Auto-Immune Hemolytic Anemia

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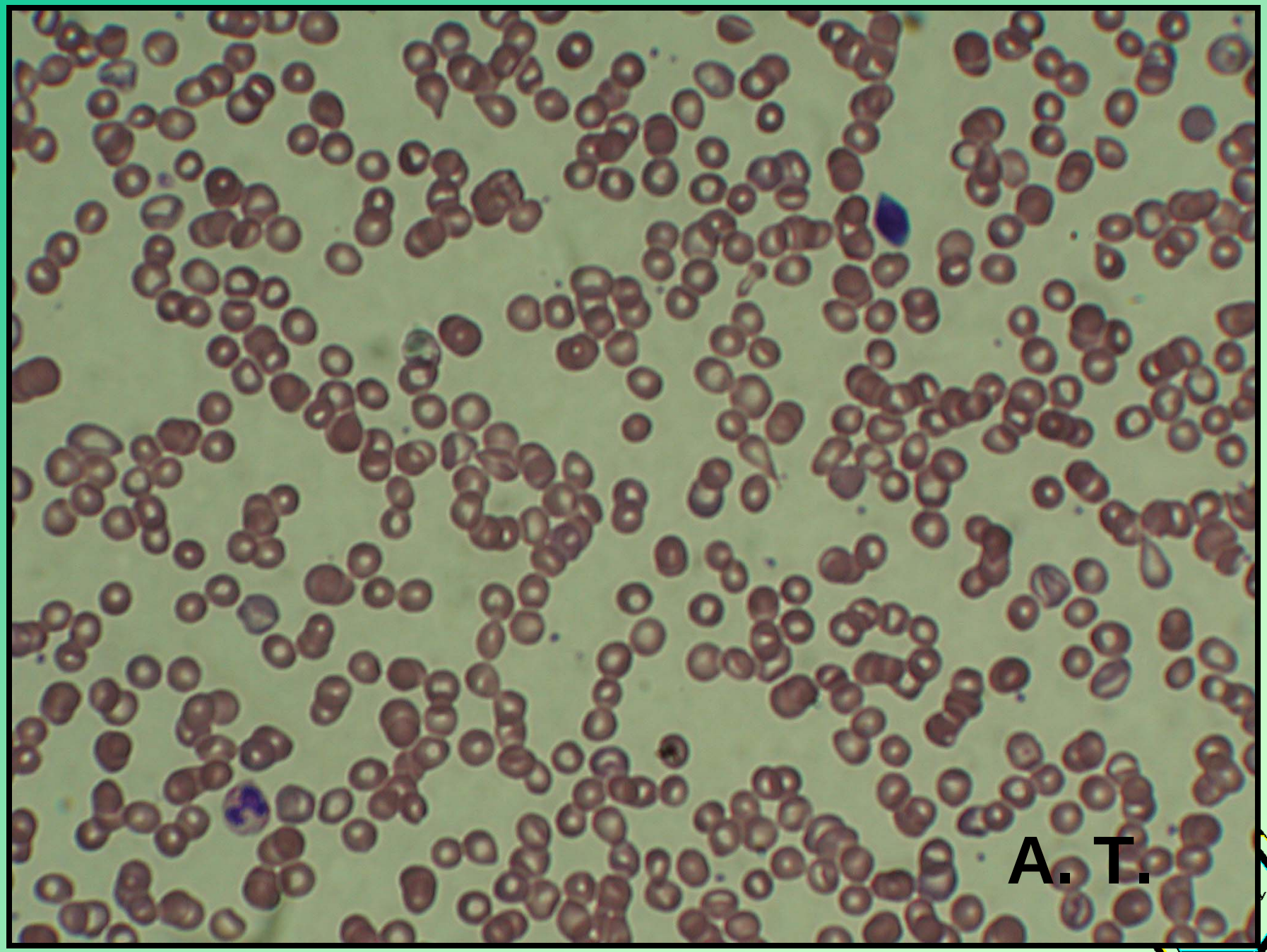
Case Number 1

- AT: 67 y.o. man with auto-immune hemolytic anemia
- Presented in 1965 with initial episode of AIHA treated successfully with short course of steroids

Case, Continued

- In adulthood developed NIDDM, CAD and hypercholesterolemia; s/p coronary bypass and stent placement
- Prior to referral was found to be newly and severely anemic:
  - Hematocrit 24%, MCV 115, Retics 12.7%
  - Bilirubin 1.4 all indirect
  - WBC 6,700 78% PMN, platelets 136,000
  - Normal B12, folate and ferritin
- Peripheral blood smear…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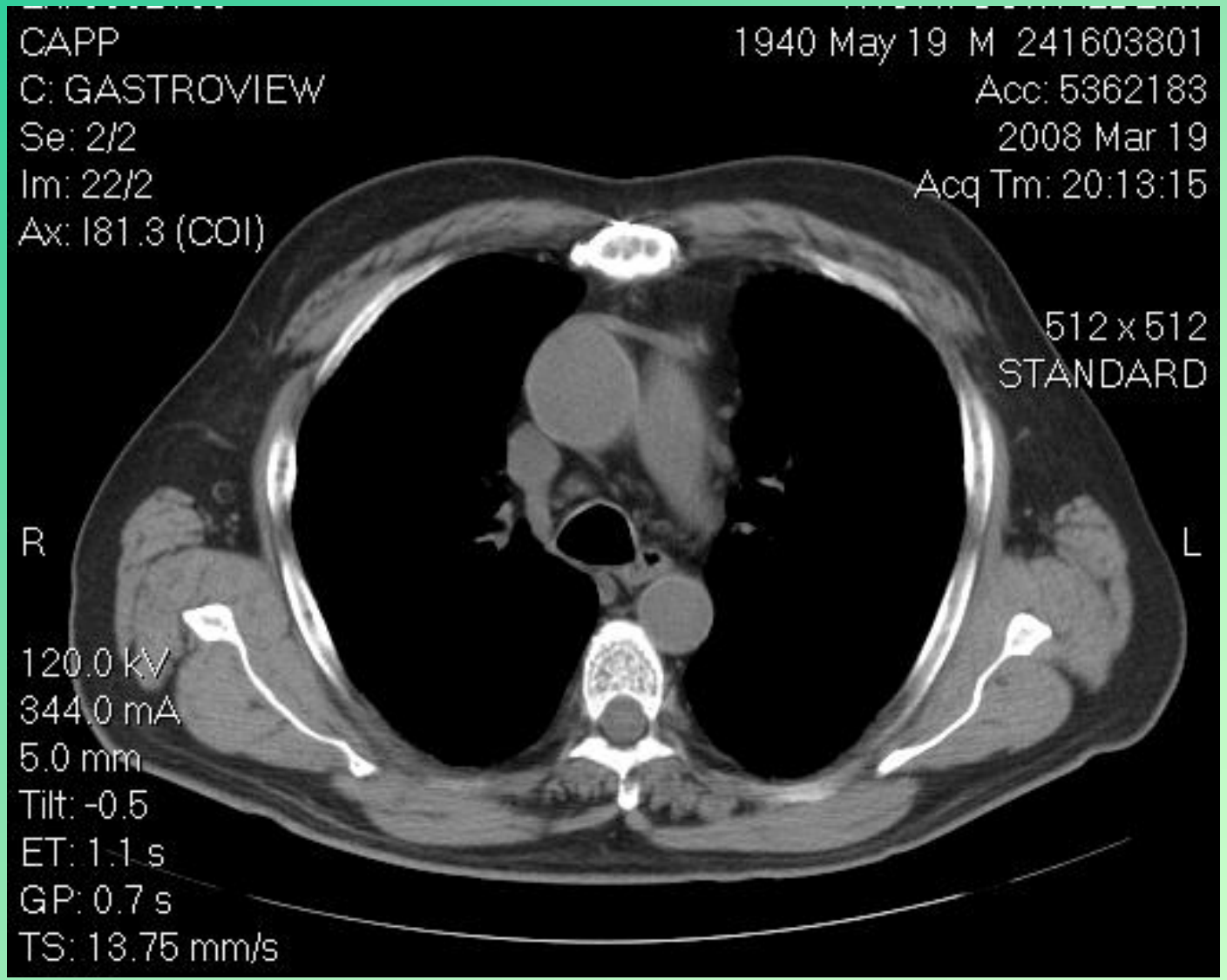
Case, continued

