

Di Guglielmo's syndrome

First described in 1923 and named after Giovanni Guglielmo. It is classified as an M6 subtype of acute myeloid leukaemia (AML). It is characterised by large numbers of nucleated red cells appearing in the bone marrow and circulating blood volume.

Pathogenesis

The disease develops in 3 stages:

- Erythemic myelosis: there is anaemia and presence of bizarre red blood cells.
- Erythroleukaemia: characterised by a prominence of myeloblasts in the bone marrow, amegakaryocytic thrombocytopenia and reduced granulopoiesis, leading to neutropenia.
- Acute myeloid leukaemia (AML): the bone marrow is replaced by leukaemic blast cells.

Aetiology

In erythroleukaemia, megaloblastic change coexists with leukaemic changes in the marrow. The causative agent must therefore cause megaloblastosis and be mutagenic at the same time. This sort of change can result from an inadequate supply of any of the four nucleotides in DNA, and it is suggested that an inadequate supply of mutagenic cytosine could be responsible for all the changes seen.^[1]

Epidemiology

Incidence

It is uncommon in children, incidence peaking in the 4th and 7th decades of life.^[2] There is a slight male predisposition. It accounts for 3–5% of all acute myeloid leukaemias (AML); it also forms 20–30% of all secondary leukaemias.^[3]

Risk factors

- Myelodysplastic syndrome (MDS)
- Ionising radiation
- Previous chemotherapy
- Family history (rare familial form – autosomal dominant with variable penetrance) ^[4]

Presentation

Classic presenting features include:

- Pallor
- Fever
- Hepatosplenomegaly
- Anaemia, thrombocytopenia and circulating blasts

Symptoms

- Tiredness, exertional dyspnoea
- Occasionally easy bruising/bleeding
- Fever, bone pain, moderate weight loss
- Arthralgia
- Commonly there is superimposed fungal infection
- Meningism is very rare and indicates CNS involvement

Signs

- The disease is characterised by invasion of the pathological erythroid elements into the spleen, liver, lymph nodes, heart, skin, muscle, oesophagus, stomach, adrenals, kidneys and gonads.
- There is focal necrosis of the spleen.
- Pallor, sometimes petechiae, bruising, gum and nose bleeding, hepatosplenomegaly, lymphadenopathy, retinal haemorrhage.

- In erythroleukaemia: refractory anaemia, splenomegaly present for a long time before nucleated red cells appear in the blood.

Investigations

- FBC shows pancytopenia.
- Blood smear shows nucleated red cells at different stages with pathological features (macrocytosis, schistocytes, blast cells <50%, thrombocytopenia).
- Bone marrow biopsy shows prevalence of erythroid elements with anaplastic/dysplastic changes and reduced megakaryocytes.
- Check B12 and red cell folate to exclude pernicious anaemia.
- LFTs to check lactate dehydrogenase and uric acid, which may be raised.
- Rheumatoid factor, antinuclear antibody, Coombs' test, and immunoglobulins should be evaluated. Autoantibodies and hypergammaglobulinaemia have been reported in patients with erythroleukaemia who have joint or bone pain.
- Flow cytometry and cytogenetics confirm diagnosis and help in assessing prognosis (some chromosomal abnormalities are less favourable than others).
- CXR and CT/MRI scanning are usually performed as staging examinations. Echocardiogram is used to assess cardiac function before chemotherapy.
- Bone marrow aspiration and biopsy are critical in making the diagnosis of acute erythroleukaemia.

Associations

There is an association with autoimmune abnormalities, eg arthritis, peripheral neuropathy, vasculitis, iritis, myositis.^[5] No causal relationship has been found.^[6]

Management

The approach to the treatment of acute erythroleukaemia is similar to the approach used for other subtypes of acute myeloid leukaemia (AML).

Remission induction:

- This usually involves treatment with 2 chemotherapy drugs, cytarabine (ara-C) and an anthracycline drug such as daunorubicin or idarubicin.
- If induction is successful, no leukaemia cells will be found in the blood, and the number of blast cells in the bone marrow will be less than 5% within a week or two. Induction is successful in about 40% to 80% of all AML patients.^[7]

Consolidation (post-remission) therapy:

This may consist of:

- Several courses of high-dose cytarabine (ara-C) chemotherapy
- Allogeneic (donor) stem cell transplant
- Autologous stem cell transplant

Multidrug resistance gene - MDRI- expression correlates with unfavourable cytogenetic aberrations and is responsible for poor response to chemotherapy and short survival time. MDR modulators, eg cyclosporin A and verapamil, are being assessed for their ability to overcome this resistance. A less favourable outcome may be observed in:

- Elderly patients
- Patients with secondary erythroleukaemia, usually after treatment with alkylating agents
- Patients with unfavourable cytogenetics

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