*Project S.E.N.S.O.R. News

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Hypersensitivity Pneumonitis – Identifying the Causal Agent

Hypersensitivity Pneumonitis (HP) is a difficult disease to diagnose, particularly to identify the causal antigen. Since the primary treatment modality is to remove the patient from exposure, identification of the causal antigen is extremely important. A patient whose disease is recognized at an early stage and is removed from exposure will usually have complete reversal of their symptoms, as well as reversal of their radiographic and pulmonary function abnormalities.

We previously described a cluster of HP patients in southwest Michigan associated with machining (i.e. grinding, drilling) metal while using water based metal working fluids (coolants) (Gupta and Rosenman, 2006).These cases with ground glass changes on their high resolution chest CT scans, restriction and decreased diffusing capacity on their pulmonary function testing were diagnosed early in the development of their disease and had reversal of their findings one to six months after removal from exposure.

Unfortunately many patients with HP are first thought to have common conditions, such as pneumonia or sarcoidosis and the association of their lung symptoms with an exposure is not appreciated. Commercially available hypersensitivity panels that measure IgG antibodies in the patient's serum to bacteria, fungus or bird protein may be useful in identifying the causal antigen (See Appendix I).

However, in a large percentage of HP patients these commercially available tests are negative since the causal antigen in the environment of the patient is not included in the commercially available panel. Another issue is that antibodies may be present after exposure to one of these antigens in the absence of disease, so a positive result, although suggesting the importance of that antigen in the etiology of the patient's HP, may be a marker of exposure but not involved in the pathophysiology of the disease.

Hypersensitivity Pneumonitis (HP) — (Extrinsic Allergic Alveolitis)

HP was first described in farmers in the late 1800's (Farmer's Lung Disease) and there are now approximately 50 known types with descriptive names such as Mushroom Worker's Disease, Hot Tub Lung, Sauna Taker's Disease, etc. HP is an immunologically mediated disease from inhalation of nondigestible antigens that act as adjuvants, fix complement and initiate a cell mediated process. Typically, the cause of HP is a microbial agent, but, for example, in Pigeon Breeder's Disease the agent is a bird protein and for others, the agent can be certain chemicals, such as TDI (toluene diisocyanate), which can cause both asthma and HP.

If a patient smokes cigarettes, they probably do not have HP. HP is often confused with recurrent "pneumonia". A HRCT that describes infiltrates with a ground glass appearance is commonly the initial test result that raises suspicion for the disease. Granulomas are found on lung biopsy. Although oral prednisone will reduce symptoms, with continued exposure patients will progress to irreversible fibrosis even with steroid treatment.

To explore ways to facilitate recognition and treatment of HP, Dr. Millerick-May, Assistant Professor of Medicine at Michigan State University, with previous industrial experience in toxicology/industrial hygiene, has partnered with Shelley Schmidt, M.D., of the Department of Pulmonary & Critical Care Medicine at the University of Michigan, on a pilot project. The pilot project consisted of 17 patients with definite and probable HP (Table 1).

Environmental samples were collected at the 17 patients' homes and workplaces. Serum was collected from the patients for testing with the commercially available antigens and antigens identified from the environmental samples collected from each patient's home and workplace. Antigens from the environmental samples were identified via immunodiffusion assay with the patient's serum, isolated via standard microbiological techniques and using 16S sequencing techniques. Asymptomatic disease-free family members and/or co-workers were recruited as controls and their serum similarly tested. Since not all people exposed to these antigens become ill, HLA typing to investigate individual genetic susceptibility was also performed on patients and controls.

In order to assess if the positive antigens are initiating an immune response in individuals testing positive to multiple antigens, we plan to utilize flow cytometry to assess cytokine production and lymphocyte proliferation.

The results to date on the 17 patients are:

One or more 'positive' antigens identified for 6 patients. Up to 18 antigens identified in one patient.

