Intralesional Bleomycin for Angiolymphoid Hyperplasia

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The Cutting Edge: Challenges in Medical and Surgical Therapeutics

REPORT OF CASES

CASE 1

A 51-year-old woman presented with a 4-year history of slightly pruritic, bleeding papules on her right ear. Approximately 2 years earlier, the lesions had been excised, but they had recurred the following year and had increased in number within the past 3 months. The dermatologic examination revealed 5 violaceous, erythematous soft papules ranging from 3 mm to 1 cm in diameter in the helix and on the upper lateral postauricular region of the right ear (Figure 1). The results of the systemic examination were normal, without evidence of lymphadenopathy. Routine laboratory tests, including a complete blood cell count, erythrocyte sedimentation rate, routine blood biochemical profile, complete urinalysis, IgE level, antistreptolysin-O and C-reactive protein assessments, and x-ray imaging of the chest, demonstrated no abnormalities. Histopathologic examination of a punch biopsy specimen revealed angiolymphoid hyperplasia with eosinophilia (ALHE) (Figure 2).

CASE 2

A 28-year-old woman presented with a 1-year history of generalized pruritic hemorrhagic papules on her right ear. The papules, which initially were small, itchy, and acneiform, had extended to the posterior auricular region during the last 3 months. The patient also had small, itchy, pimplelike lesions on her body, which had appeared almost simultaneously. There was no history of insect bite or trauma. On dermatologic examination, the helix of the right ear was erythematous and swollen, and there were a number of purple, erythematous, soft papules and nodules ranging from 0.5 to 3 cm in diameter on the helix and postauricular region (Figure 3). On the abdomen, midline of the back, extensor aspects of both forearms,
and bilateral pretibial regions, there were numerous erythematous, excoriated papules with hemorrhagic crusting. Three lymph nodes, approximately 1 cm in diameter, were palpable on the right postauricular and cervical region ipsilateral to the ear lesions. The results of the systemic examination were normal. Routine laboratory tests revealed an elevated level of IgE (1150 IU/mL) and eosinophilia (7.4%). The histopathologic diagnosis was reported as ALHE (Figure 4).

**THERAPEUTIC CHALLENGE**

Angiolymphoid hyperplasia with eosinophilia is a proliferative vascular lesion of skin and mucosa membrane.1-5 The most common treatments are local surgical excision, intralesional corticosteroid therapy, and laser ablation with continuous-wave carbon dioxide, argon laser, or 585-nm pulsed-dye laser.5 The rate of recurrence after surgical excision is as high as 33% to 50%.5 In case 1, the lesions recurred and increased in number after surgical excision. Because surgical excision was not successful, we prescribed bleomycin sulfate therapy, which had been locally used, with success, in proliferative lesions of skin such as verruca and lymphangioma. The exceptionally promising therapeutic response in case 1 prompted us to use bleomycin in the second case, in which the lesions were widespread and unsuitable for surgical excision.

**SOLUTION**

In case 1, intralesional bleomycin sulfate therapy was initiated at a dosage of 0.2 U (0.1 mg) once a month. The dose of the second injection was increased to 0.4 U. No systemic or local adverse effects, such as swelling, Raynaud phenomenon, scarring, or pigment alteration, were observed. The pain was mild to moderate but always tolerable and subsided within 30 minutes after the injection. The lesions completely disappeared at the end of the fifth month, and therapy was discontinued. After 9 months of follow-up, the patient still had no recurrence.

In case 2, intralesional bleomycin therapy was used in the same way as in case 1. All the lesions were injected with bleomycin, and the therapy was repeated once a month for 5 months. The protocol was interrupted because of pregnancy after the fifth injection. In both cases, all the lesions completely disappeared (Figure 5 and Figure 6). During the follow-up, no new lesions occurred.