- Anti-globulin test positive for anti-IgG
- Anti-C-3 was negative
- Therefore diagnosed with so-called warm-reacting IgG AIHA.
- No symptoms to suggest underlying cause such as lupus or lymphoma
- On no drug associated with AIHA
- Underwent further evaluation:
  - ANA negative
  - CT C/A (ins. co refused to allow pelvis (!!))…

CT of Chest



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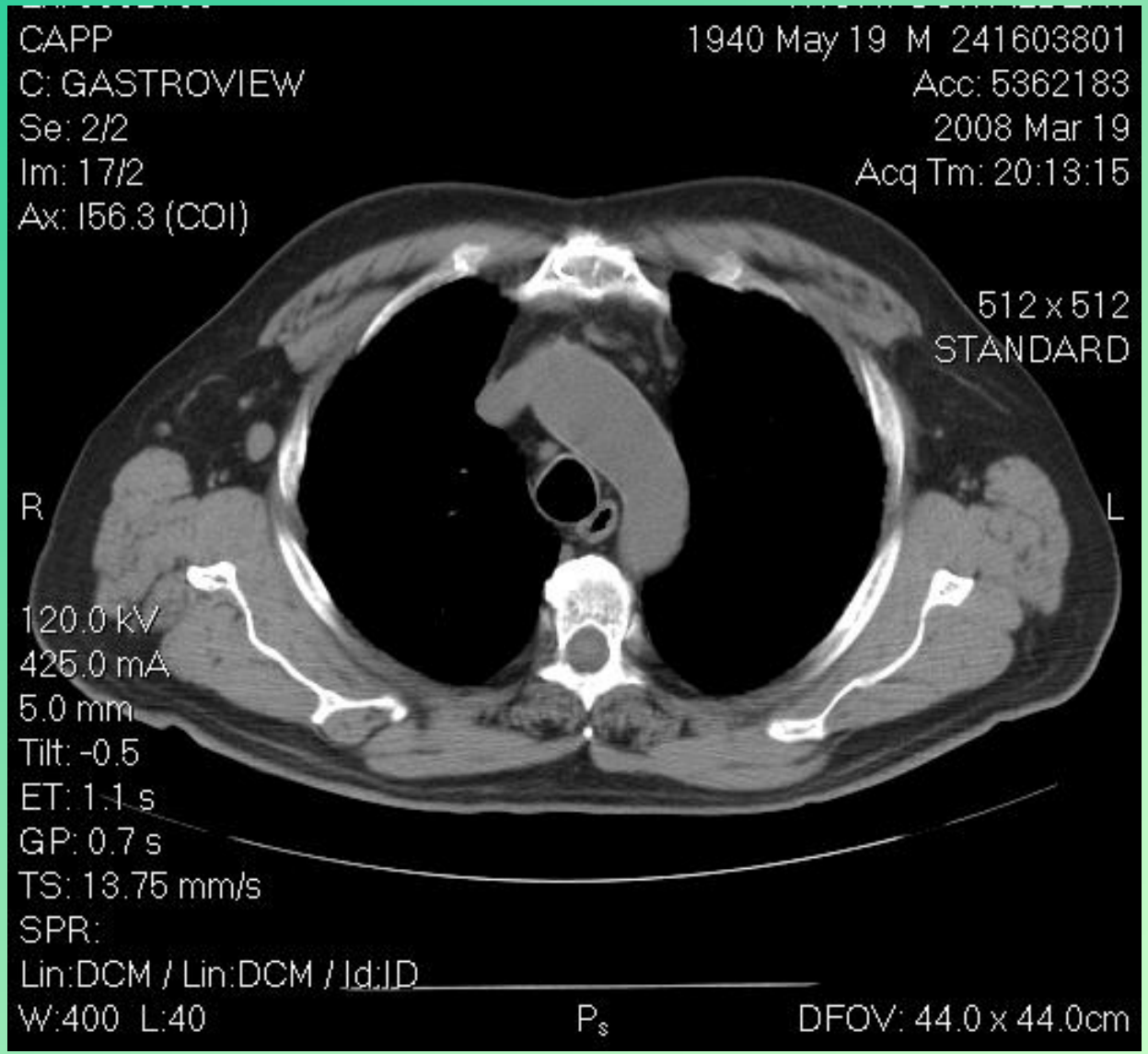
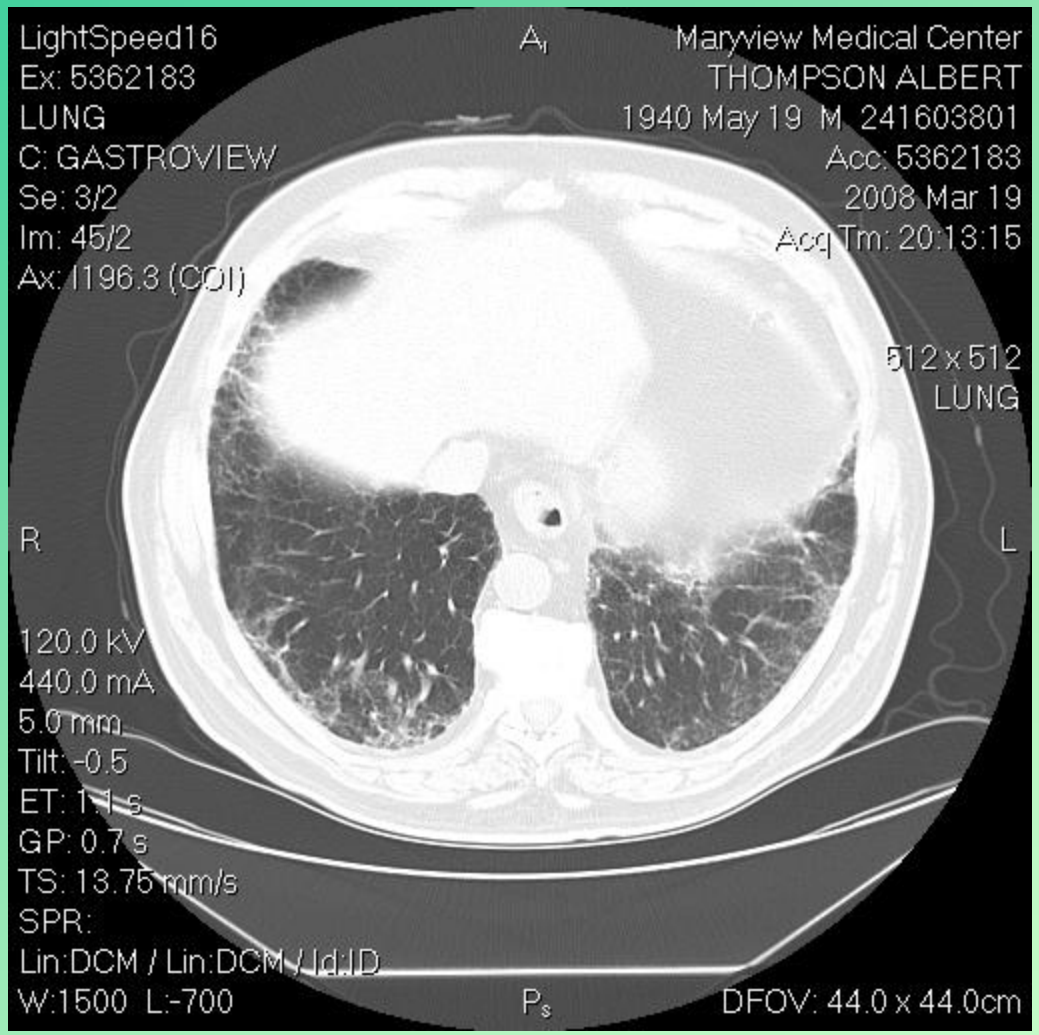
CT Chest, cont.



