THE AMERICAN JOURNAL of MEDICINE®

Recalcitrant Grysbovski's Keratoacanthomas with Good Response to Cimetidine

To the Editor:

Grysbovski generalized multiple keratoacanthoma (GGMK) represents a rare disabling skin condition of follicular origin, in which hundreds of pruritic tiny disseminated nodules with a central hyperkeratotic plug appear sporadically, especially on the sun exposed areas. The disease follows a progressive course with gradual disfigurement consisting of sclerotic transformation of the skin and mask-like facial expression with bilateral ectropion. Etiopathogenic factors include ultraviolet light, human papilloma virus (HPV), trauma, chemical carcinogens and immunosupression.[1] Modern treatment using retinoids and immunosupressors have a limited efficiency and several side effects. We report a severe case of GGMK with lack of response to the conventional therapies which has been successfully treated with cimetidine.

PRESENTATION

A 45-year-old Caucasian woman presented with a 3-month history of hundreds of tiny keratotic papules disseminated all over the body and buccal mucosa, with predominance on sun exposed areas (Figure 1A). Over the next several months, she developed generalized cutaneous induration with confluent papules, commencing with facial skin and spreading caudally. This resulted in severe pruritus and discomfort.

DIAGNOSIS AND MANAGEMENT

The diagnosis of GGMK was established by physical examination, a negative family history together with characteristic histological features (skin fragments with a central core of keratin surrounded by thickened squamous epithelium showing minor atypia and occasional dyskeratotic cells). General examination, screening blood tests, faecal occult blood, chest X-ray, mammography and cervical smear detected no evidence for internal malignancy. Using a polymerase chain reaction approach we investigated paraffin-embedded specimens of 7 biopsies sampled from skin kerathoacantomas(5), oral lesions(1) and normal skin(1) for the presence of HPV DNA. All specimens were positive for HPV type 20; in addition two lesions were also positive for types 15 and 4, respectively.

Early unsuccessful therapies included Acitretin (0.5 mg/kg, 3 months), followed by Metothrexate (15 mg/week, 2 months); the lesions continued to develop, creating a serious cosmetic problem that resulted in distress and difficulties in the patient's social life. Following the lack of response to the mentioned therapies we administrated cimetidine 2.4 g/day, for its immunoregulatory effects previously reported in skin diseases of HPV causation like warts and papillomas. Just three months later we observed the complete resolution of more than 95% of the lesions, and a significant regression of agglomerate tumors (Figure 1B). An attempt to discontinue cimetidine after 4 months resulted in dramatic development of new lesions. The treatment was restarted at the same dose for 3 months, and the remission was maintained with 1.2 g/day until the present, the drug being well tolerated.

COMMENT

GGMK is a particular type of keratoacanthoma with progressive course and unsatisfactory therapeutic outcome.[1] Significant numbers of CD5+ and CD4+ cells invading the epidermis and increased number of infiltrating T lymphocytes expressing the interleukin-2 receptor have been reported as evidence for an immunologically mediated process in keratoacanthoma regression.[1] Cimetidine, the most studied H2-receptor antagonist, has been shown to possess a tumor-suppressive effect in several cancers (e.g. gastric, colon, salivary glands, melanoma); it acts directly on tumor growth by blocking the cell growth-promoting activity of histamine (via activation of H_2 receptors), and supresses cancer cell migration and adhesion to endothelial cells;[2] moreover, through its immunomodulatory effect, cimetidine enhances the effector immune response to tumor cells.[2]

Treatment with cimetidine, devoid of systemic side effects of immunosuppressive and retinoid medications, may be considered an alternative for a subset of GGMK cases.

Funding source in preparation of this manuscript: Department of Dermatology, University of Colorado. No pharmaceutical company contributed as funding source.

Conflict of Interest: Adrian Baican states no conflicts of interest. David Norris states no conflicts of interest. Stanca Birlea states no conflicts of interest.

All authors had access to the data and a role in writing the manuscript. Dr Baican contributed to the acquisition of the data; he diagnosed and treated the case presented. Drs. Birlea, Baican and Norris contributed to the manuscript concept.

Address correspondence to: Stanca Birlea, MD, PhD, Department of Dermatology and Human Medical Genetics Program, University of Colorado Denver, Anschutz Medical Campus, PO Box 6511, MS 8300, Aurora, Colorado 80045, USA.

E-mail address: Stanca.Birlea@ucdenver.edu

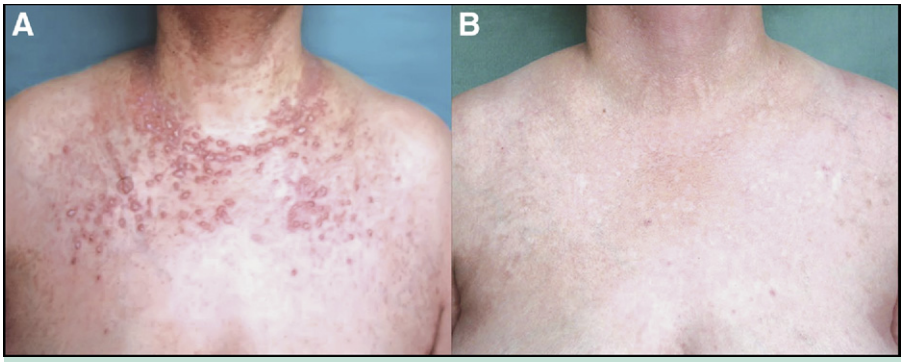

Figure 1 Clinical presentation of the case before therapy with cimetidine(1A) and after(1B).

Although cimetidine has showed variable results in warts and papillomas, we believe that the therapeutic response depends in particular on the patient immunological status, being relevant in cases in whom deficient cellular mediated immunity plays a role in the disease causation.

Adrian Baican[a]
David A. Norris[b]
Stanca A. Birlea[b,c]
[a]*Department of Dermatology, University of Medicine and Pharmacy, Cluj-Napoca, Cluj, Romania*
[b]*Department of Dermatology, University of Colorado Denver, Aurora*
[c]*Human Medical Genetics Program, University of Colorado Denver, Aurora*

doi:10.1016/j.amjmed.2009.11.014

References

1. Kavanagh GM, Marshman G, Hanna MM. A case of Grysbovski's generalized eruptive keratoacanthomas. *Australas J Dermatol*. 1995; 36:83-85.
2. Natori T, Sata M, Nagai R, et al. Cimetidine inhibits angiogenesis and suppresses tumor growth. *Biomed Pharmacother*. 2005;59:56-60.