Ministry of Defence

Synopsis of Causation

Polycythaemia/Myeloproliferative Disease

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Disclaimer

This synopsis has been completed by medical practitioners. It is based on a literature search at the standard of a textbook of medicine and generalist review articles. It is not intended to be a meta-analysis of the literature on the condition specified.

Every effort has been taken to ensure that the information contained in the synopsis is accurate and consistent with current knowledge and practice and to do this the synopsis has been subject to an external validation process by consultants in a relevant specialty nominated by the Royal Society of Medicine.

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1. Definition

1.1. The myeloproliferative disorders are a group of disorders defined by the presence of an abnormally high number of peripheral blood cells in the absence of any other identified cause.

1.2. This Synopsis will consider conditions where either too many red blood cells (polycythaemia rubra vera, or primary proliferative polycythaemia) or platelets (essential thrombocythaemia) are produced in the bone marrow. Although exhibiting some similarities, the myeloproliferative disorder dominated by a high white cell count, chronic myeloid leukaemia, is sufficiently different in behaviour and aetiology to be best considered in a separate synopsis. Idiopathic myelofibrosis (agnogenic myeloid metaplasia) is another related condition not considered here.

1.3. Myeloproliferative disorders are caused by an abnormal clone of cells that has acquired a survival advantage, thereby suppressing normal haemopoiesis. They can, therefore, be considered malignant disorders. However, the malignant clone behaves in an indolent manner and most clinical problems are manifest as haemostatic complications, most importantly myocardial infarctions and strokes.

1.4. A significant problem with the diagnosis of these disorders is that high platelet and red blood cell counts may be caused by several other conditions. Some of these disorders can be excluded fairly easily. However, others cannot and some cases which have been diagnosed as myeloproliferative may not be clonal disorders. The importance of these distinctions is often uncertain.

2. Clinical features

2.1. The incidence is about 1-2 per 100,000 per year in the UK and, unlike most malignancies, this is not thought to vary greatly in different regions of the world.

2.2. The median age of presentation is about 60. The incidence increases with age, following an approximately third power relationship with age (incidence = k.age^3).

2.3. Although the crude incidence is increasing this reflects the above age-specific incidence and an increasingly elderly population. The age-specific incidence appears to be constant.

2.4. Most cases present as a result of a full blood count taken for an unrelated reason and no specific symptoms can be ascribed to the disease. Otherwise, presentation can occur through directly ascribable symptoms or complications.

2.5. Directly ascribable symptoms include those resulting from hyperviscosity (tiredness, headache, disturbed vision, confusion, paraesthesia); other symptoms may include aquagenic itching, night sweats, weight loss, erythromelalgia and other symptoms presumed secondary to poor microcirculation. There may also be symptoms of splenomegaly (pain, early satiety) and symptoms of peripheral vascular disease especially with essential thrombocythaemia.

2.6. Complications include: intravascular thromboses (both arterial and venous) migraine, gout, bone pain, transformation to acute myeloid leukaemia, transformation to myelofibrosis and an increased incidence of peptic ulceration.

2.7. Venous thromboses are most common in the usual sites, for example, lower limb deep venous thromboses, although there is an increased proportion of "unusual" sites involved, notably the liver, giving a Budd-Chiari syndrome.

2.8. As well as thromboses the platelets behave abnormally and there is a bleeding predisposition, sometimes manifest during operations.

2.9. The diagnosis of primary proliferative polycythaemia is suspected when the proportion of blood taken up by red blood cells is over 52% in males or 48% in females. The diagnosis of essential thrombocythaemia is suspected when the platelet count is raised above 400.10^9/L. for more than 2 months.[1]

2.10. Diagnosis of primary proliferative polycythaemia requires the demonstration of a circulating red cell mass in excess of about 36ml/kg (depending on the normal range) with a normal arterial O_2 saturation. The demonstration of splenomegaly, thrombocytosis, leukocytosis, eosinophilia or basophilia aids the diagnosis. Diagnosis of essential thrombocythaemia requires a platelet count above the upper end of the normal range for more than 2 months and is supported by the same features as primary proliferative polycythaemia. Other supportive evidence may also be provided by a cytogenetic abnormality (present in 10-20% of cases), low erythropoietin levels, apparently clonal haemopoiesis, the demonstration of endogenous erythroid colonies or the presence of the JAK2 V617F mutation. The diagnosis of myeloproliferative disorders is therefore dependent on excluding other causes of raised blood counts and supported by

the presence of other features, most of which may occur in the absence of a myeloproliferative disorder. There is no accepted single diagnostic test. Some cases, therefore, which turn out to be clearly myeloproliferative do not, initially, fulfil these criteria. Conversely and less commonly, other cases fulfil the criteria for a myeloproliferative condition but other causes for the abnormalities subsequently become apparent.

