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Five Cases of Keratoacanthoma with Perineural Invasion Treated with Mohs Micrographic Surgery: Clinical-Histopathological Correlations and Surgical Management

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1. Introduction

Keratoacanthomas (KAs) typically present as rapidly growing papules that develop into crateriform nodules with hyperkeratotic plugs, primarily on sun-exposed areas in elderly, light-skinned individuals [1-3]. KA is a common epidermal tumor with a controversial classification, often debated whether it is a benign pseudomalignancy with self-regressing potential or a pseudo-benign tumor that can progress into invasive squamous cell carcinoma. Historically, KAs were sometimes considered a variant of cutaneous squamous cell carcinoma (cSCC) [1,3]. However, many dermatologists now view KAs as distinct entities with unique molecular gene signatures, though the "World Health Organization Classification of Tumors" still regards KAs as a well- differentiated SCC [4]. The exact etiology of Keratoacanthoma is unknown, but several factors are proposed to contribute to its development. Physical injury is believed to act as a second insult to a preceding oncogenic insult, such as UV radiation exposure which if chronic can be a significant risk factor. Older age, male sex, and UV radiation exposure-sensitive phenotypes are associated with KA development [5]. Occupational exposure to substances like coal tar, oils and even burns. Involvement of viruses (ex. HPV), immunocompromised states, transplant grafts, and increased Langerhans' cell activity have been suggested [6]. Ferguson-Smith–type multiple KA is characterized by an autosomal dominant inheritance pattern and is believed to arise from a single gene mutation 7. The genetic background of multiple familial KA and the role of the Wnt signaling pathway are highlighted 8. BRAF Inhibitors used for advanced metastatic melanomas, can lead to dermatological side effects including KAs and SCCs 4,8. Eczema, atopic dermatitis, psoriasis, scleroderma, and xeroderma pigmentosum have also been implicated 6. Smoking and Alcohol are independently associated with KA development [5].

While the classic form is solitary, which is the most frequent presentation, where a single lesion appears. It typically manifests as a rapidly growing, dome-shaped papule or nodule, often with a central keratin-filled crater, predominantly on sun-exposed areas of the body, such as the face, neck, and extremities. These lesions may spontaneously regress, and many are biopsied due to their clinical and histological similarities with squamous cell carcinoma [9]. Multiple Keratoacanthomas encompasses various conditions where individuals develop multiple lesions. These can arise sporadically, in the context of underlying inherited syndromes, or in association with chronic inflammation. Ferguson-Smith Type Multiple Keratoacanthoma (Familial KA / Multiple Self-Healing Squamous Epithelioma) is an autosomal dominant (AD) inherited disorder is characterized by the sudden appearance of multiple, recurrent skin tumors resembling well-differentiated SCC or KA, often during adolescence. These lesions tend to regress spontaneously, leaving atrophic scars.

Grzybowski Syndrome is an extremely rare condition, this syndrome involves the acute onset of hundreds to thousands of small, generalized eruptive KAs, primarily affecting middle-aged adults. Witten-Zak Syndrome is another form of multiple familial KAs. Muir-Torre Syndrome is characterized by the presence of multiple KAs, along with sebaceous skin tumors,

and an increased risk of internal malignancies, particularly gastrointestinal and genitourinary carcinomas [10,11,7,12]. Keratoacanthoma Centrifugum Marginatum is a rare variant of KA that can be solitary or multiple and is characterized by progressive peripheral growth with central atrophyic healing, leading to annular or 'coral reef-like' lesions. Unlike typical KAs, often lacks spontaneous remission and can have a larger diameter [13]. Giant Keratoacanthoma refers to KAs that grow to an unusually large size while not always classified as a distinct type based on etiology, the sheer size can present unique clinical challenges related to local tissue destruction.

2. Histology

Histologically are defined as squamoproliferative lesions with buttressing of the edges, a variable keratin plug, and nests of squamous epithelium with distinctive, slightly paler eosinophilic cytoplasm. A KA is an exo endophytic growing squamous proliferative tumour with a characteristic central keratin plug, surrounded by epidermal lips, forming a relatively well-defined symmetrical structure. Histopathological features typically include squamous proliferation, acanthosis, hyperkeratosis, inflammation, micro abscess formation, eosinophilic ("glassy") cytoplasm, and collar-like surrounding epithelium [8]. Controversy exists regarding the differentiation of KA from SCC. Although some dermatopathologists regard KAs as a subgroup of SCC, others consider them self-resolving benign epidermal lesions. Molecular studies suggest KA and SCC are distinct entities with unique molecular signatures [3,9]. However, the presence of aggressive histological features such as infiltration of nerve sheaths, blood vessels, or subcutaneous structures, along with mitosis, nuclear atypia, and dyskeratosis, has led to the proposal of KA as a clinicopathologic subtype of cSCC [14]. Some classifications also include categories like KA with malignant transformation, KA-like SCC, and infundibular SCC (crateriform) [15,16].

3. Dermoscopy

The dermoscopic appearance of keratoacanthoma was characterized by concentric structures, including a central crater containing a keratin mass or crust, surrounded by white structures and peripheral vascular patterns. In the second clinical case presented by Wang et al. in the same article, the dermoscopic evaluation revealed a lesion with a more prominent and polymorphic vascular pattern. This included dotted vessels, linear irregular vessels, and arborizing vessels, along with evidence of central haemorrhage [17].

4. Confocal Microscopy

Confocal microscopy was utilized to further characterize the lesion. The examination revealed refractile scale or crust within the stratum corneum, accompanied by an atypical honeycomb pattern and architectural disarray of the stratum granulosum. Additionally, parakeratotic cells-identified as dark-cantered nucleated cells-were observed in the stratum corneum, along with large, round nucleated cells within the stratum granulosum. In the second clinical case, confocal imaging also demonstrated the presence of dendritic cells in the stratum spinosum, an increased number of inflammatory cells, and linear or round vessels traversing the dermal papillae within the dermis [17].

