(neoplasia). Casos de MDS são agora classificados como os que possuem anormalidades genéticas definidoras e os que são morfologicamente definidas. Acrescentou-se também a diferenciação entre MDS com baixa contagem de blastos (MO<5% e no SP < 2%) e MDS com aumento no número de blastos, esta por sua inclui MDS com fibrose (MDS-f). A LMA relacionada à MDS (AML-MR), foi definida como ≥20% de blastos expressando um fenótipo e abrigando alterações citogenéticas e moleculares específicas (mutação em um dos 8 genes - SF3B1, ZRSR2, ASXL1, EZH2, BCOR, U2AF1, SRSF2, STAG2). Conseguimos classificar o caso relatado como portador de MDS com fibrose (MDS-f) ao diagnóstico, e após evolução do quadro como LMA relacionada a MDS (AML-MR), com mutação no gene ZRSR-2. **Conclusão:** A classificação WHO 5ªedição (2022) agrega novas possibilidades de classificação para os neoplasmas mieloides.

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ATM DNA METHYLATION ASSOCIATED WITH POOR PROGNOSIS AND LEUKEMIA TRANSFORMATION IN MYELODYSPLASTIC SYNDROME PATIENTS

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Myelodysplastic syndrome (MDS) is a clonal disease of hematopoietic progenitors with a risk of progressing to acute myeloid leukemia. MDS etiology is mainly related to age, but one of the risk factors is exposure to pesticides that causes aberrant reprogramming of the genome by DNA methylation. The aim of this work was evaluating the methylation profile of genes acting in the single-strand DNA (ssDNA) repair (CSA, CSB, XPA, XPC and XPG) and double-strand DNA (dsDNA) repair (ATM, BRCA1, BRCA2, LIG4 and RAD51), and its relationship with gene expression. The analysis was performed using bone marrow samples from 56 MDS patients, 69 farmers exposed to pesticides and 10 controls without exposition or MDS. The methylation profile and gene expression were evaluated using pyro-sequencing technique and quantitative real-time PCR. Regarding ssDNA repair genes, in cases with MDS, patients under 60 years old showed a higher methylation for the XPA and CSB genes than patients over 60 years old ($p = 0.008$; $p = 0.017$). Furthermore, XPA showed increased methylation levels in initial forms of MDS ($p = 0.019$). The MDS group presented a higher percentage of XPA methylation than exposed farmers ($p = 0.000$) and the control group ($p = 0.011$). In the prognostic classification, lower risk presented higher methylation than high-risk ($p = 0.027$). Among the dsDNA repair genes methylation in MDS patients, only ATM gene showed significant results with increase of methylation levels in (1) males ($p = 0.037$); (2) patients aged up to 60 years ($p = 0.002$) and (3) those who progressed to AML ($p = 0.016$). Regarding the methylation between the groups of exposed farmers, MDS advanced forms and controls, we also detected significant differences with levels always increased in the control group: ATM (control group vs. farmers $p = 0.000$), BRCA1 exposed vs. control group, $p = 0.001$; MDS vs. control, $p = 0.001$;), BRCA2 (farmers vs. control, $p = 0.027$; MDS vs. control, $p = 0.004$), LIG4 (farmers vs. control, $p = 0.001$; MDS vs. control, $p = 0.012$) and RAD51 (farmers vs. controls, $p = 0.047$). The correlation analysis between methylation and expression showed a positive and strong correlation for LIG4 gene in the advanced forms MDS group ($r = 0.798$) and a positive and weak correlation for BRCA1 gene in the exposed farmers group ($r = 0.340$). Surprisingly, in the ssDNA repair genes, the expression and methylation of both farmers and MDS patients were not correlated, suggesting that the change in the expression of these genes is not motivated by the DNA methylation mechanism. Furthermore, the analysis of dsDNA repair genes in this study corroborates the phenomenon of relative hypermethylation in some DNA repair genes in MDS.

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VERY COMPLEX KARYOTYPE IN YOUNG MYELODYSPLASTIC SYNDROME PATIENT AFTER CHRONIC EXPOSURE TO CHLOROFORM

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Introduction: Myelodysplastic Syndrome (MDS) is marked by biological and clinical heterogeneity, characterized by dysplasia in the bone marrow and blood cells with the presence of cytopenias. MDS is recognized as a disease in elderly

