When the House Party Protocol *Goes Wrong…*

HKSCCM interhospital GR 21/5/2013

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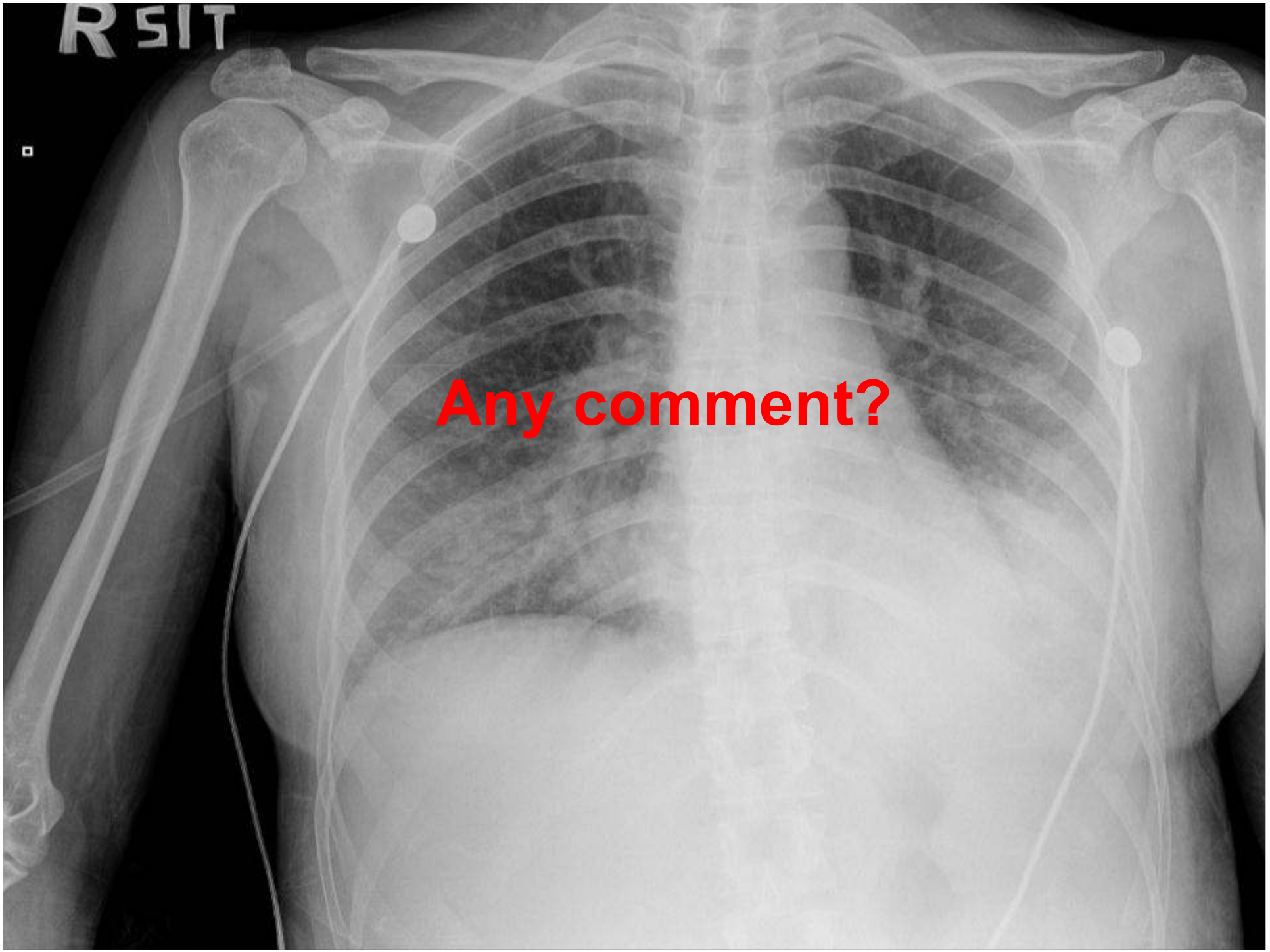
Dr Chan Yat Fat, Alfred

- 40/F
- Unremarkable past health

- p/w fever/cough/sputum 3 days on 8/2/2013, admitted to medical ward
- TOCC neg
- BP 144/84 ST 149bpm Temp 38
- WBC 411, Blast cell 369.9 (90%), Hb 8.2, Plt 71
- INR 1.4 APTT 35.4
- K 2.8 Cr 69 Bili/ALP normal ALT 67 CK 115 LDH 1931 Ca 2.14


R SIT
Any comment?

- **TMH HEMATOLOGY**
  - **CAP + AML**
  - **TAZOCIN/ZITHROMAX/TAMIFLU**

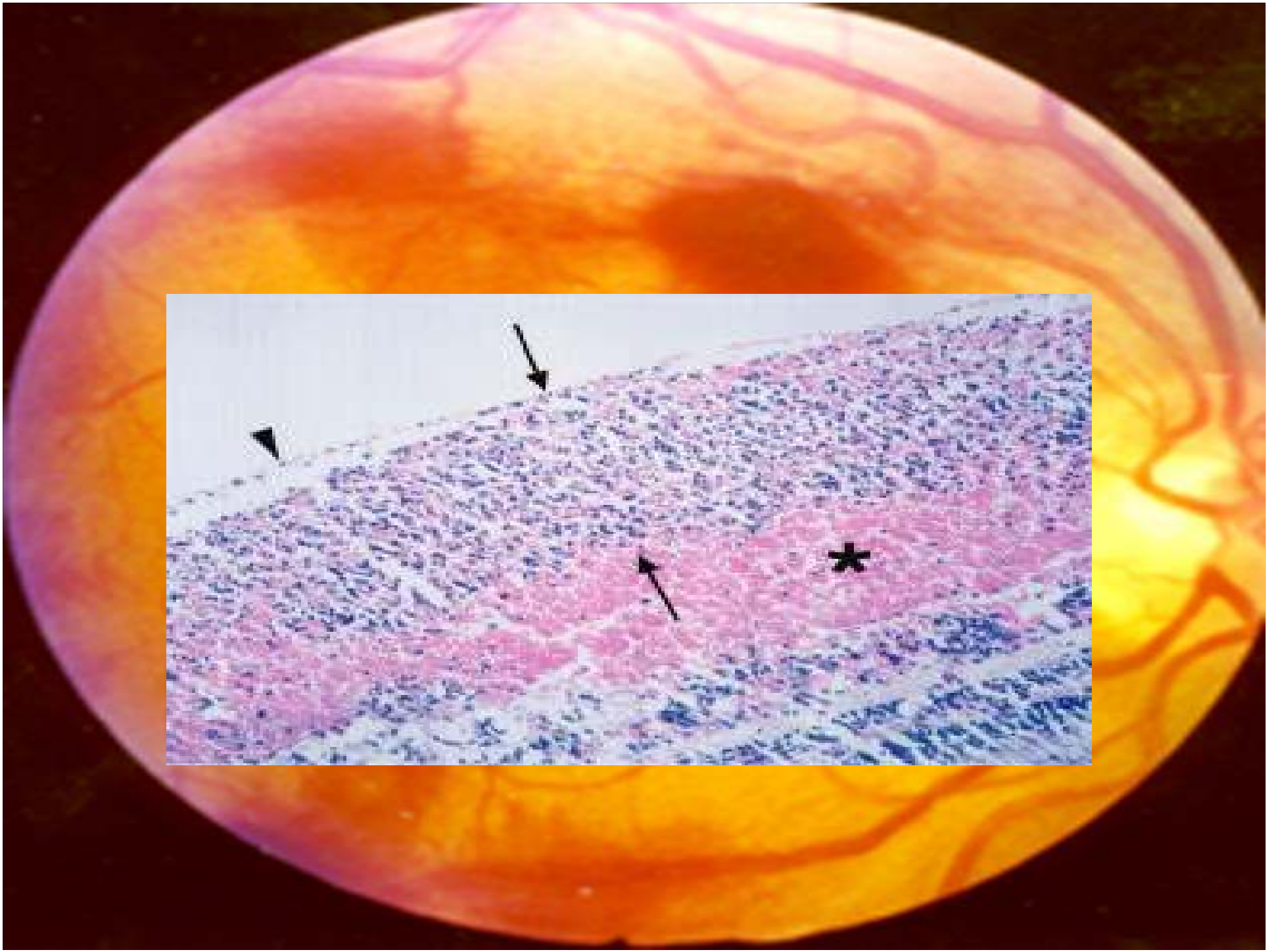
WBC 411→Any treatment?

