

A case of fibromyalgia syndrome with anaphylaxis induced by intradermal injection of purified protein derivative

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Abstract When a 36-year-old woman with fibromyalgia syndrome (FMS) underwent the tuberculin test, urticaria developed on her trunk at 30 min after intradermal injection of purified protein derivative. Although the urticaria resolved, fever, facial edema, and generalized urticaria occurred after 8 h. A patient with FMS who developed a systemic allergic reaction after an intradermal skin test has not been reported. We should pay attention to anaphylactic reactions after intradermal injection in patients with FMS.

Keywords Anaphylaxis · Fibromyalgia syndrome · Intradermal injection · Purified protein derivative

Introduction

Fibromyalgia syndrome (FMS) is characterized by widespread chronic pain and tenderness at specific sites of the body. It is known to be associated with various other symptoms, physical, central nervous system, and neuropsychiatric symptoms, in addition to pain [1–5]. It has been reported that 46.8 % of FMS patients have allergic diseases such as allergic rhinitis, conjunctivitis, or asthma [6, 7], and it can be difficult to distinguish FMS patients with these symptoms from patients with multiple chemical sensitivity [8–10]. However, a case of FMS with a systemic

allergic reaction after intradermal injection has not been reported.

By the way, tuberculosis is still a major cause of death in many countries. Tests such as sputum smear, culture, and chest X-ray examination are used for diagnosis of tuberculosis. In Japan, the tuberculin test is performed to detect infection in healthcare professionals who are at risk of occupational tuberculosis as well as to screen persons who have been exposed to a source of infection. Purified protein derivative (PPD) is used for this test. After injection of PPD, various local symptoms such as itching, erythema, rash, urticaria bullosa, and necrosis have occasionally been reported as adverse reactions. However, the reports on systemic symptoms such as fever and edema are few [11–13]. Here we report a rare case of a patient with FMS who developed a systemic allergic reaction to PPD.

Case report

The patient was a 36-year-old woman with photosensitivity reaction and food allergy (yams) who was taking oral contraceptives for treatment of endometriosis. She had a history of bacille Calmette–Guérin (BCG) vaccination, and she had positive reactions in the past tuberculin tests. In May 2008, she had pain of the right shoulder and fingers, followed by generalized pain, so she visited the Neurology Department of a university hospital. No neurological abnormalities were found, and she was followed up. She was admitted to the Neurology Department of another university hospital in 2009 because she had persistent pain accompanied by numbness. After detailed examination, no abnormalities were found except that antithyroid antibody was positive, and she was discharged from the hospital. Subsequently, she presented to our hospital in March 2010.

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She had 11 specific points of tenderness (left and right trapezius muscles, second ribs, lateral epicondyle, greater trochanter, supraspinatus muscle, and right buttock) on palpation.

Urinary examination was within normal limits. White blood cells, hemoglobin, hematocrit, and platelet were 4200/ μ l, 12.5 g/dl, 38.1 %, and 223,000/ μ l, respectively. Eosinophils of 1.0 % were within the normal range. Liver function tests showed aspartate aminotransferase of 20 IU/l and alanine aminotransferase of 23 IU/ml. Renal function tests showed blood urea nitrogen of 13 mg/dl and creatinine of 0.51 mg/dl. On endocrinological tests, thyroid-stimulating hormone and free T4 were 5.892 μ U/ml (normal limits 0.34–3.88 μ U/ml) and 1.18 ng/dl (normal limits 0.95–1.74 ng/ml), respectively. Anti-microsome antibody and anti-thyroglobulin antibody were 6400 titer (normal limit <100 titer) and 100 titer (normal limit <100 titer), respectively, indicating chronic thyroiditis. IgG of 1323 mg/dl, IgA of 283 mg/dl, IgM of 105 mg/dl, and IgE of 128 IU/ml were within the normal range. On serological tests, C-reactive protein (0.23 mg, normal limits 0–0.4 mg/dl), anti-nuclear antibody (<40 titer, normal limit <40 titer), rheumatoid factor ($\leq$ 5.0 IU/ml, normal limits 0–19 IU/ml) were within normal limits. Anti-SS-A antibody and anti-SS-B antibody were negative. She was diagnosed as having fibromyalgia [14, 15] complicated by chronic thyroiditis and hypothyroidism. Nonsteroidal anti-inflammatory drugs (NSAIDs), neurotrophin, an antidepressant, a low-dose thyroid hormone preparation, and a vitamin preparation were prescribed. She was followed up at the outpatient clinic, and her tender points decreased to 7.

