

BBTS 2017

Clinical Case Study 3

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Case 3

- A 70 year old lady with a past medical history of sarcoidosis visited her GP feeling generally unwell
- Symptoms:
 - Shortness of breath on exertion
 - Palpitations
 - Fatigue
 - Recent viral illness
 - Weight loss (8lb in 8 weeks with no dietary modifications)
- Travel history included a recent stay in Abu Dhabi

- Social history
 - Fit and well non-smoker, teetotal
 - Continues to work in office based role
 - Lives with partner
 - Originally from Pakistan, planning trip to Pakistan in Feb
- On examination:
 - No palpable lymphadenopathy in axillae or cervical area. One lymph node in left groin, approximately 1cm x 1cm in size
 - Splenomegaly, enlarged to level of umbilicus
 - Chest clear
 - Heart sounds normal, no added murmurs

- Urgent bloods done by GP later that day:

FBC				
Mild neutropenia				
HB	*	87	g/L	118 - 148
RBC	*	3.25	$\times 10^{12}/L$	3.88 - 4.99
Haematocrit	*	0.256	L/L	0.390 - 0.440
Mean Cell Volume	*	78.7	fL	80.0 - 100.0
MCH	*	26.9	pg	28.0 - 33.0
Platelets	*	69	$\times 10^9/L$	150 - 400
WBC	*	1.8	$\times 10^9/L$	3.5 - 11.0
Neutrophils	*	1.0	$\times 10^9/L$	2.0 - 7.5
Lymphocytes	*	0.7	$\times 10^9/L$	1.0 - 3.5
Monocytes	*	0.1	$\times 10^9/L$	0.2 - 0.8
Eosinophils		0.0	$\times 10^9/L$	0.0 - 0.4
Basophils		0.0	$\times 10^9/L$	0.0 - 0.2
WBC Differential				
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Film confirms pancytopenia ? known cause. Suggest repeat.				

- GP contacted haematology registrar via switch to ask for further advice. Patient asked to attend haematology day ward the following day for further investigations given the symptoms reported.

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HB	*	79	g/L	118 - 148
RBC	*	2.89	$\times 10^{12}/L$	3.88 - 4.99
Haematocrit	*	0.226	L/L	0.390 - 0.440
Mean Cell Volume	*	78.5	fL	80.0 - 100.0
MCH	*	27.3	pg	28.0 - 33.0
Platelets	*	66	$\times 10^9/L$	150 - 400
WBC	*	1.7	$\times 10^9/L$	3.5 - 11.0
Neutrophils	*	0.9	$\times 10^9/L$	2.0 - 7.5
Lymphocytes	*	0.7	$\times 10^9/L$	1.0 - 3.5
Monocytes	*	0.1	$\times 10^9/L$	0.2 - 0.8
Eosinophils		0.0	$\times 10^9/L$	0.0 - 0.4
Basophils		0.0	$\times 10^9/L$	0.0 - 0.2
Reticulocytes				
Reticulocytes		56	$\times 10^9/L$	20 - 110

- Progressively pancytopenic
- More investigations requested:
 - Blood film
 - Biochemistry (renal profile, liver function, calcium profile)
 - LDH
 - Serum Immunoglobulins
 - B12/Folate/Ferritin
 - Glandular fever slide test
 - HIV/Hepatitis B/C screen
 - Clotting screen
 - Group and Save sample
- CT Chest/Abdo/Pelvis
- Bone marrow aspirate and trephine

- Group and Save – 1st sample 16/11/16 – sample sent to local RCI lab

BloodBank

BloodBank

B,16.0025294.N

O

Pos

Antibody Screen: Positive

Units Reserved:

For Use On:

2ND SAMPLE REQUIRED :

Direct Antiglob Test : Weak Pos (Manual)

NSEA, NSAHG

Units Reserved:

For Use On:

A FURTHER GROUP SAMPLE IS REQUIRED PRIOR TO COMPONENT ISSUE

- On further questioning...
- Patient has never received a blood transfusion
- She has had one medical termination of pregnancy at 6 weeks gestation on medical advice, no other pregnancies

- Local RCI lab had great difficulty identifying the antibodies and samples were sent on to IBGRL
- In the meantime...
 - Patient was well though easily fatigued and tired
 - She attended haematology day ward twice weekly for blood counts whilst other investigations ongoing

- Two weeks later...