Leukostasis

- WCC >= 100X10^9/L defines hyperleukocytosis
- characterised by intravascular accumulation of blasts occupying the vascular lumen, without or without the presence of fibrin
- Function of the blast cells less deformable than mature myeloid cells → intravascular plugging
- High metabolic activity of blast and local production of various cytokines contribute to underlying cellular hypoxia

Leukostasis – medical emergency!

- CNS, eyes and lungs
  - Others: extremities, kidneys, heart and penis
- Dyspnea/stupor and WCC>100 in the absence of clear etiology → presumptive diagnosis of leukostasis
- Fundoscopic exam is most helpful in establishing the diagnosis
- Clinical picture can be less typical/ WCC <100 in rapidly increasing blast / monocytic variant



Treatment of leukostasis

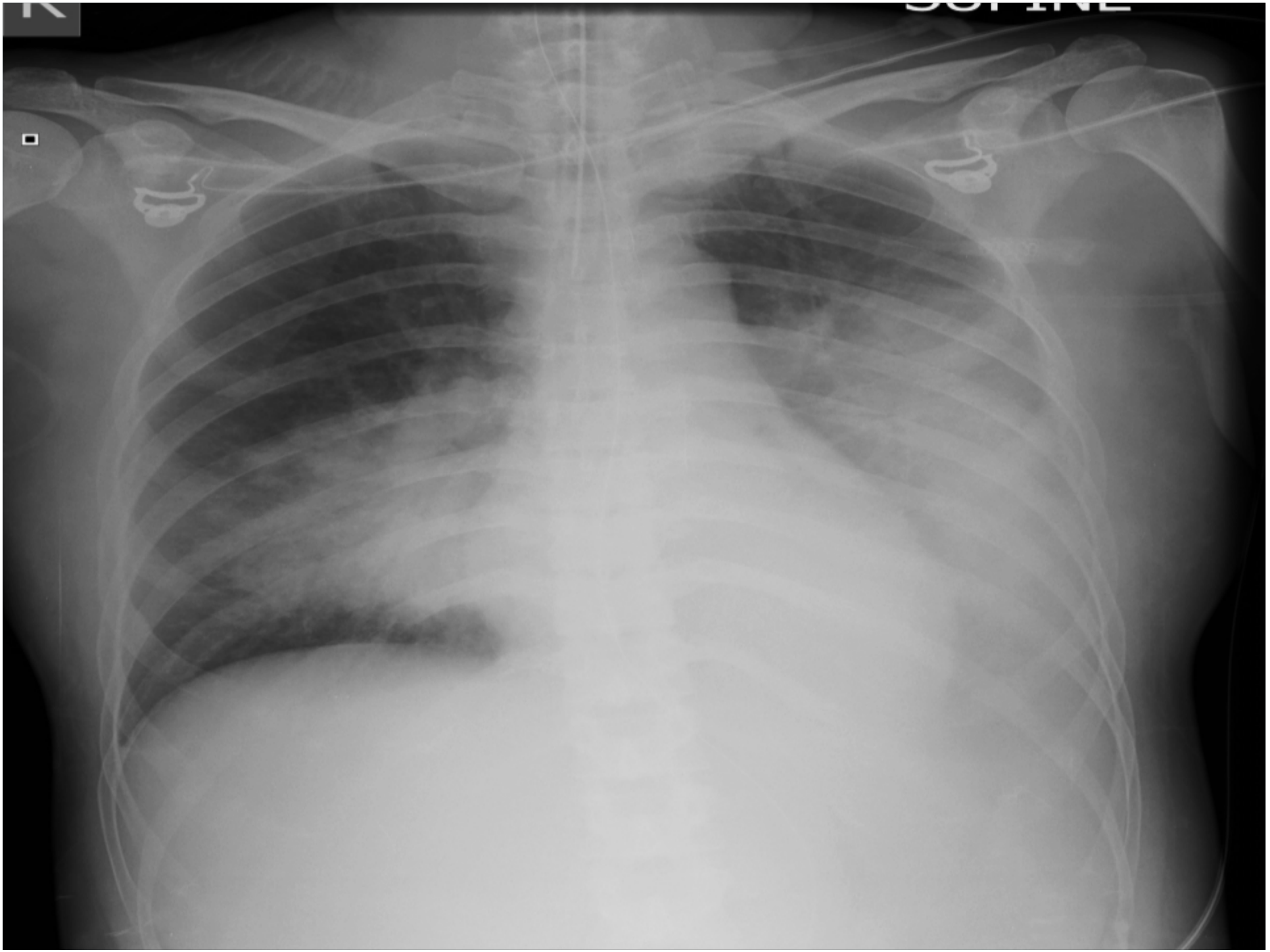
- Chemotherapy with induction agents/ high dose hydroxyurea
- No prospective randomised trial of leukapheresis/ venesection for any outcome benefit
- Cranial irradiation for neurologic symptoms
- Dexamethasone recently proposed as it inhibit upregulation of adhesion molecules on leukemia and endothelial cells
- Avoid PRBC transfusion

Management by haematology team

- venesection done x 2 units
- started on hydroxyurea and chemotherapy (cytarabine/daunorubicin) since 9/2 with allopurinol, rasburicase coverage

Next day…

- To TMH ICU for worsening resp failure, intubated
- Refractory hypoxemia on FiO2 1.0


R
SUPINE

- Transferred to PYNEH for VV-ECMO 10-15/2/13
- Echo and USG :
  - good LV/RV systolic fxn, hyperdynamic with kissing wall movements, no RWMA, trace AR, mild TR, rim of pericardial effusion
  - hepatosplenomegaly, bil kidneys no hydronephrosis

- on arrival, WBC improving trend after chemotherapy; down to 91.5
- Hb 7.4 plt 21
- INR 1.9 APTT 62.4

- TMH hematologist : not a case of M3 and unlikely differentiation syndrome
- Developed pancytopenia afterward, requiring frequent transfusion of PC and plt conc

Microbiology

- NPA 9/2
  - PCR for Respiratory syncytial virus +
- Endotracheal aspirate 10/2
  - Respiratory syncytial virus viral antigen +ve

Respiratory Syncytial Virus

- Enveloped RNA virus of the family *Paramyxoviridae*, within the genus *Pneumovirus*
- Usually confined to winter and spring
- Associated with significant morbidity and mortality in leukemia
- Mortalilty of RSV pneumonia in HSCT 5-100%
- Up to 80% of RSV-associated URI in HSCT may progress to LRTI
- Risk of progression greatest in lymphocytopenia
- Paucity of literature about RSV infection in non HSCT leukemia

Whimbey E. RSV infection in immunocompromised adults. Dcurr Clin Top Infect Dis 2000

Respiratory Syncytial Virus in non-HSCT

- Few studies reported to date suggest the epidemiology, clinical course and treatment response mirror findings in HSCT recipients
- RSV seems to be frequent cause of life-threatening infection
  - Elderly, persistent myelosuppression, commorbidies, high APACHE II score and pneumonia

Treatment

- Nebulised Ribavirin
  - Nucleoside analog with good in vitro activity against RSV
  - Early use shown to reduce morbidity and mortality in adult HSCT with RSV infection

McColl RSV in adult BMT recipients 1998

- Combination therapy
  - + IVIG: improved survival in HSCT in uncontrolled studies

Whimbey E 1995

  - + RSV-specific monoclonal Ab: Not well studied
  - + corticosteroid: uncontrolled studies on lung transplant

? Treating all leukemia with RSV infection

Considerations

- Cost
- Safety profile
  - Miscarriage, tetratogenicity
  - AE: Chronic eye/skin irritation, SOB
- Discomfort of ribavirin administration
- Conflicting results from studies
  - Many have good outcome without treatment
  - Small sample size < 20 patients

Characteristics and outcome of respiratory syncytial virus infection in patients with leukemia

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ABSTRACT

Background and Objectives

Little is known about respiratory syncytial virus (RSV) infection in patients with leukemia. The aim of this study was to determine the characteristics, and the outcome of RSV infection with or without therapy with aerosolized ribavirin in leukemia patients.

