An Overwhelming Postsplenectomy Infection Syndrome Associated with Diabetes Mellitus

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A 72-year-old male diabetic patient was admitted due to autoimmune hemolytic anemia (AIHA). We started 1mg/kg weight of prednisolone daily and multiple daily insulin infusion for hyperglycemia. Gall bladder cancer and early stage gastric cancer were then diagnosed. We removed the gall bladder and the spleen for treatment of AIHA without prednisolone for better control of diabetes mellitus. Five weeks later, endoscopic gastromucosal resection (EMR) was performed for gastric cancer. The patient suffered from fever and respiratory failure after 4 days. Chest computed tomography showed consolidation, bronchial wall thickening and a ground glass appearance in bilateral lungs. Although the sputum and blood culture were negative, β -D-glucan and mannan antigen increased. Neutrophilia (87%) was shown. The WBC count had not increased (7300/ μ l) compared with the CRP elevation (21.8mg/dl). Therefore, we diagnosed overwhelming postsplenectomy infection syndrome followed by atypical pathogen infection. We used ciprofloxacin and fosfluconazol, respirator at low tidal volume ventilation, sivelestat sodium hydrate and methylprednisolone for respiratory failure and regular insulin aiming for a blood glucose range of from 80 to 140mg/dl. The patient subsequently recovered. (Kitakanto Med J 2009 ; 59 : 275~280)

Key Words : autoimmune hemolytic anemia, postsplenectomy, diabetes mellitus

Introduction

The incidence of infection is higher than normal in diabetic patients and complications result in death more frequently.^{1,2} The relationship between postsplenectomy and severe infection, termed overwhelming postsplenectomy infection (OPSI) syndrome is documented by illness evolving from good health to death within a day.^{3,4} The infections are most often due to pneumococcus, Haemophilus influenza type b and meningococcus, but any bacterial agent may cause the rapid onset of septicemia, meningitis and pneumonia.⁵ Here, we report a recovered case of OPSI syndrome associated with diabetes mellitus treated with intensive care.

Case Report

A 72-year-old male was admitted due to shortness of breath at rest. His weight was 60kg at 20. His maximal weight was 80kg at 61. After that his weight had gradually decreased to 60kg at 66. Diabetes mellitus was indicated at age 66. From the age of 69 he had started conventional insulin therapy (Novorapid 30mix total dose from 20-22 units) and the HbA1c had ranged from 6.3 to 6.7%. He had not suffered other diseases up to that point. He had shortness of breath on effort and general fatigue over the previous 4 weeks. The symptoms had deteriorated gradually. He had smoked 20/day for 40 years and had drunk ethanol (23g/day). His father also had diabetes mellitus. His physical examination showed the following : height 169cm, weight 60kg (body mass index :

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Table 1 Laboratory data on the 1st day

Urinalysis		Chemistry		TRG	77mg/dl
protein	(-)	AST	56mU/ml	CRP	0.3mg/dl
glucose	(-)	ALT	13mU/ml	FBG	117mg/dl
blood	(-)	LDH	800mU/ml	HbA1c	4.5%
aceton	(-)	ALP	207mU/ml	GAC-Ab	0.3u/ml
pH	5	γ -GTP	9mU/ml	urineCPR	35 μ g/day
Hematology		totalprotein	7.2g/dl	Cer	67.5ml/min
RBC	144 $\times 10^4/\mu$ l	albumin	3.9g/dl	UAE	2.7mg/gCr
Hb	6.5g/dl	T-Bil	6.3mg/dl	Serology	
Ht	17.8%	I-Bil	4.5mg/dl	STS	(-)
MCV	123	STT	9.4U	HBsAg	(-)
Reticulocyte	276%	TTT	4.6U	anti-HCVAb	(-)
platelet	39.4 $\times 10^4/\mu$ l	BUN	17.3mg/dl	Coombstest	
WBC	10500/ μ l	Cr	0.9mg/dl	direct	(+)
Baso	1%	UA	3.2mg/dl	indirect	(-)
Eosino	1%	Na	137mEq/l	Coldagglutinin	(-)
Seg	66%	K	4.4mEq/l	ANA	(-)
Lymph	23%	Cl	102mEq/l	DNA-Ab	(-)
Mono	8%	Ca	9.1mg/dl	Bonemarrow	
		amylase	62su/dl	NCC	293000/ μ l
		T-CH	142mg/dl	Megakaryocyte	63/ μ l
		HDL-CH	41mg/dl		

