Session #2557
Interesting Cases I – Saturday, March 14, 2020

Case Report #1

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Case Title
Dual blockade of type 2 inflammation with mepolizumab and dupilumab for treatment of EGPA

Summary
A 13-year-old male with severe persistent asthma and chronic sinusitis with nasal polyps is diagnosed with ANCA-negative eosinophilic granulomatosis with polyangiitis (EGPA) when he presents with eosinophilic pneumonia and granulomatous inflammation is found on nasal polyp biopsy. He was started on mepolizumab 100mg monthly for severe persistent asthma, then increased to 300mg monthly, however his disease progresses. He has multiple hospitalizations for asthma exacerbations and sinus infections, undergoes endoscopic sinus surgery, and becomes steroid-dependent. A trial of rituximab fails to achieve clinical improvement and side effects of chronic steroid use become more evident. Dupilumab is started at a loading dose of 600mg and continued at a dose of 300mg monthly. Within 1 month, dupilumab led to significant improvement in nasal symptoms and lung function. He is able to wean steroids. This case suggests that the combination of mepolizumab and dupilumab may be an effective treatment option for patients with EGPA.

Patient Presentation
A 13 year-old-male of Mexican descent initially presented at age 12 with a two-year history of fatigue, shortness of breath, and chronic nasal congestion. He was previously diagnosed with asthma and allergic rhinitis. He had been treated with allergen immunotherapy in Mexico and started omalizumab monthly with persistence of his symptoms. He had 11-12 emergency department visits and 4-5 hospitalizations per year due to asthma exacerbations and sinus infections including one admission with pansinusitis and pre-septal cellulitis requiring IV antibiotics (Figure 1). He was prescribed antibiotics and steroids nearly every other month, which were initially effective, but then symptoms progressed. Subsequently, he was started on chronic steroids at 15mg prednisone daily. He also developed an eczematous rash on his arms. Family history was significant for a paternal aunt with lupus and diabetes in multiple relatives, however no asthma, eczema, allergic rhinitis, urticaria, or vasculitis. He showed normal growth and development, received all schedule vaccinations, and was doing well in school.

Diagnosis
The diagnosis of eosinophilic granulomatosis with polyangiitis (EGPA) was made as he met four out of the six criteria according to the American College of Rheumatology. Specifically he had the

following: 1) asthma, 2) >10% peripheral blood eosinophils, 3) pulmonary opacities, and 4) paranasal sinus abnormalities. He was diagnosed with ANCA-negative EGPA.

Testing

The patient was admitted to the hospital for acute respiratory distress. Routine laboratory studies demonstrated peripheral eosinophilia (absolute eosinophil count 1600 cells/uL) with a normal IgE level (162 kU/L). CT scan was done to more closely evaluate the airways and showed bilateral patchy airspace consolidation and ground glass opacities with upper lobe predominance (Figure 2). Bronchoscopy was done to rule out pulmonary infection. Bronchoalveolar lavage demonstrated a mixed infiltrate with eosinophilia (eosinophils 19%, macrophages 30%, 39% neutrophils, and 9% lymphocytes). Fungal serologies, gram stain, and AFB culture were negative. Lung biopsy was deferred given the concern for low diagnostic yield while on systemic steroids, however tissue was obtained from endoscopic sinus surgery which showed numerous eosinophils, Charcot-Leyden crystals, and large histiocytic aggregates without necrosis consistent with granulomas. Vasculitis was not identified. Rheumatologic workup was undertaken, however ANCA was negative. Skin biopsy of his eczematous arm rash showed a perivascular lymphohistiocytic infiltrate, but no vasculitis, eosinophilic infiltrate, or granuloma formation. Spirometry shortly after diagnosis revealed an FVC of 59% predicted (ppd), FEV1 of 35 ppd, FEV1/FVC of 52 ppd, and an FEF 25-75% of 11 ppd with post bronchodilator change of 2% for FEV1 and 29% for FEF 25-75%. Fractional excretion of nitric oxide (FENO) was elevated at 75.

