

Case Report

PAPAIN-INDUCED ASTHMA: A MAN WITH DYSPNEA FROM DAWN TILL DUST

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ABSTRACT

A 52-year-old man, a current smoker (40 pack years) with unremarkable medical history, was referred to the outpatient pneumology clinic because of recent complaints of shortness of breath and wheezing, which were relieved by inhaled bronchodilators. Serial peak expiratory flow (PEF) measurements showed a clear rise in PEF during the weekend and a fall on the evening after the first day of the week. It also showed that evening values were always lower than morning values. During a holiday, a slow but persistent rise in PEF was observed. Such a pattern is highly suggestive for occupational asthma. A detailed description of his job revealed papain exposure. After a positive specific IgE and skin prick test for papain the diagnosis of papain induced asthma was made. When an allergy and serious lung function impairment is proven against products encountered in a work related situation, not improving after maximal preventive measures, the patient is advised to change job.

Key words: Papain, occupational asthma, serial peak expiratory flow, occupational allergy, dust

CASE PRESENTATION

A 52-year-old man, a current smoker (40 pack years) with unremarkable medical history, was referred to the outpatient pneumology clinic because of recent complaints of shortness of breath and wheezing, which were relieved by inhaled bronchodilators. Clinical examination was normal (body mass index 24 kg/m²) except for bilateral inspiratory and expiratory wheezing on auscultation.

He had worked in various jobs, including a factory with exposure to hydrochloric acid and sulfuric acid, an industrial

bakery (for ten years) and a fishmeal factory with heavy exposure to dust. He had left the latter job due to intractable sneezing and nasal congestion. Since the past two years he had worked as an operator in a small factory that produced papain. He was seen annually by the company doctor who performed spirometry on a yearly basis.

Pulmonary function revealed a moderate obstructive impairment (FVC 120% predicted, FEV₁ 51% predicted) that was reversible after bronchodilator administration (FEV₁ +23%). Exhaled nitric oxide (FeNO) was high at 70 ppb (normal value < 20 ppb). Single breath diffusing capacity for carbon monoxide (DLCO) was low normal (73%). A chest radiograph showed no abnormalities. The patient was initially advised to stop smoking and also asked to perform serial peak expiratory flow (PEF) measurements twice a day during two months. These serial PEF measurements showed a clear rise in PEF during the weekend and a fall on the evening after the first day of the week; evening values were always lower than morning values. During a holiday, a slow but persistent rise in PEF was observed (figure 1). Such a pattern is highly suggestive for occupational asthma.

A detailed description of his job revealed that he was involved in the production of papain. He worked with two other colleagues in the production department. Papain is there imported as either powder or flakes from Congo. The papain powder is manually loaded into silos and, after being mixed with sugar, is packed according to specific customer demands. During this filling, dust is released. The papain flakes are hoisted from bags into a silo, again releasing dust. The silo contains a mixture of water and acetone, which causes the flakes to dissolve. The mixture is pushed through filters and the water and acetone evaporates so only solid matter remains. Hereafter sugars are added and dilutions created.

He described his job as dusty, and worked wearing gloves and respiratory protection in the form of a mask. Originally a P3 dust mask was used. Later on a full ventilated protective suit with hat and gloves was used, resulting in less symptoms.

