oral

MDPI

Systematic Review

The "Epulis" Dilemma. Considerations from Provisional to Final Diagnosis. A Systematic Review

Paola Costa [1,†], Matteo Peditto [1,†], Antonia Marcianò [2,*], Antonio Barresi [1] and Giacomo Oteri [1]

[1] Postgraduate School of Oral Surgery, Department of Biomedical, Dental Sciences and Morphofunctional Imaging, University of Messina, 98125 Messina, Italy; pa.costa@hotmail.it (P.C.); matteopeditto@gmail.com (M.P.); barresiantonio@hotmail.it (A.B.); giacomo.oteri@unime.it (G.O.)
[2] Department of Clinical and Experimental Medicine, University of Messina, 98125 Messina, Italy
* Correspondence: antmarciano@unime.it
† These authors contributed equally to this paper.

Abstract: "Epulis" is a widely used term to describe a localized gingival enlargement. However, a wide range of neoformations might present as localized, slow-growing, asymptomatic gingival masses. A systematic review was conducted to outline the pathological entities that were provisionally dignosed as "epulis" and whose final diagnosis was made after microscopic examination. An electronic search of PubMed, Google Scholar and Scopus databases from January 2000 to February 2021 was performed. An initial search of the databases identified a total of 864 documents, and after a careful process of screening and selection, 14 studies were included in this systematic review and processed for data extraction. The results show that histological examination, sometimes combined with immunohistochemistry, might reveal a wide spectrum of lesions, including hamartomatous lesions, non-neoplastic lesions, benign and malign neoplasms and metastases from distant cancers.

Keywords: epulis; gingival overgrowth; oral tumor; provisional diagnosis; reactive lesions; histology; immunohistochemistry

Citation: Costa, P.; Peditto, M.; Marcianò, A.; Barresi, A.; Oteri, G. The "Epulis" Dilemma. Considerations from Provisional to Final Diagnosis. A Systematic Review. *Oral* **2021**, *1*, 224–235. https://doi.org/10.3390/oral1030022

Academic Editor: Francisco Javier Silvestre

Received: 8 June 2021
Accepted: 28 July 2021
Published: 5 August 2021

1. Introduction

Localized, slow-growing, asymptomatic gingival masses are commonly indicated as "epulis". The usage of the term "epulis" as a diagnosis is well established among clinicians. However, the diagnosis of "epulis" is simplistic and inaccurate [1]. In fact, "epulis", from the Greek ἐπουλίς, literally means "over the gingiva". Thus, the term refers to the location of the neoformation and does not represent a specific pathological entity.

The occurance of masses over the gingiva may be due to different types of underlying pathological changes [2]. According to etiologic factors and pathologic changes, gingival enlargments can be classified as: inflammatory enlargements, drug-induced enlargements, enlargements associated with systemic diseases or conditions, neoplastic enlargements and false enlargements [3].

Localized enlargements can be further divided into three sub-types [3]:

- Isolated (enlargements limited to gingiva adjacent to one or two teeth);
- Discrete (isolated sessile or pedunculated enlargements);
- Regional (enlargements that involve gingiva around three or more teeth in one or multiple areas of the mouth).

Reactive lesions, or focal reactive overgrowth of the gingiva (FROG) [4], are the most common neoformations that lie beneath the so-called "epulis" [4,5].

Those neoformations are: pyogenic granuloma, peripheral giant cell granuloma, giant cell fibroma, fibrous hyperplasia and peripheral ossifying fibroma. They do not have a neoplastic origin and represent an exaggerated repairing and remodeling response to stimulus [6–11].

Drug-induced enlargements are mainly due to anti-convulsants, calcium channel blockers and immunosuppressants [12,13].

Systemic diseases or conditions exaggerate the usual gingival response to local irritation [2]. Localized gingival overgrowths that appear during pregnancy are often called "pregnancy tumor" or "granuloma gravidarum". The pathogenesis is thought to be related to the increase in sex hormones that might stimulate the synthesis of angiogenic growth factors [12,14].

Localized gingival enlargemnts have been reported in patients with neurofibromatosis, Sturge–Weber syndrome and leukemia [12,15,16].

Neoplastic enlargements can be benign or malignant [1]. Among the benign entities are nerve sheath tumors, such as neuroma and schwannoma, and vascular tumors, such as hemangioma. Among the malignant entities are verrucous carcinoma, lymphoma, sarcomas and metastasis [1].

Masses originated from different pathological changes might look very similar in shape and color. They take the form of a discrete sessile or pedunculated mass which, in dentate patients, occurs on the interdental papilla, the buccal or the palatal/lingual surface of a tooth, whereas in edentulous or partially dentate patients, it occurs on the alveolar ridge and might be close to an ill-fitting prostheses. The color may vary considerably (pink, pale pink, red or blue) [2].

Thus, the histopathological exam and, when appropriate, an immunohistochemical evaluation are mandatory to make a correct diagnosis [1,17,18].

The management of the patient should never be underestimated and depends on the nature of the lesion. Based solely on the clinical aspect, local gingival enlargements might be misdiagnosed [19]. To rationally approach these neoformations, the clinician should own a comprehensive knowledge of the pathological entities that might occur over the gingiva.

