ABSTRACT
A cohort of head and neck cancer patients, without exposure to tobacco and alcohol, presented with multiple preneoplastic and neoplastic lesions, the natural history of which may span several decades. Examination of these cases provides an opportunity to study the relationship between genetic, morphological, and clonal progression in these fields and establish whether they represent a unique presentation of squamous cell carcinoma. The presence of a common novel microsatellite allele, a common breakpoint or concordant allelic imbalance at multiple loci, reveals that a high proportion of these serial lesions arise due to spread of a precursor. The tumors arising in these patients were typically nonaggressive, although metastases developed at a late stage, supporting the notion that the genotype results in a phenotype with a propensity for lateral spread, rather than invasion. Different genetic aberrations were detected in morphologically similar phenotypes such that no consistent early or late events were associated with development of premalignant lesions. Combining information about the clinicopathological features and histological examination of the margins with that derived from clonality analysis reveals that a subgroup of patients, without exposure to the traditional risk factors associated with this disease, developed multiple clonally related oral lesions and represents a unique presentation of head and neck squamous cell carcinoma. We suggest the term clonal cancerization to describe multiple premalignant and malignant lesions when there is conclusive evidence that they arise due to lateral spread from a common precursor.

INTRODUCTION
The ability to subject histological material to genetic analysis has provided new insight into the origin of multiple preneoplastic and neoplastic lesions arising in the oral cavity. An early progression model for head and neck cancer, based on comparing the spectrum of aberrations identified in unrelated lesions showing hyperplasia, dysplasia, and frank invasive SCC, identified AI at 3p and 9p as among the earliest changes (1, 2). However, a significant number of cases with AI at these chromosomal arms did not develop a tumor, showing the limitation of relying on a restricted number of markers. Addition of more microsatellites at eight chromosomal arms, which are frequently altered in these tumors, improves prediction of tumor development such that the risk of a malignancy developing in the upper aerodigestive tract over 5 years approaches 75% in fields where the oral mucosa harbors AI at two or more critical loci (3). The importance of AI at regions 3p, 9p, and 17p in terms of predicting tumor development for head and neck cancer patients has been validated by Rosin et al. (4) and by the use of case-control methodology (5).

Preliminary study of recurrent preneoplastic lesions arising at a single site in patients with head and neck cancer patients has confirmed that AI at 3p, 11q13, 13q21, 8p21–22, 14q24, and 17p13 are all associated with histological progression (6). To date, no aberrations associated with mild, moderate, and severe dysplasia have been identified (5), suggesting that a variety of genetic events result in similar morphological changes. However, the study of more cases may reveal that the temporal order of genetic events is also important.

Genetic analysis has also revealed that a proportion of paired preneoplastic and neoplastic lesions arising in the head and neck region are clonally related to the index lesion (6–12) and that some tumors, considered to be second primaries based on conventional clinicopathological criteria, are incorrectly diagnosed because they are clonally related to the index lesion. Many of these studies have used the presence of AI affecting polymorphic sequences at chromosomes 3p and 9p to determine clonality (6, 8–12). However, because these aberrations are frequently detected in the head and neck tumors, their presence in serial lesions arising in the same patient does not provide conclusive proof of a common clonal origin. In contrast, novel microsatellite alleles occur rarely and at random and provide excellent markers of clonality with the proviso that relying on a single approach to determine clonality may underestimate the true frequency of clonally related lesions (8–10).

To date, microsatellite assay has not been used to study the relationship between genetic, morphological, and clonal progression in multiple preneoplastic and neoplastic lesions, arising in the same case, to shed light on the molecular pathogenesis of this process and establish whether there is any evidence for proposing that patients developing multiple oral lesions repre-
sent a subgroup with a unique presentation of head and neck squamous cell carcinoma.

