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Research Article

Keratoprosthetics as a visual rehabilitation method in patients with graft-versus-host disease

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ABSTRACT

The article is concerned with the treatment of a patient with allogeneic hematopoietic stem cell transplantation (HSCT) complicated by graft-versus-host disease with severe ocular manifestations. Hematopoietic stem cell transplantation is the standard therapy for a number of hemoblastoses and hereditary blood diseases, ensures the restoration of the immune system, however, in 40–60% of cases it is complicated by the development of graft-versus-host disease, with a five-year survival rate of no more than 40%. Patient S., 22 years old, was admitted to the ophthalmological center of St. Petersburg Multifield Hospital No. 2 in 2019 with a diagnosis of "Acute keratitis, corneal ulcer of both eyes". History of hematopoietic stem cell transplantation in 2018, complicated by graft-versus-host disease with multiorgan damage development was present. In total during the period 2019–2022, 7 tectonic keratoplasties were performed on both eyes, as well as penetrating keratoplasty on the left eye. After inflammation setback and left eye vascularized corneal leukoma formed, in December 2022, the first stage of keratoprosthetics (installation of the support element) was performed, and in May 2023, the second stage (implantation of the optical cylinder) took place. Visual acuity in one month after the implantation of the keratoprosthesis increased from light perception to 20/100, no correction possible. The use of "classical" methods of corneal ulcer perforation treatment in patients with graft-versus-host disease is ineffective due to the severe ocular surface xerosis, and keratoprosthetics seems to be the only effective method for restoring visual functions.

Keywords: keratoprosthetics; Fyodorov–Zuev keratoprosthesis; corneal neovascularization; graft-versus-host disease; allogeneic hematopoietic stem cell transplantation; keratitis; dry eye syndrome.

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Научная статья

Кератопротезирование как метод зрительной реабилитации пациентов с реакцией «трансплантат против хозяина»

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АННОТАЦИЯ

Статья посвящена случаю лечения пациента с аллогенной трансплантацией гемопоэтических стволовых клеток, осложнившейся реакцией «трансплантат против хозяина» с тяжёлыми глазными проявлениями. Трансплантация гемопоэтических стволовых клеток — стандартная терапия ряда гемобластозов и наследственных заболеваний крови, обеспечивающая восстановление иммунной системы, однако в 40–60 % случаев осложняющаяся развитием реакции «трансплантат против хозяина», с пятилетней выживаемостью, не превышающей 40 %. В офтальмологический центр СПб ГБУЗ «Городская многопрофильная больница № 2» в 2019 г. поступил пациент, 22 года, с диагнозом «острый кератит, язва роговицы обоих глаз». В анамнезе трансплантация гемопоэтических стволовых клеток в 2018 г., осложнившаяся развитием реакции «трансплантат против хозяина» с мультиорганным поражением. Всего за период 2019–2022 гг. было выполнено 7 тектонических кератопластик на обоих глазах, а также сквозная кератопластика на левом глазу. После стихания воспалительного процесса и формирования васкуляризированного бельма роговицы левого глаза в декабре 2022 г. был выполнен первый этап кератопротезирования (установка опорного элемента), а в мае 2023 г. — второй этап (имплантация оптического цилиндра). Острота зрения через месяц после выполнения кератопротезирования увеличилась с правильной светопроекции до 0,2 н/к. Применение «классических» методов лечения перфорации язвы роговицы при реакции «трансплантат против хозяина», как правило, неэффективно из-за выраженного ксероза глазной поверхности, и кератопротезирование представляется единственным эффективным методом восстановления зрительных функций.

Ключевые слова: кератопротезирование; кератопротез Фёдорова – Зуева; бельмо роговицы; реакция «трансплантат против хозяина»; аллогенная трансплантация гемопоэтических стволовых клеток; кератит; синдром сухого глаза.

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INTRODUCTION

Currently, allogeneic hematopoietic stem cell transplantation (HSCT) is the standard of care for many hematologic malignancies and inherited hematopoietic disorders [1]. HSCT involves the suppression of the recipient's hematopoiesis and the transplantation of the donor's hematopoietic stem cells (bone marrow, peripheral blood, or umbilical cord blood) to restore the patient's immune system. However, in 40–60% [2] of cases, HSCT is complicated by graft-versus-host disease (GVHD), which is an immune response to the recipient tissue [3, 4], with a five-year survival rate not exceeding 40% in cases of multiple organ involvement [5].

