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Application of diglycidyl methylphosphonate ointment for the treatment of actinic keratosis, Bowen's disease and basal cell carcinoma under the control of dermatoscopy

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ABSTRACT

Non-melanoma skin cancer (NMSC), which includes basal cell (BCC) and cutaneous squamous cell (cSCC) carcinomas in its structure, is the leading among malignant skin tumors (MST). Among the measures for the prevention of invasive forms of MST, the detection and treatment of early forms, which for cSCC include actinic keratosis (AK) and Bowen's disease (BD) can be mentioned. The use of topical drugs is an alternative method in case of impossibility of surgical removal and radiation therapy of MST for the treatment of AK in the presence of "carcerization fields" and location in esthetically demanding areas. According to the literature, the use of diglycidyl methylphosphonate ointment gives a clinical positive effect in the treatment of MST. A series of cases of diglycidyl methylphosphonate drug use for the treatment of AK, BD and BCC under the control of dermatoscopy is described.

Objective. To determine the effectiveness of the diglycidyl methylphosphonate ointment application for the treatment of AK, BD and BCC with low risk of recurrence in the presence of contraindications or patient's refusal from treatment by method of choice in accordance with the current clinical guidelines under the control of dermatoscopy.

Material and methods. The study was conducted on the basis of the PRMU's center of diagnosis and treatment of skin tumors. Dynamic clinical and dermatoscopic changes of 5 elements of AK, 3 elements of BD and 1 element of BCC on the therapy with diglycidyl methylphosphonate ointment are described.

Results. The use of diglycidyl methylphosphonate ointment for the treatment of AK, BD and BCC elements has shown good clinical and cosmetic results.

Conclusion. Dermatoscopy is an additional objective method of evaluating the effectiveness of AK, BD and BCC topical therapy. Dynamic monitoring for residual dermatoscopic signs is recommended in case of pronounced clinical effect from the diglycidyl methylphosphonate ointment use for the treatment of AK and BD.

Keywords: *malignant skin tumors (MST), diglycidyl methylphosphonate ointment, actinic keratosis, Bowen's disease, basal cell carcinoma.*

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Introduction

Currently, interest in the prevention of malignant skin neoplasms (MSNs) has increased due to growing number of identified cases. Non-melanoma skin cancer (NMSC), including basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), takes the first place in Russia in general structure of MSNs according to the data for 2020 [1].

Cumulative ultraviolet (UV) irradiation is the main trigger factor of NMSC. The increase of morbidity is associated with the prolongation of UV-effects due to the increment of population life expectancy, changes in clothing style and the decrease in the ozone layer. Other causes include some genetic diseases and immunosuppression. There are no background processes for NMSC, and pre-malignancies, including actinic keratosis (AK), are identified only in the development of SCC [2].

The AK can be developed by 3 scenarios over time: spontaneously regress, remain stable and transform into SCC. Evaluation of the frequency of each scenario is difficult because, for example, in case of spontaneously regressive foci their subsequent recurrence is described in 15-53% of cases [3]. The transformation frequency of single AK in SCC structure is assessed from

0.025 to 20% for a year according to the meta-analysis results [4]. In case of multiple AK foci (>5) the probability of malignant transformation increases [5].

Currently, probable signs of malignant transformation include AK density in palpation, bleeding, rapid growth in diameter, redness and ulceration [4]. Clinical and dermoscopic features of the beginning of AK transformation into SCC are disputable until the present that requires to treat all AK foci [6].

The active detection and treatment of disease's early forms can be considered as measures of MSNs secondary prevention. MSNs prevention is especially relevant for invasive forms because their development reduces the quality and expectancy of patients' life and associates with economic costs [7]. Thus, the detection and treatment of AK and Bowen's disease (BD) refers to the prevention of MSNs invasive forms.

Treatment possibilities of NMSC local stages include primarily surgical treatment, and in case of contra-indications to it — radiation therapy, application of topical drugs and physical methods [8, 9].

The most common localization of neoplasms, namely open skin areas, that include face, scalp, decollate, forearms, should be considered when choosing the AK treatment method. These are esthetically demanding areas where you should prefer cosmetically sparing exposure methods.

The theory of "cancerization field", according to which there are subclinical transformed cells in the epithelium periphery, should be taken into account when choosing treatment in the case of multiple AK and/or BD foci. According to this theory, the exposure area in treatment should be larger than the area of visible foci [10, 11].

Methods of physical destruction (radio-wave destruction, laser, cryodestruction, electrocoagulation, etc.) influence only directly in the place of the applied impact, without involving peripheral tissue. Topical and photodynamic therapy can be attributed to the methods that can be applied in the treatment considering "cancerization field" [12].

Glyciphon is approved in the Russian Federation among topical drugs for AK treatment in accordance with the instructions for use and with the possibility of impact on surrounding tissues. The preparation is produced in the form of ointment for topical application, the active substance is di(2,3-epoxypropyl) ester of methyl-phosphonic acid. The drug is also registered as a medicinal agent for external application for treatment of stage I SCC, BCC (including reccurences after surgery or radiation treatment), BB, marketing authorization LP-№(003693)-(RG-RU) dated 15.11.2023.

According to the current Russian literature, the use of *Glyciphon* ointment gives a significant clinical positive effect in the treatment of NMSC [13]. Dermoscopy has become a routine method of additional examination, allowing to suspect MSNs. We present a description of a case series of the *Glyciphon* drug use for the treatment of AK, BD and BCC under the control of dermoscopy.

Material and methods

The study was conducted on the basis of the center of diagnosis and treatment of skin tumors of the PRMU.

Criteria for inclusion of patients in the study:

— presence of clinical and dermoscopic signs of AK;

— presence of clinical, dermoscopic signs and pathomorphological confirmation of BD and BCC;

— BCC of low recurrence risk if the patient has contra-indications or refuses treatment by method of choice according to the current clinical guidelines and the availability of regulatory documentation (case conference) from a highly specialized institution on the basis of the order of the Ministry of Health of the Russian Federation №116n dated 19.02.2021 "On approval of the Procedure for provision of medical care to adults in oncological diseases" (with changes and additions);

— absence of previous treatment.