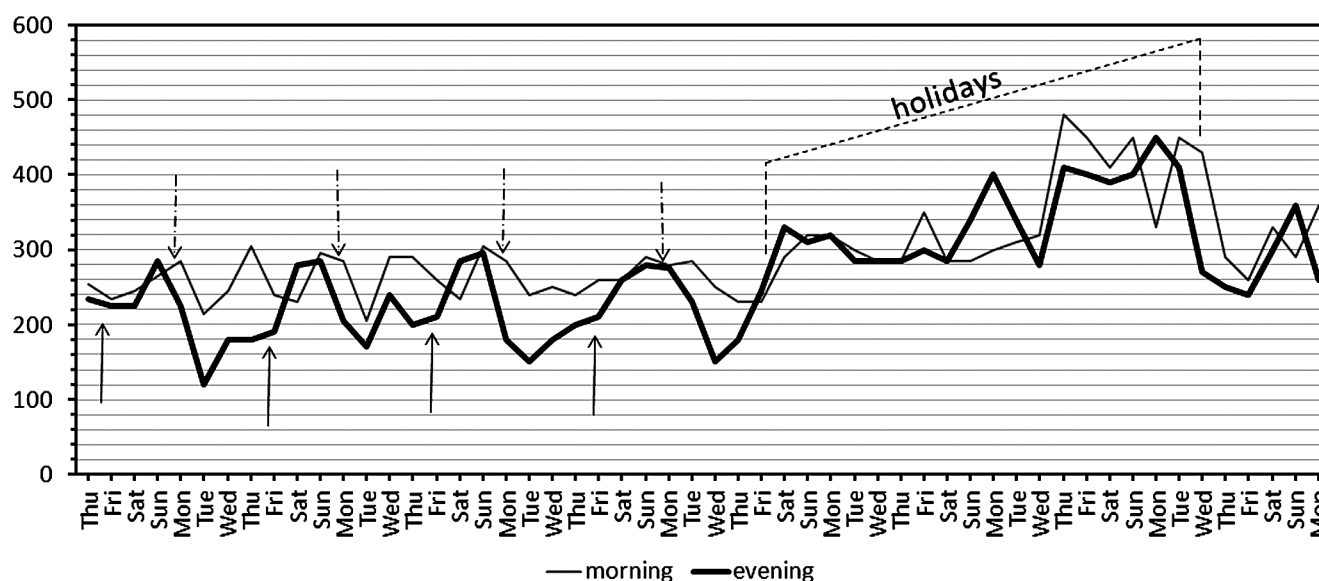


Figure 1: Self-measured peak expiratory flow (PEF) measured twice daily (each morning and evening) for two months. The Y-axis shows PEF values in L/min and the X-axis shows dates. The gray line indicates the morning values and the black line the evening values. Full arrows indicate the evening before the weekend, line-dot arrows indicate Monday morning values. The dashed line indicates a period of holiday.

The P3 filter filters at least 99.95% of airborne particles. He mentioned that his coworkers also had respiratory complaints, and that everybody developed acute redness of the skin when in contact with papain. There were no reports of allergies in his coworkers.

Skin prick tests were strongly positive for house dust mite and birch pollen; skin prick tests with a freshly prepared suspension (in 30% glycerin and 0.75% sulfite) of papain from the factory was strongly positive with 1% papain and mildly positive with 0.1% papain. Determination of specific IgE to papain via the RAST gave a value higher than 100 Ua/mL. Due to the ongoing symptoms under treatment and maximal preventive protection in the working environment, the patient was advised not to work with papain any longer. A file for compensation of occupational asthma was introduced. The company doctor was informed of our recommendations.

DISCUSSION

Papain is a cystein protease hydrolase enzyme that is present in the latex of papaya (*Carica papaya*, paw paw fruit). The latex of the green fruit contains two proteolytic enzymes, namely chymopapain and papain. Though the former is most abundant, the latter has twice the proteolytic potency. Papain has numerous applications. In the food industry, papain is widely used for tendering meat or clarifying beer and other drinks, as well as in other manufactured foods (1). Other industrial uses of papain include the treatment of wool or silk, and of hides before tanning. Medical uses include topical applications for the debridement of necrotic tissue and it is occasionally used for treating stings of jellyfish or hymenoptera although the latter should be avoided, as the literature shows no effect of papain (2). Placebo effects and the benefit of counter-irritation may account for the anecdotal benefit of

rubbing crystalline papain on normal skin near the sting site (3). Papain is also sold as an over the counter digestive medicine in alternative medicine. Papain may be present in contact lens cleansing fluids, toothpaste (as a teeth-whitener) and in cosmetics (e.g. abrasive creams) (4). Furthermore, it is used in biochemical laboratories, more specifically in immunology where papain is known to cleave the Fc portion of immunoglobulins from the Fab portion.

