THE IMMUNOPATHOLOGY OF HYPERSENSITIVITY REACTIONS

VINCENT A. MARINKOVICH, M.D.

Clinical Associate Professor, Stanford Medical School, 801 Brewster Avenue, Suite 220, Redwood City, CA 94063, Telephone: (650) 482-2800, Fax: (650) 482-2802

ABSTRACT

Overactivity of the immune system, either allergy (IgE) or hypersensitivity (non-IgE) is responsible for more illness than is generally appreciated, even by the medical profession. The least understood are the non-IgE mechanisms which involve either immune complex formation (type III of Gell and Combs) or direct killer T-cell involvement (type IV). Type III reactions may be localized with a large deposition of antigen at a focal point where immune complexes are formed and tissue damage ensues including necrosis. This is termed the Arthus reaction. A systemic dissemination of antigens will provoke a systemic inflammatory reaction which is most closely modeled by the well studied acute and chronic serum sickness reaction. Serum sickness was identified as the constellation of symptoms which followed the administration of antitoxins (antisera given for infectious disease before the advent of antibiotics) which were derived from non-human sources, most often horses. Chronic serum sickness was observed when otherwise healthy subjects were given repeat doses of antisera experimentally over relatively short periods of time. The symptoms observed in spontaneous and experimental serum sickness included fatigue, rash, cognitive changes, myositis, arthritis, headache, weight-loss, cardiovascular symptoms etc., which are often seen during heavy chronic exposure to fungal spores. The dynamic nature of circulating immune complexes, their complexity, their rapidly changing exquilibrum patterns and their pathogenicity must be appreciated before the clinician can properly interpret the patterns of illness his patients' describe. The best simple test identifying and thereby allowing the avoidance of serum sickness is a specific IgE test to a panel of high exposure antigens including fungi, food and occupational antigens.

KEY WORDS

Mechanisms of Hypersensitivity, Immune complexes, Immunopathology of fungal reactions

There is considerable controversy about the potential health hazards from exposure to fungal elements which is fueled by the growing amount of litigation involving this issue. Workers, homeowners, students who become ill, identify the potential source of symptoms as a contaminated environment and sue their companies, home builders or school authorities respectively for compensation. The litigation process with hired "expert" testimony from both sides of the controversy does little to add to our knowledge of the health hazards or safety limits on exposure to fungi. Health care professionals have to be aware of the potential for illness fol-

lowing exposure to fungi and sufficiently alerted to the possibility of a fungal cause of the illness to arrive at a correct diagnosis and thereby help their patients.

There are three commonly recognized sources of fungal exposure, which have the potential to produce disease. These come via airborne routes in the form of spores, volatile compounds and l fragments; ingestion as a food contaminant or food additive or by-product of food processing; and via direct contact from colonization of skin, mucosal surfaces and the alveoli of the lungs. Since different fungi from different sources share common surface proteins, the immune response to fungi may crossreact and avoidance measures in treating hypersensitivity reactions must identify and correct all sources of contact.

Mycotoxins are the most respected of fungal products for their potential to cause serious illness through their direct biochemical action on key body functions. Aflatoxin is known to be among the most potent of carcinogens and the toxin released by *stachybotris* is believed to have caused deaths in exposed infants. Other toxins can affect various hormonal, neurological and other body functions to produce serious health effects. They are so effective in certain biological activities that they have been harnessed by the pharmaceutical and food industries to commercial use such as antibiotics, immune suppressants to control graft rejection, cholesterol control, and enzymatic activity in food processing and preservation. Mycotoxins are produced by some fungi under specific growth conditions and are relatively rare causes of human illness. Hyperactive immune systems responding to the influx of fungal antigens following chronic exposures are much more likely to be a cause of symptoms in most individuals. Since hypersensitivity states develop only after relatively long exposure times, children under ten years of age do not have significant antibody titers to fungi unless they have experienced very high exposure levels, while normal mature adults living in temperate or tropical climates commonly show sensitivity to fungi and experience symptoms following unusual exposures. These symptoms often follow exposures by one or two days, are not recognized for what they are, and are likely to be diagnosed as a virus infection.

