Pleural Fluid Levels of Vascular Cell Adhesion Molecule-1 Are Elevated in Eosinophilic Pleural Effusions*

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**Study objectives:** The mechanisms responsible for the accumulation of eosinophils in pleural fluid are not fully understood. The objective of the present study was to examine the relationship between pleural fluid eosinophilia and the levels of vascular cell adhesion molecule (VCAM)-1, eotaxin, RANTES (regulated upon activation, normal T-cell expressed and secreted), and interleukin (IL)-4 in pleural effusions.

**Patients and methods:** Thirty-one patients with eosinophilic pleural effusion (EPE) [eosinophil percentage > 10% of the pleural fluid nucleated cells] and 10 patients without EPE were evaluated. VCAM-1, eotaxin, RANTES, and IL-4 in all pleural fluids were measured using enzyme-linked immunosorbent assay kits. IL-5 levels of the same fluids were measured in a previous study.

**Results:** VCAM-1, eotaxin, and RANTES but not IL-4 were detectable in the pleural fluids. The mean level of VCAM-1 in EPE (336 ± 85 ng/mL) was significantly higher (p = 0.011) than that in the noneosinophilic effusions (260 ± 34 ng/mL) [mean ± SD]. VCAM-1 levels were significantly correlated with the eosinophil count and percentage in all pleural fluids (r = 0.43, p = 0.005, and r = 0.37, p = 0.019, respectively). Multiple linear regression analysis disclosed that both IL-5 (β, 0.63; p < 0.001) and VCAM-1 (β, 0.27, p = 0.025) are independent predictors of the number of eosinophils in all pleural fluids. RANTES and eotaxin did not differ significantly between EPEs and non-EPEs, and were not correlated with the number of pleural fluid eosinophils.

**Conclusion:** The levels of VCAM-1 are increased in EPE, suggesting that VCAM-1 is important in the pathogenesis of EPE. Neither eotaxin nor RANTES is associated with pleural fluid eosinophilia.

**Key words:** chemokines; cytokines; eosinophilic pleural effusion; eotaxin; interleukin-5; vascular cell adhesion molecule-1

**Abbreviations:** CABG = coronary artery bypass grafting; EPE = eosinophilic pleural effusion; IL = interleukin; LDH = lactate dehydrogenase; MCP = monocyte chemotactic protein; RANTES = regulated upon activation, normal T-cell expressed and secreted; VCAM = vascular cell adhesion molecule

Eosinophilic pleural effusion (EPE), defined by an eosinophil percentage of ≥10% of the nucleated cells in the pleural fluid, is most commonly related to the presence of blood or air in the pleural cavity; however, it may be associated with a variety of other pleural or systemic diseases. Although 5 to 8% of exudative pleural effusions are eosinophilic, little is known about the pathogenesis of EPE.

Tissue accumulation of eosinophils is believed to involve increased eosinophil production, migration to tissues, and extended survival at the site of inflammation. The increased production and increased survival of eosinophils are promoted by interleukin (IL)-5, granulocyte/macrophage colony-stimulating factor, and IL-3. Beside these functions, IL-5 is also an eosinophil chemoattractant. Tissue migration is mediated by numerous agents, including the chemotactic factors and adhesion molecules. A variety of chemokines are chemoattractants for eosinophils. These chemokines include the macrophage inflammatory peptide-1 (CCL3), RANTES (regulated upon activation, normal T-cell expressed...
and secreted) [CCL5], monocyte chemotactic protein (MCP)-2 (CCL8), MCP-3 (CCL7), MCP-4 (CCL13), eotaxin (CCL11), eotaxin-2 (CCL4), and eotaxin-3 (CCL26).\(^4\) Movement of eosinophils from the intravascular space into tissues requires the adhesion of the eosinophil to the endothelial cell.