5. Clinical Course

The evolution of keratoacanthoma is characterized by a distinct pattern of development, typically involving three stages. A proliferative stage when KAs manifest as rapidly growing papules that quickly develop into crateriform nodules. A mature stage when KAs reach full size, forming a dome-shaped tumour with a central keratin plug and finally an involution stage marked by spontaneous regression, often due to apoptosis, leading to the tumour's resolution [8]. Despite this characteristic self-limiting nature, the behaviour of KAs can be uncertain, with potential for local tissue destruction and unpredictable resolution times. Approximately 25% of KAs can develop into SCCs. This highlights the ongoing debate on whether KA is a pseudo malignancy with self- regressing potential or a pseudo-benign tumour that can progress to invasive SCC. Some views describe KA as an "aborted squamous cell carcinoma" that only in rare instances evolves into a progressively growing SCC and here comes up the question of the criteria that can guide treatment approach [2,18].

6. Molecular and Pathological Insights into Evolution

The relationship between KA and SCC is complex and still debated. While they share clinical and histopathological similarities, molecular studies suggest that KAs and SCCs are distinct entities with unique molecular gene signatures. Mutations in the RAS pathway may be key for KA [19]. The classic multistep model of carcinogenesis, involving mutations in tumor suppressors like TP53 and additional driver oncogenes, provides mechanistic insight into progression from actinic keratosis to cSCC [20]. The rapid regression often seen in KAs is thought to be due to the upregulation of the apoptosis (programmed cell death) pathway [21]. This contrasts with SCC, where uncontrolled cell proliferation is a hallmark. Immunohistochemical analysis of apoptosis-associated proteins and keratinocyte proliferative activity (e.g., p53, Bcl-2, Ki-67, PCNA) can provide arguments to differentiate KA and SCC [22]. A conceptual model proposes that UV-mutated or activated infundibular stem cells, driven by an oncogenic RAS pathway linked with the Wnt/beta-catenin pathway, are central to KA proliferation and terminal keratinization. This pathway is also thought to be involved in hair follicle development and wound healing, suggesting a common origin or shared mechanisms with some forms of SCC [23]. The close resemblance can make definitive differentiation difficult 3. Pathological classifications sometimes include categories like "KA with malignant transformation" or "KA-like SCC" as part of the broader evolutionary spectrum [16]. The World Health Organization still classifies KAs as a well-differentiated SCC. There is considerable controversy in differentiating KA from SCC, impacting management, classification, and diagnosis [9].

7. Treatment Modalities

The treatment of Keratoacanthomas is influenced by their uncertain behavior, potential for local tissue destruction, variable final size, and unpredictable resolution time. While spontaneous involution can occur, treatment is typically pursued. A biopsy is generally recommended before treatment to differentiate KA from SCC [2]. Various treatment options are available, categorized into lesion and field-directed therapies. The choice depends on factors such as the number and localization of lesions, duration since onset, patient age, compliance, and comorbidities. For solitary lesions, surgical excision is a common and effective treatment option, though intralesional injections of chemotherapeutic agents like methotrexate or 5-fluorouracil are also utilized [2].

Topical imiquimod cream, photodynamic therapy, and radiotherapy represent additional non-surgical approaches for managing individual keratoacanthomas [3]. Curettage and electrodessication could also be considered a variant of treatment associated with a recurrence rate of approximately 12.5% [2]. Cryotherapy can also be combined with curettage and electrodessication with recurrence rate of 2.2% [24]. Other treatment modalities could be considered CO2 laser and Nd: YAG, topical tretinoin gel which has shown rapid regression of lesions in cases of multiple KCM or even systemic treatment with Acitretin [18,25,26]. For larger or recurrent lesions, or those in anatomically challenging areas, Mohs micrographic surgery may be preferred due to its precise tissue sparing and high cure rates, offering a comprehensive approach to complete tumour removal while preserving surrounding healthy tissue. Mohs surgery is frequently used due to overlapping features with invasive cSCC. The recurrence rate for KAs treated with MMS is approximately 0.8% [2].

Comparative studies on Keratoacanthomas often focus on differentiating them from cSCC and evaluating treatment efficacy. A retrospective, 3-year chart review comparing KAs and invasive cSCC treated with MMS found that the mean number of MMS stages required was statistically different ($p < .001$) between KA (1.28) and invasive cSCC (1.52). The percentage of cases cleared in 1 stage was significantly higher for KA (77.2%) compared to invasive cSCC (58.9%) ($p < .001$). Recurrence rates were 0% for KAs and 1.1% for invasive cSCC, but this difference was not statistically significant ($p = 242$) [27]. In terms of intralesional treatments, a study comparing intralesional methotrexate versus 5-fluorouracil (5-FU) found that both are highly efficient and relatively inexpensive. A study with 20 KA patients (9 males, 11 females, mean age 49 ± 8.98 for MTX group and 43.3 ± 7.5 for 5-FU group) showed that after 5 sessions of MTX, 70% achieved complete regression, 20% partial response, and 10% no response. None of the patients in this study developed recurrence during follow-up [28]. The recurrence rates of KAs treated with standard surgical excision, MMS, and electrodesiccation and curettage have been shown to be approximately 0.9%, 0.8%, and 12.5%, respectively [2].

8. Methods

This study was a retrospective, observational case series involving five patients who underwent Mohs micrographic surgery (MMS) for histopathological confirmed keratoacanthoma (KA) with perineural invasion, all localized in the facial region. The procedures were performed at the Dr. Leventer Mohs Centre in Bucharest, Romania, between 2019 and 2025.

