Haematological manifestations in HIV

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AWACC 2013

Cytopaenias in HIV

- Most common complication of HIV
- Anaemia is most common cytopaenia
- ITP occurs in 30%, may be first manifestation of HIV

Laboratory approach to cytopaenia

- FBC, diff, smear
- Retic count → haemolysis/peripheral loss or production problem
- UE/LFT/LDH/CMP
- Nutritional deficiencies: B12/Folate/Iron studies
- Hepatitis B/EBV/Parvo
- BMAT low threshold

Some causes of Anaemia

Decreased RBC production	Increased Red cell loss
HIV itself	Haemolysis
Opportunistic infections	Blood loss
Drugs	Hypersplenism
Nutritional deficiencies	
Malignancy	

Drugs causing cytopaenias

Drug	Cytopaenia
AZT	Anaemia, Neutropaenia
D4T	Neutropaenia, thrombocytopaenia
Bactrim	Anaemia, Neutropaenia, Thrombocytopaenia
INH/Rifampicin	Anaemia, Neutropaenia, Thrombocytopaenia
Fluconazole	Anaemia, Leucopaenia, Thrombocytopaenia

Case 1…Ms PN

- Consulted for patient with Bicytopaenia
- 35/40 pregnant

- From History:
- On HAART, CD4 235, started in pregnancy, uncertain VL
- Diagnosed 11 weeks previously with B12 deficiency, had received B12 injections
- Hb was 6,4 at time, now 11.3
- Persistently low plts -->last count 54
- Normal WCC
- No renal impairment

Investigations

- Normal MCV/MCH
- Coombs negative
- B12 started to improve (low normal) / Folate normal
- Iron studies normal
- Hep B negative
- Rest of viral screen was negative
- US abdomen nad

- Impression: Multifactorial causes
- B12 deficiency, corrected with injections-> accounts for improving Hb
- Low platelets (?ITP/ pregnancy related thrombocytopaenia)

Management plan

- Review history: No transfusions, only had 2x B12 injections
- Assessment: B12 deficiency (Inadequately replaced) and ? ITP

- Plan:
- Replace B12 appropriately
- Start prednisone
- Patient delivered few days later
- Reviewed in clinic 2/52 later
- FBC completely normal with plts of 233

Learning point

- Good history
- Replace B12 appropriately
- 1000mcg x 5/7 → weekly x 4/52 → monthly

Thrombocytopaenia

- Thrombotic Thrombocytopaenic Purpura (TTP)
- ITP
- Drugs
- Opportunistic infections
- Hypersplenism (due to chronic liver disease)
- Malignancy

Isolated Thrombocytopaenia

- Low threshold to do a BMAT
- Might pick up Bone marrow infiltrations or opportunistic infections
- Prednisone 1mg/kg/day
- Polygam to optimise for surgery
- Splenectomy
- Prophylaxis
  - Vaccines: Pneumococcal and Meningococcal prior to splenectomy
- Pen VK 250mg bd (2 years)

Case 2

- Ms SB →16 years old
- Pregnant → 24/40
- CD4 356, HAART naïve
- Initial complaint: Lower abdominal pain and haematuria

