ANNALES
UNIVERSITATIS MARIAE CURIE-SKŁODOWSKA
LUBLIN – POLONIA
VOL. LX, N 2, 183 SECTIO D 2005

Chair and Department of Dermatology, Medical University of Lublin.

KATARZYNA FRANASZCZUK, MONIKA PIETRUSIEWICZ, DOROTA KRASOWSKA

Keloids – pathogenesis and treatment

Keloid is a tumour composed of fibrous tissue and formed either in the place of injury (secondary keloids) or without any visible cause (spontaneous keloids) (12). Clinically, keloids are hard tumours of elongated or irregular shape, often with extensions. The skin that covers them is smooth, mat-white or livid-red (12). In the region of keloid there are no elastic fibres, hair follicles and sweat or oil glands (23).

Keloids develop as a result of excessive production of collagen, which may be stimulated by interleukin 1 (IL-1β), and its decreased degradation (23). In the region of keloids there is increased activity of proline hydrolase. This enzyme is responsible for post-translation hydroxylation of proline residues composed into polypeptide chain of collagen (15). Collagen synthesis in the region of keloids is twenty times higher in comparison with healthy skin. At the same time, increased collagen synthesis is accompanied by smaller increase in the activity of collagenases (23).

In connection with the increased activity of fibroblasts, there is an increase in the synthesis of glycosaminoglycanes and fibronectin within keloids (23). A considerable multiplication of fibroblasts is probably related to mutation of the gene p53, situated on the chromosome 17p13.1. This gene codes phosphoprotein, which in normal conditions inhibits cell growth and induces their apoptosis. It is supposed that mutation within the gene p53 disturbs the balance between the proliferation and death of fibroblasts and in this way they contribute to formation of keloids (9). The rate of apoptosis in cells isolated from keloids is considerably reduced in comparison with cells that originate from healthy skin (19). With the use of polymerase chain reaction combined with the analysis of heteroduplexes, single strand conformation polymorphism (PCR/SSCP) and DNA sequencing, the existence of gene p53 mutation in fibroblasts deriving from keloids was confirmed. These changes were not observed in cells isolated from a healthy tissue of the same patients. With all the patients there was a mutation discovered within the fourth exon consisting in the change of arginine into proline. Irregularities were also confirmed within the fifth and the sixth exon (19). Fibroblasts isolated from patients are more sensitive to the activity of the transforming growth factor β2 (TGF-β2), in comparison with the fibroblasts of healthy controls. In keloids there were also found incorrect proportions of collagen I, III and IV (23), whereas the enzymatic studies showed a considerably reduced level of metaloproteinase-9 and an increased level of metaloproteinase-2. Also, an increased number of inhibitors of collagenase, α1-antitrypsin and α2-macroglobulins is observed (9).

It seems that the development of keloids is genetically originated. Susceptibility to their occurrence is inherited by an autosomal, dominant or recessive way. Antigens of histocompatibility complex of the class I and II such as HLA-B14, HLA-B21, HLA-Dw16, HLA-Dw35, HLA-DR5 and HLA-DQW3 play an important role (23). These changes appear three times more often with women. Moreover, there was observed an increased frequency of keloid occurrence with dark-skinned and people with blood group A (23). In certain parts of the body keloids appear more often. The most predisposed

places are: the region of sternum, ear lobes, shoulder girdle, elbows and face. It is claimed that the turgor of the skin also plays a part in the development of keloids, which may justify their more often occurrence over the sternum and near the elbows (4).

There are many methods of treatment of keloids but there is not one generally accepted algorithm of conduct. There are often relapses and adverse events. That is why prevention is considered to be the best therapy. Contemporary methods of treatment include: surgical, pharmacological and physical treatment.

A surgical excision of the lesion is a frequently used method, despite a high index of relapses – from 45% to 100% (9). Remarkably fewer relapses occur when a surgical intervention is combined with injections of steroids (below 50% of relapses), interferon a (about 20% relapses), radiotherapy (below 10% relapses), magnetotherapy or laserotherapy (9, 23).

In pharmacological treatment, a method of choice is using glycocorticosteroids (GKS) in the form of injections. Steroids reduce collagen synthesis through inhibition of collagen pro-a1(I) transcription. Moreover, they reduce the amount of glycosaminoglycanes, inhibit cell proliferation and have anti-inflammatory effect. Injections of triamcinolon are usually used in the doses of 10–40 mg/ml in 4/5-week cycles, after previous excision of the lesion (9). Adverse events of this method include hypopigmentation, atrophy, telangiectasia, necrosis, ulceration and features of the Cushing syndrome (11).

