Open Forum Infectious Diseases

MAJOR ARTICLE

Alpha-Gal Syndrome in the Infectious Diseases Clinic: A Series of 5 Cases in Central North Carolina

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Background. Alpha-gal syndrome (AGS) is a recently described allergy to galactose-α-1,3-galactose, an oligosaccharide present in mammalian meat. AGS can present with angioedema, urticaria, and anaphylaxis arising 3–6 hours after ingestion, although symptoms such as gastrointestinal distress, fatigue, and arthralgias are also reported. Because AGS appears to be associated with tick bites, patients may present to infectious diseases (ID) clinics for evaluation.

Methods. We documented a series of 5 patients referred to the University of North Carolina ID Clinic between 2020 and 2022 for various tick-borne infections that were found to have symptoms and laboratory testing consistent with AGS. Patients were subsequently referred to the Allergy and Immunology Clinic.

Results. Patients were referred to the ID Clinic for persistent symptoms following positive tick-borne disease testing or presumed tick-borne infection. All patients had an elevated alpha-gal immunoglobulin E and clinical presentation consistent with AGS. Common symptoms included episodic gastrointestinal distress (eg, cramping, nausea, diarrhea), fatigue, arthralgias, and subjective cognitive impairment, but a notable absence of severe anaphylaxis. Four patients were seen by at least 1 nonallergy specialist prior to referral to ID. Patients reported substantial improvement in their symptoms following dietary restriction.

Conclusions. ID physicians should be aware of AGS as a cause of persistent, nonspecific symptoms following a tick exposure or tick-borne illness. Further research is needed to determine the prevalence of alpha-gal sensitization and AGS following tick-borne bites.

Keywords. alpha-gal allergy; food allergy; tick-borne disease; ticks.

Alpha-gal syndrome (AGS) is a term that describes the protean clinical manifestations of an allergy to galactose-α-1,3-galactose (herein "alpha-gal"), an oligosaccharide found in the tissue of nonprimate animals [1]. AGS is more commonly known as the "red meat allergy" as affected individuals develop symptoms after consuming mammalian meat products including beef and pork. AGS was first noted in a subset of patients enrolled in clinical trials of the monoclonal antibody cetuximab who experienced infusion-related anaphylaxis or urticaria. Further investigation revealed that these reactions occurred in patients who had preexisting immunoglobulin E (IgE) antibodies specific for glycosylation on the Fab fragment of the monoclonal antibody [2]. Notably, a disproportionate number of reactions occurred at clinical sites located in the Southeastern United States (US), an observation that prompted investigation of environmental risk factors unique to the region [3, 4]. While preliminary studies of fungal allergens and helminths were unrevealing, tick-borne exposure emerged as a leading hypothesis, given (1) similarities in the spatial distribution of the cetuximab reactions and tick-borne diseases such as spotted fever rickettsiosis and ehrlichiosis and (2) anecdotal patient reports of adverse responses to red meat ingestion after tick bites [4]. Initial supporting evidence of an association between AGS and tick bites came from Australia [5], and has been followed by a number of epidemiological studies in the US and Europe [6, 7].

Throughout much of the southeastern US, the lone star tick (*Ambylomma americanum*) (Figure 1) is the most frequently encountered tick, often representing >90% of ticks collected in field studies [8, 9]. The geographic range of the tick, which exhibits aggressive and nondiscriminatory biting habits, has expanded substantially over the past 3 decades [10–12]. The alpha-gal antigen is thought to be transmitted to humans via

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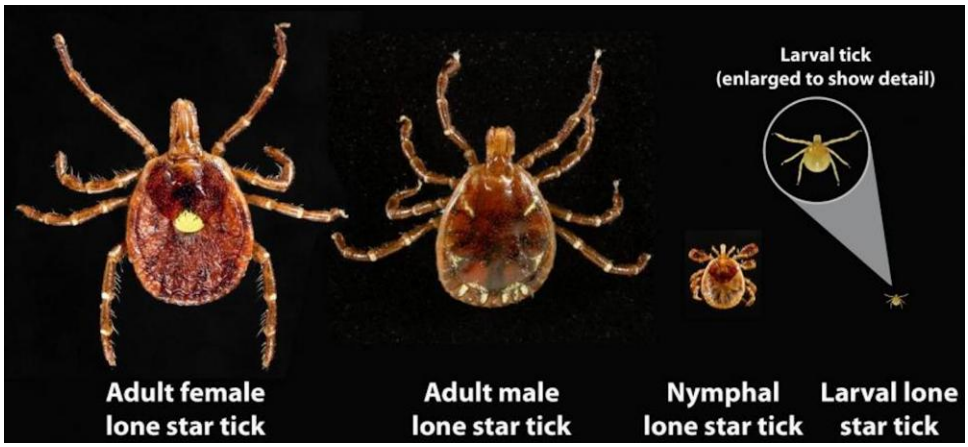

