CCM inter-hospital grand round

Transfuse or not ?

- Speaker : Dr. ChowCW (CMC ICU)
- Chairman : Dr. Wong WT (CMC ICU)

Our patient

- M/21
- Good past health.
- Presented to General Practitioner for intermittent fever, headache and dizziness for 2 days.
- Noted pallor by GP and blood test arranged.
- Found severe anaemia and referred to A&E for admission. Hb: 4.8 g/dL checked by private lab.
- Admitted to medical ward through A&E on 22nd September 2012 for management of anaemia.

History

- Intermittent epigastric pain for few months.
- No tarry stool, haemetemesis or coffee ground vomiting.
- No significant change of bowel habit
- No significant weight loss.
- Deny intake of over counter analgesia.

Physical Examination

- Stable Blood pressure and heart rate.
- Afebrile. No cervical, axillary or groin lymphadenopathy.
- No organomegaly. Chest clear. No murmur.
- Per rectal examination: yellowish stool.
- CXR : Clear.
- ECG : Sinus tachycardia with no ischaemic change.

Initial blood test

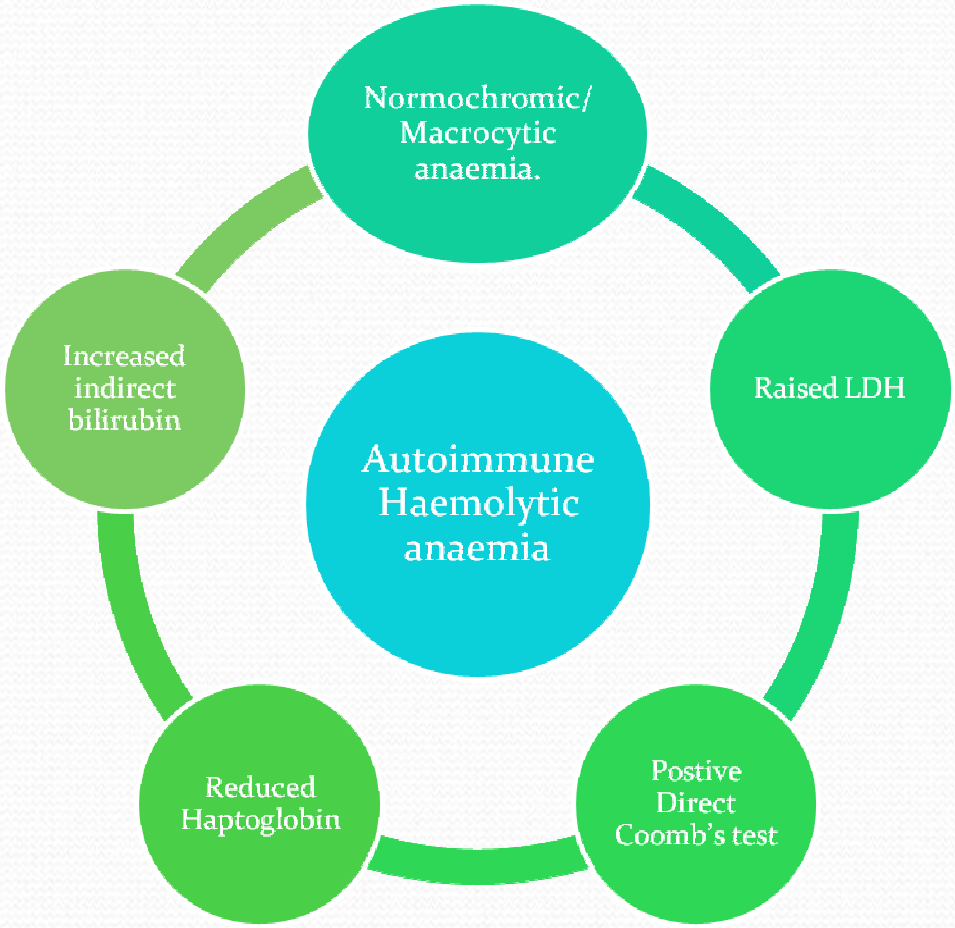
- Haemoglobin: 4.2g/dL Haematocrit: 11.5%
- MCV 102.8fL. MCH 37.1pg. MCHC 36.1g/dL
- WCC 4.3 Plt: 219
- Blood film: Anisocytosis +, Elliptocytosis +, Macrocytosis +.
- Retic count 0.1%.
- Clotting normal

Further blood test

- Vitamin B12 255pmol/L (133-675pmol/L)
- Serum Folate: 12.8 nmol/L (>6.8nmol/L)
- Iron: 38 umol/L (8.1-32.6umol/L)
- TIBC 42umol/L (44.8-76.0umol/L)
- Iron Saturation 90% (20-50%)

Further blood test

- Direct Bilirubin 3umol/L (1-4umol/L)
- Total Bilirubin 49umol/L (6-26umol/L)
- LDH: 416 U/L (58-233U/L)
- Haptoglobin: <0.06g/L (0.36-1.95g/L)
- Direct Coomb's test positive
- Indirect Coomb's test positive
- Urine toxicology found paracetamol
- G6PD Screening negative


Normochromic/ Macrocytic anaemia.
Raised LDH
Postive Direct Coomb's test
Reduced Haptoglobin
Increased indirect bilirubin
Autoimmune Haemolytic anaemia

Type and screen

- Antibody was detected during type and screen.
- In view of the symptomatic severe anaemia, proceed to transfusion with phenotypically matched blood.
- No previous history of blood product transfusion.

