

Modern challenges of allergic bronchopulmonary aspergillosis diagnosis and management

Finding from a case study with a history of rituximab use



Allergic bronchopulmonary aspergillosis (ABPA) is an exaggerated reaction to *Aspergillus fumigatus* antigens with a complex pathogenesis that is not fully clarified. The diagnosis sometimes can be a challenge because there is no universal consensus on the diagnostic criteria originally proposed by Rosenberg et al¹ and later modified.² ABPA is established by a combination of clinical, immunologic, and radiologic findings, but in clinical practice some patients do not fulfil all criteria at a given time. Nonetheless, serum immunoglobulin (Ig) E has been advocated to play a key pathogenic role in the disease, and the increase in total serum IgE levels is accepted as a major criterion of initial diagnosis and of disease activity and exacerbations.

We report on a 75-year-old woman with a history of follicular lymphoma (the second most frequent non-Hodgkin lymphoma) treated with rituximab and bendamustine until complete remission (the last cycle was 3 years previously) and then with rituximab maintenance every 2 months.³ Rituximab, an anti-CD20 B-cell–depleting chimeric antibody, has radically changed the prognosis of B-cell non-Hodgkin lymphoma but can induce or aggravate acute or persistent secondary humoral immunodeficiency, as occurred in the present patient whose previous IgG levels had partly recovered (total IgG 469 mg/dL, normal 700–1,600 mg/dL; IgA 40 mg/dL, normal 70–400 mg/dL; IgM <17.3 mg/dL, normal 40–230 mg/dL); antibody responses to diphtheria, tetanus, and *Streptococcus pneumoniae* were not tested. She was referred to the severe asthma unit in the hematology department with suspected ABPA. At the first visit, anamnesis and complementary explorations showed persistent mild-to-moderate asthma of 50 years that had been poorly controlled during the previous 2 months (daytime and night-time dyspnea and wheezing, daily need for reliever medication, limitation of her usual activities; Asthma Control Test score 11 points,⁴ forced expiratory volume in the first second 68% of predicted, fractional exhaled nitric oxide 82 ppb).^{5,6} The loss of asthma control also was associated with malaise, dysthermia, and productive cough with thick brownish expectoration, described as bronchial plugs.¹ The patient reported recurrent asthmatic exacerbations in recent years but no recurrent bacterial sinopulmonary infections. Blood count performed 1 month previously was normal (300 eosinophils/mm³, total IgE 3.70 KU/L, *A fumigatus*–specific IgG 11 mgA/L, *A fumigatus*–specific IgE 0.03 KU/L). *Aspergillus niger* was isolated from sputum cultures, and only saprophyte flora was identified. No cell differential was performed on the sputum collection. No bronchoalveolar lavage or lung biopsy examination

was performed. We performed prick tests that were negative for common aeroallergens, including *Aspergillus* species and other fungi. At that point, she did not fulfill any immunologic criteria required for ABPA diagnosis. Nevertheless, the clinical suspicion was high, so we extended the study because of her humoral immunodeficiency secondary to rituximab.⁷

The second blood work showed a total IgE level of 11 KU/L; specific IgE reactions to *A fumigatus*, *Mucor racemosus*, *Penicillium notatum*, and *Cladosporium herbarum* (r Asp f 1, 2, 4, 6, Alt a 1 <0.35 KU/L); a blood eosinophil count of 1,500/mm³; and an *Aspergillus* species-specific IgG level of 41 mgA/L. Sweat chloride and cystic fibrosis transmembrane conductance regulator tests showed negative results. High-resolution chest computed tomogram displayed central bronchiectasias, high-attenuation mucus, mucus impactions, tree-in-bud opacities, and areas with a mosaic pattern.⁸

Therefore, even in the absence of an IgE response, the final diagnosis was ABPA, central bronchiectasias, and high-attenuation mucus in this patient with secondary humoral immunodeficiency based on the clinical symptoms, sputum cultures positive for *Aspergillus* species, specific IgG positive for *Aspergillus* species, and blood eosinophilia and radiologic criteria. Asthma controller treatment was adjusted to gravity and control levels,^{5,6} and she was prescribed oral prednisone starting with 1 mg/kg with a progressive decrease, in addition to voriconazole and prophylactic trimethoprim plus sulfamethoxazole, with good clinical response and improved lung function. Six months later, the patient was asymptomatic and without opportunistic infections (Asthma Control Test score 24, forced expiratory volume in the first second 84% of predicted, specific IgG to *A fumigatus* 21 mgA/L). Clinical and serologic improvements after specific treatment confirmed the ABPA diagnosis in this challenging case.

The pattern of the main clinical, laboratory, and spirometric parameters over time is presented in Table 1.

