Case Report

Dramatic Improvement of Psoriatic Arthritis by Infliximab in a Patient Refractory to Conventional Therapy Presenting with Elevated Serum β-D-glucan

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Abstract

A 55-year-old Japanese man, with psoriasis and psoriatic arthritis for the past 15 years, was under relatively good conditions and ambulant on conventional therapy. After voluntary discontinuation of the drugs in February 2007, he became completely bedridden and a pressure ulcer developed at the sacral region by immobilization due to joint pain. Because of the inadequate response and side-effects of oral prednisolone and cyclosporine A, infliximab was started despite increased levels of serum β-D-glucan, which was against the guidelines in Japan. Skin and articular symptoms surprisingly improved after the treatment, along with normalization of serum levels of β-D-glucan. He is now back to his completely normal life.

（Key words：infliximab, psoriasis, psoriatic arthritis, β-D-glucan）

Case report

A 55-year-old Japanese man was admitted to our hospital on March 16, 2007 for generalized erythematous plaques and severe polyarthritis. He had been suffering from psoriasis vulgaris for the past 15 years. He had received oral etretinate and topical corticosteroid therapy until 1 month before the admission, when he discontinued them of his own accord. After discontinuation of drugs, erythematous plaques and polyarthralgia deteriorated abruptly and he became completely bedridden. Eventually, he developed a pressure ulcer and he was transferred to our hospital in an ambulance. On admission, he had generalized erythematous plaques, pustules and erosions with thick exfoliation on his face, trunk and extremities（Figure 1A, B）. Auspitz's phenomenon was observed. There was a Grade II pressure ulcer at the sacral region without any signs of necrosis or infection（Figure 1C）. His bilateral shoulder-, elbow-, wrist-, knee- and ankle-joints and all proximal interphalangeal joints of the hands were markedly swollen and intensely tender. The Psoriasis Area and Severity Index, the tender joint count, and the swollen joint count on admission were 40, 31, and 11, respectively. A thick white fur on the oral mucosa was observed and *Candida* species were detected in it by microscopy. No abnormal findings were found in the chest or abdomen. Laboratory studies showed the following values: white blood cell count, 18,240/μL, with 86% neutrophils,6% lymphocytes, 3% eosinophils, and 5% monocytes; serum albumin, 1.6 g/dL; serum creatinine, 0.5 mg/dL; C-reactive protein, 24.0 mg/dL; and anti-CCP antibody, < 5.0 U/mL. Antinuclear anti-

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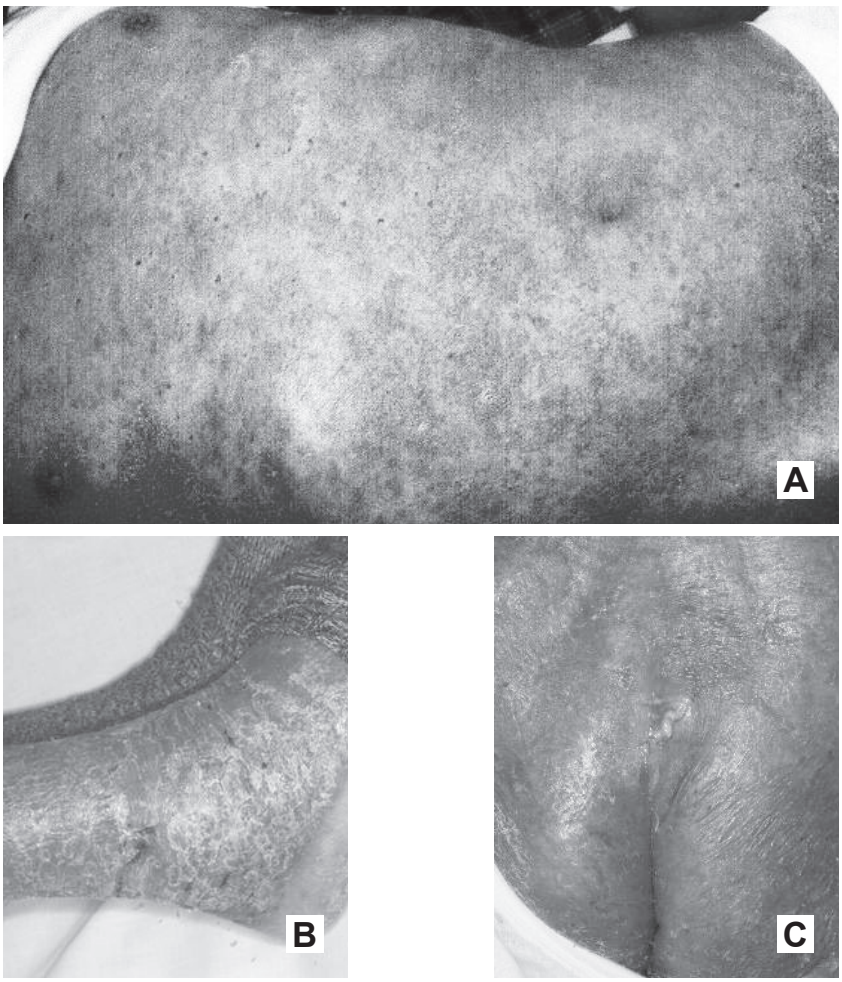

