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ORIGINAL ARTICLES

CASE REPORT

Acute Flaccid Paralysis in Enterovirus 71 Encephalomyelitis

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Background: Enterovirus 71 (EV 71) is now considered to be an important pathogen in infants and children with acute flaccid paralysis (AFP). Its clinical course is usually thought to be benign compared with that of poliomyelitis.

Methods: From 2000 to 2002, we treated seven infants or young children infected with EV 71 with the stereotypical clinical presentation of flaccid paralysis-associated symptoms of encephalitis with prominent brainstem involvement. We analyzed the correlation between the clinical features and outcomes.

Results: Three of seven patients presented with autonomic dysfunction with accompanying left ventricular failure; one died rapidly within 12 hours after admission and the other two survived via left ventricular assist device (LVAD) support in the acute stage of the illness, but residual swallowing difficulty remained. Four cases without left ventricular failure survived the acute illness. However, one died of valproic acid related fulminant hepatitis occurring on the 24th day after discharge and three had residual limb paralysis.

Conclusions: AFP in EV 71 encephalomyelitis is not always benign in infants and young children, especially when patients have autonomic dysfunction and overwhelming left ventricular failure. We emphasize that close monitoring of vital signs and performing serial echocardiograms are essential in cases of AFP caused by EV 71 encephalomyelitis.
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Key words: AFP, EV 71, encephalomyelitis

INTRODUCTION

Enterovirus 71 (EV 71), of the family Picornaviridae, was first recognized in 1974 after isolation studies were performed from a series of patients in Califoria who had severe neurologic diseases between 1969 and 1973[1]. EV 71 infection clinically presents as hand-foot-mouth disease (HFMD), herpangina or central nervous system (CNS) disorders. In cases of CNS infection, it has been reported that the various neurological syndromes include aseptic meningitis, encephalitis, acute flaccid paralysis (AFP), Guillain-Barre syndrome, acute transverse myelitis, acute cerebellar ataxia, opso-myoclonus syndrome, benign intracranial hypertension, and febrile convulsion[2, 3].

From April to July 1998, an epidemic outbreak of EV 71 infection developed in Taiwan and resulted in 78 deaths (19.3%). Moreover, according to the reports of Taiwan's Center for Disease Control for EV 71 infection, fatalities continued for four consecutive years; 9 in 1999 (25.7%), 41 in 2000 (14.1%), 58 in 2001 (14.8%), and 30 in 2002 (18.5%). These cases had neurological manifestations with altered levels of consciousness, opsoclonus, myoclonus, tremor, cra-

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nial nerve palsy and acute limb paralysis. Autonomic dysfunctions such as cold sweating, tachycardia, and hypertension followed by cardiopulmonary failure or heart failure were also noted. Most patients died rapidly within 12 hours after admission.

From 2000 to 2002, 9 patients diagnosed as encephalomyelitis presenting with AFP were seen at our hospital. 7 out of 9 were confirmed to have EV 71 infection. In this report, we present the clinical spectrum, laboratory findings and neuroimaging studies of AFP in EV 71 encephalomyelitis.

MATERIALS AND METHODS

Clinical definitions

Antecedent illness was defined as systemic symptoms that developed before the onset of neurological symptoms. This included HFMD or herpangina. HFMD means vesicular lesions over the hands, feet and mouth, and sometimes in the buttocks. Intraoral lesions were often ulcerated.

Encephalomyelitis with prominent brainstem involvement (rhombencephalomyelitis) was characterized by clinical presentations of altered levels of consciousness, ataxia, tremor, opsoclonus, myoclonus, gaze paresis, bulbar palsy, autonomic dysfunctions including cold sweating, tachycardia, and hypertension, and AFP. AFP was defined as acute onset of weakness of one or more limbs and lack of reflexes.

Extraneurological symptoms included pulmonary edema or cardiac dysfunction. Pulmonary edema was characterized by a rapid process with respiratory distress, tachypnea and often produced a frothy, pink-tingled sputum. Chest X-ray (CXR) may show a diffuse perihilar infiltrate (butterfly distribution). Ventricular dysfunction of the heart was defined as the left ventricular ejection fraction (EF) being less than 60% (normal 64-83%) and the left ventricular fractional shortening (FS) being less than 25% (normal 28-44%). EF is calculated as $(LVED)^3$-$(LVES)^3/(LVED)^3$ and FS is calculated as (LVED-LVES)/LVED, where LVED is the left ventricular (LV) dimension at end-diastole and LVES is the LV dimension at end-systole[4].

CASE REPORTS

From 2000 to 2002, a total of 9 infants or young children diagnosed as encephalomyelitis presenting with AFP were admitted to our ward. Among them, 7 patients with HFMD were documented as having EV 71 infection by virology studies. There were 4 male and 3 female patients, aged from 9 months to 3 years and 6 months.

Case 1: Female, 2 years 4 months

On day 3 of illness, the patient suffered from sudden onset of flaccid paralysis of the left arm. Ten hours later, she was admitted to our pediatric intensive care unit (PICU) because of sudden onset of pale appearance and drowsiness. Upon admission, she had grunting breath, cold sweating and opsoclonus. Her vital signs were body temperature (BT) 34.6°C, heart rate (HR) 162/min, respiration rate (RR) 31/min, and blood pressure (BP) 137/96 mmHg. Pink foamy sputum was also noted. Echocardiogram showed ventricular hypokinesia (EF:27%; FS:12%). CXR revealed diffuse pulmonary edema without cardiomegaly. Hyperventilation therapy, intravenous immunoglobulin (IVIG) and inotropic agents were given immediately. Follow-up CXR was done 3 hours later showing improvement of the pulmonary edema. However, persistent tachycardia up to 236/min and hypertension up to 132/67mmHg developed lasting 6 hours. Sudden onset of hypotension and gradual bradycardia developed. She died 10 hours after admission.

Case 2: Male, 2 years 7 months

On day 3 of illness, the patient suffered from drowsiness and myoclonus. He was admitted because of acute flaccid paralysis of the right arm on day 4. On admission, his vital signs were BT 37.3°C, HR 165/min, RR 25/min, and BP 94/51mmHg. Echocardiogram was performed immediately and the result showed normal ventricular contraction (EF:70%; FS:33%). CXR revealed no evidence of pulmonary edema. Supportive treatment with hyperventilation therapy and IVIG were given. No heart dysfunction was noted in a series of follow-up echocardiograms. On Day 11, brain magnetic resonance imaging (MRI) revealed abnormal signal intensity over the right medulla oblongata. He was discharged with paralysis of the right arm. During the four-month follow-up at our clinic, he still had weakness and hyporeflexia of the right arm with mild grasping power, but no antigravity function.

Case 3: Male, 1 year and 8 months

On day 3 of illness, the patient developed acute onset of flaccid paralysis of the right leg. He was sent to a local hospital for observation. Unfortunately, sudden onset of pale appearance, cyanosis, myoclonus and drowsiness occurred 8 hours later. His vital signs were BT 37.8°C, HR 170/min, RR 40-60/min, and BP 115/78mmHg. Immediate intubation and IVIG were given and he was transferred to our hospital. On arrival, he had cold extremities, opsoclonus, myoclonus, and pink frothy secretion from the endotreacheal tube. His vital signs were HR 165/min and BP 78/42mmHg. Echocardiogram showed left ventricular dysfunction (EF:39%; FS:18%). CXR revealed bilateral pulmonary edema without cardiomegaly. He had the same clinical course as case 1. Because the left ventricular function was progressively deteriorating and not responding to the inotropic agents, emergent left ventricular assist device (LVAD) was employed. Fifty-six hours later, LVAD was removed as left ventricular function recovered. However, respiratory and swallowing difficulties were found during the recovery stage. He received tracheostomy and was fed by nasogastric tube. Brain MRI was performed 2 months later and showed abnormal signal intensity at the lower pons, medulla oblongata, and whole spinal cord (Fig 1). He received regular OPD follow-up and his swallowing function improved very slowly. His nasogastric tube and tracheostomy tube were removed 1 year 6 months and 1 year 9 months later, respectively. At present, his neurological conditions show only a mild right limping gait.

Case 4: Female, 1 year 10 months

On day 3 of illness, the patient developed myoclonic jerks and gaze paresis. Acute flaccid paralysis of the bilateral lower legs developed on day 4, so she was admitted to our hospital. On admission, her vital signs were BT 37.2°C, HR 150/min, RR 26/min, and BP 106/59mmHg. Echocardiogram showed normal ventricular function (EF:69%; FS:33%) and the CXR was negative. Supportive treatment with IVIG and hyperventilation therapy was performed. Brain MRI was performed 18 days after admission, which disclosed abnormal signal intensity over the dorsal aspect of the pontomedullary junction (Fig 2). Valproic acid (10mg/Kg/Day) was prescribed because of frequent myoclonic jerks. On the day of discharge, neurological examinations showed mild weakness of the bilateral lower legs, right gaze paresis and myoclonic jerks. Two weeks after discharge, her mother found her feeling very sleepy. She was sent to our

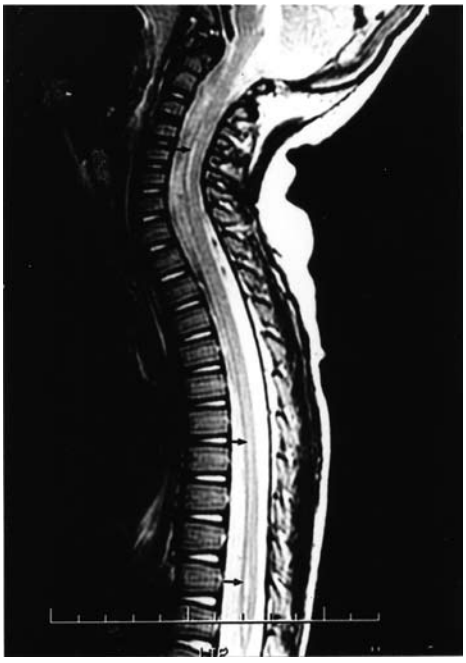

Fig. 1 Sagittal section of the brain MRI of case 3 (TR:4000, TE:93.5/Ef).
High signal intensity was found at the dorsal aspect of lower pons, medulla oblogata (arrow head), and the cervical to lumbar spinal cord (arrows).

