淋巴瘤治疗中的药物性肺损伤

北京大学人民医院呼吸与危重医学科 卢冰冰 2014-4

§1 药物性肺损伤
Drug Induced Lung Injury （DLI）

- 药物性肺损伤是由特定药物引起的发生在肺、气道、胸膜、肺血管的药物不良反应

Consensus statement for the diagnosis and treatment of drug-induced lung injuries. Respiratory Investigation.2013

流行病学

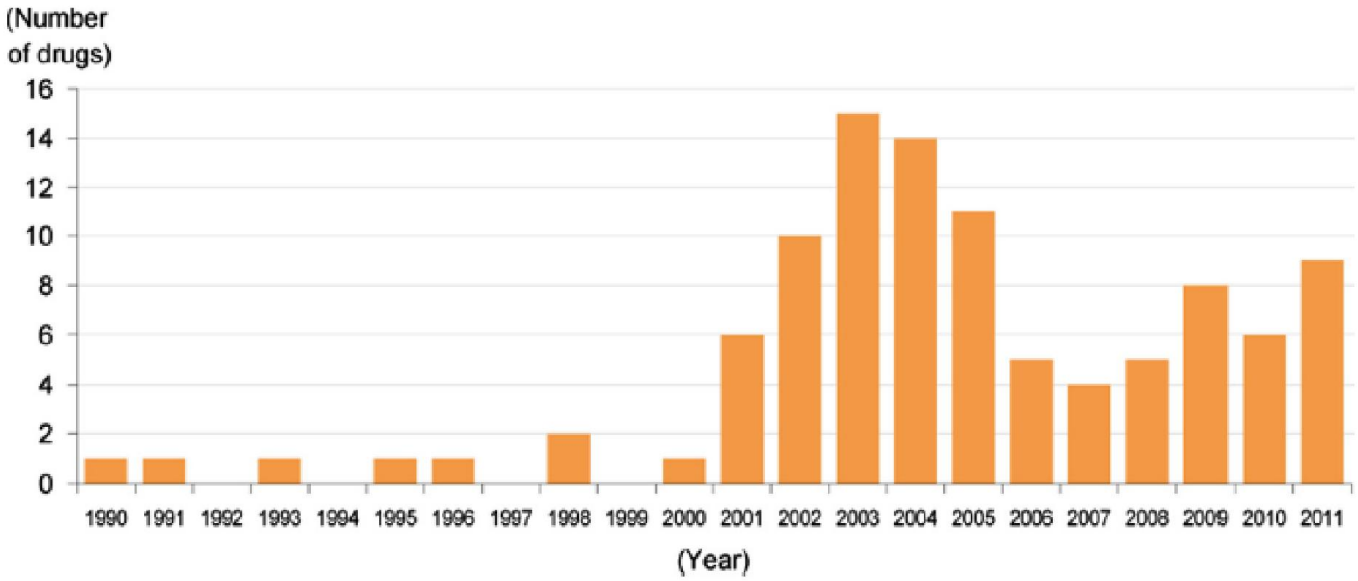


Fig. 1 – Number of drugs that have been reported to cause drug-induced (interstitial) pneumonia. The number of drugs that have been reported to cause drug-induced (interstitial) pneumonia between 1990 and 2011 according to data reported in the Pharmaceuticals and Medical Devices Safety Information (Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour & Welfare) is shown.

Consensus statement for the diagnosis and treatment of drug-induced lung injuries. Respiratory Investigation.2013

Table 2 – Number of case reports of suspected drug-induced interstitial pulmonary diseases from 2004 to 2009[a]

Drug type	Year					
	2004	2005	2006	2007	2008	2009
Anticancer drugs, non-molecularly targeted	322	339	355	388	399	393
Anticancer drugs, molecularly targeted	348	236	174	197	417	341
Gold drugs	1	3	3	3	1	2
Antimicrobial drugs/antifungal drugs	68	70	69	56	64	61
Chinese herbal drugs	36	47	36	32	33	49
Interferons	34	63	80	50	45	49
Antirheumatic drugs, non-biological	175	150	136	122	107	91
Antirheumatic drugs, biological	16	48	59	49	64	94
Anti-inflammatory analgesics	28	36	19	33	29	25
Psychotropic drugs	21	14	31	15	18	13
Antihypertensive drugs	28	32	38	43	50	46
Others[b]	167	154	161	172	232	218
Total	1244	1192	1161	1160	1459	1382

[a] The numbers of case reports filed with the PMDA were extracted from the Japanese Adverse Drug Event Report database (Reference [5]).
[b] Include drugs that do not fall into any of the specific categories listed. Among these drugs, there have been relatively large numbers of reports for the following categories of drugs: antiviral drugs, antithrombotic drugs, and anti-arrhythmic drugs.

Consensus statement for the diagnosis and treatment of drug-induced lung injuries. Respiratory Investigation.2013

Table 13 – Frequency of interstitial pneumonia and lung injuries caused by anticancer drugs.

Drug name		Frequency (%)
Paclitaxel (Taxol®)	紫杉醇（泰素）	0.54
Docetaxel hydrate (Taxotere®)	多西他赛	0.1
Amrubicin hydrochloride (Calsed®)	氨柔比星	2.2
Gemcitabine hydrochloride (Gemzar®)	盐酸吉西他滨（健择）	1.50
Pemetrexed (Alimta®)	培美曲塞（力比泰）	3.6
Vinorelbine (Navelbine®)	长春瑞滨（诺维本）	2.45
Irinotecan (Campto®, Topotecin®)	培洛霉素	1.30
Peplomycin sulfate (Pepleo®)	伊立替康	6.90
Bleomycin (Bleo)	博来霉素	10.20
Cisplatin (Briplatin®, Randa®)	顺铂	0.38
Carboplatin (Paraplatin®)	卡铂（伯尔定）	0.1
S-1 (TS-1)		0.3

Created based on data from package inserts and interview forms as of October 2011.

引起DLI的药物分类

- 非分子靶向抗肿瘤药
- 分子靶向抗肿瘤药
- 抗风湿病药（MTX、生物制剂）
- 干扰素（α-IFN、β-IFN）
- 免疫抑制剂（CTX、CYA、FK-506、AZ）
- 抗心律失常药：乙胺碘呋酮
- 其他：抗菌药物、中草药，等