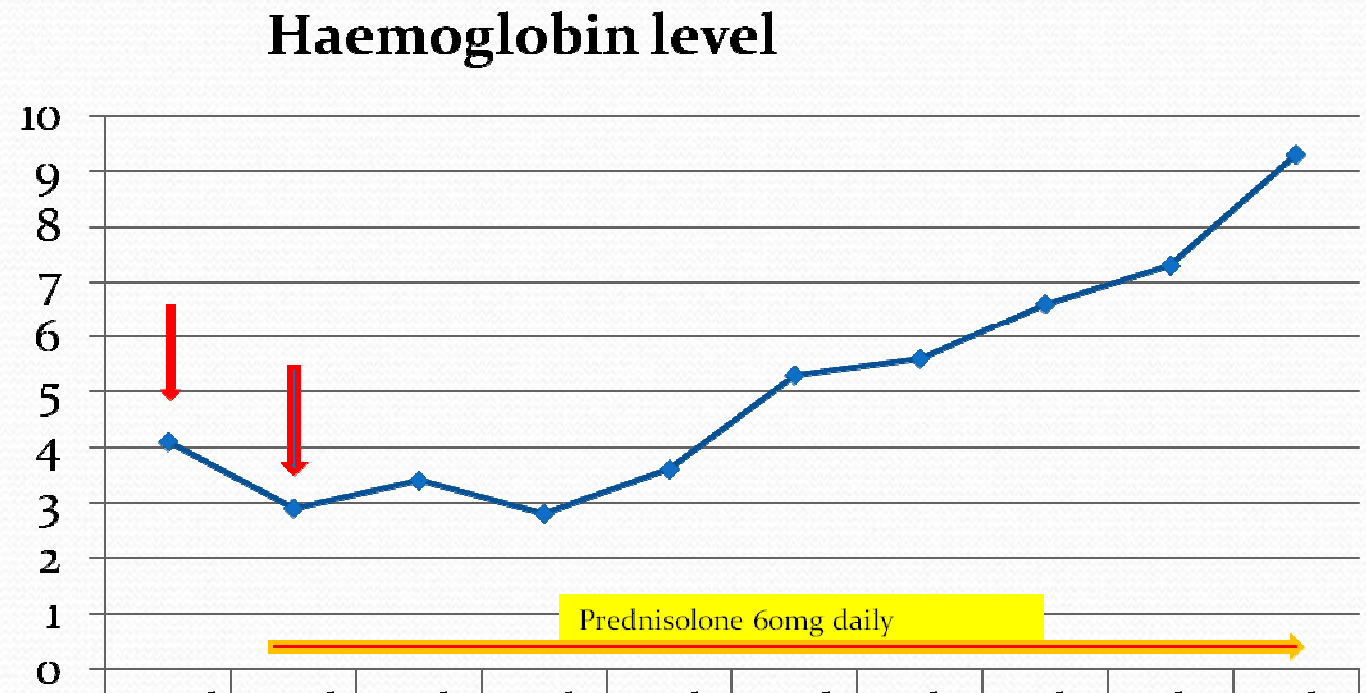
Transfusion reaction

- At around 22:00 on 22nd Sep 2013, pack cell was ready and transfusion started.
- Noted transfusion reaction just after blood transfusion
- High fever, Temp 39 degree
- Tachycardia, HR 150/min
- Chills and rigor
- Transferred to ICU for close monitoring.
- Sepsis work up including lumbar puncture performed
- Started on empirical Rocephin

Transfusion reaction.

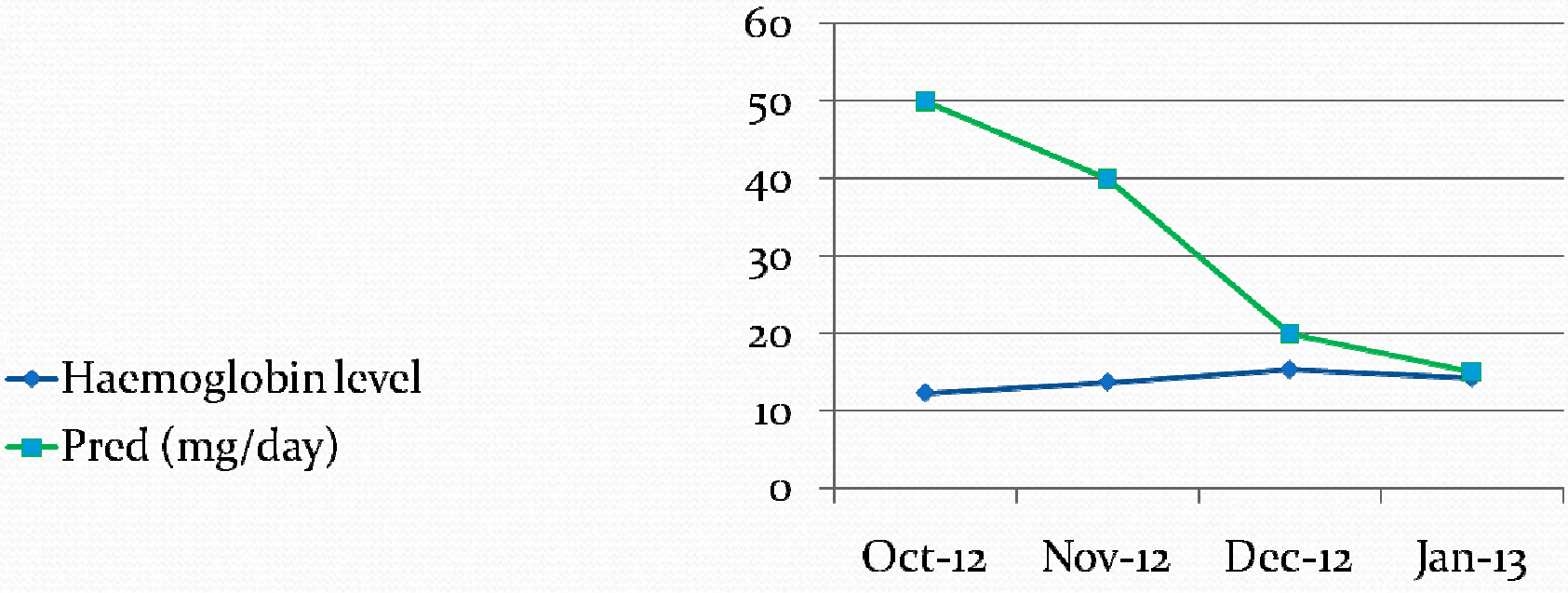
- Second attempt of blood transfusion in ICU on 23rd Sep 2013
- Given Hydrocortisone 200mg iv
- Started Prednisolone 60mg daily
- Started in a low rate of 100ml/hr
- Developed SOB, chills and rigor.
- High fever, Temp 39.6 degree
- Also found hamaturia from foley

Progress in hospital



	22nd Sep	23rd Sep	24th Sep	26th Sep	29th Sep	2nd Oct	4th Oct	6th Oct	8th Oct	11th Oct
Haemoglobin level	4.1	2.9	3.4	2.8	3.6	5.3	5.6	6.6	7.3	9.3

Progress after discharge



	Oct-12	Nov-12	Dec-12	Jan-13
Haemoglobin level	12.3	13.7	15.3	14.2
Pred (mg/day)	50	40	20	15

