

Subacute Development of Polymyalgia Rheumatica (PMR) In Diabetic Patient with Clinical Efficacy of Tocilizumab and Xultophy

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Article Info

Article History:

Received: 16 March, 2022

Accepted: 20 March, 2022

Published: 23 March, 2022

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DOI:
<https://doi.org/10.36266/RJSHP/123>

Abstract

The patient is 76-year-old men with previous history of type 2 diabetes mellitus (T2DM) in 2012, acute myocardial infarct (AMI) in 2015 and dyslipidemia in 2017. He had no health or medical problems of rheumatism and joints. As his social and sports history, he was an excellent long-distance runner with the similar level to Olympian Kenji Kimihara during 14-30 years old. He worked hard from 38 years as city assembly member. In 2019, he continued low carbohydrate diet (LCD) with decreased HbA1c from 9.0% to 6.3% for half year. In autumn 2021, he developed subacute generalized arthralgia and muscle weakness with elevated HbA1c 10.6%. He was diagnosed as polymyalgia rheumatica (PMR). For treatment, prednisolone was not effective, and then he was provided Tocilizumab (Actemra). It showed remarkable efficacy for symptom improvement and normalized C-reactive protein (CRP) 8.3 to <0.1 mg/dL, matrix metalloproteinase-3 (MMP-3) 610 to 79 ng/mL. For glucose control, he was initiated insulin human 4-4-4 to 14-14-14 units, followed by Xultophy 18 to 5 doses with satisfactory glucose variability. HbA1c was remarkably decreased from 10.6% to 6.4 % about 2 months. Various discussion perspective was described, and this article will be hopefully useful for future practice and research.

Keywords: Low Carbohydrate Diet (LCD); Polymyalgia Rheumatica (PMR); Tocilizumab (Actemra); Matrix Metalloproteinase-3 (MMP-3); Xultophy (Ideglira)

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Introduction

The author and collaborators continued to present various research concerning metabolic syndrome, sports, orthopedics, rehabilitation, bone and muscle problems and others. Among them, recent development of medical research, diagnosis and treatment includes chronic autoimmune and rheumatoid related diseases. Rheumatoid arthritis (RA) is well-known disease and it affects about 1% of adult people [1]. These related diseases have multifactorial pathophysiology, including polymyalgia rheumatica (PMR), Giant cell arteritis (GCA) and Takayasu's arteritis (TAK). Three diseases have common pathophysiology, and are characterized for their extensive vascular remodeling leading to stenosis and occlusion [2]. Historically, PMR was reported by Barber with clinical investigation of 12 cases [3]. Their symptoms were characterized for wide-spread muscular pain such as stiff neck, shoulder, lower back and thigh. Regarding the diagnosis of PMR, several former guidelines were found such as Chuang et al. [4], Healey et al. [5], Bird et al. [6] and Jones et al. [7]. In recent decades, common standard guideline would be applied from 2012 criteria by European League against Rheumatism (EULAR)/ American College of Rheumatology (ACR) [8]. Regarding the

development of research for PMR, RA and related diseases, several kinds of inflammatory biomarker, immunological antibodies were reported and used until now. They include C-reactive protein (CRP), blood segmentation rate (BSR), rheumatoid factor (RF), matrix metalloproteinase-3 (MMP-3) and Anti-cyclic citrullinated peptide antibody (ACPA) [9]. For the diagnostic method for RA, the sensitivity has been reported as the order of MMP-3 > RF > ACPA [10]. On the other hand, ACPA shows extremely higher specificity of 90% or more for RA [11]. Consequently, current situation enables the evaluation of various laboratory biomarkers for differential diagnosis for rheumatoid related diseases. Author's research group continued clinical practice in wider range of non-communicable diseases (NCDs) [12]. Our diabetic studies include the development of a low-carbohydrate diet (LCD), meal tolerance test (MTT), continuous blood glucose monitoring (CGM) [13]. Furthermore, studies of oral hypoglycemic agents (OHA), antidiabetic agents, glucagon-like peptide-1 receptor agonist (GLP-1RA), liraglutide, xultophy and others are included [14-16]. We have recently experienced an impressive patient with T2DM. LCD treatment showed clinical effects, and after that he developed PMR in subacute progress. Insulin and xultophy were provided for diabetic control, and Tocilizumab (Actemra) was applied for PMR.

