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Genetic predisposition syndromes: When should they be considered in the work-up of MDS?

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Myelodysplastic syndromes (MDS) are clonal hematopoietic disorders characterized by cytopenias, ineffective hematopoiesis, myelodysplasia, and an increased risk of acute myeloid leukemia (AML). While sporadic MDS is primarily a disease of the elderly, MDS in children and young and middle-aged adults is frequently associated with underlying genetic predisposition syndromes. In addition to the classic hereditary bone marrow failure syndromes (BMFS) such as Fanconi Anemia and Dyskeratosis Congenita, in recent years there has been an increased awareness of non-syndromic familial MDS/AML predisposition syndromes such as those caused by mutations in *GATA2*, *RUNX1*, *CEBPA*, and *SRP72* genes. Here, we will discuss the importance of recognizing an underlying genetic predisposition syndrome a patient with MDS, will review clinical scenarios when genetic predisposition should be considered, and will provide a practical overview of the common BMFS and familial MDS/AML syndromes which may be encountered in adult patients with MDS.

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Introduction

Ms. A is a 22-year-old female who presented with progressive fatigue and pancytopenia. Complete blood count revealed a white blood cell count of 2.7 · 10^3/μl, hemoglobin of 9.1 g/dl with an elevated mean corpuscular volume of 115 fl, and a platelet count of 86 · 10^3/μl, with a low absolute neutrophil count of 490 · 10^3/μl. Past medical history was notable for frequent bacterial infections, a cervical conization procedure for Human Papilloma Virus (HPV)-associated cervical intraepithelial neoplasia and lymphedema of her left lower extremity as a child. There were no toxic exposures, and she was taking no medications. Family history was unremarkable. On physical examination, Ms. A was a well-appearing young woman of normal stature, with no abnormal physical findings. A bone marrow aspirate and biopsy revealed a hypocellular marrow with erythroid dysplasia and an expansion of myeloblasts, consistent with MDS. Cytogenetic studies revealed monosomy 7. Due to the patient's young age, an inherited BMFS was suspected. Testing for Dyskeratosis Congenita and Fanconi Anemia was negative. Based on her presentation, she was clinically diagnosed with Emberger Syndrome. After *GATA2* genetic testing became available, a *de novo* pathogenic *GATA2* gene mutation was confirmed. She and her family received genetic counseling. No other family members were affected. She elected to proceed with fertility preservation, and subsequently underwent a bone marrow transplant. She is currently doing well.

The 2008 World Health Organization (WHO) classification defines myelodysplastic syndromes as a group of clonal hematopoietic stem cell disorders characterized by cytopenias, dysplasia in one or more myeloid cell lines, ineffective hematopoiesis, and increased risk of acute myeloid leukemia (AML) [1]. Historically defined by blast percentage and dysplastic morphology, MDS is now known to be driven by the sequential acquisition of clonal genetic changes through somatic mutations as well as gain or loss of chromosomal regions. Recurrent mutations found in MDS disrupt key regulatory pathways including RNA splicing (*SFSB1*, *SRSF2*, *U2AF1* and *ZRSR2*), epigenetic modifier genes (*TET2*, *DNMT3A*, *IDH1*/*IDH2*, *ASXL1*, *EZH2*, and *SETBP1*), regulators of transcription (*RUNX1*, *BCOR*, *ETV6*), DNA repair (*TP53*), signaling pathways (*NRAS*, *KRAS*, *CBL*, *JAK2*, *FLT3*, *NF1*), and cohesins (*STAG2*) [2].

The incidence of MDS increases with age, with 86% of MDS patients diagnosed over the age of 60 years; the median age at diagnosis is 76 years [3]. Based on the 2001 Surveillance, Epidemiology, and End Results (SEER) data, the incidence of MDS in patients younger than 40 is estimated at 0.14 per 100,000, but rises to over 36 per 100,000 in patients 80 years and older [4]. In children, MDS is exceedingly rare, with an annual incidence of 0.8–4 cases per million [5]. Sporadic, or primary MDS, the most common type of MDS diagnosed in the elderly, is thought to be multifactorial and to arise due to the cumulative age-related genetic damage. In contrast, secondary MDS can frequently be traced to cytotoxic exposures, such as alkylating agents and topoisomerase inhibitors, radiation, and certain environmental and occupational toxins such as benzene, agricultural chemicals and solvents [6]. In pediatric patients, MDS is strongly associated with cytotoxic exposures, classic hereditary BMFS, non-syndromic familial MDS/AML predisposition syndromes, or long history of acquired aplastic anemia [5] (Fig. 1). With the increasing knowledge of hereditary BMFS and familial MDS/AML syndromes, there is

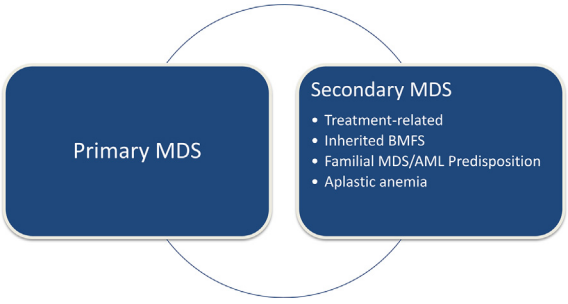

Fig. 1. Primary and secondary myelodysplastic syndromes.