PULMONARY INFILTRATES, ASTHMA AND EOSINOPHILIA DUE TO *ASCARIS SUUM* INFESTATION IN MAN

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Abstract Four male students who had been exposed to a massive dose of *Ascaris suum* ova, a parasite that is endemic to pigs, manifested the clinical picture of pulmonary infiltrates with eosinophilia and asthma. The two patients with the most widespread pulmonary infiltrates also had elevated IgE immunoglobulin levels, IgM precipitating antibody to *A. suum* antigen, and the most marked eosinophilia, thus suggesting the participation of an immune reaction in the pathogenesis of both the pulmonary lesions and the eosinophilia. The immune response may also have had a protective function since the patients with the most marked immune response to the ascaris antigen also had a minimal worm burden.

DURING the Winter Carnival weekend, around February 1, 1970, four male university students ingested a festive meal maliciously seasoned with large quantities of embryonated *Ascaris suum* ova. This large roundworm of pigs is morphologically similar to the ascaris lumbricoides which infects man. The results of this bizarre experiment were observed 10 days to two weeks later. The students, in rapid succession, presented themselves to the Emergency Department of the hospital with the symptoms and signs of lower-respiratory-tract disease, the more severely ill being in acute respiratory failure. The clinical syndrome of massive pulmonary infiltrates, asthma and eosinophilia developed. The correlation between the humoral immune response and the clinical and radiologic features of these cases is the subject of this report.

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Abbreviations Used

LDH:	lactic dehydrogenase
P_{CO_2}:	partial pressure of carbon dioxide
P_{O_2}:	partial pressure of oxygen
SGOT:	serum glutamic oxalacetic transaminase

CASE REPORTS

CASE 1. A 25-year-old student was admitted to the hospital approximately 2 weeks after ingestion of the *A. suum* ova with a 3-day history of cough, dyspnea, anorexia and fever. On admission, he was cyanotic and in acute respiratory failure. The temperature was 37.8°C, the pulse 120, and the respirations 22. Examination of the chest revealed marked bilateral crepitation over both lower lung fields, as well as asthmatic wheezing throughout the lung fields. Generalized urticaria developed on the day after admission, clearing in

48 hours. X-ray examination (Fig. 1A) showed extensive opacification of the lungs bilaterally. A specimen of arterial blood, drawn with the patient breathing room air, disclosed that the partial pressure of oxygen (Po_2) was 37 and the partial pressure of carbon dioxide (Pco_2) 25 mm of mercury, and the pH was 7.45. The hematocrit was normal; the white-cell count was 21,000, with 14 per cent eosinophils (absolute count, 2940), 7 per cent stab forms, 60 per cent neutrophils, 12 per cent lymphocytes and 7 per cent monocytes (Fig. 2). The biochemical findings were normal except for transient elevation of the serum glutamic oxalacetic transaminase (SGOT) and alkaline phosphatase. A liver scan indicated the presence of hepatomegaly. A brain scan and radiologic studies of the stomach and small bowel gave normal results. Four days after admission; *A. suum* larvae were isolated from both the sputum and the gastric washings (Fig. 3). No ascaris worms were detected in the stools.

Serum-protein electrophoresis showed a slight reduction in albumin and an increase in the alpha$_2$ and beta globulins. Quantitation of the immunoglobulins indicated an increase in both the IgM (Table 1) and IgE (Table 2) immunoglobulins. IgM precipitating antibodies to *A. suum* antigen were identified both by agar-gel diffusion and by immunoelectrophoretic techniques (Fig. 4).

The admission diagnosis was bronchopneumonia, and vigorous antibiotic therapy was given, with no response. The marked eosinophilia prompted the search for parasites, which were found in the sputum as noted above. This led to the institution of prednisone therapy, with dramatic results since his lungs were clear within 72 hours.

CASE 2. A 23-year-old student was admitted to the hospital approximately 10 days after ingestion of the ascaris ova with presenting symptoms and signs similar to those in Case 1. He