In 1990 Lee and Ping described positive effects of calcium antagonists in the therapy of keloids. These drugs have an influence on the depolymerization of actinium filaments. Additionally, they stimulate the production of collagenase, which leads to the reduction of the fibrous tissue synthesis (8). Verapamil and other drugs from this group inhibit the synthesis of extracellular matrix, and thus of collagen, glycosaminoglycanes and fibronectin (7). Verapamil inhibits incorporation of proline into collagen and it simulates the synthesis of pro-collagenase. Moreover, it reduces the excessive production of interleukin 6 (IL-6) and vascular epithelial growth factor (VEGF) in fibroblasts localised in the middle part of keloids (10). It has been proved that injections of 2.5 mg/ml of verapamil hydrochloride combined with silicone application used as a continuation of surgical treatment, are an important step ahead in the therapy of keloids (8).

In the therapy of keloids also 5-fluorouracil (5-FU) is used, which belongs to pyrimidine analogues of antimetabolic activity. This drug inhibits excessive collagen production by fibroblasts. Until recently, it was used in combination with other methods of therapy. However, it occurred that it is also effective in monotherapy, especially of keloids lasting longer than 5 years. Side-effects of the therapy include melanosis, painfulness, erythema on the spot of injections, local thinning of tissues and ulceration in the region of injection (11).

Imiquimid represents a new class of drugs used in dermatology. It stimulates a natural response of the body through the synthesis of cytokines, such as interferon, the tumour necrosis factor (TNF), IL-12 and the activation of NK cells, macrophages, lymphocytes B and Langerhans' cells. It is commonly used in the treatment of warts of sex organs, flat warts, perirectal warts and molluscum contagiosum (1). The study conducted by Berman and co-authors proved that imiquimid 5% cream reduces to a considerable extent the risk of keloids relapses after a surgical operation (1, 2). The only noted side-effects are mild local reactions, which withdraw after a discontinuance of the therapy.

Interferon is also used in the treatment of keloids. Its effect consists in inhibition of excessive synthesis of collagen and glycosaminoglycanes (GAG) by fibroblasts (13). There are reports that confirm the effectiveness of intrafocal injection of interferon-γ (INF-γ). Using interferon α-2b (INF-α-2b) is considered to be ineffective (20).

Heparin can contribute to suppression of the growth of keloids, through inhibiting the proliferation of fibroblasts and production of collagen and through stimulation of the development of growth factors

such as bFGF and TGF-beta 1 (5). In Poland there are specimens in the form of creams – Cepan and gels – Contractubex (17).

Retinoids are often applied in the treatment of keloids. These drugs cause the lowering of fibroblast proliferation and collagen synthesis. The effects of the treatment are visible after 8–12 months of drug application and after 6 months of oral administration (23).

Silicon dressings, silicon gels (Dermatix) and bandages with zinc are also applied. Ready-made dressings, such as Topigel, Sil-K or Epiderm should be used from 12 to 24 hours a day for many days (4). The bandages' mechanism of action is based on inhibiting the activity of lysylooxidase (23). This enzyme oxidatively deaminates ε-amine groups in some radicals of lysine and hydroxylysine, which leads to the development of transverse bonds in the structure of collagen (15).

Physical methods are also used in the treatment of keloids. One of them is radiotherapy. The impact of X-rays on keloids is not fully known (23). Roentgen rays destroy fibroblasts and they lower the synthesis of mRNA pro-a1(I) collagen, fibronectin and b-actin (9). One should remember about potential carcinogenic activity of X-rays (3, 23). They should be used with particular caution as far as children and adolescents are concerned, especially on areas of increased risk of neoplasia, such as the chest and thyroid (3).

One kind of radiotherapy is postoperative local radiotherapy with the use of iridium 192. The above method of treatment was described for the first time by Nicolettis and Chassagne (6). The studies show that the use of only radiotherapy gives a large percentage of relapses (50–100%), whereas its association with a surgical procedure increases the curative effect. The advantage of this method is undoubtedly the easiness of performing the operation, short period of hospitalisation (48–72 h), limited area of X rays' activity and effectiveness comparable to external irradiation. The most common side--effect is local hyperpigmentation. Moreover, there is a risk of inducing malignant neoplasms in the region of the breast and neck (6).

Cryotherapy is the next method. The course of treatment is based on the performance of three cycles of freezing and defreezing lasting for 30 s once a month (22). Two to 10 cycles are performed. The results of treatment are better in the white race (23). Zouboulis and co-authors obtained a very good response for the treatment from 32.3% of the patients, good from 29%, weak from 29% and the lack of response from 9.7% of the patients (22, 23). At the same time they observed that the number of cycles and the duration of lesion influences the result of treatment. The patient's age and sex, the place of the lesion, as well as the kind of previous treatment do not have an influence on the final result (22). The most frequently observed side-effects include pain and local hypo-or hyperpigmentation of skin (22).

