SEQUENTIAL INDUCTION OF APL&STIC ANEMIA AND ACUTE LEUKEMIA BY CHLORAMPHENICOL

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Chloramphenicol is a widely used antibiotic. It is also well known to cause some potentially lethal complications such as aplastic anemia, acute leukemia and paroxysmal nocturnal haemoglobinuria Al though development of aplastic anemia is relatively more frequent, evidence in favour of acute leukemia caused by chloramphenicol is mostly circumstantial. Very rarely, aplastic anemia caused by chloramphenicol may degenerate into acute leukemia. We describe a case who developed aplastic anemia following chl oramphenicol treatment. Bone marrow done at that time was severely aplastic with no evidence of leukemia. Her bone marrow improved completely with resolution of pancytopenia. Six months later she was again found to have pancytopenia. Bone marrow examination this time confirmed her to be suffering from acute mycloid leukemia. This sequential development of aplastic anemia and acute leukemia carries some interesting pathogenetic implications.

CASE REPORT

A twenty year old lady was admitted to the Aga Khan University Hospital with complaints of fever and generalized weakness. Two months back she had developed high grade fever. Her widal test for salmonella typhi was positive at a titre of 1:320. She was treated with chloramphenicol. Her fever subsided but two weeks later she developed increasing weakness and pallor. She was taken to a local clinic, found to be severely pancytopenic and transferredto this hospital. On examination she was found to be very pale. There was no lymphadenopathy. Liver was slightly enlarged and splenic tip was barely palpable. Her haemoglobin was 8g/dl, WBC 700/cmm and platelets 84,000/cmm. Bone marrow examination revealed a hypocellular marrow (Figure 1).