The general progress of this case and some discussion will be described in this article.

Case Presentation

The patient is 76-year-old men with previous history of type 2 diabetes mellitus (T2DM) in 2012, acute myocardial infarct (AMI) in 2015 and dyslipidemia in 2017. He had no health or medical problems of rheumatism and joints. His diabetic control was not stable until 2018, and then he was introduced to our diabetic clinic in 2019. From his situation, he was advised to continue super-LCD meal, which was successfully conducted. His HbA1c was decreased from 9.0% to 6.3% and stable for years.

His medical problems can be summarized until September 2021 in the following. They were i) T2DM, ii) coronary artery disease (CAD), iii) hypertension, iv) dyslipidemia, v) gastroesophageal reflux disease (GERD). His medication included linagliptin 5mg, Metformin 750mg, acetylsalicylic acid (Bayasprin) 100mg, Lansoprazole 15mg, Rosuvastatin calcium 2.5mg, imidapril hydrochloride 2.5mg, bisoprolol fumarate 1.25mg, which were provided once in the morning. During Sept-Oct 2021, he worked rather hard associated with some strain on his joints, muscles and lower back. It is not clear that this episode may be related or not to current medical progress. From Nov 2021, he developed subacute progress of pain, stiffness and muscle weakness in the shoulder and lower back. He visited orthopedic and dermatology clinics and was diagnosed as possible infection of joint or skin. He received antibiotics and an intra-articular injection, but these treatments could not improve his problems. Consequently, he was on further evaluation of possible collagen disease or rheumatoid related disease.

Physical Examination

Physical exam in Nov 2021 showed no remarkable abnormality of consciousness, vital signs, conversation, lung, heart and abdomen. However, he showed significant strain and muscle weakness in the neck, shoulder, low back and thigh. By applying standard manual muscle testing (MMT), the decreased muscle levels were trace in the neck, shoulder, upper arm, forearm and hand, poor in the low back, thigh, calf and foot [17, 18]. His sensory function examination was intact in upper and lower extremities. His stature showed 170.5cm, 53.3 kg and BMI 18.3 kg/m².

Data of Various Exams

The results of biochemical data in Dec 2021 were as follows: AST 12 U/L, ALT11 U/L, γ -GT 17 U/L, LDH 140 U/L (110-220), TP 6.0 g/dL, T-C 113 mg/dL, HDL-C 51 mg/dL, LDL-C 45 mg/dL, TG 121 mg/dL, UA 3.1 mg/dL, BUN 23 mg/dL, Cr 0.72 mg/dL, eGFR 80.2 mL/min/1.73m², Na 136 mEq/L, K4.5 mEq/L, Cl 100 mEq/L, RBC 3.60 x 10⁶ / μ L, Hb 10.8 g/dL, Ht 33.9%, MCV 94.2 fL (80-98), MCH 30.0 pg (27-34), MCHC 31.9 g/dL (31-36), WBC 10500 / μ L (lymph 12.7%, mono 7.0%, neutro 79.7%), Plt 24.9 x 10⁴ / μ L, post-prandial blood glucose 529 mg/dL, HbA1c 10.6%.

CRP 7.5 mg/dL, MMP-3 219 ng/mL (37-121), RF 8 IU/mL (<15), ACPA 0.1 mg/dL (<0.3), blood segmentation rate (BSR) 78 mm/1hr. His ECG revealed within normal limit, and chest and bone X-rays showed negative for significant changes.

