# Aplastic Anaemia Evolving into Myelodysplastic Syndrome

Pages with reference to book, From 380 To 381

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## Introduction

Acquired aplastic anaemia is a clonal disorder of multifactonal origin[1,2]. The ~pathophysiology of this disorder is still not clear Presumably the multiple incriminating factors include an intrinsic derangement of haematopoiesis, immune mediated damage to bone marrow and genetic predisposition[3,4]. The long term complications of the aplastic anaemia include clonal evolution into disorders like Paroxysmal Nocturnal Haemoglobiniiria (PNH), Myelodysplastic Syndrome (MDS) and Acute Non-Lymphoblastic Leukaemias (ANLL) seen especially in non-grafted cases[2,5-8]. These clonal changes are usually seen in the patients who receive immunosuppressive therapy e.g., ALG with or without cyclosporin and corticosteroids. The MDS cases evolving from aplastic anaemia have shown chromosomal aberrations similar to those seen in secondary MDS e.g., trisomy[8], monosomy[7], monosomy 5, del 5q and del 7q etc[6-9]. This suggest that clonal evolution is the result of therapy, although the mechanism is not clear.

It is extremely unusual to see clonal evolution in patients of aplastic anaemia who recoverspontaneously orwiththe use of androgemc steroids or have been transplanted[6,8]. Some of these cases are probably hypoplastic MDS or hypoplastic ANLL right from the beginning[10]. Such cases deteriorate rapidly and die within a short time. We report a case ofaplastic anaemia who was treated only with androgens and recovered. After a period of six years, during which he remained almost symptom free, he eventually developed Chronic Myelomonocytic Leukaemia (CMML).

## Case Report

A 16 years old young male presented in our institute in 1990 with a 2 months history of epistaxis, fever and purpunc spots developing over his entire body. One month prior to this illness he had sprinkled DDT over his bed to kill bed bugs and slept over it fora couple of days (acommonpractice to kill bed bugs during summer). He had been to many general practitioners and a ENT specialist for these symptoms and had been treated with antimalarial (Amodiaquine), antibiotics (Suipharnethoxazole + Trimethopnm) and silver nitrate nasal packs for epistaxis.

At presentation, physical examination showed few purpuric spots on upper and lower limbs. Peripheral blood smear showed pancytopenia (haemoglobin 7.2 g/dl, total leukocyte count 0.8x109/l, absolute neutrophil count 0.34x109/l, platelet count 19x109/l and reticulocyic count 0.05%). Bone marrow aspiration and trephine biopsy showed markedly hypocellular marrow. On the basis of these findings he was diagnosed as a case of severe aplastic anaemia. He was treated with supportive therapy (blood transfusion) and oxymetholone (Anapolone) 50 mg twice daily. After continuous use of oxymethoclone for 8 months his blood counts improved and he became transfusion independent (haemoglobin 13.5 g/dl, absolute neutrophil count 2.5x109/1, platelet count 135x109/l and reticulocyte count 1.8%). However he started complaining of frequent abdominal pain.. The liver function tests were within normal limits (serum bilirubin 15 umol/i, alanine amino tranferase 20 u/I and alkaline phosphatase 225 u/I). Abdominal ultrasound examination was also unremarkable. A Ham's test, urine haemosiderin, sucrose lysis test and flow cytometeric analysis for CD59 were repeatedly negative.

From 1991 to 1996 he remained transfusion independent. His platelet count occasionally went down to

as low as 60x109/l but recovered with short courses of oxymetholone. Cytogenetic studies were carried out in 1993 proved to be unremarkable. In December, 1996, during routine check up his peripheral blood revealed 10% blasts and 18% monocyles with dysplastic features (total leukocyte count 0.8x109/l , haemoglobin 12.6 g/dl, platelet count 79xl09/l and reticulocyte count 1.5%). Bone marrow aspiration showed 12% blasts and he was diagnosed as a case of chronic nwelomonocytic leukaernia. However, he did not receive any active intervention at this stage.
After five months he returned with high grade fever and bilateral subconjunctival haemorrhages. His peripheral blood smear showed 20% blasts (total leukocyte count 9,9xl09/l, haemoglobin 11.7 g/dl and platelet count 102x109/l). At this time his cytogenetic analysis (short term unstimulated cultures) revealed monosomy 7 in 70% metaphases. He was given low dose Ara C (15 rng subcutaneous twice daily), ciproxin 500 mug and cimetidine 400 ing twice daily. He refused hospital admission and went back to his village. Five months later his brother informed us of his death from the illness.

**Discussion**

The frequency of transformation of aplastic anaemia cases to PNH, MDS and acute leukemias varies from 10-15%[6,7]. One study has reported the risk of clonal evolution as high as 57% at eight years follow up in cases of aplasiic anaemia[5]. The interval between initial manifestation of the disease and appearance ofclonal change is extremely variable, ranging from few months to 20 years.[6]
Insecticides like chiorophenthane (DOT), parathion and chiordane etc have been reported as aetiological agents in cases ofaplastic anaemia in literature[11]. The first indication for clonal evolution to MDS or ANLL may come from abnormal kaiyotype. However, the chromosomal studies in cases of aplastic anaemia particularly at the time of diagnosis have always proved disappointing mostly due to lack of availability of enough metaphases for the analysis[5,6]. In one study carried out in our institute chromosomal changes were seen in 22% cases of aplastic anaemia suggesting the possibility of having hypoplastic MDS inaproportionofcases. All these cases did not survive enough to develop frank phenotypic evolution. When clonal evolution does occur, the abnormal karyotype seen are those which are associated with secondary cases and have poor prognosis. The evolution is therefore considered to be secondaiy to immunosuppressive therapy[9,12].
This case is usual in the sense that the patient was managed with oxymetholone alone without any immunosuppressive therapy. The patient responded well to this therapy and became transfusion independent in eight months. Search in the literature has shown that all the cases showing clonal evolution were either on androgens with corticosteroids or on immunosuppressive therapy and it was rare to find a patient surviving for six years[6,13]
The chromosomal abnormality i.e., monosomy[7], seen in this case is one of the commonest abberation seen in MDS with poor prognosis[9,14]. But chromosomal abberations seen in MDS have no predilection for any special FAB subtype[11,14].
There are many questions yet to be answered regarding clonal evolution in aplastic anaemia cases. Whether really a proportion of severe aplastic anaemia cases actually are hypoplastic MDS or it is the therapy which alters the immune systemandcauses mutationand/orpromotes the emergence of the mutant clone already present? Whether severe aplastic anaemia itself is a malignant disorder and prolonged survival with modem therapeutic modalities is enough for the emergence of malignant clone'? These queries can only be answered with development of more refined cytogenetic techniques and employment of more sensitive PCR based procedures for detection of specific clonal changes in aplastic anaemia cases especially at the time of diagnosis.

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