Inclusion criteria consisted of histological confirmed KA with perineural invasion, tumour localization in high- risk anatomical areas, treatment with MMS, and the availability of complete surgical and histopathological records. Data were collected from medical records and histopathology reports considering patient demographics, tumour characteristics (location, size, histologic subtype), number of Mohs stages required, type of reconstruction performed and postoperative outcomes. Surgical procedure was cantered on Mohs, using standard techniques, involving horizontal frozen-section excision with complete peripheral and deep margin control. Each surgical stage included en face tissue mapping. Tumour clearance was confirmed histologically before initiating reconstruction. All procedures were conducted under local anaesthesia and sedation. Reconstruction was performed immediately after histological confirmation of tumour clearance. The reconstruction technique was selected based on the size, depth, and anatomical location of the surgical defect. Closure methods included primary closure, local advancement flaps, and rotation flaps. Follow up was made at a two-to-three-month intervals for the first year. Considering ethics this study was conducted in accordance with the ethical norms, having the written informed consent of all patients for both surgical treatment as well as publication of anonymized data and photos.

9. Case 1

An 86-year-old male presented with a lesion on the tip of the nose that had been evolving over a six-week period. The tumour measured 28 × 25 mm at presentation. Excision was performed using Mohs micrographic surgery. Histopathological analysis revealed perineural invasion, necessitating a second surgical stage to achieve complete clearance. The final surgical defect 35 x 30 mm reflecting the extent of subclinical spread.

Reconstruction was made with two stage frontal flap with section of the pedicle at 3 week interval.

Histopathological examination: A cutaneous specimen was obtained via Mohs micrographic surgery, properly oriented, sectioned, and embedded in three cryostat blocks. Histological examination revealed areas of squamous cell carcinoma exhibiting features of keratoacanthoma, with invasion into the subcutaneous adipose tissue and multiple focal areas of perineural invasion. Two additional surgical stages were performed and processed into three additional frozen blocks. The final resection margins were free of tumour, with no residual carcinoma identified.

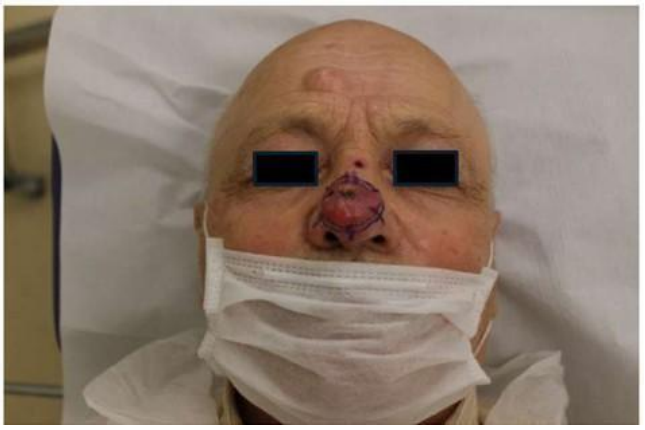

Figure 1.1: Initial presentation.

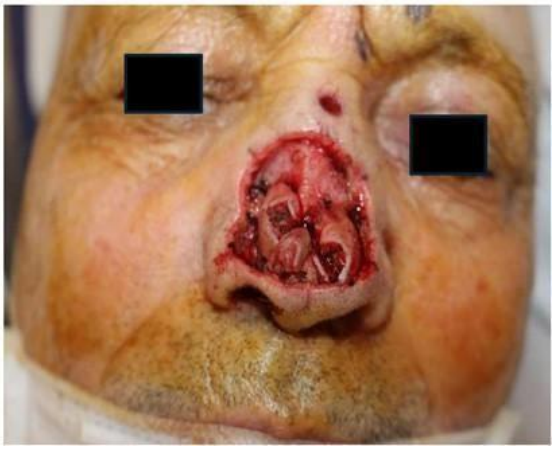

Figure 1.2: Final Defect.

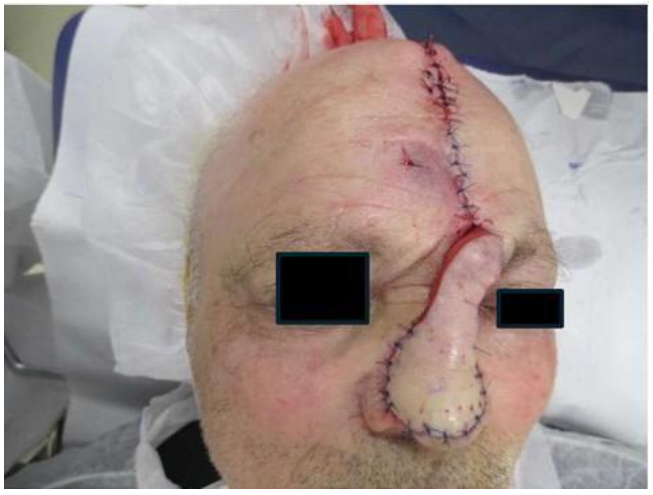

Figure 1.3: Frontal flap first stage.

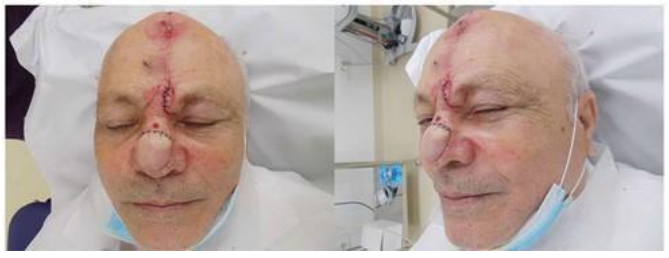

Figure 1.4: Frontal Flap Second Stage.

