

## Verrucous Carcinoma, Then and Now

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**The salient clinical and pathological features of verrucous carcinoma, as first described by Ackerman in 1948, are reviewed. Two case reports are presented. The first concerns a personal experience with a patient who had five surgical procedures for multifocal oral verrucous carcinoma and remains alive and well 28 years after her initial treatment. The second report highlights the remarkable story of President Grover Cleveland's secret surgery for verrucous carcinoma of the palate in 1893. Current concepts about the management of this uncommon tumor are reviewed, as well as some recent investigations that deal with its etiology. *Am J Surg.* 1998; 176:000-000. © 1998 by Excerpta Medica, Inc.**

Fifty years have passed since Lauren V. Ackerman<sup>1</sup> first used the term "verrucous carcinoma" (VC) to describe an unusual and indolent variant of oral squamous carcinoma (SCC). His observations were based on 26 men and 5 women who received treatment for this unusual tumor during his years as a pathologist at Ellis Fishel State Cancer in Columbus, Missouri. Tobacco chewing seemed to be a significant etiologic factor in what subsequently came to be known as Ackerman's tumor. Aged men were most often afflicted in his series, and most of the tumors involved the cheek mucosa (18 patients) or the lower gum (8 patients).<sup>1</sup>

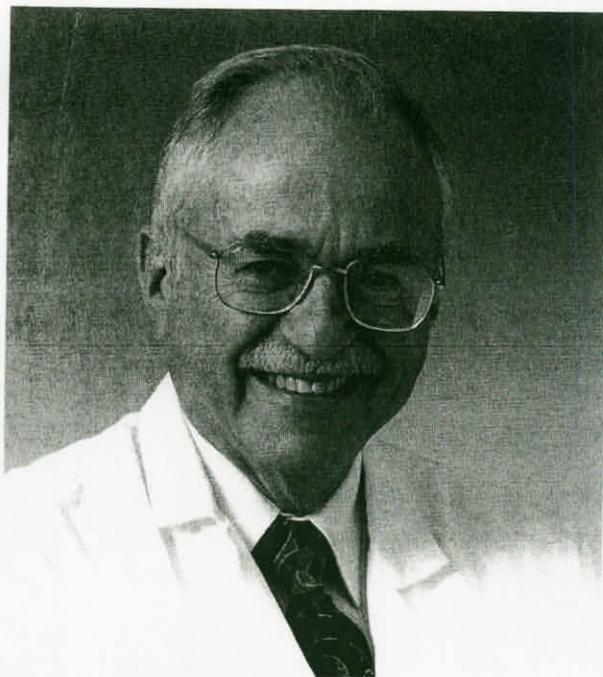
Grossly, these lesions were rather sparsely described as "pebbly, mamillated" in appearance, or "piled up in rugal folds with deep cleftlike spaces between them. . . ." Microscopic features included prominent surface keratin, downgrowth of club-shaped fingers of hyperplastic epithelium that push, rather than infiltrate, deeply toward an intact basement membrane, and a prominent inflammatory reaction in the adjacent tissues.

Extension of the tumor along the surface was typical in these patients. Cheek mucosal lesions, for instance, would extend into the sulci and eventually destroy bone. Some of these tumors even reached the cutaneous surface of the cheek or involved the external aspect of the oral commissure. The tendency to erode, rather than infiltrate, was well described, and he emphasized that regional node metastasis, confirmed in only 1 of his patients, is quite uncommon. No instance of distant spread was observed in his series.

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Although Ackerman's original report in 1948 long antedates contemporary staging and offered few clinical details, many of the tumors he described had to be sizeable. Eleven of his 31 patients required a composite resection, and the tumor was considered too extensive for surgery in 2 others. To this day, biopsy errors are common, and delay in diagnosis remains a problem. Even with a good tissue sample that includes the interface of the tumor with the host, the diagnosis of carcinoma may still prove elusive because the epithelial component of these tumors is so well differentiated and the basement membrane remains intact.

