Background

Multicentric Castleman disease (MCD) is a polyclonal lymphoproliferative disorder associated with cytokine-induced systemic inflammation, lymphadenopathy and multi-organ failure.

The annual incidence of MCD in the USA is ~16001.

Kaposi sarcoma herpes virus (HHV-8) is the driver in ~50% of MCD cases2 (HHV-8-MCD), whereas the remaining HHV-8-negative (idiopathic or IMCD).

Diagnosis and detection of IMCD is difficult due to limited etiological understanding and heterogeneous presentation – clinical, laboratory, and histopathological abnormalities overlap with infectious, autoimmune and oncological diseases.

Siluixinab (anti-interleukin(IL)-6), is the only FDA-approved therapy and is efficacious in ~34% of cases of IMCD.3

Novel drug targets to induce and maintain remission in IL-6 blockade refractory IMCD are urgently needed.

Objectives

- Molecularly define IMCD.
- Identify predictors of response to anti-IL-6 therapy.
- Gain insights into the pathogenesis of IMCD.

Methods

SomaLogic SomaScan was used to measure ~1,300 serum analytes from 92 pretreatment IMCD patients during disease flare (n = 75 collected as part of NCT01024036), and 20 of each: HHV-8-MCD, Hodgkin lymphoma (HL), and rheumatoid arthritis (RA).

1,178 analytes passed QC, were log2 transformed, and capped at the 25th and 97.5th percentiles. Clinical and laboratory data were collected at the time of sample draw.

A modified CHAP scale was used to calculate disease activity: C-reactive protein, hemoglobin and albumin.

Response to anti-IL-6 therapy was determined in NCT01024036.

Data analysis was performed using Medidata Rave Omics Machine learning platform and R v3.4.4.

Proteome-Defined IMCD: Clustering of pretreatment proteomic data for IMCD patients identified six clusters that ranged in size from seven to 27 subjects. No associations with race, site, sex, age, or batch were observed. Analytes identified among the strongest differentiators included cytokines, chemokines and inflammatory molecules (Fig 1).

Predictors of anti-IL-6 response

As compared to the other clusters, one cluster demonstrated a significant association with response to anti-IL-6 therapy (p<0.05; 65%, (11/17) vs 19% (5/27), higher disease activity (p=0.01), and higher IL-6 levels (p<0.01) (Fig 2).

Insights into IMCD pathogenesis:

Analysis across the entire study population separated HHV-8-MCD, HL, and RA into distinct clusters. IMCD patients did not form a single or unique cluster. A subset of IMCD patients demonstrated similar, but not overlapping, proteomic profiles to those of HL (Fig 3).

Results

This study represents the first use of high-quality serum proteomic data to study a rare non-malignant lymphoproliferative disorder.

IMCD is a molecularly heterogeneous disease.

Previously, no proteome-distinctively IMCD subtypes or disease states exist.

Proteomic signatures can be used to inform treatment options.

Overlapping proteomic profiles among Hodgkin lymphoma and a subset of IMCD patients provide etiological insights.