



CHEST[®]

Official publication of the American College of Chest Physicians



Alpha 1-antitrypsin deficiency and common variable hypogammaglobulinemia in a patient with asthma.

N D Phung, R T Kubo and S L Spector

Chest 1982;81:112-115
DOI 10.1378/chest.81.1.112

The online version of this article, along with updated information and services can be found online on the World Wide Web at:

<http://www.chestjournal.org/content/81/1/112.citation>

CHEST is the official journal of the American College of Chest Physicians. It has been published monthly since 1935. Copyright 2007 by the American College of Chest Physicians, 3300 Dundee Road, Northbrook IL 60062. All rights reserved. No part of this article or PDF may be reproduced or distributed without the prior written permission of the copyright holder.
(<http://www.chestjournal.org/site/misc/reprints.xhtml>) ISSN:0012-3692

A M E R I C A N C O L L E G E O F



P H Y S I C I A N S[®]

suture line must be in contact with the blood stream, as happens in shunts in which the vessels shunted remain patent after closure of the prosthetic shunt. Similar aneurysms might, therefore, appear in other types of palliative procedures involving the use of conduits and closure of the anastomotic stoma may be preferable to simple ligation of the shunt. Changes in suture material, however, have been effective in markedly decreasing suture failure as a cause of anastomotic aneurysms,⁴ making this complication improbable.

REFERENCES

- 1 Weldon CS. Complications of systemic pulmonary artery shunts. In: Complications of intrathoracic surgery, Cordell AR, Ellison RG, eds. Boston: Little, Brown, 1979
- 2 Haroutunian LM, Neill CA. Pulmonary complications of congenital heart disease: Hemoptysis. *Am Heart J* 1972; 84:540-59
- 3 Sumner DS, Strandness DE. False aneurysms occurring in association with thrombosed prosthetic grafts. *Arch Surg* 1967; 94:360-62
- 4 Moore WS. Anastomotic aneurysms. In: Vascular surgery, Rutherford RB, ed. Philadelphia: WB Saunders, 1977

Alpha₁-Antitrypsin Deficiency and Common Variable Hypogammaglobulinemia in a Patient with Asthma*

Nguyen D. Phung, M.D.;† Ralph T. Kubo, Ph.D.;‡ and Sheldon L. Spector, M.D., F.C.C.P.§

Severe alpha₁-antitrypsin deficiency with phenotype PiZZ was found in association with common variable hypogammaglobulinemia and hyperreactive airways disease in a 34-year-old patient. Immunologic studies demonstrated normal cellular immunity but impaired responses to influenza and pneumococcal antigens. Investigations of the mechanism of hypogammaglobulinemia revealed no intrinsic B cell defect, synthesis abnormality, or impairment of secretion of immunoglobulins. A serum suppressive factor was present and probably accounted for the hypogammaglobulinemia.

Alpha₁-antitrypsin is a protease inhibitor that is believed to play an important role in the pathogenesis of emphysema.¹ Severe deficiency of this protein, often associated with phenotype ZZ or SZ, leads to clinical emphysema in early adulthood.² Common variable hypogammaglobulinemia is a heterogeneous group of disorders,³ frequently associated with recurrent sino-bronchopulmonary infections, bronchiectasis, gastroin-

testinal abnormalities, and a high degree of susceptibility to neoplasia.⁴

There is no known association between immunoglobulin deficiency and α_1 -antitrypsin deficiency. We describe a patient with α_1 -antitrypsin deficiency, common variable hypogammaglobulinemia, hyperreactive airways disease, and the ZZ phenotype.

CASE REPORT

The patient was a 34-year-old man in good health until 1976, when progressive dyspnea on exertion developed. An open lung biopsy in March 1977 showed panacinar emphysema. Severe α_1 -antitrypsin deficiency with phenotype ZZ was then diagnosed. After referral to National Jewish Hospital, his history of frequent respiratory tract infections, wheezing, and rhonchi prompted further investigation. Both panhypogammaglobulinemia and hyperactive airways disease were documented. The latter diagnosis was confirmed by a positive histamine and methacholine inhalation challenge⁵ and favorable response to bronchodilators.