There are two types of GVHD: acute and chronic. The main criterion for differentiation is the time of onset of the complication; an acute reaction occurs in the first 100 days after HSCT, and a later reaction is considered to be chronic [6]. Acute GVHD is based on a cellular (T cell) response to the recipient tissue, while the chronic form is an autoimmune disease involving humoral immunity (B cell) and immune auto-aggression against both donor antigens and recipient tissues [3].

The main target organs for GVHD include the gastrointestinal tract, skin, liver, and lung, which are rich in antigen-presenting cells [3]. The lacrimal and salivary glands, the epithelium of the respiratory tract, and the bile ducts are usually also involved [5].

Ocular signs of GVHD include severe dry eye syndrome (DES) due to involvement of the bulbar and tarsal conjunctiva and abnormal changes in the lacrimal and meibomian glands [7]. Hyperkeratinization of the meibomian gland epithelium, leading to gland blockage, contributes to meibomian gland dysfunction [8]. In the early stages, GVHD manifests as conjunctivitis [9] with nonspecific complaints (burning, pain, redness, foreign body sensation, and dryness), which may be further complicated by filamentary keratitis (lacrimation, photophobia, blepharospasm, decreased visual acuity) with the potential for corneal ulceration [10]. Involvement of the bulbar and tarsal conjunctiva is associated with symblepharon, cicatricial entropion of the lower and upper eyelid, and trichiasis [11]. Ocular lesions are common in patients with GVHD, but in less than 2% of cases they progress to ulceration with corneal perforation, which is an unfavorable factor in terms of patient survival [12].

CASE REPORT

On October 9, 2019, a patient, male, 22 years old, was admitted to the Ophthalmologic Center of St. Petersburg City Multidisciplinary Hospital No. 2 with the diagnosis of acute keratitis and bilateral corneal ulcer. The patient had a history of HSCT for aplastic anemia in 2018, complicated by GVHD involving the skin (Figure 1), lungs (right pneumonectomy, 2018), and gastrointestinal tract (malabsorption syndrome). Since May 2019, he had bilateral eye pain, tearing, and photophobia. Since August 2019, he was followed-up by an ophthalmologist at the local clinic and was diagnosed with bilateral conjunctivitis. The patient was treated with an antibiotic (tobramycin) and a corneal protector (dexpanthenol). However, no significant effect was reported. At the end of September 2019, the patient noted a rapid decrease in visual acuity in both eyes, increased pain, and bilateral eye dryness. The patient presented to St. Petersburg Diagnostic Center No. 7 (Ophthalmology) and was referred to St. Petersburg City Multidisciplinary Hospital No. 2.

On admission, uncorrected visual acuity of the right and left eyes was 0.04 and 0.1, respectively, and significant xerosis of the ocular surface with bilateral corneal ulceration was reported.

Treatment was initiated with subconjunctival injections of ceftriaxone 0.05 g with dexamethasone 0.002 g (once a day), instillations of levofloxacin 0.5% and dexamethasone 0.1% (4 times a day), cyclosporine 0.05% (twice a day), lubricant with hyaluronate 0.3% (8 times a day), ophthalmic ointment with vitamin A 250 IU (once a day at night), as well as intravenous dexamethasone (initial dose 16 mg per day, followed by a decrease of 4 mg every 2 days) but it did not improve the ocular surface condition.

Despite the treatment, one week later, corneal ulcers perforated in both eyes, requiring surgical treatment. Given the extensive ulcerated defect, a tectonic keratoplasty was performed with a porous polytetrafluoroethylene plate, but one week later, it was torn off due to suture failure. The next surgical procedure was bilateral keratoplasty with sclera desiccated with silica. Unfortunately, this surgery also failed to stabilize the process, and repeated surgeries were required in both eyes.

