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內文：

I. Abstract:

1. Case

A case of crystal storing histiocytosis(CSH) of the upper lip and cheek in a 51-year-old woman.

2.Literature(80 cases)

41 men and 39 women, mean age of 59 and 61 years, Forty-six patients (58%) had localized CSH, The remaining 34 patients (42%) had generalized CSH primarily involving bone marrow, liver, lymph nodes, spleen and/or kidney. Treatment and prognosis varied according to the underlying disease. A classification of CSH based on etiology and/or associated disease and chemical composition of the crystal is proposed.

II. Introduction:

(1) Crystal-storing histiocytosis (CSH), a rare condition in which crystalline material accumulates in the cytoplasm of histiocytes, is typically associated with disorders that express monoclonal immunoglobulins, such as multiple myeloma (MM), lymphoplasmacytic lymphoma (LPL), and monoclonal gammopathy of undetermined significance (MGUS).

(2) With few exceptions, the crystalline material within the histiocytes is of kappa light chain origin without a consistent affiliation with any specific heavy chain. More recently, other variants of CSH have also been described in which the crystalline material is not an immunoglobulin. Among these include clofazimine- induced CSH, Charcot-Leyden crystal-associated CSH, and CSH associated with hereditary cystinosis.

Table 1 Proposed classification of CSH

According to etiology and/or associated disease	According to crystal
1. Hematopoietic	1. Immunoglobulin
A. Multiple myeloma	A. Type
B. Extramedullary plasmacytoma	(1) Heavy chain
C. Lymphomas	(2) Light chain
	B. Clonality
2. MGUS-Amyloid	(1) Monoclonal
	(2) Polyclonal
3. Drugs	(3) Indeterminate
A. Clofazimine	
	2. Clofazimine
4. Allergic-autoimmune	
A. Rheumatoid arthritis	3. Charcot-Leyden
B. Eosinophilic colitis	
C. Mastocytosis	4. Other
D. Hypereosinophilic syndrome	A. Cystine
	B. Silica
5. Metabolic	
A. Cystinosis	
6. Inflammatory-reactive	
A. Pulmonary infections	
B. Plasma cell granuloma	
C. Crohn's disease	
D. *Helicobacter pylori*	
7. Other	
A. Silica	

CSH crystal-storing histiocytosis, *MGUS* monoclonal gammopathy of undetermined significance

III.Case Report

1. Clinical history

A 51-year-old Caucasian woman presented to her local physician with a 1.5 cm submucosal swelling of the left upper lip and cheek of 2 weeks duration. There was no lymphadenopathy.

Medical history: osteoarthritis, hypothyroidism, elevated platelet count, and an unknown pulmonary infection treated with tetracycline.

