ambulatorial. Durante o seguimento foi disponibilizado laudo de biópsia de medula óssea com possível infiltração por neoplasia linfoproliferativa T e assim pausado protocolo HLH 94 para tratamento específico. **Conclusão:** Visto a raridade da HLH não há ensaios clínicos em adultos determinando tratamento e o mesmo é baseado principalmente no estudo prospectivo pediátrico HLH 94. O diagnóstico deve ser prontamente aventado em caso de síndromes febris associadas a citopenias e hiperferritininemia e o tratamento precoce é fundamental para redução de mortalidade.

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LOW MOLECULAR DIVERSITY AND GENOTYPIC-PROGNOSTIC ASSOCIATIONS IN FOLLICULAR LYMPHOMA (FL): IDENTIFICATION OF NEW BIOLOGICAL MARKERS BY LARGE-SCALE GENE MICROARRAY

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Introduction: FL has heterogeneous biological behavior, variable clinical outcomes, and a natural history marked by histological transformation (HT). The management of FL and its outcomes are highly dependent on staging (CS) and tumor burden (TB). The identification of new molecular biomarkers is crucial, not only to understand FL's biology, but also, can guide better prognostic stratification, and determine new therapeutic targets. This study aims to outline the GEP in tissue samples from FL categorized by CS and TB using a large-scale gene microarray platform with subsequent expansion by RT-qPCR. **Methods:** This study involved 219 FL cases. FL patients were categorized into early-stage disease (I/II) (ES), advanced-stage (AS) (III/IV) with low tumor burden (LTB), and AS with high tumor burden (HTB) according to GELF criteria. The experimental phase involved 126 FFPE samples. Firstly, 42 samples (12 ES, 11 AS-LTV, 12 AS-HTV, 6 control lymph nodes and 1 control HELA) were submitted to the array using the *Clariom D Array Human* platform. The identification of differentially expressed genes (DEGs) between the 4 groups used the *Transcriptome Analysis Console* by the eBay ANOVA method. Bidimensional PCA sought to identify discriminatory DEGs clusters. A comparison between pairs was subsequently performed. The 7 most discriminatory DEGs were selected for a cohort expansion by RT-qPCR. **Results:** According to CS and TB, 14.6% of FL cases were categorized as ES, 17.8% as AS-LTB, and 67.6% as AS-HTB. With a median follow-up of 80.7 months, the median OS was 208.2, 130.5, and 126.3 months for ES, AS-LTB, and AS-HTB,$p = 0.249$. The median PFS was 113.3, 110.7, and 59.5 months, for the same groups, $p = 0.018$. The array identified 135,750 genes comparisons between the control, ES, AS-LTB, and AS-HTB. PCA analysis was not able to identify discriminatory DEGs clusters among the 4 groups. Pairwise comparative analysis identified 1913 DEGs among the 4 groups. Of these, 1759 (91.9%) were DEGs between FL and healthy controls, but only 218 (11.3%) were DEGs among the 3 different FL subgroups, evidencing a low molecular diversity in FL when categorized by CS and TB. In the cohort expansion by qRT-PCR, 7 pre-selected DEGs based on the microarray were tested, including the genes *GNG7*, *ITGAM*, *AZN1*, *TIMD4*, *IL7R*, *PTGS2*, and *MTTL10*. The comparison between the median expression of these genes among the 3 FL's groups showed that the expression of the *ILR7* was downregulated with the progression of the disease, with marked hypoexpression in AS-HTB patients. These data may suggest downregulation of *IL7R* gene in the FLs natural history. We found that hypoexpression of the *GNG7* ($p = 0.024$) and *PTGS2* ($p = 0.090$) were associated with higher rates of disease progression/relapse, and hypoexpression of the *GNG7* ($p = 0.006$) was associated with a higher probability of HT, highlighting the potential prognostic impact of these molecular biomarkers. Finally, we established phenotypic-genotypic associations, as hypoexpression of *ITGAM* was associated with higher rates of B-symptoms ($p = 0.017$) and bulky disease ($p = 0.026$), as well as hypoexpression of *IL7R* was correlated with a higher probability of bulky ($p = 0.025$) and extranodal involvement ($p = 0.016$). **Conclusion:** Although CS and TB are strong determinants of the prognostic heterogeneity of FL, this study did not find high molecular diversity by this categorization. We observed a relatively homogeneous GEP with low biological diversity in FL presenting different disease evolution phases. Moreover, new molecular biomarkers potentially implicated in FLs natural history, prognostication and specific clinical phenotypes were revealed.