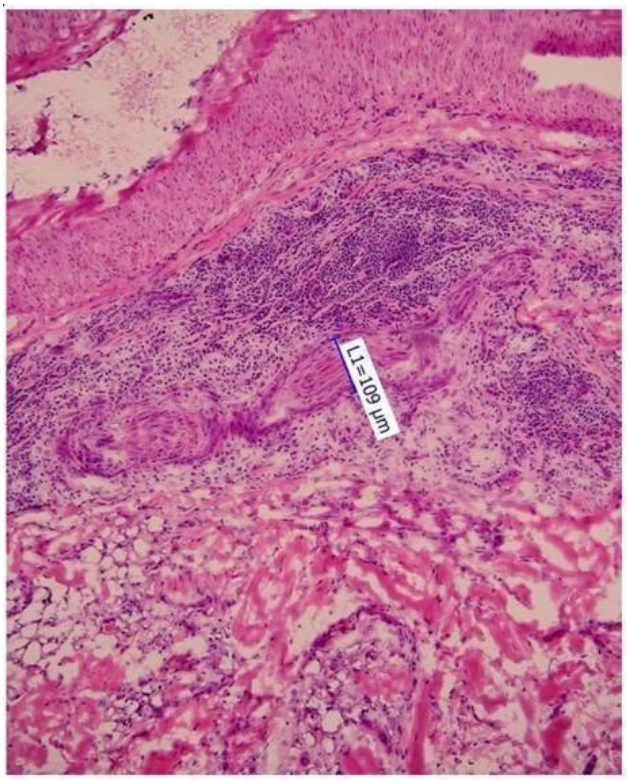

Figure 1.5: Histology.

10. Case 2

A 61-year-old male presented with a rapidly growing lesion located on the tip of the nose. The tumour initially measured approximately 8 × 9 mm, with the patient reporting a noticeable increase in size over a two-week period. The tumour was excised using Mohs micrographic surgery. Intraoperative histopathological examination revealed perineural invasion, necessitating additional surgical stages. A total of three stages were required to achieve complete tumour clearance, as the excision had to follow the trajectory of the involved nerve. The final surgical defect measured 20 × 13 mm, significantly larger than the initial tumour due to the extent of subclinical spread. Reconstruction was made with direct closure of the defect presenting slight elevation of the left ala.

Histopathological examination: A cutaneous specimen obtained during the first stage of Mohs micrographic surgery was oriented, dissected, and embedded in frozen tissue for histological analysis. Histopathological examination confirmed the presence of keratoacanthoma extending into the subcutaneous tissue. Three additional stages were performed, with each corresponding specimen embedded in separate frozen blocks.

Sections from Stages II and III revealed evidence of perineural invasion accompanied by chronic perineural inflammation. The final specimen (Stage IV) demonstrated clear surgical margins and showed the same nerve branch without any residual tumour.

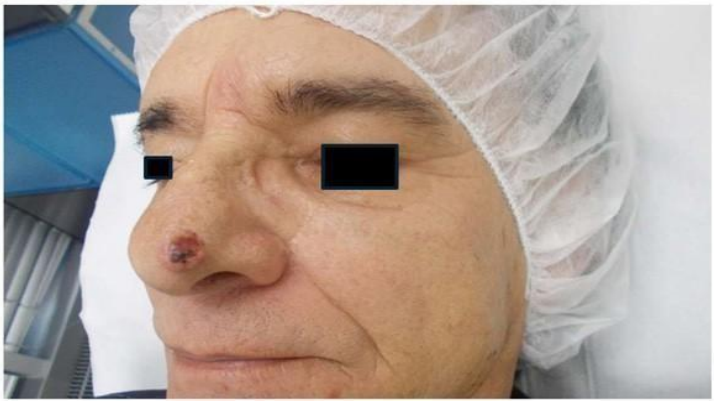

Figure 2.1: Initial Presentation.

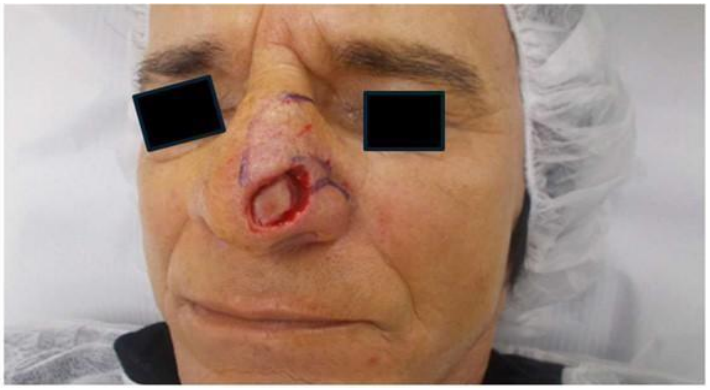

Figure 2.2: Final Defect.

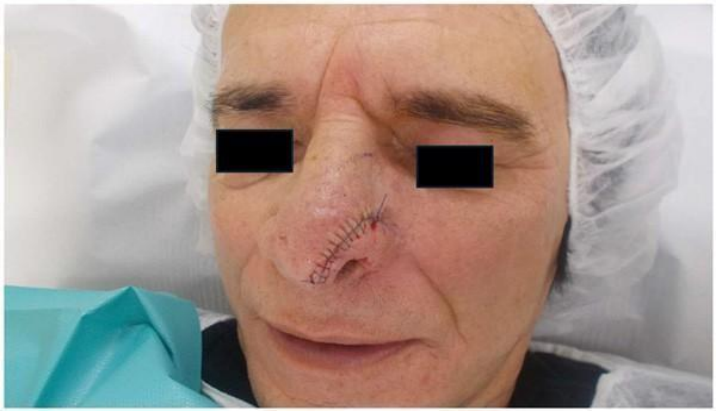

Figure 2.3: Direct Closure.

