

Mantle-Cell Leukemia: Lessons in Life and Death

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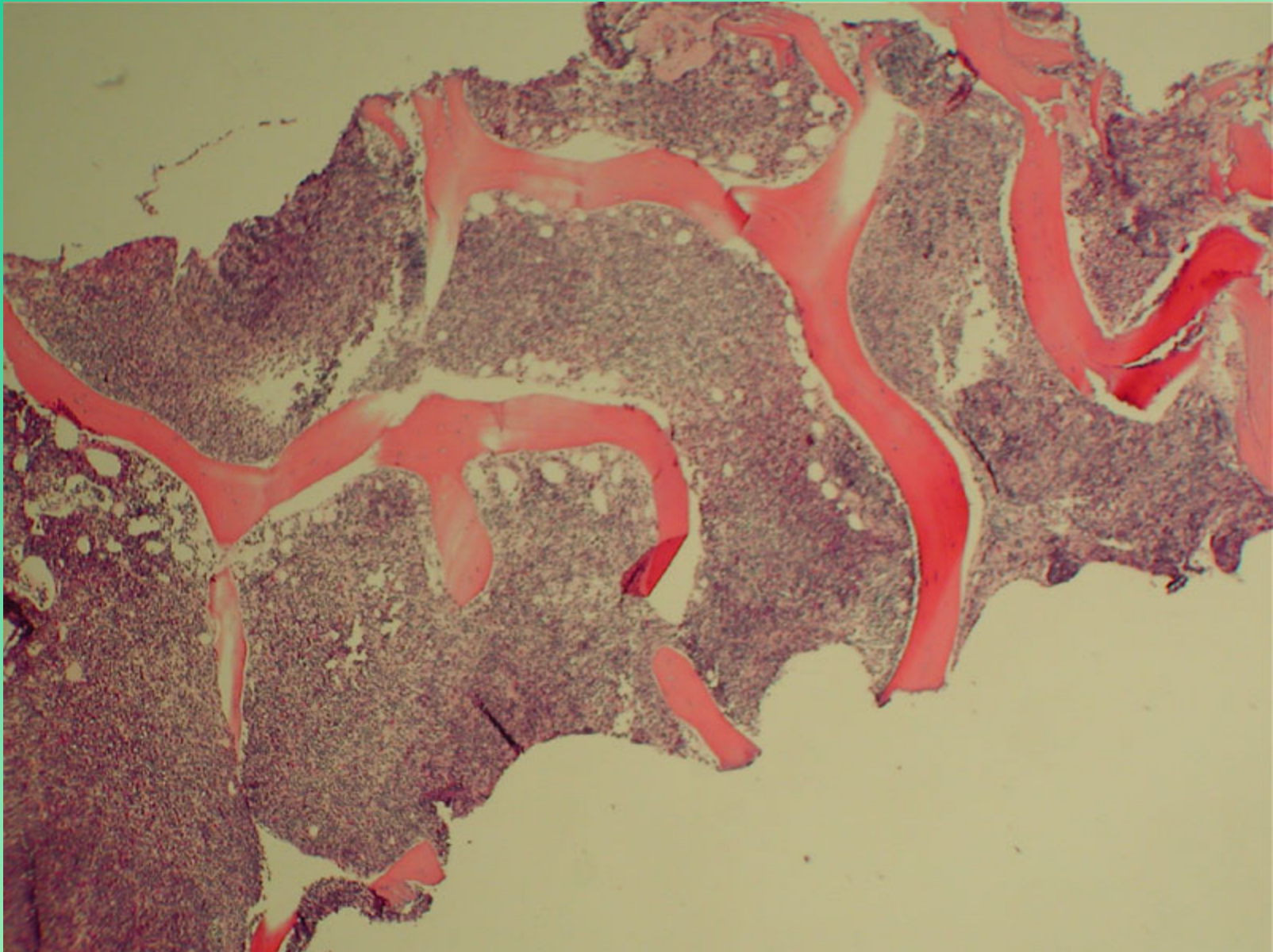


Case Presentation

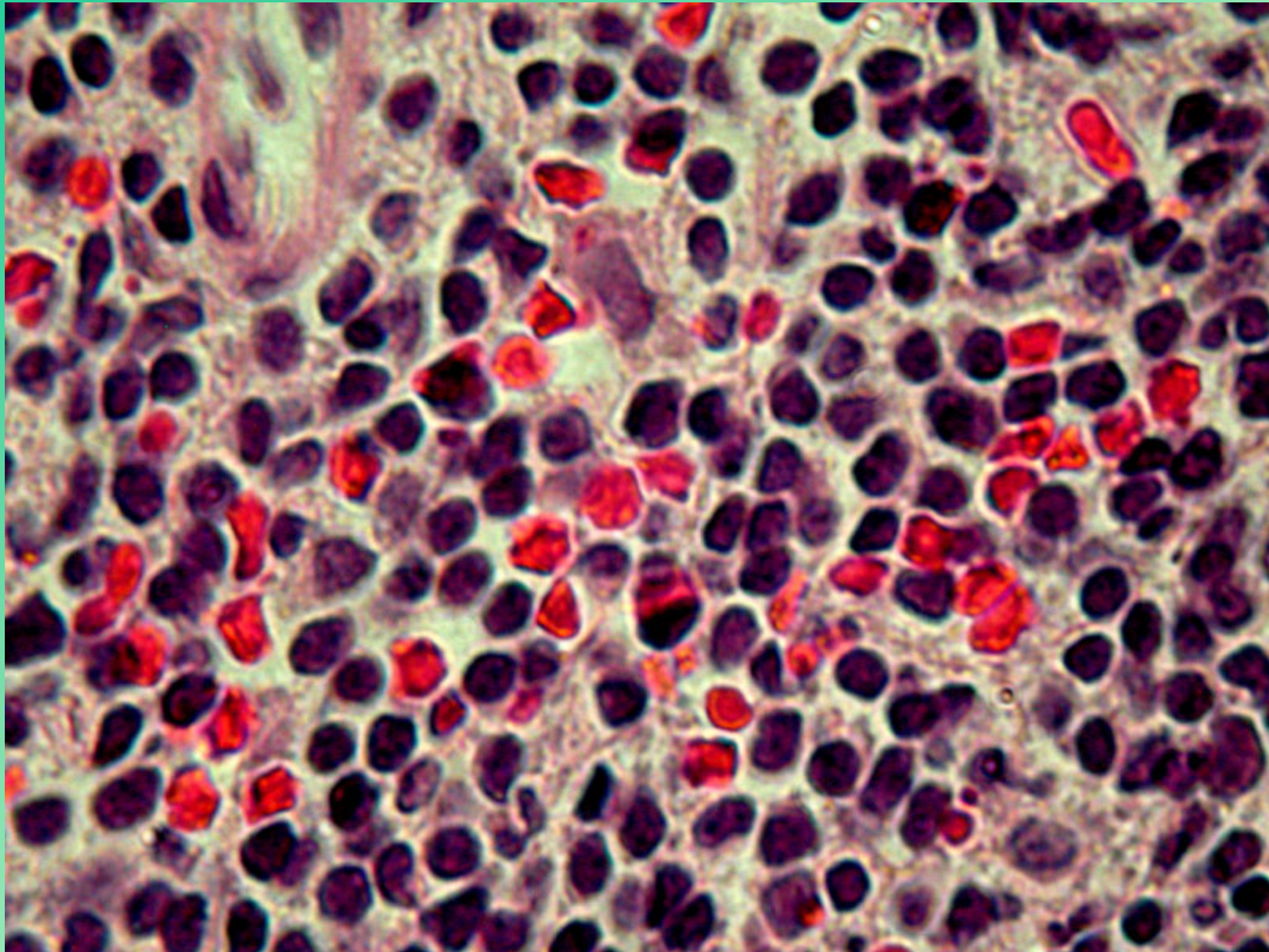
- 60 y.o. man PhD engineer inventor presented in December, 2003 with very enlarged spleen
- CBC: Hematocrit 26.7/Hgb 8.6
- WBC: 155,800 with 99% lymphocytes
- Platelet count: 59,000
- Bone Marrow Biopsy...