The literature on papain-induced asthma shows only a handful of cases. The affected subjects mostly worked in pharmaceutical plants, pharmacy, factories and industrial kitchens (5-7). The high rate of sensitization in papain exposed workers suggests that this proteolytic enzyme is a potent allergen.

Positive skin-prick reactions to papain, as well as asthma attacks and/or nasal symptoms after exposure to papain have been described in both atopic and non-atopic subjects (6).

The potent proteolytic (and elastolytic) properties of papain also represent a potential threat of other injury to the respiratory tract. Thus, emphysema has been produced in rats, hamsters, rabbits and dogs after the inhalation or intratracheal instillation of papain. However, no evidence of emphysema caused by papain exposure has been reported in humans. Nevertheless, prolonged exposure to papain powder in factory workers seems to produce some form of symptomatology in almost all of them. This can be fatigue, cough, chest pain, wheezing, shortness of breath, sneezing, rhinitis, eye dryness, lacrimation, nasal congestion, urticaria, itchy or swollen eyelids and occasionally even anaphylaxis or death (6).

In the exposure to papain, two factors are important: atopy and exposure intensity. Atopic workers developed symptoms and IgE anti-papain antibodies much earlier than non-atopic workers. Exposure intensity on the other hand correlated with symptoms and immune response and was a factor more important than duration of exposure (7). Prior sensitization is

another important factor. When accidentally exposed to high amounts of papain, highly sensitized patients can develop anaphylactic shock and even death (6). It is believed that extensive measures should be taken to eliminate the risk of sensitization and consequently illness. High-risk patients should avoid exposure, workers should be monitored by immunoserological and pulmonary function tests and proper safety measures need to be taken. Previous studies suggest a high frequency of developing papain sensitisation. Baur et al. reported seven out of eleven workers with occupational exposure to papain who developed immediate hypersensitive reactions, predominantly asthma and rhinitis (5). Likewise, Novey et al. found that of the twenty-three employees at a pharmaceutical plant manufacturing a new product containing papain, twelve had respiratory symptoms of cough, wheezing, dyspnoea or chest pain. Atopic workers developed pulmonary symptoms and anti-papain antibodies significantly sooner after papain exposure than did the others. The workers who had the greatest amount of dust exposure per work-day had significantly more pulmonary symptoms (7).

The initial evaluation of workers exposed to proteolytic enzymes such as papain should always include an extensive history with job description, duration of exposure prior to symptoms, description of workplace, protective measures, length of daily exposure and temporal relationship between symptoms. Ongoing communication with health personnel from the working place is important, not only for evaluation of the source but also afterwards, for prevention.

Further diagnosis needs more than an occupational history and positive skin prick test, though skin prick testing is essential in the diagnosis as it is more sensitive than dosing specific IgE in vitro. Lung function decrease is needed in association with exposure to the causative agent. Serial daily peak flow measurement is one good solution, but sometimes, when the diagnosis remains unclear, a provocation test is needed with the specific enzyme. Another possibility is peak flow measurement with a workplace challenge test. Other tests included are an assessment of atopic status by percutaneous testing to allergens and to the enzymes encountered at work. Although not routinely used, immunoblot has also been used in the detection (8). When an allergy and serious lung function impairment is proven against products encountered in a work related situation, not improving after maximal preventive measures, the patient

needs to change job, as did the case-patient, with excellent respiratory recovery since.

In a nonoccupational setting, the most widespread exposition to papain is by its use as a meat tenderiser. In the United States, about 95 percent of the meat tenderisers used, are either papain or bromelain and home cooking accounts for 90 percent of its use. Meat tenderising alternatives to papain do exist (Ficin from fig trees, acid-based marinades, slow-cooking, cutting or pounding) and more recently, the United States Department of Agriculture also approved protease preparations from *Aspergillus oryzae*, *Aspergillus niger* and *Bacillus subtilis* (9). Use of papain meat tenderisers in daily cooking is considered safe although these enzymes are also potential ingestive allergens and may represent an unrecognized cause of an allergic reaction following a meal. Occasional case-reports of hypersensitivity reaction to papain through ingestion of papain tenderised beef have been described (10).

CONFLICT OF INTEREST: None.

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