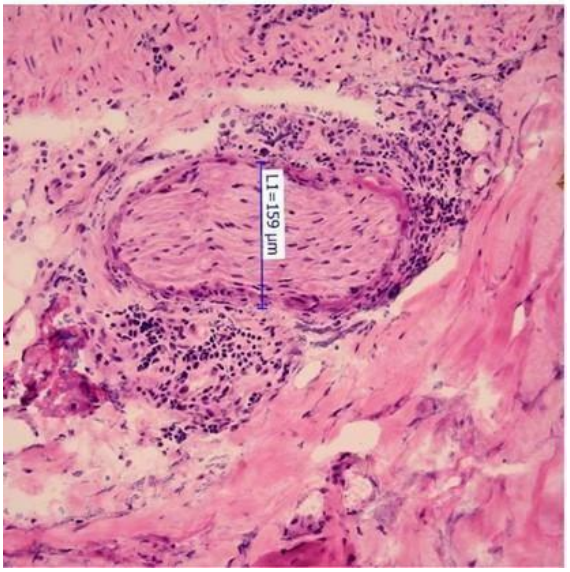

Figure 2.4: Histology.

11. Case 3

A 50-year-old female presented with a rapidly developing lesion on the nasolabial fold (upper cutaneous lip and nose ala on the left side), with a reported growth period of just two weeks. Mohs micrographic surgery was performed for excision. Due to perineural invasion and deep tumour extension reaching the facial bone plane, a total of six surgical stages were required to achieve complete tumour removal. The final surgical defect measured 30 × 27 mm, indicating significant subclinical extension along the nerve pathway.

Histopathological examination: A cutaneous specimen obtained during Mohs micrographic surgery was oriented, dissected, and embedded in a frozen tissue block. Histopathological analysis revealed invasive, well- differentiated squamous cell carcinoma involving the reticular dermis, adipose tissue, and striated muscle. Two additional stages were performed, with tissue embedded in four supplementary frozen blocks. Perineural invasion was identified in the first additional stage. The final stage revealed areas of dense lymphocytic and neutrophilic inflammatory infiltrate in the reticular dermis and striated muscle layer, containing atypical cells with an epithelioid appearance. Further evaluation using permanent paraffin-embedded sections and immunohistochemistry is recommended to confirm the cellular origin of the carcinoma.

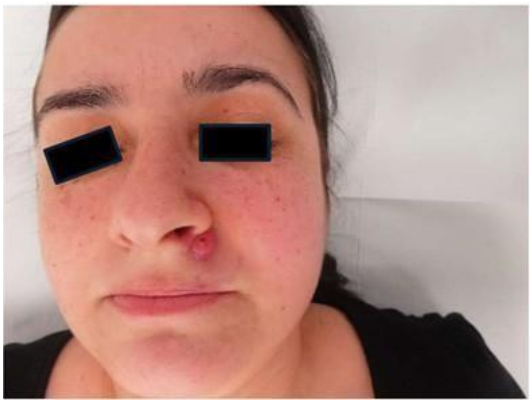

Figure 3.1: Initial Presentation.

Figure 3.2: Final Defect.

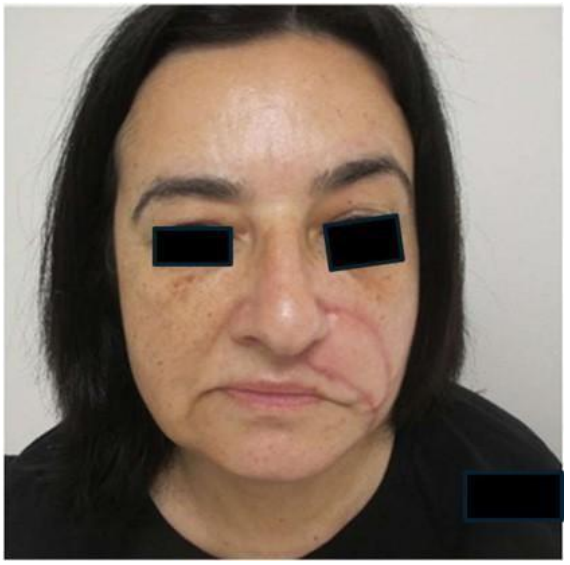

Figure 3.3: Island Flap.

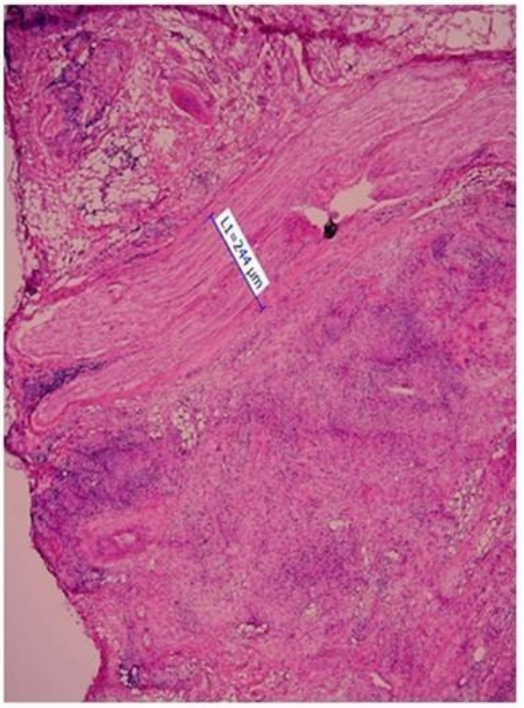

Figure 3.4: Histology.

12. Case 4

A 41-year-old male presented with a lesion located on the right upper cutaneous lip, measuring 9 × 9 mm. The tumour was excised using Mohs micrographic surgery. Histopathological evaluation revealed perineural invasion. To achieve complete tumour clearance, three additional surgical stages were required. The final surgical defect measured 17 × 18 mm, indicating significant subclinical extension along the nerve pathway.