He had smoked minimally (four packs a year) for three years, stopping several years before admission. He was retired and had worked with paint and plywood.

His family history was remarkable in that his mother had an α_1 -antitrypsin phenotype SZ and chronic bronchitis. His father was asymptomatic, with MZ phenotype. A paternal uncle died of cancer of the esophagus at the age of 40 years, with emphysema diagnosed at autopsy. A paternal cousin was found to have 40 mg/dl α_1 -antitrypsin. The patient had no siblings and no children.

Pertinent findings on physical examination included dry rales at the lung bases and early bilateral posterior subcapsular cataracts. A chest x-ray film showed pleural tenting on the right side and platelike atelectatic changes in the left mid-lung field. A sinus x-ray film showed a soft-tissue density of the inferior floor of the left maxillary. Pulmonary function testing showed the following results: hyperinflation of the lung with a vital capacity of 5.74 L (114 percent of normal), residual volume of 5.28 L (328 percent predicted) and total lung capacity 11.02 L (158 percent predicted). Flow rates showed airway obstruction with FEV₁ of 2.26 L (54 percent predicted), FEV₁/FVC ratio of 43 percent, and FEF 25-75% 0.82 L (14 percent). Specific conductance was decreased at 0.06 L/cm H₂O/L/sec (26 percent predicted). Diffusing capacity (Dco) was 13.8 ml/min/mm Hg (42 percent predicted).

The methacholine bronchial inhalation challenge was positive, with a 36 percent fall of FEV₁ after five breaths of 0.31 mg/ml. The histamine bronchial inhalation challenge also was positive, with a 27 percent fall in FEV₁ after five breaths of 2.5 mg/ml.

MATERIALS AND METHODS

Determination of IgG, IgA, IgM, α_1 -antitrypsin levels, P₁ phenotyping, enumeration of T and B cells, and *in vitro* lymphocyte stimulation studies with phytohemagglutinin and pokeweed mitogen (PWM) were done with standard techniques. Cytoplasmic immunoglobulins and immunoglobulin biosynthesis studies were done as previously described.⁶

Specific Antibody Response Studies

Isohemagglutinins were measured by standard hemagglutination inhibition techniques. The patient was given a

*From the National Jewish Hospital and Research Center and the University of Colorado Medical School, Denver.

†Fellow in Allergy-Clinical Immunology.

‡Assistant Professor in Microbiology and Immunology.

§Senior Staff Physician.

Reprint requests: Dr. Spector, National Jewish Hospital and Research Center, 3800 East Colfax, Denver 80206

Table 1—Family History

	IgG, mg/dl	IgA, mg/dl	IgM, mg/dl	α 1-AT, mg/dl	α 1-AT Phenotype
Patient	262	18	27	32	ZZ
Father	969	197	42	152	MZ
Mother	678	56	49	106	SZ
Normal values	953 \pm 206	114 \pm 47	134 \pm 49	196 \pm 41	MM

booster of DPT, and tetanus titers were determined before and two weeks after the challenge. Additionally, titers were drawn before and three weeks after administration of 0.5 ml of trivalent influenza vaccine (Parke-Davis stock 4-4079-510) and polyvalent pneumococcal vaccine (Pneumovax, Merck Sharp & Dohme, No. 4666). Influenza titer determinations were done by a hemagglutination inhibition technique.⁷ Pneumococcal titers were measured by a radioimmunoassay technique developed and performed in Dr. Schiffman's laboratory.⁸

RESULTS

The α ₁-antitrypsin and immunoglobulin levels of the patient and his parents are indicated in Table 1. The patient had panhypogammaglobulinemia and a very low α ₁-antitrypsin level. The phenotypes are also shown. The patient had ZZ; his parents were heterozygous for P^z with borderline low values of α ₁-antitrypsin. Of interest was that the mother had panhypogammaglobulinemia, although to a lesser degree than her son. The father also had low IgM values.