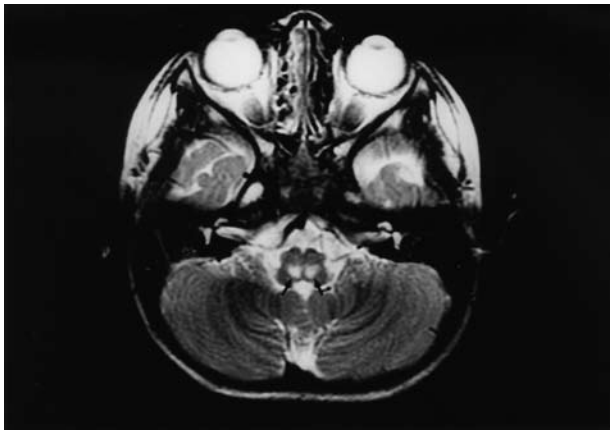

Fig. 2 Coronal section of the brain MRI of case 4 (TR:4000, TE:94.8/Ef).
Ovoid lesions at the dorsal aspect of the pontomedullary junction with high signal intensity were noted (arrows).

emergency room for help where liver function impairment was noted with a GOT level of 2576 U/l (8-38U/l), a GPT level of 3037 U/l (4-44U/l), a total bilirubin level of 6.2 mg/dl (0.1-1.2 mg/dl), and a direct bilirubin level of 4.0 mg/dl (0-0.2 mg/dl). She was sent to another hospital where her valproic acid level was measured of 36.8mg/dl. Blood exchange transfusion was performed, but she died of fulminant hepatitis on the 24th day after discharge.

Case 5: Male, 9 months

On day 4 of illness, the patient was admitted because of acute onset of flaccid paralysis of right arm. On admission, he had irritability, opsoclonus and myoclonus. His vital signs were BT 37°C, HR 130/min, RR 32/min, and BP 107/83 mmHg. Supportive treatment with hyperventilation therapy and IVIG were given. He had normal heart function (EF:75%; FS:36%) initially. However, progressive tachycardia up to 180/min and hypertension up to 175/106 mmHg developed lasting about 5 hours. Follow-up echocardiogram showed rapid deterioration of left ventricular function (EF:46%; FS:22%). CXR revealed no pulmonary edema. Based on the previous successful experience of case 3, LVAD was performed. Ninety-three hours later, LVAD was removed as left ventricular function returned normal. However, respiratory and swallowing difficulties were found in the recovery stage. He needed tracheostomy with ventilator support and nasogastric feeding. Brain MRI was performed 22 days after admission and showed multiple abnormal signal intensities over the dorsal aspect of the brainstem and cervical spinal cord. During follow-up 1 year and 6 months later, he still had swallowing dysfunction and needed respirator support at nighttime (Ondine curse). Neurological examinations showed alertness, but his gross motor function revealed head lag, inability to sit alone and paralysis of the right arm without grasping power.

Case 6: Female, 3 years and 6 months

On day 2 of illness, the patient suffered from myoclonic jerks. Sudden onset of flaccid paralysis of right arm developed on day 3. On admission, she had clear consciousness and her vital signs were BT 37.2°C, HR 106/min, RR 21/min, and BP 106/65 mmHg. Echocardiogram showed normal heart function (EF:81%; FS:48%) and CXR was negative. Supportive treatment with IVIG was given. Cervical spine MRI was performed 5 days after admission and revealed increased signal intensity from C2 to C7. She was discharged with right arm weakness. During follow-up 10 months later, her right forearm had antigravity ability and could grasp objects, but she still could not elevate the right shoulder.

Case 7: Male, 1 year and 11 months

On day 3 of illness, the patient suffered from frequently myoclonic jerks. On admission, he had drowsiness and his vital signs were BT 37.6°C, HR 160/min, RR 20/min, and BP 105/67 mmHg. Echocardiogram showed normal heart function (EF:72%; FS:35%) and CXR was negative. Supportive treatment with IVIG was given. Sudden onset of left arm weakness developed on day 4. Brain and cervical spinal cord MRI were performed on day 5 of illness and it showed abnormal signal intensity over the medulla oblongata and C2 to C6. He was discharged with left arm paralysis presenting with withdrawal to pain, but no antigravity power.

Virology study

The diagnosis of EV 71 infection was based on isolation of the virus by culture or reverse-transcription polymerase chain reaction (RT-PCR). Specimens from throat swabs, stool swabs, cerebrospinal fluid were collected on the day of admission. Monolayers of Vero cells were used for virus isolation. Indirect immunofluorescence assay was used for visualization. The cells were incubated at 36oC for at least 14 days in culture medium (2% FBS with EMEM; Gibco) to find a characteristic enteroviral cytopathic effect screened by using a Pan-Entero Blend (3360, Chemicon International, Temecula, Calif.). EV 71 was identified by monoclonal antibody 3324 which is specific for EV 71. All positive results were reconfirmed by neutralization with type specific pools of immune sera. We also use serotype-specific RT-PCR as described by Brown et al [5] to identify EV 71 for rapid diagnosis.

RESULTS

The clinical manifestations, laboratory and neuroimaging findings are summarized in Tables 1 and 2. In our 7 cases, symptoms of encephalomyelitis,

Table 1. Clinical manifestations

Case	Sex	Age	Day of admission	Physical S/S (onset day)			Neurological S/S (Onset day)				S/S of autonomic dysfunction		Foamy discharge	Mana-gement	Outcome
				Fever	Oral ulcers	Rashes H&F	Myocl-onus	Opso-clonus	Gaze paresis	AFP	Others	H/T	Tachyc-ardia	Cold sweating			
1	F	2y4m	(D4)	+ (D1)	+ (D1)	+ (D1)	-	+ (D4)	-	LA (D3)	Drowsy (D4)	+	+	+ (D4)	+ (D4)	IVIG + HV	Death
2	M	2y7m	(D4)	+ (D1)	+ (D1)	+ (D1)	+ (D3)	-	-	RA (D4)	Drowsy (D3)	-	+	-	-	IVIG + HV	Alive, RA weakness
3	M	1y8m	(D4)	+ (D1)	-	+ (D1)	+ (D4)	+	-	RL (D3)	Drowsy (D4)	-	+	-	+ (D4)	IVIG + HV + LVAD	Alive, Rt limping gait
4	F	1y10m	(D4)	+ (D1)	+ (D1)	+ (D1)	+ (D3)	-	+ (D3)	Bil.L(D4)	-	-	+	-	-	IVIG + HV	Died of VPA related fulminant hepatitis
5	M	9m	(D4)	+ (D1)	+ (D2)	+ (D2)	+ (D4)	+ (D4)	-	RA (D4)	Irritable(D4)	+	+	-	-	IVIG + HV + LVAD	Alive, RA paralysis Res/swallow. difficulty
6	F	3y6m	(D4)	+ (D1)	-	+ (D2)	+ (D2)	-	-	RA (D3)	-	-	-	-	-	IVIG	Alive, RA paralysis
7	M	1y11m	(D3)	+ (D1)	+ (D3)	+ (D2)	+ (D3)	-	-	LA (D4)	Drowsy (D3)	-	+	-	-	IVIG	Alive, LA paralysis

AFP= acute flaccid paralysis; Bil.L= bilateral legs; F= female; H&F=hands and feet; H/T= hypertension; HV=hyperventilation therapy; IVIG=intravenous globulin; LA= left arm; LVAD= left ventricular assist device; M= male; m= months; RA= right arm; Res/swallow.=respiration/swallowing; RL= right leg; S/S= symptoms and signs; VPA=valproic acid; y= years

including altered levels of consciousness, myoclonus, opsoclonus, gaze paralysis and limb flaccid paralysis were noted on day 3 to 4 of onset of hand-foot-mouth disease (HFMD). 6 of 7 cases had autonomic symptoms such as cold sweating, and tachycardia with or without hypertension. 3 of 6 were accompanied by left ventricular failure; 2 of 3 presented with pulmonary edema. Case 1 quickly died of cardiopulmonary failure; case 3 and case 5 survived the acute stage of the illness via LVAD therapy. Case 3 recovered gradually, but case 5 still had swallowing and respiration difficulties. 4 other cases without left ventricular failure all recovered from acute illness by supportive treatment with IVIG injection with or without hyperventilation therapy. Case 4 died of valproic acid related fulminant hepatitis on the 24th day of illness in the recovery phase; cases 2, 6 and 7 had residual limb paralysis.

In cerebrospinal fluid (CSF) studies, all cases had increased intracranial pressure. 4 of 7 cases had pleocytosis (white cell counts more than 10/cumm). All had negative results for bacterial cultures, viral cultures and RT-PCR. All cases were documented as being EV 71 infection from throat swabs; 3 cases had positive results of virus cultures and RT-PCR, 2 had positive findings of virus cultures, and the remaining 2 had positive RT-PCR results. Brain MRIs with or without the spinal cord MRIs were performed in all cases except for case 1. Among them, 5 of 6 patients had abnormal signal intensity over the dorsal aspect of the pons and/or medulla oblogata; 3 out of 5 also showed abnormal signal in the spinal cord. Case 6 had abnormal signal intensity over the cervical spinal cord only.