Hence, the aim of this review is to point out those pathological entities that, after the clinical evaluation, were provisionally dignosed as "epulis" and whose final diagnosis was made after the microscopic examination.

2. Materials and Methods

The study has been registered in the international prospective register of systematic reviews, PROSPERO—registration number CRD42021241595.

2.1. Eligibility Criteria

Inclusion criteria:

- Scientific articles published from January 2000 to February 2021;
- Scientific articles published in English language;
- Case reports and case series;
- Mention of provisional diagnosis of "epulis";
- Final diagnosis supported by histological/immunohistochemical analysis.

Exclusion criteria:

- Papers with no clear report of clinical case;
- No provisional diagnosis of "epulis";
- Lesions not in oral cavity or in a location not well specified in title and/or abstract;
- Animal studies;
- In vitro studies;
- Final diagnosis not supported by histological/immunohistochemical analysis.

2.2. Literature Search Strategy

A systematic search of the literature was performed using PubMed and Google Scholar databases. Search strategies are highlighted in Table 1.

Table 1. Search strategies.

Database	Search Terms
PubMed	epulis AND (oral OR gingiva) AND (immunohistochemistry AND histology)
Google Scholar	"epulis *" AND ("oral" OR "gingiva *") AND ("immunohistochemistry *" AND "histology *")
Scopus	epulis AND oral * OR gingiva * AND immunohistochemistry * AND histology *

Note: *. Multiple spelling variations.

2.3. Study Selection

The search strategy for identification of relevant studies following the PRISMA guidelines is presented in Figure 1.

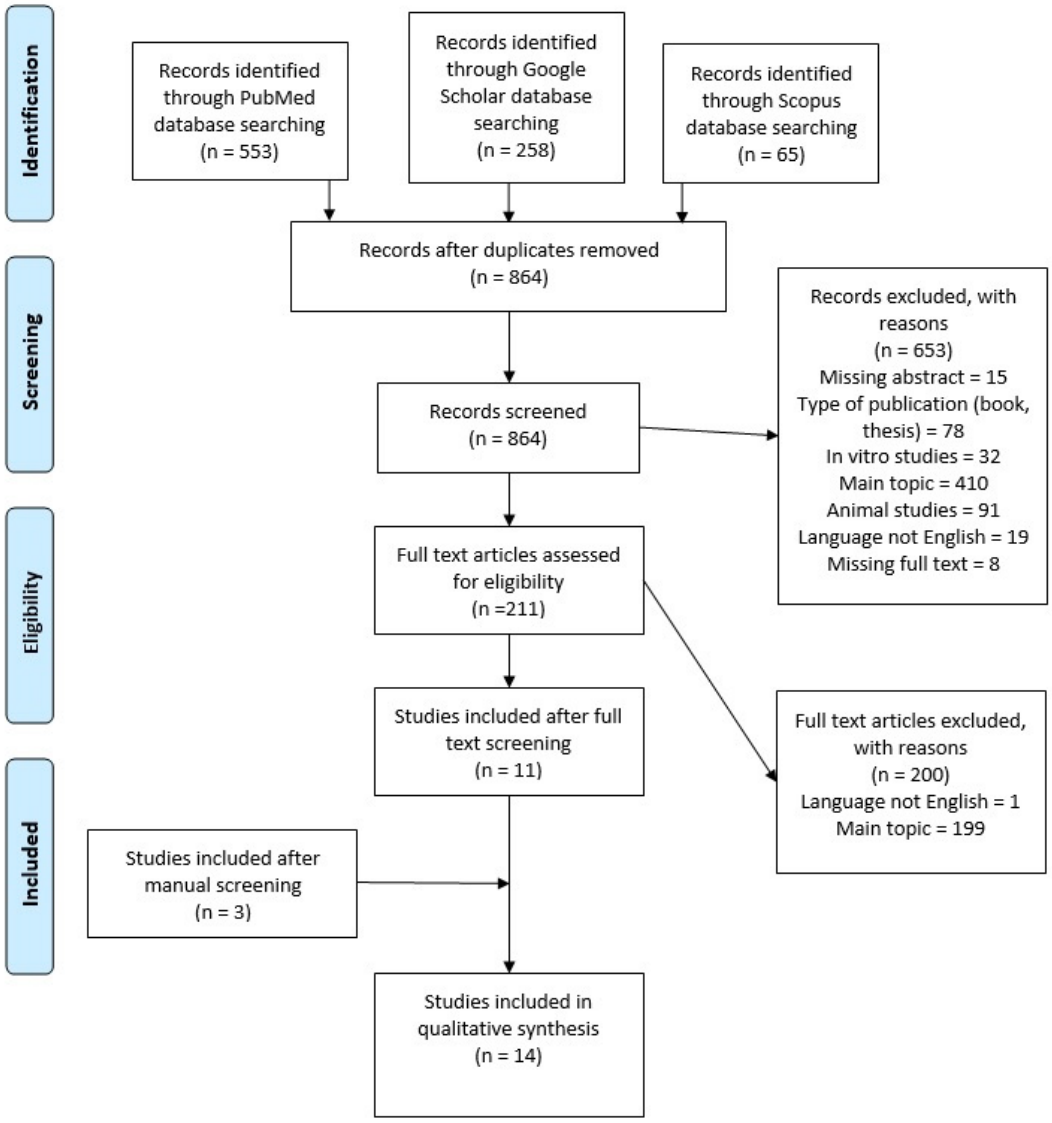

Figure 1. PRISMA flow diagram.

