How Would You Diagnose This Woman's Growing Asymptomatic Nodule?

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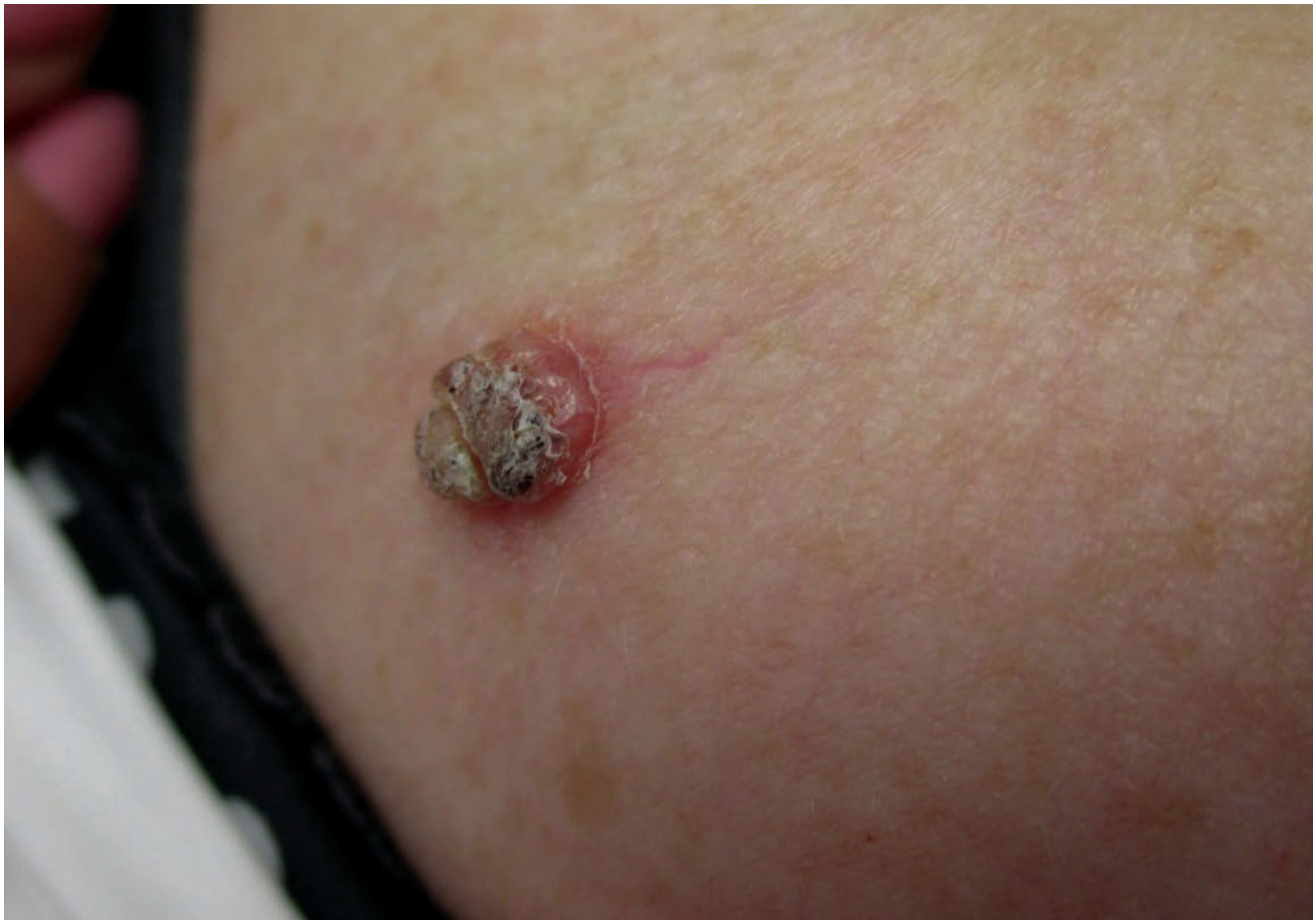

A 52-year-old white woman presented with an asymptomatic solitary nodule on the right breast. The lesion was first noted 5 months prior as a small papule and evolved to its current size over a period of 2 months. There was no history of trauma to the site. The patient was otherwise healthy. She was a non-smoker and not on any medications. There was a family history of skin cancer.

PHYSICAL EXAMINATION

On examination, the nodule was dome-shaped and had a central keratinous crater. There was no regional or systemic lymphadenopathy.

