

# A Calv(el)cade of Infection

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PETER MACCALLUM CANCER CENTRE

# THE CASE: Mrs. CF

61 year old woman with 4 year Hx of:

- Multiple Myeloma
  - 1<sup>st</sup> Dx 2007
- Myeloma treatment:
  - Anthracycline-based induction
  - Repeated relapse and salvage therapies
    - Autologous transplant 2009
    - Alkylating agents in combination with dexamethasone and novel agents

# Myeloma treatment

- Dec 2007 to Dec 2010
  - adriamycin
  - depsipeptide and bortezomib (Velcade©)
  - cyclophosphamide, dexamethasone, lenalidomide (Revlimid©)
  - melphalan autologous stem cell transplant (2009)
  - cyclophosphamide, dexamethasone, lenalidomide

# Myeloma treatment

- Jan 2011 to Aug 2011
  - lenalidomide
  - cyclophosphamide, dexamethasone, lenalidomide
  - cyclophosphamide, dexamethasone, bortezomib
  - dexamethasone, bortezomib, thalidomide

# Myeloma progression

- Marked progression
  - Rising paraprotein levels
  - Multiple lytic lesions
  - Symptoms of hyperviscosity
  - End organ dysfunction
    - Renal impairment
    - Anaemia, neutropenia

# Infective complications

- April 2009
  - Culture negative febrile neutropenia
  - Septic shock requiring ICU admission
- September 2009
  - *Serratia marcescens* septicemia
  - Secondary to tunneled line (port) : removed
- September 2009
  - Primary Varicella Zoster
  - Treated with IV aciclovir
  - Remained on valaciclovir prophylaxis

# Infective complications

- April 2010
  - Campylobacter bacteraemia
  - Requiring admission to ICU
- Noted to have hypogammaglobulinaemia
  - IVIG replacement monthly
- Known to be VRE colonised

# Presenting episode

- Admitted electively on 17/8/11
- DTPACE
  - dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide and etoposide
- Prophylaxis :
  - Bactrim (ceased on admission)
  - Fluconazole 200mg/daily
  - Valaciclovir 500mg/daily
- Day 5 : Neutropenia  $< 0.1$
- Day 8 : Febrile neutropenia
  - Fevers, sweats, rigors
  - No localising symptoms
  - Treated with piperacillin-tazobactam 4.5g/TDS

# Progression

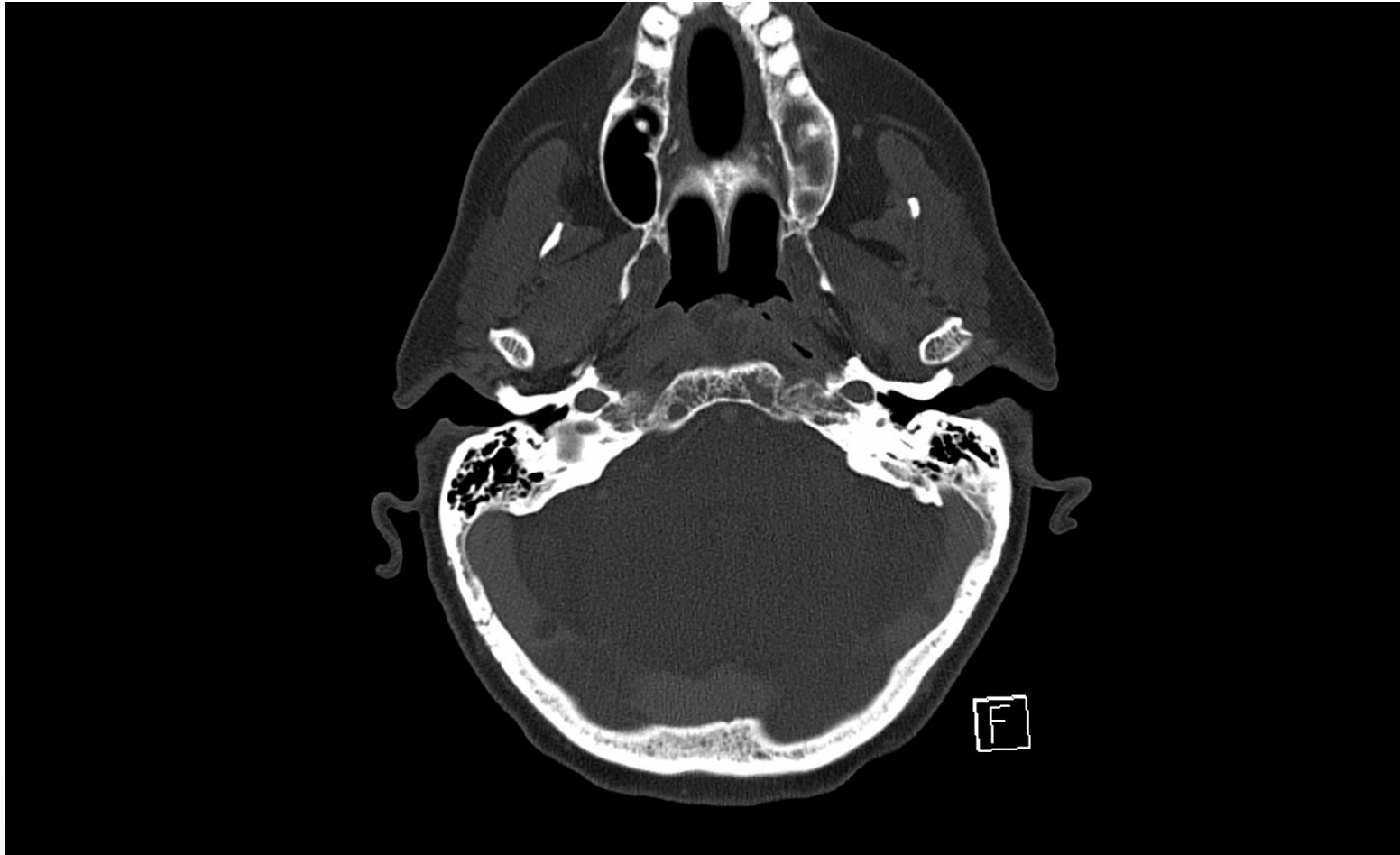
- Day 10 : Positive BC
  - GNB:
    - 6/6 bottles
    - Peripheral, both lumens of PICC
  - GPC:
    - 4/6 bottles
    - Both lumens of PICC
  - Teicoplanin added with loading
  - Septic screen results
    - CXR no consolidation
    - Urine no growth