An initial search of PubMed, Google Scholar and Scopus databases identified a total of 876 documents. Twelve records were excluded because they were duplicates. Titles and abstracts of retrieved studies were screened and all the studies that did not meet the inclusion criteria were excluded. Thus, 653 records were excluded after reading titles and abstracts due to type of publication (book or thesis), main topic, in vitro studies, animal

studies, language (other than English) and incapability to retrieve the abstract and/or the full text.

The full texts of 211 articles were then screened, and 199 articles were excluded because the main topic was not relevant for the purpose of this review and 1 record was excluded because the full text was not in English. Furthermore, a manual search of the reference lists of all selected studies was performed and 3 studies were additionally included after full-text reading. The articles selected for full-text reading were examined from two authors and those that were lacking relevant information for the purpose of this review were excluded. Any controversy was resolved with the aid of a third reviewer, selected among the authors.

Ultimately, 14 studies were included in the systematic review and processed for data extraction.

2.4. Risk of Bias

In order to evaluate the methodological quality of included studies, reviewers used the JBI Critical Appraisal Checklist for Case Reports Studies (Table 2). Items 1, 6, 7, 9 and 10 were not useful for the purpose of this review, thus items 2, 3, 4, 5 and 8 were used in the quality assessment.

Table 2. JBI Critical Appraisal Checklist for Case Reports Studies.

JBI Critical Appraisal Checklist for Case Reports
1. Were the patient's demographic characteristics clearly described?
2. Was the patient's history clearly described and presented as a timeline?
3. Was the current clinical condition of the patient on presentation clearly described?
4. Were diagnostic tests or assessment methods and the results clearly described?
5. Was the intervention(s) or treatment procedure(s) clearly described?
6. Was the post-intervention clinical condition clearly described?
7. Were adverse events (harms) or unanticipated events identified and described?
8. Does the case report provide takeaway lessons?

3. Results

3.1. Quality Analysis of the Included Studies

Quality analysis showed that all the studies but one were highly valuable for the purpose of this review (Table 3).

Based on the items used in the quality assessment, the studies finally included in this review comprised:

- Patient's history inclusive of any systemic disease, drug taken, pregnancy, previous diagnosis of malignant tumors or specification of state of good health;
- Occurrence and evolution of the neoformation as well as description of location, extension, shape, size, margins, color, surface and consistency;
- Provisional diagnosis of "epulis" or "epulis" considered in differential diagnosis with other lesions;
- Radiographic examinations (if taken);
- Surgical treatment and type of biopsy (incisional or excisional);
- Histological evaluation;
- Immunohistochemical evaluation (if perfomed);

Table 3. Summary of the JBI Critical Appraisal Checklist for Case Reports Studies for the selected studies.

Authors	Items					Overall Appraisal
	2	3	4	5	8	
Alqahtani et al. (2013) [20]	Y	Y	Y	Y	Y	Included
Chiarelli et al. (2012) [21]	Y	Y	Y	U	Y	Included
Jeyaraj et al. (2013) [22]	Y	Y	Y	Y	Y	Included
Kawamura et al. (2007) [23]	Y	Y	Y	U	Y	Included
Lu et al. (2020) [24]	Y	Y	Y	Y	Y	Included
Montebugnoli et al. (2010) [25]	Y	Y	Y	Y	Y	Included
Moser et al. (2011) [26]	Y	Y	Y	Y	Y	Included
Raghunath et al. (2016) [27]	Y	Y	Y	Y	Y	Included
Shah et al. (2009) [28]	Y	U	Y	Y	Y	Included
Sowmya et al. (2015) [29]	U	Y	Y	Y	Y	Included
Sumida et al. (2012) [30]	N	Y	Y	U	Y	Included
Tripathi et al. (2017) [31]	Y	Y	Y	Y	Y	Included
Truschnegg et al. (2016) [32]	U	Y	Y	Y	Y	Included
Wu et al. (2017) [33]	Y	Y	Y	U	Y	Included
Kalele et al. (2016) [34]	N	N	N	N	Y	Not Included

Legend: Y = yes, N = no, U = uncertain.

3.2. Data Extraction

The data extracted from the fully read articles included: provisional diagnosis, final diagnosis and location of the lesion (Table 4).

Table 4. Data extracted from included studies.

Authors	Provisional Diagnosis	Final Diagnosis	N. of Cases	Localization	
				Maxilla	Mandible
Alqahtani et al. [20]	Epulis	Leiomyomatous hamartoma	1	1	
Chiarelli et al. [21]	Epulis	Metastasis from breast angiosarcoma	1		1
Jeyaraj et al. [22]	Pyogenic granuloma Peripheral giant cell reparative granuloma Fibrous epulis Giant cell epulis Fibroma	Plasma cell granuloma	1	1	
Kawamura et al. [23]	Epulis	Metastasis from rectal cancer	1	1	
Lu et al. [24]	Epulis	Plasma cell granuloma	1	1	
Montebugnoli et al. [25]	Fibrous epulis	Low-grade myofibroblastic sarcoma	1		1

