

Protracted anaphylaxis developed after peginterferon α -2a administration for chronic hepatitis C

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Side effects occurring immediately after administration include headache, nausea, and influenza-like symptoms, such as fever and joint pain. However, reports of anaphylactic shock are extremely rare. Here we report a patient with protracted anaphylaxis who suffered shock symptoms after peginterferon α -2a administration for chronic hepatitis C. Although the patient improved temporarily with shock treatment, symptoms of anaphylaxis recurred. As peginterferon is often administered on an outpatient basis, it is important to recognize life-threatening side effects that may develop in a protracted manner.

Key words: Peginterferon α -2a; Anaphylaxis; Anaphylactic shock; Protracted anaphylaxis; Chronic hepatitis C

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Core tip: This is the first report that describes a case involving anaphylactic shock that developed after peginterferon administration. Moreover, our case showed protracted anaphylaxis, in which symptoms appear hours after exposure to the causative substances and temporarily improve with treatment but recur twice within hours. Protracted anaphylaxis is rare; its incidence accounts for less than 20% of all cases of anaphylaxis. There are few case reports regarding this condition, and its pathophysiology has not yet been established.

Abstract

Peginterferon is a key drug used to treat chronic viral hepatitis that is known for causing various side effects.

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INTRODUCTION

Anaphylaxis is a hypersensitivity reaction that causes systemic symptoms to abruptly appear, and if severe, they could be fatal. This adverse reaction is believed to be caused by immunological or non-immunological mechanisms. In recent years, protracted anaphylaxis, in which symptoms appear hours after exposure to causative substances, and biphasic anaphylaxis, in which symptoms temporarily improve with treatment but recur within hours, have been reported^[1,2]. However, there are few case reports regarding these conditions, and their pathophysiologies have not yet been clarified. In this study, to the best of our knowledge, we report for the first time a case of protracted anaphylactic shock that developed after peginterferon α -2a administration.

CASE REPORT

The patient was a 61-year-old Japanese male. During a follow-up examination with his local doctor for hypertension and type 2 diabetes, blood tests showed elevated liver enzyme deviations (aspartate aminotransferase, 89 IU/L; alanine aminotransferase, 189 IU/L). As a result, the patient was referred to our hospital for further examination and diagnosed with chronic hepatitis C (serotype 2) *via* blood test. No findings indicated hepatitis B or human immunodeficiency viral infections. We judged the patient to be a candidate for peginterferon α -2a (Pegasys®) monotherapy and admitted him to our hospital, considering that this was the first time he received this drug. The patient was generally in good condition upon hospitalization, and blood testing revealed his liver enzyme deviation was within the normal range. Apart from an elevated fasting blood glucose level (125 mg/dL) associated with his diabetes, no other blood-related abnormalities were noted. The patient received amlodipine (20 mg) and irbesartan (100 mg) each morning for hypertension. He had no known medication or food allergies or any relatives with a history of asthma or hereditary angioedema.

After hospitalization, a skin prick test was performed on the upper left arm using undiluted peginterferon α -2a with no clear allergic reaction such as rash or itching. Therefore, we subcutaneously injected 180 μ g of peginterferon α -2a into the patient's upper left arm; no adverse reactions were initially observed. However, 1 h and 20 min after injection, the patient complained of generalized itching and fever before temporarily losing consciousness. Erythema appeared from the patient's face to his trunk, and all four limbs were sweating profusely. His blood pressure decreased (66/48 mmHg), along with his blood oxygen saturation (SpO₂, 88%; room air). Consequently, the patient was diagnosed with anaphylactic shock and fluid loading was initiated. After intramuscular injection of epinephrine (0.5 mg) and intravenous injections of

chlorpheniramine (5 mg) and hydrocortisone (200 mg), his blood pressure increased to 142/70 mmHg, the itching subsided, and shock treatment was stopped. Subsequently, the patient underwent careful follow-up observation.

However, 3 h after peginterferon administration, the patient complained of recurrent itching, nausea, and abdominal pain. Although his blood pressure had decreased slightly (120/58 mmHg), the possibility of recurring anaphylaxis was considered, and he was again given an intramuscular injection of epinephrine (0.5 mg) and intravenous injection of hydrocortisone (300 mg). Subsequently, the patient's blood pressure increased and itching improved, but the erythema and nausea persisted. Furthermore, maintaining a 98% SpO₂ required delivery of 10 L/min oxygen by mask with reservoir bag. Due to his lack of improvement, we performed plain chest and abdominal computed tomography to determine whether the patient had intestinal or pulmonary edema. Results indicated no clear abnormalities in the lung area, but edematous changes were found primarily in the mucosa of the small intestine. Because the patient's voice had become muffled since the onset of initial shock symptoms, laryngeal fibroscopy was performed that revealed mild swelling of the larynx without edema of the vocal cords; thus, tracheal intubation was not performed.

Five hours after peginterferon administration, the patient again complained of recurrent itching and his blood pressure decreased substantially (80/48 mmHg). As the patient appeared to be in anaphylactic shock, a third intramuscular injection of epinephrine (0.5 mg) was given with methylprednisolone (1000 mg). Afterward, the patient's SpO₂ gradually improved, as did his symptoms of hypotension and itching. Oxygenation was discontinued 15 h after administration and the patient was allowed to resume meals following withdrawal of nausea and abdominal pain. No recurrence of abdominal pain was observed and erythema of the trunk disappeared approximately 24 h after administration. Because of the long half-life of peginterferon α -2a in blood, the patient remained under careful observation during his entire hospital stay. No recurrence of anaphylactic symptoms occurred and he was discharged on hospital day 8. Peginterferon treatment was not resumed thereafter. The patient was followed-up for 2 years on an outpatient basis, during which he had no recurrence of anaphylaxis.

