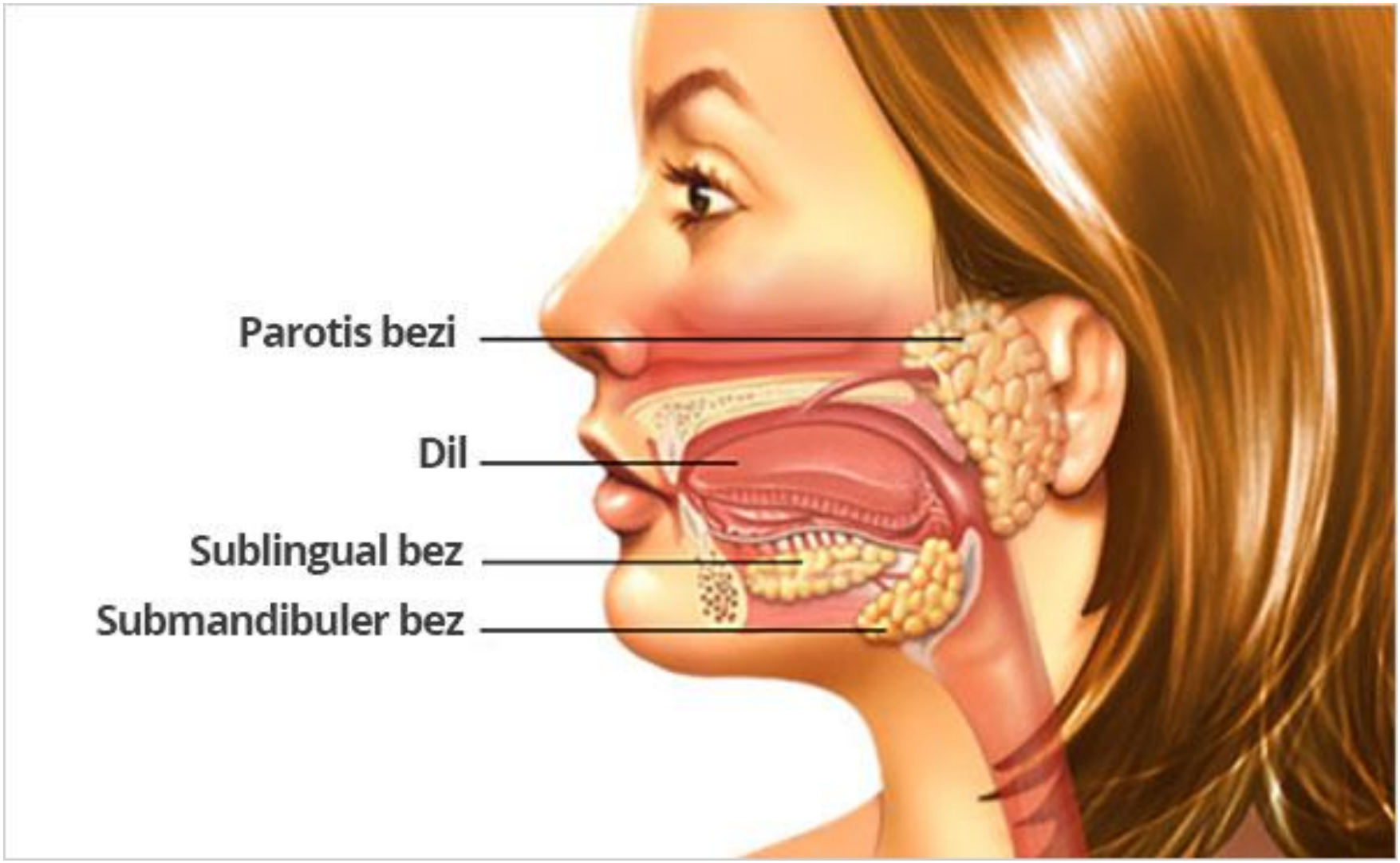
# TÜKÜRÜK BEZİ BİYOPSİSİ

Gonca Karabulut
Ege Üniversitesi Tıp Fakültesi
İç Hastalıkları - Romatoloji




**Major Tükürük Bezleri:**

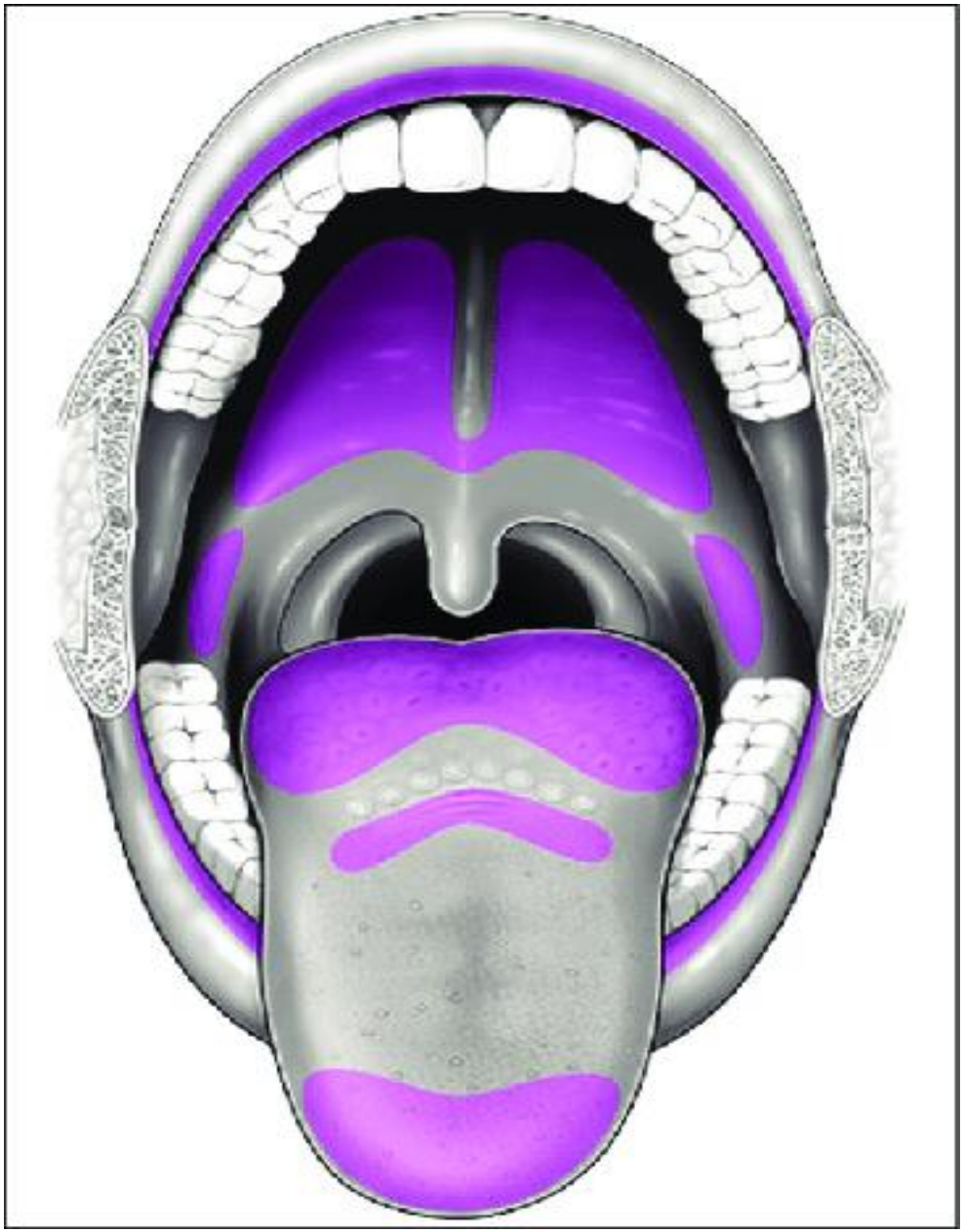
•Parotis Bezi: Kulak önü tükürük bezi

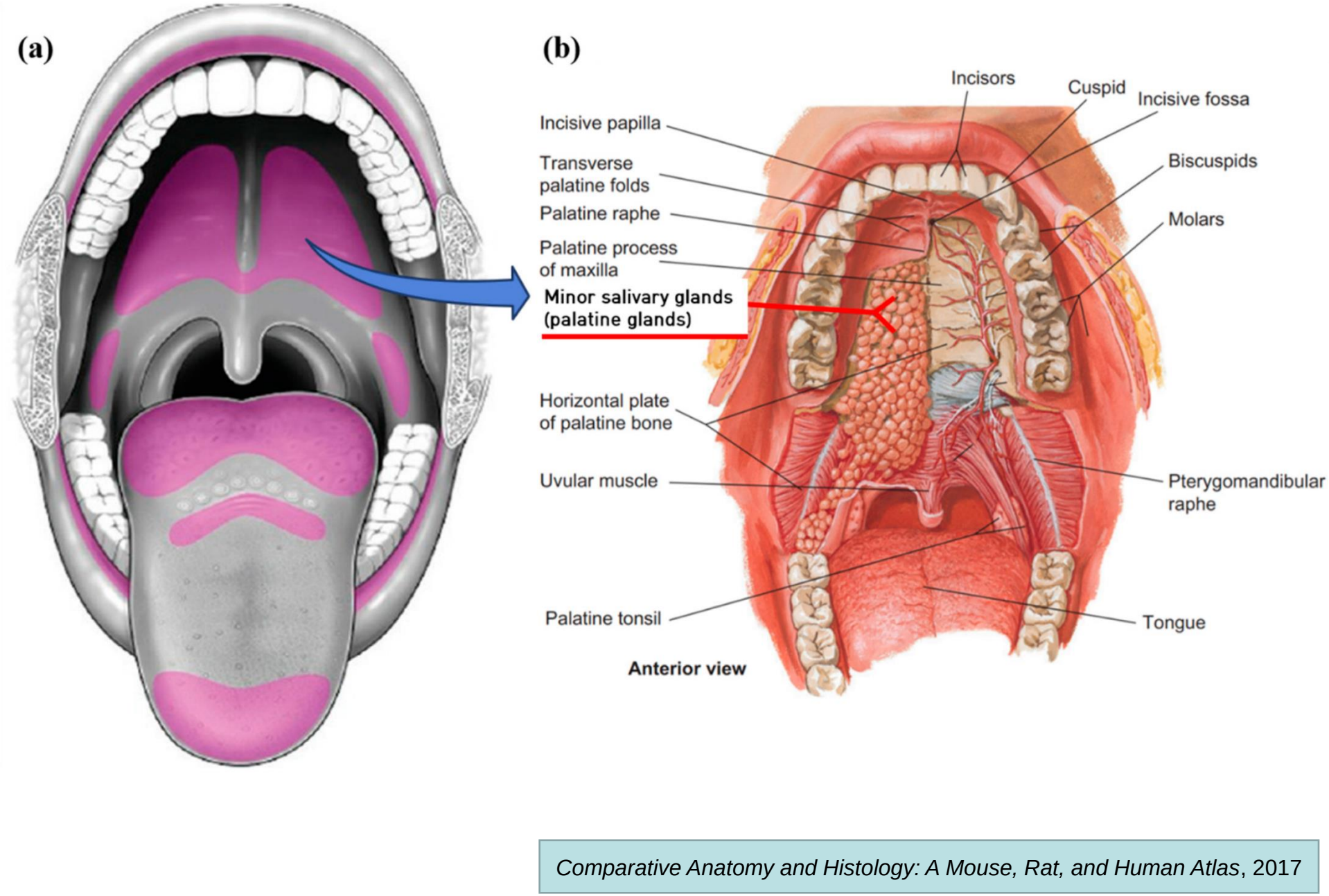
•Submandibuler Bez: Çene altı tükürük bezi

•Sublingual Bez: Dil altı tükürük bezi

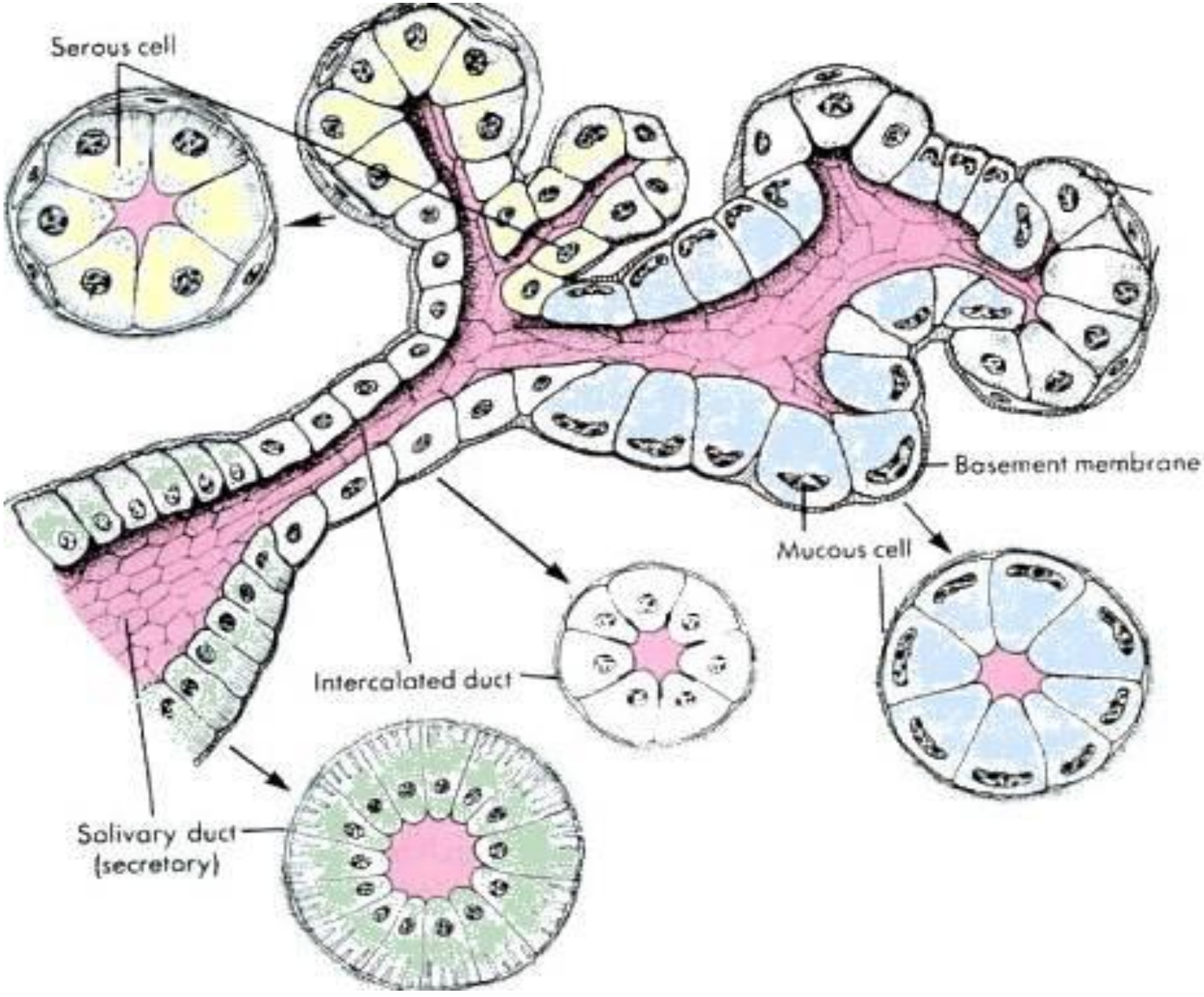
## Minör tükürük bezleri

- Üst solunum yolları
- 600-1000






*Comparative Anatomy and Histology: A Mouse, Rat, and Human Atlas*, 2017


Serous cell
Basement membrane
Mucous cell
Intercalated duct
Salivary duct
(secretory)