Design and Methods

We reviewed the records of 52 leukemia patients with RSV infection seen at our institution between October 2000 and March 2005.

Results

The median age of the patients was 47 years (range, 1-83 years). Most patients were male (65%) and had acute leukemia (65%); 46% had received salvage chemotherapy and 62% corticosteroids before RSV infection. Compared to the 25 patients with upper respiratory tract infection (URI), the 27 patients with pneumonia had a higher median APACHE II score at the time of the first assessment at the hospital for respiratory symptoms (11 vs 16), and a higher rate of corticosteroid treatment in the month preceding the infection (48% vs 74%) (all $p \leq 0.05$). Twenty-four (46%) patients received aerosolized ribavirin. Patients who presented with URI and were treated with ribavirin were less likely than non-treated patients to develop pneumonia (68% vs 96%, $p<0.01$) and possibly die of pneumonia (6% vs 36%, $p=0.1$). Multiple logistic regression analysis identified high APACHE II score and lack of ribavirin treatment as independent predictors of progression to pneumonia ($p=0.01$). Five patients (10%) died within 30 days of RSV infection; all had pneumonia.

Interpretation and Conclusions

RSV infection is associated with significant morbidity and mortality in leukemia

Aerosolised ribavirin

- Daily dose of 6g at a concentration of 20mg/ml for 18 hrs/day
- Median duration: 7 days, given at least 4 days
- Small-particle aerosol generator unit via face mask inside a scavenging tent

Findings

- Aerosolised ribavirin at the stage of URI may prevent pneumonia in some subsets of patient
- Preemptive therapy for URI
  - Some subsets at risk of developing pneumonia
    - Males
    - High APACHE II
    - Prolonged lymphocytopenia
    - Recent corticosteroid

? Established RSV pneumonia may still benefit

Progress in PYNEH

- Neb Ribavirin given
- ECMO decannulated on 15/2/2013
- Bone marrow exam: aparticulate marrow aspirate. Cytochemical study on blast of peripheral blood showed AML. Favour monocytic lineage
- Cytoreduction regime chemotherapy
  - Hydroxyurea and '3+7' daunorubicin and cytarabine
  - Post D2 3+7 good cytoreduction: WCC 9.8
- Mild tumor lysis syndrome given rasburicase/ allopurinol
- Kick of fever despite tazocin, switched to meropenem on 18/2

Progress

- Transferred back to TMH ICU on chemo D11 (19/2)
- In Stable condition, transferred to haematology ward
- Developed Neutropenic fever on D12 (20/2)
- ALP 37 ALT 114 ALP 37
- Cr 107→289 on D15 (23/2)
- USG kidney
  - Left kidney 9.4cm Rt kidney 14.3cm
  - Trace perinephric collection, no hydronephrosis

Fever on D12 , in Haematology ward

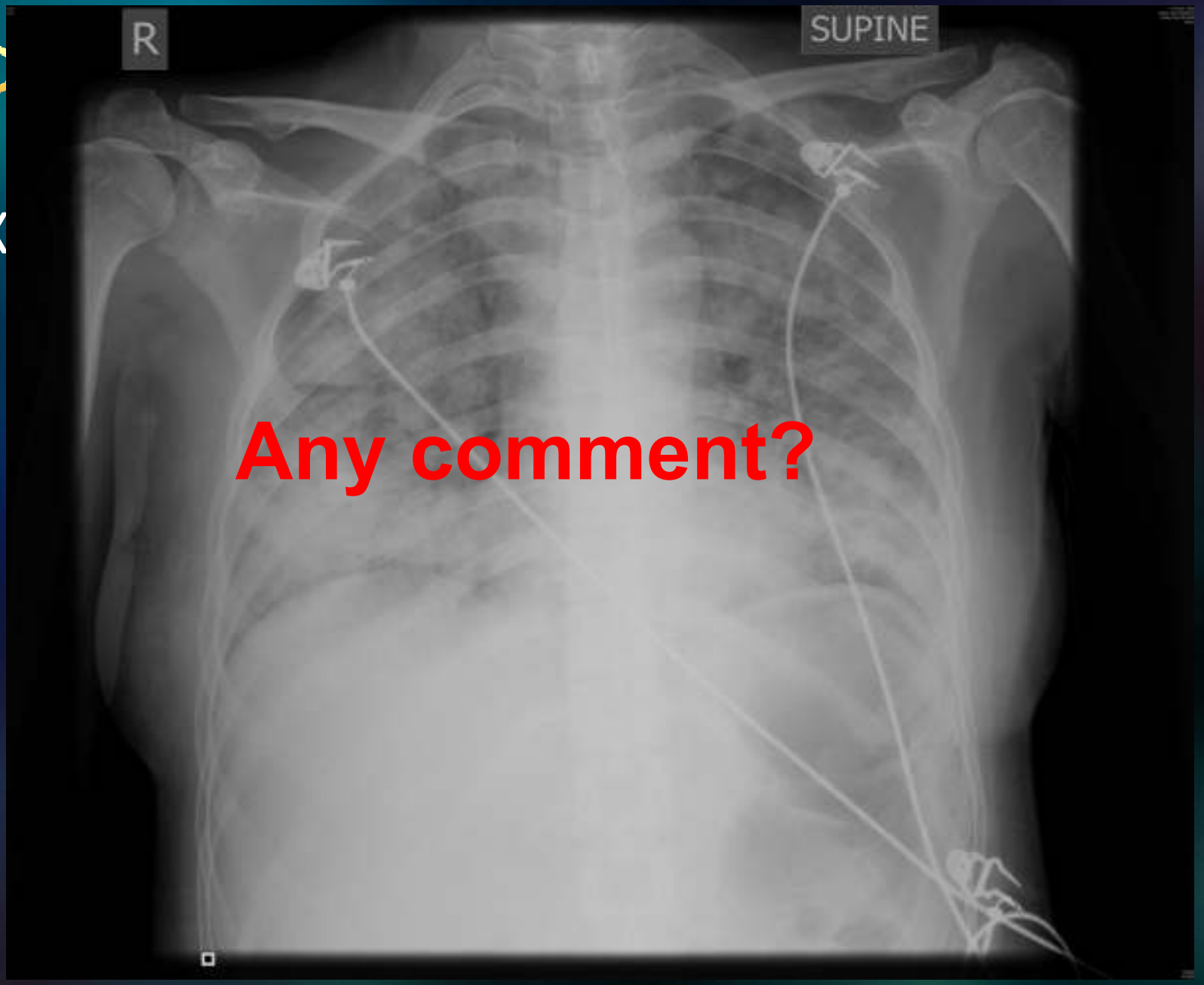
- Hb 7.8 WCC 0.2 plt 31 on D11
- LDH 1916
- Negative sputum / blood c/st
- Antimicrobial therapy
  - Meropenem since D10
  - Vancomycin since D17
  - Micafungin since D18
  - Septrin since D19
  - Doxycycline since D20