PATIENTS AND METHODS

Eleven consecutive cases, presenting to one of us (M. P.) with at least three lesions with histological evidence of hyperplasia, dysplasia, verrucous, or invasive SCC at different sites in the oral cavity, between 1978–1996, were identified for study. Cases presenting with a recurrent dysplastic lesion at the same site as the initial biopsy were excluded from the series to ensure that we were analyzing spreading and progression within a field and not multiple recurrences at the same site. All cases were monitored regularly, and repeat biopsies were performed: if a new lesion appeared at a different site; if there was a change in the appearance or size of a patch of altered mucosa; or to determine whether there was histological evidence of progression. The histological diagnosis and location of each premalignant and malignant lesion, together with any associated risk factors, are shown in Table 1 and Fig. 1. All biopsies were reviewed with the histopathologist who initially reported the case. Cases presenting with a single premalignant and malignant lesion, together with any associated risk factors, are shown in Table 1 and Fig. 1. All biopsies were reviewed with the histopathologist who initially reported the case.

When biopsies were carried out, one-half was snap-frozen in liquid nitrogen and stored at −70°C, and the remaining portion was processed for conventional histology. Sections from each sample were stained with H&E, and the grade of dysplasia (mild, moderate, or severe) was determined by the pathologists at each collaborating center. The term “atypia” was used to describe changes that fell short of a diagnosis of dysplasia. Venous blood was stored in NaCl-EDTA tubes and kept at −20°C until required.

All cases under review during 1993–1999 with three or more lesions with evidence of dysplasia or frank invasive carcinoma (see Table 1) were offered chemoprevention in a pilot study with isotretinoin, which is currently unlicensed for this indication. All patients enrolled into this open study were treated with isotretinoin, 30 mg/day for 9 months, followed by long-term maintenance with 10 mg/day. Treatment commenced within 6 months of index tumor development (cases 1, 5, 6, and 10) or after the appearance of a second (cases 2, 7–9, and 11) or third (case 4) tumor. These patients were also given advice about dietary modification to minimize cancer risk and reviewed every 4–6 months.

Microdissection, DNA Extraction, and Microsatellite Analysis. Ten-µm frozen or paraffin-embedded sections of each keratotic, dysplastic lesion and the matched verrucous and invasive SCC were mounted onto microscope slides covered with double-sided sticky tape and stained with toluidine blue for microdissection. The epithelium was separated from the underlying connective tissue, and the greater proportion of the stroma was removed from the tumors using an ophthalmic scalpel under a stereomicroscope (3). Each sample analyzed contained <30% contaminating connective tissue or stromal cells. To ensure that sufficient sample was processed and to avoid the possibility of artifacts due to inadequate template, at least 30 sections were microdissected for 5–10-µm biopsies.

To prepare DNA, samples were digested in 100 µl of lysis buffer, 50 mM KCl, 10 mM Tris-HCl (pH 8.3), 2.5 mM MgCl₂, 0.01% gelatin, 0.45% NP40, 0.45% Tween 20, and 60 µg/ml proteinase K (Roche Diagnostics Ltd., Lewes, United Kingdom) and incubated overnight at 55°C. Digested products were purified with phenol-chloroform, and DNAs were recovered using the ethanol precipitation method. Control DNA was extracted from Research Genetics (Huntsville, AL). Thirty pmol of primers for these polymorphic microsatellite markers were obtained from Research Genetics (Huntsville, AL). Thirty pmol of the forward primer were end-labeled with 0.8 MBq [32P]ATP

<table>
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<th>Case</th>
<th>Age at diagnosis</th>
<th>Sex</th>
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<th>Alcohol</th>
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<td>nil</td>
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<tr>
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<td>nil</td>
<td>nil</td>
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</tr>
</tbody>
</table>

* DoC, died of cancer.
and 0.5 μl of the labeled primer was used for each PCR reaction. PCR products generated in a total volume of 25 μl containing 50 ng of DNA, 1.5 pmol of each primer, 2.5 mM of 10× reaction buffer [50 mM KCl, 100 mM Tris-HCl (pH 8.3), 15 mM MgCl2, and 0.01% w/v gelatin], 1.2 mM of each deoxynucleotide triphosphate, 1.25 units of Taq Polymerase (Promega, Southampton, United Kingdom), and water to the total volume as described previously (15). Normal and tumor DNA were subjected to 28 cycles of 95°C for 30–75 s, 55–65°C for 60–75 s, and 72°C for 60 s in a temperature cycler (Perkin-Elmer, Warrington, United Kingdom), followed by a 5-min extension at 70°C. Products were separated by gel electrophoresis in denaturing 6% polyacrylamide-7M urea and autoradiographed for 24–48 h. Labeled M13mp8 was included as a sequencing ladder to facilitate sizing of the alleles (10).

