

Review

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Posted Date: 1 September 2025

doi: 10.20944/preprints202508.2218.v1

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Review

# Keratoacanthoma: New Insight into Pathogenesis and Management of the Disease

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## Abstract

Keratoacanthoma (KA) is a rapidly growing epithelial neoplasm characterized by clinical and histopathological features that often overlap with well-differentiated squamous cell carcinoma (SCC), posing diagnostic challenges. This review provides a comprehensive overview of KA, emphasizing advances in non-invasive diagnostic techniques such as dermoscopy, reflectance confocal microscopy (RCM), and line-field confocal optical coherence tomography (LC-OCT), which improve lesion characterization and differentiation from SCC. We discuss the histopathological phases of KA and highlight key features aiding in diagnosis. Furthermore, we explore the emerging role of human papillomavirus (HPV), particularly  $\beta$ -genus types, as a cofactor in KA carcinogenesis through modulation of apoptosis and DNA damage response pathways, especially under ultraviolet (UV) radiation exposure. Therapeutic strategies remain centred on complete surgical excision; however, alternative treatments, including radiotherapy, cryotherapy, topical agents, and systemic retinoids, are discussed with their respective benefits and limitations. Finally, we review current HPV vaccines and novel vaccine candidates targeting a broad spectrum of mucosal and cutaneous HPV types, alongside promising off-label therapeutic applications. This review underscores the importance of integrated diagnostic and therapeutic approaches to optimize KA management and highlights future directions in understanding its pathogenesis and treatment.

**Keywords:** keratoacanthoma; human papillomavirus; non-melanoma skin cancer; dermoscopy; reflectance confocal microscopy; line-field confocal optical coherence tomography; carcinogenesis; therapies; vaccines

## 1. Introduction

Keratoacanthoma (KA) is classified among the non-melanoma skin cancers (NMSC), typically arising on the head and neck areas. It is still controversial whether KA is a distinct neoplasm or a subtype of well-differentiated squamous cell carcinoma (SCC). Although the exact cause of KA remains uncertain, ultraviolet (UV) rays play a significant role in its development, rendering fair-skinned individuals particularly vulnerable. Other potential triggers include human papillomavirus (HPV), immunosuppression, immunodeficiency, trauma, radiation, chemicals, cell-cycle-modulating medications, and foreign bodies [1]. Additionally, KA is more commonly seen in older adults, particularly those with prolonged sun exposure or immunosuppression, and it occurs more frequently in men than in women. KA is thought to originate from the hair follicle and can appear in solitary, multiple, or eruptive forms, with the solitary type being the most prevalent [2]. Clinically,

the most common presentation is a solitary lesion measuring 1 to 2 cm in diameter. Less common variants include giant KA—defined as a solitary tumor larger than 20 mm, typically found on the eyelid or nose—and KA centrifugum marginatum, characterized by peripheral expansion with central healing, which can also exceed 20 mm in diameter [3]. Typically, KA progresses through three clinical phases: a proliferative phase, a stabilization phase, and a regression phase [4]. Several signaling pathways have been implicated in KA pathogenesis, including the Wnt/retinoic acid pathway, B-Raf, H-Ras, p27, and the Hedgehog signaling pathway [5–8].

Some patients affected by specific genetic syndromes, such as Muir-Torre syndrome, *xeroderma pigmentosum*, Ferguson-Smith disease, Witten-Zac syndrome, and Grzybowski syndrome, may present multiple KAs [9,10]. The last syndrome is characterized by thousands of eruptive KAs that could resolve over several months, and tumors may also develop in the airway. The appearance of the tumors may resemble milia or eruptive xanthomas [9].

Regarding therapy, surgery with traditional excision or Mohs micrographic surgery is considered the gold standard treatment, mainly for single forms of KA. Other therapies that have been proposed include radiation, destructive therapies, topical therapies, and systemic therapies. However, to date, there is no consensus guideline on alternative therapies for KAs, except for surgery. Some case series report the use of methotrexate and interferon injected into the tumor, and tretinoin used for multiple-type KA [11–13].

This article aims to explore the key aspects of KA, including its clinical presentation, pathogenesis, histological aspects, and the available treatment options, providing an insight into the management of this tumor.

## 2. Epidemiology of Keratoacanthoma

Epidemiological data about KA are still inconsistent due to underestimation arising from shared morphological features with SCC, especially in the case of well-differentiated SCC. The reported incidence of KA ranges between 100 and 150 cases per 100,000 individuals [14,15]. Recently, the KA peak incidence has shifted toward the age group 65 to 71 years from 50 to 69 years observed in the 1990s [16]. Men are more often affected than women [16]. KA affects mostly fair-skinned people and has not yet been reported in native Australians [14]. Major risk factors include excessive UV exposure, radiation, immunosuppression, chronic non-healing wounds, and HPV infection, as also reported for well-differentiated SCC [17]. In addition, cutaneous trauma (e.g., laser therapy, resurfacing procedures, or surgery) has been reported as an additional risk factor in KA development, suggesting that dysregulated inflammatory responses may play a further role in its pathogenesis [18,19].