Figure 1. Male and female adult lone star tick (*Amblyomma americanum*) with juvenile (eg, nymphal and larval) stages shown for comparison. Picture from Centers for Disease Control and Prevention.

the saliva of the lone star tick. Once the alpha-gal antigen is introduced into a person's skin following a tick bite, it can stimulate an IgE antibody response and lead to the development of an allergy to red meat and other mammalian products [13, 14].

AGS can develop at any age and typically manifests 4–6 weeks after the offending tick bite. The most overt symptoms are similar to a typical food allergy, including angioedema, urticaria, and anaphylaxis [15]. Yet, unlike other IgE-mediated allergic reactions, AGS reactions are often delayed, emerging 3–6 hours after mammalian meat consumption [16]. The occurrence and severity of reactions can also vary with the amount of meat consumed. It is also important to recognize that milder presentations of AGS, including gastrointestinal (GI) distress, arthralgia, or pruritis, may occur. Furthermore, some individuals with elevated alpha-gal IgE levels may not experience any symptoms and are categorized as "sensitized," as opposed to having AGS. Together, the delayed and varied clinical presentations often confound timely and accurate diagnosis [17].

Lone star ticks are also vectors for a range of bacterial pathogens such as *Ehrlichia*. Thus, patients may present with an acute febrile illness more typical of ehrlichiosis 5–10 days after the tick exposure only to develop AGS-like symptoms in the subsequent weeks to months, often having completed directed or empirical antimicrobial therapy. As patients may seek care when new symptoms emerge after completion of antibiotics, it is important for infectious diseases (ID) physicians to be aware of AGS as a late sequela of tick exposure, particularly in areas where lone star ticks are prevalent.

METHODS

Data Collection

Cases described herein were patients referred to the University of North Carolina (UNC) ID Clinic for evaluation of various tick-borne diseases. Patients were evaluated and found to have symptoms and laboratory evidence consistent with AGS. Eligible cases were prospectively identified between 2020 and 2022 by one of the authors (R. M. B.), who provides patient care for patients with tick-borne diseases at the clinic. Patients were subsequently referred to the UNC Allergy and Immunology Clinic, where they were seen by another author (S. P. C.), who specializes in the diagnosis and management of AGS. For each case, we reviewed the medical record and abstracted relevant demographic information, clinical histories, and the results of laboratory testing (Table 1).

Patient Consent Statement

The case series did not require individual patient consent or review by the UNC Institutional Review Board as all patient interactions and resulting data were collected solely for nonresearch purposes [18].

RESULTS

Patient 1

Patient 1 was a woman from central North Carolina referred to the ID Clinic for Rocky Mountain spotted fever (RMSF). Her gastrointestinal symptoms, described as sharp midepigastric pain and excessive eructation, along with severe fatigue, started 3 months prior. She was unaware of a tick exposure, but noted frequent outdoor activity such as hiking, which prompted her primary care physician to test for tick-borne diseases. Serological testing for *Borrelia burgdorferi* was negative, but her *Rickettsia* immunoglobulin G (IgG) returned at a titer of 1:64. She was started on a 14-day course of doxycycline, after which her testing was repeated and returned at a titer of 1:128. She did not recall subjective improvement in her symptoms with antibiotic treatment.

