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內文：

Wegener's granulomatosis

Abstract

1. A multisystem disease
2. Characterised by necrotizing granulomatosis of the upper and lower respiratory tracts, disseminated vasculitis (血管炎) 1 如下 and glomerulonephritis (腎絲球炎) 2 如下 Note 1

他的臨床表徵和牽涉到的器官其實相當廣泛。今天這個案例可以讓我們知道 Wegener's granulomatosis 和特定的 oral lesion 的關係。若是不了解這些 lesions 不僅會延遲診斷和治療計畫，甚至可能導致潛在性的致命結果。

Case Report

這個4歲的小朋友是一個地區醫院 department of oral and maxillofacial surgery 接到的 case。他的主訴是 *a lesion on his left buccal gingivae which was apparently growing in size, painful bleeding gums and oral ulcers since 4 months ago*。他是雙胞胎中的老大，在36週的時候剖腹抱出來，development history 並不明顯，過去曾有 glue ear 3 如下的病史影響聽力。

檢查結果顯示為 *florid erythematous gingival hyperplasia with desquamation in the palatal aspect*。他同時有 nasal obstruction with mucus in the nose。

The gingivae were biopsied under GA and a number of hematological tests were also conducted。Biopsy 的結果是 *non-specific granulomatous inflammation with epithelioid granulomas*，這確定了我們臨床所下的診斷 - Wegener's granulomatosis (WG)。在初步的治療中有獲得改善 - 讓小孩服用了2個禮拜份的 *co-trimoxazole* 和 *prednisolone* Note 2。但是仍然可以發現 swelling on the labial aspect of the gingivae with erythema and hyperplasia over the interdental papillae。

這位小朋友被緊急轉送到 local university hospital 接受小兒科醫師的會診，進行評估是否牽涉到多重器官，雖然本人並沒有 systemic complaints，而且是 symptom free。在服用了 prednisolone 3個月後，gingival hyperplasia 的問題被徹底解決，現在維持 1 mg 劑量的 prednisolone 已經1年了，沒有任何症狀。

Differential Diagnosis

根據病史，在 etiology 可以下的 DD 有 tuberculosis, aspergillosis (黴菌症) or sarcoidosis (類肉瘤病) and even Crohn's disease，其他可以考慮的 entities 包括了 leukemia, Churg-Strauss disease, polyarteritis nodosa (結節性多動脈炎) and scurvy (壞血病)。

Investigations

診斷 Wegener's granulomatosis 必須靠：

1. A raised PR3-ANCA [proteinase 3 antineutrophil cytoplasmic antibodies, 正式的名稱為 cytoplasmic-antineutrophil cytoplasmic antibodies (c-ANCA)] Note 3

2. Histopathological confirmation

在輕微的案例中(就像這個case)，有高達40%的個體不會有升高的PR3-ANCA。雖然檢驗PR3-ANCA仍然是個具爭議性的診斷工具，但是仍會用於biopsy沒有特殊發現的病患。其他的檢查有renal function tests, urinalysis (dipstick/proteinuria/haematuria), full blood count including erythrocyte sedimentation rate(ESR) and chest X-ray。

在這個案例中，laboratory investigations可以發現到顯著升高的platelets ($735 \times 10^9/L$)⁴ 如下、升高的ESR (30 mm/hr)⁵ 如下和microcytic anaemia(小球性紅血球)，雖然c-reactive protein (6 mg/L)仍然在正常值之內。從胸部X光可以發現心臟大小在正常範圍內，同時peri-hilar有些許發炎的現象，但是並沒有證據顯示parenchymal lung lesions/cavitations。

這個小朋友在初步的治療有獲得改善，但是仍然可以找到lesions on the labial aspect of the gingivae with erythema and hyperplasia over the interdental papillae。現在仍舊持續服用prednisolone，並且定期接受小兒科的診察追蹤。

Oral Findings

Wegener's disease在口中的特徵 – strawberry gums [Note 4](#)