Lung Windows



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Case Management

- With diagnosis in hand, without underlying disease definable, started on Prednisone at 60 mg/day; diabetes immediately went out of control necessitating addition of insulin
- Rapid decrease in retics and rise in hematocrit
- When tapering of Prednisone attempted retics remained somewhat elevated and hematocrit stayed in 20's as dose of Prednisone was reduced to 20 mg/day
- What to do next….

Options for Management

- Keep on Prednisone indefinitely – unpalatable given array of side effects:
  - Diabetes
  - Accelerated bone mineral loss
  - Altered host resistance
  - Cataract formation
  - Propensity to cause upper GI bleeding
- Take his spleen out
- Add a second drug…which drug?

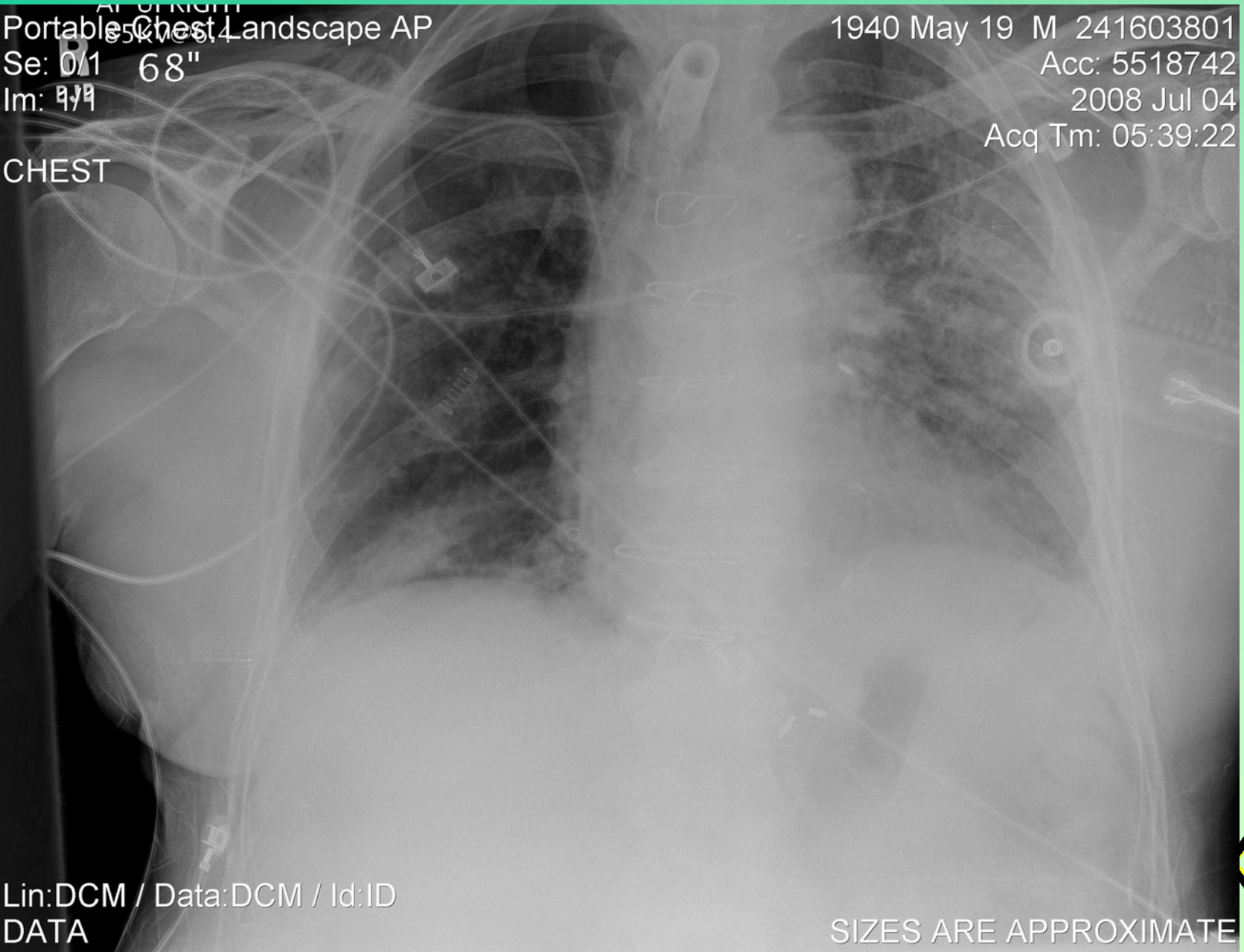
Management, continued

- Choices of drug:
  - Immunosuppressant
    - Cyclosporine
    - Cyclophosphamide
    - Azothioprine
  - Anabolic Steroid
    - Danazol
  - Anti-B-cell monoclonal antibody (Rituximab)

