Idiopathic multicentric Castleman Disease (iMCD) is a rare, atypical lymphoproliferative disorder with significant morbidity and mortality and unknown etiology. (Fig. 1)

A fundamental question is whether iMCD should be considered an infectious disease caused by an as-yet-unknown pathogen, an autoimmune disease caused by autoantibodies, an autoinflammatory disease caused by genetic mutations, or a neoplastic disease caused by somatic mutations in a clonal cell population.

Idiopathic Multicentric Castleman Disease (iMCD)

- Cytokine Storm
- Lymphadenopathy
- Histopathological Abnormalities
- Healthy
- iMCD

Do autoantibodies contribute to iMCD pathogenesis?

We constructed two custom bead-based protein arrays to screen serum samples for autoantibodies from iMCD patients and healthy controls. (Fig. 2, Table 1, and Fig. 3)

1) The Connective Tissue Disease (CTD) array consisted of 52 antigens associated with traditional CTDs. Antigens are separated by six subcategories of CTDs (Scleroderma, Myositis/Overlap Syndromes, Systemic Lupus Erythematosus SLE/Lupus, Granuloma Syndromes, GI/Endocrine, DNA-Associated, and Inflammation/Infection).

2) The Anti-Cytokine Autoantibody (ACA) array included 38 cytokines, chemokines, and cell surface proteins.

Autoantibodies associated with Connective Tissue Disorders (CTD) are prevalent in iMCD patients

- Overall, 46% of iMCD subjects were positive for a CTD autoantibody compared to 17% of HCs (OR 4.1, P = 0.005). (Fig 4A)
- Cytokine autoantibodies associated with Myositis and SLE (red box) trended higher in iMCD patients (but did not pass multiple testing correction).

Serum samples were analyzed using a FlexMap3DTM instrument (Luminex Corp.). Binding events were measured as Median Fluorescence Intensity (MFI). Serum samples were considered “positive” for autoantibodies targeting a specific antigen if the normalized MFI was greater than 5 standard deviations (SDs) above the average MFI for HC or an MFI value > 3,000 units.

Cytokine Storm

Autoantibody levels fluctuate over time and may fluctuate based on disease state. Investigation of specific autoantibodies in iMCD is ongoing.

Conclusions

1) Overall, 46% of iMCD subjects were positive for a Connective Tissue Disorder (CTD) autoantibody compared to 17% of HCs (OR 4.1, P = 0.005).

2) Although not surviving multiple hypothesis correction, autoantibodies associated with myositis and SLE trended higher in iMCD patients.

3) IgG autoantibodies associated with CTDs, including anti-Mi2, anti-SRP54, anti-La, anti-Ro, and anti-Histone H3 were common in iMCD compared to HC.

4) Anti-cytokine autoantibodies (ACA) were common in iMCD patients

5) Autoantibodies fluctuate over time, and may fluctuate based on disease state. Investigation of specific autoantibodies in iMCD is ongoing.