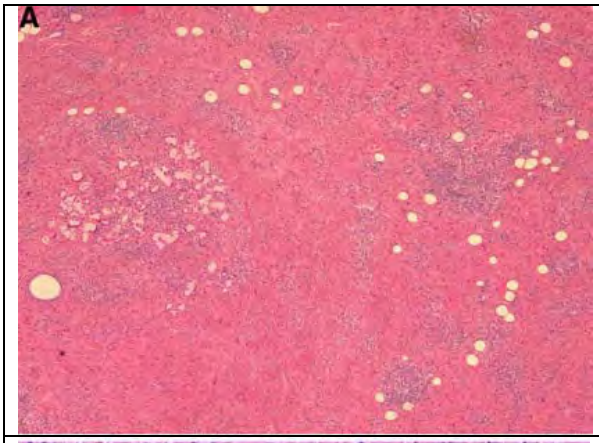
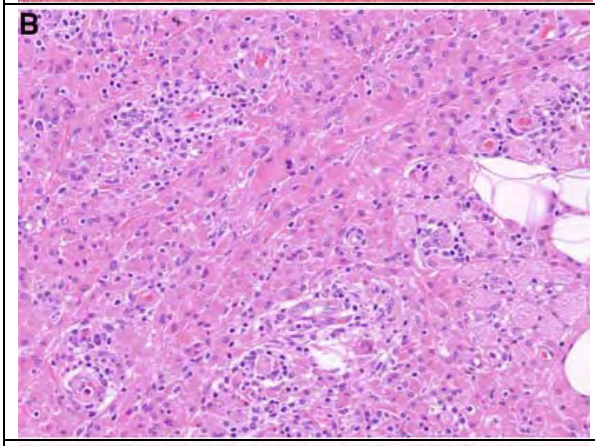
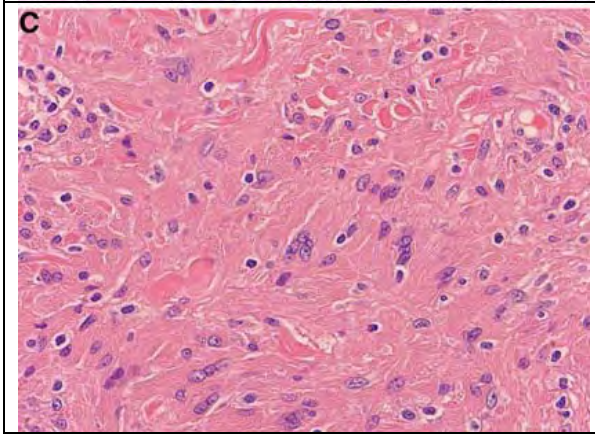
A whole-body scan performed 7 months prior to presentation showed multifocal degenerative joint changes with no evidence of metastatic disease. The mass was thought to be a pleomorphic adenoma and was subsequently excised.

2. Pathology (Gross)

The specimen consisted of a 1.5 × 1.3 × 1.0 cm firm, yellow–brown, poorly demarcated soft tissue mass that varied on cross section from grey–white to yellow–tan.

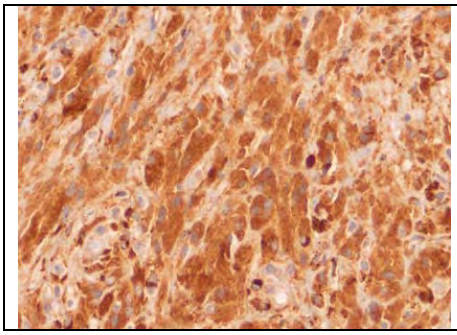
3. Microscopic

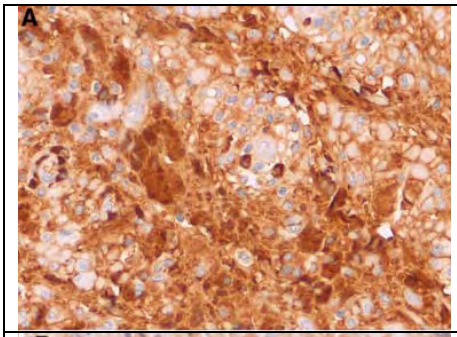
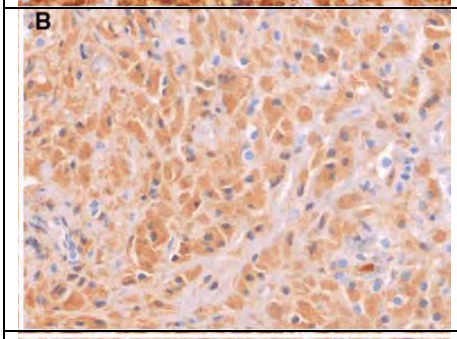
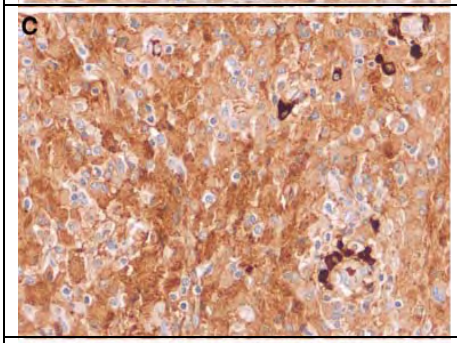
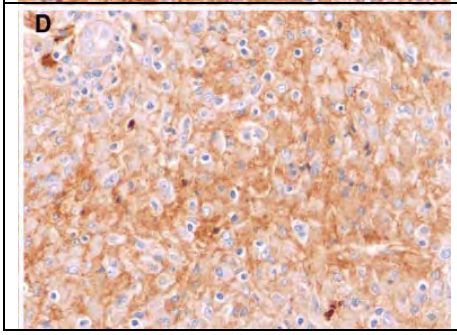
Hematoxylin and eosin stained sections

