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tion.[3–5] In our case, endovascular stenting was not appropriate, and this resulted in the need for complete embolization of the right pulmonary artery. The consequent large physiologic mismatch was believed to be the etiology of the patient's hypoxia; therefore, we proceeded to obliteration of right lung ventilation. In a period of 2 months from presentation, the patient has been since decannulated and is progressing in rehabilitation.

Conclusions

Massive hemoptysis is a significant risk of endobronchial brachytherapy. Pulmonary artery pseudoaneurysm can result at a delayed time from initial therapy. This entity can be successfully managed through bronchoscopic and endovascular techniques.

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Allergic Bronchopulmonary Aspergillosis After Infliximab Therapy for Sarcoidosis*

A Potential Mechanism Related to T-Helper Cytokine Balance

Marc A. Judson, MD, FCCP

We report a case of allergic bronchopulmonary aspergillosis (ABPA) that occurred in a man receiving infliximab for systemic sarcoidosis. His symptoms associated with ABPA were temporally related to his infliximab infusions. We suspect that infliximab disrupted the T-helper (Th) type 1-Th2 lymphocyte balance such that Th2 cytokines were left relatively unopposed, promoting the development of ABPA.

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Key words: allergic bronchopulmonary aspergillosis; cytokine; infliximab; sarcoidosis

Abbreviations: ABPA = allergic bronchopulmonary aspergillosis; IL = interleukin; SURT = sarcoidosis of the upper respiratory tract; Th = T-helper; TNF = tumor necrosis factor

Infliximab is a monoclonal antibody directed against tumor necrosis factor (TNF)-α. Clinical studies have suggested that infliximab may be useful in the treatment of sarcoidosis.[1–3] There is a sound rationale for this therapy because TNF-α is released by macrophages in patients with sarcoidosis,[4] and TNF-α is thought to be integrally involved in the development of the granulomatous inflammation.[5] Infliximab is useful with other diseases associated with a T-helper (Th) type 1 pattern of inflammation such as psoriasis,[6] Crohn disease,[7] and rheumatoid arthritis.[8]

It has been suggested that disrupting the Th1-Th2 balance by down-regulating Th1 cytokines may result in manifestations of Th2 diseases.[9] Indeed, severe atopic dermatitis has been reported after institution of infliximab in a case series,[9] which has been attributed to infliximab causing a switch toward Th2-mediated reactions.

We report a case of allergic bronchopulmonary aspergillosis (ABPA) that developed in a patient with multisystem sarcoidosis after he had been placed on infliximab therapy. To our knowledge, this is the first such reported case; and it supports the hypothesis that patients receiving infliximab are at risk of developing Th2-related diseases.

Case Report

A 47-year-old white man was referred for the management of multisystem sarcoidosis. He had pulmonary sarcoidosis diagnosed by mediastinoscopy 14 years earlier, lupus pernio facial skin lesions, nasal crusting, and epistaxis consistent with sarcoidosis of the upper respiratory tract (SURT), and a history of lacrimal gland and conjunctival sarcoidosis. He had no history of asthma, wheezing, or atopy. He had received therapy with prednisone, hydroxychloroquine, and minocycline over the years primarily for dyspnea, lupus pernio, and SURT. He found that his dyspnea, lupus pernio, and SURT would flare when his prednisone dose was lowered to < 25 mg every other day. Table 1 shows his initial pulmonary function tests performed in March 2006. While receiving 20 mg of prednisone every other day, he was placed on infliximab, 5 mg/kg every 6 weeks, and within 3 months (by April 2007) he noted marked improvement in his breathing and clearing of lupus pernio skin lesions, nasal crusting, and epistaxis. His pulmonary function tests improved as shown in Table 1.

Over the next year, his local physician lowered his prednisone dose to 5 mg daily while the patient continued to receive infliximab. After 3 months on this low prednisone dose, the patient returned (July 2008) complaining of dyspnea and wheezing that had worsened over several weeks. These symptoms had occurred within 24 h after his previous infliximab infusion. He had no recurrence of lupus pernio skin lesions, SURT symptoms, or eye problems. He also complained of coughing up "bronchial casts." His physical examination was only remarkable for wheezing on chest auscultation. His pulmonary function is displayed in Table 1. Blood test results revealed the following: WBC count,

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Table 1—*Drug Doses and Spirometry*

Variables	Dosing Dates		
	March 2006	April 2007*	July 2008†
Prednisone dosing	20 mg every other day	20 mg every other day	5 mg/d
Infliximab dosing	None	5 mg/kg IV at wk 0, 2, 6, 12	5 mg/kg IV, every 6 wk
FVC, L (% predicted)	4.92 (97)	5.58 (111)	4.63 (92)
FEV_1, L (% predicted)	3.14 (84)	3.25 (88)	2.81 (76)
FEV_1/FVC ratio	0.64	0.58	0.61

*Patient had started infliximab therapy 3 months earlier.
†Prednisone dose lowered to 5 mg daily 3 months earlier.

6,290/mm^3 with 10% eosinophils; serum IgE, 8,319 IU/mL; aspergillus-specific IgE, 55.6 kU/L (highly positive; normal, < 0.05 [Labcorp; Burlington, NC]); and aspergillus-specific IgG, 5.59 kUA/L (highly positive; normal, < 0.05 [Labcorp; Burlington, NC]). A chest CT scan showed mediastinal lymphadenopathy and scattered small alveolar opacities but no bronchiectasis. Even without the presence of bronchiectasis, the diagnosis of ABPA is secure serologically.[10] His prednisone dose was raised to 20 mg daily with resolution of his symptoms within 2 weeks. However, even with this prednisone dose, 24 h after his next infliximab infusion he noted recurrent wheezing and a cough productive of bronchial casts that continued for 1 week.

Discussion

To our knowledge, this is the first case reported of ABPA occurring after a patient had been treated with infliximab. Although it is possible that this relationship was coincidental, there is a plausible explanation for these findings. Infliximab is a chimeric antibody directed against TNF-α, a cytokine associated with both Th1-dependent and Th2-dependent inflammatory reactions. Nevertheless, infliximab may have disrupted the Th1-Th2 balance so that in our patient, Th2 cytokines predominated. Another potential mechanism to explain our findings is that infliximab may have decreased interleukin (IL)-12 production, which has been reported to cause T cells to progress to a Th2 phenotype.[11] The T-lymphocyte response in ABPA is skewed toward a Th2 response, manifested by the production of Th2 cytokines including IL-4, IL-5, IL-10, and IL-13,[12] causing an allergic inflammatory pattern. It is possible that the development of ABPA was further enhanced by lowering the patient's corticosteroid dose because of successful response of his sarcoidosis to infliximab. We conclude that this case suggests that ABPA, like atopic dermatitis,[9] represents another Th2-associated disease that may occur as a result of infliximab therapy.

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