Allergists have accepted the role that fungal spores can play in eliciting allergy symptoms in susceptible individuals. This is akin to the effects of other airborne organic particles such as pollen, animal dander's and insect dust. The illness affects only individuals programmed genetically to make large quantities of specific IgE antibodies on exposure to relatively small amounts of allergen. This is a type I immunopathology as defined by Gell and Coombs (1) and involves the release of pre-formed histamine and other biologically active cytokines from sensitized mast cells and basophils. Symptoms include watery nasal discharge, sneezing paroxysms, itching of the naso-oro-pharyngeal mucosa and tearing eyes and can be significantly disabling. It has been suggested that perhaps five percent of the population may be affected in this way by fungi.

Far more elaborate and damaging immune responses can be elaborated by the body following exposure to large amount of fungal particles, especially when the exposure is chronic. These illnesses were originally described in association with various occupational exposures in unprotected workers such as farmer's lung, bagassosis in sugar cane workers and many others. More recently such conditions have been identified and studied in office workers whose workplace is contaminated by fungi, especially in buildings with closed ventilation systems. The disease has also been described in individuals exposed to swamp coolers or contaminated air condi-

timers in the home. These symptoms can occur in all individuals with normal immunity because they are ultimately manifestations of a robust immune response to a heavy airborne fungal load with consequential overload of clearing mechanisms or macrophages, and the activation of inflammatory processes.

The mechanisms of disease produced by heavy, chronic exposure to airborne fungal elements are classified as Types III and IV immunopathologys (Gell and Coombs) and involve antibodies, primarily IgG, and activated, sensitized lymphocytes. The best single marker of such an immune response is specific serum IgG which can help identify the fungal causes of the illness and lead to remediation to remove fungal sources of exposure. The only known treatment for the condition is cessation of exposure. Once the hypersensitivity has developed, all sources of fungi must be removed including treatment of colonization and a mold-free diet.

The spectrum of symptoms produced by exposure of healthy, normal individuals to heavy doses of fungal elements varies from throat or nasal irritation to severe incapacitating influenza-like illness with malaise, rash, muscle soreness, joint stiffness and pain, fever, night sweats, weakness, headaches, and mental changes including cognition. In the patient with diminished resistance such as the very old or very young, the chronically ill such as patients with diabetes, patients with suppressed immunity as a result of cancer chemotherapy or organ transplantation; and patients with AIDS, certain fungi will invade the body with disastrous consequences including death.

When foreign materials (antigens) enter the body's tissues for the first time a series of events is initiated which leads to the formation of specific antibody which combines with the antigen and leads to its rejection from the body by the action of scavenger cells or macrophages. The antigen-antibody unit is called an immune complex and it is rapidly taken up by the macrophages under normal circumstances. When the antigen is a virus, the viral-antibody complex is removed from the circulation, the infection is over leaving a temporary state of immunity. If the antigen is a fungal spore continually being broadcast into the air by a contaminated air conditioning unit, the "infection" never stops. The immune state is repeatedly or continually challenged to cope with large numbers of foreign invaders. The macrophage system can become saturated and complexes can no longer be safely removed from the circulation. The complexes may be then removed by tissue deposition into the skin, blood vessel walls and specific organs such as the lungs or kidneys leading to rashes, vasculitis, alveolitis (lungs) and glomerulo-nephritis (kidneys) respectively.

The behavior of circulating immune complexes is determined by several semi independent variables such as absolute and relative concentrations of antigen and antibody in the circulation, the solubility of the complex, and its size and surface charges. There are three important antigen-antibody equilibria which determine the pathogenicity of the complex and the clinical course of the exposures. In antigen excess the stable complex consists of an antibody with an antigen at each of its two binding sites. At antibody excess the stable complex consists of an antigen with a different single antibody at each of its recognized epitopes or antibody reactive sites. At more equal concentrations of antigen and antibody, the complexes are at equivalence and can grow to enormous size. The most pathogenic equilibrium is near equivalence. Because of the nature of the antigen-antibody binding site, the complexes can easily shift from one equilibrium to another as relative concentrations of antigen and antibody

shifts. This complexity in the disposition in the body makes it difficult to study the phenomena and even more difficult for the clinician to understand its ever changing effects on the patient.

