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Case report

Minocycline-induced acute eosinophilic pneumonia: A case report and review of the literature☆

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ABSTRACT

Acute eosinophilic pneumonia (AEP) can be a challenging diagnosis and is often initially misdiagnosed as one of the more common pneumonia syndromes such as acute respiratory distress syndrome. Early bronchoalveolar lavage (BAL) is critical in distinguishing the diagnosis to initiate proper management. The etiology of AEP is unknown, though many drugs have been implicated, including minocycline.

Minocycline is commonly used for pneumonia, acute bronchitis, urinary tract infections, and acne and is likely the cause of AEP in our patient. There are 26 case reports of minocycline-induced AEP. In most cases, outcomes were favorable and symptoms rapidly resolved upon discontinuation of minocycline, with 11 cases employing steroids, one case twelve hours of CPAP and another 5 days of intubation. None resulted in mortality. Although it is difficult to evaluate without further studies, steroids should be recommended for minocycline-induced AEP, especially for those with severe or persistent symptoms.

1. Introduction

Acute eosinophilic pneumonia (AEP) can be a challenging diagnosis and is often initially misdiagnosed as one of the more common pneumonia syndromes. Early bronchoalveolar lavage (BAL) is critical in establishing a diagnosis to initiate proper management. There have been numerous drugs implicated in the development of AEP. Twenty-six have been reported in the English literature. We describe a case consistent with minocycline-induced eosinophilic pneumonia.

2. Case summary

An 87-year-old male initially presented to the emergency department with right hand cellulitis after being bitten by his pet dog. Past history included coronary artery disease, TIA, hypertension, hyperlipidemia, osteoporosis, and glaucoma. He previously smoked a few cigarettes per day but quit 60 years ago. He denied any other illicit drug use. One dose of intravenous ampicillin/sulbactam was administered in the emergency department. The wound was thoroughly washed. The patient was then discharged to complete a course of oral amoxicillin/clavulanate. Three days later he was seen in orthopedic clinic for follow up. Continued significant erythema, edema, and warmth of the wound and hand were noted prompting hospitalization. Three days of intravenous ampicillin/sulbactam and vancomycin were administered with improvement. He was discharged to complete a 10 day course of oral amoxicillin 875 mg/clavulanate and minocycline. Twelve days after discharge he presented again to the emergency room for ankle pain after a misstep. He also described 10–15 loose, non-bloody bowel movements in the 24 h prior to admission. History was otherwise unremarkable.

Vitals revealed a fever to 102.7 F, hypotension to 90/62, tachycardia at 108 beats per minute, tachypnea to 22 breaths per minute and an oxygen saturation of 87% while breathing ambient air. On evaluation he was breathing and speaking comfortably. Faint crackles were auscultated. A 3/6 systolic murmur loudest at the apex and a flat JVP were noted. His hand exhibited mild erythema and an eschar on the dorsal hand without excessive warmth. There was mild left ankle warmth and edema. Laboratory studies reflected a leukocytosis to 20.8 k/uL with 74% neutrophils, 20% lymphocytes, and 2.8% eosinophils. Creatinine was slightly elevated at

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1.38 mg/dL with normal liver enzymes. A chest radiograph demonstrated small bilateral effusions and vague bilateral upper lobe lung infiltrates (Image 1). He was diagnosed with an ankle sprain but was hospitalized for severe sepsis, pneumonia and acute kidney injury. Intravenous ertapenem, vancomycin, and azithromycin given recent antimicrobial use in addition to oral metronidazole for possible C. difficile colitis.

Worsening tachypnea and hypoxia developed on hospital day 2 in addition to ongoing fevers. Supplemental oxygen at 4 L per minute via nasal cannula was required to maintain oxygen saturation in the low 90s. A complete blood count with differential was obtained demonstrating a new eosinophilia to 22.8% with ongoing leukocytosis at 17.3 k/uL. Repeat chest film revealed interval worsening of a diffuse alveolar filling pattern concerning for acute respiratory distress syndrome. Small bilateral pleural effusions persisted. Computed tomography of the chest revealed diffuse bilateral airspace disease with ground glass attenuation involving all lobes along with moderate bilateral pleural effusions (Images 2 and 3).

