模拟狼疮及抗核抗体陷阱

北京协和医院　费允云

临床表现

* 发热： 80%，热型不定

* 皮肤： 颊部蝶形红斑，盘状红斑，网状青斑，冻疮样皮损，雷诺现象，光过敏，脱发

* 骨、肌肉： 关节痛 90%，关节炎 10%，2% 的病人符合 RA 的诊断标准

  关节痛特点：多关节，对称性，阵发性，

  骨无菌坏死

  肌痛肌无力，肌炎仅占 5%

* 呼吸系统：肺胸膜病变 18%~90%

胸膜炎：24%，70% 为双侧，30% 为单侧

狼疮肺炎：30%

肺动脉高压：14%

肺间质纤维化：1%~6%

* 泌尿系统

狼疮肾炎：病理 100%，50% 发病时，80% 发病 5年内，50% 病人死于尿毒症

- 血液系统

70% SLE 慢性贫血，10% 溶血性贫血，Coombs 试验＋ ,WBC 下降，PLT 下降

消化系统

25%~50% 的 SLE 有消化系统症状

10% 的 SLE 为首发症状

8% 厌食，呕吐，恶心

8%~40% 腹痛

4%~8% 急性胰腺炎

10%~30% 肝脏肿大和肝功异常

* 心血管系统：心脏病变 50%~55%

心包炎：尸检 80%，平均 50%~60%，35% 有临床症状，协和医院资料 27% 有心包炎

心肌病变：尸检 50%

心内膜炎：15%~60% 非细菌性疣状心内膜炎，协和医院尸检 4/9，可影响心瓣膜

心律失常：34%~70%

冠状动脉病变：42%

高血压：40%~70%，协和医院住院病人为 57%

生殖系统

妊娠对母体的影响

妊娠对胎儿的影响

新生儿狼疮综合征

有关的抗体：ACL，抗 SSA/Ro

- 与SLE 相关的主要抗体

ANA　　A-ds-DNA

A-Sm　　A-U_1-RNP

A-SSA/Ro　A-SSB/La

A-rRNP　　ACL　　LEC

抗体与临床表现的相关性

抗体	相关表现
抗 ds-DNA	严重 SLE，弥漫性 LN，CNS-SLE，心，肺
抗 Sm	膜增殖 LN，光过敏
抗 RNP	Raynaud 征，肺，肌
抗 SSA	皮肤，口眼干，NLS
抗 SSB	同上
APL	APS
抗 scl-70	SSc 或发展或 SSc 的倾向

抗DNA抗体

抗ds-DNA与肾脏损伤

ANA+抗ds-DNA+肾脏损伤

SLE可能性90%

随诊疾病过程100%

- 颊部红斑

特异

要除外：阳光性多形红斑

酒糟鼻

药物反应

- 高滴度 **ANA**

加非感染性浆膜炎，**SLE** 可能的重要标志

加肌痛（归入 **SLE** 鉴别中）

- 盘状红斑 → **SLE**

多年病史

血液、肾、**CNS**、骨骼肌肉

- 特异性低的征象

脱发、肌痛乏力

低热、**Raynaud** 征

C_3、C_4↓

WBC、Hb、PLT↓

光过敏（**UVB 300~320nm**）

反复流产

不稳定的精神状态（**50%** 的可能性）

SLE 诊断的可信度

	可信度（%）	ANA	免疫实验指标	临床征象
肯定	90	≥ 1:80	抗 ds-DNA 或 Sm	蛋白尿
	80	≥ 1:160		颊部红斑
	80	≥ 1:160	低补体	浆膜炎
大概	70	≥ 1:160	低补体	盘状红斑
可能	60	≥ 1:160	RNP、SSA、SSB	淋巴细胞（1000/mm³）
			ACL 抗体	PLT↓、coombs 阳性的贫血
	50	≥ 1:160	无异常	无专业人员证实的光过敏，颊部红斑，非特异皮肤损伤，荨麻疹
不象	25	≥ 1:160	无异常	严重的疲乏、关节痛、肌痛