Criteria for exclusion of patients from the study:

— AK, BD or BCC in the periorbital region.

The study included 10 patients: 7 women and 3 men. The age of the patients was from 70 to 81 years, the mean age was 75,2 years. The cases of treatment with *Glyciphon* ointment of 5 AK elements, 3 BD elements and 1 BCC element (4 women and 1 man) are shown in the article. The Canon EOS 750D digital SLR camera was used to record the clinical picture, and the Heine delta 20t dermoscope in polarized mode was additionally applied for the dermoscopic pattern fixation with ultrasonic gel as an immersion and adapter. The duration of patients' follow-up at this writing was 1 year.

Results

Clinical case 1

Patient *A.*, 76 years old, complained about the onset of nasal skin neoplasm. The element existed for about a year, subjectively not disturbing, not bleeding. At presentation: a pink macule 5 mm in diameter on the skin of the back of the nose, grey scale on the surface **(fig. 1, a)**. The unstructured gray area was visualized in dermoscopic examination, on the periphery — pink pseudonet **(see fig. 1, b)**.

A preparation with keratolytic effect, namely 5% salicylic acid ointment, was prescribed externally to increase the informativeness of dermoscopic examination.

A diagnosis of AK was made based on clinical and dermoscopic data. It was recommended to use the *Glyciphon* ointment according to the daily under bandage scheme.

In view of the persistence of AK dermoscopic signs after 6 days of the ointment application, it was recommended to continue the *Glyciphon* ointment use according to the once a day under bandage scheme. Erythema, single serous crusts and pigmentation on the AK periph-

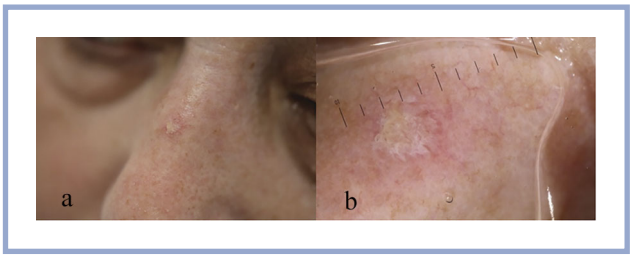


Fig. 1. **Patient *A.* before initiation of treatment.**
a — clinical, b — dermatoscopic picture.

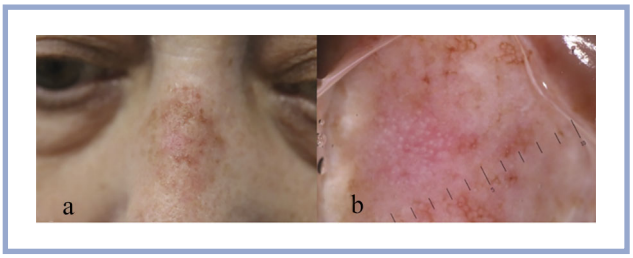


Fig. 2. **Patient *A.* after 10 days of treatment with *Glyciphon* drug.**
a — clinical, b —dermatoscopic picture.

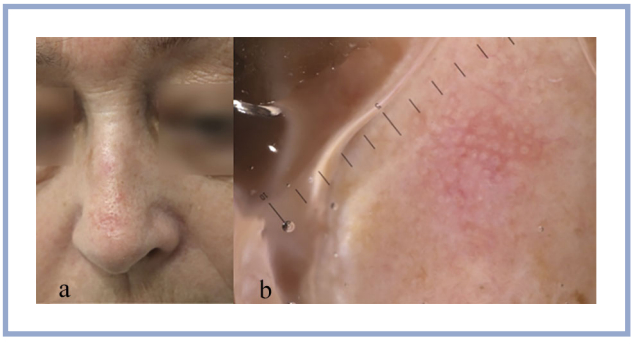


Fig. 3. **Patient *A.* 1.5 months after drug withdrawal.**
a — clinical, b — dermatoscopic picture.

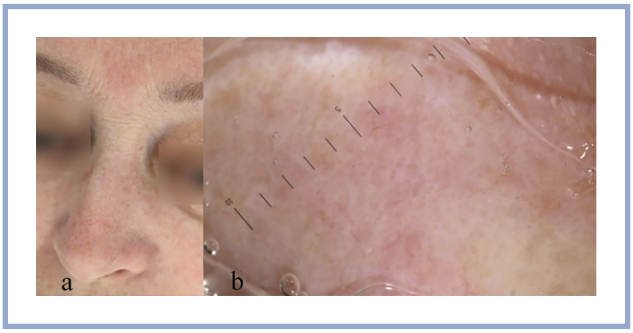


Fig. 4. **Patient *A.* 1 year after treatment.**
a — clinical, b — dermatoscopic picture.

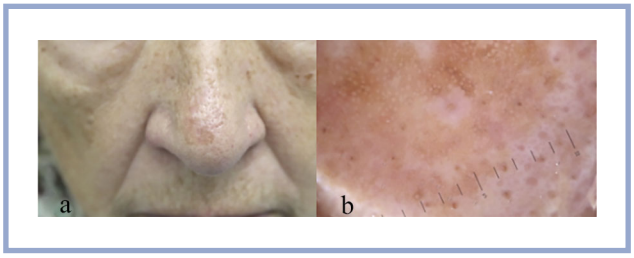


Fig. 5. **Patient *B.* before initiation of therapy.**
a — clinical, b — dermatoscopic picture.

ery **(fig. 2, a)** were visualized on examination after 10 applications totally from the first day of therapy, on examination using dermoscope — increased pigmentation area of the pink pseudonet **(fig. 2, b)**.