	擴散開的嗜酸性histiocytes 和淋巴漿細胞聚集浸潤小唾液腺、脂肪組織和骨骼肌 (×40 magnification).
	Histiocytes 有極度不透明、嗜酸性的細胞質，呈圓形和卵圓形的細胞核、灰白色的核染色質，淋巴球和漿細胞都是成熟的 (×200 magnification).
	可看到histiocytes的細胞質內有結晶狀的條紋 (×400 magnification)

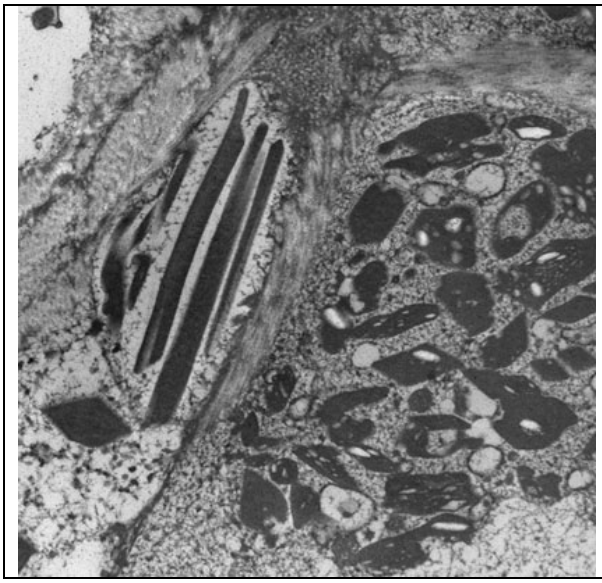
4. Histochemistry and Immunohistochemistry

從測驗immunoglobulins 的免疫化學染色可以看到histiocytes內有明顯的結晶狀內含物。

	Histiocytes are strongly positive for CD68 (×400 magnification)

	Immunostain for IgM heavy chain is strong and diffuse.
	IgG heavy chain is diffuse but relatively weak.
	可以看到lambda light chain 在染色下的免疫反應無論是在histiocytes 和漿細胞內部的很強烈，表示IgM lambda light chain restriction.
	Kappa light chain is weakly positive (×400 magnification)

5. Electron Microscopy

	Electron microscopy reveals elongated and rhomboid shaped dense crystals within the cytoplasm of histiocytes. Some of the crystals contain clear vacuoles (×11,500 magnification)

6. Final Pathologic Diagnosis

Crystal-storing histiocytosis, immunoglobulin variant, associated with a mild lymphoplasmacytic infiltrate exhibiting IgM lambda light chain restriction.

The patient should be evaluated for an underlying lymphoproliferative or plasma cell disorder.

7. Follow-up

a. No additional foci of CSH were found.
b. no evidence of lymphadenopathy or hepatosplenomegaly.
c. peripheral blood count was normal
d. serum protein analysis was significant for slightly increased total protein of 8.2 g/dL (normal range = 6.2–8.0 g/dL), increased gamma globulins of 1.7 g/dL (normal range = 0.6–1.6 g/dL) and beta-microglobulin of 3.32 mg/L (normal range = 0.00–2.51 mg/L).
e. 尿液分析並沒有檢查到monoclonal bands的存在，血液檢查也沒有發現monoclonal proteins。
f. No additional foci of CSH were detected in the marrow.
g. A repeat complete skeletal imaging survey was negative for blastic or lytic lesions or osteopenia.
h. working clinical diagnosis of“possible monoclonal gammopathy of undetermined significance (MGUS)”based on the borderline to slightly elevated serum proteins and histologic findings.
i. Asymptomatic, n o treatment was recommended, just follow-up.
j. At last examination (*8 months* since her diagnosis of CSH), there has been no significant change in her physical condition or laboratory data.

