Mission Impossible with Anti-Vel

BBTS September 2014

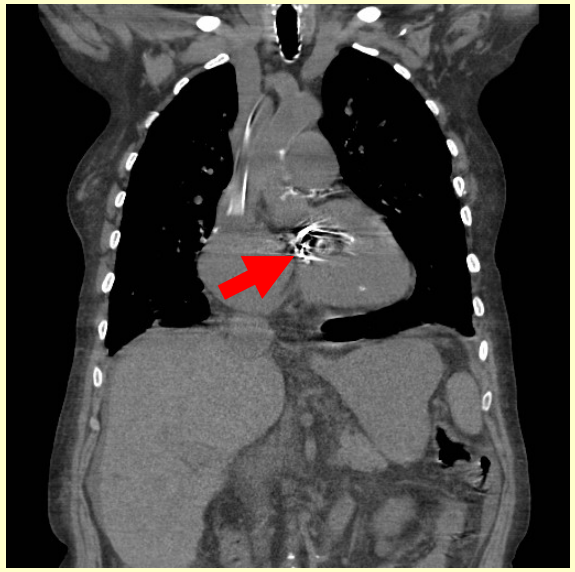
Stephanie Stone, Sheffield Teaching Hospitals
Helen Kilgallon, NHSBT Sheffield

74 yr old female

Presented to ENT May 2013:

4/52 bilateral nasal obstruction and intermittent epistaxis

No B symptoms

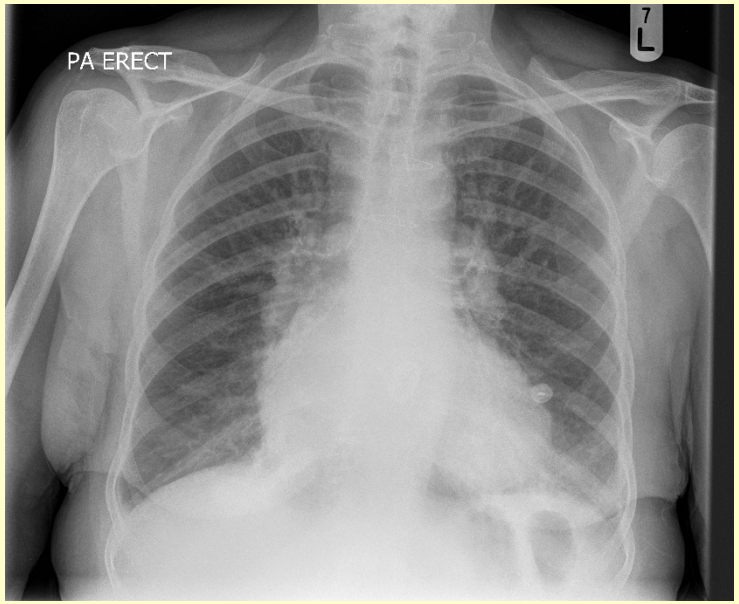


Past medical history:

- Metallic mitral valve replacement 1974: Warfarin INR 3-4
- Dilated left atrium, AF, Pulmonary HTN
- Angina, COPD
- Type II DM, CKD stage 4, Gout, Bullous pemphygoid

Social history

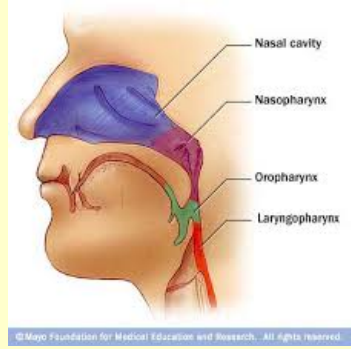
- Retired, lives alone
- 4 daughters – first in 1957
- Ex smoker
- No regular ETOH
- Exercise tolerance 25-40 yards
- ECOG performance status 2
- Independent of activities of daily living



Drug history

- No known drug allergies – mild allergic reaction to blood component 2012
- Warfarin
- Digoxin 125mcg od
- Furosemide 40mg bd
- Pravastatin 40mg on
- Candesartan 8mg od
- Linagliptin 5mg od
- Quinine 300mg od
- Betahistine 8mg tds

Examination and investigations



Fibre optic examination: large post nasal mass – Fine needle aspiration taken

2cm cervical LN. No other palpable LN/hepatosplenomegaly/masses

Hb 97 Mcv 92 Platelets 287 Wbc 6.9 Lymph 0.6 Reticulocytes 248

B12 394 Folate 8.0 Ferritin 252 Bil 10 Alt 40 Alb 44 LDH 708

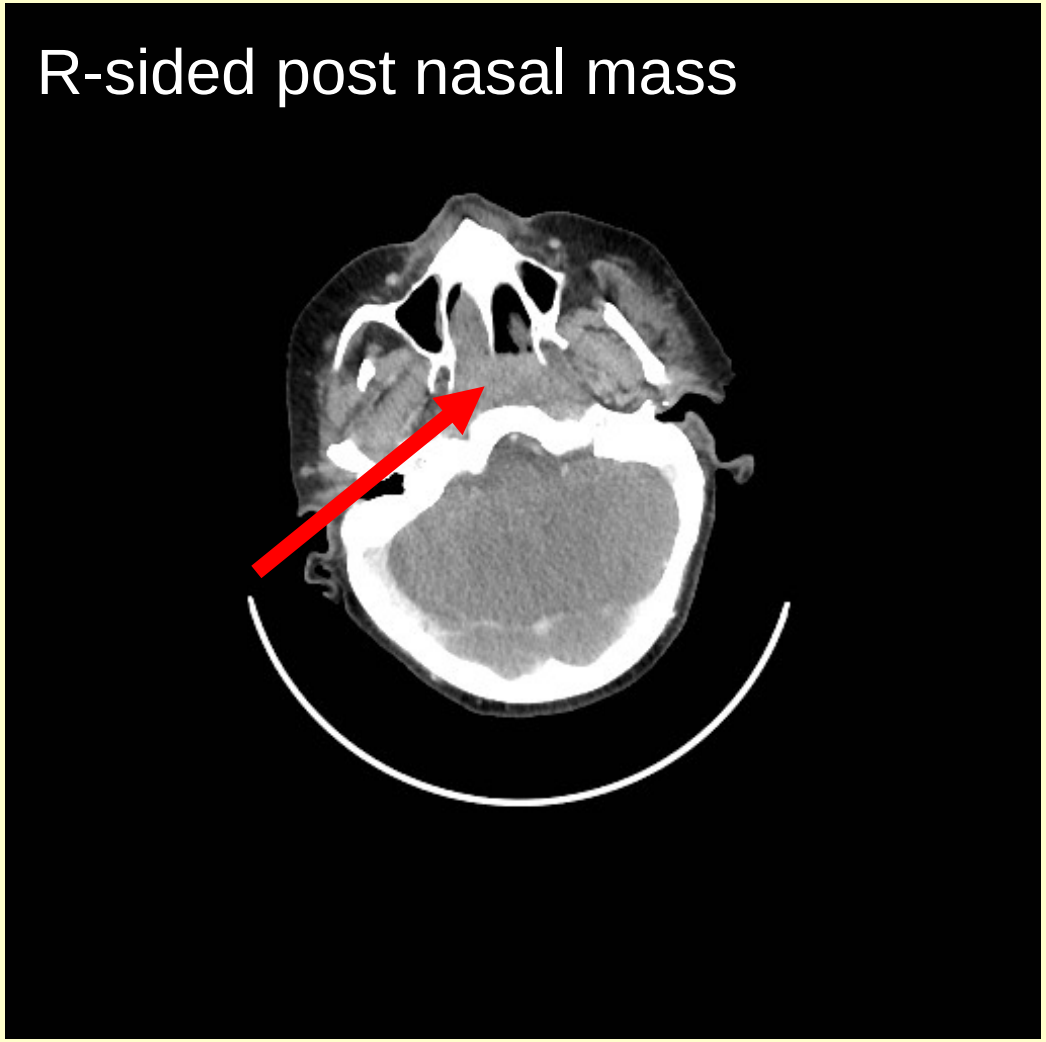
DAT –ve Haptoglobin normal Immunoglobulins normal

