

Development of eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome) and brain tumor in a patient after more than 7 years of omalizumab use: A case report

International Journal of
Immunopathology and Pharmacology
2015, Vol. 28(1) 134–137
© The Author(s) 2015
Reprints and permissions:
sagepub.co.uk/journalsPermissions.nav
DOI: 10.1177/0394632015572567
iji.sagepub.com


S Borekci,¹ O Aydin,² G Hatemi³ and B Gemicioglu¹

Abstract

Omalizumab is a monoclonal anti-immunoglobulin E antibody used for the treatment of severe perennial allergic asthma. Previous reports have suggested that omalizumab treatment can be associated with the development of eosinophilic granulomatosis with polyangiitis (EGPA) (formerly known as Churg-Strauss syndrome) and an increased risk of malignancy. Long-term risks of omalizumab treatment are not very well defined. Here, we report the case of a 75-year-old woman with concurrent occurrence of EGPA and brain tumor after more than 7 years of omalizumab treatment. The possibility of EGPA should be borne in mind during long-term treatment with omalizumab. Despite the absence of definitive data, an association may also exist between the development of malignancy and omalizumab use.

Keywords

anti-IgE, asthma, Churg-Strauss syndrome, eosinophilic granulomatosis with polyangiitis, malignancy, omalizumab

Date received: 11 September 2014; accepted: 19 December 2014

Omalizumab (Xolair; Novartis, Horsham, UK) is a monoclonal anti-immunoglobulin E (IgE) antibody¹ which has been recommended since 2006 for the management of patients with severe asthma who have high serum IgE levels as a part of the global strategy for asthma management and prevention.² Omaluzimab is indispensable for many patients with severe asthma since it allows the control of asthma symptoms and discontinuation of inhaled and/or systemic steroids, which are associated with several side effects. Due to a relatively shorter clinical experience with omalizumab, long-term adverse effects are not very well known, despite reports suggesting an association between the development of eosinophilic granulomatosis with polyangiitis (EGPA) and a trend for increased risk of malignancies. EGPA is characterized by a systemic necrotizing eosinophilic vasculitis affecting small and medium-sized vessels. The diagnosis of early EGPA is challenging as it may cause a number of non-specific initial signs and

symptoms.³ Asthma is almost always a part of the clinical picture. According to American College of Rheumatology Criteria, at least four of the six following parameters are required for a diagnosis of EGPA: (1) asthma; (2) eosinophilia >10%; (3) neuropathy; (4) non-fixed pulmonary infiltrates; (5) paranasal sinus abnormality; and (6) the presence of extravascular eosinophils in a biopsy specimen.⁴ Certain treatment modalities for asthma including omalizumab have been proposed to trigger the onset

¹Pulmonology Department, Istanbul University, Cerrahpasa Faculty of Medicine, Istanbul, Turkey

²Pathology Department, Istanbul University, Cerrahpasa Faculty of Medicine, Istanbul, Turkey

³Rheumatology Department, Istanbul University Cerrahpasa Faculty of Medicine, Istanbul, Turkey

Corresponding author:

Şermin Börekçi, Pulmonology Department, Cerrahpasa Faculty of Medicine, Istanbul 34303, Turkey.
Email: serminborekci@yahoo.com.tr

of EGPA symptoms.⁵⁻⁷ One of the two principal hypotheses put forward to explain this association involves a direct effect of omalizumab in triggering EGPA, and the second hypothesis points to the unveiling of EGPA signs and symptoms after the removal of suppression by inhaled or systemic corticosteroids upon switching to omalizumab.⁸ Also, a possible link between omalizumab and malignancies has been reported. In a study by Busse et al., the incidence of malignancies in patients receiving omalizumab and in controls were 4.5% and 4.1%, respectively.⁹ The majority of these malignancies were observed during the first year of omalizumab use and they included malignancies such as breast cancer, non-melanoma skin cancer, prostate cancer, malignant melanoma, parotid neoplasms, in addition to others. This issue is also underscored in the website of the manufacturer of omalizumab (Xolair; Novartis, Horsham, UK).¹⁰

We report here the unusual case of a late and simultaneous occurrence of EGPA and brain tumor after nearly 7 years of omalizumab use in a 75-year-old female patient.