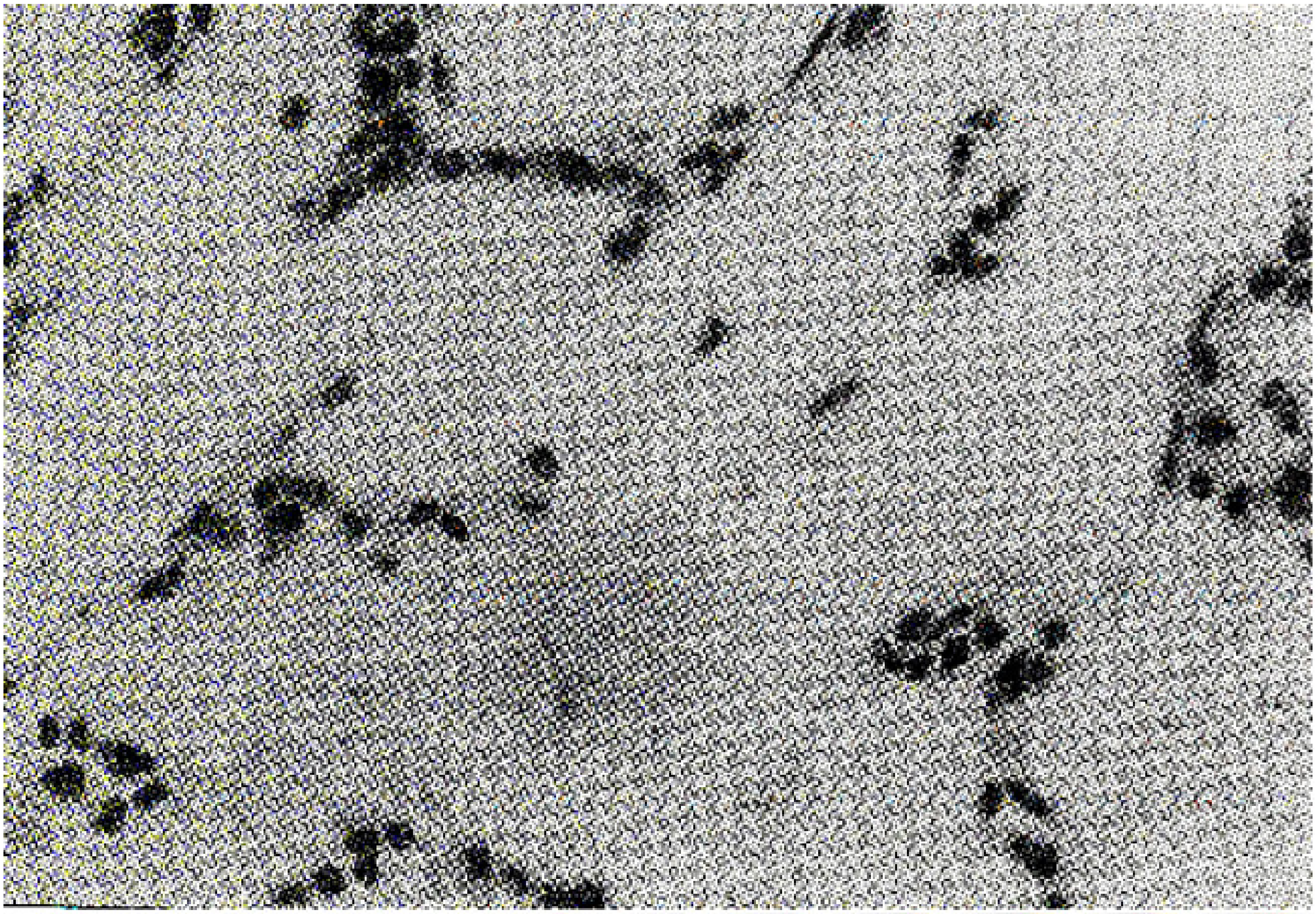

Figure 1.First admission: Bone marrow aspirate showing marked hypo cellubrity.

She was found to have F. coli bacteremia and treated with antibiotics. Over the next few days, her blood counts improved. Repeat bone marrow examination was normal. She was discharged with haemobglobin of 10.9g/dl, WBC 5100/cmm with sixty percent neutrophils and a normal platelet count. The patient remained symptom-free for the next six months. She then started having weakness, anorexia and body aches. She was readmitted to this hospital with fever. Blood examination revealed haemoglobin 3.8g/dl, WBC 4700/cmm with seventy-five percent blasts and platelet count of 10,000/cmm. Bone marrow aspirate showed hypercellular marrow heavily infiltrated with blasts (Figure 2).

