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When treating sick joints harms lungs, Ixekizumab induced pleural effusion

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ABSTRACT

Immunological therapies have provided a multitude of new and effective treatment strategies for various disease states. While monoclonal antibody therapy benefits many patients, side effects are widely variable. here we present a case of pleural effusion complicating psoriatic arthritis treatment.

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INTRODUCTION

Immunological therapies have provided a multitude of new and effective treatment strategies for various disease states. While monoclonal antibody therapy benefits many patients, some agents have been linked to pulmonary toxicity and pneumonitis. Pleural effusion and pleurisy have not previously been described as a side effect of immunological therapy. Here we present a case of unilateral, hemorrhagic, lymphocytic pleural effusion in a 50-year-old female caused by Ixekizumab, an interleukin-17 (IL 17) inhibitor, treated with corticosteroids resulting in complete resolution.

CASE PRESENTATION

50-year-old female with psoriatic arthritis, hypertension and type II diabetes mellitus presented to the emergency department (ED) with shortness of breath. Right lower lobe pneumonia was suspected based on chest x-ray. She was discharged on a course of oral levofloxacin. The patient presented again to the ED two days later with new, right sided chest pain and worsened dyspnea.

Upon presentation, the patient reported right sided, pleuritic chest pain and cough productive of clear phlegm. She endorsed dyspnea at rest that worsened with exertion. Vital signs were significant for hypoxemia with O2 saturation of 88% on room air (RA), tachycardia and tachypnea; other vital signs were within reference. Physical examination revealed a female in moderate respiratory distress. Auscultation showed decreased air entry bilaterally with dullness to percussion at the right lung base. Laboratory workup was significant for leukocytosis of 17,900 with neutrophilic predominance, elevated ESR and CRP but otherwise was unremarkable with the exception of elevated serum creatinine which normalized with gentle hydration (Table 1).

Chest x-ray showed right lower lobe infiltrate with small pleural effusion (Image 1).

Empiric treatment with vancomycin and cefepime was started for presumed parapneumonic effusion. Over the following 48 hours, the patient's dyspnea continued to worsen. Repeat x-ray showed worsening effusion, chest computed tomography (CT) showed normal lung parenchyma and significant effusion with no signs suggestive of infection or empyema

Table 1. Initial Laboratory Results		
	Serum Value	Reference Range
WBC	17,900	4,800-10,800
RBC	5.01	4.2-5.4 million
Hgb	12.9 g/dL	12-15 g/dL
Hct	41.5 %	36-47 %
Platelets	225000	150,000-450000
Neutrophils	15,900	1,500-7,500
Lymphocyte	1,100	1,000-4,500
Monocyte	800	1- 1000
Eosinophils	0	0-5,000
Basophils	0	0-200
Sodium	138 mmol/dL	135-145 mmol/L
Potassium	4.1 mmol/dL	3.5-5.1 mmol/L
Chloride	108 mmol/dL	96-108 mmol/L
Serum bicarbonate	20 mg/dL	21-32 mg/dL
BUN	11 mg/dL	7-22 mg/dL
Creatinine	1.4 mg/dL	0.6-1.1 mg/dL
Glucose	184 mg/dL	70-100 mg/dL
Procalcitonin	< 0.05	0.10 - 0.25 ng/mL
ESR	48	0 - 26 mm/HR
CRP	19.4 mg/dL	0 - 0.29 mg/dL
T - spot	Negative	Negative
HIV 1/2 Ab and P24 Antigen	Negative	Negative
Respiratory Virus Panel	Negative	Negative