The recommended course of applications for AK is 5—10 procedures according to the instructions for use of *Glyciphon* ointment, in this connection the further use of the drug was discontinued.

The preservation of AK signs was observed on examination 1,5 months after the drug withdrawal according to the clinical and dermoscopic data **(fig. 3)**. Patient was taken under case follow-up.

There were no clinical and dermoscopic signs of AK **(fig. 4)** at the control examination after 1 year, during which no additional methods of treatment were applied.

Clinical case 2

Patient B., 80 years old. Came to an appointment with complaints of neoplasm on the nasal tip onset. The duration of the element's existence was difficult to establish. On examination there was a light brown macule with distinct boundaries on the nasal tip skin on the right **(fig. 5, a)**. The following signs have been confirmed on the dermoscopic examination: brown pseudonet, white perifollicular areas, keratotic plugs, annular grain structures **(see fig. 5, b)**. Based on clinical and dermoscopic data, the diagnosis of pigmented AK was determined.

Glyciphon drug was recommended externally for the treatment according to the daily under a bandage scheme. There was intensification of AK brightness, development of erythema on examination 1 week after, and on dermoscopic examination — enhancement of pigmentation and partial destruction of pseudonet **(fig. 6)**. After 10 days, it is recommended to continue the off-label use of the drug due to the preservation of dermoscopic signs of AK according to the decision of the case conference (The Federal Law of 21.11.2011 № 323-FL "The basis for health protection in the Russian Federation").

A regression of AK was observed clinically, and dermoscopic signs preserved **(fig. 7)** at the repeat visit after 14 days from the treatment initiation.

Considering this, it was decided to prolongate the treatment, but after both 21 days and 28 days from the therapy initiation the strawberry pattern was visualized on dermoscopy, while according to the clinical examination there was a regress of AK **(fig. 8)**.

There were no signs of AK **(fig. 9)** on visual and dermoscopic examination after 1 year. The patient has used only suncreens over the last year.

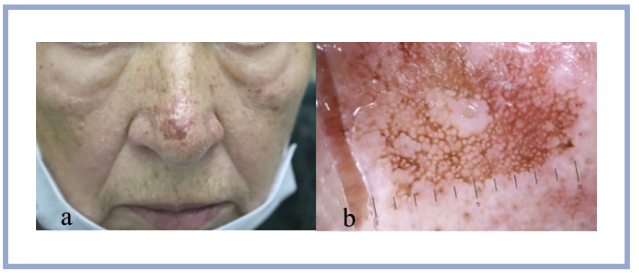


Fig. 6. **Patient *B.* after 7 days from initiation of therapy.**
a — clinical, b — dermatoscopic picture.

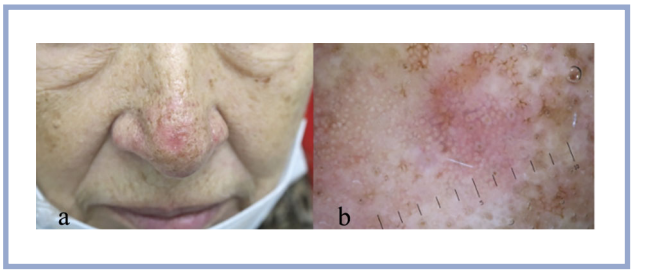


Fig. 7. **Patient *B.* after 14 days from initiation of therapy.**
a — clinical, b — dermatoscopic picture.

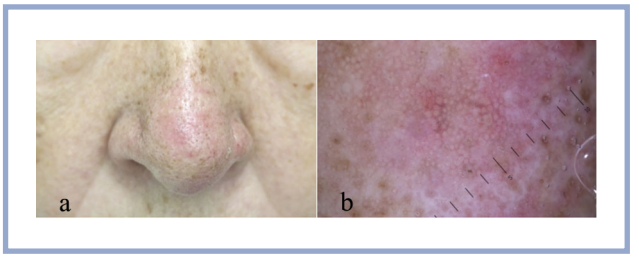


Fig. 8. **Patient *B.* after 28 days from initiation of therapy.**
a — clinical, b — dermatoscopic picture.

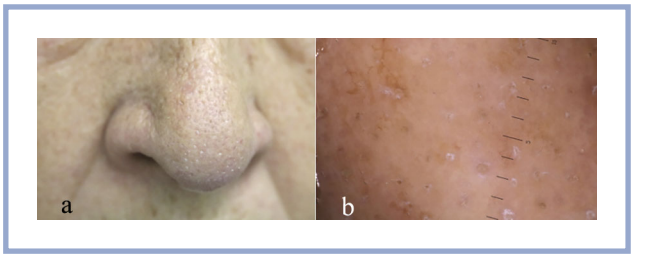


Fig. 9. **Patient *B.* 1 year after the therapy.**
a — clinical, b — dermatoscopic picture.

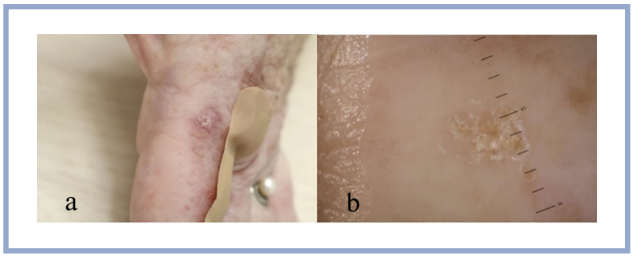


Fig. 10. **Patient *I.*, BD focus №1 before treatment initiation of BD focus №1.**
a —clinical, b — dermatoscopic picture.

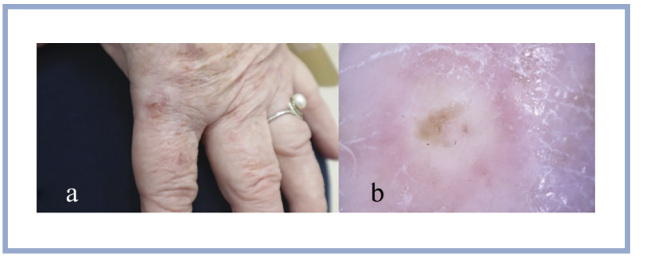


Fig. 11. **Patient *I.*, BD focus №1 after 14 days of *Glyciphon* ointment use.**
a — clinical, b — dermatoscopic picture.

