Role of Inflammation in Benign Salivary Gland Tumor Etiopathogenesis: An Evaluation through the Blood Inflammatory Biomarkers

Vincenzo Abbate,1 Simona Barone,1 Giovanni Dell’Aversana Orabona,1 Paola Bonavolontà,1 Maria Rosaria Galdiero,2 Leonardo Cristinziano,2 Luca Modestino,2 Giorgio Iaconetta,2 Luigi Califano1

1Department of Neurosciences, Maxillofacial Surgery Unit, Reproductive and Odontostomatological Sciences, University of Naples Federico II, Naples NA, Italy
2Department of Translational Medical Sciences (DiSMeT), Center for Basic and Clinical Immunology Research (CISI), University of Naples Federico II, Naples NA, Italy
3Department of Medicine, Surgery and Odontoaiatrics, Neurosurgery Unit, University of Salerno, Via Giovanni Paolo II 132, 84084 Fisciano, Salerno, Italy

Abstract

Objectives: To investigate the immune inflammatory profile in patients affected by benign salivary gland tumors (SGTs) by evaluating the blood inflammatory biomarkers.

Methods: A retrospective chart review was performed between January 2015 and April 2020, collecting the data of all patients admitted for benign SGTs in our maxillofacial surgery unit. A total of 191 patients were divided into two groups: 94 with Warthin’s tumor (WT group) and 97 with pleomorphic adenoma (PA group) at histological diagnosis. The third group consisted of 90 patients randomly selected as the control group (C group).

Results: The most relevant correlations were found by analyzing the values of some inflammatory biomarkers among the three groups. The neutrophil-to-lymphocyte ratio was found significantly higher in patients in the PA (p<0.005) and WT (p<0.001) groups than in patients in the C group. Similarly, the systemic immune-inflammation index was found significantly higher in patients in the PA and WT (p<0.005) groups than in patients in the C group. The platelet-to-lymphocyte ratio was significantly higher in patients in the PA group than in patients in the WT (p<0.05) and C groups (p<0.05).

Conclusion: In both WT and PA groups, the inflammatory status of the patients was found altered. Thus, inflammation and the immune system seem to have a role in the genesis of these benign salivary neoplasms whose etiopathogenesis is still debated.

Keywords: Salivary gland tumors, blood inflammatory biomarkers, NLR, SII, PLR, Warthin’s tumor, pleomorphic adenoma, tumor etiopathogenesis


Address for correspondence: Vincenzo Abbate, MD. Department of Neurosciences, Maxillofacial Surgery Unit, Reproductive and Odontostomatological Sciences, University of Naples Federico II, Naples NA, Italy
Phone: +39 0817462370 E-mail: vincenzo.abbate@unina.it
Submitted Date: March 09, 2022 Accepted Date: April 28, 2022 Available Online Date: June 06, 2022
*Copyright 2022 by Eurasian Journal of Medicine and Oncology - Available online at www.ejmo.org
OPEN ACCESS This work is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License.
Inflammatory blood biomarkers such as the neutrophil-lymphocyte ratio (NLR), the platelet-to-lymphocyte ratio (PLR), and recently the systemic immune-inflammation index (SII) reflect the balance between host inflammation and immune status. They are frequently discussed in the literature and their efficacy as prognostic indicators in malignant tumors is now unanimously recognized. However, it is not yet clear whether they can also play a role in benign tumors, especially for the salivary glands.[1]

Benign salivary gland tumors (SGTs) are the most frequent types, corresponding to 54%–79% of the total SGTs, while malignant tumors account for 21%–46%.

Pleomorphic adenoma is the most common SGT. It accounts for nearly 50% of all neoplasms occurring at this anatomical site. The second most frequent is Warthin’s tumor, also called papillary lymphomatous cystadenoma, which corresponds to 4%–14% of all tumors.[2]

Even though a strong association with smoking, ionizing radiation, viruses, and autoimmune disease was found, the etiopathogenesis of these tumors is still largely unknown.[3]

Smoking may trigger ductal hyperplasia and oncocytic metaplasia in preexisting lymph nodes.[4]

The exact etiopathogenesis of pleomorphic adenomas is also still unknown. Genetic and environmental risk factors appear to be involved.[5]

The tumor responds to hyperplastic pathogenesis: cells proliferate and change the cytoarchitecture of the tissue to extend through normal glandular parenchyma in the form of finger-like pseudopodia, leading to a high recurrence rate after surgery. Besides this, there is a potential for malignant transformation into carcinoma ex pleomorphic adenoma in less than 5%.[6]

Such evidence suggests that the inflammatory status of the patients may be altered, and it could contribute to the etiopathogenesis of these tumors.

