Proceedings

Molecular Genomics in Precision Hematopathology

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Abstract: This section focuses on the molecular tools employed in precision hematopathology. Dr. Xia Li in her presentation led us through a new journey to genomics and precision medicine by discussing the utilization of fluorescence in situ hybridization (FISH), polymerase chain reaction (PCR), and next generation sequencing (NGS) in the diagnosis and treatment of adult hematological malignancies, whereas Dr. Kristian Schafernak vividly discussed the utility of chromosomal microarray (CMA) to compensate for the specimen insufficiency and less sensitive cytogenetic studies in the evaluation of suspected pediatric hematolymphoid malignancies with numerous exemplary cases, and concluded that CMA is a valuable tool that seems to be underutilized.

Keywords: ALL, AML, CMA, FISH, MRD, NGS

A New Journey to Genomics and Precision Medicine

It is known that genetics and genomics both play roles in health and disease. Genetics refers to the study of genes and the way that certain traits or conditions are passed down from one generation to another. Genomics describes the study of a person's whole genes (the genome).

Genetic testing has been utilized in pathological diagnosis, clinical prognosis, risk stratification, and therapeutic guidance for the conditions such as prenatal (infertility and *in vitro* fertilization), postnatal (inborn diseases) and cancers (acquired diseases).

Many genetic testing methods are widely used in molecular pathology labs. The common assays include cytogenetics, florescence *in situ* hybridization (FISH), and cytogenomics in cytogenetics labs, polymerase chain reaction (PCR), sequencing (Sanger, pyrosequencing, and next generation sequencing (NGS)), and gene expression profile in molecular labs.

Individuality is determined by ancestry, environment, culture, and experience. These will affect risk of disease, response to treatment and side effects to the medications. Precision medicine is a revolutionary approach to patient care. It uses advanced genetics and molecular testing or big-data analytics to help clinicians to craft the best treatment strategies for patients. In this regard, precision medicine is to administer the right drug, at the right dose, to the right person, at the right time.

Although precision medicine has paved a stellar path for the treatment of cancer, it relies heavily on precision pathology, as part of precision medicine which still faces challenges in optimizing patients' interests in prioritizing use of limited specimens, par-

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ticularly irreplaceable tissue samples. A major problem is simply the imbalance between available patient specimen and tests to be ordered. Since limited patient samples are often used in morphology, immunohistochemistry (IHC), FISH, NGS DNA/RNA sequencing, PCR, or clinical trials, etc. Pathologists often face a dilemma in prioritizing the assays that serve the best interest of patients. Therefore, communications between pathologists and geneticists are becoming more and more important.

There are many genetic biomarkers used in hematopathology practice (see Table 1). For example, in AML patients, there are numerous mutations and fusions associated with diagnosis, prognosis and therapeutic decision [1]. Tests are usually performed sequentially, and it takes a long time to give results. NGS is the solution to reduce the number of assays, turn-around time (TAT) and sample size. The clinical utility of the multiple biomarker testing using NGS includes screening, diagnosis, prognosis, monitoring minimal residual disease and predicting individual's response to treatment. During the disease monitoring, any mutations identified may change the treatment strategy, which is so called targeted therapy.

NGS is also known as massively parallel sequencing. Millions of reads generated by NGS are aligned to a reference sequence and are being analyzed by sequencing software. Analysis is computationally intense with high-throughput and low cost. NGS enables to test many genes on a single assay with a very small amount of sample and very short TAT. It has fundamentally changed the paradigm of clinical practice. A study from 4,656 patients with hematological disorders identified the most common mutations including *TET2* (7.5%), *DNMT3A* (5.04%), *TP53* (4.37%), *JAK2* (3.9%), *ASXL1* (3.03%), *SF3B1*, and *CSDE1* (2.84%), *FLT3* ITD/TKD, *IDH1/2*, *NPM1*, *WT1*, and *NRAS* (1.5-2%) (Figure 1) and fusions including *BCR::ABL1*, *CBFB::MYH11*, *PML::RARA*, *RUNX1::RUNX1T1*, *KMT2A* and *RUNX1* rearrangements (<2%)(Figure **??**) [2]. Among these samples, *KIT* mutations presented in 15% core-binding factor AML with *CBFB::MYH11*, and 23% core-binding fac-