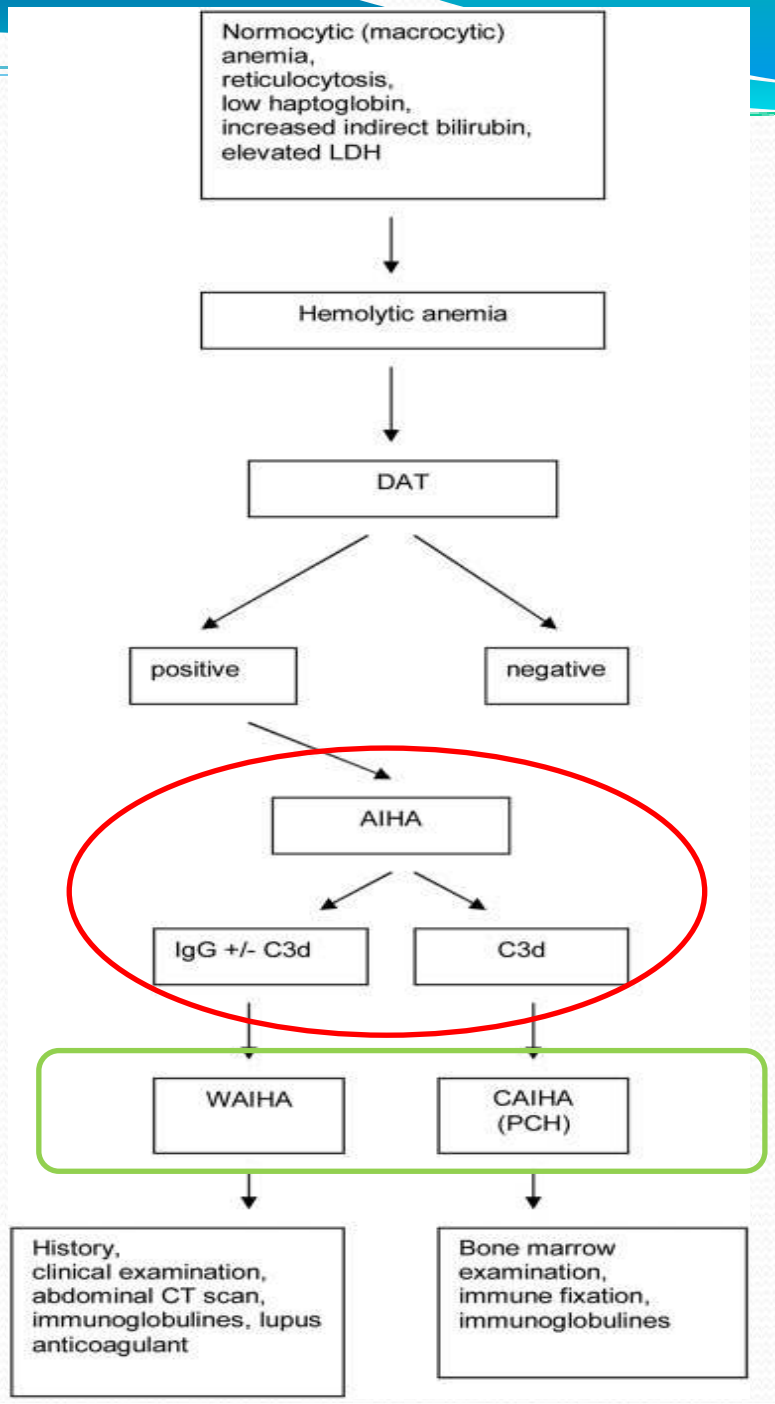

Normocytic (macrocytic) anemia, reticulocytosis, low haptoglobin, increased indirect bilirubin, elevated LDH
Hemolytic anemia
DAT
positive
negative
AIHA
IgG +/- C3d
C3d
WAIHA
CAIHA (PCH)
History, clinical examination, abdominal CT scan, immunoglobulines, lupus anticoagulant
Bone marrow examination, immune fixation, immunoglobulines

Table 1. Main characteristics of various types of autoimmune hemolytic anemia.

AIHA type	Epidemiology/ type of hemolysis	Rate of secondary AIHA	Autoantibody isotype	Optimal temperature	DAT pattern	Eluate	Autoantibody specificity (targeted antigens)
Warm AIHA	~70–80% of all AIHAs Adults > children (mean age 3 years) EV hemolysis, subacute onset (sometimes abrupt with associated IV hemolysis)	~50% of the cases (see Box 1)	IgG >> IgA, IgM	37°C	IgG ± C_3d	IgG	Broad specificity towards antigens of the Rhesus system
Cold agglutinin syndrome	~20–30% of all AIHA cases in adults. Age >50 years EV hemolysis	Mainly secondary Monoclonal IgMκ gammopathy in 90% of the cases ± features of definite clonal B-cell lymphoproliferative disorder	IgM >>> IgA or IgG Cold agglutinins titer >1/500	4°C	C_3d	Negative	I antigen > i >> Pr
Cold transient AIHA	Children and young adults IV hemolysis	Infections (*Mycoplasma pneumoniae*, Epstein–Barr virus)	Polyclonal IgM Cold agglutinins titer ≥1/64	4°C	C_3d	Negative	I > i antigens
Paroxysmal cold hemoglobinuria	Children (rare ++), exceptional in adults Acute IV hemolysis	Infections (*M. pneumoniae*, virus)	IgG (Donath–Landsteiner hemolysin)	>30°C	C_3d	Negative	P + c antigens (two-phase hemolysin)
Mixed-type AIHA	Adult Mainly EV hemolysis	Mainly B-cell lymphoma	IgG, IgM ± AF ~1/500	Wide range (4–37°C)	IgG ± C_3d	IgG	Polyreactivity

AF: Autoimmune feature; AIHA: Autoimmune hemolytic anemia; DAT: Direct antiglobulin test; EV: Extravascular; IV: Intravascular.

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Box 1. Main disorders or conditions associated with warm autoimmune hemolytic anemia (secondary cases).

Hematologic disorders & lymphoproliferative diseases

- Chronic lymphoid leukemia†
- Acute lymphoblastic leukemia‡
- Large granular lymphocytic leukemia
- B-cell lymphoma†
- Angioimmunoblastic T-cell lymphoma
- Hodgkin lymphoma
- Castleman disease
- Myelodysplasias
- Myelofibrosis

Solid tumors

- Thymoma
- Ovarian dermoid cyst
- Carcinoma

Autoimmune & inflammatory diseases

- Antiphospholipid syndrome
- Rheumatoid arthritis
- Ulcerative colitis
- Pernicious anemia
- Myasthenia gravis
- Autoimmune hepatitis
- Giant cell hepatitis†
- Thyroiditis
- Sarcoidosis
- Eosinophilic fasciitis
- Systemic lupus erythematosus

Infections

- Virus: Epstein–Barr virus†, hepatitis C
- Bacteria: tuberculosis, brucellosis, syphilis

Drugs [17,18]

Primary immunodeficiencies

- Common variable immunodeficiency
- Hyper IgM syndrome‡
- ALPS‡
- IPEX syndrome‡
- APECED syndrome‡

Others

- Pregnancy
- Post-allogenic bone marrow transplantation, post-liver or small bowel transp
- Rosai–Dorfman disease

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Direct Coombs Test

- Positive
- Anti-IgG: Very Strong
- Anti-C3d: Very Strong
- Warm Antibody Autoimmune Haemolytic Anaemia (AIHA)