DISCUSSION

Acute flaccid paralysis (AFP) could result from acute anterior myelitis, acute myelopathy, peripheral neuropathy, or disorders of the neuromuscular junction, the muscle or systemic disease. In the past, poliomyelitis was the major cause of AFP. Since the eradication of the poliovirus, polio-like syndrome caused by non-polio viruses has been reported such as coxackieviruses, echoviruses, enteroviruses 70 and 71[6-10]. Enterovirus 71 (EV 71) has become an important cause of AFP because of a number of recent epidemics. Literature review[11-15] show that most cases had a benign clinical course resulting in complete

Table 2. Laboratory results and neuroimage findings

Case	CSF						EV-71 culture			RT-PCR for EV-71			Image				
	WBC	N:L	Protein	Sugar	Culture	IP/FP (mmH_2O)	CSF	Throat	Rectal	CSF	Throat	Rectal	CXR	ECG		MRI	
													PE	EF	FS	Brain	Spinal cord
1	12	2:8	36	47	_	180/ND	_	+	ND	_	+	ND	+	27	12	ND	ND
2	34	8:25	72	113	_	230/160	_	+	_	_	_	_	_	70	33	MO	ND
3	0	0:0	111	92	_	210/190	_	+	_	_	+	+	+	39	18	P+MO	C-L cord
4	330	34:64	143	63	_	260/200	_	+	_	_	_	_	_	69	33	P+MO	ND
5	8	4:4	35	82	_	165/160	_	_	_	_	+	+	_	46	22	P+MO	C-cord
6	4	2:2	32	72	_	180/180	_	+	_	_	+	_	_	81	48	N	C2-7
7	65	57:8	48	85	_	180/148	_	_	ND	_	+	_	_	72	35	MO	C2-6

C-L cord=cervical to lumbar spinal cord; CSF= cerebrospinal fluid; CXR=chest X-ray; ECG=echocardiogram; EF=ejection fraction;
EV-71= enterovirus 71; FS= fraction shortening; IP/FP=initial pressure/final pressure; MO=medulla oblongata;
MRI=magnetic resonance imaging; N=normal; ND= not done;N:L= neutrophil:lymphocyte; P=pons;
RT-PCR= reverse-transcription polymerase chain reaction; PE=pulmonary edema; WBC= white cell count;

recovery or mild residual paralysis

EV 71 associated with fatal paralytic disease, however, was first described in a severe epidemic of the central nervous system (CNS) disease occurring in Bulgaria in 1975. Of 705 patients, 149 (21%) developed polio-like paralysis and 44 died[16]. In the Bulgaria outbreak, all fatal cases of paralytic diseases were characterized by meningoencephalomyelitis with medullary involvement. It has also been reported that some cases of AFP with EV 71 infection became fatal during the outbreaks in Malaysia in 1997[17,18] and in Taiwan in 1998[19]. Clinical symptoms of the fatal cases included encephalomyelitis with brainstem involvement. In our cases, in addition to the clinical presentation of AFP, 5 of 6 cases had brainstem involvement either documented by MRI or noticed by clinical signs. These findings indicate that the clinical symptoms of encephalomyelitis associated with acute flaccid limbs may be a sign of serious danger. We also found in our surviving cases, only one patient had mild residual weakness of the right leg in long-term follow up, whereas the remaining 4 cases still had neurological sequelae of prominent limb weakness.

In Malaysia ‘s 1997 and Taiwan ‘s 1998 outbreaks, a unique clinical presentation of cardiopulmonary failure or rapid progressing left ventricular dysfunction evolving to quick death was described. In the past, pulmonary edema was thought to be the cause of death[17-20] because most clinics did not perform the echocardiograms during the acute deterioration of illness. Recently, left ventricular failure has been determined to be the cause of death[21-23]. It has also been reported that acute neurologic insult may cause a catecholamine storm and “a panic myocardium”, manifestation with autonomic dysfunctions and progressing left ventricular failure, ultimately resulting in rapid death[8,24]. In our study, 6 out of 7 cases had autonomic dysfunction presenting with tachycardia, hypertension or both. Among 6 cases, 3 had clinical manifestations of progressing left ventricular dysfunctions; 2 of 3 had pulmonary edema and 1 case only had ventricular dysfunction.

For clinical treatment, we used LVAD to reverse rapidly deteriorating left ventricular function in the acute stage and in the event of conventional therapy failure[23]. In our report, 3 cases had ongoing left ventricular failure; 1 died rapidly and the other 2 receiving LVAD therapy in the acute stage of illness survived. Case 3 had nearly complete recovery of neurological functions except for mild residual limb weakness. Case 5, however, had prominent neurologic sequelae in terms of swallowing and respiration difficulties, and profound limb paralysis. On the other hand, 4 cases without left ventricular failure survived the acute stage of illness via supportive treatment.

We conclude that AFP in EV 71 encephalomyeli-

tis is not always benign, and is sometimes fatal. Close monitoring of vital signs and frequent echocardiograms are crucial in cases showing signs of autonomic dysfunction, especially progressive tachycardia or hypertension. EV 71 is important for the differential diagnosis of critical paralytic disease in patients with HFMD during an epidemic, especially in infants and young children.

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病毒 71 型腦脊炎引起之急性肢體無力麻痺

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背景：腸病毒 71 型（Enterovirus 71; EV71）目前已被認為是造成嬰兒及兒童急性肢體無力麻痺的重要病因之一，它的臨床過程常被認為比小兒麻痺病毒造成的急性肢體無力麻痺來得良性。

方法：從 2000 年到 2002 年，我們治療七位感染腸病毒 71 型的嬰兒及兒童，臨床上，他們均出現典型肢體無力麻痺且同時合併腦幹腦炎的症狀，我們分析臨床表現與預後的相關性。

結果：七位病童中，三位出現自主神經功能失調合併左心室衰竭，一位病童於住院後十二小時快速死亡，兩位病童在急性期時需左心室輔助器維持生命，但恢復期時仍有吞嚥功能障礙；四位病童在急性期時不需左心室輔助器協助，其中一位病童於出院後第二十四天因帝拔癲引起猛爆性肝炎死亡，其餘三位肢體麻痺的情況仍持續存在。

結論：腸病毒 71 型腦脊髓炎在嬰兒及兒童造成的急性肢體無力麻痺並非總是良性的，特別是當病童合併自主神經功能失調及左心室衰竭的症狀時。因此，密切監測生命徵兆及追蹤心臟超音波在腸病毒 71 型腦脊髓炎合併急性肢體無力麻痺的病童是很重要的。

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關鍵詞：急性肢體無力麻痺，腸病毒 71 型，腦脊髓炎。

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Immunomodulatory Effects of Lactic Acid Bacteria in Patients with Perennial Allergic Rhinitis

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Background: Lactic acid bacteria can alleviate the disease severity of atopy and, prevent the development of allergies, possibly via their ability to modulate the immune response.

Purpose: We aimed to examine the clinical efficacy, safety, and immunological effects of *Lactobacillus paracasei-33* (LP-33) in patients with mite-induced perennial allergic rhinitis.

Methods: In this randomized, double blind, placebo-controlled study, 57 subjects were assigned to the LP-33 group (n = 41) and the placebo group (n = 16), based on consumption of yogurt with or without LP-33 for 12 weeks. Relative changes of symptom scores after intervention were used for primary outcome measure. We also assessed the changes of immunological parameters, including interferon (IFN)-γ, interleukin (IL)-4, and total serum immunoglobulin (Ig) E at enrolment and after 12 weeks of treatment.

Results: Consumption of LP-33 fortified fermented milk demonstrated significantly greater improvement in symptoms ($P < 0.05$) during the intervention and follow-up period. LP-33-treated subjects had a significant increase in IFN-γ level (33.77 ± 6.93 pg/mL vs. 41.05 ± 8.75 pg/mL, $P = 0.001$) and reduction in IgE level (732.53 ± 229.20 IU/mL vs. 579.96 ± 125.99 IU/mL, $P = 0.032$). No subjects reported any adverse side effects.

Conclusion: Patients who consumed LP-33-fortified fermented milk had significantly less symptoms of allergic rhinitis. The mechanisms were probably due to the immunomodulatory effects of probiotics. This may further provide a novel and safe approach to perennial allergic rhinitis.

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Key words: ***Probiotic, Allergic rhinitis, Lactobacillus paracasei***

INTRODUCTION

Because the increasing trend of atopy has emerged during an era of strict hygiene practice and successful infection control in the developed countries, the concept was proposed that this was linked to decreasing and insufficient exposure to microbial agents[1, 2]. According to the "hygiene hypothesis" [3], changing interactions between humans and intestinal microflora may affect the immune balance at the mucosal level, thereby predisposing to allergic disease by a deviation to T_H2 immune response[4]. Animal study demon-

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strates that a lack of adequate microbial stimulation of the intestinal immune system in early life increases the risk factors of allergic diseases[5]. Seropositivity to orofecal microbes (hepatitis A virus, *Toxoplasma gondii*, and *Helicobacter pylori*)[6, 7] is inversely correlated with IgE levels and onset of allergic sensitization. Epidemiological studies demonstrate a low prevalence of respiratory allergies had been reported in children living the traditional lifestyle in anthroposophic communities[8] and farming communities[9].

Recently, there were many clinical studies providing evidence to support the administration of probiotics in prevention and treatment of atopic disease. Majamaa et al. compared the response to a hydrolyzed whey formula alone or in combination with *Lactobacillus casei* GG (LGG) in cow's milk-sensitive infants with atopic dermatitis. The probiotic group had a significantly greater improvement in the intensity and extent of atopic eczema during a 1-month study period[10]. In the most promising demonstration of the potential for probiotics in a clinical study to date, Kalliomäki et al. published the results of a landmark study recently. They provided the probiotic *Lactobacillus rhamnosus* perinatally to infants at risk for atopy. In the active treatment group, the frequency of atopic eczema in infants at age 24 months was one-half that of the placebo group (23% vs. 46%, respectively). The authors suggested intestinal microflora could be a natural endogenous immunomodulators for prevention of atopic diseases [11].

We therefore investigated the clinical efficacy, safety profile, and immunological effects of LP-33 on subjects with perennial allergic rhinitis induced by house-dust mites. In addition, we focused on whether specific immune responses shifted to a T_H1 status after probiotic intervention.

MATERIALS AND METHODS

Subjects

Potential subjects were invited from an allergy clinic of the Pediatrics Department of China Medical University Hospital during a screening period. The Ethics Committee of the hospital approved this study. Informed written consent was obtained from each patient and from a parent or legal guardians of eligible children if the patient was under age 18. All subjects completed a questionnaire on rhinitis symptoms before entering the study. Subjects were eligible if they were older than age 6 years and had a history of physician-diagnosed perennial allergic rhinitis for more than 1 year. All subjects showed sensitization to *Dermatophagoides pteronyssinus* (Dp), as evaluated by intradermal skin testing (wheal $\geq$ 3 mm), with a titer of specific IgE to Dp of more than 3.5 IU/L, which was determined using the CAP system (Pharmacia Diagnostics, Uppsala, Sweden). Potential subjects were excluded if they had participated in another clinical study during the past 1 month; were pregnant or planning to be pregnant; were taking any prescribed steroid medications (oral, parenteral, or both); had smoked during the past 6 months; or had been diagnosed as having immunodeficiency diseases, active infectious sinusitis, or cow's milk protein allergy.