Management, continued

- While being maintained on Prednisone at 20 mg/day, he received four doses of Rituximab at 375 mg/m^2
- While awaiting a response he became acutely ill with fever and shortness of breath and was admitted to the hospital with bilateral pulmonary infiltrates
- X-rays…

Chest X-ray upon admission



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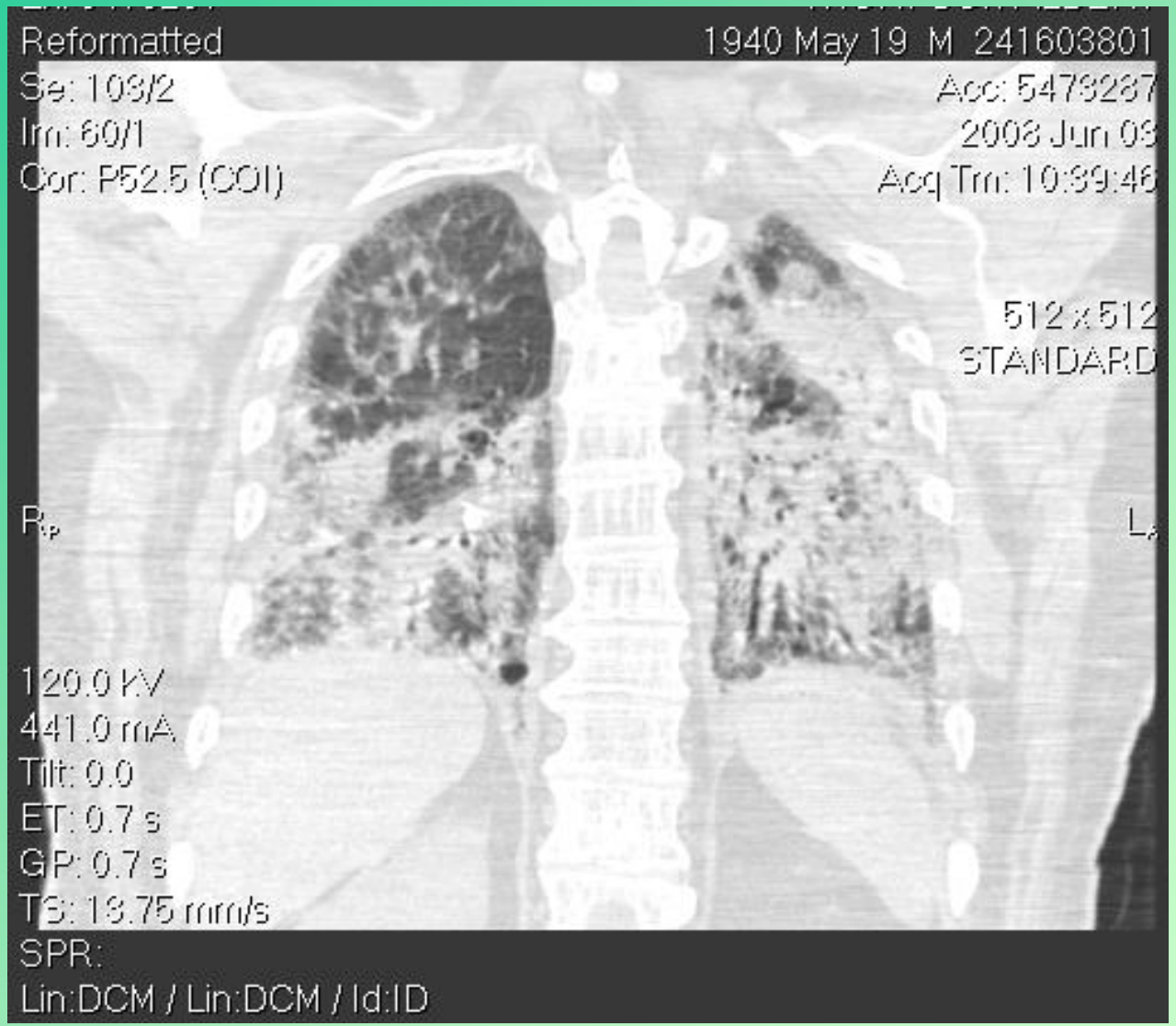
Chest CT



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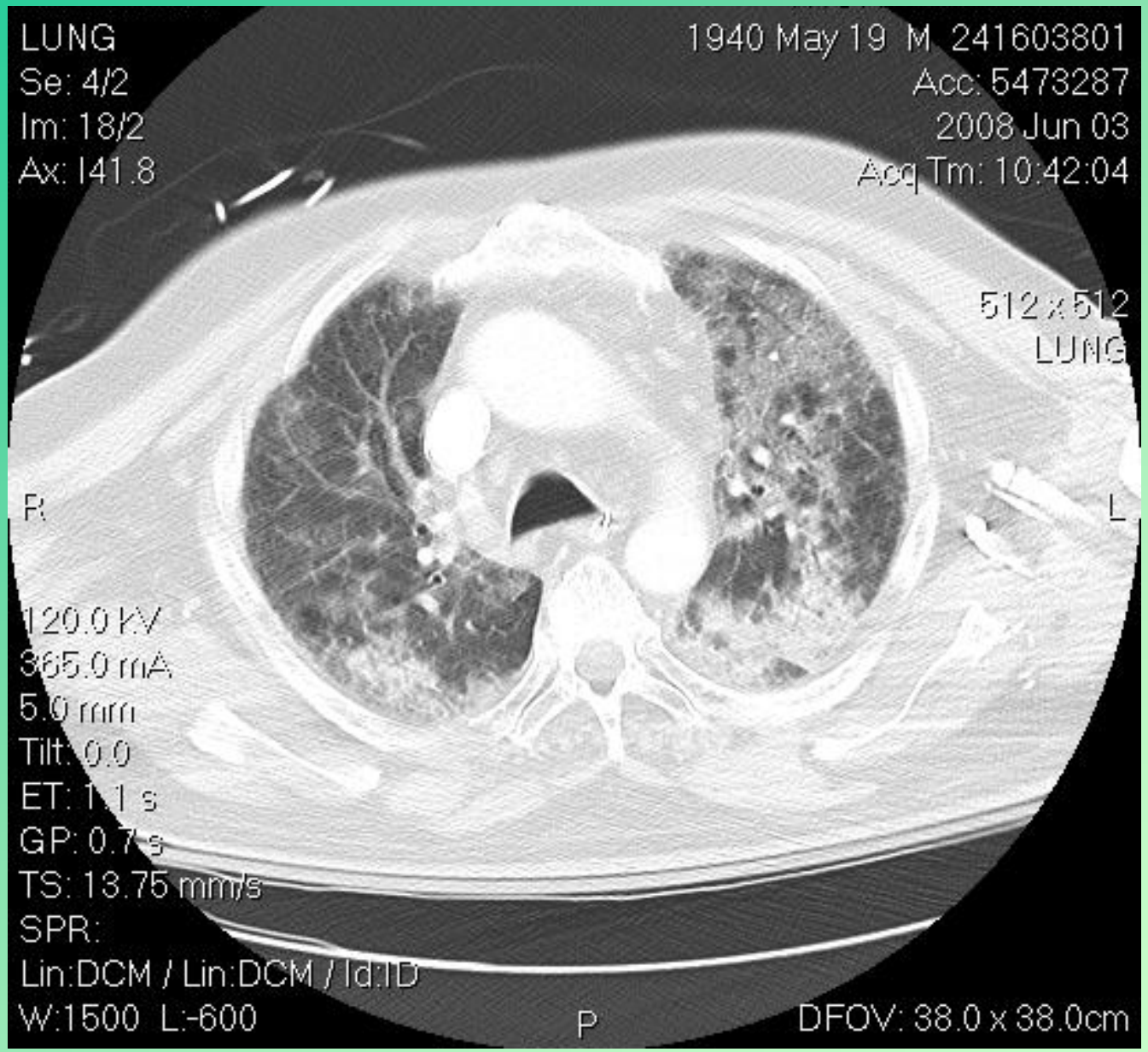
Chest CT