Table 1: Landscape of Hematology Biomarker Testing

Biomarker/Gene	Therapeutic Target	Assay	Cancer Type	Drug
FLT3 ITD/TKD (mutation)	FLT3	NGS/PCR	AML	midostaurin, sorafinib
IDH1 (mutation)	IDH1	NGS, PCR	AML	ivosidenib, AG-881
IDH2 (mutation)	IDH2	NGS, PCR	AML	cytarabin, enasidenib, AH-881
CBF/MYH11 (translocation)	CBFB	FISH, NGS, PCR	AML	gemtuzumab ozogamicin + chemotherapy
KIT (mutation)	KIT	NGS, PCR	AML with core-binding factors	no drug, but with poor prognosis
PML/RARA (translocation)	PML/RARA	FISH, NGS, PCR	APL	all-*trans* retinoic acid
BCL2 (mutation)	BCL2	NGS, PCR	CLL, AML	venetoclax
BCR/ABL1 (translocation)	ABL1	FISN, NGS, PCR	CML	imatinib, nilotinib
BCR/ABL1 (translocation)	ABL1	FISN, NGS, PCR	CML (imatinib-resistant)	dasatanib
JAK2 (mutation)	JAK2	NGS, PCR	PV	ruxolitinib
EZH2 (mutation)	EZH2	NGS, PCR	follicular lymphoma	tazemetostat

https://www.cancer.gov/about-cancer/treatment/types/targeted-therapies/targeted-therapies-fact-sheet

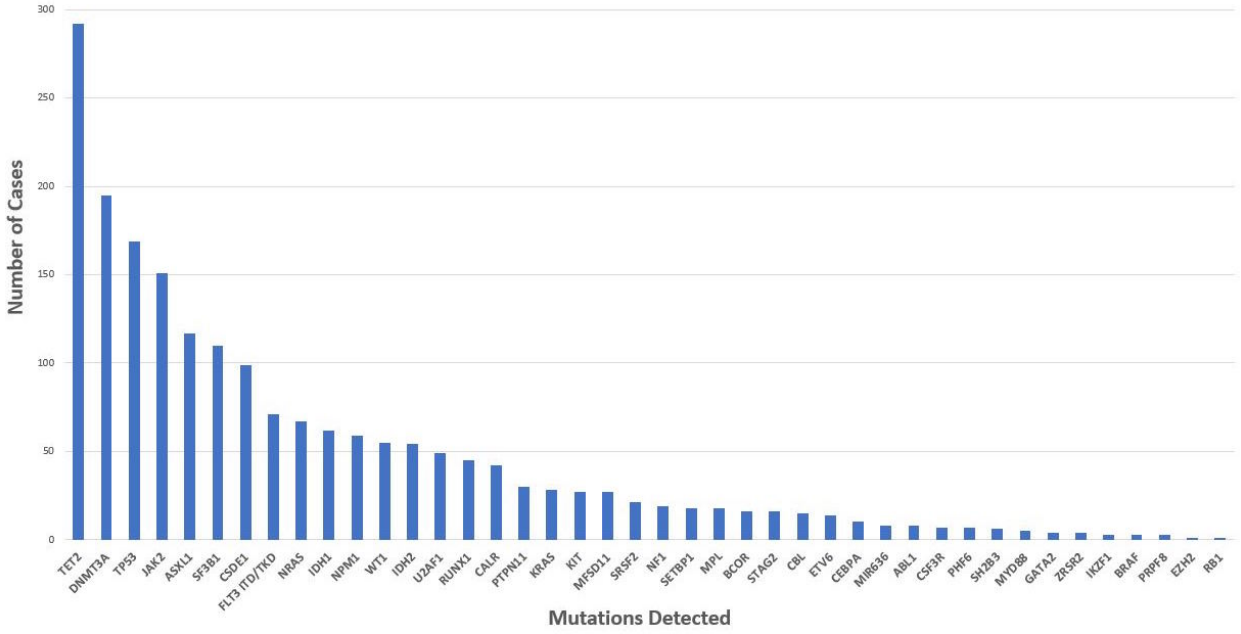

Figure 1: Molecular profile for myeloid malignancies by NGS (mutations) (n=4656)