Table 1. Select Demographic, Clinical, and Laboratory Information of Cases

Characteristic	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Demographic					
Age, y	60s	60s	30s	50s	50s
Sex	Female	Male	Female	Female	Female
Race/ethnicity	NH White	NH White	NH White	NH White	NH White
Referral information					
Month	August	September	December	May	May
Indication	RMSF	RMSF	Lyme disease	RMSF	Diarrhea
Prior treatments	Doxycycline	Doxycycline and amoxicillin	Doxycycline	Doxycycline	Doxycycline
Total duration	14 d	≥35 d	≥30 d	28 d	7 d
Exposure					
Known tick exposure	Unknown	June	June	September	April
Tick identification	Unknown	LST	Unknown	Unknown	Unknown
Onset postexposure	Unknown	3 wk	1 mo	2 wk	2 wk
Symptoms					
Subjective fever/chills	…	…	X	X	X
Rash (description, if present)	…	Erythema migrans	Initial eschar	…	Urticarial
Arthralgia or myalgia	…	X	X	X	X
Fatigue	X	X	X	X	X
Lightheadedness/flushing	X	…	X	…	…
Nausea/vomiting	…	…	X	…	X
Abdominal cramping	X	…	X	X	X
Diarrhea	…	…	X	…	X
Cognitive impairment	X	…	X	…	…
Anaphylaxis	…	…	…	…	…
Other	Sleep issues	…	Worsening of asthma	…	…
Self-reported food triggers	Not noted	Dairy	Honey-roasted peanuts	Not noted	Not noted
Tick-borne disease testing					
Lyme EIA	<0.91	<0.91	<0.91	<0.91	<0.91
Lyme Western blot	…	…	…	…	…
SFGR	1:64 → 1:128	1:128 → 1:256	<1:64	<1:64 → 1:128	<1:64 → 1:128
Ehrlichia	1:256	<1:64 → <1:64	<1:64	…	<1:64 → 1:128
Other diagnostic evaluation prior to referral	Referral to gastroenterologist; abdominal ultrasound and CT	ANA and RF testing, knee arthrocentesis	Colonoscopy for chronic nausea, vomiting, and diarrhea (unremarkable); referral to cardiology for tachycardia	Abdominal CT, colonoscopy, rheumatology referral	Abdominal CT, EGD, coloscopy with biopsies
Alpha-gal IgE, kUA/L[a]	2.06	12.5	16.0	5.28	0.66

Abbreviations: ANA, anti-nuclear antibody; CT, computed tomography; EGD, esophagogastroduodenoscopy; EIA, enzyme immunoassay; IgE, immunoglobulin E; LST, lone star tick; NH, non-Hispanic; RF, rheumatoid factor; RMSF, Rocky Mountain spotted fever; SFGR, spotted fever group rickettsia.

[a]Reference range <0.1 kUA/L. Level of allergy: absent, <0.35 kUA/L; low, 0.35–0.69 kUA/L; moderate, 0.70–3.49 kUA/L; high, 3.50–17.5 kUA/L; very high, >17.5 kUA/L.

She was referred to a local gastroenterologist and underwent abdominal imaging that incidentally identified polyps in the gallbladder, which were not thought to be the cause of her symptoms. She was advised to consider elective cholecystectomy at a later date. When seen in the ID clinic, she was still experiencing GI symptoms and fatigue. Further review of systems elicited mild cognitive impairment described as "brain fog" along with poor sleep. Serological testing for *Ehrlichia* demonstrated reactive IgG titers at 1:256, while alpha-gal IgE was elevated in the "moderate" range. She was advised to restrict her diet to exclude mammalian meat and was referred to the Allergy Clinic, where she was seen approximately 1 month later. At that time, she noted substantial interval improvement in her symptoms and was advised to continue dietary restrictions.

Patient 2

Patient 2 was a man from central North Carolina referred to the ID clinic for RMSF after finding a tick attached to his upper back in the summer. He was uncertain of the duration of attachment, but suspected the exposure occurred while mowing his yard approximately 5 days prior to discovery. The tick was removed, sent to the state public health laboratory for identification, and eventually confirmed as a lone star tick. He developed a large, circular area of erythema consistent with erythema migrans (Figure 2), but no constitutional symptoms. He was seen by a local physician, who prescribed a 10-day course of doxycycline. The rash resolved with antibiotic treatment, at which point he stated that he was feeling well.

