DIFFERENTIAL GENE EXPRESSION OF SIRTUINS (SIRT1 TO SIRT7) REVEALS POTENTIAL ROLES IN MYELODYSPLASTIC NEOPLASM PATHOBIOLOGY

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Introduction: Sirtuins (SIRTs) are a group of proteins that play a crucial role in various cellular processes, including DNA repair, metabolism, and aging. They have been the subject of significant research interest, particularly in relation to cancer. SIRTs have been implicated in promoting cancer progression by inhibiting cell death pathways and facilitating cancer cell survival. Additionally, some studies have linked increased *SIRTs* family (*SIRT1* to *SIRT7*) gene expression activity to developing drug resistance in cancer cells, making treatment more challenging. Recently, in a systematic review, our group highlighted the scarcity of studies that establish the role of *SIRTs* genes in the pathobiology of Myelodysplastic neoplasm (MDS). **Objective:** To assess the gene expression profile of *SIRTs* (*SIRT1*, *SIRT2*, *SIRT3*, *SIRT4*, *SIRT5*, *SIRT6*, and *SIRT7*) in relation to the pathogenesis and prognostic progression of MDS. **Methodology:** This analysis included a cohort of 80 elderly patients diagnosed with MDS and bone marrow samples from 10 healthy individuals. MDS patients were diagnosed based on the World Health Organization (WHO) criteria and stratified according to the prognostic criteria established by the International Prognostic Scoring System-Revised (IPSS-R). We assessed the gene expression levels of *SIRTs* using the Real-Time PCR Gene Expression (RT-qPCR) method. **Results:** We observed low expression of *SIRT2* ($p = 0.009$), *SIRT3* ($p = 0.048$), *SIRT4* ($p = 0.049$), *SIRT5* ($p = 0.046$), *SIRT6* ($p = 0.043$), and *SIRT7* ($p = 0.047$) in MDS patients compared to the control group. Additionally, we found increased expression of *SIRT4* ($p = 0.029$) in patients aged 60 or above. Furthermore, we identified increased expression of *SIRT2* ($p = 0.016$) and *SIRT3* ($p = 0.036$) in patients with hemoglobin levels below 8 g/dL, increased *SIRT4* ($p = 0.036$) in patients with dyserythropoiesis, decreased expression of *SIRT2* ($p = 0.035$), *SIRT4* ($p = 0.035$), and *SIRT7* ($p = 0.037$) in patients with dysgranulopoiesis, increased *SIRT1* ($p = 0.027$) in patients with dysmegakaryopoiesis, and increased *SIRT4* ($p = 0.043$) in patients with the presence of ring sideroblasts. We also observed high expression of *SIRT2* ($p = 0.045$) and *SIRT3* ($p = 0.033$) in patients with cytogenetic alterations and increased expression of *SIRT2* ($p = 0.004$), *SIRT3* ($p = 0.005$), and *SIRT4* ($p = 0.033$) in healthy patients compared to those with a normal karyotype. **Discussion and conclusion:** In summary, we identified significantly differential gene expression of *SIRTs* members in MDS. We identified variations in the expression of *SIRTs* in cell dysplasias in all 3 cell lines present in BM, as well as variations of *SIRTs* in patients with very low hemoglobin levels, demonstrating the relationship of these genes with the disease. These defunctions lead to dysplastic and oncogenic characteristics capable of triggering the disease and its prognostic characteristics. Our results revealed significant clinical associations regarding the expression of *SIRT2*, *SIRT3*, *SIRT4*, *SIRT5*, *SIRT6*, and *SIRT7* genes, demonstrating their potential involvement in the pathogenesis and progression of MDS.

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SÍNDROME MIELODISPLÁSICA PEDIÁTRICA COM SIDEROBLASTO EM ANEL UMA NOVA VARIANTE EM SF3B1E ANORMALIDADES CROMOSSÔMICAS CLONAIS: RELATO DE CASO

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As síndromes mielodisplásicas com sideroblastos em anel (SMD-SA) são desordens clonais que apresentam grave displasia eritróide e discreta granulocitica e megacariocitica. A doença tem curso clínico benigno e resulta do acúmulo de ferro nas mitocôndrias ocorrendo apoptose e eritropoese ineficaz. Cursa com anemia macrocítica, HgF elevada e sinais sistêmicos de acúmulo de ferro, refletidos pelo aumento da ferritina e ferro livre, independentes de transfusão. Pela 5ªedição da OMS e Consenso Internacional-2022, a SMD-SA é considerada se houver 5% de sideroblastos em anel e mutação somática do gene *SF3B1*. Na infância, as SMDs são doenças raras (<5%) sendo as SMD-AS <1%. Dois casos já foram descritos: um com monossomia 7, sem investigação genética e outro em A.Fanconi com *SF3B1* mutado. Aqui descrevemos uma paciente com SMD-AS com mutação de significado incerto (VUS) no gene *SF3B1 e* alterações cromossômicas clonais, -7/del(7q),+11,+22. **Relato de caso:** Paciente, 11 anos, parda, sexo feminino, procedente de Viçosa-PE. Admitida no CEONHPE em 2018, aos 7anos, para investigação de anemia macrocítica - dosagens de Vit.B12 e ácido fólico normais. A

