

Immunodeficiency and other clinical immunology

Hypersensitivity pneumonitis caused by soybean antigens

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Since 1929, when it was first introduced in infant diets, soybean has been described as a cause of a variety of allergic reactions (i.e., urticaria, angioedema, gastrointestinal symptoms, asthma, and anaphylaxis).¹ In 1990 this antigen was listed as an agent causing occupational disease when a soybean-dependent asthma epidemic occurred in Barcelona and Cartagena, Spain, after a dust discharge into the air.² The partially characterized antigens were 14 and 8 kd molecular weight proteins found highly concentrated in soybean hull.^{3,4}

We now describe other soybean hull antigens as a new cause of hypersensitivity pneumonitis (HP) in a research agronomist who was exposed to them for a long time.

CASE REPORT

A 45-year-old female agronomist had been working on veterinary diet research for 20 years. She specialized in research of the efficacy of several animal diets that contained soybean, oleins, and fats as principal components. Her laboratory was adjacent to an animal farm where rabbits were being raised. Seventeen years ago, she had an episode of chest pain, fever (39° C), mild dyspnea, and chills over a 10-day period. Chest roentgenogram revealed a right middle lobe infiltrate. Lobar pneumonia was suspected and successfully treated with antibiotics. She had a recurrent, nonproductive cough

Abbreviations used

BAL: Bronchoalveolar lavage
DL_{CO2}: Carbon dioxide diffusion in the lungs
HP: Hypersensitivity pneumonitis

and residual pharyngitis for weeks. Four similar episodes in different pulmonary lobes followed the initial occurrence. After December 1990, she continued to have more frequent symptoms (one episode per month). Symptoms included low-grade fever (37.5° C), mild chest pain, and asthenia, along with recurring pulmonary infiltration. Complete relief of symptoms was not observed between episodes. In July 1991 she was admitted to the hospital because of acute lingular infiltration. Blood analysis demonstrated leukocytosis (73.6% granulocytes) and hypoxemia (partial pressure of oxygen = 72 mm Hg). Results of laboratory studies were nondiagnostic. A perfusion lung scan was not compatible with pulmonary embolic disease. Bronchoalveolar lavage (BAL) produced copious mucus secretions containing 50% macrophages, 45% neutrophils, and 5% lymphocytes (Fig. 1, A). Cultures of transbronchial biopsy specimens were negative for bacteria, mycoplasma, fungi, and mycobacteria. Biopsy specimens revealed a fibrinous, hemorrhagic exudate present in the alveoli with lymphoid interstitial infiltration and no ciliary abnormalities (Fig. 1, B). Results of viral serology tests were negative. Results of humoral studies (quantitative analysis of immunoglobulins, including IgG subclasses, complement, isohemagglutinins) and cellular immunity studies (anergy panel, lymphocyte phenotyping, mitogenic assays, and leukocyte function [phagocytic and oxidotic burst studies]) were normal. Results of tests for rheumatoid factor, antinuclear antibody, and antineutrophil cytoplasm antibody were negative. Chloride level in sweat was normal. Results of pulmonary function tests performed 2 months later were normal (lung volumes, spirometry, carbon dioxide diffusion in the lungs [DL_{CO2}] and blood gases).

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Received for publication Nov. 5, 1993; revised June 28, 1994; accepted for publication July 15, 1994.

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J ALLERGY CLIN IMMUNOL 1995;95:622-6.

