CASE REPORT

Hypopigmented large-cell acanthoma of the eyelid

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A B S T R A C T

Large-cell acanthoma is an asymptomatic, slightly keratotic, usually hyperpigmented epidermal lesion that is mostly seen in the sun-exposed skin of middle-aged or elderly people. It is characterized by extraordinarily large keratinocytes that can reach up to twice their normal size without a change in the nucleus/cytoplasm ratio. Here, we describe a chronic case of large-cell acanthoma that involved the whole upper eyelid of a 67-year-old man for at least 15 years. The lesion was almost depigmented and demonstrated altered consistency of the eyelid, causing lax and folded skin. The lesion responded to treatment with topical tretinoin and urea. This case verifies the benign character of large-cell acanthoma and demonstrates how it may have atypical presentations.

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I N T R O D U C T I O N

Large-cell acanthoma (LCA) is an asymptomatic, slightly keratotic, usually hyperpigmented epidermal lesion that is mostly seen in the sun-exposed skin of middle-aged or elderly people. LCA is characterized by extraordinarily large keratinocytes.1 Here, we present a case of LCA that demonstrated a number of atypical clinical findings related to color, size, site of occurrence, and secondary skin changes.

C A S E   R E P O R T

A 67-year-old man was referred to our institution complaining of skin texture change with thick and loose skin of the left upper eyelid that had been present for at least 15 years. He had been subjected to intense and long-term sun exposure because he had worked as a farmer throughout his life. His medical history was negative for previous skin malignities and periocular trauma. He presented with no eye- or plaque-related symptoms. A thick, whitish, glossy plaque involving almost the whole left upper eyelid was noted on dermatological examination. The lesional skin showed shallow pits in some areas. In addition, the skin of this area was looser, more folded, and redundant than its counterpart. His facial skin showed signs of photodamage with multiple solar lentigines, solar elastosis, and increased skin wrinkling (Figures 1A, B). An incisional biopsy of the lesion was performed, and a predisagnosis of lichen scleroatrophicus or chronic lichenified dermatitis was considered. The microscopic features included hyperkeratosis, hypergranulosis, acanthosis, slight pleomorphism, and hyperchromatism of the basal layer. The most striking finding was the unusually large size of keratinocytes, while the cells in the nonlesional border were of normal size. The dermis demonstrated edema and mononuclear inflammation. Solar elastosis was minimal (Figures 2A, B, C). Based on the microscopic features, a diagnosis of LCA was made. PCR examination of the biopsy specimen for determination of the high-risk group of Human papillomavirus (HPVs) that are more likely to induce development of cancer (HPV-16, 18, 31, 33, 35, 39, 45, 52, 53, 56, 58, 59, 66, and 70) was negative. Before the histopathological examination reached a definitive conclusion, empiric treatment with twice-daily administration of topical mometasone furoate had already been started. After 1 week of therapy, the lesion was aggravated with a prominent verrucous surface (Figure 3A). Because the diagnosis of LCA was confirmed by the histopathological examination, topical steroid treatment was suspended. The patient was treated with topical tretinoin and 10% urea cream, and relatively satisfactory results were achieved within 1 month (Figure 3B).

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Discussion

LCA was first described in 1970 by Pinkus as a benign neoplasm of the epidermal cells with distinctive histopathological features.\textsuperscript{1,2} The case presented here adds some new information regarding LCA.

Clinically, LCA is usually a solitary, sharply demarcated, slightly scaly lesion that is <10 mm in diameter. The lesion commonly presents as a hyperpigmented maculopapule and grossly resembles solar lentigo or seborrheic or actinic keratosis. Skin-colored or hypopigmented lesions have been infrequently reported.\textsuperscript{1,2} The only reported case of achromic LCA presented on the dorsal hand of an elderly woman and was described by Ambrojo et al.\textsuperscript{3} That white and verrucous lesion demonstrated the absence of melanin, but the density of the melanocytes was not different from that of the adjacent epidermis. In our case, the plaque was markedly hypopigmented, almost white in most areas. Decreased melanin may clinically account for the hypopigmentation, although there wasn’t enough of a specimen to verify this finding using any type of special stain. We believe that the light reflecting from the skin folds and the hyperkeratotic surface may also have contributed to the whitish color. Another interesting clinical feature of our patient was the large size of the lesion. It was about 3.5 cm in diameter, covered the entire upper eyelid, and involved the upper and lateral orbital circle. Skin laxity was prominent at first sight, probably due to the large area involved.