# Progression

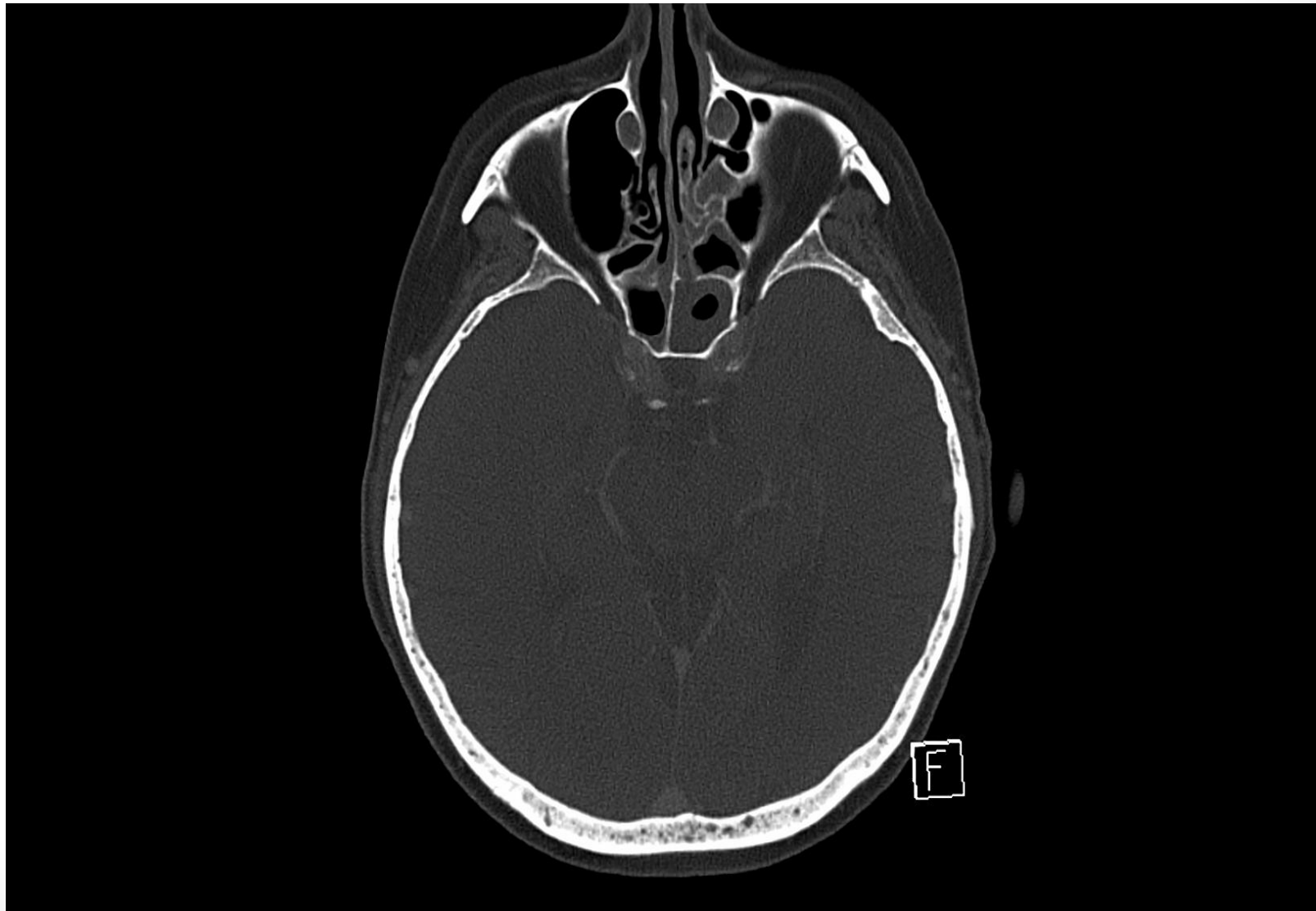
- Day 11 :
  - ID involvement
    - Enterococcus *faecium*
      - Vancomycin resistant
      - Teicoplanin sensitive MIC 1.0 microg/ml
    - Klebsiella *pneumoniae*
      - Resistant to amoxicillin
      - Sensitive to augmentin, gentamicin, pip-taz, ciprofloxacin
  - Symptoms
    - Frontal headache, postural
    - Non meningism
    - Sinus congestion
- PICC line removed

