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Original Research

CRITICAL CARE MEDICINE

Circulating Thymus- and Activation-Regulated Chemokine/CCL17 Is a Useful Biomarker for Discriminating Acute Eosinophilic Pneumonia From Other Causes of Acute Lung Injury*

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Background: **The presentation of acute eosinophilic pneumonia (AEP) closely resembles that of acute lung injury (ALI)/ARDS, including its idiopathic form, acute interstitial pneumonia (AIP). AEP usually lacks peripheral eosinophilia at the acute phase; therefore, the establishment of serum biomarkers for AEP would be clinically useful.**

Methods: **We measured the levels of thymus- and activation-regulated chemokine (TARC)/CCL17, eotaxin/CCL11, KL-6, and surfactant protein-D (SP-D) in serum for patients with acute parenchymal lung diseases including AEP (n = 17), AIP (n = 13), pneumonia-associated ALI/ARDS (n = 12), and alveolar hemorrhage (n = 7). To evaluate diagnostic ability, each marker was estimated by measuring the area under the receiver operating characteristic curve (AUC).**

Results: **Serum TARC/CCL17 levels of AEP patients were much higher than those of patients in other disease groups. More importantly, high circulating TARC/CCL17 levels were observed in AEP even at acute phase when peripheral eosinophilia was absent. TARC/CCL17 showed the largest AUC, and the TARC/CCL17 levels with cutoff points from 6,259 to 7,039 pg/mL discriminated AEP from other syndromes with sensitivity and specificity of 100%. The KL-6 level was low in most patients with AEP, and the sensitivity was 81.6% in cutoff with 100% specificity. The AUC for eotaxin/CCL11 and SP-D was small, with values of 0.73 (95% confidence interval [CI], 0.60 to 0.86) and 0.53 (95% CI, 0.31 to 0.64), respectively.**

Conclusions: **This study indicates that the measurement of circulating TARC/CCL17 and KL-6 is useful for discriminating AEP from other causes of ALI.** ***(CHEST 2007; 131:1726–1734)***

Key words: acute eosinophilic pneumonia; acute lung injury; KL-6; serum biomarker; thymus- and activation-regulated chemokine

Abbreviations: AEP = acute eosinophilic pneumonia; AHS = alveolar hemorrhage syndrome; AIP = acute interstitial pneumonia; ALI = acute lung injury; AUC = the area under the receiver operating characteristic curve; CI = confidence interval; p-ALI = pneumonia-associated ALI/ARDS; SP-D = surfactant protein-D; TARC = thymus- and activation-regulated chemokine

Acute eosinophilic pneumonia (AEP) is characterized by an acute febrile illness with severe hypoxemia, diffuse pulmonary infiltrates, and an increase in BAL eosinophils.[1,2] AEP may be a common pathway of lung inflammation in response to a variety of possible antigens such as cigarette smoke,[3,4] dusts,[2,5] fungi,[6] and drugs,[7] and it usually

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demonstrates an excellent prognosis. The pulmonary presentation of AEP closely resembles that of acute lung injury (ALI) and its more severe form, ARDS and its idiopathic form, acute interstitial pneumonia (AIP).[8,9,10] AEP should be distinguished from ALI/ARDS and AIP because of its uniform prompt response to steroid therapy and uniformly good prognosis in AEP, as opposed to the low rate of steroid responsiveness and the high mortality rate in ARDS and AIP.[11] A previous investigation[12] defined the histologic pattern of AEP as eosinophilic infiltration with diffuse alveolar damage, which is shared by ARDS and AIP, and only massive eosinophil infiltration can distinguish both conditions. An analysis of the BAL fluid can help in distinguishing AEP from AIP and ALI/ARDS in that the latter is usually associated with neutrophils without a significant number of eosinophils.[11] In contrast to the presence of conspicuous BAL eosinophils in AEP, blood eosinophilia is usually not prominent at presentation[3]; therefore, clinicians may sometimes misdiagnose AEP. Moreover, the BAL procedure is not always available at every hospital, while this procedure also sometimes may even worsen the patient's condition. Hence, the establishment of diagnostically useful serum biomarkers for AEP would be of great value.