For 2019–2022, a total of 7 tectonic keratoplasties were performed on both eyes and a full-thickness cornea

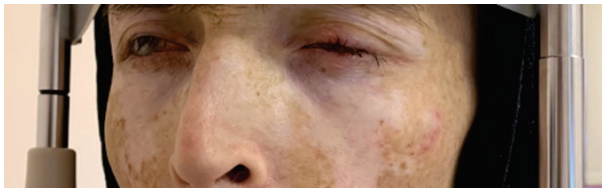

Fig. 1. Appearance of the patient, skin manifestations of graft-versus-host disease: poikiloderma, skin depigmentation
Рис. 1. Внешний вид пациента, кожные проявления реакции «трансплантат против хозяина»: пойкилодермия, депигментация кожи

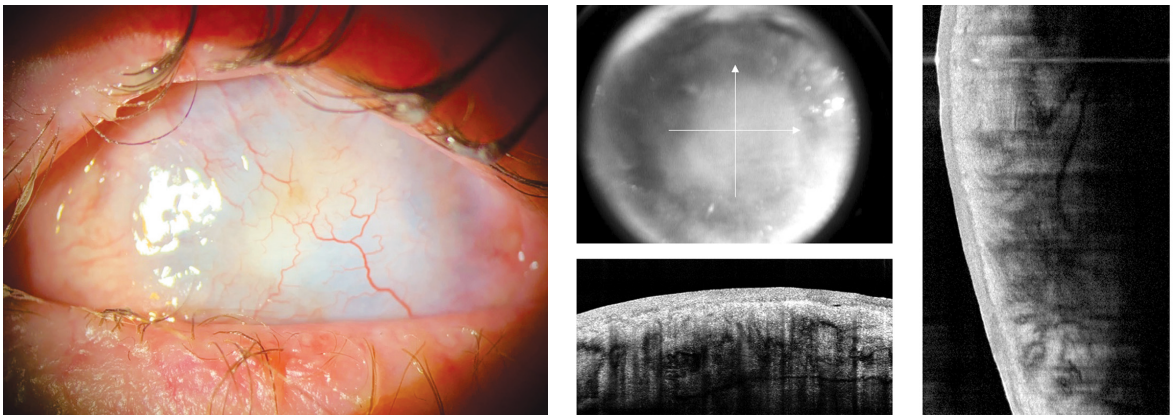

Fig. 2. The state of the left eye before the first keratoprosthetics stage: vascularized corneal leukoma with central thickness of about 1 mm
Рис. 2. Состояние левого глаза перед первым этапом кератопротезирования: сформировавшееся васкуляризированное бельмо роговицы 5-й категории с толщиной в центре около 1 мм

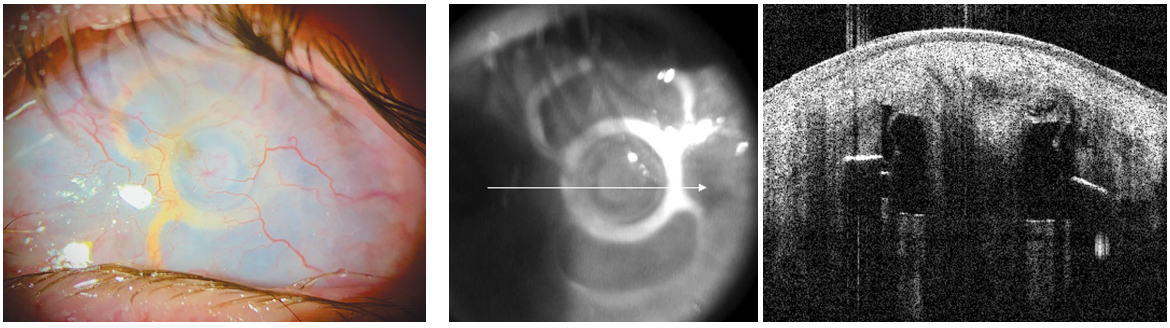

Fig. 3. The results of the first stage of Fyodorov–Zuev keratoprosthesis implantation into the left eye (positioning of the support keratoprosthesis element into vascularized leucoma of the left eye cornea)
Рис. 3. Результаты первого этапа кератопротезирования (установка опорного элемента кератопротеза Фёдорова – Зуева в толщу васкуляризированного бельма роговицы левого глаза)

transplant was performed on the left eye. It should be noted that one of the tectonic keratoplasties involved the left intracapsular cataract extraction. Considering the impossibility of adequate control of retinal and optic nerve status and the inevitable development of secondary glaucoma due to synechial block of the iridocorneal angle, bilateral Ahmed valve implantation was performed in 2020. In the left eye, the silicone drainage was removed due to exposure of the valve tube and development of symblepharon.