Figure 1 Skin manifestations on admission. (A) Multiple erythematous plaques and pustules on the trunk. (B) Erythematous plaques with silver scales on the right ankle. (C) Grade Ⅱ pressure ulcer at the sacral region.

body was negative. Serum β-D-glucan was positive at 53.7 pg/mL. Serum *Candida* antigen was weakly positive at 2-fold by latex agglutination test. Neither *Cryptococcus* nor *Aspergillus* antigen was detected in serum. Repeated bacterial and fungal cultures of sputum, urine, blood and feces were all negative. A chest X-ray showed localized pleural thickening at the bilateral apices of the lung; a chest computed tomography showed old inflammatory changes only. An upper gastrointestinal endoscopy revealed a gastric ulcer on the anterior wall of antrum with no evidence of esophageal candidiasis. An echocardiography showed normal wall motion and no vegetations.

A diagnosis of psoriatic erythroderma and severe psoriatic arthritis was made. Treatment was started with 200 mg/day cyclosporine A, topical corticosteroid, and topical tacrolimus. Itraconazole was also administered for oral candidiasis for 8 days. Skin and joint manifestations moderately improved and the white fur on the oral mucosa completely disappeared. Serum β-D-glucan was also high at 65.2 pg/mL on

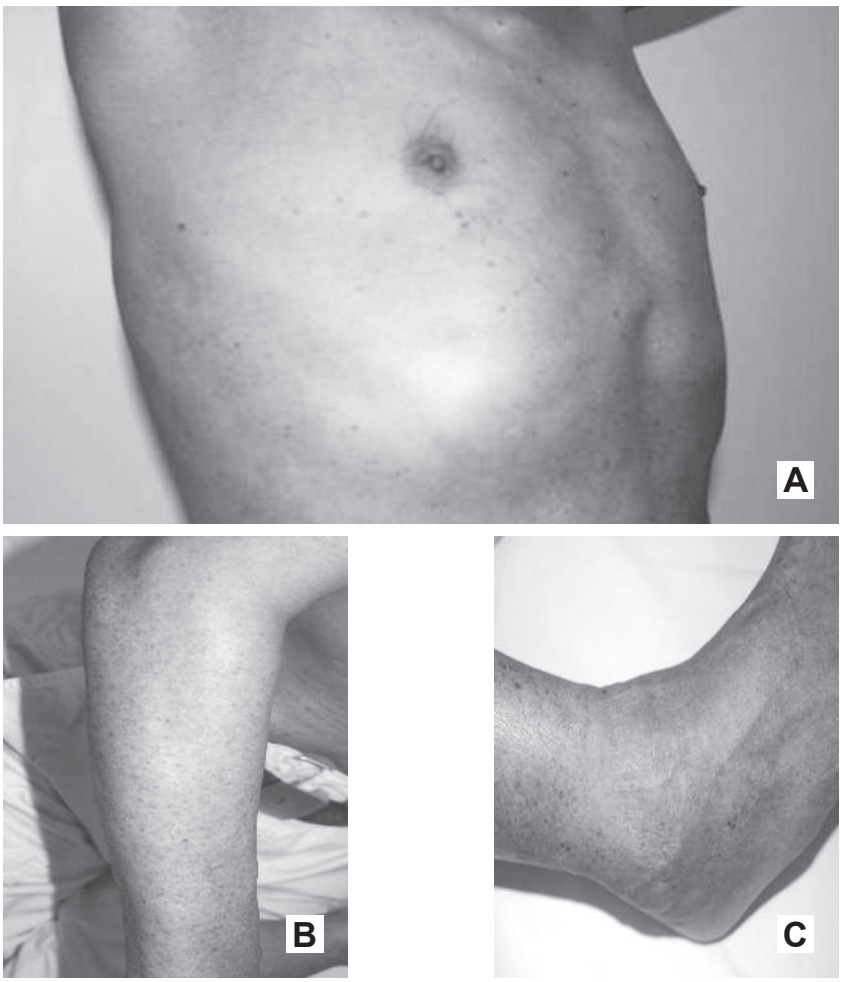

Figure 2 Skin manifestations after 2 infusions of infliximab. Note the remarkable improvement of the skin lesions on the trunk（A）, the right forearm（B）, and the right ankle（C）.