Vascular-cell adhesion molecule (VCAM)-1, which is expressed on the endothelial surface, interacts with the \(\beta 1\)-integrins (expressed on the eosinophil surface) and facilitates eosinophil tissue migration.\(^4\) VCAM-1 is induced by IL-4, tumor necrosis factor-\(\alpha\), and IL-13.\(^4\)

The aim of the present study was to determine if the pleural fluid levels of four molecules involved in eosinophil tissue migration (VCAM-1, eotaxin, RANTES, and IL-4) differ between eosinophilic and non-EPEs, are correlated with the number or the percentage of eosinophils in the pleural fluid, and are related to the amount of blood in the EPEs. We hypothesized that the pleural fluid levels of VCAM-1, eotaxin, RANTES, and IL-4 would be higher in eosinophilic than in non-EPEs, and that their levels would correlate with the percentage and absolute eosinophil count. We further hypothesized that the levels of VCAM-1, RANTES, eotaxin, and IL-4 would be higher in the hemorrhagic than the nonhemorrhagic EPEs, and that they would correlate with the RBC count in the EPEs, since the presence of blood in the pleural cavity is one of the major conditions associated with EPE.

**Materials and Methods**

The Institutional Review Board of Saint Thomas Hospital approved this study, and all patients signed an informed consent. An EPE was defined as an effusion with eosinophils accounting for \(> 10\%\) of the nucleated pleural fluid cells. Forty-one pleural fluid samples—31 eosinophilic and 10 noneosinophilic samples—were selected from a total of \(> 1,000\) pleural fluids collected from patients who underwent thoracentesis in our hospital between September 1, 1997, and June 1, 2000. The pleural fluids were randomly selected to have the following distribution: 31 eosinophilic and 10 noneosinophilic pleural fluids. The specific diagnoses for patients with EPE were post-coronary artery bypass graft (CABG) pleural effusions \((n = 22)\), metastatic lung cancer \((n = 3)\), idiopathic pleural effusion \((n = 2)\), congestive heart failure \((n = 1)\), and nephrotic syndrome \((n = 1)\). The fluids were selected so that approximately the same number would be bloody \((RBCs > 100,000/\mu L)\) and nonbloody \((RBCs \leq 100,000/\mu L)\). Ten post-CABG noneosinophilic pleural effusions were also studied as controls because the majority of the eosinophilic effusions were post-CABG. Five of the noneosinophilic pleural fluids were bloody, and five were nonbloody. A post-CABG effusion was defined as an effusion that developed within the first 3 months after CABG with or without heart valve replacement with no other identifiable causes \((e.g.,\) congestive heart failure, chylothorax, or infection). Forty of the pleural fluid samples in the present study had been included in a previous study of IL-5 in pleural effusions.\(^7\)

At the time of the thoracentesis, pleural fluid was collected in an ethylene diamine tetra-acetic acid tube for measurement of total and nucleated cell counts, and in a plain glass tube for protein and lactate dehydrogenase (LDH) analysis. Red and nucleated cell counts were obtained by manual microscopy. The differential nucleated cell counts were obtained by manually counting 100 cells on a Wright-stained smear after the cells had been concentrated by cytocentrifugation at 2,000 revolutions per minute for 10 min. Protein and LDH concentrations were measured using a Vitro Model 950 automated analyzer (Johnson & Johnson; New York, NY). The pleural fluid for chemokine analysis was collected in a citrate-treated glass tube and immediately centrifuged at 3,000 revolutions per minute for 20 min at 4°C. The supernatant was stored at \(-70^\circ\)C until analysis. The levels of VCAM-1, eotaxin, RANTES, and IL-4 in all pleural fluids were measured using enzyme-linked immunosorbent assay kits (R&D Systems; Minneapolis, MN). The minimal detectable levels are 2 ng/mL, 5 pg/mL, 8 pg/mL, and 0.13 pg/mL, respectively.

**Statistics** Since the absolute values of pleural fluid nucleated cell count, eosinophil count, RBC count, LDH, and eotaxin levels were not normally distributed, values for these measurements are reported as median (intraquartile range) and were logarithmically transformed for the statistical analysis. Data from the rest of the variables were reported as mean \(\pm SD\). Comparisons between groups were assessed by a Student unpaired \(t\) test. Pearson correlation analysis was performed to examine for possible significant correlations between quantitative variables. Stepwise linear regression analysis was performed to assess whether the various cytokines were independently correlated with the numbers and percentage of eosinophils in the pleural fluid. For this analysis, the number or the percentage of eosinophils in the pleural fluid was the dependent variable, while the VCAM-1, eotaxin, RANTES, and IL-5 levels (measured in the previous study\(^7\)) were the independent variables. A \(p\) value \(< 0.05\) was considered significant. For statistical analysis and construction of figures, the SPSS 10.0 statistical program (SPSS; Chicago, IL) was used.