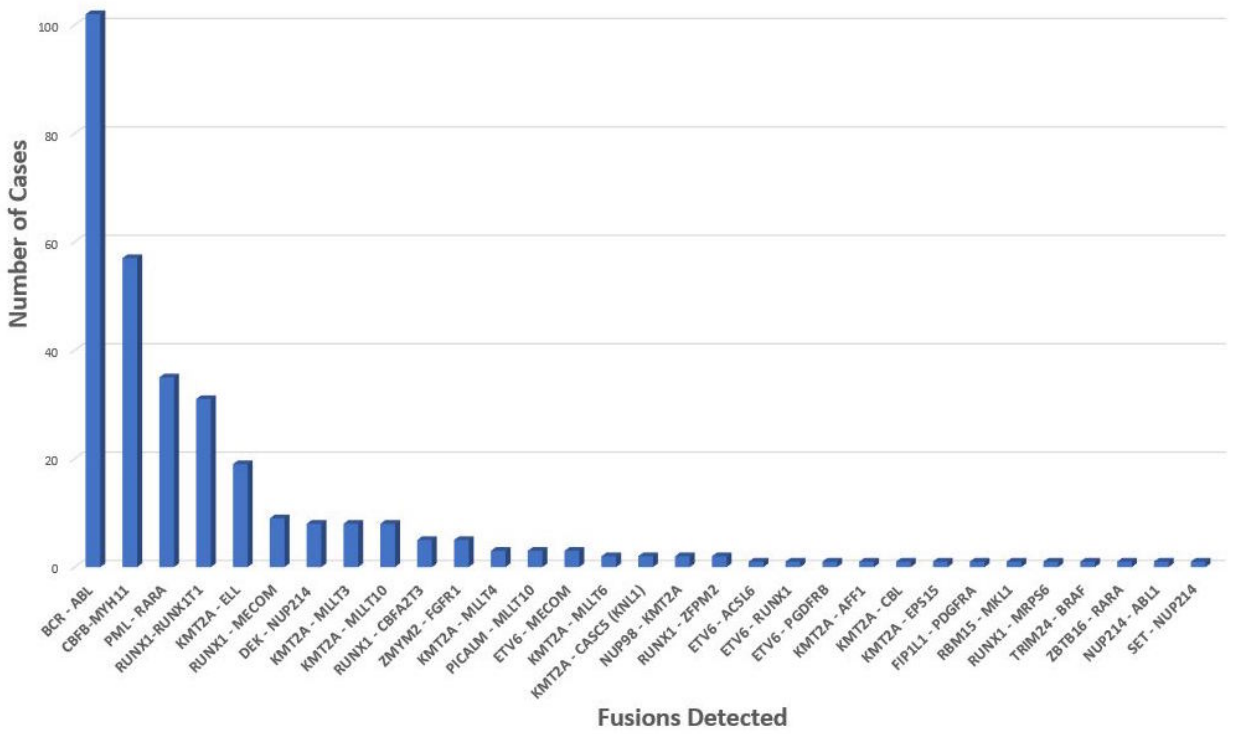

Figure 2: Molecular profile for myeloid malignancies by NGS (fusions) (n=4656)

tor AML with *RUNX1::RUNX1T1*. *FLT3* mutations (ITD/TKD) presented 3.6% core-binding factor AML with *CBFB::MYH11*, and 10% core-binding factor AML with *RUNX1::RUNX1T1*. The presence of both *KIT* and *FLT3* mutations has changed the prognosis from favorable to poor in these patients.