## 3. Etiology

The etiology of KA is still not completely understood. It is presumed to originate from the hair follicle, usually located on the hair-bearing, sun-exposed parts of elderly individuals, and it is characterized by a triphasic trend of rapid development, stabilization, and regression, which mimics the hair cycle [20,21]. Multiple factors have been suggested, including UV radiation exposure, chemical carcinogens, immunosuppression, medications, genetic predisposition such as mutations of p53 or H-Ras, viral infection by HPV, and cutaneous trauma or surgery to the location [22].

In the literature, cases of KA have been reported after COVID-19 vaccination, including both multiple and eruptive KA and solitary KA strictly located on the site of vaccination [23,24]. It has been hypothesized that the onset of KA after vaccination may have been initiated by an immune-mediated, pro-inflammatory mechanism.

KA is widely reported also after cutaneous trauma, including tattooing [25], site injection of cosmetic collagen filler [26], and at the recipient site of skin graft [27].

KA can also be triggered by medications, including BRAF inhibitors (such as pembrolizumab) [28], but also kinase inhibitor drugs (such as sorafenib), PD-1 inhibitors (such as sintilimab) [29], and immunosuppressive disease-modifying antirheumatic drugs - DMARDs- (such as leflunomide) [30].

KA may also be associated with various genetic syndromes: Muir-Torre syndrome (MTS), multiple self-healing squamous epithelioma (MSSE, Ferguson-Smith syndrome), multiple familial KA of Witten and Zak (MFKWZ), *xeroderma pigmentosum* (XP), multiple self-healing palmoplantar carcinoma (MSPC), *incontinentia pigmenti* (IP), and eruptive KA of Grzybowski [31].

Recently, the key role of HPV in cutaneous keratinocyte tumors development has been highlighted [32]. Beta-HPVs have been reported as the main etiologic agent of SCC in patients with *epidermodysplasia verruciformis* (EV) and organ transplant recipients [33]. Several studies have shown that samples from KA contain HPV DNA in more than 90% of cases, unlike well-differentiated SCC, suggesting a co-factor role for HPV [34].

Epidemiological studies have pointed out that SCCs are associated with beta-HPV infections more often than the general population [35]. However, their role in NMSC progression in the general population is still unclear [35].

In a recent systematic review, 321 KAs were analysed for the presence of different HPV genotypes, detecting a high presence of beta genus types (50.31%) and an equal proportion between alpha (24.84%) and gamma (24.84%) genera [32]. However, most of the HPV types found in NMSC were the consequence of multiple infections with different HPV types, which were detected at very low viral loads (<1 copy/1000 cells), depending on the polymerase chain reaction (PCR) primers, which raises the issue of bias in detecting only HPV types with high similarity to the primers employed, potentially overlooking others [36].

#### 4. Clinical Manifestations

KA is usually a solitary and sporadic tumor [2]. It can vary from a few millimeters up to more than 20 mm in KA centrifugum marginatum [3]. KA usually starts as a small papule, while the mature KA is a dome-shaped, well-demarcated umbilicated nodule with a hyperkeratotic plug in the center [2]. KA usually arises on sun-exposed areas and evolves in three clinical stages, namely proliferative, mature, and resolving [2]. This process usually occurs within 4 to 6 months and can lead to atrophic hypopigmented scars [2]. Rarely, solitary KA can arise on mucous membranes, mostly in the oral cavity [37–44]. Several studies suggest that KA arises more frequently on non-chronically sun-damaged skin (i.e., chest or arms) while SCC always arises in the context of severely photodamaged skin, usually surrounded by actinic keratosis and/or associated with a field of cancerization. According to these proposed classifications, KA can be clinically recognized as a rapidly growing nodule with a central crateriform area not surrounded by signs of the field of cancerization, while well-differentiated SCC develops upon sun damage and actinic keratosis, proposing a possible different etiopathogenesis between the two tumors.

Multiple KAs are rare and can be sporadic or familial. Multiple KAs centrifugum marginatum belong to the first group and are characterized by a coral reef-like appearance [45]. Rarely multiple KAs can be associated with *prurigo nodularis* [46]. Multiple familial KAs can be described in multiple MSSE, an autosomal-dominant skin cancer condition characterized by multiple SCC-like locally invasive cutaneous tumors, also known as Ferguson-Smith disease [47]. Furthermore, patients affected by generalized eruptive KA (GEKA) of Grzybowski develop multiple eruptive KAs, especially on sun-exposed areas, such as the face and the upper trunk, and on intertriginous areas [48,49]. Finally, several KAs develop in patients with multiple familial KAs of Witten and Zak type, a disease that is still not well characterized and combines clinical features of MSSE and GEKA in the same patient [50,51].