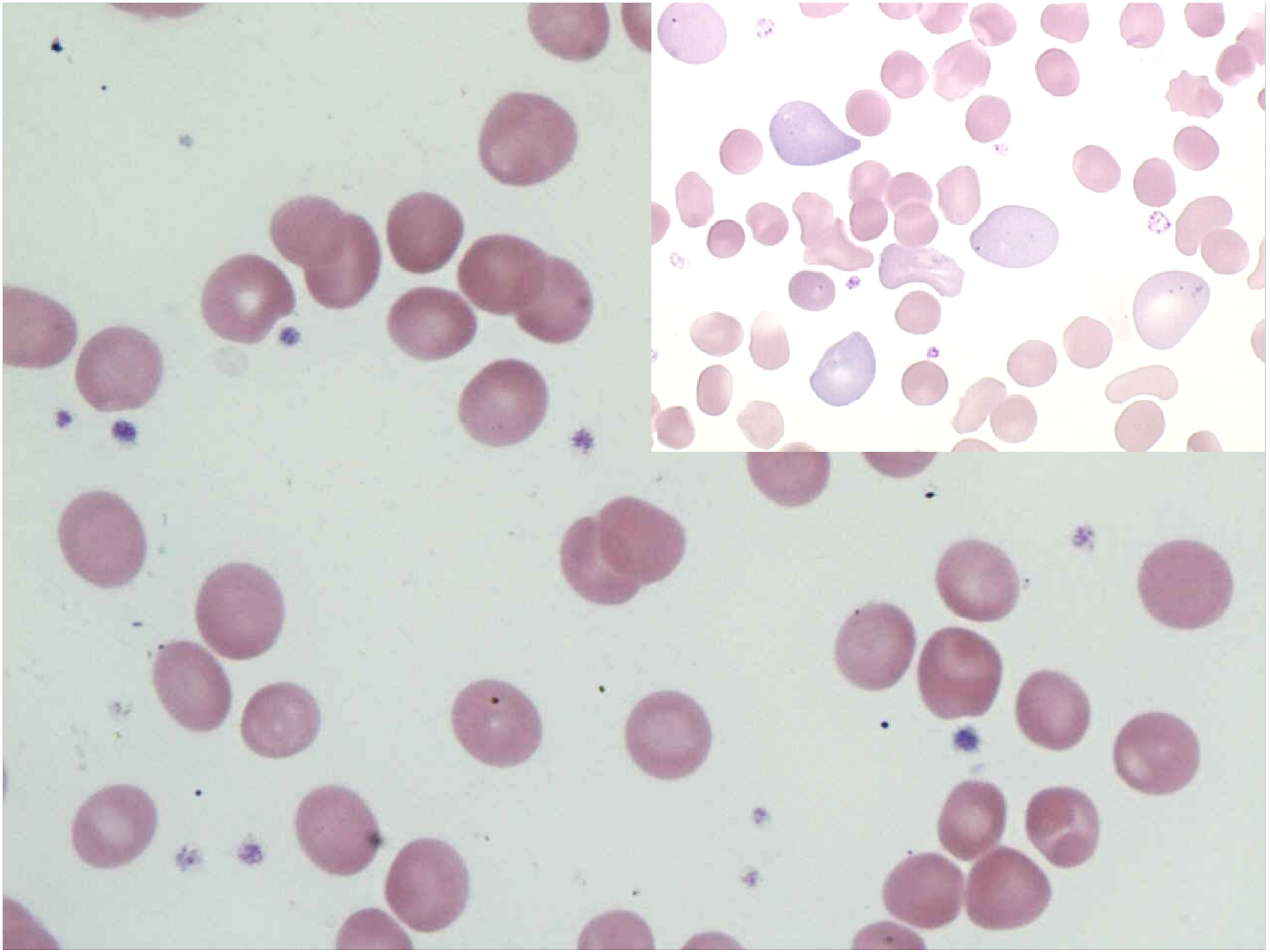
Primary or Secondary

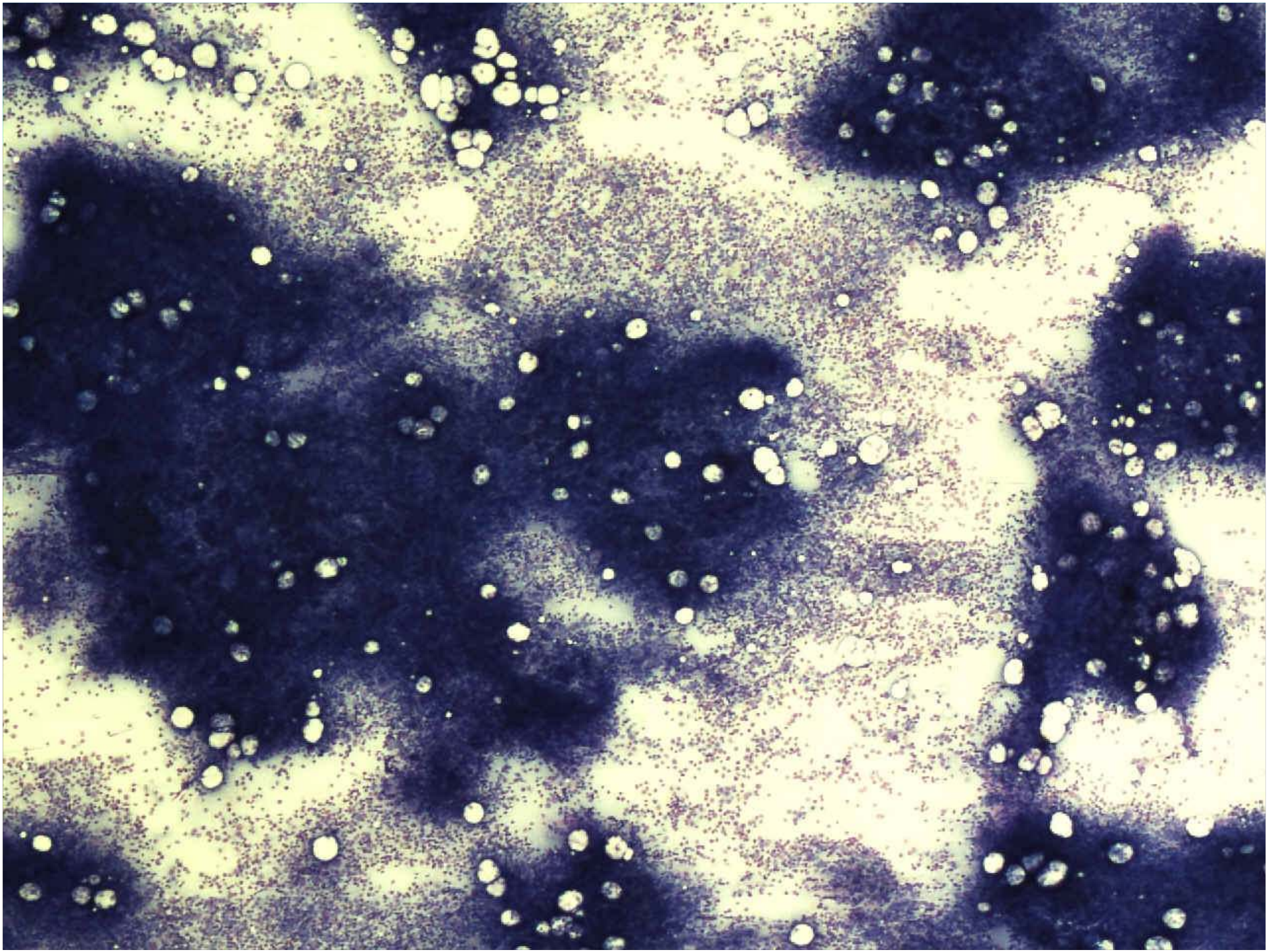
- Anti-Nuclear Antibody negative
- Anti-ds DNA negative

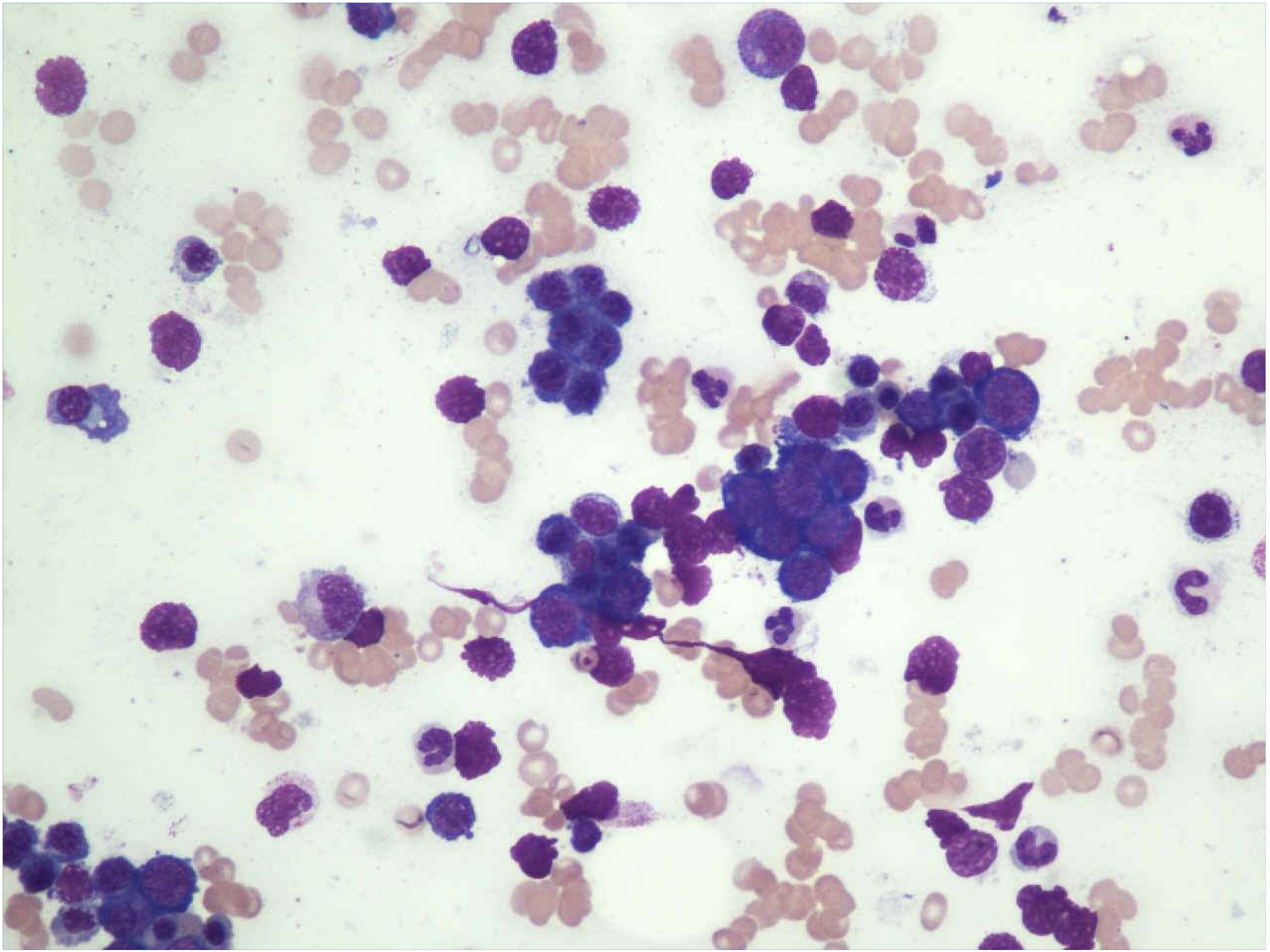
- Malaria Screening negative.
- Anti-HIV negative
- IgM Antibody to Parvovirus B19 negative.
- IgM Antibody to Dengue Virus negative
- Antibody Titre to Adenovirus, Chlamydia, Coxiella, Influenza A/B and Mycoplasma all not raised

