

foram relatados sugerindo padrão de herança autossômica recessiva. Assim como no caso apresentado as manifestações clínicas aparecem nos primeiros meses de vida, ocorrendo neutropenia grave com infecções e sem resposta a G-CSF, anemia e plaquetopenia progressivas e flutuantes. Presença de hematopoiese extramedular, com esplenomegalia, hepatomegalia, nefromegalia, baixo ganho ponderal e eventualmente adenomegalia. Em alguns casos foram também relatados hipergamaglobulina, osteoesclerose e reação periosteal, atraso do DNPM. Alguns pacientes também apresentaram trombastenia, porém isso não foi avaliado em nosso paciente. Em todos os pacientes relatados a BMO mostrou ser hiper celular, com hiperplasia mieloide e proeminente fibrose reticulínica, porém em nosso paciente não foi possível coleta de material adequado para análise. Quanto ao tratamento, por ser tratar de quadro muito raro, poucos pacientes foram submetidos a TMO aparentado, e assim como o nosso caso, alguns tiveram sucesso. **Conclusão:** Mutação no gene VPS45 deve ser considerado em pacientes com neutropenia, associada a outras citopenias, hematopoiese extramedular e mielofibrose, e rapidamente encaminhados para TMO.

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ASSOCIAÇÃO ENTRE INFECÇÃO POR CHLAMYDOPHILA PNEUMONIAE E ANEMIA HEMOLÍTICA AUTOIMUNE HIPOPROLIFERATIVA NA INFÂNCIA: UM RELATO DE CASO

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Objetivos: Relatar o caso de uma criança com anemia hemolítica autoimune (AHAI) mediada por auto-IgG associada a infecção de vias aéreas por *Chlamydomphila pneumoniae*. **Materiais e métodos:** Descrição de história clínica e exames laboratoriais a partir de revisão de prontuário e discussão por meio de revisão da literatura. **Relato de caso:** Criança de 8 anos, sexo masculino, havia apresentado sintomas respiratórios há 2 semanas, quando iniciou quadro de fraqueza, dor abdominal e febre. Ao exame físico, apresentava prostração, palidez e icterícia, sem outras alterações. Os exames laboratoriais demonstraram hemoglobina (Hb) 5,9 g/dL (11.5-14.5), reticulócitos 9945/ μ L (> 27.000), bilirrubina indireta 2,8g/dL (0.1-0.9) e haptoglobina < 10 mg/dL (30-200). O teste de anticorpos irregulares mostrou reatividade contra todas as hemácias do painel, inclusive o autocontrole, indicando a presença de autoanticorpo de especificidade indeterminada e confirmando a hipótese diagnóstica de anemia hemolítica autoimune a quente. Para definição de agente etiológico foi solicitado painel molecular de agentes infecciosos, que detectou infecção por *Chlamydomphila pneumoniae*. Iniciado tratamento com metilprednisolona 30mg/kg e Claritromicina,

porém o paciente manteve queda contínua de Hb (nadir 4,1 g/dL), sendo necessárias transfusões de concentrado de hemácias com compatibilidade estendida, após genotipagem eritrocitária. Devido a refratariedade à 1ª linha de tratamento e reticulocitopenia grave, realizou-se mielograma, que evidenciou hipocelularidade e parada de maturação da série eritróide, e imunofenotipagem, que não demonstrou anormalidades. O PCR para Parvovírus/ Eritrovírus foi negativo. Realizados 2 ciclos de imunoglobulina endovenosa, porém o paciente persistiu com quadro de anemia e reticulocitopenia acentuadas, com suporte transfusional quase diário, totalizando 10 concentrados de hemácias em 14 dias. Optado por introdução de terapia imunossupressora de segunda linha com ciclofosfamida (500 mg/m² dose única). Após 48h, houve progressiva ascensão de reticulócitos e, posteriormente, de Hb, com normalização do hemograma após 33 dias de tratamento. **Discussão:** A apresentação de AHAI na faixa etária pediátrica costuma ser variável em evolução e gravidade, com grande heterogeneidade etiológica. Encontramos apenas 2 casos descritos na literatura de AHAI associada a infecção por *Chlamydomphila pneumoniae*, nenhum em pediatria, e sem associação com acentuada reticulocitopenia, a qual geralmente ocorre na infecção por Parvovírus / Eritrovírus. Em relação ao tratamento da AHAI, em adultos e crianças a terapêutica de segunda linha escolhida costuma ser Rituximabe ou esplenectomia. Descrições de taxas de resposta à Ciclofosfamida são ao redor de 50-70% dos pacientes. Em crianças, há poucos dados. No caso em questão, a resposta ao tratamento com ciclofosfamida traz enfoque a uma opção terapêutica de menor custo e maior acessibilidade para a população, muitas vezes preterida frente às demais opções terapêuticas atuais. **Conclusão:** Este caso evidencia uma associação raramente descrita na literatura entre infecção por *Chlamydomphila pneumoniae* e AHAI, desta vez em cenário pediátrico. Além disso, ilustramos o manejo transfusional frente a um quadro agudo grave e destacamos o uso da ciclofosfamida como uma medicação eficaz de segunda linha para o tratamento dessa condição.