8. Literature Review

80 acceptable cases of CSH were identified through a PubMed search of the English literature from 1950 to 2010 (until September)

Table 2 Review of 80 cases of CSH from the literature

Men (n = 41)	
Age, average (range)	59 (38–75)
Women (n = 39)	
Age, average (range)	61 (17–81)
	Number of cases (%)
1. CSH with underlying LP-PCD	72 (90%)
A. Multiple myeloma	23 (31.9%)
B. Lymphoplasmacytic lymphoma	17 (23.6%)
C. Paraproteinemia/MGUS	15 (20.8%)
D. Plasma cell dyscrasia/neoplasm, not further specified	4 (5.6%)
E. B-cell lymphoma	11 (15.3%)
MALT/EMZL	6
MZL	2
B-cell lymphoma (not classified)	2
F. Other LP-PCD[a]	2 (2.8%)
2. CSH with unknown history	1 (1.2%)
3. CSH without underlying LP-PCD	7 (8.8%)
Lung	3
Stomach	1
Brain	1
Base of tongue	1
Upper lip/cheek	1

LP-PCD lymphoproliferative or plasma cell disorder, *MALT* mucosa-associated lymphoid tissue lymphoma, *EMZL* extranodal marginal zone lymphoma, *MZL* marginal zone lymphoma

[a] Including diagnoses of reticuloendotheliosis and purpura hemorrhagica

a. Only cases describing immunoglobulin crystals within histiocytes were considered for this review. Non-immunoglobulin variants are addressed separately in the ”Discussion”section.
b. The cases were subdivided into two categories: (1) localized CSH (L-CSH), defined as a single deposit involving only one organ or site (2) generalized CSH (G-CSH), defined as involving two or more distant organs or sites.
c. The following data, if available, were tabulated for each case: gender, age, site(s) of CSH, localized versus generalized, association with other diseases (MM, LPL, MGUS, etc.), symptoms, treatment, prognosis, and type and clonality of immunoglobulin within the histiocytes.

IV. Discussion

1. The accumulation of crystalline material within the cytoplasm of histiocytes is an uncommon condition known as CSH.
2. Based on etiology and/or associated disease and the chemical composition of the crystal, CSH can be classified as shown：

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LP-PCD lymphoproliferative or plasma cell disorder, *MALT* mucosa-associated lymphoid tissue lymphoma, *EMZL* extranodal marginal zone lymphoma, *MZL* marginal zone lymphoma

[a] Including diagnoses of reticuloendotheliosis and purpura hemorrhagica

3. 90% of cases were associated with an underlying LP-PCD, and most of these patients had either MM, LPL, or MGUS.
4. 7 cases (7/80 or 8.8%) that were not related to a clonal LP-PCD was a female predominance and an association with diseases with an inflammatory background.

Table 5 CSH without underlying clonal lymphoproliferative or plasma cell disorder

Author	Age/sex	Patient history/underlying disease	Duration of symptoms	Symptoms/indication for work up	Organ(s) involved by CSH
Bosman [7]	73 F	Rheumatoid arthritis, polyclonal hypergammaglobulinema	Unknown	Mass at the base of tongue	Base of tongue and hypopharynx
Jones [3]	54 F	Plasma cell granuloma	Unknown	None/incidental finding	Lung
Ionescu [20]	50 F	Rheumatoid arthritis	Unknown	None/incidental finding	Lung
Joo [21]	56 F	*H. pylori* + gastritis, polyclonal plasma cell proliferation	2 weeks	Dyspepsia, gastric pain	Stomach
Lee [29]	64 M	Lung abscesses, possible tuberculosis (?), history of asbestos exposure	7 months	Cough, fever, unresolved lung nodules	Lung
Kaminsky [22]	27 F	Crohn's disease	Unknown	Localized neurologic deficits	Brain
Present case, 2010	51 F	Arthritis, hypothyroidism, pulmonary infection treated with tetracycline	Unknown	Upper lip/cheek swelling	Upper lip/cheek mucosa and submucosa

