Int J Clin Exp Pathol 2015;8(1):818-823
www.ijcep.com /ISSN:1936-2625/IJCEP0003393

*Original Article*

# Dysplastic changes in erythroid precursors as a manifestation of lead poisoning: report of a case and review of literature

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Received October 26, 2014; Accepted December 22, 2014; Epub January 1, 2015; Published January 15, 2015

**Abstract:** Dysplastic changes in erythroid precursors occur not only in patients with hematologic diseases, but also those with other diseases. Here, we report on a patient that presented with dysplastic changes in erythroid precursors due to lead poisoning from the intake of Chinese folk remedies.

**Keywords:** Lead poisoning, dyserythropoiesis, bone marrow

## Introduction

Dysplastic changes in erythroid precursors occur in patients with hematologic diseases, such as myelodysplastic syndromes, pyruvate kinase deficiency and hereditary stomatocytosis [1-3]. These changes can also occur in patients with infectious diseases (e.g. dengue virus-associated hemophagocytic syndrome, visceral leishmaniasis and malaria) [4-6], autoimmune diseases (disseminated lupus erythematosus) [7], and other diseases as well as those who used certain medicines [8, 9]. Here, we report on a patient presenting with dysplastic changes in erythroid precursors due to lead poisoning from the intake of Chinese folk remedies.

Lead is a common environmental pollutant and humans can be exposed to it from many sources, including air, food, dust, soil and water. In adults, occupational exposure is the main cause of lead poisoning [10-16]. In Asia, traditional practices, such as folk remedies, may be another important source of lead exposure [17-20]. The symptoms of lead poisoning include abdominal pain, confusion, headache, anemia, irritability, and, in severe cases, seizures, coma and death [21]. Because the symptoms of lead poisoning are nonspecific, misdiagnoses and/or missed diagnoses often occur, especially in sporadic cases.

## Case report

In July of 2014, a 60-year-old female patient presented with fatigue, pallor, chest tightness, shortness of breath after physical activity, poor appetite and skin hyperalgesia. She visited several hospitals and was examined multiple times. Blood tests found macrocytic anemia, an ALT of 151 U/L, an AST of 142 U/L, a serum total bilirubin of 49 μmol/L, and a serum direct bilirubin of 20 μmol/L (**Table 1**). Other tests performed, all of which fell within normal parameters, included serum folic acid, vitamin B12, ferroprotein, LDH, fecal occult blood, urine bilirubin and urobilinogen, as well as acranial, chest and abdominal CT scan, gastroscopy and colonoscopy. She received a red blood cell transfusion, but continued to feel progressively worse. In particular, she complained of abdominal pain in her skin over her entire body and feeling faint. One month later, she was determined to be anemic by our department.

Upon physical examination, her body temperature was 36°C, respiratory rate was 18 breaths/min, pulse rate was 87 beats/min and blood pressure was 138/86 mmHg. She had pale conjunctiva with yellow skin and sclera, mild tenderness upon deep abdominal palpation, and painful skin across her entire body. The results of laboratory tests were as follows: WBC $4.9\times10^9$ cells/L, RBC $2.49\times10^{12}$ cells/L, Hb 71

**Table 1.** Changes of blood test results before and after $CaNa_2$-EDTA therapy of lead poisoning patient

| | WBC (4-10×10$^9$/L) | Hb (113-151 g/L) | MCV (82-95 fl) | MCH (27-31 pg) | MCHC (320-360 g/L) | Ret (0.5-1.5 %) | PLT (100-300×10$^9$/L) | ALT (5-40 U/L) | LDH 109-245 (U/L) | TBIL (5-20.5 uM/L) | DBIL (1.7-6.8 uM/L) | Blood lead (200-400 ug/dL) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Before treatment | 4.9 | 71 | 94.4 | 28.5 | 302 | 13.7 | 224 | 23.3 | 187 | 63.4 | 35.2 | 630 |
| After treatment | 5.0 | 119 | 84.3 | 27.9 | 331 | 0.87 | 119 | 10.3 | 110 | 11.7 | 3.0 | 200 |

