Two Common Diagnostic Challenges of Juvenile Myelomonocytic Leukemia

Jinjun Cheng[1], Sarah Harney[1], David Jacobsohn[1], and Reuven Schore[1]

[1]Children's National Hospital Center for Cancer and Blood Disorders

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Jinjun Cheng MD PhD[1,3,4*], Sarah Harney MD[1, 2], David Jacobsohn MD[1, 2], Reuven Schore MD[1,2*]

1. Center for Cancer and Blood Disorders, Children's National Hospital, Washington, DC
2. Department of Pediatrics, The George Washington University School of Medicine and Health Sciences, Washington, District of Columbia, USA
3. Division of Pathology and Laboratory Medicine, Children's National Hospital, Washington, DC
4. Departments of Pathology and Pediatrics, The George Washington

University School of Medicine and Health Sciences, Washington, District of Columbia, USA

***Correspondence to:**

Jinjun Cheng, MD, PhD

Pathology and Laboratory Medicine Division

Children's National Hospital

Room 1629, 111 Michigan Avenue NW

Washington, DC 20010-2970

Telephone: 202-476-4311

Fax: 202-476-4030

Reuven Schore, MD

Center for Cancer and Blood Disorders

Children's National Hospital

Associate Professor of Pediatrics

The George Washington University School of Medicine and Health Sciences

111 Michigan Avenue NW

Washington, DC 20010

Phone: 202-476-2800

Fax: 202-476-5685

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List of abbreviations:

Abbreviation	Full term
JMML	Juvenile Myelomonocytic Leukemia
AML	Acute Myeloid Leukemia
MPN	Myeloproliferative Neoplasm
NS-MPD	Noonan Syndrome-associated Myeloproliferative Disorder
ICC	International Consensus Classification
WHO	World Health Organization
COG	Children's Oncology Group

Discussion:

We report two pediatric cases of JMML with diagnostic challenges.[5] The first patient had a KRAS mutation which is a diagnostic criterion for JMML, but was also found on genomic testing to have a translocation of *NUP98::NSD1* , which makes this case qualify as an AML according to the recent 5th WHO and International Consensus Classification (ICC) classifications.[4,10] Notably, a few JMML patients have been reported with structural rearrangements that are typically associated with AML (e.g. inversion 3 and*NUP98::NSD1*).[6] *NUP98::NSD1* translocations can be missed on routine karyotyping and are independently associated with very poor prognosis.[11]These patients, including our first patient, require aggressive treatment and in fact may respond well to JMML therapy.

The ICC classification includes a distinct entity of Noonan syndrome–associated myeloproliferative disorder (NS-MPD), to characterize patients with Noonan syndrome and germline mutations in*PTPN11* , *KRAS* , *NRAS* or *RIT1* experiencing a transient myeloproliferative disorder in the first year of life.[12] These patients may be appropriately managed with close observation or mild chemotherapy.[5,13] A recent study of a cohort of patients with NS-MPD further shows variable clinical outcomes.[14] The disease onset within 1-year-old age and high VAF of *PTPN11* mutation in our second patient raised a differential diagnosis of NS-MPD. However, this mutation was confirmed to be somatic in nature; and the blasts show aberrant immunophenotype.[15] Hence, the findings fit JMML, and the patient received chemotherapy followed by BMT. Interestingly, Glu76 Lys of PTPN11 has been the most affected residue in JMML.[16]

In summary, our JMML cases demonstrate some common diagnostic pitfalls. It is important to recognize these unusual features of JMML and further risk stratify JMML, especially because rare JMML may self-resolve,[14,17] and a significant percentage of JMML relapse after BMT.[18]

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