# Progression

- Day 13 : CT Brain and sinuses



# Progression

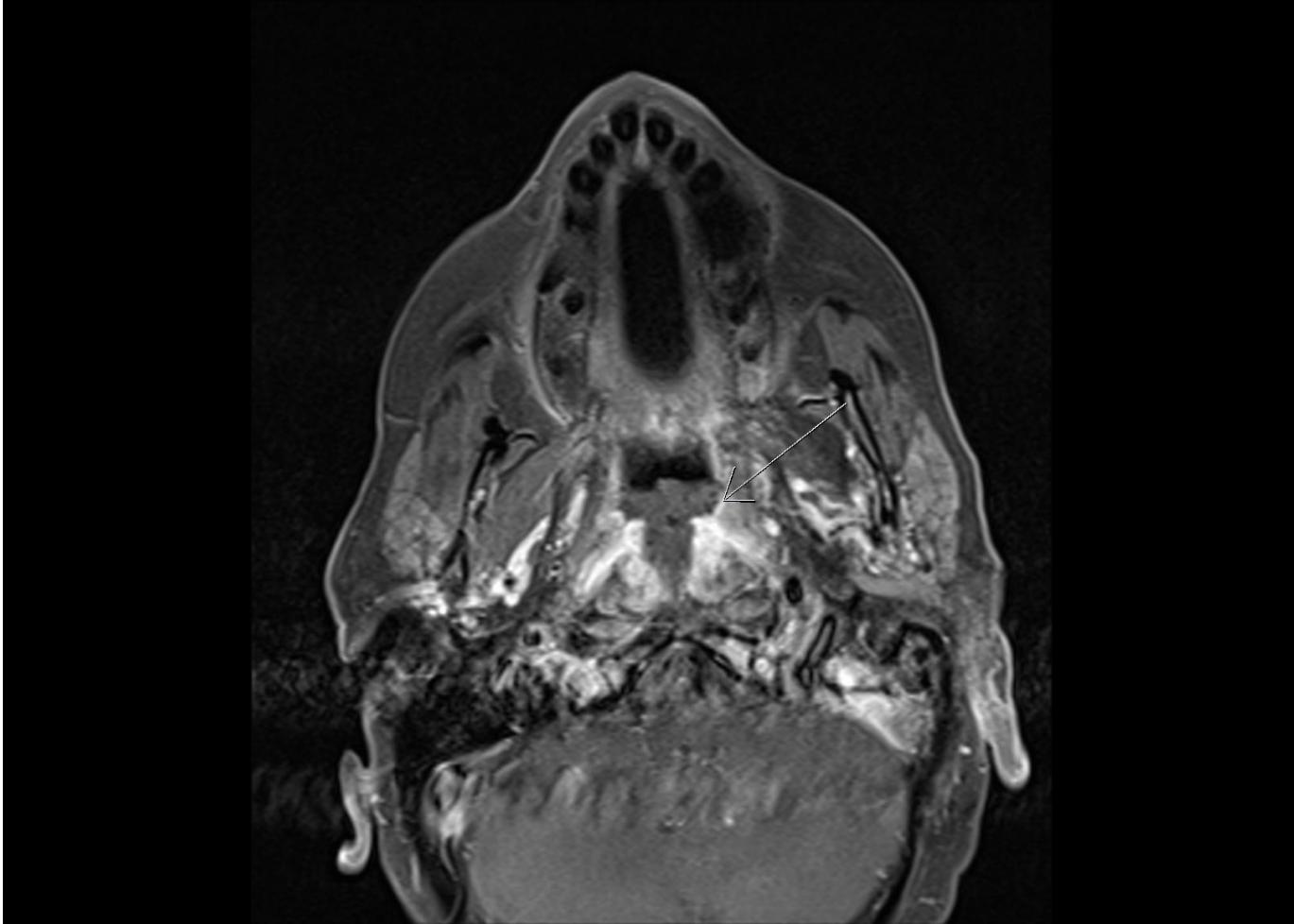


# Progression

- Day 13 : CT Brain and sinuses
- Report:
  - Opacification of left sphenoidal sinus with possible air-fluid level
  - Minimal thickening of mucosa elsewhere
  - Prominent soft tissue density at at adenoids
    - Possible retention cyst
    - Infection remains a possibility
- ENT review +/- biopsy suggested
  
- Day 14 : New neurology
  - “blurring of left sided vision”
  - Ongoing headache
  - Pip-taz changed to meropenem for CNS penetration

# Progression

- Day 14 : MRI Brain and neck



# Progression

- Day 14 : MRI Brain and neck
- Report:
  - Sphenoidal sinus mucosal thickening
  - No evidence of bone destruction
  - Hyperintensity at posterior margin of nasopharynx
    - Breaching mucosa with debris in posterior wall
    - T1 signal loss base of skull
- Antimicrobial changes:
  - Commenced on liposomal amphotericin (ambisome)
  - Teicoplanin changed to linezolid

