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Recurrent Fever, Aphtous Stomatitis and Chronic non-bacterial Osteomyelitis in a patient with Trisomy 8 associated autoinflammation

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Systemic autoinflammatory diseases (SAIDs) are characterized by episodes of systemic inflammation, caused by dysregulation of the innate immune system. Mendelian-inherited pathogenic variants in distinct genes may account for these diseases in a significant proportion of patients, however, disease-causing variants may present with variable expressivity. Furthermore, pathogenic germline variants that may explain the disease phenotype cannot be detected in the majority of patients, particularly in those suffering from “complex” SAIDS, e.g. PFAPA-syndrome or chronic non-bacterial osteomyelitis (CNO), as the most common SAIDs in children. Interestingly, non-Mendelian inheritance of somatic variants has increasingly been described to account for or modify the clinical phenotype of SAIDs.

A 13-year-old girl was presented to our pediatric department with a history of recurrent fever and oral ulcers and pain in the legs. Recurrent episodes with fever, aphthous stomatitis and pharyngitis, that responded well to corticosteroids, started at the age of 18 months and the diagnosis of PFAPA-syndrome was made. At the age of 5 years, the fever episodes suspended, while aphthous stomatitis continuously persisted since then. Additionally, the patient reported severe pain in the legs since the age of 11 years.

Whole-Body MRI displayed multifocal lesions with bone edema and contrast-enhancement in the right proximal femur metaphysis, both tibial metaphyses as well as right talus/calcaneus compatible with CNO. Her differential blood count showed mild neutropenia (1300/µl) and macrocytosis (MCV 101 fl). Vitamin B12-deficiency was ruled out. Bone marrow aspirates did not show significant dysplastic alterations. However, cytogenetic analysis revealed a 47, XX+8 karyotype in 68% of the analyzed interphase nuclei. These genetic alterations remained unchanged in a 6-months follow-up analysis without significant signs of dysplastic alterations and could also be detected in 64% of peripheral blood mononuclear cells suggesting either constitutional or acquired mosaicism.

Whereas short-term treatment of corticosteroids alleviated skeletal pain, long-term treatment with colchicine had no impact on the oral ulcerations. Hence, TNF-α inhibition (adalimumab) was initiated and the patient is in clinical remission since then.

Acquired Trisomy 8 is a common finding in myelodysplastic syndrome (MDS) and in conjunction with MDS associated with inflammatory disorders, e.g. Behcet-spectrum like symptoms. Additionally, increased prevalence of periodic fevers and/or aphthous stomatitis has been reported in rare patients with constitutional trisomy 8 mosaicism. We herein present a patient with complex autoinflammatory symptoms most likely associated to an acquired or constitutional trismomy 8 mosaicism. Current experiments are ongoing to dissect the distribution of aneuploid cells within distinct cell lineages and correlate this to potential aberrant gene expression and function.