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OUTCOMES AND TOXICITY PROFILE IN ELDERLY DIFFUSE LARGE B-CELL LYMPHOMA PATIENTS (DLBCL): A REAL-WORLD AND COMPARATIVE STUDY INVOLVING THREE DIFFERENT DOSE-MODULATED ANTHRACYCLINE-BASED IMMUNOCHEMOTHERAPY REGIMENS IN LATAM

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Introduction: DLBCL commonly affects the older population. Elderly patients often present high-risk molecular profile, lower tolerability to chemotherapy, and poor outcomes. In this setting, attenuated therapeutic regimens, such as R-miniCHOP and R-miniCHOP of the elderly, have emerged for this fragile population. Albeit its relevance, response rates, clinical outcomes, and toxicities of these regimens remain

poorly understood, because these individuals are usually excluded from controlled trials. Therefore, this study aims to assess the outcomes, determine survival predictors, and compare responses and toxicities between R-CHOP, R-mini-CHOP, and R-miniCHOP of the elderly protocols in the management of elderly DLBCL patients. **Methods:** This retrospective, observational, and single-center study involved 185 DLBCL patients older than 70 years, treated at USP, from 2009 to 2020. Endpoints included ORR, OS, PFS. Survival curves were constructed using the KM method and the Log-Rank test was used to assess the relationship between variables and outcomes. The chi-square test and the Kruskal-Wallis test were applied to assess statistically significant differences in clinical characteristics, adverse event profile, and responses between different treatment modalities. Univariate analysis was performed using the Cox test and multivariate analysis by Cox regression method. The results were presented in HR and 95% CI, and a *p-value* ≤0.05 was considered significant. **Results:** The median age at diagnosis was 75 years, and 58.9% were female. Comorbidities were prevalent, including 19.5% with immobility, 28.1% with malnutrition and 24.8% with polypharmacy. Advanced clinical stage (III/IV) was observed in 72.4%, 48.6% had bulky ≥ 7 cm, 63.2% had B-symptoms, and 67.0% presented IPI ≥ 3. Among the 182 (98.4%) effectively treated cases, 57.1% received R-CHOP, 18.0% R-miniCHOP, 13.2% R-miniCHOP of the elderly, and 1.7% were palliated using R-CVP. The ORR for the whole cohort was 68.1%, with CR achieved in 65.9%. ORR was 72.1% for R-CHOP, 70.6% for R-miniCHOP, and 45.6% for R-miniCHOP of the elderly, p = 0.040. Although R-miniCHOP of the elderly regimen promoted lower ORR, patients in this group had higher rates of unfavorable clinical-laboratory findings, including hypoalbuminemia (p = 0.001), IPI ≥ 3 (p = 0.013), and NCCN-IPI ≥ 3 (p = 0.002). With a median follow-up of 6.3 years, the estimated 5-year OS and PFS were 50.2% and 44.6%, respectively. The estimated 2-year OS was 82.0% for R-CHOP, 67.5% for R-miniCHOP, and 48.1% for R-miniCHOP of the elderly, p = 0.003. The estimated 2-year PFS was 61.1% for R-CHOP, 56.4% for R-miniCHOP, and 20.5% for R-miniCHOP of the elderly, p = 0.005. Although correlated with increased OS and PFS in comparison to attenuated protocols, R-CHOP regimen was associated with higher rates of severe neutropenia (p = 0.003), but not translated into febrile neutropenia (p = 0.907), therapy interruption (p = 0.671), or higher early mortality rates (p = 0.681). In multivariate analysis, age≥75 years (HR: 2.08, p = 0.001), neutrophilia (HR: 2.18, p = 0.007), low lymphocyte/monocyte ratio (HR: 1.98, p = 0.010), and clinical stage III/IV (HR: 2.36, p = 0.003) were predictors of decreased OS. **Conclusion:** In this large and real-life LATAM cohort, we demonstrated that DLBCL patients older than 70 years still do not have satisfactory outcomes, with half of cases not reaching 5 years of life expectancy after diagnosis. Although a significant portion of older DLBCL patients is highly fragile and ineligible for enhanced regimens, attenuated anthracycle-based protocols promoted remarkably inferior outcomes compared to those achieved by the R-CHOP.