- Three patients, each with past/present history of 'farming' exposure tested positive to >5 discrete antigens. Of those, two had 'controls' that tested positive to bulk samples, but neither tested positive to the same isolate as their 'matched' case. A 'matched' control with the same 'farm' exposure was not available for serum collection for the remaining patient.

Table 1: Characteristics of Study Population (n=17)

Gender	
Male	**7**
Female	**10**
Age (range, years)	**47 - 77**
HP Diagnosis	
Definite	**11**
Probable	**6**
Type	
Inflammatory	**2**
Fibrotic	**13**
Unknown	**2**
Time Between Onset of Symptoms and Diagnosis (years)	
<1	**1**
1-3	**8**
>3	**8**

Of the 11 patients where 'positive' antigens were not identified from environmental samples:

- Five of the patients have fibrosis with stable pulmonary function tests and are likely not currently exposed to the causal antigen.

- In two patients, it is likely that exposure still occurs intermittently, but access to the environment from which to collect the antigen was not possible (i.e. out of state family member's home).

- Repeat sampling will be scheduled for late spring/early summer in 4 patients where it is believed that exposures of interest still may occur, but due to timing of original sampling (late fall/winter/early spring), antigen may not have been present in sufficient quantities during bulk collection.

- It is possible that current use of immunosuppressant drugs is causing a false negative finding in the immunoassay.

The source of most of the patients for this pilot project was a tertiary pulmonary clinic. Therefore, patients may have had symptoms for prolonged periods, in some cases years, before a diagnosis of HP was made (Table 1) and environmental sampling was initiated. Most patients in this small cohort already have fibrosis which may explain why environmental sampling in 65% did not result in identification of an antigen. This emphasizes the importance of early recognition of the etiologic agent and assessment of the patient's environment in order to identify the causal antigen from which the patient needs to be removed.

If you have questions about patients with possible HP or patients where we may be able to assist evaluating their environment, please call at 1-800-446-7805.

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Reference

Gupta A, Rosenman KD. Hypersensitivity Pneumonitis Due to Metal Working Fluids: Sporadic or Under-Reported? American Journal of Industrial Medicine; 2006; 49:423-433.

Appendix I. Antigens Included in HP Test Panels by Laboratory

	QUEST*		Mayo* Clinic	ARUP*			IBT*
Antigen	HP Evaluation	HP Screen	HP Panel IgG Ab	HP Extended panel (Farmers)	HP I Panel	HP II Panel	HP Panel
Micropolyspora faeni	X	X	X	X	X		X
Saccharomonospora viridis	X	X		X		X	
Thermoactinomycetes vulgaris	X	X	X		X		X
Thermoactinomycetes sacchari	X			X		X	
Thermoactinomycetes candidus	X	X		X		X	
Aspergillus fumigatus	X	X	X				X
Aspergillus flavus						X	
Aspergillus fumigatus #1, #2, #3, and #6				X	X		
Aspergillus fumigatus #2, and #3						X	
Aspergillus fumigatus #1, and #6					X		
Alternaria tenuis	X						X
Aureobasidium pullulans	X			X	X		X
Cladosporium herbarum	X						
Penicillium notatum or chrysogenum/notatum	X						X
Phoma spp or phoma betae	X						X
Trichoderma viride	X						X

***Testing Available for IgG Antibodies to Bird Proteins:**

ARUP HP Extended Panel—pigeon serum plus eleven micro organisms

ARUP HP I—pigeon serum plus five micro organisms

IBT Bird Fancier's Precip Panel I—pigeon, parakeet and parrot droppings and serum, canary and cockatiel serum and finch droppings

IBT Bird Fancier's Precip Panel II—same as I plus aspergillus fumigatus and asperigillus pullulans

Mayo Clinic Avian Antigen Panel - pigeon, parakeet, cockatiel and parrot droppings and serum

Quest HP Evaluation - Mixed Feathers IgG, pigeon dropping plus 12 micro organisms

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*PS *Remember to report all cases of occupational disease!*

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