Asymptomatic Multicentric Castleman Disease: a Potential Early Stage of Idiopathic MCD

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Introduction: In 2017, the Castleman Disease Collaborative Network (CDCN) published the first international, evidence-based consensus diagnostic criteria for HHV-8 (human herpesvirus-8) negative/idiopathic multicentric Castleman disease (MCD), a rare and sometimes life-threatening disorder involving systemic inflammatory symptoms, polyclonal lymphoproliferation, cytopenias, as well as multiple organ system dysfunction. According to this consensus, HHV-8 negative MCD was regarded as idiopathic MCD (iMCD) due to unknown etiology. However, there was a group of HHV-8 negative MCD patients who did not exhibit symptoms indicative of a hyperinflammatory state and therefore did not meet the minor criteria of iMCD proposed by CDCN. It was still unknown whether this subgroup of patients, regarded as asymptomatic MCD (aMCD), represented a 'pre-stage' of iMCD, which would eventually suffer from clinical and laboratory abnormalities over time, or if these patients belonged to a unique subset of MCD patients. Herein, we conducted a multicenter, retrospective study focusing on the follow-up information and potential transformation of aMCD patients, trying to figure out whether these patients would eventually exhibit inflammatory symptoms and laboratory abnormalities and transform into iMCD.

Methods: This observational, retrospective study enrolled aMCD patients from 2000 to 2021 in 26 Chinese medical centers. The inclusion criteria for aMCD patients who were eligible for this study were: HHV-8 negative MCD patients who met both major criteria (histopathologic evidence plus ≥ 2 lymph node stations involvement) but did not fulfill the minimal requirements of minor diagnostic criteria (at least 2/11 minor criteria with ≥ 1 laboratory criterion) proposed by CDCN.. Patients were followed until March 31, 2023 and survival status was documented. The time-point when a patient developed symptoms and/or new laboratory abnormalities and fulfilled the CDCN diagnostic criteria of iMCD was recorded.

Results: 114 patients with aMCD were enrolled, with a male to female ratio of 1:0.9. The median age at diagnosis of aMCD was 45.5 years (range: 10-79 years). Adult patients accounted for 92.1%. After diagnosis of MCD, although the patients did not have inflammatory symptoms or laboratory abnormalities, 43 patients (37.7%) received treatment targeting MCD. 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). Gender, age at diagnosis of aMCD, extent of lymph node involvement (the same side or both sides of diaphragm), pathological subtype and systemic therapy targeting MCD were not associated with the probability of transformation to iMCD. 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 rate of patients who maintained aMCD was 94.9% while the 5-year estimated survival rate of patients who ultimately transformed to iMCD was 83.3%. Transformation to iMCD was an important predictor of death (log-rank p=0.01, Figure 1).

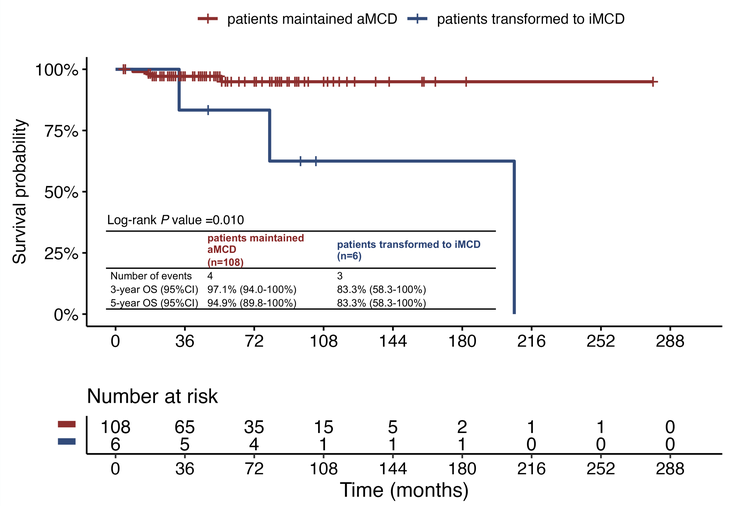

Fig 1. Survival curves of patients who maintained aMCD and those who transformed to iMCD.

Conclusion: aMCD might be regarded as a potential early stage of iMCD that does not need immediate treatment but should be closely monitored