Here is an example how biomarker testing impacts patient care. The patient was a 49-year-old female who was diagnosed with FLT3-positive AML in 2018. She was treated with midostaurin, an FDA-approved drug for treating new AML with *FLT3* mutation and achieved remission. She had stem cell transplant in 2019, relapsed in 2021 with approximately 18% blasts on bone marrow biopsy. All her biomarker testing including flow, IHC, karyotyping, FISH, NGS, AML measurable residual disease (MRD) and *FLT3*-ITD by PCR came back positive. Chromosome analysis showed a complex karyotype with clonal evolution and FISH detected *CBFB* deletion in 83% of cells; NGS and PCR analyses detected *FLT3* and several other mutations; flow and morphology analyses demonstrated high blast level. She was treated with gilterinitib and venetoclax, which target mutated FLT3 and BCL2 in relapsed AML, and achieved remission afterwards. In July of 2021, she had the second relapse with approximately 12% blasts on bone marrow biopsy. All her biomarker testing results again came back positive, like her previous results. She was treated again with gilterinitib and venetoclax and achieved remission. In this case, genetic testing as part of precision pathology played an important role in disease diagnosis, risk stratification, treatment decision and disease monitoring. The abnormal clone(s) identified by cytogenetics and FISH, and mutations by NGS are the key indicators for confirmation of the relapse in disease. These indicators help oncologist to make decisions for further treatment. This example illustrates the importance of genetic testing in precision medicine.

Several new assays are being developed in our lab. A new Leukemia Fusion Panel by multiplex PCR has just been launched which detects 30 fusions including more than 155 transcripts (Table 2). The clinical application includes diagnosis of acute and chronic leukemias, such as AML, CML, ALL, CMML, MDS, etc. This assay can not only detect RNA transcripts of fusion genes extracted from bone marrow or leukemic blood using a RT-qPCR procedure, but also has a much shorter TAT than karyotyping and NGS. The second launched assay is Ph-like ALL FISH panel which identifies the gene rearrangements for *CRLF2*, *JAK2*, *EPOR*,

Table 2: Fusions Detected by Leukemia Fusion Panel

No.	Translocation	Fusion Gene	No.	Translocation	Fusion Gene
1	t(9;11)(p22;q23)	*KMT2A::MLLT3*	16	t(6;9)(p23;q34)	*DEK::NUP214*
2	t(15;17)(q24;q21)	*PML::RARA*	17	t(X;11)(q24;q23)	*KMT2A::SEPTIN6*
3	t(8;21)(q22; q22)	*RUNX1::RUNX1T1*	18	t(16;21)(p11;q22)	*FUS::ERG*
4	t(4;11)(q21;q23)	*KMT2A::AFF1*	19	t(5;12)(q33;p13)	*ETV6::PDGFRB*
5	t(12;21)(p13;q22)	*ETV6::RUNX1*	20	t(11;19)(q23;p13.1)	*KMT2A::ELL*
6	t(1;19)(q23;p13)	*TCF3::PBX1*	21	t(11;17)(q23; q21)	*KMT2A::MLLT6*
7	t(11;19)(q23;p13.3)	*KMT2A::ENL*	22	t(5;17)(q35;q21)	*NPM1::RARA*
8	t(9;22)(q34;q11)	*BCR::ABL1*	23	t(3;5)(q25;q34)	*NPM1::MLF*
9	del(1)(p32)	*STIL::TAL1*	24	t(11;17)(q23;q21)	*ZBTB16::RARA*
10	t(10;11)(p12;q23)	*KMT2A::MLLT10*	25	t(1;11)(q21;q23)	*KMT2A::MLLT11*
11	inv(16)(p13;q22)	*CBFB::MYH11*	26	t(1;11)(p32;q23)	*KMT2A::EPS15*
12	t(3;21)(q26; q22)	*RUNX1::MECOM*	27	t(9;12) (q34;p13)	*ETV6::ABL1*
13	del(4)(q12)	*FIP1L1::PDGFRA*	28	t(16;21)(q24;q22)	*RUNX1::CBFA2T3*
14	del(9)(q34)	*SET::NUP214*	29	t(3;21)(q26; q22)	*RUNX1::RPL22*
15	t(17;19)(q22;p13)	*TFPT::HLF*	30	t(6;11)(q27;q23)	*KMT2A::AFDN*