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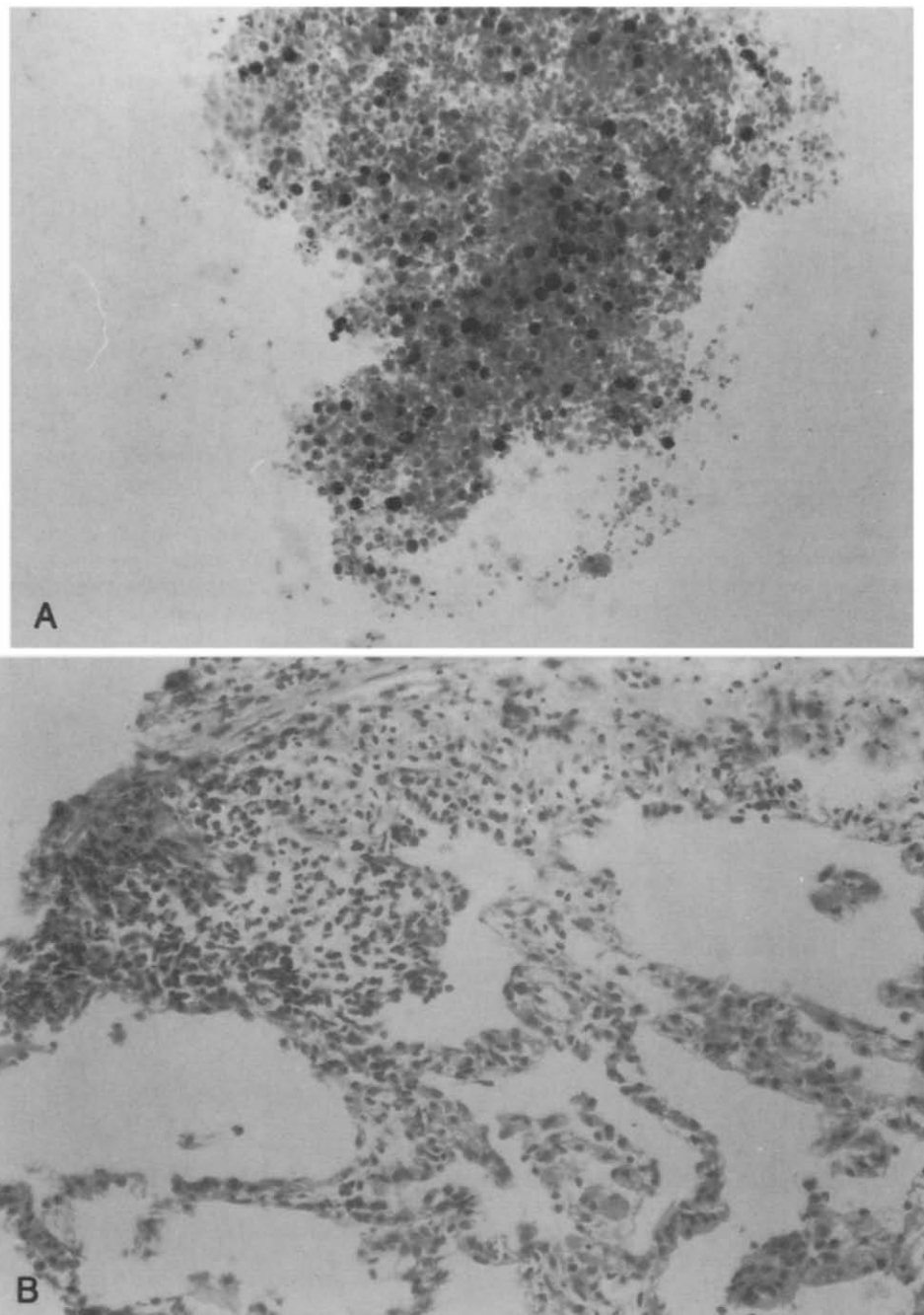


FIG. 1. A, BAL. The cellular composition of the BAL is mainly macrophages with only some isolated lymphocytes. (Papanicolaou stain; $\times 100$.) **B, Transbronchial biopsy specimen.** Alveolar septa show a moderate to mild degree of lymphoid infiltrate without evidence of collagen deposition. (Hematoxylin-eosin stain; $\times 250$.)

The patient was then referred to our Section to be evaluated for possible HP. She did not recall her initial exposures but related her more recent episodes to intense exposures to 10 different animal fodders during the preceding year (she had three different infiltrates). Results of delayed hypersensitivity tests were positive, and precipitins to fodders containing soybean were

present. Total IgE was normal; precipitins, specific IgE and IgG to bird droppings, fungi, animal dander, and other non-soybean-containing fodders were absent. The 100% soybean powder to which she was exposed was run on a gel for isoelectric focusing. It displayed an identical pattern to a commercial soybean extract (Dome/Hollister-Stier; Miles-Martin Div., Madrid, Spain) (Fig. 2).