0 = 不可能；25 = 有问题、不象；50 = 可能；75 = 大概；100 = 绝对

严重和威胁生命的表现

对大剂量 GC 有效

血管炎

SLE 严重的皮损

多关节炎

多浆膜炎

心肌炎

狼疮肺炎

增殖性 LN

溶贫

弥漫性 CNS-SLE

严重认知障碍

脊髓病

周围神经受损

狼疮危象：高热、卧床不起

对 GC 反应差的症状

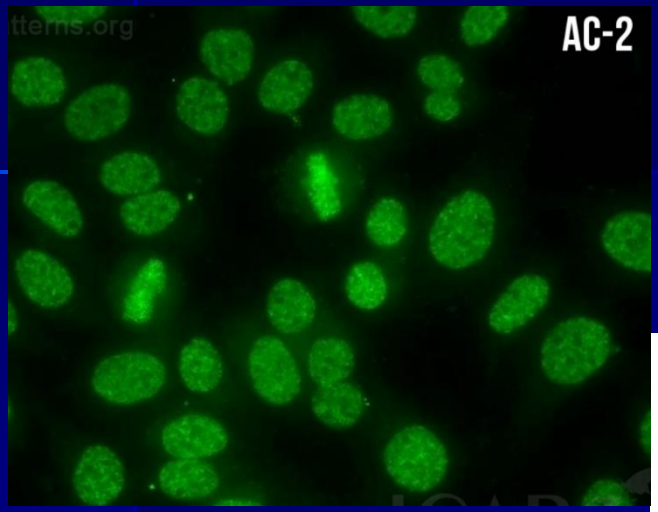
血栓

中末期肾病、VLN

有抗药性的血小板下降、溶贫（少许）

精神症状（非 SLE 引起）

致密颗粒型（dense fne speckled, DFS）



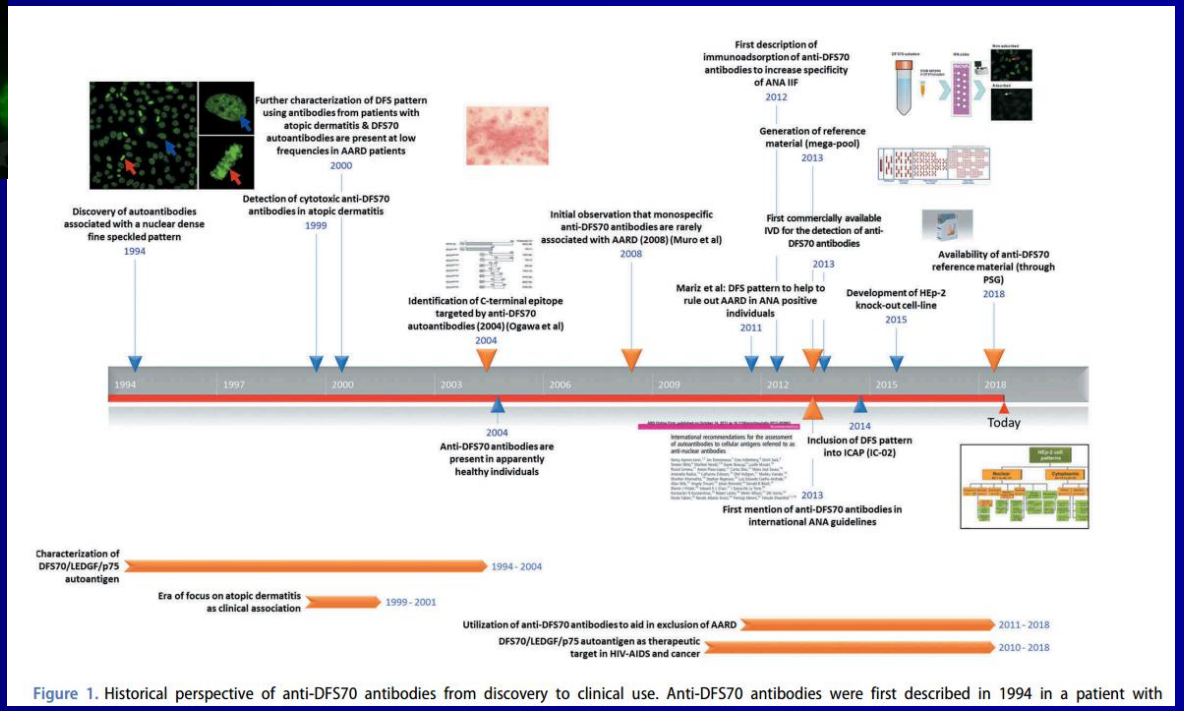
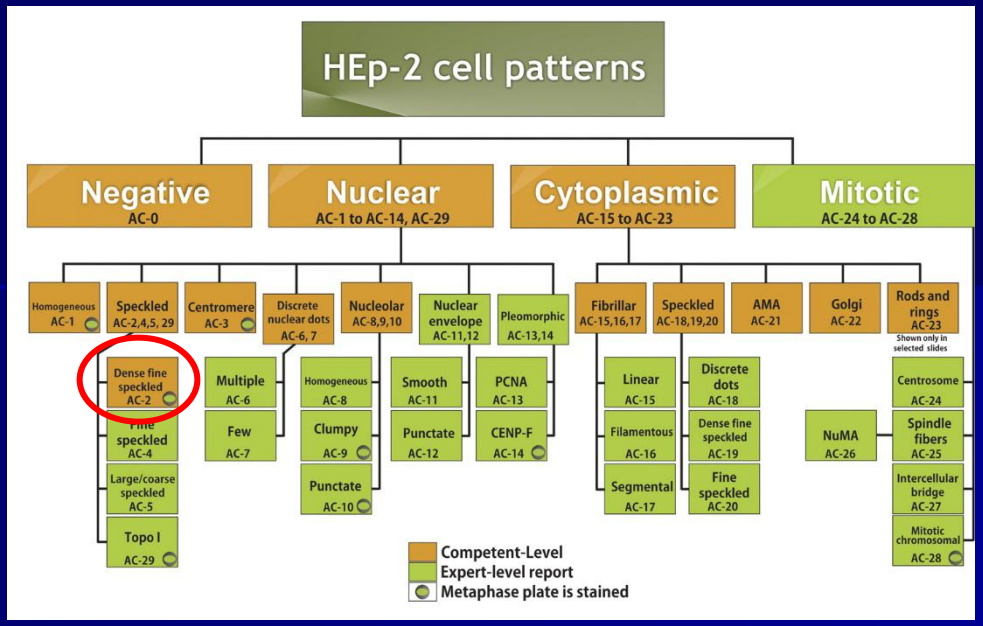


Figure 1. Historical perspective of anti-DFS70 antibodies from discovery to clinical use. Anti-DFS70 antibodies were first described in 1994 in a patient with

https://www.anapatterns.org

Expert Rev Clin Immunol. 2019 Mar;15(3):241-



AC-2 DENSE FINE SPECKLED

- Commonly found as high titer HEp-2 IIFA-positive in apparently healthy individuals or in patients who do not have a systemic autoimmune rheumatic disease (SARD) 9
- The negative association with SARD is only valid if the autoreactivity is confirmed as being directed to DFS70 (also known as LEDGF/p75) and if no other common ENA is recognized 20, 21
- Both in apparently healthy individuals as well as patients who do not have a SARD the AC-2 pattern may be caused by autoantibodies to other antigens than DFS70 22

Note: Confirmatory assays for anti-DFS70 antibodies may be available only in specialty clinical laboratories.

DFS与SARD负相关？？结论解读需严谨

Ann Rheum Dis. 2019 Mar 12. pii: annrheumdis-2018-214436.

Table 1 Antinuclear antibodies (ANA) in systemic lupus erythematosus (SLE) by immunofluorescence (IFA) and solid phase immunoassay

Reference	No of SLE patients	IFA (% SLE patients positive)	Solid phase assay (% SLE patients positive)	Solid phase assay method
9	55	91% (1:80)*	87% 89% 78%	Radim SpA EIA Zeus EIA VarElisa ReCombi (Pharmacia)
11	53	91% (>1:50)	49%	Athena Multilyte
16	71 (including SLE, DLE, drug-induced)	98% (1:40)	91%	RADIAS (Bio-Rad)
17	34	76% (>1:160)	62%	ELIA Pharmacia
19	202	87%	75%	VarElisa ELISA
30	50	84% at 1:50 80% at 1:100 76% at 1:200	40% 56%	AntiNucleosomes GmbH QUANTA Lite (INOVA)
28	38	92%	79%	QUANTA Lite (INOVA)
32	192	99% (81%)†	75.5%	Bioplex
33	35	97% (>1:160)	100% 94% 100% 60% 62%	Quanta Life Bio-Rad Relisa VarElisa UniCap

*Indicates the dilution used if reported in the paper.
†Two different percentages are reported in the paper.