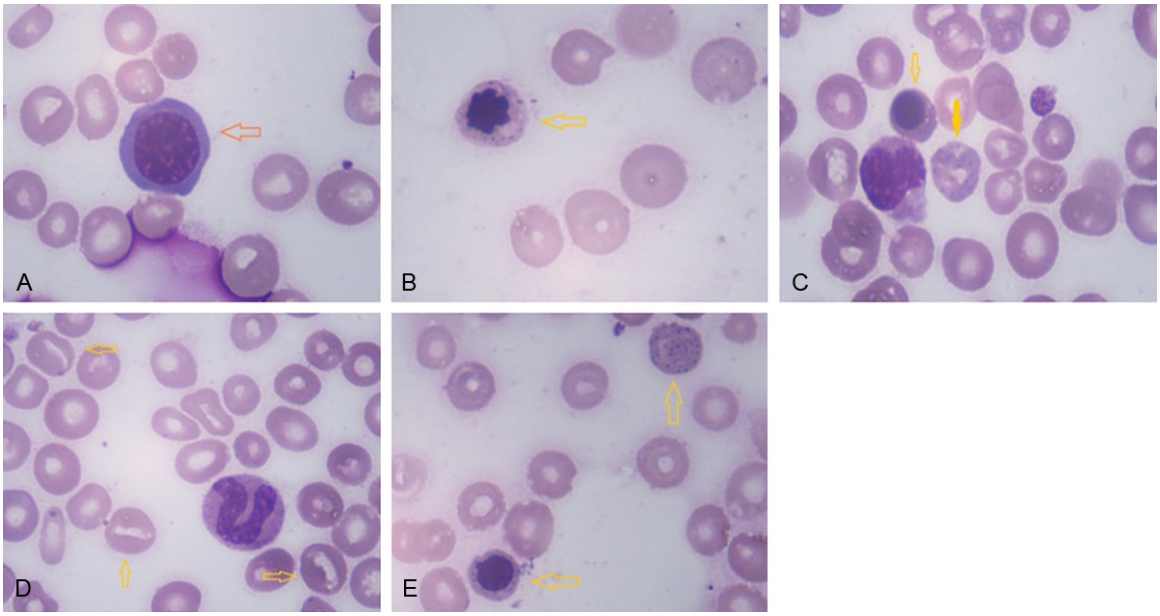


**Figure 1.** Dysplastic changes in erythroid precursors in bone marrow smear. A. Anisocytosis and megaloblastic erythroblast (open orange arrow). B. Segmented erythroid cell (open orange arrow). C. Anisocytosis, carbon nucleated red cell (open orange arrow) and basophilic stippling of erythrocyte (solid orange arrow). D. Anisocytosis and stomatocytes (open orange arrow). E. Erythrocytes of basophilic stippling (open orange arrow).

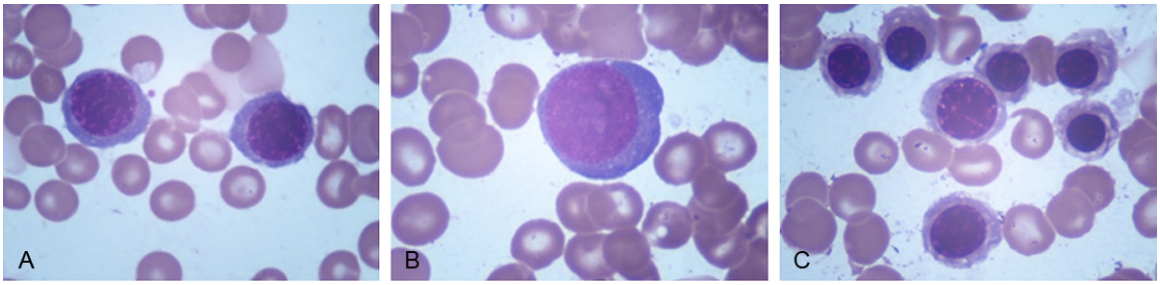


**Figure 2.** Normal erythroid precursors in bone marrow smear after $CaNa_2$-EDTA therapy.

g/L, Hct 23.5%, MCV 94.4 fl, MCH 28.5 pg, MCHC 302 g/L, PLT 224×10$^9$/L, Ret 13.7%, ALT 23.3 U/L, AST 30.1 U/L, serum total bilirubin 63.4 umol/L, serum direct bilirubin 35.2 umol/L, and urobilinogen and urobilirubin were negative. Bone marrow smears revealed dysplastic changes in erythroid precursors (**Figure 1**). Of the cells in the smear, 28% of them were dysplastic erythroid precursors.