She developed urticaria on her trunk at 30 min after intradermal injection of PPD when she underwent the tuberculin test before starting her job as a healthcare worker in April of the same year. Although the urticaria resolved after approximately 30 min, fever (38.5 °C) and facial edema occurred subsequently (Fig. 1), and systemic urticaria recurred after 8 h. Although she went to another hospital, she did not have any prescription. The fever subsided on the following day, facial edema resolved by 2 days after PPD injection, and urticaria disappeared by approximately 2 weeks after injection of PPD. Her tender point count increased to 10. A blood test about 2 weeks after the occurrence of anaphylactic symptoms showed white blood cell count 5,100/ μ l, eosinophils 0 %, and IgE level 108 IU/ml, thus all within normal limits. Moreover, because the tuberculin test results showed negative conversion, malignant lymphoma and sarcoidosis were suspected, and the patient was examined for these conditions. However, the superficial lymph nodes were not palpable, and the values of angiotensin-converting enzyme and soluble interleukin-2 receptor were within the normal range, with no abnormal findings in chest radiography images.

Discussion

In the present case, urticaria appeared on the trunk first at 30 min after intradermal injection of PPD, and resolved after approximately 30 min. Then, fever and facial edema occurred subsequently, and systemic urticaria recurred after 8 h. Facial edema resolved by 2 days, and urticaria disappeared by approximately 2 weeks after injection of PPD. This case has food allergy and has been taking NSAID. NSAID is known as a possible anaphylactic cotrigger by facilitating allergen absorption from the gastrointestinal tract in a case of food allergy [16]. Therefore, naproxen might be related to anaphylaxis in this case. Hypersensitivity symptoms have infrequently been reported as adverse reactions immediately after injection of PPD, including itching, erythema, rash, urticaria, and local symptoms such as bullosa or necrosis, but the reports on patients with systemic symptoms such as fever, and facial swelling are few. Systemic symptoms of the present case were regarded as biphasic and protracted anaphylaxis [17–23]. Biphasic anaphylactic reactions have been found to develop in as many as 20 % of anaphylactic reactions [17, 18, 20, 21, 23], and can be less severe (one-third), equally severe (one-third), or more severe (one-third) than the initial reaction [19, 20]. The second-phase reaction has been described as occurring between 1 and 8 h after the initial reaction [19]. Systemic urticaria of the present case was recurred after 8 h. A delay in the administration of epinephrine and too small a dose of epinephrine given for the primary response have also been mentioned as risk factors of second-phase reaction [22], so she should have been administered epinephrine for the primary response.

Recently, abnormal overexpression of mast cells (MCs) in skin biopsies of FMS patients has been reported [24]. According to this report, a significantly increased number of MCs in the papillary dermis was seen and MCs were uniformly distributed around blood vessels and appendages. MCs are easily stimulated by a number of chemical triggers to degranulate and release several proinflammatory products. Moreover, it has been reported that FMS might trigger chronic urticaria [25]. In the present case, there might be a possibility that systemic allergic reactions developed as a result of overexpressive MCs in the papillary dermis being stimulated by intradermal injection of PPD.

By the way, Froeschle et al. [12] reported 24 cases of serious or life-threatening hypersensitivity reactions to tuberculin tests performed between October 1, 1989 and November 30, 2000. According to their report, the incidence rate of the reactions was 0.08 % reported reactions per million doses of tuberculin. Youssef et al. [13] reported 26 cases of serious hypersensitivity reactions to tuberculin tests performed between 1998 and 2005, and the incidence



Facial edema at eight hours after injection of PPD

At 4 days after injection of PPD

Fig. 1 Facial edema after intradermal injection of PPD. Facial edema resolved by 2 days after PPD injection

rate of the reactions was 1 per million doses. With reference to their report, the incidence of serious hypersensitivity reactions after tuberculin tests becomes less than 1 per million doses, which can be considered as a very rare adverse effect. In the report by Youssef et al., cases that exhibited a serious allergic reaction to tuberculin test for the first time were included. On the other hand, the present case had positive reactions in the past tuberculin tests. However, she developed systemic allergic reactions and showed negative reaction to the tuberculin test this time. It is necessary to consider the mechanisms of serious hypersensitivity reactions to tuberculin tests more.

In conclusion, we report a case of FMS complicated by biphasic anaphylaxis following intradermal injection of PPD. We recommend that PPD-induced anaphylaxis is kept in mind before PPD injection in patients with FMS, because anaphylaxis can be a fatal or life-threatening syndrome.

Conflict of interest None.

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