Clinical case 3

Patient I., 70 years old. Complained about the onset of multiple rashes on the skin of upper and lower extremities. At presentation, there were multiple round/oval pink-red macules with scaling on the skin of the upper extremities' extensor surfaces, a macule with indistinct boundaries, with scaling on the surface was on the skin of the front surface of the left tibia. The common AK, BD diagnoses were determined according to clinical, dermoscopic data and based on histological examination. A staged treatment was planned, the first stage of which was the treatment of BD foci. The patient refused surgical treatment. *Glyciphon* was prescribed in regimen according to the instruction based on the case conference decision from highly specialized institution according to the order of the Ministry of Health of the Russian Federation № 116n dated 19.02.2021 "On approval of the Procedure for provision of medical care to adults in oncological diseases" (with changes and additions). Dynamic changes of clinical and dermoscopic pattern are presented not for all elements.

The BD focus № 1 was localized on the skin in the region of the metacarpal-phalanx joint of II left finger **(fig. 10)**.

Glyciphon ointment was prescribed externally to the element for 14 days. The crust formed on the element's surface in 14 days during reexamination **(fig. 11)**.

Erythematous macule and unstructured area that is corresponding to microerosion remained after 1 month of treatment **(fig. 12)**.

A pink macule **(fig. 13, a)** was visualized after 3 months, and then after 10 months, in dermoscopy — linear tortuous vessels on a pink background **(see fig. 13, b)**.

The second BD focus was localized on the dorsal surface of the left wrist and was presented by a blue plaque with desquamation on the surface **(fig. 14, a)**, on dermoscopic examination – unstructured areas that are corresponding to squama and crusts, glomerular vessels on a pink background **(see fig. 14, b)**.

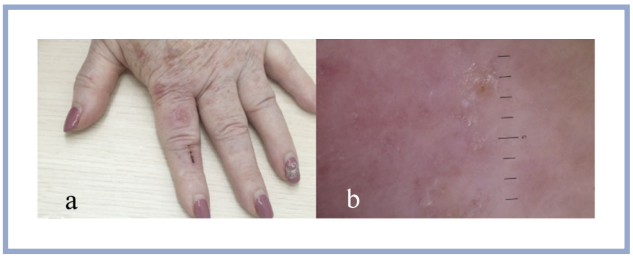


Fig. 12. **Patient *I.*, BD focus №1 1 month after 2-week application of *Glyciphon* ointment.**
a — clinical, b — dermatoscopic picture.

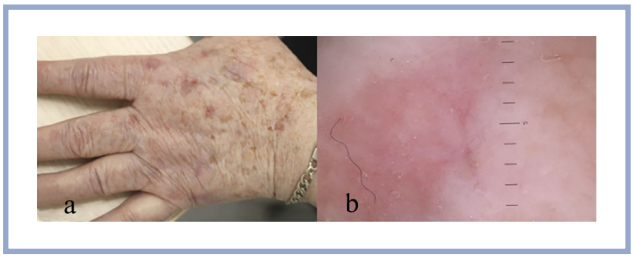


Fig. 13. **Patient *I.*, BD focus №1 10 months after 2-week application of *Glyciphon* ointment.**
a — clinical, b — dermatoscopic picture.

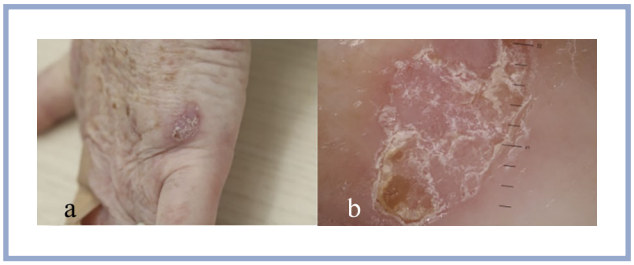


Fig. 14. **Patient *I.*, BD focus №2 before initiation of treatment.**
a — clinical, b —dermatoscopic picture.

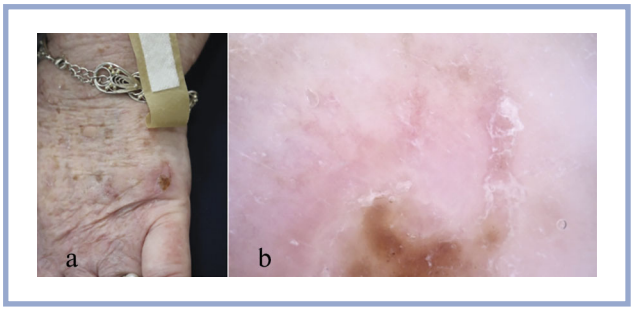


Fig. 15. **Patient *I.*, BD focus №2 after 14 days of *Glyciphon* ointment application.**
a — clinical, b — dermatoscopic picture.

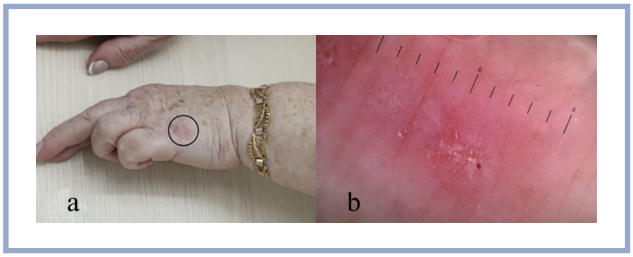


Fig. 16. **Patient *I.*, BD focus №2 after 3 months of *Glyciphon* ointment application.**
a — clinical, b — dermatoscopic picture.

