XIAOLI WU, MD, PHD. ZHEN GAO, MD, PHD. WEI LIU, MD, PHD
Department of Plastic and Reconstructive Surgery, Shanghai Research Institute of Plastic and Reconstructive Surgery, Shanghai 9th People's Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China

Surgery and chemotherapy of keloids: use of low dose 5-FU for treatment and relapse prevention

Keloid is invasive and difficult for controlling its growth and thus is considered as a benign skin tumor. Clinical therapies of keloid remain unsatisfied including surgery, cryotherapy, radiotherapy and others because these treatments often lead to new trauma which can trigger keloid regrowth.[1,2] 5-Fluorouracil (5-FU) has been reported in keloid therapy using a dose of 40-50mg/ml[3,4], which may be difficult for long time treatment.

Our group has developed a chemotherapy regime by using low dose 5-FU with a concentration lower than 4mg/ml. Intralesional injection of 5-FU along with triamcinolone acetonide (less than 8mg/ml) was employed for keloid treatment.[5] This chemotherapy is usually performed once a month with a total therapy time around two years, and the injection interval can be prolonged or drug dose be reduced gradually with symptom improvement and scar flattening until the keloid scar is completely resolved. We have utilized this method to treat keloids of earlobe, chest, shoulder, back and other regions in a large quantity of patients.

Our experience showed that such a therapy regime is successful in term of improving symptoms and flattening and softening keloid scar. Generally, intralesional injection of 5-FU could significantly inhibit angiogenesis and reduce erythema and thus reduce itching and pain. Importantly, simultaneous injection of steroid along with 5-FU could enhance degradation of keloid matrices leading to scar softening and flattening. Although improvement of clinical symptom and complete flattening of scar can be achieved usually within 6 months, small nodules as a means of regrowth need a long term therapy (around 2 years) to completely cure the disease *(Figure 1).* In some difficult cases, an even longer time of therapy is required to achieve expected clinical outcome. More importantly, this therapeutic regime resulted in a much higher cure rate and a much lower recurrence rate when compared to what have been reported in the literatures.

Surgical excision has long been used for keloid treatment and the high recurrence rate is the shortcoming that limits its wide applications in keloid treatment. Based on the success of this chemotherapy, we further explored the possibility of treating keloids using low dose chemotherapy for preventing post-surgical relapse. Earlobe keloid becomes the first target because of the easiness of handling. Keloids on patients' earlobes with typical sizes of 1-2 centimeters in diameter were first excised for its core removal while maintaining its out layer soft tissue in order to close the wound primarily. Intralesional injection of low dose 5-FU and steroid was given once a month since 3-4 weeks post-operation. The results showed that such a therapeutic regime can not only mostly keep the natural shape of earlobe, but also results in enhanced efficiency in curing keloid and preventing relapse. For the majority of patients, earlobe keloids can be completely resolved within one year post-surgery with drug injection once a month or two months without recurrence. Longer treatment time period remains needed for some difficult cases, but almost all of them can be completed cured without recurrence given a longer enough treatment.

Chest keloid remains a challenge because of its relatively less response to treatment and a higher recurrence rate when comparing to earlobe keloid, and high tension in this area is likely to cause this problem. In the initial stage, we have per-

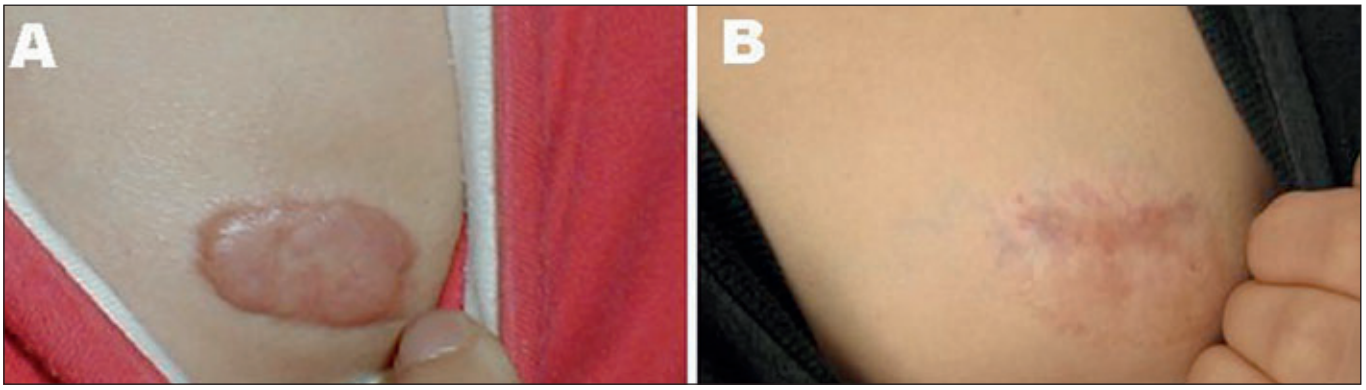

Figure 1. Low dose 5-FU injection for chest keloid therapy.
(a) before treatment. (b) 6 years follow-up after 13 months of injection therapy with both 5-FU and steroid.