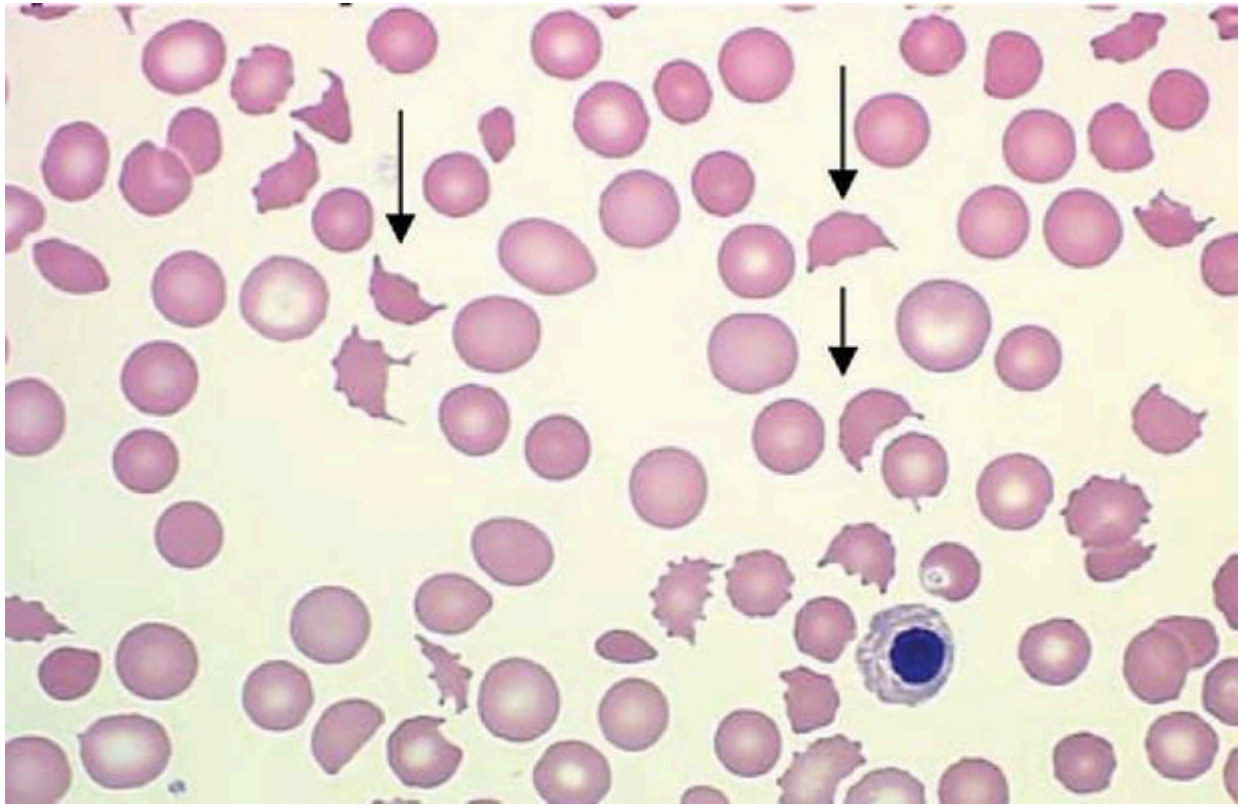
- Examination: Apyrexial, pallor, no lymphadenopathy
- Petechiae +
- No chronic liver disease, no hepatosplenomegaly
- No neurological impairment

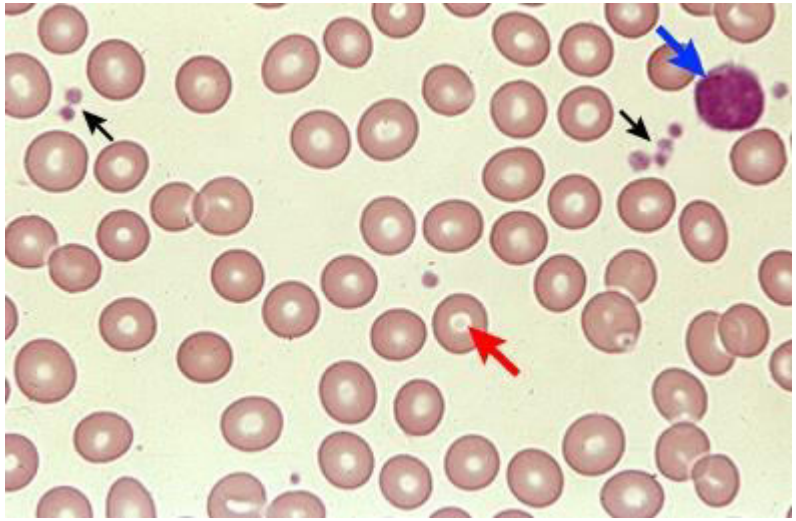
Initial investigations

- FBC: HB 7.3 Plts 24 WCC 10
- UE/LFT normal,
- LDH elevated -882 (N:100-190)
- Iron studies normal
- B12/Folate normal
- INR normal
- ANF neg
- Coombs neg

Initial management

- Smear not followed up
- ITP suspected
- Started on steroids
- Haematology consulted after 10/7 when no platelet increment noted





Considerations in patient

- HIV associated TTP

Unlikely:

- HIV associated ITP
- Gestational thrombocytopenia

TTP Pentad

- Thrombocytopenia
- Microangiopathic Haemolytic Anaemia (MAHA)
- Fluctuating neurological signs
- Renal impairment
- Fever

Differences

- No classical Pentad
- Pathogenesis is different
- Treatment is different: Responds to plasma infusion, rate of relapse low, HAART essential

HIV: A changing landscape

- Incidence 15-40x that of non-infected individuals
- >80% of TTP cases in SA found to be HIV+
- Missed diagnosis

HIV associated TTP

- TTP may be the initial presenting feature of HIV disease

- Remission is dependent upon improving the immune status of the patient.