By October 2022, the process had stabilized with a vascularized leukoma and partial symblepharon in both eyes. The visual acuity of both eyes was equal to the correct light projection. The patient required constant lubrication therapy.

To restore visual function, it was decided to perform optical keratoprosthetics using the Fedorov–Zuev prosthesis [13] in the left eye. Sufficient thickness of the cornea in the center (about 1 mm) (Fig. 2) allowed performing the first stage of the keratoprosthetics (Fig. 3) in December 2022, i.e., implanting a full-thickness 8 mm supporting element into the vascularized corneal leukoma.

The postoperative period was uneventful, with no evidence of protrusion of the keratoprosthesis supporting element (outside or into the anterior chamber). Six months later, in May 2023, the second stage of the keratoprosthetics was performed: implantation of a 58 D optical cylinder with a protrusion height of 1.5 mm (Fig. 4).

The postoperative period was uneventful, with no signs of infection or external filtration, and the patient reported an improvement in uncorrected visual acuity to 0.02. Sonography showed a flat serous detachment of the choroid, which resolved with instillations of dexamethasone 0.1% (4 times daily) for 1 week. A small blood clot behind the optical cylinder was lysed within 2 weeks. Uncorrected visual acuity improved to 0.1. In the postoperative period, in addition to dexamethasone, the patient received instillations of levofloxacin 0.5% (4 times daily for 10 days) and continued therapy with lubricants containing hyaluronate 0.3% (8 times a day).

At discharge, the left fundus was ophthalmoscoped. The optic disc was pale and well-defined with a cup-to-disc ratio of 0.4. There were no focal macular or peripheral gross abnormalities. Optical coherence tomography of the macula and optic disc showed no structural changes in the examined areas of the fundus (Fig. 5).

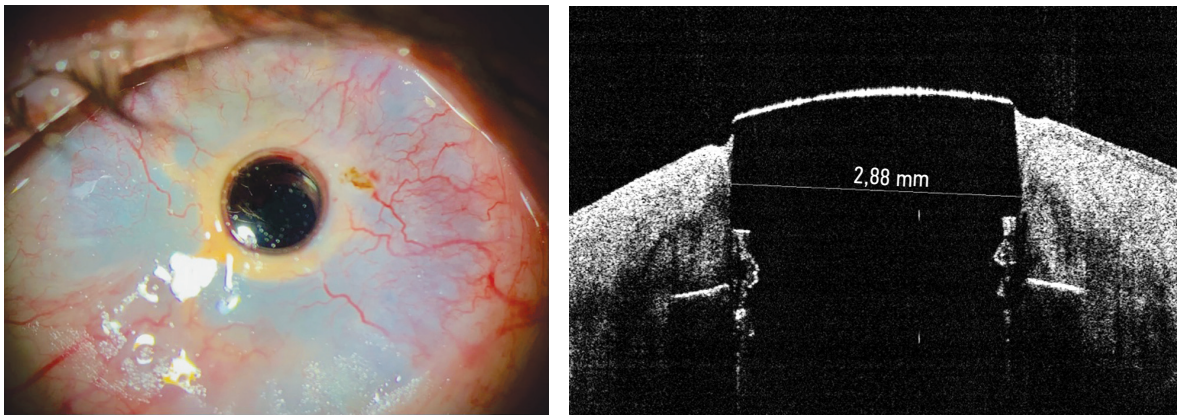

Fig. 4. The results of the second stage of the Fyodorov–Zuev keratoprosthesis implantation on the left eye (positioning of the optical cylinder into the support keratoprosthesis element)
Рис. 4. Результаты второго этапа кератопротезирования (установка оптического цилиндра) на левом глазу