Table 1. Patients presenting with LN with or without extra-renal manifestations of SLE who did not develop positive serology

Author	Cases (total in article)	Age, years[a]	Initial clinical or pathology findings	Initial negative lab tests	IF	Late clinical or pathology findings	Immunosuppressive treatment	Outcome
Adu et al. [22], 1983	2 (17)	23	Nephrotic syndrome, membranous and mesangial GN, immune deposits at multiple sites	ANA, dsDNA, C3, C4	IgG, IgA, C3, C4	Membranous GN	None	No extra-renal manifestations or elevated dsDNA after 2–6 years
		40	Proteinuria, hypertension, mesangiocapillary GN, immune deposits at multiple sites	ANA, dsDNA, C3, C4	IgG, C3	Mesangiocapillary GN	None	No extra-renal manifestations or elevated dsDNA after 2–6 years
Enriquez et al. [26], 1988–1989	3 (3)	22 months	Anasarca, nephrotic syndrome thought to be idiopathic minimal change disease	ANA, ENA, C3, C4, CIC	IgG, IgM, IgA, C1q, C3	Nephrotic syndrome	PRED 60 mg/m^2/day for 3 doses → CYC 1 mg/kg/day, AZA 1 mg/kg/day	Nephrotic syndrome resolved 19 months out
		24 months	Nephrotic syndrome, edema	ANA, C3, C4, CIC	IgG, IgM, IgA, C1q, C3, C4	Fever, abdominal pain, nephrotic syndrome	PRED 60 mg/m^2/day → AZA 1 mg/kg/day, CYC 1 mg/kg/day → PRED 10 mg/m^2/day	Nephrotic syndrome resolved for 1 year at last follow-up
		4	Nephrotic syndrome, edema	ANA, C3, C4 CIC, VDRL	IgG, IgM, IgA, C1q	Rash, proteinuria	PRED 60 mg/m^2/day → PRED, AZA 1 mg/kg/day, CYC 1 mg/kg/day	Proteinuria resolved for 6 months at last follow-up
Cobeñas et al. [2], 2003	1 (1)	5 months	Malaise, pallor, purpuric rash, ITP, Coombs negative anemia	ANA, DNA, ANCA, anti-phospholipid antibodies, anti-Sm, anti-RNP, anti-SSA, anti-SSB, anti-histone antibodies, Coomb's test	IgG, IgA, IgM, C3, C5b-9, C1q	Hemolytic anemia, thrombocytopenia, direct Coombs (+) → low C3 and C4, → edema, nephrotic syndrome	PRED → MPP, IVIG → PRED → PRED, CYC → AZA	Proteinuria improved, no follow-up reported
Kim et al. [20, 29], 2009	1 (1)	16	Arthritis, rash, photosensitivity, synovitis, lymphopenia, mild pericardial effusion, leukocytoclastic vasculitis without immune deposits on skin biopsy	ANA, anti-dsDNA, ENA, anti-phospholipid antibodies, C3, C4, anti-cardiolipin Ab, lupus anticoagulant, anti-RNP, anti-Sm, anti-Ro, anti-LA, RF	IgG, IgA, C3, fibrinogen, C1q	Abdominal pain, proteinuria	CYC monthly, high dose steroids	Proteinuria improved, serologies remained negative at 2 years
Huerta et al. [23], 2012	2 (4)	50	Edema, nephrotic syndrome, hematuria, hypertension, renal insufficiency	ANA, anti-DNA, C3, C4	IgG, C1q, C3, kappa, lambda	Pulmonary edema, renal artery stenosis	PRED 1 mg/kg/day × 1 month tapered over 7 months → CYC unsuccessful → HD	Renal insufficiency persists, serologies negative at 3.5 years from diagnosis
		46	Fever, vomiting, edema, nephrotic syndrome, hematuria, hypertension renal insufficieny	ANA, C3, C4, anti-DNA	IgG, IgM, IgA, C3, kappa, lambda	Worsening renal function	PRED, CYC (did not tolerated CYC) → MMF	HD-dependent 5 months after treatment, serologies negative at 8 months
Elcioglu et al. [19, 28], 2014	1 (1)	48	Arthritis, fatigue, weight loss, oral ulcers, synovitis, diarrhea, proteinuria, hematuria	ANA, anti-dsDNA, RF, anti-CCP, ANCAs, anti-RNPs, anti-SSA, anti-SSB, anti-Sm, anti-cardiolipin antibodies	IgA, IgG, IgM, C1q, C3		Salazopyrin, MPP (for presumed seronegative rheumatoid arthritis) → HCQ 400 mg/day, MPP 1 g/day × 3 days, CYC 1 g/day × 1 day → MPP 48 mg/day	Symptoms resolved, ESR and urinalysis normalized at 2 months

Table 2. Patients presenting with LN with or without extra-renal manifestations of SLE who underwent treatment and afterwards developed positive serology

Author	Cases (total in article)	Age, years	Initial clinical or lab findings	Initial negative lab tests	IF	Late clinical findings	Late (+) serology	Time to (+)	Immunosuppressive treatment	Outcome
Cairns et al. [30], 1979	3 (11)	19	Nephrotic syndrome, acute renal failure	ANF, LE prep	IgA, IgM, C3 then IgM, IgG, C1q, C3, C4	Proteinuria	ANF, CH_{50}, C3, anti-DNA (borderline)	6 years	Steroids, AZA	No clinical symptoms, positive serology
		16	Nephrotic syndrome	ANF	Third biopsy: IgM, C4, IgA, IgG, C3, C1q	Proteinuria	ANF, anti-DNA, low CH_{50}	5 months	Steroids	Proteinuria persisted
		23	Idiopathic glomerular disease	ANF, anti-DNA, complement	IgM, C3	Unknown	ANF, low CH_{50} → anti-DNA	5–6 years	Steroids	No clinical symptoms
Gianviti et al. [24], 1999	3 (17)	9	Proteinuria, hematuria, acute renal failure	ANA, anti-dsDNA, complement, anti-cardiolipin, anti-U1 RNP, anti-Sm, anti-SSB, anti-SSA, anti-Scl-70, PCNA, anti-Jo-1	IgG, IgA, +/− IgM, C1q, C3	Renal failure → fever, arthralgias, asthenia, hemolytic anemia, thrombocytopenia	ANA, dsDNA	5 years	MPP 15 mg/kg/day qod × 3 days → PRED 2 mg/kg/day × 1 month tapered to 0.5 mg/kg qod × 4 months, CYC 2 mg/kg/day × 9 weeks → PRED 1 mg/kg/day	Renal transplant 7 years after diagnosis with positive serology at 9 years post-diagnosis
		8	Autoimmune thrombocytopenia, hemolytic anemia → nephrotic syndrome, direct Coombs (+)	Coomb's positive, ANA, anti-dsDNA, complement, anti-cardiolipin, anti-U1 RNP, anti-Sm, anti-SSB, anti-SSA, anti-Scl-70, PCNA, anti-Jo-1	IgG, IgA, +/− IgM, C1q, C3	None	ANA, dsDNA	4–8 years	MPP 15–20 mg/kg qod × 3 days → PRED 1 mg/kg/day × 2 months then 0.3–0.5 mg/kg qod, chlorambucil 0.2 mg/kg/day × 6 months	Nephrotic syndrome resolved with positive serology at 7 years
		10	Proteinuria, hematuria	ANA, anti-dsDNA, complement, anti-cardiolipin, anti-U1 RNP, anti-Sm, anti-SSB, anti-SSA, anti-Scl-70, PCNA, anti-Jo-1	IgG, IgA, +/− IgM, C1q, C3	None	ANA, dsDNA, U1-RNP (1:400)	10 years	CYC 2 mg/kg/day × 2 months, PRED 0.8 mg/kg/day × 1 month then 0.5 mg/kg qod × 3 months → PRED 1 mg/kg/day × 1 month then 0.5 mg/kg qod, AZA 2 mg/kg/day	No clinical symptoms, serologies remained positive at 10 years
Ozdemir et al. [31], 2005	1 (1)	28	Oliguria, edema, hypertension, pulmonary congestion, ascites, anemia, renal insufficiency, nephrotic syndrome	ANA, anti-dsDNA, C3, C4, p-ANCA, c-ANCA, immunoglobulin	IgA, IgM, IgG, C1q, C3, fibrin	Fever, pulmonary infiltrates, renal failure	ANA	Not specified	PRED → MPP, CYC	Proteinuria and renal function improved, serology became positive, follow-up period not specified

