**Polymorphous Low-Grade Adenocarcinoma of the Upper Lip: 11 cases of an Uncommon Diagnosis.**

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**Statement of Clinical Relevance**

Although PLGAs are rarely found in the upper lip, by describing the clinical and pathological features of this multi-institutional series we highlight this uncommon clinical presentation, a feature of note for both clinicians and pathologists.

**Abstract**

**Objective:** To describe an international case series of polymorphous low-grade adenocarcinoma (PLGA) affecting the upper lip.

**Material and Methods:** Over a 30-year-period the files of five pathology services were reviewed for PLGA cases affecting the upper lip. Hematoxylin and eosin-stained slides were reviewed by three oral and maxillofacial pathologists and the microscopic features were described. Clinical data were retrieved from patients' medical records.

**Results:** The review identified 11 upper lip PLGAs, with a complete set of clinical data available for 5 cases. There was male predominance (1.2:1) and a mean age of 58.7 years. Most cases presented as small asymptomatic swellings resembling benign tumors. All patients were surgically treated and no recurrence or metastases were reported in the 8 cases from which follow-up data was available. Microscopically, the typical polymorphic architectural arrangement of PLGA was seen in all cases, with lobular, trabecular, papillary and cribriform patterns identified. Perineural invasion, normal gland entrapment, Indian filing and concentric growth were frequently identified.

**Conclusion:** PLGA must be included in the list of differential diagnoses of tumors affecting the upper lip because of its similar clinical presentation to benign entities. The follow-up data available from 8 of 11 cases suggests that these tumors follow a low grade clinical course, similar to the majority of palatal cases of PLGA.

**Keywords:** Polymorphous low-grade adenocarcinoma; lip; PLGA; minor salivary glands; salivary gland tumors.

## Introduction

Salivary gland tumors are an uncommon group of neoplasms that account for approximately 3-10% of all head and neck tumors[1]. Their morphological and clinical heterogeneity is well-known, which can lead to a wide differential diagnosis and incorrect diagnoses.

Among salivary gland malignancies, polymorphous low-grade adenocarcinoma (PLGA) clearly illustrates such diagnostic difficulty. Before its original recognition as an independent entity in 1983, most cases of PLGA were included in the spectrum of adenoid cystic carcinoma (AdCC) and therefore, both entities share numerous microscopic overlaps[2-5]. On the other hand, in contrast to AdCC, PLGA is virtually restricted to the intra-oral minor salivary glands, especially from the palate, where it usually reveals an indolent growth pattern[6].

The identification of PLGA in other intra-oral sites is uncommon and when such presentation is recognized it frequently raises a range of diagnostic possibilities. Canalicular adenoma and pleomorphic adenoma are by far the most common salivary gland tumors affecting the upper lip and both entities can occasionally reveal histologic similarity to PLGA, which can uncommonly be found in this location[1, 7-10]. As a consequence, careful clinical and pathological examination should be applied to ensure a malignant salivary gland tumor is not missed.

Hence, in the current manuscript we aimed to describe the clinicopathological features of an international series of PLGA cases affecting the upper lip to better characterize this exceptionally uncommon clinical presentation.

## Material and Methods

A retrospective analysis of the archives of five diagnostic oral pathology services was carried out covering a 30-year-period from 1983 to 2013 (1996 to 2013 for the Brazilian centers). The units supplying cases were specialist Oral and Maxillofacial Pathology Services, namely: Piracicaba Dental School, UNICAMP (Brazil), Oral and Maxillofacial Surgery and Traumatology Service, University of São Paulo (Brazil), School of Clinical Dentistry, University of Sheffield (UK), School of Dentistry, University of Pretoria (South Africa) and Texas A&M University Baylor College of Dentistry. (Dallas, USA). Databases of all departments were reviewed for salivary gland malignancies and cases diagnosed as PLGA involving the upper lip were retrieved. New 4µm, hematoxylin and eosin (H&E)-stained sections were reviewed by three oral pathologists to confirm the original diagnoses conformed to the guidelines of the World Health Organization Classification of Salivary Gland Tumors[11]. Demographic data including gender, age, ethnicity, symptomatology, duration, size, treatment and follow-up were gathered from patients' medical records. During histological examination, data

regarding microscopic pattern, presence of Indian filing, concentric growth, perineural invasion, entrapment of normal glands, pattern of invasion and stromal features were carefully described.