Written informed consent was obtained from the daughter of the patient to use the data of the patient's file.

Case description

A 75-year-old woman with a diagnosis of allergic asthma had been receiving omalizumab (300 mg/month) since September 2006. She was found to have sensitization to alternaria and dermatophagoides pteronyssinus allergens with a specific IgE level of 98 IU/mL. Before starting anti-IgE treatment, she was receiving high dose inhaled corticosteroids (fluticasone 1000 µg/d), salmeterol 100 µg/d, and montelukast sodium 10 mg/d, with frequent need for systemic corticosteroids. Despite regular treatment with these drugs, she experienced asthma attacks every 2–3 months. Within 4 months of the initiation of omalizumab, optimum control of asthma was accomplished with elimination of the need for systemic corticosteroids, reduction of daily fluticasone dose to 500 µg/d, and discontinuation of montelukast. Her chest X-ray was normal. After 81 months of omalizumab use, she presented with shortness of breath and symmetrical purpuric rashes in both legs. Laboratory tests showed an elevated acute phase response, total IgE level of 32.9 IU/mL, and

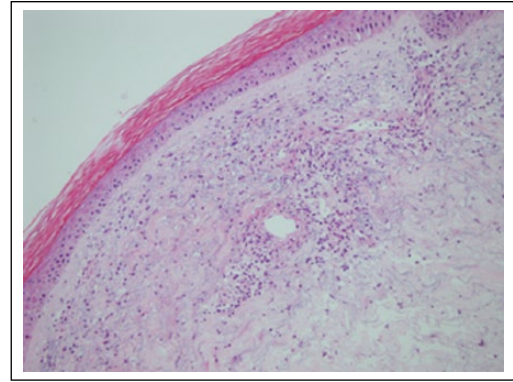


Figure 1. Skin biopsy showing leukocytoclastic vasculitis (hematoxylin-eosin staining, X100).

borderline positive ANA. Anti-dsDNA, cANCA, pANCA, RF, and anti-CCP were negative. The histological examination of skin biopsy revealed infiltration of the vessel wall with polymorphonuclear leukocytes in all layers of dermis together with fibrinoid necrosis, compatible with leukocytoclastic vasculitis (Figure 1). Thorax CT scan showed bilateral interlobular septal thickening, ground glass opacities, and subpleural microcysts. Bronchoscopy showed normal findings, but the patient did not consent for a biopsy. Infection was ruled out with negative procalcitonin level and bronchial lavage and blood cultures. Although this patient did not fulfill ACR criteria, the typical lung parenchymal findings together with leukocytoclastic vasculitis in this patient with asthma supported the diagnosis of EGPA. Blood eosinophil count was within normal limits (150/µL) at that time, but this may have been caused by the omalizumab treatment.

Omalizumab was discontinued due to the lack of safety information on its use in patients with EGPA. Deltacortil 1 mg/kg/d was used for 3 weeks, after which all skin lesions disappeared and lung lesions regressed (Figure 2A and B, before and after Deltacortil treatment). However, her asthma symptoms deteriorated despite treatment with fluticasone 1000 µg/d and salmeterol 100 µg/d, and she had two severe asthma attacks in the following month. Omalizumab was re-initiated together with corticosteroids, with careful follow-up. Subsequently, asthma control was achieved and she had no signs or symptoms of vasculitis flare. However, 6 months later (after a total duration of 87 months of omalizumab use) she presented with severe headache and syncope.