Histopathological examination: A cutaneous specimen was obtained via Mohs micrographic surgery, sectioned, and embedded in a single frozen block. Histological evaluation revealed keratoacanthoma-type squamous cell carcinoma, with invasion into the striated muscle layer and evidence of perineural invasion. Three additional stages were performed; each embedded in separate frozen blocks. The final surgical margins were free of tumour, with no residual malignant lesions identified.

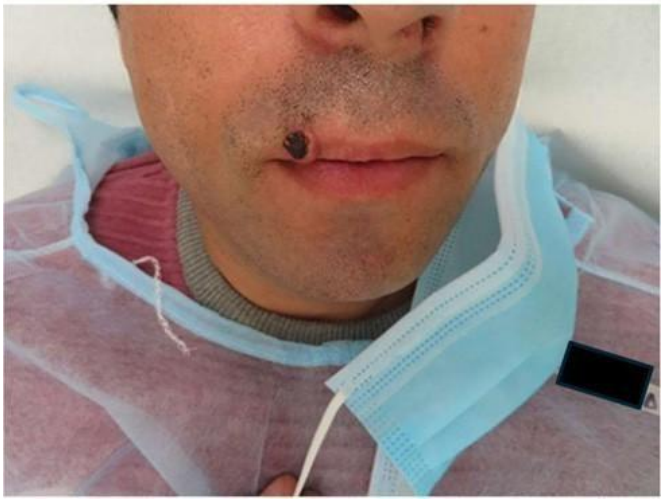

Figure 4.1: Initial Presentation.

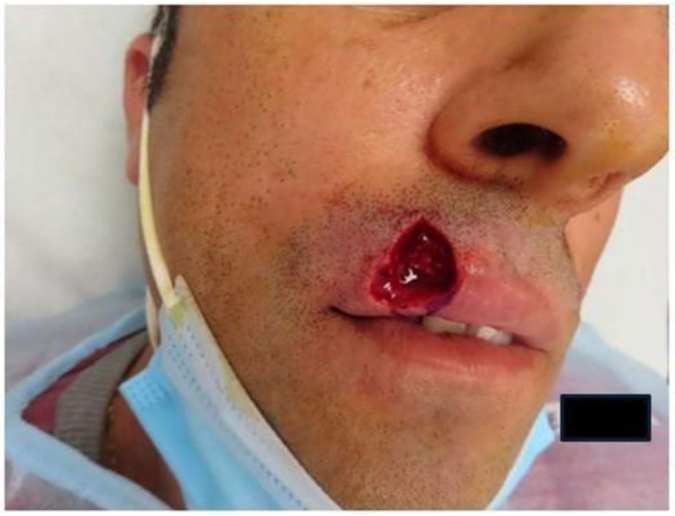

Figure 4.2: Final Defect.

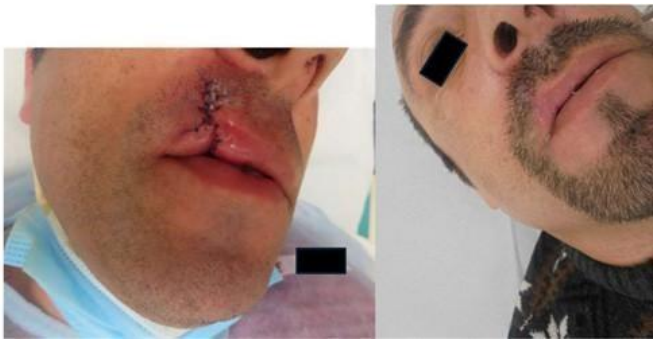

Figure 4.3: Direct Closure with Wedge Excision.

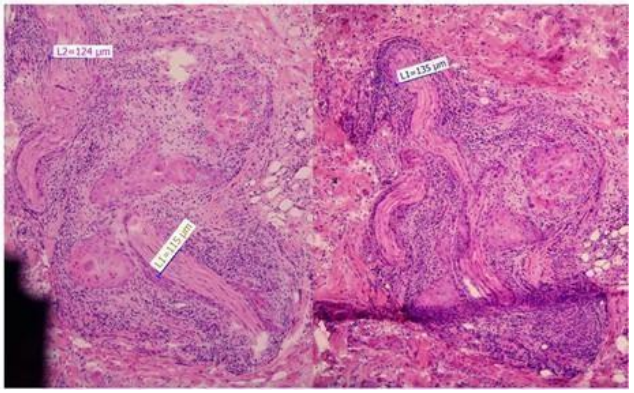

Figure 4.5: Histology.

13. Case 5

A 35-year-old female presented with a rapidly growing lesion on the ala nasi, evolving over an eight-week period. The tumour measured 18 × 15 mm on initial assessment. Mohs micrographic surgery was initiated, and histopathological analysis after the first stage revealed perineural invasion and deep tumour infiltration extending beneath the nasal cartilage. Three additional stages were required due to continued tumour presence. At the fourth stage, perineural invasion was again confirmed histologically. Complete tumour excision was achieved after the fifth stage. The final surgical defect measured 25 × 35 mm, reflecting extensive subclinical spread and deep invasion.

Histopathological examination: A cutaneous specimen obtained during Mohs micrographic surgery was oriented, dissected, and embedded in a frozen tissue block. Histopathological analysis revealed invasive, well- differentiated keratoacathomatous type squamous cell carcinoma involving the dermis, muscular, mucosal and submucosal layer of the nose. Five additional stages were performed, with tissue embedded in five supplementary frozen blocks. Perineural invasion was identified in the first stage. Further evaluation using permanent paraffin-embedded sections and immunohistochemistry were associated for evaluation of the surgical margins. The final surgical margins were free of tumour, with no residual malignant lesions identified.