HB	*	66	g/L	118 - 148
RBC	*	2.43	$\times 10^{12}/L$	3.88 - 4.99
Haematocrit	*	0.188	L/L	0.390 - 0.440
Mean Cell Volume	*	77.6	fL	80.0 - 100.0
MCH	*	27.0	pg	28.0 - 33.0
Platelets	*	53	$\times 10^9/L$	150 - 400
WBC	*	1.7	$\times 10^9/L$	3.5 - 11.0
Neutrophils	*	0.9	$\times 10^9/L$	2.0 - 7.5
Lymphocytes	*	0.7	$\times 10^9/L$	1.0 - 3.5
Monocytes	*	0.1	$\times 10^9/L$	0.2 - 0.8
Eosinophils		0.0	$\times 10^9/L$	0.0 - 0.4
Basophils		0.0	$\times 10^9/L$	0.0 - 0.2
Reticulocytes				
Reticulocytes		56	$\times 10^9/L$	20 - 110

- IBGRL had not yet identified the specificity of the antibody detected and asked the ward for more blood for further analysis.
- Investigations:
 - Blood film confirmed pancytopenia.
 - Biochemistry raised LDH (356), bilirubin slightly elevated at 34, no haematinic deficiency
 - HIV / Hep B and C negative
 - CT scan – significant splenomegaly with maximum transverse diameter of 14.5cm
 - Bone marrow aspirate non-diagnostic

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 - CT scan – significant splenomegaly with maximum transverse diameter of 14.5cm
 - Bone marrow aspirate non-diagnostic
- Decision made to start steroids, as a holding measure to improve anaemia and patient wellbeing until trephine available
 - Blood not transfused at this time

Case 3

Question 1

Working diagnosis?

1. Splenic Marginal Zone lymphoma
2. Alternative as yet undetected tropical/infectious disease
3. Lymphomatous process leading to significant autoimmune haemolysis with pan-reactive panel
4. Primary autoimmune haemolytic anaemia
5. Alternative solid tumour malignancy

- Two units of phenotype-matched blood are now available from Colindale
- Patient admitted for transfusion and admits she feels symptomatic of her anaemia
- Explained to patient there are risks with transfusion of blood products but also risks associated with progressive anaemia – patient consented

- Pre-blood transfusion FBC

HB	*	60	g/L	118 - 148
RBC	*	2.11	$\times 10^{12}/L$	3.88 - 4.99
Haematocrit	*	0.165	L/L	0.390 - 0.440
Mean Cell Volume	*	78.2	fL	80.0 - 100.0
MCH		28.2	pg	28.0 - 33.0
Platelets	*	22	$\times 10^9/L$	150 - 400
WBC	*	1.8	$\times 10^9/L$	3.5 - 11.0
Neutrophils	*	1.3	$\times 10^9/L$	2.0 - 7.5
Lymphocytes	*	0.4	$\times 10^9/L$	1.0 - 3.5
Monocytes	*	0.0	$\times 10^9/L$	0.2 - 0.8
Eosinophils		0.0	$\times 10^9/L$	0.0 - 0.4
Basophils		0.0	$\times 10^9/L$	0.0 - 0.2
Reticulocytes				
Reticulocytes		24	$\times 10^9/L$	20 - 110

- First unit of blood transfused over 3 hours without incident, completed at 18.30
- Observations stable during transfusion but on re-checking an hour later:
 - Temperature 39.2
 - Respiratory rate 17
 - Oxygen saturations 98% on room air
 - Blood pressure 180/71
 - Heart rate 104
- On call junior doctor reviewed within 30 minutes, patient found to be relatively well. Discussed with haematologist on call who advised treating as neutropenic sepsis, and send haemolysis screen to assess for transfusion reaction
- Transfusion lab informed, second unit of blood not administered. Unit sent back to lab for further investigation

- Two hours later:
 - Frank haematuria
 - Some nausea and loose stools
 - No abdominal or flank pain
 - No further temperatures, tachycardic
- Investigations:
 - Haemoglobin post transfusion 57 (60 prior to transfusion)
 - Urea 9.5, eGFR 56 (previously >90, therefore an acute kidney injury)
 - ALT 101, bilirubin 99, GGT 62 (all acute changes, previously normal)
 - Haptoglobin haemolysed
 - Urine - frank haematuria
- Impression: **haemolytic transfusion reaction**
- Reviewed by on call consultant following morning; explained to patient nature of reaction and proposed treatment plan

Case 3

Question 2

What is the next best treatment option?