CSF1R, *ABL1*, *ABL2*, and *PDGFRA*. This assay can be ordered as a reflex test in patients with negative *BCR::ABL1* and *ETV6::RUNX1* fusions. An NGS hematology molecular profile is currently being validated on Genexus, a platform that will reduce TAT from 3-5 days to 2 days, which will greatly benefit patients with newly diagnosed acute leukemia. An ultrahigh sensitive NGS assay (with 0.05-0.1% allele frequency) is also being validated for detecting minimal residual disease of myeloid disorders. The assay includes 3 panels: DNA panel to detect single nucleotide variants (SNVs) and insertions/deletions (indels), RNA panel to detect fusions, and microhaplotyping (MHT) DNA panel to detect chimerism. This assay will help monitoring patients with disease progression.

In summary, precision medicine revolutionizes healthcare from "one-size-fits-all" to a targeted and individualized approach. The decisions are made with individual's unique clinical, molecular, and lifestyle information. Compared to the individual gene testing, genetic biomarker panel testing reduces TAT, sample size and patient/healthcare cost. NGS testing provides a more comprehensive genetic profile of hematologic malignancies and aids in diagnosis, prognosis, and treatment of these disorders, and it has changed the paradigm of cancer therapy.

Utility of Chromosomal Microarray in the Evaluation of Suspected Pediatric Hematolymphoid Malignancies

Cancer is a genetic disease, and indeed many entities in the WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues [3] are defined by recurrent cytogenetic and molecular genetic abnormalities, particularly many of the ones we see in pediatric patients. A challenge we face, working at a large freestanding children's hospital without a cytogenetics (CG)/fluorescence *in situ* hybridization (FISH) lab or a partner adult hospital, is ensuring that children suspected of having an hematolymphoid malignancy receive the most accurate diagnosis. Compounding the problem is the fact that a not insubstantial proportion of the bone marrow aspirates we receive are aparticulate and paucicellular, which has negative downstream implications for chromosome analysis and minimal residual disease testing, for example.

Because we were frequently receiving cytogenetics reports from our reference lab with either no growth or a suboptimal number of metaphase cells, we started to take advantage of the option to add-on chromosomal microarray (CMA) or make it an automatic reflex in cases with insufficient metaphases or normal CG results. In parallel, our own genomics lab went live with CMA for constitutional disorders. If we could determine that CMA added value for oncology, we might decide to validate CMA for mosaicism because tumor samples will always contain some normal cells and their DNA. The interested reader is directed to [4] for a discussion on CMA workflow and how, using unique non-polymorphic oligonucleotide probes across the genome and genotype-able single nucleotide polymorphism (SNP) probes, calls are made for copy number alterations, absence or loss of heterozygosity, and mosaicism.

We retrospectively reviewed the results of 276 CMA cases from 234 patients in the last 6 years, from January 1, 2015 to December 31, 2021. These were all done at a reference lab, ARUP Laboratories in Salt Lake City, UT. In terms of the other techniques applied to these samples, all but 2 CMA cases had CG (274 cases, 99.3%), and nearly 92% (253 cases) had FISH. Only about 14% (38 cases) had molecular (MOL) testing, mostly a myeloid malignancies mutation panel by next generation sequencing or the Foundation Medicine FoundationOne heme assay, done on cases with a high pretest probability of malignancy (e.g., new cases of acute myeloid leukemia or AML); CMA was mostly done as a reflex test (249 cases, 90.2%), though it was run in parallel with CG in 6 cases (2.2%), added-on in 19 cases (6.9%) and done without CG in 2 cases (0.7%).