Discussion

1. First description – Friedrich Wegener, 1936
2. Three main clinical criteria (**ELK**) – Godman and Churg, 1954
E – upper airway and related structures、**L** – lung、**K** – kidney
3. Etiology – unknown [Note 5](#)
但是證據顯示為一種autoimmune disease，一般也認為ANCA扮演重要角色
4. Average untreated survival – less than 1 year. [Note 6](#)
5. 口內可能產生表現的機率雖然很少，但是對於WG牽涉到多重器官前是很重要的判斷。
6. **Classic Wegener's granulomatosis**會包含以下三種特徵：
 - 1) **necrotizing granulomatous inflammation of upper and lower respiratory tracts**
 - 2) **systemic vasculitis of small arteries and veins**
 - 3) **focal glomerulonephritis**
 However, not all patients show involvement of all three areas and virtually any area can be involved.[Note 7](#)
7. 有6%的病人可以發現oral or pharyngeal involvement，但是oral lesions as initial signs卻是相當少的。
8. Oral lesion：
 - 1) 最常見的是**friable granularhyperplastic gingivitis**，一般稱之為**strawberry**

gums

- 2) 可能伴隨 *alveolar resorption and tooth mobility*
- 3) *Persistent mucosal ulcerations usually buccal but may also occur of the palate or pharynx*
9. The disease may remain localized to the mouth for several weeks or months before multi-organ involvement occurs.
10. Oral history 對於早期診斷是很重要的，特色是 vasculitis 和 necrotizing granulomas。Gingival enlargement is a direct manifestation of Wegener's granulomatosis and it may be pathognomonic.

References

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Note from Oral & Maxillofacial Pathology (Neville, Damm, Allen, Bouquot) 297~300**Note 1.**

The *initial* description of the syndrome by Wegener included necrotizing granulomatous lesions of the respiratory tract, necrotizing glomerulonephritis, and systemic vasculitis of small arteries and veins. [back_1](#)

Note 2.

The drugs of choice are *cyclophosphamide* and *prednisone*, but this approach is not without serious potential side effects. [back_2](#)

Note 3.

Indirect immunofluorescence for serum antibodies directed against cytoplasmic components of neutrophils has been used to support a diagnosis of Wegener's granulomatosis. There are two reaction patterns of these antineutrophil cytoplasmic antibodies :

1. Perinuclear (p-ANCA)
2. Cytoplasmic (c-ANCA)

Cytoplasmic localization (c-ANCA) is the most useful and is present in 90% to 95% of case of generalized Wegener's granulomatosis. [back_3](#)

Note 4.

An *early* manifestation of Wegener's granulomatosis and has been documented before renal involvement in most cases. The affected gingival demonstrates a *florid and granular hyperplasia*.

The **buccal surfaces** are affected more frequently, and the alterations are classically confined to the **attached gingival**. The process appears to begin in the **interdental region** and demonstrates lateral spread to adjacent areas. [back 4](#)

Note 5.

1. An abnormal immune reaction secondary to a nonspecific infection.
2. An aberrant hypersensitivity response to an inhaled antigen.
3. A possible hereditary predisposition has been mentioned in some cases. [back 5](#)

Note 6.

The mean survival of untreated patients with disseminated classic Wegener`s granulomatosis is 5 months. 80% of the patients are dead at 1 year and 90% within 2 years. However, the prognosis is better for the limited or superficial forms of the disease. [back 6](#)

Note 7.

1. **Classic Wegener`s granulomatosis** :
Patients initially show involvement of the upper and lower respiratory tract; if the condition remains untreated, renal involvement often rapidly develops.
2. **Limited Wegener`s granulomatosis** :
There is involvement of the respiratory system without rapid development of renal lesions.
3. **Superficial Wegener`s granulomatosis** :
Patient exhibits lesions primarily of the skin and mucosa. In this form of the disease, systemic involvement develops slowly.