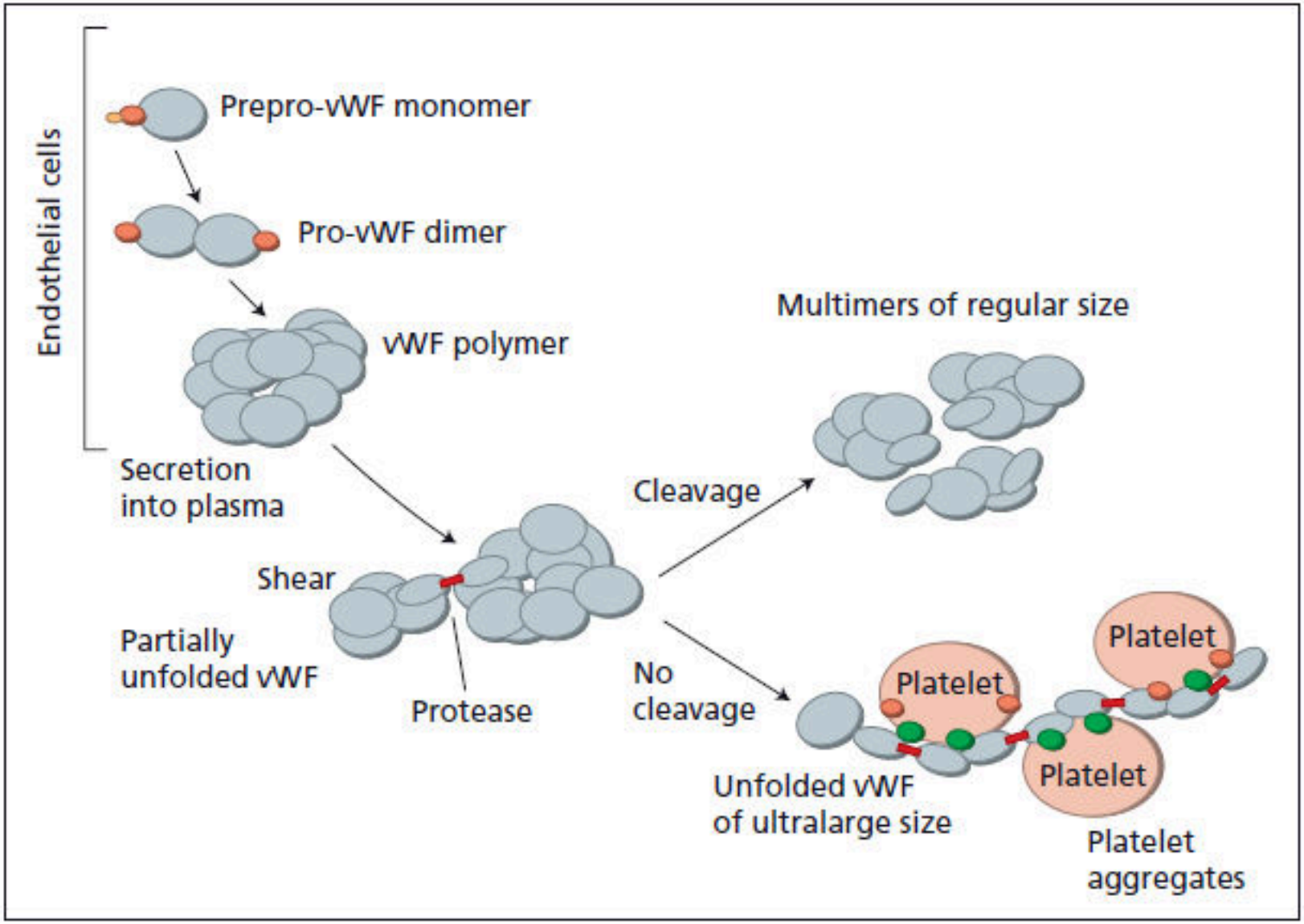
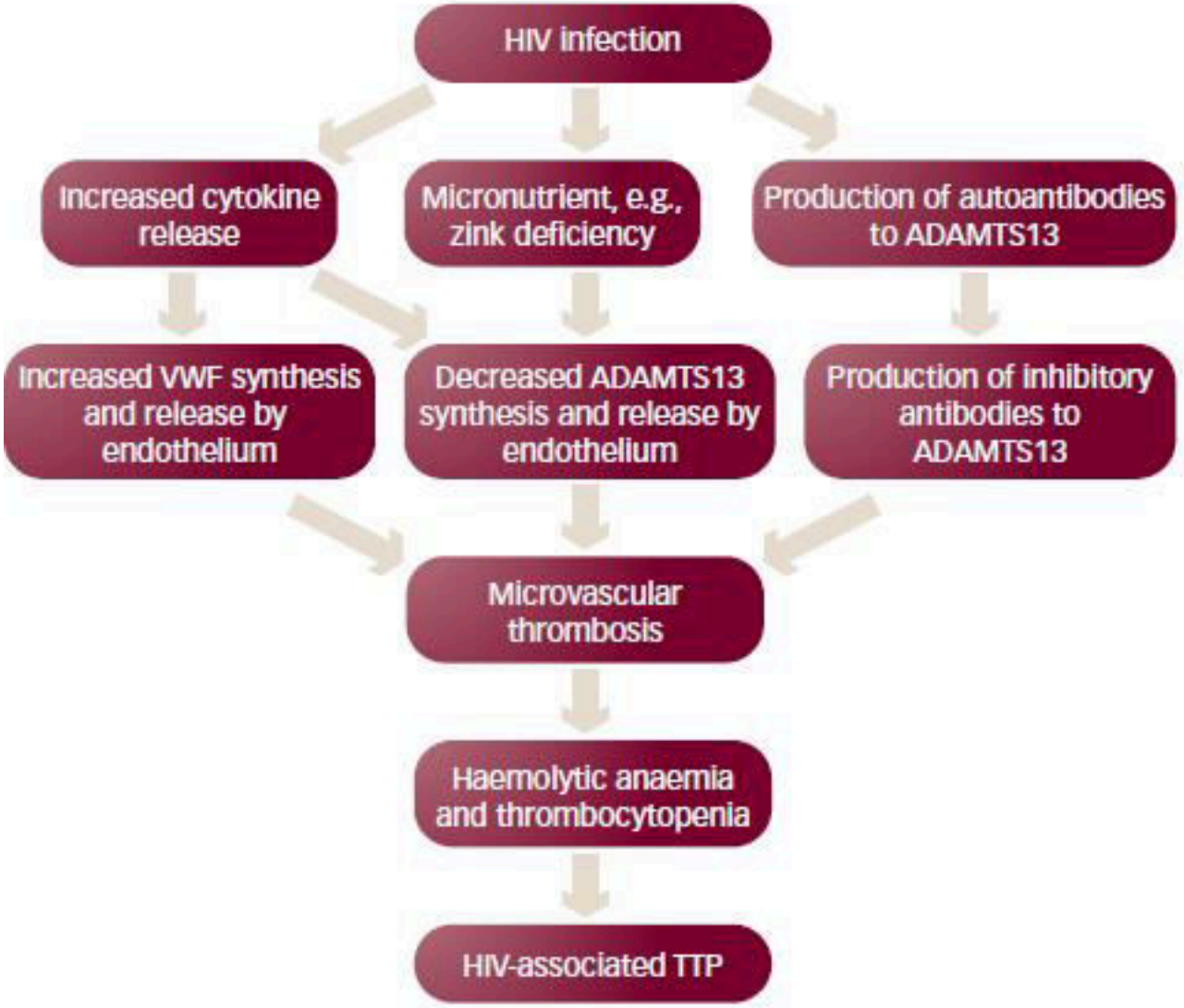