What's Your Diagnosis?

A. Basal cell carcinoma
B. Squamous cell carcinoma
C. Keratoacanthoma
D. Pyogenic granuloma

Answer: Keratoacanthoma

Keratoacanthoma is an epithelial neoplasm characterized by a sharply demarcated nodule with a central keratin-filled crater, rapid growth in the proliferative phase, variable period of lesion stability, and potential for spontaneous involution. The condition was first described by Hutchinson in 1889.[1]

EPIDEMIOLOGY

Individuals in their 40s to 60s are most commonly affected.[2] The male to female ratio is 2:1.[3] The condition is most common in fair-skinned individuals.[3]

ETIOPATHOGENESIS

It is believed that keratoacanthoma derives from the infundibulum of the hair follicle.[3] Changes in the expression of genes involved in epidermal cell proliferation, cell adhesion, and cell survival may play a pivotal role in the development of keratoacanthoma.[3] In this regard, mutations of the tumor suppressor gene *p53* and the apoptosis regulatory protein gene *bcl-2/Bak* are implicated in the pathogenesis.[4] Moreover, mutations in the transforming growth factor beta receptor and mismatch repair genes have been reported in multiple self-healing squamous epithelioma (MSSE, also known as multiple keratoacanthomas of Ferguson-Smith type or Ferguson-Smith syndrome) and keratoacanthomas in Muir-Torre syndrome, respectively.[5]

Ultraviolet radiation is a major predisposing factor.[4] Other predisposing factors include Caucasians with Fitzpatrick skin phototypes I, II or III, genetic predisposition, trauma, immunodeficiency, medications (eg, sorafenib, vemurafenib, dabrafenib), chemical carcinogens (eg, tar, pitch, cigarette, polyaromatic hydrocarbons), and, possibly, certain types of human papillomavirus infection.[3,6]

HISTOPATHOLOGY

Histological findings include epidermal hyperplasia, overhanging epithelial lips, central keratin-filled crater, keratinocytes with glassy eosinophilic cytoplasm, sharp demarcation between tumor nests and surrounding stroma, and mixed inflammatory infiltrate in the dermis.[2-4] The tumor does not extend into the dermis to a depth below the eccrine glands.[2]

CLINICAL MANIFESTATIONS

According to the number, size, and distribution, several clinical variants of keratoacanthoma have been described—namely, solitary keratoacanthoma, giant keratoacanthoma, subungual keratoacanthoma, mucosal keratoacanthoma, keratoacanthoma centrifugum marginatum, MSSE, generalized eruptive keratoacanthomas of Grzybowski, and multiple keratoacanthomas of Witten and Zak.[3,6]

Solitary keratoacanthoma is the most common variant.[3] Typically, solitary keratoacanthoma presents as an asymptomatic, firm, solitary, pink or skin-colored, dome-shaped nodule with a central keratin-filled crater, as is illustrated in the present case.[6] Sites of predilections include sun-exposed areas such as the face, neck, and hands as well as areas of previous trauma. Solar-induced freckles, solar lentigines, and actinic keratoses may be found in the surrounding areas. The lesion is characterized by rapid growth and achieves an average size of 1-2 cm in the first few weeks.[6] The lesion then stabilizes and may regress spontaneously over several months.

Arbitrarily, a giant keratoacanthoma refers to a keratoacanthoma >2 cm in diameter.[7] A giant keratoacanthoma can be locally invasive and destructive.

A subungual keratoacanthoma develops on the nail bed and is usually painful. Typically, it presents as a crescent-shaped soft tissue mass with erosion of the underlying bone. Although a subungual keratoacanthoma is locally aggressive, it does not metastasize.

Mucosal keratoacanthoma develops on mucosal surfaces such as those in the oral cavity, lip, conjunctiva, nasal cavity, and genitalia. Mucosal keratoacanthomas may also be seen in patients with generalized eruptive keratoacanthomas of Grybowski.[3]

Keratoacanthoma centrifugum marginatum is characterized by progressive peripheral expansion with a raised rolled-out margin, central healing, and atrophy.[8] The most common locations are dorsa of hands and feet.[8] Lesions are large, reaching up to 20 cm.[2] Keratoacanthoma centrifugum marginatum is differentiated from giant keratoacanthoma by absence of downward vertical growth and destruction of underlying tissue.[8]

MSSE is seen predominantly in Scottish kindreds. The condition has as an autosomal dominant mode of inheritance and the responsible gene has been mapped to chromosome 9q22-q31.[2,4] MESS often presents as hundreds of keratoacanthomas through adolescence and onward.