1. Further phenotype-matched unit of blood with IV steroid cover
2. Arrange urgent plasma exchange for presumed primary autoimmune haemolytic anaemia
3. Treat as presumed lymphoma with chemotherapy as may be anaemic due to bone marrow infiltration (trephine still awaited)
4. Trial rituximab (monoclonal antibody immunotherapy) for presumed primary autoimmune haemolytic anaemia
5. Trial high dose IV steroids and IV immunoglobulins

- The patient agreed to trial high dose IV steroids and IV immunoglobulins. It was explained to the patient that this may prevent a clinical diagnosis of lymphoproliferative disease being made if trephine not diagnostic
- She continued to feel symptomatic of anaemia (fatigue, breathlessness, occasional pre-syncope) and remained on IV antibiotics for neutropenic sepsis. Haematuria resolved.
- Refused further red cell transfusion. Agreed to platelet transfusion after long discussion (transfused without incident)

- NHSBT informed team they were having difficulty in cross matching the patient's blood, and were unable to match for **M**
- Report awaited from Bristol given unlikely to be a clinically significant antibody
- The unit of blood provided had been phenotype matched and cross-matched with plasma; genotype matched blood awaited

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- Report awaited from Bristol given unlikely to be a clinically significant antibody
- The unit of blood provided had been phenotype matched and cross-matched with plasma; genotype matched blood awaited
- **Medical team felt this was likely autoimmune haemolytic anaemia driven by underlying high grade lymphoma in the bone marrow – imperative to ascertain diagnosis**

Bone Marrow Trephine Report

- 26 days after initial presentation...

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The bone marrow trephine is not ideal for sub-classifying B-cell non-Hodgkin lymphoma due to site-specific diagnostic discordance that can be present. Suggest correlate with lymph node biopsy for a definitive diagnosis.

FINAL DIAGNOSIS

Bone marrow, trephine biopsy:

- Diffuse large B-cell lymphoma (DLBCL), NOS.
- ICD-O3 9680/3 (WHO 2008).

Conclusion

FINAL DIAGNOSIS

Bone marrow, trephine biopsy:

- Diffuse large B-cell lymphoma (DLBCL), NOS.
- ICD-O3 9680/3 (WHO 2008).

Diffuse Large B Cell Lymphoma

- Most common sub-type of Non-Hodgkin Lymphoma (30% of patients with NHL)
- An aggressive cancer, survival without treatment is measured in months
- Risk factors associated with shorter overall or relapse-free survival include age >60, higher than normal LDH, Clinical stage (III or IV) and number of involved extra-nodal sites and score calculated based on this
- Estimated survival rates at 4 years range from >90% to those with low scores to <60% for those with high scores

- The following day diagnosis was explained, consent obtained for R-CHOP immuno-chemotherapy and administered that same day
- Treatment administered without incident; however progressive symptomatic anaemia

- Full blood count done 6 days after chemotherapy commenced

FBC				
HB	*	45	g/L	118 - 148
RBC	*	1.60	x10 ¹² /L	3.88 - 4.99
Haematocrit	*	0.129	L/L	0.390 - 0.440
Mean Cell Volume		80.5	fL	80.0 - 100.0
MCH		28.4	pg	28.0 - 33.0
Platelets	*	28	x10 ⁹ /L	150 - 400
WBC		3.5	x10 ⁹ /L	3.5 - 11.0
Neutrophils		2.9	x10 ⁹ /L	2.0 - 7.5
Lymphocytes	*	0.7	x10 ⁹ /L	1.0 - 3.5
Monocytes	*	0.0	x10 ⁹ /L	0.2 - 0.8
Eosinophils		0.0	x10 ⁹ /L	0.0 - 0.4
Basophils		0.0	x10 ⁹ /L	0.0 - 0.2
Reticulocytes				
Reticulocytes	*	15	x 10 ⁹ /l	20 - 110

Case 3

Question 3

What is the next best treatment option?

1. Transfuse further unit(s) of phenotype-matched blood
2. Increase dose of steroids to prednisolone 200mg
3. Bring forward next cycle of chemotherapy by 7 days to be given at 14 days (in 8 days time)
4. Arrange urgent plasma exchange
5. Commence erythropoietin and repeat high dose IV immunoglobulins

- Erythropoietin commenced, and high dose IV Immunoglobulins given the following day after discussion with NHSBT consultant

- Erythropoietin commenced, and high dose IV Immunoglobulins given the following day after discussion with NHSBT consultant
- Two days later...

HB	*	41	g/L	118 - 148
RBC	*	1.36	$\times 10^{12}/L$	3.88 - 4.99
Haematocrit	*	0.110	L/L	0.390 - 0.440
Mean Cell Volume		80.8	fL	80.0 - 100.0
MCH		29.7	pg	28.0 - 33.0
Platelets	*	9	$\times 10^9/L$	150 - 400
WBC	*	0.4	$\times 10^9/L$	3.5 - 11.0
Neutrophils	*	0.1	$\times 10^9/L$	2.0 - 7.5
Lymphocytes	*	0.2	$\times 10^9/L$	1.0 - 3.5
Monocytes	*	0.0	$\times 10^9/L$	0.2 - 0.8
Eosinophils		0.0	$\times 10^9/L$	0.0 - 0.4
Basophils		0.0	$\times 10^9/L$	0.0 - 0.2

