

Transient Eosinophilic Granulomatosis with Polyangiitis-Like Vasculitis During Omalizumab Therapy: A Case Report

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Abstract: A 67-year-old Caucasian female presented in August 2019 to our rheumatology service, with 3 days history of severe neck pain and right-sided headache with aches in both shoulders and arms and mild stiffness. Other symptoms included mild jaw claudication. She had recently returned from Majorca after an uneventful two-week trip. She had a background of severe allergic asthma and allergic rhinitis, well controlled with omalizumab which was started in 2016, based on persistently high IgE. Her sister suffers from a type of vasculitis and is currently on steroids. The patient is an ex-smoker and drinks two bottles of wine a week. She had high inflammatory markers with raised eosinophilic count and was admitted for further work up to rule out infection and to commence steroid after for a likely diagnosis of eosinophilic granulomatosis with polyangiitis. Shortly after admission to the acute assessment unit, she became confused and febrile. An extensive work up ruled out infection, and she was started on steroids and treated for acute hyponatremia. Omalizumab was stopped. She improved and was discharged on a tapering dose of steroids and was weaned off completely within 4 months. Her inflammatory markers returned to normal as well as her eosinophilic count, with complete resolution of her presenting symptoms.

Keywords: EGPA, ANCA, vasculitis, Churg-Strauss syndrome, eosinophilia, anti-IgE antibodies

Introduction

Omalizumab is a recombinant humanized antibody of IgG1k subclass targeted against IgE for the treatment of moderate to severe asthma. It is unclear whether omalizumab can cause eosinophilic granulomatosis with polyangiitis (EGPA), however different reports described the occurrence of EGPA while on omalizumab in patients with asthma or vasculitic urticaria. Interestingly, omalizumab is used to treat asthma in EGPA with success. We report a case of a lady, who was on omalizumab for more than 3 years presenting with EGPA like vasculitis which resolved completely after treatment with steroids and discontinuation of omalizumab.

Case Presentation

We present a case of a 67-year-old, right-handed, retired administrator female, referred urgently by her GP to the rheumatology service, with 3-days history of severe neck pain radiating to both shoulders and shoulder blades with aches in both

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arms. She also had a severe persistent headache in the right temporal and orbital areas. Both her headache and neck pain were severe and only marginally helped with analgesia including paracetamol, ibuprofen and codeine. She also had jaw pain on chewing as well as exquisite pain over her temple and occipital region. She had some neck stiffness but no restriction to movement of the neck or shoulders. She had no muscle stiffness or symptoms around her pelvic girdle or lower limbs. There was some blurring of vision but no visual loss or diplopia and there was no limb claudication. She also complained of episodic sore throat with odynophagia. She denied fever, sweats or weight loss; however, her appetite was reduced. There were no respiratory, gastrointestinal, urinary or neurological symptoms. There were no other extra-articular features and no history of altered sensorium. She had been on a holiday to Majorca 2 weeks prior to the presentation and had a background of severe allergic asthma and allergic rhinitis diagnosed in 1996 with multiple environmental allergies. Because of persistently raised IgE and recurrent asthma exacerbation, she was commenced on omalizumab injections in 2016. Azithromycin 250 mg three times a week was also added over the months October to April for better control. Short courses of steroids for asthma exacerbations were given once or twice a year during omalizumab therapy. She also had previous septoplasty and chronic plaque psoriasis of the extensor surfaces of the upper limb since her teenage years, tolerated and treated with calcipotriol (as monohydrate) and betamethasone (as dipropionate) ointment with the last flare up in 2009 treated with narrow-band phototherapy (UVB) and emollient creams.

Her regular medication included omalizumab 375 mg fortnightly subcutaneous injections, Symbicort 200/6 Turbo haler (120-dose) one puff twice daily and Dymista 137 µg/dose/50 µg/dose nasal spray one puff twice daily.

Family history revealed a sister with a type of vasculitis and currently on steroids. Her father suffered from osteoarthritis. She is a widow and has three children who are fit and well. She gave up smoking 40 years ago and drinks two bottles of wine a week and lives independently on her own.

On examination, she looked well, and general peripheral examination was unremarkable. Peripheral pulses were well palpable. There was no lymphadenopathy or bruit. Her blood pressure was high at 198/106 in the right arm and 198/107 in the left arm. She weighed 54 Kg. She did not have any temporal artery tenderness and

both temporal arteries were well palpable, however she had some tenderness over frontal and ethmoidal sinuses. There were no peripheral stigmata of vasculitis or connective tissue diseases. The rest of the clinical examination was unremarkable including the musculoskeletal system.