**Results**

Following our retrospective archive retrieval, 12 cases originally diagnosed as PLGA affecting the upper lip were identified. After careful histological review (KDH, FF and DB), one case was excluded from the study as its appearances were more consistent with low grade carcinoma ex-pleomorphic adenoma. Eleven cases remained for analysis, although a full set of clinical data was only available for 5 of these cases. The relative incidence of upper lip PLGA diagnoses in the context of overall case load and other salivary gland tumours diagnosed are presented in Table 1. Further detailed data on the incidence of salivary gland tumours from Sheffield have been previously published[12].

**Table 2** summarizes the demographic data obtained with the final sample. The male-to-female ratio was 1.2:1, the mean age was 58.5 years (median: 56 years, range from 41 to 77 years). Where patient reported data was available (n=6), the tumors were predominantly asymptomatic (n=5), but in one case the patient reported a numb sensation. A mean time of duration of 20.6 months (range 1 – 48 months) was reported by patients and during clinical examination lesions presented as submucosal, slow-growing, small diameter tumors **(Figure 1A)**, although one large neoplasm was also found **(Figure 1B)**. Surgery was the therapeutic modality applied for all patients whose treatment data was available and no recurrence or metastases were described in the 8 cases for whom follow-up data was available.

Microscopic features of cases are depicted in **Table 3**. Some tumours were markedly multilocular, particularly the larger ones. Some had been excised with overlying oral mucosa and the tumours have a variable relationship with this: some extended very close whilst in others there was a clear zone of connective tissue separation. No ulceration was noted in any of these cases. In keeping with the polymorphous description, all described histologic growth patterns could be found in the cases presented with the lobular subtype the most frequently encountered. Focal cribriform or trabecular areas were identified in most tumours and papillary cystic areas were occasionally noted. The ductal structures in the trabecular form were single layered, with no apparent luminal and ab-luminal components. Presence of Indian filing (54.5%), perineural invasion (54.5%) **(Figure 1C),** concentric growth (36.4%) **(Figure 1D)** and entrapment of normal glands (36.4%), all features often described in cases of PLGA, were also variably seen in our samples. A collagenous stromal

compartment was the most frequently described, but no marked stromal desmoplasia was identified. In some cases, tumor islands were embedded in a surrounding myxo-collagenous stroma.

Cytologically, the neoplastic cells presented the typical bland “washed-out”, round nuclear appearance, with scattered evident nucleoli only occasionally found. Nuclear pleomorphism and mitoses were largely absent and only focal hyperchromasia was noted. Most tumors displayed a pushing type of infiltration into the surrounding structures, however some, showed infiltration of small islands of tumour into the adjacent minor salivary gland tissue (for example, case 1) or fat (for example, case 5). Figure 2 shows representative photomicrographs from cases 1, 4, 6 and 9. The virtual microscopy images for these case are available as supplementary material

**Discussion**

PLGA is an uncommon malignant salivary gland tumor that reveals an indolent clinical behavior and only rarely develops local or distant metastases. It is virtually always diagnosed in minor glands of the oral cavity, and the palate is by far the most affected subsite[13]. In the current paper we describe the pathological and microscopic features of a number of cases of this unusual clinical presentation of PLGA, highlighting the importance of including such entity in the list of differentials before and during clinical management of these patients. Although most epidemiologic studies describe involvement of other intra-oral locations, PLGA cases involving the upper lip only rarely are described in these studies. There are less than 20 cases in the published literature presented as individual case reports and in case series of minor salivary gland tumours or PLGA generally [8-10, 14-19]. There are currently only two published cases presenting similar detail: in each case, the patient was an elderly female, and in one, the lesion recurred[14, 15]. In the larger series, the data is not presented in sufficient detail to bear direct comparison with our cases, but the overall proportions of PLGAs and frequency of the lesion in the upper lip are comparable to that seen in the contributing centers of this series. The clinical data for some of these cases is, unfortunately, incomplete as was also the case in our series (table 2).