Table 3 Sites of localized CSH cases

Localized CSH (N = 46)	
Region/organ/tissue	Number (%)
1. Head and neck	16 (35%)
Eye/orbit[a]	6
Oral, pharyngeal and sinonasal mucosa	3
Cervical lymph nodes	2
Soft tissue	2
Parotid and periparotid lymph nodes	1
Skin	1
Brain	1
2. Lung and pleura	11 (24%)
3. Bone marrow	5 (11%)
4. Kidney	5 (11%)
5. Lymph nodes[b]	2
6. Gastrointestinal mucosa	2
7. Skin[b]	2
8. Body fluids	2
9. Heart	1

[a] Including the ocular adnexa

[b] Other than head and neck region

Table 4 Sites of generalized CSH Cases

Generalized CSH (N = 34)	
Organ/tissue site	Number (%)
Bone marrow	33 (97%)
Liver	16 (47%)
Lymph nodes	15 (44%)
Spleen	15 (44%)
Kidney	13 (38%)
Gastrointestinal mucosa	7 (21%)
Lung	4 (12%)
Adrenals[a]	4 (12%)
Heart[a]	3 (9%)
Pleura[a]	3 (9%)
Peritoneum	3 (9%)
Bone	3 (9%)
Skin	2 (6%)
Pancreas[a]	2 (6%)
Testis[a]	2 (6%)
Thyroid[a]	1 (3%)
Dura and pia mater[a]	1 (3%)
Mesentery[a]	1 (3%)
Thymus	1 (3%)
Pericardium[a]	1 (3%)
Bladder[a]	1 (3%)
Parotid	1 (3%)
Conjunctiva[a]	1 (3%)
Tongue[a]	1 (3%)
Sinonasal mucosa	1 (3%)
Connective tissue	1 (3%)
Adipose tissue	1 (3%)
Ascites	1 (3%)

[a] Organs involved by generalized CSH at autopsy only

5. Although most cases of CSH occur in patients with a previous wellestablished diagnosis of MM, LPL, or MGUS, we have identified at least 7 cases in which the

diagnosis of CSH led to the discovery of a simultaneous, previously unrecognized LP-PCD and/or paraproteinemia.

6. In another three cases, CSH preceded the diagnosis of a LP-PCD by"a few months", 7 months, and 4 years, respectively.
7. Majority of patients with CSH present clinically with an asymptomatic mass or swelling, often associated with a yellow or tan hue.
   (1) De Alba Campomanes et al.- an orbital CSH in a 66-year-old man that was associated with 上瞼下垂、眼球突出、眼外肌麻痺.
   (2) Sailey et al.- discuss a cardiac CSH in a 64-year-old man that was responsible for 經常性心房心律不整、頭暈.
   (3) Kapadia et al.- mention an 18-year-old woman with a "symptomatic"CSH of the right lateral wall of the nasopharynx extending to the soft palate (specific symptoms not indicated).
8. Most CSH：
   (1) range in size from microscopic to 4 cm.
   (2) 由嗜酸性上皮狀到紡錘狀的組織細胞組成 with poorly defined margins.
   (3) 細胞核扁平，呈現圓形或是卵圓形，內含小核仁.
   (4) 顯微鏡下可見到不同比例和成熟度的淋巴細胞、漿細胞擴散或是微微聚集起來.
   (5) The histiocytes are strongly positive for CD68 and negative for desmin, muscle-specific actin, myoglobin, S-100 protein and CD1a.
   (6) The crystals 通常在PTAH染色下呈現藍色，在 PAS stain下呈陽性.
   (7) On immunohistochemical analysis, the crystals are typically monoclonal but in some instances may be polyclonal or even fail to stain.
      i. 組織固定的不夠理想
      ii. 晶體的蛋白質被一些抗原所遮蓋
      iii. 蛋白質抗原性降低而分子結構改變
      iv. the fact that the crystals are truly not of immunoglobulin origin and represent one of the other CSH variants
   (8) 在電子顯微鏡下，結晶是很緻密的，附有膜的，且呈現細長的、矩形狀的、菱形狀的排列，有些甚至含有小空泡。
9. The specific type of heavy chain was mentioned in only 37 cases, and of these, 14 were IgM, 10 IgG, 6 IgA, and 7 polyclonal. The light chain component was documented in 51 cases, and of these, 33 were kappa, 8 lambda, and 10 polyclonal.
10. 對於CSH的結晶形成的確切機制目前尚未清楚，我們推測有幾種因素：從簡單的生產過剩、分泌異常，到受損的免疫球蛋白分泌都有可能，例如近端腎小管功能障礙.
11. Crystallogenesis is more related to the type of light chain (particularly kappa) rather than to a specific heavy chain.
12. Lebeau et al.的研究中提到一個73歲罹患G-CSH男性的stored kappa light chain的結構有幾個位置被胺基酸置換，他們認為異常的結構改變很可能就是CSH的發病主因，造成蛋白質結晶和影響內部溶解酶的降解，而化療也會造成類似如此結構的改變，誘發CSH的形成。
13. 病理學家們應審慎注意CSH的評估，常見的誤診像是在顯微鏡下histiocytes細胞質的深嗜伊紅和opaque的特性常常會混淆其他內含物、晶體、條紋(like our case)。在多數的CSH case中，由於histiocytic component占了大部分，讓檢驗

