

a total challenge dose of 0.06 g protein/kg divided into 3 feedings over a total of 45 minutes with a 4-hour observation time. Consequently, he received 10 mL orange juice every 15 to 20 minutes, with a total of 30 mL given. Before the challenge, we secured intravenous access, and a complete blood count with differential was obtained. One hour and 30 minutes after the final dose, he developed repetitive emesis every 10 to 15 minutes lasting 2 hours. No urticaria, rhinorrhea, nasal congestion, wheezing, diarrhea, or other symptoms of anaphylaxis occurred during the challenge. Complete blood count with differential obtained 30 minutes into his reaction revealed a significant increase in his absolute neutrophil counts from 1,920 cells/ μ L to 3,420 cells/ μ L. Evaluation of fecal leukocytes and eosinophils was inadvertently not done. After his episodes of emesis, he became tachycardic and lethargic, for which a normal saline bolus was given. After rehydration, the boy returned to baseline with no additional management needed. Based on the positive OFC, the diagnosis of FPIES was made. We recommended our patient strictly avoid orange juice as well as other citrus products. On follow-up, our patient had experienced 1 mild episode of emesis after ingesting pineapple. He had no further emergency room visits or hospitalizations for emesis.

To our knowledge, this case is the first report of FPIES to orange juice. As is often the case with FPIES, our patient had been misdiagnosed on multiple occasions with viral gastroenteritis, and the possibility of IgE-mediated food allergy was entertained. However, based on clinical history, as well as negative skin prick testing and specific IgE level to orange juice, we opined that IgE-mediated food allergy was unlikely. We therefore proceeded to OFC and were able to confirm the diagnosis of FPIES to orange juice. When managing patients with repetitive emesis, diarrhea, dehydration, or lethargy,

in addition to evaluating for common causes, we encourage clinicians to consider the possibility of FPIES induced by unusual agents such as oranges or other citrus fruits.

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Prolonged hypogammaglobulinemia after adjuvant rituximab for Hodgkin's lymphoma presenting with refractory urticaria

Rituximab is a monoclonal anti-CD20 antibody approved by the Food and Drug Administration for the treatment of B-cell malignancies and rheumatoid arthritis. Interestingly, rituximab is also being used off-label for a multitude of other disorders. Although it is well known that rituximab causes transient decreases in peripheral B-cells and serum immunoglobulins, they generally return to normal within 6 to 9 months after therapy. However, evidence of prolonged alteration of the B-cell compartment leading to loss of isotype-switched CD27+IgM-IgD- memory B-cells and subsequent hypogammaglobulinemia is increasing.^{1,2} Studies have shown that patients who received rituximab therapy as an adjuvant to stem cell transplantation or as a treatment for autoimmune disease have an increased risk of prolonged hypogammaglobulinemia in some cases up to 6 years and longer.^{2–4}

We describe a case of a 47-year-old woman who was referred to our clinic for refractory urticaria. Pertinent medical history included Hodgkin lymphoma and consequent autologous stem cell transplantation 6 years earlier. She was initially treated with high-dose chemotherapy followed by 3 cycles of rituximab, ifosfamide, carboplatin, and etoposide therapy in 2005 before autologous stem cell transplantation in 2006. In 2008, immunoglobulin (Ig) G and IgA levels were found to be greater than 2 standard deviations below the age-related mean, consistent with hypogammaglobulinemia.

Quantitative immunoglobulin levels were IgG of 246 mg/dL (650–1,600 mg/dL), IgA less than 15 mg/dL (40–350 mg/dL) but normal IgM of 281 mg/dL (50–300 mg/dL). Unfortunately, she was lost to follow-up until our evaluation in January 2012. Recent history included 4 sinus infections requiring antibiotics during the past 12 months with no history of any recurrent infections. Repeat immunoglobulin levels were IgG of 34 mg/dL, IgA less than 15 mg/dL, and elevated IgM of 338 mg/dL. Rubella, rubeola, tetanus, diphtheria, and streptococcal IgG antibodies were all undetectable. Initial flow cytometry indicated a normal T-cell population and a normal total B-cell number. However, B-cell subset evaluation revealed a low percentage of CD27+IgM-IgD-switched B-cells (0.1%; 0.4–2.3%). CD27+IgD+ (nonswitched) memory B-cells were normal (0.4%; 0.2–2%). CD20/IgA+ and CD20/IgG+ B-cells were completely absent, but CD20/IgM+ B-cells were present in normal numbers, reflecting the lack of isotype-switched B-cell receptors. This supports the mechanism of impaired isotype switching leading to a paucity of surface and secreted IgG and IgA. Intravenous immunoglobulin replacement was initiated, with serum IgG rising to 600 to 800 mg/dL with no subsequent infections, and her urticaria was controlled with daily antihistamine therapy. Although chronic urticaria has been described in common variable immune deficiency, this is a unique case in a patient with Hodgkin lymphoma treated with rituximab combined chemotherapy presenting with refractory urticaria and hypogammaglobulinemia.