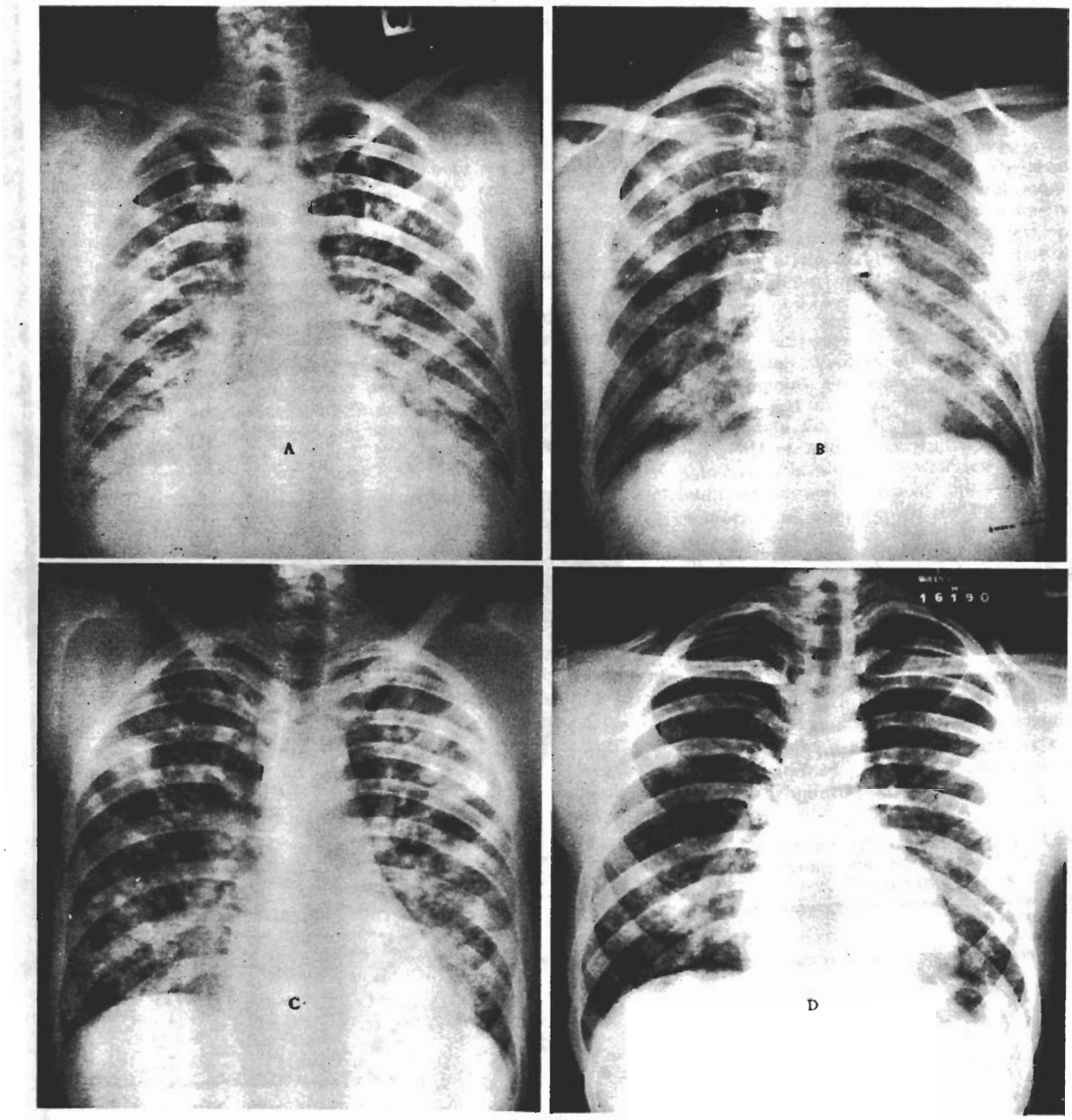

Figure 1. X-ray Films of the Chest of Cases 1 (A), 2 (B), 3 (C) and 4 (D) (for Details, See Text).

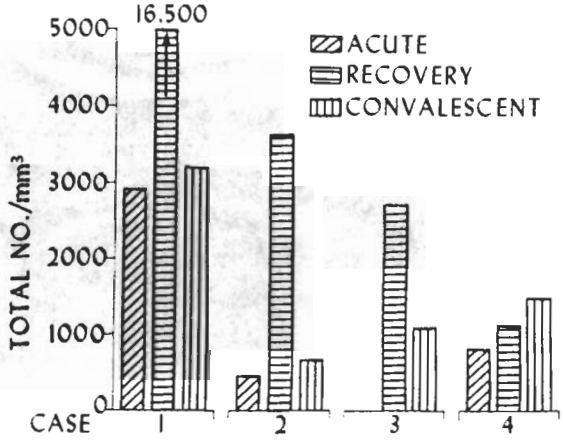

Figure 2. Blood Eosinophilia of the Four Patients during the Acute, Recovery and Convalescent Phases of Their Illnesses.

was cyanotic, in acute respiratory failure, with a Po_2 of 34 and Pco_2 of 44.5 mm of mercury and a pH of 7.37. X-ray study (Fig. 1*B*) indicated massive pulmonary infiltration throughout the lung fields. The hematocrit was normal, the white-cell count was 22,800, with 2 per cent eosinophils (absolute count, 456), 72 per cent neutrophils, 9 per cent lymphocytes, 5 per cent monocytes and 12 per cent stab forms.