Clinical Progress

From various results of the history, physical exam and laboratory data, he was diagnosed as aggravated status of T2DM and PMR associated with arthralgia and muscle weakness. Immediately, treatments for the diseased condition were initiated (Figure 1). He was provided prednisolone per os for PMR, and he felt clinical effect on the 1st day. However, his arthralgia and muscle weakness have exacerbated again on the next day. He refused to continue prednisolone. Furthermore, administration of rapid insulin human was begun, but he could not use the pencil-type insulin agent. The reason was that his grasping power was so poor to trace degree, then he could not turn the knob on the scale or push the button. He could not check blood glucose at home, because he did not have enough power of fingers and hands necessary for glucose measurement. From late Dec, he could start human injection 3 times a day, then his blood glucose control was gradually improved (Table 1). Successively, insulin therapy was changed into Xultophy administration. The provided amount of Xultophy was gradually decreased from 18 doses to 5 doses. From early March, he could start to work again due to complete improvement of arthralgia and general malaise. For the therapy of PMR, he was initiated to be given Tocilizumab (Actemra) 162mg per 2 weeks. On the first injection at early January, his arthralgia and muscle weakness of lower extremities were rather improved. Furthermore, the second injection has brought almost disappearance of arthralgia and the third injection gave him almost good muscle power of lower extremities. As to the laboratory data, C-reactive protein (CRP) showed normalization from 8.3 mg/dL to < 0.1mg/dL about 2 months. HbA1c values were remarkably decreased from 10.6% to 6.4 % about 2 months (Figure 1).

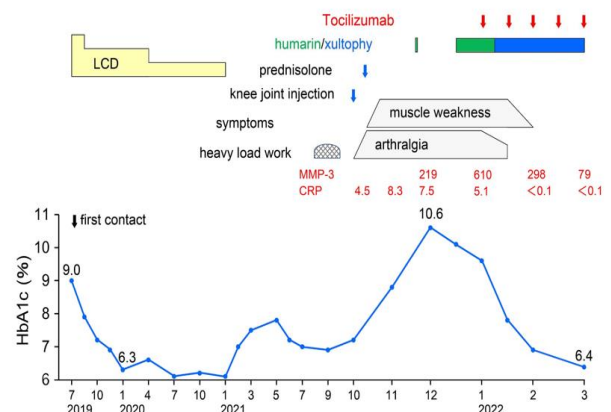


Figure 1: Clinical progress of the case with T2DM and PMR.

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prednisolone. Furthermore, administration of rapid insulin human was begun, but he could not use the pencil-type insulin agent. The reason was that his grasping power was so poor to trace degree, then he could not turn the knob on the scale or push the button. He could not check blood glucose at home, because he did not have enough power of fingers and hands necessary for glucose measurement. From late Dec, he could start human injection 3 times a day, then his blood glucose control was gradually improved (Table 1). Successively, insulin therapy was changed into Xultophy administration. The provided amount of Xultophy was gradually decreased from 18 doses to 5 doses. From early March, he could start to work again due to complete improvement of arthralgia and general malaise. For the therapy of PMR, he was initiated to be given Tocilizumab (Actemra) 162mg per 2 weeks. On the first injection at early January, his arthralgia and muscle weakness of lower extremities were rather improved. Furthermore, the second injection has brought almost disappearance of arthralgia and the third injection gave him almost good muscle power of lower extremities. As to the laboratory data, C-reactive protein (CRP) showed normalization from 8.3 mg/dL to < 0.1mg/dL about 2 months. HbA1c values were remarkably decreased from 10.6% to 6.4 % about 2 months (Figure 1).