The samples were mostly non-targeted bone marrow aspirates (255; 92.4%) and a few leukemic peripheral blood samples (21; 7.6%), the latter typically sent to get a head-start on testing if the oncologists were not planning to do a marrow over the weekend; for that reason, some of the patients had paired peripheral blood and bone marrow samples, or could have had multiple samples on account of bilateral staging marrows or rapidly sequential marrows because they didn't meet the 25% Children's Oncology Group bone marrow blast threshold to establish a diagnosis of acute lymphoblastic leukemia (ALL), or they had an inherited bone marrow failure syndrome that predisposed them to malignancy thereby necessitating annual surveillance marrows.

In terms of disease categories or indications for bone marrow or peripheral blood examination, 107 cases were for diagnosis, staging or follow-up of B-lymphoblastic leukemia/lymphoma, with 18 for T-lymphoblastic leukemia/lymphoma, 13 for AML, 9 for myelodysplastic syndrome (MDS), 1 for essential thrombocythemia, 1 for Noonan syndrome myeloproliferative disorder, 2 for RAS-associated leukoproliferative disorder, 1 for myeloid leukemia of Down syndrome, 3 for blastic plasmacytoid dendritic cell neoplasm, 1 for peripheral T-cell lymphoma, 31 for various bone marrow failure states and germline predisposition to myeloid neoplasia, 82 for cytopenia, 1 for abnormal imaging, 5 for cytosis, and 1 for hyperinflammatory state. Appropriate FISH testing was done for the various neoplasms, for example, the AML FISH panel was done on AML cases and the MDS FISH panel was performed on MDS cases but also on many of the cytopenia cases. A Ph-like panel was not initially available for cases of B-lymphoblastic leukemia (B-ALL) but was ordered heavily later in the study period.

Overall, the "hit rate" for detecting an abnormality was 11.3% for CG (31/274 cases), 53.6% for CMA (148/276), 33.2% for FISH (84/253), and 78.9% for MOL (30/38); again, MOL was used sparingly and in cases with a high pretest probability of showing an abnormality, and there is a bias in our data in that CMA was typically done reflexively when CG didn't grow or showed normal results. Sixty CG cases (21.9%) had fewer than 15 analyzable metaphase cells, and 23 (8.4%) actually had zero metaphases: Suboptimal/inadequate specimens represented 50 (19.6%) of 255 non-targeted bone marrow aspirates, nine (45%) of 20 peripheral blood samples, and the 1 core biopsy sent for CG due to the aspirate being a "dry tap." Of the cases with abnormalities detected by CG, 58.1% had acquired, 38.7% had constitutional (commonly, trisomy 21), and 38.7% had both acquired and constitutional abnormalities. For abnormal CMA cases, 68.9% had acquired, 21.6% had constitutional, and 9.5% had both acquired and constitutional abnormalities.

Hit rate varied widely by leukemia subtype, and some results were expected, though others were not. For example, while CMA showed acquired abnormalities in all 17 cases of B-ALL with *ETV6::RUNX1*, none were the driver, which was identified in all 17 cases by FISH; CG was positive in only 1 case (5.9%) and did not identify the driver (as it is cryptic on CG), showing no growth or a suboptimal mitotic index in 8 of the 17 cases. There were 20 cases of B-ALL with hyperdiploidy, and the driver was identified in 100% of cases by CMA and 95% by FISH, but CG was positive in only 2 cases, 1 showing hyperdiploidy and 1 showing +21c, with 14 cases of no growth or suboptimal mitotic index. B-ALL with hypodiploidy was identified in all 4 cases by CMA and although FISH was abnormal in all 4 cases, 3 were incorrectly called hyperdiploid due to masked hypodiploidy (from endoreduplication of the hypodiploid clone); only case was hypodiploid on CG, as another showed a normal karyotype and 2 cases had no growth or a suboptimal mitotic index. FISH was the best test for B-ALL with *BCR::ABL1* or *BCR::ABL1*-like features, though CMA was able to detect the driver in half of the *BCR::ABL1*-like cases and in 1 of 3 cases harboring the *BCR::ABL1* translocation. Chromothripsis was seen in 8 of 8 iAMP21 cases by CMA, with FISH only identifying the driver (RUNX1 amplification)