**Results**

Detectable levels of VCAM-1 and eotaxin were present in every fluid examined, and detectable levels of RANTES were found in the majority of the effusions. Levels of RANTES were below the detectable levels in 10 samples: 7 samples from post-CABG patients with EPE, 1 sample from a patient with parapneumonic EPE, and 2 samples from the control group. Levels of IL-4 were below the detectable levels in all fluids examined. In three different patient groups, measurements of either eotaxin, RANTES, or VCAM-1 were not done. The mean level of VCAM-1 in EPEs \((336 \pm 85\) ng/mL) was significantly higher \((p = 0.011)\) than the mean level in the non-EPEs \((260 \pm 34\) ng/mL) [Fig 1]. Moreover, the VCAM-1 levels were significantly correlated with the absolute count and the percentage (Fig 2) of the eosinophils in all pleural fluids \((r = 0.43, p = 0.005\), and \(r = 0.37, p = 0.019\), respectively).
The mean levels of eotaxin and RANTES did not differ significantly between eosinophilic and non-eosinophilic fluids (Table 1). There was no significant correlation between the levels of eotaxin or RANTES and the absolute count or the percentage of the eosinophils in pleural fluids. Pleural fluid levels of VCAM-1, eotaxin, and RANTES levels did not differ between post-CABG and other eosinophilic pleural effusions (Table 2).

When the data were analyzed for the subgroup of patients with post-CABG effusions (22 with EPE and 10 with non-EPE), the results were similar to those for the entire group. The mean level of VCAM-1 in EPEs (327 ± 80 ng/mL) was significantly higher (p = 0.02) than the mean level in the non-EPEs (206 ± 54 ng/mL), while RANTES and eotaxin levels did not significantly differ between EPEs and non-EPEs (p = 0.5 and p = 0.18, respectively). The VCAM-1 levels were significantly correlated with the absolute eosinophil count (r = 0.46, p = 0.008) and marginally correlated with the percentage of the eosinophils in all post-CABG pleural fluids (r = 0.39, p = 0.056). There was no significant correlation between the absolute count or the percentage of the eosinophils and either RANTES levels (r = 0.18, p = 0.33, and r = −0.46, p = 0.8, respectively) or eotaxin levels (r = 0.23, p = 0.2, and r = 0.2, p = 0.26, respectively).

Multiple stepwise linear regression analysis disclosed that both IL-5 (β, 0.63; p < 0.001) and VCAM-1 (β, 0.27; p = 0.025), but not eotaxin or RANTES, are independent predictors of the number of eosinophils in all pleural fluids. The mean RANTES level was significantly higher in bloody (35.5 ± 30 pg/mL) than in nonbloody (12.6 ± 19 pg/mL) fluids (p = 0.006), when all the fluids were included in the analysis. When only bloody fluids were considered, RANTES levels tended to be higher in eosinophilic rather than noneosinophilic fluids, but the difference was not statistically significant (40.5 ± 30 pg/mL vs 29 ± 26 pg/mL, p > 0.05). There was a significant correlation between the pleural fluid level of RANTES and the RBCs in eosinophilic (r = 0.554, p = 0.001) and all the pleural effusions (r = 0.519, p = 0.003) [Fig 3]. The mean levels of VCAM-1 and eotaxin did not differ significantly between bloody and nonbloody fluids. There was no significant correlation between the levels of VCAM-1 or eotaxin and the RBC count in pleural fluids.

When only the post-CABG effusions were examined, RANTES levels but not VCAM-1 or eosinophil levels were significantly higher in bloody than in nonbloody fluids (p = 0.002, p = 0.56, and p = 0.28, respectively). Additionally, RANTES levels but not VCAM-1 or eosinophil levels were significantly correlated with the RBCs in post-CABG pleural effusions (r = 0.42, p = 0.17; r = 0.1, p = 0.57; and r = 0.1, p = 0.59, respectively).