The patient received treatments to alleviate her symptoms, including red blood cell transfusions, but failed to improve. Anemia should not have caused the patient's diverse symptoms, suggesting there must be another etiology. She lived in a nearby village and neither her family nor any others in her village displayed similar symptoms. However, she had taken folk remedies two months prior for almost a month

**Table 2.** Other reasons which may cause dyserythropoiesis of peripheral blood

| Reasons | Morbidity of dyserythropoiesis | References |
|---|---|---|
| Pyruvate Kinase Deficiency | Unavailable | [1, 2] |
| Hereditary Stomatocytosis | Case report | [3] |
| Dengue Virus-associated Hemophagocytic syndrome | Case report | [4] |
| Visceral Leishmaniasis | Case report | [5] |
| Malaria | 67% | [6] |
| Disseminated Lupus Erythematosus | Case report | [7] |
| Ellis-van Creveld Syndrome | Case report | [8] |
| Medicine Usage | Case report | [9] |

**Table 3.** Possible features of blood or marrow erythroid of lead poisoning patients

| Location | Features of erythoid | Incidence | References |
|---|---|---|---|
| Blood | Normocytic normochromic anemia | Common | [31-34] |
| | Anisocytosis | Common | |
| | Polychromasia | Common | |
| | Basophilic stippling of erythrocytes | Common | |
| Marrow | Rare nucleated erythrocyte | Rare | |
| | Hyperreactive erythropoiesis | Common | |
| | Incomplete differentiation especially with basophilic stippling of erythroid progenitor cells | Common | |

because of a lumbar vertebral fracture. It was then that her symptoms started, suggesting that the folk remedies were involved and, through them, there may have been an accumulation of heavy metals in her body. Samples of her blood and urine were sent to Nanjing Occupational Disease Precaution Clinic for heavy metal testing. It was determined that the level of lead in her blood had increased to 630 μg/dl, but her mercury level was normal. Therefore, she was diagnosed with lead poisoning. She received $CaNa_2$-EDTA therapy and her symptoms improved. One month after starting treatment, her blood hemoglobin had increased, serum bilirubin returned to normal and blood lead level became 490 μg/dl. Two months after starting $CaNa_2$-EDTA therapy, her blood lead level had decreased to 200 μg/dl and her blood hemoglobin (**Table 1**) and bone marrow smear (**Figure 2**) were normal.

## Discussion

When it comes to lead exposure, herbal remedies are not usually mentioned as a source. However, patented Chinese and other Asian remedies have been previously reported to be contaminated or adulterated with heavy metals such as lead, arsenic, mercury and cadmium and, therefore, may be a health hazard to those who take them. A portion of the Chinese population, especially those without a basic education, use folk remedies to cure chronic health problems. An increasing number of experimental and clinical trials concerning Chinese medicines have been performed, and some have concluded that Chinese medicines may provide an alternative treatment for some diseases. However, some folk remedies have no scientific basis and, despite the unwillingness of registered doctors to prescribe them, are sometimes taken by patients. Koet al [22] reported that at least 83 of 240 (32%) Asian patented medicines were adulterated by undeclared pharmaceuticals or heavy metals. Severe cases of lead poisoning have been reported in children after they took contaminated herbal remedies [23-30]. The patient described in this case report took oral folk remedies for approximately one month to promote healing of her lumbar vertebral fracture. By comparing her diet and living environment to her family members, it was determined that the only possible etiology for her symptoms were the Chinese folk remedies she found an elevated level of lead. As she had no remnants of the folk remedy and could not get the medicine again, we were unable to directly measure the lead in the folk remedy. However, based on the evidence at hand, the folk remedy was concluded to be the leading cause of the lead poisoning.

