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Answers for the CME: Patients with high haemoglobin and negative for JAK2 mutation

1. FTTFT

2. T T F F T

3. T T F T T

1. JAK2 positive polycythaemia is diagnosed when the dual criteria of a high haematocrit (>0.52 in men, >0.48 in women) or raised red cell mass (>25% above predicted) and a mutation in JAK2 are fulfilled.

Often, we forget the existence of JAK2-negative polycythaemia vera (which is not synonymous with secondary polycythaemia).

Diagnosis requires A1-A4 plus another A or two B criteria.

A1-A4

A1 – Raised red cell mass (>25% above predicted) OR haematocrit ≥0.60 in men, ≥0.56 in women, A2 – Absence of mutation in JAK2, A3 – No cause of secondary erythrocytosis, A4 – Bone marrow histology consistent with polycythaemia vera.

plus, another A

A5 – Palpable splenomegaly, A6 – Presence of an acquired genetic abnormality (excluding BCR-ABL1) in the haematopoietic cells.

or two B criteria

B1 – Thrombocytosis (platelet count >450×10^9/L),B2 – Neutrophil leucocytosis (neutrophil count >10×10^9/L in non-smokers, ≥12.5×10^9/L in smokers), B3 – Radiological evidence of splenomegaly, B4 – Low serum erythropoietin.

Accordingly the haematocrit for diagnosis of JAK2 negative PV **is higher than for JAK2 positive PV (haematocrit ≥0.60 in men, ≥0.56 in women)**. All secondary causes have to be excluded as JAK2 negative PV is also an autonomous proliferation. Similar to JAK2 positive PV **splenomegaly** is seen and is a criterion as is **increased white cell and platelet counts** and **trilineage bone marrow hyperplasia**. **Serum erythropoietin is low** and this too is similar to JAK2 positive PV. The presence of an acquired genetic abnormality supports the diagnosis of JAK2 negative PV. However, it does **not include BCR-ABL1 mutation**. Mutations that have been described include SH2B3 (LNK), TET2 and DNMT3A mutations.

2. The other reason a patient is JAK2 negative is obviously because the high Hb is due to a secondary cause and a thorough search for a secondary cause needs to be undertaken. Routine tests would include serum erythropoietin (EPO), arterial oxygen saturation (SaO2), renal /liver function tests, serum ferritin, 2D echo, lung function tests and imaging (USS and CT).

Identifying hypoxia (which leads to secondary erythrocytosis) can be done by using a pulse

oximeter and a **SaO2 of <92% has been shown to be associated with an absolute erythrocytosis**. However, this test is unreliable in certain instances. Although carbon monoxide poisoning, **high oxygen affinity haemoglobins** and sleep apnoea syndrome are conditions that cause hypoxia, **pulse oximetry in these conditions may give normal results.**

EPO levels are high in hypoxic conditions, exogenous administration or endogenous overproduction.

In **Chuvash erythrocytosis there is a defect in the oxygen sensing pathway due to a defect in the VHL gene**. Therefore, there will be **cellular hypoxia leading to increased EPO**. Other congenital defects of hypoxia include EPO receptor defects, other defects in oxygen sensing pathway (mutations in EGLN1 or EPAS1), high oxygen-affinity haemoglobins and 2, 3-BPG deficiency.

Parathyroid neoplasms secrete parathormone which in turn will cause hypercalcaemia

3. Acquired causes for hypoxia are **central hypoxic processes** such as chronic lung disease, right-to-left cardiopulmonary vascular shunts, carbon monoxide poisoning, smoker's erythrocytosis, **sleep apnoea** and high altitude.

Local renal hypoxia is induced by renal artery stenosis, end-stage renal disease, **hydronephrosis** and renal cysts (polycystic kidney disease).

Pathological EPO producing tumours include hepatocellular carcinoma, renal cell cancer, cerebellar hemangioblastoma, parathyroid carcinoma/adenoma, uterine leiomyoma, pheochromocytoma and meningiomas. **Papillary carcinomas of the thyroid gland have not been described as EPO producing tumours**.

Other causes of erythrocytosis include drug-associated (erythropoietin, androgen preparations, **diuretics**), alcohol excess and **post renal transplant erythrocytosis**.

Therefore, a systematic and comprehensive investigation comprising serological tests, lung and cardiac function tests and imaging is needed to identify a secondary cause in patients who do not demonstrate a JAK2 mutation.

References

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