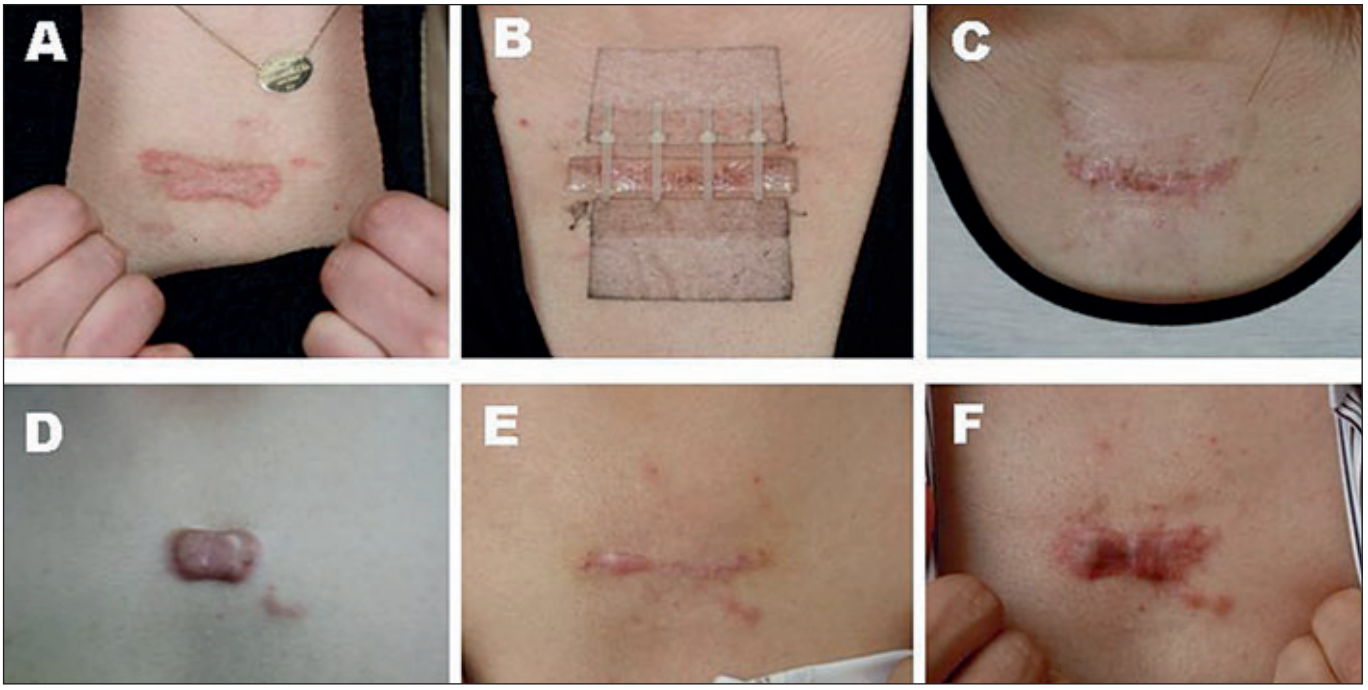

Figure 2. Comparison of therapeutic results between tension-reduction (top panel) and non tension-reduction (*bottom panel*) surgical approaches. *Top:* (a) before treatment; (b) one month post-surgical excision with tension reduction device; (c) six months post-surgical treatment with 3 injections. *Bottom:* (d) before treatment; (e) one month post-surgical excision without tension reduction device; (f) six months post-surgical treatment with injection once a month.

formed complete surgical excision of small and medial sized keloids that allowed for primary wound closure. Chemotherapy was then given at 3-4 weeks post-operation and usually once a month. Comparing to injection therapy, surgery combined with injection can relatively shorten the therapeutic time and reduce drug amount in general, however, keloid recurrence with stretched-widened scar is quite often observed and a relatively long time of injection therapy is needed to completely cure keloid and control its recurrence.

Realizing that tension reduction may play an important role in treating high tension area keloids such as chest, a tension reduction approach was employed using a device which is tape based and able to transfer the wound tension to nearby normal unwounded skin. With this device, even a bigger sized keloid can be surgically removed followed by the application of this device that needs to be worn for minimal 3 months or preferred 6 months. The clinical results showed that part of the patients did not need chemotherapy or need only a few injections to fully cure the disease. For other patients, low dose chemotherapy remains needed to completely control keloid recurrence. In general, much shorter treatment time period is needed comparing to that without the device, because the rate and extent of regrowth are much lower and less compared to those without device even the same dose and frequency of drug injection are applied to both groups. Additionally, a thick linear scar is usually observed in cured patients instead of a stretch-widened scar in cured patient who did not wear the device *(Figure 2)*. Afterwards, the same approach has also been applied to the treatment of keloids with success in other high tension areas such as shoulder, extremity or back.

In summary, we have developed a chemotherapy regime with low dose 5-FU and steroid based on the hypothesis that this may efficiently inhibit angiogenesis and fibroblasts proliferation during and post degradation of keloid matrices or after keloid removal and thus is able to better control keloid relapse. Importantly, the low dose chemotherapy agent not only allows for long time therapy without obvious side effect, but also avoids tissue necrosis which is likely to cause new wounding and trigger a new fibrotic process. Furthermore, with reduced vascularity of treated keloid by 5-FU, steroid can be better retained at the injection site to increase drug efficiency and reduce side effect. Our clinical experience indicates that such a strategy may further improve therapeutic efficiency when combined with surgical therapy given the fact it is also ~~able~~ able to control post-surgical recurrence. More importantly, combination of chemotherapy with tension reduction by using related devices may represent future direction of keloid treatment in high tension zones. ■

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