Most patients who are experiencing symptoms from exposure to environmental fungi exposure have become hypersensitive and are usually in the antigen excess side of equivalence at the time they seek medical care. Removing the source of exposure may temporarily (one to two weeks) lead to an increase in symptoms as the patient's moves through equivalence and into antibody excess. At this time, even small exposures produce exaggerated symptoms because of the move into equivalence. The patients must be forewarned of this phenomena before it happens because it increases compliance.

If the patient has had previous infections involving exposed surfaces which have caused tissue damage or scarring, the possibility of fungal colonization increases. This would include chronic sinusitis, pneumonia or gastroenteritis. In these cases, a fungal component of the disease must be suspected and a therapeutic trial of an antifungal may be necessary. Nystatin, econazole and miconazole are poorly absorbed and are effective in treating colonization of the G.I. tract. The more soluble anti-fungals itraconzole, terbenafine and fluconazole may be helpful in reaching the lungs, nails or sinuses.

Treating a hypersensitive (to fungi) patient who is heavily colonized with a fungus (e.g. *aspergillus*) with an effective antifungal (e.g. itraconzole) will almost always produce a Jarisch-Herxheimer (J.H.) reaction due to the inability of the bodies clearing mechanisms to dispose of the surge in immune complexes following initiation of therapy. It is, therefore, prudent to begin treatment with low doses of antifungal and progress upward every few days to a week as the patient tolerates the therapy. The symptoms of a J-H reaction are flu-like with malaise, fever, headache, gastroenteritis, myositis, nasal congestion, CNS disturbances, etc. When they occur, the treatment should be temporarily interrupted to allow the patient to recover, and then resumed at the last tolerated dose for a few weeks before trying to increase the dose again. J-H reactions can occur at any stage as the dosage is being increased and may occur after therapeutic levels are safely reached should there be a sudden increase in ambient fungal levels or following ingestion of a food containing a significant fungal component.

The quantity of fungal elements in foods is not appreciated by the general public, by nutritionists, and even by physicians specializing in the treatment of food allergy. Only the food scientists really know the full extent of fungal usage in foods and they often do not show this on package labels. Chocolate, tea and soy sauce are fermented by *aspergillus* species. The Lactase used to remove lactose from milk for milk-intolerant patients is an *aspergillus* product. Malt extracts, dough conditioners and amylase used in baking are all of fungal origin. Most commercial fruit juices are not only extracted from moldy fruit but have had fungal cellulases added to the pulp to increase yields. Citric acid, a major acidulant/preservative used in processed foods is an *aspergillus* fermentation product, not a lemon extract. All tomato products are laced with fungal derivatives, and of course, all foods become moldy in time and frequent grocery shopping is essential to a mold-free diet.

The best studied human model of immune complex-mediated illness following chronic exposure to absorbed antigen is chronic serum sickness. There is considerable experimental data on this subject published in the middle third of this century (2). This work was, of course, stim-

ulated by the adverse effects of horse serum (antitoxin) administration for the treatment of diphtheria and tetanus, but the elements are the same as seen in fungal hypersensitivity disease. Figure II lists the common clinical symptoms seen in serum sickness and demonstrates how widespread are the possible adverse effects one can expect from circulating immune complexes.

Circulating immune complexes containing IgG or IgM antibodies are highly inflammatory acting on serum complement which triggers the activation of a cascade of enzymes which play various roles in the destruction and removal of foreign materials from the body. Two of these components, C'3 and C'5, are known to cause the release of histamine from mast cells thus mimicking the Type I allergy reaction although delayed in time from minutes for the IgE activation to hours for the C'3, C'5 action. Because of the time requirement for antigen uptake, complex formation, macrophage overload and tissue deposition, Type III hypersensitivity reactions are delayed by hours or days from the time of exposure. This makes it more difficult to appreciate the cause-effect relationship of exposure to illness. Type IV cellular reactions are similarly delayed in onset.

By understanding the nature of a hypersensitivity reaction, its multiple interactives, it's delayed onset and the widespread nature of its inflammatory potential, an extremely complicated system can be better appreciated. The underlying principles can be applied to a better understanding of human hypersensitivity diseases caused by exposure to relatively benign, common, non- mycotoxin producing fungi.

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