

CASE REPORT

만성 C형간염 환자에서 페그인터페론 알파 2a에 의해 반복적으로 발생한 지방층염

송준석, 손주현, 정재윤, 민지희, 최원석, 김원중, 표주연¹

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Repeated Panniculitis Induced by Pegylated Interferon Alpha 2a in a Patient with Chronic Hepatitis C

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Pegylated interferon alpha (PEG-IFN- α) is widely used to treat chronic hepatitis C in combination with ribavirin. Many adverse effects of PEG-IFN- α , such as hematologic, psychologic, dermatologic, immunologic, and other abnormalities, have been reported, and some serious adverse events lead to PEG-IFN- α treatment discontinuation. For very rare adverse events such as panniculitis, there are no established guidelines on whether to continue PEG-IFN- α treatment. Published reports on panniculitis induced by PEG-IFN- α 2a are sparse. Herein we report a case of repeated occurrences of panniculitis in a patient with chronic hepatitis C, leading to treatment cessation. (**Korean J Gastroenterol 2016;67:272-276**)

Key Words: Panniculitis; Peginterferon alfa-2a; Hepatitis C; Adverse effects

INTRODUCTION

Hoofnagle and colleagues¹ first used interferon alpha as a potential treatment for patients with non-A non-B chronic hepatitis. Thereafter the combination of interferon and ribavirin were the main treatment agents for chronic hepatitis C. Many new direct-acting antiviral agents are now a part of treatment for chronic hepatitis C, but pegylated interferon (PEG-IFN) is still being used, especially for genotype 2, in Korea. However, PEG-IFN has a number of adverse effects, some severe enough to require halting interferon treatment. Dermatological adverse events induced by PEG-IFN include pruritus, alopecia, dermatitis, dry skin, and injection site

infection.² There are some case reports of panniculitis induced by PEG-IFN- β ,³⁻⁵ but only one case report about panniculitis induced by PEG-IFN- α was published in Korea.⁶ There is no report of repeated occurrences of panniculitis induced by PEG-IFN- α . So we report a case of repeated panniculitis induced by PEG-IFN- α 2a, with literature review.

CASE REPORT

A 50-year-old woman with body weight of 44 kg was admitted because of tenderness in the left lower abdomen accompanied by a nodule that occurred one day prior. Skin color at the site was reddish, and the nodule size was about 6×6 cm (Fig. 1).

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One year prior, she was diagnosed incidentally with chronic hepatitis C in a private clinic, and came to our hospital. At that time, serum complete blood cell counts and serum liver function test was within normal range. There was no abnormal finding on abdominal computed tomography. Her HCV PCR level was 6,980,000 IU/mL, and the genotype was 2a/c. She received outpatient monitoring for six months. After six months, her HCV PCR level was 6,770,000 IU/mL. In liver biopsy to determine whether to start the treatment, periportal fibrosis was observed, and treatment with PEG-IFN- α 2a (180 μ g/week) and ribavirin (800 mg/day) was started. No specific side effect was observed after the first subcutaneous injection of PEG-IFN- α 2a on the right lower abdomen at the hospital, but after the second subcutaneous injection of PEG-IFN- α 2a, self-administered on the left lower abdomen at home, she felt severe pain and a nodule in the injection site, and came to our hospital on the next day.

At admission, initial blood pressure was 100/60 mmHg, pulse rate 80/min, respiration rate 18/min, and body temperature 37.5°C. On physical examination, a subcutaneous nodule with reddish discoloration of overlying skin and tenderness was observed on her left lower abdomen. The laboratory findings were white blood cell $2.8 \times 10^3/\mu\text{L}$, hemoglobin 10.6 g/dL, platelets $159 \times 10^3/\mu\text{L}$, total protein 7.2 g/dL, albumin 4.0 g/dL, calcium 8.2 mg/dL, inorganic phosphorus 3.3 mg/dL, serum urea nitrogen 10 mg/dL, serum creatinine 0.6 mg/dL, estimated glomerular filtration rate was 106 mL/min/1.73 m², AST 25 U/L, ALT 20 U/L, total bilirubin 0.4 mg/dL, PT 10.5 sec, and CRP 0.15 mg/dL. In the soft tissue ultrasound, 6×2×6 cm sized edematous thickening at the in-

jection site was observed. In the Doppler ultrasound, vascularity in deep space was increased, indicating severe inflammation. Abscess, hematoma and necrosis were not observed (Fig. 2). With a diagnosis of panniculitis caused by PEG-IFN- α 2a, we treated her with oral prednisolone 20 mg once a day and acetaminophen 650 mg/tramadol hydrochloride 75 mg twice a day for two weeks. After the two weeks of treatment, her symptoms improved, and her left lower abdominal skin lesions completely recovered. After considering and explaining the benefits and risks of the PEG-IFN- α 2a, we decided to restart the same treatment. The third PEG-IFN- α 2a subcutaneous injection on the right lower abdomen produced no complication. However, after the fourth at the different location from the first injection site on the left lower abdomen, she felt the same pain and nodule at the injection site as before. A punch skin biopsy from the lesion was performed, measuring 0.3 cm in diameter and 0.5 cm in depth. Histologically, the pathologic examination showed superficial and deep perivascular and interstitial lymphocytic infiltrates. Unfortunately, we could not obtain sufficient subcutaneous fat tissue. However, a few degenerated adipocytes were noted in the adjacent eccrine glands and small vessel. The epidermis was unremarkable (Fig. 3). After re-treatment with oral prednisolone 20 mg once a day and acetaminophen 650 mg/tramadol hydrochloride 75 mg twice a day for two weeks, her symptoms and skin lesion completely resolved. However, the repeated occurrence of panniculitis led us to discontinue PEG-IFN- α 2a and ribavirin treatment. We are considering oral direct acting antiviral agents as her new treatment agents.