21kg/m²), blood pressure 128/70mmHg, pulse rate 83/min, temperature 36.7°C. The conjunctiva was anemic and icteric. Fundoscopic examination showed no diabetic retinopathy. There were no abnormalities in the neck and chest. The spleen was palpable two fingerbreadths beneath the left costal margin. There was no skin eruption. Body surface lymph nodes were not palpable. Deep tendon reflexes were normal. A sensory exam showed nothing unusual. Laboratory data were as follows: chest X-ray film was normal. Electrocardiogram was within the normal range. Urinalysis showed glucose (-), protein (-), acetone (-) and blood (-). The white blood cell (WBC) count was 10500/ μ l (basophil 1%, eosinophil 1%, segmented leukocyte 66%, lymphocyte 23%, monocyte 8%); the red blood cell count was 144 $\times 10^4/\mu$ l, hemoglobin; 6.5g/dl and reticulocyte; 276. Platelet count; 39.4 $\times 10^4/\mu$ l. Liver function showed AST; 56mU/ml, ALT; 13mU/ml, LDH; 800mU/ml, total bilirubin; 6.3mg/dl, indirect bilirubin; 4.5mg/dl, total protein; 7.2g/dl, albumin; 3.9g/dl, total cholesterol; 142mg/dl, high density lipoprotein-cholesterol; 41mg/dl, triglyceride; 77mg/dl and C-reactive protein (CRP): 0.3mg/dl. Fasting blood glucose was 117mg/dl and HbA1c; 4.5%. The glutamic acid decarboxylase (GAD) antibodies were negative. The urinary C-peptide was 35 μ g/day, with an urinary protein excretion rate of 2.7mg/gCr. Immunological test showed the direct Coombs test (+), in direct Coombs test (-), cold agglutinin (-), antinuclear antibodies (-) and DNA-antibodies (-). Bone marrow puncture showed nuclear cell count; 293000/ μ l and megakaryocytes; 63/ μ l with erythroblast

hyperplasia (Table 1). We diagnosed autoimmune hemolytic anemia (AIHA) because of an anemia with increased reticulocytes and erythroblast hyperplasia, indirect bilirubin increase and positive Coombs test. We started 60mg (1mg/weight) of prednisolone daily and multiple daily insulin infusion for varied blood glucose levels. The Hb elevated. Three weeks later the patient suffered from epigastric pain and the AST, ALT, LDH, ALP and γ -GTP became elevated. An abdominal echogram showed intrabladder tumor with gall bladder wall thickening, indicating cholecystitis with gall bladder cancer. Moreover, a gastro fiberscope showed early stage gastric cancer. We administered 4g of piperacillin daily for cholecystitis. Then liver function recovered. When the prednisolone was reduced to 30mg/day, we removed the gall bladder (after diagnosed gall bladder cancer) and the spleen for treatment of AIHA without prednisolone use. Four weeks after the operation, we stopped prednisolone and after a week endoscopic gastromucosal resection (EMR) was performed (Fig. 1). Four days after EMR, the patient suffered from fever (38.5°C), tachycardia (120/min) and respiratory failure (pH 7.412, PCO₂ 35.4 Torr, PO₂ 35.8 Torr and HCO₃ 22.0mEq/l after the inhalation of 6l/min oxygen). The chest x ray film showed multiple granular lesions in bilateral middle-lower lung fields (Fig. 2). The ultracardiocchogram did not show abnormal valve and wall motion, and bilateral dilatation. The chest computed tomography showed a ground glass appearance at the anterior area, bronchial wall thickening and consolidation at the posterior area in the bilateral lower lobes (Fig. 3). An abdominal computed tomography

Fig. 1 Clinical course
EMR* : endoscopic gastromucosal resection

Fig. 2 Chest X-ray film shows multiple granular lesions in the bilateral middle-lower lung fields.