Laserotherapy is another way of treatment. Using this method exclusively does not reduce the relapse index, but its association with glycocorticosteroids (GKS) brings much better results. The first laser applied in treatment of keloids was the argon laser. Haemoglobin and melanin are good absorbents of light emitted by this kind of laser and that is why it is so useful in the treatment of lesion of pigmentary origin (4). Its mechanism is based on coagulation of skin vessels that leads to local anoxia and to lowering pH of tissues, which causes lysis of granulocytes and release of enzymes (23). The effect of argon laser is limited to structures situated at the depth up to 1 mm (23); its effectiveness in the treatment of keloids was estimated at 50% (23).

Neodym laser Nd : YAG emits continuous radiation with the wavelength of 1064 nm (4, 23). The laser beam runs together with the red beam of the visible light. The radiation may be let pass through an ice-cube, so the skin surface stays cool and in this way the risk of scar occurrence declines (11). Neodym laser Nd;YAG gives better curative results than the argon laser. It inhibits DNA replication and owing to it the collagen synthesis is inhibited (23).

Laser Erbium : YAG produces infrared radiation with the wavelength of 2940 nm. Thanks to this, it is possible to remove superficial skin layers (23). This laser can be used not only in the treatment of keloids but also hypertrophied and post-acne scars (23).

Fleshlamp-Pumped Dye Laser (FPDL) emits yellow light with the wavelength of 585nm. It is used in the treatment of vascular naevi with infants and children (11). Its effectiveness in the case of keloids amounts to 57–83%, after 6 months of therapy (23).

In the treatment of keloids there is also compressive therapy, for it has been proved that excessive production of collagen slowly disappears as a result of compression. The effectiveness of this method is directly proportional to the length of the treatment. Constant compression lasting longer than 8–12 months reduces the filling pressure to 20–25 mmHg. The dressing should be applied as soon as possible after healing of the wound (up to 3 months). The time of compression may be shorter in the case of combining the pressure therapy with surgical procedure (23).

In the case of keloids situated on ear lobes are applied so-called "zimmer splints". The research conducted by R. Russel and co-authors showed keloid reduction by at least 50% with every patient out of 30 after a year. The treatment included lesions with the diameter of 5 cm. After previous injection of glycocorticosteroids (GKS) patients were recommended to carry splints during the day (and also at night if they were well tolerated) for the period of minimum 6 months (18). The curative effect is the result of local hypoxia and degeneration of fibroblasts (18, 21). A common side-effect of this method is ulceration caused by too large pressure on soft tissues. Moreover, during the treatment may appear bleedings, increased susceptibility to infection and even ear necrosis. A modification of typical clips is U-loop clips. They allow for the regulation of both the amount and the direction of the applied pressure and in this way avoidance of adverse events (21).

Many methods are used in the treatment of keloids, but none guarantees complete cure. Each therapy has its limits. Choosing a therapy, one should take into account a few factors such as the patient's age, duration and position of lesions. Radiotherapy should be avoided in the case of children and young people. Laserotheraphy is particularly effective with people of fair complexion and skin of type one (23). Obtaining a positive result in the case of cryotherapy correlates with the duration time of the lesion and the number of conducted cycles (22). An occlusive dressing should be applied as soon as possible after the healing of the wound (up to 3 months). The best results are obtained in the case of lesions situated on dorsal surfaces of hands and feet (23). Using compression is also very effective in the case of keloids situated on ear lobes.

To sum up, it should be stated that there is no ideal method of keloid treatment. Effectiveness of used therapies is still unsatisfactory. The obtained results are different and they are often accompanied by side-effects. Therefore, association of surgical treatment with intrafocal injections of glycocorticosteroids is still the most common method in the keloid therapy.

CONCLUSIONS

1. There are many methods in the treatment of keloids but none guarantees a complete cure.
2. Each therapy has its limits or occurrence of side-effects.
3. Despite the progress in keloid treatment, the most common method is surgical excision associated with intrafocal injections of glycocorticosteroids.
4. The problem of keloid treatment remains open.