Generalized eruptive keratoacanthomas of Grzybowski is characterized by a sudden generalized eruption of hundreds to thousands of small (1-3 mm), follicular, skin- or flesh-colored papules with central umbilication that may contain a central horny, keratotic plug.[9,10] The onset is usually between the fifth and seventh decades of life. The sex ratio is equal. The condition usually affects the skin and, less commonly, the mucous membrane.[9,10] Sun exposed areas are predominately affected with prominent facial involvement, leading to ectropion and a masked facies of tumors (sign of Zorro).[9] Intense pruritus is common.[9]

Multiple keratoacanthomas of Witten and Zak is characterized by multiple larger cherry-sized nodules, intermediate pea-sized lesions, and smaller follicular papules.[2,4] The condition has as an autosomal dominant mode of inheritance. The age of onset is usually in childhood.

In addition, keratoacanthomas may be part of Muir-Torre syndrome and xeroderma pigmentosum.[2,3]

DIAGNOSIS

The diagnosis is usually clinical, based on its distinctive clinical history. Dermoscopy of the lesion reveals keratin crust/scale, central keratin mass, white keratin pearls, white circles, white structureless zones, hemorrhage centrally and in areas of keratinization, glomerular vessels, linear irregular vessels, atypical vessels, and hairpin vessels.[11,12] Unfortunately, these features may also be present in squamous cell carcinoma.[11,12] Because of a lack of clinical features that can reliably distinguishing keratoacanthoma from squamous cell carcinoma, a biopsy with a sample of sufficient depth should be considered.

DIFFERENTIAL DIAGNOSIS

Differential diagnosis includes squamous cell carcinoma, basal cell carcinoma, Merkel cell carcinoma, hypertrophic actinic keratosis, seborrheic keratosis, verruca vulgaris, pyogenic granuloma, prurigo nodularis, giant molluscum contagiosum, deep fungal or mycobacterial infection, and nodular Kaposi's sarcoma.[3,4]

COMPLICATIONS

Occasionally, keratoacanthoma may metastasize.[2] Vascular and perineural invasion may also be observed.[13] For lesions that have undergone spontaneous resolution, some may leave atrophic and hyperpigmented scars. In patients with generalized eruptive keratoacanthomas of Grzybowski, the associated ectropion and a masked facies of tumors are cosmetically unsightly and together with the intense pruritus have an adverse effect on the quality of life.

PROGNOSIS

In approximately 50% of cases, spontaneous resolution of the tumor occurs within 4 to 9 months of achieving maximal size. Subungual and mucosal keratoacanthomas and keratoacanthoma centrifugum marginatum usually do not regress.[2,4] The recurrence rate is 3% to 5%, depending on the treatment modality.[5]

MANAGEMENT

Some suggest watchful observation of the lesions and to await spontaneous resolution. Should a patient elect to defer treatment, regular close follow-up with serial photography of the lesion is recommended. Most others believe that keratoacanthoma is a variant of squamous cell carcinoma or within the same spectrum and it is wise to treat keratoacanthoma rather than to monitor for its spontaneous resolution since a clinically presumed keratoacanthoma may in fact turn out to be a squamous cell carcinoma on histopathology.[2] The choice of the treatment method should be individualized depending on the physician's comfort level with the various treatment options, the type of keratoacanthoma, the location, number and size of lesions, and the preference of the patient.

Surgical excision is the treatment of choice for a solitary keratoacanthoma. Other treatment options include electrodessication and curettage, cryosurgery, intralesional 5-fluorouracil or methotrexate, topical imiquimod or 5-FU, and laser therapy; some therapies are used in combination.[3,4] For a large keratoacanthoma in a sensitive location not amenable to surgery, intralesional 5-fluorouracil or methotrexate should be considered.[4,14] For multiple keratoacanthomas, treatment options include oral retinoids, oral cyclophosphamide, and superficial radiotherapy.[4,15]

Avoidance of sun exposure especially during hours of peak ultraviolet intensity (11 am to 4 pm), regular use of broad-spectrum sunscreens, avoiding tanning salons, and wearing of protective hats and clothes when outdoors should be emphasized to reduce scarring and prevent recurrence.

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