## 4. Dermoscopy

Dermoscopic examination of KA may present several distinct features that help in differentiating it from other skin tumors [52]:

1. Central Keratin Plug: One of the hallmark features of KA is the presence of a central, well-defined, yellowish or whitish keratin plug. This central crater is visible in most cases and is a key diagnostic feature.

2. Rolled Border: The lesion typically displays a smooth, well-demarcated, and elevated border that is slightly rolled. This appearance is characteristic of KA and helps in differentiating it from other tumors that may have irregular borders.

3. Vascular Patterns: Dermoscopy often shows vessels that are linear, dotted, or hairpin-shaped in the peripheral areas of the lesion. These vessels may be more prominent around the edge of the keratin plug, contributing to the lesion's raised appearance. Inflammatory and hyperplastic changes in the epidermis contribute to these vascular patterns.

4. Homogeneous Pink or White Background: The background of the lesion may show a homogeneous pink or white color due to the underlying inflammatory changes and epithelial proliferation. This feature, when seen with the characteristic keratin plug, helps in the diagnosis.

5. Yellowish Structures: Apart from the keratin plug, the lesion may exhibit yellowish areas or streaks within the lesion, which correspond to the presence of keratinized material beneath the surface.

6. Regular Pattern: In most cases, the dermoscopic pattern of KA is regular, with no irregular pigment network or atypical vessels, which further helps to differentiate it from malignancies such as melanoma.

Dermoscopically, it is not easy to differentiate KA from SCC because they share some common features [53]. Keratin has the highest sensitivity to differentiate KA and SCC from other amelanotic nodules, while white circles have the highest specificity, and they are typically detected in SCC tumors but not in KA. Another important clue for differentiating SCC from KA is the predominantly white color, more frequently detected in SCC, which histologically corresponds to fibrosis and hyperkeratosis. These dermoscopic findings, together with dot vessels, are helpful for the diagnosis of KA and SCC [52].

## 5. Reflectance Confocal Microscopy (RCM) and Line-Field Confocal Optical Coherence Tomography (LC-OCT)

As previously explained, KA is a rapidly growing epithelial neoplasm that often poses diagnostic challenges due to its clinical and histological similarities with well-differentiated SCC. Non-invasive imaging techniques such as reflectance confocal microscopy (RCM) and line-field confocal optical coherence tomography (LC-OCT) have emerged as valuable tools for the real-time, in vivo evaluation of skin tumors, offering near-histologic resolution without the need for tissue excision.

RCM allows a face imaging of the epidermis and superficial dermis, generally reaching a maximum depth of approximately 200–250 microns. This limitation in penetration depth may hinder complete visualization of thick lesions such as KA, which often exhibits marked central hyperkeratosis and deep epidermal proliferation. Nevertheless, RCM can provide useful information, particularly at the lateral and superficial portions of the tumor [54]. On RCM analysis, KA typically presents with epidermal hyperplasia and architectural disarray, often accompanied by a large, highly reflective central structure corresponding to the compact keratin plug. The surrounding keratinocytes may appear atypical, yet they tend to preserve an organized honeycomb pattern, distinguishing KA from more aggressive forms of SCC. Vascular features such as dilated and tortuous capillaries within the dermal papillae, as well as perivascular inflammatory infiltrates, are frequently observed and may support the diagnosis [55].

On the other hand, LC-OCT, with its capacity to acquire both vertical (B-scan) and horizontal (*en face*) images and a penetration depth of up to 500 microns, offers a more complete structural assessment of KA compared to RCM [56]. The hallmark feature of KA in LC-OCT analysis is the presence of a cup-shaped epidermal invagination filled with a hyperreflective material, corresponding to the crateriform morphology and central keratin seen histologically. The surrounding epidermis typically appears markedly thickened, with abrupt lateral transition zones separating the lesion from the adjacent normal skin. In the vertical plane, broad strands and islands of keratinocytes can often be seen extending downward into the dermis, mimicking the appearance of histologic sections. Although cytological details are not as clearly defined in LC-OCT as in RCM, the architectural pattern is usually well visualized and can aid in distinguishing KA from invasive SCC [57].

Despite their utility, both RCM and LC-OCT have inherent limitations that must be considered. The depth of penetration may be insufficient to evaluate the full extent of the lesion, particularly at the base, and the dense keratin content can attenuate signal penetration, reducing image quality. Furthermore, distinguishing KA from well-differentiated SCC remains challenging, especially in cases where the imaging captures only a portion of the lesion. The interpretation of images is also observer-dependent and may vary based on the examiner's level of experience and training.

Nonetheless, these techniques can serve as helpful adjuncts in the clinical evaluation of KA, especially in cases where biopsy is contraindicated, where the lesion is in regression, or when monitoring over time is required. The correlation between imaging findings and histopathology, particularly regarding the overall architecture, further supports their integration into the diagnostic pathway for KA.