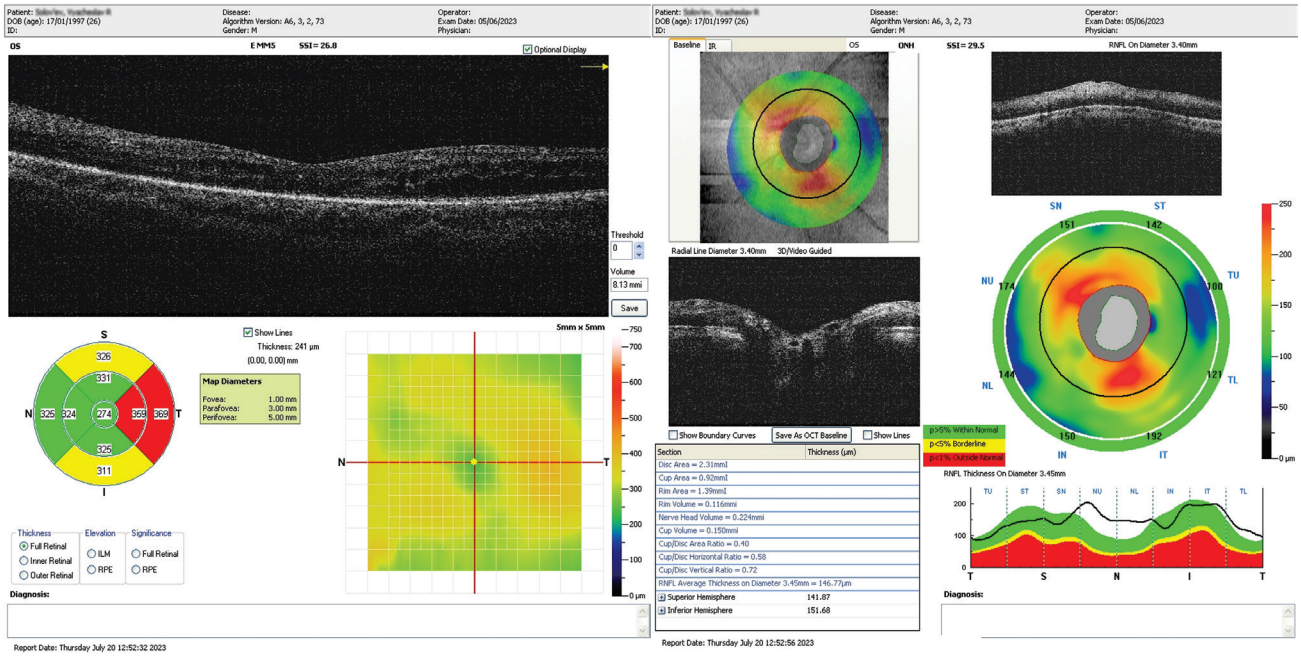

Fig. 5. Optical coherence tomography of macular area and optic nerve head of the left eye
Рис. 5. Оптическая когерентная томография макулярной зоны и диска зрительного нерва левого глаза

At 1 month postoperatively, uncorrected visual acuity was 0.2 in the left eye, and the supporting element and optical cylinder of the keratoprosthesis were correctly positioned with no evidence of protrusion.

Six months after surgery, the uncorrected visual acuity of the left eye remained the same (0.2), and the position of the supporting element and the optical cylinder of the keratoprosthesis did not change (Fig. 6).

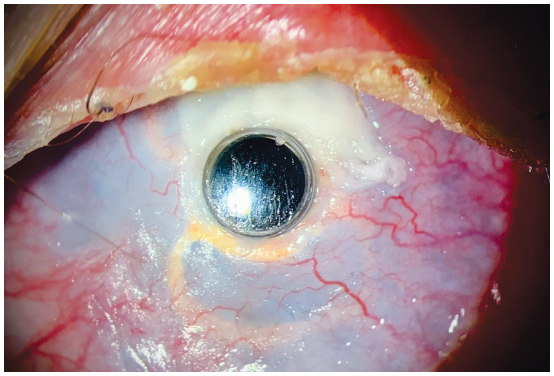

Fig. 6. Biomicroscopic appearance six months after the second stage of keratoprosthetics
Рис. 6. Биомикроскопическая картина через полгода после второго этапа кератопротезирования

DISCUSSION

The treatment of severe ocular symptoms of GVHD is a challenging task due to the ineffectiveness of "conventional" anterior segment reconstructive surgery (amniotic/tectonic/lamellar/penetrating keratoplasty) in the

setting of severe dry eye syndrome and limbal failure with corneal conjunctivalization [10]. After unsuccessful tectonic and penetrating keratoplasties, the immune-mediated inflammatory process stabilized with leukoma of the left eye (Filatov–Bushmich category V) [14]. The presence of symblepharon clearly required keratoprosthesis as the only possible method to restore visual function in this setting [15].

