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Abstract

本篇回顧文章總結了下列五類關於唾液腺病理學的新發現：

1. Immunohistochemistry
   (1) Luminal cell component – CD117
   (2) Abluminal cell component – p63 or mapsin
2. Molecular genetics
   (1) pleomorphic adenoma – translocation involving PLGA1 or HMGA2
   (2) mucoepidermoid carcinoma – MECT1-MAML2 fusion
3. Newly recognized tumor types
   (1) sclerosing polycystic adenosis
   (2) sclerosing mucoepidermoid carcinoma with eosinophilia
   (3) keratocystoma
   (4) adenoma with additional component (lymphadenoma, lipoadenoma and adenofibroma)
   (5) cribriform adenocarcinoma of the tongue
   (6) signet ring adenocarcinoma of minor salivary gland
4. Known tumor entities with new findings
   (1) salivary duct carcinoma – 新的次分類 (mucinous, micropapillary and sarcomaoid variants)
   (2) intraductal carcinoma – 命名確認 (controversies in terminology)
   (3) mucoepidermoid carcinoma – 新的分級參數與次分類 (grading parameters and oncocytic variant)
   (4) epithelial-myoepithelial carcinoma – 新的次分類
   (5) small cell carcinoma – 大部份的cases與Merkel cell carcinoma有關
   (6) extra-nodal marginal zone B-cell lymphoma – 與特定基因translocation有關
   (7) chronic sclerosing sialadenitis – 與IgG4相關之sclerosing disease 的要素之一
5. Progression of salivary gland tumors
   (1) 良性腫瘤的malignant transformation
   (2) 由low-grade 進展為high-grade carcinoma
   (3) 原位癌的dedifferentiation或stromal invasion

Introduction

本篇文章回顧了去十年所累積關於唾液腺腫瘤與類腫瘤疾病的新資訊，文章重心在於具有診斷重要性的發現與新觀念。

What is new in immunohistochemistry?

唾液腺之結構可分為兩類

(1) luminal cells – acinar and ductal cells
(2) abluminal cells – myoepihtelial and basal cells
acini與intercalated ducts是由myepithelial cells 所包圍，接下來的conducting portion則是由basal cells所支持。

利用immunohistochemistry來區分luminal 與abluminal cells有助於了解唾液腺複雜的結構、幫助診斷。

Markers for luminal cells

低分子量cytokeratin (CK, eg: CAM5.2)，carcinoembryonic antigen 或epithelial membrane antigen對luminal cells為陽性反應。

CD117對正常唾液腺細胞為陰性反應，對唾液腺腫瘤的luminal cells則經常呈現陽性。這可用來找出腫瘤中rudimentary或abortive glands。之前宣稱CD117再唾液腺腫瘤中對adenoid cystic carcinoma具有相當的專一性並未得到證實，雖然CD117會在ductal cells表現，但將一種特定針對adenoid cystic carcinoma的tyrosine kinase receptor inhibitor (imatinib)用於臨床實驗上證實對治療

ACC沒有助益。

Markers for abluminal cells
高分子量cytokeratin (eg:34βE12或CK14)，或針對myoepithelial cells 的免疫組織化學染色。
(1) 針對myoid proteins的免疫組織化學染色，eg: muscle-specific actin、smooth muscle actin或calponin。
(2) p63 –最近變得熱門，對basal cell與myoepithelial cell皆呈現nuclear immunoreactivity。無專一性，squamous cells與其腫瘤細胞也會呈現陽性反應。
(3) CD10 – myoepithelial cells呈陽性反應，無專一性。
(4) mapsin – 一種tumor suppressor，屬於myoepithelial marker。在正常唾液腺中，mapsin會出現在myoepithelial cell的核與質中。對具有雙重分化 (ductal cell-myoepithelial cell) 的唾液腺腫瘤 (eg: pleomorphic adenoma、basal cell adenoma、adenoid cystic carcinoma、epithelial-myoepithelial carcinoma)，myoepithelial component會呈現強陽性反應，而ductal component則會呈現陰性或局部弱陽性反應。Mapsin雖可顯現腫瘤的myoepithelial component，卻對myoepithelioma或myoepithelial carcinoma 缺乏專一性，因為其他腫瘤 (eg: colorectal cancer、lung cancer、oral cancer) 也會呈現陽性反應，而且並不少見 (not uncommonly)。