Treatment

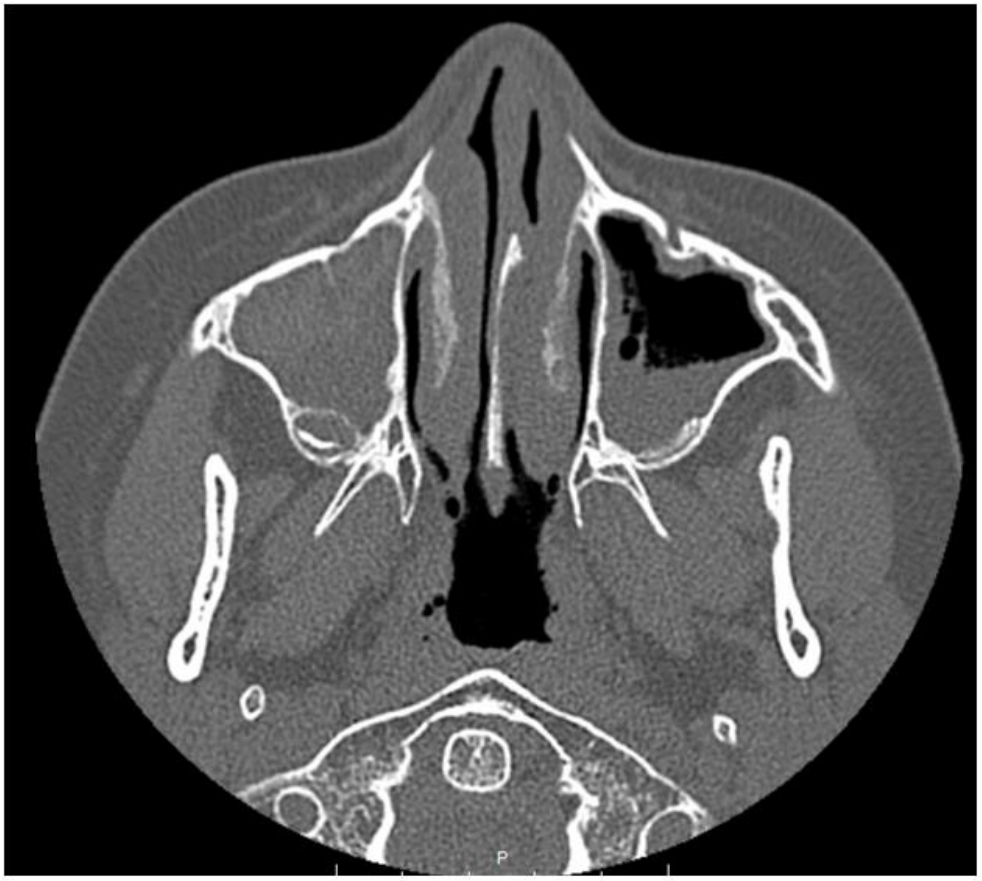
He was initially treated with mometasone furoate 200mcg/formoterol fumarate dehydrate 5mcg two puffs twice daily, fluticasone nasal spray two sprays daily, albuterol as needed, and prednisone 15mg daily. The patient's symptoms improved, however he developed significant flares when prednisone taper was attempted. He started anti-IL5 therapy, mepolizumab, which has been shown to be efficacious in the management of EGPA. While his overall lung function and eosinophilia improved, symptoms persisted with frequent exacerbations, thus the decision was made to undergo a trial of rituximab for refractory and relapsing EGPA. He received two infusions of 1000mg of rituximab, but symptoms did not improve. Spirometry was now concerning for the development of fixed obstruction. Additionally, nasal symptoms were chronic and progressive despite multiple debridements and an intensive endoscopic sinus surgery with total bilateral ethmoidectomy with inferior turbinate reduction. He also began developing steroid-associated complications including bone density loss and adrenal insufficiency. We chose to add dupilumab on to his treatment regimen. Since dupilumab had been approved for chronic rhinosinusitis with polyps, our thought process was that it may be active in the upper airways. The rationale for continuing mepolizumab was to try to achieve a synergistic effect of dual type 2 inflammation blockade. Additionally, dupilumab has been associated with a transient increase in peripheral eosinophilia in phase III asthma studies and caution is necessary in patients with hyper-eosinophilic conditions. Therefore, we maintained mepolizumab to try to address this potential increase in peripheral eosinophilia with dupilumab.