Fig. 1. The skin lesion was reddish and edematous, and the size of subcutaneous nodule was 6×6 cm.

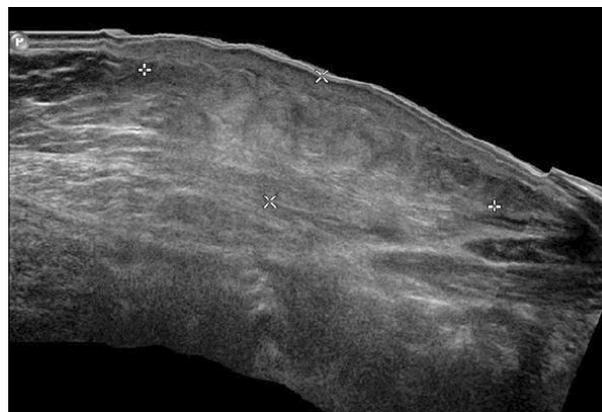


Fig. 2. Ultrasonographic findings. Soft tissue ultrasound shows cellulitis, panniculitis and myositis of the left abdominal wall compatible with chemical-induced inflammation.

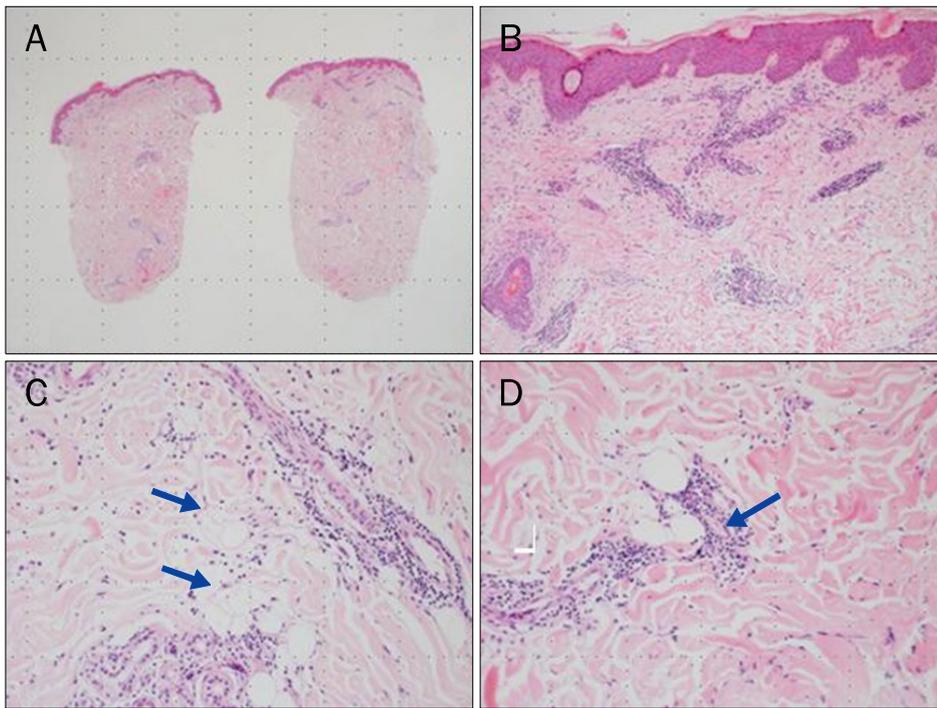


Fig. 3. Microscopic findings of the punch biopsy specimen (H&E). (A) Histology of bisected tissue section of abdominal skin lesion ($\times 12.5$). (B) Superficial perivascular and interstitial lymphocytic infiltrates ($\times 100$). (C) Deep perivascular and interstitial lymphocytic infiltrates ($\times 200$) (arrows). (D) In deep dermis, a few degenerated adipocytes with lymphocytic infiltration ($\times 200$) (arrow).

DISCUSSION

The patient in this case was given a total of four PEG-IFN- α 2a subcutaneous injections. Upon the second injection and the fourth injection, panniculitis developed at the injection site at the different location. To our knowledge, no case has been published about repeated occurrences of panniculitis induced by PEG-IFN- α 2a subcutaneous injection in the same patient.