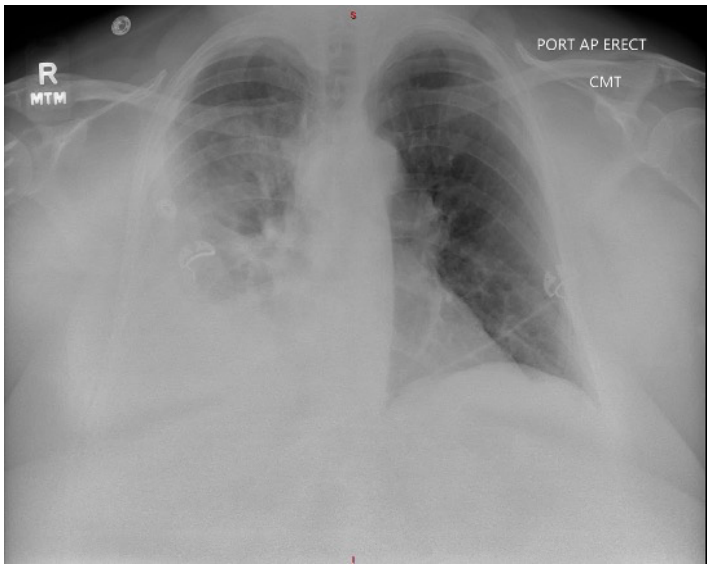

IMAGE 1: Chest x-ray on presentation

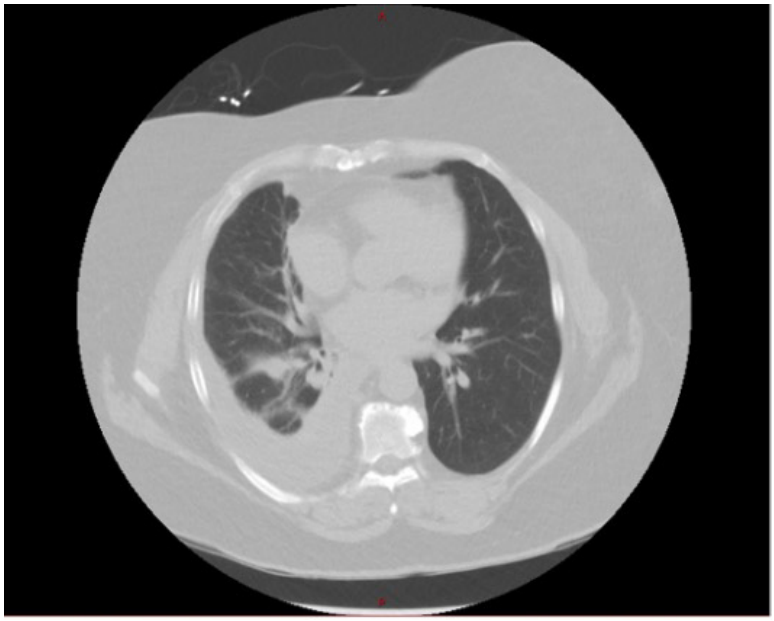

IMAGE 2: Initial chest CT scan

Table 2. Pleural Fluid Analysis		
	Pleural Fluid	Reference Range
RBC	59,733	2-1000 mm^3
WBC	1,285	<1000 mm^3
Glucose	73	~ Plasma
Lymphocyte	60	2-30%
Monocyte	5	30-70%
Eosinophil	1	0%
LDH	711	<50% plasma LDH
ADA	8 IU/L	<20 IU/L
Protein	4.5 g/dL	1-2 g/dL
Albumin	2.1 g/dL	3.4-5.4g/dL
Gram, Acid Fast and Fungus Stain.	All Negative	No organism
Acid Fast and Fungus culture	Negative after 6 weeks	Negative
Cytology	Mixed inflammatory cells, negative for malignancy	-

(Image 2).

Further inquiry into the patient's recent medical history revealed a recent course of Ixekizumab for psoriatic arthritis. The last injection (second one) was two weeks prior to the onset of the patient's dyspnea.

Thoracentesis was performed and 750 mL of serosanguinous fluid was removed. Analysis revealed a hemorrhagic, exudative effusion with a lymphocytic predominance (Table 2).

Autoimmune and connective tissue disease workup was unremarkable as well as common tumor markers (Table 3).

Microbiologic workup was also unrevealing, yielding negative blood, sputum and pleural fluid culture as well as negative gram, acid fast bacilli and fungal stains. Initially, the patient was started on non-steroidal anti-inflammatory drugs (NSAID), for which she showed minimal response. After pleural fluid analysis, the patient was transitioned to oral steroids with rapid resolution of dyspnea and pleuritic chest pain. Patient's supplemental oxygen requirement diminished and functional capacity improved. The patient was discharged on oral prednisone 60 mg daily with a 6-week tapering dose.

Table 3. Autoimmune Analysis

	Serum	Reference Range
C3	187	90-180mg/dL
C4	28	10-40mg/dL
P-ANCA	<1:20	0-1:20
C-ANCA	<1:20	0-1:20
Antihistone Antibody	1.2	0-0.9 IU/mL
Antinuclear Antibody	>1:80	0-1:80
Anti-double stranded DNA	<1	0-9 IU/mL
RNP	0.3	0-0.9 IU/mL
Smith	<0.2	0-0.9 IU/mL
Anti-Chromatin Antibody	<0.2	0-0.9 IU/mL
Sjogren's SSA Antibody	<0.2	0-0.9 IU/mL
Sjogren's SSB Antibody	<0.2	0-0.9 IU/mL
Anticentromere B Antibody IgG	<0.2	0-0.9 IU/mL
Anti-Scleroderma-70 Antibody	<0.2	0-0.9 IU/mL
Anti-Jo-1 Antibody	<0.2	0-0.9 IU/mL
CA19.9	9	0-35 U/mL
CA15-3	15.2	0-25 U/mL
CA 125	11.5	0-35 U/mL
CEA	1.3	0 -3 ng/mL

The patient was seen in pulmonary outpatient clinic four weeks after discharge. Repeat x-ray showed complete resolution of pleural effusion (Image 3).

