48 Monte Carlo Crescent
Kyalami Business Park
Kyalami, Johannesburg, 1684, RSA
Tel: +27 (0)11 463 3260
Fax: + 27 (0)86 557 2232
Email: ThistleQA@LGCgroup.com
www.thistle.co.za

Please read this section first

The HPCSA and the Med Tech Society have confirmed that this clinical case study, plus your routine review of your EQA reports from Thistle QA, should be documented as a "Journal Club" activity. This means that you must record those attending for CEU purposes. Thistle will not issue a certificate to cover these activities, nor send out "correct" answers to the CEU questions at the end of this case study.

The Thistle QA CEU No is: MTS 17/011

Each attendee should claim ONE CEU point for completing this Quality Control Journal Club exercise, and retain a copy of the relevant Thistle QA Participation Certificate as proof of registration on a Thistle QA EQA.

DIFFERENTIAL SLIDES LEGEND

CYCLE 51 SLIDE 4

POLYCYTHAEMIA VERA (PV)

Polycythemia Vera (PV, PCV) (also known as erythremia, primary polycythemia, Vaquez disease, Osler-Vaquez disease and polycythemia rubra vera) is a neoplasm in which the bone marrow makes too many red blood cells. It may also result in the overproduction of white blood cells and platelets. Most of the health concerns associated with PV are caused by the blood being thicker as a result of the increased red blood cells. It is more common in the elderly and may be symptomatic or asymptomatic. Common signs and symptoms include itching (pruritus), and severe burning pain in the hands or feet that is usually accompanied by a reddish or bluish coloration of the skin. Patients with PV are more likely to have gouty arthritis. Treatment consists primarily of phlebotomy.

Signs and symptoms

Patients with PV can be asymptomatic. A classic symptom of PV is pruritus or itching, particularly after exposure to warm water (such as when taking a bath), which may be due to abnormal histamine release or prostaglandin production. Such itching is present in approximately 40% of patients with PV. Gouty arthritis may be present in up to 20% of patients. Peptic ulcer disease is also common in patients with PV; most likely due to increased histamine from mast cells, but may be related to an increased susceptibility to infection with the ulcer-causing bacterium H. pylori. Another possible mechanism for the development for peptic ulcer is increased histamine release and gastric hyperacidity related with PV.

A rare but classic symptom of PV (and the related myeloproliferative disease essential thrombocythaemia) is erythromelalgia. This is a sudden, severe burning pain in the hands or feet, usually accompanied by a reddish or bluish coloration of the skin. Erythromelalgia is caused by an increased platelet count or increased platelet "stickiness" (aggregation), resulting in the formation of tiny blood clots in the vessels of the extremity; it responds rapidly to treatment with aspirin. Patients with PV are prone to the development of blood clots (thrombosis). A major thrombotic complication (e.g. heart attack, stroke, deep venous thrombosis, or Budd-Chiari syndrome) may sometimes be the first symptom or indication that a person has PV. Headaches, lack of concentration and fatigue are common symptoms that occur in patients with PV as well.

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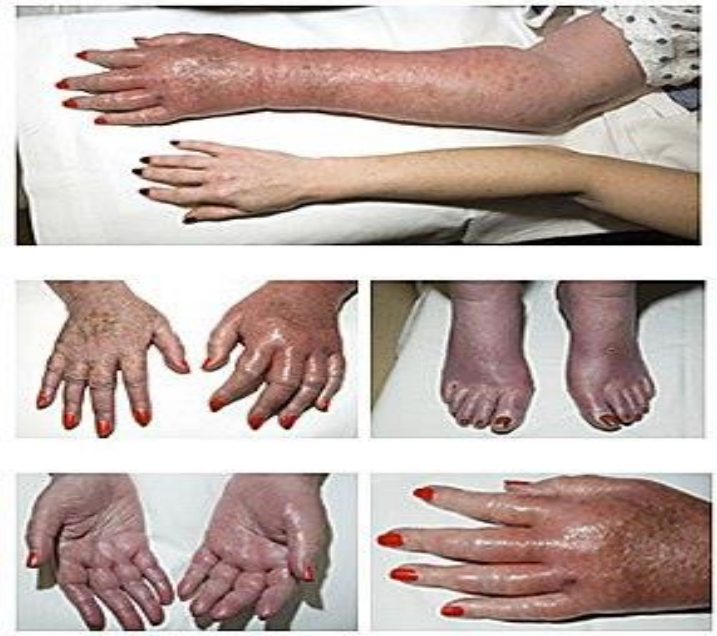

Figure 1: Erythromelalgia in a patient with longstanding polycythemia vera

Pathophysiology

PV, being a primary polycythemia, is caused by neoplastic proliferation and maturation of erythroid, megakaryocytic and granulocytic elements to produce what is referred to as panmyelosis. In contrast to secondary polycythemias, PV is associated with a low serum level of the hormone erythropoietin (EPO). Instead, PV cells often carry a mutation in the tyrosine kinase (JAK2), which acts in signaling pathways of the EPO-receptor, rendering those cells hypersensitive to EPO.