The trachea was intubated to permit flexible fiberoptic bronchoscopy given the degree of compromise in hypoxemia and respiratory mechanics. BAL and transbronchial biopsies were obtained from the right side. A trial of liberation from mechanical ventilation immediately post procedure failed. The patient was reintubated, and mechanical ventilatory support was initiated. By the next morning an FiO2 of 0.80 was required to maintain saturations in the low nineties. A pneumothorax developed in the right hemithorax and a chest tube was placed. Initial blood cultures identified streptococcus parasanguinus in 2 out of 2 specimens. Urine culture grew >100 K colony forming units of Klebsiella. C. dificile toxin returned negative without further diarrhea. Urine legionella antigen and coccidiodes IgG and IgM returned negative. Antimicrobials were tailored to ampicillin/sulbactam and ciprofloxacin.

Analysis of the BAL sample revealed 515 nucleated cells per microliter, of which 6% were neutrophils, 5% lymphocytes, and 15% eosinophils. Transbronchial biopsies demonstrated marked eosinophilia in both the alveolar and interstitial spaces. Bacterial, fungal, mycobacterial and viral stains and cultures were negative. Methylprednisolone was started at 125 mg every 6 h.

The following morning leukocytosis decreased to 13.5 k/uL with a precipitous drop in eosinophilia to 8.3%. By hospital day six the patient had defervesced with marked improvement in gas exchange. He was successfully liberated from mechanical ventilation with supplemental oxygen requirements improving to 3 L per minute via nasal cannula. There was normalization of eosinophilia to 0.1% with marked improvement in air space disease on imaging (Image 4). Solumedrol was transitioned to oral prednisone of 60 mg daily. Ciprofloxacin was discontinued as Klebsiella in the urine was determined to be a contaminant, given urinalysis was negative for

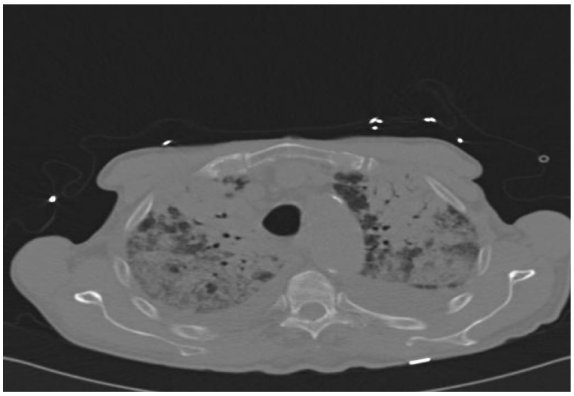

Image 2. Computed tomography of the chest revealed diffuse bilateral airspace disease with ground glass attenuation involving all lobes along with moderate bilateral pleural effusions.

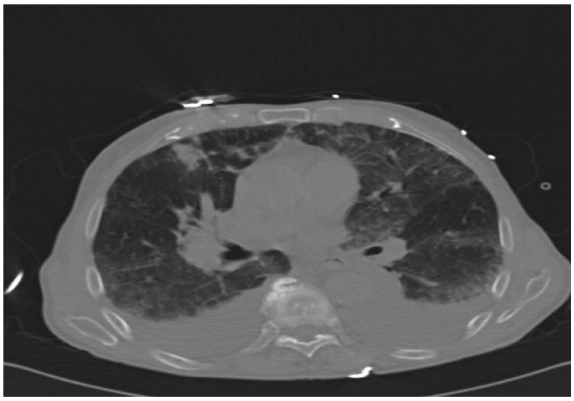

Image 3. Computed tomography of the chest revealed diffuse bilateral airspace disease with ground glass attenuation involving all lobes along with moderate bilateral pleural effusions.

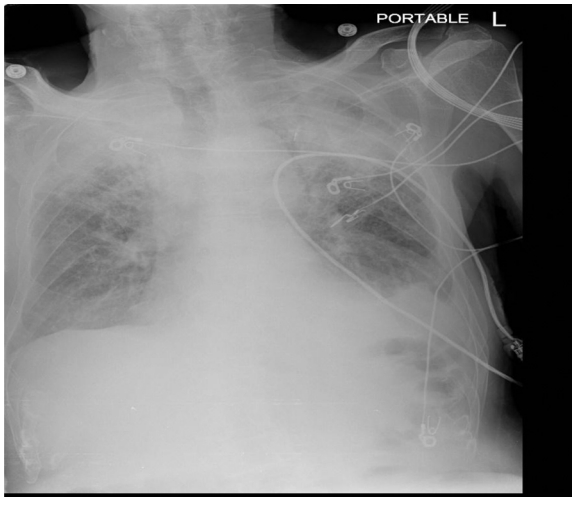

Image 1. Admission Chest Radiograph demonstrated small bilateral effusions and bilateral upper lobe lung infiltrates.