Endothelial cells
Prepro-vWF monomer
Pro-vWF dimer
vWF polymer
Secretion into plasma
Shear
Partially unfolded vWF
Protease
Cleavage
Multimers of regular size
No cleavage
Platelet
Platelet
Platelet
Unfolded vWF of ultralarge size
Platelet aggregates

Figure 1: Proposed Mechanism for the Initial Onset of HIV-associated Thrombotic Thrombocytopenic Purpura



Evidence for Plasma infusion

- Prospective study by Novitsky et al Groote Schuur Hospital
- Compared HIV associated TTP with HIV negative TTP
- All HIV+ patients responded to FFP infusions and their platelet count and serum LDH levels normalized significantly faster than the HIV negative group

Treatment of HIV-TTP

- Plasma infusion
  - FDP (Freeze dried plasma) 30ml/kg/day (can add loop diuretic)
- Adjunctive corticosteroids
  - Prednisone 1mg/kg/day
- Folate
- Aspirin once plts > 100
- If no response in 72 hours→ plasma exchange

Outcome of patient

	Platelet count
DOA	24
Consult:	13
2/7 of FFP	53
4/7 of FFP	132
8/7 of FFP	229

Differences between ITP and TTP

	ITP	TTP
Clinical	Bleeding	"Clotting" Multi-organ involvement
Laboratory	No fragments	Fragments
Treatment	HAART steroids	HAART Steroids FDP Plasma exchange