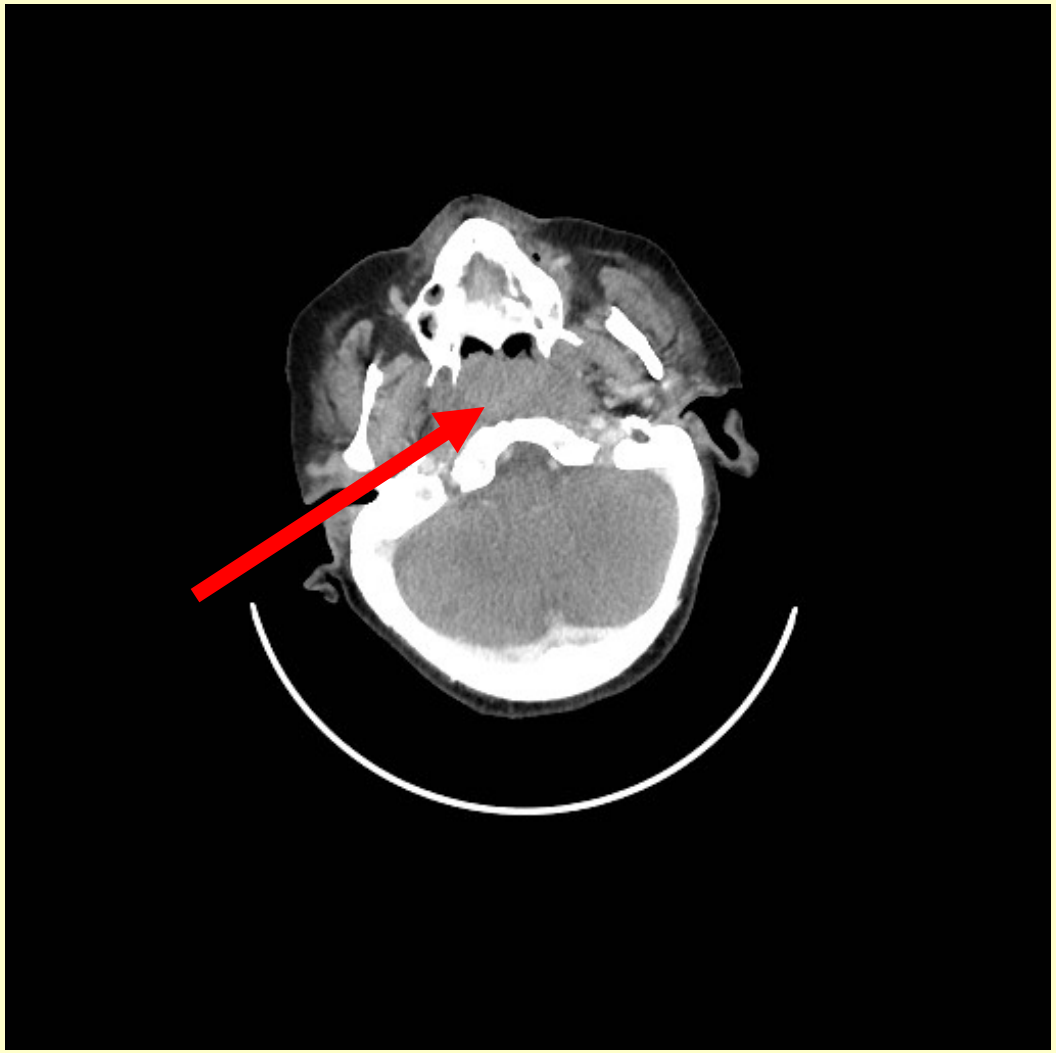
HIV/Hep B/C serology normal

Bone marrow: normal

Echo: good LV function, dilated LA, moderate TR, increased PA pressure

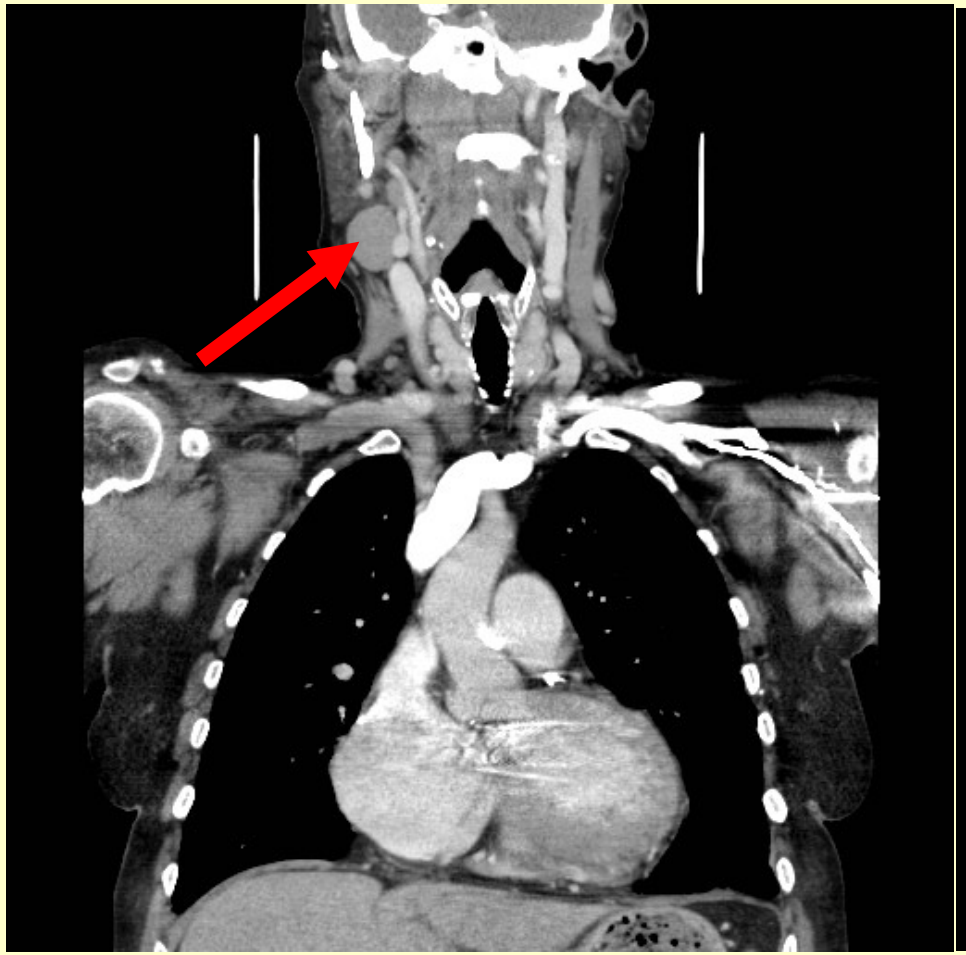
CT neck, chest, abdomen and pelvis