Low Power Bone Marrow Biopsy



High Power Bone Marrow Biopsy



Case Presentation, cont.

- Flow cytometry on bone marrow:
- CD 20 + CD 5 +
- FMC7 +
- CD23 –
- Cytogenetics: 11;14 translocation in 166/200 cells studied by FISH analysis
- Monoclonal λ light-chain on cell surface
- Diagnosis of Mantle Cell lymphoma/leukemia made on the above bases



Case Presentation, continued

- Treated with 6 cycles of “R-CHOP” and went into solid clinical remission with disappearance of splenomegaly and normalization of peripheral blood counts
- FISH not repeated on marrow or blood
- Referred to Bone Marrow Transplant Unit at MCV for consideration of high-dose therapy and stem-cell rescue



Case Presentation, continued

- At recommendation of MCV he received three additional cycles of higher intensity chemo consisting of Rituxan, Ifosfamide with Mesna, Carboplatin and Etoposide (R-ICE) to reduce amount of minimal residual disease prior to transplant
- Then went back to MCV for more chemo with stem-cell mobilization



Case Presentation, continued

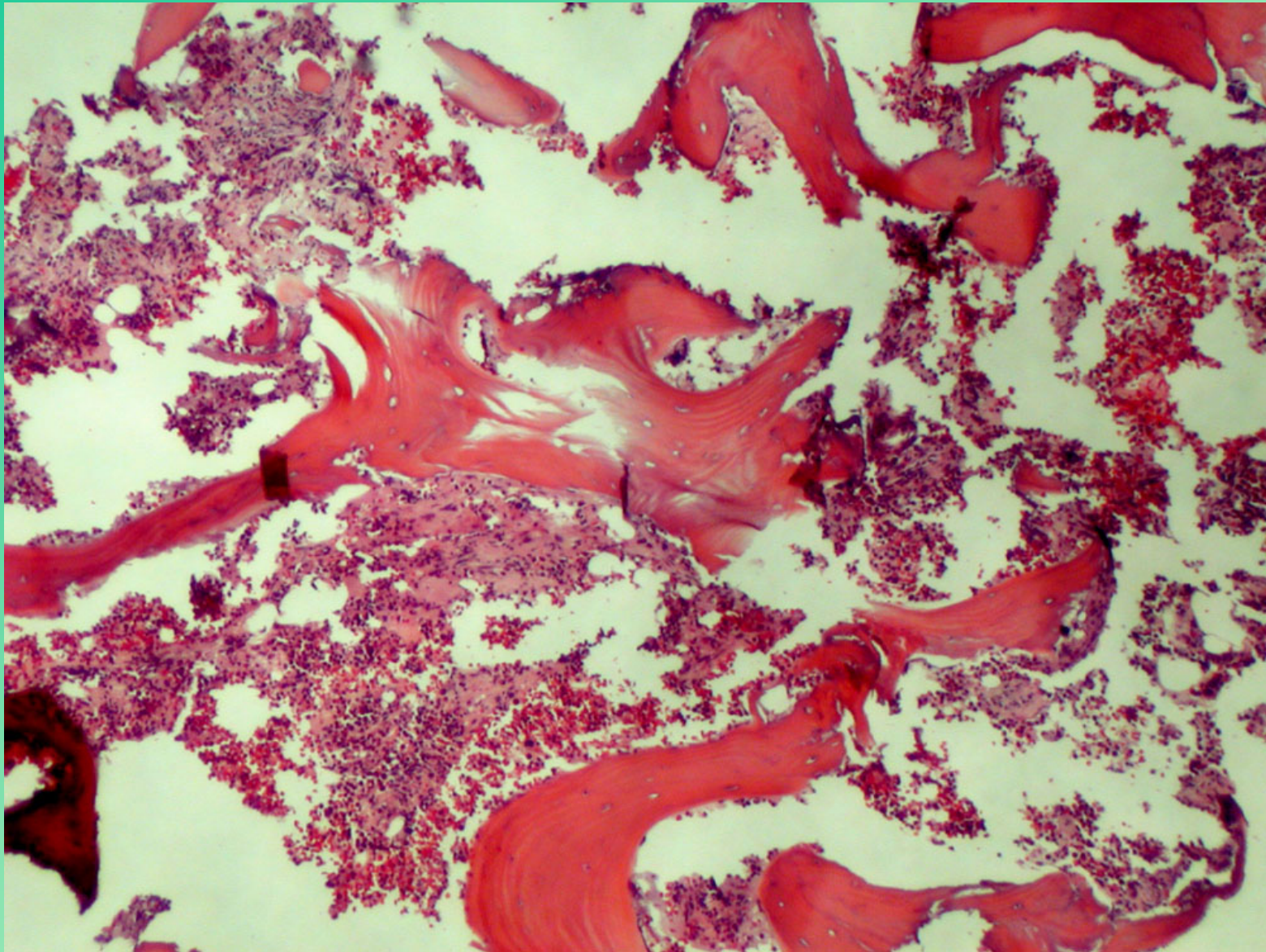
- In December, 2004 after much therapy and preparation he received his transplant:
- BEAM therapy (high-dose BCNU followed by high-dose ARA-C and etoposide followed by high-dose melphalan)
- Then he received stem-cell reinfusion
- Tolerated well; discharged from MCV on G-CSF and numerous antibiotics, anti-fungals and anti-virals
- Never developed a serious infectious complication
- Took months to recover his former vigor



Case Presentation, continued

- At his request, Bone-Marrow biopsy performed in April, 2005....





Case Presentation, continued

- At his request, Bone-Marrow biopsy performed in April, 2005: normal morphologically and by cytogenetics
- Deemed to be in hematologic and cytogenetic remission
- After much consideration and with considerable intellectual input from patient (risk-benefit analysis) he was treated with pulse maintenance Rituxan every six months for two years
- Continued well although developed periodic severe neutropenia usually associated with otherwise trivial viral infections



Case Presentation, continued

- In May, 2007 developed Herpes Zoster of face with some minimal disseminated zoster
- Felt ill with low-grade fever
- Admitted after failing to improve on oral Famvir
- Improved quickly on intravenous Acyclovir
- No post-herpetic neuralgia or other sequelae



Case Presentation

- In May, 2008, 3.5 years after ABMT he became ill again
- Admitted to hospital in California while traveling with severe bronchopneumonia
- Hematocrit 25 at that time
- By the next month his white count was rising rapidly and his disease was in obvious relapse
- Flow cytometry on peripheral blood confirmed same malignant cells as with original presentation



Case Presentation, continued

- Admitted to Maryview ill for re-induction with R-CHOP
- Because of persistence of respiratory symptoms CT scan done which revealed multiple pulmonary emboli....
- Anticoagulated gingerly in light of low platelet count
- WBC fell quickly but rose again before he could be retreated....functionally R-CHOP resistant