- D20 (28/2): Respiratory failure required intubation and shock on NA
- E4V2M6
- Fever+
- Generalised petechaie

- Transferred to TMH ICU again

Bac

- CX



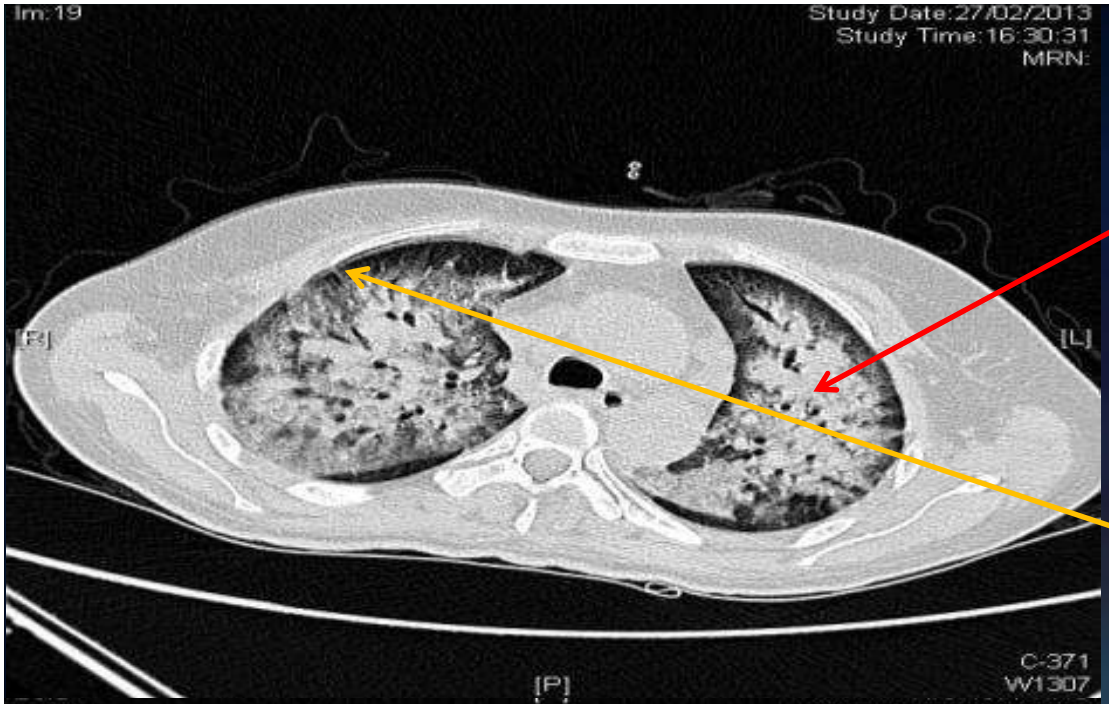
Respiratory failure in leukemia

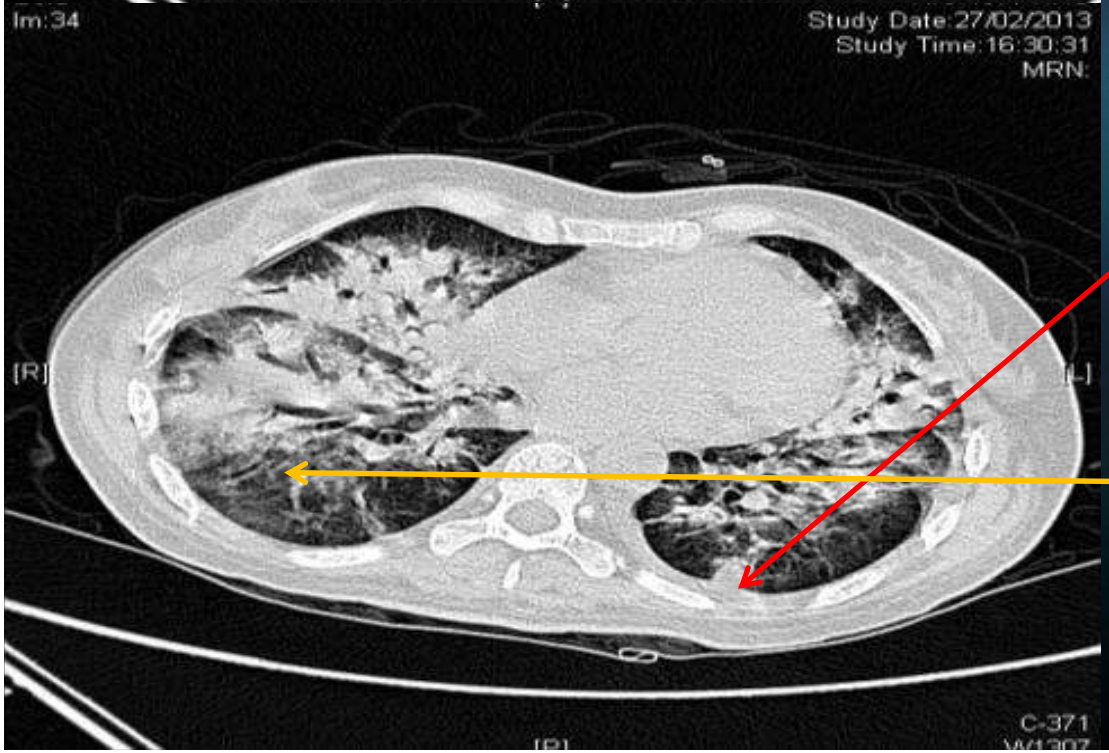
- Infection
  - Viral/ bacteria/Fungal…
  - MDR
- Neoplastic
  - Pulmonary haemorrhage
  - Organising pneumonia
  - Toxic pneumonitis
  - Pulmonary leukemic infiltration
  - Acute lysis pneumopathy
  - Alveolar proteinosis
- Others: PE, CHF, fluid overload, TRALI…

Pulmonary complications in patients with hematological malignancies requiring ICU admission

- 10 years observation in a resp ICU
- 42% infectious; 27% non-infectious
- 31% undetermined even after autopsy
- 23/37 (62%) died in non-transplanted patients
- 47/52 (90%) in died in bone marrow recipients
- Mortality was 68/76 (90%) for ventilated cases compared to those not requiring (2/13; 15%)

Eur Respir J 1998; 12: 116–122





Consolidation mixed with ground-glass

Thickened interstitium at peripheries

Nodules

Thickening of peribronchial tissue

Infection?

- Peripheral WCC 0.6 Hb 10.1 plt 27
- BAL for PCP/ CMV/bacteria/proteinosis negative
- CMV PP65 antigenemia negative
- Candida parapsilosis from serial lower respiratory cultures
  - TA 28/2, BAL 1/3

Questions

- Does it mean Invasive Fungal Infection?
- What else can be done to test?
- When Should we start antifungal therapy
  - Prophylaxis
  - Empirical
  - Pre-emptive
- What to be given?

Does it me
Infection?

EORTC/MSG c

- Prolonged Neutropenia >10 days and fever
- Lower respiratory tract disease with lung infiltrates on CT
- Candidial yeast grew on BAL not regarded as microbiological factor

Proven IFI: histology/culture from a normally sterile site which was clinically or radiologically infected

Probable IFI : Requires host, clinical AND microbiological factors

Possible IFI: host, clinical or microbiological factors

Is it useful in leukemic patients?

- Prompt and definitive diagnosis difficult
  - Low yield of microbiological cultures
    - Use of antifungal prophylaxis
  - Invasive procedures for histology rarely possible
  - Various causes for lung infiltrates
  - These criteria are made for clinical trials
    - High false negative rate at autopsy
      - 75% died without diagnosed in life (Chamilos et al 06)

What else can be done to test?