## 6. Histology of Keratoacanthoma

Differentiating KA from well-differentiated SCC on routine histology can be tricky due to shared features. Furthermore, inadequate biopsies fail to include the complete tumor architecture, leading to a diagnosis of SCC and potentially overtreatment [58]. KA histopathological features depend on the development phase, namely, proliferative, mature, and regressive phases [59]. The proliferative phase is characterized by marked hyperkeratosis and exophytic or endophytic proliferation of pale squamous cells in lobules that can resemble distorted infundibular structures, which become more cystic and hyperkeratotic in a later stage, coalescing into a central keratin plug [60]. In the mature stage, most peripheral tumor islands infiltrate the edges of the central mass [60]. Typically, the peripheral keratinocytes show enlarged, pink, glassy-appearing cytoplasm, a low nuclear-to-cytoplasmic ratio, and minimal nuclear atypia [60]. In addition, a mixed infiltrate of inflammatory cells can be commonly detected [60]. Regressing lesions show a well-formed crater of keratin with thinning of the surrounding squamous epithelium, reduced squamous lobules, and underlying dermal fibrosis [60]. The most significant histopathological features that help to confirm the diagnosis of KA are symmetry, the absence of extension beyond the sweat glands, lack of infiltration or desmoplasia, and the little-to-moderate nuclear atypia [61]. Some cases of metastatic KA have been reported in the literature [62]. However, it could be possible that in these cases either a SCC has arisen within a KA [63] or a SCC with a distinct follicular pattern of differentiation was misdiagnosed as KA [64]. In addition, it has been reported that immunocompromised patients with large KA have developed metastasis of unclear significance [65].

## 7. Human Papillomavirus and Carcinogenesis

HPV belongs to the Papillomaviridae family, which includes more than 440 genotypes of small DNA viruses, classified into five genera:  $\alpha$ ,  $\beta$ ,  $\gamma$ ,  $\mu$ , and  $\nu$  [66]. Only a few of them, mainly within  $\alpha$  and  $\beta$  genera, can cause significant risks to human health and have received the most attention from researchers [67].

HPV particles are characterized by the presence of circular, 7.9-kb double-stranded DNA included in a nonenveloped icosahedral capsid constituted by 360 copies of the L1 protein [68] and a smaller amount of L2 gene product [69]. The HPV genome encodes eight main expressed proteins: the core proteins involved in genome replication (E1 and E2), the core proteins involved in virus assembly (L1 and L2), and the accessory proteins (E4, E5, E6, and E7). A fusion protein with regulatory functions, E8<sup>E2C</sup>, was also described [70]. Whereas the core proteins are highly conserved among all HPV genotypes, the accessory proteins are highly variable [71]. E6 and E7 are considered the major HPV oncoproteins, required to establish persistent infection and propagation of both  $\alpha$  and  $\beta$  HPVs and for malignant transformation of the host cell [72,73] and thus represent attractive antitumoral drug targets [74].

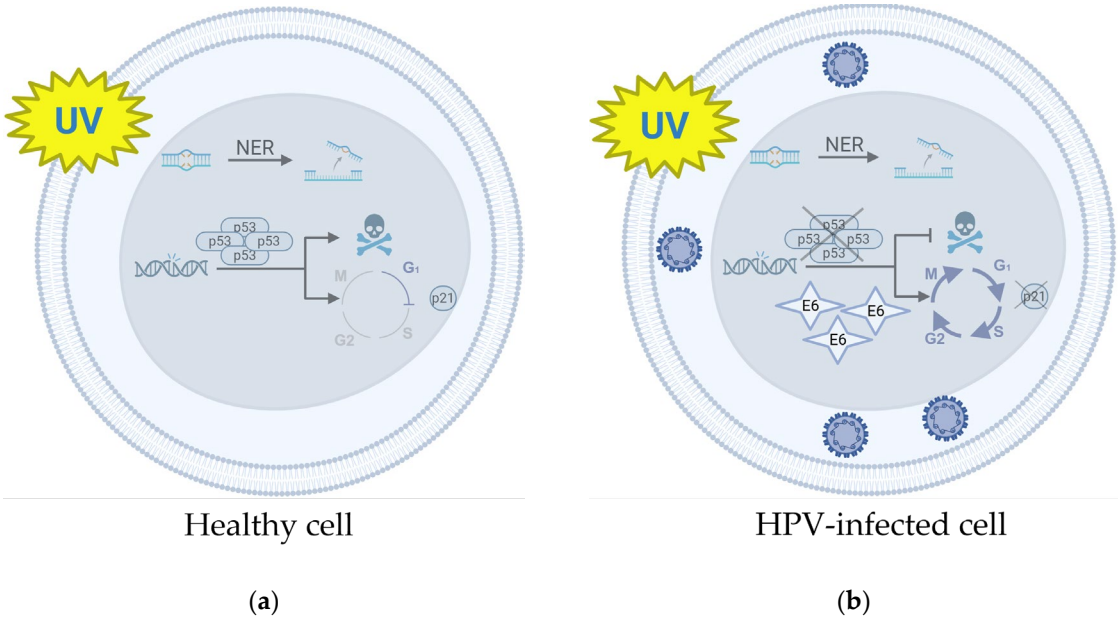
The types  $\alpha$  and  $\beta$  of HPV show significant differences in tissue tropism:  $\beta$  types can infect only cutaneous anatomic sites, whereas  $\alpha$  types predominantly infect mucosal tissues. Among  $\alpha$  types, it is important to distinguish between high-risk (HR)  $\alpha$ HPVs, such as 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59 genotypes, which show a tissue tropism limited to mucosal tissues, and low-risk (LR)  $\alpha$ HPVs, which can infect both cutaneous and mucosal tissues. Generally, infections sustained by  $\beta$  types remain subclinical, but certain infections, mainly those caused by HPV5 and HPV8, can become clinically relevant, leading to the development of NMSC in high-risk patients (e.g., immunocompromised organ-transplant individuals or patients affected by the genetic disorder EV) [75–77].