模拟狼疮的疾病

- 皮肤病变；
- 病毒感染：细小病毒**B19**感染；**HIV**；
- **I**型干扰素病；
- **MAS**
- **Castleman**；
- **Kikuchi-Fujimoto**病；
- 免疫缺陷疾病

模拟狼疮的疾病

- 坏死性淋巴结炎；
- **GVHD**；
- **T**细胞淋巴瘤；
- 白血病；
- **ALPS**：自身免疫性淋巴增殖综合征；
- **Prolidase deficiency**

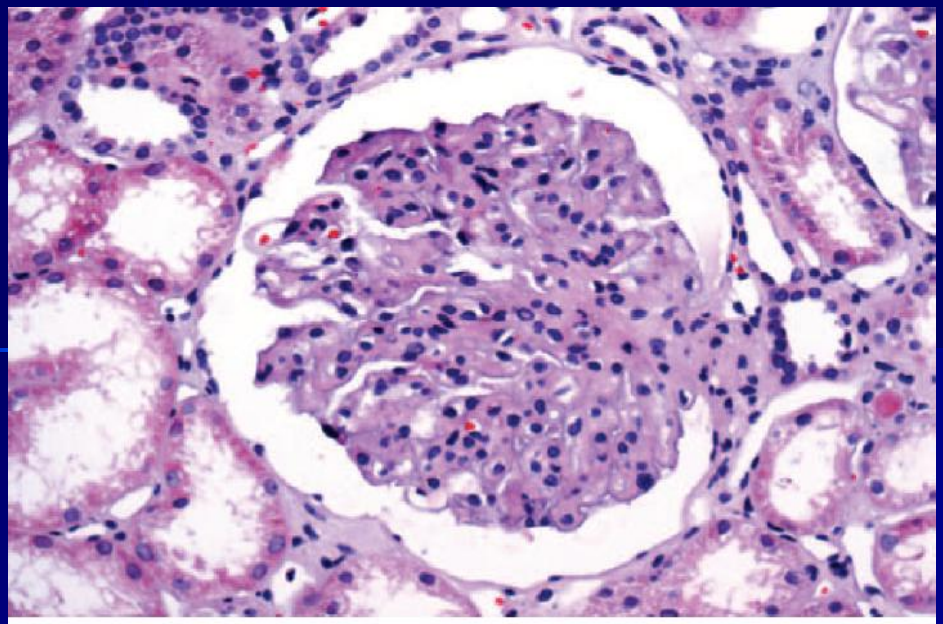


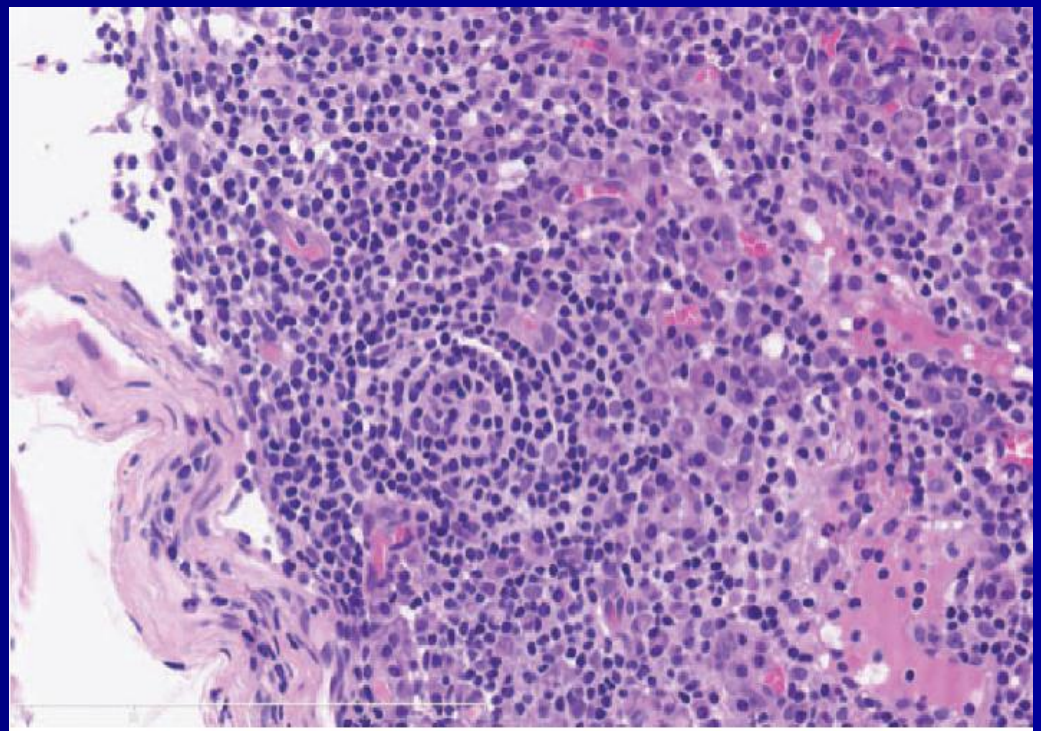
Figure 1. Kidney biopsy: endocapillary proliferative glomerulonephritis.