Protocol

This was a randomized, double-blind, placebo-controlled intervention study examining the effect of probiotic LP-33 on aspects of symptom change and immunological markers of allergic rhinitis. At the baseline visit, we recorded characteristics of all subjects enrolled. A comprehensive medical and allergic history was taken for eligible subjects, especially including a history of allergic rhinitis and the medications used for its control. A physical examination, including check of vital signs, was performed at each visit. The intervention period consisted of visit 2, visit 3, and visit 4. The interval between visits was 4 weeks. All qualified subjects were randomly assigned to consume fermented milk with or without LP-33 fortification. According to body weight (with an arbitrary cutoff of 30 kg), subjects were assigned to consume one or two bottles (200 ml each) of fermented milk daily. Four weeks after the intervention period, patients received examinations and questionnaires to assess the follow-up effects (final visit).

In the placebo formula, each milliliter of milk contained 10^6 colony-forming units (CFU) of live *Streptococcus thermophilus* and 10^5 CFU of *Lactobacillus bulgaricus*. The LP-33 formula was further fortified with *Lactobacillus paracasei* (10^7 CFU/mL). The two preparations of formula were designed to resemble each other as indistinguishably as possible in package, color, olfaction, and palatability. The dairy product was prepared fresh at the plant during the study period and distributed to the participants every 14 days.

One piece of questionnaire was administered

to all subjects or their parents at all five visits. This questionnaire consists of five domains (nose symptoms, eye symptoms, practical problems, other symptoms, and activity limitation) and 20 items corresponding to them. The symptom scores are indexed on a 5-point scale for each item. Subjects rated the frequency of symptoms as 0 indicating none to 4 indicating most of the time. They also rated the level to which the symptoms bothered them, with 0 indicating not at all and 4 indicating extremely.

Subjects discontinued the study if they had a respiratory tract infection complicated by an episode of sinusitis. They withdrew due to other factors, such as moving away, poor adherence, or severe adverse effects (diarrhea, abdominal pain, etc.).

Blood sampling and immunologic assays

Peripheral blood samples were obtained by venipuncture from subjects at the start and the end of the 12-week intervention period. The specimens were assayed using microparticle enzyme immunoassay for quantitative measurement of total serum IgE level (IMx® Total IgE assay, Abbott laboratories, Japan). Each cytokine assay involves anti-cytokine monoclonal antibody-coated microwells and a complementary working detector preparation (one-step incubation of biotinylated antibody/avidin reagents) to capture the cytokine in the sample (PharMingen for IL-4 and IFN-γ). Measurement by reading absorbance at 405 nm fluorescence yields the amounts of immune complex formed on the surface of the microwells. The results were quantitated against the standard curves generated using known amounts of recombinant cytokines, according to the instructions of the manufacturer. The sensitivity of the IL-4 and IFN-γ assay was 0.5 pg/mL and 5 pg/mL, respectively. All assays were performed in duplicate and the mean value was used for interpretation.

Evaluation of safety

At each visit, we checked vital signs of subjects and inquired of all subjects about whether any adverse effects (such as abdominal pain, vomiting, diarrhea, and febrile episodes of unknown causes) emerged during the past month. All of the reported adverse effects were recoded.

Statistical analysis

Values of outcome measures are reported as means ± SD. Because the symptom scores and the concentration of plasma mediators might have been non-normally distributed, we used nonparametric tests. Intra-group comparisons were performed using the Wilcoxon's rank sum test and between-group comparisons were performed using the Mann-Whitney U test. A value of $P < 0.05$ indicated statistically significance difference.

RESULTS

Subjects and baseline characteristics

Of the 60 subjects who were screened, 57 were eligibly enrolled and randomly assigned to the LP-33 group ($n = 41$) and the placebo group ($n = 16$). The important baseline characteristics of both groups are shown in Table 1. The two groups did not differ significantly in terms of demographic variables, including age, body weight, and gender distribution. There was no significant difference in personal and family history of allergy between the groups. The distribution of classes (from 0 to 6) of specific IgE to Dp was well matched between the treatment and placebo groups at baseline. There was no significant difference in the sensitization rate to cockroach, egg white, and shrimp between the groups.

Percentage changes of frequency variable

As shown in Table 2, relative to baseline score, at 4 time points every subject in both groups experienced a drop (presented as positive percentage change) in symptom score in all domains. Nose symptoms score at 8 weeks decreased to a significantly greater degree ($P = 0.001$) in the LP-33 group compared with placebo group. Compared with the placebo group, the relative change in eye symptoms score at 8 weeks, 12 weeks, and 16 weeks differed significantly in the LP-33 group. At 4 weeks, 8 weeks, and 12 weeks, the mean percentage change of practical problems in the LP-33 group differed significantly (all $P < 0.05$) from the placebo group. Except at 4 weeks, the LP-33-treated subjects experienced a significantly greater drop in score of other symptoms compared with the placebo-treated subjects. In the LP-33 group, furthermore, the reduction of activity limitation score at both 12 weeks and 16 weeks differed significantly from the placebo group ($P = 0.018$, and $P = 0.036$, respectively). The total

Table 1. Demographics and baseline characteristics of the study subjects (n = 57)

		LP-33 (n = 41)		Placebo (n = 16)		P value
Age (y)		16.22 ± 1.89		14.00 ± 2.03		0.979[a]
Body weight (kg)		39.63 ± 2.43		40.39 ± 4.05		0.894[a]
Gender	♂	19	(46.3)*	10	(62.5)	0.273
	♀	22	(53.7)	6	(37.5)	
Bottle(s) of milk	1	16	(39.0)	6	(37.5)	0.915
	2	25	(61.0)	10	(62.5)	
Asthma	+	24	(58.5)	7	(43.8)	0.314
	−	17	(41.5)	9	(56.8)	
Urticaria	+	1	(2.4)	1	(6.3)	0.486[+]
	−	40	(97.6)	15	(93.8)	
Atopic dermatitis	+	5	(12.2)	2	(12.5)	0.999[+]
	−	36	(87.8)	14	(87.5)	
Atopy of family	+	29	(70.7)	9	(56.3)	0.356
	−	12	(29.3)	7	(43.8)	
Classes of Dp[†] IgE	1-2	5	(12.8)	3	(21.4)	0.204
	3-4	19	(48.7)	3	(21.4)	
	5-6	15	(38.5)	8	(57.1)	
Egg white	+	5	(19.2)	1	(10.0)	0.655[+]
	-	21	(80.8)	9	(90.0)	
Shrimp	+	4	(15.4)	1	(10.0)	0.999[+]
	-	22	(84.6)	9	(90.0)	
Cockroach	+	3	(11.5)	0	(0.0)	0.545[+]
	-	23	(88.5)	10	(100.0)	

aData analysis used the Mann-Whitney U test.
+Data analysis used Fisher's exact test; the other items used chi-square test.
*The number in parenthesis is the percentage (%).
†:Dp: *Dermatophagoides pteronyssinus*.

score decreased to a significantly greater degree at 4 weeks, 8 weeks, 12 weeks, and 16 weeks after enrollment in the LP-33 group, compared with the placebo group (P = 0.042, P = 0.000, P = 0.001, and P = 0.001, respectively).

Percentage changes of level of bother variable

As shown in Table 3, percentage change of nose symptoms at 8 and 12 weeks differed significantly (P = 0.006 and P = 0.035, respectively) between the two groups. In the LP-33 group, there was a significantly greater percentage of change in eye-symptoms score at 8, 12, and 16 weeks [P = 0.032, P = 0.016, and P = 0.004, respectively] compared with the placebo group. Furthermore, compared with the placebo-treated subjects, the LP-33-treated subjects experienced a significantly greater drop in score of practical problems at all time points. On the other hand, the percentage change of other symptoms did

Table 2. Percentage changes of score in frequency variable as a function of time of intervention and follow-up (weeks)

	Intervention period			Follow-up
	Week 4	Week 8	Week 12	Week 16
Nose symptoms				
LP-33 (%)	38.42 ± 4.50	42.31 ± 4.60	37.51 ± 4.92	38.47 ± 5.07
Placebo (%)	25.30 ± 7.25	13.81 ± 6.10	20.99± 8.00	24.20 ± 6.52
P value	0.097	0.001*	0.052	0.132
Eye symptoms				
LP-33 (%)	44.52 ± 6.32	51.33 ± 5.82	38.43 ± 6.00	52.43 ± 6.44
Placebo (%)	31.99 ± 10.25	24.51 ± 8.00	3.13 ± 2.27	10.20 ± 5.20
P value	0.333	0.017*	0.001*	0.001*
Practical problem				
LP-33 (%)	43.55 ± 5.43	43.39 ± 5.29	34.76 ± 5.24	26.87 ± 4.78
Placebo (%)	19.98 ± 7.31	7.11 ± 3.37	11.31 ± 7.25	14.93 ± 5.64
P value	0.014*	0.000*	0.007*	0.195
Other symptoms				
LP-33 (%)	50.01 ± 5.75	54.05 ± 5.80	42.54 ± 5.85	62.87 ± 5.58
Placebo (%)	40.89 ±10.80	24.67 ± 7.58	19.40 ± 7.53	34.31 ± 8.46
P value	0.383	0.007*	0.022*	0.010*
Activity limitation				
LP-33 (%)	47.75 ± 6.30	62.39 ± 6.01	46.02 ± 6.46	61.41 ± 5.41
Placebo (%)	28.55 ± 10.49	44.43 ± 11.22	19.61 ± 8.50	37.08 ± 9.35
P value	0.059	0.165	0.018*	0.036*
Total score				
LP-33 (%)	43.23 ± 4.69	49.28 ± 4.45	38.20 ± 4.76	42.59 ± 4.52
Placebo (%)	25.31 ± 6.69	15.78 ± 5.39	10.72 ± 5.72	16.00 ± 5.09
P value	0.042*	0.000*	0.001*	0.001*

1. Data analysis used the Wilcoxon's rank sum test.
2. *Significantly different from the placebo group at the same week, $P < 0.05$.
3. % in parentheses (percentage change): Dividing absolute change (baseline score - score at the time after intervention) by baseline score.

not differ significantly between the two groups during the study period. In the LP-33 group, there was a significantly greater reduction in score of activity limitation at 12 and 16 weeks compared with placebo group ($P = 0.007$, $P = 0.040$, respectively). Compared with placebo group, there were significantly greater reductions ($P < 0.05$) of total score during the study period in the LP-33 group.

