CASE REPORT

Development of Churg-Strauss syndrome with severe multiple mononeuropathy after leukotriene receptor antagonist treatment in one of the monozygotic twins with asthma

Bożena Targońska-Stępniak[1], Maria Majdan[1], Grzegorz Haberek[2], Ewa Papuć[3], Kinga Wnukowska[2]

1 Department of Rheumatology and Connective Tissue Diseases, Medical University of Lublin, Lublin, Poland
2 Department of Neurology, Regional Railway Hospital, Lublin, Poland
3 Department of Neurology, Medical University of Lublin, Lublin, Poland

KEY WORDS

Churg-Strauss syndrome, leukotriene receptor antagonists, montelukast, neuropathy, vasculitis

ABSTRACT

Several cases of Churg-Strauss syndrome (CSS) have been reported in asthmatic patients treated with leukotriene receptor antagonists (LTRAs). It is not clear whether LTRA is a causative factor in the development of vasculitis. We present the case of a 26-year-old patient, who developed severe central and peripheral neuropathy after a short-term treatment with LTRA, followed by gastrointestinal perforation and bleeding. The patient was successfully treated with high-dose glucocorticoids, immunoglobulins, and cyclophosphamide. His monozygotic twin brother treated for asthma does not meet classification criteria for Churg-Strauss syndrome at the moment, but his condition is being monitored. Both asthma and rheumatology specialists should consider the possibility of CSS development in patients treated with LTRAs.

Correspondence to:
Bożena Targońska-Stępniak, MD, PhD, Katedra i Klinika Reumatologii i Układowych Chorób Tkanki Łącznej, Uniwersytet Medyczny w Lublinie, ul. Jaczewskiego 8, 20-950 Lublin, Poland, phone: +48-81-724-47-90, fax: +48-81-724-45-15, e-mail: bozena.stepniak@am.lublin.pl
Received: September 11, 2009.
Revision accepted: October 26, 2009.
Conflict of interest: none declared.
Pol Arch Med Wewn. 2009; 119 (11): 761-764

INTRODUCTION Churg-Strauss syndrome (CSS) is a rare form of systemic vasculitis, characterized by eosinophilia, asthma, and necrotizing small-vessel vasculitis.[1,2] The American College of Rheumatology classification criteria include asthma, eosinophilia >10%, neuropathy, pulmonary infiltrates, paranasal sinus abnormalities, and extravascular eosinophilia.[1] Over the last decade, several cases of CSS in asthmatic patients receiving leukotriene receptor antagonists (LTRAs) have been reported.[3-6]

We describe a patient with asthma, who developed severe, life-threatening manifestations of CSS after a short-term treatment with one of LTRAs, montelukast. His monozygotic twin brother treated for asthma does not meet classification criteria for CSS.

CASE REPORT A 26-year-old man with a 1-year history of moderate asthma was treated with inhaled β_2-agonists (formoterol 0.024 mg/day, fenoterol 0.1 mg in case of dyspnea), and inhaled steroid (beclomethasone 0.5 mg/day). There were no signs of atopic or other diseases. His brother, a monozygotic twin, had been similarly treated for asthma for the last 3 years. In July 2008, the patient was diagnosed because of increased cough and dyspnea. Chest radiograph showed no abnormalities. The results of laboratory tests were as follows: erythrocyte sedimentation rate (ESR) of 16 mm in the first hour, white blood cell (WBC) count of 13.89 × 109/l with 24.9% eosinophils, proteinuria (163.6 mg/dl), erythrocyturia, and cylindruria (control urinalysis was recommended). Other laboratory findings were within normal ranges. The differential diagnosis of eosinophilia and proteinuria was not performed. Spirometric parameters were as follows: forced vital capacity (FVC) 3.13 l (58%), forced expiratory volume in 1 second (FEV_1) 1.55 l (34%), FEV_1% of vital capacity (FEV_1%VC) 45.06%, peak expiratory flow (PEF) 4.08 l/s (40%). Electrocardiogram