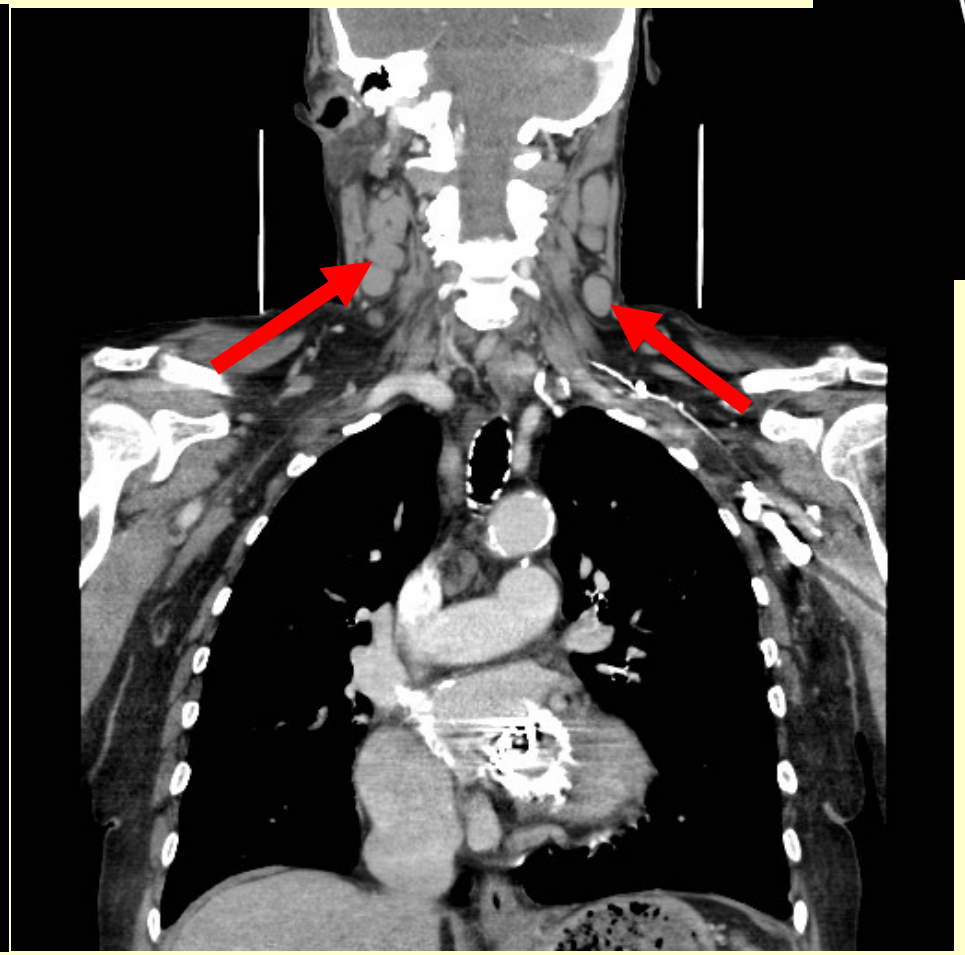


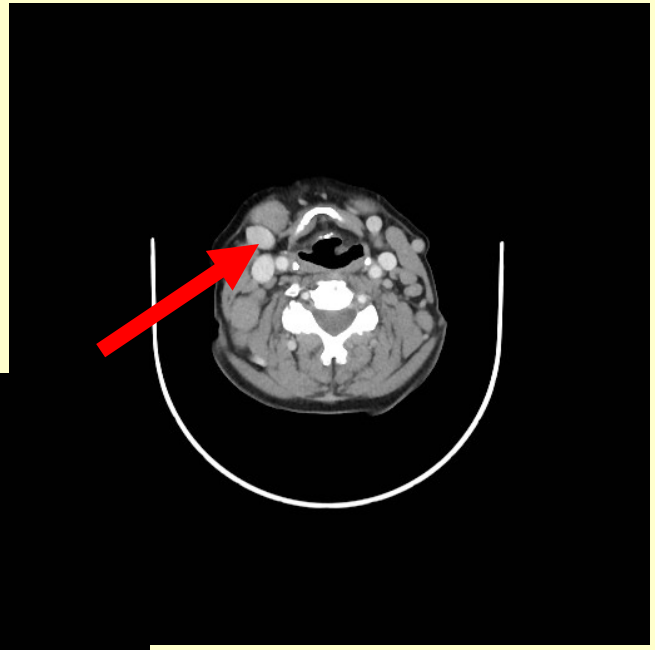


CT chest, abdomen and pelvis

Multiple cervical and mediastinal lymph nodes

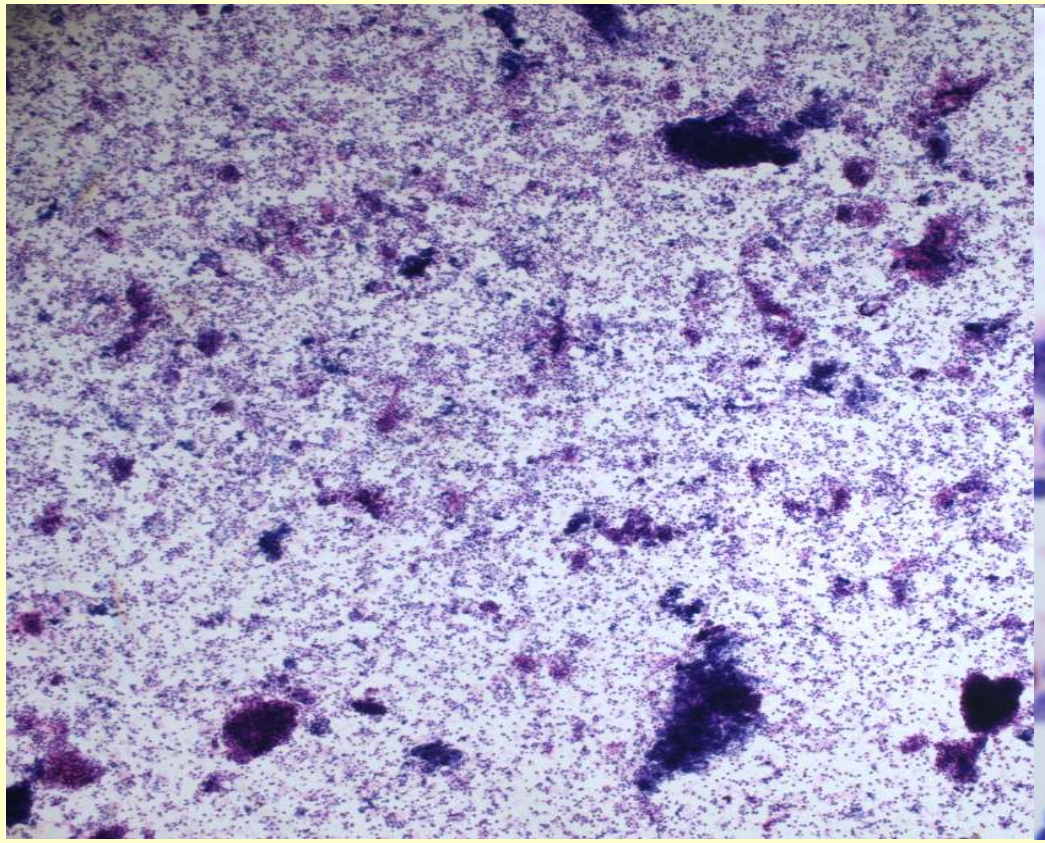