- Serum galactomanan
  - Polysaccharide component of the cell wall of Aspergillus species, released during hyphal growth
  - Approved by US FDA for surveillance of invasive aspergillosis in immunocompromised patients
    - SE 0.71 (95% CI: 0.68-0.91)
    - SP 0.89 (95% CI: 0.88-0.90)
    - Variable cut–off 0.5-1.5
  - Pitfalls
    - False negative: fungal prophylaxis
    - False positive: piperacillin-tazobactam, cross-reacting antigens from other fungi, gut GVHD

Marr KA et al. Detection of galactomanan antigenemia by enzyme immunoassay for the diagnosis of IA. J Infect Dis 2004

- 1,3- β -D-glucan
  - Panfungal antigen , not specific for any fungi
  - SE for candidiasis 78-81% depending on cut-off value
  - False-positive: HD with cellulose membrane, cephalosporin, carbapenems, ampicillin-sulbactam
  - Adjunctive test

Pickering JW. Evaluation of a (1→3)- β -D-glucan Assay for diagnosis of IFIs. J Clin Microbiol 2005

- PCR of fungal ribosomal DNA
  - allows rapid and early detection of IFIs
  - SE 92.5% , SP 94.6%
  - Still investigational and standardisation of test needed before it can be used clinically

When Should we start antifungal?

Prophylactic, Empirical or pre-emptive

When should we start antifungal?

Prophylaxis

Meta-analysis 2007 (J. Clin. Oncol)– 64 RCT

reduced overall mortality significantly . RR 0.84 NNT 43.
reduced IFIs by 50%.

* allo-HSCT and induction chemotherapy for AL

- Patients with high risk
  - Itraconazole (solution>tablet)
  - Posaconazole (> itraconazole in RCT)
- Intermediate risk
  - According to local incidence rates and individual risk

Fluconazole most widely studied, gold-standard in Stem cell transplant (Meta-analysis: Kanda et al., Cancer 2000)

- Not effective after myelosuppressive treatment for acute leukemia
- not active against molds and some candida species
- Emergence of resistant candida strains and aspergillus

Table 1. Risk stratification of invasive fungal infection in hematological patients.

High risk	Intermediate risk	Low risk
Prolonged neutropenia $<0.1 \times 10^9$ /l for >3 weeks, or $<0.5 \times 10^9$ /l for >5 weeks	Fungal colonization at one site with neutropenia 0.1–0.5 x 10^9/l for 3–5 weeks	Autologous SCT
Unrelated or mismatched SCT	Fungal colonization at more than one site	Lymphoma
GVHD	AML	Childhood ALL
High-dose cytarabine	TBI	
Corticosteroids >1 mg/kg with neutropenia $<1 \times 10^9$/l for >1 week	Allogeneic matched sibling donor SCT	
Corticosteroids >2 mg/kg for >2 weeks	Neutropenia 0.1–0.5 $\times 10^9$/l for <3 weeks Antibiotics + lymphopenia $<0.5 \times 10^9$/l Old age Presence of central venous catheter	

ALL: Acute lymphoblastic leukemia; AML: Acute myeloid leukemia; GVHD: Graft-versus-host disease; SCT: Stem-cell transplantation; TBI: Total body irradiation.

Prentice HG. Towards a targeted, risk-based, antifungal strategy in neutropenic patien
Br. J. Haematol. 2000

When should we start anti-Fungal treatment?

- Under debate
- Empirical approach
  - start antifungal treatment in patients with neutropenic fever not responding to antibiotics, irrespective of results of microbiological or radiological investigation
- Pre-emptive
  - treat on the basis of clinical, imaging and/or laboratory findings indicative of IFIs in at-risk patients

Pre-emptive approach

- Pros
  - Reported to have Antifungal use reduced by 78%
    - Limited studies
    - Depends heavily on SE and SP tests for IFI
- Cons
  - mortality of untreated IFIs or delayed treatment reaches 100%
  - Incidence of IFIs signficantly higher in pre-emptive arm during induction chemotherapy. Non-inferior in lower risk group. *Cordonnier C. Empirical versus preemptive antifungal therapy for high risk, febrile, neutropenic patients: a randomised, controlled trial. Clin. Inf. Dis.*
- Whether to adopt depends on availability of intensive screening and rapid diagnostics

Empirical antifungal therapy for persistent neutropenic fever remains the mainstay approach

Still recommended in IDSA, NCCN and ECIL
And all panels restrict this strategy to expected duration of neutropenia of at least 10 days

What to be given?

- Empirical treatment
  - Amphotericin B, LAMB, itraconazole and caspofungin are approved for empirical treatment of IFIs in susceptible patients

For our patient

- Very ill patient
- Poor immunity
- Compatible radiology finding (At least partially)
- No rapidly reversible cause being more likely

Progress

- Persistent lung shadow for 2 weeks
- Blood cell counts out of pancytopenia
- On PS mode, FiO2 0.4
- Still rather stiff lung and static imaging abnormality

Anything we missed and reversible?

Acute lysis pneumopathy ? leukemic infiltration?

strong association with AML M5

Acute lysis pneumopathy

- presumably pathologically related to the destruction of fibroblast cells in the pulmonary circulation
- These cells release cytokines and cytotoxic enzymes, which promotes inflammation in the lungs, with subsequent airspace infiltration and hypoxia
- Animal models have shown that **monocytic cells have a predilection for the pulmonary circulation**, probably as a result of monocyte-endothelium interaction.
- all patients experienced acute worsening of respiratory status within hours of chemotherapy initiation

Acute lysis pneumopathy

- Supportive care
- Ensuring adequate nutrition and maintaining electrolyte homeostasis
- Prompt recognition and therapy directed toward the tumor lysis syndrome is crucial

leukemic infiltration?

Can absence of hyperleukocytosis exclude it?