Three weeks later, he developed diffuse arthralgia most prominent in the shoulders and knees, severe enough to make it difficult to stand from a sitting position. He returned to the local clinic, now approximately 2 months after the initial exposure, where he was prescribed a 30-day course of amoxicillin, which was subsequently switched to doxycycline. He reported no improvement on the extended course of antibiotics. Serological testing for *B burgdorferi* and *Ehrlichia* was negative but testing for *Rickettsia* demonstrated reactive IgG antibodies at a titer of 1:128. Due to ongoing arthralgia and unilateral knee swelling (the site of a prior injury), he underwent arthrocentesis that yielded 40 cc of benign-appearing aspirate. Subsequent cell counts and culture were unremarkable, with pathologist review noting the presence of many monocytes, lymphocytes, and polymorphonuclear leukocytes, but no crystals.

He was referred to a local ID provider where he underwent repeat serological testing for *Rickettsia*, which was reactive at a titer of 1:256. Inflammatory markers including C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were within normal limits. He was referred to the UNC ID Clinic for a second opinion nearly 4 months postexposure. Testing for alpha-gal IgE was high and he was initiated on a restricted diet and referred to the Allergy Clinic, where he started twice-daily oral antihistamines, one of the therapeutic options for AGS, with improvement in his symptoms.

Patient 3

Patient 3 was a woman from northeastern North Carolina referred to the ID clinic for suspected Lyme disease. She recalled finding 1 tick attached to the lateral aspect of her breast the prior summer. The tick was removed but left a self-described "crater" on her breast. The following week, she developed subjective fever and chills followed by severe, unremitting vomiting that lasted for nearly a month. She was taken to a local community hospital where she was given a syndromic diagnosis of coronavirus disease 2019 (COVID-19) despite negative severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) testing. Her GI symptoms persisted and she returned to the local hospital a few days later, where she was tested for Lyme disease and prescribed a 7-day course of doxycycline without improvement. Serological testing for *B burgdorferi*, the causative agent of Lyme disease, was negative.

Over the coming months, nausea and vomiting became less frequent and more episodic. Associated symptoms included abdominal cramping, diarrhea, lightheadedness, arthralgia most prominent in hips and knees, more frequent asthma exacerbations, and difficulty with concentration and short-term memory—described as "brain fog." She saw her primary care physician approximately 5 months after onset of symptoms and received an additional 30-day course of empirical doxycycline for Lyme disease, which reportedly only made her feel worse. At her visit to the ID Clinic, which took place approximately 7 months after her tick exposure, she reported a worsening of symptoms with ingestion of honey-roasted peanuts, many of which contain gelatin made from beef and cattle byproducts. Serological testing for tick-borne diseases was negative, but alpha-gal IgE was elevated. She was subsequently referred to the Allergy Clinic for evaluation of AGS, but was lost to follow-up and did not follow through with the appointment.

Patient 4

Patient 4 was a woman from central North Carolina who was referred to the ID Clinic for RMSF. The previous fall, she returned home after walking in a wooded area and found 8 ticks attached to her legs, some of which were reportedly engorged. She subsequently developed erythematous lesions at several bite sites that enlarged, and, in some areas, coalesced. Approximately 2 weeks later, she developed fatigue, diffuse myalgia, and subjective fever that she described as similar to when she had infectious mononucleosis. She underwent testing for SARS-CoV-2, which was negative.

While the mononucleosis-like symptoms resolved, approximately 1 month later, she experienced severe, cramping abdominal pain that localized to the left lower quadrant for

