False-positive Elevation of Beta-D-glucan and Aspergillus Galactomannan Levels Due to Mendelson’s Syndrome after Rice Aspiration

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Abstract:
Both 1,3-beta-D-glucan (BDG) and galactomannan (GM) are polysaccharide components of the fungal cell wall. Although elevated levels of serum BDG and Aspergillus GM suggest invasive fungal infection or Pneumocystis pneumonia and aspergillosis, respectively, it is also necessary to consider the possibility of false-positives. We herein report a 68-year-old man with marked elevation in serum BDG and GM levels accompanied by Mendelson’s syndrome after rice aspiration. With the improvement of Mendelson’s syndrome, his serum BDG and GM levels decreased. The false-positive serum BDG and GM findings may have been due to his aspiration of food containing them. It is important to take a detailed history of aspiration in addition to making a conventional differential diagnosis in patients with pneumonia with elevated serum BDG and GM levels.

Key words: beta-D-glucan, Aspergillus galactomannan, false positive, aspiration pneumonia, Mendelson’s syndrome, inhalation

(Intern Med 61: 2935-2939, 2022)
(DOI: 10.2169/internalmedicine.8805-21)

Introduction

1,3-beta-D-glucan (BDG), a polysaccharide glucose polymer, is a constituent of the fungal cell wall (1) and thus a useful serum marker for the diagnosis or monitoring of invasive fungal infection or Pneumocystis pneumonia (PCP) (2). However, false-positive BDG findings not related to invasive fungal infection, have been reported in some conditions, including hemodialysis with cellulose membrane filters, use of fungal-derived antimicrobial agents, infusion of blood products containing immunoglobulins or albumins, massive mushroom intake and bacteremia due to certain bacteria (3-10).
Galactomannan (GM) is also a polysaccharide component of the cell wall of some fungi or plants. Aspergillus GM is used as a beneficial serum marker for invasive aspergillosis infections. Similar to BDG, false-positive GM findings have been reported in cases involving beta-lactam antibiotics or immunoglobulins administration, certain bacterial infections and aspiration pneumonia (11-14). However, the relationship between food aspiration and increased serum BDG and GM levels is not well known.
We herein report a case of an immunocompetent man with marked elevation of serum BDG and GM levels accompanying Mendelson’s syndrome after rice aspiration. Af-
After treatment with antibiotics only, the patient recovered from Mendelson’s syndrome, and the serum BDG and GM levels gradually decreased.

**Case Report**

A 65-year-old man was brought to another hospital by ambulance due to acute respiratory failure after lunch. He had a history of pulmonary tuberculosis at 20 years old as well as a 30-pack-year smoking history. His regular medications were tadalafil and dutasteride for benign prostatic hyperplasia. He had no history of recent usage of antibiotics and blood products. Chest computed tomography (CT) revealed bilateral upper lobe predominant ground-glass opacity, and he was hospitalized (we defined the day of onset as day 1). The patient was initially diagnosed with bacterial pneumonia and treated with antibiotic therapy [ampicillin-sulbactam (ABPC/SBT) and minocycline] and systemic corticosteroids [prednisolone (PSL), 40 mg/day]. On day 4, it turned out that his serum BDG levels on admission (Fungitec G Test MKII “Nissui”; Nissui Pharmaceutical, Tokyo, Japan) had increased to >300 pg/mL. Due to suspected PCP, he was started on treatment with a trimethoprim-sulfamethoxazole combination. The patient was then transferred to our hospital during the day.

Upon admission to our hospital, the patient was alert, with a respiratory rate of 24 breaths/min and peripheral capillary oxygen saturation (SpO₂) of 96% under oxygen administration at 2 L/min by nasal cannula. His other vital signs were stable. A physical examination revealed late inspiratory fine crackles over the bilateral lung fields.

Laboratory tests revealed a white blood cell count of 11,460/mm³, erythrocyte sedimentation rate of 20 mm/h, C-reactive protein concentration of 5.11 mg/dL and immunoglobulin G level of 1,102 mg/dL. The KL-6 level was 274 U/mL, which was within normal limits (<500 U/mL). BDG (β-glucan test Wako; Fujifilm Wako Pure Chemical, Osaka, Japan) and *Aspergillus* GM antigen (Platelia Aspergillus Ag; Bio-Rad Laboratories, Marnes-la-Coquette, France) levels were markedly elevated at 435.5 pg/mL and >5 index, respectively. The patient was negative for human immunodeficiency virus (HIV) antigens and antibodies. His peripheral blood culture tests were negative.

Chest CT revealed bilateral upper lobe-predominant centrilobular ground-glass opacity and consolidation, which were relatively typical of aspiration pneumonia but not of PCP and pulmonary aspergillosis (Fig. 1). The BDG level in the bronchial lavage fluid was 911.0 pg/mL by dilution measurement. Culture of the bronchial lavage fluid showed positivity for non-hemolytic *Streptococcus* and negativity for both fungi and acid-fast bacilli. A polymerase chain reaction was negative for *Pneumocystis jirovecii*. A pathological examination by hematoxylin-eosin stain and Grocott’s methenamine silver stain detected a large amount of food residue in the bronchial lavage fluid and no evidence of fungal infection.