individuals. About 86% of MDS cases are diagnosed at age ≥ 60 and less than 10% of patients are younger than 50. Recurrent cytogenetic abnormalities are present in 40% to 60% of cases. Cytogenetic analysis plays an important role, whether in the diagnosis or classification of the disease. Recently, the new international molecular prognostic score system (IPSS-M) reinforces the valuable prognostic contribution of cytogenetics in MDS in both survival and leukemic evolution. **Objective:** To report a chronic chloroform exposure as a trigger capable of inducing DNA damage. **Case report:** Chronic exposure to a genotoxic agent has been linked to MDS chromosomal abnormality. Among these, chloroform, and an inorganic halide derivative of hydrocarbons can induce the DNA lesion. A 24-year-old male patient with a marked history of 10-year chloroform exposure sought medical attention for anemia, fainting, and unintentional weight loss. He was diagnosed with Myelodysplastic Syndrome and refractory anemia with excess blasts (RAEB II) with initial tests: Hb = 5 g/dL; neutrophils=320/mm3; platelets= 18 x 109/L. Bone marrow aspiration showed 15% myeloblasts, immunohistochemistry profile showed CD34+, CD117+ in blasts and cytogenetic analysis showed a very complex karyotype: 45,XY,del(6)(q22),-7,add(9) (q12),del(12)(p11.2),del(17)(p13),del(20)(q12),add(21(p13)[17]/46, XY[3]. Chemotherapy with azacitidine was performed as a bridge to bone marrow transplantation, but the patient evolved into sepsis, dying eight months after diagnosis. **Conclusion:** The pathogenesis of MDS reflects the heterogeneity of the disease, thus, comprises multiple steps and includes factors that can be endogenous and/or exogenous. Therefore, this unusual case shows the extreme importance of investigating possible recurrent and/or occupational exposures in these patients combined with cytogenetics analyses.

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CYTOGENETIC BICLONAL ABNORMALITIES IN PEDIATRIC AND ADULT PATIENTS WITH MYELODYSPLASTIC SYNDROME: CLINICAL IMPLICATIONS

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Objective: Myelodysplastic syndrome (MDS) comprises a heterogeneous group of clonal hematopoietic stem cell diseases. MDS is characterized by dysplasias, cytopenias and an increased risk of acute myeloid leukemia (AML) evolution. MDS has a higher incidence in elderly patients, and is rare in pediatric patients. Cytogenetic analysis is an important laboratory tool for diagnosis, prognosis and clinical decision-making for MDS patients. Chromosome alterations can be detected in 30-50% in MDS. The most frequent chromosomal abnormalities are: del(5q), del(7q)/-7, +8, del(11q), del(12p), del(17p), del(20q) -Y. Rare cytogenetic abnormalities usually are considered as intermediate group in the Revised International Prognostic Scoring System (IPSS-R), as the cytogenetic biclonal abnormalities. However, this group of chromosomal abnormalities may be reported to help to elucidate its clinical implications in *de novo* MDS. The aim of this study was to report rare cases of cytogenetic biclonal alterations in pediatric and adult patients with *de novo* MDS and their clinical implications. **Materials and methods:** This study included 7 patients with MDS, being 3 pediatric patients and 4 adult patients from a cohort of 1056 *de novo* MDS patients. Chromosomal and clinical studies were carried out in 1056 MDS patients, being 200 pediatric patients and 856 adult patients, between 2000-2022. Cytogenetic analyses were performed in bone marrow cells by G-banding and fluorescence *in situ* hybridization (FISH). **Results:** A total of 7 (0.66%) patients with *de novo* MDS (7/1056) had biclonal cytogenetic abnormalities, being 4 (0.48%) adult patients (4/856), and 3 (1.5%) pediatric patients (3/200). The mean age of adult patients was 67.5 (60-73 years old), and pediatric patients were 10 (6-13 years old). Most of the patients (57%) were classified as advanced stages (MDS-EB-1, MDS-EB-2 and MDS-EB-t) and dysplasias in more than one lineage (71%). The cytogenetic biclonality in adult patients involved the clones with the chromosomal alterations: del(11q),del(20q)/del(12p); Y/del(17p); del(11q),+21/del(6q); i(17q)/hyperdiploidy karyotype; and in pediatric patients del(17p)/del(12p); +X,+8/add(7p); +8/+21. **Discussion:** Biclonal cytogenetic alterations are uncommon findings, with a frequency between 1.6%-6.5% in MDS. Although we studied a large cohort of MDS patients the frequency of these alterations was lower than literature (0.66%). It is important to note that most studies included secondary or therapy-related MDS and AML which generally have a higher chromosomal instability. In our results, the chromosomal instability in these clones involved common cytogenetic alterations: del(11q), del(12p), del(17p) and +8, but the prognostic value of this distinct cytogenetic clones still needs to be elucidated. The mechanisms for the development of unrelated cytogenetic clones remain to be elucidated, especially because it is unclear if these clones are in fact two independent clones, representing a true biclonality, or a clonal evolution derived from a common precursor with a submicroscopic molecular genetic change. **Conclusion:** Our study shows new insights into biclonal cytogenetic abnormalities in *de novo* MDS, demonstrating for the first time, from a large cohort of *de novo* MDS patients, the frequency of cytogenetic biclonality in pediatric and adult patients.

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EVOLUÇÃO DA SÍNDROME DE FOURNIER, EM PACIENTE COM SÍNDROME MIELODISPLÁSICA: RELATO DE CASO

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