Acute Rise in Serum Immunoglobulin E Concentration in Pulmonary Thromboembolism

Hironori Takekawa, M.D.; Kenji Miyamoto, M.D.; Etsuro Yamaguchi, M.D.; Mitsuru Munakata, M.D.; and Yoshikazu Kawakami, M.D., F.C.C.P.

Events mediated by immunoglobulin E (IgE) may be related to platelet activation and aggregation, and there may be an association between IgE and pulmonary thromboembolism (PTE). Fourteen patients with PTE were studied with regard to serum concentrations of IgE, IgA, IgG, IgM, fibrinogen, and D-dimer and with regard to blood neutrophil, lymphocyte, platelet, and eosinophil counts during acute and recovery phases. The serum IgE concentration increased during the acute phase to 402±310 IU/ml and decreased afterwards in all patients. The increase in serum IgE concentration lagged a few days behind that of the serum D-dimer concentration, indicating later IgE produc-
tion than thrombus formation and lysis. Infarction and pleural fluid accumulation developed in patients with a high initial serum IgE concentration. These results indicated a relationship between serum IgE concentration and the pathophysiology of PTE. Serum IgE may be an indicator of the severity of PTE and provide insight into its pathogenesis, thereby facilitating the diagnosis of PTE.

(Chest 1993; 104:61-64)

IL-4 = interleukin-4, PAF = platelet-activating factor, PTE = pulmonary thromboembolism, TGF-β = transforming growth factor-β

The number of patients with pulmonary thromboembolism (PTE) has increased recently, although this figure in Japan is still only one tenth of that in the United States. The main reason, among many possible factors, why patients with PTE are rare in Japan may be racial or dietary differences. Also, another reason may be that few Japanese women take oral contraceptives. One of the other reasons may be the difficulty in diagnosing PTE. Lung perfusion scintigraphy and pulmonary angiography are not available in every Japanese hospital. We desire a ready adjunct for diagnosing PTE.

We incidentally observed a patient with PTE whose serum IgE concentration increased during the acute phase, before it declined to its initial values prior to the onset of PTE. He had no allergic symptoms.

A recent article reported an increased serum concentration of immunoglobulin E (IgE) during the acute phase in patients with myocardial infarction. Another report demonstrated an increased serum IgE concentration in male patients with previous myocardial infarction, previous stroke, or current large-vessel peripheral arterial disease. Events mediated by IgE are related to platelet activation and aggregation. Thus, IgE may be closely related to thrombosis.

We hypothesized that serum IgE concentration increases during the acute phase in patients with PTE due to a mechanism similar to that at work in myocardial infarction. If this hypothesis is correct, IgE will be a new tool for the diagnosis of PTE and a means to obtain deeper insights into its pathogenesis and pathophysiology. To verify this hypothesis, we examined changes in serum IgE concentration in patients with PTE during acute and recovery phases.

Materials and Methods

We studied 14 patients (6 men and 7 women [mean age, 52±15 years (+SD)] with PTE during the 3 years from 1989 to 1991. The diagnosis of PTE was based on a typical history of sudden onset, mismatched pulmonary perfusion and ventilation scintiscans, and abnormal pulmonary angiograms. We examined eosinophil, neutrophil, lymphocyte, and platelet counts of the peripheral blood and also serum concentrations of fibrinogen, D-dimer, IgE, IgA, IgG, and IgM. We examined chest x-ray films to see whether infarction or pleural fluid developed during the clinical course. Serum IgE concentrations were determined by a radioimmunosorbent method at least twice, once in the acute and again in the recovery phase. We define the first 15 days after the onset of PTE as the acute phase and after the acute phase as the recovery phase.

No patient had a personal and familial history of allergic rhinitis, allergic dermatitis, bronchial asthma, or urticaria. No patient had hypersensitivity angitis or allergic granulomatous angitis. Stool examinations were negative for parasites in all of the patients.

Results are expressed as the mean ± SD. The intergroup comparison was done with paired Student's t test. Differences were considered significant when the p value was less than 0.05.

Results

Table 1 shows the clinical characteristics and serum IgE concentrations in 14 patients with PTE. This table shows the highest IgE values during each phase. Two of the 14 patients had had at least 1 prior pulmonary infarction. There was a consistent pattern of change in the IgE level; serum IgE concentration significantly increased during the acute phase and decreased afterwards to basal level. Pulmonary infarction and pleural fluid accumulation developed in patients with serum IgE concentrations that were

*From the First Department of Medicine, School of Medicine, Hokkaido University, Sapporo, Japan. Reprint requests: Dr. Takekawa, 1st Department of Medicine, Hokkaido University School of Medicine, Kita 15, Nishi 7, Sapporo 060, Japan.
higher than normal (>250 IU/ml). Ten patients were treated with heparin, and ten patients underwent thrombolytic therapy with urokinase or tissue plasminogen activator. There was no relationship between serum IgE concentrations and the treatment regimen. In 3 patients with serum IgE concentrations of 500 IU/ml or more during the acute phase, deep venous thrombosis caused the thrombus. In three patients with serum IgE concentrations of 90 IU/ml or less during the acute phase, the cause of the thrombus was iatrogenic. All the patients had an uneventful course after discharge from our hospital.

Table 2 shows the results of a comparison between the two phases. The highest values during each phase are shown in this table. The serum D-dimer concentration during the acute phase is the value before initiation of thrombolytic therapy. Serum fibrinogen and D-dimer concentrations and platelet counts in the acute phase were significantly higher than in the recovery phase. The blood neutrophil, lymphocyte, and eosinophil counts did not change significantly between the acute and the recovery phase. The following are two representative cases described in detail.

