# Idiopathic Myelofibrosis

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- Mr C.C. 55 year old gentleman with an ethanol abuse problem presenting to MAU with progressively worsening dyspnoea on exertion.

- Clinically found to have massive splenomegaly down to RIF.

# Investigations

- FBC – WCC - 33.6
  Hgb - 6.1g/dL
  Plt - 575

Leukoerythroblastic film with tear drop poikilocytes

- BM – Aspirate: haemodilute sample with platelet clumps and clumps of dysplastic megakaryocytes, predominantly micromegakaryocytes.
- BM – Trephine: 10-20% cellularity. Occasional dysplastic megakaryocytes seen. No increase in blast cells.
- Increased reticulin Grade 3 – 4.
- BCR-ABL –ve. JAK2 –ve.

- Started on Hydroxyurea.
- Several problems including a cardiac arrest following blood transfusion on the day unit.
- Recently deceased 15/07/05

# Definition

- Idiopathic myelofibrosis (IMF) or myelofibrosis with myeloid metaplasia (MMM) is a chronic stem cell disorder characterised by :
  - Bone marrow fibrosis
  - Extramedullary haematopoiesis
  - Splenomegaly
  - Leukoerythroblastic blood picture

# Incidence

- Reported incidence of 0.5 – 1.3/100,000
- Median age 60 years

# Aetiology

- Unknown.
- Some links to radiation and benzene exposure.

# Historical Perspective

- First described by Heuck in 1879.
- Dameshek first postulated it was one of the members of the myeloproliferative group of disorders in 1951.
- Recently, more light has been shed on the pathogenesis , although this has yet to be translated into clinically relevant advances.

# Pathogenesis

- The fact that IMF is a clonal disorder has been demonstrated by a study of the X chromosome inactivation patterns of G-6-PD in a heterozygote for this gene.
- Recently FISH analysis has shown that also B and T cells are involved.
- Karyotypic analysis has shown that the fibroblast proliferation is not clonal and not part of the underlying malignant clone.

- In IMF there is an increased number of circulating CFU-GEMM pluripotent stem cells and also lineage-restricted stem cells of myeloid lineages i.e. BFU-E, CFU-GM and CFU-Meg.

- This is all reflected in a high peripheral CD34 count.

# Cytogenetics

- Over the last 15 years the publication of the data collected on 256 well characterised cases of IMF have revealed that the commonest abnormalities in descending order of frequency are:
  - 13q- (25%)
  - 20q-
  - Partial duplication of the long arm of chromosome 1
  - Others including trisomy 8, abnormalities of chromosomes 7 and 9.
- Of note, no single one or combination of cytogenetic abnormalities are specific to IMF, since they are found in other disorders such as PRV, ET and MDS.

- Extensive mapping and mutational screening of 13q- and 20q- has not identified any candidate genes, suggesting that haplo-insufficiency may be a common mechanism.

- The incidence of cytogenetic abnormalities in IMF is less in younger patients, explaining the generally better prognosis in young individuals.

- ~33% of patients presenting with IMF have an abnormal karyotype, increasing to ~90% in acute transformation, a finding which supports the multi-step hypothesis of leukaemogenesis.

- Recently, a JAK2 mutation (Val617Phe) has been reported in 30-40% of IMF patients by 4 groups including one local group.

- This mutation which also occurs in 96% of PV patients and 40% of ET patients, almost certainly is important in that it confers growth factor independence in myeloid cell groups.

- STAT5 has been reported to be constitutively activated in IMF, and this may occur by mechanisms independent of JAK2 mutations.