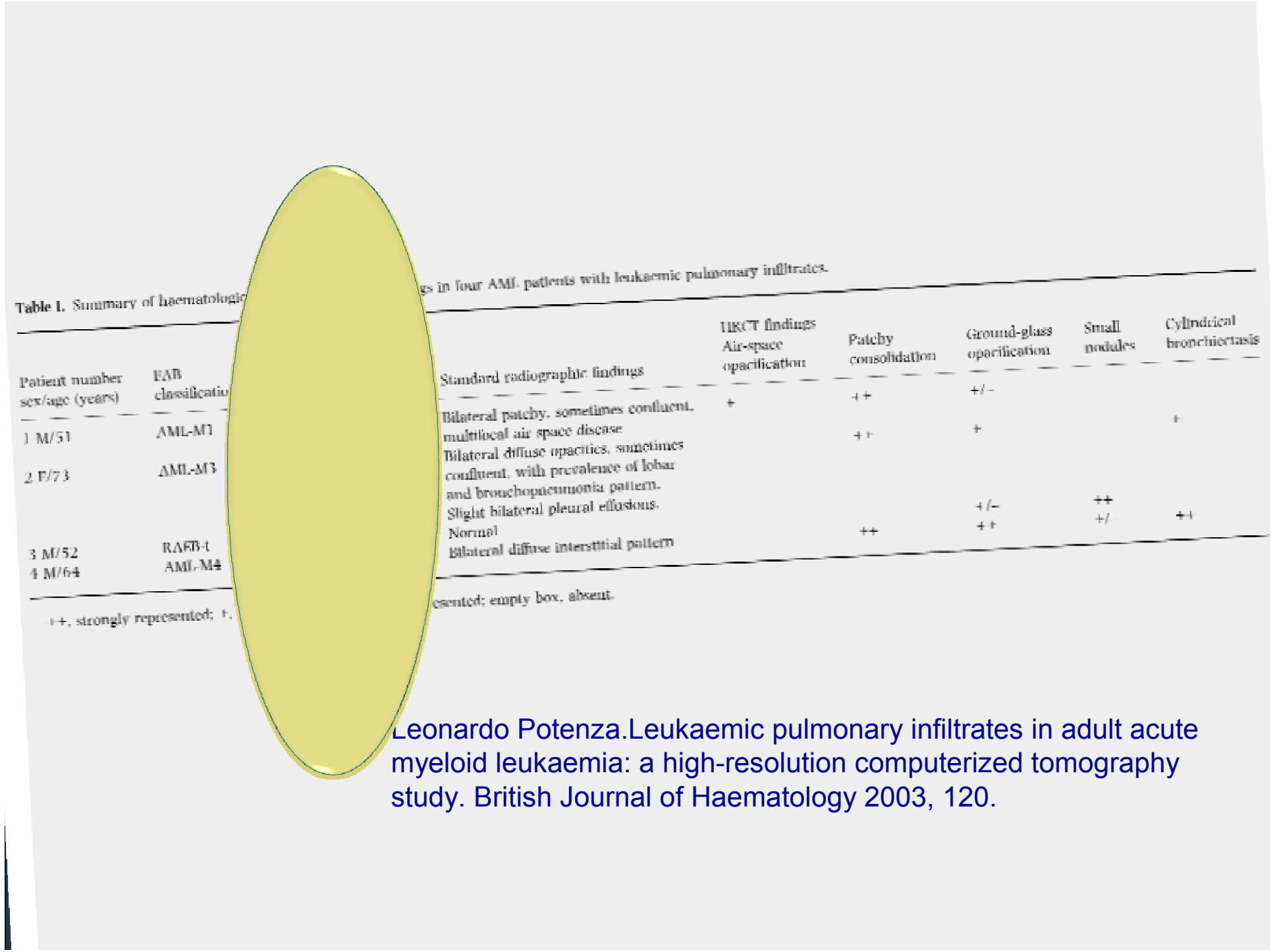


Table I. Summary of haematologic gs in four AML patients with leukaemic pulmonary infiltrates.

Patient number sex/age (years)	FAB classificatio	Standard radiographic findings	HRCT findings Air-space opacification	Patchy consolidation	Ground-glass opacification	Small nodules	Cylindrical bronchiectasis
1 M/51	AML-M1	Bilateral patchy, sometimes confluent, multifocal air space disease	+	++	+/−		
2 F/73	AML-M3	Bilateral diffuse opacities, sometimes confluent, with prevalence of lobar and bronchopneumonia pattern.		++	+		+
3 M/52	RAEB-t	Slight bilateral pleural effusions.			+/−	++	
4 M/64	AML-M4	Normal		++	++	+/	++
		Bilateral diffuse interstitial pattern					

++, strongly represented; +, esented; empty box, absent.

Leonardo Potenza.Leukaemic pulmonary infiltrates in adult acute myeloid leukaemia: a high-resolution computerized tomography study. British Journal of Haematology 2003, 120.

Leukemic pulmonary infiltration

- Reported in patients without hyperleukocytosis
  - the type of blasts and their affinity for the pulmonary endothelium may be involved in the development of ARDS
  - AML M5 have predilection for pulmonary circulation
- No established clinical criteria to firmly exclude or include diagnosis
- No single low cutoff value for peripheral leukocyte or fibroblast counts that excludes this diagnosis.
- The index of suspicion should be particularly high in patients with monocytic leukemia, especially when the peripheral blast cell count is high or increases rapidly

Radiographic changes

- Most striking abnormality

interstitial thickening

- Along lymphatics in the peribronchovascular, septal, and pleural interstitial tissue
- Pulmonary nodules and focal homogeneous opacities

Leukemic pulmonary infiltration

- Diagnosis
  - based on **histologic or cytologic studies** and negative findings from a comprehensive investigation for more common causes
  - retrieval of leukemic cells by BAL
  - blast cell count above 40% in peripheral blood
- Retrospective confirmation by effectiveness of chemotherapy in improving respiratory function

Acute Monocytic Leukemia Presenting as Acute Respiratory Failure

Élie Azoulay, Fabienne Fieux, Delphine Moreau, Guillaume Thiery, Philippe Rousselot, Antoine Parrot, Jean-Roger Le Gall, Hervé Dombret, and Benoît Schlemmer

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Acute respiratory failure revealing acute monocytic leukemia is rare. We report 20 patients admitted to the intensive care unit (ICU) with three remarkable features: (*1*) rapidly progressive respiratory distress revealing acute leukemia, (*2*) monocytic leukemia, and (*3*) respiratory status deterioration after chemotherapy initiation. The median age was 50 years (17–72 years), and respiratory symptoms started 2 days (0–15 days) before ICU admission. The median leukocyte count was 98,250/mm^3 (800–529,000), with circulating monocytic cells in all of the patients but one. Bone marrow examination was diagnostic of monocytic leukemia in all patients. At presentation, respiratory rate was 33 (18–50) per minute, and Pa_{O_2} on room air was 44.5 mm Hg (30–60). Chest radiographs revealed unilateral alveolar infiltrates (n = 1), bilateral alveolar infiltrates with (n = 3) or without (n = 11) pleural effusion, or diffuse interstitial infiltrates (n = 5). Alveolar hemorrhage was the main bronchoalveolar lavage finding, with monocytic cells retrieved from four patients. Respiratory function deteriorated after cancer chemotherapy initiation in all patients. Of the 15 patients who required mechanical ventilation, 10 died. Leukemic pulmonary infiltration as the first manifestation of acute mono-

15). Acute lysis pneumopathy can develop at chemother initiation in these patients (16–18). In contrast, leukemic i tration of the lungs has been reported in acute leukemia pati without hyperleukocytosis, suggesting that the type of blasts their affinity for the pulmonary endothelium may be involve the development of acute respiratory distress syndrome (1

We report 20 patients with acute respiratory failure fi leukemic pulmonary infiltration or leukostasis caused by a leukemia. These cases deserve special attention for three sons: respiratory impairment was the presenting manifesta of undiagnosed acute monocytic leukemia; all patients myeloid leukemia of the AML5 subtype; and respiratory fu tion deteriorated in all 20 patients within a few hours a chemotherapy initiation, suggesting a need for intensive unit (ICU) admission before starting chemotherapy.

METHODS

- 20 patients admitted to the intensive care unit (ICU) with three remarkable features:
  - (1) rapidly progressive respiratory distress revealing acute leukemia
  - (2) monocytic leukemia
  - (3) respiratory status deterioration after chemotherapy initiation in all
- median age was 50 years (17-72 years)
- respiratory symptoms started 2 days (0-15 days) before ICU admission.
- Chest radiographs revealed unilateral alveolar infiltrates (n = 1), bilateral alveolar infiltrates with (n = 3) or without (n = 11) pleural effusion, or diffuse interstitial infiltrates (n = 5)
- Alveolar hemorrhage was the main bronchoalveolar lavage finding, with monocytic cells retrieved from four patients

- Leukemic pulmonary infiltration as the first manifestation of acute monocytic leukemia should be recognized
- Index of suspicion should be particularly high in patients with monocytic leukemia
- Especially when the peripheral blast cell count is high or increases rapidly
- 50% died in the group of Azoulay et al.

Go back to our case…

- Transbronchial lung biopsy
  - atypical cells

To be or not to be, that is the question…

?Open lung biopsy

- 63 patients with hematologic malignancy to undergo 67 open lung biopsies for abnomality
- Specific diagnosis was only found in 41 (62%) of the biopsies, with changes in therapy being made in 37 (57%)
- Focal radiographic abnormality have higher yield than diffuse (79% versus 36%, $p < 0.003$)
- Malignancy found in 18% of cases
- Neutropenia or cases on ventilator lower yield

AM J RESPIR CRIT CARE MED 2000;161:723–729.