Social and Sports History

He had been an excellent athlete for long. He started long distance running at the age of 14, and obtained good achievement associated with high evaluation. He entered Chukyo University in Nagoya, and became the captain of the athletic club. At the age of 28 years, he competed with Kenji Kimihara (1941-) who won the silver medal in Mexico Olympic in 1968 (Figure 2). He continued running until 30 years old. He was working in the Naruto city hall office, and was elected to the Naruto city assembly member at the age of 38. Regarding his past history, there was no remarkable non-communicable diseases (NCDs). He had the episode of right knee injury due to falling down during marathon competition at the age of 25 years. Otherwise, he had no medical problems for orthopedics.



Figure 2: Long distance athletic race of Igata and Kimihara
 a) Katsuo Igata: 3rd author of this article at 28 years old
 b) Kenji Kimihara: Silver medalist (Mexico Olympian 1968)
 The race was held in Jan 4, 1972, Tokushima, Japan.

Table 1: Clinical progress of blood glucose and treatment.

Time progress		Blood glucose (mg/dL)			Treatment		Work
Month	Date	morn 6:00	noon 11:30	night 20:00	humarin (units)	Xultophy (doses)	
Dec	3				4-4-4		none
	7				6-6-6		
	17				8-8-8		
	21		225	107	10-10-10		
	25	193	114	129	12-12-12		
Jan	4	172	262	111	14-12-12		work
	9	157	162	143	14-14-14		
	12	115	147	166		16	
	14	111	109	152		18	
	16	93	96	130		17	
	20	87	123	152		15	
	22	83	79	118		14	
	25	83	86	154		12	
	29	98	108	206		10	
	Feb	1	88	127	136		
3		110	97	161		7	
5		102	108	170		6	
8		102	85	137		4	
12		121	99	166		5	
15		129	97	184		6	
24		123	89	132		7	
26		91	83	193		7	
27		108	86	196		5	
28		108	104	170		5	
Mar	1	94	119	245		5	work
	2	130	97	164		5	
	3	99	96	149		5	
	5	109	102	149		5	
	6	104	114	189		5	

Discussion

The case described in this report has some clinical problems, which can be roughly divided into two aspects. One is the diabetic area, including LCD, insulin treatment and the administration of Xultophy. Another is rheumatoid related clinical area, including the diagnosis and treatment of PMR. In this discussion, several perspectives would be described in this order. The latest guidelines for diabetes were published by ADA in January 2022 [19]. The basis of diabetic treatment is nutritional therapy, which is shifting from calorie restriction (CR) to current low carbohydrate diet (LCD) [20]. LCD was started by Atkins, Bernstein and others in Europe and the United States [21]. Furthermore, LCD, CR and Mediterranean diet were compared in Dietary Intervention Randomized Controlled Trial (DIRECT) Group [22]. On the other hand, authors research group has begun LCD in Japan [23]. We have established Japan LCD promotion association (JLCDPA) and continued to raise awareness of beneficial LCD from medical and social points of view [24]. We have proposed three types of super-LCD, standard-LCD and petite-LCD so that everyone can apply LCD clinically [25]. These have carbohydrate calorie ratio of 12%, 26% and 40%, respectively. In this case, standard-LCD was advised to be continued, and his HbA1c was improved from 9.0% to 6.3% for half year, indicating enough clinical efficacy with no problems. After that, he has continued to apply LCD at suitable degree according to his daily life. Consequently, LCD seems to be effective and safe strategy for nutritional therapy [26]. This case developed hyperglycemia due to inflammatory situation and then fast-acting insulin human was started from 4-4-4 units and increased to 14-14-14-units [27]. This improved daily profile of blood glucose with stable glucose variability. Then, the treatment