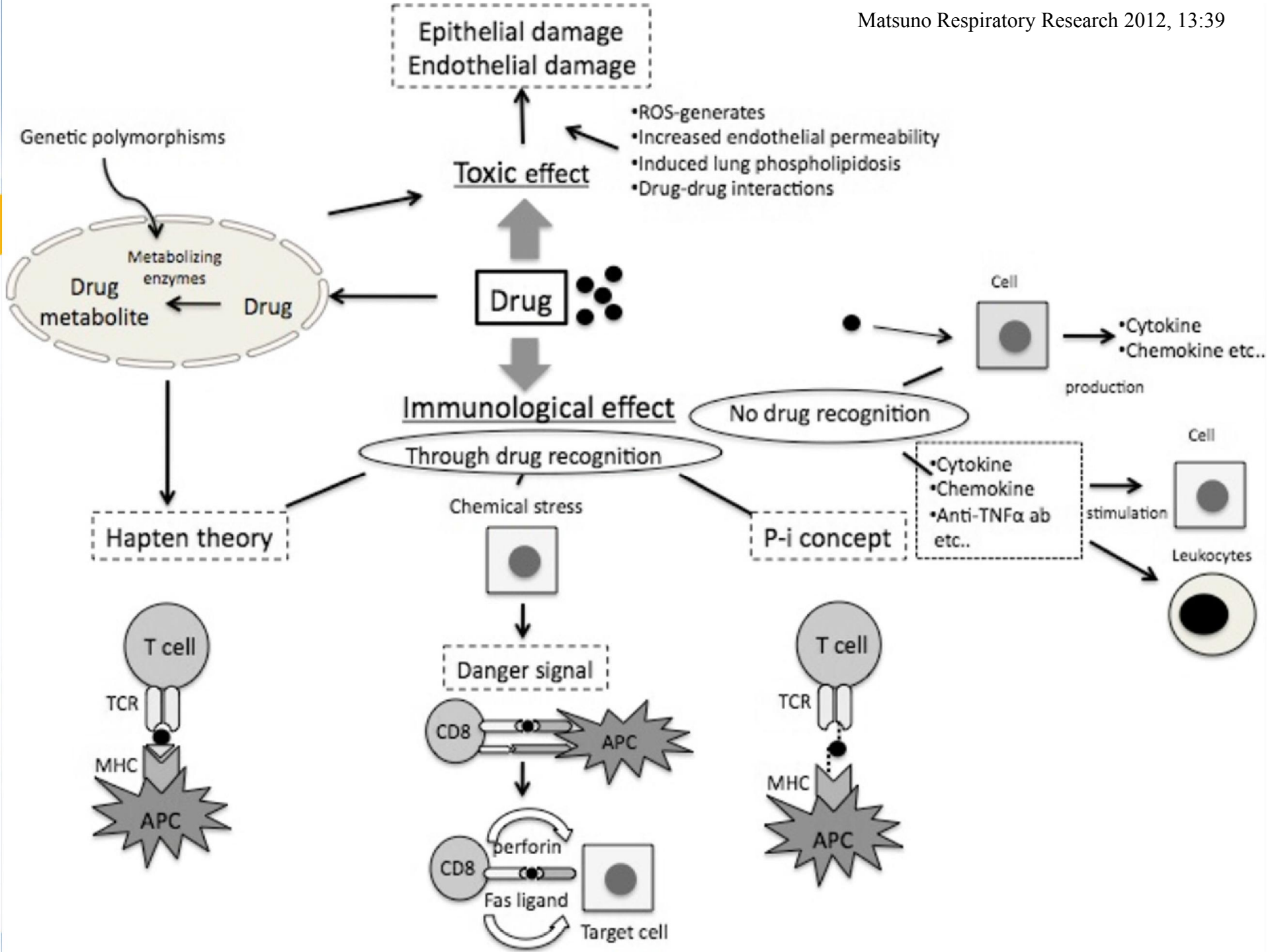
DLI的发病机制

- 细胞毒作用介导的肺损伤

药物直接或间接损伤肺泡上皮细胞、肺血管内皮细胞及气道上皮细胞；降低肺泡上皮的修复能力

- 免疫机制介导的肺损伤

药物作为半抗原或模拟抗原成分

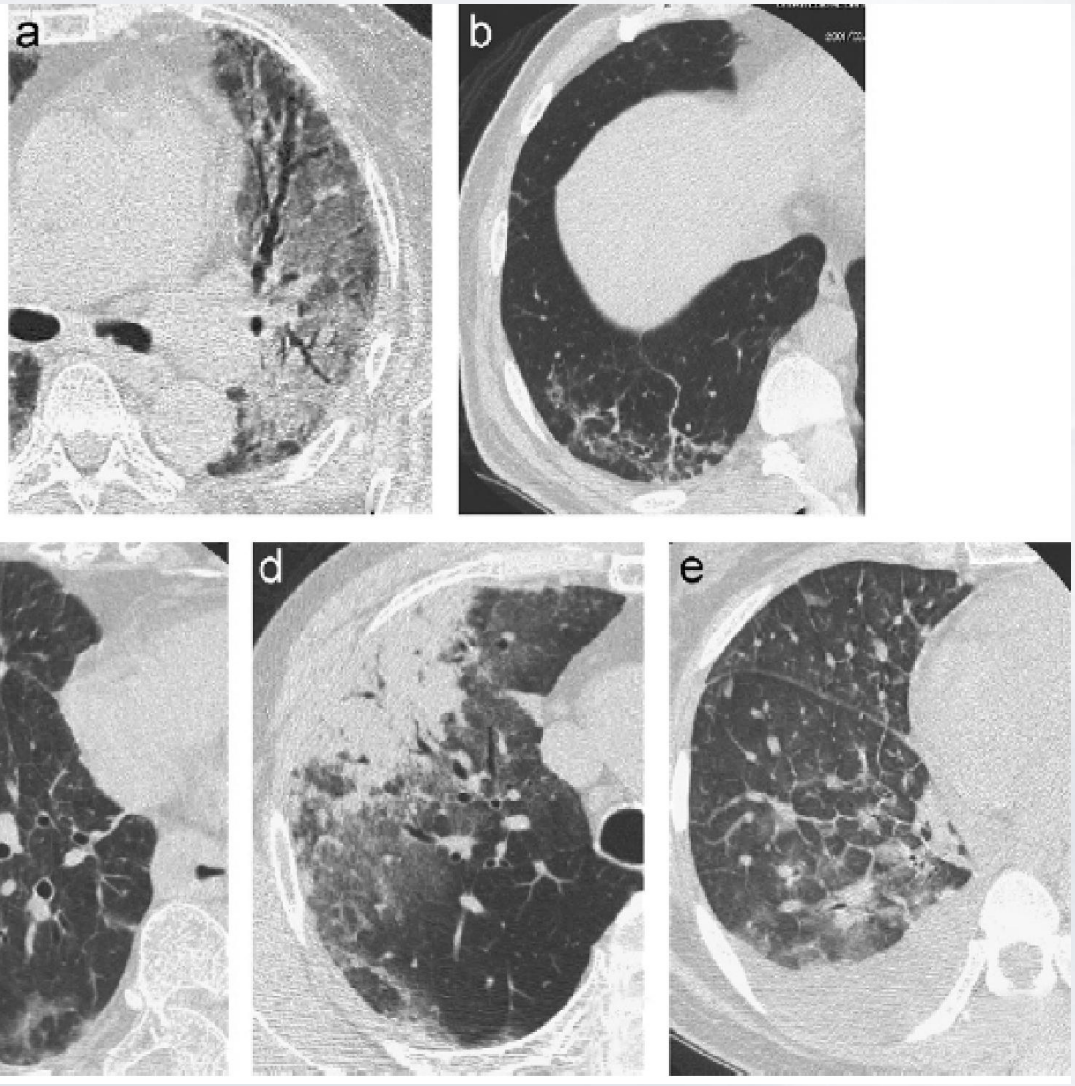

Epithelial damage
Endothelial damage
•ROS-generates
•Increased endothelial permeability
•Induced lung phospholipidosis
•Drug-drug interactions
Genetic polymorphisms
Toxic effect
Metabolizing enzymes
Drug metabolite
Drug
Drug
Cell
•Cytokine
•Chemokine etc..
production
Immunological effect
No drug recognition
Through drug recognition
Cell
•Cytokine
•Chemokine
•Anti-TNFα ab etc..
stimulation
Leukocytes
Hapten theory
Chemical stress
P-i concept
T cell
TCR
MHC
APC
Danger signal
CD8
APC
T cell
TCR
MHC
APC
perforin
CD8
Fas ligand
Target cell

DLT的临床表现

- 起病：急性、亚急性、慢性
- 临床症状：发热、胸膜性胸痛、干咳、活动后气短，少数伴咯血
- 支气管肺泡灌洗液（BALF）：细胞分类大多数为淋巴细胞性肺泡炎，嗜酸细胞性肺炎时分类可见嗜酸细胞比例增加。既可以CD_4为主，也可以CD_8为主
- 影像学特点：弥漫性间实质浸润，可伴有胸腔积液

DLI的影像学-HRCT特点

- 弥漫性肺泡损伤（DAD）
- 非特异性间质性肺炎（NSIPS）
- 过敏性肺泡炎（HP）
- 机化性肺炎（OP）
- 嗜酸粒细胞性肺炎（EP）



a. 弥漫性肺泡损伤（DAD）
b. 非特异性间质性肺炎（NSIPS）
c. 过敏性肺泡炎（HP）
d. 机化性肺炎（OP）
e. 嗜酸粒细胞性肺炎（EP）

Respiration Medicine.2008;102:892-898

药物性肺损伤的诊断标准

1	可疑药物的用药史，已知该药能够引起药物性肺损伤	询问病史时应注意患者的其他用药史：非处方药、保健品、非法麻醉药，等
2	患者的临床表现符合既往药物性肺损伤的相关报道	临床表现包括临床症状和体征、影像学特点、病理学特征
3	引起临床表现的其他病因已被排除	鉴别诊断：肺部感染、心源性肺水肿、基础肺病的急性加重
4	停药后临床表现获得缓解	病情可自行缓解或在应用糖皮质激素后缓解
5	再次用药后临床症状加重	不建议药物激发试验，但当患者要求用药并在保证安全性的前提下可再次用药