Previous investigations have shown several molecules to be involved in AEP pathogenesis. In particular, some chemokines are considered to contribute to eosinophilic inflammation, which may be detectable in serum as well as BAL fluids. Eotaxin/CCL11, the most potent chemokine for eosinophils, was exclusively elevated in the BAL fluids of patients with eosinophilic pneumonia.[13] Thymus- and activation-regulated chemokine (TARC)/CCL17, a functional ligand for CCR4, was also elevated in the BAL fluids only from patients with eosinophilic pneumonia among diffuse lung diseases.[14,15] Serum levels of eotaxin/CCL11 and TARC/CCL17 have been shown to be elevated and associated with disease activity in other types of allergic diseases, such as atopic dermatitis or bronchial asthma, thus suggesting that these chemokines in the circulation may reflect *in situ* eosinophilic inflammation in these syndromes,[16–19] whereas KL-6 and surfactant protein-D (SP-D) are expressed on regenerated type II pneumocytes and moved into the bloodstream in patients with interstitial pneumonia[20,21] as well as ALI/ARDS.[22,23] The elevation of KL-6 and SP-D may reflect alveolar epithelial cell damage or re-epithelialization in the pathogenesis. Although the histopathology of AEP has previously been demonstrated to be diffuse alveolar damage with eosinophilic infiltration,[12] circulating KL-6 levels were not elevated in five cases in the publication by Daimon et al.[24] The aim of this study was to establish diagnostically useful biomarkers of AEP in order to discriminate this syndrome from other causes of ALI such as AIP, pneumonia-associated ALI/ARDS, and alveolar hemorrhage.

Materials and Methods

Patient Recruitment

The diagnosis of AEP was established based on a modification of the criteria proposed by Philit et al,[25] as follows: (1) acute febrile illness; (2) bilateral diffuse infiltrates on chest radiography; (3) hypoxemia with PaO_2 on room air < 60 mm Hg, and/or oxygen saturation on room air $< 90\%$; (4) lung eosinophilia, with $> 25\%$ eosinophils on BAL differential cell count; and (5) no evidence of infection. We excluded any case with an exacerbation of allergic bronchopulmonary aspergillosis by measuring the specific Ig levels against *Aspergillus fumigatus*. ALI and ARDS were diagnosed according to the North American-European Consensus Conference definition of ALI/ARDS including the acute onset of bilateral pulmonary infiltrates, a PaO_2/fraction of inspired oxygen ratio < 300 mm Hg for ALI and < 200 for ARDS, and no evidence of left atrial hypertension.[26] The exclusion criteria in this study were ALI/ARDS cases secondary to extrapulmonary origin such as sepsis, trauma, burns, or a postsurgical operation. Any patients having severe immunocompromised conditions were also excluded. AIP was diagnosed based on the clinical, radiologic and histopathologic findings as characterized by acute respiratory failure of unknown etiology with severe hypoxemia, diffuse lung infiltrates, and evidence of diffuse alveolar damage either at lung biopsy or at autopsy. The diagnosis of alveolar hemorrhage was made by harvesting bloody samples with BAL and then determining the presence of hemosiderin-laden macrophages.[27]

BAL and Blood Sample Collection

After informed consent was obtained from the subjects, BAL was performed principally to make a diagnosis. Briefly, a fiberoptic bronchoscope was wedged into the right middle lobe bronchus or into the left lingula. Saline solution was instilled in two to three aliquots of 50 mL, and then BAL fluid specimens from the subjects were collected. The cells were stained with May-Grünwald-Giemsa solution, and a differential count was performed on 300 cells. Blood samples were obtained from clotted blood following centrifugation at 1,500*g* at 4°C for 10 min, and then were stored at − 80°C until the measurements were performed.

Measurement of TARC/CCL17, Eotaxin/CCL11, KL-6, and SP-D

The level of each marker was measured using commercially available specific kits according to the protocol of each manufacturer. The concentrations of TARC/CCL17 and eotaxin/CCL11 were measured using an enzyme-linked immunosorbent assay (R&D Systems; Minneapolis, MN). The coefficients of variation for the chemokines assays were within 10%. The upper and lower limits of detection for TARC/CCL17 were 2,000 pg/mL and 7 pg/mL, respectively. The detectable doses of eotaxin/CCL11 by the enzyme-linked immunosorbent assay kit were from 5 to 1,000 pg/mL.

The levels of KL-6 were measured by a sandwich-type electrochemiluminescence immunoassay kit (Picolumi KL-6; Sanko

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