3. Markers for prognosis
(1) Ki67 –使用最廣泛的免疫組織化學染色。High Ki67 index與下列腫瘤的poor overall survival有關，包含mucoepithelial carcinoma、acinic cell carcinoma與adenoid cystic carcinoma。
(2) p53 –與survival無顯著關係。
(3) NM23 protein – 與tumor metastasis有關，減少或過度表現都曾被顯示與increased metastasis及poor prognosis有關。
  (a) cytoplasmic NM23 staining – 出現在pleomorphic adenoma、adenoid cystic adenoma與mucoepidermoid carcinoma，彼此間呈現陽性細胞的頻率無顯著差異。
  (b) nuclear NM23 staining – 只出現在具有metastasis的惡性唾液腺腫瘤中，可用於預測惡性唾液腺腫瘤的轉移。
(4) Membrane-bound mucins in mucoepidermoid carcinoma – MUC1、MUC4、MUC5AC。
  (a) high MUC1表現與high histological grade、高復發率、高轉移率及short disease-free interval有關。
  (b) high MUC4表現與low histological grade、低復發率及long disease-free interval有關。
  (c) MUC5AC – 可用來區別high grade mucoepidermoid carcinoma與SCC。
(5) CD43 – T cell與histiocyte的marker，偏好在adenoid cystic carcinoma中表現。
  One study – ACC:100%，PLGA: 7%，monomorphic adenoma: 12%
  Another study – ACC: 48%，其他SGTs：0%
  可用於診斷ACC。

What is new in molecular genetics?
特定基因的translocation在pleomorphic adenoma與mucoepidermoid carcinoma都曾被報告過，但仍需進一步的探索這對診斷這兩種腫瘤的潛在價值。

Pleomorphic adenoma
70% pleomorphic adenoma病例的cytogenetic aberrations可分為下列三類：
1. Rearrangement of 8q12 -- 39%
(1) 不同chromosome之間cryptic translocation
  Target gene：PLAG1
  Partner gene：CTNNB1 (β-catenin)，in t(3;8)(p21;112)
  LIFR (leukaemia inhibitory factor)，in t(5;8)(p13;q12)
  SII (transcription elongation factor SII)
  兩者fusion → dysregulated expression of PLAG1 by swapping promoter region。
(2) 同一chromosome之間cryptic rearrangement
  fusion的產物CHCHD7-PLAG1或TCEA1-PLAG1 → 造成PLAG1的overexpression。

2. Rearrangement of 12q13-15 – 8%

Target gene：HMGA2

2. Partner gene：FHIT (fragile histidine triad gene) in t(3;12)(p14.2;q145)
NFIB (nuclear protein involved in transcriptional regulation) in ins(9;12)(p23;q12q15)
造成DNA與mRNA分開，使得HMGA2的表現失調。

Sporadic，clonal changes 與8q12、12q13-15無關 – 23%

PLGA1與HMGA2 gene translocation只在pleomorphic adenoma中出現可，進一步利用RT-PCR或螢光in situ hybridization的方式來幫助診斷。

Mucoepidermoid carcinoma

1.在70%的cases中可發現t(11;19)(q21;p13)的Translocation
MECT1 (mucoepidermoid carcinoma traslocated-1) – 19p13
MAML2 (mastermind-like gene family) – 11q21
MECT1與MAML2因translocation而fusion形成新的protein會表現在各種type的mucoepidermoid carcinoma中。這種基因改變打破了Notch signaling pathway。

2.呈現MECT1-MAML2 fusion-positive的病人們與MECT1-MAML2 fusion-negative的病人相較，具有顯著減少的復發率、轉移率以及與腫瘤有關的死亡率，fusion-positive存活年限的中位數為10年，而fusion negative為1.6年，可作為有用的prognostic marker。

3. 傳統的cytogenetic或molecular genetic研究發現Warthin's tumor中也會出現MECT1-MAML2 fusion，最近以RT-PCR及in situ hybridization檢測後則沒有發現MECT1-MAML2 fusion。

Adenoid cystic carcinoma

1. 最常出現overexpression的為basement membrane and extracellular martrix proteins of myoepithelial cells的encoding gene，e.g.：laminin-β1、versican、biglycan、type IV collagen-α1。

2. 最少被表現為proteins of acinar-type differentiation 的encoding gene，eg：amylase、carbonic anhydrase、salivary proline-rich proteins。

3. Loss of heterozygosity in chromosome 6q23-25也曾在76% ACC cases中發現。

Newly recognized entities

Sclerosing polycystic adenosis

1. Clinical features and new evidence of its neoplastic nature
   (1) first characterized in 1996
   (2) resembling fibrocystic change of the breast
   (3) still under-recognized and frequently misdiagnosed，e.g.：ACC
   (4) clinical features
      (a) Age：9-80 yrs，mean age – 33~44.5 yrs
      (b) Gender：female/male – 3/2
      (c) Location：most in major salivary gland，rare in oral minor salivary gland
      (d) Growth：slow growing mass
      (e) Recurrence：1/3
      (f) Metastasis or mortality：no report
   (5) new evidence
      before：pseudoneoplastic benign entity
      now：利用human androgen receptor assay進行clonal分析，發現 這種疾病為clonal，因此可能是neoplastic。