Diagnosis

Physical exam findings are non-specific, but may include enlarged liver or spleen, plethora, or gouty nodules. The diagnosis is often suspected on the basis of laboratory tests. Common findings include an elevated hemoglobin level and hematocrit, reflecting the increased number of red blood cells; the platelet count or white blood cell count may also be increased. The erythrocyte sedimentation rate (ESR) is decreased due to an increase in zeta potential. Because PV results from an essential increase in erythrocyte production, patients have a low erythropoietin (EPO) level.

In primary polycythemia, the red blood count may be as high as 8 - 9 x 10^{12}/l and the hematocrit may be as high as 70 to 80%. In addition, the total blood volume sometimes increases to as much as twice normal. The entire vascular system can become markedly engorged with blood, and circulation times for blood throughout the body can increase up to twice the normal value. The increased numbers of erythrocytes can cause the viscosity of the blood to increase as much as five times normal. Capillaries can become plugged by the very viscous blood, and the flow of blood through the vessels tends to be extremely sluggish.

As a consequence of the above, people with untreated PV are at a risk of various thrombotic events (deep venous thrombosis, pulmonary embolism), heart attack and stroke, and have a substantial risk of Budd-Chiari syndrome (hepatic vein thrombosis), or myelofibrosis. The condition is considered chronic; no cure exists. Symptomatic treatment can normalize the blood count and most patients can live a normal life for years. The disease appears more common in Jews of European extraction than in most non-Jewish populations. Some familial forms of PV are noted, but the mode of inheritance is not clear.

A mutation in the JAK2 kinase (V617F) is strongly associated with PV. JAK2 is a member of the Janus kinase family and makes the erythroid precursors hypersensitive to erythropoietin (EPO). This mutation may be helpful in

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part of the LGC Group

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making a diagnosis or as a target for future therapy. Following history and examination, the British Committee for Standards in Haematology (BCSH) recommend the following tests are performed:

- full blood count/film (raised haematocrit; neutrophils, basophils, platelets raised in half of patients)
- JAK2 mutation
- serum ferritin
- renal and liver function tests

If the JAK2 mutation is negative and there is no obvious secondary causes the BCSH suggest the following tests:

- red cell mass
- arterial oxygen saturation
- abdominal ultrasound
- serum erythropoietin level
- bone marrow aspirate and trephine
- cytogenetic analysis
- erythroid burst-forming unit (BFU-E) culture

Other features that may be seen in PV include a low ESR and a raised leukocyte alkaline phosphatase.

The diagnostic criteria for PV have recently been updated by the BCSH. This replaces the previous PCV Study Group criteria.

JAK2-positive PCV - diagnosis requires both criteria to be present:

A1	High erythrocyte volume fraction (EVF or haematocrit) (>0.52 in men, >0.48 in women) OR raised red cell mass (>25% above predicted)
A2	Mutation in JAK2

JAK2-negative PCV - diagnosis requires A1 + A2 + A3 + either another A or two B criteria:

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	Palpable splenomegaly
A5	Presence of an acquired genetic abnormality (excluding BCR-ABL) in the haematopoietic cells
B1	Thrombocytosis (platelet count >450 * 109/l)
B2	Neutrophil leucocytosis (neutrophil count > 10 * 109/l in non-smokers; > 12.5*109/l in smokers)
B3	Radiological evidence of splenomegaly
B4	Endogenous erythroid colonies or low serum erythropoietin

Treatment

Untreated, PV can be fatal. Research has found that the "1.5-3 years of median survival in the absence of therapy has been extended to at least 10-20 years because of new therapeutic tools." As the condition cannot be cured, treatment focuses on treating symptoms and reducing thrombotic complications by reducing the erythrocyte levels.

- Phlebotomy is one form of treatment, which often may be combined with other therapies. The removal of blood from the body reduces the blood volume and brings down the hematocrit levels below 45 for men or 42 for women; in patients with PV, this reduces the risk of blood clots. It has been observed that phlebotomy also improves cognitive impairment.
- Low dose aspirin (75–81 mg daily) is often prescribed. Research has shown that aspirin reduces the risk for various thrombotic complications.

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- Chemotherapy for polycythemia may be used, either for maintenance, or when the rate of bloodlettings required to maintain normal hematocrit is not acceptable, or when there is significant thrombocytosis or intractable pruritus. The tendency of some practitioners to avoid chemotherapy if possible, especially in young patients, is a result of research indicating possible increased risk of transformation to acute myelogenous leukemia (AML).
- Other therapies include interferon injections, and in cases where secondary thrombocytosis (high platelet count) is present, anagrelide may be prescribed.
- Bone marrow transplants are rarely undertaken in polycythemia patients; since this condition is non-fatal if treated and monitored, the benefits rarely outweigh the risks involved in such a procedure.
- There are indications that with certain genetic markers, erlotinib may be an additional treatment option for this condition.

Epidemiology

Polycythemia Vera occurs in all age groups, although the incidence increases with age.

References

1. https://en.wikipedia.org/wiki/Polycythemia_vera

Questions

1. Discuss the pathophysiology of PV.
2. What are the diagnostic considerations for PV?
3. Discuss the signs and symptoms of PV.