Castleman 模拟SLE1例

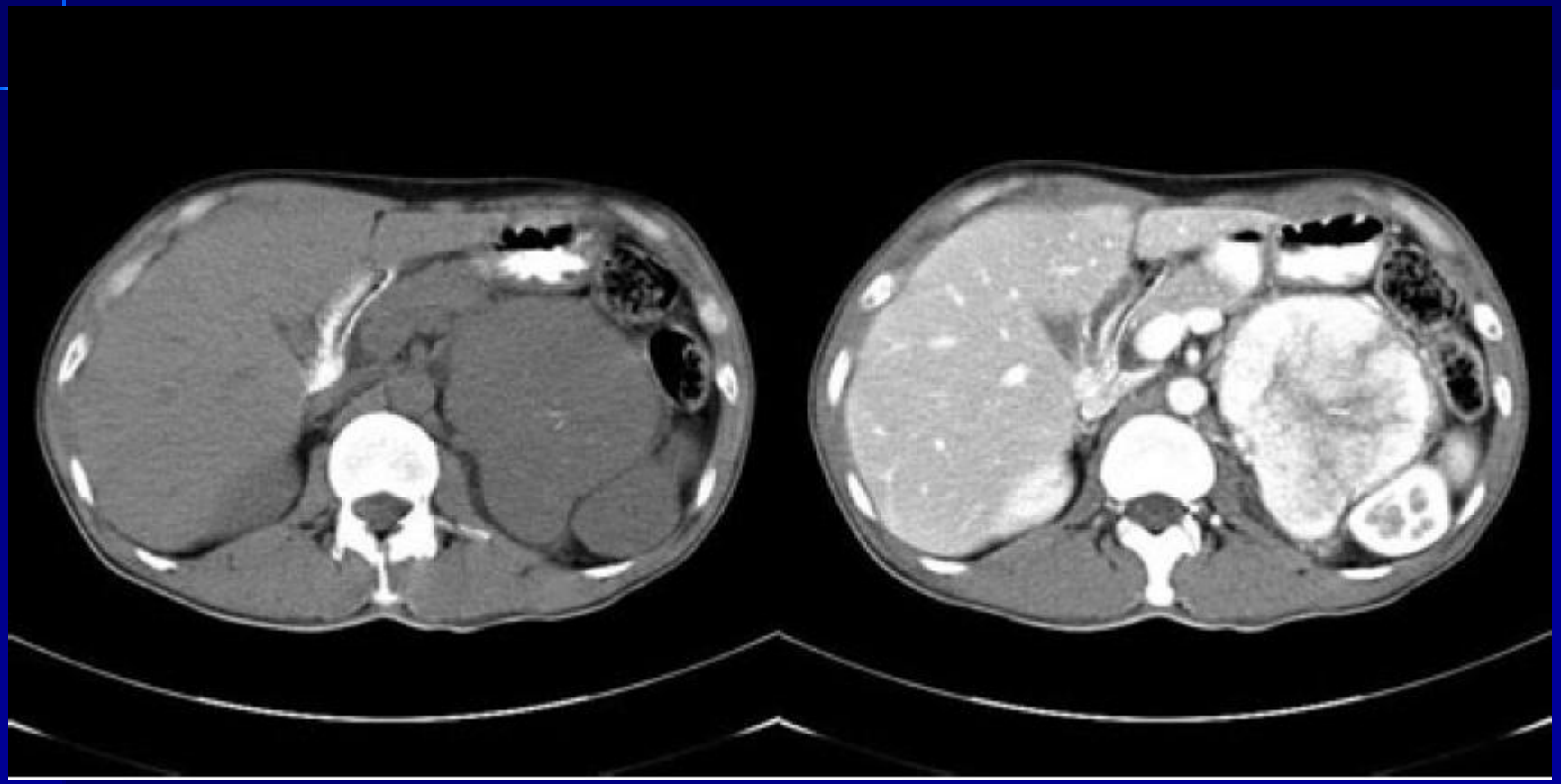
低补体；
蛋白尿、血尿；
血小板减少；
淋巴结肿大；
发热；
自身抗体阴性

肾活检：毛细血管内增生性肾小球肾炎

淋巴结活检



Castleman 模拟SLE1例：腹膜后占位



干咳、口腔溃疡、舌头肿大，浅表淋巴结（-），无肝脾大；

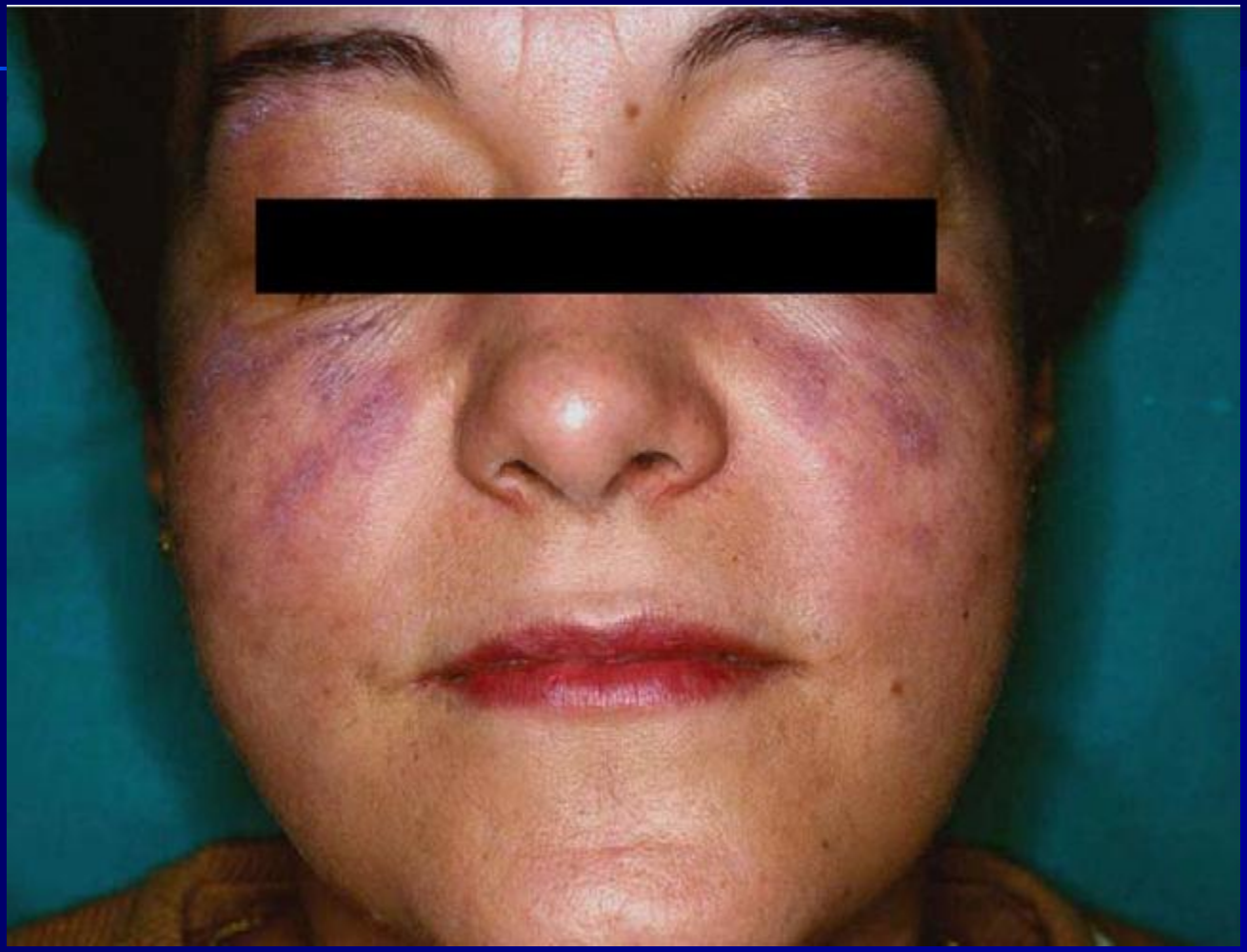
ANA（+）S 1：320，抗dsDNA（+），补体轻度减低

Castleman 模拟SLE

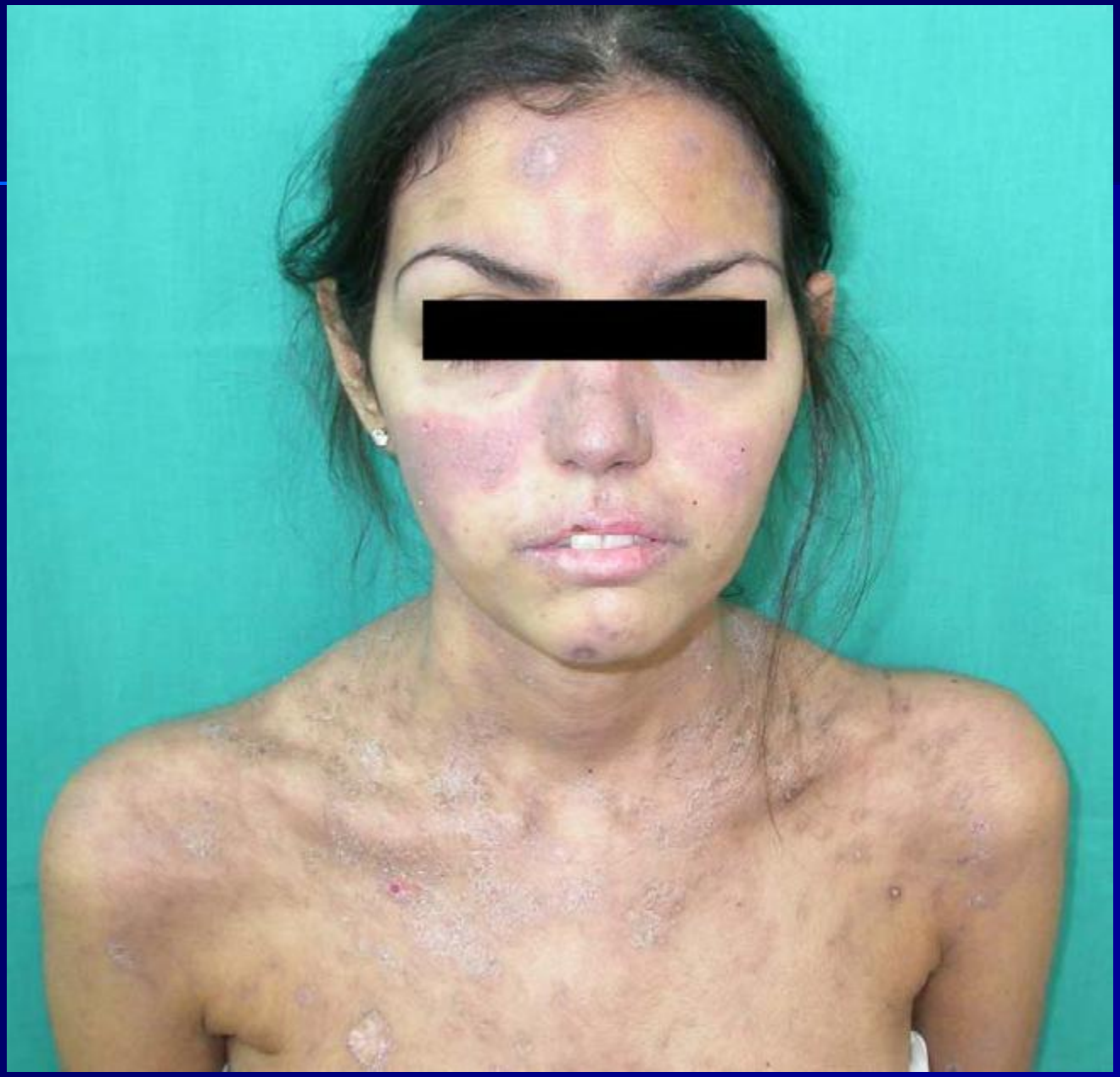
Table 1 Castleman's disease preceding or contemporary to rheumatic diseases

No	Age/sex	CD	Rheumatic disease	Systemic manifestation	Laboratory data	Treatment	Response	Reference
1	49/F	MCD, PC	Suspected SLE/SjS	Lymphadenopathy, polyserositis, parotid enlargement	AIHA, AITP, leukocytosis, hypoalbuminemia, proteinuria, ANA, DNA, SSA, SSB, ACA	CYC+PD+ vincristine, AZP	Resolution	9
2	39/F	MCD, PC	Suspected SLE/SSc	Arthralgia, fever	Coombs test, ANA, SSA, RNP	PD	Resolution	7
3	60/M	MCD, mixed	Suspected SLE	Renal dysfunction with proteinuria	AITP, ANA, RNP, DNA, ACA	PD	Death	7
4	46/F	UCD, HV	Suspected SSc/MCTD	Raynaud's phenomenon, sclerodactyly, nail fold bleeding	ANA, ENA	Not accessed	Not accessed	7
5	60/F	MCD, PC	MCTD	Lymphadenopathy, splenomegaly, POEMS	Anemia, ANA, RNP, RF, hypergammaglobulinemia, HLA-DR4	PD, CYC, melphalan	Remission	8
6	21/F	MCD, PC	Suspected SLE	Polyserositis, spleen rupture, leukocytoclastic vasculitis	ANA, SSA, LAC	PD		5
7	23/M	MCD, HV	Not described	Raynaud's phenomenon	AIHA	Rituximab	Remission	6
8	41/M	UCD, HV	Suspected SLE	Oral ulcer, multiple coffee bean-colored spots, bronchiolitis obliterans	Lymphopenia, ANA, DNA, Histone	Surgical resection, MTX, PD	Resolution	Described case