HR- $\alpha$ HPVs are strongly carcinogenic, even though the infection seems to be a necessary but insufficient element for neoplastic transformation. Conversely,  $\beta$ HPVs are not intrinsically carcinogenic but behave as facilitators for cancer initiation, by interfering with apoptotic pathway activation upon UV damage [78,79]. As is well-known from the literature, UV-B rays (290–320 nm) are considered strong physical factors damaging macromolecules (i.e., DNA, proteins, lipids) and, in turn, cell integrity [80]. The result of UV-induced DNA damage is represented by specific photoproducts, such as the pyrimidine dimers, resulting from the covalent bond of two adjacent pyrimidine bases [80]. Normally, these photoproducts are efficiently removed by the Nucleotide Excision Repair (NER) pathway [81]. If not properly repaired, pyrimidine dimers can lead to mutations [82]. DNA damage response activates the oncosuppressor proteins p53 and p21<sup>waf1</sup> that arrest the cell cycle. The p53 protein, which is considered the “guardian of the genome”, undergoes some post-translational modifications, mainly phosphorylation and acetylation, which regulate the assembly of p53 monomer into a tetramer, inhibit its degradation, and induce its transcriptional activity, allowing the expression of the cell-cycle inhibitor p21<sup>waf1</sup> or the activation of apoptotic pathways [83,84]. P53 has been extensively reported as the best-characterized target of HPV E6 oncoprotein [85]. The HR- $\alpha$ HPV E6 oncoprotein promotes degradation of p53 via the interaction with the E6-associated protein (E6AP) ubiquitin ligase. This interaction allows the formation of an intermediate ternary complex E6-E6AP-p53, resulting in the ubiquitination and proteasome-mediated degradation of the cellular oncosuppressor [86–88]. In contrast, most of the  $\beta$ HPV E6 oncoproteins do not interact with E6AP and do not degrade p53, but interfere with both acetylation and phosphorylation of p53, finally inhibiting the assembly of the p53 monomer into a tetramer [89,90] (Figure 1). However, some important exceptions have been reported: E6 protein from HPV49, HPV75, and HPV 76 genotypes behave similarly to  $\alpha$ HPV E6 protein [91]; E6 protein produced by HPV38 and HPV92 can interact with E6AP and stabilize p53 [92,93]. Moreover, the stabilization of wild-type p53 mediated by E6 from HPV38 results in the accumulation of  $\Delta$ Np73 [94], which is the carcinogenic isoform of p73 and works as an antagonist of p53 itself [95]. In detail, HPV38 E6 and E7 stabilize  $\Delta$ Np73 by inducing its I $\kappa$ B kinase beta (IKK $\beta$ )-mediated phosphorylation, finally increasing its half-life [96]. Other intracellular targets for  $\beta$ HPV E6 oncoprotein have been extensively investigated: BAX and BAK are two proapoptotic factors belonging to the BCL-2 family, transcriptionally regulated by p53 and involved in mitochondrial membrane permeabilization occurring during the apoptotic process, required for the release of cytochrome c and other proapoptotic proteins in the cytosolic space [97].  $\beta$ HPV E6-induced, proteasome-mediated

degradation of BAK is the result of its interaction with  $\beta$ HPV E6 in an E6AP-dependent manner [98–100]. Conversely, the exact mechanism of  $\beta$ HPV E6-induced degradation of BAX has not yet been elucidated.

The other major HPV oncoprotein is E7. For HR- $\alpha$ HPV types, the interactions of E7 with its targets, i.e., the retinoblastoma protein (pRb) [101], p107 [102], p130 [103,104], PTPN14 [105,106], PTPN21 [107], and Memo1 [108], have been extensively investigated and characterized. The sequence of E7 oncoproteins from both  $\beta$ HPV and HR- $\alpha$ HPV types contains the LXCXE motif, which is directly involved in the binding of E7 to pRb [109]. In the case of HR- $\alpha$ HPV types, this interaction triggers the proteasome-mediated pRb degradation and abrogates its negative regulation of cell cycle progression in infected cells. In particular, pRb binds to and inhibits transcription factors belonging to E2F family, controlling S-phase entry [110]. Nevertheless, the presence of the LXCXE in E7 sequence does not seem sufficient to allow this effect in  $\beta$ HPV host cells. Indeed, the ability to interact with pRb with an affinity quite similar to that shown by HR- $\alpha$ HPV E7, and to promote its destabilization has been reported only for HPV38 E7 [111]. For  $\beta$ HPV, the effects of E7 interactions are less well understood, but in general do not seem able to interfere with pRb activity in the infected cell.

