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Journal Reviews

Leukotriene receptor antagonists and Churg-Strauss Syndrome: an association with relevance to dermatopathology?

It may seem unusual to have this month's journal reviews focus on journals such as *Seminars in Respiratory Critical Care*,[2] *Pharmacoepidemiology and Drug Safety*,[4] and *Clinical Rheumatology*,[8] but given a recent chance encounter of a skin biopsy with a granulomatous vasculitis with eosinophils from a pediatric patient on montelukast, I felt the topic warranted discussion. Over the years, it has been controversial whether there is a causal relationship between leukotriene receptor antagonists (LTRA) and Churg-Strauss Syndrome (CSS) or whether the concommitant withdrawal from corticosteroids is responsible for unmasking the syndrome. CSS is rare in adults and even rarer in children, which confounds the process of determining causality. The use of LTRA within the general population is not uncommon and it is yet unclear whether the incidence of CSS is increasing or whether recent awareness of a possible association may be inducing a reporter bias. As LTRA are being considered for other conditions, the future recognition of biopsy specimens with features of CSS will be important, particularly within the pediatric population, as any detectable increase in incidence within this population subset will yield information on the strength of the association. To our knowledge, the phenomenon of CSS in patients on leukotriene receptor antagonists has not been reported in the dermatopathology literature; it does exist and perhaps with this month's journal reviews, we may all become familiar with the possibility and remain particularly vigilant with respect to the pediatric population.

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Leukotriene receptor antagonists and Churg-Strauss Syndrome: an association with relevance to dermatopathology?

–Christine Jaworsky

One of the most challenging areas in dermatopathology is the nosologic interpretation of inflammatory dermatoses. Of these, many are caused by medications and present a wide array of microscopic findings, from spongiotic to lichenoid dermatoses to pseudolymphoma. Histological findings may also be modified by an underlying disease state, which further complicates interpretation. Churg-Strauss Syndrome (CSS) or allergic angiitis and granulomatosis is an unusual disorder that was first described in 1951.[1] It is characterized by the triad of asthma, eosinophilia, and necrotizing vasculitis. Although its incidence has been one to three cases per million per year,[1] recently there have been more frequent reports of patients with asthma who received medications known as leukotriene receptor antagonists (LTRA) and later have been found to have concomitant CSS, leading to questions of possible causality.[2] Most articles in the literature are case reports of one or several patients, which although are limited in the determination of causality, are useful for signal detection and the generation of hypothesis. DuMouchel et al.[3] reviewed postmarketing surveillance data from the Federal Drug Administration's database of the voluntary Adverse Event Reporting System (AERS) and suggested a relationship between CSS and LTRA. The study included postmarketing adverse event reports from 1997 to 2002 and contained 337 cases of CSS in patients on LTRA. Such a study, however, may be subject to reporting bias, whether it is under-reporting or over-reporting.

One population-based nested case control study[4] was performed on three US managed care organizations and a US national health plan and analyzed 13.9 million patients. In their study there were 4700 patients who used drugs for asthma, matched to 47 patients who were suspected of having or were diagnosed with CSS. This study was based on drug dispensing rather than actual use and excluded medications dispensed within 60 days of the onset of CSS. Based on these limitations, only 6 of 47 patients with CSS were exposed to LTRA 2 to 6 months prior to the onset of CSS. The authors concluded that although there was no association between CSS and LTRA, they could not, however, exclude some association with treatments for asthma, given the low incidence of CSS.

At the epicenter of discussions about asthma, CSS, and LTRA, are the leukotrienes themselves. Leukotrienes are naturally occurring inflammatory derivatives of arachadonic acid, which have long been suspected to play a role in asthma. Of the many inflammatory compounds released or generated by eosinophils and mast cells, cysteinyl leukotrienes (CysLT) cause contraction of smooth muscles in the bronchial tree, secretion of mucus, and increased vascular permeability in the lungs. Two CysLT receptors (type 1 and type 2) have been identified in the human airway. Specifically, these receptors exist within smooth muscle cells and airway macrophages, as well as on other pro-inflammatory cells including eosinophils and other myeloid stem cells.[5] Within the group of leukotrienes (LTB4, LTC4, LTD4, and LTE4), leukotriene B4 is a chemoattractant for neutrophils and eosinophils.[6] This is of interest because eosinophilia is one criterion for the diagnosis of CSS.