Table 4. *Cont.*

Authors	Provisional Diagnosis	Final Diagnosis	N. of Cases	Localization	
				Maxilla	Mandible
Moser et al. [26]	Epulis Pyogenic granuloma peripheral giant cell Lipoma Myxoma Neurofibroma Schwannoma Leiomyoma	Metastasi from malignant mesothelioma	1		1
Raghunath et al. [27]	Fibrous epulis Pyogenic granuloma Peripheral giant cell granuloma	Leiomyomatous hamartoma of the maxilla	1	1	
Shah et al. [28]	Epulis	Metastasis from breast cancer	1	1	
Sowmya et al. [29]	Epulis	Oral focal mucinosis	1		1
Sumida et al. [30]	Epulis	Angiosarcoma	1		1
Tripathi et al. [31]	Pyogenic granuloma peripheral giant cell GranulomaFibrous epulis	Plasma cell granuloma	1		1
Truschnegg et al. [32]	Epulis	Peripheral ossifying fibroma	30	17	13
		Fibroma/fibrosis	27	15	12
		Giant cell lesion	12	6	6
		Granuloma pyogenicum	8	3	5
		Hyperplastic squamous epithelium	7	5	2
		Granulation tissue	5	3	2
		Peripheral odontogenic fibroma	3		3
Wu et al. [33]	Epulis	Metastasis from gastric adenocarcinoma	1	1	

3.3. Main Results of the Review

From the 105 selected clinical cases, 101 lesions were initially diagnosed as epulis. As per the remaining four, epulis was considered in the differential diagnosis alongside reactive lesions and/or benign tumors. Three authors reported that the tentative diagnosis of epulis was made by the family dentist rather than the clinical center of reference. The following final diagnosis were made after histological examination of the excised samples:

- Peripheral ossifying fibroma;
- Fibroma/fibrosis;
- Giant cell lesion;
- Granuloma pyogenicum;
- Hyperplastic squamous epithelium;
- Granulation tissue;
- Peripheral odontogenic fibroma;
- Leiomyomatous hamartoma;
- Plasma cell granuloma;
- Oral focal mucinosis;
- Low-grade myofibroblastic sarcoma;

- Angiosarcoma;
- Metastasis of malignant mesothelioma;
- Metastasis from breast cancer;
- Metastasis from gastric adenocarcinoma;
- -Metastasis from rectal cancer;
- Metastis from breast angiosarcoma.

4. Discussion

Localized chronic gingival enlargements are frequently detected by clinicians and the management requires a rational approach. These neoformations occur with the following characteristics [1–3,20–33,35,36]:

- Develop on the buccal/palatal/lingual side or extent from buccal to palatal/lingual side along the interdental papillae;
- Self-limited and solitary growth;
- Progressively increasing in size over a variable period of time;
- Variable size (usually about 1 or 2 cm in diameter);
- Nodular/ovoid shaped;
- Smooth or irregular surface;
- Well-defined margins;
- The same color as the surrounding normal mucosa/pale pink/red/blue;
- Sessile or pedunculated;
- Soft/hard on palpation;
- Spontaneous bleeding/ulcerated surface might be present.

A careful collection of data regarding the medical history of the patient must always be the first step to take in the process that will lead the clinician to the final diagnosis. Sometimes the medical history might be not relevant at all, whereas at other times it might be of great help.

As regards the patient's medical history, the clinician should investigate the following aspects [37]:

- Systemic diseases;
- Medications taken;
- Pregnancy;
- Previous diagnosis of malignant tumors.

A previous diagnosis of a malignancy at a distant site should make the clinician consider the possibility that a metastasis occured over the gingiva [36,38].

Time of appearance, eventual recurrence, any change in shape, color and consistency and spontaneous bleeding and ulceration are relevant details.

Clinical examination must include a good descriptive evaluation of the neoformation as well as the assessment of oral hygiene and the presence of traumatic factors [32]. With the sole clinical examination, a provisional and not a definitive diagnosis might be formulated. The term "epulis" can be provisionally used to describe the overgrowth that occurs over the gingiva. Surgical treatment should be preceded by cause-related therapy and elimination of plaque retentive factors in attempts to modify etiological factors. The choice between an excisional or incisional biopsy might be challenging. Incisional biopsy instead of complete excision of the lesion should be taken into consideration when one or more of the following features are present [17,23,25,26,28,30]:

- Persistent ulceration;
- Multiple and irregularly spherical in shape enlargements;
- Induration or fixation over time;
- Unusual pigmentation;
- Lymphadenopathy;
- Unexplained tooth mobility,
- Paraesthesia;

- Irregular bone loss at radiographic examination;
- History of cancer.

A detailed investigation through a histopathological examination is mandatory for the final diagnosis. Immunohistochemical evaluation is also of great help, especially in the most challenging scenarios.

The microscopic evaluation might reveal a wide spectrum of lesions, including hamartomatous lesions, non-neoplastic lesions, benign and malign neoplasms and metastases from distant cancers.

Hamartomas are rare findings in the oral cavity and may derive from various tissues [39].