体检

肺部听诊

胸部影像学

CXR或HRCT

症状和体征

干咳　　呼吸困难、肺部啰音

胸部影像学

CXR或HRCT

症状和体征

皮疹、干咳、气短、呼吸困难、肺部啰音

胸部影像学

CXR或HRCT

实验室检查

血常规、生化、动脉血气分析、CPR、ESR、BALF细胞分类

鉴别诊断（感染，等）

-血CMV抗原/DNA

-血G&GM

-痰病原学（细菌、真菌、抗酸杆菌，涂片及培养或DNA）

-BALF：PCP涂片/DNA

BALF

肺组织病理学

药物性肺损伤

基础肺部疾病发展或急性加重

合并肺部感染或其他

用药前　　用药期间　　怀疑药物性肺损伤　　确诊

药物性肺损伤的治疗原则

- 非心源性肺水肿
- ALI/ARDS
- 弥漫性肺泡损伤（DAD）

→ 静脉激素冲击治疗
甲强龙500-1000mg/d×3d
→ 细胞毒药物

- 非特异性间质性肺炎（NSIP）
- 机化性肺炎（OP）
- 过敏性肺泡炎（HP）
- 嗜酸粒细胞性肺炎（EP）

→ 口服激素治疗
强的松 0.5～1g/kg·d
→ 非细胞毒药物（过敏性）

临床特征　　激素用法　　发病机制

预后

- 预后与病理类型有关
- 大部分过敏性肺泡炎（HP）、机化性肺炎（OP）、嗜酸粒细胞性肺炎（EP）对停药及激素反应良好
- 弥漫性肺泡损伤（DAD）预后不良

§2 病例分享

来自非淋巴瘤患者的经验

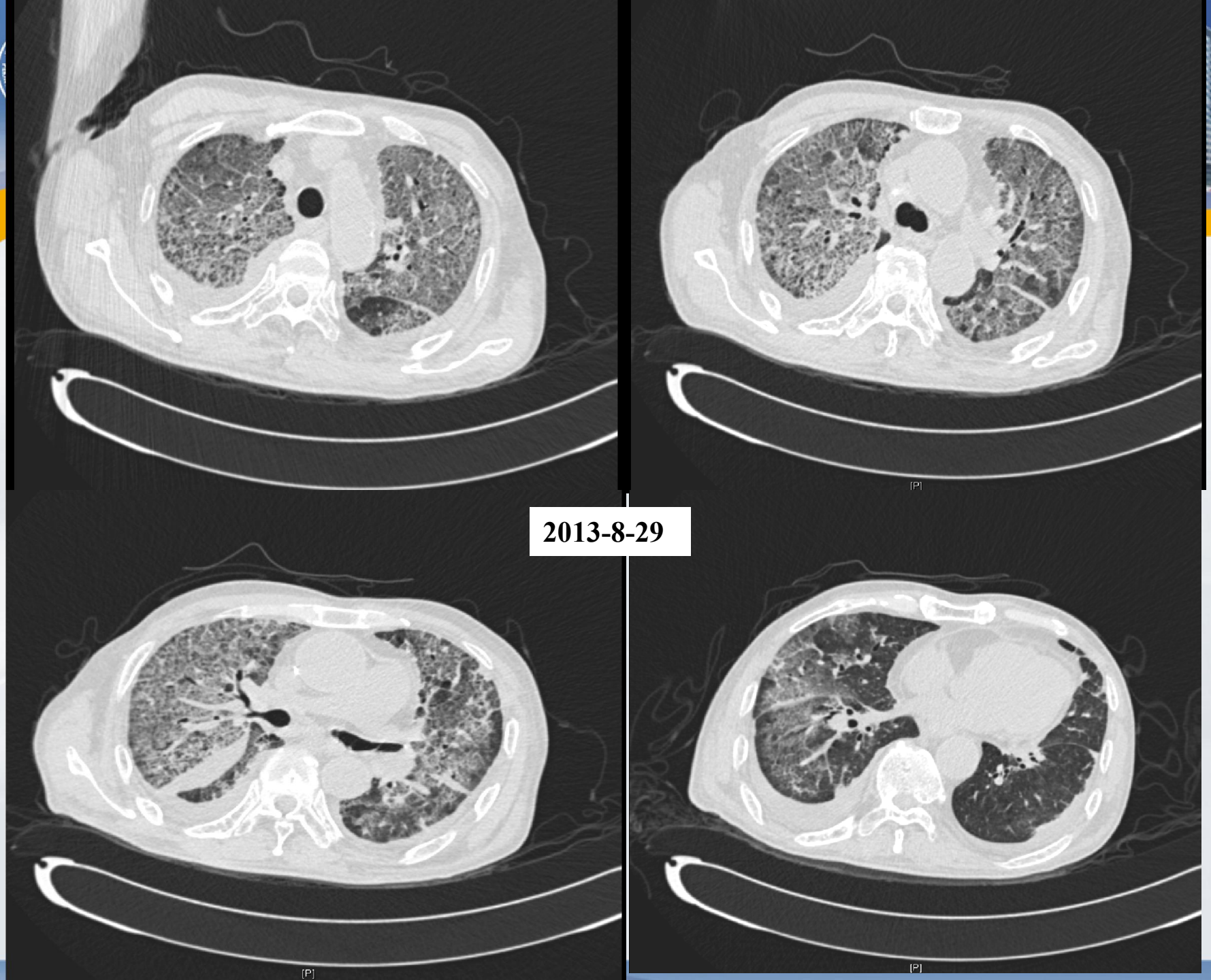
CASE 1

- 虞FX，RA， 服用MTX 7.5mg/w及来氟米特 3-4月后就诊
- 主诉：干咳伴活动后气短
- 可疑药物：MTX
- 治疗：甲强500mg IV×3d，序贯并逐渐减量

- MTX-induced pulmonary toxicity may induce the release of free oxygen radicals, such as nitric oxide, and various cytokines, such as IL-1β, TNF-α, and TGF-β.

2013-8-25

2013-9-3


2013-8-29

支气管灌洗液细胞计数及分类

- 2013-08-29：巨噬细胞57.00%，LY 27.00%，分叶核细胞15.00%，嗜酸性粒细胞0%

- 2013-09-03：巨噬细胞31.00%，LY 62.00%，分叶核细胞7.00%，嗜酸性粒细胞0%

病原学

- 病毒指标

-2013-08-29血：CMV-DNA、EB病毒扩增荧光检测、微小病毒B19核酸均阴性

-2013-08-29支气管镜灌洗液：CMV-DNA阴性

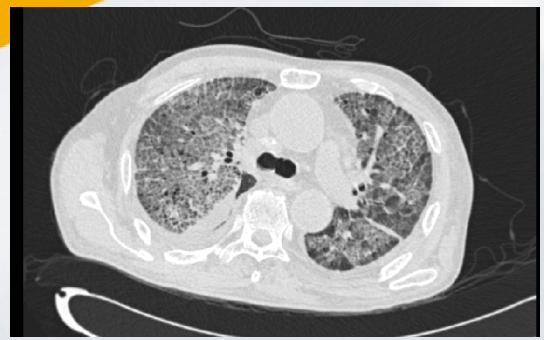
- 2013-09-03支气管镜灌洗液：CMV-DNA、EBV、ADV均阴性

PCP涂片及DNA：阴性

- 普通细菌涂片与染色支气管分泌物：阴性
- 浓缩查结核杆菌支气管分泌物：阴性
- 真菌培养支气管分泌物：热带念珠菌及白色念珠菌（考虑定植）

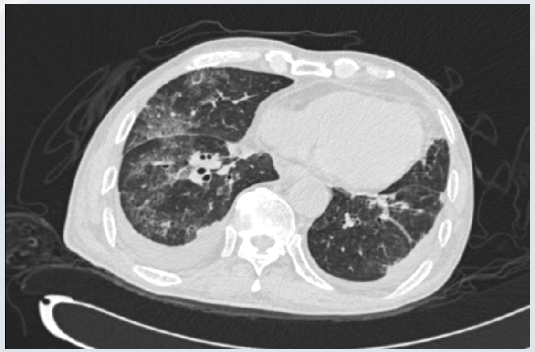
2013-9-5

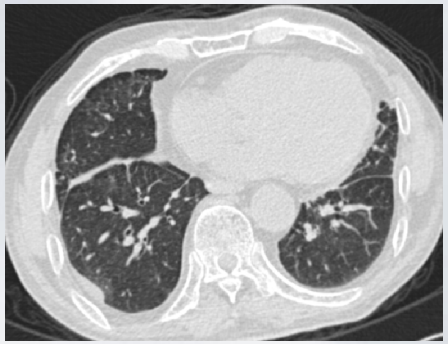
2013-10-3









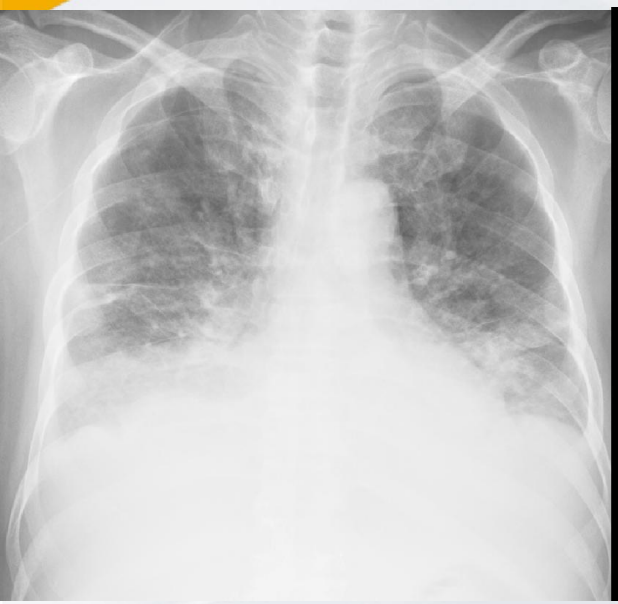


2013-8-29　　2013-9-6　　2013-11-4

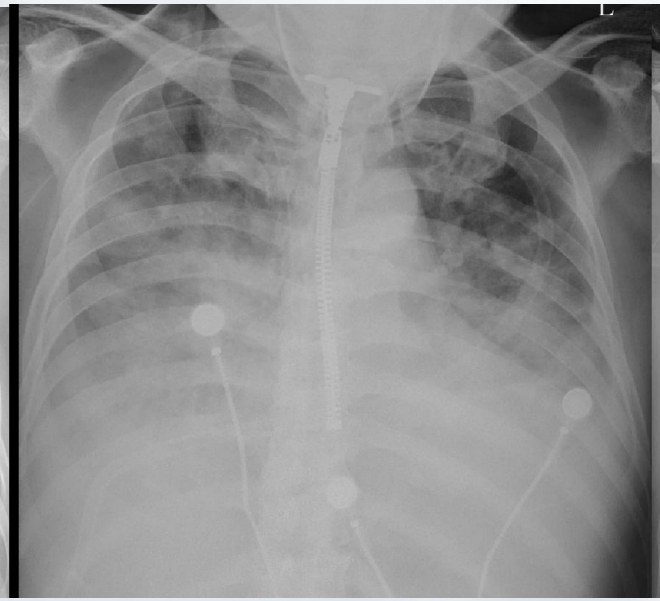
CASE 2

e.g. 王YF，男，51y

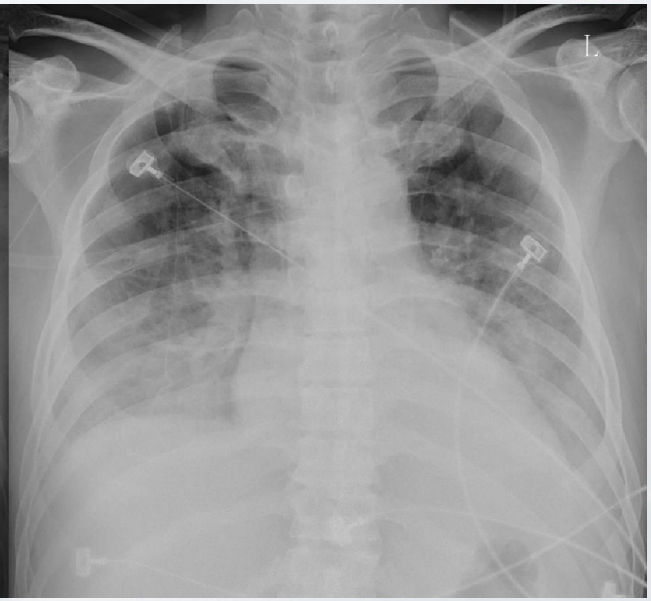
- 主诉：确诊ALL 4月余，呼吸困难2周
- 可疑药物：BCR-ABL（+），达沙替尼间断用药2月余
- 治疗：甲强500mg IV×3d，序贯并逐渐减量