In his discussion of treatment options, Ackerman expressed a clear preference for surgery, a view shared by most head and neck oncologists today. Although local recurrence was noted in 8 of 14 patients (57%) who received radiation as definitive treatment, he believed this modality offered a reasonable chance for control when the lesions were small and relatively superficial.

Reflecting on the reason for local recurrence, Ackerman used language that mirrors the concept of "field cancerization" proposed by Slaughter et al.<sup>2</sup> "The cause for recurrence is unknown," he said, ". . . but certainly there must be a predisposition of the epithelium over a wide area to become malignant." I would like to emphasize this point with the case history of a remarkable woman who I first encountered early in my career. I owe much of what I know about VC to her travails over the years. Moreover, I never cease to be amazed at the courage and endurance she continues to display despite my repeated surgical attacks.

### CASE REPORT

A 58-year-old Cuban woman gave a 7-week history of palate irritation when she came to my office in June 1969 with a white, warty lesion of the left hard palate. She had been a 3-pack-per-day smoker, and biopsy elsewhere had been read as epidermoid carcinoma. The lesion extended from the left upper bicuspid region to the tuberosity and reached the midline. There was no cervical adenopathy.

Treatment consisted of a peroral partial maxillectomy with split thickness skin graft, and the pathology report described a SCC that infiltrated bone. (Material not available for review.) She did well with a dental obturator until October 1983, more than 14 years after her initial surgery, when a left lower molar tooth became loose. On examination, there was a 2.5-cm warty tumor in the left lower gingiva extending from the retromolar to the premolar area. Pseudoepitheliomatous hyperplasia was favored on biopsy, but VC could not be excluded. A composite resection was performed in conjunction with left supraomohyoid neck dissection. VC was the final diagnosis, with in-situ carcinoma involving one lateral margin. All excised lymph nodes were negative.

In January 1984, more than 10 years later, at the age of 83, a new 15-mm lesion appeared in the left cheek mucosa not far from the scar of the previous composite resection. Peroral resection again confirmed the diagnosis of SCC, but it was not clear whether this was a recurrence or another primary.

Four months later, peroral resection of a 1-cm nodule within the substance of the left cheek anterior to the last excision yielded metastatic SCC in fibroadipose tissue, presumably a lymph node replaced by tumor. Two months later, she required a left subtotal parotidectomy for a 2-cm periparotid lymph node metastasis. Adjunctive radiation therapy was considered at this point, but was not thought to be feasible.

In November 1994, 5 months later, a new nodule appeared in the soft tissue overlying the body of the left mandible, apparently a metastasis in a lymph node adjacent to the facial artery. This was confirmed by needle biopsy, and treatment consisted of a permanent I<sup>125</sup> implant. The patient had no sign of residual or recurrent tumor when last seen 3 years later at the age of 86, 28 years after her initial procedure.

An important lesson to be learned from the above case history is that prolonged follow-up may be necessary to appreciate the potential for multicentricity in patients with VC. This raises an interesting thought about another, high-profile patient—arguably one of the most fascinating case histories in the lexicon of cancer treatment—who died of other causes 15 years after presumably successful treatment of what, in retrospect, was VC of the upper jaw.<sup>3-6</sup>

### CASE REPORT

The year was 1893, and Grover Cleveland, the 22nd and the 24th president of the United States (and the only president to serve two nonconsecutive terms) was facing a crucial personal and political challenge. It was only a few months into his second term, and the nation's economy was deteriorating sharply. Unemployment was high, banks were closing, and export volume was shrinking. Following

the Sherman Silver Act of 1890, a major contributory factor to what was later called "the panic of '93," there had been a major shift from gold to silver. The 53rd Congress had failed to enact remedial legislation. With US gold reserves at a dangerous low, world confidence in the American economy was crumbling. The need for strong leadership from the White House was obvious.