In assessing humoral immunity, the natural isohemagglutinins showed a borderline anti-B titer of 1:16 (patient was blood group A). The patient had good antibody response to tetanus antigen, with pre- and post-immunization titers of 1:2048 and 1:65,536, respectively; however, there was no response to A Brazil influenza virus and minimal response to A Texas and B Hong Kong viruses, the latter pre- and post-titers being 1:16 and 1:32, respectively. The antibody response to 12 different pneumococcal antigens were clearly abnormal compared with controls (Table 2). The pre-immunization values were much lower than normal controls (except serotype 6A), despite the fact that the patient had

a pneumococcal vaccine injection one year before this study and had many respiratory infections, some presumably caused by pneumococcal infection. Also the antibody response, as reflected by the ratio of pre- and post-immunization values, was less than that of control subjects in at least six serotypes.^{1,4,8,9}

Cell-mediated immunity was normal as assessed by delayed hypersensitivity skin tests. Enumeration of T and B cells was normal (74 percent and 8 percent, respectively), as were lymphocyte stimulation studies with phytohemagglutinin and PWM.

The ability of the patient's B lymphocytes to produce immunoglobulins was assessed by determining the number of cells that were positive for cytoplasmic immunoglobulins in cell cultures stimulated with PWM for seven days. Stimulation of both the normal and patient lymphocytes cultured with PWM resulted in an increase in the number of cytoplasmic immunoglobulin containing plasma cells (12 percent and 8.5 percent, respectively) compared with the unstimulated cultures (0.5 percent). The number of cytoplasmic immunoglobulin-containing cells enumerated was comparable to the number of B lymphocytes detected in the patient's peripheral blood, which is in the normal range. In a subsequent experiment, when the patient's serum was added to a culture of lymphocytes from a normal subject or from the patient, no increase in cytoplasmic Ig-positive cells could be detected in cultures stimulated with PWM compared with unstimulated cultures (data not shown). Cell viabilities were not altered by the addition of the patient's serum compared with a normal AB⁺ serum, and, thus, these results suggest the presence of an inhibitory or suppressive substance in the patient's serum capable of preventing the mitogen-induced differentiation of B lymphocytes.

The synthesis of immunoglobulins by the patient's lymphocytes stimulated with PWM for seven days was comparable to the immunoglobulin synthesis of the normal subject lymphocyte culture. These results are consistent with the increase in the number of cytoplasmic immunoglobulin-containing cells following stimulation with PWM. Polyacrylamide gel analysis of the anti-immunoglobulin immune precipitates of the culture supernatant fluids revealed the presence of IgM and

Table 2—Pneumococcal Serotype

Serotype	1	3	4	6A	7	8	9	12	14	18	19	23
Pre-Immunization*	129	41	216	126	38	59	38	15	50	69	35	302
Post-Immunization†	289	221	516	216	90	422	200	98	133	292	105	515
Ratio	2.2	5.4	2.7	1.7	2.4	7.2	5.3	6.6	2.7	4.2	2.9	1.7
Control‡												
Pre-Immunization*	282	190	912	93	234	115	316	339	1148	141	145	562
Control‡												
Post-Immunization*	1551	1235	4742	223	514	1736	3634	1202	3214	1198	160	1686
Ratio	5.5	6.5	5.2	2.4	2.2	15.1	11.5	3.6	2.7	8.5	1.1	3.0

*Antibody response expressed as antibody nitrogen in ng/ml.

†Mean values of 27 normal control subjects.

IgG heavy and light chains for both the normal subject and the patient, indicating that there was no impairment in immunoglobulin secretion by plasma cells of the patient. The difference in the intensity of the μ and QA heavy chain bands in the fluorograms of the immunoglobulins secreted by the normal subject's and by the patient's cells probably are due to individual variation in response to PWM.⁸ Thus, immunoglobulin synthesis and secretion by the patient's lymphocytes *in vitro* appears to be normal.