2. Pathological features
   (1) well circumscribed and partially encapsulated
   (2) proliferation of microcysts、ducts and acinar structures in a sclerosing stroma。

(3) 局部淋巴球浸潤
(4) 腺樣組織呈lobular pattern
(5) 不等程度的表皮增生，形成solid aggregate與篩狀結構
(6) 狹窄的管腔，使人聯想到sclerosing adenosis of breast
(7) 腺狀上皮細胞具有foamy、vacuolated、mucinous 的外觀，有一些細胞會有large，brightly eosinophilic granules
(8) 40%-75%的cases會有ductal epithelial atypia，由mild dysplasia至carcinoma in situ

3. Immunohistochemical stain
(1) positive：EMA、BRST-2(常用乳癌marker)
(2) focal positive：oestrogen (雌激素) receptor、progesterone (黃體素) receptor
(3) negative：c-erbB2(致癌基因，常用乳癌marker)

Sclerosing mucoepidermoid carcinoma with eosinophilia
1.Clinical features
(1) 一種不常見的甲狀腺腫瘤，發生於Hashimoto thyroiditis，臨床進展緩慢
(2) 曾有2個形態類似的原發性病例發生在主要唾液腺
(3) 為low-grade malignancy
(4) 資料有限，無法確定這代表一種截然不同的獨立疾病，或是mucoepidermoid carcnoma的一個分支。

2. Pathological features
(1) 具有infiltrated border
(2) 嚴重的慢性發炎細胞與嗜酸性白血球浸潤
(3) low nuclear grade
(4) 大部份細胞呈現squamoid外觀與部份角化，glandular structure與squamoid islands混合，或形成有空腔的小管。

Keratocytoma
1. Clinical features
(1) 非常罕見，只有3 cases
(2) Age：3-38 years (children or young adult)
(3) location：parotid gland
(4) recurrence after complete excision：nil
(5) 易被誤判為well-differentiated SCC

2. Pathological features
(1) multicystic lesion with creamy material;
(2) multiple cystic structures lined by stratified squamous epithelium with ortho- or parakeratosis，缺乏granular layer，管腔中充滿lamellated keratin
(3) solid nests of squamous cells
(4) fibrotic stroma with chronic inflammatory cell infiltration
(5) foreign body reaction when keratin extruded from the ruptured cysts

Adenoma with additional stromal compoenent
最近數種具有addiotional stomal component的adenoma被舉出，additional component包括：lymphoid cell, adipose cells, 或fibrovascular stroma。

Lymphadenoma
1.為這個group中最重要的腫瘤，因為可能會被誤診為惡性腫瘤。Lymphadenoma是一種 adenoma accompanied by a dense lymphoid infiltrate，與sebaceous lymphadenoma類似 (除了缺乏sebaceous component)。可能不能視為distinctive tumor type，只能看作basal cell adenoma 或cystadenoma 伴隨a heavy lymphoid infiltrate。

2. Clinical features
(1) 所有的cases都發生在parotid gland。

(2) 完全切除即可治癒。

3. Pathological features
(1) well circumscribed
(2) admixed adenomatous and lymphoid components
(3) adenomatous component會形成相交通的trabeculae、islands、solid tubules、cystically dilated glands filled with proteinaceous materials，或papillary structures (Fig. 7)
(4) cyst或gland-lining cells 為cuboidal to columnar，沒有明顯的celllular atypia
(5) solid islands或trabeculae則是由basaloid cells組成
(6) lymphoid component為lymphocytes與plasma cells, lymphoid follicle可能有也可能無
(7) 一些cases中，lymphoid component太明顯以致於蓋過epithelial component，使得腫瘤看起來像lymphoma，可用PAS stain染epithelial islands的basement membrane來確認

4. differential diagnosis
(1) lymphoepithelial carinoma – definite nuclear atypia, invasive growth，significant mitotic activity，squamous rather than glandular differentiation
(2) lymphoepithelial sialadenitis – lymphoadenoma有明顯border
(3) metastatic carcinoma in lymph node – lymphoadenoma缺乏nuclear atypia

Lipoadenoma(sialolipoma)
1. Clinical features
(1) Age：wide range
(2) Gender：male predilection
(3) Location：major or minor salivary gland
(4) Growth：slowly growing mass
(5) 完全切除即可治癒

2. Pathological features
(1) well encapsulated
(2) benign tumor consisting of adipose tissue admixed with adenomatous glands
(3) 腫瘤90%為adipose tissue
(4) 一些cases會產生oncocytic change、ductal dilatation with fibrosis、sebaceous differentiation or squamous metaplasia
(5) glandular component為陷進去的腺樣組織或是組成tumor一份子仍不清楚