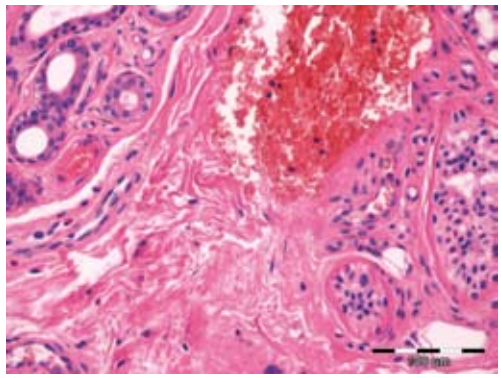


FIGURE A biopsy specimen from a finger of the patient showing vasculitis, eosinophil infiltration, histiocytes, and granuloma formation

showed the right bundle branch block. The patient was treated with theophylline (600 mg/day) and antibiotic (amoxicillin with clavulanic acid) due to pharyngitis; the inhalatory treatment was maintained. In early August 2008, he was started on montelukast 10 mg/day in order to improve asthma control. The treatment was discontinued after 7 days because of neurological disorders. In mid-August 2008, we observed a 1-week deterioration in the patient's condition; after the fourth dose of montelukast, painful paresthesia occurred in the right upper and left lower limbs with progressive muscle weakness and paresis. The patient was admitted to the Department of Neurology. Neurological examination revealed central paresis of the right facial nerve and symptoms of multiple mononeuropathy (paresis of the left radial, left median, and right peroneal nerves). Laboratory results were as follows: ESR 66 mm in the first hour, C-reactive protein 22.2 mg/l, WBC 12.4–23.0 $\times 10^9$/l with 24.6–43.4% eosinophils, proteinuria 500 mg/day. Antinuclear antibodies were negative, while perinuclear antineutrophil cytoplasmic antibodies (p-ANCA) were positive (69.8 U/ml). Computed tomography (CT) of the lungs showed bilateral, peripheral interstitial infiltrates. CT cranial scanning showed thickening of paranasal sinus mucosa. Electromyogram showed advanced asymmetric, axonal, multiple mononeuropathy with demyelinization features. Skin biopsy revealed perivascular eosinophilic infiltrates and eosinophilic granulomas (FIGURE). The treatment with intravenous (IV) glucocorticoid (GC) (methylprednisolone 1500 mg) was started, followed by oral prednisone 80 mg/day and oral cyclophosphamide (CYC) 100 mg/day for 7 days. On admission to the Department of Rheumatology and Connective Tissue Diseases, the patient was hypertensive (180/120 mmHg). He was in a poor general condition, presented with signs and symptoms of malnutrition and flaccid tetraparesis, and was not able to move on his own. Laboratory tests showed the following results: WBC 14.11 $\times 10^9$/l with 1.4% eosinophils, increased activity of muscle enzymes (creatine kinase 396 U/l and lactate dehydrogenase 306 U/l), high ferritin (1370 ng/ml) and low immunoglobulin G levels (479 mg/dl), persistent proteinuria (687 mg/day, with protein to creatinine index [0.97]). The presence of p-ANCA specific for myeloperoxidase (MPO-ANCA) was confirmed. Antinuclear and anticardiolipin antibodies were negative. Rheumatoid factor immunoglobulin M was positive (24.3 IU/ml). Neurological examination revealed peripheral, asymmetric, mainly motor (but also sensory) multiple mononeuritis involving predominantly the left radial and median nerves, right ulnar and radial, both peroneal and right facial nerves, as well as the involvement of the autonomous nervous system (such symptoms as dilated pupils, tachycardia 110/min). Examination of cerebrospinal fluid showed no significant abnormalities. The patient was treated with IV GC (methylprednisolone 4.0 g overall), immunoglobulins (0.6 g/kg for 4 days) and IV CYC (0.6 g on first dose), followed by oral prednisone (60 mg/day). On the sixth day of treatment, he developed severe abdominal pain caused by perforation of the small intestine and gangrenous cholecystitis with diffuse stercoral peritonitis. The patient was operated on and regional resection of the ileum and cholecystectomy was performed. Three weeks later eventration occurred due to the wound dehiscence, and the patient was reoperated. After the first operation, IV GC treatment was continued (hydrocortisone and methylprednisolone). After the second operation, oral prednisone was started (60 mg/day) with dosage tapered over the next 6 weeks to 40 mg/day. CYC treatment was continued, four IV doses were given every 2 weeks (2.2 g overall). Pharmacological treatment was accompanied by progressive rehabilitation and dietary treatment. A gradual improvement of the neurological state was observed; however, symptoms of sensorimotor neuropathy persisted. Laboratory parameters normalized, except for mild proteinuria and erythrocyturia. The patient is currently in a stable condition on 20 mg/day prednisone and monthly IV pulses of CYC. He is intensively rehabilitated and his functional ability is improving. The twin brother was carefully examined. Slight eosinophilia (8.6%) was detected, with negative ANCAs and no signs of internal organ involvement.