Roll et al⁵ described the characteristic regeneration of the B-cell subset population after treatment with rituximab in rheumatoid

arthritis patients. Immature B-cells are the first subset to return followed by naïve B-cells, which constituted most of the peripheral B-cells. CD27⁺ memory B-cell recovery was shown to be delayed and remained low for over 2 years. Furthermore, persistent in vitro failure of naïve B-cells to differentiate into mature B-cells or plasma cells in the presence of interleukin (IL)-2, IL-6, IL-10, IL-15, and B-cell activating factor in patients treated with rituximab combined chemotherapy has also been described.^{6,7} These findings further support the conclusion that rituximab combined chemotherapy may induce persistent B-cell maturation and differentiation arrest with subsequent hypogammaglobulinemia.

In addition to rituximab, several anti-CD20 monoclonal antibodies are in development for use in a variety of conditions, which will undoubtedly increase the number of patients exposed to these agents. The medical community should be made aware that the loss of memory B-cells and hypogammaglobulinemia with an increased risk of infection will likely become a more prevalent problem. Currently, B-cell subset characteristics and serum immunoglobulin levels are not universally evaluated before, during, or after treatment with rituximab and these evaluations appear to be warranted. Prolonged or perhaps permanent alteration of the B-cell compartment, which can have an indistinguishable clinical presentation and B-cell phenotype as common variable immune deficiency and certain hyper IgM syndromes (eg, activation-induced cytidine deaminase/uracil-DNA glycosylase and inducible T-cell costimulator deficiencies), may result from rituximab therapy and are not readily recognized or differentiated based on the evaluation of CD19⁺ B-cells alone.⁸ Delay in diagnosis and complicated evaluation of these patients can and should be avoided with appropriate baseline values. Based on our experience and review of the literature, we recommend acquiring a comprehensive baseline evaluation of the B-cell compartment as well as quantitative immunoglobulin levels before, during, and after rituximab therapy. Finally, the risk of persistent hypogammaglobulinemia and its associated comorbidities, as well as related long-term health concerns such as consequent chronic

intravenous immunoglobulin therapy should be seriously considered before recommending rituximab therapy, particularly in conditions that have other viable alternative treatments.

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A case report of bell pepper anaphylaxis: Could 1, 3- β -glucanase be the culprit allergen?

A 34-year-old woman was referred to our outpatient clinic after presenting with anaphylaxis. After eating red bell pepper she immediately presented with plantar and palmar itching, urticaria, stupor, and breathing impairment. Hypotension (80/50 mmHg) and low oxygen saturation (88%) were recorded at the emergency unit.

One month after that, she presented with a second episode of palmar and plantar itching and skin rash, immediately after eating a sauce containing crude red peppers. The symptoms resolved with self-administered adrenaline and antihistamines.

She reported a history of oral allergic syndrome to peach, walnut, and chestnut and immediate urticaria when using latex gloves, but she had never been studied by an allergist. She did not have any other medical condition; she denied respiratory symptoms and avoided red and green pepper, peach, and nuts.

We performed a skin prick test (SPT) with commercial extracts of fruits, vegetables, latex, nuts, and common aeroallergens (ALK Abelló, Madrid, Spain) and prick by prick with red and green pepper

(*Capsicum annuum*). Red or green pepper oral challenge was refused by the patient. Total and specific immunoglobulin (Ig) E was determined by the ImmunoCAP system (Thermo Scientific, Uppsala, Sweden).

A molecular diagnosis panel using microarray technology was performed using the ImmunoCAP ISAC (immuno solid-phase allergen chip) method (Thermo scientific).¹

Red and green peppers were extracted for 90 minutes at 4°C with phosphate buffer and analyzed by tricine sodium dodecyl sulphate polyacrylamide gel electrophoresis method under nonreducing conditions. Proteins were transferred to nitrocellulose membranes and incubated with patient serum about 18 hours. After that, they were incubated with anti-human IgE monoclonal antibodies and rabbit IgG anti-mouse antibodies labeled with peroxidase (Calbiochem, Nottingham, United Kingdom). Buffer incubation without serum was used as negative control. IgE binding proteins were detected by chemiluminescence (Amersham Bioscience) following the manufacturer's instructions. The same method was performed with peach.²

The SPTs with commercial extract were positive to red pepper and tomato and negative to other *Solanaceae* (eggplant and potato).