Case Presentation, continued

- Referred back to MCV
- He arrived at MCV with pneumonia, was hospitalized there and convalesced slowly
- Grew *e. coli* and a fungus from his blood
- Before he could be re-treated (this time with Velcade and Rituxan) he was admitted to Maryview with mental-status deterioration and found to be in renal failure

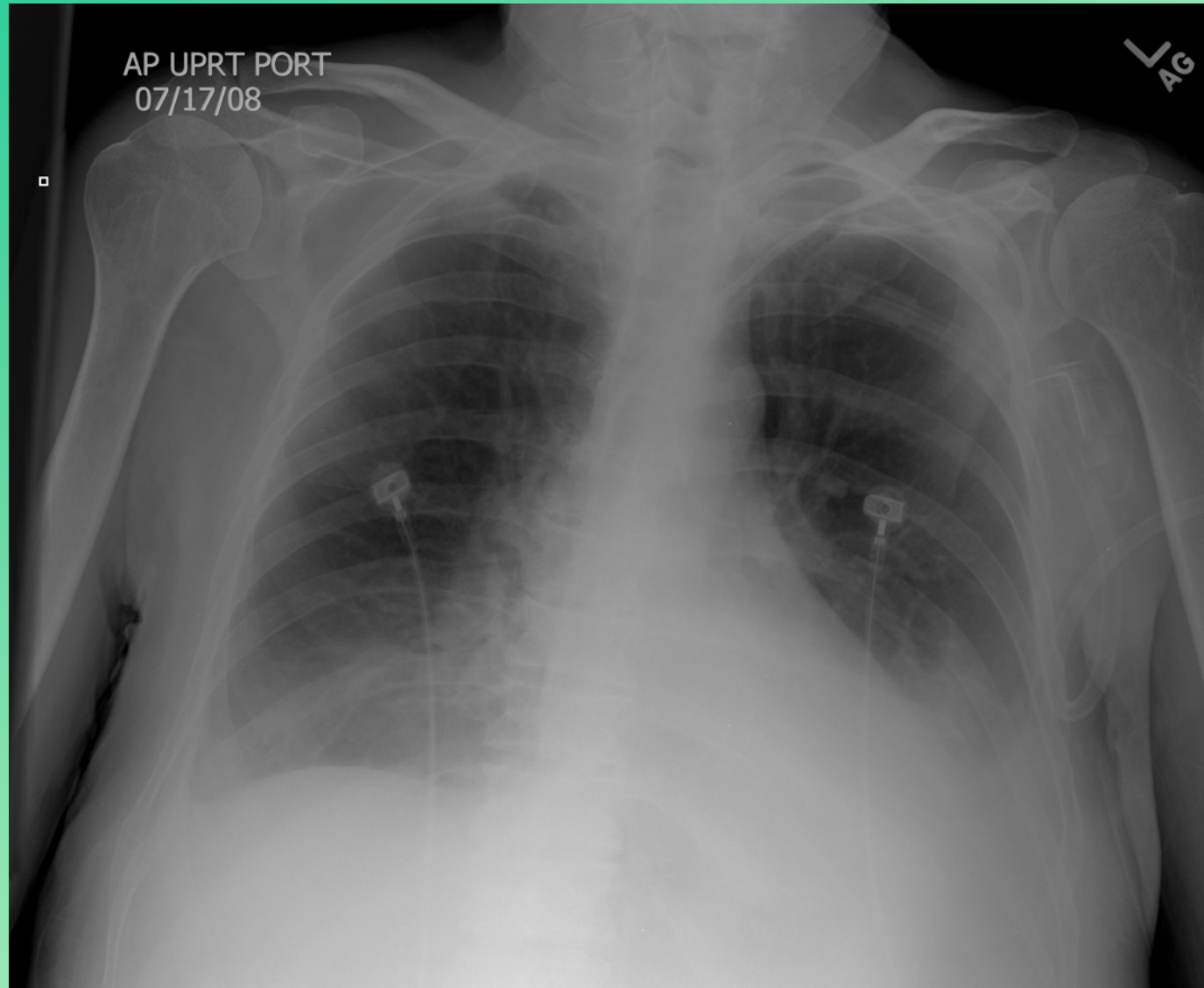


Case Presentation, continued

- Evaluation of renal failure included imaging studies to rule out obstruction and vigorous rehydration to rule out volume depletion as contributing factor
- X ray studies....



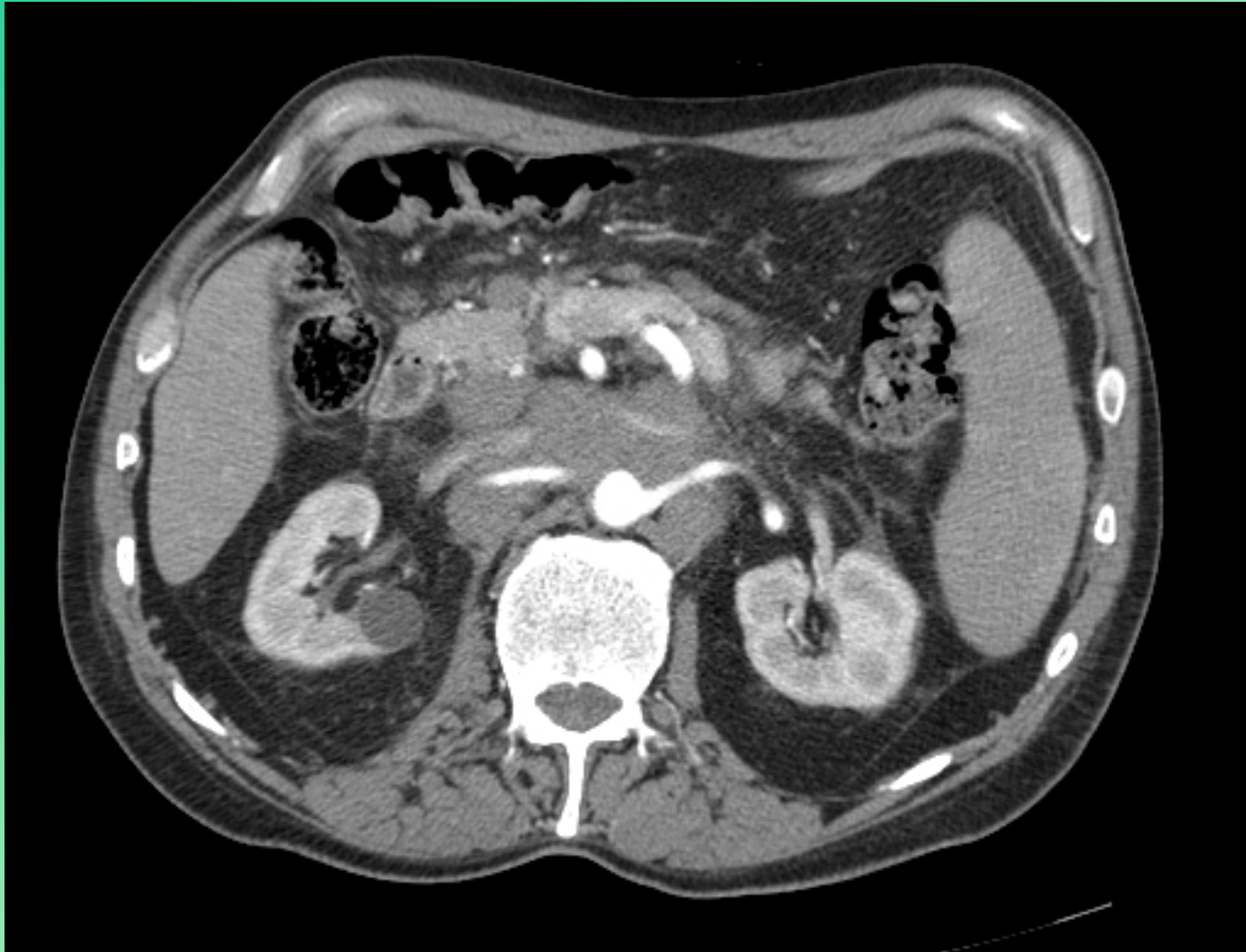
Bilateral pulmonary infiltrates – pneumonia vs. CHF