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Key word & other references

1. 血栓閉塞性血管炎(vasculitis obliterans, 簡稱血管炎)是四肢中、小動脈一種節段性、週期性、非特異性的發炎,致血管壁增厚、彈性減弱、血流通過緩慢,最終導致血栓形成、四肢出現缺血症狀,甚至壞疽、潰瘍。本病於1908年由伯格首先提出,故又稱伯格氏病(Berger`s disease)。 [vasculitis](#)
2. 急性腎絲球腎炎又稱為急性腎炎(acute glomerulonephritis)。主要是指腎臟中,最小功能單位的腎絲球體發生彌漫性的炎症反應。通常半數以上的罹患者會先產生上呼吸道感染的病症,如扁桃腺炎、支氣管炎等情況,其伴隨而來的病症還有膿痂疹(皮膚上先形成紅斑塊然後出現中央化膿的皮膚病)、猩紅熱、膿瘍以及淋巴腺炎。 [glomerulonephritis](#)
3. 油耳朵(glue ear)是耳內油脂分泌旺盛,使得耳朵像被膠封住了一樣;如果不常清理,會慢慢出現半聾狀態。 [glue ear](#)
4. 血小板正常值為 $150000 \sim 400000/\mu\text{L} = 150 \sim 400 \times 10^9/\text{L}$ [platelet](#)
5. CRP (C-Reactive Protein, C-反應蛋白)
陰性： $< 5 \text{ mg/L}$
c-反應球蛋白,在細菌發炎性感染會出現陽性
ESR (Erythrocyte Sedimentation Rate, 血球沉降速率)
男性： $0 \sim 15 \text{ mm/hr}$ 女性： $0 \sim 20 \text{ mm/hr}$
血球沉降速率,於風濕性關節炎、風濕熱、肺炎、腎炎、代謝性中毒、懷孕3個月後、貧血、梅毒等增加 [ESR](#)

Comment

Q1 Strawberry tongue所對應的特殊疾病是？

A1 Strawberry gingivitis - Wegener`s granulomatosis ;
 Strawberry gingivitis - Kawasaki disease, toxic shock syndrome, and scarlet fever.

Strawberry tongue is the appearance of tongue with inflamed red papillae, giving an appearance of strawberry.

Q2 治療用的藥物其作用是？

A2 **cyclophosphamide**

典型的烷化劑(alkylating agent)，可以導致細胞凋亡(apoptosis)，但有些獨特的表現。

Usage : breast, lung, ovary, testis, bladder carcinomas, bone & soft tissue sarcoma, Hodgkin`s and non-Hodgkin`s lymphomas, lymphocytics leukemias, neuroblastoma, Wilm`s tumor of childhood, multiple myeloma, lupus nephritis

Dosage : 1. 單一藥物Cyclophosphamide進行連續性治療時的常用口服劑量是每天1 ~ 2.5 mg/kg，分數次服用。調整口服劑量的最佳指標是依照疾病的反應率和白血球數目(維持3500-4000/uL)。

2. 當少數情況需要單一藥物的間歇性高劑量治療時，靜脈注射40 ~ 50mg/kg，分成2~5天給予，此時需要同時靜脈輸液(生理食鹽水500~1000 ml)。

3. 因為Cyclophosphamide由腎排出，因此嚴重腎衰竭病人需要靜脈注射烷化劑時可以考慮其它的藥，如mechlorethamine或thiotepa。

Prednisone

為一種類固醇。

Usage : adrenocortical insufficiency, anti-inflammation, collagen disease, allergic states, neuropathic pain

Dosage : Adult – 5~80 mg/d

Child – 0.1~2 mg/kg/d,

Max : 60~80 mg/d

題號	題目
1	Strawberry gingivitis發生時，通常是位於gingiva的_____，並且受限在_____。 (A) buccal surfaces; free gingiva (B) buccal surfaces; attached gingiva (C) lingual surfaces; free gingiva (D) lingual surfaces; attached gingiva
答案(B)	出處：Oral & Maxillofacial Pathology P 298
題號	題目
2	Wegener`s granulomatosis有3種次分類，請依照病程進展的速度，由快到慢進行排序： (A) limited > superficial > classic (B) limited > classic > superficial (C) classic > limited > superficial (D) superficial > classic > limited
答案(C)	出處：Oral & Maxillofacial Pathology P 298