The time could not have been worse for a presidential health crisis. During a social call at the White House, Major Robert M. O'Reilly, Cleveland's physician, was asked to examine a "rough place" in the roof of the president's mouth that had been present for 4 or 5 weeks. Concerned by what he saw, scrapings were taken and were examined anonymously by a pathologist at the Army Medical Museum (now the Armed Forces Institute of Pathology), who thought the diagnosis was probably "epithelioma." At this point, Dr. Joseph Decateur Bryant, a New York City surgeon and personal friend of the president, was summoned. On examination 4 days later, he visualized a quarter-sized, ovoid, ulcerated lesion on the left hard palate extending from the inner surface of the molar teeth to within one-third inch of the midline, slightly overlapping the soft palate. A second biopsy, read at Johns Hopkins Hospital, confirmed the diagnosis of "epithelial carcinoma."

Cleveland reluctantly proposed a July 1 date for surgery provided it could be performed without public disclosure of his illness. All agreed that any suspicion of presidential infirmity might aggravate the panic and propel the nation toward bankruptcy. It was his idea to arrange for the use of the yacht *Oneida*, owned by his good friend Commodore Elias Benedict, which was moored off lower Manhattan in the East River. With political concerns foremost in his mind, Cleveland was reassured that he would be able to appear at a special session of Congress that he would convene on August 7th for the purpose of repealing the Sherman Act. The stated purpose of his trip was to be rest and relaxation at Gray Gables, the president's summer home on Buzzard's Bay in Massachusetts.

The high drama associated with Cleveland's surgery in a makeshift operating room on the yacht *Oneida* while cruising up the East River has been told and retold. In addition to Drs. O'Reilly and Bryant, the team consisted of Dr. William Keene, eminent professor of surgery from Jefferson College, Dr. John Erdmann, Bryant's assistant, Dr. Edward Janeway, a prominent New York internist, and Dr. Ferdinand Hasbrouck, a New York dentist skilled in the use of nitrous oxide.

One half hour past noon on July 1st, as the *Oneida* cruised up the East River at half speed, the president was positioned in a chair, nitrous oxide anesthesia was induced, and both left upper premolar teeth were extracted. Peroral exposure was enhanced by a special cheek retractor that Keene had bought in Paris some years previously (now standard equipment). After topical application and injection of cocaine, an incision was made through gingival and palate mucosa to the underlying bone. Supplemental ether inhalation was then used to facilitate a partial maxillectomy, including the left upper alveolus from the first bicuspid to just behind the last molar tooth, the hard palate to the midline, and a small portion of the soft palate.

Only at this point was it appreciated that the tumor had extended into the antrum, involving the floor around the roots of the molar teeth. For this reason, the remaining left maxilla, exclusive of medial wall and infraorbital plate, was apparently removed in piecemeal fashion, and the cavity was packed with iodoform gauze. The 1 hour and 20 minute procedure was well tolerated. Hemostasis had been achieved with pressure, hot water, and at one point, galvanocautery. It was Keen's estimate that the blood loss was "probably about 6 ounces."

Recovery was remarkably uneventful, and official Washington was oblivious to what had transpired when Cleveland debarked from the yacht 4 days later (July 5th) and walked to his waterfront residence. The secrecy was preserved when, on July 17th, he rejoined the surgical team on board the *Oneida* for a second procedure to remove some "suspicious tissue" noted by Bryant on examination a week after the first operation. The two procedures had produced a defect of 2.5 by 13/16 inches, but relatively normal speech was restored by a vulcanized rubber prosthesis fabricated by Dr. Kasson Gibson, a New York dentist—so much so that members of Congress were unaware of any change in Cleveland's voice when he addressed the special session on two occasions. His efforts were largely responsible for repeal of the Silver Act that October and the gradual restoration of fiscal stability.

Cleveland remained in relatively good health until late in his retirement, when he developed gastrointestinal symptoms. Until his death in July 1908 at age 71, there had been no recurrence of his oral tumor. Although the death certificate attributed his demise to cardiac and respiratory problems, Erdman asserted years later that the actual cause was obstruction related to "intestinal carcinoma."

