

including AVA are currently unclear. Insect stings, infections, and other events or conditions that occur at the time of onset of CIndU or shortly before may be coincidental or may have triggered the development of CIndU without being responsible for its persistence. Even in cases where CIndU patients were treated for a “cause,” for example, a chronic infection, and experienced remission of their CIndU, this does not prove a causal relationship. CIndU remission may have occurred spontaneously, or the antibiotic treatment may have cured the CIndU by eradication of another infection or by off-target effects. Most suspected causes of CIndU, insect stings for example, cannot be eradicated and are, therefore, not of therapeutic relevance. A search for underlying mechanisms, in the management of patients with CIndU including AVA, does not usually benefit patients, but rather raises false hopes of a possible cure, incurs costs, may lead to ineffective treatment, and can delay appropriate treatment. We suggest to consider all cases of AVA, until we know the cause(s) of this disease, as primary.

VA is a rare form of CIndU. The global chronic urticaria registry (CURE, www.urticaria-registry.com) of the GA²LEN network of urticaria centers of reference and excellence (UCAREs, www.ga2len-ucare.com) can help to collect more cases of VA and to increase our knowledge of VA.^{9,10} Identifying and characterizing the underlying causes and pathogenesis of CIndUs including AVA is of the highest priority and may allow for the development of novel and better treatments including curative treatments. When we have more data and a clear understanding of the etiopathogenesis of VA, revising its classification may be possible and helpful.

Kanokvalai Kulthanan, MD^a

Patompong Ungprasert, MD, MS^b

Sompol Tapechum, MD, PhD^c

Chuda Rujitharanawong, MD^a

Rungsima Kiratiwongwan, MD^a

Kanyalak Munprom, MD^a

Dorothea Terhorst-Molawi, MD^d

Marcus Maurer, MD^d

^aDepartment of Dermatology, Faculty of Medicine Siriraj hospital, Mahidol University, Bangkok, Thailand

^bClinical Epidemiology Unit, Department of Research and Development, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand

^cDepartment of Physiology, Faculty of Medicine Siriraj hospital, Mahidol University, Bangkok, Thailand

^dDermatological Allergy, Allergie-Centrum-Charité, Department of Dermatology and Allergy, Charité-Universitätsmedizin Berlin, Berlin, Germany (corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, Berlin Institute of Health, Berlin, Germany).

No funding was received for this work.

Conflicts of interest: The authors declare that they have no relevant conflicts of interest. Received for publication February 6, 2021; accepted for publication February 9, 2021.

Corresponding author: Marcus Maurer, MD, Dermatological Allergy, Allergie-Centrum-Charité, Department of Dermatology and Allergy, Charité-Universitätsmedizin Berlin, Charitéplatz 1, 10117 Berlin, Germany. E-mail: Marcus.Maurer@charite.de.

REFERENCES

- Pastor-Nieto MA, Gatica-Ortega ME, de-la-Campa LV, Gimenez-Arnau AM. Proposal for a new classification of vibratory urticaria/angioedema. *J Allergy Clin Immunol Pract* 2021;9:2542-3.
- Kulthanan K, Ungprasert P, Tapechum S, Rujitharanawong C, Kiratiwongwan R, Munprom K, et al. Vibratory angioedema subgroups, features, and treatment: results of a systematic review. *J Allergy Clin Immunol Pract* 2021;9:971-84.