Fig. 3 Chest computed tomography shows a ground glass appearance at the anterior area, bronchial wall thickening and consolidation at the posterior area in the bilateral lower lobes.

showed nothing particular in liver and kidneys. The white blood cell (WBC) count was 7300/ μ l (basophil 0%, eosinophil 0%, segmented leukocyte 87%, lymphocyte 10%, CD4 431/ μ l, CD8 295/ μ l, monocyte 3%); and hemoglobin; 11.7g/dl. Liver function showed AST; 81mU/ml, ALT; 60mU/ml, LDH; 321mU/ml and Fasting blood glucose; 179mg/dl. The CRP was 21.8mg/dl, IgG; 1415mg/

dl, IgA; 403mg/dl and IgM 179mg/dl. Urine pneumococcal Ag and legionella Ag were negative. Although the 2-set blood culture was negative, the sputum culture showed *Candida albicans*. β -D-glucan was 1390pg/ml and mannan antigen 6 u/ml The sputum pneumocystis DNA was negative (Table 2). Fundoscopic examination showed no retinal exudates indicating fungal infection. We diagnosed OPSI syndrome followed by hospital acquired infection after EMR. The patient was moved to the inten-

Table 2 Laboratory data 39th days after postsplenectomy

Hematology		Chemistry		Infection	
RBC	406 × 10 ⁴ /μl	AST	81mU/ml	UrinepneumococcalAg	negative
Hb	11.7g/dl	ALT	60mU/ml	UrinelegionellaAg	negative
Ht	39.2%	LDH	321mU/ml	endotoxin	1.0pg/ml
platelet	15.2 × 10 ⁴ /μl	ALP	244mU/ml	β-D-glucan	1390pg/ml
WBC	7300	BUN	25.6mg/dl	mannanAg	6u/ml
Baso	0%	Cr	0.9mg/dl	SputumcultureCandidaalbicans	
Eosino	0%	Na	142mEq/l	SputumPneumocystis (DNA)	negative
Seg	87%	K	3.6mEq/l	cytomegalovirusWBC	negative
Lymph	10%	Cl	105mEq/l	Bloodculture	negative
CD4	41.9%	FBG	179mg/dl		
CD8	28.6%	CRP	21.8mg/dl		
Mono	3%	IgG	1415mg/dl		
		IgA	403mg/dl		
		IgM	179mg/dl		
		Bloodgas (nasal O ₂ 6l/min)			
		pH	7.412		
		Pco ₂	35.4Torr		
		Po ₂	35.8Torr		
		HCO ₃	22mEq/l

Fig. 4 Clinical course

sive care unit where in addition to fosfluconazol for candida infection and 600mg of ciprofloxacin for other bacterial infection, he was put on a respirator at low tidal volume ventilation. He was given 250mg of sivelestat sodium hydrate and 1000mg of methylprednisolone for a three day period and then 40mg of prednisolone for respiratory failure. Administration of regular insulin aimed for a blood glucose range of 80 to 140mg/dl. When blood glucose levels fell below 60mg/dl, insulin dosage was decreased. At

levels above 180mg/dl, it was increased. The patient's fever decreased and his respiratory condition improved. The chest x-ray film improved and the CRP became negative and β-D-glucan decreased (Fig. 4). After the patient did not take prednisolone, he had pneumococcal vaccination.