Splenomegaly



Normal-sized kidneys with normal collecting systems

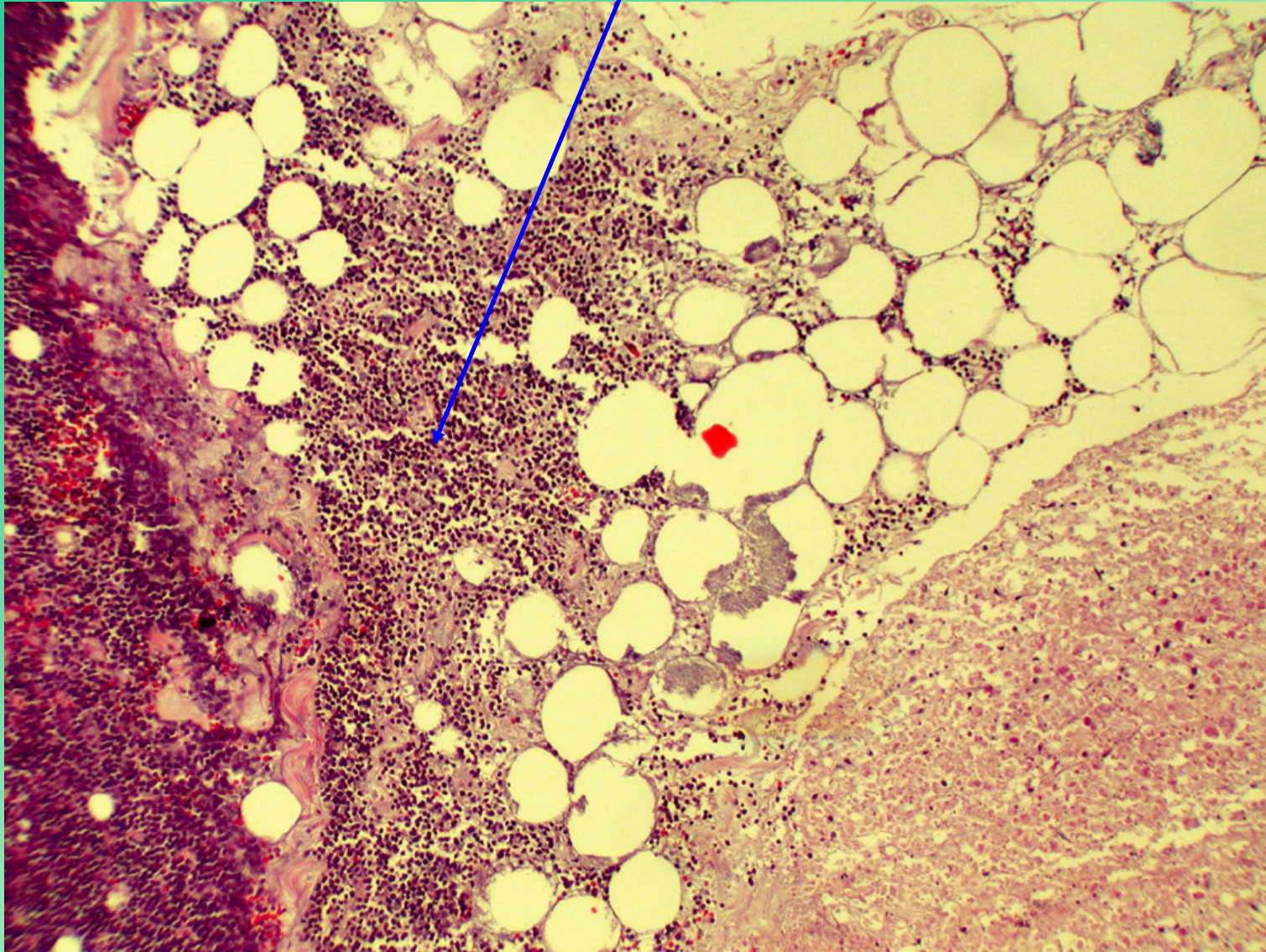


Case Presentation, continued

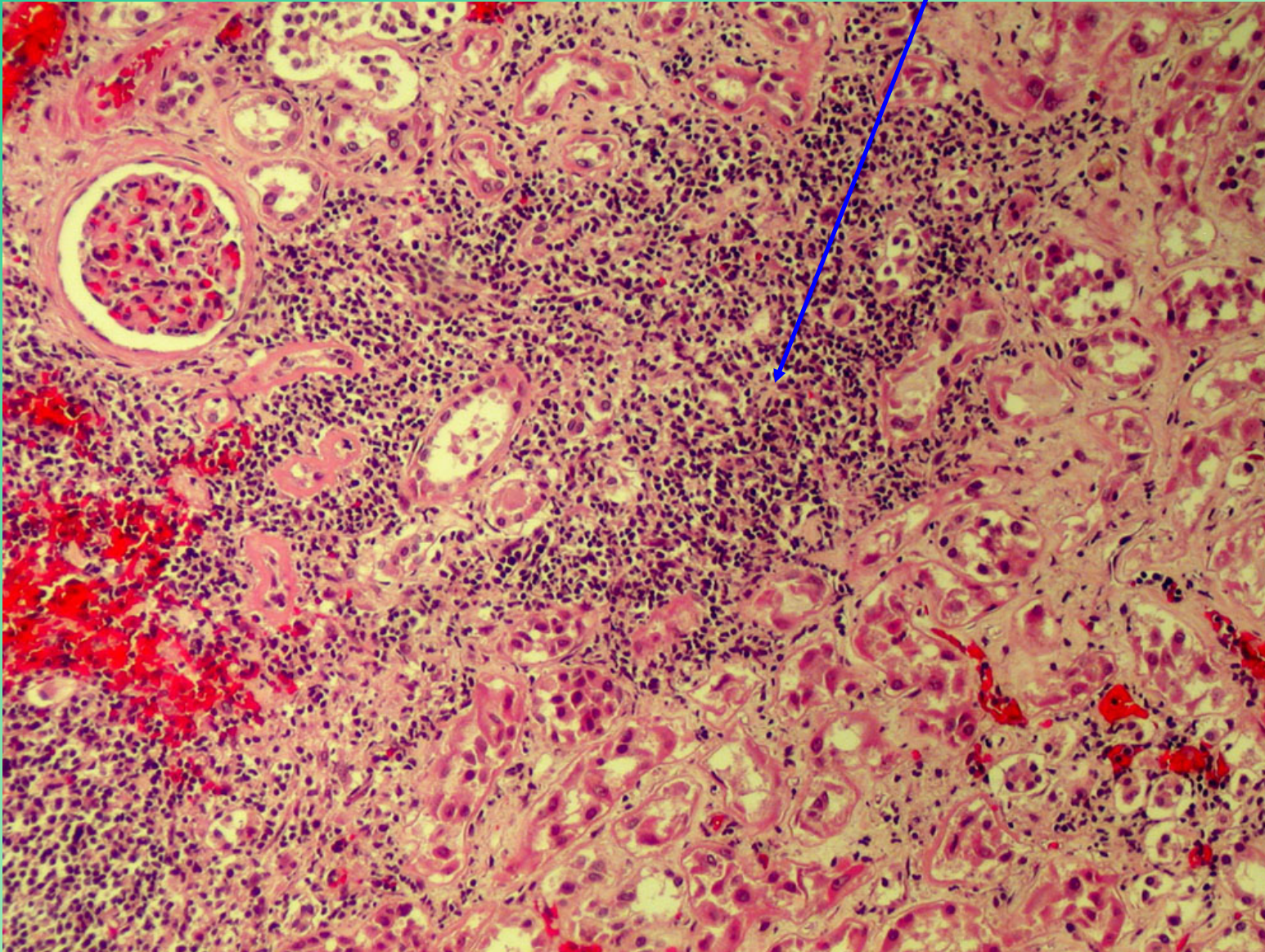
- Evaluation of renal failure included imaging studies (see above) to rule out obstruction and vigorous rehydration to rule out volume depletion as contributing factor
- Clinical diagnosis of lymphomatous infiltration of kidneys as cause of uremia entertained as diagnosis of exclusion, with literature support
- Family at this point insisted that aggressive measures be withdrawn and he died peacefully on July 22, 2008
- Autopsy performed...