April 5. However, anti-fungal agents were not administered because there was no evidence of active fungal infection or infection with *Pneumocystis jirovecii*. The dose of cyclosporine A was reduced to 100 mg/day because serum creatinine level increased from 0.5 to 2.0 mg/dL and the trough level of cyclosporine A increased to 350 ng/mL. As a result, skin and articular symptoms were aggravated. Oral prednisolone elevated his intra-ocular pressure and had to be stopped. In May, tender joint and swollen joint count increased and the patient complained of severe pain and difficulty standing. Although serum level of β-D-glucan was still high at 32.4 pg/mL, repeated examination did not reveal any evidence of active fungal infection. Eventually, we recommended him to accept the treatment with infliximab even under the condition of an increased serum level of β-D-glucan. An informed consent was obtained from the patient.

On May 16, 2007, the first administration of infliximab（200 mg）was infused along with 2 mg oral methotrexate weekly. Skin and articular manifestations dramatically improved after two infusions of infliximab（Figure 2）. Serum levels of β-D-glucan were completely normalized after the treatment. Cy-

closporine A, topical corticosteroid, and topical tacrolimus became unnecessary and were discontinued. He is now on the regular infliximab infused every 2 months without any serious adverse events. The clinical course after admission is depicted in Figure 3.

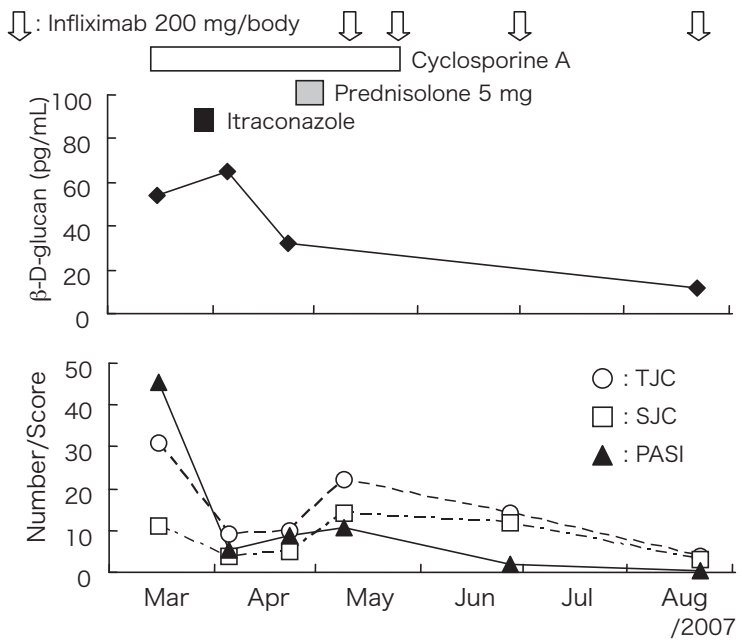

Figure 3 Clinical course of the present case. Closed diamond represents the serum levels of β-D glucan, open circle represents the tender joint counts, open square represents the swollen joint counts, and closed triangle represents the Psoriasis Area and Severity Index (PASI) scores.