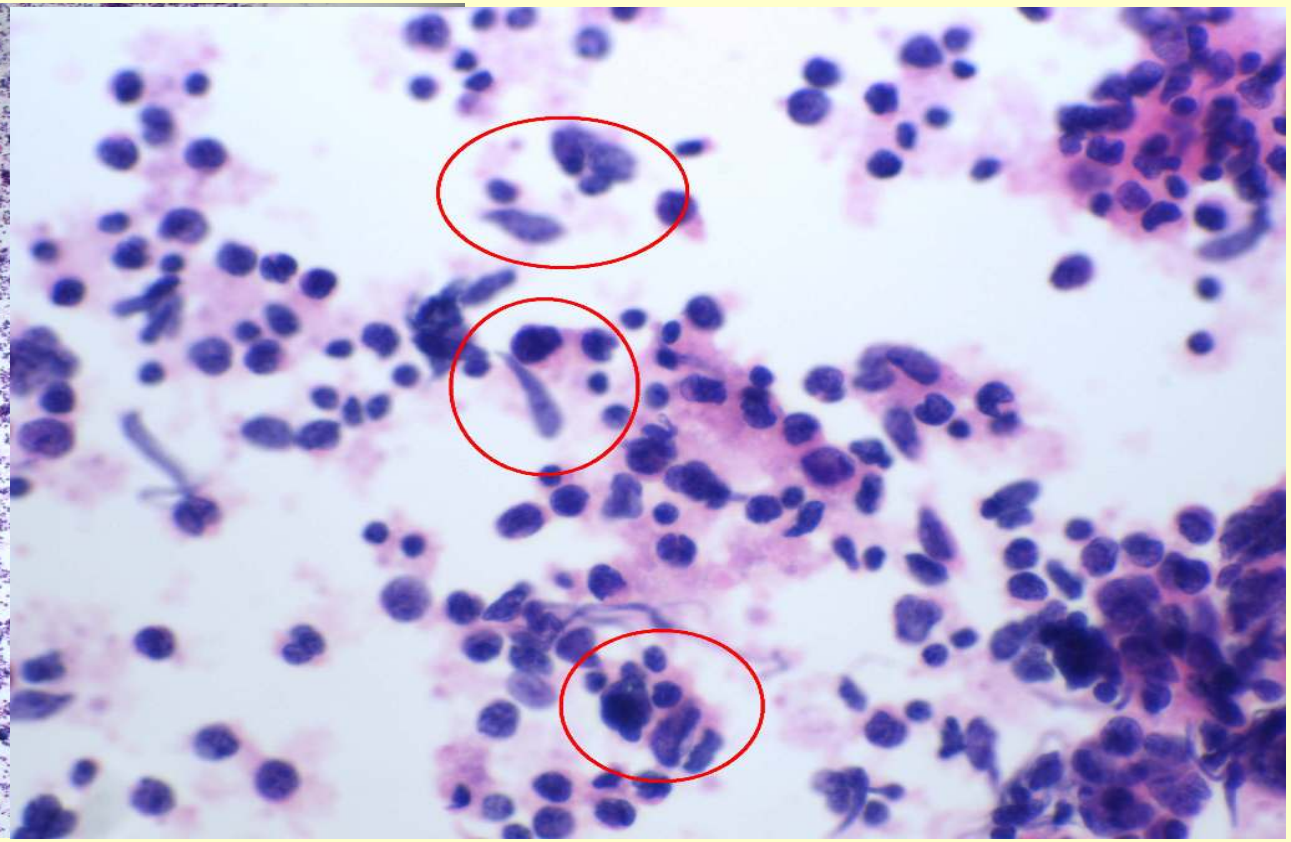


Fine needle aspiration

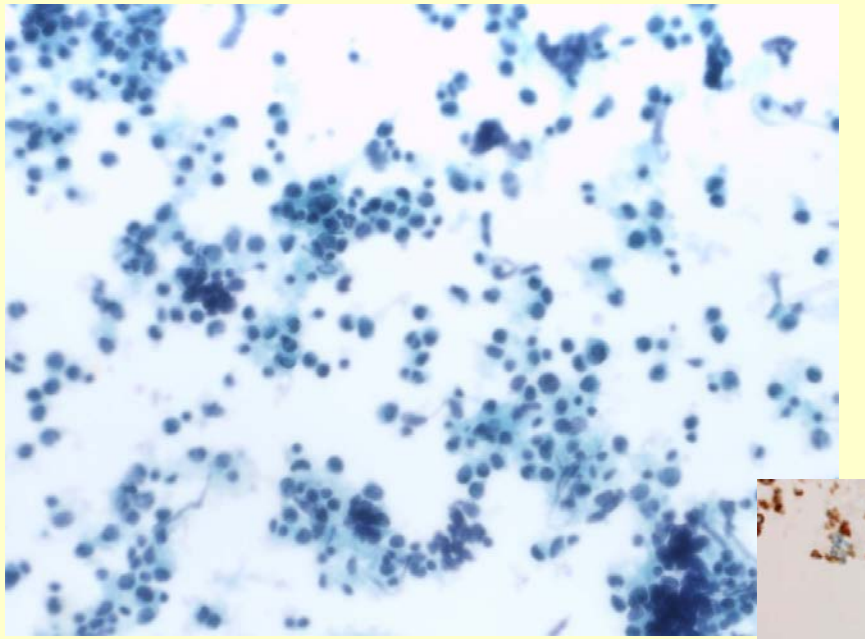
High grade cell Non Hodgkins Lymphoma: CD 45 + CD 20 +



H +E low power



H + E high power



Pap stain

CD 20

Leucocyte common antigen (CD 45)