- Boyden SE, Desai A, Cruse G, Young ML, Bolan HC, Scott LM, et al. Vibratory urticaria associated with a missense variant in ADGRE2. *N Engl J Med* 2016;374:656-63.
- Epstein PA, Kidd KK. Dermo-distortive urticaria: an autosomal dominant dermatologic disorder. *Am J Med Genet* 1981;9:307-15.
- Patterson R, Mellies CJ, Blankenship ML, Pruzansky JJ. Vibratory angioedema: a hereditary type of physical hypersensitivity. *J Allergy Clin Immunol* 1972;50:174-82.
- Rose MH. Vibratory urticaria associated with bladder-wall infection with the yeast *Torulopsis glabrata*. *J Allergy Clin Immunol* 1989;84:408.
- Astarita C, Savoia A, De Bartolomeis F. Venom-dependent vibration-induced anaphylaxis: a new hazard following large local reactions from hymenoptera stings. *J Investig Allergol Clin Immunol* 2014;24:282-3.
- Maltseva N, Borzova E, Fomina D, Bizjak M, Terhorst-Molawi D, Košnik M, et al. Cold urticaria—what we know and what we do not know. *Allergy*. 2021;76:1077-94.
- Maurer M, Metz M, Bindslev-Jensen C, Bousquet J, Canonica GW, Church MK, et al. Definition, aims, and implementation of GA²LEN Urticaria Centers of Reference and Excellence. *Allergy* 2016;71:1210-8.
- Weller K, Giménez-Arnau A, Grattan C, Asero R, Mathelier-Fusade P, Bizjak M, et al. The Chronic Urticaria Registry: rationale, methods and initial implementation. *J Eur Acad Dermatol Venereol* 2021;35:721-9.

<https://doi.org/10.1016/j.jaip.2021.02.037>

Thoracic conidiobolomycosis: Invasive or allergic?



To the Editor:

Yeoh et al¹ describe a challenging case of invasive conidiobolomycosis managed with mepolizumab. However, the index case described by the authors appears to be an allergic inflammatory response to *Conidiobolus*. A Th2 response to the fungi (elevated eosinophils and total IgE), histopathology showing eosinophil-rich inflammation, a prolonged course lasting for nearly a year, and a good response to glucocorticoids and mepolizumab suggest an allergic inflammation. Also, a lack of progression of invasive infection despite high-dose glucocorticoids and mepolizumab therapy implies otherwise.² The clinical and radiologic presentation described by the authors probably represents bronchocentric granulomatosis. However, the authors have not presented computed tomography images.

The authors rightly cite the example of allergic bronchopulmonary aspergillosis,³ wherein such presentations are previously described.⁴ *Aspergillus fumigatus* is the most extensively studied of the environmental fungi pathogenic to humans. A spectrum of manifestations can occur in humans (saprophytic colonization, allergic response, and invasive) depending on the fungal burden and the host immune response. A similar allergic reaction to fungi other than *A. fumigatus* has been well described.⁵ Although the clinical presentation and available investigations suggest an allergic response to *Conidiobolus*, the performance of skin testing or demonstration of IgE against the culture filtrate antigens of the *Conidiobolus* isolate would help in confirming the allergic nature.⁶

The distinction between allergic and invasive forms is important because high doses of glucocorticoids and immunomodulatory treatments may be harmful in the invasive variety of thoracic or disseminated conidiobolomycosis.

Valliappan Muthu, MD, DM
Ritesh Agarwal, MD, DM

Department of Pulmonary Medicine, Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh, India.

No funding was received for this work.

Conflicts of interest: The authors declare that they have no relevant conflicts of interest. Received for publication February 27, 2021; accepted for publication March 1, 2021.

Corresponding author: Ritesh Agarwal, MD, DM, Department of Pulmonary Medicine, Postgraduate Institute of Medical Education and Research, Chandigarh 160012, India. E-mail: agarwal.ritesh@outlook.in.

REFERENCES

1. Yeoh DK, Saunders T, Butters C, Burgner D, Bryant PA, Cain TM, et al. Refractory thoracic conidiobolomycosis treated with mepolizumab immunotherapy. *J Allergy Clin Immunol Pract* 2021;9:2527-30.
2. Liu AY. Infectious implications of interleukin-1, interleukin-6, and T helper type 2 inhibition. *Infect Dis Clin North Am* 2020;34:211-34.
3. Agarwal R, Chakrabarti A, Shah A, Gupta D, Meis JF, Guleria R, et al. Allergic bronchopulmonary aspergillosis: review of literature and proposal of new diagnostic and classification criteria. *Clin Exp Allergy* 2013;43:850-73.
4. Agarwal R, Srinivas R, Agarwal AN, Saxena AK. Pulmonary masses in allergic bronchopulmonary aspergillosis: mechanistic explanations. *Respir Care* 2008;53:1744-8.
5. Chowdhary A, Agarwal K, Kathuria S, Gaur SN, Randhawa HS, Meis JF. Allergic bronchopulmonary mycosis due to fungi other than *Aspergillus*: a global overview. *Crit Rev Microbiol* 2014;40:30-48.
6. Chowdhary A, Agarwal K, Randhawa HS, Kathuria S, Gaur SN, Najafzadeh MJ, et al. A rare case of allergic bronchopulmonary mycosis caused by *Alternaria alternata*. *Med Mycol* 2012;50:890-6.