There was a significant correlation between LDH
levels in all the pleural fluids and the levels of RANTES ($r = 0.39, p = 0.013$), eotaxin ($r = 0.65, p < 0.001$), but not VCAM-1 levels ($r = 0.235, p = 0.145$). There was no significant correlation between pleural fluid nucleated cell count and the levels of RANTES ($r = 0.25, p = 0.13$), eotaxin ($r = 0.018, p = 0.91$), and VCAM-1 levels ($r = 0.23, p = 0.15$). Similarly, there was no significant correlation between the percentages of neutrophils and lymphocytes and the levels of RANTES, eotaxin, or VCAM-1.

**Discussion**

The primary findings of the this study are as follows: (1) detectable levels of VCAM-1 and eotaxin were present in every fluid examined and detectable levels of RANTES were found in the majority of the fluids, whereas levels of IL-4 were below the detectable levels in all fluids examined; (2) VCAM-1 levels were significantly higher in eosinophilic effusions than in noneosinophilic effusions and were significantly correlated with the absolute number and

<table>
<thead>
<tr>
<th>Variables</th>
<th>Eosinophilic Pleural Fluids</th>
<th>Nonbloody</th>
<th>Noneosinophilic Pleural Fluids</th>
<th>Bloody†</th>
<th>Nonbloody</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, No.</td>
<td>13</td>
<td>18</td>
<td>5</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>WBC, $\times 10^9$/μL</td>
<td>2.5 (0.2–10)</td>
<td>1 (0.25–3.75)</td>
<td>2.6 (2.5–9.5)</td>
<td>0.7 (0.22–0.72)</td>
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<tr>
<td>Eosinophils, μL</td>
<td>581 (46–7100)</td>
<td>243 (40–2700)</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>RBC, $\times 10^3$/μL</td>
<td>233.75 (102.5–1515)</td>
<td>3.812 (0.4–95)</td>
<td>507.5 (256–625)</td>
<td>3.75 (0.48–4.6)</td>
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<tr>
<td>LDH, IU/L</td>
<td>1,491 (488–5475)</td>
<td>460 (259–3338)</td>
<td>1,313 (1,159–1,513)</td>
<td>324 (209–424)</td>
<td></td>
</tr>
<tr>
<td>VCAM-1, ng/mL</td>
<td>345.2 ± 81.8</td>
<td>327 ± 88.6</td>
<td>259.3 ± 47.2</td>
<td>244.7 ± 63.4</td>
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</tr>
<tr>
<td>RANTES, pg/mL</td>
<td>40.5 ± 30.1</td>
<td>14.7 ± 21.3</td>
<td>23.3 ± 29.2</td>
<td>6.8 ± 9.2</td>
<td></td>
</tr>
<tr>
<td>Eotaxin, pg/mL</td>
<td>95.5 (37–259)</td>
<td>80.5 (19–823)</td>
<td>58 (25–137)</td>
<td>29 (24–67)</td>
<td></td>
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</tbody>
</table>

*Data are presented as median (intraquartile range) or mean ± SD unless otherwise indicated.
†RBC count $>100,000$/μL.
§Significant difference between eosinophilic and noneosinophilic effusions ($p = 0.011$).
\$Significant difference between bloody and nonbloody effusions ($p = 0.003$).
percentage of the eosinophils in all fluids; (3) multiple stepwise linear regression analysis revealed that both VCAM-1 and IL-5 levels are independent predictors of the number of the eosinophils in pleural fluid; (4) RANTES levels were significantly higher in bloody than in nonbloody effusions and were significantly correlated with the number of RBCs in the fluids; and (5) there was a significant correlation between pleural fluid LDH levels and the levels of RANTES and eotaxin in the fluid.

The present study focused on four molecules involved in the mobilization of eosinophils from the bone marrow into the blood and their subsequent recruitment into sites of inflammation: VCAM-1, eotaxin, RANTES, and IL-4. To the best of our knowledge, this is the first report in which VCAM-1 was measured in the pleural fluid. Pleural fluid levels of VCAM-1 were significantly higher in EPEs than in the noneosinophilic effusions, and the VCAM-1 levels were significantly correlated with the absolute count and the percentage of the eosinophils in all pleural fluids. Moreover, multiple linear regression analysis disclosed that VCAM-1 is independently associated with the number of eosinophils in all pleural fluids.