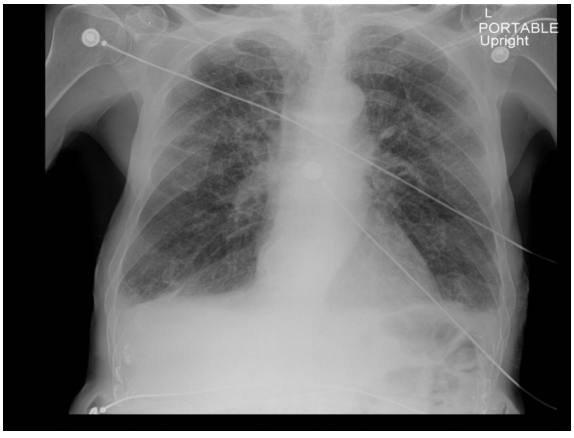

Image 4. Three weeks after oral steroid therapy, marked resolution of bilateral infiltrates and improvement of bilateral effusions are seen.

signs of active infection. The chest tube was removed after resolution of an air leak on hospital day 15. Transthoracic echocardiogram revealed no evidence of endocarditis and repeat blood cultures were sterile. A 14 day course of vancomycin was completed for streptococcus parasanguinous bacteremia. After rehabilitation the patient was discharged on day 30.

3. Discussion

3.1. Demographics

Less than 200 cases of AEP have been reported to date. The mean age of onset is 29 years [1], with no gender preference. There does not appear to be a regional predilection. Cases have been reported throughout the United States (Colorado, Ohio, Kentucky, Massachusetts, Georgia) and all around the world, including Belgium, France, Japan, and Korea.

3.2. Etiology

The etiology and pathophysiology of AED is unknown. However, it is postulated that stimuli activate T-lymphocytes which, in turn, initiate eosinophil accumulation in the lung. There is a developing body of data implicating cytokines as a mediator. Selective activation of eosinophils by IL-5 produced by T-lymphocytes may be the inciting event resulting in eosinophil-rich alveolar exudates [1]. It has been estimated approximately 40% of patients with AEP have a history of smoking. It is speculated that recent changes in smoking habits, such as restarting after cessation, is associated with the development of AEP [2]. About 66% of patients with AEP are current smokers [1–3]. In Uchimaya et al., change in smoking habits correlated with AEP. While all but their 33 AEP patients were smokers, interestingly 23 (69.7%) had just started smoking within one month prior to AEP onset [4]. Some patients have reported unusual outdoor activities including gasoline tank cleaning, cave exploration, plant repotting, smokehouse cleaning, and motocross racing prior to the onset of symptoms [3]. Paragonwestermani has been implicated in one case report as an infectious cause of AEP [5].

Numerous drugs have been associated with eosinophilic pneumonia, however fewer drugs have met the clinical criteria for the syndrome of AEP. These include BCG vaccination [6], daptomycin [7], minocycline, amiodarone [8], fludarabine, intramuscular progesterone, sertraline, venlafaxine [9], ibuprofen [10], mesalazine suppository [11], and marijuana [12].

3.3. Clinical characteristics

In descending order the most common symptoms at presentation are rapid onset of fever, dyspnea, non-productive cough, and tachypnea, in previously healthy individuals. A more subacute presentation over a few weeks has been described. Progression to life-threatening respiratory failure can occur within a few hours. Chest pain is present in 73% of patients and is typically pleuritic. Myalgias are present in approximately half of patients. Crackles are auscultated in about 80% of patients, with 13% having both wheezes and crackles, but 20% of patients are clear [13].

3.4. Laboratory findings

The most widely used criteria for diagnosis of AEP was proposed by Philit et al. in their analysis of 22 patients (Table 1). Arterial oxygen saturation, chest radiograph and BAL are essential for diagnosis, as are blood, sputum, and BAL cultures to rule-out infectious etiologies. Patients generally lack peripheral blood eosinophilia at presentation. In a case report of 22 patients, mean WBC at the time of hospitalization was 20.7×10^9/L with a standard deviation of 10.9 while mean peripheral eosinophil count was $0.98 \times 10^9/L \pm 1.5$ [1]. Patients often present with a neutrophil predominance, later in the course of hospitalization, peripheral blood eosinophilia is seen in most patients. In the same study the percentage of eosinophils on BAL was 53 ± 19%. There is a mixed cellular infiltrate with eosinophils dominating in the BAL, with an average of 20% lymphocytes and 15% neutrophils [3]. There generally is not neurophilia or lymphocytosis on BAL in drug-induced eosinophilic pneumonia. Peripheral blood IgE level can be either normal or elevated in AEP. Lung biopsy is not essential in the diagnosis of AEP except for the purpose of excluding other diseases that may mimic AEP.

