Serum proteomics reveals distinct subtypes associated with treatment response in idiopathic multicentric Castleman disease

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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 ~1600[1].
- Kaposi sarcoma herpes virus (HHV-8) is the driver in ~50% of MCD cases[2] (HHV-8-MCD), whereas the remaining are HHV-8-negative (idiopathic or iMCD).
- Diagnosis and treatment of iMCD is difficult due to limited etiological understanding and heterogeneous presentation – clinical, laboratory, and histopathological abnormalities overlap with infectious, autoimmune and oncological diseases.
- Siltuximab (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 $\log_2$ transformed, and capped at the 2.5th 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, *h*emoglobin and *a*lbumin.
- 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.

RESULTS

Proteomically define 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 include cytokines, chemokines and inflammatory molecules (Fig 1).

Predictors of anti-IL-6 response:
As compared to the other clusters, cluster one demonstrates 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 patents demonstrated similar, but not overlapping, proteomic profiles to those of HL (Fig 3).

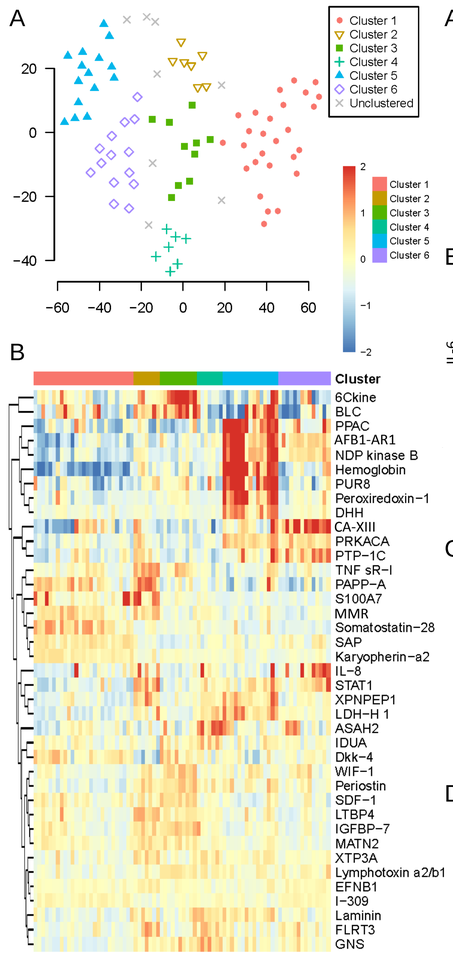
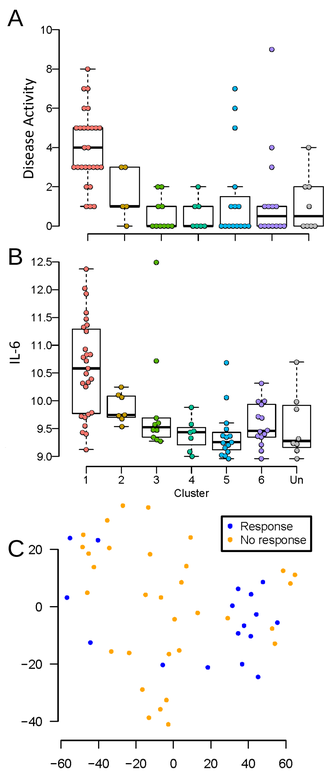


Fig. 1. (A) Cluster analysis of iMCD patients. (B) Heat-map of the top differentially expressed genes between the identified clusters of iMCD patients.



Cluster	Evaluable	Response	Rate (%)
1	17	11	65
2	2	**0**	0
3	8	**1**	13
4	4	**0**	0
5	10	**3**	30
6	3	**1**	33
Unclustered	5	**1**	20
All	49	17	35

Fig. 2. (A) iMCD disease activity, (B) IL-6 levels, and (C and D) response to anti-IL-6 therapy by Cluster.

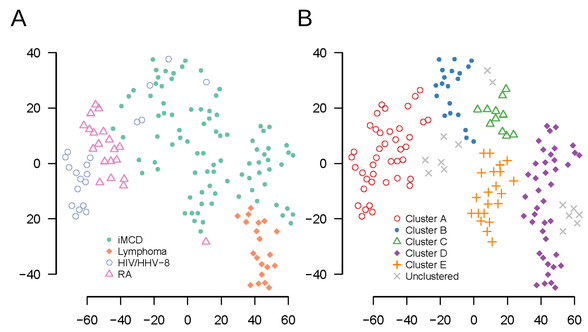


Fig. 3. (A) tSNE plot of the entire study population. (B) Clustering analysis of entire study population demonstrates proteomic similarities among Hodgkin lymphoma and a subset of iMCD patients.

CONCLUSIONS

- **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 undiscovered proteomically-distinct 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 provides etiological insights.**

Conflict of Interest Disclosure: MG is employed by Janssen Pharmaceuticals. CT and MPR are employed by and have equity ownership in Janssen Pharmaceuticals. MW is a consultant to and receives research funding from Amgen, Bristol Myers Squibb, Crescendo Biosciences, Sanofi/Regeneron, and UCB Pharmaceuticals. MB has received honoraria from Merck, Gilead, ViiV, and Janssen Pharmaceuticals. YM receives research funding from Kyowa Hakko Kirin, Astellas, Ono, Eisai, and Pfizer. PB, ABA, JW, and JB are employed by and have equity ownership in Medidata Solutions. SM, LK, and DL are employed by Medidata Solutions. SS and JM are consultants to Medidata Solutions. AF has received honoraria from Janssen Pharmaceuticals. DF receives research funding from Janssen Pharmaceuticals. DS, JRR, CSN, SKP, NS, ADP, and FvR have nothing to disclose.

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