VCAM-1 is an adhesion molecule, which is mainly expressed on the intraluminal endothelial surface and interacts with the β1-integrins that are expressed on the surface of the eosinophils. It connects eosinophils to the endothelial surface and facilitates their subsequent migration to the peripheral tissues. Increased serum levels of soluble adhesion molecules including VCAM-1 are believed to be the result of vascular injury or endothelial activation related to systemic inflammation in the following conditions: in smokers and patients at risk for coronary heart disease, with the acute coronary syndrome, after cardiopulmonary bypass, and in patients with multiple sclerosis, hepatic cirrhosis, rheumatoid arthritis, and vasculitis. Serum VCAM-1 also appears to be marker of angiogenesis in breast cancer. Finally, there are two reports demonstrating increased serum levels of soluble VCAM-1 in eosinophil-related disease: in patients with severe

### Table 2—VCAM-1, RANTES, and Eotaxin Levels in Post-CABG and Other EPEs*

<table>
<thead>
<tr>
<th>Variables</th>
<th>Nonpost-CABG (n = 9)</th>
<th>Post-CABG (n = 22)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>VCAM-1, ng/mL</td>
<td>361.1 ± 96.2</td>
<td>327.4 ± 80.2</td>
<td>0.11</td>
</tr>
<tr>
<td>RANTES, pg/mL</td>
<td>19.1 (4.9–69)</td>
<td>11.0 (0–47)</td>
<td>0.33</td>
</tr>
<tr>
<td>Eotaxin, pg/mL</td>
<td>92.5 (56.5–150.5)</td>
<td>87.5 (29.7–182)</td>
<td>0.94</td>
</tr>
</tbody>
</table>

*Data are presented as mean ± SD or median (interquartile range).
asthma and in patients with nasopharyngeal carcinoma and tumor-associated eosinophilia.12

There are several possible explanations for the elevated VCAM-1 levels in pleural fluid. First, the VCAM-1 possibly came from blood and reflected the endothelial activation for facilitating eosinophil migration to the pleural cavity. VCAM-1 is comparable in size to albumin (100 kd) and could diffuse from the blood to the pleural fluid. The correlation between the pleural fluid VCAM-1 levels and the number and percentage of pleural fluid eosinophils supports this explanation. This possibility cannot be evaluated because we did not measure serum levels. Second, VCAM-1 could be overproduced locally as the result of pleural inflammation and related angiogenesis, but we see no reason for the EPE to have more inflammation-related angiogenesis than the non-EPE. Moreover, this notion does not explain the correlation between the VCAM-1 levels and the number of eosinophils in pleural fluid. A third explanation may be related to the observation of Luna and coworkers, who found a mild pulmonary eosinophilic vasculitis associated with EPE due to spontaneous pneumothorax. If there is pulmonary eosinophilic vasculitis with EPE, then the endothelial-derived VCAM-1 may move from the vessel to the interstitial tissue and then to the pleural space. Finally, the possibility that VCAM-1 is locally produced by pleural mesothelial cells cannot be ruled out.20 Mesothelial cell VCAM-1 expression has been also detected in other inflammatory conditions, ie, an animal model of peritonitis; however, whether pleural mesothelial cell VCAM-1 production is responsible for at least some of the VCAM-1 in pleural fluids remains to be demonstrated.

Eotaxin and RANTES belong to CC chemokines and are chemoattractants for the eosinophils.5 In the present study, there was neither a significant difference in the levels of eotaxin between EPE and non-EPE nor a significant correlation between the pleural fluid levels of eotaxin and the number of pleural fluid eosinophils. Our findings differ from those reported by Yokoyama and associates, who measured the pleural fluid levels of eotaxin in 47 pleural fluid samples including only nine EPEs and found a significant correlation between the eotaxin levels and the eosinophils count and percentage. One possible explanation for these discrepant findings is that most patients in the present study had post-CABG effusions while none of the patients in the study by Yokoyama et al had post-CABG effusions. Given that eotaxin is considered a potent eosinophilic chemoattractant, one might expect that its pleural fluid levels would be significantly higher in EPE than in non-EPE; however, eotaxin is not the only factor that contributes to eosinophilic recruitment at the site of inflammation. In certain cases, other chemotactic factors may have the primary role in attracting eosinophils, depending on the condition that cause EPE.

