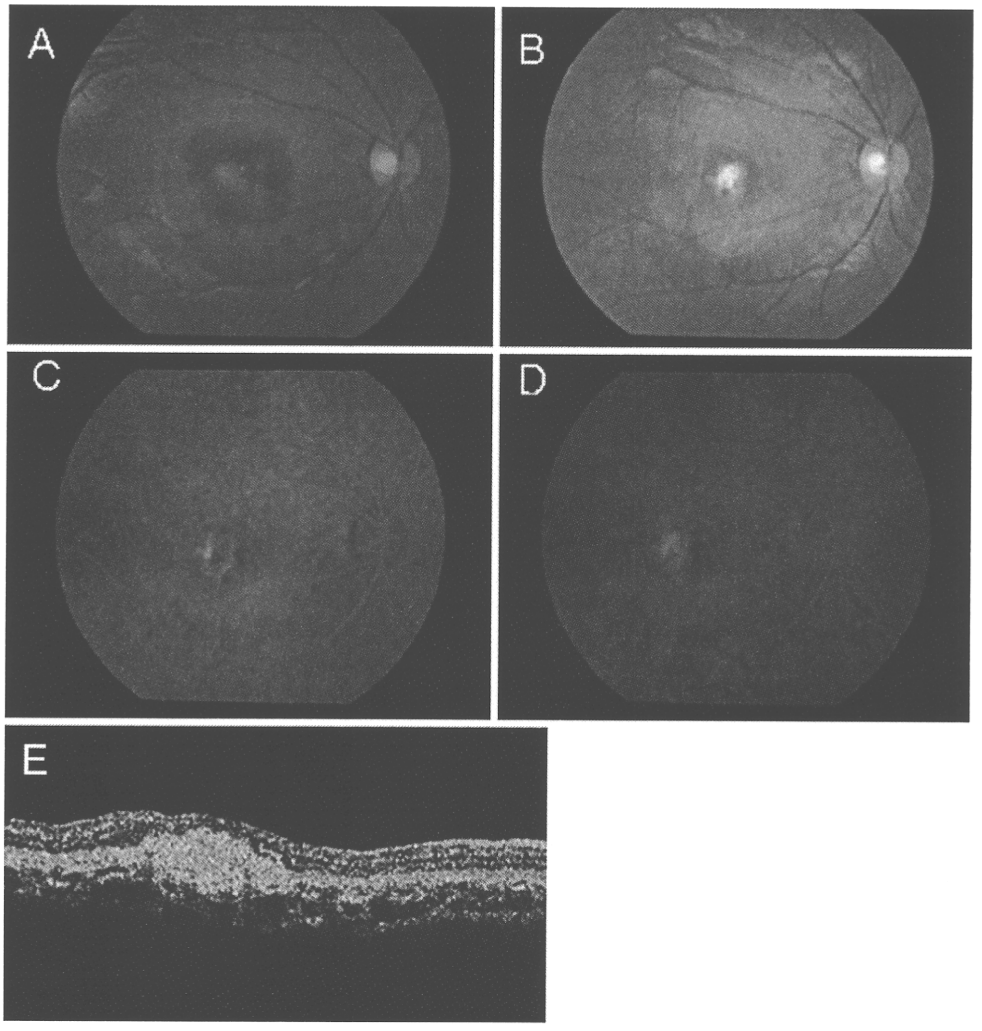

Figure 1A–E. Fundus images of the current case. **A** When the patient was 11 years old, the fundus of his right eye showed a yellow lesion resembling exudates or fibrous tissue surrounded by subretinal hemorrhage in the macula. **B** When he was 13 years old, the fundus showed a yellow lesion resembling fibrous tissue. **C, D** Fluorescein angiography showed leakage with fibrous tissue remaining in the right macula (**C** early phase; **D** late phase). **E** Optical coherence tomography demonstrated a highly reflective mass extending not only to the outer retinal layer and retinal pigment epithelium but also to the Bruch's membrane and choroidal tissue.

patient, and the time of the injury and initial examination were prolonged.

There is a correlation between the energy of a laser and the degree of chorioretinal damage it can cause. The output power of handheld laser pointers is commonly from 1 to 5 mW. Mild thermal retinal injuries might be caused by a 5-mW laser, if it is stared at for more than 10 to 20 s;[1] this suggests that the chorioretinal damage in our patient, which probably induced the CNV, was caused by the frequent and repeated exposure to the low-energy laser beam.

The prognosis of this patient is unclear, because the interval between the first laser exposure and the development of the CNV was long in comparison to previously reported cases. The patient is being carefully followed for the possible reactivation of the CNV.

Keywords: choroidal neovascularization, laser pointer, macular injury

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Spontaneous Closure of a Stage 2 Macular Hole Without Detachment of the Posterior Hyaloid

Stage 2 macular holes occasionally close spontaneously after hyaloid membranes with pseudo-opercula become separated from the surface of the retina. However, we observed spontaneous closure of a stage 2 macular hole without release of the vitreofoveal traction. This case was documented by means of optical coherence tomography (OCT).

Case Report

A 52-year-old man complained of metamorphopsia in his left eye. He was referred to a nearby clinic, and a macular hole in the left eye was diagnosed. He did not report any trauma. About 2 weeks later, he came to our clinic at Akita University Hospital. His best-corrected visual acuity was 20/16 in the right eye and 20/160 in the left. Slit-lamp examination showed no remarkable findings. Biomicroscopic examination did not reveal posterior vitreous detachment (PVD). OCT (Zeiss OCT3; Zeiss-Humphrey Systems, Dublin, CA, USA) showed the presence of a stage 2 macular hole with perifoveal cyst formation (Fig. 1A). The hole measured 336 μm in diameter and was partially covered with a retinal flap. A posterior hyaloid was present and adhered to the edge of the hole (Fig. 1B). Around the macular hole, there was a shallow PVD. He did not have any other ocular diseases such as diabetic retinopathy, retinal vein occlusion, macular telangiectasia, or uveitis.

Four months later, the patient's best-corrected visual acuity had improved to 20/30. OCT seemed to show the presence of an outer retinal bridge over the macular hole (Fig. 1C, D), indicating a spontaneous macular hole closure in process. The perifoveal cysts were no longer apparent. However, the patient still felt metamorphopsia in his left eye, and the posterior hyaloid remained adhered to the retinal flap (Fig. 1E). To release this adhesion and close the hole completely, we performed a pars plana vitrectomy. During the operation, we used triamcinolone acetonide to visualize the vitreous and observed the hyaloid attachment to the macular hole. We did not peel the internal limiting membrane because the macular hole was already bridged and we thought that releasing the attachment was sufficient to close the hole completely. At the end of the operation, air tamponade was used.

Seven days after the surgery, OCT showed the presence of a thick bridge and a well-defined retinal hyporeflective space interrupting the inner high-reflective layer (Fig. 2A). Seven months after surgery, the patient's best-corrected visual acuity remained at 20/30. The hyporeflective space had become quite small. Two and a half years after surgery, his best-corrected visual acuity was 20/20. OCT (Spectralis HRA+OCT; Heidelberg Engineering, Heidelberg, Germany) showed that the hyporeflective space no longer existed and the foveal morphology had progressed to almost normal (Fig. 2B).

Comments

As the use of OCT has become more common, many cases of spontaneous closure of macular holes have been reported.[1–4] Four explanations have been proposed for the