The lactic dehydrogenase (LDH), alkaline phosphatase and SGOT were all markedly elevated, and a liver scan indicated hepatomegaly. *A. suum* parasites were not detected in sputum or stools. However, no gastric washings were done in this case, and the sputum, which was scanty, was sent for parasite study 48 hours after prednisone therapy had been instituted. Numerous stool studies were done during the worm stage of this infestation. Serum protein electrophoresis showed an increase in alpha$_2$ and gamma globulins and a

Figure 3. *A. suum* Larva (4 Mm Long) Isolated from the Sputum of Case 1.

Table 1. Serum Immunoglobulin Levels of the Four Patients during the Acute (A), Recovery (R) and Convalescent (C) Phases of Their Illnesses.

Case No.	IgG	IgA	IgM
		mg 100 ml	
1:			
A	1200	175	425
R	1300	200	480
C	1200	165	270
2:			
A	1200	165	270
R	1500	83	188
C	1200	39	106
3:			
A	1000	430	155
R	900	300	148
C	980	190	116
4:			
A	760	220	70
R	800	240	120
C	860	200	75
Normal	800-1600	75-420	50-200

reduction in albumin. The IgM and IgE immunoglobulins were elevated, and IgM precipitating antibodies to *A. suum* antigen were identified both by agar-gel diffusion and by immunoelectrophoretic technics.

A course of prednisone therapy was given, with good results. X-ray examination showed some residual densities in the lungs that persisted for several months; however, 6 months after admission the x-ray film was normal. The hospital course was complicated by the development of thrombophlebitis of the right leg 13 days after admission. There was no evidence of pulmonary embolism, and the patient responded to a course of heparin therapy.

Case 3. A 21-year-old student was admitted to the hospital approximately 2 weeks after exposure to the *A. suum* ova with symptoms and signs similar to those in the previous cases. He was also cyanotic, and in marked respiratory distress, with a Po_2 of 48 and Pco_2 of 31.5 mm of mercury and a pH of 7.46. X-ray study (Fig. 1*C*) indicated that the pulmonary involvement was less marked, in that the infiltrates showed a patchy distribution with slightly less confluence as compared to the more homogeneous pattern seen in Cases 1 and 2. The white-cell count was 15,500, with 90 per cent neutrophils and 10 per cent lymphocytes (eosinophils were increased in the recovery phase). The alkaline phosphatase, SGOT, LDH and liver scan were normal. *A. suum* larvae were detected in the gastric washings, and 4 weeks after ingestion of the ova, many immature worms were found in the stools.

Serum protein electrophoresis showed a slight reduction in albumin and an increase in alpha$_2$ globulins. Only the IgE globulin level showed a borderline elevation in this case, and no precipitins to the ascaris antigen were detected. The patient responded to a short course of prednisone with rapid clearing of the pulmonary infiltrates.

Table 2. Serum IgE Immunoglobulin Levels* of the Four Patients during the Acute, Recovery and Convalescent Phases of Their Illnesses.

Case No.	IgE Level		
	Acute Phase	Recovery Phase	Convalescent Phase
		ng/ml	
1	3450	2300	1800
2	2100	350	225
3	700	525	355
4	353	405	335

*Determinations done by Dr. S.G.O. Johansson, of Uppsala, Sweden (normal value, 0-500 ng/ml[12]).

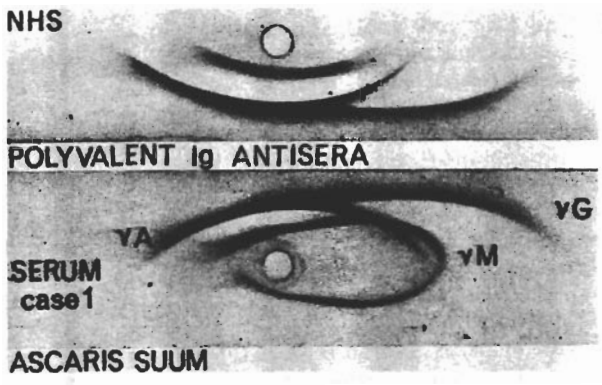

Figure 4. Immunoelectrophoretic Pattern of Case 1, Indicating that the Precipitin Band to the *A. suum* Antigen Has γM Mobility.