Adenofibroma
1. very rare neoplasm
2. admixture of adenomatous gland and a fibrocellular stroma
3. glands會有metaplastic change(eg：oncocytic metaplasia)或cystic dilation
4. stoma由spindly cells 所組成，這些spindly cells呈現CD34+，而且缺乏myoepithelial features（S-100、actin與p63為negative）

Cribriform adenocarcinoma of the tongue
1.1999年，Michal et al提出8個cases，並命名為cribriform adenocarcinoma
2.目前仍不清楚這是否是為distinctive tumor type或只是PLGA的一種variant，但與後者相對照，cribriform adenocarcinoma只發生在tongue且cervical lymph node metastasis頻率也高出許多(100%)。
3. Pathological features
(1) 具有不同的生長pattern -- solid、microcystic、follicular、cribriform與papillary
(2) 腫瘤細胞具有一致且經常重疊的細胞核，chromatin呈現vesicular或ground glass的樣子(Fig. 8)
(3) 無明顯mitotic activity、necrosis或haemorrhage

Signet-ring cell (mucin-producing) adenocarinoma of minor salivary gland
1. Clinical features

(1) mean age：56.4 yrs
(2) location：所有的cases都發生在口腔中的minor salivary gland
(3) exophytic mass fixed to underlying tissue
(4) low-grade malignant neoplasm with no recurrence or metastasis after excision

2. Pathological features
(1) 腫瘤為infiltrative，形成狹窄平行的strands，其中散布small tumor nests或單獨的tumor cells
(2) Signet ring 細胞佔大部份，其細胞質中有一個至數個mucin vacuoles，細胞核偏離中心
(3) 小部份tumor cells具有eosinophilic或clear cytoplasm
(4) mild cytological atypia, rare or absent of mitotic figures，no necrosis，mucin pool只在一個case中出現，perineural invasion也不常見

Known tumor entities with new findings
Salivary duct carcinoma
最近有數種variants被發表出來，對診斷並不會造成問題因為典型的salivary duct carcinoma都會至少佔腫瘤的局部部份。

1. Mucin-rich variant – areas of mucinous/colloid carcinoma，可見到clusters of carcinoma cells(with or without cytoplasmic mucin) float in mucin pools

2. Invasive micropapillary variant – 形成morule-like tumor cell clusters，沒有fibrovascular cores，並且被一圈clear space所包圍，形態上類似micropapillary variant of breast or urothelial carcinoma。比傳統的salivary duct carcinoma更aggressive (Fig. 9A)。

3. Sarcomatoid variant – 具有sarcomatoid component，由anaplastic spindly cells、怪異的多核細胞、rhabdoid cells以及osteosarcomatous cells(罕見, Fig. 9B)所組成。這些anaplastic cells常顯示有focal immunochemistry and ultrastructural evidence of epithelial differentiation。觀念上，作者將這個variant 視為一種salivary duct carcinoma去分化(dedifferentiation)後的form。

Intraductal carcinoma：the controversies in terminology
1. Concept：pure intraductal proliferation of tumor cells，所有的tumor islands周圍都有完整的myoepithelial layer包圍，具有low malignant potential，行為類似breast的intraductal carcinoma。
2. 1983年第一次被描述(Chen)，在2005年WHO分類中仍不是a recognized entity。此命名並沒有被廣泛接受，其原因可能為一些具有pure intraductal-like growth的salivary duct carcinoma仍具有aggressive course，而且在轉移的腫瘤中有時也可看到intraductal-like component。作者認為這些觀察可歸因於"intraductal-like"這個term被無區分(indiscriminate)的使用，它通常表示invasive growth而非genuine in situ growth。
3. 在已發表的文獻中常被稱為low-grade salivary duct carcinoma，作者認為實際上這些cases不是屬於pure intraductal carcinoma就是intraductal carcinoma with microinvasion。作者也認為使用intraductal carcinoma 比low-grade salivary duct carcinoma更適合，這可避免與more aggressive 的salivary duct carcinoma 產生混淆。新WHO分類中採用"low grade cribriform cystadenocarcinoma"這個名詞，這引起更多誤解，作者與Weinreb等學者並不推薦採用這個命名。Intraductal carcinoma到底代表conventional salivary duct carcinoma的precursor 還是一種完全分開獨立的entity仍待釐清。
4. Clinical features
(1) Location：最常發生於parotid gland，與salivary duct carcinoma相同，也會侵犯小唾液腺。
(2) Prognosis：完全切除後結果很好，沒有metastasis或mortality。復發可歸究於incomplete excision。放著假以時日invasive component會發生。
5. Pathological features
(1) multiple smoothcontoured ducts expanded by epithelial proliferation forming cribriform, fenestrated, solid-comedo, micropapillary or Roman-bridge patterns, 結構類似乳房的atypical ductal hyperplasia 或 intraductal carcinoma (Figure 10A).
(2) 組成細胞通常顯示低至中度的 cytological atypia，有時高度cellurlar atypia也會出現 (Figure 10B). 這些細胞也會展現 apocrine features. Tumor islands 周圍的 myoepithelial cell layer在光學顯微鏡下可能很明顯也可能不明顯。