The low grade behavior of most PLGAs is consistent with its clinical presentation. As with previous descriptions of PLGA[20], in the current sample we found submucosal slow-growing lesions with a steady evolution, some present for 4 years duration and most commonly presenting as small diameter neoplasms, although one occasional case presented as a large telangiectatic tumor. El-Naaj *et al*.[6] reported that PLGA cases affecting the lip tend to present in smaller sizes, possibly due to an earlier recognition by the patient. Despite its hallmark microscopic feature of neural involvement, pain or paresthesia is usually not reported by the patients[10]. This was exemplified in our series, where

numbness of the affected lip was described by only one patient, suggesting that the simple histologic presence of perineural growth might not be a reliable parameter to predict a painful clinical presentation of this lesion. A similar observation in AdCC was reported by Speight and Barrett (2009)[21] where only 25% of the cases demonstrating nerve involvement seemed to be associated with clinical signs and symptoms. In contrast, other neurotropic malignancies like pancreatic carcinoma demonstrate a strong association between perineural invasion and pain[22]. Hence, since we failed to identify any well conducted study investigating such association in the context of PLGA, and considering that pain and perineural invasion are clinicopathological features frequently evaluated as prognostic determinants, we believe that a better understanding of their direct correlation might be of relevance to improve the knowledge about the clinical and biological behavior of PLGA, demanding, therefore, further efforts and investigations in this line.

The male predominance observed in our study is in contrast to the frequently female preponderance described for PLGA[13, 20]. On the other hand, most of our patients were diagnosed in the sixth and seventh decades of life, which was in accordance with general PLGA descriptions[20]. Despite pooling cases from four continents, 9 of the 11 patients were white which limits the possible variation due to differing ethnicities. All patients with treatment data available had surgery to remove the lesions with no signs of recurrence nor regional or distant metastases during their follow-up period, although this data was not available for all patients. This confirmed the indolent behavior of this tumor and that surgery is the current therapeutic approach for patients affected by PLGA[13, 20]. The absence of distant spread of PLGA is an important feature that distinguishes it from the recently recognized cribriform adenocarcinoma of the tongue/minor glands (CATS) [23], which is characterized by a more aggressive behavior with frequent metastases and recurrences. The dominant cribriform architecture and nuclear features similar to papillary thyroid carcinoma described in CATS[18] were not present in our PLGA case series. The recently described PRKD1 mutations in PLGA may further help to define this entity in cases where there is diagnostic uncertainty[24].

It is important that PLGA forms part of the differential diagnosis of salivary gland tumours of the upper lip, despite their preponderance in the palate. Special attention for distinguishing PLGA from the more common benign tumors affecting the upper lip including pleomorphic adenoma and canalicular adenoma is also warranted, especially in small biopsy specimens, although in some cases this may prove difficult. No specific clinical feature can be found in PLGA to differentiate it from its benign counterparts, although the presence of the telangiectasia on the surface of the tumor has previously been suggested as an indicator of malignancy[25]. Although PLGA is rarely found in the upper lip, by describing the clinical and pathological features of this multi-institutional series we

highlight this uncommon clinical presentation, a feature of note for both clinicians and pathologists. In our series, none of the tumours for which we had follow up data recurred, emphasizing low-grade behavior.

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## Figure Legends

**Figure 1.** Clinical and microscopic features of upper lip PLGA. **A)** Cases more commonly presented as a small, normal colored and non-ulcerated nodules resembling benign tumors. This photograph is from case 3. **B)** More aggressive appearing lesions were also found. In this case the tumor exhibited larger size with an irregular and telangiectatic surface (Case 4). **C)** Perineural involvement was a frequent microscopic finding in the sample analyzed (example from case 4). **D)** Concentric growth pattern was found in 36.4% of the cases (example from case 4).

**Figure 2.** Representative photomicrographs of Case 1 (A&B), showing entrapment of minor salivary gland (A) and a concentric growth pattern round an entrapped duct (B); Case 4 (C&D), showing a lobular growth pattern (C) and a focus of perineural infiltration (D); Case 5 (E&F), showing infiltration into adjacent fat (E) and mixed growth pattern, including cribriform areas and focal ducts (F); Case 9 (G &H), showing cribriform islands of tumour (G) and peripheral “Indian filing” (H). High resolution version of the images are available as eSlide: VM00426 (Case 1). eSlide: VM00427 (Case 4); eSlide: VM00428 (Case 5); eSlide: VM00429 (Case 9)