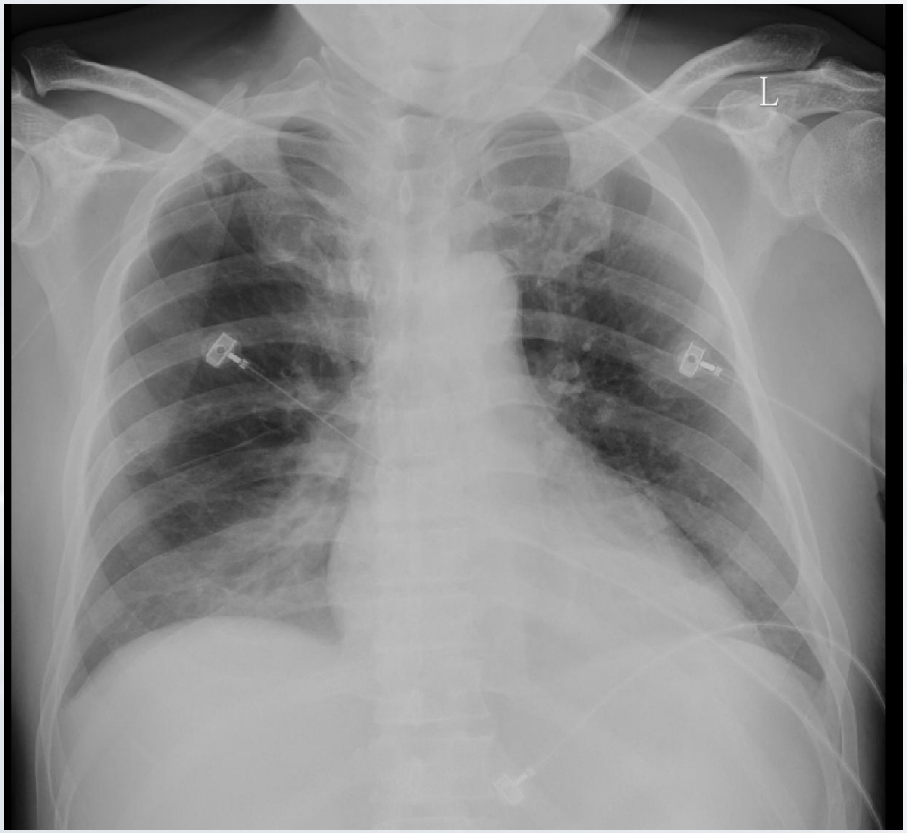
2014-2-4



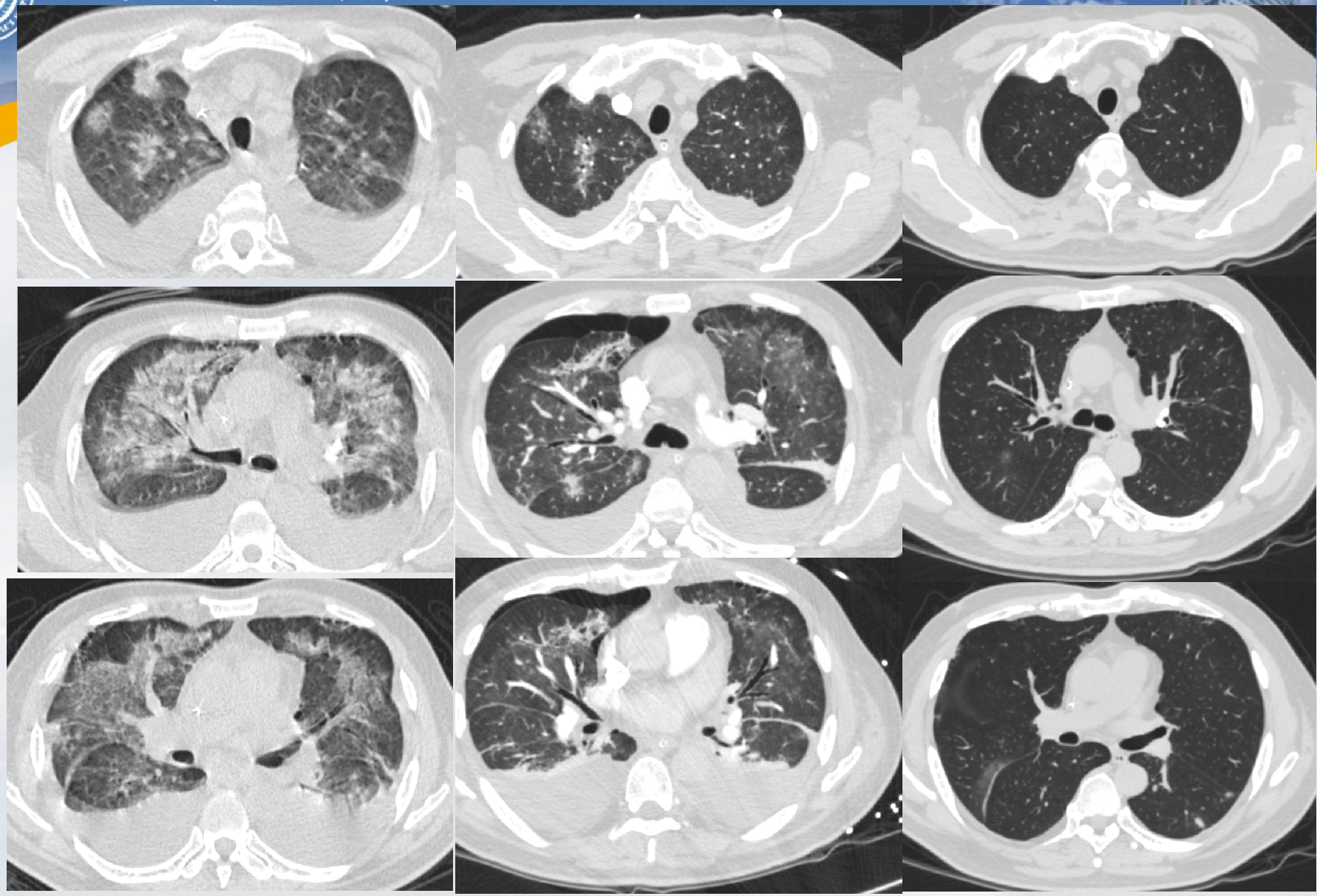
2014-2-6



2014-2-9



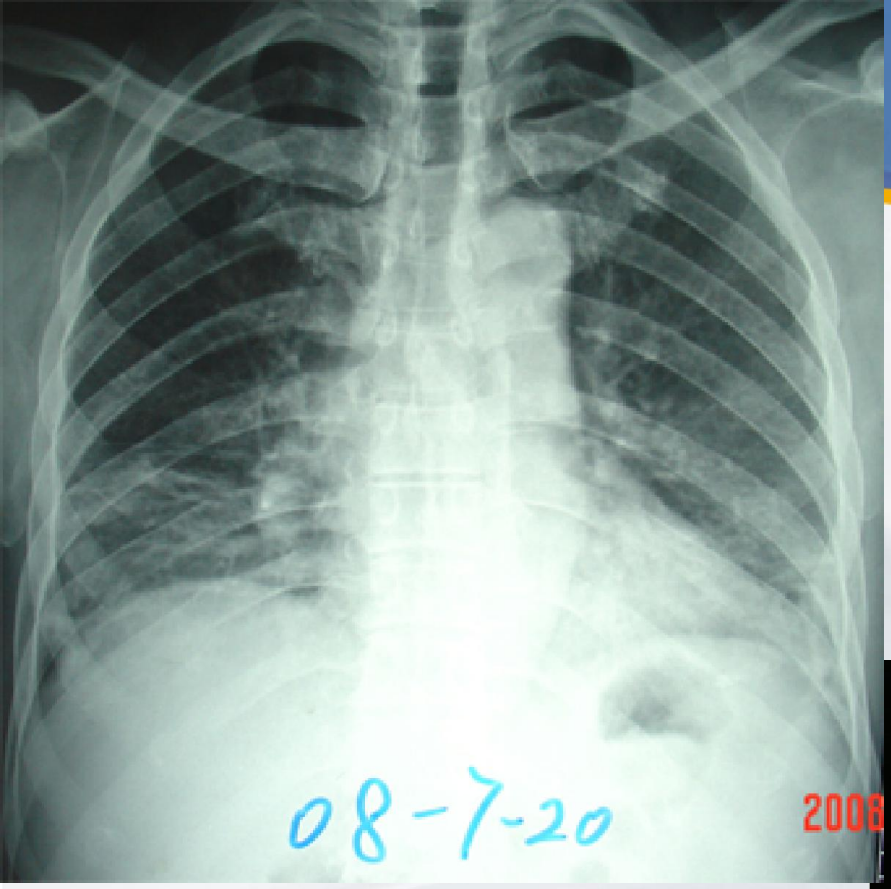
2014-2-15



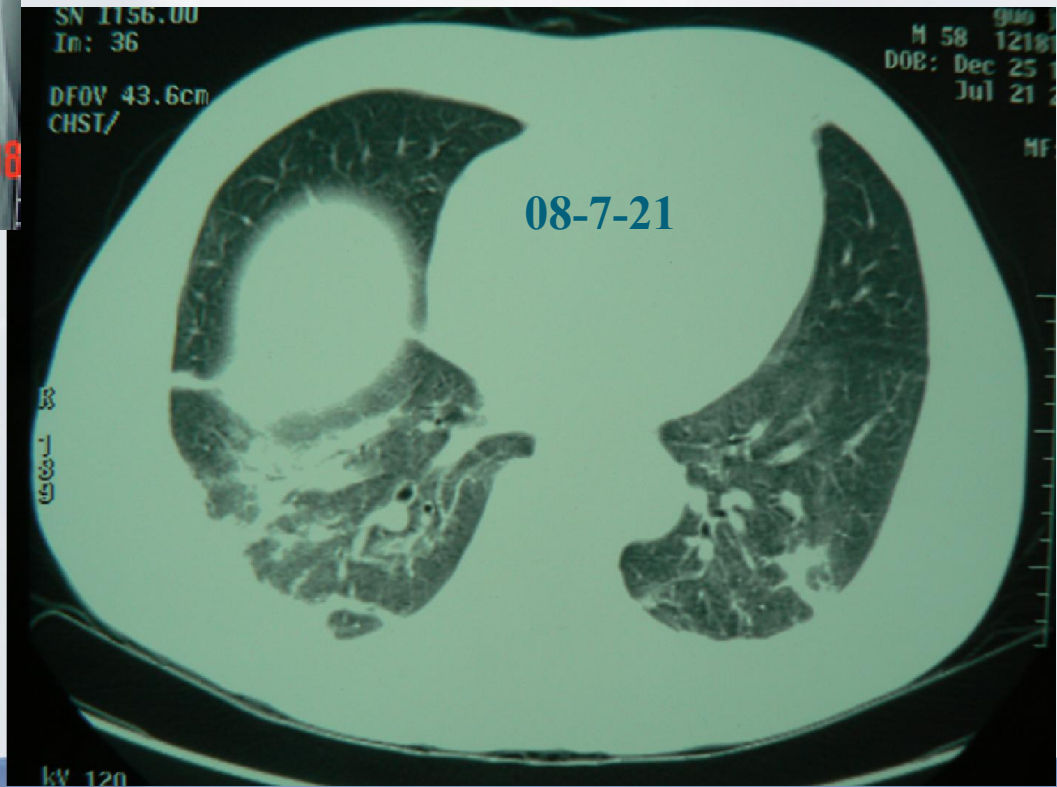
2014-2-7　　2014-2-11　　2014-2-24

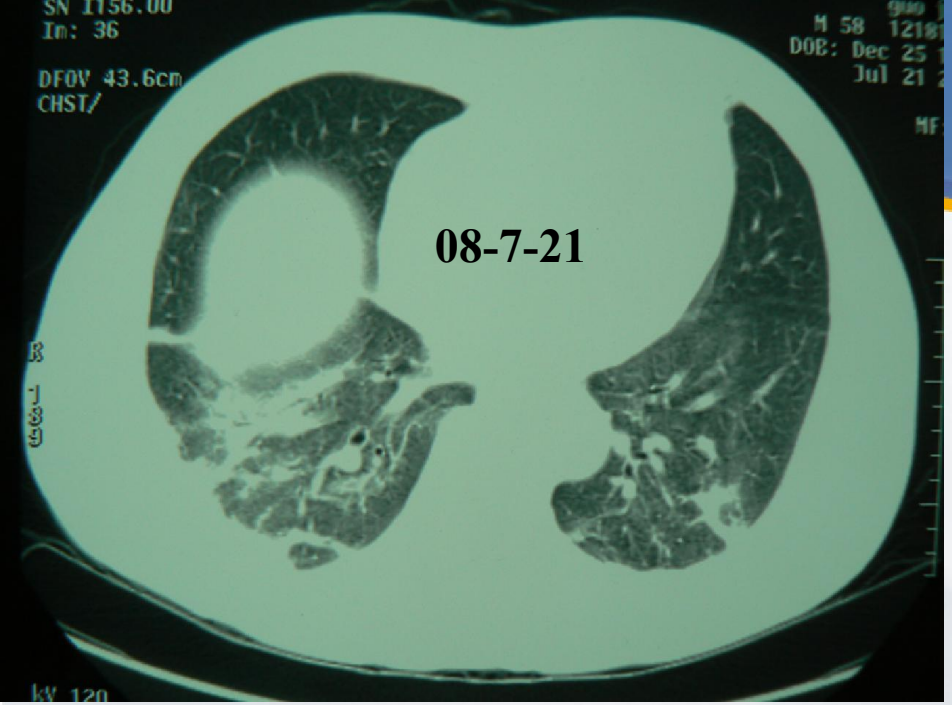
CASE 3

- 郭J，男，因“咳嗽、气短” 08-7-21入院
- 5个月前丙肝，2月前α干扰素300万u qod im
- 入院时：HCV-RNA 1.453×10^5copy/ml



•PH 7.49，$PaCO_2$ 36mmHg，PaO_2 48mmHg

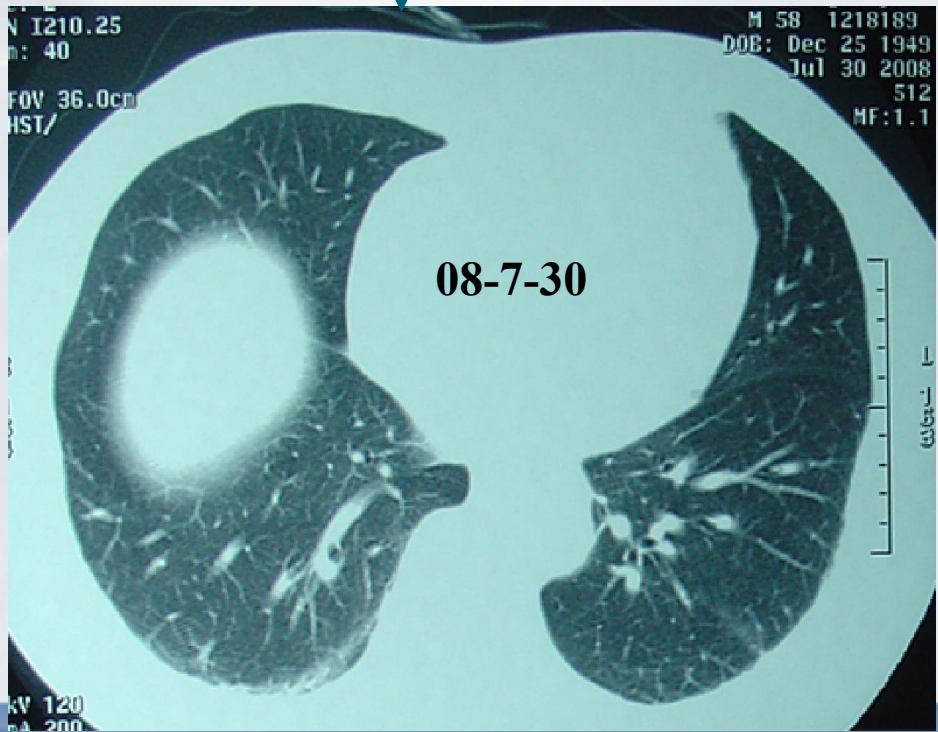




•08-7-30支气管镜：支气管粘膜炎症

肺泡灌洗液：巨噬45%，淋巴55%

•PH 7.41，$PaCO_2$ 40mmHg，PaO_2 78mmHg



•措施：停用干扰素治疗

•诊断：药物性肺损伤

§3 淋巴瘤患者的药物性肺损伤

淋巴瘤患者的抗肿瘤药物

- 细胞毒药物

  烷化剂：环磷酰胺、异环磷酰胺

  抗微管药物：长春新碱

  DNA拓扑异构酶Ⅱ抑制剂：依托泊苷

  蒽环类抗生素：阿霉素（多柔比星）、米托蒽醌

  铂类：顺铂、卡铂、奥沙利铂

  抗代谢药：阿糖胞苷、吉西他滨、甲氨蝶呤

- 生物制剂：美罗华

Methotrexate Induced Lung Injury in a Patient with Primary CNS Lymphoma: a Case Report

Figure 1. Figure showing normal tracheobronchial tree, vessels and normal lung parenchyma.