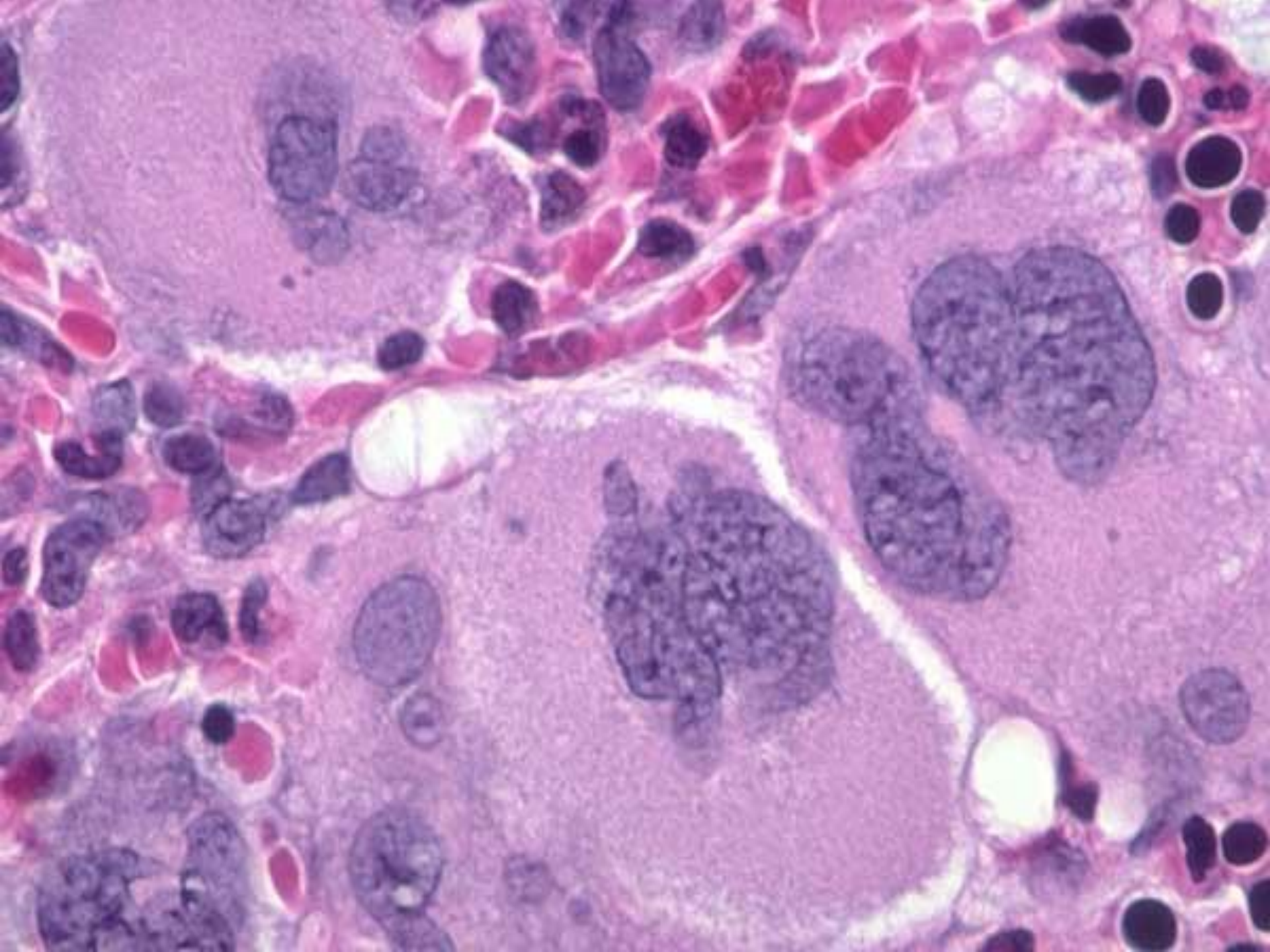
- The exact significance of both JAK2 mutations and STAT5 activation in relation to clinical, diagnostic, prognostic and therapeutic variables is still unknown.

- Myelofibrotic stroma has a complex structure.
  - Increased total collagen including both interstitial and subendothelial collagens, namely Types I,III,IV,V and VI.
  - Excessive deposition of fibronectin, laminin, tenascin and vitronectin.
  - Increased neovascularisation.

- The fibrosis has been found to be secondary to secretion of PDGF and TGF-B by the abnormal megakaryocytic clone occurring in IMF.