3. Aetiology

3.1. Like all clonal disorders, myeloproliferative disorders are caused by acquired somatic mutations. There are numerous karyotypic abnormalities described in association with the condition. The associated genetic abnormalities are often unknown, although it has recently been established that about 40% of cases of essential thrombocythaemia and about 80% cases of primary proliferative polycythaemia are associated with an activating (V617F) mutation in the JAK2 gene, which explains the hypersensitivity to erythropoietin.

3.2. Although cases that fulfil the above criteria for polycythaemia rubra vera are nearly always clonal, almost half of cases that fulfil the criteria for essential thrombocythaemia cannot be demonstrated to be clonal. These cases appear to have a lower risk of thrombosis associated with them although further work is needed on whether these cases are truly myeloproliferative disorders.

3.3. Risk factors for the development of myeloproliferative disorders are poorly researched, especially compared to the leukaemias. There is no consensus on whether any single risk factor is linked to myeloproliferative disorders apart from family history, which is present in under 1% of cases.[2] Other risk factors that have been implicated are Jewish ancestry, history of blood donation, hair dye use (>10 years), living in houses built with materials containing high concentrations of gamma-emitting radionuclides or radon for longer than a decade, and selected occupations (electrical workers, shoemakers, physicians and occupations using solvents and glues).[2,3] However, none of these risk factors has been confirmed in other studies.

3.4. A major question concerning risk factors is therefore whether extrapolation from more extensive studies on leukaemias is justified. On one hand, it is almost certain that both myeloproliferative disorders are caused by somatic mutations. Other more clinically important, and therefore better researched, malignancies have been linked with exposure to mutagens (notably radioactive exposure and chemical carcinogens like chemotherapy, certain solvents and smoking) and it seems unlikely that, given sufficient research, the myeloproliferative disorders would be different. On the other hand, each malignancy is caused by a different range of mutations and the mutagens that increase the mutation rate of those specific sites, added to the background rate seen in all humans, can be difficult to elucidate. For instance, one of the most clear cut epidemiological links described in this area followed the dropping of 2 atomic bombs at the end of World War Two. A highly significant peak of chronic myeloid leukaemia, which can be classed as a myeloproliferative disorder, followed in Hiroshima but was not found at Nagasaki. In neither case was a statistically significant excess of other myeloproliferative disorders seen. However, it is well documented that certain forms of radioactivity (e.g. strontium) can cause these disorders in animal models.

3.5. Although it is plausible that exposure to mutagens and radioactivity might cause primary proliferative polycythaemia or essential thrombocythaemia no risk factor associated with military service can currently be unequivocally blamed for the development of the disease.

4. Prognosis

4.1. Myeloproliferative disorders follow a progressive course, with the exception of rare but well documented cases of chronic myeloid leukaemia spontaneously remitting. The only cure is bone marrow transplantation but this can only be justified in exceptional cases, for example, aggressive disease in a young patient. Data from previous decades described a poor prognosis with a median survival of 18 months. However, this poor figure represented cases presenting in a more advanced stage of disease and, more importantly, there was inadequate treatment at that time. The disease now generally presents earlier and treatment is more effective.

4.2. **Treatment**

4.2.1. The mainstay of treatment is controlling the haematocrit, or platelet count and changing it into, or at least nearer to, the normal range. This unequivocally decreases the frequency of the most frequent complication, thrombosis. Venesection is the treatment of choice for control of high haematocrits. Pharmaceutical treatment is the mainstay for essential thrombocythaemia. Chemotherapy is usually in the form of hydroxycarbamide (until recently, termed hydoxyurea). Second line choices include busulfan, 32P, alpha-interferon and anagrelide.