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ASSOCIATION BETWEEN GENETIC VARIANTS IN TPMT AND NUDT15 AND THIOPURINE TOXICITY IN CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKEMIA

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Introduction and objectives: Acute lymphoblastic leukemia (ALL) is characterized by accelerated proliferation of blasts in the bone marrow, reducing the production of normal blood cells and leading to accumulation of immature cells. Chemotherapeutic treatment of ALL is crucial for achieving

remission and curing these patients. However, some patients might experience toxic effects as a consequence of variations in thiopurine metabolism, including TPMT and NUDT15 enzymes. In Brazil, there is a lack of studies that demonstrate the clinical association between drug toxicity in ALL treatment and genetic variants in genes related to thiopurine metabolism. The main objective of this study was to estimate the toxicity risk regarding polymorphisms of TPMT (rs1142345, rs1800460 e rs1800462) and NUDT15 (rs116855232) in children with ALL. **Material and methods:** Pediatric patients diagnosed with ALL were included in the study. Recurrent gene fusions were identified by RT-qPCR and the copy number alterations were evaluated with MLPA. Genotyping was performed for TPMT and NUDT15 genes using allele quantification assays with TaqMan probes. Hardy-Weinberg Equilibrium and odds ratio tests were conducted for statistical analysis of clinical and genetic data to assess the association between toxicity and genotype. **Results and conclusion:** A total of 154 individuals aged 0–18 years with ALL were analyzed, comprising 63 (40.9%) females and 91 (59.1%) males. Most patients (81.2%) had a common B-cell ALL subtype. Genotyping analysis showed heterozygous genotype frequencies of 7.8% for TPMT rs1142345, 2.6% for rs1800460 and 3.3% for rs1800462, while no variant genotype was found for NUDT15. Patients exhibited various manifestations of treatment toxicity, with febrile neutropenia (51.3%) being the most common. No significant association was found between genetic variants and toxicity symptoms. Considering that only patients with NM phenotype underwent thiopurine dosage adjustments during treatment, our study highlights the lack of clinical adherence to genotyping results for the thiopurine dosage adjustment in patients with the IM phenotype. This may impact their susceptibility to toxicity manifestations that might worsen their clinical condition. This study underscores the importance of pharmacogenetics in personalizing ALL treatment, offering potential to improve clinical outcomes by customizing thiopurine doses according to each patient's genetic profile. Supported by: CNPq, FAPERJ, Ministério da Saúde, Swiss Bridge Foundation.

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ACQUIRED HEMOPHILIA A IN A 3-YEAR-OLD PEDIATRIC PATIENT: A CASE REPORT OF RARE AND POTENTIALLY FATAL BLEEDING DISORDER

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Introduction: Acquired hemophilia A (AHA) is a rare severe autoimmune bleeding disorder with significant morbidity and mortality mainly occurring in older adults (average age 75). The condition is extremely rare in children. It is characterized by autoantibodies against coagulation factor VIII (FVIII), resulting in increased clearance and neutralization

of FVIII leading to bleeding. Preventing and managing bleeding and inhibitor eradication are the mainstays of treatment. The outcome in pediatric patients seems more favorable than in adults because the inhibitors usually resolve more quickly and in a higher rate of patients. Yet we report a case of a child with AHA who had a lethal outcome 10 days post AHA diagnosis. **Case:** A 3-year-old female with history of fever, viral URTI and non-bloody diarrhea was diagnosed with parainfluenza infection. After two weeks, she developed progressive, total body edema with large ascites, and pleural effusions, mild acute kidney disease (creatinine 55 $\mu\text{mol/L}$), hypoalbuminemia (albumin 22 g/L), elevated inflammatory markers (CRP 60.5 mg/L, ferritin 434.1 $\mu\text{g/L}$), and bicytopenia [normocytic anemia (Hgb 69 g/L) with reduced reticulocyte count 36.2x10⁹/L and reduced platelet count (17x10⁹/L)]. She showed no findings of hemolysis, and peripheral smear showed only occasional schistocytes. Initially, she had a normal INR and fibrinogen but had a prolonged PTT at 83.3 sec which failed to correct with mixing study (she tested negative for lupus anticoagulant). After 4 days, the PTT prolonged further to 148.4 sec, and mixing study continued to show absence of correction. She started having some bruises, and a forearm hematoma where a peripheral IV was inserted. Further testing showed a FVIII level of < 1% whilst all other factors were within normal range. A high titer inhibitor (10 BU) was demonstrated by Bethesda assay. Extensive investigation was conducted to identify the underlying inflammatory condition, and differential diagnosis included atypical HUS, TTP (although ADAMTS-13 was normal), vasculitis and Castleman/TAFRO (given thrombocytopenia, anasarca, fever, renal dysfunction, elevated IL-6 at 11.6 pg/mL, as well as mild hepatomegaly and extensive, but small volume lymphadenopathy shown by abdominal CT). PCR testing for HHV-8 was negative. Bone marrow and lymph node biopsies were not pursued due to bleeding risk. She was started on rFVIIa 40 $\mu\text{g/kg}$ (initially given prior to procedures, then increased to every 4 hours, then every 2 hours), and immunosuppressive therapy with intravenous methylprednisolone (30 mg/kg/day). PTT initially responded decreasing from 148 to 101 sec. However, on the third day after starting steroids, her PTT increased to 123 sec. On the fourth day of steroids, her left pupil was noted to be fixed and dilated. An urgent CT showed extensive bilateral subdural bleeds for which she underwent urgent decompressive craniotomy. Massive transfusion protocol was activated, and despite rFVIIa 90 $\mu\text{g/kg}$ given every hour, tranexamic acid, platelet transfusions and FFP her subdural bleeding continued at which point further treatment was stopped and she passed. **Conclusion:** AHA is extremely rare in children but can be life-threatening. AHA should be suspected when a patient with no previous history of bleeding presents with bleeding, and an unexplained prolonged PTT. The awareness of such condition is essential for starting treatment. Despite treatment, poor outcome is still possible as seen in our case.

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