Transient loss of the Y-chromosome in an elderly man with anemia and lead poisoning: Chance occurrence or a clonal marker of the underlying hematological abnormality?

One of the most important environmental and occupational pollutants is lead. Cytogenetic damage is known to occur to many individuals exposed to lead, e.g., outdoor and car painters, traffic policemen, gasoline station attendants, etc.[1] Chronic lead exposure affects many organ systems leading to a gradual decline in the so-called *safe* blood lead levels over time.

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We report a 60-year-old man who presented with pallor and abdominal pain. Clinical examination showed mild hepatomegaly without splenomegaly. Laboratory investigations revealed leukocytes 6,700/μL with normal differential, hemoglobin 10.9 gr/dL, hematocrit 32.7%, MCV 88.8 fl, MCH 29.6pg, platelets 281,000/μL, total bilirubin 0.44 mg/dL and LDH 181IU/L. Examination of the peripheral blood smear showed extensive basophilic stippling, while a bone marrow examination revealed dyserythropoiesis with intense basophilic stippling of the bone marrow red cell precursors. Bone marrow cytogenetics revealed loss of the Y chromosome in 3 out of 20 metaphases. On questioning the patient, he admitted consuming large amounts of a local self-made spirit called *raki*. Since this spirit is frequently produced into lead-containing boilers, we suspected chronic lead poisoning and measured lead levels in his blood. Indeed, a high blood lead concentration (75 μg/dL) was detected (upper level of normal for blood lead in our laboratory 20 μg/dL). To investigate the matter further, we confirmed a high lead content (17 mg/L) in a sample of the raki he used to consume. Although there are no official upper limits for raki lead content in Greece, the raki lead concentration in our case was much higher than the local upper limit set for wines (0.2 mg/L) or for other spirits in countries of the European Union. For example, in Ireland for drinks and cocktails the limit is 1 mg/l, for brandy or beer it is 0.5 mg/l, while in Germany the upper limit for wine and its products is 0.3 mg/L. Since dimercaptosuccinic acid is not commercially available in Greece, we decided to treat our patient with penicillamine[2] 500 mg bid for 2.5 months and until the urine ‰-aminolevulinic acid dropped to <4.5 mg/L, the upper limit of normal for urine ALA in our laboratory, compared to 62 mg/L before treatment. At the same time, we advised him to completely refrain from raki. A year later we repeated all blood and bone marrow examinations. The hemogram had now normalized showing leukocytes 7,400/μL with normal differential, hemoglobin 14.9 g/dL, hematocrit 45.9%, MCV 94.1 fl, MCH 30.7 pg, MCHC 32.6 g/dl, and platelets 247,000/μL, while the peripheral blood smear showed normal morphology with complete resolution of the basophilic stippling. Bone marrow morphology and karyotype were normal. According to the International System for Human Cytogenetic Nomenclature (ISCN 2005), an abnormal clone exists if 3 cells have loss of the same chromosome, which was exactly the case in our patient. Moreover, the normal karyotype after penicillamine therapy in this patient supports that the loss of the Y chromosome may be a clonal marker of the lead and alcohol-induced hematological abnormality. However, the low percentage loss (3 out of 20 cells) is in total agreement with the mean percentage loss of 36.8%±21.5% that has been described in elderly men without any association to disease.[3,4] Moreover, in elderly men with no evidence of haematological disease, this loss may be transient.[4] Therefore, the transient loss of the Y chromosome in our patient was most likely a chance occurrence and not due to lead poisoning and/or alcohol intake. Lead exposure reduces the DNA repair capacity and can cause chromosomal aberrations and structural abnormalities, such as gaps, breaks, and sister chromatid exchanges.[5,6] Moreover, chronic ethanol intoxication can lead to chromosome damage that persists for a long time constituting a risk factor for development of neoplasias.[7] Chromosome and biochemical (blood lead, erythrocyte protoporphyrin, ‰-aminolevulinic acid dehydratase activity of red blood cells) studies conducted in 18 healthy females occupationally exposed to lead and in 12 comparable female controls showed significantly increased rates of metaphases with chromatid and chromosome aberrations in the exposed versus controls.[8] Loss of the Y chromosome has been described as a good prognostic factor is myelodysplastic syndromes (MDS)[9] for which evidence is accumulating for an association between occupational and/or environmental exposures.[10] However, since lead poising is well-known to cause anemia and dyserythropoiesis, and since the hematological and cytogenetic findings in our elderly male patient were transient, MDS is not the correct diagnosis in this case. In conclusion, this teaching case emphasizes the diagnostic dilemma for the potential association of lead and alcohol to cytogenetic abnormalities in the face of aging and suggests that elderly patients with anemia should be investigated for potentially treatable occupational and/or environmental exposures.

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