A temporal artery ultrasound scan did not reveal any ultrasound evidence of temporal arteritis. Initial investigations are summarized (Table 1).

She was admitted to the acute assessment unit for further investigations and to rule out infection before commencing her on steroids for a likely diagnosis of EGPA.

Two days later, she developed a fever and became confused. She was noted to have an ejection systolic murmur on cardiac examination. Repeat blood tests showed profound hyponatremia (Table 2). A CT scan of the head and neck followed by a brain MRI showed enhancing soft tissue mass at the right submandibular area of indeterminate nature, but was otherwise normal. Arterial spine labelling MRI, MR

Table 1 Initial Investigation

Laboratory Test	Value	Reference Range
Hematology		
White blood count	19.8 ×10 ⁹ /l	4–11
Neutrophil	8.8 ×10 ⁹ /l	2–7.5
Eosinophil	8.7 ×10 ⁹ /l	0.1–0.4
Hemoglobin	125 g/L	115–160
Mean corpuscular volume	95.4 fl	77.0–98
Platelets	587 ×10 ⁹ /l	150–400
Coagulation profile	Normal	
Biochemistry		
Erythrocyte sedimentation rate	84 mm/hr	5–15
C reactive protein	135 mg/L	<5
Bone, liver and renal profile	Normal	–
Creatinine kinase	70 u/l	25–200
Thyroid stimulating hormone	0.91 mU/L	0.27–4.2
Immunology		
Proteinase 3 antibody	0.3 IU/mL	<2
Myeloperoxidase antibody	34.0 IU/mL	<3.5
Extractable nuclear antigen	Negative	–
Complement 3	1.79 g/L	0.75–1.65
Complement 4	0.34 g/L	0.14–0.54
Immunoglobulin G	12.27 g/L	6.0–16.0
Immunoglobulin A	3.73 g/L	0.9–4.5
Immunoglobulin M	1.43 g/L	0.5–2.0
Immunoglobulin E	605 KU/L	<100
Rheumatoid factor	<10.3 IU/mL	<20
Thyroid peroxidase antibodies	Negative	–
Antinuclear antibodies screen	Negative	–

Table 2 Further Investigations

Laboratory Test	Value	Reference Range
Chemistry		
Sodium	122 mmol/L	133–146
Potassium	5 mmol/L	3.5–5.3
Chloride	88 mmol/L	95–108
Bicarbonate	25 mmol/L	22–29
Urea	4.9 mmol/L	2.5–7.8
Creatinine	36 µmol/L	50–120
eGFR	>90 mL/min	
CRP	106 mg/L	<5
Urine		
Urine sodium	21 nmol/L	–
Urine osmolality	613 mOsmol/kg	50–1200
Urine creatinine	3571 µmol/L	–
Urine protein	0.16 g/L	–
Protein creatinine ratio	44.8 mg/mmol	<20
Urinary cortisol creatinine ratio	604 nmol/nmol/L	5–55
Urine cortisol	6763 nmol/L	–
Urine creatinine	11,189 µmol/L	–
Urine culture	Positive <i>E. coli</i>	
Microbiology		
<i>Borrelia burgdorferi</i> IgG/IgM	Not detected	
HIV 1 and 2 antigen/antibodies	Not detected	
Treponemal antibodies	Not detected	
Others		
Serum electrophoresis: pattern associated with inflammation/infection, Gamma region proteins: normal pattern		

Note: The urine sample was taken after commencing the patient on steroids.

Venography of the cerebral veins and MR angiograph of the circle of Willis showed no acute large hemispheric subdural collection, The FLAIR suggests multiple white matter, basal ganglia, and pons as well as general subcortical changes due to underlying small vessel cerebrovascular disease. No mass effect or midline shift was seen. The paranasal sinuses demonstrate right circular mucosal thickness.

An EEG was requested based on a neurologist's advice to rule out encephalitis. It showed bi-frontal abnormalities with emphasis on the left and possible minor temporal involvement. There was no evidence to point strongly to diffuse encephalitis, however focal encephalitis was possible but the distribution of abnormalities was not typical of herpes simplex and there were no periodic complexes to

point to this condition. She was started on acyclovir which was discontinued after 3 days as lumbar puncture was normal with no growth after 48 hrs and cerebrospinal fluid (CSF) polymerase chain reaction (PCR) for Herpes simplex type 1 and 2, varicella zoster, parvovirus and enterovirus was negative.