in 4 of 7 cases, 1 only after reanalysis following CMA. *ZNF384*-rearrangement could be identified in B-ALL by CMA and MOL (*EP300* was suspected to be the partner gene when a small subset of blasts expressed myeloperoxidase). Finally, there was a case of B-ALL with hyperdiploidy and *BCR::ABL1* which were cytogenetically cryptic but both drivers were correctly identified by both CMA and FISH. Interestingly, a case of AML with *CBFB::MYH11* was cryptic on CG and FISH but detected by CMA. As one would expect, AML cases with mutations in *CEBPA*, *NPM1*, or *RUNX1* could only be detected by MOL. All cases of T-ALL showed abnormalities on CMA, and 1 case had a constitutional abnormality, deletion 17p12, that is associated with hereditary neuropathy with liability to pressure palsies, explaining severe neuropathy that developed from chemotherapy and subsequently resulted in dose modifications. CMA showed a greater mean number of abnormalities for ALL compared to AML/MDS and was highest for B-ALL with hypodiploidy and iAMP21.

The second largest category in our study was the cytopenia cases. Constitutional abnormalities were observed by CMA in 16 cases, including +21c, 3 cases with increased total autosomal homozygosity (which increases the possibility of a recessive condition and in 1 case raised the possibility of sexual abuse within the family), 2 cases of 22q11.2 deletion (incidentally identified DiGeorge syndrome), terminal 2p duplication/subtelomeric 12q deletion, 5q14.1 gain, 10q22.3-q23.2 deletion syndrome, 16p11.2 loss/microdeletion syndrome, 22q11.21 gain, and Xq24 loss (Nascimento form of syndromic X-linked mental retardation); some of these are variably associated with developmental phenotypes. A further 2 CMA cases showed acquired abnormalities: 1 incipient B-ALL (see below in paragraph), and 1 new case of aplastic anemia which had copy neutral-loss of heterozygosity (CN-LOH) on the short arm of chromosome 6 extending to the telomere, which involved the HLA locus, suggesting poor response to immunosuppressive therapy alone. Four of 81 cytopenia cases showed a cytogenetic abnormality, which in all 4 cases was +21c. Only 1 of 74 cytopenia cases had an abnormality identified on MDS FISH, and it was actually a case of "possible aplastic anemia" with stromal damage and +8 on FISH (with normal CG but gains of chromosomes 8 and 10, deletion 9p, 20p gain, 20q CN-LOH, and partial deletion of 20q, raising the possibility of lymphoblastic leukemia). These abnormalities disappeared on repeat bone marrow examination 9 days later, but the patient ultimately declared herself as having B-ALL 1 month later, so FISH and CMA ensured close follow-up.

An interesting finding that emerged from our CMA data was deletion of *TBL1XR1* on chromosome 3, in 5 B-ALL patients. Knockdown of this gene results in glucocorticoid resistance [5]. Steroids are important for the treatment of ALL, and 4 of our 5 cases with *TBL1XR1* deletion were positive for minimal residual disease at the end of induction.

In summary, for a lab like ours, CMA helps to overcome the problem of not getting specimens into culture right away. CMA added more value (and shows more abnormalities) for precursor lymphoid neoplasms (though irrelevant for T-ALL classification) than for myeloid neoplasms, in which MOL performed the best, especially for identifying gene fusions and single nucleotide variants. MDS FISH had virtually no utility for cases with adequate CG. Finally, although unrelated to the indication for testing, CMA reveals a not insignificant number of unexpected and potentially important secondary/constitutional findings. Although there are certainly guidelines for CMA in neoplastic disorders [6,7] and even literature on how useful CMA can be in various hematologic neoplasms, including in the pediatric setting [8-18], it seems like we might be underutilizing a very valuable tool.

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