DISCUSSION

Anaphylaxis is a potentially fatal hypersensitivity reaction that causes severe symptoms to rapidly appear throughout the body. A common symptom is an immediate allergic reaction mediated by IgE. In such cases, exposure to a certain allergen establishes sensitization, after which, repeated exposure stimulates

release of chemical mediators from mast cells in tissue or eosinophils in blood, leading to a range of symptoms^[3]. Typically, shock symptoms usually appear immediately after allergen exposure and rapidly worsen but respond quickly to timely appropriate treatment, such as epinephrine. However, sometimes the case of anaphylaxis differs from typical cases because it originates from the first exposure to a drug, such as an iodine contrast agent^[4] or certain anticancer drugs (taxanes)^[5], and develops hours after antigen exposure^[1,2]. Recently The European Academy of Allergy and Clinical Immunology proposes that anaphylaxis are categorized into two classes “allergic anaphylaxis” and “non-allergic anaphylaxis”^[6]. Because our patient had never previously been given peginterferon α -2a, shock symptoms appeared after initial administration, and he had negative skin prick test, we believe that a non-IgE-mediated mechanism was involved.

The side effects of peginterferon are broadly classified into two types: those which appear relatively quickly after initial administration and those appearing after multiple dosage. The former is known to include mainly headaches, rash, and influenza-like symptoms, such as fever and joint pain. Although anaphylaxis is included as a possible side effect on the enclosed peginterferon α -2a manufacturer product sheets^[7], its frequency is not mentioned. The fact that there was also no mention of anaphylaxis in two large-scale studies regarding the side effects of alfa interferon^[8,9] or a review of the side effects of peginterferon and ribavirin combination therapies^[10] suggests that it is a relatively rare side effect. Our MEDLINE search of reports on anaphylaxis developing after interferon administration revealed only two cases, both of which administered interferon β as part of their treatment for multiple sclerosis. Therefore, our report is the first case of anaphylaxis occurring in a patient undergoing treatment for hepatitis with peginterferon.

The first^[11] of the aforementioned cases was a 34-year-old female who underwent alternate day administration of interferon β -1a. Fifteen minutes after administration, the patient exhibited rash, respiratory distress, and decreased blood pressure. She was given an intradermal injection of epinephrine and administered corticosteroids and antihistamines, after which her condition improved. A skin test was used to diagnose an IgE-mediated allergy to interferon β -1a. The second case^[12] was a 21-year-old female administered with interferon β -1a for 6 months. Ten minutes after administration, she complained of respiratory distress and facial erythema was noticed; her blood pressure decreased and she lost consciousness. She regained consciousness upon administration of chlorpheniramine and hydrocortisone, and her blood pressure increased after a drip infusion of physiological saline solution. There was no mention of any allergies.

The course of anaphylaxis can be used to classify it into three types: monophasic, biphasic, and protracted anaphylaxis^[2]. A small-scale case series is the only study we found regarding protracted anaphylaxis, which develops hours after antigen exposure and progresses despite treatment. Unfortunately, little is known regarding its clinical characteristics and mechanisms at this time. Of all anaphylactic reactions, biphasic anaphylaxis accounts to almost 20% of all cases^[2,13]. The two previously reported anaphylaxis cases following interferon β administration mentioned above^[11,12] were monophasic, as symptoms appeared directly after drug administration and quickly improved with shock treatment. However, our patient exhibited protracted anaphylaxis, as symptoms developed more than 1 h after administration, temporarily improved with shock treatment, then recurred repeatedly, including repeated itching and decreased blood pressure.

Our case was characterized by severe protracted anaphylaxis. Brown^[14] proposed grading scores for anaphylaxis and defined serious anaphylaxis as that exhibiting hypoxia, hypovolemia or neurologic compromise, typically manifested by collapse. Although our case suffered serious anaphylaxis that met the requirements of this definition, it was recently reported by Lee *et al.*^[15] that there is a relationship between antihypertensive medication and serious anaphylaxis. Thus, the involvement of antihypertensive medication in our case is possible. However, there has not been any report on a relationship between antihypertensive medication and protracted anaphylaxis. In recent years, there have been successive reports of patients developing protracted anaphylaxis after administration of monoclonal antibodies, which have long half-lives in blood^[16]. This suggests that the long blood half-life of peginterferon α -2a influenced the development of protracted anaphylaxis in our patient. However, there have been no previous reports of anaphylactic shock caused by peginterferon; therefore, more data on patients with the same condition is required to understand the extent of peginterferon involvement in the pathological mechanism of anaphylaxis. As peginterferon α -2a is often administered on an outpatient basis, care should be taken regarding life-threatening side effects that may develop in a protracted manner.

COMMENTS

Case characteristic

A 61-year old patient who had not previously received on any antiviral therapy for chronic hepatitis C.

Clinical diagnosis

Anaphylactic shock.

Differential diagnosis

Pulmonary edema.

Laboratory diagnosis

Apart from an elevated fasting blood glucose level (125 mg/dL) associated with

his diabetes, no other blood-related abnormalities were noted.

Treatment

Intramuscular injection of epinephrine and intravenous injections of chlorpheniramine and hydrocortisone.

Experiences and lessons

As peginterferon is often administered on an outpatient basis, it is important to recognize life-threatening side effects that may develop in a protracted manner.

Peer-review

It's a very interesting case report. May be the long acting action of pegylated interferon has something to do in the protracted anaphylactic reaction.

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