CASE 4. A 23-year-old student was admitted to the hospital 2 weeks after ingestion of the *A. suum* ova with a 3-day history of anorexia, dry cough and exertional dyspnea. He was not cyanotic or in respiratory distress, and examination of the chest showed scattered crepitations in both lung bases and only occasional asthmatic wheezes were heard. The Po_2 was 80, and the Pco_2 24.5 mm of mercury, and the pH was 7.45. X-ray examination (Fig. 1*D*) showed no gross infiltration but some minimal nodular densities were noted in the middle and lower fields of the lung bilaterally. The white-cell count was 12,500, with 2 per cent eosinophils, 82 per cent neutrophils, 13 per cent lymphocytes and 3 per cent monocytes. The SGOT, LDH, alkaline phosphatase and liver scan were normal. *A. suum* larvae were found in gastric washings, and a massive number of immature ascaris worms were found in the stools 4 weeks after exposure to the ova. Serum protein electrophoresis, $beta_{1C}$ globulin level and immunoglobulin quantitation were all within normal limits, and no precipitating antibodies to *A. suum* antigen were found in the serum.

The small nodular densities present on admission increased slightly during the next 2 days, with a migratory pattern characterizing the pulmonary infiltrates. During the next few days there was complete clearing of the lung densities without therapy.

DISCUSSION

Ascaris Life Cycle

The life cycle of the *A. suum* parasite in the pig is similar to that of the ascaris lumbricoides in man, with the production of similar clinicopathological manifestations.[1] After the pig swallows the infective eggs, the liberated larvae burrow into the intestinal wall, travel via the bloodstream to liver and lung, break out into the alveoli, migrate up the bronchial tree and re-enter the intestine. The larvae grow rapidly in the small intestine; five stages are recognized, and the adult worm stage is reached in 50 to 55 days and eggs may be recovered from the stool 60 to 62 days after infection. In three of the cases reported above fourth-stage larvae were identified. In the pigs the larvae produce widespread degeneration of liver cells, and in Cases 1 and 2, there was biochemical evidence of transient hepatocellular damage.

The life cycle of the parasite in these cases indicated a specific time sequence. The early intestinal phase, as indicated by anorexia, nausea, and vomiting, occurred seven to 10 days after ingestion of the ova. The larval migration phase (pulmonary infiltrates) occurred 10 to 14 days after ingestion, and gradual larval maturation, with the appearance of immature worms (late larval stage), in the stools, 29 days after ingestion. All patients were given a course of piperazine seven weeks after infestation, before the expected adult worm stage, which eradicated the parasites. Thus, the adult worms were not detected, and as a consequence no ascaris ova were found in their stools. Details concerning human *A. lumbricoides* and other nematode infections have been given elsewhere.[2-4]

Humoral-Antibody Response

Analysis of the protein-polysaccharide antigens of *A. suum* and other nematode parasites indicates the presence of multiple determinants, some antigenic, stimulating host production of precipitating antibodies, and others allergenic, responsible for reaginic IgE production.[5-8] Similar dual antibody responses were observed in some of these patients. The IgG and IgA levels (Table 1) were normal in the four patients, but the IgM levels were elevated in Cases 1 and 2 and precipitating antibodies to the ascaris antigen were also detected in these patients' serum specimens both by agar-gel diffusion and by immunoelectrophoretic analysis. Figure 4 shows the immunoelectrophoretic pattern of Case 1, indicating that the ascaris antibody had IgM mobility. The IgD and $beta_{1C}$ complement levels were also normal in the four cases.

Increased circulating IgE globulins have been reported in many parasitic infections such as ascariasis,[9] capillariasis,[10] trichinosis[11] and visceral larvae migrans.[8] The IgE levels of three of these patients (Table 2) were also elevated and bore no relation to the atopic background of the patient. Ishizaka[13] has demonstrated that the IgE antibody is the mediator of most of the reaginic activity in the serums of allergic persons. Thus, Case 1, who had the highest IgE levels, also was the only patient in whom generalized urticaria developed.

Blood Eosinophilia

An impressive laboratory feature of these cases was a blood eosinophilic leukocytosis, which almost invariably reached its peak during the recovery phase of the illness (Fig. 2) when the symptoms were subsiding and the pulmonary infiltrates as demonstrated by x-ray study were regressing. It is also worthy of note that the peak humoral antibody levels (Tables 1 and 2) preceded the eosinophilia in most of these cases. The delayed blood eosinophilia in ascaris infestation has been recorded by other investigators[2,14] and also correlates with the findings of Voorhorst[15] that, in mice infected with ascaris, a sizable increase in eosinophils does not occur until after antigen and antibody interactions have taken place.