Overall,  $\beta$ HPV represents a cofactor that can enhance the effects of UVB damage. Indeed, the presence of  $\beta$ HPV confers resistance to the cell towards apoptosis as well as increases the susceptibility to UVB-mediated DNA damage [112].



**Figure 1.** Best-characterized molecular mechanism involved in carcinogenesis occurring in HPV-infected skin cell. UV radiation induces damage on DNA, which is normally repaired by the Nucleotide Excision Repair (NER) pathway. If NER fails and the DNA damaged is maintained, in the healthy skin cells (a) p53 tetramer is activated, leading to apoptosis and p21-mediated cell cycle block in G1 phase. When NER pathway fails in the skin cell infected by  $\beta$ -HPV (b), the presence of E6 interferes with the assembly of p53 monomer into tetramer, finally resulting in loss of apoptotic pathway activation and cell cycle progression.





## 7. Therapy

The first-line therapy for KA remains the complete surgical removal. However, about 8% of KAs may exhibit a recurrence after complete surgical excision [113]. Radiotherapy (RT) and cryotherapy are physical therapies for treating KAs. Although the effectiveness of RT on KA has been demonstrated [114–116], RT is rarely used. Indeed, RT is generally unsuitable for younger patients, and the several doses required make it burdensome for older patients. Furthermore, RT may induce eruptive KAs [117]. However, RT could be an option for cosmetically sensitive, non-operable regions. Although cryotherapy has not been widely studied as a therapeutic option, its effectiveness has been



reported in about 87% of KAs [118]. Photodynamic therapy (PDT) belongs to the group of physical therapies, too. However, only limited data are available on the use of PDT for KAs. On the one hand, PDT has been reported as effective in treating KAs, but on the other hand, the development of KAs after PDT use has been reported [119]. The argon lasers have also been used for KAs. Solitary KAs of the face and auricles were successfully treated in 65% of the patients, while 35% achieved healing with mild scarring [120]. Topical 5-fluorouracil (5-FU) and imiquimod represent two valuable alternatives for KAs. 5-FU is an inhibitor of thymidylate synthase, disrupts DNA synthesis, and leads to lethal DNA damage [121]. Topical 5-FU has a good safety profile and could be considered as a first-line treatment for KAs, particularly in cosmetically sensitive areas [122]. Indeed, the use of topical 5-FU led to a complete resolution of the lesion within six weeks in a retrospective analysis [122]. 5-FU can also be used for intralesional applications [123]. An average of three injections in three weeks has been reported as effective [123]. Furthermore, 5-FU has been effectively used in combination with systemic retinoids [124] and Er:YAG lasers [13]. Topical 5% imiquimod, a toll-like receptor 7 and 8 agonist able to stimulate immune response, also represents an effective alternative for treating KAs topically. However, imiquimod should be applied for 9 - 11 weeks, three to four times a week, to obtain a complete remission [125]. Systemic therapies for KAs include retinoids and erlotinib. Systemic retinoids act with several mechanisms, including inhibition of keratinization and Wnt-related KAs proliferation, modulation of terminal differentiation of epidermal cells, and an increase in both IL-2 production and mitogen-induced lymphocyte proliferation [5]. Oral retinoids represent a valuable option for generalized eruptive KAs of Grzybowski and Ferguson-Smith disease [126–128]. Erlotinib, an epidermal growth factor receptor (EGFR) inhibitor, has also been proposed for the treatment of resistant, multiple KAs [129]. However, experience with it is still limited. A summary of the above-described therapeutic options for the treatment of KAs is provided in Table 1.

**Table 1.** Summary of currently available therapeutic options for the treatment of KA.

Therapy type	Description	Mechanism	Effectiveness
 surgical	Complete surgical removal	Surgical removal with histopathological control	Gold-standard, but ~8% recurrence
	Radiotherapy	Energy	Effective, but rarely used
 physical	Cryotherapy	Targeted destruction of lesions via Cold	Effective (~87%), but not widely studied
	PDT <sup>1</sup>	Locally activated drug	Limited available data
	Argon laser	Laser	Effective for solitary KA <sup>2</sup>
 topical	Local application of 5-FU <sup>3</sup>	Inhibition of DNA synthesis	Very effective, first-line treatment
	Imiquimod	Local immune response activation	Effective
 systemic	Retinoids	Control of proliferation, differentiation, and immune response	Valuable option for generalized eruptive KA <sup>2</sup>
	Erlotinib	EGFR <sup>4</sup> inhibition	Still limited experience