## Table legends

**Table 1.** Details of the Pathology services presenting cases to this series, including the incidence of all minor salivary gland tumours, total PLGAs (all sites) and salivary gland tumours in the upper lip, accessioned from 1983 to 2013 (Sheffield, Dallas and Pretoria) and 1996-2013 (Brazil: [a]shorter time presented due to lack of consistent records). [1]includes: Pleomorphic adenoma (46), Basal Cell adenoma/Canalicular Adenoma (55), PLGA (4), Adenoid Cystic carcinoma (9), Mucoepidermoid Carcinoma (1), Adenocarcinoma NOS (4) and Carcinoma-x pleomorphic adenoma (1). [2]includes: PLGA (1). No further breakdown available. [3]includes: 1 adenoid cystic carcinoma (1), Canalicular adenoma (8), Pleomorphic Adenoma (4), and PLGA (3). [4]includes: Pleomorphic adenoma (30), PLGA (3), Adenoid Cystic carcinoma (2), Carcinoma-x pleomorphic adenoma (1), Canalicular adenoma (5), Mucoepidermoid carcinoma (1), Papillary cystadenoma (1).

**Table 2.** Clinical features of PLGA cases affecting the upper lip. NK = Not Known; NED = No Evidence of Disease

**Table 3.** Microscopic findings of PLGA cases affecting the upper lip. High resolution version of the images marked * are available as eSlide: VM00426 (Case 1). eSlide: VM00427 (Case 4); eSlide: VM00428 (Case 5); eSlide: VM00429 (Case 9)

| | Sheffield | Dallas | Pretoria | Brazil[a] |
|---|---|---|---|---|
| Total accessioned cases | 55750 | 145710 | 29603 | 24313 |
| Number of minor salivary tumours | 463 | 728 | 461 | 254 |
| Number of PLGAs (total) | 72 | 16 | 44 | 23 |
| Number of upper lip minor gland tumours | 120[1] | 77[2] | 16[3] | 43[4] |
| Number of upper lip PLGAs | 4 | 1 | 3 | 3 |