- A number of observations support the concept that these megakaryocytic lineages play a pivotal role in the pathogenesis of the disease.

- Structural and maturational defects in megakaryocytes are quite common in IMF.
- The first tangible evidence of the role of the clonal megakaryocytes in the development of fibrosis came from a study by Castro-Malaspina in 1981.
- This demonstrated that the megakaryocytes in IMF stimulated fibroblast proliferation in vitro. PDGF was the first factor incriminated in this event by this study
- Further studies demonstrated the importance first of TGF-B, calmodulin and others.



- A mechanism whereby these mediators are released has also been postulated:
  - The megakaryocytes secrete high levels of P-selectin which aid in neutrophil/eosinophil rolling.
  - These leukocytes, by a process called emperipolesis are surrounded by the megakaryocytes, activated and cause death of both cells releasing the PDGF and TGF-B.

- Several mouse models have supported the pivotal role of the clonal megakaryocytes in the pathophysiology of the disease.

- It has been found that mice which oversecreted TPO and underexpressed GATA1 developed myelofibrosis by the PDGF and TGF-B mechanism hinted to previously.

# Clinical Features

- Asymptomatic in 25%
- Commonest symptoms:
  - Symptoms of anaemia
  - Abdominal discomfort
- Others:
  - Systemic manifestations such as fever, night sweats, malaise and weight loss
  - Bone pain
  - Bleeding
  - Extramedullary haematopoiesis may present according to the organ involved

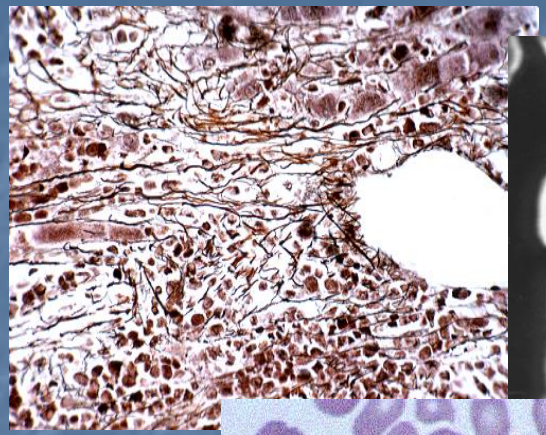
# Commonest Causes of Death

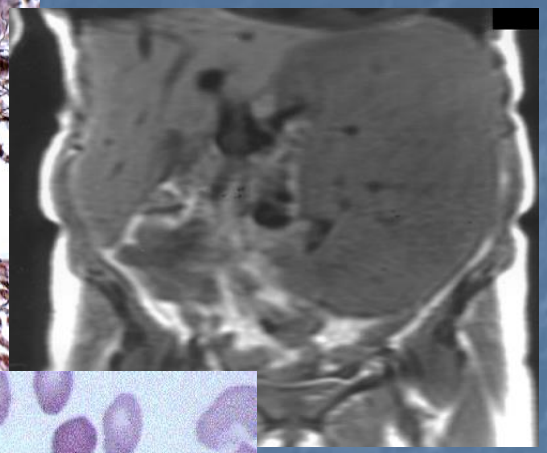
- Infection
- Bleeding
- Cardiac Failure
- Acute Leukaemic Transformation (~15%)