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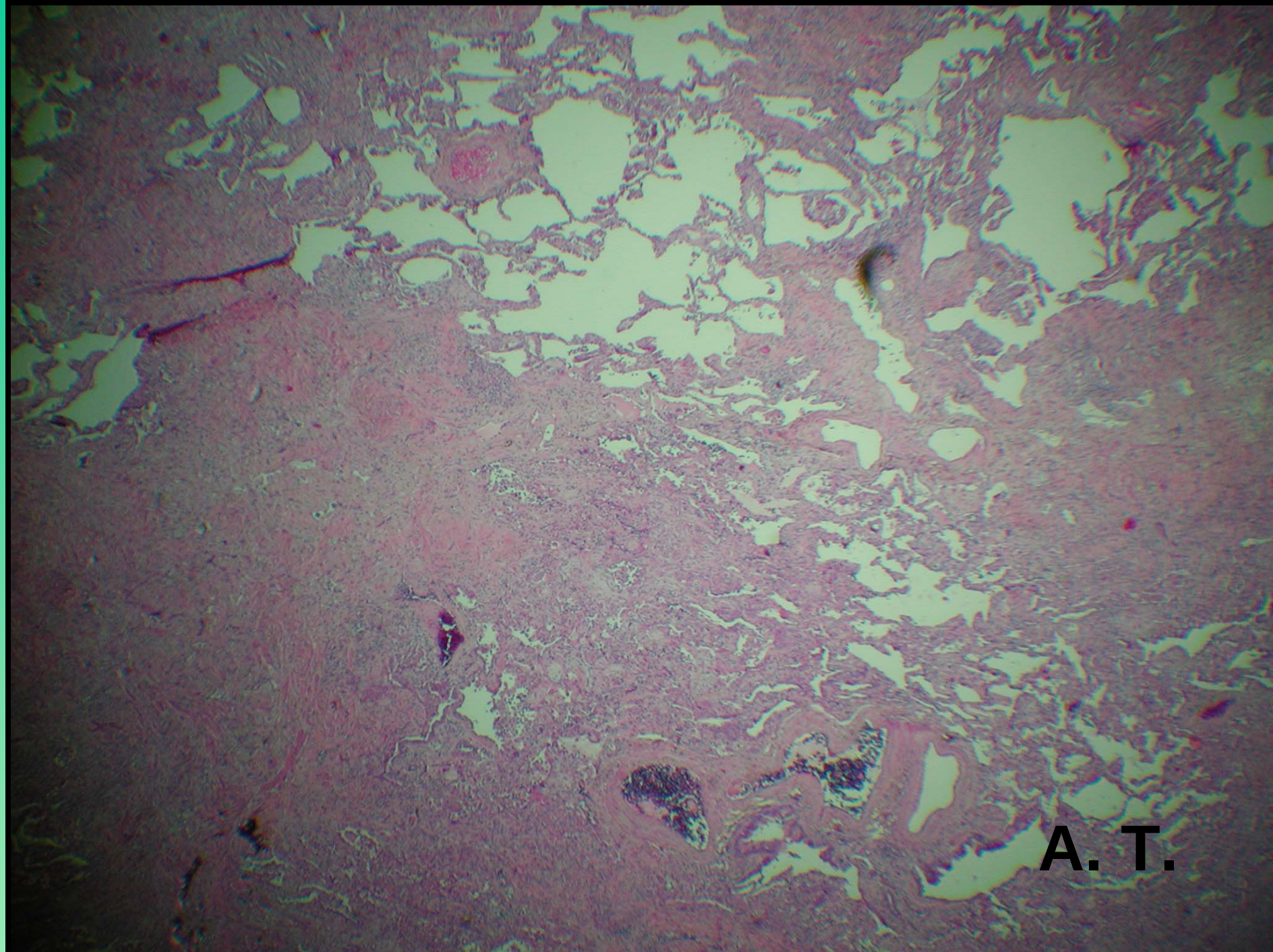
Management, continued