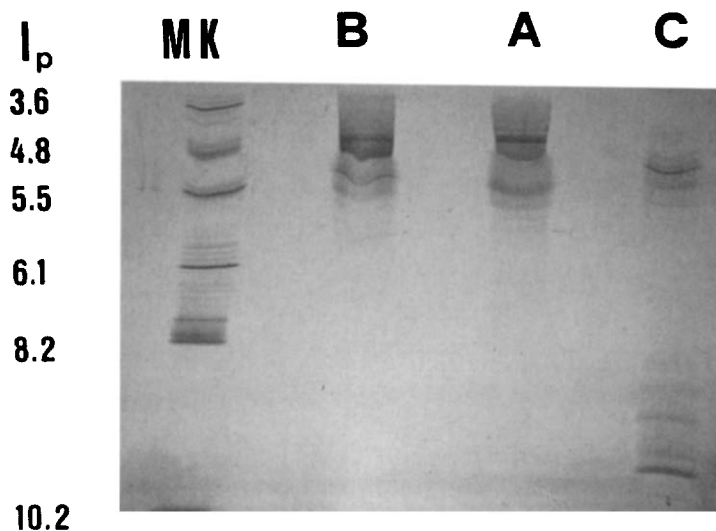


FIG. 2. Soybean agarose isoelectric focusing. Observe the identical pattern obtained with commercial whole soybean and the soybean provided by the patient. *Lane A*, patient's soybean; *lane B*, commercial soybean; *lane C*, soybean hull. *MK*, Isoelectric point markers.

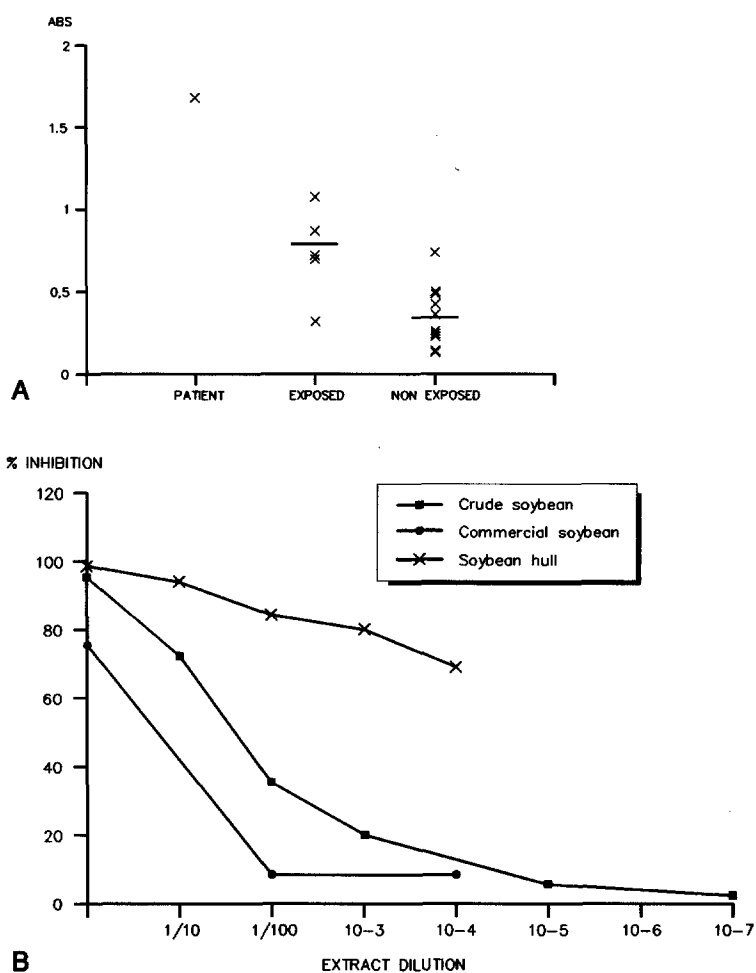


FIG. 3. Specific IgG to soybean extract. Soybean-coated ELISA microtiter plates were used to detect specific IgG. **A**, Increased levels were detected in sera of patient and exposed population compared with nonexposed population. **B**, IgG inhibition ELISA. Patient's serum IgG-soybean complex was strongly inhibited by commercial soybean and purified hull extracts.