MTX 1g/m^2

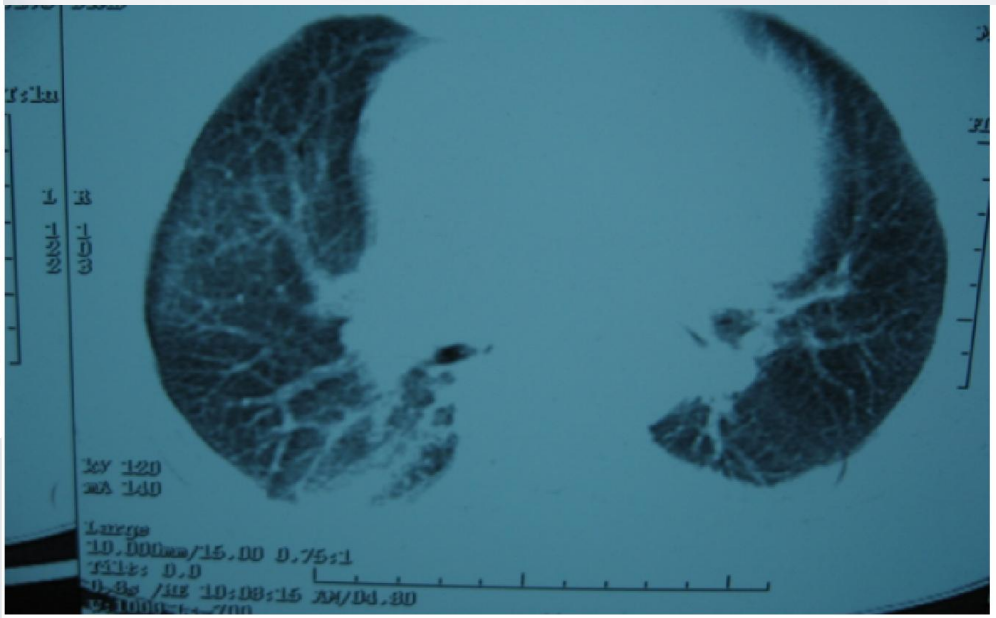


Figure 4.

Figure 2,3,4. HRCT chest [after giving methotrexate], showing normal tracheobronchial tree, vessels but lung parenchymal changes in the form of b/l patchy ground glass opacities with b/l basal atelectasis.

Figure 4 A 75-year-old man with HL. Following chemotherapy, diffuse ground-glass opacification and subpleural reticulation can be seen throughout the lung parenchyma, attributed to NSIP secondary to bleomycin. The patient had no respiratory symptoms.

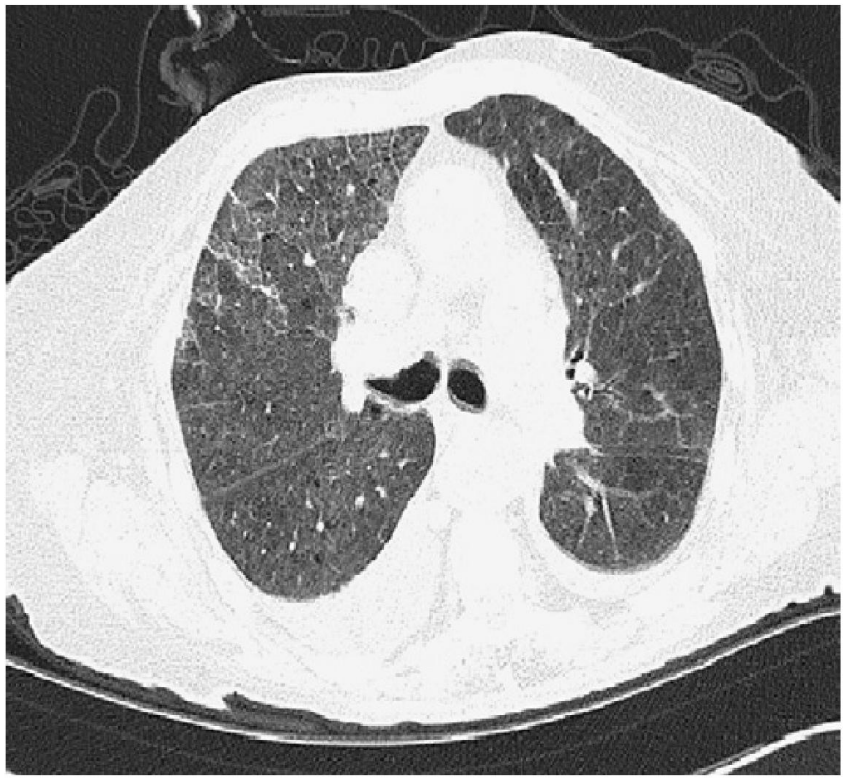
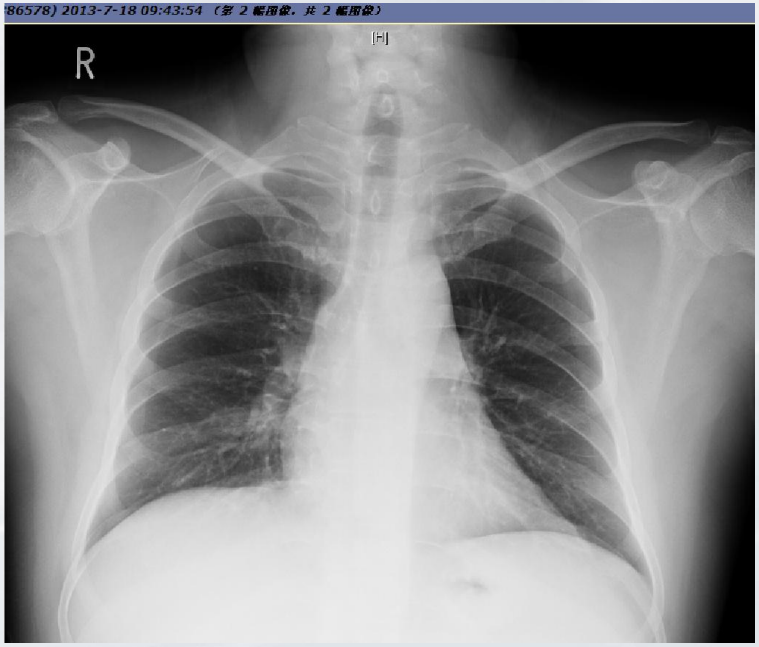


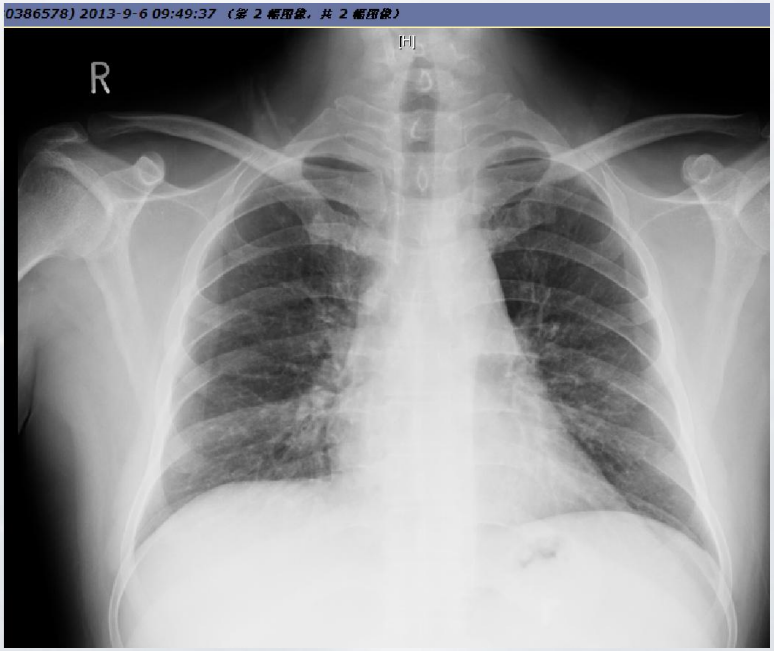
Figure 5 A 81-year-old man with diffuse large B-cell lymphoma. Following chemotherapy, there is ground-glass change and peripheral interlobular septal thickening in the right middle lobe. These were also present in all other pulmonary lobes. Findings were attributed to rituximab and resolved following withdrawal of the drug. The patient had only mild respiratory symptoms.

Case 4

- 何XJ，男，40y
- 免疫性血小板减少（ITP），病程2月
- 曾经应用口服强的松及环孢素，效不佳
- 给予静点美罗华（利妥昔单抗）100mg/w，连续4周
- 2013年9月6日出现呼吸困难