We did not find any significant difference in RANTES levels between EPE and non-EPE, or a significant correlation between the levels of RANTES in the pleural fluid and the number of pleural fluid eosinophils. This finding is in agreement with that of Smit and coworkers, who analyzed the pleural fluid in 23 patients with spontaneous pneumothorax and found no relationship between RANTES levels and eosinophils count and percentage. Similar results were also reported by Yokoyama et al.2 When these three studies are taken together, the results indicate that the presence of RANTES in the pleural fluid may not be an important factor in EPE pathogenesis.

We examined if eotaxin, RANTES, or VCAM-1 were correlated with the pleural fluid RBC count, given that blood in the pleural space is among the most common conditions associated with EPE. Bloody pleural effusions had significantly higher concentrations of RANTES than the nonbloody effusions, and there was a significant correlation between pleural fluid RANTES levels and the RBC count. Bloody EPE did not contain significantly more RANTES than bloody non-EPE. Thus, the RANTES levels in pleural fluid are more closely correlated with the RBC count than the number of eosinophils. The mechanism of RANTES production or transmission into the pleural cavity when there is a bloody effusion is not known. There is evidence that RANTES can be produced by leukocytes and platelets, but we did not find any significant correlation between pleural fluid RANTES levels and pleural fluid leukocyte counts. While RANTES may be produced by erythroblasts, there is no evidence of its production by mature circulating RBCs; however, our data indicate that the RANTES associated with the presence of blood in the pleural cavity is not enough to convert an effusion to EPE, an observation consistent with the notion that one chemokine may not be enough for eosinophil recruitment in the pleural cavity during the development of EPE.

The significant correlation between pleural fluid LDH and eotaxin or RANTES in all pleural effusions may simply indicate the relationship of both of these chemokines with pleural inflammation of any etiology. This possibility is compatible with the fact that inflammatory cells produce and secrete CC chemokines; however, we did not find any correlation between the pleural levels of the chemokines and any specific inflammatory cell type.

We have previously reported that EPE is charac-
characterized by increased pleural fluid levels of IL-5. Furthermore, the levels of IL-5 correlated with the number of the pleural fluid eosinophils, a relationship that others had previously reported. In the present study, multiple linear regression analysis showed that pleural fluid IL-5 level is an independent predictor of the number of pleural fluid eosinophils and had a higher β number than any of the other cytokines. These results suggest that IL-5 contributes significantly to the accumulation of eosinophils in the pleural fluid, although a correlation does not necessary suggest a causative relationship. This importance of high pleural IL-5 levels is probably related to its ability to enhance the chemotactic action of eotaxin and increase the life span of eosinophils in the pleural fluid. Given the absence of an association between eotaxin or RANTES and pleural fluid eosinophilia, we could speculate that IL-5 is a critical chemoattractant for the development of EPE in humans; however, whether and to what extent local production of IL-5 by the eosinophils contributes to the increased pleural fluid level is not known.

IL-4 levels were determined in this study because this cytokine contributes to the eosinophils chemoattracting VCAM-1 expression on the surface of endothelial cells. Moreover, eotaxin and RANTES may induce the release of preformed IL-4 by eosinophils. We did not find detectable levels of IL-4 in any pleural fluid sample. IL-4 was previously reported to be undetectable in EPE and in tuberculous pleural effusions. The absence of IL-4, combined with, as previously discussed, high IL-5 levels in EPE is consistent with the observation of Walker and coworkers, who found increased BAL IL-4 levels only in diseases characterized by increased IgE production, while BAL IL-5 levels were associated with pleural fluid eosinophilia, suggesting a role for this adhesion molecule in the pathogenesis of EPE. The data derived from the previous study, strengthened by the multiple linear regression analysis presented in the present study, suggest that IL-5 is an essential mediator for the development of EPE. RANTES levels are significantly higher in bloody effusions than in nonbloody effusions and are significantly correlated with the number of RBCs in the fluids.

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