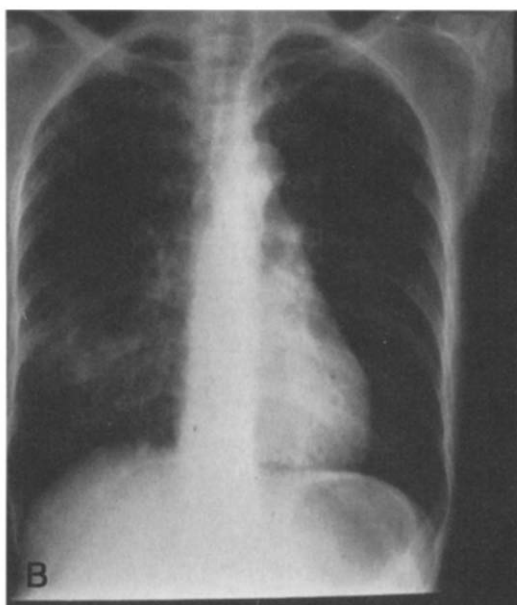
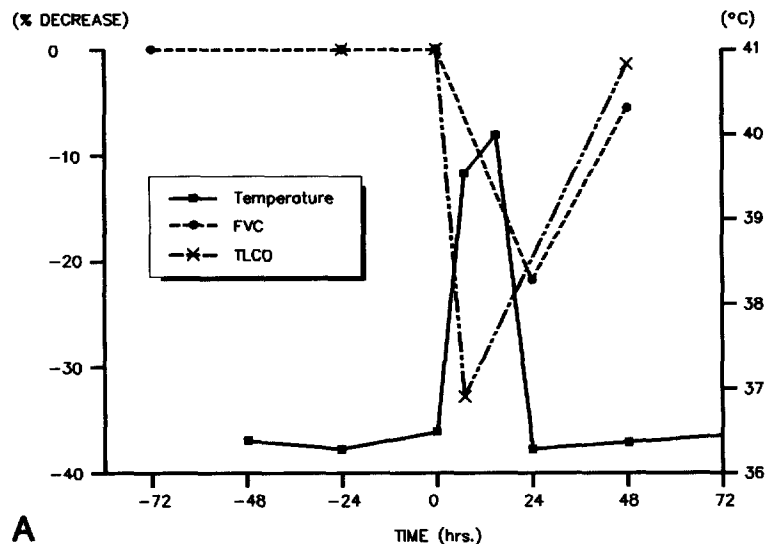


FIG. 4. Soybean inhalation challenge test. **A**, High fever and significant decreases in forced vital capacity and DL_{CO_2} were observed 6 hours after inhalation challenge (time 0 hours) with soybean extract. **B**, Right basal infiltrate 48 hours after the challenge test.

Levels of specific IgG to the suspected soybean powder, as well as to commercial soybean extract and purified soybean hull (kindly provided by Abelló Laboratories, Spain), were highly elevated as compared with those of normal and exposed populations (Fig. 3, A). Antigens were cross-reactive within the three soybean extracts as demonstrated by IgG inhibition ELISA (Fig. 3, B). Sodium dodecylsulfate–polyacrylamide gel electrophoresis and blotting with the patient's IgG showed one positive band at an apparent molecular weight of 38.5 kd.

Because of the importance of an accurate diagnosis to her professional future, the patient underwent a soybean

bronchial challenge (after a 3-month asymptomatic hiatus outside her work environment). Results of pulmonary x-ray studies, gallium lung scan, DL_{CO_2} and blood tests were normal before and after diluent challenge. Six hours after inhalation of 1 ng of soybean extract, she had a high fever (40° C), malaise, chest pain, and mild dyspnea. Crackles were heard on chest auscultation. Leukocytes measured 26,000 cells/mm³. Her forced vital capacity and DL_{CO_2} decreased by 20% and 33%, respectively, and partial pressure of oxygen decreased to 68 mm Hg. (Fig. 4, A). Gallium lung scan, high-resolution computed tomography, and chest roentgenogram revealed a right basal infiltrate at 48 hours (Fig. 4, B).

Treatment with oxygen and prednisone (1 mg/kg) resulted in a dramatic clinical and radiologic improvement. Challenge extract culture was negative for fungi, bacteria, and endotoxin. The patient has completely avoided her workplace and has remained free of symptoms for the past 2 years.

DISCUSSION

We have studied a patient with long exposure to different organic products in whom an HP to soybean proteins developed, as confirmed by a challenge test and clinical evaluation after avoidance measures were taken. Other diseases were excluded by absence of analytic and clinical features. Recurrent pulmonary infections could not be confirmed, regardless of extensive microbiologic and immunologic studies. The controverting observation of only 5% lymphocytes in BAL cytology, compared with lymphocytosis usually found in this disease, is rare but has already been described in some individuals.⁵ The exposed population revealed a higher tendency to produce soybean-specific IgG compared with the normal population but the level was much lower than that produced by the patient. None of them had work-related symptoms. Antigens responsible for this disease seem to be located in the soybean hull as demonstrated by IgG inhibition ELISAs.

HP had not previously been described as a consequence of exposure to soybeans. We emphasize this antigen as a new cause of occupational pneumonitis.

We thank Dr. E. Álvarez Fernández (Pathology Department) for the accurate description of BAL and biopsy specimens. We also thank S. López Segura (International Pharmaceutical Immunology, S.A.) and Abelló Laboratories for their contribution to this work.

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