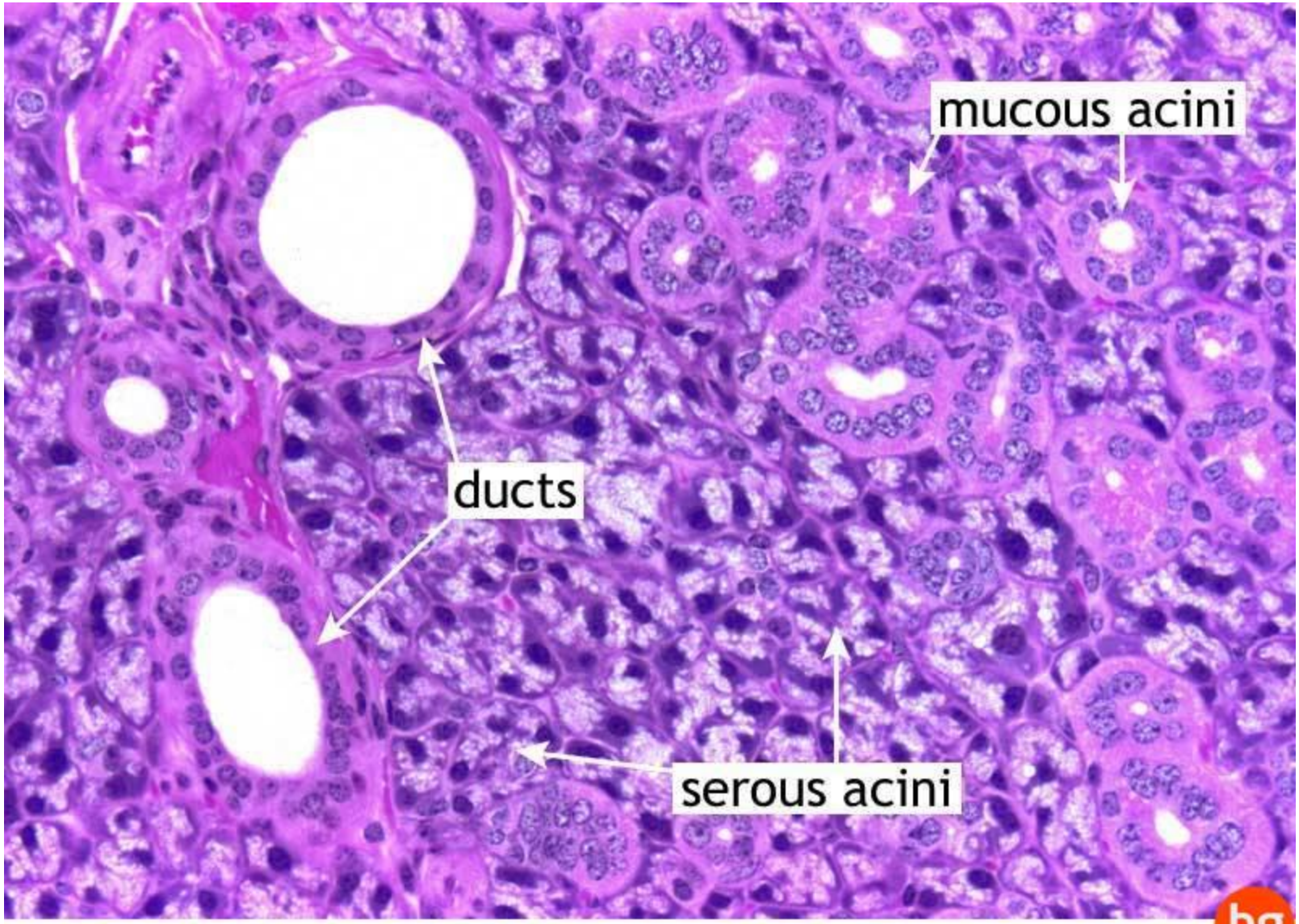


**Table 3**
Histopathological differential diagnosis of Sjögren's syndrome.

| Diagnosis | Histopathological features | References |
|---|---|---|
| History of head and neck radiation treatment | Parenchymal loss, acinar atrophy, interstitial fibrosis, duct proliferation dilated, intercalated and striated duct | [55–57] |
| Active hepatitis C infection | Pericapillar lymphocytic infiltration, no destruction of the SG ducts | [58–61] |
| HIV | Diffuse lymphoplasmacytic infiltrates of the glandular parenchyma without epithelial lesions | [62] |
| Sarcoidosis | Lymphocytic infiltration and noncaseating granulomas | [63] |
| Amyloidosis | Presence of amyloid deposits using Congo red or crystal violet | [64–66] |
| Graft versus host disease | Periductal lymphocytic infiltration, acinar atrophy and periglandular fibrosis | [67–70] |
| IgG4-related disease | Dense lymphoplasmacytic infiltrate, fibrosis with prominent storiform pattern, obliterative phlebitis, increased number of IgG4+ plasma cells/HPF | [71–73] |
| Diabetes mellitus | Acinar hypertrophy, fat infiltration in the glandular stroma, and normal-appearing epithelium | [74,75] |
| Parkinson's disease | Lewy type alfa-synucleinopathy, Immunoreactive nerve fibers | [76–78] |
| Vasculitis | Granulomatosis with polyangiitis may have diffuse necrotizing inflammation with abscess formation in addition to granulomatous features such as giant cells and aggregates of lymphocytes, epithelioid cells and vasculitis | [79,80] |
| Aging | Acinar atrophy, fibrous replacement and ductal aberrations | [81–83] |

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# Endikasyonları

- Sjögren sendromu
- Amiloidoz
- Sarkoidoz
- Hemokromatoz
- Lenfoma

Romatolojik hastalıkların tanısında;

- Anamnez
- Fizik bakı
- Laboratuar testleri
- **BİYOPSİ**

**Table 1**
2016 ACR–EULAR classification criteria for primary Sjögren's syndrome.

| Item | Description | Score |
|---|---|---|
| Focus score of ≥1 | A score determined by the number of mononuclear-cell infiltrates containing ≥50 inflammatory cells per 4 $mm^2$ of minor labial salivary gland obtained on biopsy | 3 |
| Presence of anti-SSA antibodies* | Measured in serum; only anti-Ro60 antibodies have to be considered; isolated anti-Ro52 antibodies are not specific for Sjögren's syndrome | 3 |
| SICCA ocular staining score of ≥5 | A score determined by an ophthalmologist on the basis of examination with fluorescein and lissamine green staining; scores range from 0 to 12, with higher scores indicating greater severity | 1 |
| Schirmer test of ≤5 mm per 5 min | An assay for measuring tear production by inserting filter paper on conjunctiva in the lower eyelid and assessing the amount of moisture on the paper | 1 |
| Unstimulated whole salivary flow of ≤0.1 ml per min | An assay for measuring the rate of salivary flow by collecting saliva in a tube for at least 5 min after the patient has swallowed | 1 |
| Total score | | 9 |

Four or more points are classified as Sjögren's Syndrome.

* Positive serologic results for anti-SSB/La antibodies in the absence of anti-SSA/Ro antibodies is not specific and is no longer considered to be a criterion for the diagnosis.

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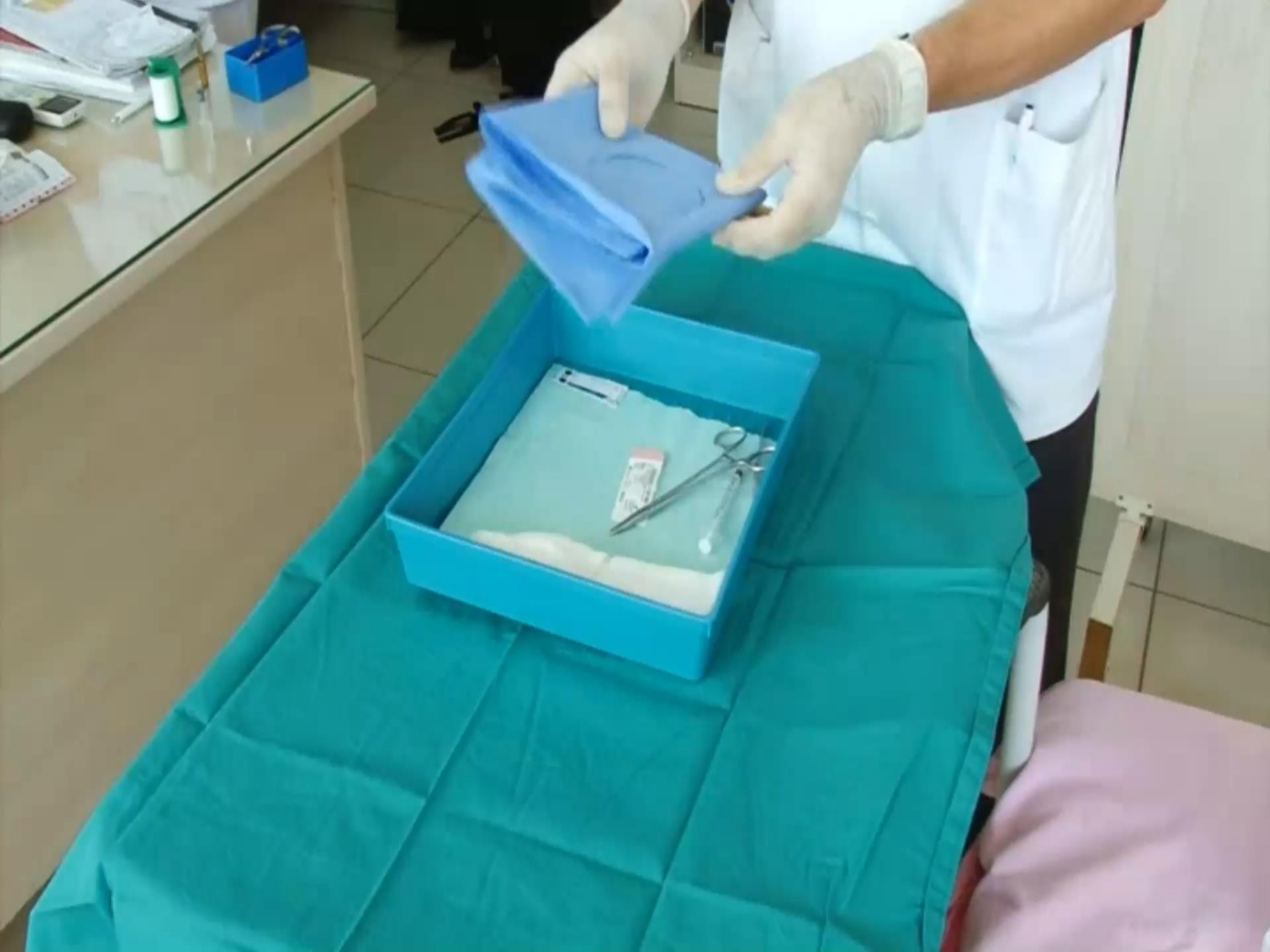
# Minör Tükürük Bezi Biyopsisi

# Biyopsi teknikleri

- **İnce iğne aspirasyon biyopsisi:** Majör tükürük bezi biyopsileri için kullanılır.
- **Punch Biyopsi:** Sütur kullanmadan dişsiz pensetle mukozanın çekilip kesilmesi (Mukoza patolojilerini aydınlatabilir.)
- **Eksizyonel dudak biyopsisi:** 1 cm'den daha küçük kesi yapılarak derin dokularla birlikte çıkarılması
- **İnsizyonel dudak biyopsisi:** 1 cm'den daha büyük alanı kapsar. Ameliyathane şartlarında dudaktaki patolojik lezyonların çıkarılmasında kullanılır.

# Biyopsinin yapılması

- Hastaya neden biyopsi yapmamız gerektiği, anlayacağı şekilde anlatılmalı
- Biyopsinin nasıl yapıldığı, süresi, yan etkileri ve biyopsi sonrası neler yapılacağı açıklanmalı
- İmzalı olur belgesi alınmalı



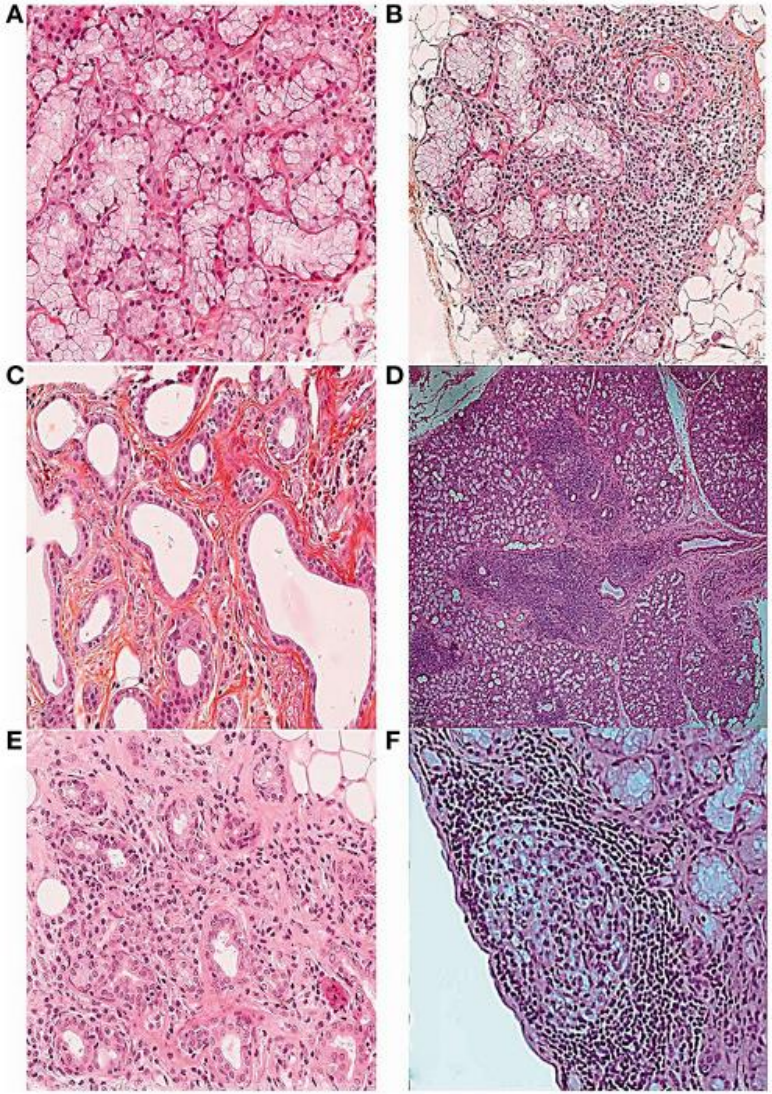
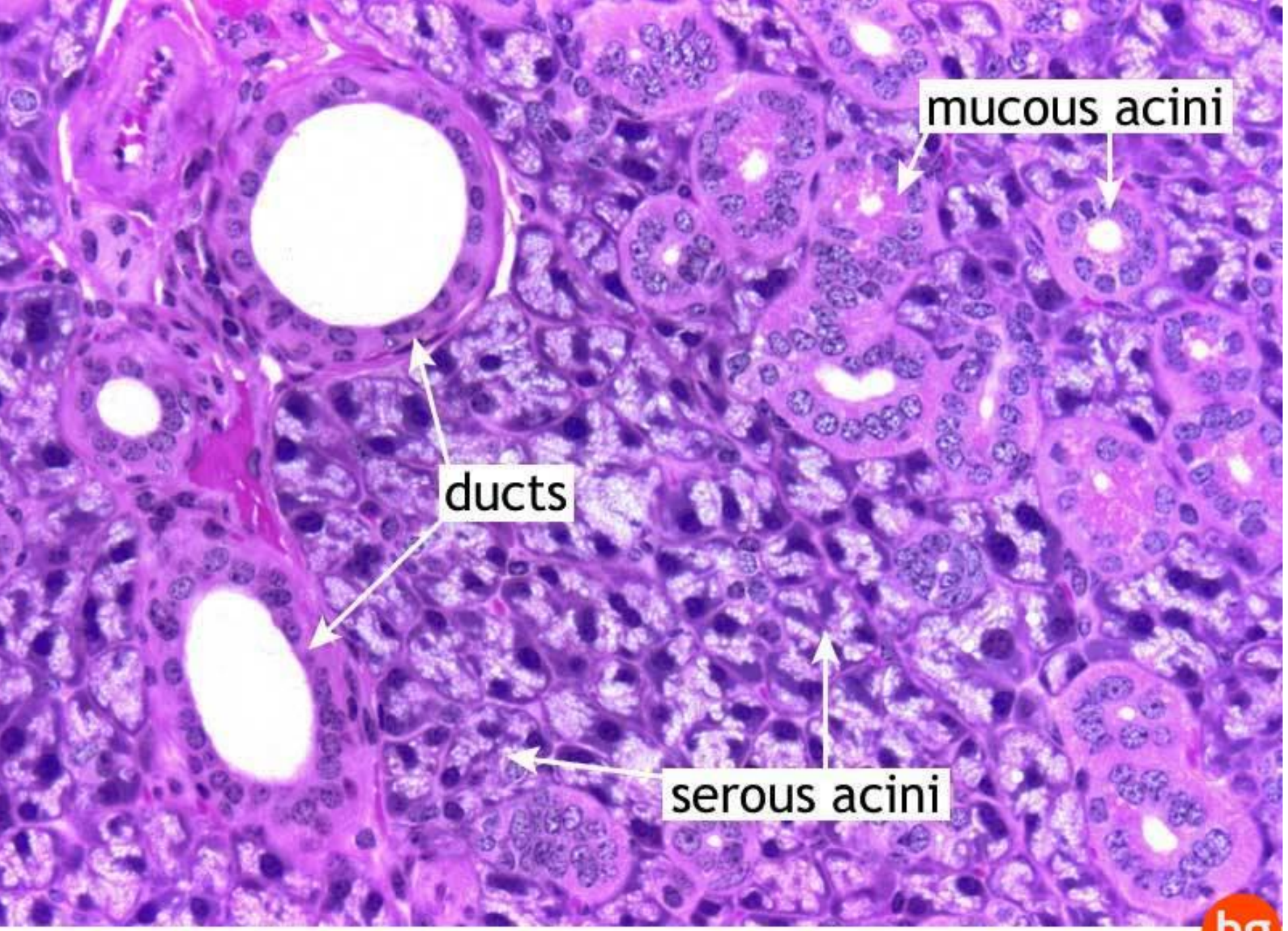
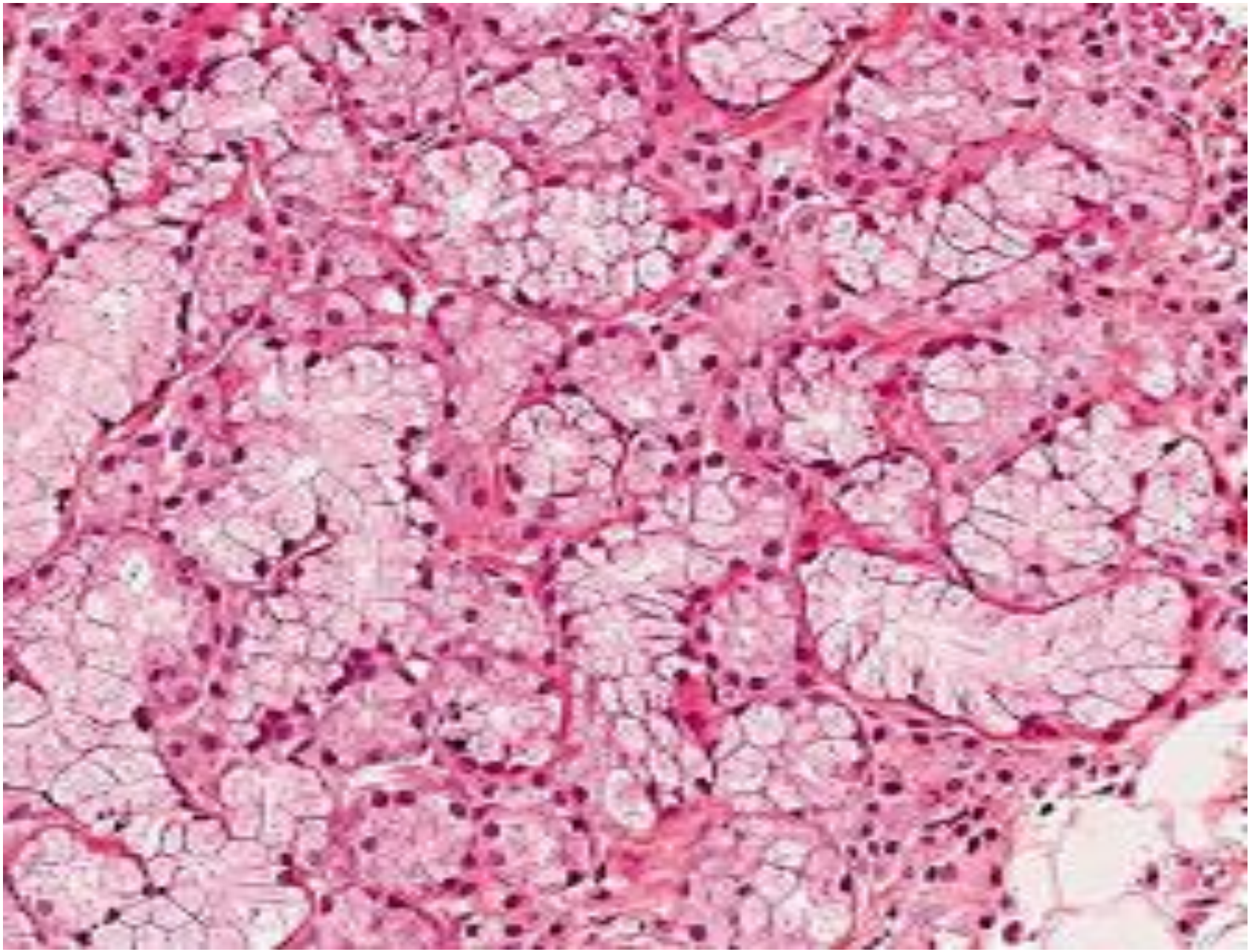



