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LEUKEMIA STEM CELLS AND MEASURABLE RESIDUAL DISEASE IN PATIENTS WITH ACUTE MYELOID LEUKEMIA UNDERGOING ALLOGENEIC BONE MARROW TRANSPLANTATION

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Introduction: Measurable residual disease (MRD) is predictive of relapse in acute myeloid leukemia (AML), including in the pre-stem cell transplant (SCT) setting. The presence of leukemia stem cells (LSCs) has been shown as another predictor of outcome in addition to MRD status. **Aim:** this study aims to assess the presence of LSC in association with MRD results and its impact on the survival of AML patients undergoing SCT. **Material and methods:** Patients, material and methods: One hundred and eleven patients with AML were retrospectively evaluated before SCT and 89 after SCT. The median age was 37 years (5-63), 47% were female, and 82 (91%) had de novo AML. The 2022 ELN risk classification was: 32% adverse, 28% intermediate, 4% favourable, and 36% with missing data. Clinical remission status was: CR1(52%), CR2(31%), ≥ CR3 (17%). The conditioning regimen were myeloablative (MAC) (59%) and reduced intensity (RIC)(41%). MRD was assessed before and after SCT using an analytically and clinically validated 10-color panel that combined backbone markers (CD33, CD34, CD38, CD 45, CD117 and HLA-DR) with markers such as CD2, CD7, CD11b, CD13, CD14, CD15, CD19, CD36, CD56, CD123, CD300e. LSC immunophenotypes (CD34+/CD38-) were identified using markers such as CD45RA, CD54, CD96, CD97, CD99, CD244, CLL1/TIM3. Samples were acquired on a BDFACSLyric flow cytometer and Infinicyt (Cytognos)TM was used for flow data analysis. At least 1 million events were evaluated per tube to achieve adequate test sensitivity. R-software v 4.1 was used for statistical analysis. The Kaplan-Meier method was used to assess overall survival (OS) and relapse-free survival (RFS). The log-rank test was used to compare the survival distributions of two or more groups. **Results:** In the pre-SCT setting, the 2-year OS and RFS of the patients were, respectively, 89% and 91% for the MRD-/LSC- group (n = 44); 66% and 66% for MRD-/LSC+ (n = 3); 63% and 53% for MRD+/LSC- (n = 49); 42% and 45% for MRD+/LSC+ (n = 15) ($p < 0.001$ and $p < 0.005$ respectively). In the post-SCT setting, OS and RFS at 2 years were, respectively, 90% and 92% for MRD-/LSC- (n = 37); 100% and 89% for MRD-/LSC+ (n = 9); 75.2% and 66% for MRD+/LSC- (n = 36); 57% and 57% for MRD+/LSC+ (n = 7) ($p = 0.001$ and $p = 0.007$ respectively). **Discussion and conclusion:** Patients with MRD-/LSC- had significantly longer OS and PFS than the other groups both pre- ($p = 0.001$) and post-SCT($p = 0.009$). MRD+/LSC+ characterized the group with the worst outcome. However, the MRD+/LSC- and MRD-/LSC+ groups presented intermediate overall survival and progression-free survival compared to the other groups, and presented similar outcomes both pre- and post-SCT. A shorter OS was observed in MRD+/LSC+ patients compared to MRD +/LSC- patients pre-SCT ($p = 0.02$), but this analysis was hampered by the small number of patients in this group (n=3). In the MRD+ patient groups, OS and RFS were higher in the LSC- group than in the LSC+ group ($p = 0.009$ and $p = 0.024$ respectively) in the post-SCT setting. These findings show the relevance of the presence of LSC in the bone marrow of patients with AML and are in agreement with some data in the literature. Although the number of AML patients and LSC+ in this cohort is small to allow a more robust evaluation, these preliminary data contributed to highlight the importance of detecting LSC in the follow-up of these patients.

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LIGASE IV SYNDROME IN A 7-YEAR-OLD BOY: CLINICAL, MOLECULAR, AND TRANSPLANTATION ASPECTS OF A RARE IMMUNODEFICIENCY DISORDER

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Introduction: Ligase IV Syndrome (LIG4) is an extremely rare autosomal recessive disorder arising from mutations in the LIG4 gene, which encodes DNA ligase IV, a crucial component of the non-homologous end-joining (NHEJ) pathway responsible for repairing double-strand breaks (DSBs) in DNA. **Case report:** The patient is a male child, born on July 11, 2017, diagnosed with constitutional severe aplastic anemia secondary to a LIG4 gene mutation, confirmed through genetic testing. This rare autosomal recessive condition is classified under ICD D61.0 and is associated with defective DNA repair mechanisms and immunodeficiency disorders. Over recent months, he has required monthly transfusions of red blood cells and platelets and exhibited persistent severe neutropenia (< 500 neutrophils/μL), increasing his susceptibility to opportunistic and severe infections. The clinical and laboratory findings, consistent with bone marrow failure, led to the recommendation of allogeneic hematopoietic stem cell transplantation (HSCT), the only potentially curative treatment in LIG4 deficiency. Between January and February 2025, the patient was admitted several times to Hospital Infantil Gonzaga for neutropenia-associated bacterial infections and transfusional support. Episodes of febrile neutropenia were managed with broad-spectrum antibiotics, including intravenous vancomycin and meropenem, with good clinical response. No allergies