In his prime, Cleveland was described as a robust, "corpulent," short-necked gentleman who had a penchant for good cigars. In unpublished notes, Hayes Martin expressed admiration for the "skill and the courage," as well as the good fortune of the surgical team. An operation that often involves significant blood loss was swiftly performed without endotracheal intubation. Recovery was rapid and uneventful, and the tumor was controlled. Keen<sup>3</sup> himself reflected that "the operation itself was as nothing compared with scores that both of us [Bryant and Keen] had performed, but on it hung . . . the destiny of a nation."

A remarkably accurate account of Cleveland's illness had appeared on August 29, 1893 in the *Philadelphia Press*, apparently leaked by Hasbrouck, which was promptly denied by his physicians and the White House. Reassured by his reappearance in apparent good health, the American public remained in the dark until 1917, when Keen<sup>3</sup> recounted the entire escapade.

Additional details have emerged in subsequent publications, especially that of Morreels<sup>4</sup> in 1967, but there was no resolution of the confusion in diagnosis until Brooks et al,<sup>5</sup> pathologists at Jefferson Medical School, finally obtained permission to prepare additional sections from what remained of the surgical specimen and reported their results in 1980. Recalling that Cleveland's palate lesion had initially been called "epithelioma," and later "sarcoma" by Keene because of the fleshy character of the tumor within the antrum, they were unsuccessful in their attempts to find

either an official pathology report or the original slides and blocks. In the new sections, however, the mucosal surface was "replaced abruptly by sheets of epithelial cells which projected above the surface of the mucosa in papillary fronds corresponding to the wart-like growths apparent grossly. In the submucosa, elongated . . . club-shaped epithelial sheets could be seen to infiltrate." There was no doubt that Cleveland's lesion fulfilled all of Ackerman's criteria for VC.<sup>5</sup>

## CURRENT STATUS

For more than 2 decades after his paper appeared, tumors that fit Ackerman's description were reported in the literature under a variety of names, including florid papillomatosis, oral florid verrucosis, verruca acuminata, verrucous squamous cell carcinoma, and papillomatosis mucosae carcinoides. By the 1970s, they were consistently termed "verrucous carcinoma" or "Ackerman's tumor," and it was clear that this uncommon lesion could arise in other areas of the body. Reported sites of origin include skin, male and female genitalia, anal canal, uterine cervix, bladder and renal pelvis, and esophagus. By the early 1980s, more than 400 cases of VC had been reported, an obvious reflection of considerable clinical interest.<sup>7</sup>

With respect to the upper aerodigestive tract, where these tumors most often arise, the oral cavity remains the most common site of origin. The incidence is highest in the cheek mucosa, gingivae, and retromolar areas. Glottic larynx is the most frequently encountered nonoral head and neck site for VC; nasal cavity, sinus, and hypopharynx (pyriform fossa) involvement has also been described. The incidence varies from 4.5% to 9%, or even higher in some centers, and elderly men are most often afflicted. By far, the largest reported experience comes from India, where oral cancer is the most common malignant tumor (27% of all cancers).<sup>8</sup>

Diagnosis continues to be a problem. In a 1980 study, Shear and Pindborg<sup>9</sup> emphasized that verrucous hyperplasia is clinically indistinguishable from verrucous carcinoma without careful histologic examination. According to them, carcinoma is characterized by extension of the lesion into the underlying connective tissue deep to the adjacent normal epithelium. They believed that both lesions can exist concurrently, and that verrucous hyperplasia can progress either to SCC or VC.

Rajendran et al<sup>7</sup> agreed that verrucous hyperplasia is an intermediate lesion, often arising in areas of leukoplakia, which can in turn lead to VC and then invasive carcinoma. Emphasizing that clinical and histologic diagnosis can be difficult, these authors cite pseudoepitheliomatous hyperplasia, well-differentiated squamous carcinoma, chronic candidiasis, and condyloma accuminatum as lesions that must be distinguished from VC. This distinction obviously requires concurrence between the clinician's appreciation of the typical verrucous appearance of the tumor and the pathologist's identification of the microscopic criteria described by Ackerman.