ALQahtani et al. [20] and Raghunath et al. [27] diagnosed an oral leiomyomatous hamartoma that arised over the gingiva. ALQahtani et al. [20] reported that the patient was in good health and the lesion appeared as a polypoid, pedunculated, light pink and soft swelling. A complete excision of the lesion was performed. The diagnosis was made thanks to histological and immunohistochemical investigations. Masson's trichrome staining allowed the authors to distinguish the smooth-muscle cells (red-stained) from the surrounding collagen fibers (blue-stained). Smooth-muscle bundles stained positive for smooth-muscle actin and desmin.

Raghunath et al. [27] reported that the patient's medical history was not relevant for the final diagnosis and the lesion appeared 6 months earlier, measured about 1.5 × 2 cm and was smooth surfaced, sessile, ovoid and soft. The lesion was completely excised. Van Gieson stain was used to differentiate the smooth muscle bundles, which stained yellow, from the collagen bundles, which stained red.

Jeyaraj et al. [22], Tripathi et al. [31] and Lu et al. [24] diagnosed a plasma cell granuloma. Plasma cell granuloma is a non-neoplastic lesion characterized by the infiltration of plasma cells, which represents the major cellular population in this type of lesion [40]. Jeyaraj et al. [22] reported a mass appearing as pinkish red, lobulated, oval, non-tender and pedunculated. Patient medical history was defined as "not contributory" for the diagnosis. The lesion was completely removed. Histological investigation showed the characteristic appearance of the plasma cells. Immunohistochemical investigation of the specimen was also perfomed: numerous cells of the connective tissue showed strong immunohistochemical positivity for CD-138, thus were confirmed to be plasma cells, and immunoglobulins by the plasma cell population expressed the lambda and kappa light chain, thus were confirmed to be polyclonal and of an inflammatory origin. Tripathi et al. [31] reported a nodular, sessile, solitary growth, measuring 2.0 cm × 1.5 cm, that occurred over the buccal gingiva of a patient in good health. The growth increased in size over a period of 8–9 months and was completely removed during surgery. The immunohistochemical evaluation showed high expression of kappa light chain and low expression of lambda chain. Plasma cell granuloma usually occurs as a solitary lesion. Lu et al. [24] reported an unusual case of plasma cell granuloma characterized by multiple gingival masses. The patient was in good health. Immunohistochemical stain revealed dense polyclonal plasma cell infiltration with positive expression of both kappa and lambda light chains.

Sowmya et al. [29] made the provisional diagnosis of "epulis" for a well-defined, pinkish, pedunculated, roughly ovoid-shaped, non-tender growth that occurred on the buccal gingiva and increased in size over a period of 3 months. The mass was completely excised. The final diagnosis of oral focal mucinosis was made after histological and immunohistochemical examinations. Immunohistochemistry ruled out other myxomatous lesions of neural origin, because cells stained positive for vimentin and negative for S-100.

Truschnegg et al. [32] reported a clinical and histopathological evaluation of a series of gingival growths defined as "epulides". Clinical investigation included periodontal evaluation by local probing of the gingival sulcus to reveal periodontal inflammation and occlusal check-up to detect occlusal trauma. Before surgical biopsy of the mass, all patients underwent periodontal pre-treatment and correction of the occlusal trauma if it was detected. Histopathological examination of the specimens solely was sufficient to make the final diagnosis, among which were lesions that belonged to the spectrum of

"reactive lesions", peripheral odontogenic fibromas, granulation tissue or hyperplastic squamous epithelium.

Montebugnoli et al. [25] reported a case of a low-grade myofibroblastic sarcoma. The patient's medical history was defined as "not meaningful" for the diagnosis. The mass was lobulated, hard on palpation, fixed on the underlying tissues, ulcerated and painful. Incisional biopsy was performed. Histological examination suggested the diagnosis of low-grade myofibroblastic sarcoma, since the specimen showed the presence of neoplastic cells immersed in a myxoid stroma and areas of necrosis and calcifications. Immunohistochemical examination revealed that the neoplastic cells were diffusely vimentin positive, focally smooth muscle actin and desmin positive and cytokeratin, CD34 and CD21 negative. Intratumoral dendritic reticular cells were positive for S-100 protein. Based on the histological and immunohistochemical examination, they made the final diagnosis of low-grade myofibroblastic sarcoma. In order to detect any bone-destructive activity an orthopantomography, a CT scan was performed. The systemic spread of the neoplasm was investigated through positron emission tomography.

Sumida et al. [30] reported a case of angiosarcoma that appeared as a well-defined, white-pink in color, soft mass with easy bleeding. The tumor cells were positive for factor VIII-related antigen, CD31, αSMA and vimentin, and negative for pancytokeratins, S100 protein, neuron-specific enolase and CD56. The Ki-67 labeling index was measured and it was more than 50%.

The oral cavity is an uncommon site for metastatic colonization. The development of tumor metastases in the oral cavity accounts for 1 to 3% of all the malignancies of the head and neck region [41].

Oral metastasis might be the first indication of an occult malignant tumor [42]. The sites of the primary tumor might be lung, kidney, liver and prostate for men, and breast, female genital organs, kidney and colo-rectum for women [43]. Oral metastatic lesions are divided into mucosal and jawbone metastases. The jawbones are more affected than the oral soft tissues [44].

