Acute Promyelocytic Leukemia (APL) or APLM is a subtype of Acute Myeloid Leukemia (AML). APL is characterized by the presence of a specific chromosomal translocation, t(15;17), which results in the formation of a new genetic fusion gene, PML-RARA. This fusion protein leads to the formation of a retinoic acid receptor (RARα) and a promyelocytic leukemia (PML) protein, which together promote the proliferation of myeloid cells. The typical morphologic features of APL include hypergranular promyelocytes, Auer rods, and faggot cells. The diagnosis of APL is based on the presence of this translocation and the characteristic clinical features.

Case Study

A 22-year-old female patient presented to her physician with symptoms suggestive of APL. Her bone marrow evaluation was normal. However, the PML/RARA dual fusion FISH test revealed an atypical abnormal fusion signal pattern (2R1G1F) in just over 84% of the interphase nuclei scored. Further investigation and close examination with metaphase FISH (M-FISH) using the dual color, dual fusion probe revealed a small red signal on top of one of the green signals, forming a fusion signal. This FISH finding confirmed a small insertion of PML from the long arm of chromosome 15 into the long arm of chromosome 17, juxtaposing the PML and RARA genes. This finding also emphasizes the importance of peer review and quality control as a necessary process to minimize false or discrepant diagnoses.

Discussion

The atypical abnormal pattern is unusual and difficult to detect. Technologist A did not detect the atypical abnormal patterns using the probes designed by all four companies. Technologist C was the only technologist in this study who correctly detected all the patterns with relatively uneven percentages of the abnormal cells. The probe position is the key factor determining the intensity of the fused red signal.

The false negative result can easily lead to misdiagnosis as well as delayed treatment. The same probe gap is around 15kb. It is thus concluded that the designated location of the probe is the main reason behind the discrepancy in the result. In addition, BAC (Bacterial Artificial Chromosome) clones and DNA printing are only two of the most ways to design and develop FISH probes. Without a FDA-standardized guideline that specifically dictates the probe design, location, and the ratio of the fluorescent materials, different companies may have different ways to produce their own probe sets. This lack of unified guidelines results in the existence of various sizes, colors, intensities, and hybridization patterns for the same probe set.

Conclusion

The literature and this case study confirm that although 92% of APL patients have the same breakpoint, some atypical APL cases may not be detectable based on probe set design. The PML/RARA dual fusion FISH test revealed an atypical abnormal pattern. The false negative result can easily lead to misdiagnosis as well as delayed treatment. The same probe gap is around 15kb. It is thus concluded that the designated location of the probe is the main reason behind the discrepancy in the result. In addition, BAC (Bacterial Artificial Chromosome) clones and DNA printing are only two of the most ways to design and develop FISH probes. Without a FDA-standardized guideline that specifically dictates the probe design, location, and the ratio of the fluorescent materials, different companies may have different ways to produce their own probe sets. This lack of unified guidelines results in the existence of various sizes, colors, intensities, and hybridization patterns for the same probe set.

The atypical abnormal pattern is unusual and difficult to detect. Technologist A did not detect the atypical abnormal patterns using the probes designed by all four companies. Technologist B and C are not able to detect this rare event detectable by FISH, which eventually activates the translation of an oncprotein factor which is important to know that the median survival of untreated APL is less than 30 days.