were reported. Given the severe bone marrow aplasia and intrinsic hypersensitivity of LIG4 deficiency patients to genotoxic agents, the medical team recommended unrelated donor HSCT with a reduced-intensity conditioning (RIC) protocol, based on recent clinical experience and established guidelines. Preparatory steps for transplantation included multidisciplinary evaluation, laboratory and imaging workup, admission to a protective environment, placement of a central venous catheter, and a conditioning regimen with fludarabine, thiotepa, and alemtuzumab. The treatment protocol also included antimicrobial prophylaxis (acyclovir, micafungin, sulfamethoxazole-trimethoprim), graft-versus-host disease (GVHD) prophylaxis (cyclosporine, mycophenolate mofetil, cyclophosphamide), adjuvant therapies (oral laser therapy and ursodeoxycholic acid), and continuous transfusion support. The planned hospitalization is approximately 60 days, followed by 4–6 months of intensive outpatient monitoring to assess for infections, GVHD, graft rejection, and chimerism. Given the severe bone marrow aplasia and intrinsic hypersensitivity of LIG4 deficiency patients to genotoxic agents, the medical team recommended unrelated donor HSCT with a reduced-intensity conditioning (RIC) protocol, based on recent clinical experience and established guidelines. Preparatory steps for transplantation included multidisciplinary evaluation, laboratory and imaging workup, admission to a protective environment, placement of a central venous catheter, and a conditioning regimen with fludarabine, thiotepa, and alemtuzumab. **Conclusion:** This case highlights the clinical complexity of LIG4 syndrome and the value of personalized transplant strategies. Genetic counseling and early screening are essential in managing inherited bone marrow failure syndromes.

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LINFO-HISTIOCITOSE HEMOFAGOCÍTICA SECUNDÁRIA À TOXOPLASMOSE DISSEMINADA, EM UM PACIENTE APÓS 12 ANOS DE TCTH ALOGÊNICO POR LEUCEMIA MIELOIDE AGUDA

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Introdução: A linfo-histiocitose hemofagocítica (HLH) é uma condição hiper-inflamatória grave e potencialmente fatal, causada pela ativação descontrolada de linfócitos T, macrófagos e células NK, resultando em tempestade de citocinas, disfunção multiorgânica e coagulopatias. Com etiologia primária (genética/familiar) ou secundária (adquirida), sendo a última mais comum e relacionada, por exemplo, com infecções, neoplasias, imunodeficiências, doenças autoimunes e uso de certas medicações. O diagnóstico precoce é essencial para o início rápido do tratamento e melhor prognóstico. **Relato de caso:** Paciente de 82 anos, com diagnóstico prévio de leucemia mieloide aguda (LMA) secundária a uma leucemia mielomonocítica crônica (LMMC), pós-transplante de células-tronco hematopoiéticas (TCTH) alogênico aparentado em 2013, com interrupção da imunossupressão em 2017. Até o momento, sem sinais de doença do enxerto contra o hospedeiro (DECH), com níveis de IgA, IgG, IgM, CD4 e CD8 dentro dos parâmetros da normalidade. Reside em um sítio em Ilhabela (SP), sem relato epidemiológico relevante. Em 2025, procurou atendimento por febre prolongada, pancitopenia, marcadores inflamatórios elevados (PCR e ferritina), triglicerídeos elevados, fibrinogênio baixo, TGO/TGP elevados e falência multiorgânica. Em avaliação medular, o mielograma evidenciou uma medula óssea (MO) hipercelular nas três séries, com figuras de hematofagocitose presente e visualização direta de taquizoítos. A biópsia da MO apresentava pesquisa imuno-histoquímica positiva para toxoplasma. O paciente apresentou risco de HLH de 93–96% segundo o HScore, com 212 pontos. A investigação infecciosa revelou sorologia inicial com IgG baixa e IgM negativa, seguida de PCR positivo para T. gondii. O teste de avidez foi baixo, e a repetição da sorologia demonstrou soroconversão com IgM reagente, sugerindo infecção aguda. Além disso, o PCR para T. gondii no LCR positivo. Portanto, compatível com o diagnóstico HLH secundária à toxoplasmose disseminada. Em uma análise retrospectiva, o paciente apresentava sorologia para T. gondii com IgG em títulos baixos 9 meses após o TCTH. **Conclusão:** Em pacientes pós-TCTH alogênico, quadros inflamatórios sem foco infeccioso definido representam um desafio diagnóstico, com diferenciais importantes entre recidiva de LMA, HLH e infecções oportunistas. No caso em questão, a toxoplasmose foi confirmada por PCR positivo e presença do parasita no mielograma, além de IgM reagente e baixa avidez de IgG para T. Gondii. A interpretação da avidez é limitada nesse contexto, devido à disfunção imunológica prolongada, sendo necessário analisar os resultados de forma integrada. Interessante notar que, mesmo após um longo período pós-TCTH, e na ausência de sinais clínicos de imunodeficiência o mesmo apresentou uma infecção oportunista grave, sugerindo um comprometimento imune persistente. A confirmação da toxoplasmose aguda disseminada em nosso paciente reforça a necessidade de vigilância contínua para agentes infecciosos, mesmo anos após o TCTH. Nestes casos, é fundamental a sinergia entre a avaliação clínica e laboratorial, uma vez que a interpretação de testes sorológicos e de avidez para patógenos deve ser feita com cautela em pacientes pós-TCTH, devido às alterações imunológicas que podem comprometer a especificidade destes exames. Essa abordagem multidisciplinar e o uso combinado de exames são essenciais para o diagnóstico e tratamento eficaz, melhorando o prognóstico desses pacientes complexos.

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