DISCUSSION

This patient had severe α_1 -antitrypsin deficiency leading to emphysema, as evidenced by lung biopsy and his clinical picture. In addition, he had hyperreactive airways disease as demonstrated by methacholine and histamine bronchial inhalation challenge and hypogammaglobulinemia. To the best of our knowledge, this patient represents the first described with α_1 -antitrypsin deficiency and the ZZ phenotype in association with panhypogammaglobulinemia. Previous studies of serum immunoglobulins in patients with chronic obstructive airways disease usually revealed a pattern of increased gammaglobulins in patients with α_1 -antitrypsin, either homozygous or heterozygous.^{10,11}

Common variable hypogammaglobulinemia is a heterogeneous group of disorders usually termed acquired in contrast with Bruton's type of agammaglobulinemia, which is an x-linked disorder.³ However, there have been reports of familial aggregations of hypogammaglobulinemia that are not x-linked Bruton's disease. Kirkpatrick et al¹² reported the existence of familial hypogammaglobulinemia with low IgM as a marker, especially on the paternal side. In our patient, findings of mild hypogammaglobulinemia in the patient's mother and a low IgM level in the patient's father was interesting in two respects. The patient's hypogammaglobulinemia was probably congenital. The presence of low IgM levels in both parents suggests that one or more genes may transmit in an autosomal codominant fashion low IgM as a manifestation of the heterozygous state and panhypogammaglobulinemia as a manifestation of the homozygous state. It is unfortunate that the patient had no siblings or children to test this possibility. However, preliminary findings in a study of 24 relatives of the patient showed that many members had low IgM values, which supports the above hypothesis. The finding of a quantitative serum deficiency as an expression of the Gm gene, which codes for the constant part of the IgG heavy chain in family members of patients with hypogammaglobulinemia,¹³ and the known linkage of the Gm gene with the Pi gene¹⁴ supports the possibility of a linkage between the Pi gene and the gene (or genes) determining hypogammaglobulinemia.

An attempt was made to elucidate the mechanism of our patient's hypogammaglobulinemia. By administering different antigens *in vivo* and measuring the antibody response, it was clearly shown that the patient had a deficient immune response. This is in contrast to many cases of common variable hypogammaglobulinemia

without immunodeficiency, *ie*, without an increased frequency of infections. Sometimes immunodeficiency can be selective.¹⁵ The patient had normal antibody responses to tetanus and some pneumococcal serotypes, but had abnormal or no response to other antigens tested. Studies *in vitro* showed that the patient had a normal number of B cells, as is usually found in common variable hypogammaglobulinemia. The response of his lymphocytes to mitogens was also normal and, in fact, upon stimulation with PWM, the patient's lymphocytes were induced to synthesize and secrete immunoglobulins in a normal fashion. In an experiment in which lymphocytes from a normal subject and from the patient were cultured in the presence of the patient's serum, we observed that following stimulation with PWM, no increase in cytoplasmic immunoglobulin-containing cells was seen as compared with unstimulated cultures. These results suggest that the presence of an inhibitory substance or substances or suppressive serum factor may be responsible for the hypogammaglobulinemia in this patient.

In summary, a patient is described with homozygous α_1 -antitrypsin deficiency, the PiZZ phenotype, hyperreactive airways disease, and common variable hypogammaglobulinemia. The hypogammaglobulinemia appears to be a congenital regulatory defect with the possibility of linkage to the Pi gene. In view of the above, more patients with α_1 -antitrypsin deficiency should have serum immunoglobulin determinations, especially those with a clinical picture of increased infections, bronchiectasis, or hypogammaglobulinemia. Studies of more patients with concomitant α_1 -antitrypsin deficiency and hypogammaglobulinemia would be necessary to shed light on the relationship between the genetic defects and the clinical course of both diseases.

ACKNOWLEDGMENT: The authors wish to thank Dr. Gerald Schiffman for performing the radioimmunoassay of the pneumococcal antibody study and Ms. Judy Franconi and Mrs. Debby Hillberg for secretarial skills. They also thank Dr. Howard M. Grey for his critical review of the manuscript.