**FIGURE 1 |** Histopathological features of the minor salivary gland biopsy in patients with SS stained with hematoxylin, eosin and saffron (16). **(A)** Normal salivary gland tissue (10×). **(B)** Focal lymphocytic sialadenitis (FLS) with perivascular or periductular aggregates of >50 lymphocytes (10×). **(C)** Dilated ducts of the minor salivary gland biopsy (10×). **(D)** FLS surrounded by normal gland tissue (4×). **(E)** Non-specific chronic sialadenitis (NSCS) with acinar atrophy, interstitial fibrosis and scattered mononuclear cell infiltrates (10×). **(F)** FLS with germinal center-like structure (10×).

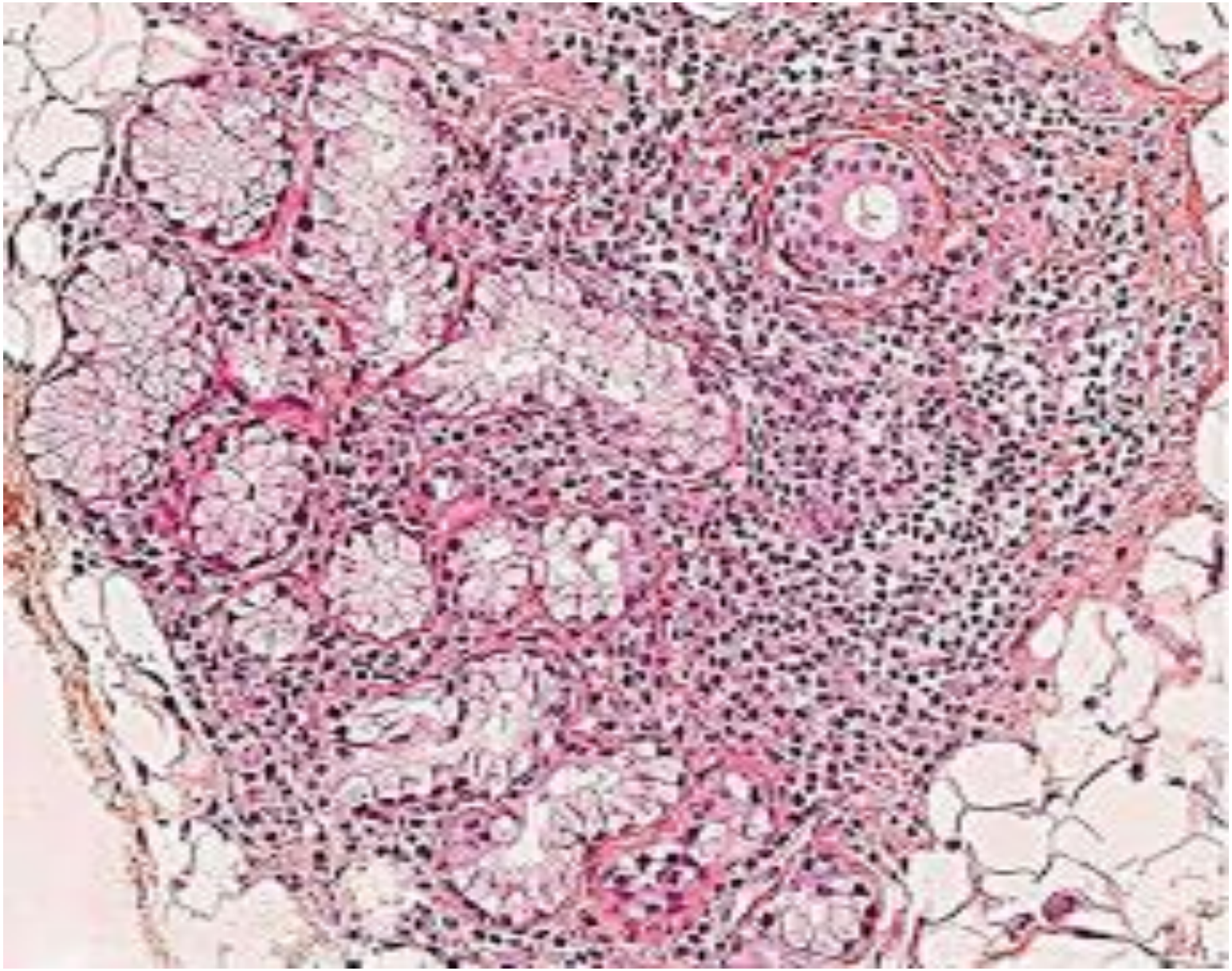
Liao L, 2022





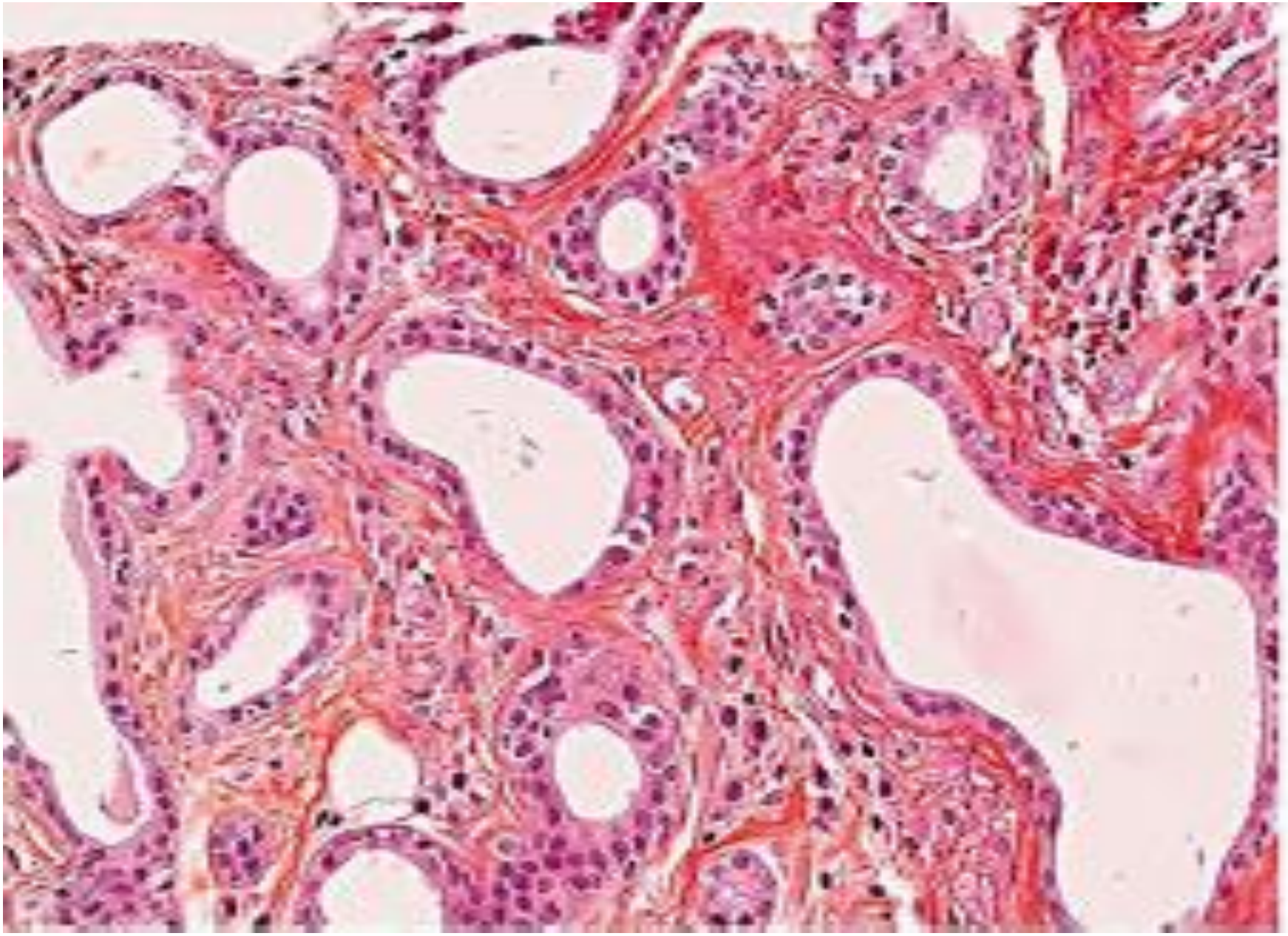
Normal
salivary gland tissue (10×).

Liao Rui, 2022



Focal lymphocytic sialadenitis (FLS) with
perivascular or periductular aggregates of >50 lymphocytes (10×)

Liao Rui, 2022



Dilated
ducts of the minor salivary gland biopsy (10×).

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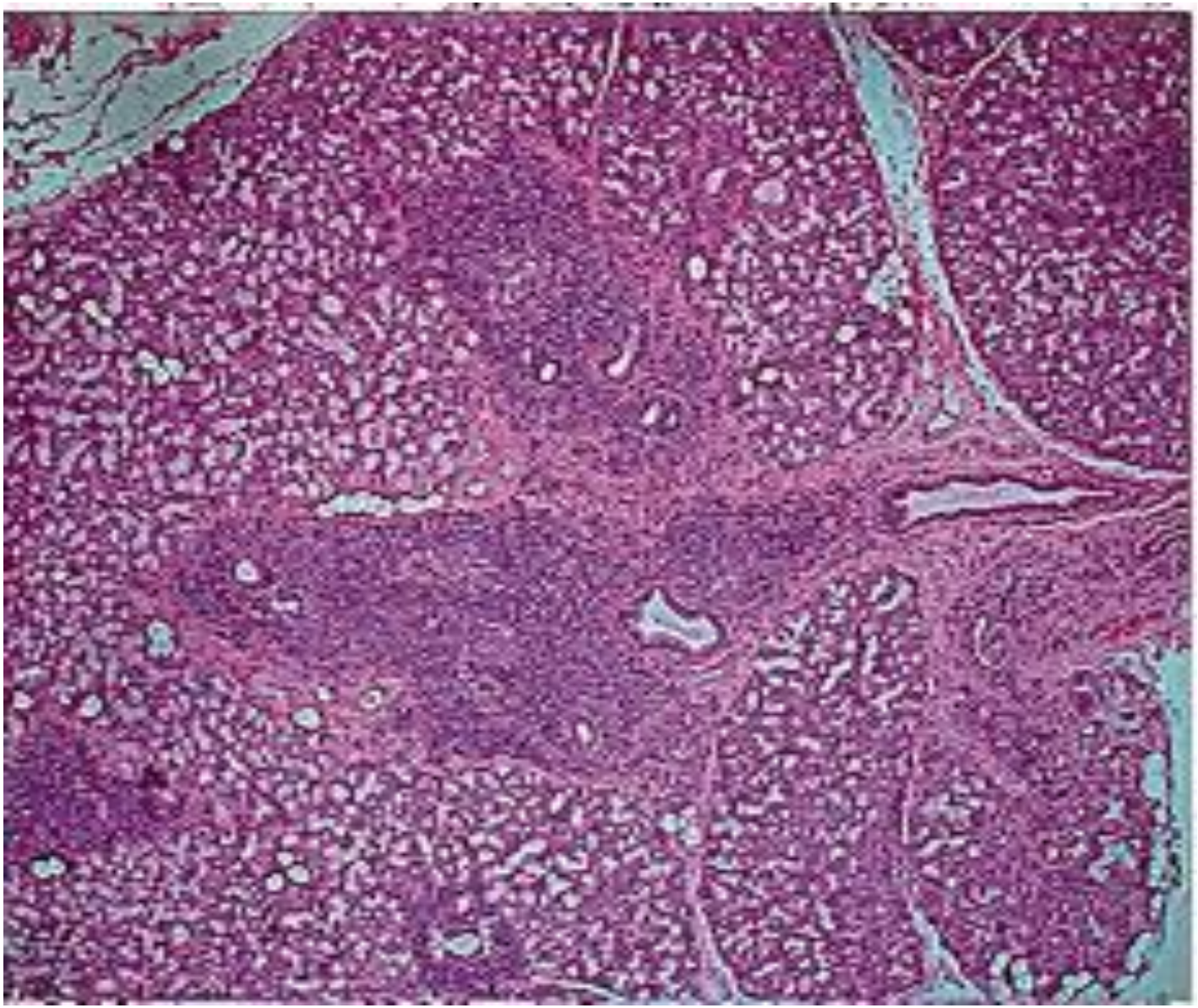
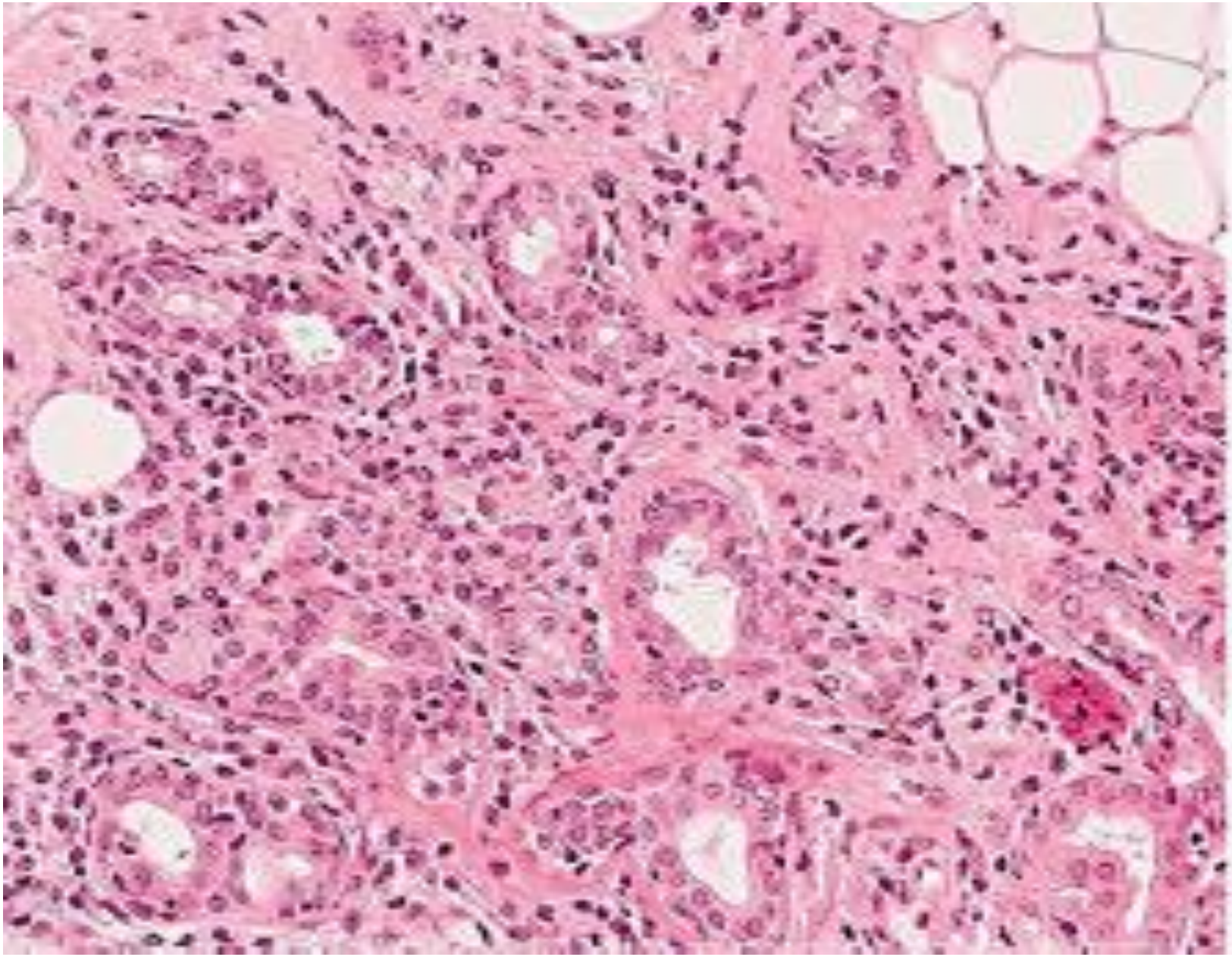