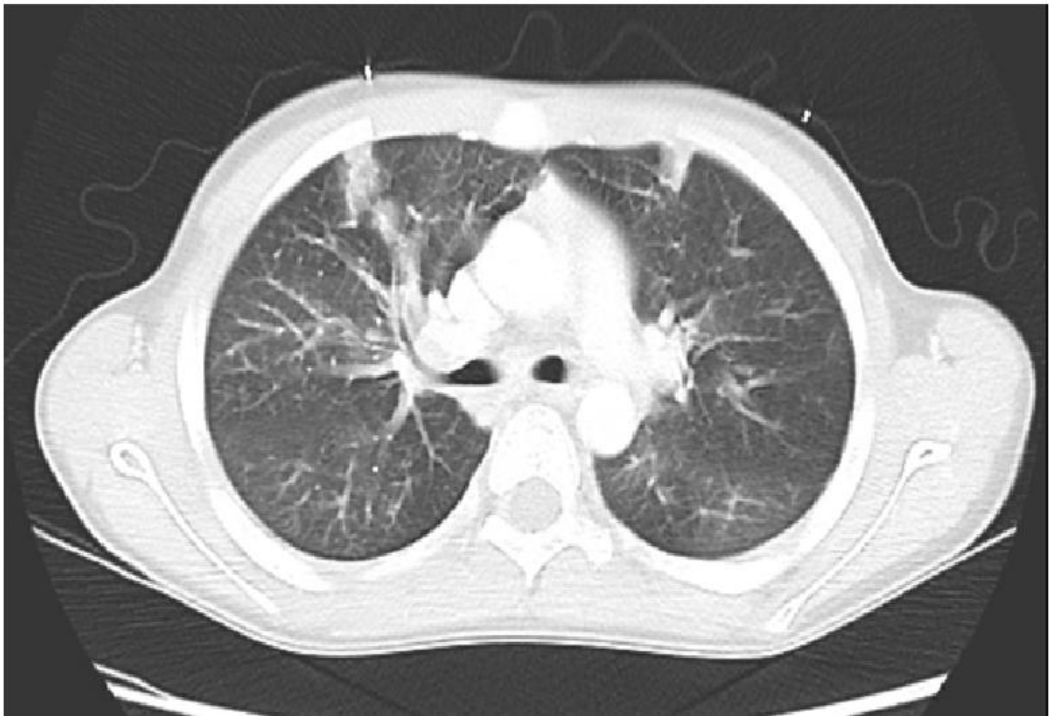
Patient Outcomes

While maintaining on mepolizumab 300 mg every month, he received a 600mg loading dose of dupilumab and was continued on 300mg monthly. He returned for a follow up appointment one month later and reported significantly improved nasal symptoms. Peripheral eosinophils reduced to zero. Spirometry showed improvement of FEV1 from 74% to 102% of predicted, improvement of FEV1/FVC from 72% to 84% of predicted, and improvement of FEF 25-75% from 45% to 98% of predicted (Figure 3). FENO improved from 65 to 18. We have begun to wean his oral steroids with assistance from endocrinology given concern for his compromised HPA axis.