Because the patient had no immunodeficiency and his radiologic findings were atypical, we ruled out PCP, aspergillosis and other pulmonary fungal infections and diagnosed him with Mendelson’s syndrome or aspiration pneumonia.
Figure 2. Therapeutic course, serum (1,3)-beta-D-glucan (BDG) levels at each sampling time and chest X-ray findings. The serum BDG level gradually decreased and eventually normalized after discharge. The X-ray findings also improved following treatment. Oxygen was administered by nasal cannula. ABPC/SBT: ampicillin/sulbactam, ST: sulfamethoxazole/trimethoprim, CT: computed tomography, BF: bronchofiberscopy, dis.: discharge

Discussion

We noted two important clinical issues in our patient. First, serum BDG and GM can show false-positive results in cases of aspiration of food containing them. Second, rice can contribute to a false-positive elevation of serum BDG levels.

In this case, although PCP, aspergillosis and deep mycosis were ruled out, marked elevations of BDG levels were observed in the serum, bronchial lavage fluid and food suspensions. While BDG is a useful marker for the diagnosis or monitoring of fungal infections, some reports have shown false-positive results in certain conditions, including use of cellulose membrane filters, fungal-derived antibiotics or blood products (6-9). However, our patient had no such histories. Furthermore, elevated serum BDG levels may be observed in certain bacteremic patients, such as those with infections caused by *Nocardia* species, *Streptococcus pneumoniae*, *Alcaligenes faecalis* and *Pseudomonas aeruginosa* (3, 4), none of which were detected in this case.

Previous studies have reported that the abundant intake of foods, such as mushrooms (5) or seaweed (10), that include polysaccharides containing glucose, may cause increased serum BDG levels. Therefore, BDG or its analogs included in
foods could contribute to the elevation of serum BDG levels. In addition, his serum Aspergillus GM antigen levels were high in spite of lack of general reasons for positivity. GM is also a kind of polysaccharide, and a false-positive elevation of serum GM antigen due to the aspiration of GM of food origin has been reported (14, 15). These cases support the explanation that aspiration of food caused the false-positive reaction of serum BDG as well as GM in this case.

Just before symptom onset, the patient had vomited and aspirated a large amount of pearl barley rice that he had eaten for lunch. We wondered whether or not the pearl barley would show cross-reactivity with the BDG assay, as it includes large amounts of beta-glucan; thus, we measured the BDG levels in (1) the supernatant of a suspension of rice and saline, (2) the supernatant of a suspension of rice with pearl barley and saline and (3) saline alone as control using the same method as that for blood serum. High BDG concentrations were detected in conditions (1) and (2), suggesting that the elevation was at least due to the aspiration of rice.

This study and previous research indicate that rice includes large amounts of BDG and GM (16). We ordinarily eat rice, which is rich in BDG and GM; however, it does not contribute to the elevation of serum BDG and GM levels. While the reason why serum BDG and GM levels became elevated following absorption through the respiratory mucosa is unclear, one possible explanation involves the fact that foods or other materials consumed orally are usually denatured by gastric juice; however, the relatively low levels of these enzymes in cases of aspiration results in less denaturation (17). In addition, the distal bronchioles and alveoli have a high surface area and adjoin capillary vessels through thin bronchiolar or alveolar walls (17, 18). Thus, during aspiration or inhalation of a large amount of material, including BDG and GM, can allow them to enter vessels easily and directly without denaturation. Through this mechanism, inhalation also allows the systemic delivery of drugs, such as insulin, that cannot be administered orally (19).

Several limitations associated with the present study warrant mention. First, the BDG tests that we used in this study do not guarantee an accurate measurement of BDG in samples other than serum and plasma. Furthermore, when measuring BDG using Limulus amebocyte lysate (LAL), inhibitors and endotoxin indicating cross-reactivity with LAL in the samples are inactivated by heating (20). We measured the BDG levels in bronchial lavage fluid or food suspensions based on previous studies that have reported the measurement of BDG in bronchoalveolar lavage fluid for the diagnosis of mycosis (21, 22). However, in those cases, the BDG tests showed false-positive results when contamination with large amounts of foreign substances, like endotoxin, developed beyond expectations. Second, we measured the concentrations of BDG in food suspensions to perform relative evaluations; thus, the values were not the actual BDG content in these foods. Third, we did not evaluate the BDG levels in other foods that the patient had eaten before the onset and did not evaluate the GM levels under the same conditions as BDG.

In conclusion, serum BDG and GM assays can show false-positive results because of the aspiration and trans-airway absorption of food containing large amounts of these molecules. It is important to determine the history of aspiration in addition to performing a conventional differential diagnosis in pneumonia patients with an unnatural elevation of serum BDG and GM levels.

The authors state that they have no Conflict of Interest (COI).

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