<https://doi.org/10.1016/j.jaip.2021.03.020>

Reply to "Thoracic conidiobolomycosis: Invasive or allergic?"



To the Editor:

We thank Muthu and Agarwal¹ for their interest in our report.² In our view, the report illustrates the blurred boundaries between infection and allergic responses to fungal pathogens and a potential role for adjunctive targeted immunotherapy in the multimodal management of complicated cases refractory to conventional approaches.

Muthu and Agarwal question whether the primary pathologic process was an allergic reaction with bronchocentric granulomatosis rather than invasive fungal infection. In our patient, baseline computerized tomography imaging of the chest showed a mediastinal mass encasing the pulmonary vessels and causing extrinsic compression of the right main bronchus (Figure 1). The location and scale of the lesion can also be appreciated from the initial fluorodeoxyglucose positron emission tomography/magnetic resonance imaging panel in our report. Fungal hyphae with surrounding eosinophilic inflammatory material (Splendore-Hoeppli phenomena) were apparent on histopathological examination of a biopsy sample, and *Conidiobolus incongruus* was identified by culture. Fluid collected at the same time by bronchoalveolar lavage was culture negative. These features match previously reported cases of invasive mediastinal conidiobolomycosis.^{3,4}

Muthu and Agarwal also highlight that glucocorticoids may be detrimental in the setting of invasive fungal infection. Corticosteroid use is indeed associated with increased susceptibility to fungal and other infections.⁵ However, there are a myriad of examples for the use of corticosteroids in an attempt to control a disproportionate and dangerous inflammatory response to invasive infection, including with fungi. Steroids are routinely used for *Pneumocystis jiroveci* pneumonia in patients with HIV⁶ and



FIGURE 1. Computed tomography of the chest at baseline showing a right-sided mediastinal mass with compression of right main bronchus and branches.

for cryptococcal meningitis complicated by immune reconstitution inflammatory syndrome.⁷ For conidiobolomycosis specifically, proliferation of Th2 lymphocyte subsets during invasive infection is well described and may be a pathogen-directed survival mechanism.⁴ In a previous case of an adolescent with disseminated conidiobolomycosis, also associated with characteristic histopathological eosinophilic inflammation, clinical and radiological response occurred after administration of corticosteroids.³

In our report, we postulated that the benefits of corticosteroid therapy were counterbalanced by suppression of Th1, Th17, and innate immune responses, preventing clearance of the fungal infection. Cure coincided with initiation of more selective immunotherapy (mepolizumab) and gradual withdrawal of steroid therapy. A recently reported case of dupilumab immunotherapy in the successful treatment of a child with refractory disseminated coccidioidomycosis adds further weight to our position that targeted immunotherapy may be beneficial in selected cases of invasive fungal infection.⁸

Daniel K. Yeoh, FRACP^{a,b}

Theresa Cole, PhD^c

Joshua Osowicki, FRACP^{d,e}

^aInfectious Diseases Department, Perth Children's Hospital, Perth, WA, Australia

^bSir Peter MacCallum Department of Oncology, University of Melbourne, Melbourne, Vic, Australia

^cDepartment of Allergy and Immunology, Royal Children's Hospital Melbourne, Melbourne, Vic, Australia

^dInfectious Diseases Unit, Royal Children's Hospital Melbourne, Melbourne, Vic, Australia

^eTropical Diseases Research Group, Murdoch Children's Research Institute, Melbourne, Vic, Australia.

No funding was received for this work.

Conflicts of interest: The authors declare that they have no relevant conflicts of interest. Received for publication March 4, 2021; accepted for publication March 4, 2021.

Corresponding author: Daniel K. Yeoh, FRACP, Infectious Diseases Unit, Perth Children's Hospital, Perth, WA 6009, Australia. E-mail: daniel.yeoh@health.wa.gov.au.