In some patients treated with rituximab or other anti-CD20 monoclonal antibodies, the measured total and specific IgE levels might decrease or might be completely suppressed, but that does not automatically imply the annulment of a clinically relevant hypersensitivity response because the allergic cascade is so complex. Recently, the use of rituximab has been extended beyond B-cell non-Hodgkin lymphoma to the treatment of a wide range of autoimmune disorders refractory to standard treatments.⁹ Hence,

Table 1
Pattern of Main Clinical, Laboratory, and Spirometric Parameters Over Time

	FEV ₁ , %	ACT	Asp f-specific IgG, mgA/L	Total IgE, KU/L	Blood eosinophils/mm ³
Before ABPA diagnosis	68	11	11	3.7	30
ABPA diagnosis	62	10	41	11	150
1-mo treatment with corticoids	82	22	31.5	4.39	20
2-mo treatment with corticoids	81	25	35.8	4.51	30
3-mo treatment with corticoids	75	25	31.3	5.11	40

Abbreviations: ABPA, allergic bronchopulmonary aspergillosis; ACT, Asthma Control Test; FEV₁, forced expiratory volume in the first second; Asp f-specific IgG, serum immunoglobulin G for *Aspergillus fumigatus*; total IgE, total serum immunoglobulin E.

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cases similar to the present case are likely to increase in allergists' daily practice worldwide.

Specifically, the suppressed IgE result complicates the already quite challenging ABPA diagnosis; therefore, in these cases, additional criteria are required for confirmation. For example, high-attenuation mucus is a characteristic computed tomographic finding in ABPA and should be actively sought, because its presence confirms the diagnosis of ABPA in patients with bronchiectasis,¹⁰ as in the present patient. Moreover, long-term treatment with systemic corticosteroids in already immunosuppressed patients implies specific prophylaxis and closer clinical follow-up. The clinical criteria are crucial when tapering the steroid dose, because IgE monitoring is unhelpful. In this case, the dynamics of specific IgG to *Aspergillus* species were parallel to the clinical improvement, but in patients with more severe hypogammaglobulinemia, this biomarker also might be useless. We believe this case brings up modern challenges to the initial diagnosis and long-term management of ABPA.

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Prospective evaluation of electronic medical record penicillin allergy documentation at a tertiary community teaching hospital



The global threat of increasing antibiotic resistance has driven regulatory organizations to advocate for the judicious and prudent use of antibiotics through robust antibiotic stewardship programs. Recently published antibiotic stewardship guidelines detail recommended strategies to optimize antibiotic use in a variety of health care settings.¹ One such strategy includes a thorough penicillin allergy history assessment and, if indicated, subsequent penicillin skin testing in patients with a reported penicillin allergy.

Obtaining an accurate and comprehensive medication history is the first step in the clinical evaluation of drug hypersensitivity.² Despite the significance of classifying and assessing potential allergic reactions, inaccurate reporting of drug allergies continues to be described across numerous platforms and contributes to the unnecessary avoidance of first-line therapies.^{3,4}

As part of a stewardship initiative to optimize antimicrobial use and promote accurate penicillin allergy assessments, we prospectively evaluated the accuracy of penicillin allergy documentation in the electronic medical record (EMR) (Epic Systems Corporation, Verona, Wisconsin) compared with patient interview responses at a 528-bed tertiary care medical center. Inpatients 18 years or older with a reported allergy to an antibiotic within the penicillin class were randomly selected between February and April 2016 to be interviewed by a pharmacist, pharmacy student, or allergist regarding their penicillin allergy. During the patient interview, the history was collected using a standardized penicillin allergy history

algorithm that assessed and categorized allergic reactions based on the Gell and Coombs classification scheme.² The penicillin allergy history obtained from the patient interview was compared with the history documented in the EMR and then classified into 1 of 8 categories (Table 1). EMR documentation was considered consistent with the patient interview if the symptoms described by the patient matched the symptoms documented in the EMR. Written informed consent, as approved by the Rochester General Hospital Clinical Investigations Committee, was obtained before interview.

The primary outcome measurement was to evaluate the accuracy of the penicillin allergy history documented in the EMR vs patient interview response. The secondary outcome measurement was to assess the accuracy of allergy documentation across the spectra of health care professionals.

A total of 100 patients were interviewed. The penicillin allergy history obtained using the algorithm was consistent with the penicillin allergy history documented in the EMR in 32 patients. The discrepancies observed in the remainder of patients are given in Table 1. Strikingly, in our patient cohort, severe or life-threatening penicillin allergies were underreported in nearly half of patients (43%). The underreporting of allergy severity is a significant patient safety concern because it may place patients who are challenged with an alternative β -lactam antibiotic at risk for unanticipated adverse reactions.

Most patients (96%) were able to describe a period in which the allergic reaction occurred; however, these data were only documented in 10% of patients. Of the 96 patients who could recall approximately when their penicillin allergy transpired, 89 patients (93%) reported a reaction that occurred greater than 10 years from the interview date. It is estimated that 80% of patients with an

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