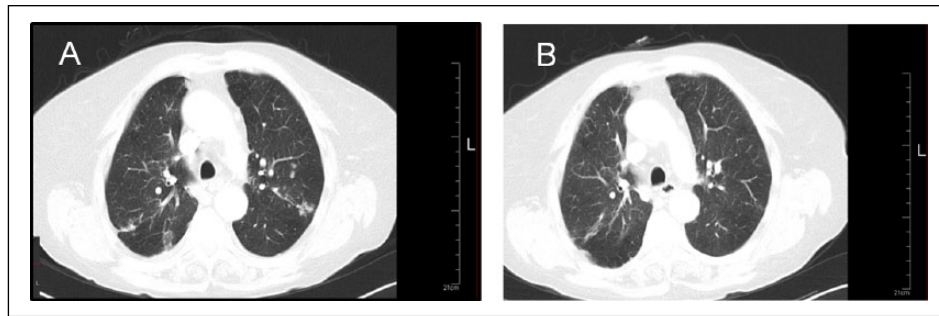


Figure 2. (A) Before Deltacortil treatment, thorax CT showed, bilateral interlobular septal thickening, ground glass opacities, and subpleural microcysts. (B) After treatment, lesions were regressed.

Cranial MRI showed multiple cranial lesions highly suggestive of malignancy (Figure 3).

The abdomen and chest CT scans and mammography of patient were normal. Moreover, the cranial MRI that had been performed 1 year previously for headache showed only non-specific gliotic changes. Although the patient did not consent for biopsy, she was diagnosed as having an advanced stage brain tumor (either primary or metastatic) clinically and radiologically, and she died in May 2014.

Discussion

The adverse effects of long-term omalizumab use are not well-defined. Our patient developed EGPA after 81 months of treatment with omalizumab, and a brain tumor after 87 months. As compared to previous reports on the possible association between omalizumab use and these disorders, our case represents the longest time interval documented between the commencement of omalizumab treatment and emergence of these conditions.

There are conflicting reports regarding the association of omalizumab and EGPA. One of the first reports suggesting this association was in 2006, by Winchester et al.⁵ On the other hand, 1 year after that report, Giavina-Bianchi et al. reported a patient with EGPA whose clinical course did not worsen with omalizumab treatment.¹¹ Two principal hypotheses have been put forward to explain a possible link between anti-IgE treatment and development of EGPA. The first is a direct effect of omalizumab in triggering EGPA, and the second is the appearance of EGPA signs and symptoms which were suppressed by inhaled or systemic corticosteroids used for asthma, after corticosteroids are stopped and switched to omalizumab.^{8,9} However,

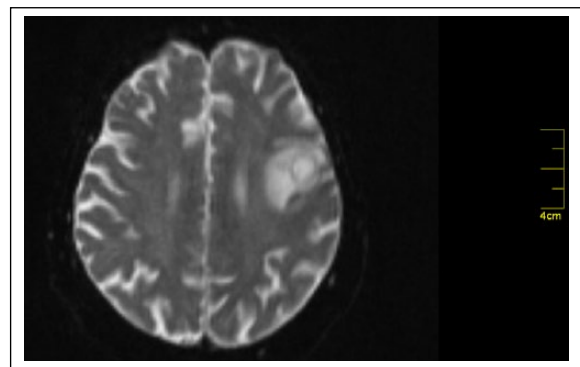


Figure 3. Cranial MR showed multiple cranial lesions highly suggestive of malignancy.

Spina et al. reported a patient developing EGPA after 16 months of omalizumab treatment, without a reduction of the oral corticosteroid dose.¹² Moreover, another patient was reported who developed EGPA during omalizumab treatment, with no use of oral corticosteroids before anti-IgE treatment.⁶ These cases suggest the presence of a causal relationship between omalizumab and EGPA. Furthermore, several recent studies supportive of such a relationship have been published.^{5,7} In contrast with most of these previous reports on the development of EGPA within the first year of omalizumab treatment, our patient was found to have EGPA after 81 months of treatment with omalizumab. This may be an indication of the long-term effects of omalizumab and relates to the following question posed by Soler et al.: ‘How long should omalizumab treatment continue, for life or not?’¹³ In addition, there are few data to guide the decision to continue/discontinue omalizumab treatment in patients developing EGPA, despite few reports showing no effect of omalizumab on the disease activity in EGPA.¹¹ Obviously, in most of the cases

including ours, the cause of EGPA is not very well understood and it might either be associated with the omalizumab treatment itself or with the reduction of inhaled steroids. However, clearly more data are needed to draw firmer conclusions on such an association.

