Co-incidental finding of pancytopenia

W Thomas and M Beveridge

ABSTRACT
A 73 year old man was found to be pancytopenic after visiting his General Practitioner for a routine health check. He had a history of spinal bulbar atrophy and hypertension. In this teaching case we discuss the investigation and immediate management of the patient, with the outcome of the case also being revealed. The case is an educational piece intended to be at the level required of candidates preparing to sit the membership of the Royal College of Physicians of the United Kingdom.

KEYWORDS: pancytopenia, differential diagnosis.

CASE REPORT
A 73 year old male retired civil servant with a background of spinal bulbar atrophy and hypertension presented to his General Practitioner (GP) for a routine health check. He was taking bendroflumethiazide, propranolol, atorvastatin and aspirin. His brother also has spinal bulbar atrophy.

The GP sent routine blood tests, which came back as follows: Haemoglobin 8.5 (13-17g/dL), Mean Cell Volume 84.9 (80-100fl), White Cell Count 3.4 (4-11 x10^9/L), Neutrophil Count 0.68 (2-8 x10^9/L), Platelets 19 (150-400 x10^9/L). A random blood sugar reading was 18 (3.9-7.8mmol/L). Renal function, bone profile and hepatic function tests were normal. The General Practitioner referred the patient urgently to the local Haematology unit for further assessment.

On further review the patient complained of tiredness but had had no infections or bleeding. There were no night sweats or recent foreign travel. Physical examination was unremarkable, with no lymphadenopathy or organomegaly.

A blood film showed marked anaemia with red cell anisopoikilocytosis, prominent tear drop cells and neutropenia with normal white cell morphology. There were no platelet clumps. A diagnostic investigation followed.

QUESTIONS
What are the differential diagnoses of pancytopenia and which causes are likely here given the findings on examination of the peripheral blood film?

Infections - Viral infections including cytomegalovirus, hepatitis A-E, Epstein-Barr virus, Parvovirus B19 and non A-E hepatitis viruses can cause aplastic anaemia1. The classical picture would be pancytopenia in a young patient who has recently had ‘slapped cheek syndrome’ from parvovirus B19 who has transient bone marrow aplasia. Tropical infections such as visceral leishmania may cause pancytopenia, splenomegaly and a polyclonal rise in immunoglobulins2. Overwhelming sepsis may also cause pancytopenia with a leucoerythroblastic blood film (myeloid precursors, nucleated red blood cells and tear drop red cells). HIV is also an important cause of cytopenias.

Medications - common medications may cause aplastic anaemia, such as chloramphenicol, azathioprine and sodium valproate. The history in this case did not have any recent medications introduced. The other very common cause of pancytopenia in modern practice would be in the context of chemotherapy.

Bone marrow disorders - tear drop cells are a key finding and clue in this case. They suggest an underlying bone marrow disorder and stress. In the context of a known active malignancy they are nearly indicative of bony metastases. Our patient did not have a known malignancy and there was nothing to suggest this on the history or physical examination, although in a man of this age metastatic prostate cancer should be considered. Other bone marrow disorders that would need to be considered are acute leukaemia (which was the diagnosis here), myelodysplasia and myelofibrosis. Splenomegaly would be especially significant in this case as it would be highly suggestive of myelofibrosis in combination with tear drop cells with pancytopenia in an elderly patient3.

B12 and folate deficiency – this may cause pancytopenia, tear drop cells and leucoerythroblastic blood findings4&5. The mean corpuscular volume in this case however is normal which would somewhat argue against B12 and folate deficiency, as
well as the fact that there were no hypersegmented neutrophils seen on the blood film. This cause is however very important given how it is easily reversible and treatable.

**Haemophagocytosis** – this is a bone marrow manifestation of severe inflammation and is a manifestation of systemic disease. It has various causes including viruses (e.g. Epstein Barr virus), malignancy and autoimmune disease. It should be considered in patients with prolonged fever, splenomegaly and cytopenias. It is diagnosed by characteristic findings on bone marrow biopsy.

**Paroxysmal nocturnal haemoglobinuria** – this is a triad of pancytopenia, thrombosis and haemolysis caused by a clonal stem cell disorder with loss of membrane proteins (e.g. CD55 and CD59) that prevent complement activation7.

**Genetic disease** – Fanconi anaemia is a rare autosomal recessive disease with progressive pancytopenia, malignancy and developmental delay. It is caused by defects in DNA repair genes.