was changed from insulin to Xultophy [28]. It is a fixed ratio of the combination of Insulin Degludec and Liraglutide (IDegLira) [29]. IDegLira has been reported to show enough medical efficacy [30]. Xultophy was started at 16 doses, increased to 18, and finally reduced to 5 doses. One of the reasons for this progress may be the clinically rapid improvement in the inflammatory response. As the administration of Xultophy, 16 doses would be standard amount in the case who has been already treated by insulin [31]. In the current case, this amount of Xultophy seemed to be adequate. The amount was decreased to 5-7 doses in late February 2022. For this period, the patient could come back to the previous work in a few months. He can change 5-7 doses of Xultophy according to his daily lifestyle, whether his work would be on or off. As described above, glycemic control has been satisfactory for Xultophy with clinical benefits. Authors et al. have presented several reports of Xultophy, in which a patient with T2DM and RA showed remarkable effect of xultophy [32]. Unlike reported cases treated by Xultophy from Europe and the United States, some cases in Japan show good glucose control with a small amount of Xultophy of 5-8 doses per day [33]. For this reasons, higher sensitivity for insulin and GLP-1RA may be involved physiologically and pharmacologically [34]. For clinical research for Xultophy, a series of European Xultophy Treatment Retrospective Audit (EXTRA) studies were observed [35]. From those data, significant relationships of HbA1c and body weight were found from real-world evidence (RWE) point of view [28].

Among rheumatic inflammatory disorders, PMR has been common for people more than 50 years [36]. PMR is characterized for its morning stiffness in the shoulder, neck and pelvic girdles. Formerly, the guideline of PMR was not clarified and several controversies were observed. Recently, however, international collaboration of American College of Rheumatology (ACR) and European League against Rheumatism (EULAR) has brought novel classification criteria of PMR [37]. As to current case, several symptoms and signs were applied to the scoring algorithm of the PMR guideline. Main four symptoms were found in the case, including morning stiffness for >45 min, pain and restricted range of motion (ROM), absence of RF or ACPA, and absence of other joint involvement [36, 37]. Consequently, this case was diagnosed as not RA but PMR. Current case was not difficult to diagnose as PMR. For laboratory biomarkers, MMP-3 showed changes in parallel to the inflammatory situation and CRP was decreased to normal level. However, differential diagnosis for rheumatic related disease has been sometimes difficult. They include RA, PMR, giant cell arteritis, and cervical radiculopathy [38]. Several information and immunological tests are required such as various complaints of arthralgia and strain, radiculopathy, CRP, RF, MMP-3, ACPA. When a patient was not diagnosed properly for elder RA, PMR or giant cell arteritis, his diseased condition might not be relieved due to insufficient steroid amount leading to possible vascular complications. MMP-3 is an enzyme that is also known as stromelysin-1. MMP-3 has been predominantly involved in the several joints destruction in RA. MMP-3 has been useful for

screening and follow up the clinical progress. Serum MMP-3 values reflect the positive activity, injury and erosion of bone and joint and predict the clinical outcome and progress in the future [39]. Consequently, MMP-3 monitoring would be beneficial for assessment and management of RA, PMR and rheumatic related diseases.

Some limitation exists for the discussion regarding this report. In his medical history, joint pain is strongly found in the right knee, and it cannot be denied that this is related to the previous episode in which he hurt his right knee when he was young. The causes for current subacute PMR development were not fully recognized. Furthermore, initial administration of prednisolone was not effective, where its pathophysiology was not clarified yet. By the treatment of Tocilizumab (Actemra) twice, general inflammatory symptoms were improved with negative CRP value. Careful follow-up the case will be required. In summary, a case suffering T2DM and PMR was described associated with remarkable efficacy by Actemra and Xultophy. This presentation and various discussion will hopefully become some reference data for future rheumatoid and diabetic practice and research.

Ethical Considerations

In current article, the case study was basically according to the standard ethics which includes the principles for the Declaration of Helsinki. Moreover, comment was also added from some data of the Ethical Guidelines for Research for Humans. Their guidelines are along with the Good Clinical Practice (GCP). The authors and collaborators have discussed enough and established an ethical committee in the hospital. It has some professional staffs including the director of the hospital, chief of the administration department, physician, head nurse, pharmacist, dietitian and legal professional. The committee has brought satisfactory discussion with applicable methods and decided the agreements for the investigation. The informed consent as well as written document were taken from this patient.

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