Interferon was the first effective treatment agent for chronic hepatitis C. The addition of a guanosine analog, ribavirin, to interferon was a major breakthrough in the treatment of HCV infection.^{7,8} The next innovation in hepatitis C treatment was the development of pegylation of the interferon molecule. Pegylation is the attachment of one or more polyethyleneglycol moieties to a biologic molecule. PEG-IFN overcome most of the limitations of the nonpegylated interferon molecule—poor stability, short elimination half-life and potential immunogenicity.^{9,10} In addition, use of PEG-IFN allows the interval between doses to be lengthened to one week. There are two commercially available forms of PEG-IFN, PEG-IFN- α 2a and PEG-IFN- α 2b, that are almost equally efficacious.

Although interferon α has a dual (direct antiviral and immunomodulatory) effect on hepatitis C, a wide spectrum of adverse effects has been noted.¹¹ Several side effects such

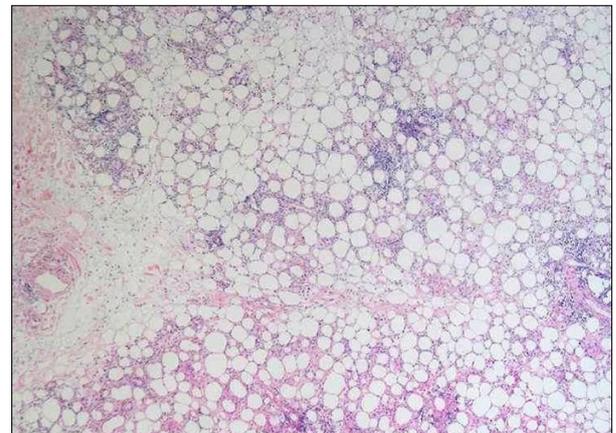


Fig. 4. Microscopic findings of typical panniculitis. Lobular panniculitis with mixed infiltration of lymphocyte and plasma cell (H&E, $\times 40$). Courtesy of Yoo et al. (Korean J Dermatol 2012;50:640-643).

as flu-like symptoms are common, especially with the initial injections, but are easily manageable. Neuropsychiatric side effects such as depression and irritability can cause much trouble and be difficult to manage. Hematologic side effects such as neutropenia, thrombocytopenia, and anemia are usually mild, although they can be dose-limiting if cell counts are too low. Because of the immunomodulatory properties, interferon can induce autoimmune side effects, the most frequent being autoimmune thyroiditis, especially in predisposed patients. Rarely, severe or life-threatening side effects

occur in 0.1% to 1% of patients; these include thyroid, visual, auditory, renal, and cardiac impairment, and pulmonary interstitial fibrosis. Dermatologic side effects such as skin rash, alopecia, dermatitis, and pruritus are common, but the panniculitis observed in this case is very rare.

Panniculitis can be defined as an inflammation of the subcutaneous tissues.¹² Pathologically there are two broad types, septal and lobular, although most lesions are composed of a mixture of each (Fig. 4). Ter Poorten and Thiers¹³ classified panniculitis by its primary histopathologic pattern: (1) septal panniculitis without vasculitis, (2) septal panniculitis with vasculitis, (3) lobular panniculitis without vasculitis, (4) lobular panniculitis with vasculitis. Despite the differing pathology, the external appearance of the lesion is the same and is defined by the hallmark subcutaneous nodule on the skin that is tender, raised, and erythematous,¹² as seen in this case.

If panniculitis was suspected, systemic disease that can cause panniculitis should be evaluated. Panniculitis associated with systemic disease includes pancreatic panniculitis, lupus panniculitis, subcutaneous sarcoidosis, calciphylaxis, leukemia and lymphoma, infectious panniculitis, and α -1 antitrypsin deficiency panniculitis.¹³

Panniculitis induced by interferon appears most common in patients with multiple sclerosis.^{3,5} The pathogenesis of the panniculitis induced by interferon has not been described completely. Heinzerling et al.⁴ described the pathogenesis immunologically. They hypothesized that panniculitis was induced by infiltration of inflammatory cells, activation of local adhesion molecules and secretion of chemokines. For interferon beta, that hypothesis has been demonstrated experimentally by Buttman et al.¹⁴ A similar immunological response may be assumed for interferon alpha, although further research is needed. Based on this background, we treated the patient with oral steroids and acetaminophen/tramadol hydrochloride for anti-inflammatory effect and for pain control.

Inafuku et al.¹⁵ reported that skin reactions associated with interferon beta-1b subcutaneous injection were dependent on the depth of injection and that no local reactions occurred following deep subcutaneous injection. They suggested that local cytokine-mediated mechanisms may initiate adverse immune reactions or that non-specific inflammation may be more likely to follow intradermal administration, and recommended vertical injection with the aim of

injecting interferon into deep subcutaneous fatty tissues. Therefore patients need to be educated to properly inject into the skin in order to avoid panniculitis.

In conclusion, we report a case of panniculitis as a very rare side effect of PEG-IFN- α 2a. Physicians should be aware and manage this rare complication properly. Considering that it might be caused by inappropriate self-injection technique, patients should be educated in injection technique to prevent or decrease local skin reactions including panniculitis.

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