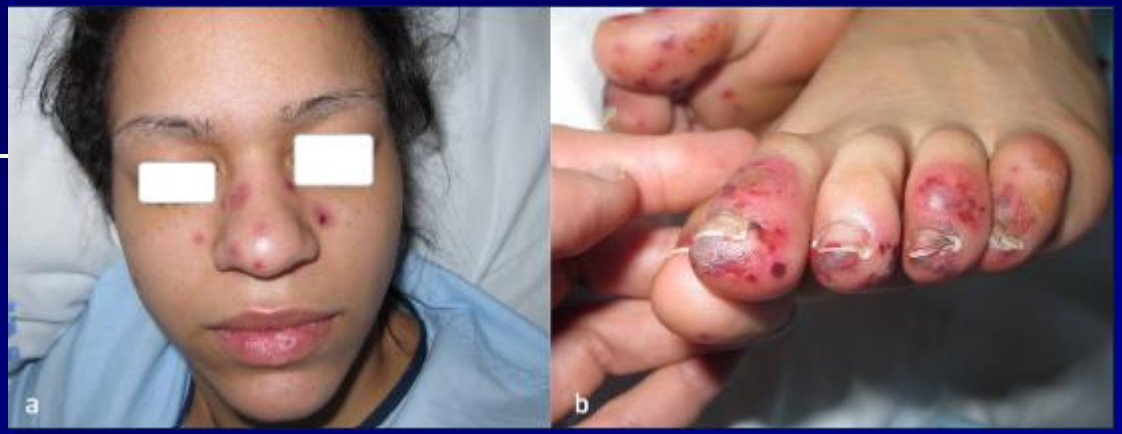
GVHD

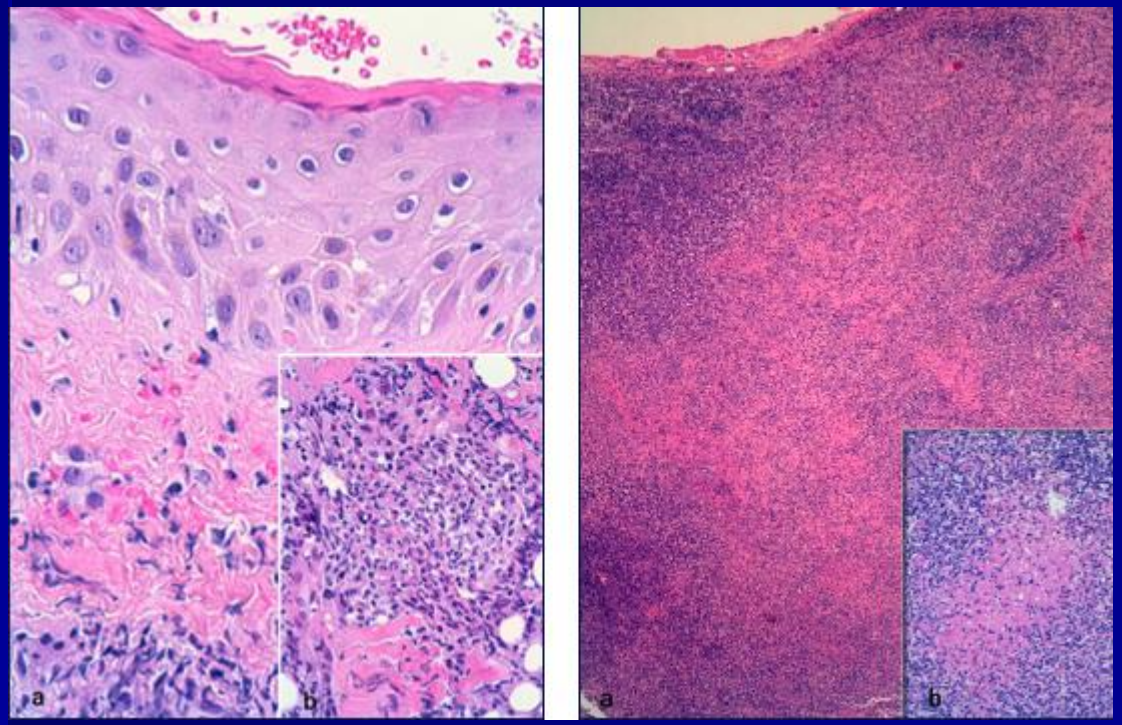


GVHD



Kikuchi disease with skin lesions mimicking lupus erythematosus





淋巴结病（宫颈）；

皮疹；

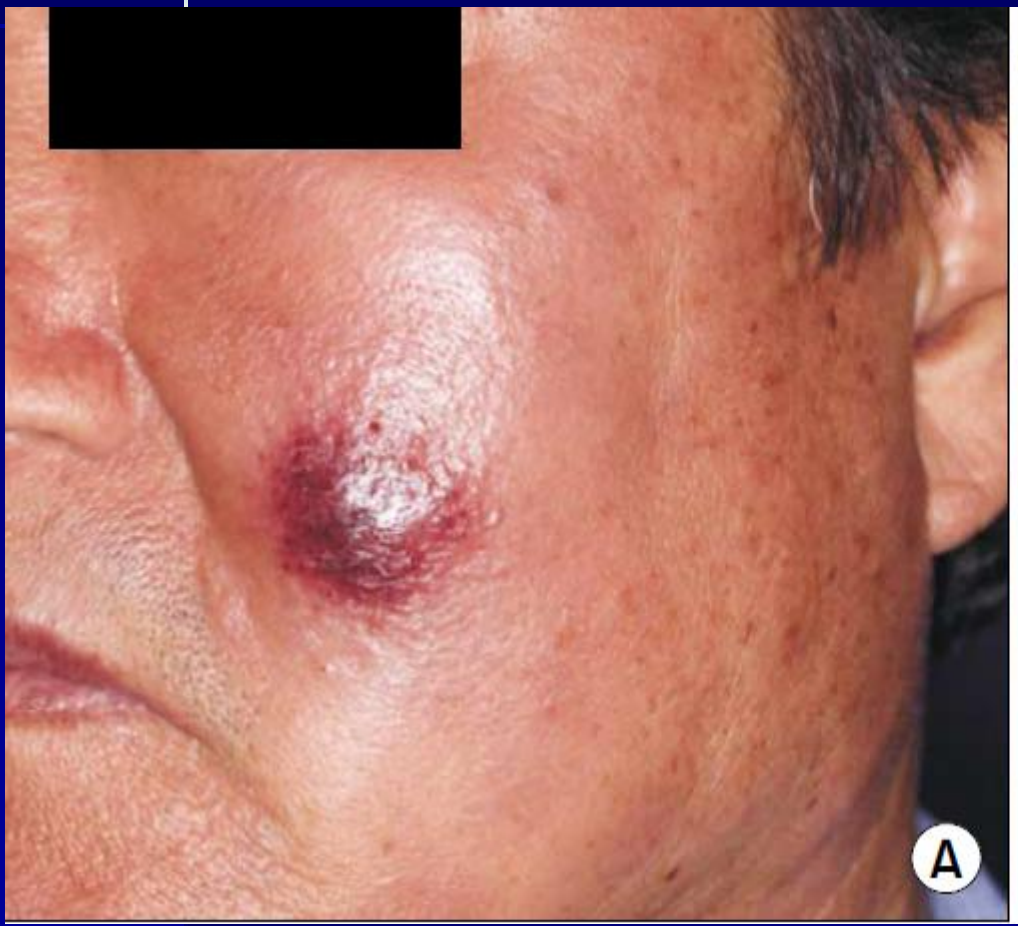
轻症肌炎；

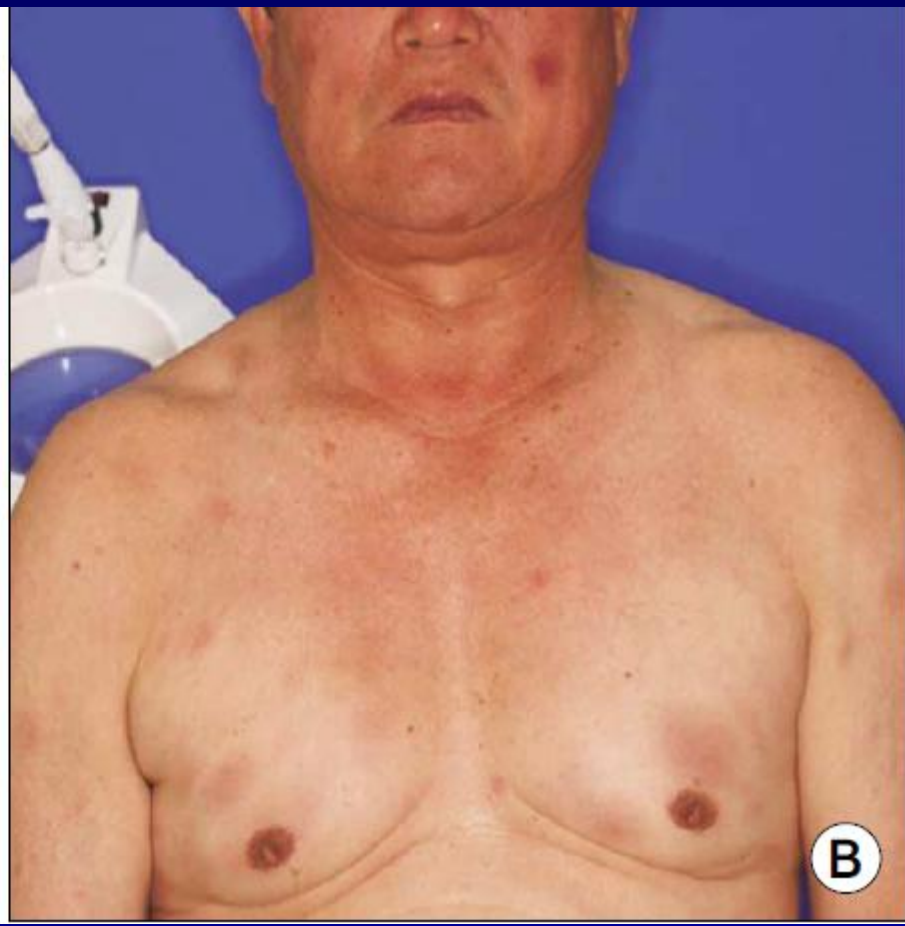
口腔溃疡；

ANA（+）S1：320；

Coombs试验（+）