The two-component Fedorov–Zuev model (1972) [13] was chosen as the keratoprosthesis because of its availability in Russia, high speed of production and delivery to the clinic. According to the literature [15], the optimal method of keratoprosthesis implantation is a two-step technique. The first step is the insertion of a supporting element of the keratoprosthesis into the corneal stroma without opening the anterior chamber, and the second step is the implantation of an optical cylinder. The two-step technique prevents some typical complications of this procedure, such as the protrusion of the support element. It also allows correcting of refractive error by replacing the optical part of the prosthesis and excising the retroprosthetic fibrous tissue in case of its growth after unscrewing the optical cylinder.

A postoperative flat serous detachment of the choroid was expected in this patient due to the hypotony after the implantation of the optical cylinder of the keratoprosthesis. However, dexamethasone instillations quickly resolved this complication.

An optical cylinder with a power of 58 diopters with an axial length of the left eye of 23.23 mm made it possible to achieve near-emmetropia in the eye, as determined by subjective refraction assessment. Unfortunately, it was not possible to evaluate postoperative refraction with an autorefractometer.

The duration of patient follow-up from the first clinic admission to the second stage of keratoprosthesis implantation was 46 months. A total of 14 operations were performed. International literature also reports challenges in treating ocular surface lesions in patients with

Table. Case series of patients with corneal ulcer treatment against the background of graft-versus-host disease, according to C.Y. Zhang, et al. [12]

Таблица. Серии случаев лечения пациентов с язвой роговицы на фоне реакции «трансплантат против хозяина» по данным C.Y. Zhang и соавт. [12]

Case	Time from HSCT to corneal perforation, months	BCVA at first eye care visit	BCVA at the follow-up visit	Number of keratoplasties	Systemic immunosuppression	Topical CS therapy
1	26	1.0	0.3	2	Prednisolone	N/A
2	29	0.35	pr. l. incerta	0	Tacrolimus, prednisolone	Yes
3	33	1.0	Anophthalmi	0	Tacrolimus, prednisolone	Yes
4	31	1.0	pr. l. certa	0	Tacrolimus, mycophenolate mofetil, ruxolitinib, prednisolone	Yes
5	6	0.3	0.2	1	Tacrolimus, prednisolone	Yes
6	152	0.6	0 (nil)	2	N/A	N/A
7	60	0.06	0.05	3	Prednisolone	N/A
8	202	0.06	0.005	0	Not used	Yes
9	98	1.0	0.005	3	Sirolimus, prednisolone	N/A
10	33	0.5	0.3	1	Not used	Yes
11	20	0.8	0.3	1	Sirolimus, mycophenolate mofetil, prednisolone	No
12	21	1.0	0.4	0	Tacrolimus, prednisolone	Yes
13	65	0.4	pr. l. certa	3	Cyclosporine, prednisolone	No
14	19	1.0	0.07	0	Sirolimus, prednisolone	Yes

Note. HSCT, hematopoietic stem cell transplantation; BCVA, best corrected visual acuity; CS, corticosteroids.

GVHD. For example, C.Y. Zhang et al. described heterogeneous treatment outcomes for this group of patients (see Table), with objective visual acuity remaining significantly reduced despite the best efforts of clinicians [12].

CONCLUSION

Graft-versus-host disease is a serious complication of hematopoietic stem cell transplantation. Ocular symptoms of GVHD include severe dry eye syndrome, which can be treated conservatively in most cases. Approximately 2% of patients develop severe keratitis with perforating corneal ulcers. In such cases, conventional treatments such as tectonic/lamellar/penetrating keratoplasty or keratoplasty with amniotic membrane transplant are ineffective due to severe ocular surface xerosis. We believe that keratoprosthetics is the only method to restore visual function once inflammation has resolved and vascularized corneal leukoma has formed.

ADDITIONAL INFORMATION

Authors' contribution. All authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published, and agree to be accountable for all aspects of the study. Personal contribution of each author: D.F. Belov — concept and writing of the article, literature review; V.P. Nikolaenko — text writing, literature review; V.P. Petukhov — collection and processing of photographic materials, literature review, writing the text of the article.

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Competing interests. The authors declare that they have no competing interests.

Consent for publication. Written consent was obtained from the patient for publication of relevant medical information and all of accompanying images within the manuscript.

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