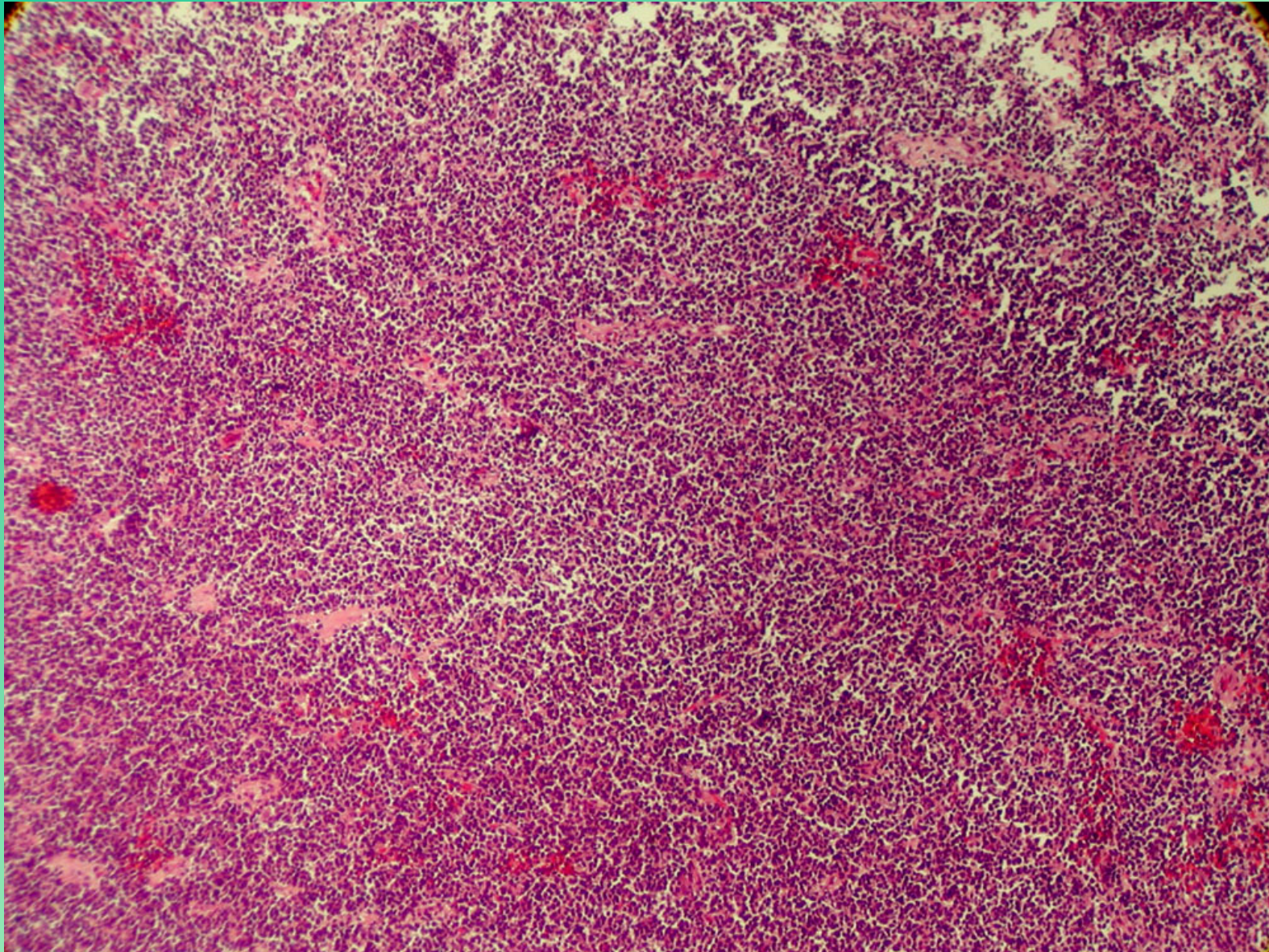
Retroperitoneal Lymph Node – extensive infiltration with lymphoma



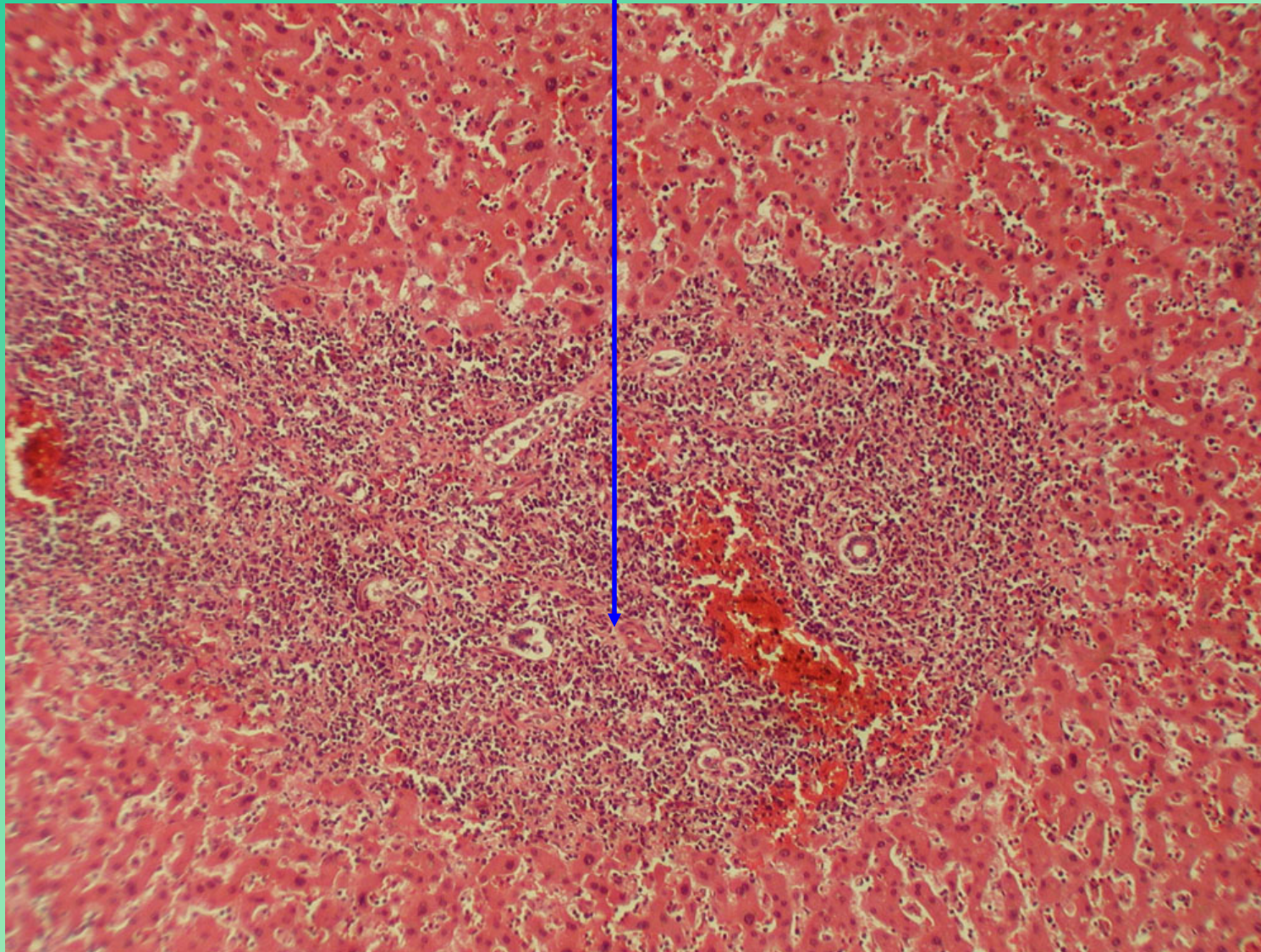
Kidneys – infiltrated with lymphoma, enough to cause renal failure