者常常忽略了其他lymphocytes or plasma cells等腫瘤的性質檢查。在一些例外的case中，有可能出現晶體和的serum的clonality是不一致的，for example, the crystals may appear polyclonal on immunostaining while a monoclonal protein is apparent in the serum.

14. 如果病患被確診患有CSH，要去找其病因，因為根據文獻的回顧，高達90%的機率病患也患有潛在的LP-PCD，所以要回顧病史、PE檢察看看是否有額外的CSH病灶出現，例如是否有淋巴結腫大、肝脾腫大、骨髓穿刺、血清和尿蛋白的檢查、骨質檢查等等。臨床醫師要注意，某些情況CSH可能同時或是早於LP-PCD的診斷，所以即使沒有診斷出罹患LP-PCD的跡象，還是要維持往後的follow-up.
15. 當然並不是所有的CSH都跟腫瘤性疾病相關聯，根據我們的回顧有8.8%的Cases伴隨著benign disorders，通常與發炎有關，例如類風濕性關節炎、肺感染和Crohn's disease.

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Present case, 2010	51 F	Arthritis, hypothyroidism, pulmonary infection treated with tetracycline	Unknown	Upper lip/cheek swelling	Upper lip/cheek mucosa and submucosa

16. CSH的治療與預後視病患相關的疾病而定。目前只有少許的文獻指出CSH對於化療和簡單切除術後的具體反應，Jones等人的研究顯示，可於4個罹患myeloma的患者在化療和骨髓移植後的切片中持續觀察到CSH。另一位54歲的女性沒有LP-PCD疾病；肺部有單獨且無症狀的CSH病灶在切除後的第10年復發。
17. 有待往後數據驗證的假說提出CSH病灶的數目可能會影響預後，G-CSH 往往比L-CSH的預後來的差；值得玩味的是，多數合併罹患CSH的Myeloma患者在確診後的存活率是5~15年，比平均中位數來的久。根據Lebeau等人的研究，合併患有CSH和Myeloma的患者往往因為細微的漿細胞浸潤和免疫球蛋白結晶，在疾病初期就診斷出來，導致存活年限得以延後。
18. 雖然immunoglobulin變異的CSH佔了極大多數，但還是有例外，通常需要依靠詳細的臨床檢查而不是切片，其中一種CSH病變是由長期服用高劑量的clofazimine所引起，clofazimine常用來治療麻瘋病和mycobacterial infections，副作用是胃毒性，常造成患者皮膚發紅和腹部不適，通常在影像判讀上可見變粗的小腸黏膜皺摺伴隨局部的淋巴結腫大，增加罹患lymphoma的可能性，所以往往需要切片。clofazimine crystals通常出現在lamina propria和淋巴結的巨噬細胞裡面，以冷凍切片觀察呈現明亮的紅色，儘管如此，將取樣組織以福馬林固定，包埋於石蠟以PAS或是免疫球蛋白染色觀察時，細長的晶體則是呈現無色和陰性的狀態。
19. 目前已知道有3例CSH與大量的Charcot-Leyden crystals沉積有關：
    (1) 78歲的女性患有嗜伊紅性結腸炎和皮膚肥大細胞增生症，在手術切除取