- He remained gravely ill with pulmonary infiltrates which did not improve, and so underwent open-lung biopsy
- Pathology….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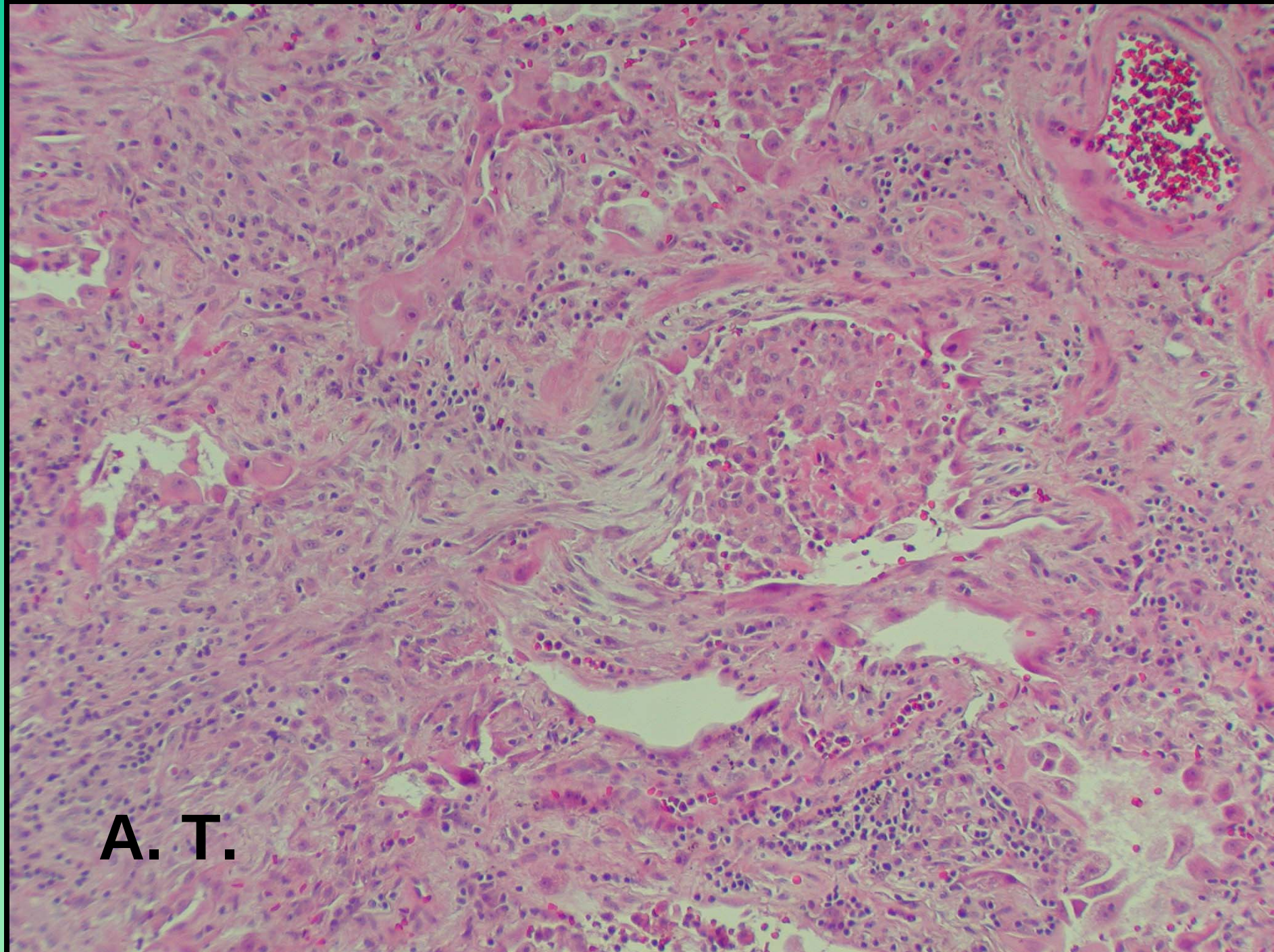
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Subsequent Course

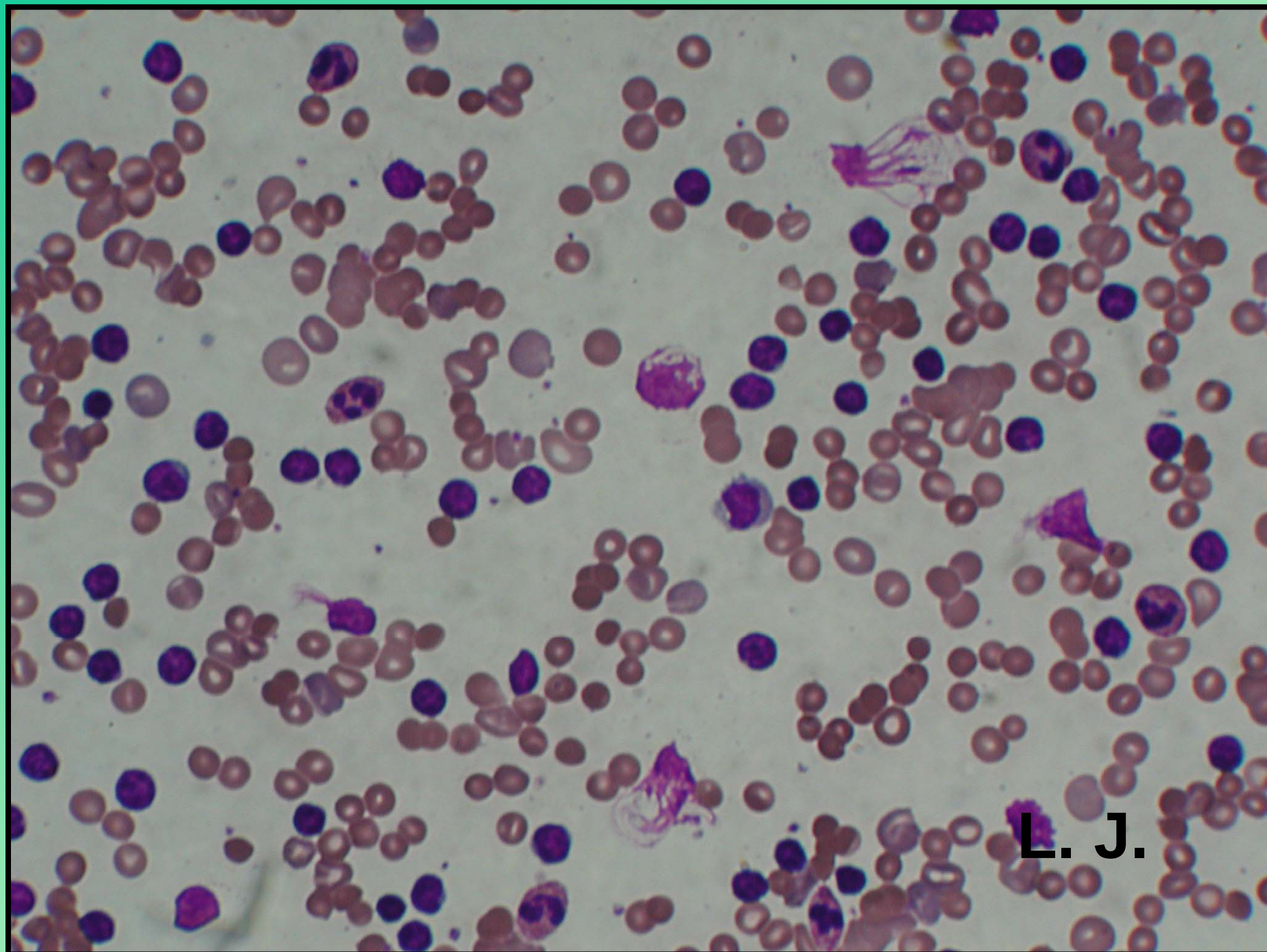
- Remained on high-dose steroids for pulmonary process, underwent tracheostomy for long-term ventilatory support and now, two months later, is getting slightly better