Therefore, the aim of this study is to investigate the immune inflammatory profile based on blood biomarkers in patients affected by benign SGTs by focusing on pleomorphic adenoma and Warthin’s tumor.

Methods

Study Subjects

Clinical records of patients with SGTs who underwent their first operation between January 2015 and April 2020 at the Department of Maxillofacial Surgery of the University of Naples “Federico II” were retrospectively analyzed.

Of the 458 reports examined, 191 patients who met the following inclusion criteria were eligible for this study: histologically confirmed Warthin’s tumor or pleomorphic adenoma; complete medical records available; and preoperative blood count.

Exclusion criteria include patients who had any inflammatory, autoimmune, acute, or chronic infection disease; history of other cancers; previous treatment with nonsteroid anti-inflammatory drugs and immunotherapy; fever; acute myocardial infarction or coronary revascularization within 6 months before surgery; and who had incomplete clinical data.

Study Methods

Patients’ clinical–pathological data such as sex, age, tumor location, and comorbidities were collected from the medical records. Based on their histological diagnoses, patients were grouped as follows: WT group (94 patients with Warthin’s tumor) and PA group (97 patients with pleomorphic adenoma).

In addition, 90 consecutive noncancer patients were randomly selected from our database and used as controls (C group).

Blood samples from each patient with a confirmed diagnosis of a SGT were taken before the first surgery at our center, as part of the preoperative workup. Serum full blood count, lactate dehydrogenase (LDH), and gamma globulin measurements were performed in certified health service laboratories in a standardized manner on automated counters. Routine laboratory data included white blood cell (WBC) count, absolute lymphocyte count (ALC), absolute neutrophil count (ANC), absolute monocyte count (AMC), absolute eosinophil count, absolute basophil count (ABC), platelets, LDH, and gamma globulin fraction and were obtained from the clinical record. From these retrospectively available preoperative biochemical data, the following scores were calculated:

- NLR by dividing the ANC by the ALC;
- PLR by dividing the absolute platelet count by the ALC;
- SII by multiplying the absolute platelet count and NLR.

Statistical Analysis

Patients’ characteristics were expressed as mean±SEM. Statistical analysis was performed using Prism 7 (GraphPad Software, San Diego, CA, USA). Quantitative or continuous variables were tested for Gaussian distribution with the Shapiro–Wilk test, and nonparametric and parametric data were further analyzed with the Mann–Whitney U test and Student’s t-test, respectively. The α for statistical significance was set at 0.05.
Results
In the first group, 94 patients with Warthin’s tumor were included (63 males and 31 females). The mean age was 60.3±11.3 years. In the second group, 97 patients with pleomorphic adenoma were included (36 males and 61 females). The mean age was 49±15.1 years. In the third cohort (healthy controls), 90 patients comprising 65 males and 25 females were included. The mean age was 52.0±16.1 years (Table 1).

The age of onset of the WT group was higher than that of the PA group (Fig. 1). No differences were found in the gamma globulin fraction (Fig. 1). No differences were found in the absolute lymphocyte and absolute eosinophil count (Fig. 2).

The WT group displayed increased LDH levels (Fig. 1), WBC (Fig. 2), AMC (Fig. 2), and ANC (Fig. 2) compared with the control and PA groups. A slight increase in ABC (Fig. 2) was also found in the WT group compared with the PA group.

NLR was significantly higher in PA and WT groups compared with the C group (Fig. 3). A similar distribution was also found for the SII value, which was significantly higher in patients in the PA and WT groups compared with those in the C group (Fig. 3).

Interestingly, PLR was significantly higher in the PA group than in the WT (p<0.05) and C groups (p<0.05) (Fig. 3).

Discussion
The current fourth World Health Organization classification of 2017 defines 11 different types of benign epithelial salivary tumors (some of them with subclassifications).[7]

The most common tumors are pleomorphic adenoma and Warthin’s tumor. Even if they are well characterized from the histopathological point of view, the etiopathogenesis is still largely unknown.