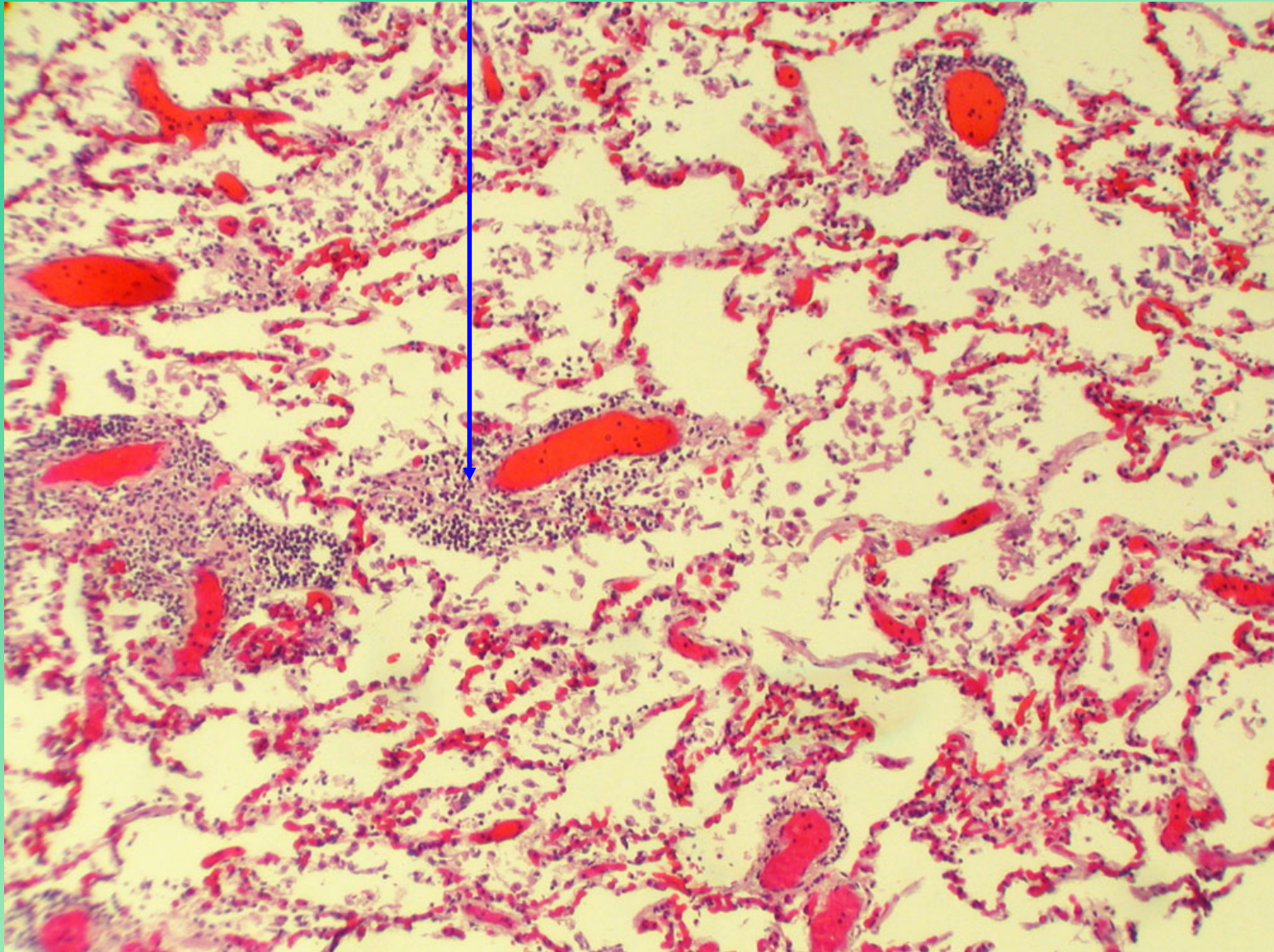
Spleen – normal architecture replaced by diffuse lymphomatous involvement



Liver – focally infiltrated with lymphoma



Lungs – focal perivascular infiltration



Cause of Death

- Organ failure secondary to infiltration with Mantle-Cell lymphoma
- Despite altered mental status there was no evidence of CNS lymphoma – either in meninges or parenchyma of brain



Mantle-Cell Lymphoma/Leukemia

- B-cell neoplasm of moderately aggressive nature
- Characteristic flow-cytometric and cytogenetic abnormalities
 - CD5, CD20, FMC7 positivity
 - CD23 negative....our patient exhibited conformity with these
 - Surface membrane IgM and IgD: λ (also seen although parent Ig class not determined)
 - 11;14 translocation almost always present although not completely diagnostic (can be seen in other NHL's)



Mantle-Cell Lymphoma, continued

- Cell morphology not pathognomonic of diagnosis
- Lymph-node appearance, when sampled, is helpful in the diagnosis
 - Can be nodular or diffuse



Prognosis of MCL

- Investigated as separate entity in one large study
- Resulted in development of “MIPI” scoring
- Multivariate analysis as to prognosis...