DISCUSSION We presented the patient with 1-year moderate asthma, who developed severe clinical manifestations of CSS, after a short-time exposure to LTRA. It is likely that the patient belonged to a subset of asthmatic population with an underlying predisposition to vasculitis. The earliest symptoms diagnosed as asthma exacerbation could be due to the first signs of systemic vasculitis (dyspnea, eosinophilia, proteinuria, erythrocyturia, right bundle branch block). However, temporal relationship between the introduction of LTRA and CSS onset suggested a probable causal relationship. It might be speculated that the clinical course of CSS had been exacerbated by the LTRA, with the occurrence of poor outcome predictors (central nervous system [CNS], gastrointestinal [GI] and cardiac involvement). Our patient developed severe CSS

symptoms, without a history of GC withdrawal, after 7 days of LTRA therapy, which is an unusually long time for drug hypersensitivity to develop. It seems that LTRA treatment unmasked and triggered the full-blown CSS.

The genetic susceptibility to CSS should be considered. The monozygotic twin brother, who also suffers from asthma and eosinophilia, might have an early stage of CSS. Clinical symptoms of CSS occurred only in one twin brother treated with LTRA, which triggered the disease.

LTRAs have been widely used in patients with asthma since the mid-1990s. Several cases of CSS have been reported in asthmatic patients treated with antileukotriene drugs (zafirlukast, montelukast, pranlukast).[3-6] It has been reported that LTRAs have a GC-sparing effect in asthma therapy.[7] It has been suggested that tapering or discontinuation of oral or inhaled GC could unmask or trigger CSS symptoms.[3] CSS might also present with an allergic response to LTRAs therapy, similarly to CSS developing as a result of hypersensitivity reactions to antibiotics (e.g., erythromycin, azithromycin).[3] One might hypothesize that LTRA treatment increases leukotriene (LT) production and aggravates vasculitis symptoms by affecting noninhibited receptors[4] and LTB_4 increase, which acts as a chemoattractant for eosinophils and neutrophils, and could lead to hypereosinophilia and vasculitis.[3]

Familial CSS in two sisters was reported, suggesting that genetic factors might confer susceptibility to the disease.[8]

The stages of classic CSS are as follows: early, prevasculitic phase (e.g., adult-onset asthma); vasculitic phase (one tissue eosinophilia [pulmonary, GI, myocardial]); systemic vasculitis.[1,3] The final diagnosis poses a challenge because individual symptoms can occur independently over a prolonged time.[3] Clinical presentation with acute neuropathy requires differentiation with Guillain-Barré syndrome.[9] Anti-MPO-ANCA appear to determine a subgroup of the patients with higher frequency of CNS and renal damage, alveolar hemorrhage, purpura, and mononeuritis multiplex.[10] Relapses are more frequent in ANCA-positive patients.[2]

There are five factors associated with a poor outcome: cardiac, CNS, severe GI involvement, creatininemia >1.6 mg/dl or proteinuria >1 g/day.[2,3] The estimated 5-year mortality rate was 26% with one factor present, 45% with two or more factors.[3]

CSS patients usually respond rapidly to GC; however, resistance to GC alone is observed in CSS with organ impairment. In patients with poor prognosis factors, immunosuppressive cytotoxic therapy (with CYC) is indicated.[1,2] In case of resistance to GC and CYC, high doses of human immunoglobulin might be effective.[1]

Asthmatic patients treated with LTRAs should be carefully monitored for symptoms of vasculitis. Both asthma and rheumatology specialists should be aware that CSS may develop in predisposed patients.