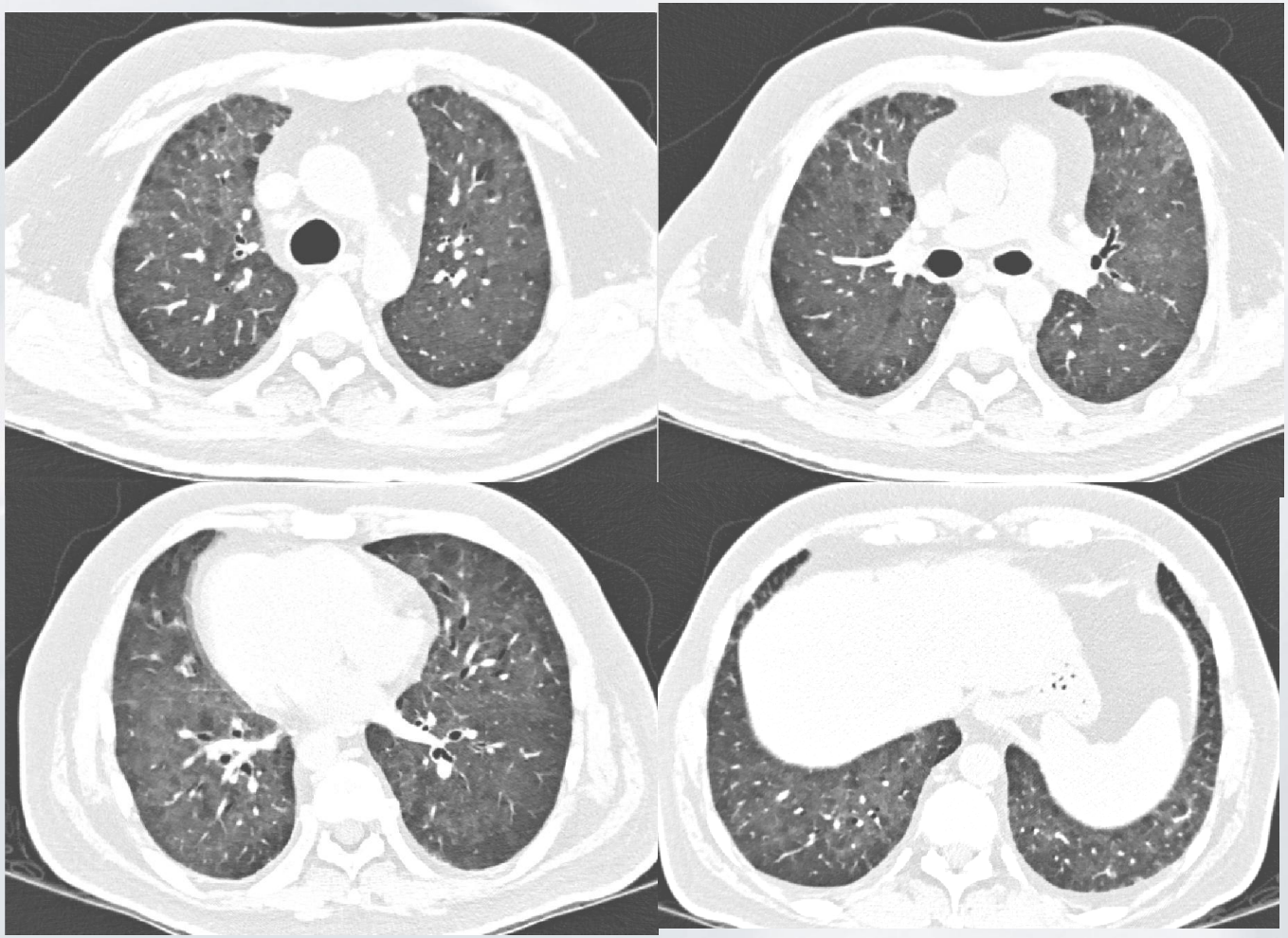


2013-7-18

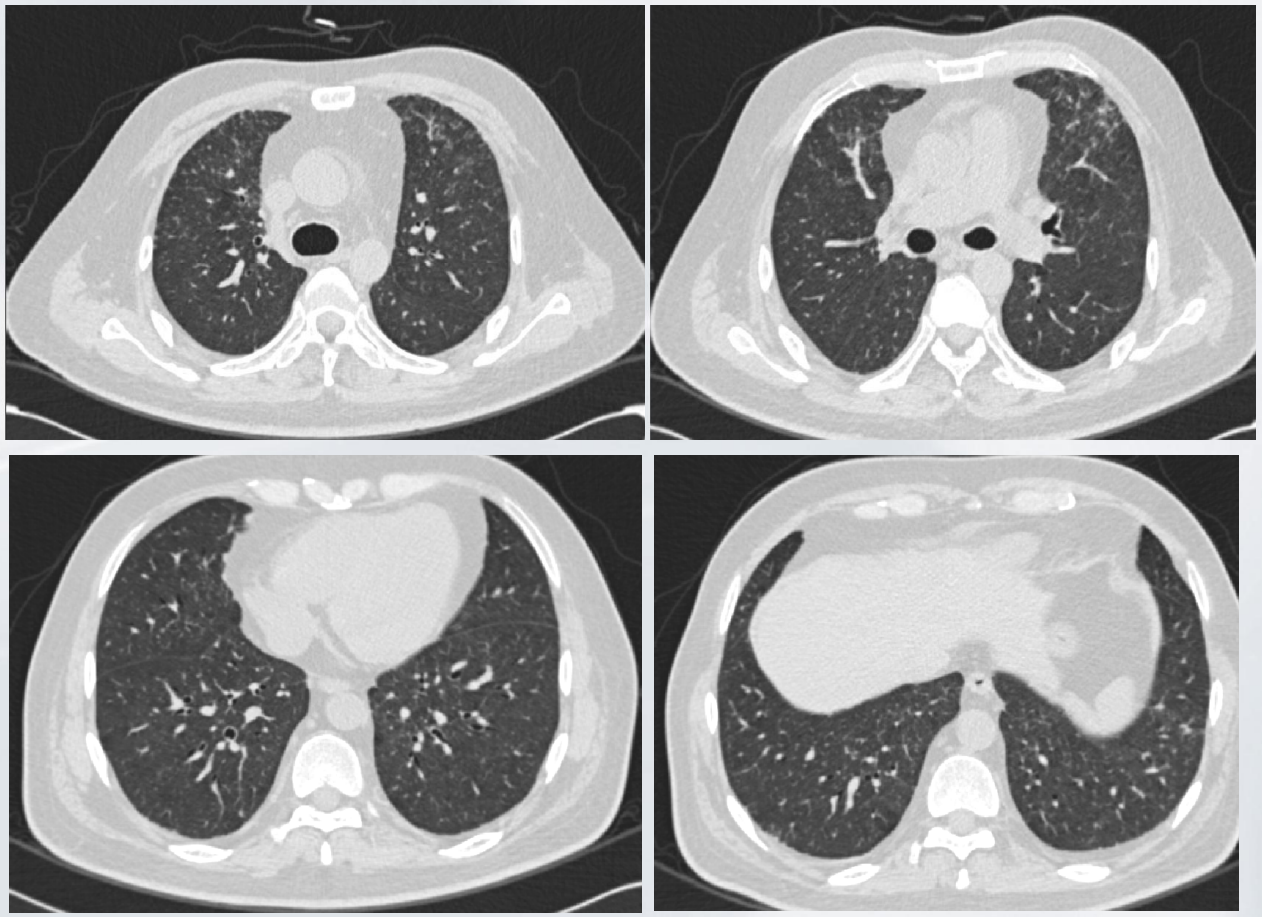


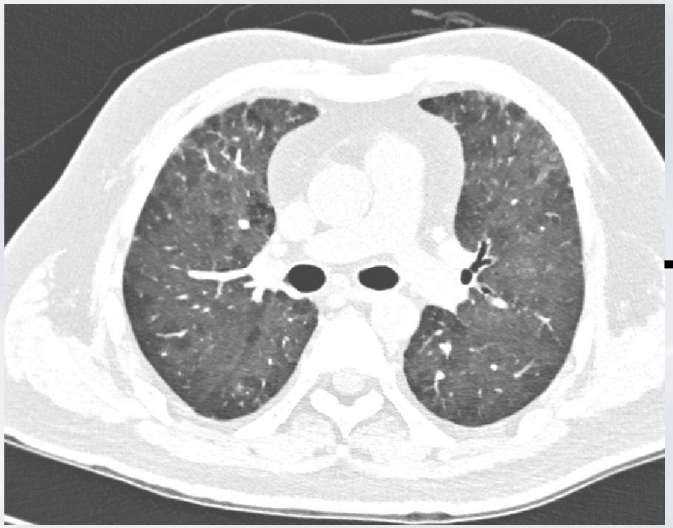
2013-9-6

2013-9-10



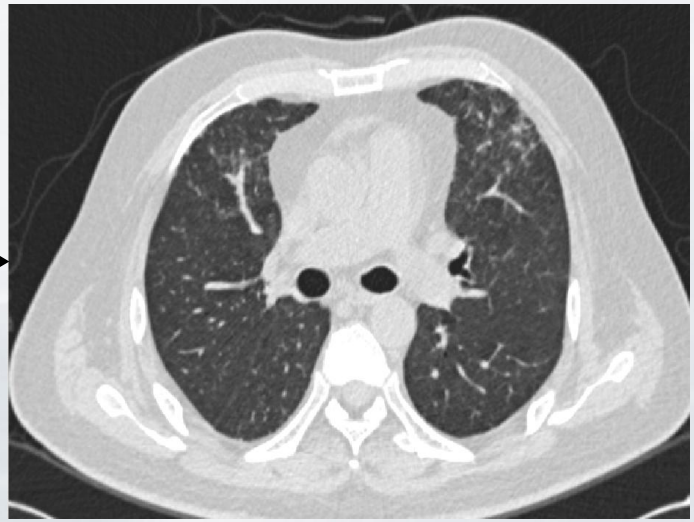
2013-9-20





2013-9-10

甲强龙80mg



2013-9-20

诊断：药物性肺损伤（美罗华）

CASE REPORT

Rituximab-induced Acute Eosinophilic Pneumonia with Diffuse Alveolar Damage: A Case Report

