Churg-Strauss Syndrome: Singulair or Silicone (or both?)

Paula R. David[1,4], Amir Dagan MD[2], Maartje Colaris MD[4], Mintsje de Boer MD[5], Jan W. Cohen Tervaert MD[5] and Yehuda Shoenfeld MD FRCP MaCR[1,3]

[1]Zabludowicz Center for Autoimmune Diseases and [2]Department of Internal Medicine F, Sheba Medical Center, Tel Hashomer, Israel
[3]Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel
[4]Faculdade de Ciências Médicas, Universidade do Estado do Rio de Janeiro, Rio de Janeiro, Brasil
[5]Faculty of Health, Medicine and Life Sciences, Maastricht University, Maastricht, The Netherlands

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Leukotriene receptor antagonists have been used successfully for asthma treatment. These drugs could induce eosinophilic granulomatosis with polyangiitis (EGPA), previously known as Churg-Strauss syndrome (CSS), in patients who are prone to develop autoimmune diseases [1] One of the most important adjuvants responsible for developing ASIA (autoimmune/inflammatory syndrome induced by adjuvants) is silicone. Patients with silicone-induced ASIA may develop CSS [2-4]. We present two asthmatic female patients diagnosed with CSS who had been exposed to both risk factors: montelukast and silicone. We discuss here how these risk factors could be associated with the development of CSS.

PATIENT DESCRIPTIONS

A 63 year old female patient presented with asthma exacerbation of 2 months duration, bilateral paresthesia in her hands, wrists and right thigh, and recurrent paranasal sinusitis. She had been diagnosed with asthma in 2005 when she was 53 years old, and since then had tried many different treatments. She had been taking systemic corticosteroids and montelukast for the last 3 years and her asthma was stable, until a few months before the current presentation when the exacerbation returned. She described a sensation of fullness in both nostrils and recurrent paranasal sinusitis. A head computed tomography (CT) confirmed pansinusitis. She also had nasal polyposis, for which she had undergone functional endoscopic sinus surgery (FESS) in 2008.

She was referred due to a painful paresthesia in her right hand that appeared a month before her presentation. It eventually subsided but reoccurred one week later, now in her left hand and right leg simultaneously. Electromyography confirmed the hypothesis of mononeuritis multiplex.

In 2007, she underwent a mammoplasty with silicone breast implants. Her last mammography, one year ago, demonstrated that the implant had ruptured and was leaking silicone. No other findings in her or her family's medical history were relevant, other than her positive skin allergy tests to house mites and her mother's polyarthritis.

Routine blood laboratory tests were all within the normal range, except for eosinophils which were increased (6300/µl), C-reactive protein (CRP) that was lightly elevated (19.5 mg/L), and high levels of immunoglobulin (Ig) E (545.7/UL). Her urine showed no abnormalities. Her induced sputum demonstrated 13% eosinophils. She was positive for anti-myeloperoxidase, despite being negative for c-ANCA and p-ANCA (cytoplasmic and perinuclear antineutrophil cytoplasmic antibodies, respectively). Rheumatoid factor (RF), antinuclear antibody (ANA), and proteinase 3 antibodies (anti-PR3) were all normal. There were no alterations in components of the complement system: C3 was 147 mg/dl and C4 was 28 mg/dl. There was no infiltration on chest X-ray, and a biopsy to seek extravascular eosinophil infiltration was not performed. She met four of the six American College of Rheumatology (ACR) criteria for CSS: asthma, history of allergies, extravascular eosinophilia, and paranasal sinus abnormalities, configuring a probable case of CSS, with positive anti-myeloperoxidase.

Our second patient was a 61 year old female who presented with dyspnea, hemoptysis, pulmonary infiltrates and arthralgia. Her IgE level was high (330 U/L) and her eosinophils were 2300/mm^3. She had been diagnosed previously with CSS. We consider this a possible relapse of the disease and restarted steroid treatment.

Her history disclosed implantation of bilateral silicone prostheses in 1980 when she was 26 years old. In 2000 the implant ruptured and was replaced by a water-based prosthesis. In 2003 she underwent another mammoplasty with a new silicone implantation.

Shortly after her first implant, she developed asthma and an allergy test to house dust mites was positive. In 2005, after her second exposure to silicone, she experienced more extensive allergies, with skin tests positive to house dust mites, grasses, dogs and cats, and her asthma became unstable. She was put on montelukast therapy.

She suffered recurrent sinusitis due to extensive nasal polyps. In 1998 a polypectomy was performed. Despite the surgery, she continued to have recurrent sinusitis. In 2000 she underwent a conchotomy and in 2005 an ethmoidectomy.