Acknowledgements We would like to thank Agnieszka Pedrycz-Wieczorska, MD, from the Department of Histology and Embryology, Medical University of Lublin, for her support during histological examination.

REFERENCES

1 North I, Strek ME, Leff AR. Churg-Strauss syndrome. Lancet. 2003; 361: 587-594.

2 Cohen P, Pagnoux C, Mahr A, et al. Churg-Strauss syndrome with poor-prognosis factors: a prospective multicenter trial comparing glucocorticoids and six or twelve cyclophosphamide pulses in forty-eight patients. Arthritis Rheum. 2007; 57: 686-693.

3 McDanel DL, Muller BA. The linkage between Churg-Strauss syndrome and leukotriene receptor antagonists: fact or fiction? Ther Clin Risk Manag. 2005; 1: 125-140.

4 Keogh KA, Specks U. Churg-Strauss syndrome: clinical presentation, antineutrophil cytoplasmic antibodies, and leukotriene receptor antagonists. Am J Med. 2003; 115: 284-290.

5 Hauser T, Mahr A, Metzler C, et al. The leukotriene receptor antagonist montelukast and the risk of Churg-Strauss syndrome: a case-crossover study. Thorax. 2008; 63: 677-682.

6 Mastalerz L, Świerczyńska M, Niżankowska-Mogilnicka E. [Anti-leukotriene drugs and Churg Strauss syndrome]. Pol Arch Med Wewn. 2002; 107: 173-176. Polish.

7 Joos GF. Which patients with asthma could benefit from using anti-leukotriene drugs: an evidence based review. Pol Arch Med Wewn. 2008; 118: 689-690.

8 Tsurikisawa N, Morita S, Tsuburi T, et al. Familial Churg-Strauss syndrome in two sisters. Chest 2007; 131: 592-594.

9 Riva N, Cerri F, Butera C, et al. Churg-Staruss syndrome presenting as acute neuropathy resembling Guillain Barré sydrome: case report. J Neurol. 2008; 255: 1843-1844.

10 Sinico RA, Di Toma L, Maggiore U, et al. Renal involvement in Churg-Strauss syndrome. Am J Kidney Dis. 2006; 47: 770-779.

OPIS PRZYPADKU

Zespół Churga i Strauss z ciężką mnogą mononeuropatią po leczeniu antagonistą receptora leukotrienów u jednego z bliźniąt monozygotycznych z astmą

Bożena Targońska-Stępniak[1], Maria Majdan[1], Grzegorz Haberek[2], Ewa Papuć[3], Kinga Wnukowska[2]

1 Katedra i Klinika Reumatologii i Układowych Chorób Tkanki Łącznej, Uniwersytet Medyczny w Lublinie, Lublin
2 Oddział Neurologii, Okręgowy Szpital Kolejowy, Lublin
3 Klinika Neurologii, Uniwersytet Medyczny w Lublinie, Lublin

SŁOWA KLUCZOWE

antagoniści receptora leukotrienów, montelukast, neuropatia, zapalenie naczyń, zespół Churga i Strauss

STRESZCZENIE

W literaturze pojawiły się opisy przypadków zespołu Churga i Strauss u chorych na astmę oskrzelową, leczonych antagonistami receptora leukotrienów (*leukotriene receptor antagonist* – LTRA). Nie jest pewne, czy LTRA odgrywają rolę czynnika wywołującego zapalenie naczyń. Przedstawiamy opis 26-letniego chorego, u którego po krótkotrwałym leczeniu LTRA rozwinęła się ciężka postać neuropatii centralnej i obwodowej, w dalszej kolejności doszło do perforacji jelit i krwawienia z przewodu pokarmowego. W leczeniu stosowano duże dawki glikokortykosteroidów, immunoglobuliny i cyklofosfamid, uzyskując dobry efekt terapeutyczny. Monozygotyczny brat bliźniak pacjenta, który leczony jest także z powodu astmy oskrzelowej, nie spełnia obecnie kryteriów klasyfikacyjnych zespołu Churga i Strauss, jednak pozostaje w obserwacji klinicznej. Reumatolodzy i alergolodzy powinni rozważać możliwość rozwoju zespołu Churga i Strauss u pacjentów leczonych LTRA.