Diagnosis and treatment

Stage 2EA high grade B cell NHL

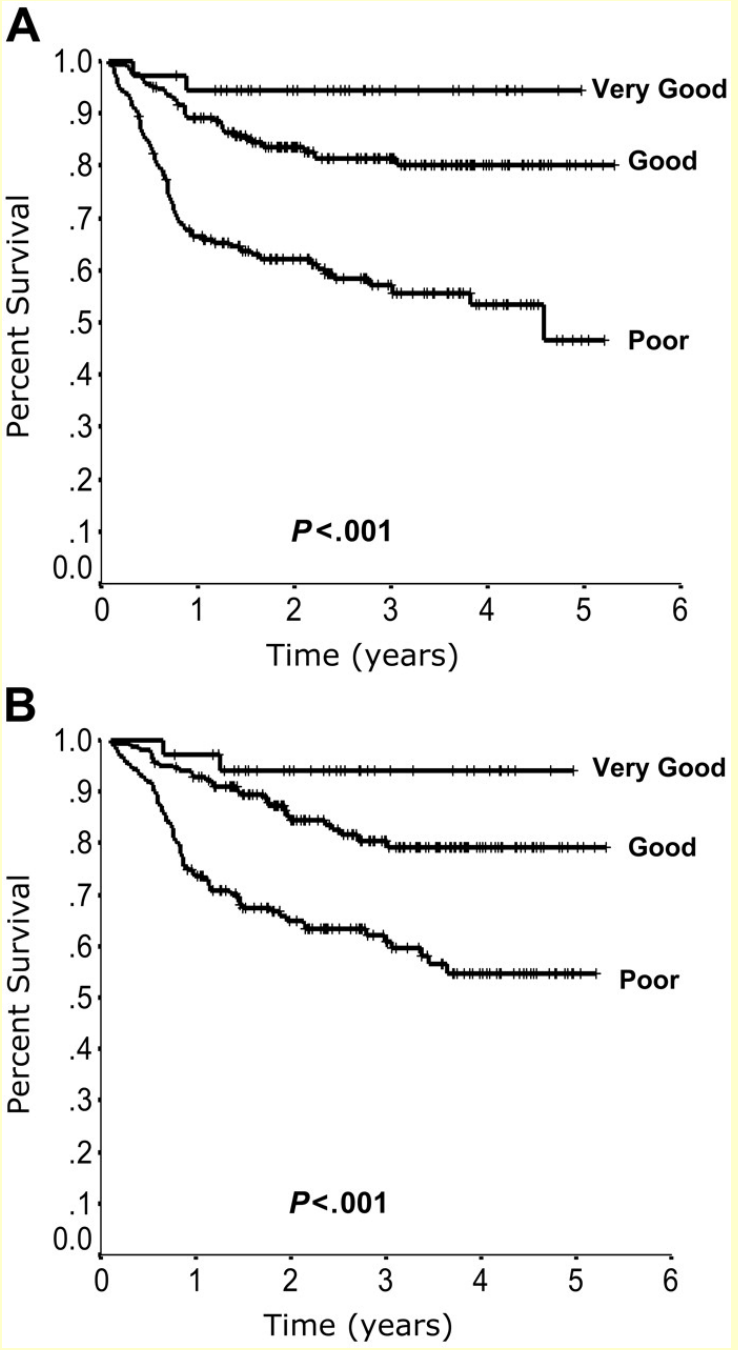
- Revised International Prognostic Index score: good

Further characterisation not possible without rpt Bx

- MDT – advised to treat clinically for aggressive NHL
  - Technically difficult biopsy
- Not for prophylactic intrathecal MTX
- No time for pre-treatment PET-CT

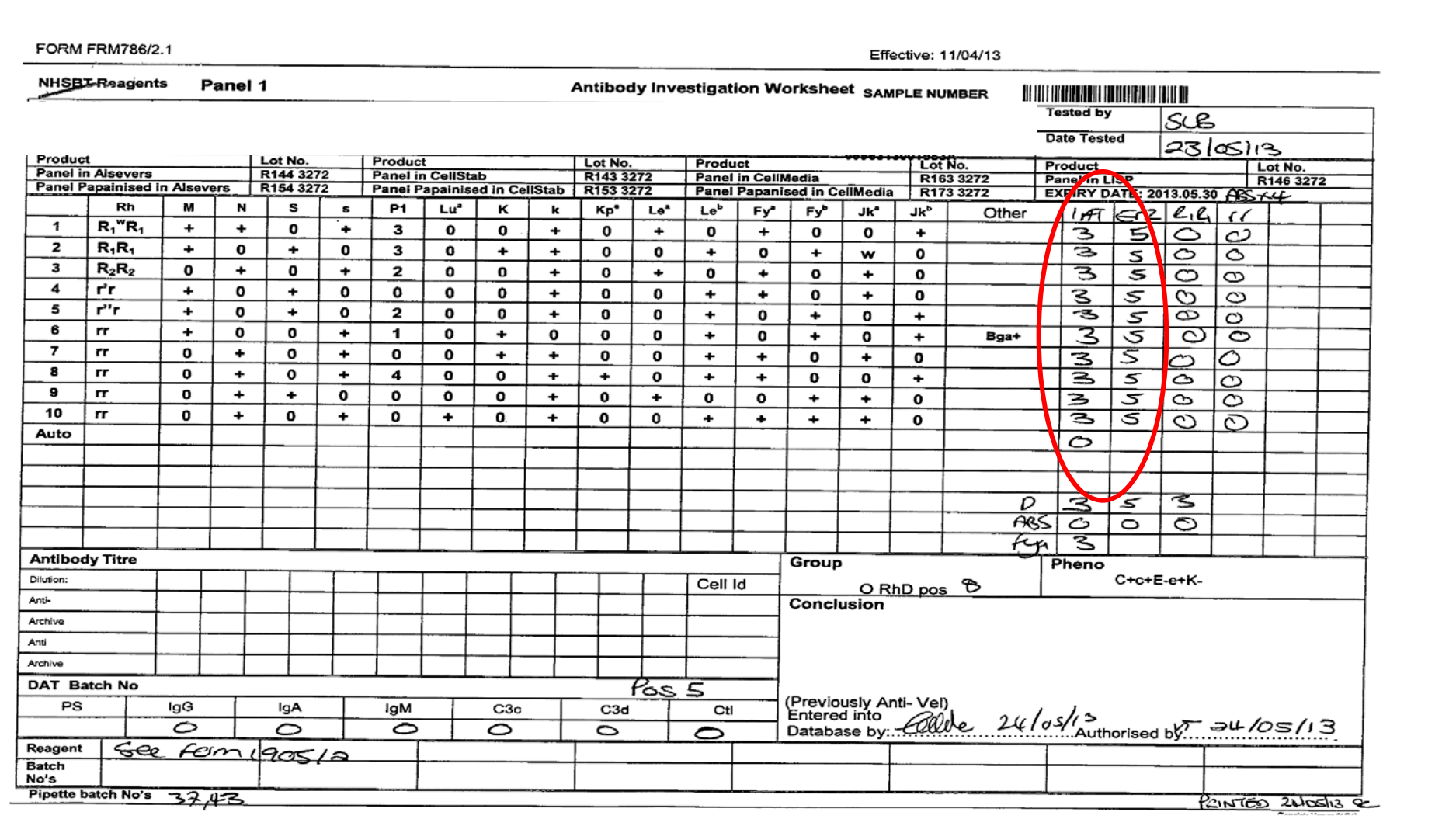
Treatment: R-CHOP chemotherapy –

- Rituximab, Cyclophosphomide, Doxorubicin,
- Vincristine, Prednisolone



Sehn et al 2007 [6]

All fairly straight forward so far…..except



FORM FRM786/2.1 Effective: 11/04/13

NHSBT Reagents **Panel 1** **Antibody Investigation Worksheet** SAMPLE NUMBER

Tested by: SLB
Date Tested: 23/05/13

Product	Lot No.	Product	Lot No.	Product	Lot No.	Product	Lot No.
Panel in Alsevers	R144 3272	Panel in CellStab	R143 3272	Panel in CellMedia	R163 3272	Panel in LISP	R146 3272
Panel Papainised in Alsevers	R154 3272	Panel Papainised in CellStab	R153 3272	Panel Papanised in CellMedia	R173 3272	EXPIRY DATE: 2013.05.30 ABS+4	