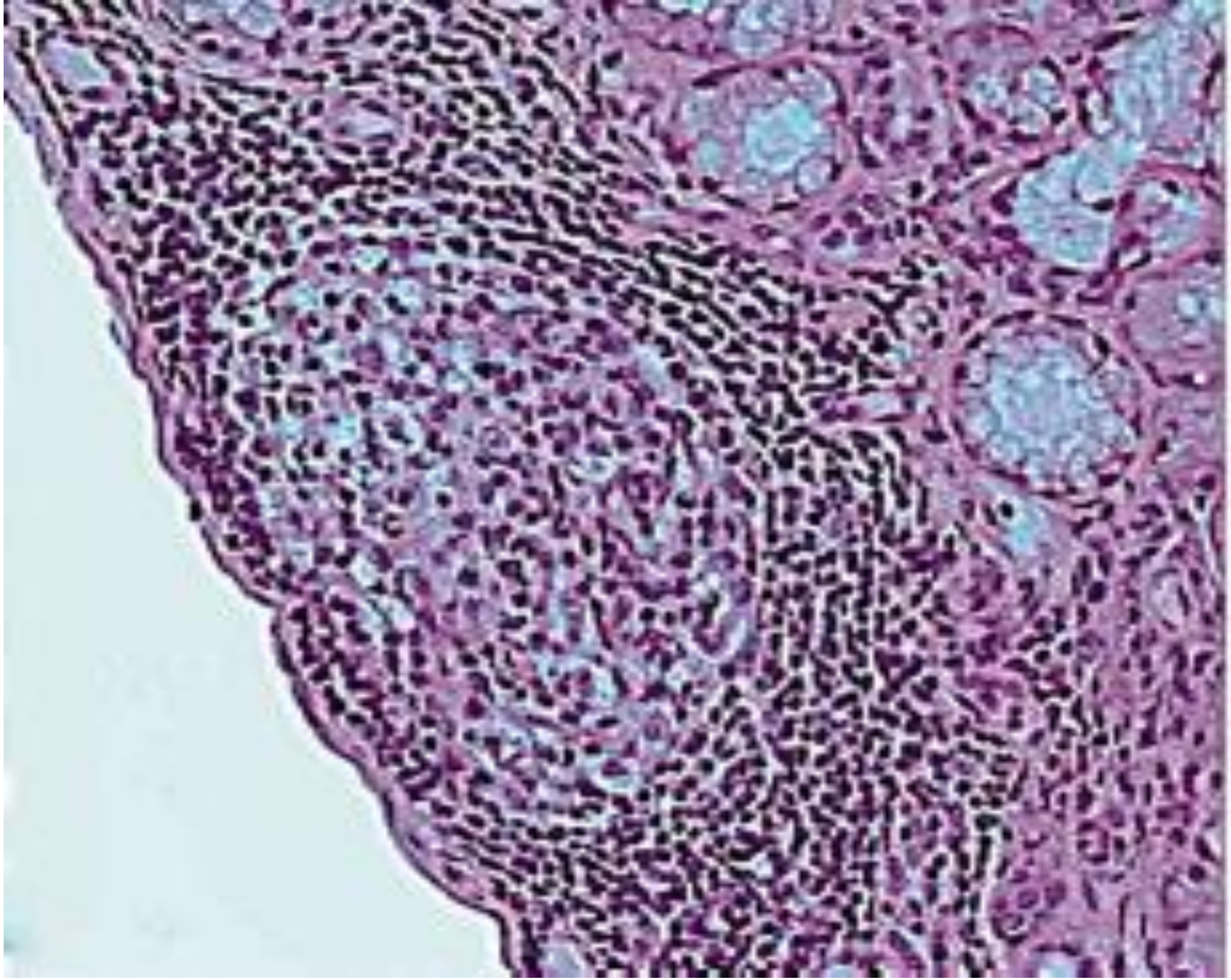
FLS surrounded by normal gland tissue (4×).

Liao Rui, 2022



Non-specific chronic sialadenitis (NSCS) with acinar atrophy, interstitial fibrosis and scattered mononuclear cell infiltrates (10×)

Liao Rui, 2022



FLS with germinal center-like structure (10×). Liao Rui, 2022

# Tükürük bezi Biyopsisinin Klinik Yönleri

- **Tanı**sal araç;

Duyarlılık;%63.5-93.7

Özgüllük; %61.2-100

- **Prediktör**; Hastalık ciddiyeti ve lenfoma gelişimi
- Klinik çalışmalarda verilen **tedaviye yanıt**ın belirlenmesi

Kroese F.G.M, 2018

# Tanı

- Foküs skor
- Tarpley
- Chisholm
- Diğer histopatolojik belirteçler

**Table 2**
Classifications used to assess minor salivary gland biopsies.

| Chisholm & Mason | | Greenspan y cols. | | Tarpley y cols. | |
|---|---|---|---|---|---|
| Grade | Lymphocytes/ 4 $mm^2$ | Focus Score | Lymphocytes/ 4 $mm^2$ | Class | Lymphocytes/4 $mm^2$ |
| 0 | None | 1 | 1 focus | 0 | Normal |
| 1 | Slight infiltrate | 2 | 2 focus (thus up to 10 focus) | I | 1 or 2 aggregates # (minimal infiltration) |
| 2 | Moderate infiltrate or less than one focus* | 12 | Confluent infiltrate | II | >3 aggregates# |
| 3 | One focus* | | | III | Diffuse infiltrate with partial destruction of acinar tissue with or without fibrosis |
| 4 | More than one focus* | | | IV | Diffuse infiltrate with or without fibrosis destroying the lobular architecture completely |

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# Minor Salivary Gland Biopsy (MSGB)

- **At least three** salivary gland lobules
- Examined area should be **>=4 mm²**

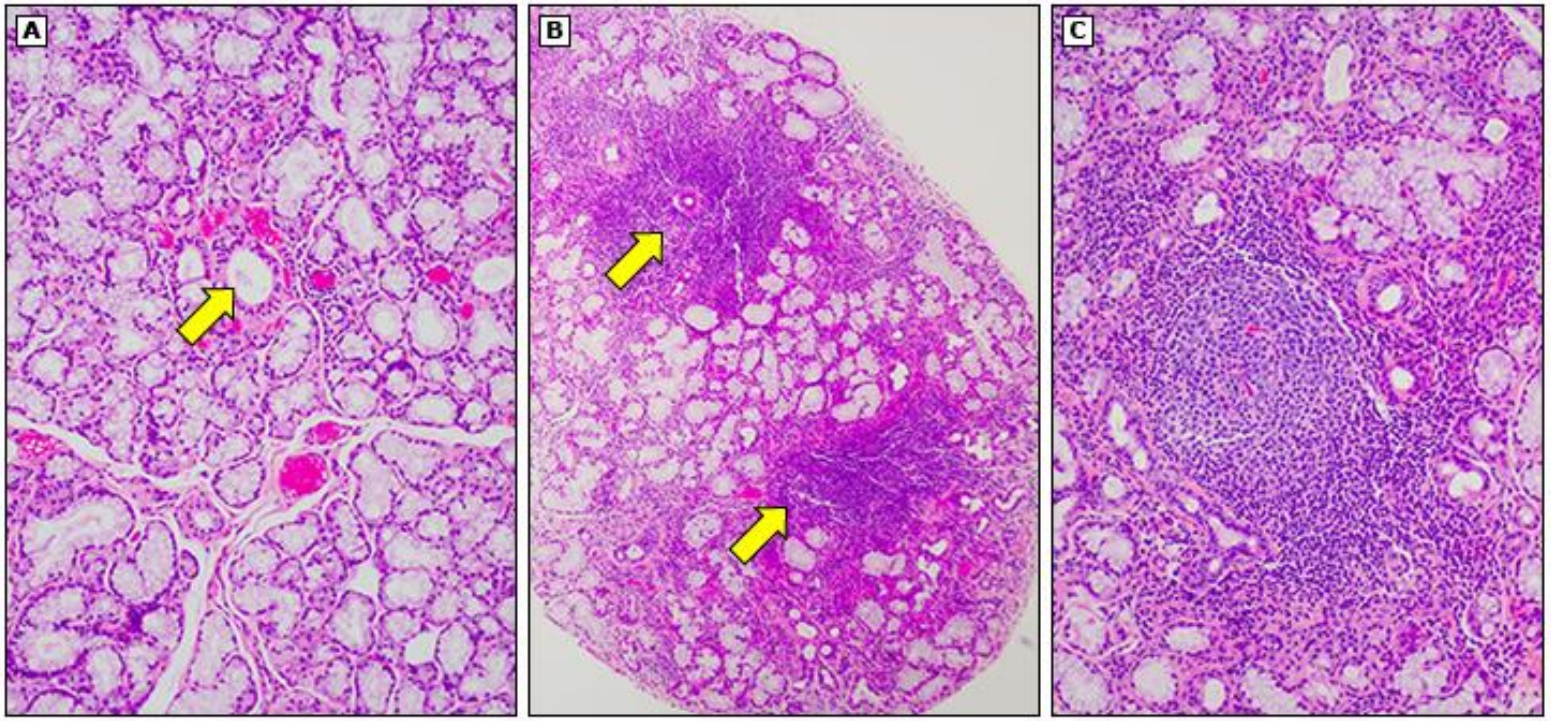
- Distinct pattern: Focal Lymphocytic Sialadenitis (FLS)

- A focus is >=50 lymphocytes in a cluster surrounding normal tissue

- If FLS present → Focus score (FS) is calculated:
  FS is number of foci in 4 mm²

- **Positive** if FS >=1

## Lip gland histopathology in Sjögren's syndrome




(A) High-power view showing a portion of a normal salivary gland lobule with mucous acini and a striated duct (arrow).

(B) Low-power view showing a salivary gland lobule with two focal areas of lymphocytic infiltration (arrows). This histopathologic pattern is known as "focal lymphocytic sialadenitis" and is characteristic of Sjögren's syndrome.

(C) High-power view of a lymphocytic infiltrate with a germinal center-like structure. These are present in approximately 20% of minor salivary gland biopsies.

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*Courtesy of Alan N Baer, MD.*

# Fokus skorunun kısıtlılıkları

- 2. cil uzman değerlendirmesi
- Diğer histolojik paternlerin varlığı

Kronik sialadenitis

Sklerozan kronik sialadenitis

Asiner atrofi

İntersitisyel fibrozis

Yağ hücre artışı

- Yaşlanma
- Foküslerin büyüklüğü

# Biyopsideki diğer histolojik belirteçler

- **Lenfoepitelyal lezyonlar**

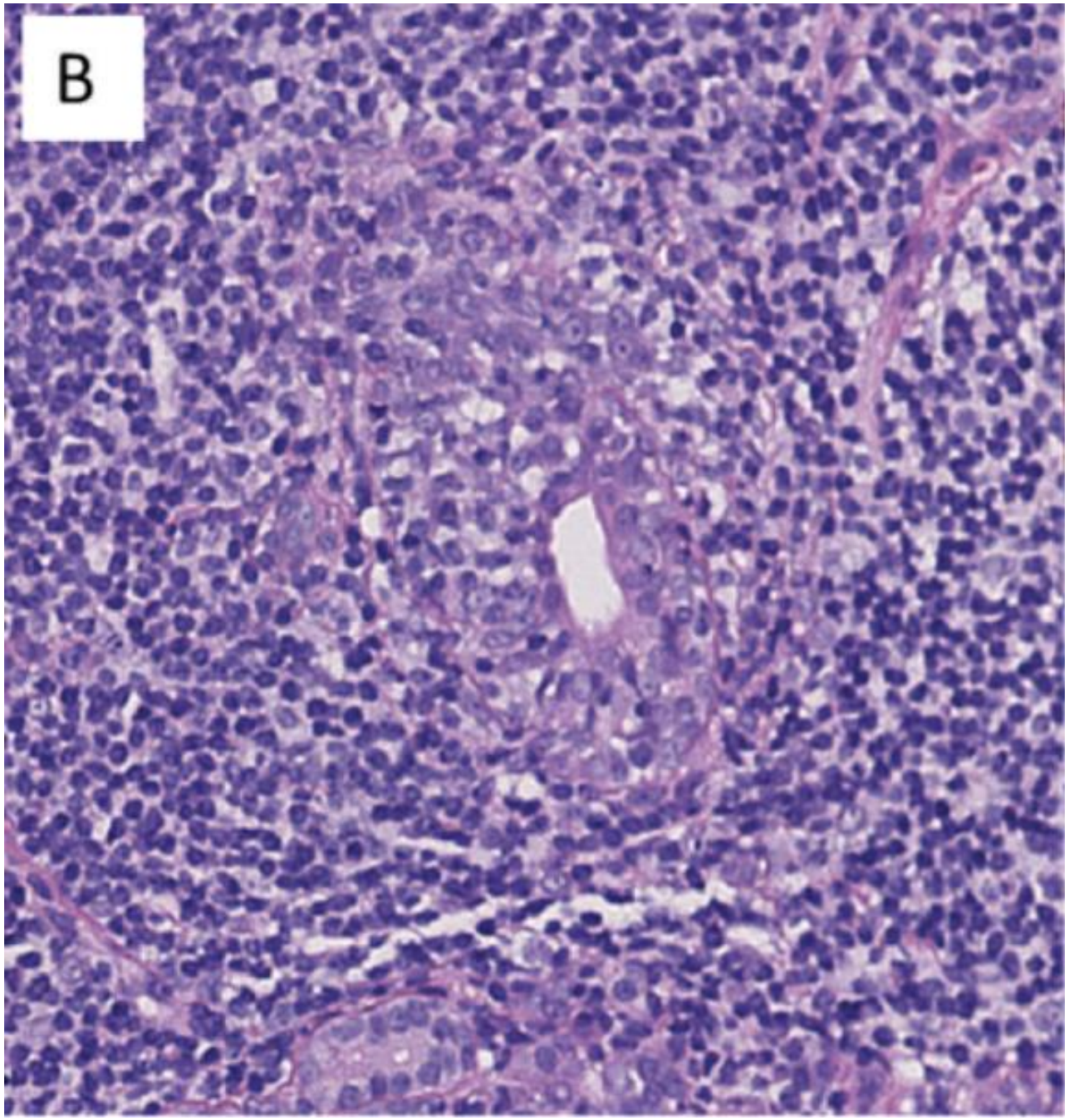
**Duktusların epitel hücrelerinin hiperplazisi ve lenfosit infiltrasyonu**