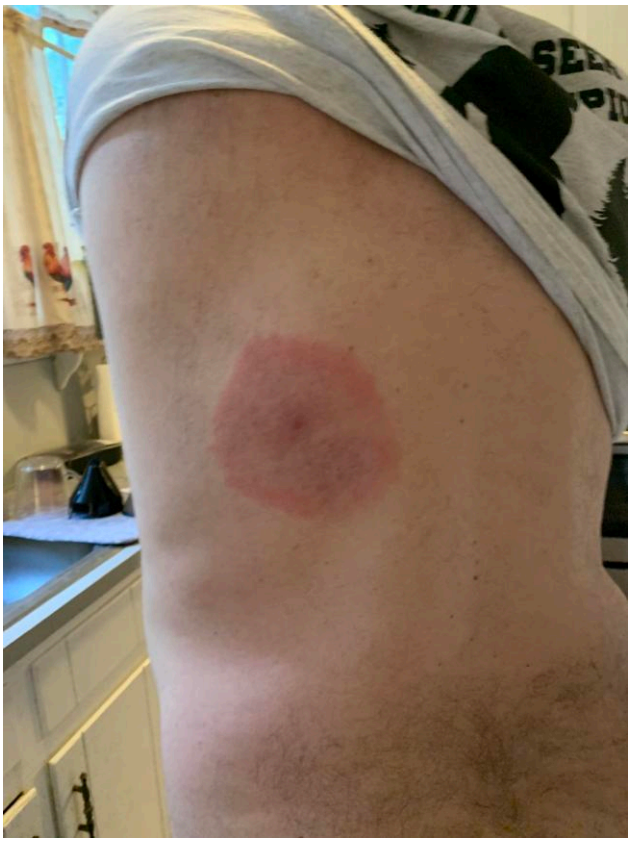

Figure 2. Patient 2: appearance of rash approximately 1 week after tick bite.

which she underwent a computed tomography (CT) scan of the abdomen and pelvis that was notable for diverticulosis without diverticulitis. Her abdominal symptoms persisted and she underwent a colonoscopy, which was unremarkable. Around the same time, diffuse arthralgia and more prominent fatigue emerged. Recalling her exposures, she asked her primary care physician to test her for tick-borne diseases. Serological testing for *B burgdorferi* and *Rickettsia* was negative. The test results were apparently misinterpreted and she received a 14-day course of doxycycline. She reported subjective improvement in fatigue following treatment and subsequently received another 14-day course of doxycycline, but the arthralgia, described as most severe in her shoulders, hips, and knees, persisted.

Due to these symptoms, along with a peripheral eosinophilia, she was referred to a local rheumatologist for possible rheumatoid arthritis. Testing for autoimmune and inflammatory markers, including antinuclear antibody, anti–cyclic citrullinated peptide antibody, rheumatoid factor, creatinine kinase, aldolase, CRP, and ESR was either negative or within normal limits. RMSF and Lyme disease remained the leading cause on the differential diagnosis, and she was subsequently referred to a hematologist for eosinophilia and another ID clinic, the latter of which declined to schedule the patient. She was then referred to our ID practice, where she was seen approximately 8 months after exposure.

At the time of visit the patient still complained of substantial arthralgia of the large joints, along with fatigue. She reported regularly eating beef and pork products, but had not associated ingestion with her symptoms. Repeat testing for *Rickettsia* returned reactive IgG antibodies at a titer of 1:128, while alpha-gal IgE was elevated in the "high" range. She was advised to restrict her diet to exclude mammalian meat and reported modest improvement in her joint pain after 1 week with substantial improvement after 3 weeks.

Patient 5

Patient 5 was a woman from central North Carolina seen in the ID Clinic after a recent hospitalization for nausea and diarrhea. Approximately 2 weeks prior to admission, she developed nausea followed by profuse watery diarrhea. She was initially seen in a local emergency department (ED) approximately 1 week after onset of symptoms. At that time, she was reporting 8–10 episodes of watery diarrhea daily. CT of the abdomen and pelvis showed liquid stool in the colon, but was otherwise unremarkable. A multiplex gastrointestinal pathogen panel was negative, as was testing for *Clostridium difficile* toxin. She was discharged from the ED with outpatient gastroenterology follow-up.

At this appointment 5 days later, she reported the interval development of diffuse arthralgia and an erythematous, macular rash over her flanks and thighs. Four days later, she underwent esophagogastroduodenoscopy and colonoscopy, both of which demonstrated normal anatomy. Subsequent pathologic examination of biopsy specimens revealed vilious blunting in the duodenum, but normal colonic mucosa. Staining for Periodic acid–Schiff and pathogens (eg, fungal, acid-fast bacilli) was negative. After the procedures, she was admitted to the hospital for dehydration.

During admission intake, she recalled being bitten by a tick approximately 1 week prior to the onset of symptoms. She was initiated on antimotility agents (eg, loperamide) and a 7-day course of doxycycline, which resulted in a decrease in the diarrhea. She was discharged home 5 days after admission. Serological testing for tick-borne disease returned after discharge and was negative. Convalescent testing at follow-up with ID, approximately 1 month after admission, demonstrated seroconversion of both *Rickettsia* and *Ehrlichia* to titers of 1:128, while levels of alpha-gal IgE were positive in the "low" range. She initiated a restricted diet and started a twice-daily antihistamine with noted improvement.