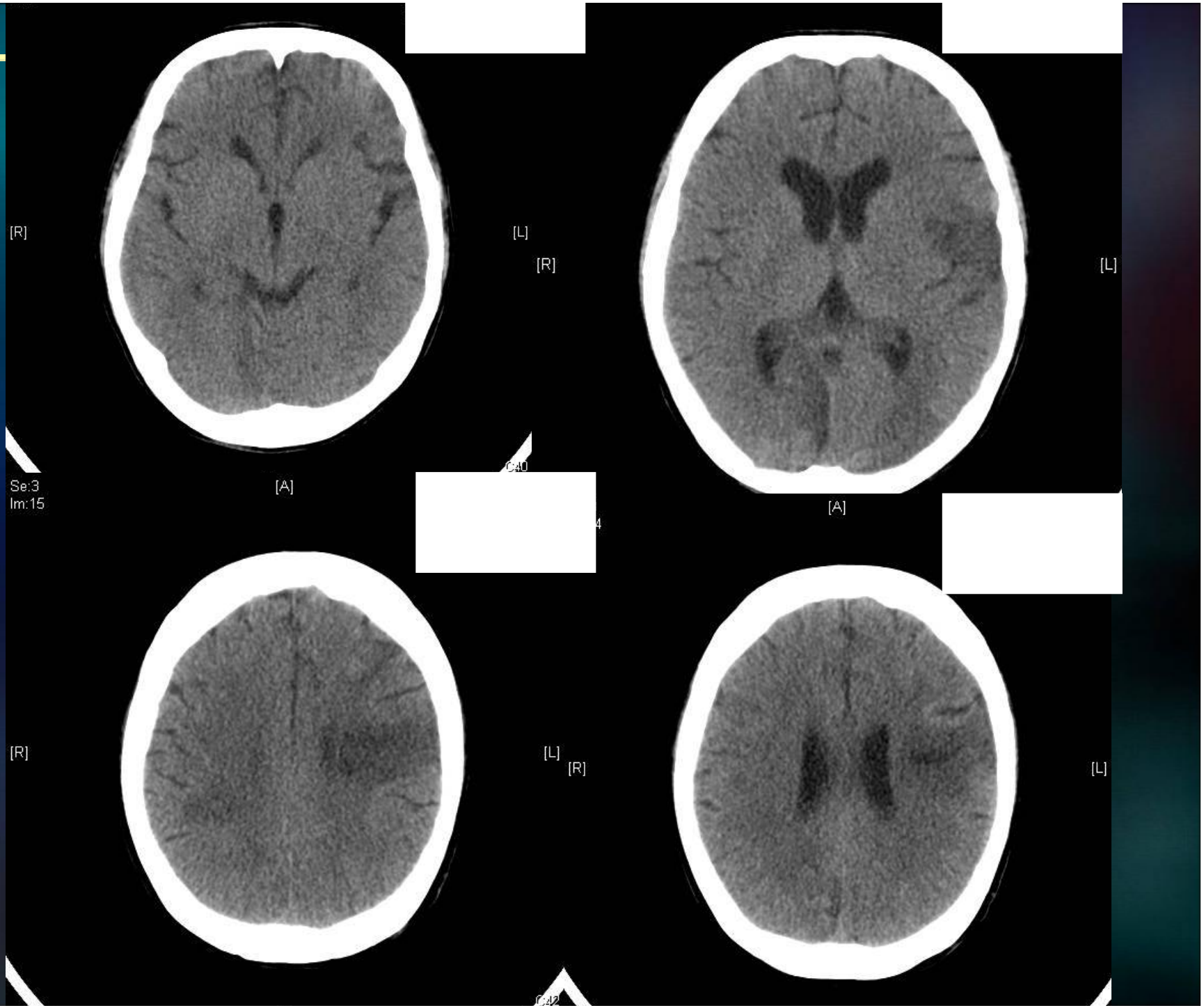
Is AML in Disease state?

- Repeat BM exam on 12/3
  - Marrow aspirate: regenerating marrow, blast accounts for 1% of total nucleated cells
  - Trephine: mild to moderately hypercellular marrow,Full myeloid maturation still seen. Blasts are not obviously increased. Megakaryocytes are moderately increased. Dx: regenerating marrow.

Neurological deterioration

- Developed Rt hemiparesis and dysphasia since 13/3
  - RUL / RLL/LUL 0/5, LUL 3/5
  - Jerk normal
- E4VTM6→ E3VTM4
- BP 179/97 P112

CT



CNS involvement in Leukemia

- Infection
  - Opportunistic CNS infection
    - cryptococcus, listeria monocytogenes, aspergillosis, nocardia, mucormycosis, toxoplasmosis, herpes simplex, varicella zoster, and JC virus Neoplastic
- Neoplastiac
  - Direct effect
    - Meningeal, parenchymal, skull base metastasis
  - Indirect effect
    - Cerebrovascular complications from hyperviscosity
    - Drug toxicity
    - Demyelination (necrotising leukoencephalopathy)

Is it CNS infiltration?

CNS leukemic infiltrates

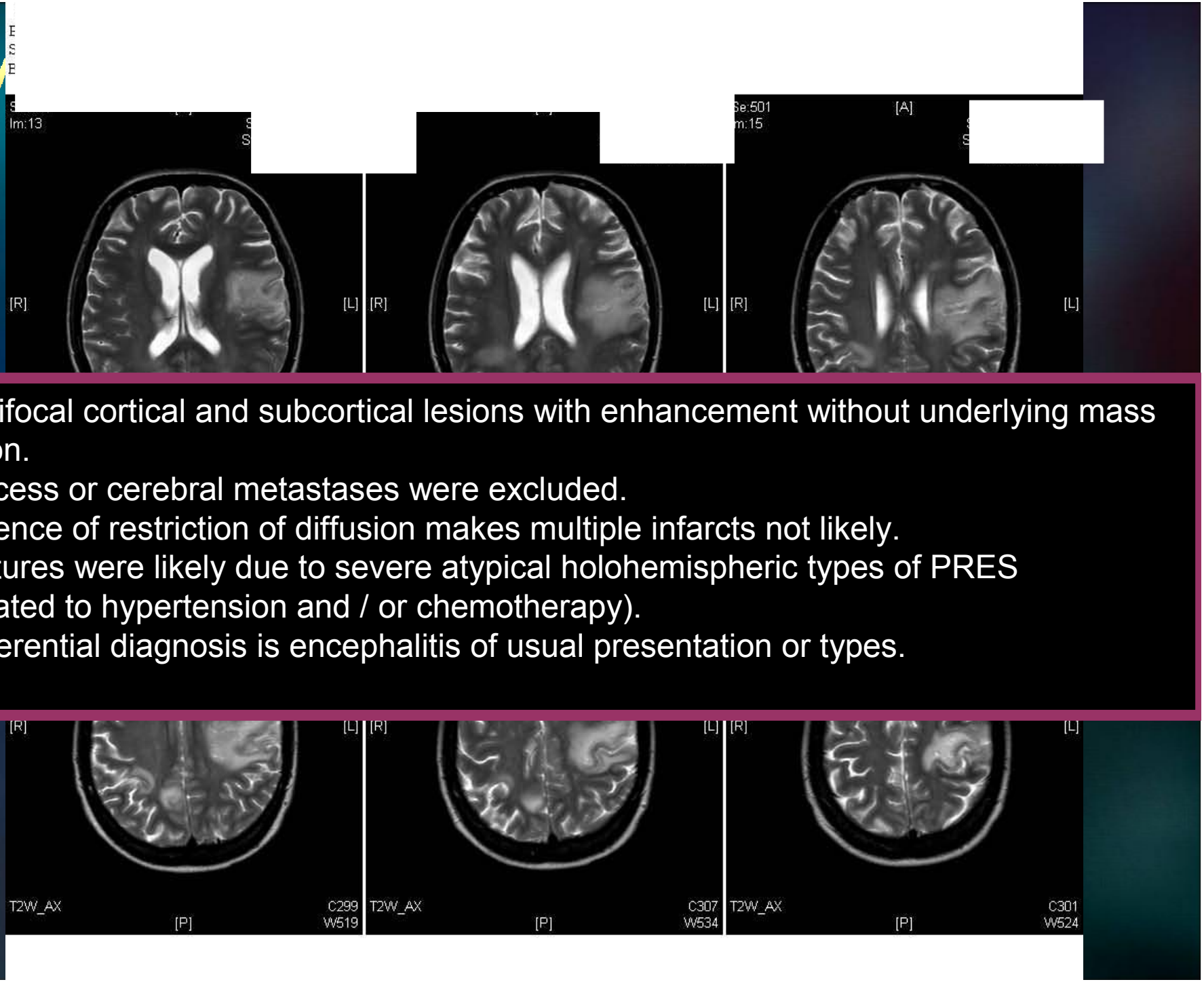
- Incidence at diagnosis/relapse 3-7%
- Pathogenesis unknown
- Interruption of tight junctions of BBB through adhesion molecules on leukemic blasts or increased permeability from vascular endothelial growth factor
- Increased risk in high WCC, high blast count, high LDH and younger age
- monocytic lineage 5.7-fold increased risk