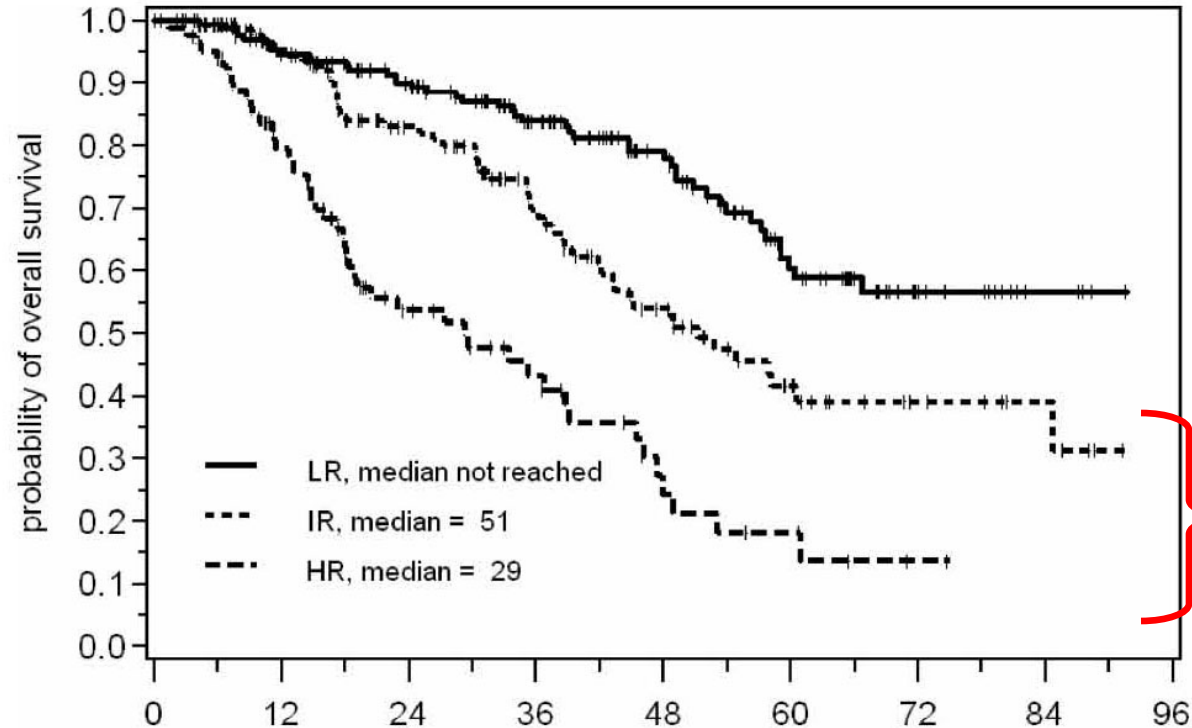
Summary of Prognostic Factors

Prognostic factor	<i>P</i>
Age >60	<.001
ECOG	.009
LDH	.006
WBC count >15,000	<.001

n=455; from Hoster et al *BLOOD* 111:558, 2008



Prognosis Over Time



Likely in this range*

	numbers of patients at risk								months since registration	
LR	180	153	131	99	69	39	15	4		
IR	145	116	83	57	37	19	9	5		
HR	84	58	29	19	8	5	1	0		

***LDH never measured but likely high**

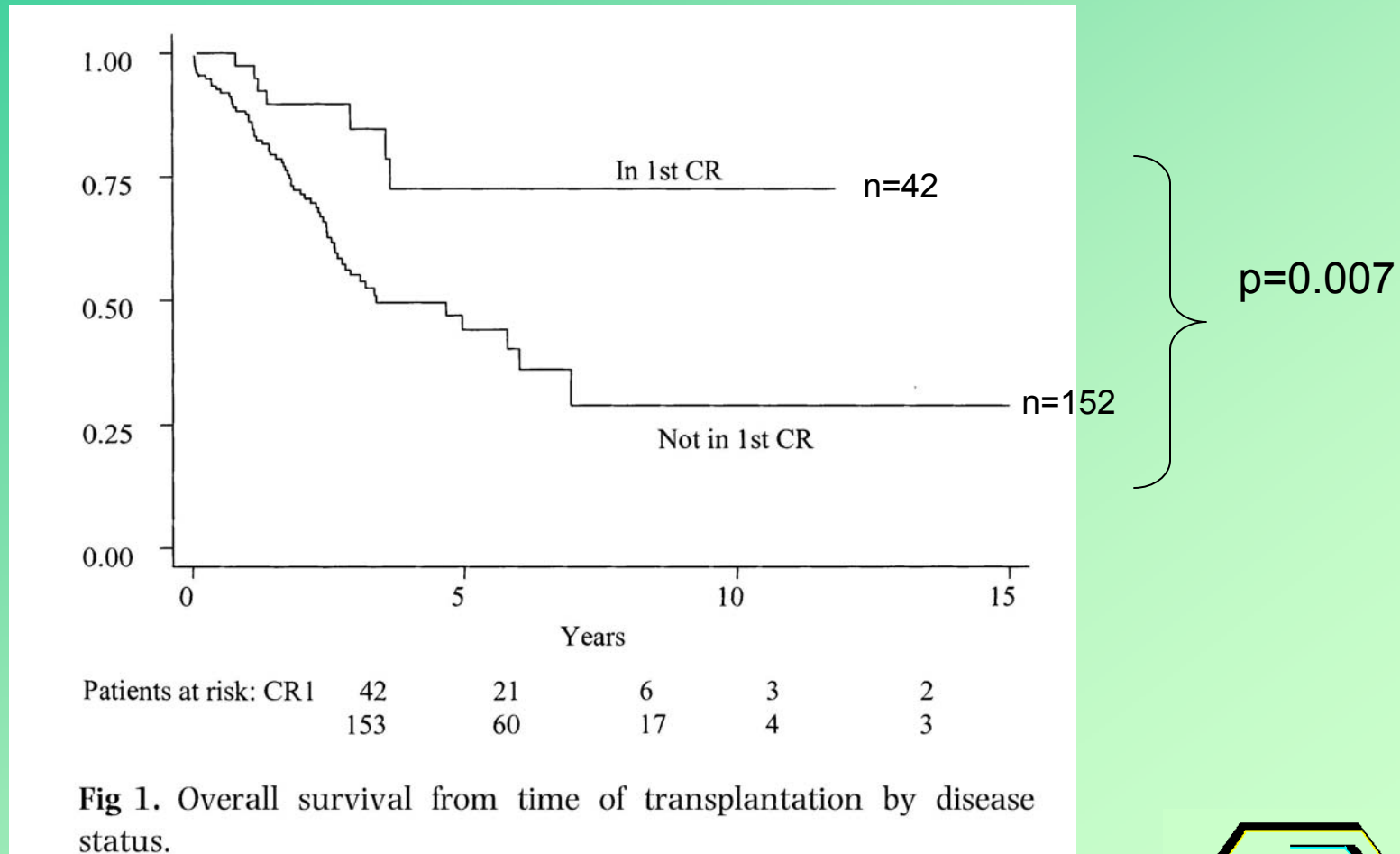


Decision to Transplant

- Natural history of disease optimally treated without transplant suggested five-year survival likelihood of 10-30%
- Transplant data reasonably robust and optimistic for patients in first remission (vs. transplant after first relapse)
- Age worrisome but he was physiologically youthful



