CASE REPORT

Eosinophilic "empyema" associated with crack cocaine use

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Smoking of crystalline cocaine, known as "crack" cocaine, has been associated with eosinophilic pneumonitis, but not with pleural effusions. We describe a patient with eosinophilic pneumonitis with an eosinophilic "empyema" after using "crack" cocaine. The illness resolved with corticosteroids. We hypothesised that his effusion would have increased levels of eosinophil cytokines that promote oedema, and found a marked increase in pleural vascular endothelial growth factor (VEGF) and smaller increases in interleukins IL-5, IL-6, and IL-8. In the setting of "crack" use, we suggest that a pleural effusion that appears grossly to be pus should be evaluated for eosinophilic inflammation. Such eosinophilic effusions may respond to corticosteroids alone, consistent with a non-infectious process driven by proinflammatory cytokines.

Pulmonary complications of inhaled cocaine include eosinophilic pneumonitis.^{1,2} We report a case of an empyema-like eosinophilic pleural effusion following the use of smoked crystalline cocaine ("crack" cocaine).

CASE REPORT

A 33 year old man presented with fever, sweats, and a productive cough 1 week after using "crack" cocaine. His previous use of "crack" cocaine had been 3 months earlier. He had no travel or sick contacts and took no medications. His temperature was 104°F and there were diffuse wheezes at the lung apices. Chest radiographs and a CT scan showed apical infiltrates and pleural effusions (fig 1). The circulating white blood cell count (WBC) was 18 200/μl with 45% eosinophils and 40% neutrophils. Antibodies to the HIV virus were negative. A blood toxicology screen showed only cocaine. Gram stain and stains of sputum for acid fast bacilli (AFB) and fungi revealed no organisms. A purified protein derivative (PPD) skin test was non-reactive. The stool was not examined for parasites.

Acute eosinophilic pneumonitis induced by "crack" cocaine was suspected. Transbronchial biopsies and bronchoalveolar lavage (BAL) of the left upper lobe were performed on day 2. The visual appearance of the tracheal and bronchial mucosa and submucosa was normal to the subsegmental level. A left pneumothorax required anterosuperior placement of a small bore catheter 2 hours later. On suction, 500 ml of pus-like pleural fluid was drained. A repeat chest radiograph showed pneumothorax evacuation but a persistent effusion. Pleural fluid analysis revealed an exudate with 177 500 WBC/μl with 80% eosinophils, lactate dehydrogenase (LDH) 2629 IU/ml (normal <132 IU/ml), glucose <20 mg/dl, total protein 4.1 g/dl (serum protein 7.7 g/dl), pH 6.9 (ABG machine), and a negative Gram stain. Cultures of blood, sputum, BAL fluid, and pleural fluid for bacteria, AFB, and fungi were negative. Aliquots of pleural fluid were processed and frozen. The BAL fluid contained many eosinophils and a few neutrophils and alveolar macrophages. Transbronchial biopsy specimens showed an acute inflammatory

infiltrate with many eosinophils, oedema, and no fibrosis, consistent with eosinophilic pneumonitis. Fungal, AFB, and Gram stains of tissue and centrifuged BAL fluid were negative.

Oral prednisone was begun at a dose of 60 mg/day. After 2 days the symptoms were improved and the pneumothorax tube was removed. He was discharged on oral prednisone 50 mg/day with a 10 mg per week tapering schedule. His illness resolved 1 month after discharge (fig 1) and prednisone was discontinued. He failed to return thereafter.

Pleural fluid was centrifuged at 8000g for 10 minutes at 22°C. Supernatants were frozen at -70°C for 3 months (within stability ranges for cytokines). Cytokine concentrations were assayed in duplicate at ≥2 dilutions. Sandwich ELISA antibody sets (R&D Systems Inc, Minneapolis, MN and BD PharMingen, Franklin Lakes, NJ for IL-5) were used to measure vascular endothelial growth factor (VEGF) and the interleukins IL-4, IL-5, IL-6, and IL-8. Concentrations were calculated from standard curves (Deltasoft; BioMetallics Inc, Princeton, NJ). The pleural cytokine levels were: VEGF, 20 ng/ml; IL-4, <4 pg/ml; IL-5, 54 pg/ml; IL-6, 132 ng/ml; IL-8, 14 ng/ml.