出的升結腸和橫結腸可見到充滿Charcot-Leyden crystals和巨噬細胞沉積的黏膜瘜肉。

(2) 另一個是91歲的女性有包括骨髓在內侵犯性的系統性肥大細胞增生症。
(3) Hypereosinophilic syndrome
(4) 以上3例都可見histiocytes腫脹和帶有鋸齒狀邊緣的嗜酸性針狀的結晶。

20. Weiss等人提出7例因疝氣手術需注射二氧化矽後長出腫塊的病人，顯微鏡下可見被膠原蛋白隔開的histiocytes和細胞內外可見到二氧化矽的結晶，此病變常被誤認為良性或是惡性的纖維組織細胞瘤；Gebrail等學者研究提出一個患有遺傳性胱胺酸症的23歲男性，因不正常的peripheral blood count而發現，在骨髓切片顯示出大量的巨噬細胞和不同形狀的結晶。
21. 與CSH做鑑別診斷要花費一段較長的時間，以下8種疾病：
    (1) Adult rhabdomyoma (ARM)
    (2) Granular cell tumor
    (3) Langerhans cell histiocytosis (LCH),
    (4) Fibrous histiocytoma
    (5) Xanthogranuloma
    (6) Gaucher's disease
    (7) Malakoplakia
    (8) Mycobacterial spindle cell pseudotumor
22. 雖然ARM和CSH都是由大量的嗜酸性球和上皮細胞組成，也都有晶體和條紋，但是卻不難區分：
    (1) ARM的晶體是"Jack straw"晶體，有Z字狀的肥厚帶，而CSH的晶體呈現平行線性排列，幾乎不出現交叉和垂直的排列。
    (2) ARM在Desmin、muscle specific actin和myoglobin呈現陽性反應，對immunoglobulins呈現陰性；而CSH恰恰好相反。
23. A granular cell tumor is positive for S-100 protein and does not contain crystals or immunoglobulins.
24. 不同於CSH的histiocytes有圓形和卵圓形的細胞核，LCH的histiocytic cells的細胞核有摺疊和凹痕像是咖啡豆。
25. Fibrous histiocytoma微觀下可見storiform pattern、更多纖維基質且缺乏晶體。
26. 雖然Xanthogranuloma常見於小孩，但是成人依然有機會罹患，對factor XIIIa呈現陽性。
27. 正常來說CSH的細胞在微觀下呈現出條紋的表現，跟Gaucher's disease的表現極為相似，但Gaucher's disease的條紋表現是由glucocerebroside而非immunoglobulins堆積而來；Gaucher cell對鐵的反應為陽性，CSH則否。
28. 雖然malakoplakia通常見於泌尿道，但近年來發現在其他部位包括頭頸部也能發生，由CD68(+) histiocytes、散亂且特異的Michaelis-Gutmann bodies甚至是細菌組成，缺乏immunoglobulins。
29. CSH因為有顯眼的紡錘狀histiocytes，所以容易與mycobacterial spindle cell pseudotumor混淆，利用抗酸桿菌染色可以很快的做區分。
30. 最後總結一下，CSH算是一種罕見的病變，其好發年齡很廣(17~81 years)且無性別偏好，可以是localized或generalized且幾乎涉及所有解剖部位；其中約90%的cases和嚴重的LP-PCD，特別是MM, LPL, and MGUS有關聯。另外約有8.8%的cases伴隨著良性的疾病，通常與發炎的有關；目前也已經發現非常稀少的non-immunoglobulin變異的CSH。

題號	題目
1	Generalized CSH 最容易影響甚麼部位? (A) Bone marrow (B) Liver (C) Lymph nodes (D) Spleen
答案(A)	出處：本篇 Journal
題號	題目
2	如果病患被確診患有 CSH，請問有病患多大的機率合併有潛在的的 LP-PCD 病症？
	(A) 90% (B) 70% (C) 50% (D) 30%
答案(A)	出處：本篇 Journal

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