Another area of research is represented by the potential link between omalizumab treatment and the occurrence of malignant conditions. In a previous report, the incidence of malignant disorders was 0.5% among subjects receiving omalizumab, as compared to 0.2% in controls. The corresponding figures in another study by Busse et al. were 4.1% and 4.5%, with no significant differences between omalizumab and control subjects.⁹ In recent clinical studies, the results were suggestive of an absence of an association between omalizumab and malignancy.¹⁴ The observation that most cancers occurred within a year from the beginning of omalizumab therapy in a recent review suggests that these malignancies were likely to be pre-existing, since drug-induced malignancies usually develop after longer exposures.¹⁵ In contrast, development of a brain tumor after 87 months of treatment with omalizumab in our patient may be considered to be indicative of a potential long-term effect of anti-IgE treatment. Certainly, the exact nature of the association between omalizumab use and the brain tumor in our patient cannot be definitely ascertained and this question awaits further research.

The case presented herein provides further support for the previous observations suggesting a link between the development of EGPA and long-term use of omalizumab, and furthermore indicates the need for further studies examining a potential association between omalizumab and development of malignancies.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

References

- Schulman ES (2001) Development of a monoclonal anti-immunoglobulin E antibody (omalizumab) for the treatment of allergic respiratory disorders. *American Journal of Respiratory and Critical Care Medicine* 164: 6–11.
- Global Initiative for Asthma (2006) *Global Strategy for Asthma Management and Prevention*. Vancouver, WA: Global Initiative for Asthma (GINA). Available at: www.ginasthma.org.
- Pagnoux C and Guillevin L (2010) Churg-Strauss syndrome: evidence for disease subtypes? *Current Opinion in Rheumatology* 22: 21–28.
- Masi AT, Hunder GG, Lie JT, et al. (1990) The American College of Rheumatology 1990 criteria for the classification of Churg-Strauss syndrome (allergic granulomatosis and angiitis). *Arthritis & Rheumatology* 33: 1094–1100.
- Winchester DE, Jacob A and Murphy T (2006) Omalizumab for asthma. *New England Journal of Medicine* 355: 1281–1282.
- Puechal X, Rivereau P and Vinchon F (2008) Churg-Strauss syndrome associated with omalizumab. *European Journal of Internal Medicine* 19: 364–366.
- Cisneros C, Segrelles G, Herráez L et al. (2013) Churg-Strauss syndrome in a patient treated with omalizumab. *Journal of Investigational Allergology and Clinical Immunology* 23: 515–516.
- Churg A, Brallas M, Cronin SR et al. (1995) Formes frustes of Churg-Strauss syndrome. *Chest* 108: 320–323.
- Busse W, Buhl R, Fernandez Vidaurre C, et al. (2012) Omalizumab and the risk of malignancy: results from a pooled analysis. *Journal of Allergy and Clinical Immunology* 129: 9838–9839.
- Novartis US and Genentech. Omalizumab (Xolair) label. Available at: www.gene.com.
- Giavina-Bianchi P, Giavina-Bianchi M, Agondi R et al. (2007) Three months' administration of anti-IgE to a patient with Churg-Strauss syndrome. *Journal of Allergy and Clinical Immunology* 119: 1279–1280.
- Spina MF and Miadonna A (2009) Role of omalizumab and steroids in Churg-Strauss syndrome. *Journal of Allergy and Clinical Immunology* 124: 600–601.
- Solèr M (2004) Omalizumab for severe allergic asthma: 7 years and open questions. *Respiration* 88: 158–161.
- Long A, Rahmaoui A, Rothman KJ, et al. (2014) Incidence of malignancy in patients with moderate-to-severe asthma treated with or without omalizumab. *Journal of Allergy and Clinical Immunology* 134: 560–567.
- Pelaia G, Gallelli L, Renda T, et al. (2011) Update on optimal use of omalizumab in management of asthma. *Journal of Asthma and Allergy* 4: 49–59.

Copyright of International Journal of Immunopathology & Pharmacology is the property of BIOLIFE, s.a.s. and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.