Case #2

- 54 y.o. man followed for three years for typical CLL
- WBC on presentation about 30,000; slowly climbed over the next three years to 50,000
- No anemia, thrombocytopenia; minimal adenopathy; no splenomegaly or constitutional symptoms
- No therapy offered (“pre-treatment phase”)

Case #2, continued

- Presented 10 days ago with sudden drop in hematocrit from 44 to 24, brisk reticulocytosis (15%)
- WBC now 98,000 almost all lymphs; platelets still normal
- Peripheral blood smear…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Case #2, continued

- Presented 10 days ago with sudden drop in hematocrit from 44 to 24, brisk reticulocytosis (15%)
- WBC now 98,000 almost all lymphs; platelets still normal
- Peripheral blood smear…
- Nodes slightly bigger
- Spleen now palpable
- Coombs test:
  - **4+ positive for IgG and C3 coating his red cells**
- Prednisone initiated; chemotherapy with Rituxan and Cytoxan just started

Case #2, continued

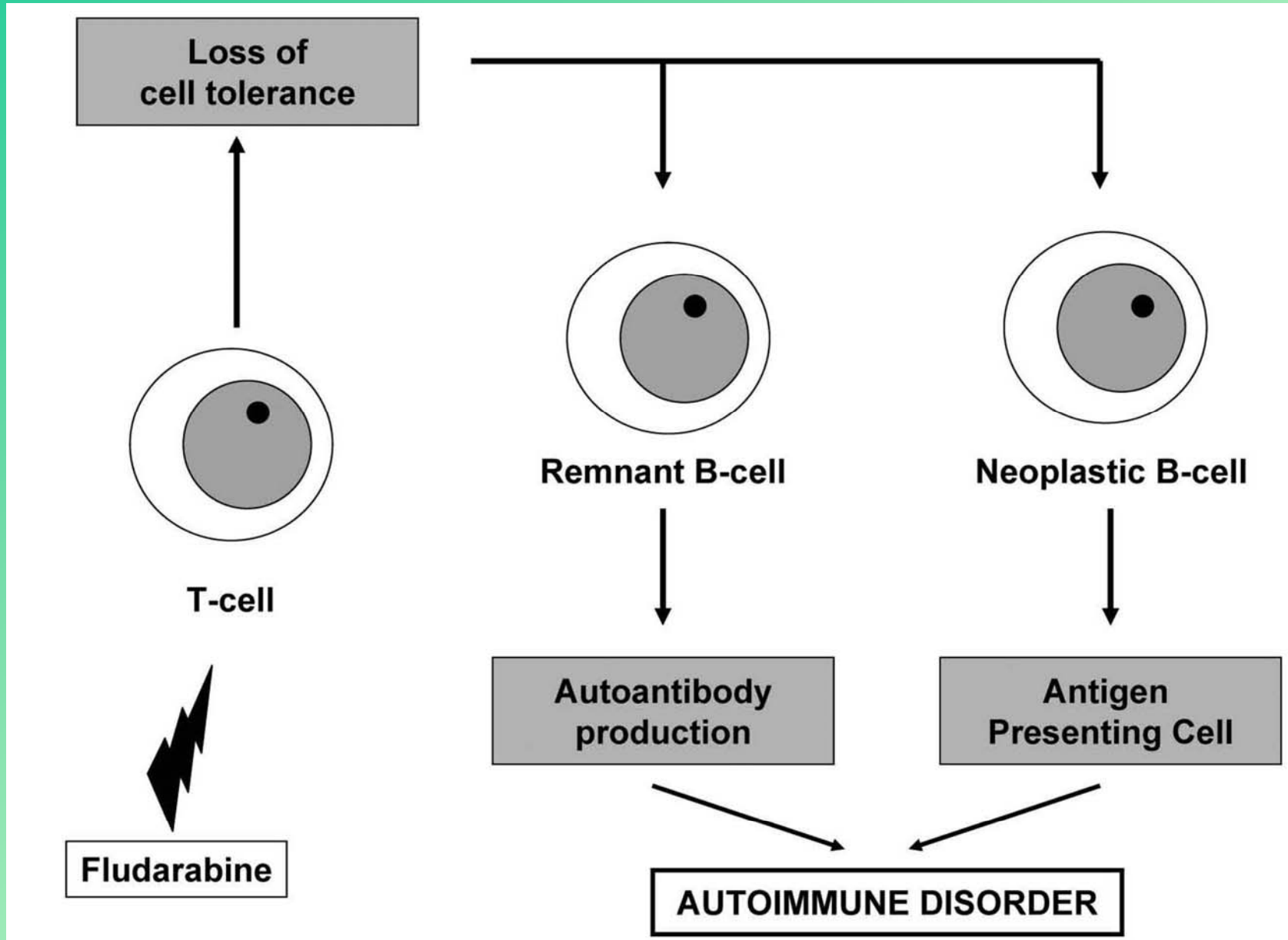
- On third day of chemotherapy his WBC is up to 206,000
- H/H = 5.6/17
- Retics 34%

- If no improvement by next week will recommend he undergo immediate splenectomy

Case #2 Therapy, continued

- Conventional first-line therapy for aggressive CLL usually includes Fludarabine
- Several well-documented reports of this drug causing AIHA in CLL patients where none previously existed…
- Therefore reluctance to use this agent
- Why should this be so?

Theoretical Basis for Fludarabine Effect



Case #2, continued

- Hence decision made to withhold Fludarabine for the moment
- Ultimate wisdom of this move to be determined
- Decision made on anecdotal evidence

Background: Terminology

- "Warm-reacting AIHA"
  - Abnormal IgG produced which reacts with proteins on red cell surface at body temperature (i.e., "warm")
  - Associated with lupus and B-cell neoplasms (CLL, non-Hodgkin Lymphoma); can be triggered when CLL treated with anti-metabolites as discussed above

IgG-Associated AIHA: Laboratory Features

- Macrocytic anemia (reticulocytes are larger than mature RBC's)
- Reticulocytosis
- ↑ LDH
- Very low or absent haptoglobin
- Occasional thrombocytopenia (Evans-Duane syndrome)
- Positive Coombs (anti-globulin) test

Positive Coombs Test

- Can be against IgG, C3 or both
- Intensity of positivity correlates with degree of hemolysis
- Can be produced by variety of drugs (classically penicillin) with or without associated hemolysis
  - Not the case with either of our patients

