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Title: Asymptomatic multicentric Castleman disease: A potential early stage of idiopathic MCD

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Summary: According to the diagnostic criteria for HHV-8 (human herpesvirus-8) negative/idiopathic multicentric Castleman disease (iMCD) proposed by Castleman Disease Collaborative Network (CDCN) in 2017, there is a group of HHV-8 negative multicentric Castleman disease (MCD) patients who do not have symptoms and hyperinflammatory state and do not fulfill the criteria for iMCD. This retrospective study enrolled 114 such patients, described as asymptomatic MCD (aMCD), from 26 Chinese centers from 2000-2021. Following diagnosis of MCD, despite the absence of inflammatory symptoms or laboratory abnormalities, 43 (37.7%) patients underwent treatment specifically targeting MCD, primarily in the form of lymphoma-like intensive chemotherapy (e.g., CHOP, R-CHOP). With a median follow-up time of 46.5 months (range: 4-279 months), 6 patients (5.3%) transformed to iMCD. The median time between diagnosis of aMCD and iMCD in these 6 patients was 28.5 months (range: 3-60 months). During follow-up, 7 patients died; three of them died from progression of MCD. Despite that 37.7% patients received systemic treatment targeting MCD, this strategy was neither associated with a lower probability of iMCD transformation nor a lower death rate. The 5-year estimated survival of all aMCD patients was 94.1% (95% CI 88.8-99.6%). Transformation to iMCD was an important predictor of death (log-rank p=0.01) (5-year estimated survival 83.3%). This study suggests that aMCD patients may represent a potential early stage of iMCD, who may not require immediate treatment but should be closely monitored.