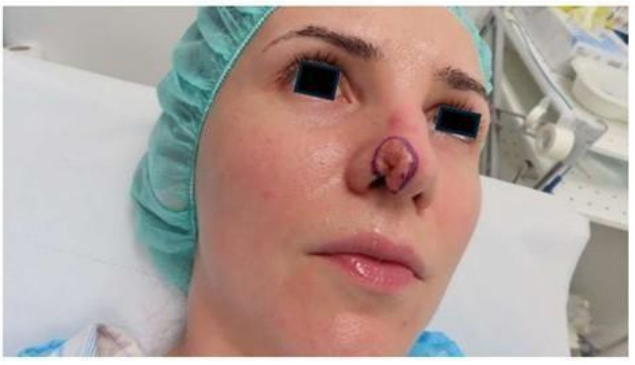

Figure 5.1: Initial Presentation.

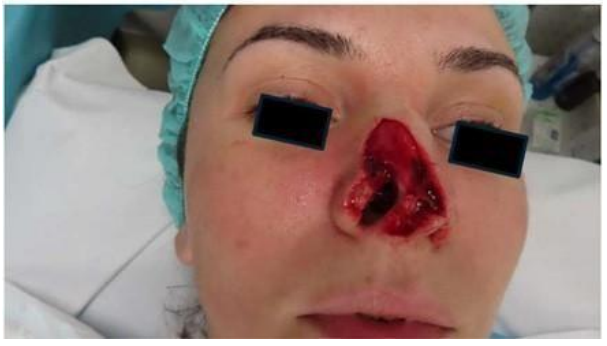

Figure 5.2: Final Defect.

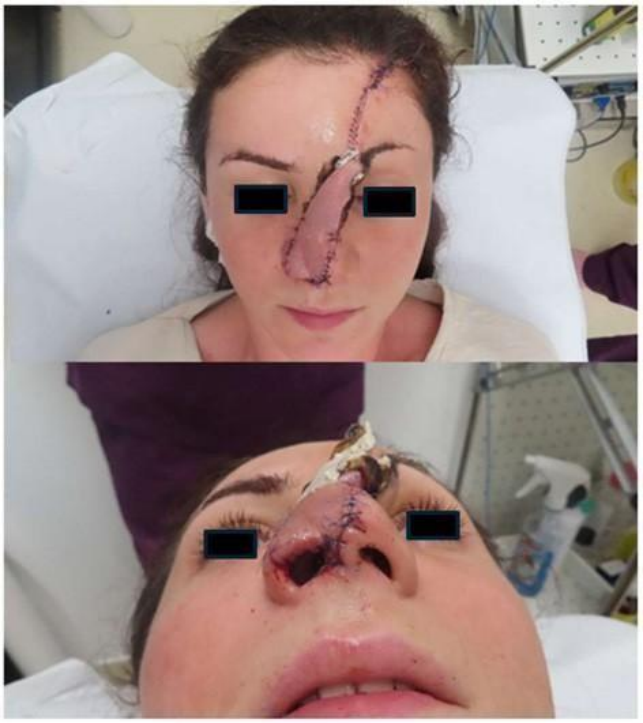

Figure 5.3: Frontal Flap First Stage.

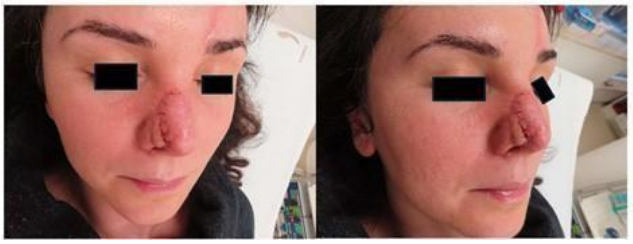

Figure 5.4: Frontal Flap Second Stage after Suture Removal.

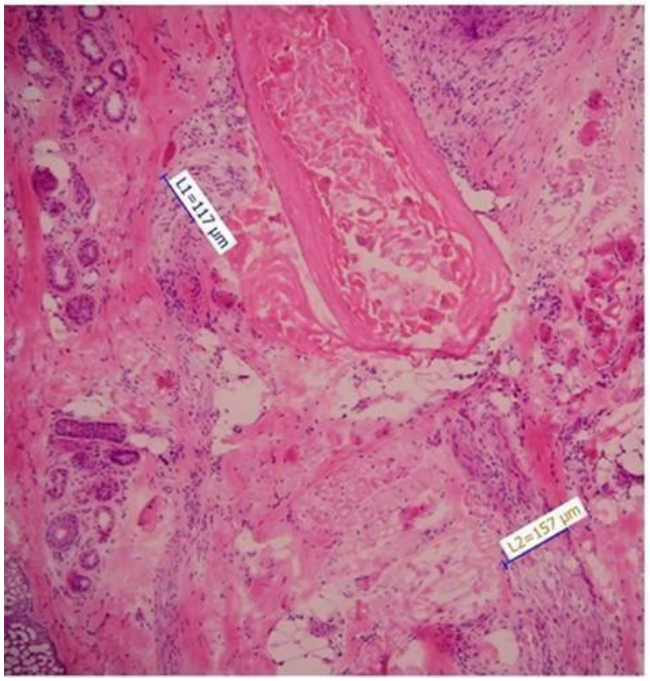

Figure 5.5: Histology.