DISCUSSION

We report an unusual eosinophilic pleural effusion that mimicked empyema in a patient with eosinophilic pneumonitis due to "crack" cocaine. The illness resolved with abstinence and prednisone. We hypothesised that the leak mediator VEGF, present in eosinophils,³ and cytokines implicated in cocaine effects (IL-6, IL-8)^{4,5} and eosinophil activation (IL-4, IL-5)⁶ would be likely to have contributed to the pleural effusion. We found the largest increase in pleural VEGF level ever reported, and increased pleural levels of IL-5, IL-6, and IL-8, suggesting potential roles for these cytokines in eosinophilic lung disease due to cocaine.

Entry of eosinophils into the pleural space in rodent models of acute systemic inflammation appears to be mediated by upregulation of endothelial adhesion molecules, not by IL-4 or IL-5.^{7,8} As cocaine upregulates endothelial adhesion molecules,⁴ it is possible that such cocaine mediated effects contributed to the marked eosinophilic pleuritis in our patient. Once present in the pleural space, eosinophils may have been the predominant source of VEGF.³ The effect of cocaine on VEGF expression or release is unknown.

The highest pleural VEGF level previously reported was 14 ng/ml in a malignant effusion.⁹ Generally, increases in pleural VEGF levels in malignant effusions⁹ (mean 0.9 ng/ml, range 0.08-14.3) and in parapneumonic effusions¹⁰ (mean 0.6 ng/ml, range 0.1-9) are 10 times less than the pleural VEGF level in our patient. IL-4 was not detectable in the effusion in our patient but IL-5 was present in a measurable amount. The expected levels of IL-4 and IL-5 in pleural effusions are unknown. IL-5 is chemotactic for eosinophils, and the IL-5 level in our patient was within the range where it triggers eosinophil chemotaxis *in vitro*.⁶ Pleural levels of IL-6 and IL-8 were high in our patient in ranges typical of acute inflammation; mean (SE) pleural levels of 76 (26) ng/ml IL-6 and 1.5 (0.9) ng/ml IL-8 have been reported in sepsis.¹¹

Figure 1 (A) Posteroanterior chest radiograph at presentation showing the presence of biapical lung infiltrates and a left pleural effusion; (B) chest CT scan of lung apices at presentation; (C) chest CT scan of lung bases at presentation; (D) posteroanterior chest radiograph at follow up visit 1 month after start of corticosteroid therapy.

Eosinophilic pleural effusions from cocaine have not been described.² In reports of pleural effusions in acute eosinophilic pneumonia, pleural pH values were 7.3 and 7.0 with normal glucose levels and no pus-like appearance.^{12, 13} As a clear eosinophilic illness and pleural effusion preceded the pneumothorax in our patient, 2 hours of pleural air was an unlikely cause of his eosinophilic pleuritis. We speculate that VEGF was a key instigator of the pleural effusion as it is a potent mediator of endothelial leakage¹⁴ that is highly expressed in eosinophils.³ VEGF release by eosinophils contributes to allergic oedema, and VEGF has been implicated as a mediator of pleural effusions.¹⁰ The level of VEGF in our patient was very high at 20 ng/ml (0.5 nM), well within the range that causes leakage in vivo.¹⁴ Glucocorticoids downregulate VEGF¹⁵ and proinflammatory cytokines¹⁶ and promote eosinophil apoptosis¹⁷; such effects probably aided resolution of the effusion in our patient.

We conclude that a pleural effusion that appears grossly to be pus in the setting of cocaine abuse should not be drained until an eosinophil predominant effusion is ruled out. If infection is excluded, an eosinophilic "empyema" in the setting of inhaled cocaine abuse should be treated with corticosteroids and may not require drainage.

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