mãe notou a criança pálida aos 3 anos, procurou assistência médica sendo tratada com sulfato ferroso, sem melhora. Foi transfundida duas vezes entre 2013-2014. Nasceu de parto cesariano com sofrimento fetal (sic) e desenvolvimento psicomotor retardado. Em 2016, fez RNM de crânio que mostrou insulto hipóxico isquêmico, disgenesia do corpo caloso, hipoplasia dos nervos e quiasma óptico.Os pais e avós maternos são consanguíneos de 1°grau. Mãe com baixa estatura e hemograma normal. Ao exame apresenta retardo mental estrabismo divergente, pescoço curto, pés equinos, palidez e leve icterícia. Ausculta cardíaca com sopro no BEEA e ECO sem HAP. Ausências de visceromegalias e adenomegalias. Os exames mostraram: Hemograma com anemia macrocítica (7,1 g%, HTC-22%, VCM- 114fL), sem outras anormalidades. Homocisteína, ácido metilmalônico urinário e cobre normais. Ferro-115 μg/dL, Ferritinemia-1408 ng/mL. Sat da transferrina = 56%. Dosagens de hemoglobina: A = 92.6%, A2 = 3% e HgF = 4,6%. A RNM do abdômen e a biópsia hepática mostram hemossiderose hepática. O mielograma apresentava hiperplasia eritroide, alterações megaloblásticas, proeritroblastos gigantes, alguns binucleados, halo perinuclear, figuras mitóticas atípicas, cariorrexe e aumento de histiócitos com pigmentos. O setor granulocitico mostrou relativa hipocelularidade, discretas alterações megaloblásticas, predomínio de granulócitos maduros e distúrbios de segmentação. A reação de Perls demonstra depósitos de ferro em histiócitos exarcebados e sideroblastos em anel em cerca de 20%. Na histologia da BMO havia intensa hiperplasia eritrocitária (CD71+) e megaloblastose parcial. Macrófagos intersticiais aumentados com pigmentos férricos (Perls). O teste da MMC sem fragilidade cromossômica e cariótipo medular confirmado por FISH revelou: 47,XX,del(7)(q34),-7,+11,+22[cp10]/46,XX[10]. O sequenciamento detectou uma variante no gene *SF3B1* não descrita: c2077+35del. A paciente foi diagnosticada com SMD-AS, está em controle clínico e laboratorial em uso de quelante de ferro. Os autores mostraram um raro caso de SMD-AS e enfatizam a importância dos estudos genéticos na investigação das SMD na infância para o correto diagnóstico e condução terapêutica.

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IMMUNOLOGICAL RESPONSE ASSOCIATED WITH DERMATOLOGICAL LESIONS IN A PATIENT WITH MYELODYSPLASTIC NEOPLASIA

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Introduction: Hematopoiesis in the bone marrow is regulated by its niche and by immune system cells. These cells are derived from bone marrow precursors and therefore immunological alterations are frequently observed in Myelodysplastic Neoplasia (MN), complex and heterogeneous disease. **Objective:** description of a clinical case through data collection from HSPE/IAMSPE-SP digital system. **Case report:** Male, 64 years old, with bipolar disorder and prolonged bicytopenia. In january/21 diagnosed with NM, myelogram: 10% of blasts with dysplastic changes in the 3 series, IPSS-R = 3.8, FISH and karyotype without abnormalities. Submitted to the AZAVIT-ABCDEF protocol (Azacitidine, erythropoietin, filgrastim associated with high dose of vitamin B1, C and D), after signing consent form (Plataforma Brasil-CAAE: 53015421000005463). Evolved with sporadic need for transfusion, in the first year he received 23 packed red blood cells. In July/22 he developed a large, ulcerated lesion with irregular and painful borders on his left leg, after being infected with COVID-19. Anatomopathological: chronic ulcer, without signs of malignancy. Follow-up and clinical evaluation suggested the diagnosis of Pyoderma Gangrenosum (PG). Treatment with high dose of corticosteroids was started, but the psychiatric condition got worse. Replaced by cyclosporine, serum level maintained around 200 ng/mL, we observed slow healing of the ulcer. In NOV/22, he presented a dense and elevated lesion in the nasal fin, computed tomography showed infiltration up to the lacrimal canal. Biopsy compatible with Bowenoid in situ carcinoma (possibly mediated by HPV), with proposal for rhinotomy. It was then decided to immediately withdraw cyclosporine. In the already healed PG region, topical corticosteroids were maintained. There was total regression of the nasal lesion, with control tomography demonstrating slight thickening. A new biopsy showed no neoplastic infiltrate. Despite the suspension of immunosuppression, there was no reactivation of PG. Complete blood count in july/23: Hb = 13.4 g/dL, leukocytes = 4770 (2/62/3/0/30/3) and platelets: 92.000/mm^3 and no need for transfusion since july/22. He's in the 27 cycles of the AZAVIT-ABCDEF. **Discussion:** NM is characterized by clonal hematopoiesis, cytopenias and dysplastic cell morphology. Among the few therapeutic options, azacitidine is being used with some benefits. PG is an uncommon neutrophilic dermatosis, but frequent in hematologic malignancies, presents as a painful inflammatory and ulcerative disorder of the skin. Neutrophils are the main actors of innate immunity and within tissues they perform several functions such as phagocytosis, cytokine production, degranulation of soluble antimicrobial substances and production of extracellular neutrophil traps to eliminate pathogens. The use of azacytidine and the Covid-19 infection may have contributed to the exacerbated and prolonged activation of neutrophils, originating PG. **Conclusion:** Immunological alterations such as autoimmune thrombocytopenia, vasculitis, PG and Sweet's syndrome are frequent in NM. The rapid recognition of inflammatory processes and the early institution of immunosuppressive treatment have an impact on the outcome of NM. However, the side effects must be weighed due to their severity, in this case the Bowenoid carcinoma.

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