# Progression

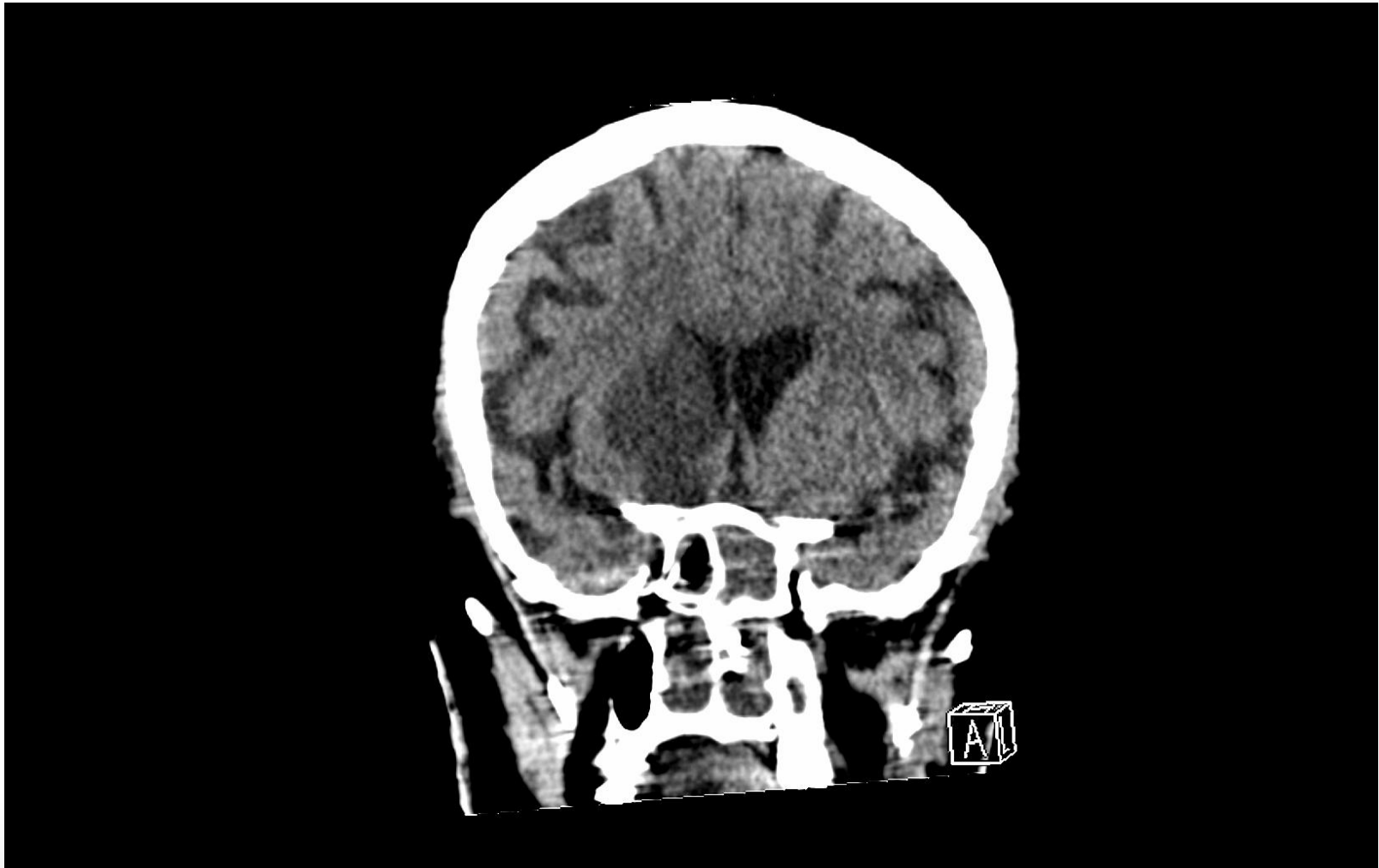
- Day 15 : New neurology
  - Sudden onset dense right sided hemiplegia
  - CT Brain : No obvious infarcts, haemorrhage
  - LP CSF : Protein 0.56, glucose 2.3 lymphocyte 0, poly 2  
No growth, Cryptococcal Ag neg
- Day 16 : Neurological decline
  - Aphasic