Leukotriene receptor antagonists, or modifiers, are orally active drugs that were introduced in the US in 1998. They inhibit leukotriene synthesis in one of two locations.[5] They either block the Cys LT type I receptor or interfere earlier in the conversion of arachidonic acid pathway by blocking 5-lipoxygenase. Cys LT type I receptor antagonists including zafirlukast, montelukast and pranlukast are approved for the prophylaxis and treatment of asthma and allergic rhinitis. They are mainly used as an alternative to low dose steroids in mild asthma and as a steroid-sparing agent in moderately severe asthma to prevent bronchospasm.[5]

In many patients, CSS onset was documented upon tapering of oral corticosteroids while on LTRA, thus invoking a debate in the literature regarding the role of LTRA in precipitating versus unmasking CSS in asthmatic patients.[7,8] Both theories have their proponents and underlying rationale. In many instances, patients were receiving LTRA for 2 days to 12 months prior to presentation with constitutional symptoms of CSS, including eosinophilia, cardiomyopathy, peripheral neuropathy, skin lesions, and CNS symptoms.[8] All were receiving oral corticosteroids with or without the addition of inhaled corticosteroids. As in idiopathic CSS where 40-75% of patients with active disease may be positive for antineutrophil cytoplasmic antibodies (ANCA), one of three reported patients were ANCA positive.[8] Since there is overlap between patients with CSS who are ANCA positive and those who are ANCA negative, similar treatment protocols for both groups with immunosuppressive agents are used. Peripheral eosinophilia has been variable. This is likely because patients with asthma receive corticosteroids, which can mask eosinophilia. Interestingly, Cuchacovich[8] noted improvement after discontinuation of montelukast within the three patients reported to have developed CSS in apparent association with montelukast.

Skin is the most common site of extrapulmonary involvement in CSS. Cutaneous lesions occur in 50 to 70% of patients with CSS[9] and are a common site of biopsy for histological documentation of the disorder. Three types of skin lesions are found in CSS, erythematous macules and papules, deep-seated subcutaneous nodules, and hemorrhagic lesions ranging from petechiae to purpura and infarcts.[10–12] Skin biopsies show a granulomatous vasculitis with eosinophils rather than a leukocytoclastic vasculitis as commonly seen in allergic vasculitides, including those to medications. There is often striking tissue eosinophilia.

CSS has been reported in patients with asthma who were receiving various LTRA such as zafirlukast,[13,14] montelukast,[7,8] and pranlukast.[15] All improved with removal of the LTRA and initiation of therapy with systemic corticosteroids with or without the addition of cyclophosphamide. Other drugs have also been implicated in CSS, including estrogens,[16] and carbamazepine,[17] macrolide antibiotics,[18] fluticasone propionate;[19] the latter two can be used as steroid-sparing treatments for asthma. Such reports are much fewer in number than those with LTRA.

It is important to be aware of the association between LTRA and CSS in asthmatic patients, even if it is not causative. These drugs may have future applications in dermatologic disorders. Although efficacy within adults with severe atopic dermatitis has not been proven,[20] controlled trials of LTRA in pediatric patients with moderate to severe atopic dermatitis are already underway.[21] It will be interesting to see whether or not CSS occurs in patients with atopic dermatitis as with asthmatic patients. If there are no reported cases of CSS within non-asthmatic patients on LTRA, then the current theory of the unmasking of an underlying CSS within asthmatic patients on LTRA would seem most likely. In the interim, seeing a skin biopsy of a granulomatous

vasculitis with eosinophils should prompt a systemic workup including blood counts to check for eosinophilia, ANCA studies, and checking the patient's list of medications for LTRA. The general recommendation is to discontinue therapy with LTRA and treat with immunosuppressive agents.

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