Loss of the Y Chromosome and Anemia: Age-Related Phenomenon or Myelodysplastic Syndrome?

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INTRODUCTION

Myelodysplastic syndrome (MDS) represents a heterogeneous hematopoietic stem cell disorder that results in abnormal cellular maturation and peripheral blood cytopenias. Balanced and unbalanced translocations are rare among patients with the myelodysplastic syndrome; however, those involving chromosomal deletions are common. [1,3] The most common deletions are loss of chromosome 5q, 7q, 20q, and 12p. Y chromosome loss (-Y) is considered a normal aging phenomenon; however, some studies have indicated a link between -Y and neoplastic changes with arbitrary cut off of greater than 75% loss [2]. Isolated loss of the Y chromosome is a frequent cytogenetic finding in MDS. A study in 2008 revealed that 14 of 142 patients (9.9%) with loss of Y developed MDS and reported a 3.8-fold increase in the risk of developing MDS with –Y [5]. It usually starts with normocytic anemia, as in our case.

CASE

We present the case of a 78-year-old gentleman with a history of multiple Transient Ischemic Attacks, Hypertension, Hyperlipidemia, Chronic Obstructive Pulmonary Disease, Benign Prostatic Hypertrophy, and Diastolic Dysfunction who was admitted to hospital with fever and was found to have Acute kidney Injury (creatinine level 6.17). He was treated empirically with antibiotics for suspicion of Sepsis, but all infectious and autoimmune workup remained negative. Once discharged after resolution of kidney injury, he was readmitted with recurrent fever (39.6°C on the second admission), rash (Figure 1), mild confusion, elevated creatinine (2.36 mg/dl), anemia (Hgb 9.8 g/dL), and markedly elevated proBNP. Troponins were positive with no ischemic change on ECG. He was diagnosed with decompensated diastolic heart failure and was diuresed accordingly. The extensive infectious disease workup was negative. Fever was considered related to Hydralazine due to its temporal relationship. Hydralazine was stopped, and the patient was also given a short course of steroids. The fever subsided, with all work up once again turned out negative. Multiple Myeloma was on the differential, however, was ruled out after standard diagnostic workup. Plasma creatinine improved during hospitalization, but his Hgb remained below 9 g/dL without any signs of GI bleed. A bone marrow biopsy was obtained. The marrow was morphologically normal (Figure 2), with no dysplasia or plasma cell neoplasm, but karyotype showed loss of Y chromosome in 90% of cells, suggestive of clonal hematopoiesis. Flow cytometry was normal. Karyotype was normal other than deletion Y, 45, X,-Y(27)/46, XY (3). MDS FISH panel was negative along with MDS FISH being negative. Based on clinical suspicion of MDS, he was started on ESA therapy with darbopoietin 300 mcg and had significant improvement in his anemia.

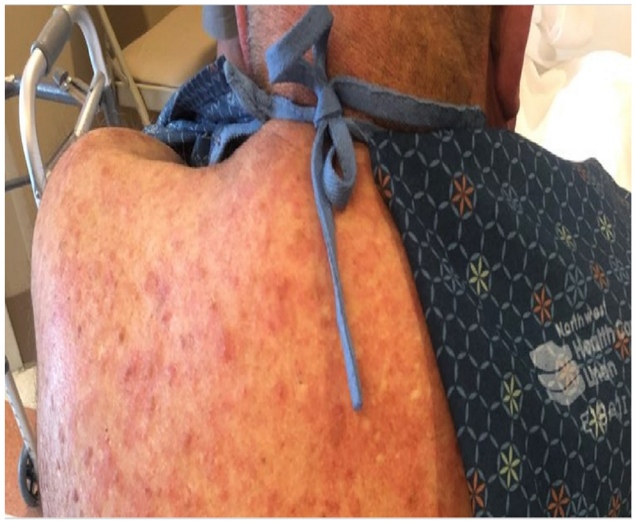

Figure 1: Rash with fever

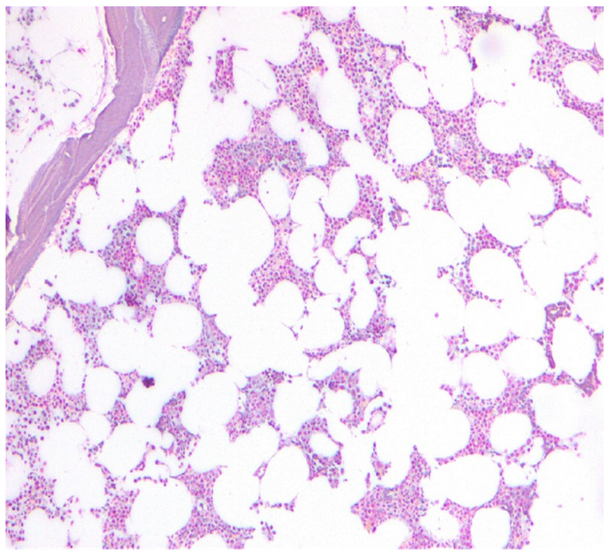

Figure 2: Negative for significant reticulin fibrosis

CONCLUSION

Deletion of Y chromosome can be a normal aging chromosome change among men, but when detected in majority of bone marrow cells, it may indicate clonal dysplastic hematopoiesis. Hematopathologists often use 75% or higher percentage of interphase nuclei carrying chromosome Y deletion as an arbitrary cut off to suggest clonal hematopoiesis. [4]

Our patient had a persistent anemia with otherwise negative work-up. His bone marrow was morphologically normal, without evidence of dysplasia. Flow cytometry was normal as well. Chromosome Y was deleted in 90% of nuclei, therefore possibility of clonal hematopoiesis was raised.[6] He was treated with darbopoietin and his anemia significantly improved.

Next generation sequencing or multi-gene panels for MDS-specific mutations are increasingly being used in routine clinical practice to aid with diagnosis, prognosis and individualized treatment of MDS. In our patient, detection of an MDS-associated mutation or chromosome deletion would have been very helpful in diagnosis of early MDS, as chromosome Y deletion could merely reflect an aging process.[2,3,4]

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