  - Decline in GCS requiring ICU admission and intubation
- Day 17 : Withdrawl of treatment
  - Sluggish, unequal pupils
  - Family meeting : Patient's previously expressed wishes
  - Positive BC !

# Progression

- Final CT Brain



# Progression

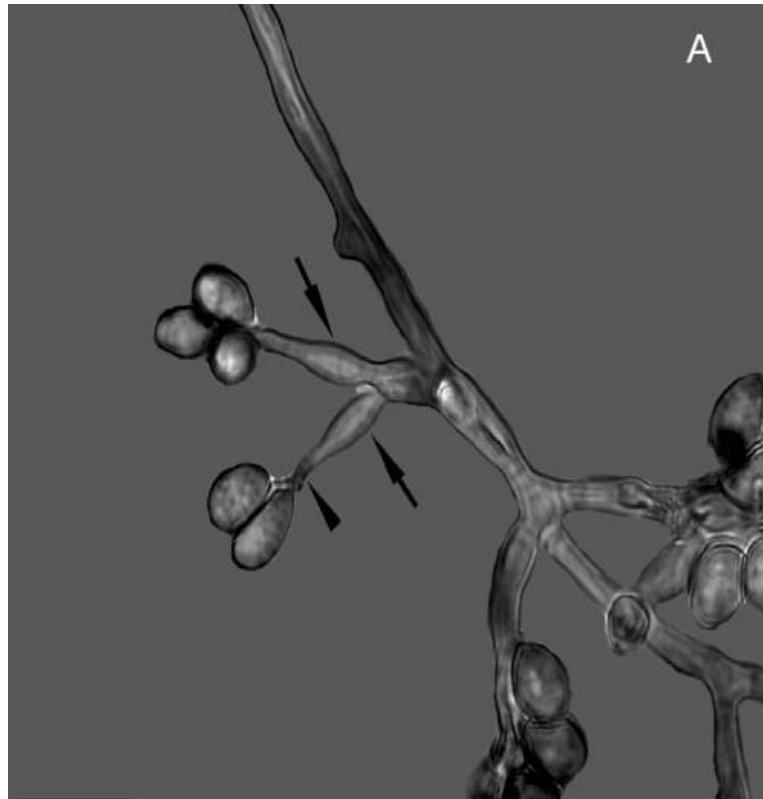


# Progression

- Causative organism?