The function of the eosinophil is unknown, but antigen-antibody complexes have long been associated with eosinophilia.[16-18] There is increasing evidence that the eosinophilia frequently observed in

certain parasitic infections may also be largely mediated by immune processes, and much of this new evidence is derived from experimental infections with trichinella spiralis in rats and mice.[19-21] These studies suggest that the eosinophilic response is dependent upon an intact-thymus-processed (T) population of lymphocytes. Since the humoral immune response is probably derived from the "bursal"-processed (B) population of lymphocytes,[22] it appears that parasitic immune reactions may be separate phenomena, and the two responses may indicate activities of different antigenic determinants stimulating different parts of the host's immune system at different times.[23] The sequence of events described above for the humoral-antibody responses and the eosinophilic response in these patients is not inconsistent with this proposal.

Asthma and Pulmonary Infiltrates

The main clinical presenting features in the more severely ill patients was the marked respiratory failure as indicated by the severe reduction in the Po_2 levels, the presence of severe dyspnea and cyanosis and the massive pulmonary infiltrates as demonstrated by x-ray examination. In addition, asthmatic wheezing was a consistent feature in all the cases, and mild wheezing persisted even after clearing of the pulmonary infiltrates had occurred. Pulmonary-function studies (Table 3) done at this latter stage, approximately 10 days after admission, indicated the presence of borderline reduction of vital capacity, but a more marked reduction of the forced expiratory volume and the maximum mid-expiratory flow rates, suggesting the presence of airway obstruction. Repeat studies three weeks later showed a return of the flow rates to more normal values in all cases.

Serial studies of the x-ray changes in the lungs of these patients indicated that the basic lesion was of the "alveolar type," with the presence of acino-nodose lesions in a nonsegmental pattern, and that the lung infiltrates had a migratory pattern.

The initial chest x-ray films of the four patients, as shown in Figure 1, indicated that Cases 1 and 2, who had the highest IgE levels as well as IgM precipitating antibody to the ascaris antigen, had the most intense opacification of the lungs. This phenomenon suggests that the pulmonary lesions not only are produced by the larvae migrating through the lung parenchyma but also are the result of the presence of the two types of antibodies, the reaginic IgE antibody (Type I)[24] being responsible for the asthma and urticaria, and the IgM precipitating antibody (Type III)[24] for the pulmonary infiltrates. The IgE antibody may also have been involved in the production of the infiltrates by mediating the release of vasoactive amines, which increase vascular permeability and thus facilitate the deposition of the antigen-antibody complexes in the lung parenchyma. These complexes may then produce an Arthus-like[25] reaction in the lung, resulting in the pulmonary infiltrates, a mechanism similar to that proposed for allergic bronchopulmonary aspergillosis.[26,27]

Worm Burden

Cases 3 and 4, with minimal antibody responses, produced the most immature worms found in the stool. In Cases 1 and 2, who mounted a marked immune response to the ascaris antigen, the antigen-antibody complexes produced probably were easily phagocytosed[28] by the polymorphonuclear and mononuclear phagocytic cells, and thus fewer larvae were available to develop into the adult worms in these patients. This observation is supported by animal studies in which rats with high antibody titers to helminths also had a reduction of worm burdens.[29]

Since the high antibody titers in those patients (Cases 1 and 2) correlate with the reduction of worm burden, the immune response to the ascaris antigen, in addition to participating in the pathogenesis of the adverse pulmonary lesions, appears to be part of a protective immune response against the *A. suum* parasites.

Table 3. Pulmonary-Function Studies.*

Case No.	Vital Capacity		Forced Expiratory Volume		Maximal Mid-Expiratory Flow Rate	
	Observed	Predicted	Observed	Predicted	Observed	Predicted
	liters		*liters/min*		*liters/sec*	
1:						
A*	4.1	5.1	52	148	1.4	4.5
B†	5.4		102		2.9	
2:						
A	3.3	4.2	20	134	0.75	3.5
B	4.3		109		3.6	
3:						
A	4.6	5.6	72	159	2.2	4.8
B	5.0		139		3.2	
4:						
A	3.2	4.4	68	138	1.3	4.0
B	3.8		94		3.8	

*10 days after admission. †Repeat studies 3 wk later.

We are indebted to Dr. S.G.O. Johansson, of Uppsala, Sweden, for measuring the IgE levels in these patients, to Dr. Paul C. Beaver, of Tulane University, New Orleans, for identification of the ascaris larvae and to Dr. Norman E. Wilks, chief, Parasitology Section of the Armed Forces Institute of Pathology, Washington, D.C., for assistance in the investigation of these cases.

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