Fig. 1 Clinicopathological features and results obtained after application of microsatellite assay to serial lesions, preneoplastic lesions, and neoplastic lesions.
Cases were considered to show AI if the ratio of the two alleles in the tumor was 50% less than that detected for the normal sample after visual inspection of the band patterns by at least two independent observers and scanning densitometry. In this and related studies, complete agreement in the interpretation of autoradiographs was obtained between the use of visual inspection and scanning densitometry. Novel microsatellite alleles were identified by the presence of one or more alleles in the biopsy specimen, which were absent in the normal DNA. All heterozygous cases were repeated at least once, and paired tumors showing conflicting genetic changes were dissected again from new slides to assure that contamination had not occurred.

**RESULTS**

Eleven cases (7 females and 4 males) presenting with 3–14 serial oral lesions were identified for analysis. All female patients were nonsmokers and nondrinkers. Two males had modest exposure to tobacco in their teens and early 20s but smoked <10 cigarettes/day. Seven of the 11 cases (cases 2, 3, 5, 7–10; see Fig. 1) came from families where one parent or a sibling died as a result of cancer.

Two cases (cases 3 and 4) presented with areas of leukoplakia showing simple keratosis. Overall, this was the most common phenotype, although subsequent lesions examined for cases 3, 7, and 8 showed moderate (cases 3 and 7) and severe (cases 7 and 8) dysplasia. Cases 3, 4, 7, and 9 had persistent leukoplakia during the period of study. Three patients developed CIS (cases 3, 6, and 7) or an exophytic tumor (case 4) before an invasive tumor. Typically, the early cancers were small, nonaggressive lesions. Only the tumors that developed in the floor of the mouth (case 5) and on the dorsum of the tongue (case 6) were associated with nodal metastases at presentation, although these developed at a late stage for cases 3 and 7. Ten cases (cases 1, 2, and 4–11) enrolled in the open pilot study with isotretinoin did not develop any new tumors after commencing therapy, although cases 4 and 9 developed new areas of leukoplakia.

The results obtained after application of microsatellite assay to screen serial biopsies obtained from these patients are summarized in Fig. 1. Cases found to have AI affecting the same allele (upper or lower) in multiple preneoplastic and neoplastic samples are highlighted. A single individual (8) showed loss of different alleles at the *D4S407* marker when the initial and subsequent dysplastic lesions were examined. Biopsies reported as showing simple keratosis (cases 3 and 4) harbored aberrations at 1–4 informative loci. In addition, the initial dysplastic lesion examined for cases 1, 3, 4, 5, and 10 showed AI at two or more loci, a finding previously reported to be associated with risk of tumorigenesis (5, 10).

Our findings show that aberrations, affecting key chromosomal areas, may be detected in the oral mucosa a decade before cancer develops (for examples, see cases 3, 4, and 7), reflecting the long natural history of the disease process in individuals without exposure to the traditional risk factors associated with head and neck cancer.

In view of the extensive nature of many of the areas of leukoplakia biopsied, we anticipated that aberrant histological features would be present at the mucosal margins, and this was confirmed by the histopathologist (see Fig. 1), although the majority of the intervening epithelium was not dysplastic. Thus,
persistent dysplasia at the left buccal mucosa in case 2 after an incisional biopsy and atypia at the ventral surface of the tongue for case 3 may have been the source of cells for the subsequent tumors that developed at the same, or adjacent, sites in the mouth. The presence of dysplasia at the margins of biopsies may also be related to development of new tumors at adjacent sites for cases 1, 3, 5, 7, and 10. The dysplastic epithelium detected at the margins of the tumors excised for case 3 was reported to continue into the minor salivary ducts, revealing the propensity of these altered cells to colonize large areas of oral mucosa. Additional dysplastic lesions also appeared in cases 4 and 9, where aberrant histological changes were detected at the margins after removal of a tumor. However, histologically clear margins were not synonymous with no risk of subsequent tumor development because additional malignant lesions developed in cases 2, 3, 6, 7, and 11, although the margins were reported as “clear.” Lesions showing all grades of dysplasia (mild, moderate, and severe) showed AI affecting similar numbers of loci, and aberrations affecting single or combinations of loci were not found to be associated with the different phenotypes.