# Progression

- Organism:



# Progression

- Day 17 :
  - Patient passed away following withdrawal of treatment
  - Positive Blood cultures (collected Day 14-16)
    - *Scedosporium prolificans*
    - 8/8 bottles
      - Lines and peripheral cultures

# Summary

- 61 yo woman with :
  - Polymicrobial bacteraemia (Klebsiella and VRE)
  - Rapid deterioration from disseminated *Scedosporium prolificans* from suspected nasopharyngeal tissue invasion
- in the setting of :
  - Neutropenia and
  - Cumulative immunosuppression from multiple treatment courses with conventional and immunomodulatory agents for myeloma

# Discussion

- Multiple myeloma & Infective risks
- Novel agents & Infective risks
- Multiply treated patients
  - Level of immunosuppression
  - Possible recommendations for prophylaxis

# Myeloma

Treatments have expanded over the last decade

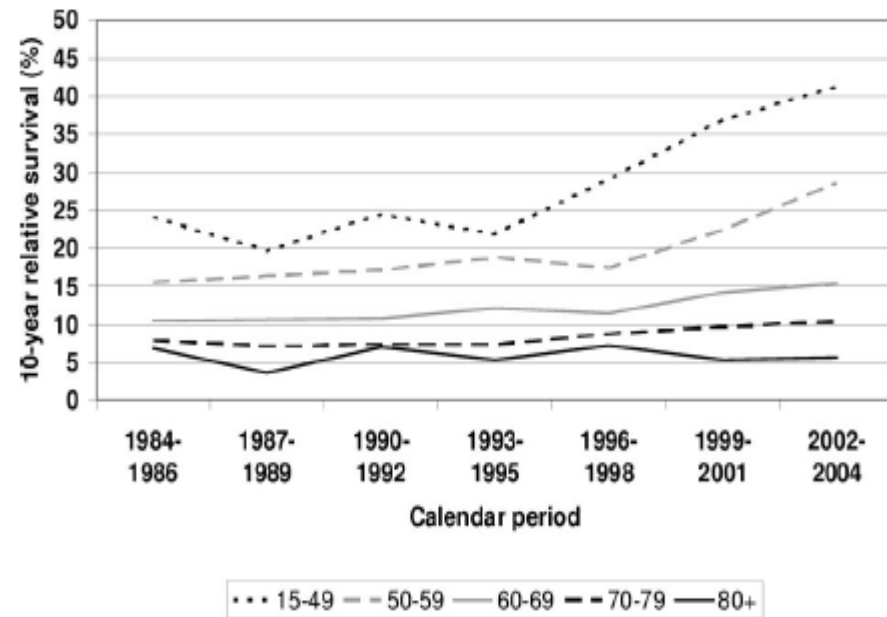
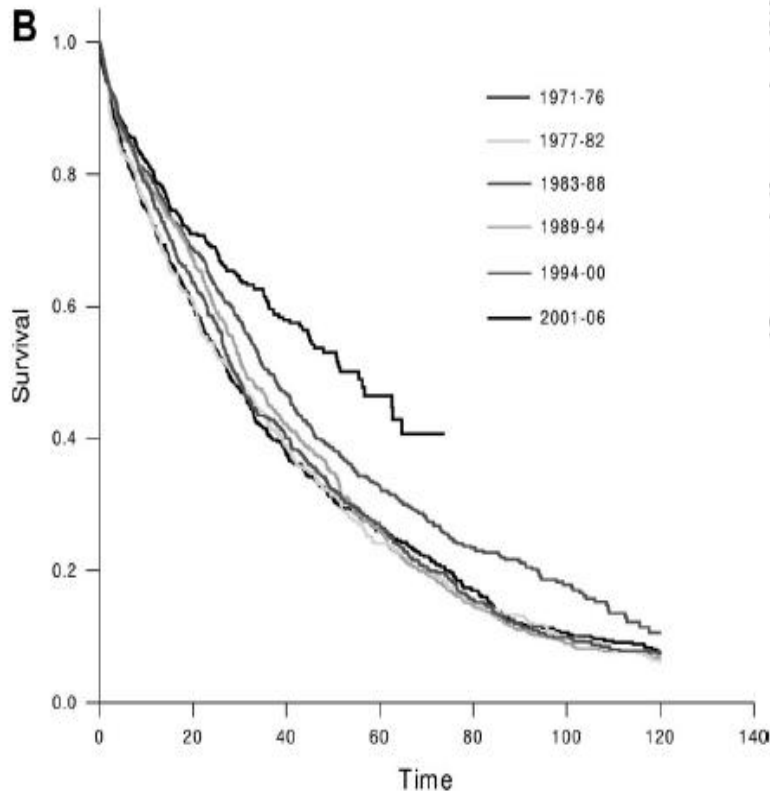
- Introduction of novel agents
- Increasing use of high dose therapy
- Increasing numbers of autologous transplants