Adres do korespondencji:
dr med. Bożena Targońska-Stępniak, Katedra i Klinika Reumatologii i Układowych Chorób Tkanki Łącznej, Uniwersytet Medyczny w Lublinie, ul. Jaczewskiego 8, 20-950 Lublin, tel.: 081-724-47-90, fax: 081-724-45-15, e-mail: bozena.stepniak@am.lublin.pl
Praca wpłynęła: 11.09.2009.
Przyjęta do druku: 26.10.2009.
Nie zgłoszono sprzeczności interesów.
Pol Arch Med Wewn. 2009; 119 (11): 761-764

INTERNA 2010 – IX Krajowa Konferencja Szkoleniowa Towarzystwa Internistów Polskich Postępy w chorobach wewnętrznych

oraz
- warsztaty specjalistyczne
- III Sympozjum „Dylematy etyczne w praktyce lekarskiej"

interna 2010

Organizatorzy
Medycyna Praktyczna
Towarzystwo Internistów Polskich

Przewodniczący Komitetu Organizacyjnego
Prof. dr hab. med. Andrzej Szczeklik

Zgłoszenia
Medycyna Praktyczna – Dział Szkoleń
ul. Krakowska 41, 31-066 Kraków
tel. 012 2934004, e-mail: interna2010@mp.pl

Cennik dla uczestników
Prenumeratorzy MP oraz członkowie TIP:
do 15 lutego 2010 r. – 350 zł
po 15 lutym 2010 r. – 400 zł
Pozostali uczestnicy:
do 15 lutego 2010 – 420 zł
po 15 lutym 2010 – 500 zł
Pakiet specjalny (udział w konferencji
+ roczna prenumerata MP):
do 15 lutego 2010 – 449 zł
po 15 lutym 2010 – 529 zł

Zapraszamy

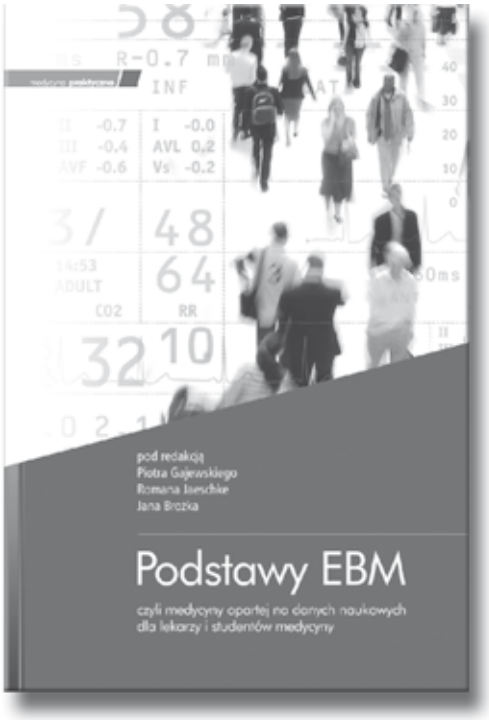
Warszawa, 25–26 marca 2010 r.
Sala Kongresowa Pałacu Kultury i Nauki

medycyna praktyczna

Podstawy EBM

czyli medycyny opartej na danych naukowych
dla lekarzy i studentów medycyny

pod redakcją
Piotra Gajewskiego
Romana Jaeschke
Jana Brożka



W kolejnych rozdziałach książki opisane zostały:

- Historia EBM
- Filozofia EBM
- Pytania kliniczne
- Ocena informacji o metodzie leczniczej, rokowaniu lub szkodliwości
- Ocena informacji o metodzie diagnostycznej
- Przegląd systematyczny i metaanaliza
- Analizy ekonomiczne
- Wytyczne praktyki klinicznej
- Źródła wiarygodnych odpowiedzi na pytania kliniczne

2008 r., format 173x246,
192 strony, oprawa twarda,
cena 40 zł (cena klubowa 36 zł),
nr katalogowy 3615

Zamówienia: tel. 0800 888 000, http://ksiegarnia.mp.pl