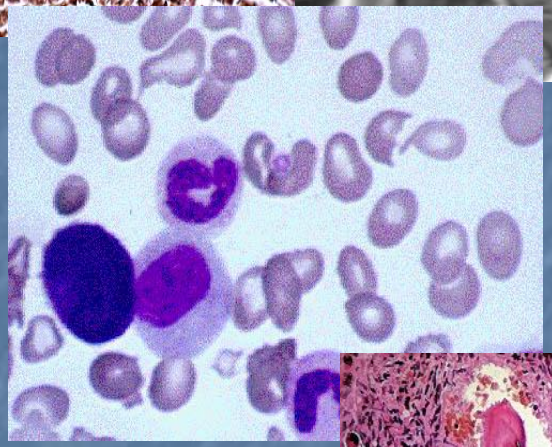
# Diagnosis

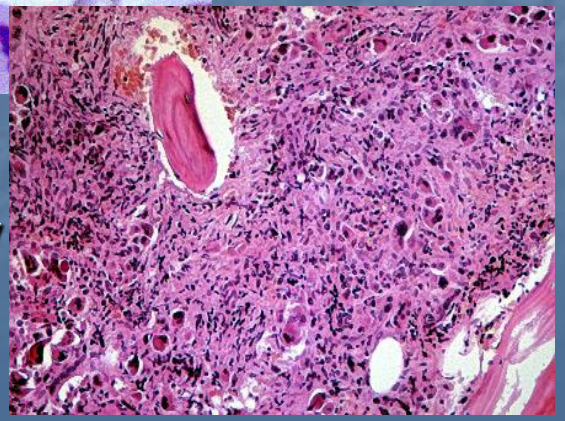
- The concept of a pre-fibrotic stage of IMF has been stressed by a number of German researchers.
- ~25% of patients with pre-fibrotic IMF present with a hypercellular marrow with granulocytic and megakaryocytic proliferation with little or no reticulin.
- The diagnosis requires careful examination of the BM and relies on clustering of megakaryocytes with hypolobulated nuclei.
- According to many German researchers pre-fibrotic IMF is often misdiagnosed as ET, since it is characterised by thrombocytosis, anaemia, splenomegaly, but no leukoerythroblastic blood picture.

- Diagnostic Criteria Proposed by Italian Group (1999):
  - Myelofibrosis
  - BCR-ABL –ve
  - Splenomegaly
  - Myeloid precursors in PB
  - Erythroid precursors in PB
  - Anisopoikilocytosis
  - Megakaryoblastic clustering in BM
  - Abnormal megakaryocyte morphology









# Prognosis

- The overall survival varies from series to series but averages about 4 years in general.
- Two scoring systems in common usage:
  - Lille Score
  - Sheffield Score

# Lille Score
# Dupriez et al. 1997 Blood

## Bad prognostic variables get 1 point each:

- Anaemia (<10g/dL)
- WCC <4x10^9/L or >30x10^9/L

  - Score 0 MS 93 mo
  - Score 1 MS 26 mo
  - Score 2 MS 13 mo

# Sheffield Score
# Reilly et al. 1997

| Age | Hgb (g/dL) | Karyotype | Median Survival (months) |
|---|---|---|---|
| <68 | <10 | N | 54 |
| | | A | 22 |
| | >10 | N | 180 |
| | | A | 72 |
| >68 | <10 | N | 44 |
| | | A | 16 |
| | >10 | N | 70 |
| | | A | 78 |

# Management

- Only curative modality is allogeneic BMT.
- Otherwise essentially palliative.

- Allo-BMT
  - Deeg et al. reported conventional allo-BMT results in 56 patients from a particular institution.
    - Median age at transplantation – 43 years.
    - Median disease duration 33 months.
    - 53 patients achieved engraftment.
    - 2 died of progressive disease
    - 18 died of other causes.
    - 3 year survival 58%
    - Better survival in those with less advanced disease.

- The evidence of a GvMF effect has led to the development of non-myeloablative allo-BMTs in IMF.

- Auto SCT is a possibility for older patients without a donor.

- Anderson, Craig et al. in 2001, reported a series of 21 patients who received single-agent busulphan at 16mg/kg, with a 2 year actuarial survival of 61%.

- However, the mainstay of treatment is palliative and includes the use of:
  - Blood and blood product transfusion (+iron chelation if necessary)
  - Early treatment of infections when they occur.
  - Thalidomide (@low-dose) and steroids in combination.
  - Androgens and steroids in combination.
  - Hydroxyurea
  - Interferon
  - Erythropoietin

- Splenectomy should not be performed routinely and has been found to be of some benefit in patients with:
  - Refractory haemolysis and or thrombocytopenia
  - Symptomatic splenomegaly
  - Significant splenic infarction
  - Severe portal hypertension
- Splenectomy does not prolong survival and is associated with morbidity & mortality of 30% and 8% respectively.