Mucosal metastases over the gingiva might resemble a reactive lesion [17]. Fukuda et al. [38] suggested that the criteria for considering an oral malignant neoplasm as metastatic are: a primary tumor with histologic verification, a second oral lesion histologically relevant to the primary tumor, a histopathologic appearance of the oral lesion distinct from that of a typical oral malignancy and exclusion of a possible direct extension from the primary tumor.

Kawamura et al. [23], Moser et al. [26], Wu et al. [33], Shah et al. [28] and Chiarelli et al. [21] reported the occurrence of gingival metastasis. Kawamura et al. [23] treated a patient who previously underwent a surgical procedure for poorly differentiated rectal carcinoma. The gingival mass presented as a red and tender swelling. The histology of the mass was similar to the histology of the primary tumor. Immunohistochemical examination revealed positive staining for cytokeratin 20 and negative staining for cytokeratin 7, estrogen, progesterone and thyroid transcription factor-1.

Moser et al. [26] reported a gingival metastasis that occurred in a patient who was diagnosed with epitheloid mesothelioma 2 years earlier. The compact, painless and ulcerated swelling appeared 6 weeks before the patient was referred to their department and increased in size during that period. There was no objective paresthesia of the mental nerve nor was lymphadenopathy discernible. Orthopantomography and a CT scan showed no signs of osteolytic activity. Microscopic examination showed a morphology very similar to the one of mesothelioma. The mesothelial marker calretinin was strongly positive in tumor cells. Positive staining for cytokeratins 5/6 and negative staining for Ber-EP4 ruled out the diagnosis of adenocarcinoma.

Wu et al. [33] treated a gingival metastasis from adenocarcinoma in a patient who previously underwent a radical gastrectomy for gastric adenocarcinoma. The growth increased in size during a period of 1 month. It appeared gray in color and showed local hemorrhage on palpation. Serum level of carcinoembryonic antigen (CEA) was elevated and a PET-CT

revealed upper gingiva involvement. Not only did the histological appearance suggest the gingival metastasis originated from gastric carcinoma, but the positive staining for CK7, CK20, Villin, and MUC2 was also detrimental to the final diagnosis.

Shah et al. [28] reported a gingival metastasis from breast cancer. CT scan showed no evidence of cortical erosion of the underlying bone. Incisional biopsy was performed. The diagnosis of a metastasis was made only based on the histological pattern of the tumor.

Chiarelli et al. [21] reported a gingival metastasis of a radiotherapy-induced breast angiosarcoma. The mass was painless, red-brownish, larger than 3 cm and covered by a yellow-grayish secretion. The microscopic examination and the immunohistochemical staining for CD34 confirmed the vascular nature of the lesion and the diagnosis of angiosarcoma metastatic to the gingiva was made.

5. Conclusions

"Epulis"is a non-specific term used for localized gingival enlargements. These enlargements might hide various pathological entities. Thus, the diagnosis cannot be based only on clinical impressions. Histological and immunohistochemical examinations help clinicians to formulate the right diagnosis. A clear medical history is necessary to rule out possible association with systemic diseases, medical treatments and pregnancy. Metastatic spread of a malignancy must also be considered. Sometimes medical history reveals nothing meaningful, even in the presence of a gingival metastasis, since it might be the first indication of a cancer of unknown origin. The clinical examination must comprise an accurate evaluation of the characteristics of the neoformation (location, extension, shape, size, margins, color, surface, consistency) and the general status of the oral cavity (level of oral hygiene, plaque retentive and traumatic factors).

Clinicians should not worry about surgical approach and prognosis of hamartomatous lesions, non-neoplastic lesions and benign neoplasms. On the contrary, the management of patients diagnosed with a malign tumor or metastasis is much more troubling. Furthermore, the clinical presentation of a malign tumor or a metastasis in the oral cavity can be deceiving, leading to a misdiagnosis. CT of the mandible/maxilla must be used to detect any bone-destructive activity under masses, although bone involvement might not always be present. Moreover, when a malign neoplasm is diagnosed, it is mandatory to detect any systemic spread of the primary neoplasm.

Author Contributions: Conceptualization, P.C., M.P. and G.O.; Methodology, P.C., M.P. and A.M.; Supervision, A.M., A.B. and G.O.; Writing—original draft, P.C. and M.P.; Writing—review and editing, A.B. and A.M. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

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

References

1. Brierley, D.J.; Crane, H.; Hunter, K.D. Lumps and Bumps of the Gingiva: A Pathological Miscellany. *Head Neck Pathol.* **2019**, *13*, 103–113. [CrossRef]
2. Glickman, I. A Basic Classification of "Gingival Enlargement". *J. Periodontol.* **1950**, *21*, 131–139. [CrossRef] [PubMed]
3. Agrawal, A.A. Gingival enlargements: Differential diagnosis and review of literature. *World J. Clin. Cases* **2015**, *3*, 779–788. [CrossRef]
4. Puranik, R.S.; Puranik, S.R. Localized Gingival Growths: Do They Belong to the Common Spectrum Called Frog? *Aust. Dent. J.* **2011**, *56*, 109. [CrossRef]
5. Tamiolakis, P.; Chatzopoulou, E.; Frakouli, F.; Tosios, K.I.; Sklavounou-Andrikopoulou, A. Localized gingival enlargements. A 390 clinicopathological study of 1187 cases. *Med. Oral Patol. Oral Cir. Bucal* **2018**, *23*, e320–e325. [PubMed]
6. Kerr, D.A. Granuloma pyogenicum. *Oral Surg. Oral Med. Oral Pathol.* **1951**, *4*, 158–176. [CrossRef]
7. Kamal, R.; Dahiya, P.; Puri, A. Oral pyogenic granuloma: Various concepts of etiopathogenesis. *J. Oral Maxillofac. Pathol.* **2012**, *16*, 79–82. [CrossRef]