Immunological parameters of allergy

The mean concentrations of total IgE, IFN-γ, and IL-4 did not differ significantly between the two groups at baseline ($P > 0.05$, data not shown). After 12 weeks of intervention, there was a significant decrease in the total IgE concentration in the LP-33 group (732.53 ± 229.20 IU/mL vs. 579.96 ± 125.99 IU/mL, $P = 0.032$). On the other hand, there was no

Table 3. Percentage changes of score in level of bother variable as a function of time of intervention and follow-up (weeks)

	Intervention period			Follow-up
	Week 4	Week 8	Week 12	Week 16
Nose symptoms				
LP-33 (%)	44.09 ± 5.29	48.29 ± 4.60	41.85 ± 5.62	39.08 ± 5.97
Placebo (%)	26.59 ± 7.84	22.59 ± 7.27	21.51 ± 8.64	28.51 ± 8.24
P value	0.088	0.006*	0.035*	0.329
Eye symptoms				
LP-33(%)	43.88 ± 6.92	50.96 ± 6.38	42.77 ± 6.70	51.77 ± 6.72
Placebo (%)	22.11 ± 8.95	27.49 ± 8.64	10.33 ± 6.39	14.38 ± 7.21
P value	0.132	0.032*	0.016*	0.004*
Practical problem				
LP-33 (%)	48.76 ± 5.83	51.48 ± 5.39	38.27 ± 6.08	39.07 ± 6.38
Placebo (%)	17.08 ± 7.10	13.80 ± 6.49	8.65 ± 5.38	11.30 ± 5.23
P value	0.004*	0.001*	0.006*	0.016*
Other symptoms				
LP-33 (%)	43.63 ± 6.49	49.03 ± 6.32	45.78 ± 6.28	59.76 ± 6.61
Placebo (%)	37.83 ± 11.32	26.97 ± 8.97	36.88 ± 11.21	37.12 ± 9.07
P value	0.704	0.441	0.484	0.088
Activity limitation				
LP-33 (%)	46.38 ± 6.30	61.37 ± 6.16	55.44 ± 6.71	60.59 ± 6.47
Placebo (%)	27.95 ± 10.33	39.58 ± 11.14	19.62 ± 8.82	37.53 ± 10.12
P value	0.066	0.099	0.007*	0.040*
Total score				
LP-33 (%)	45.30 ± 4.88	46.59 ± 5.22	38.62 ± 5.53	43.86 ± 5.51
Placebo (%)	17.91 ± 6.48	17.79 ± 5.93	12.31 ± 5.98	17.58 ± 7.22
P value	0.003*	0.003*	0.010*	0.012*

1. Data analysis used the Wilcoxon's rank sum test.
2. *Significantly different from the placebo group at the same week, $P < 0.05$.
3. % in parentheses (percentage change): Dividing absolute change (baseline score - score at the time after intervention) by baseline score.

significant change in total IgE concentration during the study in the placebo group (900.45 ± 230.88 IU/mL vs. 913.31 ± 261.29 IU/mL, $P = 0.877$). Subjects in the LP-33 group demonstrated a significant increase in the mean IFN-γ concentration (33.77 ± 6.93 pg/mL vs. 41.05 ± 8.75 pg/mL, $P = 0.001$), whereas subjects in the placebo group had a significant decrease between baseline and final results (75.05 ± 26.34 pg/mL vs. 58.34 ± 26.04 pg/mL, $P = 0.041$). However, the mean concentration of IL-4 did not change significantly in the groups at the end of intervention (Table 4).

Adverse events

The treatment was well tolerated. During the intervention and follow-up period, there were no serious adverse effects in any of 57 subjects.

Table 4. The difference of cytokines and total IgE concentration between baseline and final values in both intervention groups

Index	Baseline	Final	*P* value
Total-IgE (IU/mL)			
LP-33	732.53 ± 229.20	579.96 ± 125.99	0.032*
Placebo	900.45 ± 230.88	913.31 ± 261.29	0.877
IFN-γ (pg/mL)			
LP-33	33.77 ± 6.93	41.05 ± 8.75	0.001*
Placebo	75.05 ± 26.34	58.34 ± 26.04	0.041*
IL-4 (pg/mL)			
LP-33	158.72 ± 42.37	123.68 ± 25.63	0.629
Placebo	177.80 ± 47.99	303.18 ± 167.55	0.363

1. Data analysis used the Wilcoxon's rank sum test.
2. *Significantly different from baseline, $P < 0.05$.

DISCUSSION

In this study, the LP-33-treated subjects experienced a significant improvement in symptom control of different domains throughout the intervention period. After discontinuation of the intervention, continued improvement was observed in all but the nose symptoms domain, suggesting that subjects were less bothered by itchy eyes, had less associated symptoms, and were less limited by allergic rhinitis when they participated in their outdoors activities. These results correspond to the primary goals of treating subjects with allergic rhinitis. In addition to the present study, Van de Water et al. sought to determine the effects of probiotics to treat allergic sufferers[12]. They demonstrated that long-term consumption of yogurt, especially containing live-culture bacteria, could alleviate the allergic symptoms in both young and senior adults. Trapp et al. demonstrated that consumption of yogurt (200 g/day) containing viable bacterial culture reduced asthma symptoms in young subjects[13]. Although the results of these studies addressed the finding that probiotics have beneficial health effects, further studies are needed to provide substantial evidence for potential immunomodulatory effects.

The current management options of allergic rhinitis include preventive measures, specific antigen immunotherapy, and pharmacotherapy. Strict environmental control and avoidance of triggers for treatment and prevention of allergic rhinitis remain major tasks and are often difficult to achieve[14,15,16]. However, the efficacy of preventive measures is inconclusive[17]. Despite the advances made, management of allergic rhinitis for many patients is still discouraging and the clinical effects disappear after medication is terminated. However, preventive avoidance of triggers, pharmacotherapy, and immunotherapy has well-known positive effects on quality of life[14, 18, 19]. Recently, a growing body of evidence indicates that intestinal microbes can modulate the incidence and treatment of allergic diseases, probably via the same mechanism operating in immunotherapy[4, 20, 21]. Corroborating the epidemiological and experimental findings support the possibility that manipulation of gut microflora represents an effective therapeutic option for the management of atopic diseases.

A novel and amazing characteristic of probiotics is the "local action, global function." The present study shows that consumption of LP-33-fortified fermented milk for 12 weeks appears to significantly increase serum IFN-γ concentration and reduce serum IgE level. These results suggest the concept that exposure to probiotic LP-33 partially tilted the T_H2-biased immune system toward a balanced T_H1/T_H2 paradigm via the T_H1-promoting effects (IFN-γ enhancement) and T_H2-inhibiting effects (down-regulation of IgE synthesis) of microbial components. This finding agrees with a previous study conducted by Halpern et al.[22]. They had reported an in-vitro increase in IFN-γ concentration by isolated T lymphocytes in subjects

who consumed yogurt containing viable L. bulgaricus and S. thermophilus for 4 months. On the other hand, de Water et al. demonstrated that there was little effect on IFN-γ and total IgE level after yogurt consumption for 1 year[12]. Trapp et al. also reported that yogurt consumption for 1 year had no effect on IFN-γ concentration, total serum IgE, and specific IgE titers[13]. Combined, these studies suggest that the immunomodulatory effects of probiotics may be species-specific.

Recently, new and emerging molecular and genomic technologies have become available to investigate more commensal bacteria and the related mechanisms by which they affect the immune system[23]. Many studies, both in animal and human trials, had reported that lactobacillus (LAB) augments both humoral and cellular immunity. LAB administered orally might adhere to gut mucosa and transplant to the Peyer's patches, where secretory IgA is produced. A large body of evidence suggests that LAB stimulates systemic cellular immune response, such as phagocytosis of peripheral blood polymorphonuclear leukocytes and macrophages, tumoricidal activity of natural killer cells, and other cells[24-26]. Because LAB are Gram-positive bacteria with cell-wall components such as peptidoglycan, polysaccharide, and teichoic acid, all of which have been shown to have immunostimulatory properties[27]. Recent researches suggested that production of various cytokines is enhanced by the interaction between the cell-wall components and the surface receptors (such as Toll-like receptors) of peripheral blood mononuclear cells and lymphocytes, via NF-κB and STAT signaling pathways[28, 29].

Modern eating habits have also significantly reduced gastrointestinal exposure to a number of microfloras that commonly existed in the diet as compared with that of our ancestors. Great strides have been made toward elucidating the contribution of immunomodulatory events in probiotic bacteriotherapy to substantial clinical symptom improvement. Furthermore, previous clinical trials had proven the safety of this treatment modality. When considering a population-based public health approach to managing the increase in allergic diseases, the lower economic and psychosocial cost of the LP-33-fortified dairy products compared to prescription medications could provide a new and novel strategy for the health care of persons with allergies. On the basis of our data, we expect that well-designed, controlled studies will be forthcoming with different probiotic organisms and therapeutic dosage for the prevention and treatment of different clinical allergic disorders in children and adults.