Sjögren için karekteristik ama spesifik değil

Sınıflama ve prognozdaki önemi belli değil

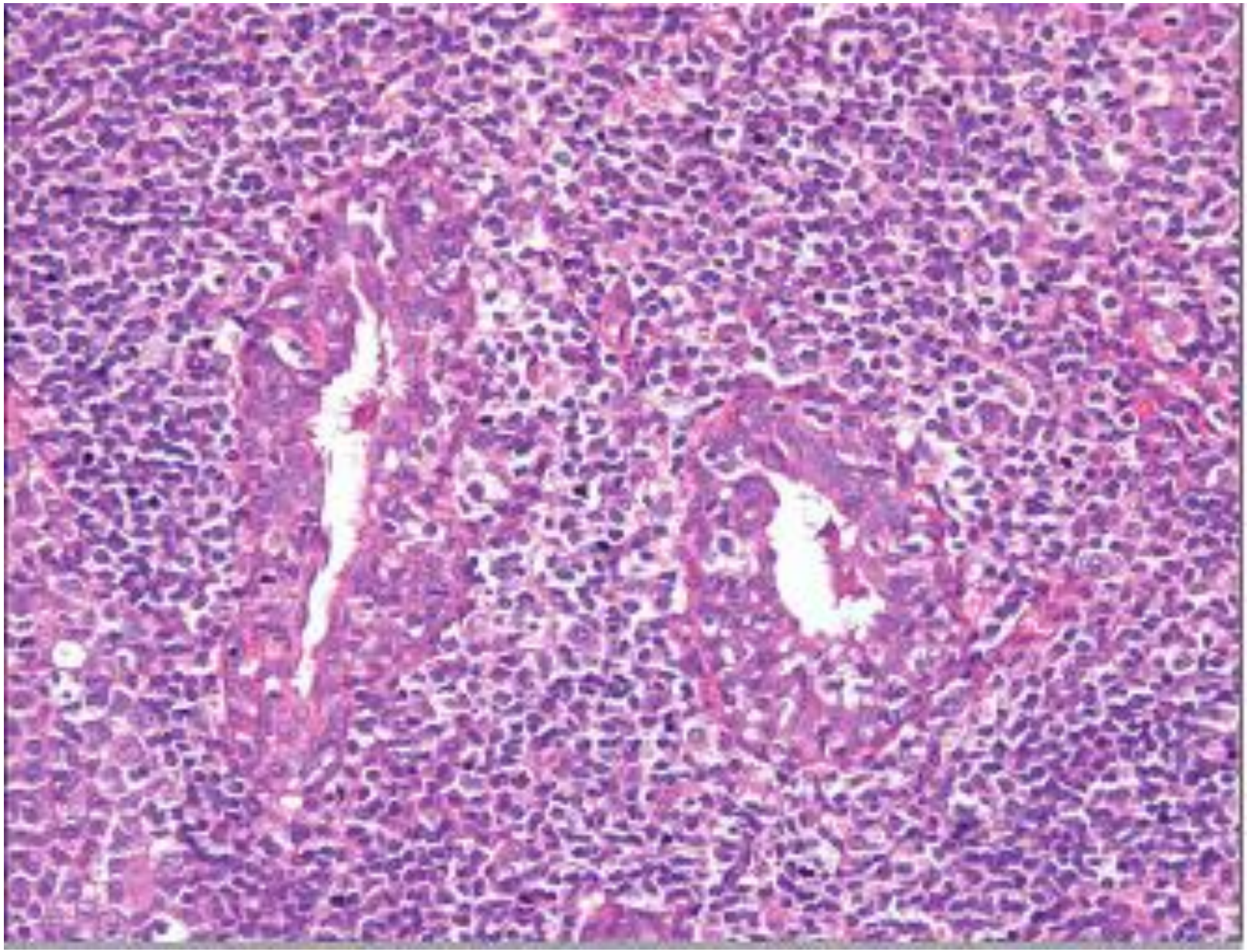
- IgA+ plazma hücrelerinin relativ azalması IgG ve IgM + plazma hücrelerinin relatif olarak artması

Kroese F.G.M, 2018




Centrally located duct forming a lymphoepithelial lesion within a focus.

Kroese F.G.M, 2018



Lymphoepithelial lesions (LELs) surrounded by lymphocytic infiltrates (20×)

Liao Rui, 2022

# Biyopsideki diğer histolojik belirteçler

- Lenfoepitelyal lezyonlar
- **IgA+ plazma hücrelerinin relatif azalması IgG ve IgM + plazma hücrelerinin relatif olarak artması**

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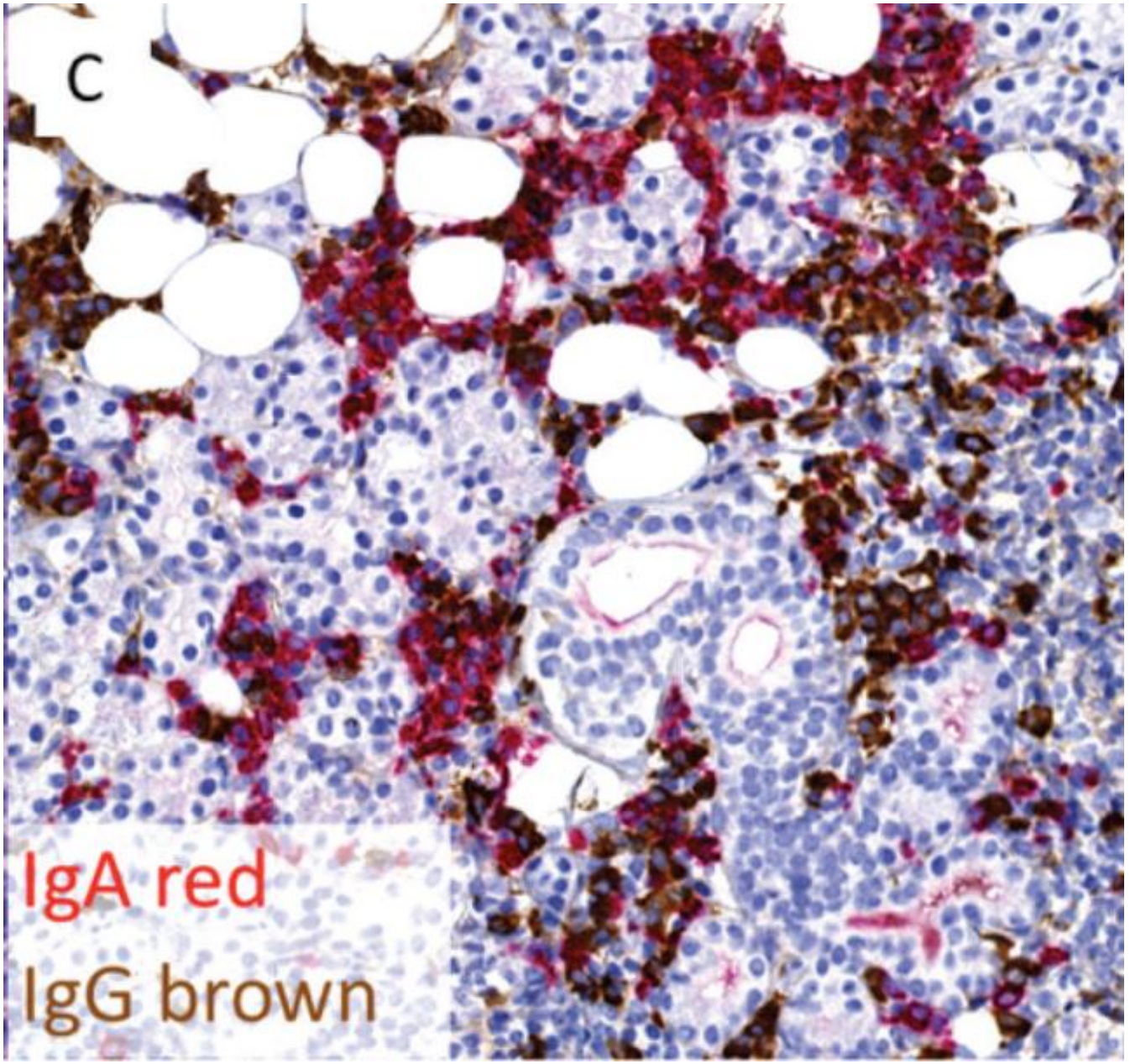


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# Hastalık ciddiyetini ve lenfogenezi belirleme

- Germinal merkez

GC+ hastalarda

Lenfoma ile ilişkili risk faktörleri daha fazla

Foküs skorları daha yüksek

FS≥3 lenfomagenezis de bağımsız risk faktörü

- Rolü tartışmalı???

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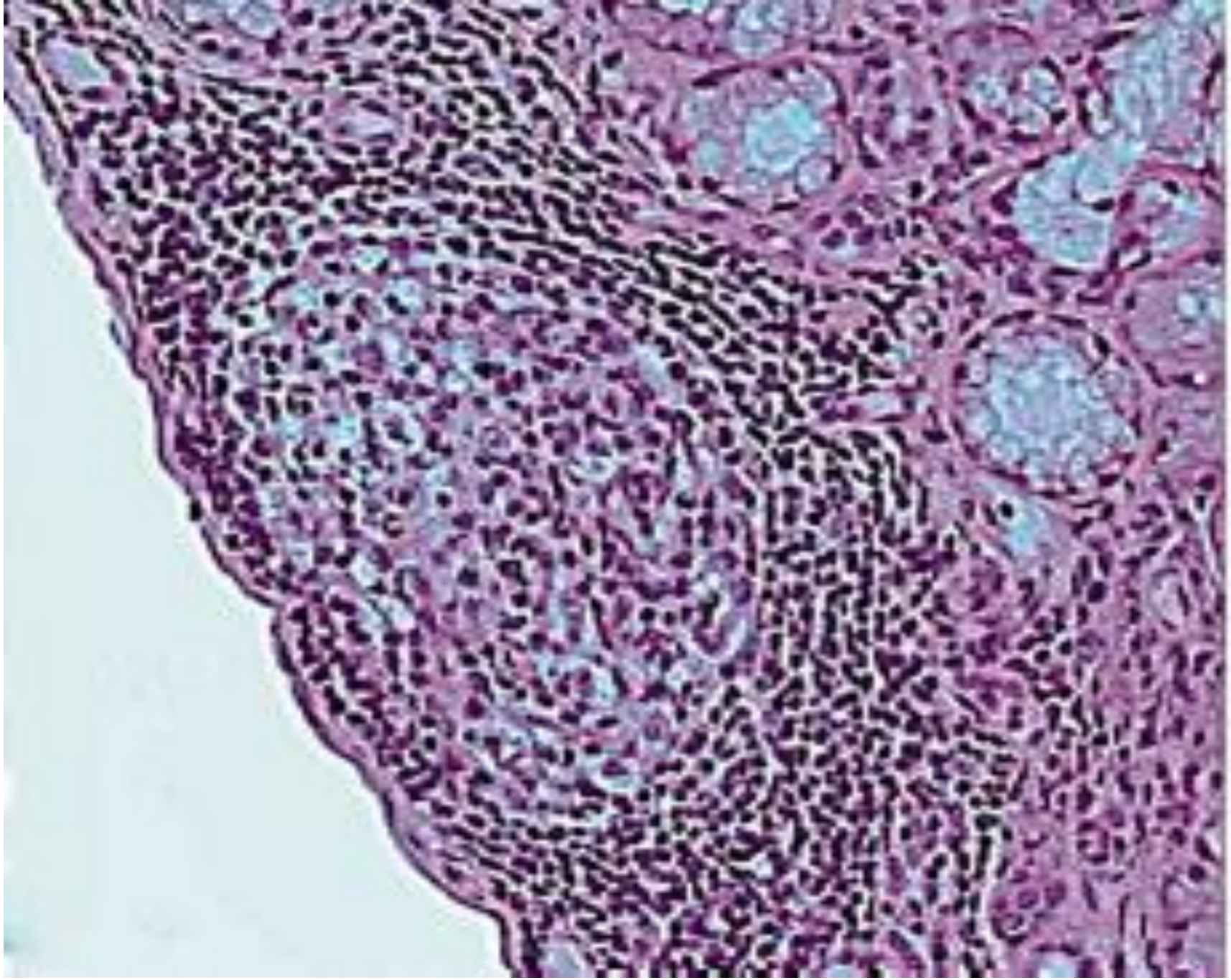

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# Klinik Çalışmalardaki rol

- Parotis biyopsisi

Aynı bez takibi

Usg, tükürük akım hızı, tükürük kompozisyonu

- FS
- CD 45 + hücre oranı
- GC
- LEL
- Fibrozis atrofi  yağ infiltrasyonu

Kroese F.G.M, 2018

# Tedaviye yanıtı belirleme

- Onaylanmış biyolojik ilaç yok
- Çalışmalarda kullanılan yöntemlerde standardizasyon yok
- Tekrar biyopsi zamanı farklı
- RTX; tükürük akım hızı stabil veya artmış
- Belimumab;??????

Kroese F.G.M, 2018

# Sonuç

- Sjögren sendromunu düşündüren klinik bulguların varlığında yeterli laboratuvar desteği yoksa tanı için en akılcı yaklaşım tükürük bezi biyopsisidir
- Lenfoma gelişimi ve hastalık ciddiyeti hakkında da bilgi verebilir
- Biyopside fokus skoru dışındaki değişiklikler de göz önünde bulundurulmalıdır

- Tükürük bezleri büyük (majör) ve küçük (minör) bezler olarak iki gruptan oluşur. Her iki tarafta kulak ön ve altında yer alan parotis tükürük bezleri, çene altı tükürük bezleri ve dilaltı tükürük bezleri majör tükürük bezleridir.
- Ağız içinde, dudak ve damakta çok sayıda küçük (minör) tükürük bezi mevcuttur. Tükürük bezlerinin görevi ağzı nemlendiren, mikroplara karşı dezenfektan etki yapan ve sindirime yardımcı enzim adı verilen proteinleri içeren tükürük salgısını üretmektir. Majör ve minör bezlerden günde 0,5 ila 1,5 litre arasında tükürük salgısı üretilerek ağız içine boşaltılmaktadır.

**Table I.** Grading systems for salivary gland biopsies of Chisholm/Mason and Tarpley (29, 42).

| Chisholm/Mason | | Tarpley | |
|---|---|---|---|
| Grade | Lymphocytes per 4 $mm^2$ of salivary gland tissue | Grade | Description |
| 0 | Absent | 0 | Normal |
| 1 | Slight infiltrate | 1 | 1 or 2 aggregates# (minimal infiltration) |
| 2 | Moderate infiltrate or less than one focus* | 2 | >3 aggregates# |
| 3 | One focus* | 3 | Diffuse infiltrate with partial destruction of acinar tissue with or without fibrosis |
| 4 | More than one focus* | 4 | Diffuse infiltrate with or without fibrosis destroying the lobular architecture completely |

*Focus: a cluster of 50 or more lymphocytes and histiocytes.
#Aggregate: approximately 50 cells (lymphocytes, plasma cells, or histiocytes).