8. Reddy, V.; Saxena, S.; Saxena, S.; Reddy, M. Reactive hyperplastic lesions of the oral cavity: A ten year observational study on North 427 Indian Population. *J. Clin. Exp. Dent.* **2012**, *4*, e136–e140. [CrossRef] [PubMed]
9. Murata, M.; Hara, K.; Saku, T. Dynamic distribution of basic fibroblast growth factor during epulis formation: An immunohistochemical study in an enhanced healing process of the gingiva. *J. Oral Pathol. Med.* **1997**, *26*, 224–232. [CrossRef]
10. Hunasgi, S.; Koneru, A.; Vanishree, M.; Manvikar, V. Assessment of reactive gingival lesions of oral cavity: A histopathological 431 study. *J. Oral Maxillofac. Pathol.* **2017**, *21*, 180. [CrossRef]
11. Reddy, V.; Bhagwath, S.S.; Reddy, M. Mast cell count in oral reactive lesions: A histochemical study. *Dent. Res. J.* **2014**, *11*, 187–192.
12. Beaumont, J.; Chesterman, J.; Kellett, M.; Durey, K. Gingival overgrowth: Part 1: Aetiology and clinical diagnosis. *Br. Dent. J.* **2017**, *222*, 85–91. [CrossRef] [PubMed]
13. Trackman, P.C.; Kantarci, A. Molecular and clinical aspects of drug-induced gingival overgrowth. *J. Dent. Res.* **2015**, *94*, 540–546. [CrossRef] [PubMed]
14. Armitage, G.C. Bi-directional relationship between pregnancy and periodontal disease. *Periodontology 2000* **2012**, *61*, 160–176. [CrossRef]
15. García de Marcos, J.A.; Dean Ferrer, A.; Alamillos Granados, F.; Ruiz Masera, J.J.; García de Marcos, M.J.; Vidal Jiménez, A.; Valenzuela Salas, B.; García Lainez, A. Gingival neurofibroma in a neurofibromatosis type 1 patient. *Med. Oral Patol. Oral Cir. Bucal* **2007**, *12*, e287–e291. [PubMed]
16. Wu, J.; Fantasia, J.E.; Kaplan, R. Oral manifestations of acute myelomonocytic leukemia: A case report and review of the classification of leukemias. *J. Periodontol.* **2002**, *73*, 664–668. [CrossRef]
17. Makos, C.P.; Psomaderis, K. A literature review in renal carcinoma metastasis to the oral mucosa and a new report of an epulis-like metastasis. *J. Oral Maxillofac. Surg.* **2009**, *67*, 653–660. [CrossRef]
18. Sikka, S.; Sikka, P.; Kaur, G.; Shetty, D.C. A review of histopathological and immunohistochemical parameters in diagnosis of metastatic renal cell carcinoma. *J. Cancer Res. Ther.* **2013**, *9*, 105–107. [CrossRef]
19. Richards, A.; Costelloe, M.A.; Eveson, J.W.; Scully, C.; Irvine, G.H.; Rooney, N. Oral mucosal non-Hodgkin's lymphoma: A dangerous mimic. *Oral Oncol.* **2000**, *36*, 556–558. [CrossRef]
20. ALQahtani, D.; Qannam, A. Oral leiomyomatous hamartoma of the median maxillary gingiva: A case report and review of the 392 literature. *Int. J. Surg. Pathol.* **2013**, *21*, 413–416. [CrossRef]
21. Chiarelli, A.; Boccone, P.; Goia, F.; Gatti, M.; De Rosa, G.; Manca, A.; Galizia, D.; Aglietta, M.; Grignani, G. Gingival metastasis of a radiotherapy-induced breast angiosarcoma: Diagnosis and multidisciplinary treatment achieving a prolonged complete remission. *Anticancer Drugs* **2012**, *23*, 1112–1117. [CrossRef]
22. Jeyaraj, P.; Bandyopadhyay, T.K.; Naresh, N.; Sahoo, N.K. Value of immunohistochemistry in diagnosing a rare case of maxillofacial 394 plasma cell granuloma masquerading as a gingival epulis. *J. Maxillofac. Oral Surg.* **2015**, *14*, 40–45. [CrossRef]
23. Kawamura, M.; Nakabayashi, Y.; Otsuka, M.; Sakata, H.; Yanaga, K. Gingival metastasis from rectal cancer. *J. Gastrointest. Surg. Off. J. Soc. Surg. Aliment. Tract* **2008**, *12*, 1121–1122. [CrossRef]
24. Lu, W.; Qi, G.G.; Li, X.J.; He, F.M.; Hong, B. Gingival Plasma Cell Granuloma: A case Report of Multiple Lesions. *J. Clin. Pediatr. Dent.* **2020**, *44*, 436–441. [CrossRef]
25. Montebugnoli, L.; Venturi, M.; Gissi, D.; Flamminio, F.; Foschini, M. Low-grade myofibroblastic sarcoma of the gingiva. *BMJ Case Rep.* **2010**, *2010*, bcr0720103166. [CrossRef]
26. Moser, S.; Beer, M.; Damerau, G.; Lübbers, H.-T.; Grätz, K.W.; Kruse, A.L. A case report of metastasis of malignant mesothelioma to the 403 oral gingiva. *Head Neck Oncol.* **2011**, *3*, 1–5. [CrossRef]
27. Raghunath, V.; Manjunatha, B.S.; Al-Thobaiti, Y. Gingival leiomyomatous hamartoma of the maxilla: A rare entity. *Case Rep.* **2016**, *2016*, bcr2015213598. [CrossRef]
28. Shah, M.Y.; Mehta, A.R. Metastasis from breast cancer presenting as an epulis in the upper gingiva. *J. Oral Maxillofac. Pathol.* **2009**, *13*, 38. [CrossRef]
29. Sowmya, G.V.; Manjunatha, B.S.; Nahar, P.; Aggarwal, H. Oral focal mucinosis: A rare case with literature review. *BMJ Case Rep.* **2015**, *2015*, bcr2014208321. [CrossRef]
30. Sumida, T.; Murase, R.; Fujita, Y.; Ishikawa, A.; Hamakawa, H. Epulis-like gingival angiosarcoma of the mandible: A case report. *Int. J. Clin. Exp. Pathol.* **2012**, *5*, 830–833.
31. Tripathi, A.K.; Kumar, V.; Singh, S.; Dwivedi, R. Oral plasma cell granuloma. *Med. J. DY Patil. Univ.* **2017**, *10*, 181–183. [CrossRef]
32. Truschnegg, A.; Acham, S.; Kiefer, B.A.; Jakse, N.; Beham, A. Epulis: A study of 92 cases with special emphasis on histopathological 414 diagnosis and associated clinical data. *Clin. Oral Investig.* **2016**, *20*, 1757–1764. [CrossRef] [PubMed]
33. Wu, Z.; Tang, J.; Li, Y.; Lu, H.; Xu, J.; Lv, D. Successful management of rare gingival metastasis from gastric adenocarcinoma: A case 416 report and literature review. *World J. Surg. Oncol.* **2017**, *15*, 141. [CrossRef] [PubMed]
34. Kalele, K.P.; Kulkarni, N.; Patil, K.P.; Nayyar, A.S.; Kulkarni, M.; Atram, P. Retrospective Analysis of Discrepancies between Clinical and Histopathological Diagnoses in Head and Neck Lesions: An Institutional Study with 10 Years Database. *OMPJ* **2016**, *7*, 1.
35. Savage, N.W.; Daly, C.G. Gingival enlargements and localized gingival overgrowths. *Aust. Dent.* **2010**, *55* (Suppl. 1), 55–60. [CrossRef] [PubMed]
36. Meyer, I.; Shklar, G. Malignant tumors metastatic to mouth and jaws. *Oral Surg. Oral Med. Oral Pathol.* **1965**, *20*, 350–362. [CrossRef]