### Case Reports

**Case 1**

This 68-year-old woman (patient 3 of Table 1) suffered from PTE twice. The chest x-ray films indicated pulmonary infarction of the left lower lobe and accumulation of pleural fluid in the first episode. Pulmonary angiograms showed the filling defects in the anterior trunk, the middle lobe artery in the right lung, the anterior segmental artery of the left upper lobe, and the interlobar artery in the left lung. The serum IgE and D-dimer concentrations changed in parallel, but the peak serum IgE concentration lagged a few days behind that of the D-dimer concentration (Fig 1). Platelet counts increased after the serum IgE concentration reached a peak value. Serum fibrinogen concentrations increased after each attack. No marked changes in serum IgA, IgG, and IgM concentrations and eosinophil counts were noted after each attack.

**Case 2**

This 72-year-old man (patient 4 of Table 1) was admitted to our hospital 3 days after onset. The chest x-ray films indicated pulmonary infarction of the lingular region of the left upper lobe and pleural fluid. Pulmonary perfusion and ventilation scintiscans showed perfusion defects in the lingular region of the left upper lobe and the lateral and posterior basal segments of the left lower lobe. The serum IgE concentration gradually increased, reached a peak on the fifth day after onset, and then gradually decreased (Fig 2). The serum fibrinogen concentration transiently increased during the acute phase. The platelet count increased a few days after the serum IgE concentration reached a peak value. There were no changes in serum IgA, IgG, and IgM concentrations and the eosinophil count. In this patient, deep venous thrombosis developed 2 months after the onset of PTE, but the serum IgE concentration did not change after the development of deep venous thrombosis.

### Discussion

The present study showed that serum IgE concentration transiently increased during the acute phase (1 to 2 weeks after the onset of PTE) and later returned to its initial level (3 to 4 weeks after the onset). The
increase in serum IgE concentration seemed to correlate with the severity of PTE, because infarction and pleural fluid accumulation developed in the patients with high initial concentrations. The serum IgE concentration was not related to the treatment regimen, because in patients the serum IgE concentration increased before treatment.

Szczeklik et al⁵ reported that serum IgE concentrations increased in myocardial infarction, reaching a peak on the seventh day, and gradually returned to the initial level 3 weeks after onset. This pattern of changes in serum IgE concentrations is similar to that in our patients with PTE. This suggests that the similar mechanism is responsible for the transient increase in serum IgE concentration in both diseases, although the organs involved are different. Furthermore, the increase in serum IgE concentration lagged a few days behind that of the serum D-dimer concentration, indicating IgE production or release later than thrombus formation and lysis.⁶

It was reported that in patients with myocardial infarction who had initial high serum IgE concentrations, severe complications were less frequent than in patients with normal value;⁵ but pulmonary infarction and pleural fluid accumulation developed in our patients with initial high serum IgE concentrations. The IgE level probably relates to the release of mediators

---

**Figure 1.** Clinical courses of IgE, D-dimer, and platelets in case 1 (patient 3 of Table 1).

**Figure 2.** Clinical courses of IgE, fibrinogen, and platelets in case 2 (patient 4 of Table 1).
(serotonin and thromboxane) which damage the bronchovascular system of the lung in PTE. Serum IgE may also be an indicator of the severity of PTE.

The possible mechanisms of the early increase in serum IgE concentration in PTE are twofold: (1) an immune response against necrotic tissue; and (2) a nonallergic response by humoral substances from emboli or related cells. In the immune response, interleukin-4 (IL-4) released from helper T cells specifically induces IgE production by B cells; IL-4-induced IgE production in man is regulated by other lymphokines. In the nonallergic mechanism, it was recently reported that platelet-activating factor (PAF) produced by mast cells, macrophages, and endothelial cells enhanced IgE production in B lymphoblastoid cells. We suggest that PAF secreted from vascular endothelial cells or lung macrophages may enhance IgE production in PTE without antigenic stimulation.

In the recovery phase, serum IgE concentration returned to its basal level. This may be the spontaneous course or may be due to chemical mediators which inhibit IgE production. Transforming growth factor-β (TGF-β) is released from platelets and is one of the mediators inhibiting IgE production. Platelet counts increased a few days after the serum IgE concentration had increased. The TGF-β released from blood platelets probably suppresses serum IgE concentration in PTE, after IgE production increases, but this assumption awaits clinical and experimental verification.

The number of eosinophils reportedly increases from the fifth to the seventh day in myocardial infarction. In our patients with PTE, blood eosinophils did not increase significantly during the acute and recovery phases. Eosinophils infiltrate the vicinity of the infarcted myocardium, but are not found around the infarcted parenchyma in PTE. Eosinophils have specific IgE receptors, but apparently are not related to the increase in serum IgE concentration in PTE.

In patient 4, deep venous thrombosis occurred 2 months after PTE without a rise in the serum IgE concentration. Thus, the transient increase in the serum IgE concentration may be related to events within the lung.

One report showed a sex difference in changes of IgE. The serum IgE concentration increased in men with previous myocardial infarction, previous stroke, or current large-vessel peripheral arterial disease, but not in women. The serum IgE concentration increased during the acute phase in our eight female patients with PTE.

In conclusion, the serum IgE concentration may be an indicator of the severity of PTE and give insight into its pathogenesis and pathophysiology. Serum IgE also may be useful for the diagnosis of PTE. To our knowledge, this is the first report demonstrating a significant relationship between serum IgE and PTE.

ACKNOWLEDGMENT: We thank Dr. H. Nagata for participating in the early phase of this study.

REFERENCES


64 Rise in Serum Immunoglobulin E in Pulmonary Thromboembolism (Takakawa et al)