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Bronchoalveolar Lavage Neutrophils and Matrix Metalloproteinase-9 in Sarcoidosis Clinical Phenotypes: Implications for Tissue Remodeling Leading to Pulmonary Fibrosis

Rafael L. Perez, MD
Thomas Jefferson University

Jeff Ritzenthaler
Thomas Jefferson University

E. Torres-Gonzalez
Thomas Jefferson University

Prarthna Chandar, MD
Thomas Jefferson University

Daniel Kramer, MD
Thomas Jefferson University

See next page for additional authors

Authors

Rafael L. Perez, MD; Jeff Ritzenthaler; E. Torres-Gonzalez; Prarthna Chandar, MD; Daniel Kramer, MD; and Jesse Roman, MD

Bronchoalveolar lavage neutrophils and matrix metalloproteinase-9 in sarcoidosis clinical phenotypes: Implications for tissue remodeling leading to pulmonary fibrosis

R.L. Perez, J.D. Ritzenthaler, E. Torres-Gonzalez, P. Chandar, D. Kramer, J. Roman; Jane & Leonard Korman Respiratory Institute; Division of Pulmonary, Allergy & CCM; Thomas Jefferson University, Philadelphia, PA.

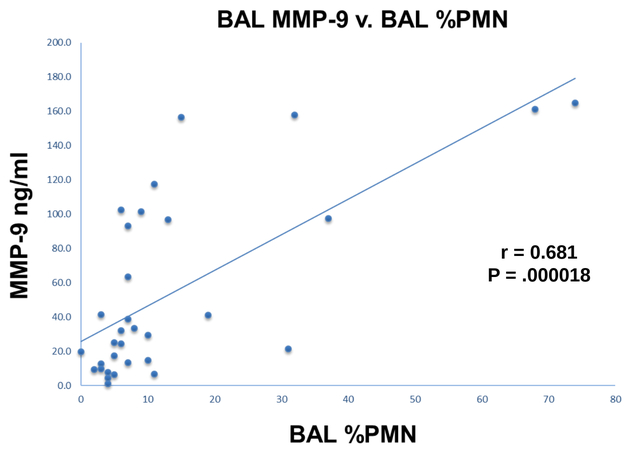
Introduction

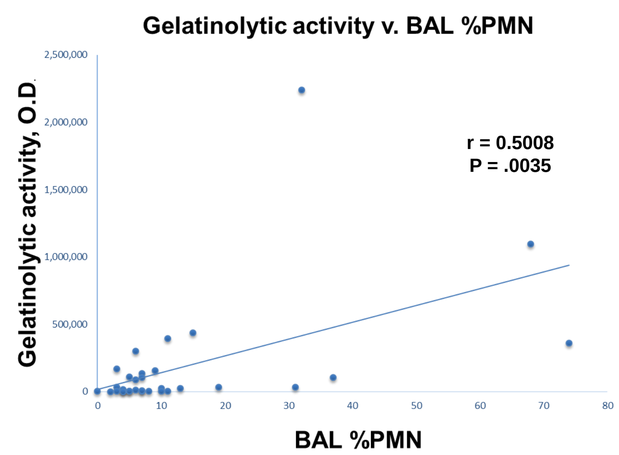
Pulmonary sarcoidosis may resolve or progress to advanced stages. Increased lung neutrophils obtained by bronchoalveolar lavage are found in advanced pulmonary sarcoidosis. Persistence of a neutrophilic alveolitis has been postulated to result in tissue injury and remodeling that leads to fibrosis and clinical features of advanced disease. Since neutrophils are a source of matrix-degrading proteins like matrix metalloproteinases (MMPs), we hypothesized that PMNs promote disease progression through the release of MMPs. **This work explores the relationship between lung neutrophils and MMP9 levels and activity and how they are associated with sarcoidosis clinical phenotypes.**

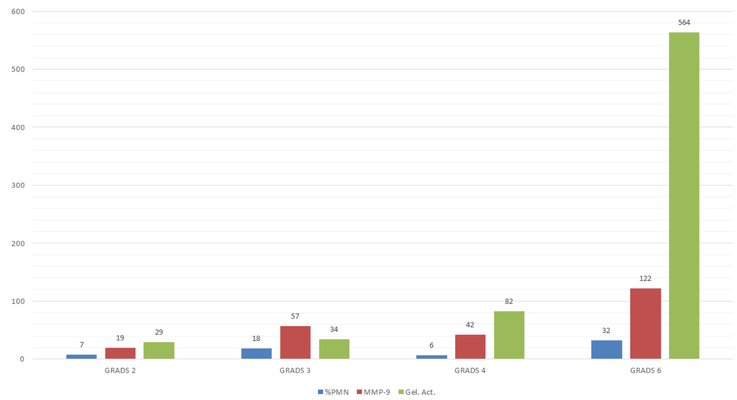
Methods

Patients undergoing bronchoscopy for the diagnosis of sarcoidosis or assessment of disease activity were classified by the 9 Genomic Research in Alpha-1 Antitrypsin and Sarcoidosis (GRADS) clinical phenotypes. Bronchoalveolar lavage fluid (BALF) percent neutrophils (%PMN), matrix metalloprotein-9 (MMP-9), ng/ml, and gelatinolytic activity, O.D./mcg total protein, were analyzed against the GRADS phenotypes.

Results







GRADS comparisons for %PMN and MMP9, ng/ml		
	%PMN	MMP9, ng/ml
2 v. 3	NS	NS
2 v. 4	NS	NS
2 v. 6	P = .017	P = .00012
3 v. 4	NS	NS
3 v. 6	NS	P = .016
4 v. 6	P = .012	P = .00248

Discussion

Our study suggests the hypothesis that a low burden of lung PMN and low matrix remodeling activity allow normal lung matrix repair as would be expected in a GRADS 2 phenotype. A high burden of lung PMN and matrix remodeling activity promote fibrosis as seen in subjects with an advanced GRAD 6 presentation. Subjects with treated stage II – III disease, GRADS 3, have a high burden of PMN similar to GRAD 6 while untreated stage II - III, GRADS 4, have significantly lower %PMN and MMP9 than GRAD 6 subjects.

Conclusions

Clinical phenotypes of sarcoidosis may reflect specific tissue remodeling paradigms that drive irreversible tissue fibrosis or repair to normal. Stage II – III lung phenotypes may remodel normally or progress to fibrosis and may be "endotyped" by the extent of neutrophilc alveolitis.

Clinical Phenotype	Presentation	Scadding Stage	Rx > 3 months	Multiorgan	Clinical course	Cardiac
1 Multiorgan	N	Any	Any	Yes	C, U	Any
2 Nonacute, Stage I, untreated	N	I	No	No	C, U	No
3 Stage II - III, treated	N	II, III	Yes	No	C, U	No
4 Stage II - III, untreated	N	II, III	No	No	C, U	No
5 Stage IV, treated	N	IV	Yes	No	C, U	No
6 Stage IV, untreated	N	IV	No	No	C, U	No
7 Acute sarcoidosis	A	I, II, III	No	Any	C, U	No
8 Remitting, untreated	Any	Any	No	Any	R	Any
9 Cardiac defining therapy	Any	Any	Any	No	C, U	Yes
A = acute; C = chronic; N = nonacute; R = remitting; U = uncertain						

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