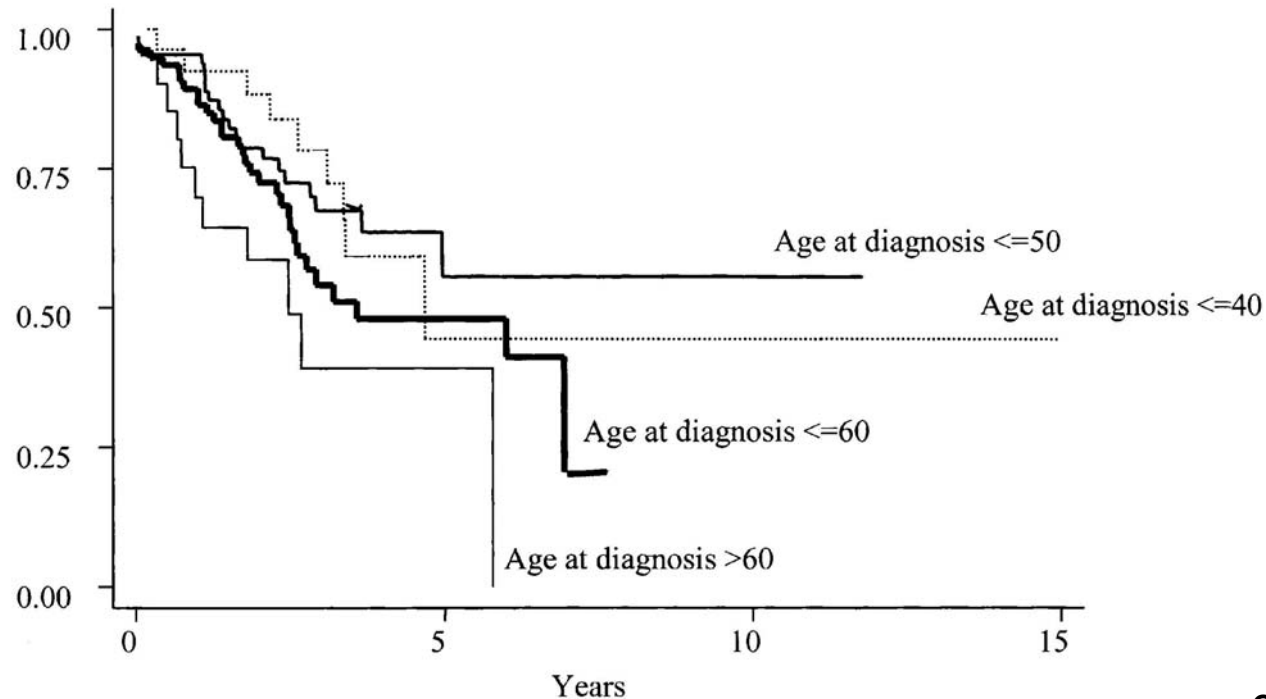
Long-Term Results from Autologous Hematopoietic Stem-Cell Transplant in MCL



From Vandenberghe *Br J Haematology* 120:793, 2003



Analysis by Age – Small Numbers but Sobering



Patients at risk:	≤ 40	28	16	3	3
	$>40 \ \& \ \leq 50$	66	32	8	3
	$>50 \ \& \ \leq 60$	79	29	11	2
	>60	21	6	3	

$p=0.041$ for
age $>$ vs. < 60

Fig 4. Overall survival and age (years) at diagnosis.



RW: Lesson in life and death

- Remarkable individual who showed courage and grace throughout his illness
- Continued to work on his engineering projects involving building machines working at the nano-particle level
- Was able to become a functioning member of the team through his extraordinary intellectual curiosity
 - Most of the time this is a speed bump for oncologists...not here
- Great personal loss for me, as he became a friend as well as patient

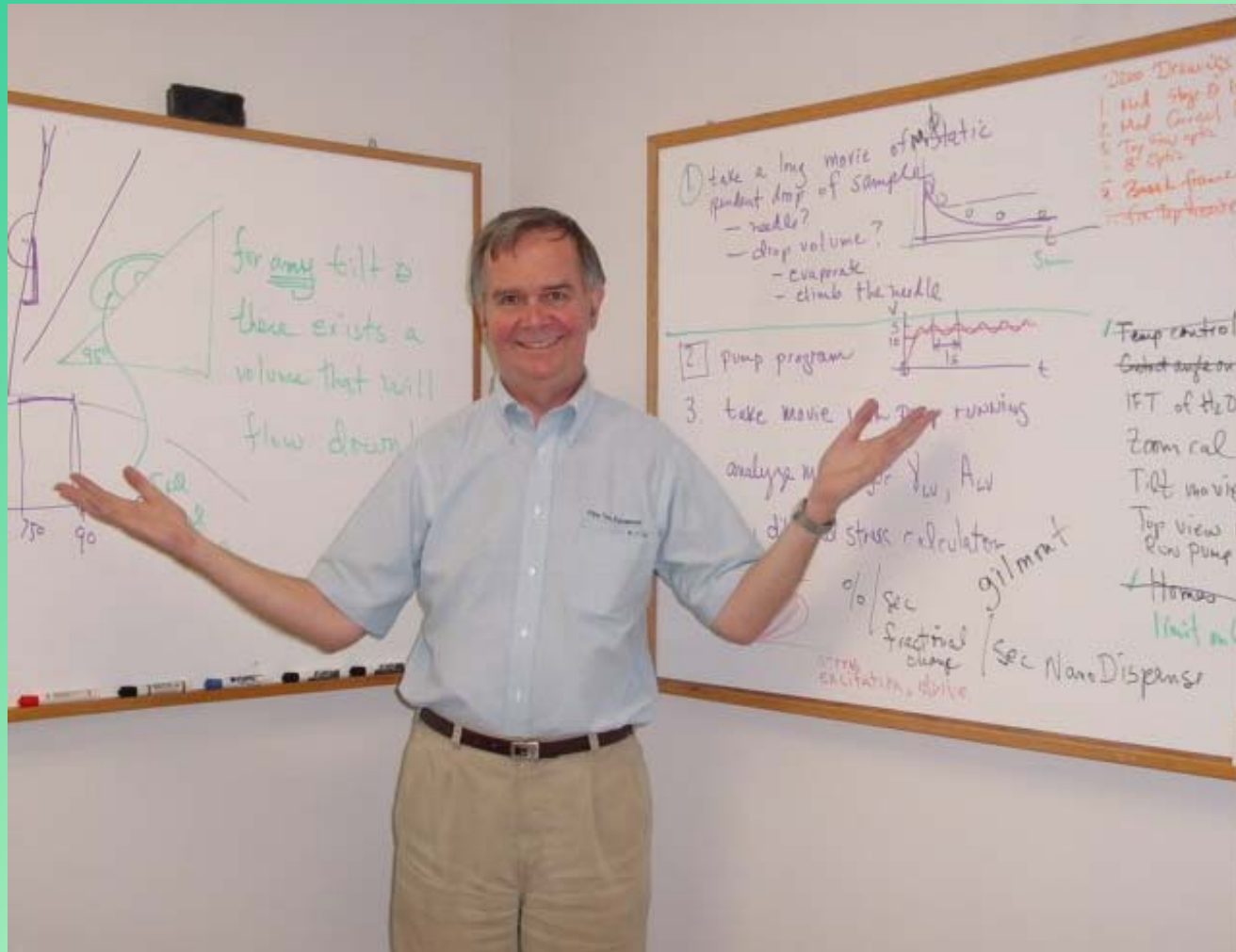


Lessons, continued

- Tumor burden at autopsy enormous
- Clinical condition belied extent of disease until the very end
- Speed of relapse and organ infiltration was very rapid – leaving his clinical team behind the curve in assessing and treating
- Unlikely to have achieved long-term survival regardless given resistance of his emerging cell line – despite being identical by flow cytometry to original cells



From First Ten Ångströms Website



At his Christmas party while in remission



For a copy of this talk....

- Visit us at the website....
- www.Starkoncology.com ...or at the office