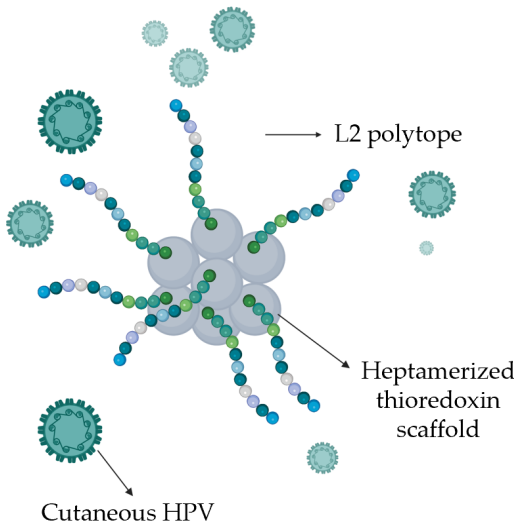
<sup>1</sup> PDT: Photodynamic therapy. <sup>2</sup> KA: Keratoacanthoma. <sup>3</sup> 5-FU: 5-fluorouracil. <sup>4</sup> EGFR: Epidermal Growth Factor Receptor.

## 8. Anti-HPV Vaccines

Three main vaccines are commercially available and approved to prevent cervical cancer caused by the most common HR-HPV genotypes: Gardasil®, Gardasil®9, and Cervarix®. They all are based on non-infectious virus-like particles (VLPs) containing the major capsid protein L1 from the specific HPV genotype they target and are approved for the prevention of premalignant ano-genital lesions (cervical, vulvar, vaginal and anal), cervical and anal cancers causally related to certain oncogenic HPV types. Gardasil® targets HPV6, 11, 16, and 18, while Cervarix® is specific for HPV16 and 18, and Gardasil®9 is a nonavalent vaccine targeting HPV6, 11, 16, 18, 31, 33, 45, 52, and 58 [130].

The employment of the three available vaccines, which are both safe and effective, had a great success for the prevention of HPV-related cancers. Nevertheless, they have several drawbacks: being based on L1, which is poorly conserved among different HPV types, they can target just the specific corresponding genotype, with incomplete cross-protection; having low thermostability, they need uninterrupted cold chains for transport and distribution, thus limiting the availability in developing countries; the manufacturing procedure is time-consuming and expensive [131]. Therefore, many efforts have been made by researchers to develop novel strategies with the aim of overcoming these drawbacks. In this regard, a research group developed PANHPVAX, which is based on the hyperthermostable thioredoxin scaffold, wherein a sequence of epitopes of the minor capsid protein L2, derived from the 20–38 amino acid region of various HPV types, has been incorporated [132]. It is noteworthy that, in contrast to L1, L2 is highly conserved among both mucosal and cutaneous HPV genotypes and carries several epitopes of linear nature, which can be inserted into various scaffolds. The safety profile and the immunogenicity of PANHPVAX, which is assumed to target mucosal genotypes of HPV, are under investigation in a phase I clinical trial, which is still ongoing [133]. Following this research line, the same research group reported the development of other promising vaccine candidates, containing the L2 polytope, i.e., a synthetic antigen composed of concatenated conserved epitopes from the L2 protein of the cutaneous HPV types, fused to the thioredoxin scaffold (Figure 2). These candidates were tested *in vivo* in both mice and guinea pigs, resulting in a broad immunization against 19 cutaneous HPV genotypes. Interestingly, the investigated vaccine prototypes elicited cross-protective neutralizing antibodies against multiple mucosal HPV types, including the HR HPV16 and HPV18, as well as some LR genotypes [134].

Finally, the intralesional administration of the nonavalent vaccine Gardasil®9 was proposed for the treatment of HPV-related recalcitrant warts in a retrospective case series [135]. In detail, within a cohort of 20 individuals (13 adults and 7 children), 12 (60%) achieved a complete response, whereas 8 (40%) exhibited a partial response. This study suggested that Gardasil®9, whose safety profile has already been demonstrated and has already been approved as a prophylactic vaccine for HPV-related cervical cancer, could also be considered as an alternative strategy for the treatment of recalcitrant cutaneous warts.



**Figure 2.** Schematic representation of new promising vaccine candidates, containing the L2 polytope of the cutaneous HPV types, fused to the thioredoxin scaffold.

8. Materials and Methods

Given the narrative nature of the present review, no predefined inclusion or exclusion criteria were established prior to the literature search.

A comprehensive search of the PubMed and Scopus databases was conducted to identify relevant publications. The key terms used for the search strategy included: “keratoacanthoma” OR “KA” AND “pathogenesis” OR “etiology” OR “human papillomavirus” OR “HPV” OR “management” OR “treatment” OR “therapy” OR “diagnosis” OR “dermoscopy” OR “reflectance confocal microscopy” OR “RCM” OR “line-field confocal optical coherence tomography” OR “LC-OCT” OR “Histopathology”. No language or publication date restrictions were applied. The database search was performed from inception to 7th August 2025. Additional relevant articles were identified by manual cross-referencing from the bibliographies of retrieved papers. Preference was given to peer-reviewed original articles, systematic reviews, meta-analyses, and significant case series that addressed the epidemiology, clinical presentation, diagnostic tools, histopathological features, molecular mechanisms, and therapeutic strategies for KA.