The key finding in this case was tear drop cells on the blood film. These are part of a leucoerythroblastic blood picture seen in bone marrow disease, malignant marrow infiltration, systemic illness and occasionally haematinic deficiency. See above for why this is unlikely to be haematinic deficiency. Although tear drop cells can occur in systemic illness such as severe infection, the history here was not in keeping with this. The diagnoses remaining therefore are malignant bone marrow infiltration or a primary bone marrow disorder (myelodysplasia, acute leukaemia or myelofibrosis). There were no features in the history pointing towards a metastatic malignancy and therefore primary bone marrow disorder is the most likely diagnosis. The diagnosis was later established as acute myeloid leukaemia on bone marrow examination.

**What investigations would help to confirm or eliminate the possible diagnoses?**

**Blood tests** including a clotting screen, liver function tests, inflammatory markers and renal function shall help to exclude other systemic disease such as disseminated intravascular coagulation, sepsis, liver disease and thrombotic thrombocytopenic purpura which may all give rise to cytopenias. Autoimmune screening may also suggest vasculitis which can cause cytopenias.

**Microbiology studies** including virology tests (e.g. human immunodeficiency virus, Epstein Barr virus and hepatitis viruses) may also be requested as appropriate given the clinical scenario and findings. Visceral leishmaniasis should be tested for according to travel history and clinical likelihood. Leishmaniasis may be identified through serology and light microscopy (for amastigotes) or polymerase chain reaction of the bone marrow aspirate. Tuberculosis could be cultured from the bone marrow is suspected.

**Haematinics** are a crucial test and the aim should be to try and withhold transfusion until these results are known in case they can easily be replaced thereby negating the need for blood products. Remember that if haematinics are not tested before transfusion then the blood products will confound the tests results.

**Bone marrow biopsy**, including aspirate and trephine are a crucial investigation for morphological examination and microbiological testing if indicated. This will distinguish the bone marrow disorders including acute leukaemia, myelofibrosis, bone marrow metastatic infiltration and myelodysplasia. Haemophagocytic syndrome may also be suggested by bone marrow examination findings.

**Imaging** if there is suspicion of an underlying malignancy (e.g. CT chest, abdomen and pelvis) and then further blood tests such as the prostate specific antigen. Ultrasound could also be used to check for splenomegaly where clinical examination has not been conclusive.

**Medication review** is vital as this may reveal the diagnosis (e.g. use of chloramphenicol)

**Flow cytometry** may be considered to investigate for an abnormal clone in the case of paroxysmal nocturnal haemoglobinuria and may be used on bone marrow samples to further evaluate the cells.

Unless a very clear cause for the pancytopenia is obvious (e.g. haematinic deficiency or malignant infiltration) then bone marrow examination is crucial for establishing a diagnosis. This will also prevent inappropriate treatments being initiated.

**What immediate management steps and advice would be given to this patient?**

General measures for pancytopenia include blood product support. Red cells and platelets can be given for symptomatic anaemia and bleeding. There is no need to transfuse platelets in the patient if there are no signs of bleeding. Alternatively he could also be treated with tranexamic acid as an alternative to avoiding risks associated with platelet transfusion. Infection should be treated urgently. Due to the neutropenia he should be advised to seek medical help if he develops a fever or sore throat. He should urgently be followed up in clinic with the results and given the contact details for the haematology department in the interim period in case he develops any problems.

The specific treatments for pancytopenia rests on the exact cause found after investigation. In this case the diagnosis was acute myeloid leukaemia arising from a background of myelodysplasia. The treatment for acute myeloid leukaemia in general, with curative intent, would consist of induction chemotherapy with DA (daunorubicin and cytosine arabinoside) followed by consolidation with further
chemotherapy, the type of which (e.g. high dose cytosine arabinoside or FLAG-Ida) would depend on the risk assessment of the disease and possible consideration of an allograft bone marrow transplant after consolidation. Currently different approaches to consolidation chemotherapy, transplantation and small molecule inhibitors are being evaluated in clinical trial (e.g. AML 17 clinical trial).

The other options, in older more frail patients where high dose chemotherapy will be very toxic, are low dose palliative chemotherapy and support with transfusion.

PATIENT OUTCOME

He has been supported with blood products (platelets and packed red cells for bleeding and anaemia respectively). After discussion with him and his wife he has elected to have palliative chemotherapy with low dose cytosine arabinoside. He will be seen regularly in the haematology clinic and day unit for review. We do not suspect a link between the leukaemia and spinal bulbar atrophy.

Competing Interests
None declared

Author Details
W THOMAS, MBBS MRCP, Core Medical Trainee Year 2, Department of Haematology, Addenbrookes Hospital, Cambridge. M BEVERIDGE, MBBS MRCP, Core Medical Trainee Year 2, Department of Haematology, Addenbrookes Hospital, Cambridge.

Correspondence: DR W THOMAS, Core Medical Trainee Year 2, Department of Haematology, Addenbrookes Hospital, Hills Road, Cambridge CB2 2QQ.
Email: whcthomas@gmail.com

REFERENCES