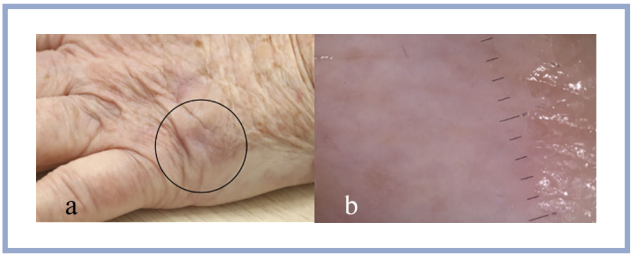


Fig. 17. **Patient *I.*, BD focus №2 after 10 months from two-week application of *Glyciphon* ointment.**
a — clinical, b —dermatoscopic picture.

Glyciphon ointment was recommended for the night under bandage for 14 days due to patient's refusal from surgical treatment. Reduction of desquamation and crust occurrence on the plaque surface **(fig. 15, a)** were found during reexamination, on dermoscopic image – occurrence of unstructured area **(see fig. 15, b)**.

Focus epithelization **(fig. 16, a)** with relevant dermoscopic features in the form of radially localized hairpin-shaped vessels around microcrusts **(see fig. 16, b)** was observed after 3 months.

The clinical and dermoscopic absence of BD signs was recorded **(fig. 17)** on reexamination after 10 months.

The BD element BB №3 was located on the front surface of the left tibia. It was also recommended to use *Glyciphon* ointment for 14 days. Erythema, crust in the center and peripheral scaling with corresponding dermoscopic manifestations were visualized after 2 weeks **(fig. 18)**.

The decision of the case conference recommended to prolongate the therapy to 21 days considering the preservation of glomerular vessels according to the dermoscopic study.

A blue macule with a crust on the left pole **(fig. 19, a)** was visualized three days after the therapy initiation, no signs of BD were detected **(see fig. 19, b)** when using a dermoscope. The application of *Glyciphon* ointment was discontinued.

The area of erythema was reduced, the crust was preserved **(fig. 20, a)** and vascular component was reduced on dermoscopic examination (black crust — the result of treatment with potassium permanganate 5% solution)

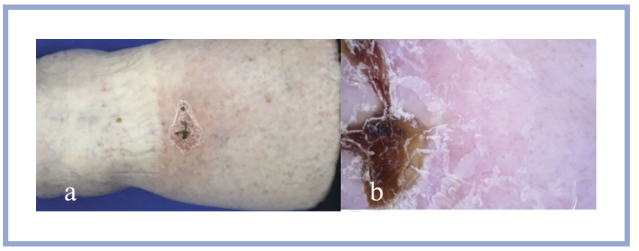


Fig. 18. **Patient *I.*, BD focus №3 after 14 days of *Glyciphon* ointment application.**
a — clinical, b — dermatoscopic picture.

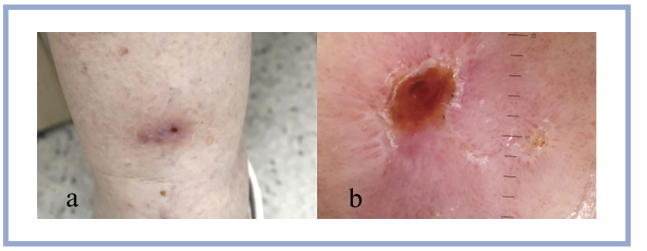


Fig. 19. **Patient *I.*, BD focus №3 after 21 days of *Glyciphon* ointment application.**
a — clinical, b — dermatoscopic picture.

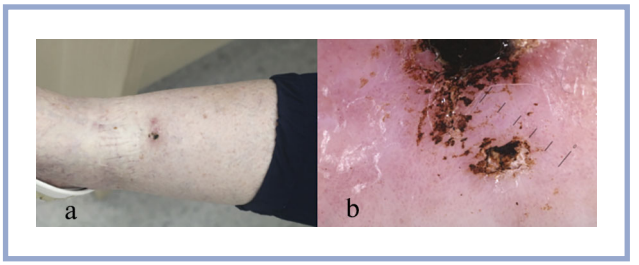


Fig. 20. **Patient *I.*, BD focus №3 after 2 weeks from three-week application of *Glyciphon* ointment.**
a — clinical, b —dermatoscopic picture.

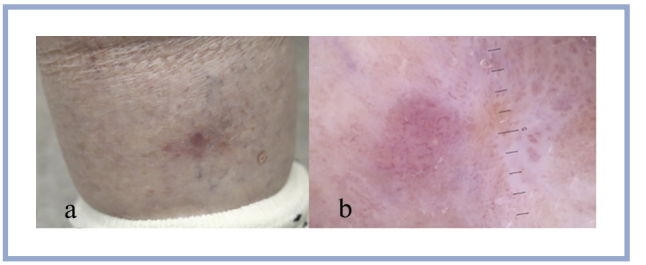


Fig. 21. **Patient *I.*, BD focus №3 1 year after three-weeks application of *Glyciphon* ointment.**
a — clinical, b — dermatoscopic picture.

(see fig. 20, b) after 2 weeks of *Glyciphon* ointment three weeks' course.

Clinical and dermoscopic absence of BD signs was observed after 2 weeks, then 3 months and after 1 year **(fig. 21)**.

Clinical case 4

Patient V., 70 years old. Complained about the onset of neoplasm on the left shoulder skin. The element existed about 5 years, subjectively did not disturb. Patient denied previous treatment. On examination 2 macules of pink color with uneven distinct boundaries were on the skin of the upper third of the front surface of the left shoulder **(fig. 22, a)**. The unstructured areas of the milky pink color, linear tortuous vessels and unstructured areas of the red color, corresponding to microerosions, were visualized with the help of the polarized dermoscope **(see fig. 22, b)**.