Discussion

The patient had clinical manifestations featuring OPSI syndrome 4days after EMR and 39days after

postsplenectomy associated with diabetes mellitus without macro- and microangiopathy. OPSI syndrome is a rare condition, but is associated with high mortality.^{3,4} A chest computed tomography showed bronchial wall thickening and consolidation at the posterior area in the bilateral lower lobes indicating transbronchial infection. *Streptococcus pneumoniae* is the most likely organism to cause OPSI syndrome. Pneumococcal vaccine, good knowledge and prophylactic penicillin are recommended in expert guidelines for the prevention of infectious complications after splenectomy.⁶ Although urine pneumococcal Ag and the 2-set blood culture were negative, and the sputum culture did not show bacterial organism, neutrophilia (87%) was shown. Therefore, OPSI syndrome may be caused by hospital acquired unknown bacterial infection after EMR in the immunocompromised condition of postsplenectomy and diabetes mellitus in our case. Moreover, the WBC count had not increased (7300/ μ l) compared with the CRP elevation (21.8mg/dl). Therefore, we administered ciprofloxacin for the consideration of atypical pathogens such as the *Chlamydia pneumoniae* infection (although we had not checked *Chlamydia pneumoniae* DNA). The 2-sets blood culture was negative and intraocular candidiasis was not shown. A chest computed tomography showed no disseminated lesion indicating septic emboli in lung. *Candida* sepsis was not considered although the β -D-glucan and mannan antigen indicating *Candida* or *Pneumocystis* infection elevated. Candidemia in critically ill patients is a significant source of mortality.⁷ Risk factors for the development of candidemia are age, malignancy, steroid use.⁸ Patients with prior surgery are at a higher risk fatality than others,⁹ compatible to our case. Splenectomy predisposes to fungal sepsis through defective phagosome formation.¹⁰ Therefore, we administered fosfluconazol in addition to ciprofloxacin and then β -D-glucan decreased. Because the sputum *Pneumocystis* DNA was negative, we did not perform the treatment for *Pneumocystis* infection. Autopsy shows that many patients with OPSI have Waterhouse-Friderichsen syndrome,³ so steroid hormone treatment in our patient was reasonable. Intensive treatment included low tidal volume ventilation that has been shown to be useful for acute respiratory failure.¹¹ The incidence of infection is higher in diabetic patients.^{1,2} Diabetes mellitus facilitates the acquisition of infection and impairs response to therapy.¹²⁻¹⁴ Diabetic patients suffering from pneumoniae with blood glucose levels of more than 200mg/dl have a poor prognosis.¹⁵ Surviving sepsis campaign guidelines recommend that the blood glucose levels should be less than 150mg/dl.¹⁶ Maintaining strict blood glucose levels from 80

to 110mg/dl by intensive insulin therapy significantly reduces morbidity more effectively than conventional insulin therapy for blood glucose levels from 180 to 200mg/dl. However, it carries a high risk of hypoglycemia.¹⁷ The blood glucose levels varied in our patient because of 1000mg of methylprednisolone over a three day period followed by 40mg of prednisolone for respiratory failure. Therefore, insulin treatment for blood glucose aimed at 80 to 140mg/dl by changing the insulin dose to less than 60mg/dl or more than 180mg/dl. A value less than 140mg/dl was the result of the guideline for management of postmeal glucose.¹⁸ After that, the patient's fever subsided. The respiratory condition and inflammatory makers improved. The patient had several diseases such as AIHA, gall bladder cancer, early gastric cancer and diabetes mellitus. We performed splenectomy for treatment of AIHA without prednisolone for better control of diabetes mellitus. Initial therapy for AIHA should be corticosteroid. However, long-term therapy may lead to significant detrimental side effects. Splenectomy has an advantage over therapeutic options in that it has the potential for complete and long-term remission.¹⁹ Both diabetes mellitus and splenectomy has induced immunocompromised condition in our patient. OPSI syndrome occurred 39 days after postsplenectomy in our case. Durations between splenectomy and onset of OPSI range from less than 1 week to more than 20 years.³ Most authorities agree that, when elective splenectomy is planned, the vaccines should be administered at least 2 weeks before the operation to optimize the antibody response. If not possible before surgery, for example in emergency splenectomy, patients should be immunized 2 weeks after the operation, taking their state of health into account.²⁰ Therefore, early vaccination is important for the prevention of remarkable infectious complication after splenectomy, particularly in diabetic patients.

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