LCA is most commonly found on the sun-exposed skin of the head, arms, trunk, and lower limbs. Our patient had also received long-term, intense sun exposure as evidenced by the facial solar lentigines. However, it is well known that the eyelids are exposed to less UV irradiation than the other parts of the face.\textsuperscript{4} Because of this, LCA located on the eyelid is a rare phenomenon. Currently, there

![Figure 1](image1.png)

Figure 1 (A) Upper left eyelid demonstrating looser and more folded skin than the right eyelid. (B) Whitish, glossy, and waxy plaque covering almost the whole eyelid.

![Figure 2](image2.png)

Figure 2 (A) General view of the lesion including the border of the lesion (arrow; hematoxylin-eosin, ×40). (B) Magnified view of the border of the lesion (arrow; hematoxylin-eosin, ×100). (C) Close-up view of the same area. Note the presence of hyperkeratosis, hypergranulosis, acanthosis, minimal pleomorphism, and the large size of the keratinocytes, while the cells in nonlesional border are of normal size. The dermis demonstrates edema and mononuclear inflammation (hematoxylin-eosin, ×200).
are only two reported cases of LCA that involved the skin of the eyelid. Both of these patients were elderly men whose lesions presented on the right upper eyelid for 3 months and 2 years, respectively. The lesions were defined as pale, hyperkeratotic plaques, similar to our case. It may be that besides UV irradiation, other unknown factors may influence the development of LCA on the eyelids.

The histopathological features of LCA are diagnostic. The sizes of the keratinocytes within the lesion are uniformly increased in proportion to the enlarged nuclei and cytoplasm that can reach twice their normal size. Other microscopic features include anaplasia, papillomatosis, hypergranulosis, and orthokeratosis. In recent years, different types of HPV, including oncogenic varieties, have been detected in multiple types of LCA lesions. However, it has also been suggested that verruca plana may be misdiagnosed as LCA, especially when multiple lesions are present, because both lesions show hyperkeratosis, acanthosis, and large keratinocytes. The critical difference between verruca plana and LCA is the presence of large cells, mainly in the upper layers of the epidermis, thereby sparing lower part. In our case, the large cells involved the whole epidermis, confirming LCA. In addition, the PCR analysis of the biopsy specimen for high-risk HPVs was also negative.

The etiopathogenesis and prognosis of LCA are still largely debatable. So far, investigators have insisted on the contribution of chronic sun damage to the pathogenesis of LCA. Several authors consider LCA to be a variant of solar lentigo, seborrhoeic keratosis, or stucco keratosis. Some early reports have suggested a relationship with actinic keratosis or Bowen's disease due to slight pleomorphism, architectural disorder, involvement of the skin appendages, and the occasional suprabasal mitotic activity in some of the lesions. Mehregan et al compared LCA with solar lentigo and actinic keratosis in terms of keratinocyte proliferation and melanocyte density using proliferating cell nuclear antigen staining and Human Melanoma Black-45 (HMB-45) staining which detects activated and neoplastic melanocytes. Solar lentigo and LCA both show an increased number of melanocytes, while actinic keratosis differs from these two maladies by demonstrating a significantly lower number of melanocytes and a higher proliferative index. However, nuclear DNA analyses by different methods have shown tetraploidy in LCA, which indicates that it is a distinct entity. Recent studies have also shown that tetraploidy may promote chromosomal aberrations and tumorigenesis due to supernumerary centrosomes and the doubled chromosome mass. Nevertheless, LCA is generally considered a benign keratinocytic neoplasm, and malignant transformation of LCA has not been reported in the skin. On the other hand, there is a recent report that describes the first case of malignant transformation of conjunctival LCA that evolved into carcinoma in situ over 6 years. Because this is the only reported case of LCA that involved a mucosal site, it is unclear whether progression to carcinoma is more likely for mucosal lesions or not. In our patient, the absence of high-risk HPVs and the lack of malignant changes over more than 15 years support the benign character of the lesion. It was amazing to observe verrucous surface changes after topical potent steroid application. This peculiar appearance may be reminiscent of cream or powder residues, however it did not vanish after washing or wiping the area. The exact cause of this reaction and its relevance to the original diagnosis of LCA is unclear, but it may be due to irritating effects of some ingredients in the cream, either the steroid itself or its base.

In conclusion, the patient reported here is interesting for a few reasons. First, it is a rare example of a nonpigmented type of LCA. Second, the lesion was unusually large and had a loose texture that had not been reported before. Third, the lesion was found in a rarely reported, relatively unexposed site. Finally, the chronic course and response to topical retinoids support its benign nature.

References