Kroese F.G.M, 2018

# Tükürük bezleri

**Majör**

- Parotis
- Submandibüler
- Submental

**Minör**

- Labial tükürük bezleri

## ACR-EULAR Classification Criteria for primary Sjögren's syndrome (pSS)

The classification of SS applies to any individual who meets the inclusion criteria,[1] does not have any condition listed as exclusion criteria,[2] and who has a score ≥ 4 when summing the weights from the following items:

| Item | Weight / Score |
|---|---|
| Labial salivary gland with focal lymphocytic sialadenitis and focus score ≥ 1.[3] | 3 |
| Anti-SSA (Ro) + | 3 |
| Ocular staining score ≥ 5 (or van Bijsterfeld score ≥ 4) on at least one eye[4] | 1 |
| Schirmer ≤ 5 mm/5min on at least one eye | 1 |
| Unstimulated whole saliva flow rate ≤ 0.1 ml/min[5] | 1 |

[1]Inclusion criteria: these criteria are applicable to any patient with at least one symptom of ocular or oral dryness (defined as a positive response to at least one of the following questions: 1) Have you had daily, persistent, troublesome dry eyes for more than 3 months? 2) Do you have a recurrent sensation of sand or gravel in the eyes? 3) Do you use tear substitutes more than 3 times a day? 4) Have you had a daily feeling of dry mouth for more than 3 months? 5) Do you frequently drink liquids to aid in swallowing dry food?); or suspicion of SS from ESSDAI questionnaire (at least one domain with positive item)

[2]Exclusion criteria: Prior diagnosis of any of the following conditions would exclude diagnosis of SS and participation in SS studies or therapeutic trials because of overlapping clinical features or interference with criteria tests:

- History of head and neck radiation treatment
- Active Hepatitis C infection (with positive PCR)
- Acquired immunodeficiency syndrome
- Sarcoidosis
- Amyloidosis
- Graft versus host disease
- IgG4-related disease

Note: Patients who are normally taking anticholinergic drugs should be evaluated for objective signs of salivary hypofunction and ocular dryness after a sufficient interval off these medications for these components to be a valid measure of oral and ocular dryness

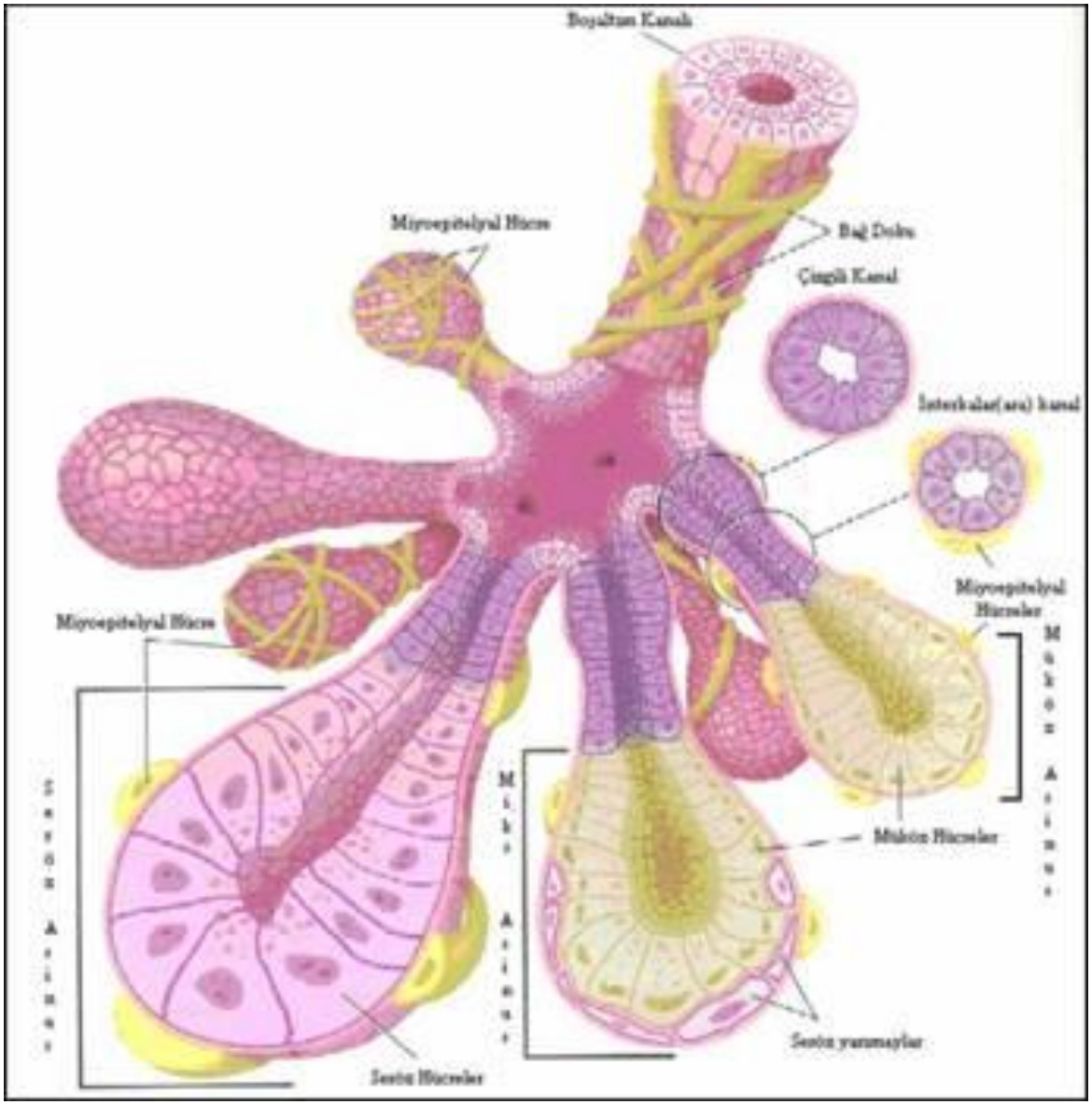
[3] The histopathologic examination should be performed by a pathologist with expertise in the diagnosis of focal lymphocytic sialadenitis, and focus score count (based on number of foci per 4 $mm^2$) following a protocol described in Daniels et al 2011 (26)

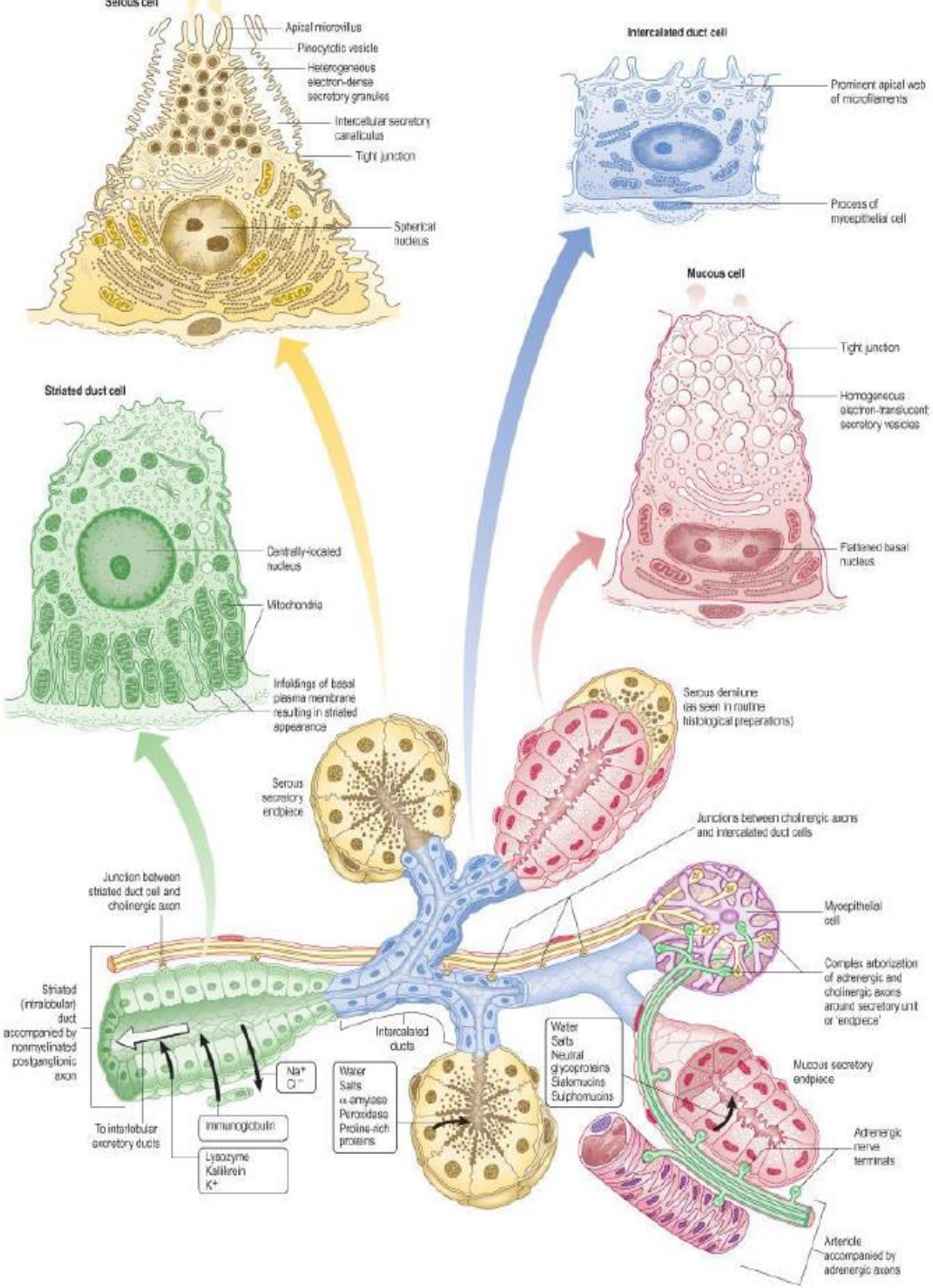
[4] Ocular staining score described in Whitcher et al 2010 (30). van Bijsterfeld score described in van Bijsterveld 1969 (29)

[5] Unstimulated whole saliva described in Navazesh & Kumar, 2008 (27)

# Histopatoloji

- Normal tükürük bezi: asiner hücreler ile tükürük kanallarından oluşur.
- Sjögren sendromunda fokal adacıklar halinde lenfositler, plazma hücreleri ve makrofajlar görülür.
- 4 $mm^2$'lik bir alanda en az 50 inflamatuar hücrenin toplanmasıyla oluşmuş kümeye Foküs denir.


Boyaltım Kanalı
Miyoepitelyal Hücre
Bağ Dokusu
Çizgili Kanal
İnterkalat(ara) kanal
Miyoepitelyal Hücreler
Miyoepitelyal Hücre
Müsöz Asinus
Müsöz Hücreler
Seröz Asinus
Karışık Asinus
Seröz Hücreler
Seröz yarımaylar