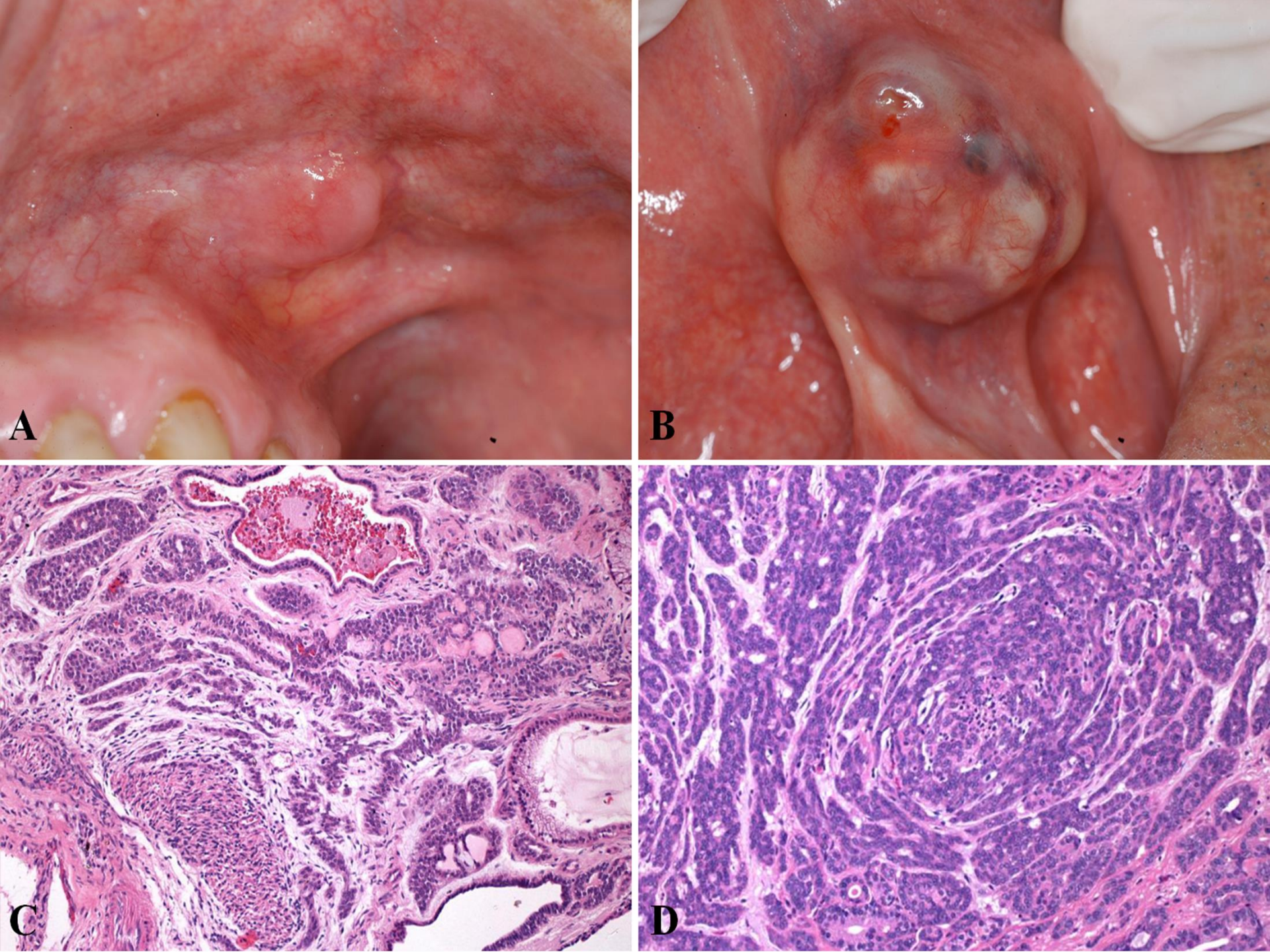
Table 1

| Case | Country | Sex | Age | Ethnicity | Symptomatology | Duration (Months) | Size (cm) | Treatment | Margins | Follow-up |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | USA | Male | 46 | White | Asymptomatic | 1 | 0.5 x 0.4 x 0.4 | Surgery | clear | NED: 2 years |
| 2 | Brazil | Male | 70 | White | Asymptomatic | 24 | 2.0 x 2.0 x 0.8 | Surgery | clear | NED: 8 years |
| 3 | Brazil | Male | 70 | White | NK | 36 | 0.3 x 0.3 x 0.2 | Surgery | clear | NED: 8 years |
| 4 | Brazil | Female | 41 | White | Asymptomatic | 48 | 2.0 x 2.0 x 1.0 | Surgery | clear | NED: 6 years |
| 5 | South Africa | Female | 56 | White | NK | 8 | 1.5 x 1.0 x 0.5 | Surgery | clear | NED: 4 years |
| 6 | South Africa | Male | NK | Black | Asymptomatic | NK | 3.0 x 2.0 x 2.0 | Surgery | involved | NED: 3 years |
| 7 | South Africa | Male | 55 | Black | NK | NK | 5.0 x 4.0 x 3.0 | Surgery | involved | NK |
| 8 | UK | Female | 51 | White | Asymptomatic | 6 | 0.7 x 0.7 x 0.3 | Surgery | fragmented | NK |
| 9 | UK | Male | 51 | White | NK | NK | 1.2 x 1.0 x 0.6 | Surgery | clear | NED: 5 years |
| 10 | UK | Female | 77 | White | Numbness | 6 | 2.0 x 1.1 x 0.8 | Surgery | clear | NED: 6 years |
| 11 | UK | Female | 68 | White | NS | 36 | 1.1 x 1.0 x 0.9 | Surgery | incisional only | NK |

**Table 2.** Clinical features of PLGA cases affecting the upper lip. NK = Not Known; NED = No Evidence of Disease

| Case | Microscopic Pattern(s) | Pattern of invasion | Indian filing | Concentric growth | Entrapment of normal glands | Perineural invasion | Stromal features |
|---|---|---|---|---|---|---|---|
| 1* | Lobular | Pushing pattern with areas of infiltration | Yes | Yes | Yes | Yes | Collagenous |
| 2 | Lobular/Trabecular/Papillary | Infiltrative | No | No | Yes | Yes | Collagenous/Hyalinized |
| 3 | Trabecular/Lobular | Pushing pattern and infiltrative areas | No | No | Yes | No | Collagenous/Hyalinized |
| 4* | Lobular/Trabecular | Pushing pattern and infiltrative areas | Yes | Yes | No | Yes | Collagenous |
| 5* | Lobular/Cribriform | Pushing pattern, well circumscribed tumor | No | No | No | Yes | Mucoid |
| 6 | Lobular | Pushing pattern with areas of infiltration | Yes | Yes | No | Yes | Hyalinized |
| 7 | Cribriform/Lobular/Papillary | Pushing pattern | No | Yes | No | Yes | Mucoid/Collageneous/Hyalinized |
| 8 | Lobular/Trabecular | Pushing pattern | No | No | No | No | Hyalinized |
| 9* | Cribriform/Lobular | Pushing pattern | Yes | No | No | No | Collagenous/Hyalinized |
| 10 | Trabecular/Cribriform | Pushing pattern | Yes | No | Yes | No | Collagenous |
| 11 | Lobular/Cribriform/Papillary | Pushing pattern | Yes | No | No | No | Collagenous |