In 2007, she was diagnosed with asthma, mononeuritis multiplex, arthralgia, hypereosinophilia (10,200/mm^3) and IgE of 2900 U/L. A test for ANCA (anti-neutrophilic cytoplasmic antibodies) was negative; she was found to have autoimmune thyroiditis with positive anti-thyroid peroxidase (anti-TPO). A skin biopsy showed leukocytoplastic vasculitis with predominant eosinophils. She was diagnosed with CSS, meeting all six American College of Rheumatology (ACR) criteria for CSS. There was no cardiac involvement. The montelukast was discontinued and she started taking prednisolone/cyclophosphamide (which after 3 months was switched to azathioprine) and thyrax. Since then, she had a relapsing respiratory tract infection with bronchiectasis and persisting recurrent nasal polyposis, with FESS being performed three times.

COMMENT

Churg-Strauss syndrome is a primary small and medium vessel necrotizing vasculitis that was first described in 1951 by Jacob Churg and Lotte Strauss. It is a member of the group of ANCA-associated vasculitides (AAV), even though ANCA may not necessarily be positive. The etiopathogenesis of CSS is still not clear but is presumed to be induced by a combination of genetic and environmental triggers. During recent years, researchers have sought some triggering factors for CSS. Those most suspected include infections, vaccination, desensitization, drugs (macrolides, carbamazepine, quinine, corticosteroid-sparing agents for asthma, leukotriene modifiers) and adjuvants. We have described two CSS patients with a history of montelukast treatment and silicone breast implants.

Montelukast, or Singulair® (Merck, USA) is a leukotriene receptor antagonist (LTRA). This class of drug has been used for asthma since the mid-1990s. It alleviates asthma by inhibiting the bond between cysteinyl-leukotrienes and their receptors in the airway cells, which prevents its sequelae (airway edema, smooth muscle contraction and pro-inflammatory effects).

A significant number of cases of CSS following LTRA therapy have been reported [1], prompting several theories to explain this association. Some authors believe that LTRA is prescribed for asthmatic patients with the most severe symptoms, which may actually be a prodromal phase of CSS. Others presume that the use of montelukast permits tapering of corticosteroid doses, thereby unmasking a preexisting CSS that had been hidden by the steroid therapy. The third hypothesis holds that montelukast indeed has a direct effect on the development of CSS since it does not inhibit leukotriene B4, which chemo-attract eosinophils and neutrophils to the vessels causing vasculitis.

A systematic study in New Zealand reviewed 140 cases of CSS in patients on montelukast reported by the Food and Drug Administration (FDA) Adverse Event Reporting System (AERS). It concluded that 9% of the cases already had the disease before initiation of the drug; 19% had tapered the corticosteroid dose, possibly unmasking a suppressed preexisting condition; and 8% had three ACR criteria for CSS when they started using LTRA and which could be compatible with a possible prodromal phase of CSS. However, in 64% of the patients the disease could not be attributed to these hypotheses, showing a potential causal association between LTRA therapy and CSS [1].

Silicones are a family of polymers consisting of an inorganic silicone-oxygen backbone with organic side groups attached to the silicone atoms. Polydimethylsiloxane is the silicone used in medication. Having long been considered an inert substance, for many years it was deployed in liquid, solid or particulate form. It has since been proven to be active in our immune system. The case of an implant leaking silicone is clear evidence that silicone is not an inert substance. Some of its low molecular weight compounds, by physical migration or engulfment and transportation in the macrophages, spread through the organism ("bleeding"), causing a histiocytic reaction in distant points of the implant. This generates granulomas, called silicomas. Moreover, specific anti-polymer IgG selectively binding to silicone particles has been found in some patients [5].

ASIA (autoimmune/inflammatory syndrome induced by adjuvants) can be triggered by any kind of silicone implant [4,6]. In the Maastricht cohort study, 34 of 100 patients were diagnosed with autoimmune diseases after silicone transplant or infusion, including 3 patients with vasculitis and one with CSS [4,6]. Also reported was the case of a CSS patient who developed the disease 8 months after having a silicone intravitreal infusion for retinal detachment treatment [3].

Our patients are compatible with the hypotheses that montelukast could lead to CSS and that silicone could be a trigger for CSS in patients prone to develop autoimmune diseases. More than that, we believe that they synergistically contributed to the onset of CSS in the cases presented here.

Goren at al. [2] described four population groups at risk of developing ASIA and recommended that they avoid exposing themselves to silicone particles and other adjuvants. These include patients with prior documented reaction to an adjuvant, patients with established autoimmune conditions, patients with a history of allergic conditions or atopic disorders, and individuals prone to develop autoimmunity (either a genetic predisposition and/or relevant environmental triggers).

We contend that asthmatic patients on montelukast should not be exposed to silicone, and vice versa. In other words, we should not prescribe LTRA to individuals with silicone implants since they are at a higher risk for developing CSS.

Correspondence
Dr. J.W. Cohen Tervaert
Faculty of Health, Medicine and Life Sciences, Maastricht University, Maastricht, The Netherlands
email: jw.cohentervaert@maastrichtuniversity.nl

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