	Rh	M	N	S	s	P1	Lu^a	K	k	Kp^a	Le^a	Le^b	Fy^a	Fy^b	Jk^a	Jk^b	Other	IAT	E2	e.h	rr		
1	$R_1^wR_1$	+	+	0	+	3	0	0	+	0	+	0	+	0	0	+		3	5	0	0		
2	R_1R_1	+	0	+	0	3	0	+	+	0	0	+	0	+	w	0		3	5	0	0		
3	R_2R_2	0	+	0	+	2	0	0	+	0	+	0	+	0	+	0		3	5	0	0		
4	r'r	+	0	+	0	0	0	0	+	0	0	+	+	0	+	0		3	5	0	0		
5	r''r	+	0	+	0	2	0	0	+	0	0	+	0	+	0	+		3	5	0	0		
6	rr	+	0	0	+	1	0	+	0	0	0	+	0	+	0	+	Bga+	3	5	0	0		
7	rr	0	+	0	+	0	0	+	+	0	0	+	+	0	+	0		3	5	0	0		
8	rr	0	+	0	+	4	0	0	+	+	0	+	+	0	0	+		3	5	0	0		
9	rr	0	+	+	0	0	0	0	+	0	+	0	0	+	+	0		3	5	0	0		
10	rr	0	+	0	+	0	+	0	+	0	0	+	+	+	+	0		3	5	0	0		
Auto																		0					
																	D	3	5	3			
																	ABS	0	0	0			
																	Fya	3					

Antibody Titre

Dilution:													Cell Id
Anti-													
Archive													
Anti													
Archive													

Group O RhD pos

Pheno C+c+E-e+K-

Conclusion

DAT Batch No Pos 5

PS	IgG	IgA	IgM	C3c	C3d	Ctl
	0	0	0	0	0	0

(Previously Anti- Vel)
Entered into Database by: [illegible] 24/05/13 Authorised by: [illegible] 24/05/13

Reagent	See form 1905/2						
Batch No's							

Pipette batch No's 3743

PRINTED 24/05/13 [illegible]

Red cell antigen testing

Blood group: O Rh D +

Rh phenotype: D+ C+ c+ E- e+ K-

Pan-reactive antibody, enhanced by enzyme

DAT –ve

? Antibody to common antigen

Vel –ve red cell panel

Number	ABO Group / Phenotype	Rarity	Additional Phenotype										
			M	N	S	s	Jk(a)	Jk(b)	Fy(a)	Fy(b)	P1	Le(a)	Le(b)
8714	O R1R2 (K-)	Vel-	+	-	+	+	+	-	-	+	+	+	-
8722	O R1R2	Vel-			N/A (Original Record Missing)								
8735	O R1r (K-)	Vel-	+	-	+	-	+	-	+	+	+	-	+
8739	O R1r (K-)	Vel-	+	+	+	-	+	-	+	+	+	+	-
8752	O R1r (K-)	Vel-	+	+	+	-	+	-	+	+	+	+	-
8758	O R1R2 (K-)	Vel-	+	-	-	+	+	+	+	+	NT	+	-
8761	O R1r (K-)	Vel-	+	+	+	-	+	-	-	+	+	+	-
8771	O R1r (K-)	Vel-	+	-	+	-	+	-	+	+	+	-	+
8772	O R1r (K-)	Vel-	+	+	-	+	+	-	-	+	+	+	-
8778	O R1r (K-)	Vel-	+	+	+	+	+	+	-	+	+	+	-
8780	O R1r (K-)	Vel-	+	-	+	+	+	-	+	-	+	+	-
8803	O R2r (Kk)	Vel-	+	+	+	-	+	+	-	+	+	-	+
8832	O R1r (K-)	Vel-	+	-	-	+	+	+	+	+	-	-	+
8833	O R1r (K-)	Vel-	+	-	+	-	+	+	+	-	+	-	+
8852	O R1r (Kk)	Vel-	+	-	-	+	+	+	+	-	+	-	+

Product	Lot No.	Product	Lot No.	Product	Lot No.
ID panel in Alsevers	R144 3266	ID panel Papainised in Alsevers	R154 3266	ID Panel in LISP	R146 3266
ID panel in CellStab	R143 3266	ID panel Papainised in CellStab	R153 3266	EXPIRY DATE : 2013.03.07	

	Rh	M	N	S	s	P1	Lu^a	K	k	Kp^a	Le^a	Le^b	Fy^a	Fy^b	Jk^a	Jk^b	Other	IAT		LISS		
1	$R_1^wR_1$	+	0	0	+	1	0	0	+	0	0	+	+	0	+	0		3	3	Wk		0
2	R_1R_1	+	0	+	0	2	0	+	+	0	+	0	0	+	0	+		3	3	2		0
3	R_2R_2	0	+	0	+	4	0	0	+	0	0	+	+	0	0	+		3	3	2		0
4	r'r	0	+	0	+	0	0	0	+	0	0	+	0	+	0	+		0	0	0		0
5	r''r	+	0	+	0	1	0	0	+	0	+	0	0	+	+	0		3	3	3		0
6	rr	+	+	0	+	1	0	+	0	0	0	+	0	+	+	0	Ch-	3	3	3		0
7	rr	0	+	0	+	3	0	+	+	0	+	0	+	0	0	+		2	3	2		
8	rr	+	0	0	+	0	0	0	+	+	0	+	+	0	0	+		3	3	2		
9	rr	0	+	+	0	3	+	0	+	0	0	0	0	+	+	0		3	4	3		
10	rr	+	0	+	0	1	0	0	+	0	0	+	+	0	+	0		3	4	3		
Auto																	IAT	0		0		0
8780	R1r	+	—	+	+	—	—	—	+	—	+	—	+	—	+	—	Vel- 0 P	3	5	3		
8703	R1R2	+	—	+	+	—	—	—	+	—	0	+	—	+	—	+	Vel-0 ABIS	0	0	0		
																	Ex	3		3.		
																					A1	0
																					A2	0

Antibody Titre

Dilution:	Kna	4Ko	4Ko	Cor								Cell Id
Anti-	8783	8704	8740	8735								
Archive	3	3	3	3								
Anti												
Archive												

Group A pos

Pheno R_1R_2K-

Conclusion Anti-Vel

DAT Batch No Pos cont - S

PS	IgG	IgA	IgM	C3c	C3d	Ctl
	0	0	0	0	0	0

Reagent					
Batch No's					

Pipette batch No's

Cross-Referenced in Primary Document: SOP883

Possible sources of allo-immunisation

4 children – 1st 1957 : No evidence of neonatal jaundice or anaemia

Cardiac surgery 1974 at NGH : 1st blood transfusion

Patient referred to NHSBT in 1964 to characterise allo Ab

Patient only remembers being made aware of anti-Vel in 1974

Brother is also phenotypically Vel -ve

Heavily transfused patient

Admission 2010 with symptomatic anaemia Hb 60 g/l :

- Haemolysis screen negative

- OGD – moderate duodenitis with stomach erosions

- Colonoscopy – angiodysplasia in caecum & descending colon

- Capsular endoscopy normal. CT CAP normal

- Required 12 x RBC and 2 litres of FFP during admission

Treatment

R-CHOP chemotherapy: 1-2 days of treatment repeated every 3 weeks

- Pancytopenia common 1-2 weeks after chemotherapy

Supportive treatment during chemotherapy:

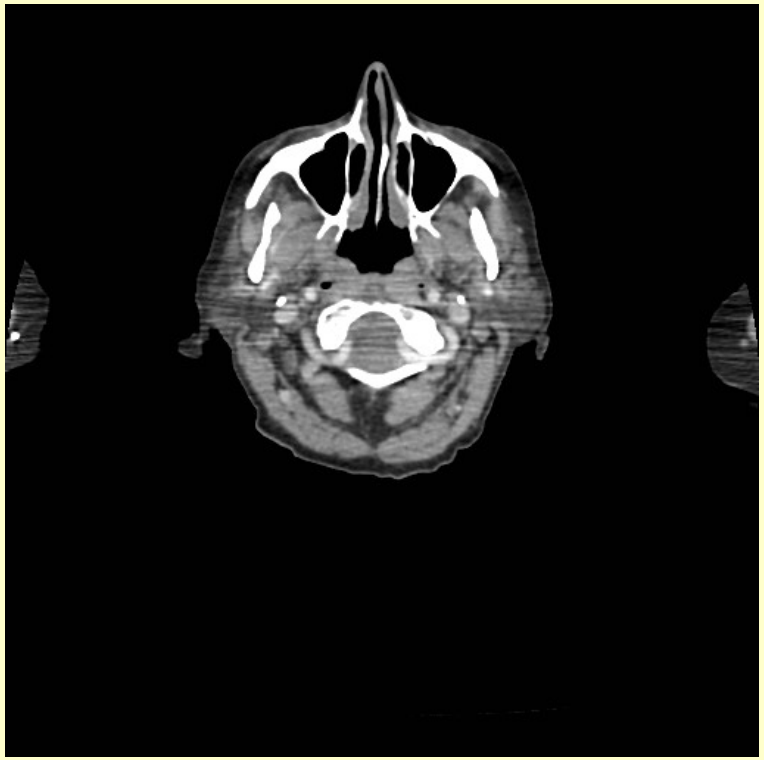
-Average of 5.8 rbc transfusions required per cycle of chemotherapy

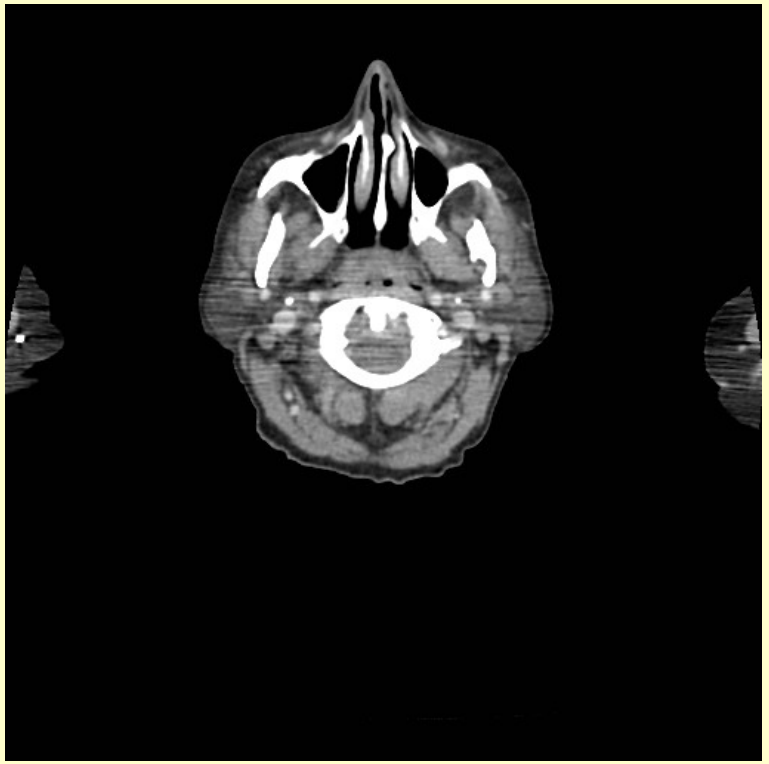
-From Dx to end of Tx: **35 x RBC**, 7 x platelets **over 6/12**

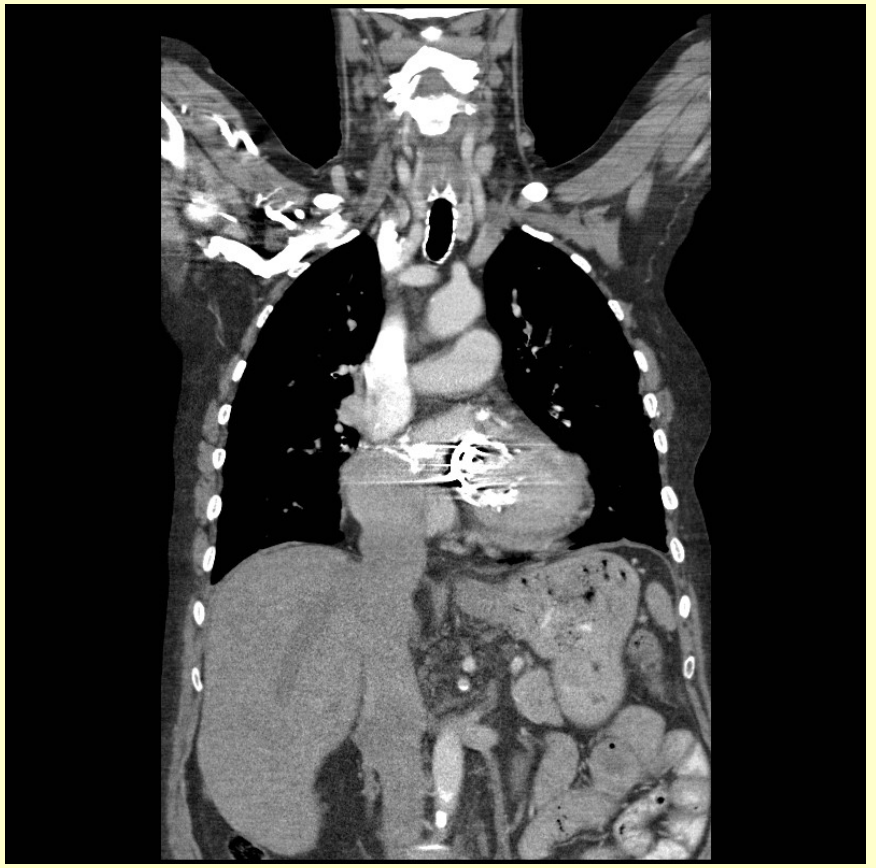
- NHSBT requested Vel-ve rbc to be available pre-chemo
- Additional ‘wet’ units searched for via NHSBT Pulse database
- Liverpool frozen blood bank