14. Discussion

Keratoacanthoma (KA) is a rapidly growing epithelial tumour with clinical and histopathological features that may overlap with squamous cell carcinoma (SCC). While spontaneous regression has been reported, its locally aggressive behaviour, potential for tissue destruction, and association with perineural invasion justify early surgical management in selected cases. Mohs micrographic surgery (MMS) is increasingly recognized as the treatment of choice for KA, particularly in anatomically and functionally sensitive locations such as the nasal ala, as can be seen in the clinical cases presented before. The advantages of MMS over conventional surgical excision lie primarily in its ability to achieve maximal tissue conservation while providing complete margin control. This is of particular importance in cosmetically and functionally critical sites, where large surgical excisions can result in significant complications. By allowing for intraoperative histopathological examination of the entire surgical margin, MMS minimizes the risk of residual tumour, which is especially relevant in cases of perineural invasion. Perineural invasion is characterized by tumour infiltration of the perineurium, specifically when at least one-third of the nerve's circumference is involved within any of its three layers [29]. This histological finding indicates tumour cells are not only in close proximity but have actively infiltrated the neural sheath, representing a significant route for tumour dissemination even in the absence of lymphatic or vascular spread [30,31]. This process, where tumor cells invade, surround, or traverse peripheral nerves, is a well-recognized pathological phenomenon across various malignancies, playing a crucial role in disease progression and patient prognosis [32]. Perineural Invasion is a significant independent risk factor for metastasis, local recurrence, and disease-specific death considering cSCC [33,34]. PNI is defined as the infiltration of the perineurium by tumour cells, involving at least one-third of the nerve's circumference. PNI can be categorized as incidental with asymptomatic behaviour, involving small peripheral nerves and clinical by being symptomatic expressing pain, numbness etc., involving larger or named nerves. Clinical PNI is associated with a significantly worse prognosis, demonstrating higher rates of local recurrence (37% vs. 17%) and mortality (27% vs. 6%) compared to incidental forms of presentation [35,36]. On the other hand as long as we consider Keratoacanthomas with perineural invasion, these lesions do not exhibit metastatic potential and rarely recur, distinguishing them behaviourally from cutaneous squamous cell carcinomas [37]. PNI is generally considered an incidental finding that does not adversely affect the biological behaviour or overall prognosis 38,39. Perineural invasion in KA is a rare but documented finding. While PNI is generally associated with aggressive behaviour in SCC, in KAs, it might be an incidental finding that does not necessarily impact the patient's outcome, particularly in the head and neck region [14,38]. A study of 40 cases of KA with PNI found that 32 patients were alive and well without recurrence or metastasis after an average follow-up of 4.5 years and between

the two cases that presented metastasis none of them where associated with perineural or perivascular ivasion. The incidence of PNI in all KAs is reported to be just over 1% 37. However, aggressive recurrences have been observed in some KAs with PNI, particularly in the head and neck region. This has led some experts to suggest that extensive PNI in such cases may warrant management strategies similar to those used for cSCC with PNI 38. Considering the associated risk of local recurrence without treatment, extension into deeper structures, and, in very rare cases, metastatic spread.

Standard wide excision may not adequately address the unpredictable subclinical extension of tumours with perineural involvement. MMS, in contrast, enables meticulous stepwise evaluation and excision of tumour extensions along nerve sheaths, thereby ensuring more reliable clearance. In the clinical cases described in this article, despite multiple stages being required, MMS allowed for complete tumour eradication while sparing as much healthy tissue as possible. Furthermore, the age of the patient and the possibility of recurrence and potential association with facial disfigurement in case of the face can guide us to choose MMS as treatment of choice in particular cases. The data reinforces the idea that while KA is histologically and clinically distinct from SCC, it should be managed with comparable rigor in selected cases to prevent undertreatment and potential adverse outcomes. Moreover, MMS provides a significant advantage in documenting perineural invasion intraoperatively, thereby guiding further management and follow-up strategies. Patients with perineural invasion require closer surveillance and, in some cases, may benefit from adjuvant therapies such as radiation. Thus, MMS not only offers therapeutic benefits but also valuable diagnostic insights that directly influence patient care. According to the 2001 publication by Amanda M Godbolt, John J Sullivan, and David Weedon in the Australian Journal of Dermatology, the spatial arrangement of lesions differed significantly between subjects experiencing perineural invasion and the control group. There was a preference for the head and neck in lesions with perineural invasion, and for the lower extremity in the control group. The same work further indicated that the elevated frequency of facial lesions in the preceding investigation could elucidate the considerable fraction of cases involving perineural invasion, given its propensity for lesions on the head and neck, particularly the lips. This may possibly mirror the rich innervation of facial skin [37].

15. Conclusions

Conclusively, MMS should be the top treatment option for KA, especially when lesions are in visually significant areas or show aggressive qualities like perineural invasion. By merging oncological safety with the preservation of tissue, it surpasses conventional removal, and its significance is particularly pronounced when microscopic features indicate a greater chance of relapse. MMS is considered the most effective therapeutic approach for keratoacanthoma, especially in situations presenting high-risk characteristics like perineural invasion or involvement of critical anatomical sites. Its stepwise margin control enables complete tumour clearance while preserving uninvolved tissue, thus minimizing both recurrence rates and cosmetic morbidity. In addition, the intraoperative identification of perineural invasion during MMS allows for appropriate adjustment of surgical management and informs the need for closer postoperative surveillance.

Keratoacanthoma represents a distinct cutaneous neoplasm with overlapping features with squamous cell carcinoma. Accurate diagnosis is essential to avoid mismanagement. Mohs micrographic surgery remains the treatment of choice for high-risk, recurrent, or diagnostically ambiguous lesions due to its excellent clearance rates and tissue-sparing capability. Awareness of rare but clinically relevant features, such as perineural invasion, further supports the importance of individualized, evidence-based therapeutic strategies in the management of keratoacanthoma. Given its superior oncologic and reconstructive outcomes, MMS should be regarded as the first-line therapeutic option for keratoacanthoma with aggressive histopathological characteristics. Future studies with larger patient cohorts are warranted to further validate its role and to establish standardized management protocols for KA with perineural invasion002E

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