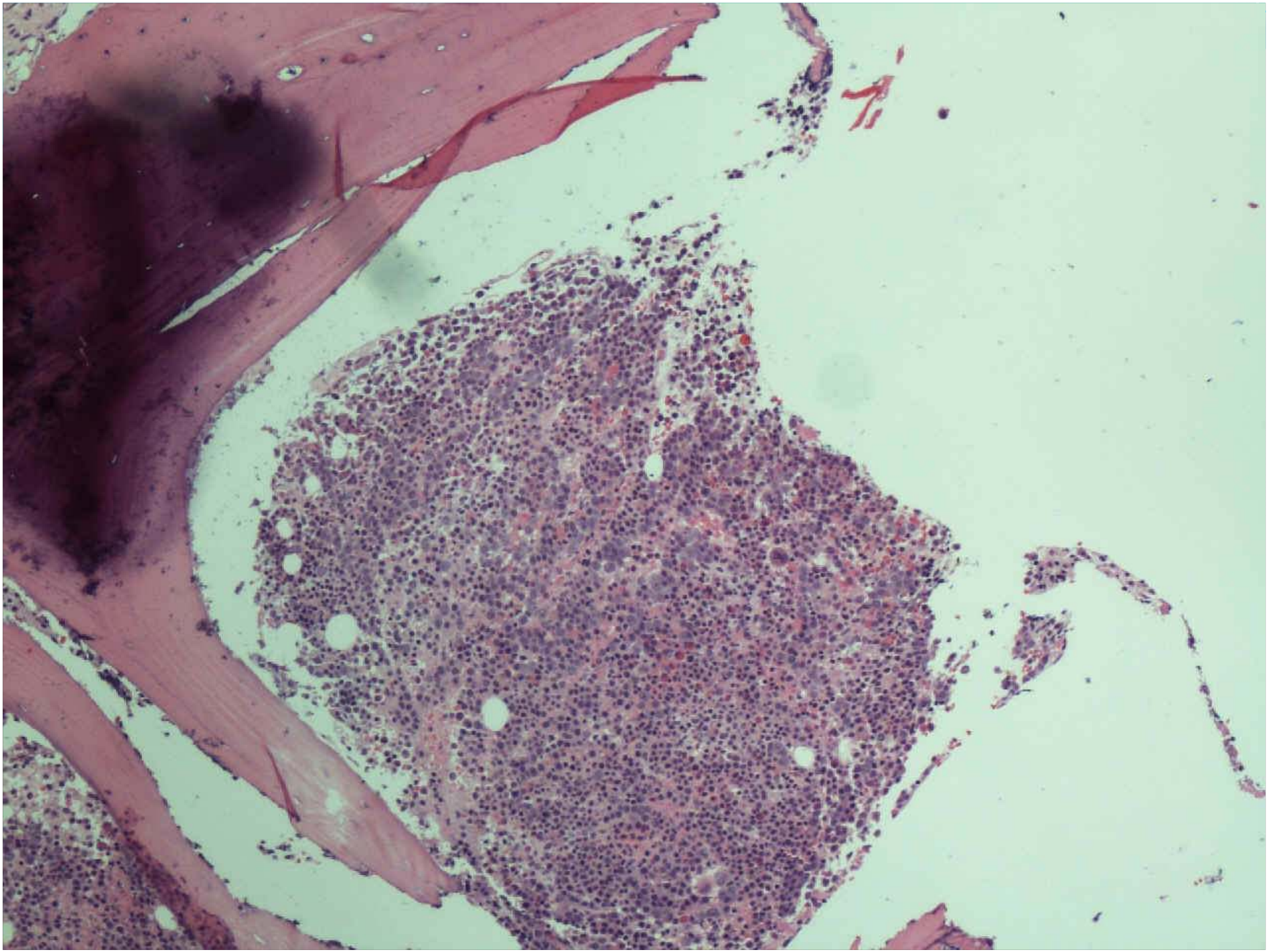
Haematopatholoy

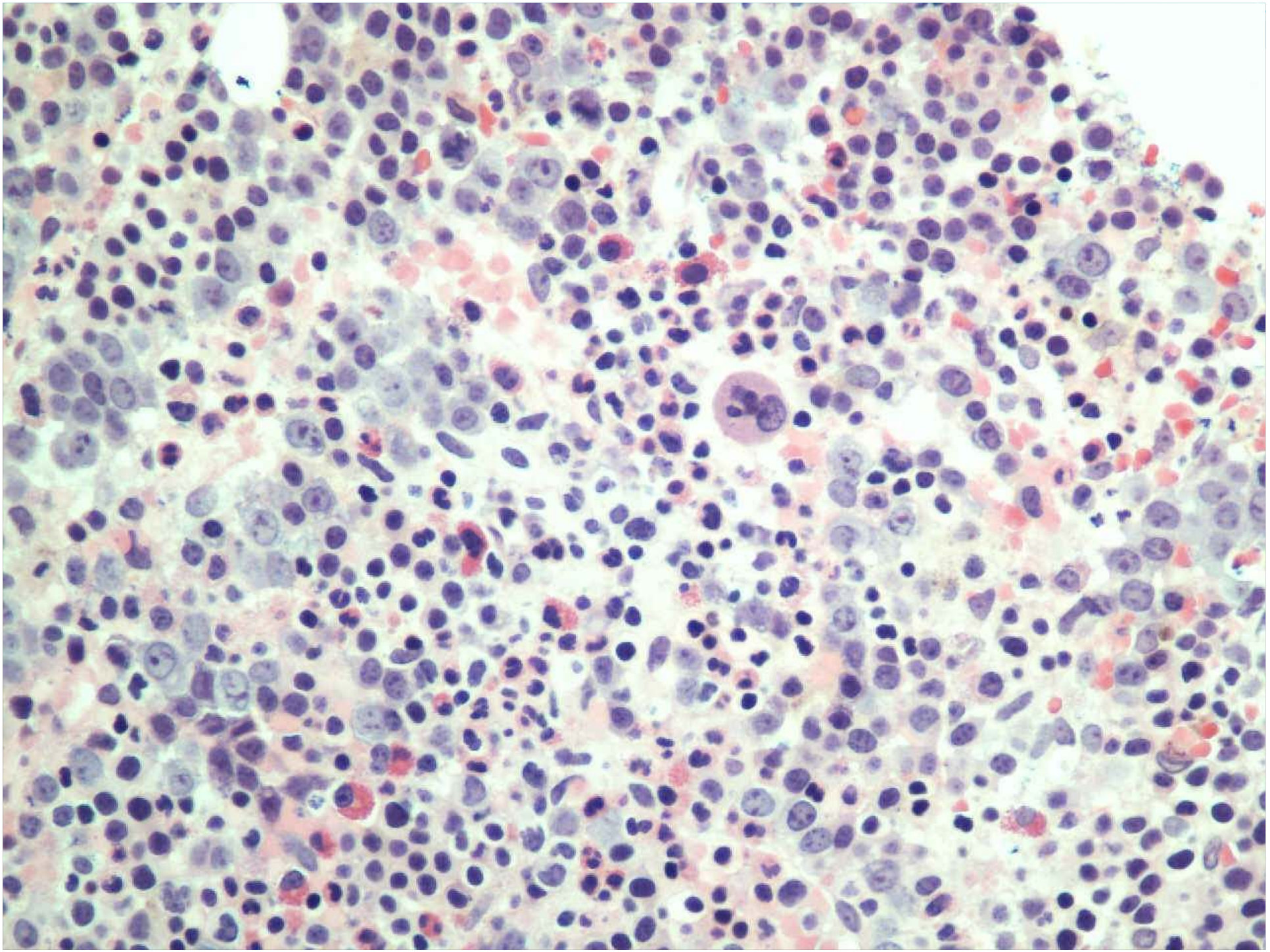
- Peripheral blood smear
- Bone marrow aspirate and trephine biopsy
- Direct and Indirect Coomb's test
- Blood transfusion and AIHA.