-Male, 69y， mantle cell lymphoma Ⅳ

-CHOP： 1 cycle

-CEOP： 7 cycles

-R-CEOP: 375mg/m^2,W1D 4 cycles

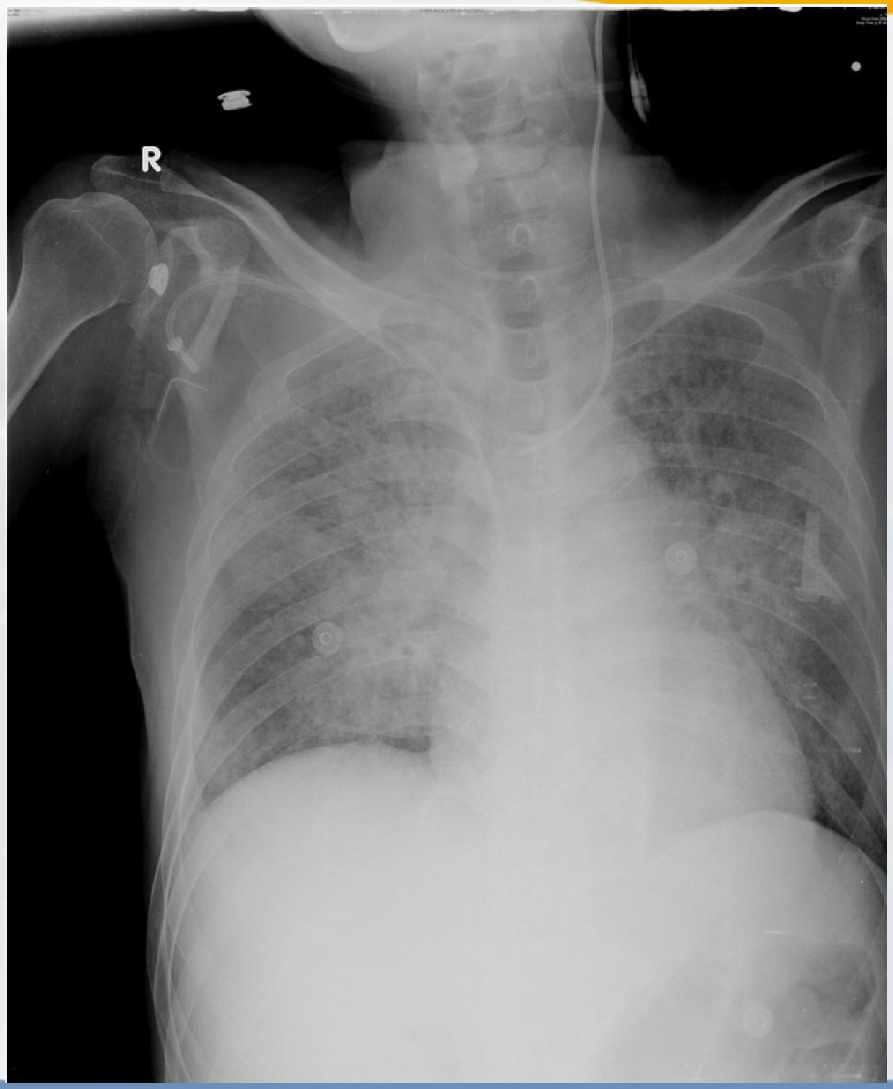
-通气支持，停药

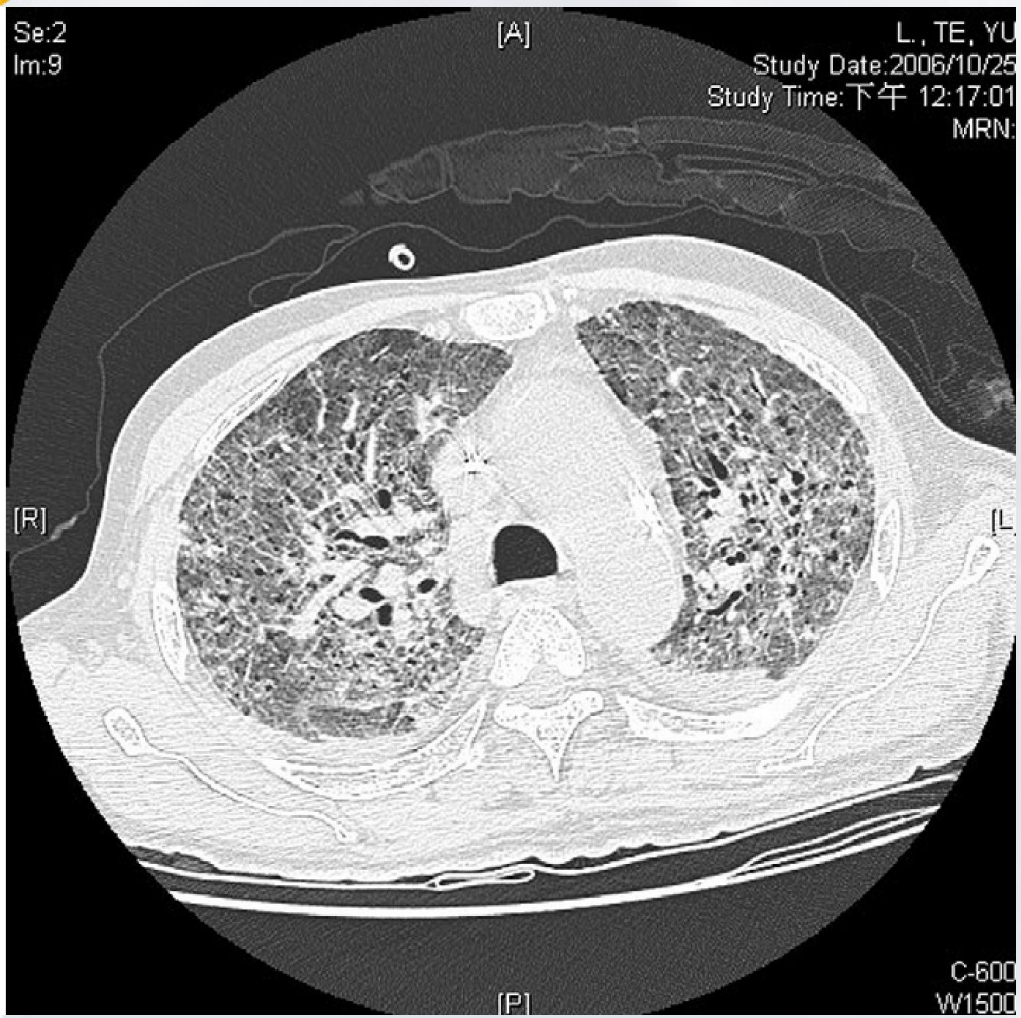
-外科肺活检：弥漫肺泡损伤

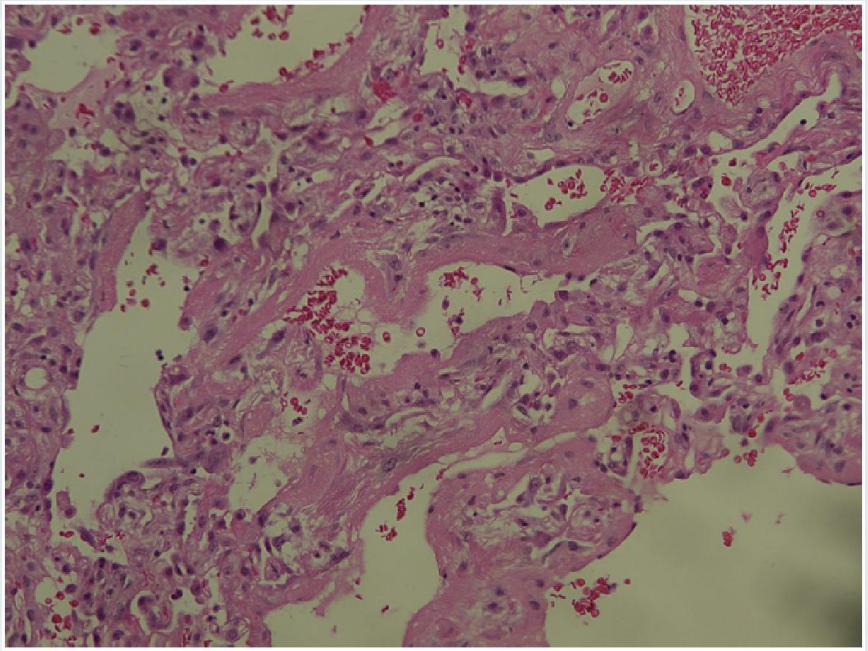
-氢化可的松：100mg, q6h

-结局：出院

-可疑药物：美罗华




Se:2
Im:9
[A]
L., TE, YU
Study Date:2006/10/25
Study Time:下午 12:17:01
MRN:
[R]
[L
[P]
C-600
W1500



- 利妥昔单抗引起肺损伤的具体机制不明
- 特点：起病多在用药后2周——2月，双肺弥漫浸润
- 肺泡灌洗液：CD4+为主的淋巴细胞性肺泡炎
- 大多数患者对糖皮质激素反应良好
- 少数患者死亡

体检

肺部听诊

胸部影像学

CXR或HRCT

症状和体征

干咳　　呼吸困难、肺部啰音

胸部影像学

CXR或HRCT

症状和体征

皮疹、干咳、气短、呼吸困难、肺部啰音

胸部影像学

CXR或HRCT

实验室检查

血常规、生化、动脉血气分析、CPR、ESR、BALF细胞分类

鉴别诊断（感染，等）

-血CMV抗原/DNA

-血G&GM

-痰病原学（细菌、真菌、抗酸杆菌，涂片及培养或DNA）

-BALF：PCP涂片/DNA

BALF

肺组织病理学

药物性肺损伤

基础肺部疾病发展或急性加重

合并肺部感染或其他

用药前　　用药期间　　怀疑药物性肺损伤　　确诊

谢 谢！