Dyserythropoiesis is most frequently seen in patients with myelodysplastic syndromes, other hematologic diseases (e.g. pyruvate kinase deficiency and hereditary stomatocytosis) [1-3], infectious diseases (e.g. dengue virus-associated hemophagocytic syndrome, visceral leishmaniasis, and malaria) [4-6] and autoimmune diseases (e.g. disseminated lupus erythematosus) [7]. Other diseases and even the use of certain medicines [8, 9] can also be sometimes accompanied by dyserythropoiesis (**Table 2**). Importantly, for patients with lead poisoning, anemia can be a symptom. Furthermore, laboratory tests may find a normocytic and normochromic anemia, anisocytosis, polychromasia and basophilic stippling of erythrocytes, and a hyperreactive erythropoiesis with basophilic stippling of erythrocytes and incomplete differentiation (especially with basophilic stippling of erythroid progenitor cells) [31-34]. In a previous case report concerning a patient with lead poisoning [34], peripheral blood smears showed extensive basophilic stippling, bone marrow smears revealed dyserythropoiesis with intense basophilic stippling of bone marrow red cell precursors, and a bone marrow cytogenetic test revealed loss of the Y chromosome in 3 out of 20 metaphases (**Table 3**). Following treatment, the peripheral blood smear showed normal morphology with complete resolution of the basophilic stippling, while the bone marrow morphology and karyotype returned to normal. In this case, our patient also had normal peripheral blood smears and bone marrow morphology following $CaNa_2$-EDTA therapy.

Exposure to lead reduces the ability to repair DNA, and, thus, may lead to chromosomal aberrations and structural abnormalities, such as breaks, gaps and sister chromatid exchanges [35, 36]. Forni et al [37] compared 18 healthy females that had occupational exposure to lead to 12 comparable female controls, and found a significantly increased rate of metaphases with chromatid and chromosome aberrations in the former cohort. Lead can affect cell membranes, and transport and energy systems, and can interfere with heme synthesis, which may explain the shortened erythrocyte survival time, anemia and elevation of bilirubin upon exposure. In particular, lead inhibits the 3 major enzymes involved with heme synthesis of δ-aminolaevulinic acid dehydratase, coproporphyrinogen oxidase and ferrochelatase as well as pyrimidine 5'-nucleotidase [38]. The patient described in this report presented not only with a normocytic, normochromic anemia and anisocytosis, but also megaloblastic erythroblasts, segmented erythroid cells, carbon nucleated red cell and stomatocytes. But further tests such as cytogenetics and examination of enzymes were not administered.

Some Asian countries have been attempting to regulate the quality of traditional remedies, and health officials in Singapore have effectively achieved such control [39]. However, the current case report underscores the importance of post-marketing surveillance for toxicity associated with herbs and dietary supplements and, corresponding with that, the public health value of case-finding.

In high-risk possession listed above, people have significantly higher blood lead levels than others. While some of these people remain asymptomatic, there are many case reports of lead poisoning that are sporadic and due to a wide range of causes like folk remedies, gunshots and infection. In conclusion, lead poisoning should be considered to limit misdiagnosis when dyserythropoiesis and other nonspecific complaints are present.

## Conclusion

Dysplastic changes in erythroid precursors are found not only in patients with hematologic diseases, but also in patients with other diseases, such as lead poisoning. When a large number of people have lead poisoning, it is easy to diagnose. However, because the symptoms of lead poisoning are nonspecific, accidental lead poisoning can often be missed or misdiagnosed. Asian folk remedies used to promote health may pose a potential hazard due to heavy metal contamination. Therefore, for patients with nonspecific symptoms who have recently taken Asian folk remedies, heavy metal poisoning should be considered. Medical toxicologists, public health agencies and poison control centers should cooperate internationally to accomplish effective post-marketing product surveillance of folk remedies.

## Acknowledgements

This work was supported by grants from the National Natural Science Foundation of China (No. 31171386 and 31371399), the Jiangsu

Province Natural Science Foundation (No. BK2011093).

## Disclosure of conflict of interest

None.

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