- Now experiencing maximum effects of chemotherapy with pancytopenia
- Long discussion with consultant as patient refusing further blood transfusion; explained there is a risk to other organs with persistent anaemia (heart, kidneys, liver etc)
- Explained to patient there is a risk with transfusion of red cells, as further haemolytic reaction may further lower haemoglobin, and haemoglobin already very low
- Patient says that for now she would prefer not to have another red cell transfusion

- The following day:

HB	*	39	g/L	118 - 148
RBC	*	1.35	$\times 10^{12}/L$	3.88 - 4.99
Haematocrit	*	0.111	L/L	0.390 - 0.440
Mean Cell Volume		82.1	fL	80.0 - 100.0
MCH		29.0	pg	28.0 - 33.0
Platelets	*	40	$\times 10^9/L$	150 - 400
WBC	*	1.2	$\times 10^9/L$	3.5 - 11.0
Neutrophils	*	0.2	$\times 10^9/L$	2.0 - 7.5
Lymphocytes	*	0.8	$\times 10^9/L$	1.0 - 3.5
Monocytes	*	0.1	$\times 10^9/L$	0.2 - 0.8
Eosinophils		0.0	$\times 10^9/L$	0.0 - 0.4
Basophils		0.0	$\times 10^9/L$	0.0 - 0.2
Reticulocytes				
Reticulocytes		42	$\times 10^9/L$	20 - 110

- However, with supportive care, time (and initiation of treatment for lymphoma...) 7 days later :

- However, with supportive care, time (and initiation of treatment for lymphoma...) 7 days later :

HB	*	63	g/L	118 - 148
RBC	*	1.98	$\times 10^{12}/L$	3.88 - 4.99
Haematocrit	*	0.184	L/L	0.390 - 0.440
Mean Cell Volume		92.9	fL	80.0 - 100.0
MCH		31.7	pg	28.0 - 33.0
Platelets		193	$\times 10^9/L$	150 - 400
WBC	*	2.8	$\times 10^9/L$	3.5 - 11.0
Neutrophils	*	1.6	$\times 10^9/L$	2.0 - 7.5
Lymphocytes	*	0.8	$\times 10^9/L$	1.0 - 3.5
Monocytes		0.4	$\times 10^9/L$	0.2 - 0.8
Eosinophils		0.0	$\times 10^9/L$	0.0 - 0.4
Basophils		0.0	$\times 10^9/L$	0.0 - 0.2

- And one week later :

HB	*	89	g/L	118 - 148
RBC	*	2.94	$\times 10^{12}/L$	3.88 - 4.99
Haematocrit	*	0.265	L/L	0.390 - 0.440
Mean Cell Volume		90.1	fL	80.0 - 100.0
MCH		30.4	pg	28.0 - 33.0
Platelets		273	$\times 10^9/L$	150 - 400
WBC		5.6	$\times 10^9/L$	3.5 - 11.0
Neutrophils		5.2	$\times 10^9/L$	2.0 - 7.5
Lymphocytes	*	0.3	$\times 10^9/L$	1.0 - 3.5
Monocytes	*	0.1	$\times 10^9/L$	0.2 - 0.8
Eosinophils		0.0	$\times 10^9/L$	0.0 - 0.4
Basophils		0.0	$\times 10^9/L$	0.0 - 0.2

- And on R-CHOP cycle 2 day 1

HB	*	95	g/L	118 - 148
RBC	*	3.10	$\times 10^{12}/L$	3.88 - 4.99
Haematocrit	*	0.283	L/L	0.390 - 0.440
Mean Cell Volume		91.2	fL	80.0 - 100.0
MCH		30.5	pg	28.0 - 33.0
Platelets		261	$\times 10^9/L$	150 - 400
WBC		3.9	$\times 10^9/L$	3.5 - 11.0
Neutrophils		2.3	$\times 10^9/L$	2.0 - 7.5
Lymphocytes		1.1	$\times 10^9/L$	1.0 - 3.5
Monocytes		0.5	$\times 10^9/L$	0.2 - 0.8
Eosinophils		0.0	$\times 10^9/L$	0.0 - 0.4
Basophils		0.0	$\times 10^9/L$	0.0 - 0.2

- In summary, this was a lady with a pan-reactive panel, autoimmune haemolytic anaemia secondary to high grade lymphoma.
- Her bone marrow was infiltrated with lymphoma, which likely contributed to her anaemia.
- Best-matched blood induced a severe haemolytic transfusion reaction.
- She responded well to initial chemotherapy but unfortunately end of treatment scan has led to second line salvage chemotherapy.
- She has had no further episodes of haemolysis.

Thank you