37. Barbe, A.G.; Röhrig, G.; Hieggelke, L.; Noack, M.J.; Derman, S.H.M. Interdisciplinary assessment and management of a patient with a fibrous gingival enlargement of unknown origin: A case report. *Clin. Case Rep.* **2020**, *8*, 159–165. [CrossRef]
38. Fukuda, M.; Miyata, M.; Okaba, K. A case series of 9 tumors metastatic to the oral and maxillofacial region. *J. Oral Maxillofac. Surg.* **2002**, *60*, 942–944. [CrossRef] [PubMed]
39. Patil, S.; Rao, R.S.; Majumdar, B. Hamartomas of the oral cavity. *J. Int. Soc. Prev. Community Dent.* **2015**, *5*, 347–353. [CrossRef] [PubMed]
40. Ide, F.; Shimoyama, T.; Kato, T.; Horie, N.; Kusama, K. Inflammatory pseudotumor and related lesions of the oral and maxillofacial 424 region: A critical reappraisal based on recent information. *Oral Med. Pathol.* **2000**, *5*, 41–47. [CrossRef]
41. Kumar, G.; Manjunatha, B. Metastatic tumors to the jaws and oral cavity. *J. Oral Maxillofac. Pathol.* **2013**, *17*, 71–75. [PubMed]
42. Hatziotis, J.C.; Constantinidou, H.; Papanayotou, P.H. Metastatic tumors of the oral soft tissues. Review of the literature and report of a case. *Oral Surg. Oral Med. Oral Pathol.* **1973**, *36*, 544–550. [CrossRef]
43. Hirshberg, A.; Berger, R.; Allon, I.; Kaplan, I. Metastatic tumors to the jaws and mouth. *Head Neck Pathol.* **2014**, *8*, 463–474. [CrossRef] [PubMed]
44. Hirshberg, A.; Shnaiderman-Shapiro, A.; Kaplan, I.; Berger, R. Metastatic tumours to the oral cavity—Pathogenesis and analysis of 439 673 cases. *Oral Oncol.* **2008**, *44*, 743–752. [CrossRef] [PubMed]