Cases 1, 4, and 7 were found to harbor a novel microsatellite allele in all serial samples analyzed (case 1 at D3S1573; case 4 at D8S133; case 7 at D8S133; Fig. 2). These shared aberrations are highlighted in Fig. 1 and provide conclusive evidence that the multiple biopsies are derived from the progeny of a single initiated clone. The signal from the novel allele is stronger in subsequent biopsies, revealing that the proportion of cells harboring the clonal marker increases as the lesion evolves (Fig. 2). Furthermore, all biopsies examined for these cases showed concordant AI at two or more of the loci tested (case 1 shows AI at D9S171, Rb, and DCC; case 4 at Rb and D9S286; and case 7, AI at D9S171 and DCC). The finding of an identical clonal marker for the index and subsequent tumors which developed in case 4 (index tumor left tongue, second tumor right fauces/buccal mucosa, and third tumor left buccal mucosa) and case 7 (index tumor right buccal mucosa and second tumor right lateral tongue) reveals that these second tumors are not second primaries, although they developed at sites separated by more than 2 cm of clinically normal mucosa.

An additional 4 cases (cases 2, 3, 6, and 10) showed concordant AI at three or more loci tested in at least three of the biopsies investigated. These aberrations are consistent, although not pathognomonic, with a common clonal origin for these serial lesions. In the absence of a clear clonal marker, it is not possible to establish categorically whether the serial lesions arising in these cases represent progression of a precursor or arise independently because of a polyclonal field effect. However, in each of these cases showing AI at multiple microsatellite markers, the degree of allelic imbalance increases as the lesion progresses from dysplasia to carcinoma (see Fig. 2), and the finding of dysplasia at the margins supports the notion that these lesions evolved from the same clone of initiated cells. Cases 8, 9, and 11 were found to harbor fewer aberrations with the microsatellites tested, such that an independent or common basis for these lesions cannot be established at present. X chromosome and p53 mutational analysis is in progress to clarify this point.

Examination of multiple biopsies of the lesions arising in case 3, ultimately resulting in widespread leukoplakia, identifies complex patterns of loss and retention of alleles, highlighting the complexity of the carcinogenic process in the oral cavity. The finding of AI at adjacent loci tested at 9p (D9S286, inja, and D9S171) for 11 of 13 biopsies examined for this case suggests a common clonal origin for these lesions. Further evidence is provided by the finding of a shared novel microsatellite allele at DCC for five lesions and keratoses for four lesions (the papilloma, two dysplastic lesions (D1 and D2), and SCC). However, this marker shows retention of heterozygosity for keratoses 1–3, the CIS, and SCC2. There are two possible explanations for these findings. The most plausible is that this novel allele evolved within a patch of mucosa on the ventral tongue, which gave rise to five subsequent lesions at adjacent sites sharing this clonal abnormality. Alternatively, this aberration may have been present at an earlier stage but was not detected in all biopsies examined because it was only present in a small proportion of the initiated cells. However, the absence of this key marker in the carcinoma in situ and SCC1, together with the varied pattern of loss and retention of alleles at p53, Rb, and D4S407, provides clear evidence of clonal heterogeneity within the field. Further evidence for the emergence of subclones is derived from examination of the varied pattern of loss and retention of alleles in the serial lesions examined for the other cases. For example, case 4 shows AI at D4S407, D9S171, and p53 for the subsequent verrucous tumors developing in this case, whereas both alleles for these markers are retained in the index tumor.