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RELATO DE CASO: LINFOMA DE CÉLULAS T/NK TIPO NASAL EXTRANODAL

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Introdução: Linfoma de células T/NK tipo nasal extranodal é um tipo agressivo de linfoma não Hodgkin que se desenvolve da transformação de células *natural killer* (NK) ou de células T citotóxicas. Possui associação com o vírus Epstein-Barr (EBV). **Métodos:** Estudo retrospectivo com coleta de dados por análise de prontuário. **Relato de caso:** Feminina, 64 anos, iniciou com lesão em região de palato dez/23, associado à emagrecimento, febre, sudorese noturna e linfonodomegalia cervical bilateral. Internada para investigação e biópsia, com anatomopatológico demonstrando proliferação linfoide atípica e efáliostoquímica sugestiva de linfoma de células T/NK EBV positivo. Realizado PET/CT para estadiamento contendo lesão expansiva de 5 cm em cavidade nasal esquerda e extensão para seios etmoidal e esfenoidal ipsilateral, além de captação em tonsilas palatinas e linfonodos cervicais altos bilaterais. Biópsia de medula óssea sem infiltração de doença e PCR de EBV negativo. Estadiado como IIB e PINK-E risco intermediário. Optado por iniciar protocolo GELOX (Gencitabina, L-Asparaginase e Oxaliplatina) em jun/24. Realizado até o momento dois ciclos de quimioterapia, com melhora da lesão, desaparecimento de sintomas B e dor local, atualmente em regime de radioterapia. Aguarda término da radioterapia para novo PET/CT e continuidade de quimioterapia. **Discussão:** Linfoma de células T/NK tipo nasal extranodal corresponde a < 2% dos linfomas de células T/NK. Possui maior predileção por população asiática e sul-americana. Cerca de 80% apresentam como sítio inicial cavidade nasal, seios paranasais, nasofaringe, orofaringe e trato digestivo alto – subtipos nasais. Aproximadamente 15-20% dos casos têm sítio primário pele, trato gastrointestinal, testículos e glândula salivar – subtipos não nasais. Menos 5% se apresentam com hepatoeslenomegalia, linfonodomegalia, envolvimento de medula óssea e fase de leucemia – subtipo agressivo de linfoma/leucemia. O diagnóstico envolve exame histopatológico, EBV positivo (universal), expressão do CD56 citoplasmático, CD3 epsilon citoplasmático ou moléculas citotóxicas (granzima B, perforinas e TIA1). O PET/CT é padrão-ouro para estadiamento, pois as células NK/T são ávidas pelo 18F-fluorodesoxiglicose. Há liberação de fragmentos de DNA do EBV com apoptose celular, sendo possível a realização de PCR quantitativo no plasma durante diagnóstico e tratamento para avaliação de resposta e prognóstico. Existem diversas escalas prognósticas, sendo mais prática a escala PINK-E (*Prognostic Index of Natural Killer Lymphoma – EBV*). A principal droga para tratamento é a Asparaginase, que induz a apoptose das células NK. É indicado quimioterapia e radioterapia, não existindo estudos comparativos entre regimes de tratamento. De modo geral, não há indicação de transplante autólogo de medula óssea. Novas terapias com inibidores do *checkpoint*, anticorpos monoclonais anti-CD30 e anti-CD38, inibidores da histona desacetilase (iHDAC) estão sendo