Lessons Learned

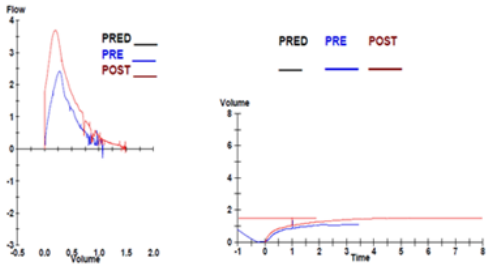
This case highlights a few important learning points and suggests avenues for future study of EGPA treatment. Importantly, we present for the first time, to our knowledge, efficacious use of dual dupilumab and mepolizumab therapy in a patient with EGPA. Exploratory endopoints from SNOT-22 suggested that dupilumab may have an impact in the upper airway as it demonstrated improvement even in co-morbid non-polyposis chronic rhinosinusitis (CRS) patients. Future research is needed to identify the subgroups of patients with EGPA who are likely to benefit from dupilumab and mepolizumab, such as those with severe persistent asthma and CRS with nasal polyposis. Additionally, further investigation is needed to identify if a loading dose of dupilumab is needed for patients with EGPA to achieve more rapid clinical remission. As well, dual therapy with mepolizumab and dupilumab may help to prevent the transient peripheral eosinophilia seen in phase III asthma studies with dupilumab. Overall, by targeting eosinophilic inflammation further upstream, through its activity against IL-4Rα subunit, more widespread inactivation of the Th2 pathway may provide an additional benefit in a subset of patients with EGPA who fail mepolizumab alone.





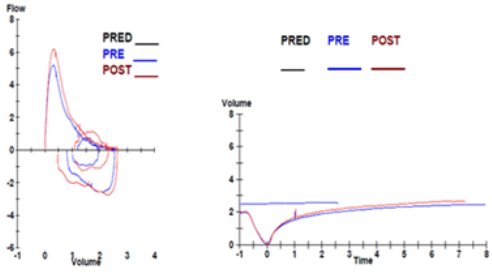
Prior to Mepolizumab

Spirometry	(BTPS)	PRED	PRE-RX BEST	PRE-RX %PRED	POST-RX BEST	POST-RX %PRED	% CHG
FVC	Liters	2.89	1.08	37	1.49	52	38
FEV1	Liters	2.54	0.87	34	1.02	40	18
FEV1/FVC	%	86	81		69		
PEF	L/sec	5.35	2.42	45	3.71	69	53
FEF25-75%	L/sec	2.88	0.90	31	0.60	21	-33
FET100%	Sec		3.42		10.89		219
MVV	L/min	140					
f	BPM						



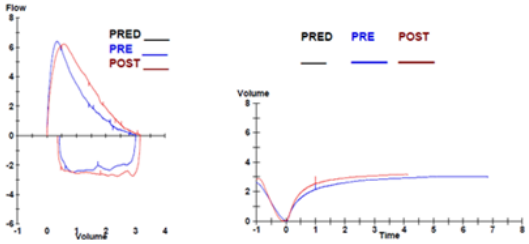
Mepolizumab 300mg subQ monthly + Rituximab 1000mg after two doses

Spirometry	(BTPS)	PRED	PRE-RX BEST	PRE-RX %PRED	POST-RX BEST	POST-RX %PRED	% CHG
FVC	Liters	3.28	2.56	78	2.66	81	4
FEV1	Liters	2.86	1.54	54	1.69	59	10
FEV1/FVC	%	85	60		63		
PEF	L/sec	6.01	5.18	86	6.14	102	19
FEF25-75%	L/sec	3.21	0.65	20	0.80	25	24
FET100%	Sec		11.58		7.18		-38
MVV	L/min	150					
f	BPM						



Mepolizumab 300mg subQ monthly

Spirometry	(BTPS)	PRED	PRE-RX BEST	PRE-RX %PRED	POST-RX BEST	POST-RX %PRED	% CHG
FVC	Liters	3.35	3.02	90	3.17	95	5
FEV1	Liters	2.94	2.18	74	2.55	87	17
FEV1/FVC	%	85	72		80		
PEF	L/sec	6.25	6.41	103	6.22	100	-3
FEF25-75%	L/sec	3.35	1.51	45	2.44	73	61
FET100%	Sec		6.84		4.14		-40
MVV	L/min	149					
f	BPM						



Mepolizumab 300mg subQ monthly + Dupilumab loading dose of 600mg followed by 300mg monthly

Spirometry	(BTPS)	PRED	PRE-RX BEST	PRE-RX %PRED
FVC	Liters	3.41	3.65	107
FEV1	Liters	2.99	3.05	102
FEV1/FVC	%	85	84	
PEF	L/sec	6.32	7.69	122
FEF25-75%	L/sec	3.38	3.30	98
FET100%	Sec		4.91	
MVV	L/min	151		
f	BPM