Identification of a cohort of patients with clonally related lesions provides an opportunity to examine the relationship between genetic and morphological progression in a patch of altered mucosa. For example, progression from mild to moderate dysplasia in case 7 is associated with AI at adjacent loci at 9p21 and the transition from severe dysplasia to CIS with AI at p53. Case 3 shows progression from keratos to verrucous tumor in the buccal mucosa associated with AI at 8p and DCC and the transition from dysplasia to invasive tumor on the tongue accompanied by AI at 4q and 8p. However, comparison of the patterns of AI associated with the keratoses, the three grades of dysplasia, and malignant lesions developing in this patient cohort does not identify any consistent early or late events associated with morphological progression. The temporal order of events is also different for each case. However, although the aberrations detected with the present assay represent only a fraction of those likely to be present, the findings suggest that similar morphological changes reflect different genetic backgrounds, and that acquisition of additional aberrations does not necessarily result in morphological progression. For example, the serial keratoses examined for case 3 (K1–4) and the dysplastic lesions biopsied for case 10 (D1 and D2) have similar phenotypes but different genotypes.

**DISCUSSION**

It is generally recognized that cases presenting with a single dysplastic lesion may develop an invasive tumor within a relatively short time frame, because the dysplasia is a precursor lesion at the margin of a developing tumor. Alternatively, malignancy may arise at another site years later, presumably because the entire mucosa is exposed to the same carcinogens. However, as highlighted in the present study, a cohort of patients presented with serial lesions, typically showing a mildly
dyplastic phenotype, over a timeframe which may span several decades. The majority of index tumors that arise in these cases show a nonaggressive phenotype, with multiple low-grade lesions, typically CIS or an exophytic tumor, developing before small $T_1$ invasive lesions are detected. These multiple preneoplastic and neoplastic lesions developed predominantly in females without exposure to tobacco or alcohol, such that the nature of the risk factors for these cases remains speculative at present. The lack of exposure to the traditional factors may explain the long natural history of the disease process and the preponderance of exophytic, low-grade tumors. Of interest is the finding that many patients’ first-degree relatives had a cancer history. Although familial factors have generally been ignored, evidence is increasing that suggests that they may be important (16, 17) and related to development of multiple tumors. Infection with human papillomaviruses may also be an etiological factor.

Current concepts of carcinogenesis predict that a tumor is more likely to develop in tissues that show moderate or severe dysplasia and harbor a significant number of genetic abnormalities. However, the present investigation extends the literature which shows that some tumors develop against a background of mild dysplasia or hyperplasia (18) and confirms that these lesions should not be regarded as “low risk.” There is also evidence that genetic aberrations can be present in clinically normal tissues (19–22), an observation that is not surprising because many tumors arise in clinically, and often histologically, normal mucosa. These observations suggest that the phenomenon of field cancerization is more widespread than previously realized and highlight the limitations of predicting risk of transformation, based on clinical and morphological features.

In the present study, AI affecting single loci or combinations of loci was not associated with the different phenotypes. Our findings do not reveal the existence of key temporal events in these fields but suggest that morphological changes reflect a plethora of different genetic events, supporting the notion that there may be multiple parallel routes to cancer.

Analysis of clonality based on the finding of shared identical microsatellite alleles has shown that, although some lesions developing within a field of cancerization arise because of independent events, a significant proportion represents spread of cells with a common clonal origin. Previous studies (2, 3, 6–9, 12) have provided evidence for a common clonal origin for paired lesions that arise in the head and neck. However, this is the first study to examine the clonal origin of multiple preneoplastic and neoplastic oral lesions that developed at different sites.

Unexpectedly, all serial biopsies examined for 3 of 11 patients (cases 1, 4, and 7) were found to harbor an identical novel microsatellite allele, indicating that these genetic aberrations occurred early in the tumorigenic process and that the lesions are clonally related. In addition, there is strong circumstantial evidence that the multiple lesions developing in 5 other cases (2, 3, 5, 6, and 10) are clonally related. All biopsies tested for these patients showed concordant AI at two or more loci examined or a common chromosomal breakpoint.