**Table 3.** Microscopic findings of PLGA cases affecting the upper lip. Virtual microscopy images are available for cases marked *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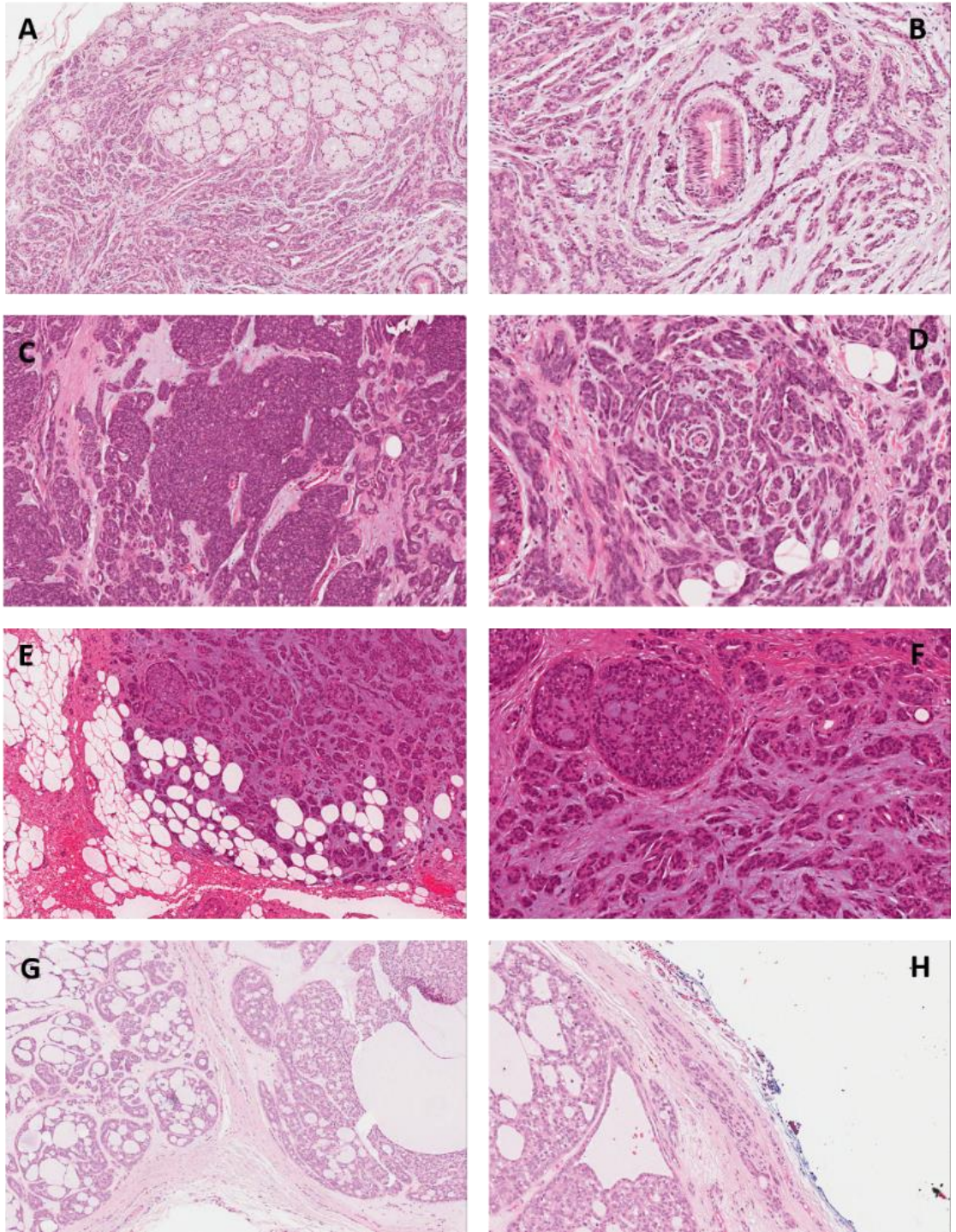
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