(3) The stroma is sclerotic and 可能具有次發性變化(secondary changes) 例如：haemorrhage, chronic inflammatory infiltrate and dystrophic calcification。

(4) 偶爾，microscopic invasive component 也會出現，可能在原發腫瘤中也可能在復發的情況下，這對臨床的重要行仍不清楚，但預後則是favorable。

6. Prerequisites of diagnosis

要診斷為intraductal carcinoma，必須以complete sampling 與immunohistochemistry 顯示每一個tumor island都有完整的myoepithelial layer，將invasive component排除(Figure 11)。

Mucoepidermoid carcinoma

Grading

1. Traditional → low grade, intermediate grade, high grade

Criteria：

(1) prominence of cysts

(2) abundance of mucus cells

(3) mitotic activity and cytological atypia

2. Evans → low grade, high grade

Criteria：intracystic space > 10%, 排除stroma與extravasated mucus所佔的區域。

3. AFIP scoring system → low grade (score 0-4), intermediate grade (score 5-6), high grade (score >= 7)

Criteria：

(1) intracystic component < 20% (score 2)

(2) neural invasion (score 2)

(3) necrosis (score 3)

(4) mitoses >=4 / 10 high power fields (score 3)

(5) anaplasia (score 4)

缺點：容易undergrade

與臨床結果的關係：

inraoral與parotid mucoepidermoid carcinomas：good correlation

submandibular：無法預測

4. Modified → adding 3 parameters

(1) lymphovascular invasion

(2) bone invasion

(3) invasion in the form of small nests and islands

Oncocytic variant (Fig. 12)

1. Rare
2. 特色：extensive presence of oncocytic cells
3. 容易誤診為oncocytoma

兩者差異：

(1) oncocytoma – pure population of cells, 偶爾有一些具有clear cytoplasm的細胞出現。

(2) mucoepidermoid carcinoma, oncocytic variant – 除了oncocytic cells, 還會出現細胞具有cytoplamic mucin，mucin-containing cystic spaces, 或non-oncocytic tumor islands

Epithelial-myoepithelial carcinoma

Oncocytic variant

1. rare
2. 特色：extensive oncocytic change in luminal cells alone or in both luminal and abluminal cells
3. 有些會有papillary growth pattern，也可能產生sebaceous cell differentiation

Double clear variant

1. 特色:clear cell change in both luminal and abluminal cells
2. 當epithelial component增生形成solid 或 cribriform的結構時，以型態來區分epithelial 與 myoepithelial cells 可能會有困難

Ancient variant

myoepithelial component 產生ancient change– hyperchromatic nuclei，smudged chromatin, random

cytological atypia, no increase of mitotic activity。

Other morphological features
1. complete lacking of clear cell change – 20%
2. sebaceous differentiation – 13.1%
3. spindle cells – formed by myopeithleial component occasionally, 可能會出現palisaded nuclei, 形成類似Verocay bodies 的結構。

Progression of epithelial-myoepithelial carcinoma
有兩種progression：
1. high grade myoepithleial carcinoma
   (1) 特色：overgrowth of myoepithelial cells with nuclear anaplasia (Fig. 13)
   (2) criteria：nuclear atypia > 20% of myoepithelial cells
   (3) prognosis：worsened
2. high grade carcinoma lacking evidence of myoepithelial differentiation
   (1) 特色：high mitotic activity, necrosis
   (2) prognosis：greatly worsened

Small cell carcinoma
1. an aggressive malignancy，超過一半的病人發生local recurrence或distant metastasis。
2. 兩種type – Merkel cell type，Pulmonary type
   73% small cell carcinoma為CK20(+)，這表示大部份的cases與Merkel cell carcinoma(CK20+)較有關連。Merkel cell type的存活時間比pulmonary type(CK20-)長。
3. Overall survival rate 為40%-50%，與cutaneous Merkel cell carcinoma相當，比conventional pulmonary 或non-pulmonary small cell carcinoma要好。

Extranodal marginal zone B-cell lymphoma of salivary gland
1.salivary gland 中最常見之lymphoma – extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue(MALT)
2.與extranodal marginal zone B-cell lymphoma相關的四種chromosomal translocation：
   (1) t(11;18)(q21;q21): API2／MALT1
   (2) t(1;14)(p22;q32): BCL10／IGH
   (3) t(14;18)(q32;q21): IGH／MALT1
   (4) t(3;14)(p14.1; q32): FOXP1／IGH.