REFERENCES

- 1 Eriksson S. Proteases and protease inhibitors in chronic obstructive lung disease. *Acta Med Scand* 1978; 203: 445-449
- 2 Morse JO. Alpha-1-antitrypsin deficiency. *N Engl J Med* 1978; 299:1045-48; 1099-1105
- 3 Geha RS, Schneeberger E, Merler E, Rosen FS. Heterogeneity of "acquired" or common variable hypogammaglobulinemia. *N Engl J Med* 1974; 291:1-6
- 4 Hermans PE, Diaz-Buxo IA, Stobo J. Idiopathic late onset immunoglobulin deficiency. *Am J Med* 1976; 61:221-37
- 5 Spector SL, Farr RS. Bronchial provocation tests. In: Weiss EB, Segal MS, eds. *Bronchial asthma: mechanisms and therapeutics*. Boston: Little, Brown and Co, 1976; 639-47
- 6 Maino VC, Kurnick JT, Kubo RI, Grey HM. Mitogen activation of human chronic lymphatic leukemia cells: I. Synthesis and secretion of immunoglobulin. *J Immunol* 1977; 118:742-48
- 7 Lennette EH, Schmidt NJ. Diagnostic procedures for

- viral and rickettsial diseases. New York: American Public Health Association, Inc, 1964:462
- 8 Sullivan JL, Ochs HD, Schiffman G, et al. Immune response after splenectomy. *Lancet* 1978; 1:178-81
 - 9 Ginsberg WW, Finkelman FD, Lipsky PE. Circulating and mitogen-induced immunoglobulin-secreting cells in human peripheral blood: evaluation by a modified reverse hemolytic plaque assay. *J Immunol* 1978; 120: 33-39
 - 10 Rozniecky J, Szmidt M, Ruta U. Immunoglobulins G, A and M and alpha-1-antitrypsin in patients with premature pulmonary emphysema. *Pneumonol Pol* 1977; 45:10-11
 - 11 Falk GA, Siskind GW, Smith JF. Chronic obstructive pulmonary disease: a subgroup of patients identified by serum alpha-1-antitrypsin and immunoglobulin concentrations. *Am Rev Respir Dis* 1971; 103:18-25
 - 12 Kirkpatrick CH, Schimke RN. Paternal immunoglobulin abnormalities in congenital hypogammaglobulinemia. *JAMA* 1967; 200:115-20
 - 13 Litwin SD, Fudenberg HH. Quantitative abnormalities of allotypic genes in families with primary immune deficiencies. *Proc Natl Acad Sci USA* 1972; 69:1739-43
 - 14 Noades JE, Cook PJJ. Family studies with the Cm: Pi linkage group. *Birth Defects* 1976; 12:341-44
 - 15 Spector SL, English GM, McIntosh K, Farr RS. Adenovirus in the sinuses of an asthmatic patient with apparent selective antibody deficiencies. *Am J Med* 1973; 55: 227-31

Usefulness of Two-dimensional Echocardiography for Detection of Ventricular Septal Aneurysm with Perforation After Acute Inferior Myocardial Infarction*

Robert S. Gibson, M.D.,† Harry L. Bishop, M.D.,†
George A. Beller, M.D., F.C.C.P.,‡
and Randolph P. Martin, M.D.§

Two-dimensional echocardiography allowed direct visualization and localization of a postinfarction ventricular septal aneurysm with rupture. Not only did this noninvasive technique permit visualization of the septal defect in this patient, but the extent of residual left ventricular contractile function was also reliably determined. The echocardiographic findings were corroborated by cardiac catheterization data and by intraoperative and histopathologic examination. Thus, in the evaluation of a seriously ill patient with complicated myocardial infarction, two-dimensional echocardiography appeared to provide anatomic and functional information that was used to guide management and predict surgical outcome.

*From the Cardiology Division, Department of Internal Medicine, University of Virginia Medical Center, Charlottesville.

†Fellow in Cardiovascular Medicine.

‡Professor of Medicine, Chief of Cardiology.