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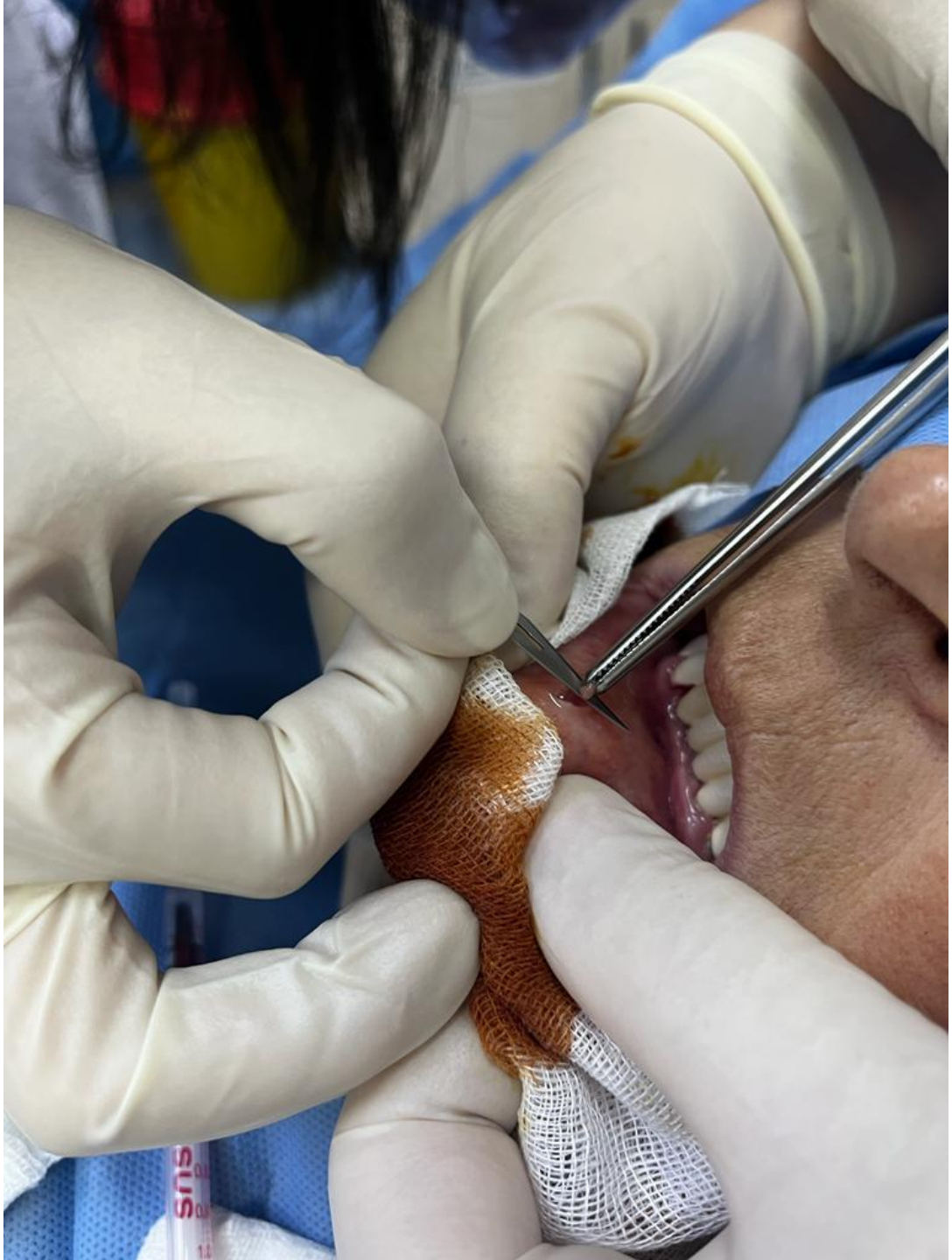
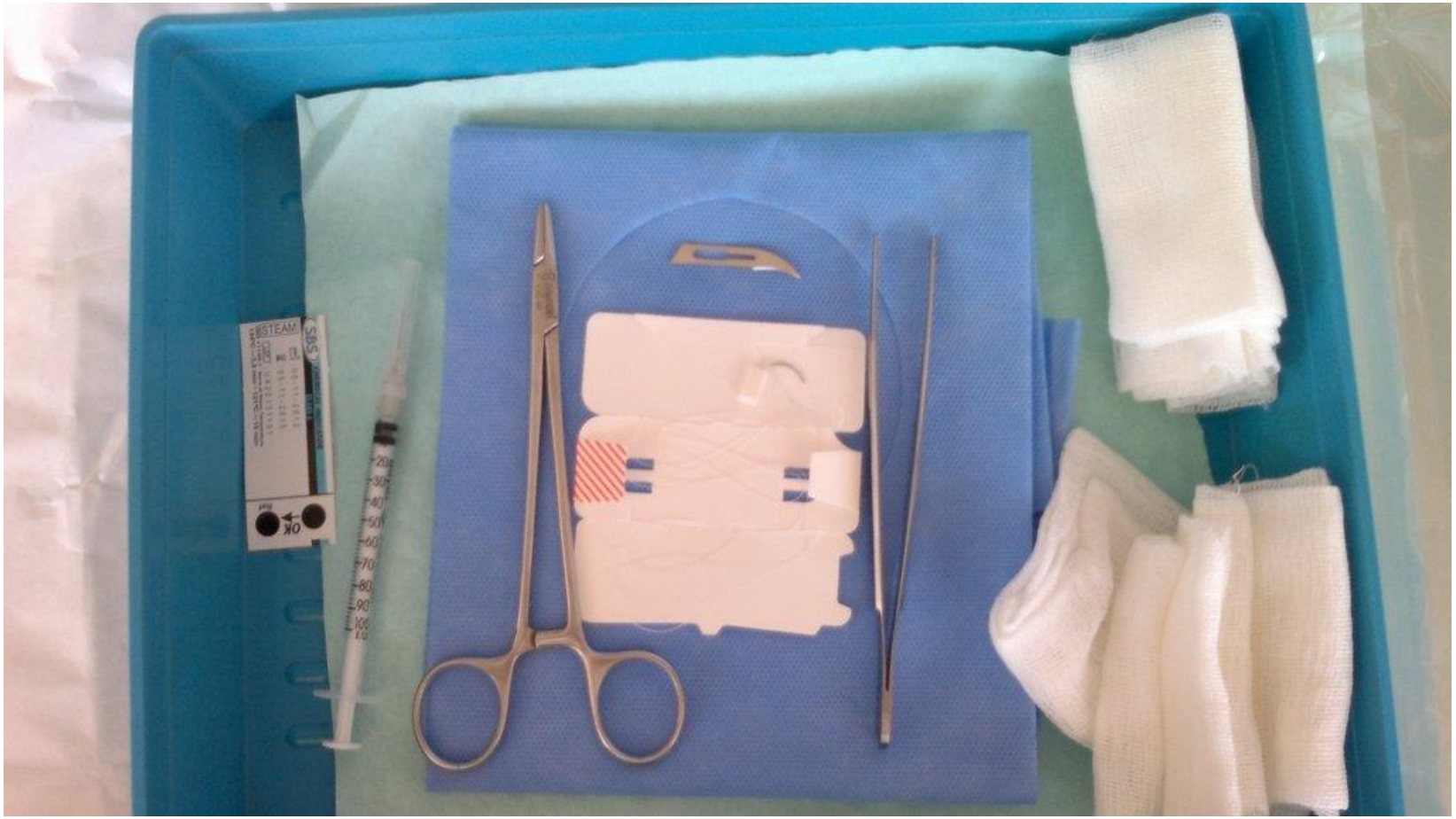
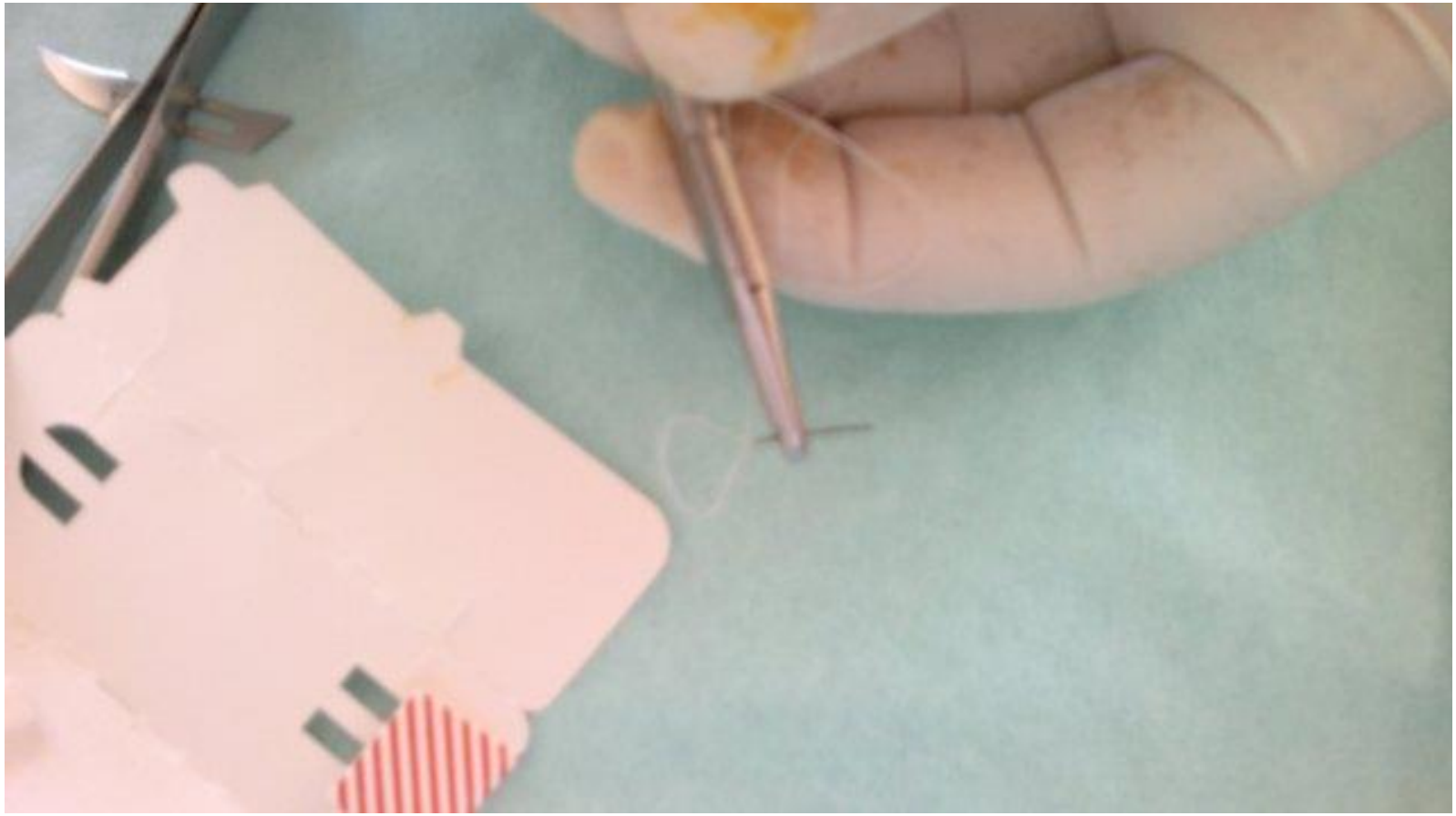
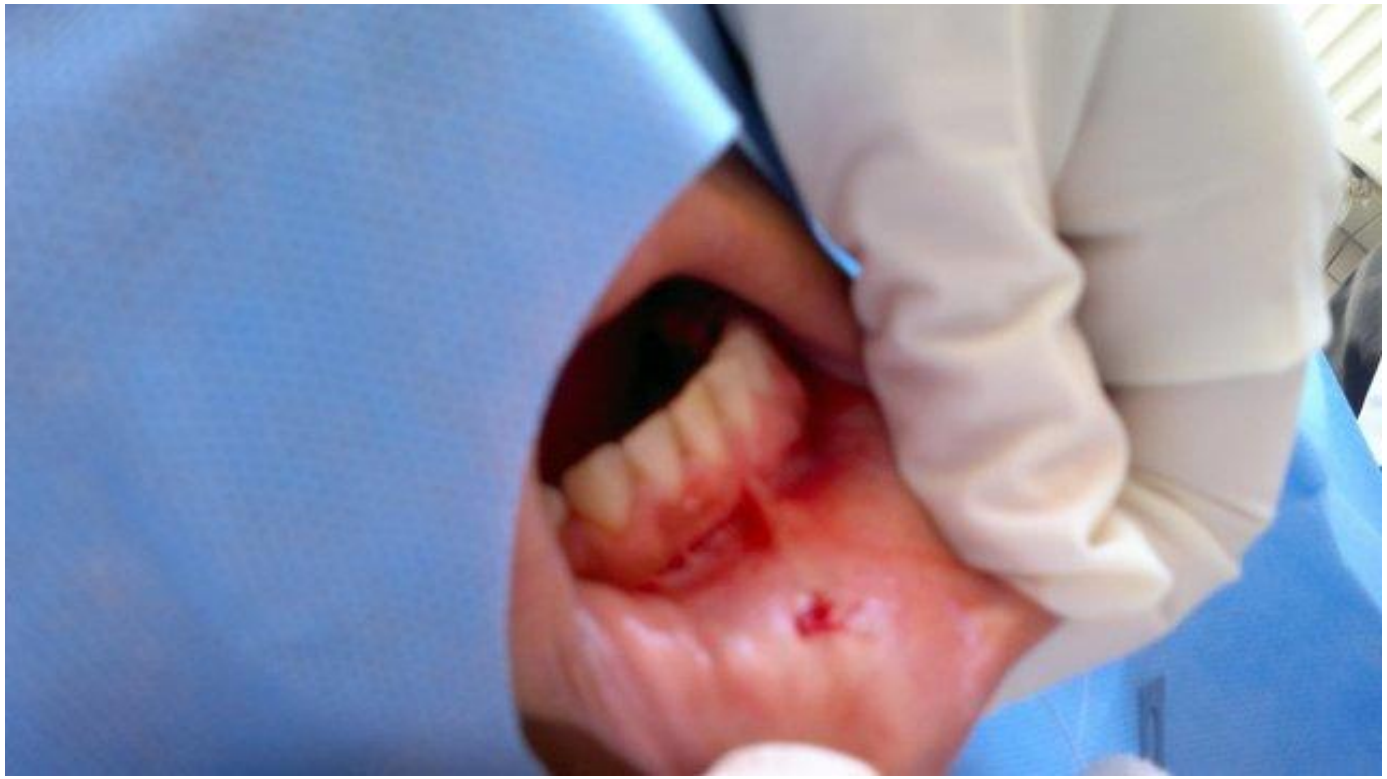
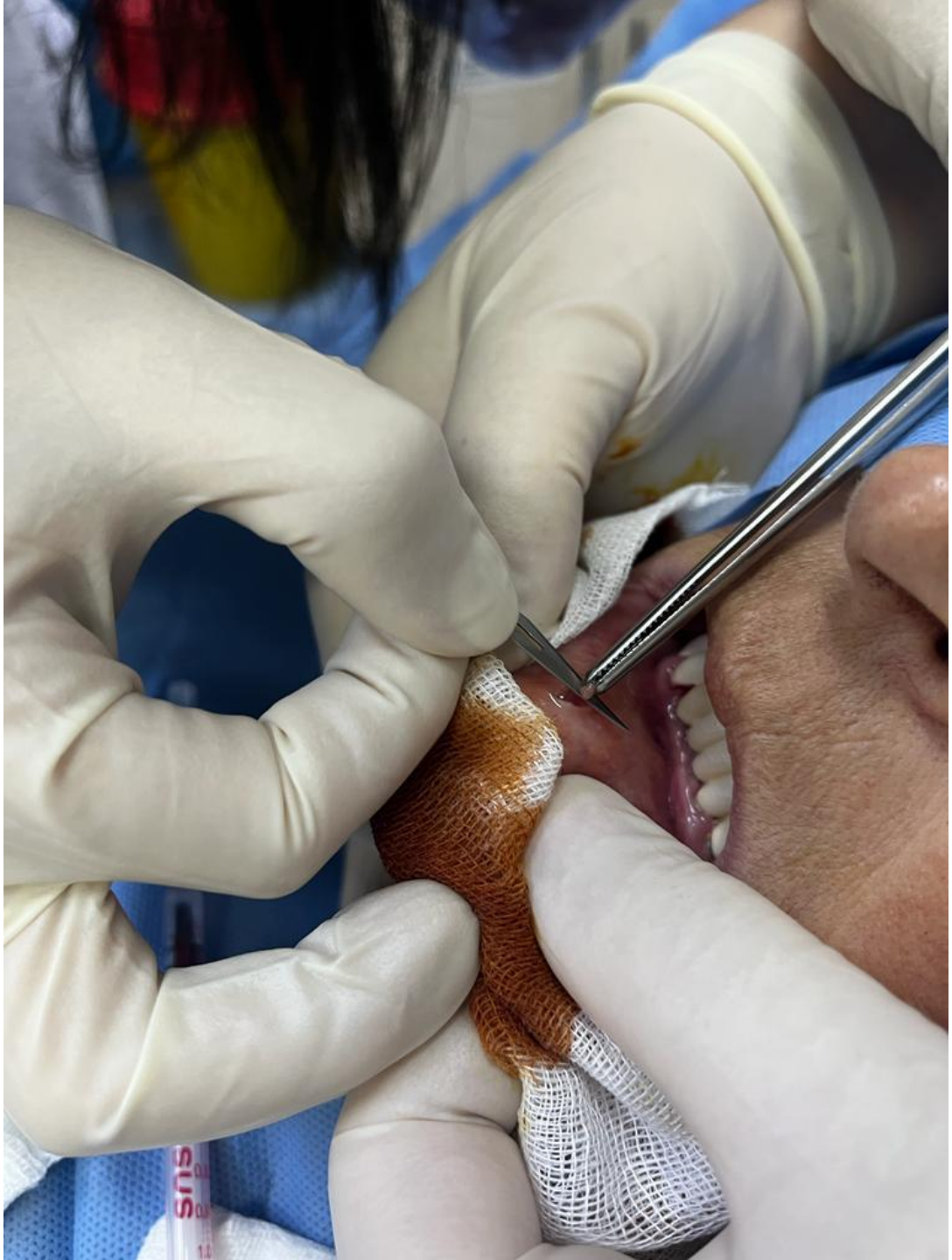
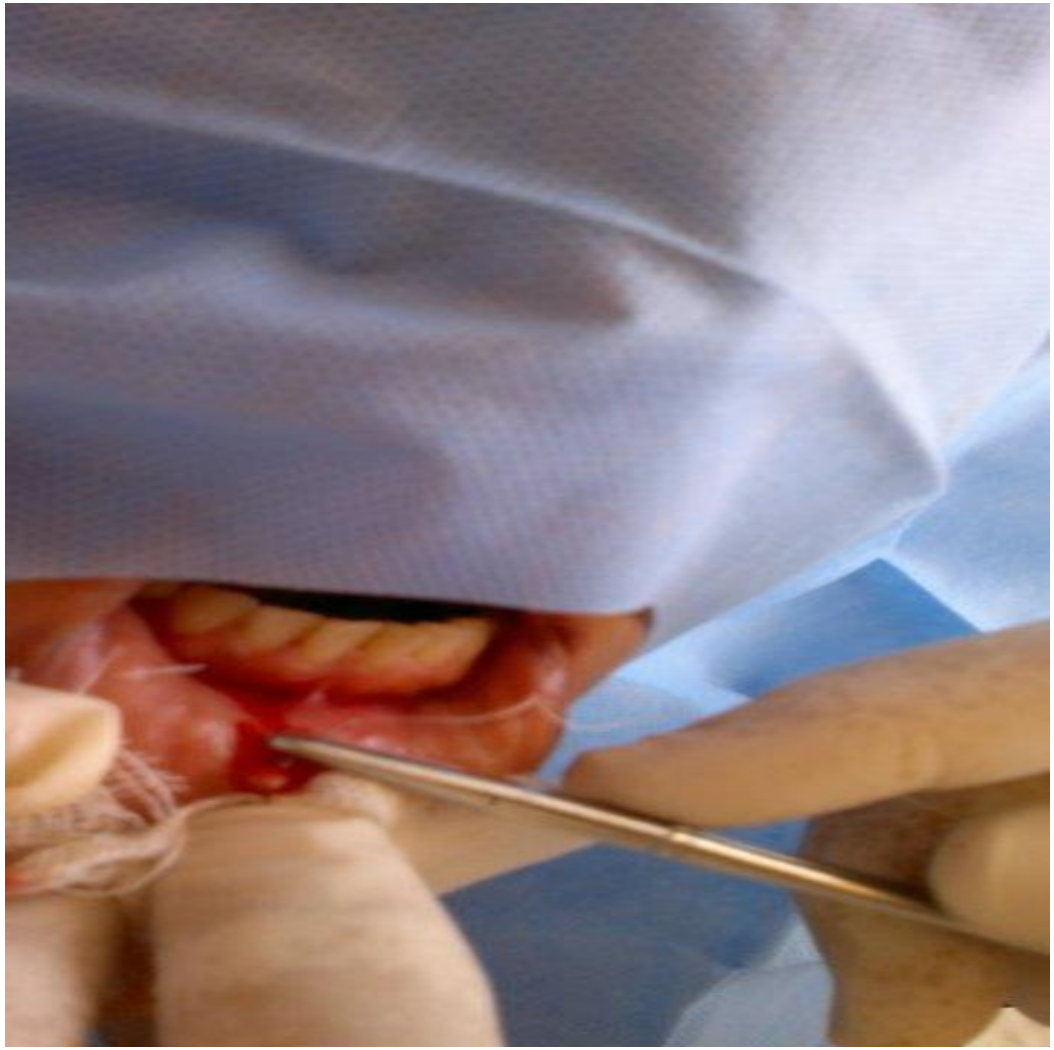