A Case of Blastic Plasmacytoid Dendritic Cell Neoplasm Initially Mimicking Cutaneous Lupus Erythematosus





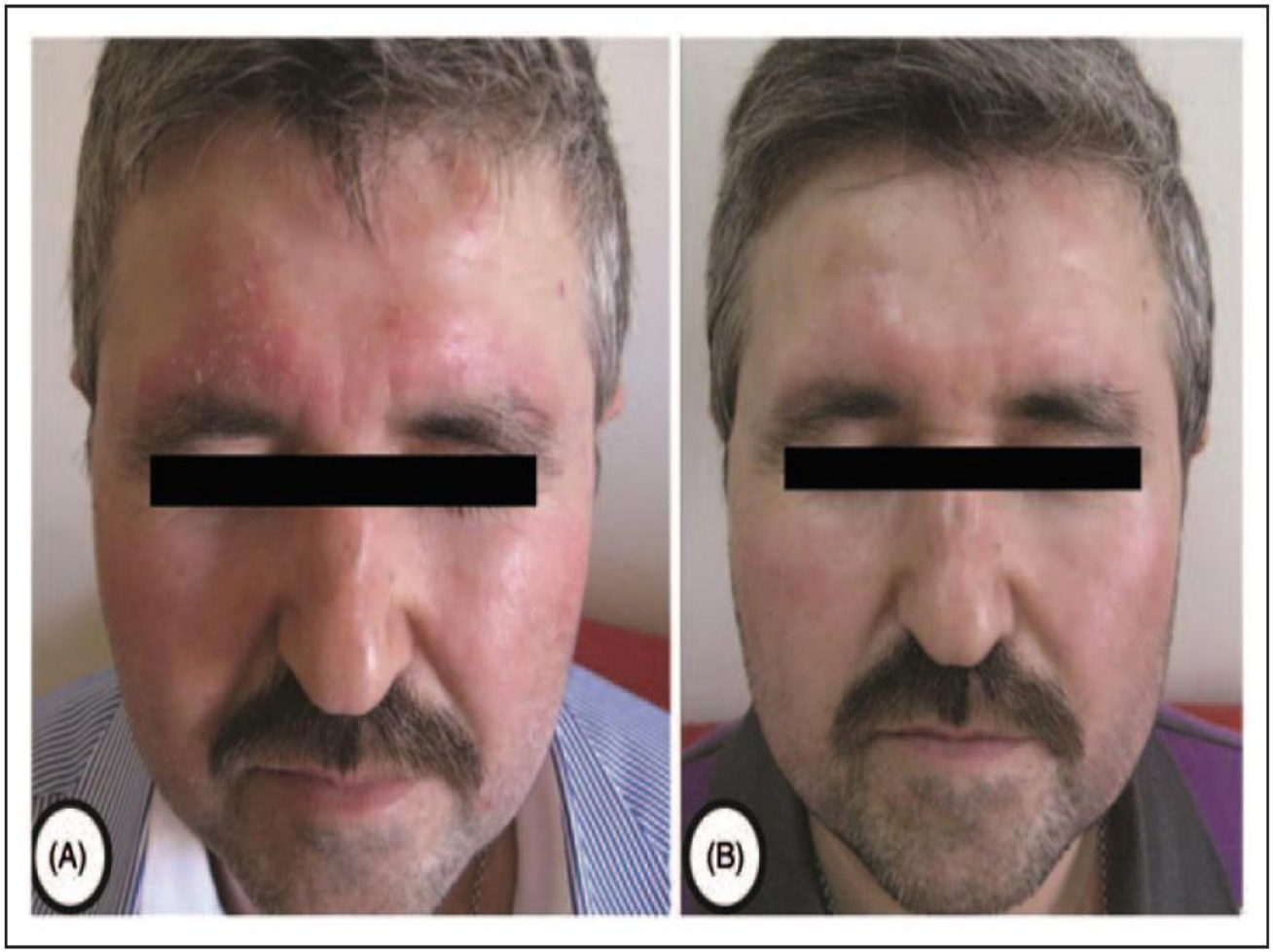


Figure 1 (A) Erythematous, well-demarcated, scaly confluent plaques on the face; (B) The skin lesions after discontinuation of treatment with infliximab.


谢谢