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乳酸菌對過敏性鼻炎患者的免疫調節作用

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背景：乳酸菌可減輕過敏症狀及避免過敏發生，機轉可能是經由其免疫調節功用。

目的：這臨床試驗將評估乳酸菌 Lactobacillus paracasei-33（LP-33）對由塵蟎引起的過敏性鼻炎的效果及安全性。

方法：這是一隨機、雙盲，對照組的研究，有 41 人飲用 LP-33 優酪乳，16 人飲用一般優酪乳，實驗期間共 12 週，主要研究目標為鼻炎症狀評分的改變。其次為免疫學的研究，如 interferon-γ（IFN-γ）、interleukin-4 及血清 IgE 的變化。

結果：飲用 LP-33 優酪乳明顯地改善過敏性鼻炎症狀（$p < 0.05$），且效果持續至追蹤期仍存在。LP-33 組的病人血中 interferon-γ 明顯上升（33.77 ± 6.93 pg/mL vs. 41.05 ± 8.75 pg/mL, P = 0.001），且 IgE 濃度下降（732.53 ± 229.20 IU/mL vs. 579.96 ± 125.99 IU/mL, P = 0.032）。兩組受試者皆無副作用產生。

結果：過敏性鼻炎服用 LP-33 優酪乳後症狀明顯改善，可能經由乳酸菌的免疫調節作用，這對日後過敏性鼻炎患者提供另一安全有效的新治療方式。

（童綜合醫誌 2008; 2: 9-18）

關鍵詞：益生菌、過敏性鼻炎、Lactobacillus paracasei

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中台灣海線腮腺腫瘤病例分析

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本研究收集了從 1996 年 1 月至 2007 年 10 月止，11 年間於童綜合醫療社團法人童綜合醫院治療共 71 例的腮腺腫瘤病人，以回溯病歷依病人性別、年齡、腫瘤大小及部位、病史、治療方式和病理報告加以分析。71 位病人男性有 38 人，女性有 33 人，比例 1.2：1。良性腫瘤有 66 例，其中以多形性腺瘤（pleomorphic adenoma；又稱混合性腫瘤，mixed tumor）最多有 39 例，男女生比為 1：1.6，其次為 Warthin's 腫瘤 (Warthin's tumor) 有 15 例，皆為男性；惡性腫瘤只有 5 例，最多為黏液上皮癌（mucoepidemoid carcinoma）。治療方式以手術為主，其中以耳下腺腫瘤切除術佔大多數有 64.8%。由本研究及文獻報告發現腫瘤大小、性別與年齡並無法判定腫瘤為良性或惡性。希望藉由本研究報告能提供中台灣海線地區腮腺腫瘤的流行病學，以供各界參考。
（童綜合醫誌 2008; 2: 19-23）

關鍵詞：parotid tumors, pleomorphic adenoma, Warthin's tumor（腮腺腫瘤，多形性腺瘤，Warthin's 腫瘤）

前　言

腮腺為人體最大的唾液腺，位於耳朵的前下方所以又俗稱耳下腺，當人在吃東西時，唾液腺會分泌大量的唾液到口腔來幫助食物的攪拌與消化。發生於腮腺的腫瘤臨床上為耳下緩慢增生的無痛性腫塊，大多為無意間發現。腮腺腫瘤的流行病學並沒有被好好討論，原因一是這些腫瘤並不常見，在所有頭頸部腫瘤中腮腺腫瘤只佔了 3%[1]，另外一個原因是大部份的腮腺腫瘤是良性，且大部分的癌症登記，包括美國國家癌症研究所的監視、流行病學和最後結果的大綱（National Cancer Institute's Surveillance, Epidemiology and End Results SEER），並沒有加入良性腫瘤，因此不同族群的腫瘤病理分型發生率的相關資料是缺乏的。而我們收集了從 1996 年 1 月至 2007 年 10 月止，11 年間到本院就診共 71 例的腮腺腫瘤病人，包括性別、年齡、腫瘤大小及部位、病史、治療方式及病理的分析結果，希望能提供中台灣海線地區腮腺腫瘤的流行病學，以供各界參考。

材料與方法

本文收集了 1996 年 1 月至 2007 年 10 月止，11 年間到本院接受良性與惡性腫瘤手術治療共 71 例的腮腺腫瘤病人。以回溯病歷調閱病人性別、年齡、手術方式、腫瘤發生時間及位置、腫瘤大小、腫瘤病理學、電腦斷層掃描及核磁共振攝影報告，並利用 SPSS 14.0 版進行統計分析。

結果與分析

一、性別與年齡：

71 個病例中男性 38 人，女性 33 人，男女比為 1.2：1；良性腫瘤中男性有 36 人，女性有 30 人；所有病例中只有 5 人是惡性腫瘤，男女生比為 1:1.5；年齡方面最大者為 79 歲，最小者為 20 歲，平均年齡為 46.3 歲，其眾數分布在 41-50 歲間，佔了 23.9%（圖一）。

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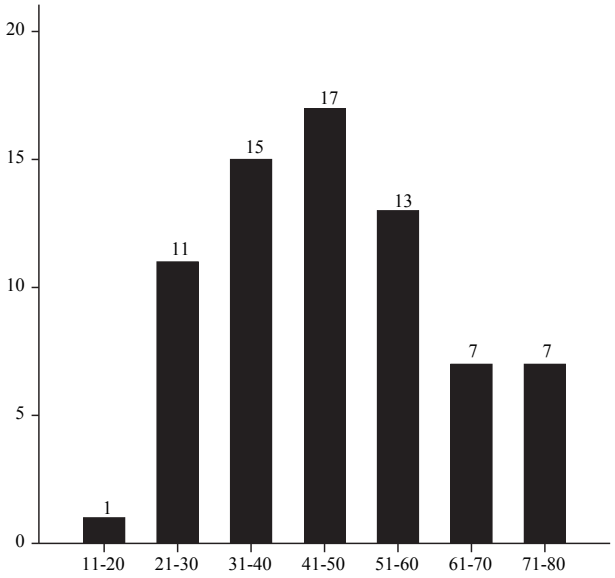

圖 1 年齡分布

二、腫瘤大小及部位：

良性腫瘤以小於等於 2 公分佔 24.1% 及 2-4 公分佔 51.9% 爲大多數，惡性腫瘤多數小於 2 公分（表一）；腫瘤發現部位在左邊者有 34 例，右邊者有 35 例。

三、病史：

腫瘤發現時間小於 6 個月有 29 例，其中良性腫瘤有 25 例，惡性腫瘤有 4 例；6 個月到 2 年者有 7 例，其中一例爲惡性；2 年以上者有 22 例，皆爲良性腫瘤。

四、影像學檢查：

有 53 例接受電腦斷層掃描檢查，其中有一例同時接受超音波掃描檢查；有 4 例接受核磁共振攝影；有 2 例只接受超音波掃描檢查；另外有 12 例無接受任何影像學檢查。

五、治療方式：

治療方式以手術爲主，其中以耳下腺腫瘤切除術佔大多數有 46 例；接受淺葉腮腺切除術者有 20 例；有 5 例是接受腮腺全葉摘除術。

六、病理分類：

病理報告良性腫瘤有 66 例，佔 98.5%，其中以多形性腺瘤最多有 39 例，男女生比爲 1：1.6，年齡爲 20-74 歲；其次爲 Warthin's 腫瘤有 15 例，皆爲男性，年齡爲 40-75 歲。惡性腫瘤有 5 例，佔 7%，其中有 3 例爲黏液上皮癌，1 例爲淋巴瘤 (lymphoma)，1 例爲鱗狀上皮細胞瘤（squamous cell carcinoma）。（表二）。

討　論

腮腺腫瘤是罕見的，只佔了所有頭頸部腫瘤中的 3%，在全身腫瘤中也只佔 0.6%[1]。一般文獻報告腮腺腫瘤以良性腫瘤爲最常見，約有 80%[2]，其中又以多形性腺瘤最多，其次爲 Warthi's 腫瘤，而惡性腫瘤則約有 19%[3]，以黏液上皮癌最常見。我們的調查和分析的文獻[2,4-11] 也與上述的結果相符合爲良性腫瘤佔腮腺腫瘤的大多數（表三）。本研究與 Tsai 等人[14] 之報告約有 7-8% 是惡性腫瘤，相似於呂等人[4] 報告的 10%。在 Sunger 等人[2] 及吳等人[5] 的報告中惡性腫瘤是以腺囊狀腺瘤（adenoid cystic carcinoma）爲最多，另外在荷蘭及日本則以腺癌（adenocarcinoma）最常見[12]。多形性腺瘤較常發現在年輕女性，平均年齡爲 36-42 歲[10,13-14]，我們的調查報告相近於之前的文獻報告好發在平均年齡爲 41.2 歲的女性。Warthin's 腫瘤則是在年長的男性較常被發現[10,13-14]，本報告 Warthin's 腫瘤皆爲男性，平均年齡爲 56.2 歲。

表 1 腫瘤大小

	良性	惡性
小於2公分	13 (24.1%)	3 60%)
2至4公分	28 (51.9%)	1(20%)
4至6公分	9 (16.7%)	0
大於6公分	3 (5.6%)	1(20%)
合　計	54 (100%)	5 (100%)

表 2 腫瘤組織病理分類

1. Pleomorphic adenoma	39 (54.9%)
2. Warthin's tumor	15 (21.1%)
3. Benign lymphoepithelial lesion	5 (7.0%)
4. Basal cell adenoma	4 (5.6%)
5. Sialadenosis	3 (4.2%)
6. Mucoepidermoid carcinoma	3 (4.2%)
7. Lymphoma	1 (1.4%)
8. Squamous cell carcinoma	1 (1.4%)
合　計	71

表 3 腮腺腫瘤良惡性比率

作　者	個案數		良性腫瘤（%）			惡性腫瘤（%）		
	良性腫瘤	惡性腫瘤	PA	WT	MA	MEC	ACC	AC
Hong et al[4]	60	10	38.6	37.1	1.4	4.3	4.3	1.4
Wu et al[5]	50	10	46.7	13.3	8.3	1.7	3.3	1.7
Pinkston et al[6]	181	31	53.3	28.3	－	9	0.5	1.5
Sunger et al[2]	192	38	66.1	17.3	－	3.0	7.4	1.7
Przewozny et al[7]	354	63	65.3	－	－	22.2	15.9	6.3
Vuhajula[8]	42	49	73.8	－	－	22.5	16.3	14.2
Ito et al[9]	256	80	77.3	16.4	－	47.5	10	－
Drivas et al[10]	101	30	44.2	22.9	3.1	5.3	1.5	2.3
Ansari[11]	63	19	93.7	－	4.8	52.6	15.8	10
本調查	66	5	54.9	21.1	－	4.2	－	－

PA: pleomorphic adenoma; WT: Warthin's tumor; MA: monomorphic adenoma; MEC: mucoepidermoid carcinoma; ACC: adenoid cystic carcinoma; AC: adenocarcinoma