**COMMENT**

Angiolymphoid hyperplasia with eosinophilia is a rare vasoproliferative disease with a benign nature.1-6 It occurs in the third to fourth decades of life, with a higher incidence in women. The etiology is unknown.1-6 The most common sites are the head and neck, particularly the region around the ears and external ear canals. Single or multiple, grouped, and dome-shaped red papules, nodules, or plaques, which are located in the subcutaneous tissue and dermis, are the most characteristic features.1-6 The condition was first described by Wells and Whimster7 in 1969. It is defined as a proliferation of skin and mucous membranes in the dermis and subcutaneous tissue that is known to originate from the vascular
lature. It mostly occurs among Asian women aged 20 to 50 years.\textsuperscript{3,8,9} The median age at presentation is 30 to 33 years.\textsuperscript{3} Our patients were 28- and 51-year-old women.

Clinically, dome-shaped papules and nodules with a relatively regular surface are the main features of the disease. They may be variable in color (red to brown) and either eroded or crusted.\textsuperscript{3,9} In approximately 85% of patients, skin lesions are located on the head and neck, particularly on the scalp, forehead, and area around the ears.\textsuperscript{1-5} They usually measure 0.5 to 2 cm in diameter, extend over an area of 0.2 to 8 cm\textsuperscript{2}, and may be painful and itchy.\textsuperscript{3} Spontaneous bleeding and pulsation are rare findings.\textsuperscript{3-5,9} Local lymphadenopathy is found in 5% to 20% of the cases, while peripheral eosinophilia is found in 20%.\textsuperscript{3,5,8,9} Although the pathogenesis is still unclear, it has been suggested that there may be some predisposing factors such as trauma, arteriovenous shunts, high blood levels of estrogens, atopic reactions, infections, and reactive hyperplasia or benign neoplasia of the vasculature.\textsuperscript{2,3,5,9}

The clinical differential diagnosis of ALHE includes Kimura disease, Kaposi sarcoma, salivary gland tumors, squamous cell carcinoma, pyogenic granuloma, angiofibroma, cavernous hemangioma, granuloma faciale, perianteritis nodosa, sarcoidosis, lymphocytoma cutis, skin metastases, and enlarged lymph nodes. Kimura disease, hemangiendothelioma, angiosarcoma, and arthropod or insect bites should be considered in the histopathologic differential diagnosis.\textsuperscript{2,3,5} In past years, Kimura disease was classified as a variant of ALHE, but today it is considered a different entity.\textsuperscript{3,5,10} Complications are rare. In severe cases, obstruction of auditory tract may result in conductive hearing loss. Orbital involvement resulting in diplopia and proptosis was reported in 1 case.\textsuperscript{3}

Generally, surgical excision is the preferred treatment; however, about one-third of lesions recur after excision. Other treatment choices are Mohs microsurgery, diathermy, cryotherapy, cautery, laser therapy (carbon dioxide laser, argon laser, and 585-nm pulsed-dye laser), radiotherapy, cessation of estrogen replacement therapy, and therapy with corticosteroids (oral, topical, or intralesional), indomethacin, imiquimod, interferon alfa, oral retinoids, pentoxifylline, intravenous vinblastine sulfate, and intralesional chemotherapeutics (vinblastine and fluorouracil).\textsuperscript{3,6,11-16}

Bleomycin is a cytotoxic agent with antitumoral, antibacterial, and antiviral activity. The drug is available as a powder. It should be reconstituted with 0.9% sodium chloride into a 1-U/mL solution. It binds to DNA, causing strand scission and elimination of pyrimidine and purine bases. At 48 hours after injection, apoptotic keratinocytes are seen in the epidermis. Possible systemic toxic effects from bleomycin therapy include myelosuppression, hyperpigmentation, hyperkeratosis, ulceration, pulmonary fibrosis, headache, nausea, vomiting, hyperthermia, and hypotension. The small volumes used in local therapy, however, do not cause systemic toxic effects. Local adverse effects such as pain, swelling, and Raynaud phenomenon have been reported.\textsuperscript{17,18} Intraligeral bleomycin has been used in the treatment of recalcitrant warts, lymphangiomas, and hemangiomas.\textsuperscript{17-20}
Patient 1 had a recurrence and an increase in the number of lesions after surgical excision. To our knowledge, there is only 1 previous report mentioning the use of intralesional bleomycin for the treatment of ALHE in the current literature.8 We report complete responses in our 2 cases. There were no recurrences during 9 months of follow-up in either patient. This positive outcome suggests that intralesional bleomycin prescribed in the indicated dosages is an effective and safe mode of therapy for ALHE.

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