Treatment recommendations have not changed appreciably since Ackerman originally advised radiotherapy (RT) for the small, superficial lesion and surgery "if at all extensive." Early enthusiasm for RT waned after the report of Demian and others<sup>10</sup> that transformation to a more ana-

plastic tumor type occurred in about 30% of patients who received curative doses of RT for VC. For the larynx in particular, it was also believed that VCs were radioresistant. Although most clinicians still prefer resection when feasible, more recent studies suggest that the radioresponsiveness and treatment results are quite similar when low-stage VCs are compared with similar SCCs.<sup>11,12</sup>

Early concerns about "malignant transformation" associated with RT have not been substantiated in more recent reports. This anaplastic evolution may relate to "hidden" areas of lesser differentiation within the tumor, but it is also likely that at least some of the reported patients whose tumors "transformed" did not, in fact, have VC. Whatever the explanation, other studies indicate that similar transformation can occur in surgically treated patients.<sup>13-15</sup>

From the outset, it has been clear that tobacco plays a significant role in the pathogenesis of VC. More than one third of the patients in Ackerman's original report were tobacco chewers, and the relationship between smokeless tobacco and verrucoid oral lesions has been established in several other studies. The habitual chewing of "pan," a mixture of betel leaf, lime, betel nuts, and tobacco, has long been implicated in the high incidence of verrucous-type oral cancers in India.<sup>16</sup> As Ferlito and Recher<sup>17</sup> pointed out years ago, however, tobacco usage is not a reasonable explanation for VC, which arises in skin, genital, and other nonaerodigestive sites.

Several investigators have focused on human papilloma virus (HPV) as a possible etiologic factor in head and neck cancer in general, and VC in particular, using archival, formalin-fixed, paraffin-embedded tissue sections, and a variety of sophisticated techniques. With the exquisitely sensitive polymerase chain reaction assay, rather than southern blot hybridization or immunohistochemistry (which are less sensitive), HPV DNA was identified in up to 85% of a cohort of patients with laryngeal VC.<sup>18</sup> Thus far, it is far from clear that HPV plays a specific role in the genesis of VC. Depending on the sensitivity of the assay and whether frozen or paraffin-embedded tissue is studied, the yield of HPV DNA seems to be similar in squamous and VC, and it is also present to a lesser extent in normal oral mucosa, benign leukoplakia, and intraepithelial neoplasia.<sup>19</sup>

Recently, there has been considerable interest in the role of molecular genetic alterations in the pathogenesis of VC. Overexpression of the p53 oncogene is similar to that which has been observed in other head and neck cancers, and there is a suggestion that HPV and p53 may work through the same pathway. When other oncogenes and indices of cell turnover were compared, there were marked differences between squamous cell carcinoma and VC that correlate with the different biology and prognosis of these tumors.<sup>20-22</sup>

### EPILOGUE

After serving 25 years as distinguished professor of pathology at Washington University School of Medicine, Ackerman left St. Louis in 1973 to join the faculty of the SUNY School of Medicine at Stony Brook, Long Island. During his long and illustrious career, which ended with

his death in 1993, he was recognized as a pathologist's pathologist. Several of his trainees now occupy positions of leadership in prestigious medical centers throughout the country. No matter that the entity he so well characterized in 1948 had actually been the subject of a case report published in 1941 by Friedell and Rosenthal<sup>23</sup> describing a patient with "papillary verrucoid carcinoma." Ackerman still deserves credit for accurately describing and focusing attention on this uncommon neoplasm. To this day, it remains a challenge in clinical management as well as a provocative model for cell biologists in search of a better understanding of oral carcinogenesis.

I wish to thank the members of the Society of Head and Neck Surgeons for the honor of serving as your president during this momentous year. Unification of the two national head and neck societies has been a remarkable achievement. I believe this ecuminism heralds a new era in which physicians of different disciplines and nationalities will receive better support in their efforts to expand our knowledge and improve treatment in head and neck oncology.

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