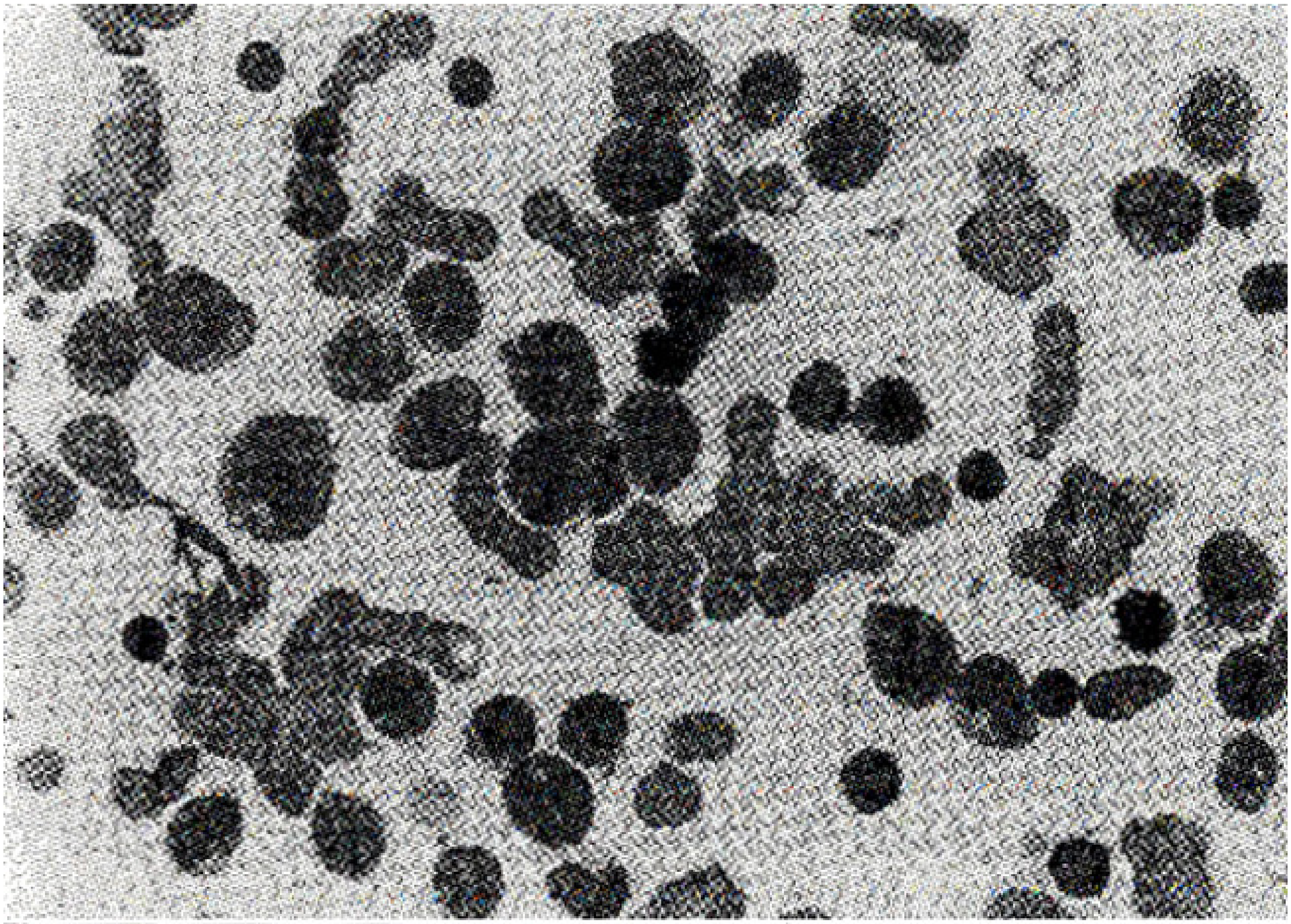

Figure 2. Acute myelomonocytic leukemia: Bone marrow infiltrated with blasts.

The blasts were PAS negative, sudan black positive and non-specific esterase positive. She was categorized as acute myelomonocytic leukemia (M4). She received induction therapy with three days of daunorubicin and seven days of cytosine-arabinoside. She responded well to this treatment and a marrow examination done three weeks later confirmed clinical complete remission of acute leukemia.

DISCUSSION

Chloramphenicol is an important antibiotic that has been widely used for a IonS time. It has been very effectively used for the treatment of typhoid fever and for several other infectious disorders of childhood. Its usage apparently is more common in the third world countries. In Pakistan, it is widely used in intravenous, oral and topical forms. Chloramphenicol is well known to cause some potentially lethal complications such as aplastic anemia, acute leukemia and paroxysmal nocturnal hemoglobinuria[1-4]. It can cause bone marrow suppression by two mechanisms. More commonly, it can cause a dose dependent, usually reversible, bone marrow suppression that initially affects eryrthroid cell line and later involves other cellular elements. Less commonly, chloramphenicol can cause an idiosyncratic, non dose-dependent, usually irreversible, most often fatal, bone marrow suppression[5]. The actual risk of developing fatal asplastic anemia after being treated with chloramphenicol is about 1 in 20,000 to 1 in 30,000[6]. This is 13 times higher incidence than the risk of aplastic anemia in the general population. It has been suggested that chloramphenicol causes dose-dependent marrow failure by affecting proliferation and maturation of differentiated cells. It is heralded by increase in serum iron, decrease in reticulocytes and vacuolization of the normoblasts[7]. Another explanation is that chloramphenicol and some of its intestinal metabolites interact with granulocyte-macrophage colony stimulating factor (GM-CSF) and the cells producing it. GM-CSF is an important factor as it stimulates the growth and differentiation of human hematopoietic progenitor cells by activating transcription of specific genes[9]. This inhibitory effect of chloramphenicol can be reversed by the use of recombinant human GM-CSF[8]. In the aplastic anaemia of idiosyncratic type, chloramphenicol affects the cellular DNA and renders the cells incapable of differentiation, In some cases a genetic predisposition of the stem cells to this inhibitory effect of chloramphenicol on the nucleic acid synthesisniay exist[10]. This effect has been observed even after topical uses of chloramphenicol[11]. Chloramphenicol has also been incriminated to cause acute non- lymphoid leukemia. This effect is similar to that of benzene, ionizing radiation and alkylating agents[12-15]. The acute leukemia may or may not be preceded byaplastic anemia[16]. Marrows cells have shown unusual chromosomal changes including vacuolization and a large telocentric marker chromosome. Similar changes have been observed in lymphoid cells cultured in the presence of chloramphenicol[17]. A population based case-control study carried out in Shanghai suggested a significant dose response relationship between the drug use and the risk ofacute leukemias[18]. Most of this evidence, however, is still circumstantial. Our patient provides a clear association ofchloramphenicol induced aplastic anemia and subsequent development of acute leukemia. Initial recovery from aplastic anemia in this case is more suggestive of dose-dependent effect rather than an idiosyncratic reaction. Chloramphenicol may have caused DNA damage while inducing aplasia, subsequently degenerating into acute leukemia. However, it is more plausible that patient may have already sub-clinical acute leukemia at the time of initial presentation and that may have made the stem cells more susceptible to the inhibitory effect of chloramphenicol. Dose- dependent type of aplasia and short time interval between aplastic anemia and subsequent acute leukemia are in favour of this hypothesis. In conclusion we have described a patient who developed chloramphenicol induced aplastic anemia, who subsequently developed acute leukemia. We hypothesize that sub-clinical leukemia may have already existed and could have increased the tendency to develop chloramphenicol induced bone marrow suppression.

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