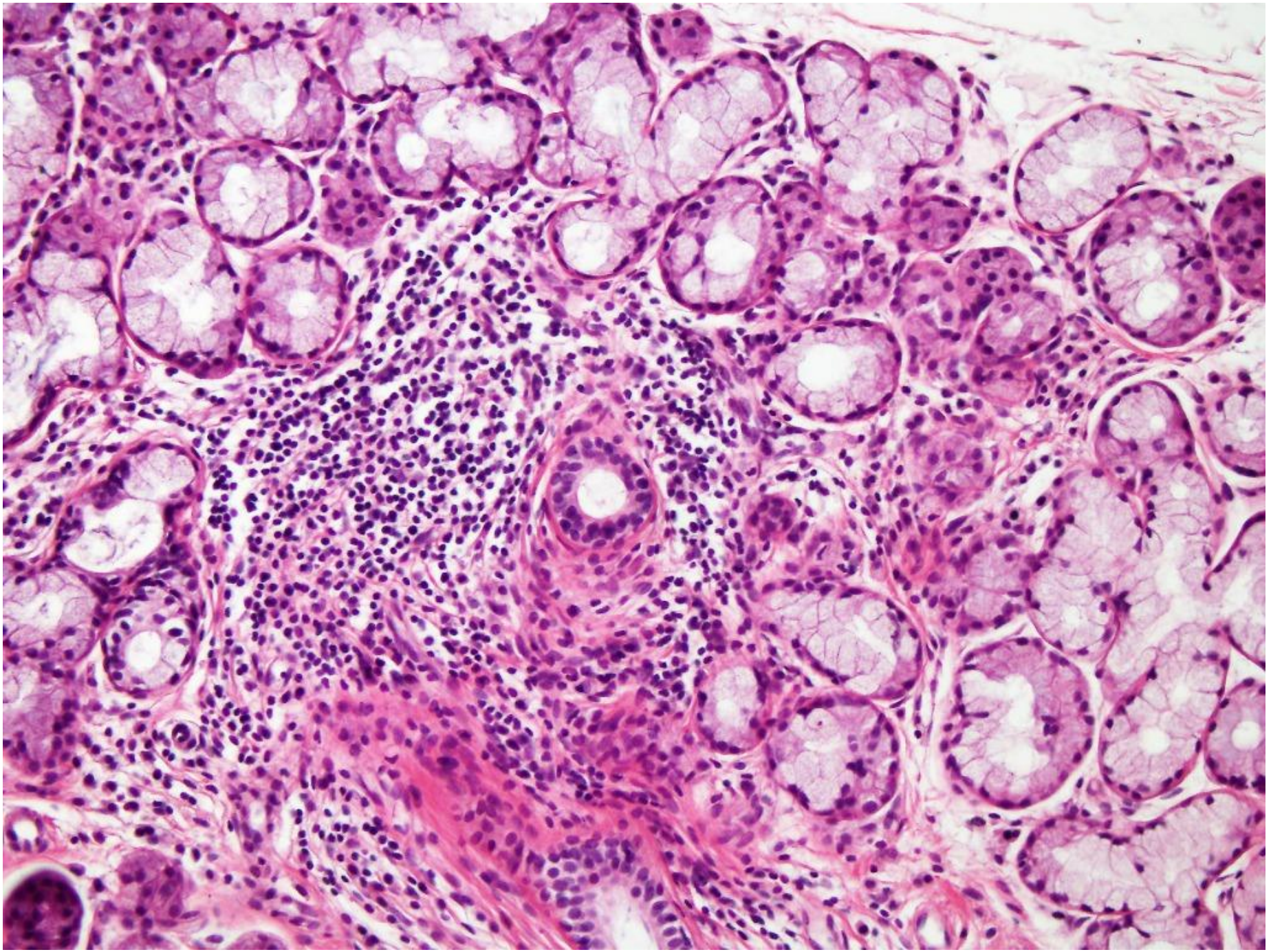

STEAM
OK

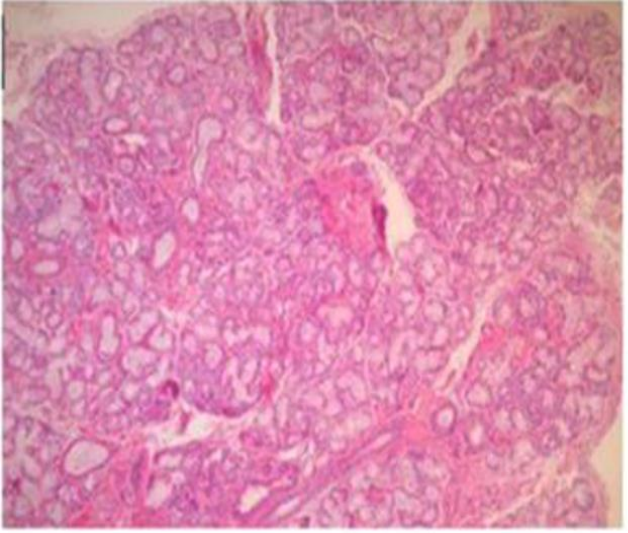




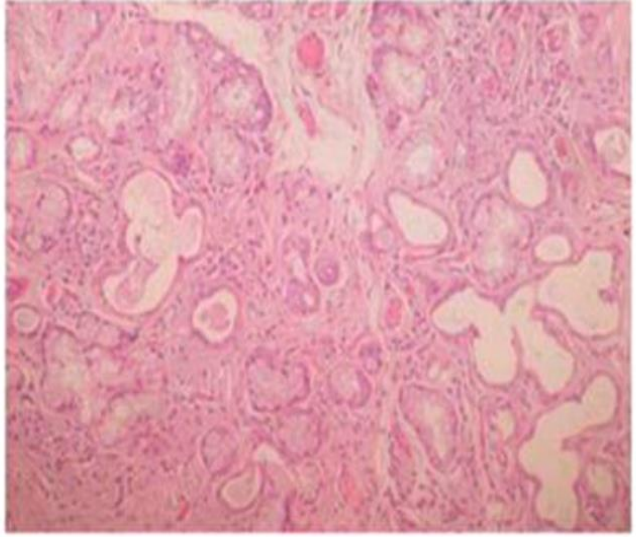




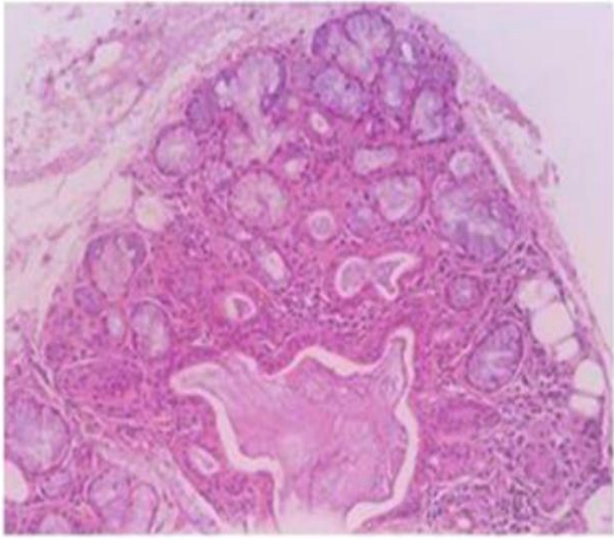




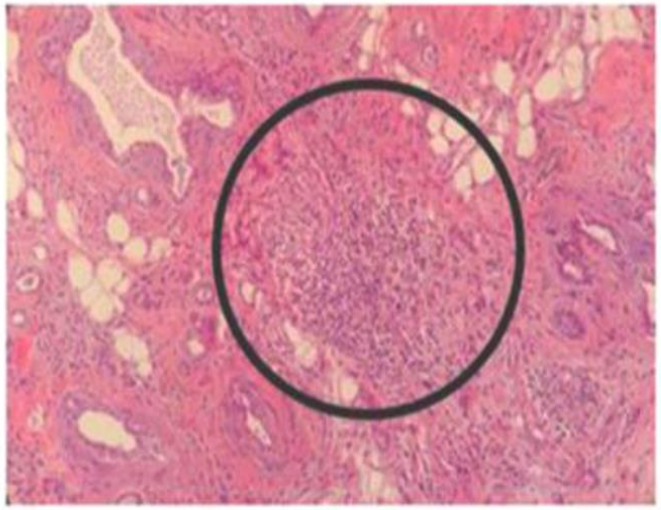
Normal salivar gland



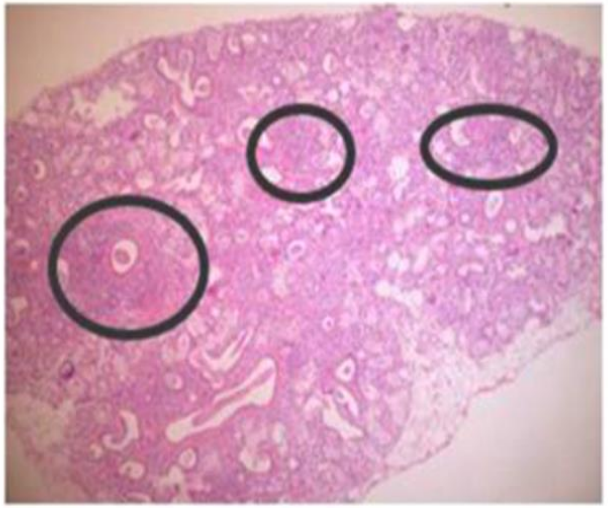
**Grade 1 Chisholm Mason *score***
Slight inflammatory infiltrate



**Grade 2 Chisholm Mason *score***
Mild inflammatory infiltrate, but <1 '*focus*' of lymphocytes per 4mm$^2$



**Grade 3 Chisholm Mason *score***
1 '*focus*' of lymphocytes and plasmocytes per 4mm$^2$



**Grade 4 Chisholm Mason *score***
>1 '*focus*' of lymphocytes and plasmocytes per 4mm$^2$

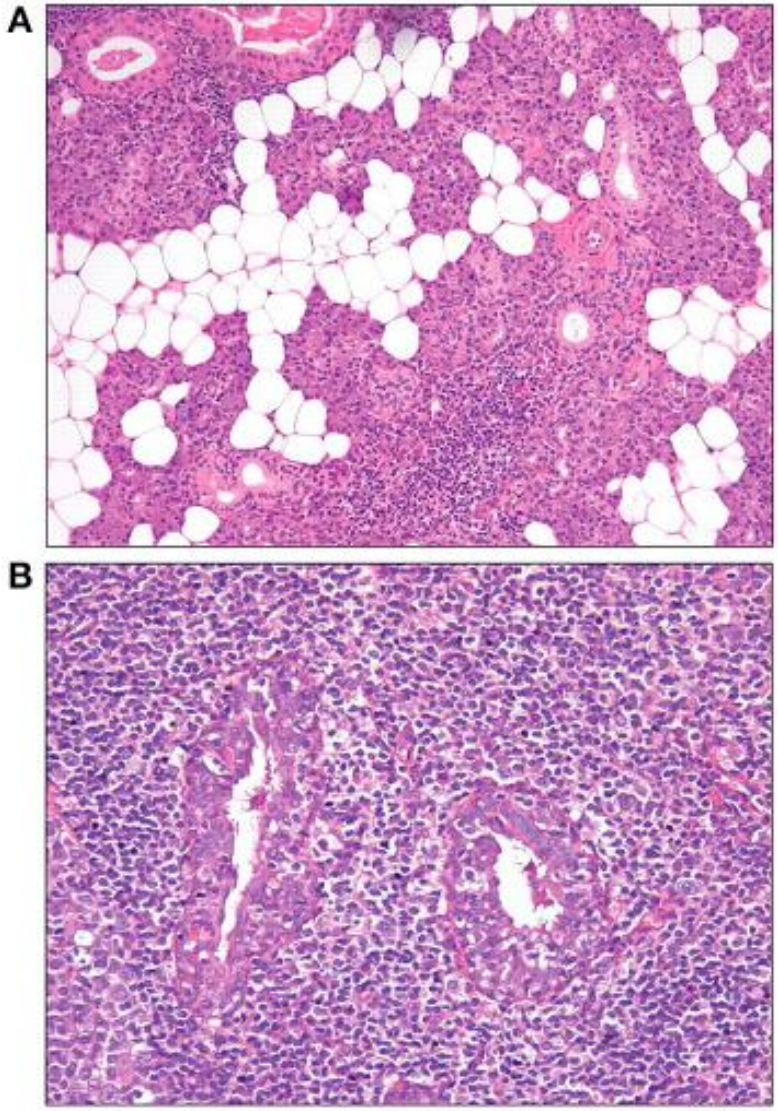
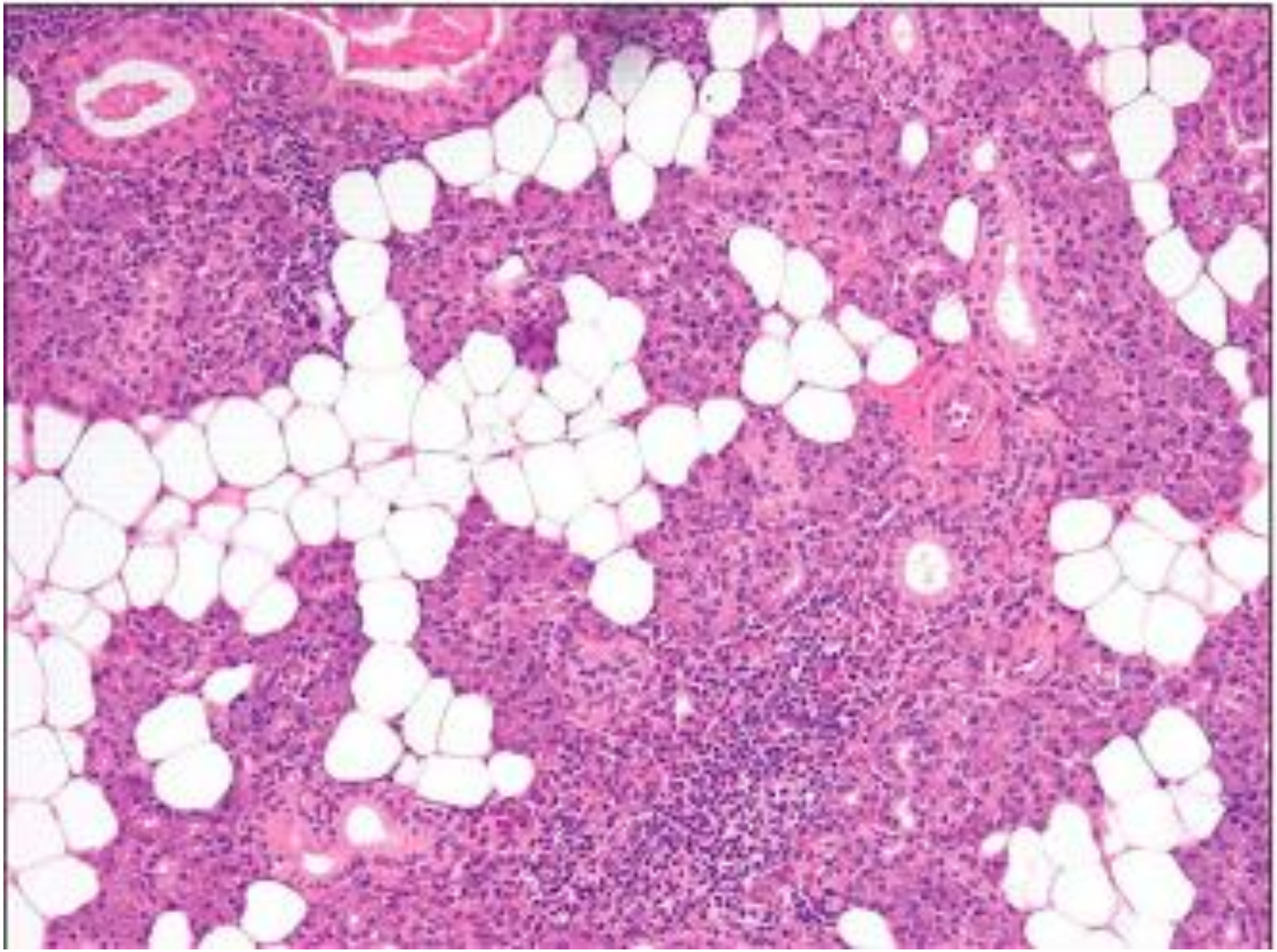



**FIGURE 2 |** Histopathological features of the parotid gland tissue stained with hemoglobin and eosin staining (57). **(A)** Adipose infiltration and periductular lymphocytic infiltrates (10×). **(B)** Lymphoepithelial lesions (LELs) surrounded by lymphocytic infiltrates (20×).

Liao Rui, 2022



Liao Rui, 2022

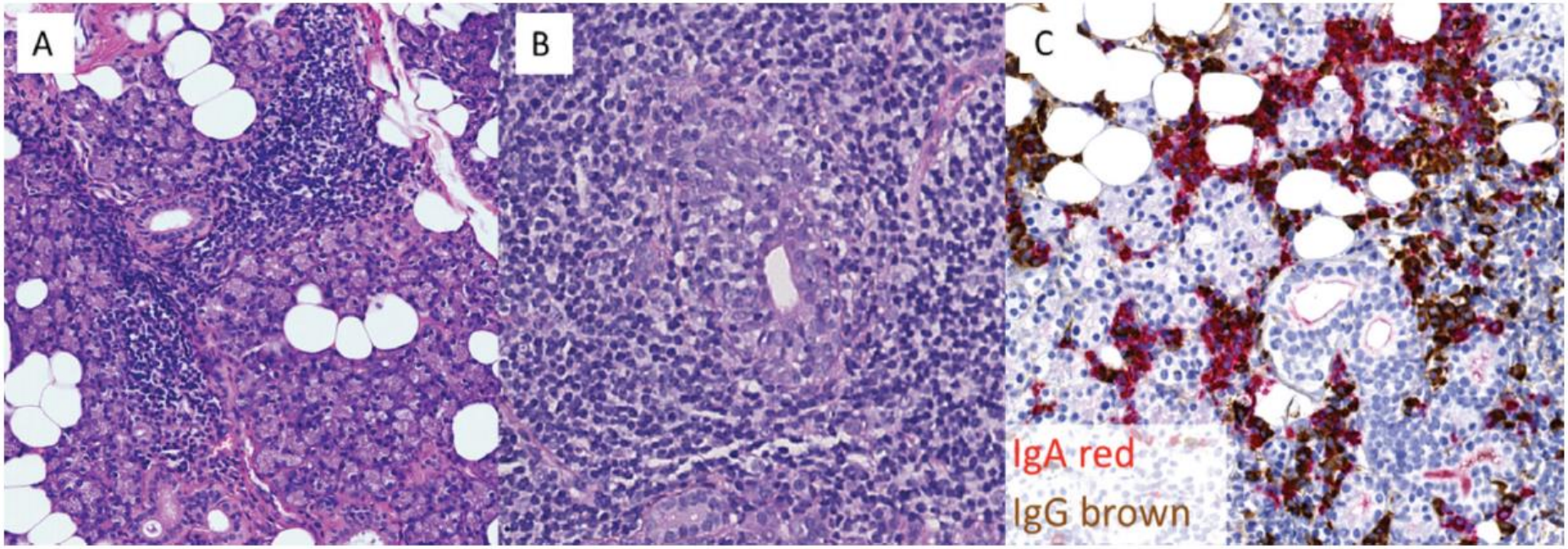



**Fig. 1.** Histopathological changes in parotid gland biopsies of pSS patients.
The examples are all from parotid gland tissue. **A**) Periductal focus surrounded by unaffected parenchyma. **B**) Centrally located duct forming a lymphoepithelial lesion within a focus. **C**) Dual staining for IgA and IgG expressing plasma cells, showing a decrease of <70%IgA expressing plasma cells.

Kroese F.G.M, 2018