Table 1. Major milestones in therapeutic options for myeloma

|      | Milestone                                | Notes   |
|------|--|---|
| 1962 | Melphalan-prednisone (MP) <sup>4</sup>   | Introduction of melphalan in the 1960s was associated with improved survival. <sup>4</sup> More intense chemotherapy regimens increased response rates, but with no improvement in survival compared to melphalan and prednisone. <sup>30</sup>   |
| 1996 | Autologous SCT <sup>6,7</sup>            | Several randomized trials demonstrated a survival advantage for this modality compared to conventional chemotherapy (CCT). <sup>5-7</sup> However, other trials either have failed to demonstrate an overall survival advantage or have demonstrated equivalent benefit from early or late ASCT. <sup>31-34</sup> |
| 1999 | Thalidomide (Thalomid) <sup>8,9</sup>    | Thalidomide has demonstrated improved response rates and progression-free survival rates compared to dexamethasone alone. When added to MP, it improves survival compared to MP alone.  |
| 2003 | Bortezomib (Velcade) <sup>12,35</sup>    | Bortezomib has improved survival compared to high-dose dexamethasone in patients with relapsed myeloma.   |
| 2003 | Tandem autologous SCT <sup>36</sup>      | Tandem SCT has improved survival compared with single transplantation, albeit in those failing to achieve a very good partial response to first transplantation.  |
| 2005 | Lenalidomide (Revlimid) <sup>10,26</sup> | Lenalidomide and dexamethasone have improved survival compared with dexamethasone in relapsed myeloma in phase III trials.  |

# Myeloma

- Increased overall survival
  - 50% increase over the last decade
  - < 50 age group



# Myeloma

- Increased survival with greater available effective treatment
  - Chronic condition
  - Multiple relapses with disease progression
  - Multiple “salvage” lines of treatment
  - Cumulative immunosuppression

# IFI risks

| Low                | Intermediate-low            | Intermediate -high                           | High                          |
|--------------------|-----------------------------|--|-------------------------------|
| Autologous<br>PBSC | Neut 0.1 to 0.5<br>< 3weeks | Neutro < 0.5 to ><br>0.1<br>> 3 to < 5 weeks | Neutro < 0.1<br>> 3 weeks     |
| Childhood ALL      | Older age                   | AML  | GVHD                          |
| Lymphoma           | Central venous<br>catheter  | TBI  | Neutro < 0.5<br>> 5weeks      |
|                    |                             | Allo matched<br>sibling donor                | High dose ara-C               |
|                    |                             |  | CS >2mg/kg > 2w               |
|                    |                             |  | CS >1 mg/kg and<br>neutro < 1 |

# New IFI risks

- Immunomodulatory, immunodepleting agents
  - Increasingly used, associated with increased IFI risk
  - Fludarabine
    - Purine analog
  - Rituximab (Mabthera©)
    - Anti CD20 monoclonal Ab
  - Alemtuzumab (Campath©)
    - Anti CD52 monoclonal Ab
- Non traditional at-risk groups
  - ALL, high grade lymphomas with vincristine containing regimens
  - CLL : multiply treated
  - ?Multiple myeloma

# Myeloma: Infection risks

- Infection contributes significantly to early deaths
  - Bacterial causes > 50%
  - Pneumonia & Bacteraemia
  - Influenza
- Related to disease & its complications
  - Age and related co-morbidities
  - Hypogammaglobulinaemia (B cell dysfunction)
  - Disruption of T cell diversity
  - Dysfunction of NK cells
  - Neutropenia
  - Renal failure

Tramontana A et al, Emerg Infec Dis 2010  
Augustson BM et al, J Clin Onc 2005  
Nucci et. al, Clin Infec Dis 2009

# Myeloma: Infection risks

- Related to treatment
  - Conventional treatment
    - Melphalan based regimens
  - Novel agents
    - Thalidomide, Lenalidomide (Revlimid©), bortezomib (Velcade©)
  - Corticosteroids
    - “Backbone” of most regimens
    - Dexamethasone doses equivalent to at least 20mg prednisolone daily
    - Significant cumulative exposure

# Myeloma: Novel agents

- Thalidomide
- Lenalidomide
- Bortezomib
- Commonly used first line singly or in combination with
  - High dose Dexamethasone