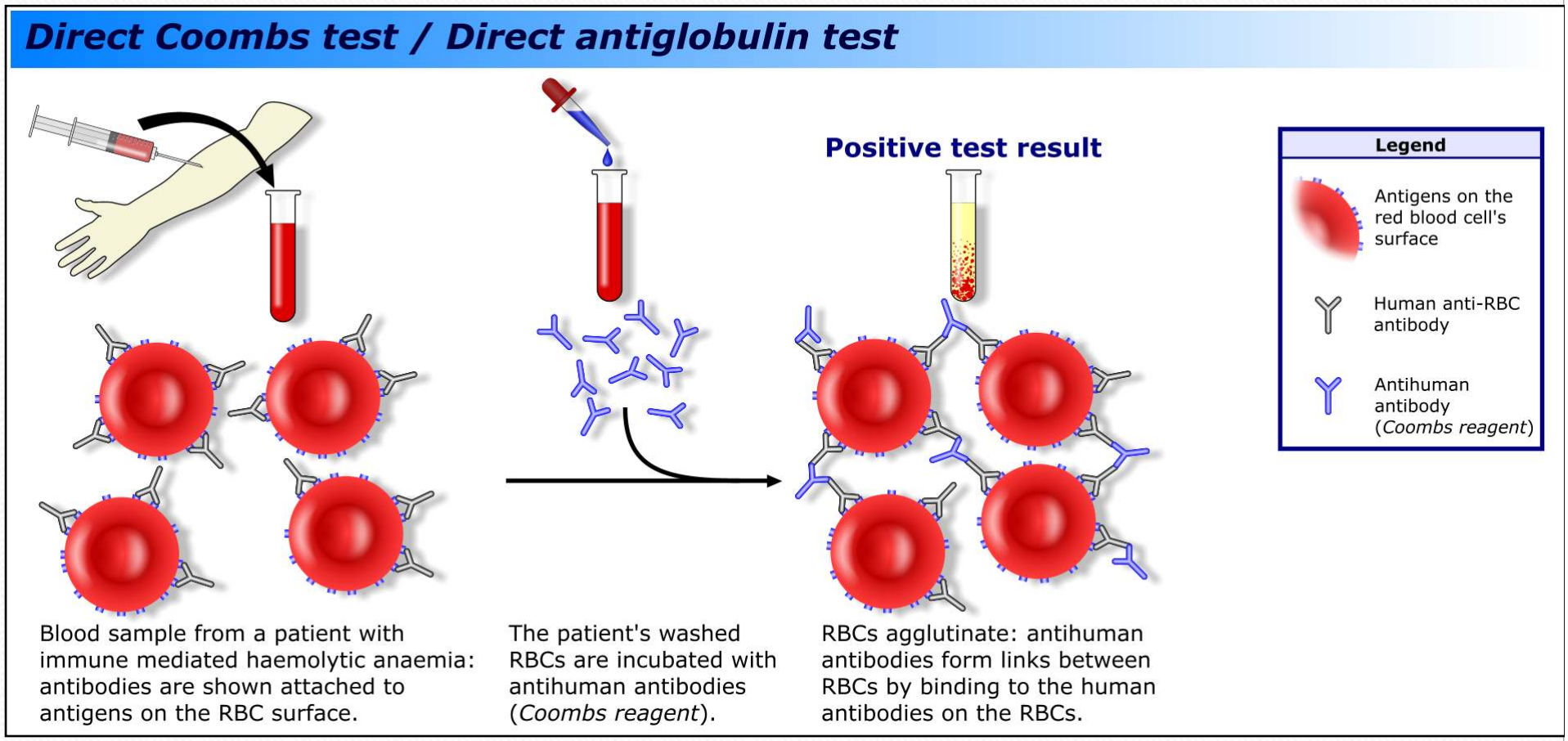




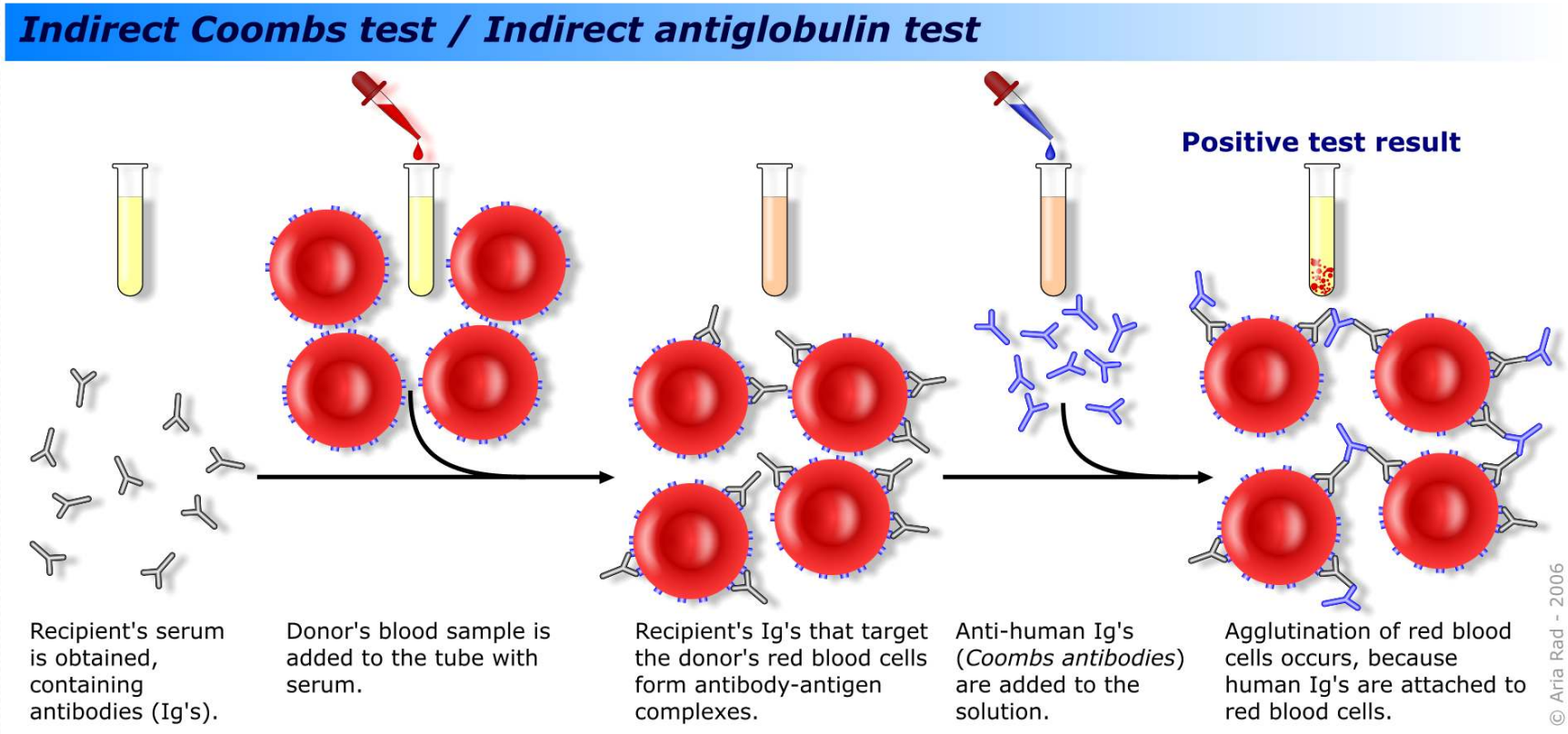




Direct antiglobulin test



Indirect antiglobulin test



How IAT is used

- Antibody screening
  - Performing an indirect antiglobulin test using patient's serum and *screening red cells*
- Cross matching
  - Performing an indirect antiglobulin test using patient's serum and *donor red cells*
- Type and screen
  - Perform a ABO Rh typing
  - Perform an antibody screening

Transfusion in AIHA

- In patient with AIHA, the autoantibody is pan reacting (i.e. it will bind to all sorts of red cells with no specificity)
- So cross matching will always give incompatible result
- What we worry is whether the patient has alloantibody (antibody against a blood group that the patient does not have e.g. anti-Jka)
- So instead of matching ABO and RhD only, we match every clinically significant minor blood group C, c, E, e, K, k, Jka, Jkb, Fya, Fyb .....

How safe

- A total of 7052 units was issued for 1685 patients; no haemolytic reactions were reported.
  - Sokol RJ, Hewitt S, Booker DJ, Morris BM. Patients with red cell autoantibodies: selection of blood for transfusion. *Clin Lab Haematol.* 1988;10(3):257-64.
- But it is not wise to over transfuse AIHA patients as rate of haemolysis is directly related to red cell concentration

2nd patient

- Mr. Y
- NS, ND
- Waiter in a Japanese restaurant
- History of epilepsy , FU CMC MODD ;
  - on Lamotrigene 50mg QD & Epilim Chrono 200mg QD
- Presented to A&E as fever, cough & sputum since 10/2/13
- Re-attended A&E on 20/2/13

History & physical examination

- Fever subsided but still cough & sputum
- Anemic symptoms with palpitation & SOB
- BP 111/72, HR 125, SaO_2 88%(room air)
- Alert & conscious
- Pallor + , Jaundice +,
- Tachypneic +,
- Chest : bilateral crep.
- CVS : HS normal, no murmur
- Abd : soft, non-tender, no palapable mass,
- PR : yellow stool

Investigations

- Hb 7.8 , WBC 30, plt 691
- MCV / Hct : N/A as RBCs was markedly auto-agglutinated,
- Ur/Cr : 6.5/68, Na 135, K 3.8
- Ca 2.08, PO_4 1.20,
- dBil 10, tBil 65, ALP 119, ALT 119, A/G 30/39
- LDH 567,
- ECG : Sinus tachycardia with HR 130/min.
