Acute lymphoblastic leukemia in a patient with fragile X syndrome: cytogenetic and molecular features

Malignancies in patients with fragile X syndrome are rarely reported. A 42-year-old man with fragile X syndrome presented with precursor B-cell acute lymphoblastic leukemia (ALL). Cytogenetic analysis showed a stemline 46, XY, t(9;22)(q34;q11) and a sideline 46,XY, t(8;14)(q24;q11), t(9;22)(q34;q11). Molecular analysis of the FMR1 gene showed a neoplastic leukemic clone possessing a full expansion of the CGG repeat, with associated aberrant methylation of the promoter CpG islands. However, analysis during morphologic remission showed that the promoter CpG island was apparently unmethylated in the regenerating normal hematopoietic cells. During subsequent relapses, the FMR1 CGG repeat was unstable, with the appearance of multiple leukemic subclones possessing different repeat expansions. Our case suggested that deregulation of the FMR1 gene might have contributed to leukemogenesis in our case.

Fragile X syndrome is the most frequent form of inherited mental retardation in males.1 It is transmitted as an X-linked dominant disorder with reduced penetrance. Affected males show a variable degree of mental retardation, mild dysmorphic features, and macroorchidism. Cytogenetically, it is marked by the presence of an inducible fragile site at chromosome Xq27.3.2 Molecularly, expansion and methylation of trinucleotide repeats of CGG at the FRAXA site is the cause of the abnormality, and results in down-regulation of the FMR1 gene, which carries the hypermutable CGG repeat in the 5' untranslated portion of its first exon.3,4 The level of expression of the FMR1 gene correlates with the clinical severity of the fragile X syndrome. Interestingly, instability of nucleotide repeats and aberrant CpG methylation, a sine qua non in the abnormal FMR1 gene in fragile X syndrome, are also commonly seen in many different neoplastic disorders as microsatellite instability and aberrant gene promoter methylation respectively.5,6 However, only very few cases of malignancies have been described in patients with fragile X syndrome. We report a unique case of acute lymphoblastic leukemia (ALL) in a patient with fragile X syndrome. A 42-year-old man with mild mental retardation and fragile X syndrome diagnosed since his teens presented with spontaneous bruising. Physical examination was unremarkable. A complete blood count showed hemoglobin (Hb): 5.9 g/dL, white cell count (WCC): 62.1x10^9/L (82% blasts), and platelet count: 9x10^9/L. A bone marrow aspiration confirmed the diagnosis of common ALL, with leukemic blasts shown to be TdT+, HLA-DR+, CD10+, CD19+, CD79a+, CD34+, and CD13+ on immunophenotyping. There was no expression of cytoplasmic or surface immunoglobulin. He was treated with combination chemotherapy (prednisolone, vincristine and adriamycin), and achieved a morphologic remission. However, several weeks later the leukemia relapsed again, and the patient died subsequently from severe sepsis. Cytogenetic analysis of the blasts at diagnosis showed a stemline 46, XY, t(9;22)(q34;q11) and a sideline 46,XY, t(8;14)(q24;q11), t(9;22)(q34;q11) [cp13] (Figure 1A). Reverse transcription polymerase chain reaction (RT-PCR) confirmed the presence of the m-BCR/ABL chimeric transcript typical of Philadelphia chromosome positive ALL (data not shown). To confirm the diagnosis of fragile X syndrome, a 72-hour culture of the peripheral blood lymphocytes under folate restriction was performed. This showed a fragile site at Xq27.3 (Figure 1B).

Unfortunately, not enough sample was left for this experiment. At subsequent relapses (Rel1 and Rel2, Figure 1B), an additional 7.0 kb band was seen, together with the 6.5 and 6.1 kb bands, suggesting that the CGG expansion was unstable in the leukemic clone during clonal evolution. To investigate if the unstable CGG expansion in the leukemic blasts was but a reflection of a generalized microsatellite...
have been reported. Although some gene product, the fragile X mental retardation gene occurred preferentially in the leukemic clone suggesting this gene might be involved in leukemic evolution/ clonal progression. In conclusion, we have presented a rare case of leukemia complicating fragile X syndrome. Our observations suggest that suppressed/ abnormal FMRP expression might be contributory to leukemogenesis. The FMRP possesses two KH motifs and one RGG box, which interact with RNA and polyribosomes. It remains to be elucidated if perturbations of these biochemical processes might contribute to carcinogenesis. Future studies of the differential deregulation of the FMR1 gene in tumors and non-tumorous tissues in patients with fragile X syndrome are required to address these issues.

References


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