REFERENCES

1. Berman B. et al.: Novel Dermatologic Uses of the Immune Response Modifier Imiquimod 5% Cream.
2. Berman B., Villa A.: Imiquimod 5% cream for keloid management. Dermatol. Surg., 29 (10), 1050, 2003.
3. Botwood N. et al.: The risks of treating keloids with radiotherapy. Br. J. Radiol., (72), 1222, 1999.
4. Braun-Falco O. et. Al.: Dermatologia. Wydawnictwo Czelej, 1464, 1671, Lublin 2000.
5. Carroll L. A., Koch R. J.: Heparin stimulates production of bFGF and TGF-beta 1 by human normal, keloid, and fetal dermal fibroblasts.
6. Clavere P. et al.: Postoperative interstitial radiotherapy of keloids by iridium 192: A retrospective study of 46 treated scars. Dermatology, (195), 349, 1997.
7. Copcu E. et al.: Combination of surgery and intralesional verapamil injection in the treatment of the keloid. J. Burn. Care Rehabil., 25 (1), 1, 2004.
8. D'Andrea F. et al.: Zapobieganie i leczenie bliznowców przy pomocy doogniskowej iniekcji werapamilu. Dermatochirurgia, (6), 16, 2002.
9. Drobnik J., Schwartz R. A.: Keloid. Post. Dermatol. Alergol., Vol. 18 (3), 200, 2001.
10. Giugliano G. et al.: Verapamil inhibits interleukin-6 and vascular endothelial growth factor production in primary cultures of keloid fibroblasts. The British Association of Plastic Surgeons, (56), 804, 2003.
11. Gupta S., Kalra A.: Bezpieczeństwo stosowania i skuteczność działania 5-fluorouracylu w leczeniu bliznowców. Dermatochirurgia, (6), 19, 2002.
12. Jabłońska S., Chorzelski T.: Choroby skóry. PZWL, 373, Warszawa 2001.
13. Jacob S. E. et al.: Topical application of imiquimod 5% cream to keloids alters expression genes associated with apoptosis. Br. J. Dermatol., (149) Suppl. 66, 62, 2003.
14. Lahiri A. et al.: Experience with difficult keloids. Br. J. Plastic Surgery, (54), 633, 2001.
15. Murray R. K., Keeley F. W.: Substancja pozakomórkowa. W: Biochemia Harpera: R. K. Murray, D. K. Granner, P. A. Mayes, V. W. Rodwell, PZWL, 833, Warszawa 1998.
16. Nanda S., Reddy B. S.: Intralesional 5-fluorouracil as a treatment modality of keloids. Dermatol Surg., 30 (1), 54, 2004.
17. Pharmindex Kompendium, MediMedia International Sp. z o.o., 171, 190, Warszawa 1999.
18. Russell R. et al.: Zimmer splintage: a simple effective treatment for keloids following ear--piercing. Br. J. Plastic Surgery, (54), 509, 2001.
19. Saed G. M. et al.: Analysis of p53 gene mutations in keloids using polymerase chain reaction – based single-strand conformational polymorphism and DNA sequencing. Arch. Dermatol., (134), 963, 1998.
20. Szepietowski J. (red.): Leczenie chorób skóry i chorób przenoszonych drogą płciową, PZWL, 333, Warszawa 2002.
21. Vachiramon A., Bamber M. A.: A U-loop pressure clip for earlobe keloid. J. Prosthet. Dent., (92), 389, 2004.
22. Zouboulis C. C. et al.: Outcomes of cryosurgery in keloids and hypertrophic scars. Arch. Dermatol., (129), 1146, 1993.
23. Żaba R.: Patogeneza i leczenie bliznowców oraz przerośniętych blizn. Przegl. Dermatol., 88 (3), 271, 2001.

SUMMARY

Keloid is a tumour composed of fibrous tissue and formed either in the place of injury or without any perceptible cause. Keloids, contrary to hypertrophied scars, grow beyond primary borders of the wound (injury). The essence of keloid development is excessive collagen production combined with its reduced degradation. The aim of this study is to discuss now available methods of keloid treatment, which include surgical, pharmacological (glycocorticosteroids, calcium-channel blockers, 5-fluorouracil, Imiquimod, interferon-γ, heparin, retinoids, silicon dressings, bandages with zinc) and physical (radiotherapy, cryotherapy, laserotherapy, compressive therapy) treatment. One should remember that none of the methods guarantees a complete cure and the treatment of choice is surgical excision associated with intrafocal injection of glycocorticosteroids.

Bliznowce – patogeneza i leczenie

Bliznowiec (keloid) to guz złożony z tkanki łącznej włóknistej powstający bądź w miejscu urazów, bądź bez uchwytnej przyczyny. Bliznowce, w przeciwieństwie do blizn przerosłych, rosną poza pierwotne granice rany (urazu). Istotą powstawania bliznowców jest nadmierna produkcja kolagenu połączona ze zmniejszoną jego degradacją. Celem pracy jest omówienie dostępnych obecnie metod leczenia bliznowców, do których należy leczenie chirurgiczne, farmakologiczne (glikokortykosteroidy, blokery kanałów wapniowych, 5-fluorouracyl, Imiquimod, interferon-γ, heparyna, retinoidy, opatrunki silikonowe, bandaże z cynkiem) i fizyczne (radioterapia, krioterapia, laseroterapia, terapia kompresyjna). Należy pamiętać, że żadna z metod nie gwarantuje całkowitego wyleczenia, a leczeniem z wyboru jest chirurgiczne wycięcie skojarzone z doogniskową iniekcją glikokortykosteroidów.