The following diagnosis was determined on the basis of visual examination, dermoscopy and histology data: superficial BCC of the upper third of the front surface of the left shoulder. This focus was classified as low risk in the assessment of a possible recurrence considering localization, the tumor morphology, the absence of immunosuppression in patient and the absence of prior radiation therapy. According to the clinical guidelines, the method of choice for low-risk BCC treatment is surgical resection, which the patient refused. The second-line method is radiation therapy, which the patient also refused. *Glyciphon* topical preparation with anti-tumor activity was prescribed daily under a bandage on elements engaging about 1 cm of surrounding tissues in accordance with the

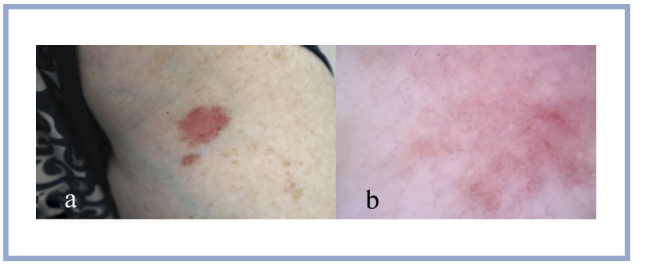


Fig. 22. **Patient *V.* before initiation of treatment.**
a — clinical, b — dermatoscopic picture.

instructions for use, clinical guidelines and on the decision of the case conference from a highly specialized institution on the basis of the order of the Ministry of Health of the Russian Federation № 116n dated 19.02.2021 "On approval of the Procedure for provision of medical care to adults in oncological diseases" (with changes and additions). An oval erosion covered with necrotic masses, located on an erythematous edematous background with indistinct uneven boundaries **(fig. 23, a)** was detected on reexamination after 10 days of drug use. According to the dermoscopy data, the unstructured areas of pink and orange (correspondence to the crusts) color, glomerular vessels **(see fig. 23, b)** were detected.

Glyciphon drug was discontinued due to the absence of BCC dermoscopic signs, a preparation based on the "cuprum—manganese—zinc" complex was prescribed externally for erosion healing. On reexamination after 18 days, post-inflammatory pigmentation was visualized at the site of the BCC, single serous crusts were preserved

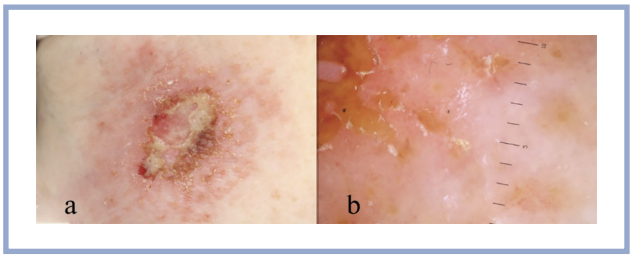


Fig. 23. **Patient *V.* after 10 days from initiation of therapy.**
a — clinical, b —dermatoscopic picture.

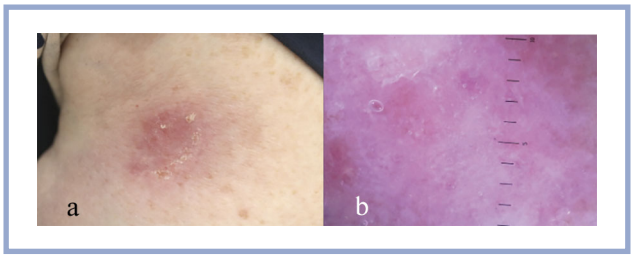


Fig. 24. **Patient *V.* 18 days after 10-day course.**
a — clinical, b — dermatoscopic picture.

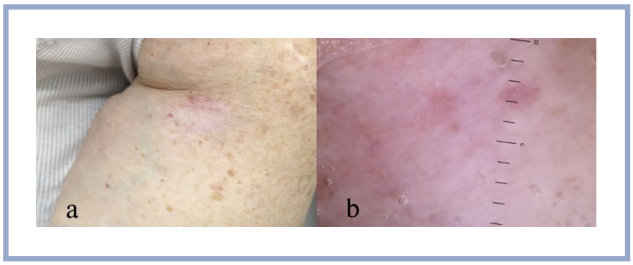


Fig. 25. **Patient *V.* 4 months after end of treatment.**
a — clinical, b — dermatoscopic picture.

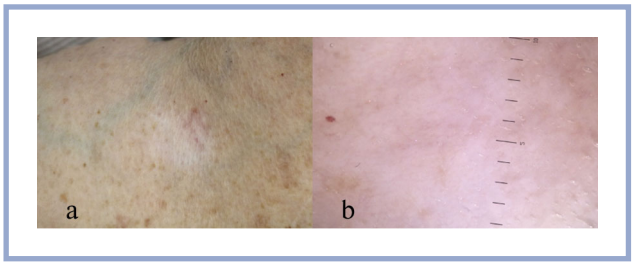


Fig. 26. **Patient *V.* 1 year after the treatment with *Glyciphon* drug.**
a — clinical, b —dermatoscopic picture.

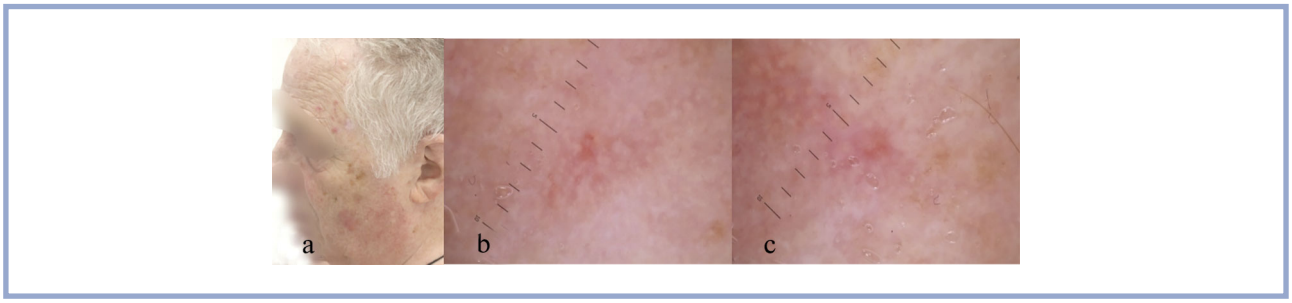


Fig. 27. **Patient *R.*, multiple AKs before initiation of treatment.**
a — clinical, b, c — dermatoscopic picture.