良性腫瘤在性別上沒有太大的差異，在呂等人[4]及 Tsai 等人[14]的報告以男生稍多，男女比爲 1.4：1 及 1.3：1，我們的調查也以男生較多，男女生比爲 1.2：1，而 Vuhajula[8] 和 Drivas 等人[10]的報告則以女生稍多，男女生比爲 1：1.8 與 1：1.5，吳等人[5]男女生的比例則約相等；在惡性腫瘤方面性別差異較大，在呂等人[4]及 Tsai 等人[14]的報告以女生爲多，男女生爲 1：2.3 與 1：2，本報告男女生爲 1：1.5，另外在 Drivas 等人[10]與吳等人[5]的文獻是以男生居多，男女生比爲 3：1 及 9：1。

本調查報告腮腺腫瘤的平均年齡爲 46.3 歲，眾數位在 41-50 歲，相似於吳等人[5]報告的平均年齡爲 44.5 歲，30-40 歲佔多數，而在呂等人[4]及 Przewozny 等人[7]報告的平均年齡則較高爲 51 歲與 57.2 歲。一般文獻報告惡性腫瘤的平均年齡高於良性腫瘤，Sungur 等人[2]、Drivas 等人[10]及 Przewozny 等人[7]報告惡性腫瘤平均年齡爲 51 歲、65.4 歲與 57.2 歲，良性腫瘤爲 35 歲、48.2 歲及 50.5 歲，在本報告良性腫瘤平均年齡爲 45.9 歲，惡性腫瘤平均年齡爲 51.2 歲，在呂等人[4]的調查中惡性腫瘤的平均年齡較低爲 37 歲。

腫瘤大小與其本身良、惡性與否是沒有直接關係的[15]，在呂等人[4]、Kamal 等人[16]及本報告腫瘤大小都以 2-4cm 最常見，而吳等人[5]報告良性腫瘤以 2-4cm 佔最多，惡性腫瘤則以大於 6cm 最多見，Dunn 等人[15]報告腫瘤平均大小爲 3cm，良惡性平均大小相近。因本報告惡性腫瘤個案數較少，故其大小較不具意義。除了腫瘤大小，根據上述性別與年齡的分析結果發現，此三項因素並無法判定腫瘤爲良性或惡性，在 Chidzonga 等人[17]與 Sullivan 等人[18]的文獻中也有相同的論點。另外 Dunn 等人[15]的報告中也指出良性或惡性腮腺腫瘤沒有偏好出現在左右邊，與本調查腮腺腫瘤發現部位的結果是相似的。

腮腺腫瘤術前較重要的檢查有細針抽取細胞學檢查和影像學檢查。通常細針抽取細胞學檢查不能當作確切的組織學診斷，只能判定腫瘤是良性或惡性，根據文獻報告細針抽取細胞學檢查在腮腺腫瘤的診斷上具有高特異性及高準確度的特性[19]。電腦斷層掃描也被證實在判斷良性或惡性腫瘤有很高的預估值[20]，它也可以區分腮腺腫瘤是位於腮腺的淺葉、深葉或腮腺外的側咽腔。在本分析報告有 74.6% 的病例經由術前電腦斷層掃描診斷爲腮腺腫瘤。

治療腮腺腫瘤的方法是以手術切除[16]。腮腺腫瘤的切除手術是挑戰性非常高的手術，原因是顏面神經從腮腺的中間經過，所以在施行腮腺腫瘤手術切除時，必須先將顏面神經小心翼翼的剝離後再將腫瘤切除，若不小心傷及顏面神經，術後發生顏面神經麻痺是非常嚴重的併發症。本文並無針對術後顏面麻痺進行討論，可再進一步研究。

本調查報告是由童綜合醫院臨床病例搜集分析研究計畫，經由醫研部研究助理李佳茹、吳宜穎、陳怡蘋於蔡青劭主任指導下完成。

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Central Taiwan Coastline Parotid Neoplasms — An Analysis of 71 cases

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In this retrospective study, we reviewed a total of 71 patients diagnosed with parotid neoplasms at Tungs' Taichung MetroHarbor Hospital within the past 11 years from January 1996 to October 2007. Patients' charts were reviewed for gender, age, tumor size and location, history of illness, treatment modality, and pathology report. Of the series of 71 patients, 38 were male, 33 were female, with a ratio of 1.2:1. Sixty-six cases were benign tumors, majority of which were pleomorphic adenomas (known as mixed tumors), with a gender ratio of male:female 1:1.6, followed by 15 cases of Warthin's tumors, all of which were male. There were only 5 cases of malignant neoplasms, most of which were mucoepidermoid carcinomas. Surgery was the treatment modality chosen in all cases; 64.8% were excision of parotid gland tumors. From this investigation and literature review, we found that tumor size, gender and age were not significantly different in the benign group or the malignant group. In sum, through this investigational effort, we hope to provide locoregional and epidemiological information on parotid neoplasms in the central Taiwan coastline area.
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Key words: parotid tumors, pleomorphic adenoma, Warthin's tumor

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Mucinous Expression in Normal Mucosa and Adenocarcinoma of Endocervix and Endometrium

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The Alcian blue stain (pH = 2.5) and the PAS (periodic acid-Schiff) stain are useful adjuncts in differentiating primary adenocarinoma of the cervix from metastatic adenocarcinoma of uterine endometrium. The former cancer type contatins variable amounts of intracellular Alcian blue positive acid mucin and PAS positive neutral mucin which may be diffuse or granular vacuole cytoplasmic pattern whithin the neoplastic growth, whereas the later usually lacks mucin within the cytoplasmic substance. The endometrial is stained only at the cell margin or facing the lumen(luminal border). In this article, cervical and endometrial adenocarcinomas were studied by histochemical staining techniques,and all data were compared with those of the controls.
(Tungs' Med J 2008; 2: 24-30)

Key words: Cervical adenocarcinoma, Endometrial adenocarcinoma, neutral/acid mucin; Alcian blue and periodic acid Schiff's stainings.

INTRODUCTION

It is often difficult to determine the site of origin of adenocarcinoma involving the endocervical and endometrial mucosa. However, this distinction is very important in view of the differences in therapy that is employed in the treatment of these tumors. Both endocervical and endometrial cells are capable of secreting mucin. In many instances, the glandular lumina of normal mucosa and tumors originating from these cells contain an amorphous mucoid material.[1-3] Based upon the premise that a tumor may retain in whole or in part of the function of its cells of origin, the mucins of endocervical and endometrial mucosa were investigated in order to determine the difference of mucin contents between these two mucosal tumors.[1-4] Differences of the intracellular mucins between normal endocervical and endometrial mucosa, and those between adenocarcinomas arising in these areas were all studied by histochemical staining techniques.

Emphasis was being focused in the comparison on of the differences in the results of the Alcian blue (pH = 2.5) and the PAS (periodic acid-staining) stainings for those specimens.

MATERIALS AND METHODS

The tissue for this study were selected from the surgical collections of Department of Pathology in Tungs' Taichung MetroHarbor Hospital. The tissues collected were included 10 normal endocervical , 10 normal endometrial, and 10 adenocarcinoma of the endometrium, and 8 adenocarcinoma of the endocervix, specimens including 2 cases of adenocarcinoma in situ. The adenocarcinomas of the endocervix and endometrium were diagnosed on the basis of Hematoxylin-Eosin (H.E.) staining and each slide were revised by the pathologist. The origin of tumor was determined on the basis of anatomical location of

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the lesion. All of the tissue samples for investigation in were based on a double-blind fashion. The tissues were fixed in a neutral-buffered 10% Formalin and embedded routinely. The sections were cut at aproximately 4 to 6μm in thickness. Sections from each specimen were stained with Hematoxylin-Eosin, Alcian bule (pH =2.5), and Periodic acid-Schiff (PAS) methods respectively.[1-9] Mucins secreted by normal cervical glands are categorized into acid mucin and neutral mucin. It stains acid mucin blue by Alcian blue (pH =2.5) and neutral mucin red by PAS. The classifications of positive degree for histochemical study were determined from 0 to 3 (grade 0: no material was available for the determination, Grade I:

Table 1. Staining in normal endocervical specimens

Cass No.	Reaction to stain									
	Alcian blue					Periodic acid-Schiff				
	Cells		Diff. reaction cytoplasm	luminal border	Extra-Cell mucin	Cells		Diff. reaction cytoplasm	Luminal border	Extra-cell mucin
	Granule	Vacuole				Granule	Vacuole			
1	2+	3+	3+	3+	3+	3+	3+	3+	3+	3+
2	2+	3+	3+	2+	2+	3+	3+	3+	2+	2+
3	3+	3+	3+	2+	2+	3+	3+	3+	2+	2+
4	3+	3+	3+	3+	2+	3+	3+	3+	3+	2+
5	3+	3+	2+	3+	2+	3+	3+	3+	2+	3+
6	3+	3+	3+	3+	2+	3+	3+	3+	3+	3+
7	3+	3+	3+	2+	2+	3+	3+	3+	3+	2+
8	3+	3+	3+	3+	3 +	3+	3+	3+	3+	3+
9	3+	3+	3+	2+	2+	3+	3+	3+	2+	3+
10	3+	3+	3+	3+	3+	3+	3+	3+	3+	3+

Note:case 1~6:normal endocervcial mucosa, case 7~8:endocervcial polyp, case 9~10: microglandular hyperplasia.

Table 2. Staining in normal endometrial specimens

Cass No.	Reaction to stain									
	Alcian blue					Periodic acid-Schiff				
	Cells		Diff. reaction cytoplasm	Luminal border	Extra-Cell mucin	Cells		Diff. reaction cytoplasm	Luminal border	Extra-cell mucin
	Granule	Vacuole				Granule	Vacuole			
1	0	0	±	+	+	0	0	0	+	+
2	0	0	0	±	±	0	0	0	+	±
3	0	0	±	+	±	±	0	0	+	±
4	±	0	±	+	+	0	0	±	+	+
5	0	±	±	±	+	±	0	±	+	+
6	0	+	0	2+	2+	0	0	0	2+	2+
7	±	±	+	+	2+	0	+	+	+	2+
8	0	0	0	+	2+	0	0	±	+	2+
9	0	0	±	+	2+	0	±	+	+	2+
10	0	0	0	+	+	0	0	0	+	+

Note:case 1~5:proliferative phase. Case 6~7:secretory phase. Case 8~10: simple to complex hyperplasia.

slight, Grade II: moderate, Grade III: Marked).[1] All of the data were collected and compared to that of a variety of controls.