- CXR : slight bilateral LZs infiltrate +

Further investigations

- Repeated Hb 7.0,
- Blood film :
  - anisocytosis,macrocytosis,poikilocytosis,polychrpmasia,
  - schiostocytes & spherocytosis
- Hepatoglobin : < 0.06 (0.36 – 1.95)
- Direct Coombs test : positive
- Indirect Coombs test : negative
- Anti-C3d Ab : positive
- GOPD screening : normal
- Cold agglutinin : 1024 titre (<32)
- NPA for Mycoplasma pneumoniae PCR : positive

Progress :

- Repeated Hb on 21/2/13 was 5.4
- One unit of packed cell was transfused on 21/2,22/2 & 23/2 with post-transfusion Hb on 24/2 : 8.1
- Hb remained static with Hb 8.3 on 25/2
- Also put on oral Klacid 500mg BD & IV Augmentin 1gm Q12H
- Able to wean off oxygen.
- To general ward on 26/2/13
- Discharged on 5/3/13
- Hb 10.1 on 4/3/13

Treatment of Warm Ab AIHA

- Transfuse or not transfuse
- First line treatment: Steroid
- Second line treatment: Splenectomy or Rituximab

Transfusion

- Individual decision
- Speed of development of anaemia
- Severe of anaemia.
- Age and clinical condition

In Vivo compatibility test

- Trial of blood transfusion with low volume in close monitoring.
- 20ml of blood and 20 minute observation

First line treatment: Steroid

- Initial dose Prednisolone 1mg/kg/day
- Methylprednisolone 250mg to 1000mg in first 3 days
- Target of Haematocrit > 30% or Haemoglobin >10g/dl
- Reduced to Prednisolone 20-30mg/day within a few weeks.
- Consider withdrawal of steroid if remained in remission while on Prednisolone 5mg per day
- Proportion of patient remained in remission after steroid withdrawal is not known, but estimated to be less than 20%.

Klaus Lechner et al. How I treat autoimmune hemolytic anaemia in adults. Blood 2010

Second line treatment

- Splenectomy and rituximab are the only second line treatment with proven short term efficacy.
- Splenectomy was recommended as the best 2nd line treatment

✓ Short term efficacy, up to 2/3 in complete remission or partial remission after splenectomy

✓ Long term success are possible. Up to 63% with Hct>30% without steroid and 21% required Prednisolone 15mg/day or less

✓ Low perioperative risk with laparoscopic procedure.