(fig. 24, a), on dermoscopic examination — the structure of normal skin with accentuated vascular pattern, unstructured areas, corresponding to crusts **(see fig. 24, b)**.

A case follow-up by oncologist according to clinical guidelines was recommended to patient. Post-inflammatory hypopigmented macule **(fig. 25, a)** was preserved on the visual examination 4 months after the 10-day course of treatment with *Glyciphon* ointment, there were no signs of BCC and local recurrence on dermoscopy **(see fig. 25, b)**.

A hypopigmented macule was preserved on examination after 1 year **(fig. 26, a)**, skin pattern of normal skin was without signs of local recurrence on dermoscopic examination **(see fig. 26, b)**.

Clinical case 5

Patient R., 81. Complained of multiple rashes on the skin of the face, torso and extremities. According to the patient, the elements have existed for more than 1 year, subjectively did not disturb. He had a history of occupational hazard — infrared radiation. Previously received treatment and was observed by an oncologist about BCC. The determined diagnosis, based on the clinical picture **(fig. 27, a, 28, a)**, dermoscopic **(see fig. 27, b, c, 28, b)** and histological examinations was multiple AK. In this case, the theory of "cancerization fields" was taken into account when choosing a method of treatment. *Glyciphon* ointment was recommended for elements engaging surrounding tissues of about 1 cm per night under a bandage for 6 days. Dynamic changes on the treatment are not presented for all elements.

After 6 days, erythema developed in the field of elements, larger in area than the initial clinical picture **(fig. 29, a, 30, a, 31, a)**. The patient experienced a burning sensation subjectively at the place of ointment application. There were still signs of AK at the same time as the vascular component was strengthened during the dermoscopic examination **(see fig. 29, b, 30, b, 31, b)**. Accord-

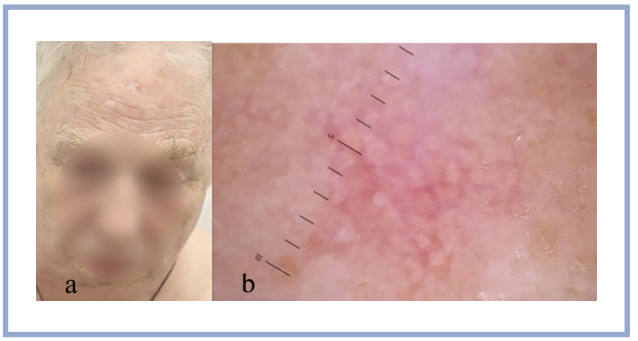


Fig. 28. **Patient *R.*, multiple AKs on the forehead skin before treatment initiation.**
a — clinical, b — dermatoscopic picture.

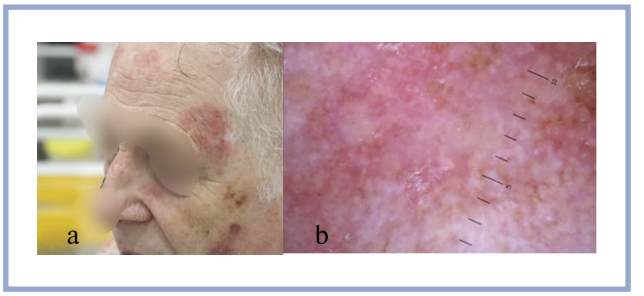


Fig. 29. **Patient *R.* after 6 applications of *Glyciphon* ointment.**
a — clinical, dermatoscopic picture.

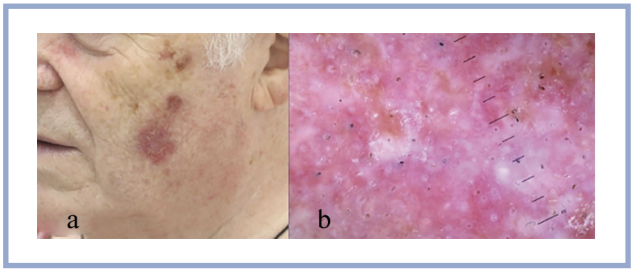


Fig. 30. **Patient *R.* after 6 applications of *Glyciphon* ointment.**
a — clinical, b — dermatoscopic picture.

ing to the instructions for use, the therapy was limited to 6 applications.

There was a complete regress of all AK foci **(fig. 32, a, 33, a)**, except one **(fig. 34, a)**, which was visualized both during clinical examination, and on dermoscopy **(see. fig. 34, b)** on examination after 11 months in the places of *Glyciphon* ointment application. No signs of recurrence were found on dermoscopic examination of other foci **(see fig. 32, b, 33, b 34, c)**.

Discussion

Our first experience of *Glyciphon* ointment use for AK, BD and BCC treatment allows us to make some estimating conclusions, that require further confirmation. Specific evolution of pseudonet with fragmented or full pigmentation followed by a decrease of the coloration intensity or pink color appearance can be the effectiveness criterion in AK. We noticed that there was a pronounced erythema around some elements of AK. It is possible to suppose that this focus is "cancerization field". The effectiveness criterion in BD can be the appearence of unstructured area in dermoscopic examination corresponding to a fibrinous membrane. The effectiveness criterion in BCC can be erosion and crust occurrence.

Selective activity of the Glyciphon drug in relation to atypical cells is visible from the presented cases, as evidenced, firstly, by a more pronounced reaction in the central part of the foci in comparison with the periphery, where, according to the theory of "field of cancerization", subclinical transformed cells may exist, secondly, a more pronounced reaction in the case of BCC treatment than BD and AK.