3.5. Radiographic findings

Characteristic radiographic findings include diffuse infiltrates, Kerley-B lines, and bilateral pleural effusions. Later mixed reticular and alveolar infiltrates can be seen which can progress to densely alveolar. CT scans in AEP show diffuse interstitial infiltrates, patchy alveolar infiltrates, or diffuse ground glass infiltrates. Infiltrates will eventually resolve, with bilateral pleural effusions resolving last.

3.6. Differential diagnosis

Because a majority of patients will meet the diagnostic criteria for ALI/ARDS it is important to distinguish between these entities. Several features distinguish AEP from ARDS. AEP is typically not accompanied by multi-organ failure, although two cases of shock was were reported [1,14]. Lastly, in ARDS neutrophils are predominant on BAL. Therefore, early BAL is critical in differentiating between AEP and ALI/ARDS. Moreover, clinicians must obtain samples from alveoli, rather than a tracheal aspirate or a bronchial washing, since AEP is an alveolitis. Other considerations in differential diagnosis includes fungal infections with as Aspergillus and Coccidioides, as well as parasitic infections with Strongyloides.

Other idiopathic eosinophilic pneumonias include simple eosinophilic pneumonia (Loeffler's syndrome) and chronic eosinophilic pneumonia (CEP). CEP was first described in 1960 and is clinically distinguishable from AEP by several characteristics. Patients with CEP are more likely to have a prior asthma history [15]. Presenting symptoms are similar except onset is insidious over weeks to months, with the presence of peripheral eosinophilia. The typical chest radiographic findings in CEP include peripheral pulmonary infiltrates as opposed to the diffuse infiltrates seen in AEP. While not a prerequisite for diagnosis, BAL can be helpful and shows an isolated increase in BAL eosinophils, generally more than

Table 1
Revised criteria for the diagnosis of idiopathic acute eosinophilic pneumonia.

Acute of onset of febrile respiratory symptoms ≤1 month duration
Bilateral diffuse opacities on chest radiography;
Hypoxemia, with PaO_2 on room air <60 mmHg, and/or PaO_2/FiO_2 300 mmHg or room air oxygen saturation <90%;
Lung eosinophilia, with >25% eosinophils on BAL differential cell count, or eosinophilic pneumonia at lung biopsy;
Absence of infection or other causes of eosinophilic lung disease. Patients generally lack peripheral blood eosinophilia

Adapted from Philit et al.

Table 2
Summary of case reports of minocycline-induced AEP.

	Age/gender	Days until symptom onset	Steroid use	Respiratory interventions	Rechallenge test	Lymphocyte stimulation
Ho [19]	36 M	7–11 days	None		ND	ND
	20 F	4 weeks	Oral prednisone 40 mg for 1 month		ND	ND
Otero [20]	55 F	4 weeks	Oral prednisone 60 mg, unreported duration		ND	ND
Yokoyama [21]	30 F	2 weeks	None		Positive	Negative
Bando [22]	65 M	5 days	Oral prednisolone 30 mg for 5 days		Positive	Negative
Sitbom [23]	53	21 days	None		ND	ND
	38	5 days	None		Positive	ND
	22	21 days	None		ND	ND
	36	14 days	Yes, unreported details		ND	ND
	28	1 day	Yes, unreported details		Positive	ND
	28	10 days	None		ND	ND
	17	12 days	Yes, unreported details		ND	ND
	43	10 days	None	Required CPAP	ND	ND
Dykhuizen [24]	36 F	7 days	Oral prednisone 30 mg for 10 days		Positive	ND
Toyoshima [25]	38 F	8 days	Three of the following patients in this study used short term oral steroids		ND	Negative
	33 M	8 days				ND
	84 F	13 days				Negative
	70 F	4 days				Negative
	67 F	12 days				Negative
	75 F	10 days				Negative
	26 M	6 days				Negative
Oddo [26]	54 F	2 weeks	IV methylprednisolone for 7 days	Required intubation	Positive	ND
Ono [27]	55 F	1 week	None		Positive	Negative

ND: not done.