這四種type的final pathway都牽涉到nuclear factor- κB，而且具有organ-specificity，例如t(11;18)主要發在消化道與肺的MALT lymphoma，而salivary gland MALT lymphomas中，有12-22%的cases具有t(14;18)(q32;q21)，其它三種則完全沒發現。一篇北美的研究則是無法在salivary gland MALT lymphoma中偵測到t(14, 18)，這篇研究所發現的abnormality為trisomy 18。
organ-specificity的原因仍不明。

Chronic sclerosing sialadenitis (Kuttner tumor)
New concept of the nature of chronic sclerosing sialadentis
1. Clinic features
   (1) Location：exclusively affecting submandibular gland
   (2) Age：middle-aged or elderly
   (3) Gender: slight male predominance
   (4) bilateral hard swelling, in advanced stage → 稱為Kuttner tumor
2. Nature
   (1) 以前—a chronic inflammatory disease resulting from inspissated secretion, stones or microliths, and perpetuated by ascending infection
   (2) 最近—belong to the spectrum of IgG4-related sclerosing disease。

IgG4-related sclerosing disease -- a syndrome characterized by involvement of one or more tissue by a chronic inflammatory cell infiltrate which includes IgG4 plasma cells, accompanied by atrophy of the normal tissue and sclerosis。一些患者患有相關自體免疫疾病(例如風溼性關節炎

)或circulating autoantibodies，血清中的IgG4, IgG, 及IgG4/IgG ratio都升高，這種疾病對類固醇療法反應佳。

Pathology
1. histological features與autoimmune pancreatitis 很類似
(1) 疾病初期，lymphoplasmacytic infiltrate around the salivary ducts.
(2) 接著產生periductal fibrosis
(3) lymphplasmacytic infiltrate 與 fibrosis逐漸變強，侵犯整個lobe，使acini萎縮(Fig. 14A)。
(4) 常產生reactive lymphoid follicles。

2. Immunohistochemitry
(1) T cells 與ducts及acini有密切關係
(2) B cells 侷限在lymphoid follicles中
(3) 有大量的IgG4+ plasma cells出現(Fig. 14B)

Progression in salivary gland tumors
腫瘤的發展是一種multistep的過程，牽涉到sequential accumulation of genetic changes。Salivary gland tumors 提供很好的機會來釐清腫瘤發生的機制，原因如下：
(1) SGTs有複雜的細胞結構
(2) SGTs有數種不同的indolent tumors，可作為累積新突變的土壤

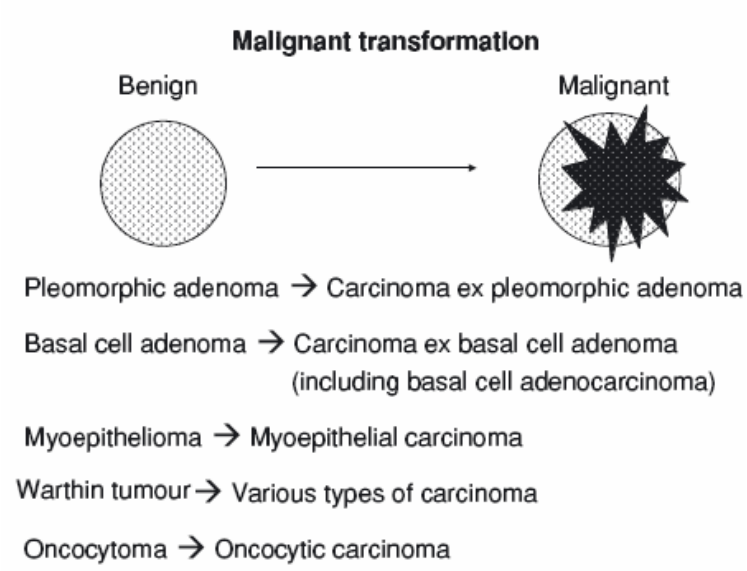

Figure 15. Progression of salivary gland tumours: malignant transformation.