§Associate Professor of Medicine, Division of Cardiology.
Reprint requests: Dr. Gibson, VA Medical Center, Box 158, Charlottesville 22908

Rupture of the ventricular septum is a rare, but often catastrophic, complication of acute myocardial infarction (MI). It can follow MI by several hours to several weeks, and the overall mortality is high: 25 percent of patients die within three days, 50 percent within one week, and 90 percent within two months after detection of the rupture.¹⁻³ Clinically, this complication may be difficult to distinguish from acute incompetence of the mitral valve.⁴ Bedside catheterization using a flow-directed balloon catheter (Swan-Ganz) has been helpful in establishing the diagnosis and quantifying the amount of left-to-right shunting at the ventricular level;⁵ however, the extent and severity of accompanying ventricular asynergy can not be appreciated.

Recently, several reports have indicated the feasibility of two-dimensional echocardiography (2D echo) for visualizing post-infarction ventricular septal defects.^{6,7} Since septal infarction and rupture are often associated with aneurysms of the adjacent ventricular wall,^{3,8} we report herein the use of 2D echo for direct visualization and localization of a ventricular septal defect with an accompanying aneurysm.

CASE REPORT

A 60-year-old man experienced new onset angina pectoris three weeks before admission. Two weeks before admission, the patient was hospitalized elsewhere because of severe chest pain associated with dyspnea. Physical examination revealed normal vital signs, bibasilar rales, and a new holosystolic murmur with an associated parasternal thrill. The ECG showed a pattern of inferior MI, and enzyme studies confirmed a recent infarct. Bedside catheterization using a Swan-Ganz catheter disclosed a left-to-right shunt at the ventricular level with Qp:Qs 2.7. The mean pulmonary wedge pressure was 21 mm Hg. After two weeks of stabilization the patient was transferred to our institution for continued treatment and surgical correction.

Upon admission, the patient was in no apparent distress, with a heart rate of 98/min and blood pressure of 110/70 mm Hg. The jugular venous pressure was normal. A prominent systolic thrill was palpable along the left sternal border, and a grade 4/6 harsh holosystolic murmur was heard over the entire precordium. There was no S₃ gallop. Bibasilar rales were present.

The ECG showed recent inferior MI with persistent ST segment elevation in leads 2, 3, and aVF. The chest roentgenogram showed mild cardiomegaly and pulmonary venous congestion.

Two-dimensional echo was performed to assess the location and size of the postinfarction ventricular septal defect (VSD), to determine the presence or absence of an inferior aneurysm, and to evaluate overall myocardial performance. A commercially available 3.0 MHz mechanical sector scanner (ATL-Mark III) was used. Complete ultrasonic examination was performed as previously described.⁹ The long axis parasternal view disclosed a normal mitral apparatus and left ventricular dimension. The outflow (anterior-basilar) portion of the ventricular septum was intact and contracted vigorously. Short axis views disclosed a discrete region of myocardial thinning and an aneurysmal bulge in the inferior-posterior septum. Although suspected, the VSD could not be visualized within the aneurysm.

Alpha 1-antitrypsin deficiency and common variable hypogammaglobulinemia in a patient with asthma.

N D Phung, R T Kubo and S L Spector

Chest 1982;81; 112-115

DOI 10.1378/chest.81.1.112

This information is current as of June 9, 2009

Updated Information & Services	Updated Information and services, including high-resolution figures, can be found at: http://www.chestjournal.org/content/81/1/112.citation
Open Access	Freely available online through CHEST open access option
Permissions & Licensing	Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: http://www.chestjournal.org/site/misc/reprints.xhtml
Reprints	Information about ordering reprints can be found online: http://www.chestjournal.org/site/misc/reprints.xhtml
Email alerting service	Receive free email alerts when new articles cite this article. sign up in the box at the top right corner of the online article.
Images in PowerPoint format	Figures that appear in CHEST articles can be downloaded for teaching purposes in PowerPoint slide format. See any online article figure for directions.

A M E R I C A N C O L L E G E O F



P H Y S I C I A N S[®]