The following PICO (Population, Intervention or exposure, Comparison, Outcome) algorithm was applied to guide the literature selection: (i) Population: patients with KA (solitary, multiple, or eruptive forms); (ii) Intervention/exposure: diagnostic and therapeutic approaches, as well as studies on etiopathogenesis and HPV involvement; (iii) Comparator: other cutaneous epithelial tumors, particularly well-differentiated SCC; (iv) Outcome: advances in understanding pathogenesis, improvements in diagnostic accuracy, and evaluation of therapeutic efficacy.

9. Conclusions

KA is a rapidly growing epithelial neoplasm that often poses diagnostic challenges due to its clinical and histological resemblance to well-differentiated SCC. Accurate diagnosis benefits from various non-invasive imaging techniques, such as dermoscopy, RCM, and LC-OCT, which allow for near-histologic, real-time in vivo evaluation, although they are limited by penetration depth and keratin density. Histopathological examination remains essential, with key features including symmetry, absence of extension beyond sweat glands, lack of stromal infiltration, and minimal nuclear atypia helping to distinguish KA from SCC. However, inaccurate biopsies may lead to misdiagnosis and overtreatment. HPVs, particularly cutaneous  $\beta$  types, act as cofactors in skin carcinogenesis by interfering with cellular responses to UV-induced DNA damage and promoting

lesion development. The complex interplay between viral factors, UV exposure, and host susceptibility continues to be an important area of research. Surgical excision remains the first-line treatment for KA, though non-surgical options—including radiotherapy, cryotherapy, photodynamic therapy, topical agents such as 5-fluorouracil and imiquimod, and systemic therapies like retinoids and erlotinib—offer valuable alternatives in select cases, especially for multiple or difficult-to-treat lesions. Available prophylactic HPV vaccines, targeting HR mucosal genotypes, have substantially advanced cancer prevention, while novel vaccine candidates based on the conserved L2 protein hold promise for broader protection against both cutaneous and mucosal HPV types. Intralesional administration of the nonavalent Gardasil®9 vaccine has also shown potential as a therapeutic approach for recalcitrant HPV-related warts.

Integrating advances in diagnostic approaches, understanding of pathogenetic mechanism, and therapeutic strategies is critical for optimizing the management of KA and HPV-associated lesions, to improve diagnostic accuracy, minimizing overtreatment, and developing more effective prevention measures.

**Author Contributions:** “Conceptualization, M.H., D.D, E.D. and L.F.; writing—original draft preparation, M.H., D.D, A.D.G., C.C (Conforti), E.D. and L.F; writing—review and editing, M.H., D.D, D.A., F.M, F.R., C.B., A.L.,G.D.L., A.D.G., A.P., C.C. (Chello), C.C. (Conforti), E.D. and L.F.; funding acquisition, D.A., A.L.. All authors have read and agreed to the published version of the manuscript.

**Funding:** This research was funded by Associazione Italiana per la Ricerca sul Cancro, AIRC, Italy, grant number IG 2021 - ID. 25899 (to A.L.); by EU funding within the NextGenerationEU-MUR PNRR Extended Partnership initiative on Emerging Infectious Diseases (Project no. PE00000007, INF-ACT) (to A.L.); by Ministero dell'Università e della Ricerca, Italy, grants PRIN 2022-cod. 20223RYYFC and PRIN 2022 PNRR - cod. P20222YKP8 (to A.L.); and by “Progetto Ricerca Corrente 2024” from the Italian Ministry of Health (to D.A.).

**Data Availability Statement:** Data is available within the article.

**Conflicts of Interest:** The authors declare no conflict of interest.

Abbreviations

The following abbreviations are used in this manuscript:

KA	Keratoacanthoma
SCC	Squamous Cell Carcinoma
RCM	Reflectance Confocal Microscopy
LC-OCT	Line-Field Confocal Optical Coherence Tomography
HPV	Human Papillomavirus
UV	Ultraviolet
MTS	Muir-Torre Syndrome
MSSE	Multiple Self-healing Squamous Epithelioma
MFKWZ	Multiple Familial KA of Witten and Zak
XP	Xeroderma Pigmentosum
IP	Incontinentia Pigmenti
EV	Epidermodysplasia Verruciformis
GEKA	Generalized Eruptive Keratoacanthoma
HR	High-Risk
LR	Low-Risk
NER	Nucleotide Excision Repair
E6AP	E6-Associated Protein
pRb	Retinoblastoma protein
RT	Radiotherapy
PDT	Photodynamic therapy
5-FU	5-Fluorouracil
EGFR	Epidermal Growth Factor Receptor



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