THE USE OF PHOTODYNAMIC THERAPY IN THE TREATMENT OF KERATOACANTHOMAS

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Abstract

The review is on treatment of keratoacanthomas using photodynamic therapy. The defining characteristic of keratoacanthoma among epithelial tumors is a rapid spontaneous regression in the case of typical keratoacanthoma and long-term persistence, recurrence and common malignant transformation to squamous cell carcinoma in the case of atypical keratoacanthoma. In recent years, photodynamic therapy which is an effective method of treatment of different types of cancer and pre-cancer diseases of the skin including actinic keratosis, Bowen's disease, basal cell carcinoma, is increasingly used in clinical practice. There are few data for photodynamic therapy in the treatment of keratoacanthoma. The analysis of the literature shows that using of photodynamic therapy in the set of treatment modalities in patients with keratoacanthoma improves the efficacy and reduces the terms of the therapy. In all investigations except one there was complete tumor regression in 100% patients with keratoacanthoma who underwent photodynamic therapy. In one study complete tumor regression was observed in 66.7% of patients with atypical keratoacanthoma after photodynamic therapy. The follow-up of patients in all analyzed studies accounted for at least 2-3 years. During this time none of the patients had evidence for recurrence. This approach has minimal restrictions for application. Thus, photodynamic therapy may become a therapeutic alternative to surgical treatment of keratoacanthoma with good clinical and cosmetic results.

Keywords: oncology, dermatology, skin diseases, skin tumors, typical keratoacanthoma, atypical keratoacanthoma, skin squamous cell carcinoma, photosensitizer, laser irradiation, photodynamic therapy.

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Keratoacanthoma's unique place among epithelial tumors of the skin is determined by its rapid spontaneous regression in cases of its typical form and long persistence, recurrence and frequent (in almost 20% of cases) transformation into squamous cell carcinoma in cases of atypical forms [1].

Several studies show an important role of genetic and immune mechanisms in the pathogenesis of keratoacanthoma [1, 2]. This is evidenced by a more pronounced local lymphohistiocytic response at the stage of stabilization and regression (compared with the tumor growth stages), more pronounced immune disorders upon atypical keratoacanthoma (reduction of the total number of blood T-lymphocytes, inhibition of the functional activity of lymphocytes in the blast transformation reaction) compared to the typical keratoacanthoma [1,3]. This role is also indicated by the proven efficacy of immune preparations in the treatment of keratoacanthoma, e.g. bemitil [1], etretinate [3], and interferon [4].

To the present day the problem of diagnostics and treatment of atypical and typical keratoacanthomas remains unsolved. In addition, to date, in the scientific community there is a point of view considering the keratoacanthoma as a highly differentiated squamous cell carcinoma, and suggesting to treat it as a squamous cell carcinoma. However, this question still causes much debate [5]. The need for treatment of keratoacanthomas is indicated by the fact that the scars as a result of spontaneous regression of the good functional and cosmetic results of PDT with photolon registered in 100% of patients should be noted keratoacanthoma can sometimes be worse in the cosmetic sense than scars after treatment.

Thus, the therapeutic intervention for keratoacanthoma is recommended not only because of the lack of reliable criteria for its differential diagnosis from the squamous cell cancer, but also to prevent the rapid tumor growth for cosmetic purposes and to achieve the minimal scarring [5,6].

There are several keratoacanthoma treatment options. The current therapy for this tumor consists of surgery, including cryotherapy with liquid nitrogen, electrodissection, excision, laser surgery, with a somewhat less popular use of radiation therapy, chemotherapy with methotrexate and 5-fluorouracil, local treatment with imiquimod, systemic therapy with retinoids and methotrexate. However, these methods of treatment do not rule out the development of a large number of recurrences, which range from 19% to 21% [6-9].

In recent years, the photodynamic therapy (PDT) is increasingly used in the treatment of skin tumors [10]. Clinical PDT has been used in our country since 1992 [11]. It has proved to be an effective therapeutic technology in dermatology for treatment of actinic keratosis, sclerosus extragenital lichen, and basal cell carcinoma [12-20]. The PDT effectiveness is shown in the combined treatment of squamous cell skin cancer and other diseases [21].

At the same time, only few publications are devoted to the issue of keratoacanthoma treatment using PDT [22-26].

The first result of keratoacanthoma PDT was presented by P.G. Calzavara-Pinton in 1995. The study reported that PDT was administered to four patients with keratoacanthoma. The emulsion of 5-aminolevulinic acid (5-ALA) in the concentration of 20% was applied under occlusive dressing for 6-8 hours and then the irradiation was carried out using the dye laser apparatus (λ = 630 nm). The procedures were performed every other day until complete clinical disappearance of the tumor was observed. All four patients had a complete response. During 3 years of follow-up, no patient showed the relapse development [22].