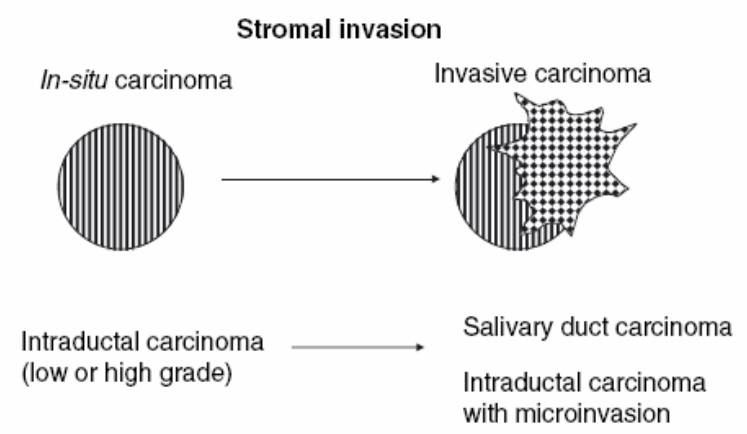

Figure 18. Progression of salivary gland tumours: stromal invasion.

Carcinoma ex pleomorphic adenoma: what's new?
Evolution of carcinoma ex pleomorphic adenoma
循序漸進式演化有時可在 carcinoma ex pleomorphic adenoma 的發展過程中被觀察到，這些不同的時期具有 prognostic significance。

1. Earliest phase
   carcinoma cells with large atypical nuclei 取代 the neoplastic ductal luminal cells，在原先的 pleomorphic adenoma 仍維持完整一層的 non-atypical myoepithelial cells (Figure 19). 這可被視為一種 carcinoma in situ，而且此時腫瘤沒有轉移的 potential.。
2. With time
   the carcinoma cells 突破了原先完整的 myoepithelial sheath並且侵犯至周圍的stroma.。若 carcinoma cells 仍局限在原先的 pleomorphic adenoma 則可視為 'intracapsular' (Figure 20)，此種情況以complete excision治療後的預後良好，只有一個case出現cervical lymph node轉移。
3. Invasion 延伸至capsule外
   此時的carcinoma ex pleomorphic adenoma 被視為 'invasive'。還可分為
   (1) minimally invasive -- tumor with minimal metastatic potential，目前在WHO的分類，tumors with invasion of < 1.5 mm from the tumor capsule
   (2) frankly invasive

在數個研究中發現良好預後出現在腫瘤已有extracapsular invasion，侵犯之深度超過capsule < 8 mm, 5 mm or 1.5 mm。臨床上, 在某些病例可能很容易去測量界定侵犯的深度，在某些病例則變得很難。

Cell types that undergo malignant change in pleomorphic adenoma
(1) 75% cases -- luminal epithelial cells 發生惡性轉變
(2) 19% cases – dual epithelial–myoepithelial differentiation
(3) 6 % cases -- pure myoepithelial differentiation

Genetic mechanisms mediating malignant transformation
1. 8q21與12q13-15 發生改變或重新排列常可在carcinoma ex pleomorphic adenoma中發現，與其 benign counterpart 類似。Pleomorphic adenoma中，12q loci失去heterozygosity的subset 具有 malignant transformation 的潛力。
   transformation.116 12q13-15的變異造成下列基因的amplification與overexpression，包括 CDK4、HMGA2與MDM2，可能代表對malignant transformation 具有影響的genetic events。
2. p53 gene 改變 -- 29–67% cases；p53 protein overexpression -- 41–75% 顯示這個基因至少在某些cases的malignant transformation中佔有一個角色。
3. c-erbB2 overexpression或amplification -- 21–82%，c-erbB2被假設可用來區分carcinoma ex pleomorphic adenoma from atypical pleomorphic adenoma (Figure 21).

Dedifferentiation of salivary gland carcinomas
'Dedifferentiation' – 即唾液腺惡性腫瘤由細胞分化良好的low grade轉變分化差的high grade，其原

來的cell line特徵以不再明顯。

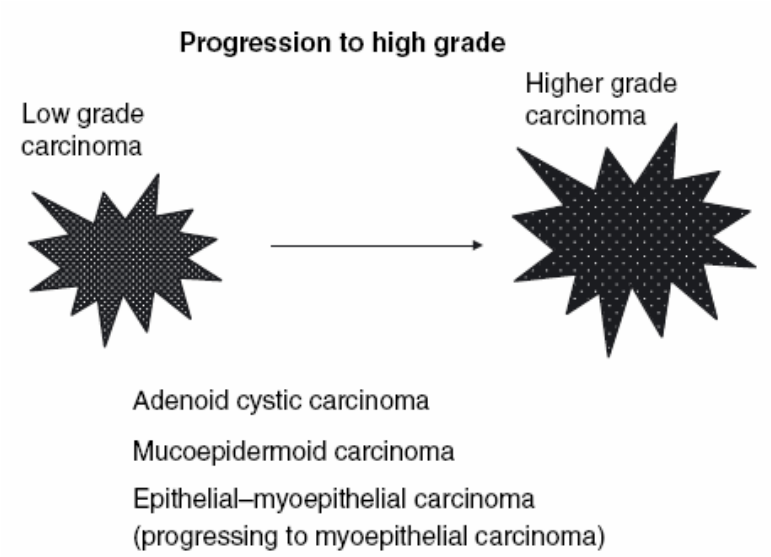

Figure 16. Progression of salivary gland tumours: progression from low grade to high grade.