Discussion

This is the first report which showed a dramatic improvement of psoriatic arthritis by infliximab in the setting of elevated serum levels of β-D-glucan. Interestingly, the serum level of β-D-glucan became completely normal after the infliximab-treatment improved his skin and articular manifestations.

Psoriasis is sometimes accompanied by an inflammatory arthritis called psoriatic arthritis. Recent reports suggest that about 40% of psoriatic patients develop irreversible joint destruction and deformity[1]. As is the case with rheumatoid arthritis, sufficient control of joint inflammation in an early stage of psoriatic arthritis has been recommended for a better prognosis, and large-scale clinical trials for anti-TNF therapy, including infliximab, showed their effectiveness[1)-3)].

This case presented with severe exfoliative erythema and polyarthritis, which caused him to be bedridden and develop a pressure ulcer on admission. Unfortunately, an elevated serum level of β-D-glucan delayed the decision to implement anti-TNF therapy.

β-D-glucan, a fungal component, has been used as a clinical marker to diagnose invasive mycoses especially in immunocompromised patients[4),5)]. However, certain causes for false positive results have been reported, including hemodialysis with cellulose membrane[6)], infusion of human albumin[7)], treat-

ment with gauze containing glucan components[8], bacterial infection[9], and several drugs, amoxicillin-clavulanic acid for example[10]. Thus, it has to be kept in mind that there are false positives and the interpretation of the result should be based upon clinical conditions, when serum β-D-glucan is determined.

In this case, all the reported factors which cause false-positive results for serum β-D-glucan were ruled out, and all the cultures, serological markers, and radiological examinations were negative for invasive fungal infection. Oral candidiasis might not have caused the elevated level of β-D-glucan because the serum level of β-D-glucan did not decrease, or rather increased after his oral candidiasis was cured. The definite cause of elevated serum levels of β-D-glucan was unclear. However, increased levels of β-D-glucan after administration of oral itraconazole indicated that the cause was other than fungal infection. In this case, it was remarkable that the serum level of β-D-glucan became completely normal after the infliximab-treatment improved his skin manifestation. Therefore, psoriatic skin derangement *per se* could have caused the elevated β-D-glucan. One possible explanation is that normal habitants of the skin such as *malassezia* species[11] invade the skin barrier damaged by psoriatic disease process, and increase serum levels of β-D-glucan.

According to Japan's guidelines for the use of infliximab for rheumatoid arthritis, negative test for β-D-glucan in serum is listed in the inclusion criteria to avoid opportunistic infections[12]. However, there are no guidelines which recommend measurement of the serum β-D-glucan in other countries, including the United States[13]and European countries[14), 15]. One reason might be that measurement of serum β-D-glucan is not popular among these countries for the diagnosis of invasive mycosis. Moreover, the risk of fungal or *Pneumocystis* infection does not have close correlation with pre-treatment determination of serum β-D-glucan.

Measurement of serum β-D-glucan was reported to be useful for the diagnosis of *Pneumocystis jirovecii* pneumonitis in immunocompromised patients with general and respiratory symptoms or pulmonary infiltration on chest X-ray[16), 17]. Therefore, we should not start biologics on patients with respiratory symptoms or radiological findings which indicate an active infection. On the other hand, infliximab is definitely a treatment of choice for patients with severe psoriatic arthritis, when conventional therapy is ineffective or needs to be discontinued due to side effects and/or adverse reactions. We should not sway due to one laboratory abnormality to implement a favourable therapy. The important thing is to comprehend patient's overall conditions when we confront a difficult case.

Reference

1）Voulgari PV, Venetsanopoulou AI, Exarchou SA et al. Sustained Clinical Response and High Infliximab Survival in Psoriatic Arthritis Patients: A 3-year Long-Term Study. Semin Arthritis Rheum 37 : 293-298, 2007.

2）Antoni CE, Kavanaugh A, Kirkham B et al. Sustained benefits of infliximab therapy for dermatologic and articular manifestations of psoriatic arthritis. Arthritis Rheum 52 : 1227-1236, 2005.

3）Van der Heijide D, Kavanaugh A, Gladman DD et al. Infliximab inhibits progression of radiographic damage in patients with active psoriatic arthritis through one year of treatment. Arthritis Rheum 56 : 2698-2707, 2007.