To investigate the murmur, an Echocardiogram showed mild Aortic Regurgitation (AR), small pericardial effusion, no haemodynamic compromise, normal size and function of both ventricles. A neck ultrasound showed dilated ducts in the submandibular salivary gland (SMG) and both parotid glands, and multinodular thyroid. As EGPA has pulmonary involvement a Chest x-ray was requested followed by high-resolution computed tomography (HRCT) scan which showed central bronchial dilatation, abnormal inflammatory/atelectasis in the left apex, no focal mass lesion in this area.

Treatment and Referrals

The below table lists the treatments recommended by each department on referral (Table 3).

Outcome and Follow-Up

During the 8-months follow-up period, she continued to improve gradually and was weaned off steroids which were given for a total of 4 months after her admission. However, she was concomitantly experiencing increasing

Table 3 Referrals and Treatments

Endocrine referral for hyponatremia: • Precipitant of decreased sodium is not clear. Impression: Acute SIAD likely secondary to vasculitis.	Treatment: • 100mg hydrocortisone IV. • 750 mL fluid restriction. • Two doses of Tolvaptan 7.5 mg OD. • Short synacthen test (SSD) in due course after steroids for vasculitis. Outcome: Sodium went up to 134, confusion resolved
Respiratory referral: Impression: Omalizumab induced vasculitis.	Treatment: • Stop omalizumab until further notice. Repeat HRCT after 3 months.
Rheumatology referral: Impression: de novo vasculitis/EGPA.	Treatment: • Methylprednisolone IV 500 mg for 3 days. Discharged on 25 mg of prednisolone reducing dose by 5mg every 2 weeks.

cough and mucous production but coping relatively well. Repeat blood tests, including inflammatory markers as well as eosinophilic count and Myeloperoxidase antibodies (MPO) were taken and were all back to normal range remaining so when repeated 2 months after steroid discontinuation. Her sodium levels remained within normal range. She was seen in the respiratory outpatient clinic and was started on prophylactic azithromycin during winter-time along with her usual inhaler and nasal spray. Moreover, she was advised not to restart omalizumab at this time.

Discussion

EGPA is a systemic necrotizing granulomatous inflammation often involving the respiratory tract, and necrotizing vasculitis predominantly affecting small to medium vessels and associated with asthma and eosinophilia.¹

There are no clinical diagnostic criteria for EGPA, however, for research purposes, the American College of Rheumatology 1990 criteria suggests the presence of EGPA if four or more of six clinical criteria in the setting of vasculitis were met: Asthma, Peak peripheral eosinophilia of >10% of the total WBC count, Peripheral neuropathy attributable to a systemic vasculitis, transient pulmonary infiltrates on chest radiographic imaging, paranasal sinus abnormality, blood vessel biopsy demonstrating extravascular eosinophils.² Our case does not fully fulfil the criteria for EGPA; however, the atypical presentation of PMR like symptoms, raised inflammatory markers, high MPO antibodies titre, eosinophilia, pulmonary infiltrates and the resolution of symptoms and abnormal biochemical markers with steroids and omalizumab discontinuation, point to the diagnosis. Vasculitis induced syndrome of inappropriate antidiuresis (SIAD) is another aspect of this atypical presentation. Histological diagnosis in this case was not applicable and the rapid response to steroids did not prompt more invasive tests.

Differential diagnosis includes infections such as toxocariasis, strongyloides stercoralis, HIV and aspergillus species, drug-induced eosinophilia, hypereosinophilic syndromes (HES), and paraneoplastic eosinophilia. In our case, serology for Lyme disease, HIV, syphilis, and spinal fluid PCR were tested initially, but because the patient improved shortly after commencing steroids, there was no need to test for parasitic infections despite her recent travel history. Hyper eosinophilic syndrome is a disease of exclusion characterized by persistently raised eosinophilic count for at least 6 months with multisystem involvement,

in our case, the eosinophilic count return to normal in less than 4 months.

Omalizumab has been implicated as a trigger for EGPA mainly during steroids withdrawal for asthmatic patients.^{3–9} However, as an exceptional option for patients with severe asthma and urticarial vasculitis, it can also be used in patients with EGPA in this context.^{10–12} Rechallenging with omalizumab can still be an option for patients with severe allergic asthma and raised IgE who do not respond to other treatment modalities.

Patient Informed Consent

Written informed consent was obtained from the patient described in this report to have the case details published. Institutional approval was not required to publish the case details.

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Disclosure

The authors report no conflicts of interest in this work.

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