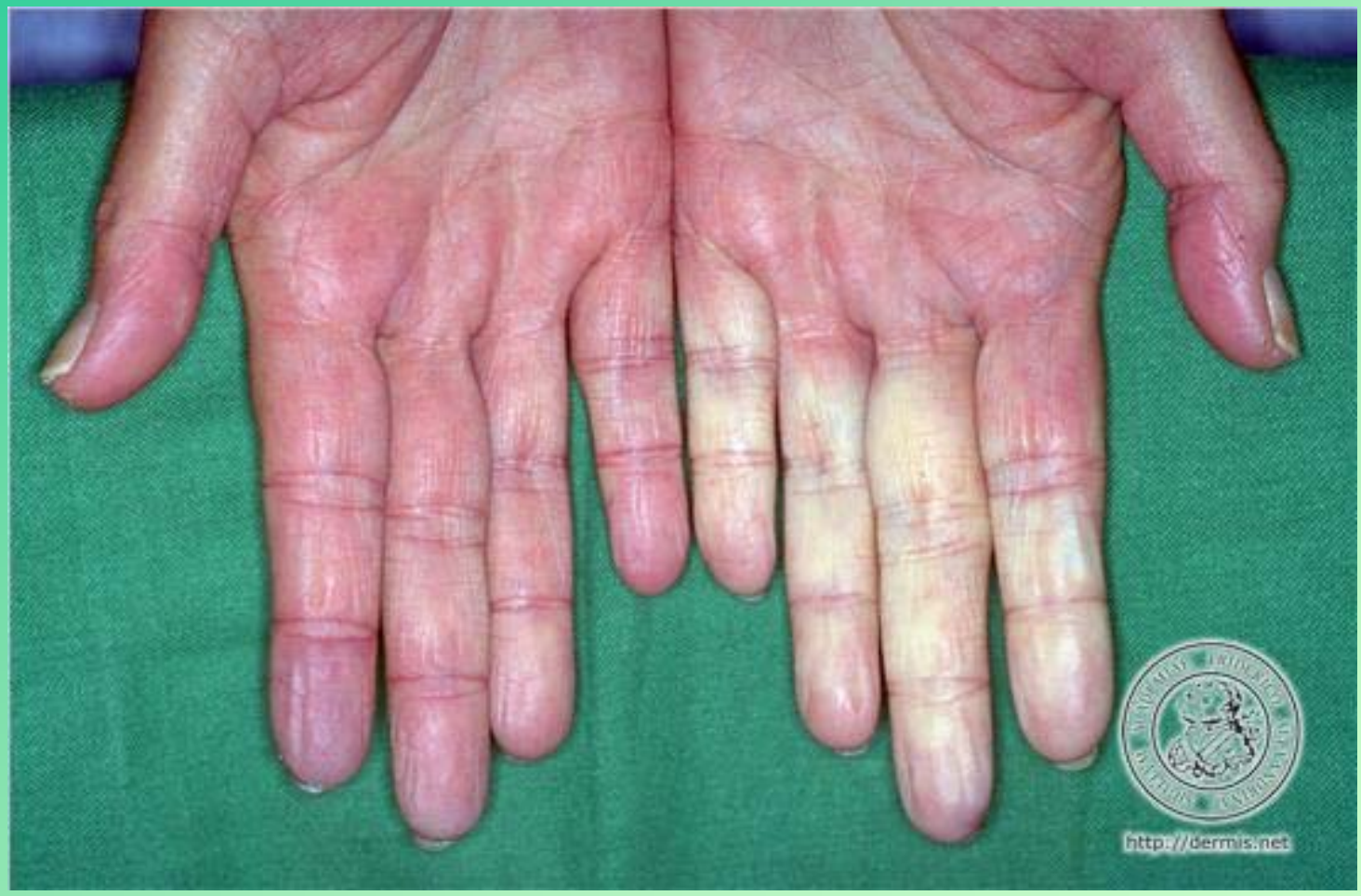
Clinical Findings in AIHA

- Anemia – can be severe enough to cause symptoms, as seen in our patients
  - Pre-existing heart or lung disease can dramatically effect impact of anemia
- Development of lymphoproliferative illness
  - Can occur after onset of AIHA; chicken and egg problem
- Hypercoagulability with venous thromboembolic disease
  - Associated with Anti-Phospholipid Syndrome
- Typically steroid responsive

Cold-Agglutinin Disease

- The other main type of AIHA
- Antibodies are usually IgM, anti-I in specificity
- Red cells agglutinate at room temperature, hence the term “cold agglutinins”
- Symptoms are those of anemia or of cryopathic phenomena
  - Acrocyanosis in the cold
- Typically steroid resistant

Acrocyanosis



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Cold Agglutinins, continued

- Span the spectrum from benign to malignant disease
  - Chronic cold agglutinins unassociated with B-cell neoplasm; hemolysis usually mild, no other symptoms
  - Caused by benign monoclonal IgM-κ
  - Can transform into aggressive B-cell neoplasm with monoclonal IgM production
  - Can be associated with Mycoplasma pneumoniae or Epstein-Barr virus infections; at times can cause brisk hemolysis; self-limited

Differential Diagnosis of Cold Agglutinins

- Paroxysmal Cold Hemoglobinuria
  - IgG, after viral infection
- Drug-induced AIHA; pathologic IgM present but no cryopathic phenomena
- Essential cryoglobulinemia; cryopathic phenomena without classic cold agglutinin protein; often mixed IgG/IgM complexes
  - Often results in hyperviscosity and cutaneous vasculitis
  - Can be associated with B-cell malignancy in which case distinction from cold agglutinin can get murky
  - Ddx that of other cutaneous vasculitis syndromes

Treatment of Cold Agglutinin AIHA

- Steroids, splenectomy of no value
- Avoidance of cold, wearing gloves in cold weather
- Rituximab of value with or without interferon
- Plasmapheresis in emergent situations
- Chronic immunosuppression with cytotoxic agents
- Treatment in general less satisfactory than for warm AIHA

Back to Our First Patient

- What caused him to develop life-threatening pulmonary toxicity?
  - B-cell depletion with Rituximab not usually associated with opportunistic infections
  - Rituximab-induced acute pulmonary toxicity very rare (<20 cases reported); steroids allegedly of benefit; not clearly so in our case
- If he recovers the problem of what to do next remains
- Hemolysis gone ?from Rituxan or prolonged high-dose steroids used to treat lung process
- ??Underlying lymphoproliferative illness remains
- Arguably immaterial to recent therapy

Back to Our Second Patient

- AIHA *should* remit with control of his underlying malignancy
- May herald reactivity of disease
- What triggered this sudden untoward event is totally unknown

Conclusion

- AIHA is a rare but serious and potentially life-threatening condition if not cured with a short course of steroids
- Complex clinical picture; confusion with other conditions possible to the unanitiated

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