CNS leukemic infiltrates

- Can be subtle or present as increased ICP, CN palsy or motor deficit
- Diagnosis based on CSF exam for cytology, immunophenotyping by flow cytometry and PCR (for leukemia specific markers)
- Gadolinum-enhanced MRI of brain and spine
  - MRI alone is neither sensitive nor specific

Lumbar Puncture

- WCC trace RC +++
- GS negative culture negative
- Fungus negative
- Protein 0.86 (blood stained)
- Glucose 3.9 (Serum 6.8)
- Negative malignant cells



Multifocal cortical and subcortical lesions with enhancement without underlying mass lesion.

Abscess or cerebral metastases were excluded.

Absence of restriction of diffusion makes multiple infarcts not likely.

Features were likely due to severe atypical holohemispheric types of PRES (related to hypertension and / or chemotherapy).

Differential diagnosis is encephalitis of usual presentation or types.

Posterior Reversible Encephalopathy Syndrome

Risk factors

- Hypertension
- Eclampsia
- Renal failure
- Immunosuppressive therapy
  - Cytosine-arabinoside, cisplatin, methotrexate, gemcitabine
  - Rituximab, bevacizumab or growth factors (erythropoietin, G-CSF)

PRES

- Mechanism is still under clarified, is an acute central nervous system disorder characterized by reversible brain **vasogenic edema**
- Mainly arising from failure of cerebrovascular autoregulation due to increased systemic BP and disruption of BBB, ? Direct endothelial dysfunction due to circulating toxin
- Primarily implicates posterior white matter

Presentation of PRES

- Cardinal sign: acute rise in diastolic BP, can occur 24 hrs or more before other symptoms
- Headache – constant, dull, non-localised
- Mental state changes
- GTC – more often multiple
- Visual disturbance
- Can be left with neurological sequalae

PRES

- Diffusion-weighted imaging (DWI) and apparent diffusion coefficient (ADC) map in magnetic resonance imaging (MRI) are most sensitive and specific to differentiate vasogenic edema of PRES from cytotoxic edema
- Commonly bilateral
- White matter of Parietal-occipital 100% , frontal 68-82%
- Less commonly postfrontal cortical/ subcortical ,brainstem, basal ganglia, cerebellum

Can MRI differentiates PRES from other CNS complications?

Table 3. Lesion location, symmetricity, and MRI signal characteristics, including contrast enhancement pattern and diffusion restriction

Lesion	Location	MRI signal	CE	DWI
PRES	Occipital=cerebellum≥parietal≥frontal≥brain stem; white matter ± cortex Usually symmetrical	T1W iso/hypo T2W hyper FLAIR hyper	None (may be + if BBB break still exists)	Not restricted (may be + if BBB break occurs)
WMD	Periventricular white matter (Subcortical U-fibers spared) Symmetric	T1W iso/hypo T2W hyper FLAIR hyper	None	Restricted (early phase)
PNE	Temporal Usually symmetric	T1W iso/hypo T2W hyper FLAIR hyper	+ subtle	Restricted ±
RN	Always limited to the affected portion of the brain Usually symmetric	T1W iso/hypo T2W hyper FLAIR hyper	+ intense heterogenous	Restricted ±
Acute ischemia	Depends on the artery involved Not symmetric	T1W iso/hypo T2W hyper FLAIR hyper	None (± if early subacute phase)	Restricted

MRI, magnetic resonance imaging; PRES, posterior reversible encephalopathy syndrome; WMD, white matter disease; PNE, paraneoplastic encephalitis; RN, radiation necrosis; T1W, T1-weighted image; T2W, T2-weighted image; FLAIR, fluid attenuated inversion recovery; CE, contrast enhancement; BBB, blood-brain-barrier; DWI, diffusion-weighted image.

Banu et al. MRI of non-neoplastic cranial complications of malignant disorders.
Diagn Interv Radiol 2008

- Mainstay of treatment
  - Control BP
    - Nicardapine, labetalol
    - Avoid clonidine and nitroglycerine
  - Hydration
  - Anti-convulsant
  - Withdrawal of offending medication and treatment of underlying systemic disease

Progress of our patient...

- BP gradually controlled with medication
- Given Micafungin for 3 weeks , out of pancytopenia
- Gradually improved and extubated on 19/3
- Obey command, Rt power 0/5, static

Summary

- New case of AML of monocytic lineage, with hyperleukocytosis and pulmonary leukostasis on presentation
- requiring urgent induction chemotherapy and ECMO support
- On presentation also had RSV chest infection treated with inhaled Ribavirin
- Further complicated with
  - neutropenic sepsis/ ?fungal pneumonia
  - severe posterior reversible encephalopathy syndrome now with neurological deficits

House party protocol:
Numerous mobile suits in action

But where is the iron man?

Questions

- We thought of many causes, were we correct?
- Can we rule out leukemic infiltration
  - Should we believe only what we see – imaging/ single biopsy/cytology…
- Should we shoot without knowing
  - Risk of further neurological damage and fatal neurological sequale
- Any change in management if proceed to more invasive procedure or repeat test…
  - Or…..time will tell…

Progress

- Acute bilateral loss of vision
- Eye 31/3/2013: ? Leukaemic retinopathy with marked edema
- MRI brain on 3/4
  - Multifocal T2W/FLAIR hyperintense lesions at bilateral cerebral/ cerebellar hemispheres, predominantly involving cortical/ subcortical regions with leptomeningeal enhancement. Overall, they show interval improvement
- FU MRI brain 8/5
  - Multiple wedge-shaped cortical/ subcortical lesions at bilateral cerebral hemispheres with evidence of early encephalomalacia

- Rehab progress 5/2013
  - BI 13 →34
  - MMSE 18 (blind)→25
  - RUL power 0 , RLL 0→3/5 LUL/LL power 4/5
  - Near blindness →→ can only perceive light.
- Haematologist:
  - Condition slowly improving, unlikely leukemic infiltration
  - Haematologically Not in relapse
  - Not for consolidative therapy meanwhile because of slow neurological recovery, ?Drug toxicity

We may not know the final answer BUT……

- Patient's general condition and functional state has deteriorated, so much that her disability makes further aggressive therapy relatively not beneficial enough to risk

Conclusion

- Different complications of leukemia as a result of the disease and treatment
  - Leukemic infiltration
  - Infection
  - PRES
- Emergencies in acute leukemia embrace multiple disciplines
- Difficult dilemma and Controversy in management

Any question?