The original clinical observation was presented in 1999 by S. Radakovic-Fijanet et al. The researchers conducted a course of treatment by PDT to a 49-year-old man with keratoacanthoma. The tumor of 3.5×2.8 cm was located on his left forearm. Due to the rapid growth of the tumor, the squamous cell skin cancer could not be ruled out clinically. After the biopsy and pathological study, keratoacanthoma was diagnosed. The surgical treatment was impeded by the fact that the tumor was located over the arteriovenous shunt, and there was a high

risk of damage to the shunt after surgical excision of the tumor, prompting researchers to try to treat the keratoacanthoma using PDT. The tumor was pretreated with 10% of salicylic acid based on petrolatum for 4 days. PDT was performed using 5-ALA. After application of 10% cream with 5-ALA at the rate of 50 mg/cm^2 to the tumor, this area was covered with adhesive tape for 20 hours. The irradiation was carried out using PTL-Penta (Switzerland), composed of Osram 250 W halogen lamp with a red filter (with the emission band of 580-680 nm) and optical fiber. The tumor irradiation power density was 150 mW/cm^2, and the light dose density was 180 J/cm^2. The irradiation was limited to the upper half of the tumor, while the lower half was shielded from light and served as a control. PDT was performed twice with a 3 week interval. 3 days after the second PDT, the irradiated half of the keratoacanthoma showed a significant regression, whereas the non-irradiated portion of the tumor remained largely unchanged. 2 months after PDT, the irradiated part of the tumor regressed completely, while the non-irradiated part still remained. Further, the non-irradiated part of the tumor was also exposed to PDT. 4 months after PDT, keratoacanthoma complete regression was achieved. Three years later there was no sign of tumor recurrence. The authors demonstrated very clearly that PDT promoted the keratoacanthoma regression, and tumor regression did not occur spontaneously [23].

In 2009, C.S. Souza et al. reported the successful treatment of a 58-year-old female patient with centrifugal keratoacanthoma of a considerable size. Keratoacanthoma area was 15x12 cm. The patient underwent PDT using photohem photosensitizer (Russia), a purified derivative of hematoporphyrin. Two sessions of PDT have been conducted. Photohem was injected intravenously at the dose of 1.5 mg/kg of the patient's body weight. After 24 hours, the laser irradiation (λ = 630 nm) was carried out with the following parameters: the irradiation power density was 130 mW/cm^2, and the light dose density was 300 J/cm^2. The treatment resulted in a complete tumor regression and a good cosmetic outcome. The patient was followed up for two years without relapse [24].

In 2012, M.M. Farias et al. reported the PDT effectiveness in the treatment of four patients (two men and two women) with solitary keratoacanthomas. Because of advanced age (71-95 years) and comorbidities, the patients could not rely on the surgical treatment. Therefore, after signing of the informed consent, the patients chose treatment with PDT. In all cases, the diagnosis was confirmed by biopsy and pathologic studies. Keratoacanthomas were located on the face of two patients, on the hand of one patient, and on the leg of one patient. The terms of keratoacanthoma development before treatment ranged from 6 to 36 months. During the PDT, the cream with methyl aminolevulinic acid (Norway) was used at a concentration of 160 mg/g. To improve the methyl aminolevulinic acid absorption, the peels were removed for 2 weeks before treatment. A thick layer (about 1 mm) of cream containing the methyl aminolevulinic acid was applied to the affected and surrounding tissues, and coated with a compression bandage. After 3 hours, the bandage was removed and the irradiation session was carried out using the lamps for photodynamic therapy (non-coherent light source, λ = 632 nm) with the following parameters: the irradiation power density was 70 mW/cm^2, the light dose density was 37 J/cm^2, and the irradiation time was 8-9 min. The patients have not performed any local or systemic analgesia. The patients reported only minor local pain and burning sensation in the area of radiation during exposure to light. PDT was repeated to all patients after 1 week, and 1 month after the first session. 7 days after the last PDT, all patients showed a complete regression of keratoacanthoma. After 3 years of follow-up, all four patients with keratoacanthoma were in remission, and the patients were very satisfied with the clinical and cosmetic results [25].

In 2012, V.A. Molochkov et al. reported the experience of keratoacanthoma treatment by PDT. The authors have shown the clinical and cosmetic efficacy of a single PDT with intralesional administration of radachlorin photosensitizer (Russia) in 6 (66,7%)

of 9 patients with atypical solitary keratoacanthomas, which is much higher than the frequency of spontaneous regression of atypical keratoacanthomas [26].

The analysis of the published data shows that the use of PDT in the range of therapeutic measures in patients with keratoacanthoma increases the therapy effectiveness, accelerates the treatment, and has the minimum number of limitations. However, despite the positive results obtained in clinical practice, for now PDT is undeservedly rarely used in the treatment of this pathology. Given the efficiency, simplicity, lack of side effects, limited contraindications during procedures, PDT can be considered the most promising direction in the treatment of keratoacanthoma, and it is quite appropriate to continue the further research of the PDT effectiveness in the treatment of various forms of keratoacanthomas.

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