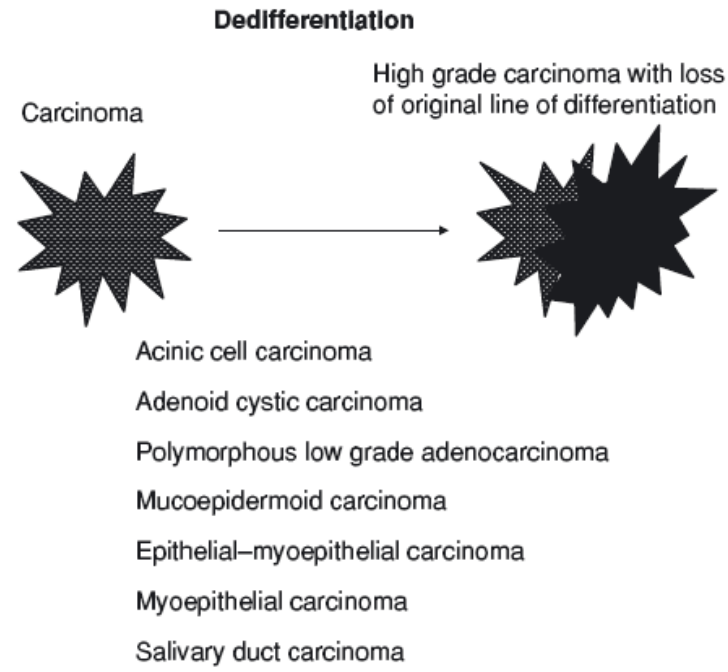

Figure 17. Progression of salivary gland tumours: dedifferentiation.

1. Acinic cell carcinoma.—第一個被觀察到有dedifferentiation的惡性SGT，被去分化的部分轉變為high-grade adenocarcinoma、poorly differentiated carcinoma 或undifferentiated carcinoma.
2. 最近幾年各種惡性SGT的dedifferentiation都有被發現，包含下列惡性SGT – mucoepidermoid carcinoma, adenoid cystic carcinoma, myoepithelial carcinoma, polymorphous low-grade adenocarcinoma, epithelial–myoepithelial carcinoma, hyalinizing clear cell carcinoma and salivary duct carcinoma. ，雖然dedifferentiation並不常見。除salivary duct carcinoma 之外，其它惡性SGT一開始都是indolent tumors，當新的genetic alterations逐漸累積，最後high-grade aneuploid carcinoma就產生了。

Clinical features

Dedifferentiation 可發生在initial tumor也可能在relapse時出現。臨床上可看到一個長期存在的腫

瘤在近期內發生快速的生長，造成bulky disease。 有些cases則是在low grade carcinoma relapse時發生快速生長。Recurrence 與metastasis 屬常見，與原先的carcinoma相較，預後普遍poor。

Common pathological features
會有明顯的invasive growth與coagulative necrosis (Figure 22)，腫瘤細胞會有明顯的nuclear atypia, pleomorphism與不正常的細胞分裂活動。通常原始腫瘤區域與去分化後的區域會緊接在一起，中間沒有過渡區(transitional zone)。

Genetic changes that mediate dedifferentiation
目前學者對於造成dedifferentiation的 molecular mechanisms 的認識仍很有限，在一些cases，數個基因被發現可能與此有關，例如：p53 mutation (accompanied by strong expression of p53 protein), increased cyclin D1 expression, c-erbB2 protein overexpression or gene amplification, and loss of expression of Rb protein。

題號	題目
1	下列發生於salivary glands的腫瘤何者不屬於malignant mixed tumor? (A) Metastasizing mixed tumor (B) Pleomorphous low grade adenocarcinoma (C) carcinosarcoma (D) Carcinoma ex pleomorphic adenoma
答案(B)	出處：Oral & Maxillofacial Pathology, P.353
題號	題目
2	下列何種組合的惡性唾液腺腫瘤常見有perineural invasion? (A) Adenoid cystic carcinoma & carcinoma ex pleomorphic adenoma (B) Acinic cell carcinoma & Adenoid cystic carcinoma (C) Pleomorphous low grade adenocarcinoma & Adenoid cystic carcinoma (D) Adenoid cystic carcinoma & salivary adenocarcinoma, NOS
答案(C)	出處：Oral & Maxillofacial Pathology, P.349~358