DISCUSSION

Monoclonal antibody therapy is a new rapidly evolving science showing great promise in the management of various disease states, from autoimmune to malignant . Still, little is understood about the potential side-effects.

Classification of T-Cell mediated immunity has expanded beyond the historical description of CD4+ and CD8+ T lymphocytes. A subset of CD4+ cell is now defined by the production of IL17, the T Helper 17 (Th17 cell). Differentiation of Th17 cells from naïve T-Cells is initiated by interleukin 6 (IL 6) and Tissue Growth Factor Beta (TGFB). Cell populations are expanded, stabilized further by Interleukin-23 (IL 23) through the expression of orphan nuclear receptor ROR-γ.[1] This system functions in protection of the host organism from the environment, specifically in the intestinal mucosa and skin. These cells reside in a preactivated state and express an array of sensory receptors that allow them to sense their surroundings.[2]

IL 17 is a proinflammatory cytokine secreted by

activated Th17 cells. The prototype member of this family is designated by the letter A (IL 17A). Five additional subtypes have been identified and cloned B, C, D, E and F. The IL 17 signaling system functions in various tissues such as articular cartilage, bone, menisci, brain, hematopoietic tissues, kidney, lung, skin and intestine.3 Signaling through IL 17 Receptor A (IL 17RA) and IL 17RC, which is highly expressed by epithelial cells, recruits neutrophils and promotes secretion of defensin-like factors and maintains tight junctions within the intestinal wall. These factors maintain mucosal tissue barrier function.[4] Recent studies have suggested a similar system within the blood brain barrier in mice.[4] Clear understanding has not yet been described in current literature. Whether a similar system exists in the pleural membrane or direct injury induced by Ixekizumab in a way similar to that described in cases of pneumonitis could not be differentiated by this report. No confirmatory pleural biopsy was taken and no bronchioalveolar lavage was done, as these tests would be invasive and were deferred because the patient responded so promptly to steroid therapy and discontinuation of the causal agent. Ixekizumab is a humanized IgG4 monoclonal antibody that selectively binds with IL 17A cytokine and inhibits its interaction with the IL17 receptor. Estimated half-life of Ixekizumab is thirteen days and time to peak is almost four days, which is consistent with the presentation of our patient5 two weeks after the second dose being in second half life of elimination. We followed an approach similar to that suggested in immunotherapy associated pneumonitis. After careful exclusion of other conditions including infectious causes, we attributed the patient's leukocytosis and neutrophilia to systemic steroids received in the ED and a negative procalcitonin level[6,7] as well as the high ESR and CRP favoring a noninfectious, inflammatory process. Autoimmunity and malignancy were shown to unlikely causes, as shown in Table 3. Pleural fluid analysis was more consistent with an inflammatory process. No malignant cells were identified on cytology and no micro-organisms where cultured also shown (Table 2).

Prednisone, 1-2 mg/kg/day was given on a tapering dose by 5-10 mg per week over six weeks with complete resolution of effusion.[6] In a clinical report, eleven out of forty three patients who experienced pneumonitis secondary to checkpoint inhibitor cancer treatments experienced recurrence of pneumonitis during drug holding and of steroid therapy. These patients received immunotherapy after resolution of pneumonitis, eleven tolerated therapy and three showed recurrent pneumonitis of equal severity.[8] The decision to restart therapy should be weighted on the severity of the disease being treated, as well as the extent of pneumonitis.[6] Our patient was given the choice and she decided not to resume immunotherapy.

CONCLUSION

Immune therapy is a rapidly evolving line of treatment modalities which have shown great efficacy in treating various disease states and are significantly impacting clinical practice. Still little is known about the potential side effects and systemic ramifications associated with their use. Here we present the first case of pleural effusion attributed to Ixekizumab. We believe this case report will serve to increase practitioner awareness of potentially serious pulmonary complications associated with immunotherapy as well as inform them of our approach to diagnosis and initial treatment which proved effective. We hope this case report serves to highlight potential systemic effects of immunotherapies which are rapidly becoming commonplace in clinical practice.

AUTHOR AFFILIATIONS

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