For this reason, an important contribution could have inflammatory biomarkers in the blood. These indices (NLR, PLR, and SII) are quoted in the literature today as useful prognostic markers in many malignant tumors such as hepatocellular carcinoma, esophageal squamous cell carcinoma, and small cell lung cancer.[8–10]

Searching the most common databases of medical literature (Cochrane, PubMed, Scopus, etc.), we found only two papers that highlighted the role of NLR in SGTs. Damar et al. in their study in 2016 analyzed preoperative NLR values in a court of 182 patients with malignant and benign SGTs. Damar et al., in their study in 2016 analyzed preoperative NLR values in a court of 182 patients with malignant and benign SGTs. The mean neutrophil percentage and NLR were significantly higher in patients with malignant SGT than in patients with benign SGTs. However, lymphocyte count and...
percentage, neutrophil percentage, and NLR were significantly different between benign and high-grade malignant parotid gland tumors. No statistically significant difference was observed among inflammatory biomarkers between benign and low-grade malignant tumors. A similar study was carried out in 2018 by Kuzucu et al., which considered the PLR index. They found a significant increase in NLR and PLR indices in malignant tumors compared with benign tumors. This increase was not evident in the control group. A similar study was carried out in 2018 by Kuzucu et al., which considered the PLR index. They found a significant increase in NLR and PLR indices in malignant tumors compared with benign tumors. This increase was not evident in the control group.

Therefore, even though the prognostic role of the inflammatory biomarkers in the malignant progression is now well described, no data are available on their role in the two most frequent benign salivary cancers. Our results showed a significant increase in NLR, PLR, and SII indices in pleomorphic adenoma and Warthin's tumor compared with the control group.

Figure 2. Continuous preoperative full blood count parameters in patients with different subtypes of salivary gland tumors. The data are shown as mean±standard deviation for the biochemical parameters that showed crude significant differences, which also remained significant after Benjamini–Hochberg correction. *<0.05, **<0.01, ***<0.005, and ****<0.001 (one-way ANOVA test with post hoc Nemenyi–Damicco–Wolfe–Dunn multiple comparison test).

Figure 3. Continuous preoperative serum inflammation-based scores in patients with different subtypes of salivary gland tumors. The data are shown as mean ± standard deviation for the biochemical parameters that showed crude significant differences, which also remained significant after Benjamini–Hochberg correction. **<0.01, ***<0.005, and ****<0.001 (one-way ANOVA test with post hoc Nemenyi–Damicco–Wolfe–Dunn multiple comparison test).
In particular, we found a significant increase in all three inflammatory biomarkers compared with the control group in Warthin’s tumors and pleomorphic adenoma, and, above all, in Warthin’s tumor group, an increase in the absolute number of LDH, WBC, neutrophils, monocytes, and basophils was noted.

Orabona et al. highlighted how self-immunity and inflammation are directly connected with Warthin’s tumor etiopathogenesis.[3]

Histologically, Warthin’s tumor is characterized by an oncocytic epithelial component forming uniform rows of cells surrounded by cystic spaces associated with a lymphoid stroma containing many germ centers. These could be the result of an immune response to some irritative stimuli, such as cigarette smoke, by residual lymphoid tissue in the salivary gland.[13]

In 1971, Allegra noted that the morphologic characteristics of the lymphoid stroma and the distribution of immunoglobulin (IgG) resembled those found in delayed hypersensitivity disease instead of normal or reactive lymph nodes.[14,15]

Recently, other reported cases revealed the infiltration of IgG4-positive plasma cells in Warthin’s tumor, which implied the possible relationship with IgG4-related disease (IgG4-RD).[16]

Thus, the inflammation would appear to play a primary role in the genesis of this tumor as confirmed by the high value of inflammatory biomarkers. These indices reflect the status of the immune system and systemic inflammation.

In the pleomorphic adenoma, inflammation could be secondarily activated by the proliferative effect of the cells which is the basis of its pathogenesis. Frequently, pleomorphic adenoma lacks a true capsule and is surrounded by a fibrous pseudcapsule of variable thickness. The tumor extends through normal glandular parenchyma in the form of finger-like pseudopodia.[17] The inflammation could be triggered by the immune system in an attempt to confine proliferative activity. This hypothesis could be confirmed by the surprisingly high values of PLR compared with the WT and C groups. In fact, platelets could act as chemotacticants to promote the inflammatory peritumoral activity essential for inhibiting intraglandular neoplastic proliferation responsible for potential malignant transformation.

Conclusion

In conclusion, our results show that inflammatory biomarkers may provide useful information about the inflammatory status of the patients affected by SGT. The analysis of the statistical values indicates that the inflammation seems to have a primary role in the genesis of Warthin’s tumor and activates secondarily in the case of pleomorphic adenoma.

This study has several limitations: this is a single-center study, mainly including a population of Italian patients, hence limiting the generalizability of our findings to other populations or ethnicities; it is a retrospective study and we cannot exclude that some patients would have unknown/unreported concomitant diseases capable of influencing hematopoiesis or systemic inflammation. A prospective trial on larger series would be advisable to confirm our preliminary results.

Disclosures

Ethics Committee Approval: The study was approved by the Local Ethics Committee.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.


References


5. Clark K. Etiology and familial inheritance of pleomorphic adenomas. Dentistry 3000 2017;5:54–8. [CrossRef]