4.2.2. Adjunct treatment should include treatment of other thrombotic risk factors, notably the use of aspirin.[4]

4.2.3. Nothing can be done to prevent the other main complication of myeloproliferative disorders, transformation to either acute myeloid leukaemia or myelofibrosis. Indeed, good evidence has now accrued that the use of busulfan and P32 increases the rate of transformation. Whether this remains true for hydroxycarbamide remains unproven.[5]

4.3. Good quality prognostic data are not available for unselected British patients. The most relevant figures come from Italy, where the overall survival at 15 years was 65% in patients with polycythaemia and 73% in those with thrombocythaemia.[6] Overall mortality compared with the general population was 1.6-fold higher ($P < 0.001$) in patients with polycythaemia but was not increased in those with thrombocythaemia (SMR = 1; $P = 0.8$).

4.4. The risks of transformation to acute myeloid leukaemia and myelofibrosis differ between reports. The cumulative 20 year risk of transformation to acute leukaemia and idiopathic myelofibrosis is about 5-20% and 1-10% by 10 years.[7-9] Transformation is associated with treatment with P32/busulfan/ pipobroman and a more advanced age.[10] In a study of younger patients (<50 years of age at diagnosis) 20 year cumulative risks of 15% for acute leukaemia and 10% for myelofibrosis were estimated. Overall survival at 20 years was 6.2%. The SMR was 5.3 indicating a mortality significantly higher than that of the general population ($P < 0.0001$).[11]

4.5. The incidence of thrombosis during follow-up is generally 0.2-3% in patients treated satisfactorily, depending mainly on the presence of other risk factors.

4.6. A point mutation V617F in the JAK2 gene has recently been described that may be the cause of 40-80% of myeloproliferative disorders. Not only will this be

helpful in the still problematic diagnosis of these conditions but may lead to the synthesis of a small molecule inhibitor of the relevant tyrosine kinase. Such a compound may improve treatment in the future.

5. Summary

5.1. The myeloproliferative disorders are a group of disorders caused by an abnormal clone of cells producing too many red cells and/or platelets which increase the risk of thromboses and may transform to acute leukaemia or myelofibrosis. Few risk factors have been identified. However, the condition can usually be treated and life expectancy is only moderately reduced.

6. Related Synopses

Leukaemia and Myelodysplastic Syndromes

7. Glossary

aquagenic itching	Itching induced by the contact of water with the skin.
Budd-Chiari syndrome	Rare liver disease in which the veins that drain blood from the liver are blocked or narrowed.
clone	A population of cells derived from a single progenitor cell.
endogenous erythroid colonies	A cluster of red blood cell precursor cells that grow without the addition of erythropoietin, a hormone that is required in healthy people.
erythromelalgia	A painful burning sensation in the limbs often associated with dilation of skin blood vessels.
erythropoietin	A hormone produced in the kidneys which regulates the production of red blood cells in the bone marrow.
essential thrombocythaemia	A condition characterised by the production of large numbers of abnormal platelets.
haematocrit	Percentage of red blood cells in blood.
haemopoiesis	The formation and development of blood cells.
haemostatic	An agent that stops bleeding.
hyperviscosity	Increased viscosity of the blood.
idiopathic myelofibrosis	A progressive disease of the bone marrow in which bone marrow is gradually replaced by fibrous tissue.
JAK2 V617F mutation	A point mutation (V617F) in the JAK2 gene thought to be the cause of up to 80% of myeloproliferative disorders.
karyotypic	Characterisation of the chromosomal complement of an individual or a species, including number, form, and size of the chromosomes.

leukocytosis	Increase in the number of white blood cells.
myeloproliferative	A group of conditions that cause an overproduction of blood cells (platelets, white blood cells, and red blood cells) in the bone marrow.
paraesthesia	Abnormal sensation, such as tingling or pins and needles.
polycythaemia	A condition in which there are too many red blood cells in the blood circulation.
polycythaemia rubra vera	A condition characterised by enlargement of the spleen and increased red blood cell production by the bone marrow. Also known as *primary proliferative polycythaemia*.
somatic mutation	Mutation occurring in the body cells of an organism, a non-heritable type of mutation.
splenomegaly	Enlarged spleen.
thrombocythaemia	An increase above normal in the concentration of the blood platelets.
thrombocytosis	The condition of having abnormally high numbers of platelets. It should be distinguished from thrombocythaemia, a spontaneous clonal overproduction of platelets that is usually persistent.
venesection	The removal of blood from a vein.

8. References

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