Case 3…Ms ZN

- 35 years old referred from EDH
- HAART for 3 years
- CD4 395, undetectable Viral load
- Constitutional symptoms
- TB x3 in past, last 1 sensitive AFB + TB
- Examination revealed pallor and lymphadenopathy

investigations

- FBC: Hb 9.8 NNA, Wcc 3.53 (ANC 1.28) Plts 282
- Smear : no fragments
- Calcium and LDH were elevated
- US abdomen showed numerous lymph nodes
- Lymph node biopsy was done

Burkitts lymphoma

- Very aggressive B cell NHL
- 1st lymphoma associated with HIV
- Incidence increasing in HAART era
- > 200x fold increase in HIV population
- HAART not decreased incidence
- 40% associated with EBV
- Rapidly dividing, doubling time of 24-48 hours

Burkitt Lymphoma

- More common when CD4 > 200
- Chronic antigenic stimulation of B cells by chronic HIV infection may be the pathogenetic mechanism
- Responds to chemotherapy
- HAART has allowed the use of high dose chemotherapy regimens

Alarm bells ring…..

Clinically:

- Lymphadenopathy, Heposplenomegaly
- Jaundice, pyrexia

Laboratory:

- Cytopaenias
- Elevated WCC (circulating blasts: Burkitts leukaemia)
- LDH/ Ca elevated
- K+ elevated
- Renal impairement

Tumor Lysis Syndrome

- High proliferation rate
- Suspect if bulky disease
- Present with:
  - Hyperkalaemia
  - Hyperuricaemia
  - Hyperphosphataemia
  - Renal failure

- Management:
- Fluids
- Urinary alkalinisation
- Allopurinol

Case 4

- 30 year old Ms GS
- HAART since June 2013
- Nadir CD4 73→290, (3/12 later), VL uncertain
- TB 2/52 prior to HAART (CXR changes, constitutional symptoms)
- Persisting symptoms, sternal mass started to slowly form
- Anaemia, thrombocytopaenia
- Extensively investigated for MDR-TB

Examination

- Pallor , no lymphadenopathy
- Sternal mass
- Temporal mass
- Hepatosplenomegaly

Continuation.....

- Investigations:
- Microcytic Hypochromic anaemia Hb 9.7, plts 112
- Normal Ca
- Elevated LDH >1000
- CT : TB spondylitis, features of bronchiectasis, Erosive lesion in relation to manubrium sternum, multiple abdominal lymphadenopathy
- Hepatomegally with multiple lesions
- Homogenously enlarged spleen
- Biopsy of sternal mass: DLBCL

Discussion on Diffuse Large B Cell Lymphoma (DLBCL)

- Most common histological subtype of NHL
- Incidence in SA is increasing exponentially primarily due to HIV pandemic
- Most patients symptomatic at presentation
- Constitutional symptoms, lymphadenopathy, hepatosplenomegaly, bone marrow involvement and cytopaenias more common in advanced stage
- Comorbidities such as TB increase the frequency and severity of clinical manifestations

Discussion

- Multiple pathologies for cytopaenias
- In this case: DLBCL and concomitant TB
- High index of suspicion in patient not improving on TB treatment
- Biopsy, Biopsy, Biopsy

Summary: What to consider in patients with Cytopaenias

- HIV induced
- Nutritional deficiency
- Opportunistic infections (eg TB)
- If Thrombocytopaenia: ITP / TTP
- Malignancy

Indications for BMAT in HIV+

- Unexplained anaemia, abnormal red cell indices, cytopenias
- Isolated thrombocytopenias
- Unexplained organomegaly or presence of mass lesions inaccessible for biopsy
- Microbiological culture for investigation of PUO

Case 5

- Mr TZ, 34 years old
- Pulmonary embolus, Right DVT
- HAART naïve, CD4 89
- Examination and rest of baseline laboratory workup was essentially normal

Acquired Thrombophilia in HIV population

- Common
- Unusual sites common
- Risk highest with advanced disease (low CD_4 and high VL) and co-existing infection and malignancies

- <u>Contributors to Hypercoaguable state:</u>
- Increased VWF
- High incidence of lupus anticoagulant and antiphospholipid antibodies
- Acquired Protein C and S deficiency

Management

- HAART
- Prophylaxis in hospitalised immobile patients
- Thrombophilia testing expensive
- NB: False + low titres of Antiphospholipid antibodies common

- Thank you for your time and attention ☺

References and acknowledgements

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- Postgraduate Haematology 2011

- Dr JP Singh, Dr N Sewpersad (IALCH department of Haematolgy)
- Various patients