4）Obayashi T, Yoshida M. Plasma (1-3)-β-D-glucan measurement in diagnosis of invasive deep mycosis and fungal febrile episodes. Lancet 345 : 17-20, 1995.

5）Moro H, Tsukada H, Ohara T et al. Clinical evaluation of performance of a new diagnostic method for deep mycosis by measuring β-glucan concentration in the blood. Kansenshogaku Zasshi 77 : 227-234, 2003.
6）Kato A, Takita T, Furuhashi M et al. Elevation of blood (1→3)-beta- D-glucan concentrations in hemodialysis patients. Nephron 89 : 15-19, 2001.
7）Usami M, Ohata A, Horiuchi T et al. Positive (1->3)-beta-D-glucan in blood components and release of from depth-type membrane filters for blood processing. Transfusion 42 : 1189-1195, 2002.
8）Nakao A, Yasui M, Kawagoe T et al. False-positive endotoxemia derives from gauze glucan after hepatectomy for hepatocellular carcinoma with cirrhosis. Hepatogastroenterology 44 : 1413-1418, 1997.
9）Digby J, Kalbfleisch J, Glenn A et al. Serum glucan levels are not specific for presence of fungal infections in intensive care unit patients. Clin Diagn Lab Immunol 10 : 882-5, 2003.
10）Mennink-Kresten MA, Warris A, Verweij PE et al. 1, 3-beta-D-glucan in patients receiving intravenous amoxicillin-clavulanic acid. N Engl J Med 354 : 2834-2835, 2006.
11）Gupta AK, Batra R, Bluhm R et al. Skin diseases associated with Malassezia species. J Am Acad Dermatol 51 : 785-798, 2004.
12）Miyasaka N, Takeuchi T, Eguchi K. Official Japanese guidelines for the use of infliximab for rheumatoid arthritis. Mod Rheumatol 15 : 4-8, 2005.
13）American College of Rheumatology Subcommittee on Rheumatoid Arthritis Guidelines. Guidelines for the management of rheumatoid arthritis 2002 update. Arthritis Rheum 46 : 328-346, 2002.
14）Ledingham J, Deighton C, on behalf of the British Society for Rheumatology Standards, Guidelines and Audit Working Group (SGAWG). Update on the British Society for Rheumatology guidelines for prescribing TNF α blockers in adults with rheumatoid arthritis (update of previous guidelines of April 2001). Rheumatology 44 : 157-163, 2002.
15）Valesini G, Montecucco C, Cutolo M. Recommendations for the use of biologic (TNF-alpha blocking) agents in the treatment of rheumatoid arthritis in Italy. Clin Exp Rheumatol 24 : 413-423, 2006.
16）Tasaka S, Hasegawa N, Kobayashi S et al. Serum indicators for the diagnosis of pneumocystis pneumonia. Chest 131 : 1173-80, 2007.
17）Iikuni N, Kitahama M, Ohta S et al. Evaluation of *Pneumocystis* pneumonia infection risk factors in patients with connective tissue disease. Mod Rheumatol 16 : 282-288, 2006.

血清β-D-glucanの上昇を伴った難治性関節症性乾癬にインフリキシマブが著効した１例

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要　約

症例は55歳男性。15年前より関節症性乾癬に対して治療を受けておりコントロール良好であった。2007年２月に自己判断にて治療薬を中止したところ，皮膚および関節症状が再燃し，著しい疼痛により離床不能となり臀部に褥創を形成するに至った。シクロスポリンA，経口プレドニゾロンによる治療を行ったが効果不充分であり副作用を認めた。血清β-D-glucanの上昇を認め，本邦の生物学的製剤の使用ガイドラインに基づけばインフリキシマブの適応外となるが，臨床所見や他の検査によって活動性の真菌感染症は否定的であったことから同意取得後にインフリキシマブを開始した。結果，皮膚および関節症状は著明に改善し，真菌感染症を発症することなく血清β-D-glucanは正常化した。現在，インフリキシマブを継続して通常の生活を送ることができている。ガイドラインは一つの指針に過ぎず，重要なことは患者の全体像を臨床的に判断することである。

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