It is recommended to carry out case follow-up of patients using dermoscopy for at least 12 months in view of the possible delayed positive effect. Dermoscopic examination is indicated in all cases, including situations with the development of positive clinical effect. Dermoscopy allows to reveal insufficient result from the conducted therapy in cases where the remaining manifestations of tumors cannot be visually identified. Combination therapy with sequential impact of both topical preparations affecting the surrounding tissues and agents with local action should be recommended to patients in case of insufficient clinical effect.

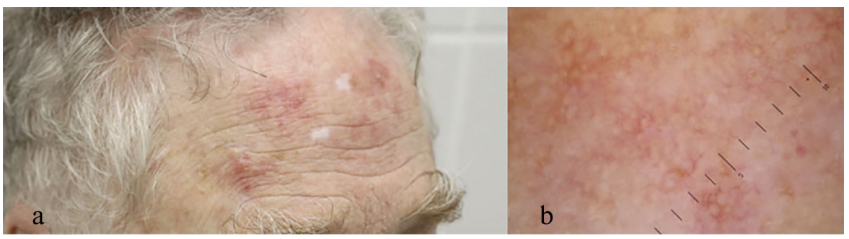


Fig. 31. **Patient *R.* after 6 applications of *Glyciphon* ointment.**
a — clinical, b —dermatoscopic picture.

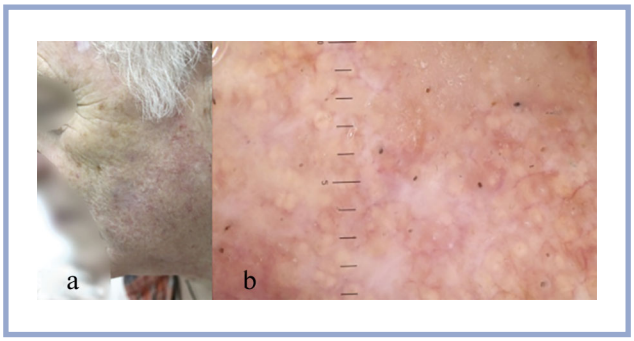


Fig. 32. **Patient *R.* 11 months after treatment.**
a — clinical, b — dermatoscopic picture.

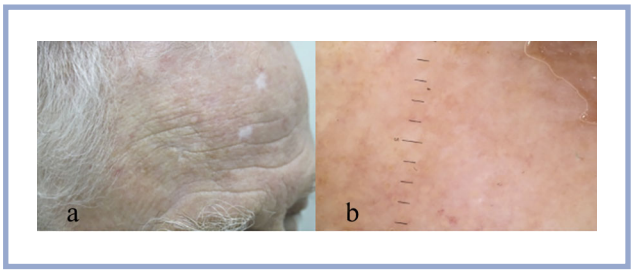
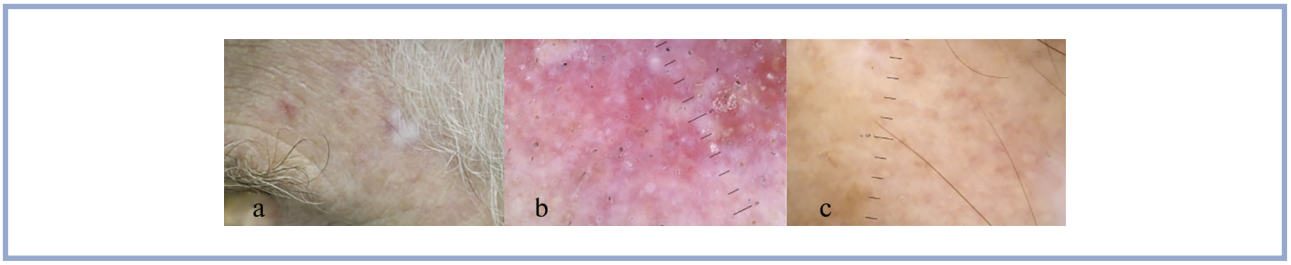


Fig. 33. **Patient *R.* 11 months after treatment.**
a — clinical, b — dermatoscopic picture.



Rice. 34. **Patient *R.* 11 months after treatment.**
a — clinical picture, single AK focus is visualized, b — dermatoscopic signs of AK, c — dermatoscopic picture without signs of AK.

Glyciphon ointment is currently the only topical drug in Russia for the treatment of multiple AK and/or BD foci allowed for use in accordance with the instructions, when it comes to "cancerization fields".

The foci were located in esthetically demanding areas in most of the presented cases, a good cosmetic effect was obtained as a result of the treatment with *Glyciphon* drug. When observing all described patients with positive effect from treatment for 1 year only in 1 case it was recorded that a post-inflammatory depigmented macule was preserved at the place of the drug use after BCC treatment. In other patients, the structure of normal skin was completely restored according to clinical and dermoscopic examination.

Conclusions

1. *Glyciphon* ointment is effective for AK and BD treatment.

2. *Glyciphon* ointment is effective for treating BCC with low risk of recurrence in the presence of contra-indications or patient's refusal of treatment by method of choice according to current clinical guidelines.

3. Dermoscopy is an objective method of evaluating the effectiveness of AK, BD, BCC topical therapy.

4. Case follow-up for residual dermoscopic signs is recommended in case of significant clinical effect from *Glyciphon* ointment application for the treatment of AK and BB.

Disclosure of information about financial and non-financial relationships and activities, and conflicts of interest: there is no conflict of interest among the authors; all patients who participated in this study were provided with Glyciphon ointment from an official representative of JSC Tathimpharmaceuticals free of charge. The support source was not involved in the development of the research plan, data collection, analysis and interpretation. The authors had access to the research data, with an explanation of the nature and scope of access, including maintaining access at the moment.

The authors declare no conflicts of interest.

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