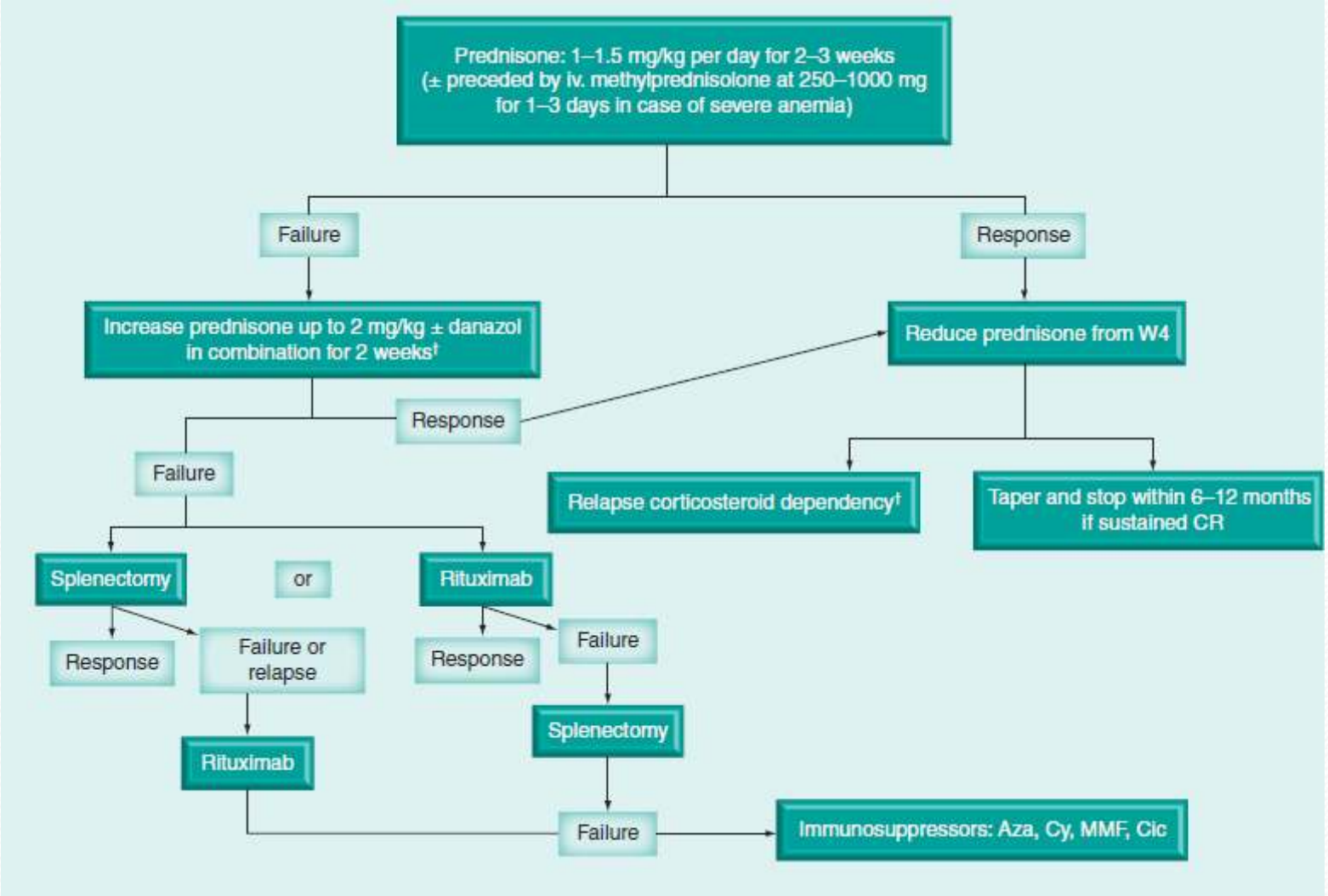
Klaus Lechner et al. How I treat autoimmune hemolytic anaemia in adults. Blood 2010

Second line treatment

- Anti-CD 20 antibody rituximab.
- Only off-label use of AIHA
- Standard regime: 375mg/m2 for 4 doses on days 1,8,15,22.
- Overall response was 82% (half complete response and half partial response).
- Major risk in severe infection.
- In favor of rituximab in case of relative contraindication for splenectomy such as massive obesity and technical difficulty.

Other second line treatment

- High dose immunoglobulin
- Danazol, a synthetic anabolic steroid with pleiotropic effects



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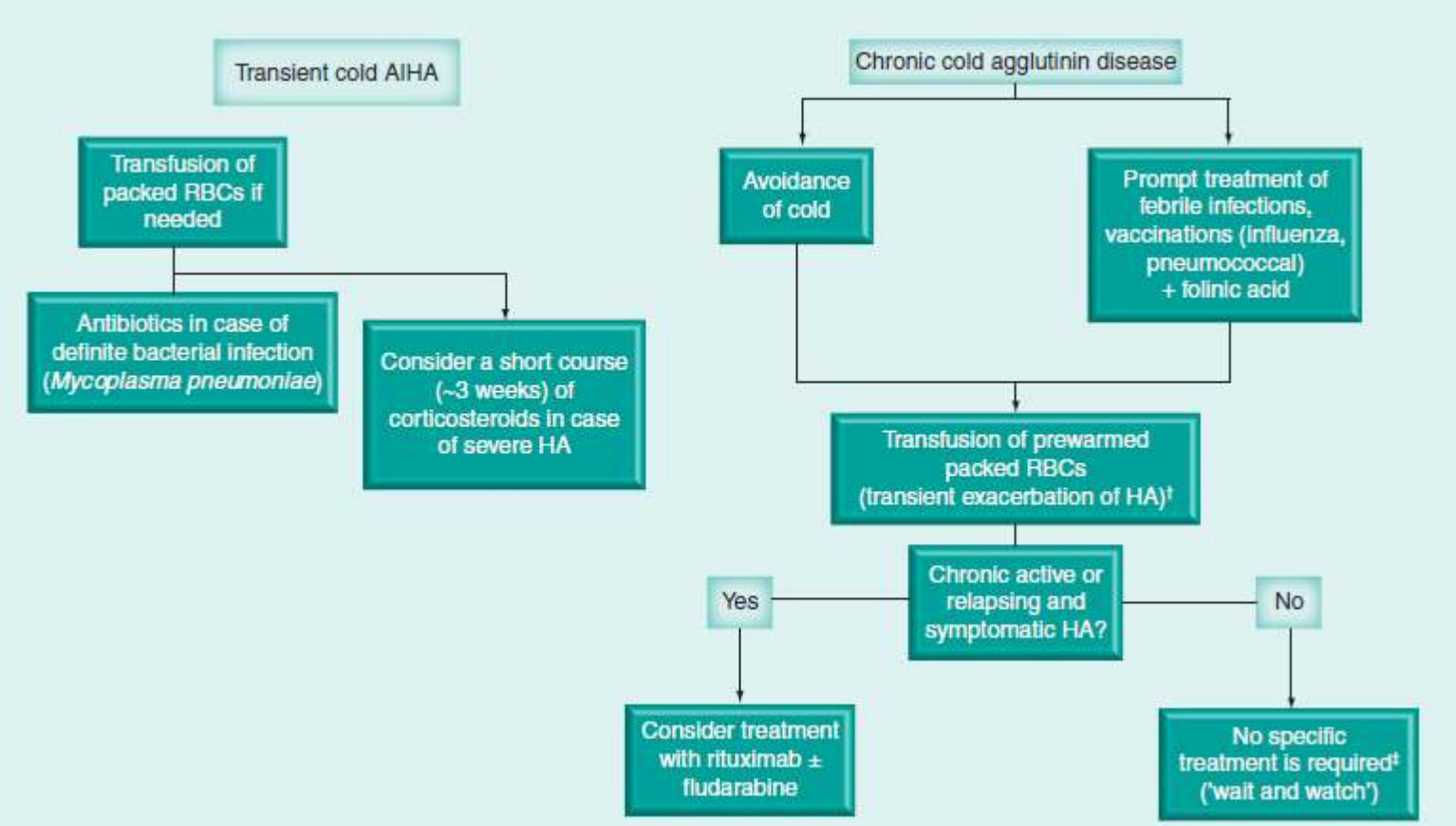
Treatment of cold agglutinin disease

- Avoidence of exposure to cold for mild form
- For more severe form, blood transfusion is not very effective because donor cells are I-positive and will be removed rapidly
- Immunosuppressive/cytotoxic treatment with prednisolone,azathioprine,or cyclophosphamide can reduce the antibody titer but the clinical efficiency is limited and S/Es may be unacceptable
- Rituximab may be a better choice



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Take Home Message

- AIHA can cause severe symptomatic anaemia.
- Decision on blood transfusion should be individualized.
- Collaboration among blood bank, red cross service and clinician is usually required for arrangement of phenotypically matched blood.
- Close monitoring is required when blood transfusion initiated, transfusion may need to be stopped.
- Steroid is the first line treatment but it takes time to work.