# Novel agents : Thalidomide

- Anti-inflammatory, anti-proliferative, anti-angiogenic, pro-apoptotic
- Not significantly myelotoxic
  - Low rates of neutropenia (5-13%)
- Immunomodulatory effects
  - Inhibits production of TNF- $\alpha$ , IL 6,12 and GM-CSF
  - Induces IL2 mediated T cell proliferation and IFN  $\gamma$  production
  - Decreases cell surface adhesion molecules
  - Augments NK cell dependent cytotoxicity

# Novel agents : Thalidomide

- Thalidomide containing regimens
  - Infection rates up to 20% (Grade 3/4)
    - 80% 1<sup>st</sup> induction course
    - Pneumonia predominant clinical infection
    - Gram negative bacteraemia
    - Fever without focus
  - In comparison to conventional regimens:
    - Significantly higher risk of infection
  - In comparison to dexamethasone alone:
    - No significant difference in infection risk

# Novel agents : Lenalidomide

- Analogue of thalidomide
- Similar range of immunomodulatory effects
  - More potent suppression
  - High rates of neutropenia
    - Up to 60%
- Lenalidomide containing regimens vs. conventional treatment
  - Similar rates of infection
- Lenalidomide-dexamethasone regimens
  - Infective risk increases in combination with dexamethasone
  - Higher rates of infection (22% vs 12% dexamethasone alone)

Kristinsson SY, Cancer J, 2010

Rao KV. Am J Health Syst Pharm. 2007

Nucci et. al. Clin Infect Dis. 2009

# Novel agents : Bortezomib

- Proteasome inhibitor
  - Induces cell apoptosis
  - Alters BM microenvironment
  - Reduced NF- $\kappa$ B activity
- Immunosuppressive effects
  - Significant reduction in CD4 cell counts
    - Median decline to 270/ $\mu$ L
    - Nadir at 6 weeks
    - 75% have CD4 < 400 during treatment
    - 34% have CD4 < 200 during treatment
    - 68% recovery to pre treatment levels

# Novel agents : Bortezomib

- Infective risks
  - No apparent increase in overall infective risk
    - Early days
  - Increased rates of VZV compared to conventional
    - 15% 1<sup>st</sup> line to 60% pre-treated
  - Aciclovir prophylaxis
    - reduces rates to baseline rate (5%)
  - CMV reactivation
    - Recent cases at local centres
      - CMV retinitis, CMV colitis

# Myeloma: Multiply treated

- Increasing patient population group
- Cumulative immunosuppression
  - Multiple lines of treatment:
    - Each regimen with its own infective risk profile
    - Lower CD4 levels with increasing cycles
- Measurement of level of immunosuppression
  - Not routinely performed
    - CD4 levels
    - Immunoglobulin levels
    - Immunospot Assays (Elispot)
  - Serve to guide decisions about infective management

# Recommendations: Pre-therapy

- Pre therapy screening
  - Hepatitis B
  - (HSV/EBV/CMV with transplant candidates)
  - TB (in presence of risk factors)
- Up to date vaccinations
  - Pneumococcal vaccinations
  - Influenza vaccinations

# Recommendations: Prophylaxis

- Dexamethasone containing regimens
  - PJP prophylaxis
  - Hepatitis B treatment/prophylaxis
  - TB prophylaxis (if appropriate)
- Bortezomib containing regimens
  - VZV prophylaxis
  - Monitor for CMV disease
- Persisting or expected prolonged neutropenia
  - Consideration of anti-fungal prophylaxis
  - Data on anti-fungal prophylaxis for non-AML patients limited

# Recommendations : ongoing

- Replacement of immunoglobulins
  - Infective risk increased with hypogammaglobulinaemia
  - Reduced risk with replacement
    - Some evidence of limited benefit pre-transplant
    - Subset of patients with severe recurrent bacterial infections

# Recommendations: Multiply treated

- Tailored to specific patients
  - Guided by previous infective complications
  - Level of cumulative immunosuppression
    - Guided by traditional measurements
    - Newer measures needed?
- Combination of some or all of the previously mentioned recommendations
  - Current supportive care guidelines are limited

# Summary

- Case of rapidly disseminated fungal infection in a patient profoundly immunosuppressed from multiple lines of therapy for myeloma
- Novel anti myeloma agents with unique infective complications
- Increasing population of patients with cumulative immunosuppression
- Potential role for routine monitoring of immune function
  - Quantifying immunosuppression
  - Guide management and prophylaxis
- Suggestions for management of multiply treated patients
  - Limited data available

# The End

- Questions? Comments?