These findings extend our knowledge about the size of patches of mucosa that may be derived from a single clone of initiated cells by demonstrating conclusively that multiple lesions developing at distinct sites, and even on the opposite side of the mouth, may be derived from clonally related cells. The presence of dysplasia at the margins of many of the lesions biopsied revealed the extent of the morphological changes. However, because not all of the epithelium examined at the margins of the biopsies examined for these cases was dysplastic, this finding suggests that any increase in the patch size does not necessarily occur in a concentric manner, and that spread of altered cells may progress in a spidery fashion, at least in a proportion of cases. Taken together, the clinicopathological features and genetic findings support the existence of a distinct cohort of patients who develop multiple, clonally related, low-grade lesions, in the absence of traditional risk factors. These lesions have a propensity for lateral spread, which results in a large patch of altered mucosa rather than invasion, a phenotype that is likely to reflect a characteristic genotype. We suggest the term clonal cancerization to describe multiple premalignant and malignant lesions arising due to lateral spread from a common precursor. This process is nested within the concept of field cancerization, as originally envisaged by Slaughter et al. (23), where an area of conditioned epithelium may break down at multiple sites producing multiple tumors or independent contiguous foci of tumor, contributing to the apparent lateral spread of a malignant lesion.

However, clonal cancerization describes a process where there is conclusive evidence that the lesions arise from a common precursor. Further studies, using multiple markers of clonality, are required to establish whether a proportion of multiple lesions considered to be “independent” on the basis of pattern of AI or discordant $p53$ gene mutations might also share a common clonal origin.

The identical clonal marker harbored by the index and second tumors that developed in cases 4 and 7 also reveals that these subsequent tumors are not second primaries, although they developed at sites separated by >2 cm of clinically normal mucosa. Thus, the present study adds to the literature which shows that a proportion of multiple tumors, defined as second primaries by conventional clinicopathological criteria (13), are clonally related (3, 6–8, 12, 14), and we suggest that, when molecular data are available, the presence of a common clonal marker should be used as a gold standard to validate clinicopathological assessment when trying to establish the relationship of any second tumor to an index lesion.

Our results confirm that application of microsatellite assay can provide useful prognostic information (1, 3–5) and that tumors may develop at some distance from the initial preneoplastic lesion (10, 18). This highlights the need to examine and protect the entire field to minimize a patient’s risk of subsequent tumor formation. Ten cases treated with isotretinoin did not develop any new tumors after commencing therapy. This preliminary evidence suggests that instigating chemoprevention when the tissue changes are molecularly benign may have mediated progression within these extensive fields of cancerization where the phenotype is predominantly mild dysplasia.

In a recent study, Mao et al. (24) showed that AI detected in pretreatment biopsies of lesions showing moderate/severe dysplasia persisted in the majority of cases after treatment with isotretinoin, IFN-$\alpha$, and $\alpha$-tocopherol. However, the cohort of patients enrolled in the present study showed a different pattern of histological features and may have reacted differently. Nev-
Progression and Clonality in Multiple Oral Lesions

Despite the studies conducted by this group (23), and the present data, reveal that it is no longer appropriate to recommend excising dysplasia back to histologically normal margins, because morphology underestimates the true extent of the problem. On the basis of these findings and our previous studies profiling genetic aberrations associated with progression (3, 5), we recommend that all dysplastic lesions showing AI at two or more key chromosomal loci are excised, and that the presence of two lesions sharing a common clonal marker, which reveals that large patches of mucosa are derived from clonally related cells, are used to identify patients that should be targeted to receive dietary advice and chemoprevention. Provided that these cases are monitored regularly and intervention planned when necessary, the history of the carcinogenic process in these patients may span several decades, such that their overall prognosis is good.

In conclusion, our findings suggest that a subgroup of predominately female patients develop multiple low-grade lesions late in life because they have lived a relatively abstemious life and have minimal exposure to the traditional risk factors. A significant proportion of these multiple lesions are derived from lateral spread of a common precursor lesion and represent a unique presentation of SCC.

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Profiling Clonality and Progression in Multiple Premalignant and Malignant Oral Lesions Identifies a Subgroup of Cases with a Distinct Presentation of Squamous Cell Carcinoma

Max Partridge, Stelios Pateromichelakis, Elaine Phillips, et al.


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