DISCUSSION

Our case series highlights how patients with AGS may be referred to ID clinics due to the temporal associations between

persistent, unexplained symptoms and tick exposures. Many patients in our series had experienced symptoms for months after the acute tick-borne illness with most having had multiple other primary care and subspecialty visits. Almost all had received multiple courses of doxycycline or other antibiotics. The delays in diagnosis and ultimately avoidable tests and procedures (eg, imaging, colonoscopy) highlight the important role that ID physicians can play in the diagnosis of AGS for the benefit of the patient. To our knowledge, this case series provides the first description of such patients presenting to ID clinics.

Tick exposure was a key element of the clinical history and had been elicited in all cases prior to referral. Notably, AGS patients often recall the inciting tick bite as being unusually erythematous and pruritic as compared to previous bites, and this reaction correlates strongly with positive alpha-gal IgE levels [15]. Yet, the presence of AGS symptoms—very different from those of a typical acute febrile illness—was frequently attributed to a persistent or incompletely treated tick-borne infection. This occurred even though tick-borne *Ehrlichia* and *Rickettsia* are not known to (1) be resistant to first-line therapies such as doxycycline or (2) establish latent infections with long-term consequences similar to those seen in later stages of Lyme disease. For these reasons, the nature, onset, and duration of symptoms provide important clues to the diagnosis. For the patients described in our case series, their symptoms began 2–4 weeks after the tick bite and persisted for months with little to no improvement after treatment with antibiotics.

While the diagnosis of AGS is challenging due to the nonspecific nature of symptoms and wide spectrum of severity, we observed that most patients presenting to our clinic reported similar clinical syndromes. GI symptoms, including bloating, cramping, nausea, and diarrhea, were most common. However, other complaints such as migratory arthralgia, fatigue, and cognitive impairment, often described as "brain fog," were reported, while IgE-mediated symptoms like urticaria and asthma exacerbations were less common. Notably, none of our patients presented with anaphylaxis, which is arguably the most widely recognized feature of AGS and would likely prompt more urgent evaluation, likely in an ED [19]. Some patients had already noted a worsening of symptoms with ingestion of certain foods, but none attributed their symptoms to mammalian meat product exposure or, more specifically, alpha-gal allergy.

Despite growing numbers of clinicians recognizing AGS as a leading cause of adult-onset anaphylaxis, fewer recognize the nonclassical manifestations of this syndrome, resulting in frequent referrals of AGS patients to nonallergy specialists. In an investigation of patients referred to a southeastern US gastroenterology clinic with unexplained GI symptoms consistent with AGS, nearly one-third of patients had positive alpha-gal IgE levels, of which 80% reported symptomatic improvement with mammalian product avoidance [20]. Even in patients who received a diagnosis of AGS from an allergist, close to half reported that they self-referred to an allergist as opposed to being directed there by a physician [17]. Evidently, increased awareness of the atypical presentations of AGS is needed across the medical community to minimize costly referrals, tests, and delays in diagnosis. Thus, ID physicians should maintain a relatively high suspicion for AGS when seeing patients with persistent symptoms following tick exposure or tick-borne infection. When considering a diagnosis of AGS, physicians should utilize alpha-gal IgE testing as confirmatory laboratory evidence alongside a patient's clinical presentation [21]. However, a positive alpha-gal IgE result (≥0.1 IU/mL or ≥0.1 kUA/L) alone is not a definitive indicator of AGS. An estimated 15%–25% of individuals in the southeastern US test positive for alpha-gal IgE, despite only a fraction of sensitized individuals developing AGS for reasons that remain unclear [14].

CONCLUSIONS

This case series illustrates the need to consider a diagnosis of AGS in patients with prolonged, nonspecific symptoms such as GI distress, fatigue, arthralgias, and mild cognitive dysfunction following a tick exposure. As symptoms may initially be attributed to an infectious cause, ID physicians have a unique opportunity to ensure the timely diagnosis of AGS and must be attuned to its more nuanced and "atypical" presentations. Given the potential for more severe manifestations such as anaphylaxis, awareness of dietary restrictions and referral for allergy evaluation are encouraged.

Notes

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