50%, with lymphocytes and neutrophils present in relatively normal percentages.

3.7. Treatment

The majority of patients have a rapid and response to corticosteroids, with clinical improvement within 24–48 h. Since approximately two-thirds of patients require mechanical ventilation, these patients should be admitted to the intensive care unit for close observation. the optimal dosage of corticosteroids and duration of administration have not been determined, intravenous methylprednisolone from 60 to 125 mg every six hours is generally used with a switch to oral prednisone after clinical improvement [13]. Oral prednisone was tapered as quickly as 10 days and as slowly as 3 months. It has been recommended to taper oral prednisone over 2–6 weeks [2,16,17]. There are some reports of patients improving spontaneously without corticosteroid treatment [1]. Most patients have complete clinical remission with no long-term pulmonary sequelae and no residual abnormalities on chest radiograph. Pulmonary function tests normalize in the majority of patients, however a minority will have residual mild restrictive changes. Relapse after steroid cessation is rare, unlike in CEP where relapse is common once treatment is stopped [3].

4. Conclusion

Minocycline is commonly used for pneumonia, acute bronchitis, urinary tract infections, and acne and is likely the cause of AEP in

Table 3
Summary of significant laboratory findings.

	White blood cells at presentation (1000/uL)	Peak eosinophilia reported (1000/uL)	IgE (IU/mL)	Percentage of eosinophils in bronchoalveolar lavage
1		2.4 (28%)		ND
2		15.2 (41%)		ND
3	12.9	5.8		ND
4	18.4	2.3 (23%)		4%
5	11.9		322	6%
6		1.2	353	27%
7		1.7	1505	50%
8		2.8	ND	55%
9		1.9	137	5%
10		1.6	ND	39%
11		0.17	600	22%
12		1.6	ND	12.5%
13		1.3	3600	ND
14	6.8	1.9 (24%)	807	13.5%
15	14.9	(0%)	1100	13.5%
16	6.4	(8%)	3675	ND
17	10.8	(1%)	2510	12%
18	8.5	(6%)	20	25.5%
19	8.2	(3%)	99	35%
20	9.8	(6%)	ND	ND
21	18.9	(0%)	620	59%
22	30.0	4.0	ND	present
23	34	4.2	ND	26.4%

ND: not done.

our patient. Our case resembles other reported cases in regards to temporal association, presentation and met diagnostic criteria. 23 case reports of minocycline-induced AEP are summarized in Table 2 and significant laboratory findings in Table 3, with a few cases in the French and Japanese literature omitted. Mean time from initiation of minocycline to symptom onset was 11 days, with a range of 1 day–4 weeks, while ours was 12 days. Peripheral eosinophilia was noted in most cases at some point during hospitalization. Time to peak of peripheral eosinophilia was only noted in six of the 23 cases which varied from hospitalization day 3–15, with our patient also lacking peripheral eosinophilia until hospital day two. Percentage of BAL eosinophilia was 25% ± 17%, reiterating the importance of early BAL to establish early diagnosis when peripheral eosinophilia is not yet present. IgE was considered positive in nine of 13 cases in which it was obtained (1180 ± 1283 IU/mL), with cut-offs used for positivity varying between 120 and 400 IU/mL.

Outcomes were generally favorable and symptoms rapidly resolved upon discontinuation of minocycline, with 11 cases employing steroids, one case twelve hours of CPAP and only one requiring intubation. None resulted in mortality. Lymphocyte stimulation was negative in all patients that were done, and thus is not a useful confirmatory test in minocycline-induced AEP. Minocycline should be avoided in patients who had a history of AEP as all patients who were re-challenged had a relapse, generally in a shorter time frame of 1–2 days. Although it is difficult to evaluate without further studies, steroids should be recommended for minocycline-induced AEP, especially for those with severe or persistent symptoms.

While ampicillin has been reported to cause pneumonitis [18], it has not been reported to be associated to fit the clinical criteria AEP, nor has vancomycin. Our patient is unlikely to have developed AEP secondary to the antibiotics he received during his second admission given his presentation on admission and the timeline of events.

He was subsequently seen in the pulmonary clinic a month after discharge. He denied any respiratory symptoms and was started on a slow three month taper of prednisone. He was also started on inhaled mometasone to ease prednisone taper.

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