Half way CT neck,chest,abdo,pelvis

No evidence of residual disease







After 5th cycle of RCHOP

Prolonged admission (4/52) October 2013

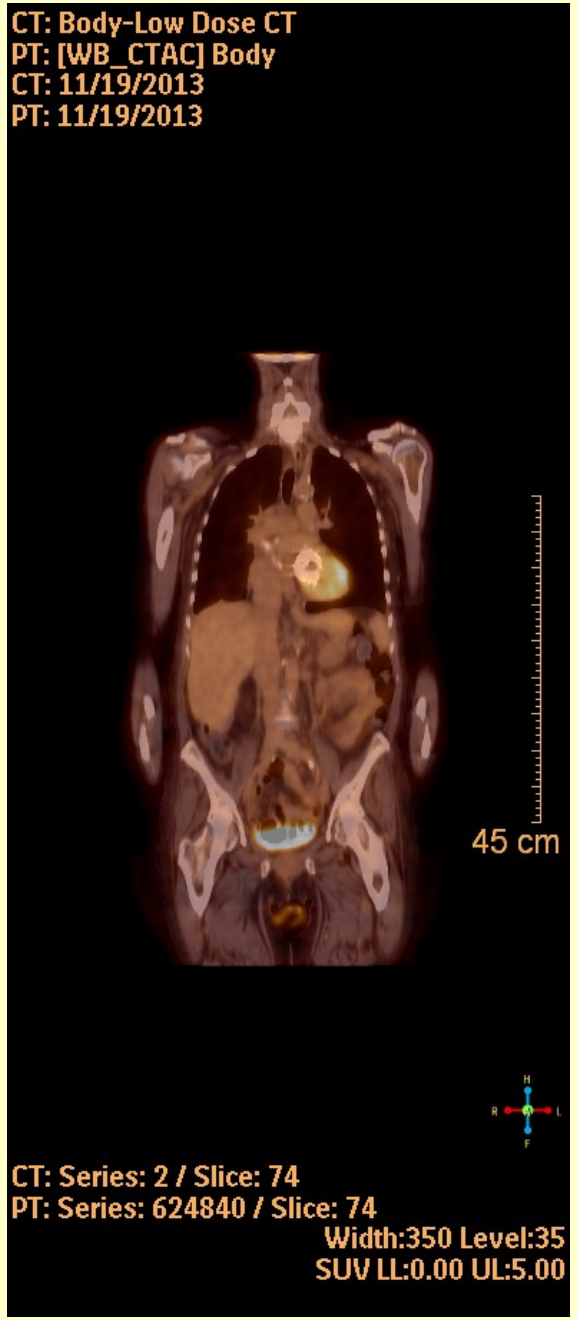
- Neutropenic sepsis & fresh PR bleeding
- Hb 61 Plt 40 Neut 0.3 INR 1.5
- Bleeding haemorrhoids banded
- 9 x rbc: 1 wet unit 8 frozen units (7 transfused)
- 3 x platelets

Isotope scan for occult GI blood loss:

- 12mls/day (normal 2ml/day)

PET CT: no residual disease

Decision made not to pursue final 6th cycle



September 2014

In remission and on 6 monthly outpatient clinic reviews

- Hb 112 Wbc 5.6 Plt 160 Neut 4.0

Increasingly frail:

- July 2014: haematoma on forehead after fall surgically debrided
- One wet unit available in Bristol
- Four frozen units in Liverpool
- Need for transfusion unlikely, so none requested

Vel antigen

First recognosed in 1952 by Susman and Miller in Mrs Vel

High incidence antigen in white Caucasians > 99% [2]

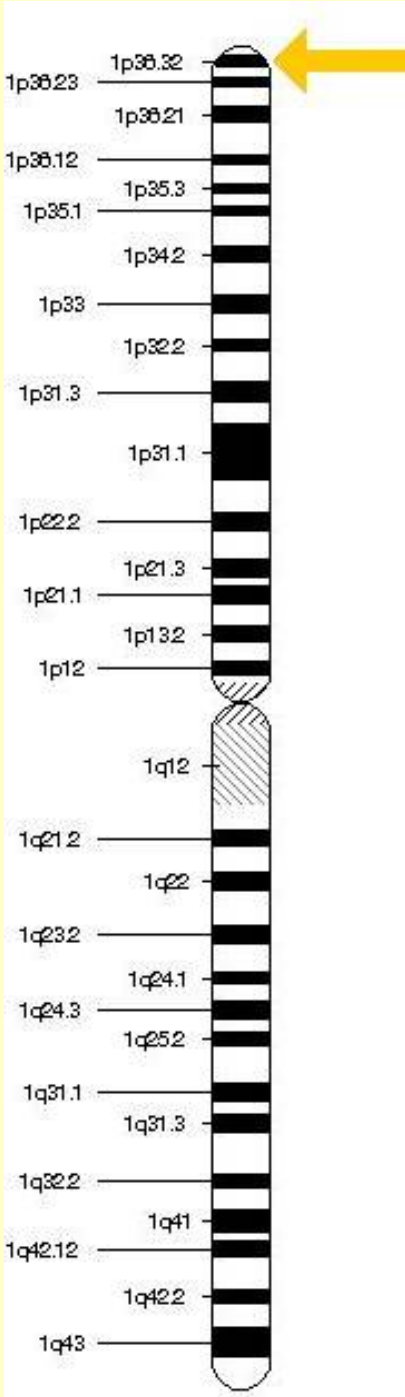
Epitope encoded by the SMIM1 gene on chromosome 1p36.32

SMall Integral trans-Membrane protein 1

- present primarily on erythroid cells [3-5]

Lack of SMIM1 may also cause reduced mean Hb conc in rbc

Not fully developed at birth; weakly expressed in infants [2]



http://ghr.nlm.nih.gov/gene/SMIM1

Vel antigen

Vel –ve phenotype: inherited as an autosomal recessive trait

Majority homozygous for frameshift deletion of 17bp in exon 3 of SMIM1 gene

Individuals heterozygous for the 17bp deletion may represent some with weak Vel antigen expression (Vel+^{W}) [3-5]

Recent proposal by ISBT that Vel should be assigned blood group system status

Association between Vel-ve phenotype and P2 phenotype [2]

Clinical relevance of anti-Vel

Not found to be naturally occurring

Usually IgM, but also IgG1, IgG3

- Able to bind complement

Implicated in both transfusion reactions and HDFN of variable severity

- Including immediate HTR
- HDFN not usual: IgM & poorly developed fetal Vel antigen [1,2]

Difficulties in providing Vel –ve blood

Estimated prevalence of Vel-ve individuals in Europe: 1 in 4,000 [4]

Anti-Vel: ‘high titre, low avidity’ antibody – easy to miss [5]

Some express low levels of Vel antigen – may incorrectly type as Vel –ve

Anti-vel doesn’t work well in adsorption-elution studies

Only recently discovery of genetic basis for Vel –ve phenotype

- Potential genotyping of blood donors to help aid Vel –ve unit shortage

National Frozen Blood Bank - Liverpool

All requests via local RCI consultant after search for wet units failed

Time taken to issue frozen unit from start of process to point of issue:

1 unit: 3.5 hrs
4 units: 7 hrs
6 units: 10 hrs

+ additional transport time

Shelf life for majority of thawed units: 3 days

Some units frozen by older method: 24 hr shelf life only

Save a life
Give Blood

Thoughts for us clinicians

Vel –ve: very rare phenotype, yet Anti-Vel clinically significant

Difficulties for those with increased demand for rare blood units

- Acquired or congenital bleeding diathesis
- Treatment or disease induced pancytopenia

- Planned need vs emergency supply
- Role for transfusion sparing strategies IV iron / EPO / cell salvage
- Forward planning and communication with local RCI lab

Large scale genotyping of donors for Vel-ve phenotype?

With kind thanks to:

Helen Kilgallon RCI lab NHSBT Sheffield

Philip Wright, RCI lab, NHSBT Sheffield

Valarie Tunnard RCI lab, NHSBT Sheffield

Dr Sunita Mane, Consultant Histopathologist, Barnsley District General Hospital

Dr Jean-Pierre Ng, Consultant Haematologist, Barnsley District General Hospital

Dr Robert Webster Consultant Haematologist NHSBT Sheffield

References

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5. B A Balliff et al. Disruption of SMIM1 causes the Vel− blood type. EMBO Mol Med 2013; 5:751–761
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Any questions?