RESULTS

Normal Tissue: In every test, endocervical and endometrial mucosa showed differences (Tables 1 and 2). The PAS and Alcian blue (pH = 2.5) reactions of the cytoplasm of endocervical cells and that of the cytoplasm of endometrial cells were differed. There were intensive (Grade 3) diffuse PAS-positive and Alcian blue-positive reactions in the cytoplasm of endocervical cells as well as strongly positive granules, vacuoles, luminal border and lumen (Fig. 1). The cytoplasm of constituent cells were stained acid mucin blue by Alcian blue (pH =2.5) and neutral mucin red by PAS in all unremarkable cervical glands, endocervical polyp and microglandular hyperplasias, indicating that both more acid, but not neutral mucins were produced . The cytoplasm of the endometrial mucosa showed only scattered foci of Alcian Blue and PAS-positive materials. The Alcian Blue and PAS positive reaction were confined to the luminal border of endometrium in all unremarkable endometrial glands (including proliferative phase and secretory phase)

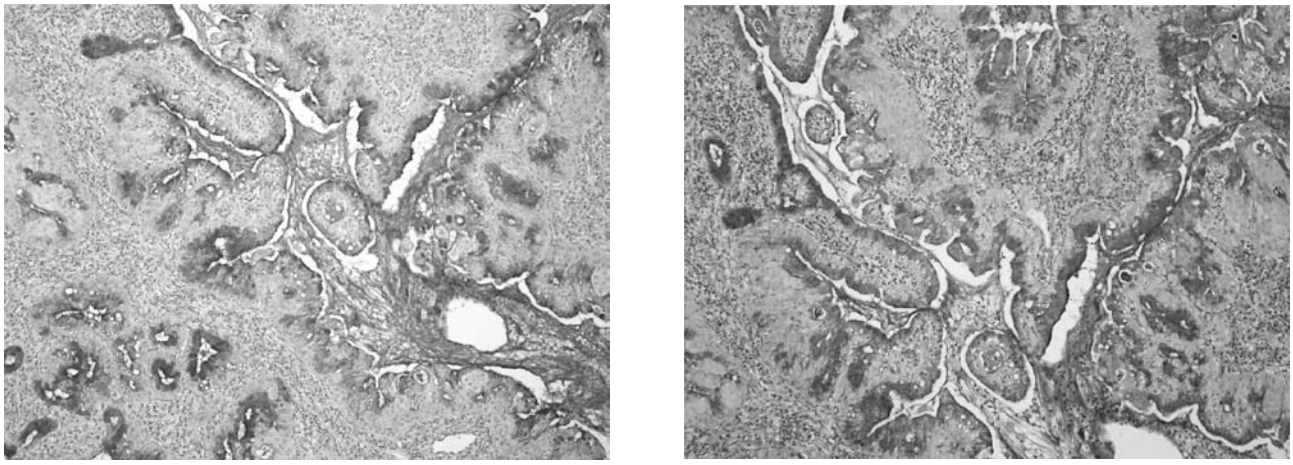

Fig. 1 A representative example of an intensive (grade 3) diffuse Alcian blue (left) and PAS (right) in the cytoplasm of the normal endocervical glands as well as strong positive granules and vacuoles of the cytoplasm (Alcain blue and PAS stains, 100X).

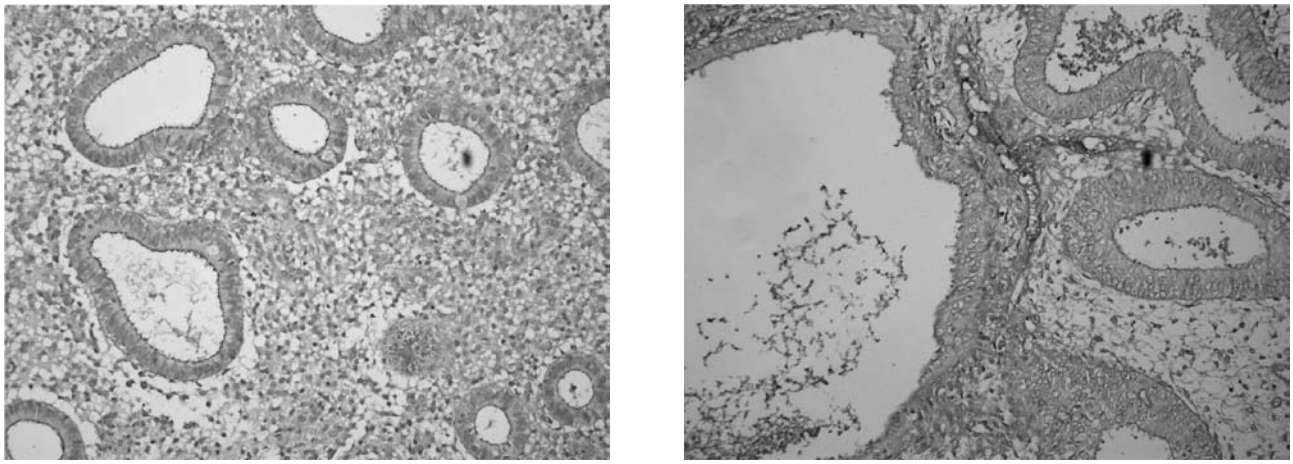

Fig. 2 A representative example of a slight to moderate (grade 1 to 2) Alcian blue positive reaction in the luminal border and lumen of the proliferative phase (left) and simple hyperplasia (right) endometrium (Alcain blue stain, 200X).

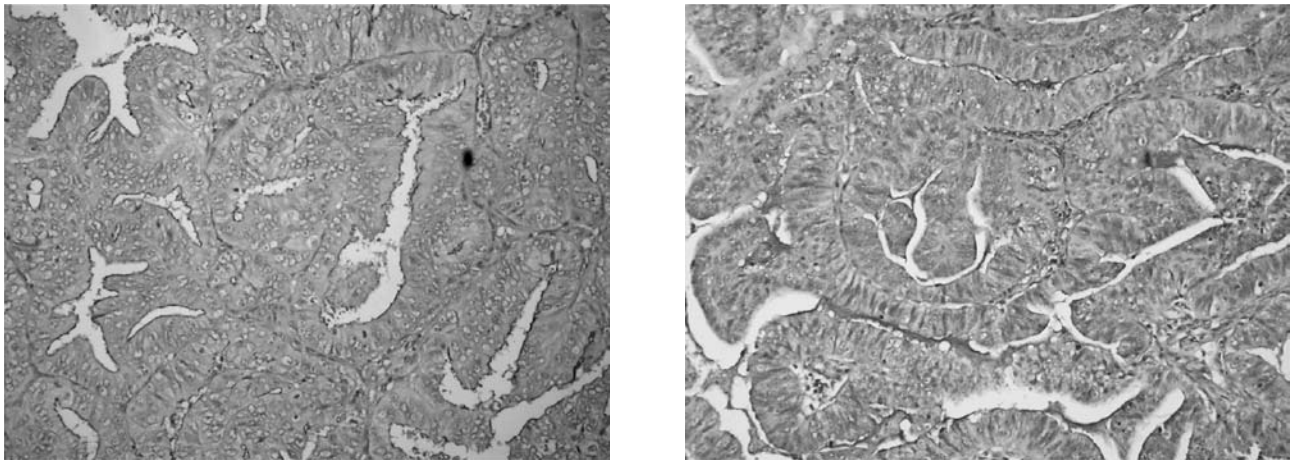

Fig. 3 A representative example of a slight (grade 1) Alcian blue positive reaction (left) and PAS positive reaction (right) in the luminal border and lumen of the endometrioid adenocarcinoma of endometrium (Alcain blue stain and PAS stains, 200X).

Table 3. Staining in adenocarcinomas of endometrium

Cass No.	Reaction to stain									
	Alcian blue					Periodic acid-Schiff				
	Cells		Diff. reaction cytoplasm	Luminal border	Extra-cell mucin	Cells		Diff. reaction cytoplasm	Luminal border	Extra-cell mucin
	Granule	Vacuole				Granule	Vacuole			
1	0	0	±	+	+	0	0	±	+	+
2	0	0	0	2+	2+	0	0	0	2+	+
3	0	0	0	0	+	0	0	0	+	±
4	0	0	±(few)	2+	±	0	0	±	2+	0
5	0	0	0	0	±	0	0	0	±	±
6	0	0	0	+	+	0	0	0	+	+
7	0	0	0	2+	2+	0	0	0	2+	+
8	0	0	0	+	+	0	0	0	+	+
9	0	0	0	2+	+	0	0	0	2+	+
10	2+	2+	+	2+	3+	2+	2+	+	2+	+

Note:case 1~8:adenocarcinoma, endometroid type, case 9: serous papillary type, case 10:mucinous type.

and glandular hyperplasias (including simple to complex hyperplasia). The lumen of the endometrium was slight to moderate positive or faintly positive in the PAS and Alcian bue reactions (Fig. 2).Thus we found that. So, both acid and neutral mucins of the unremarkable endometrium to the hyperplastic change endometrium were produced lesser amount than the endocervical glands.

Adenocarcinoma: 10 adenocarinomas of endomertium were examined. Most cases demonstrated slight PAS and Alcian bue-positive reactions on the luminal border of eudiometrical glands (Fig. 3). There were 2 cases which showed faint Alcian blue and PAS-positive cytoplasm without granule and vacuole. The mucin within lumen of the endotmetroid adenocarcinoma showed a slight to moderate PAS and Alcian bue-positive reactions. There was a moderate(grade 2) focal Alcian blue and PAS-positive reaction in the luminal border and lumen of the mucinous type adenocarcinoma of the endometrium

(in case 10) as well as positive granules and vacuoles of the cytoplasm (Table 3 and Fig 4). In adenocarcinoma of endocervix, 6 cases were well differentiated adenocarcinoma including 2 cases of adenocarcinoma in situ. Those cells had a strong positive reaction for PAS and Alcian blue stain abilities. In addition, there was only a diffuse staining of the cytoplasm as well as the granules and vacuoles. The mucin within the lumina also showed a strong positive stain (Fig. 5). One case of moderately differentiated adenocarcinoma of the endocervix also had strong positive staining of the PAS and Alcian blue in the cytoplasm. But the positive material was all confined to the top of cellular margin with only occasional PAS and Alcian bue diffuse positive foci. Granules and vacuoles of the cytoplasm were also revealed. Case number 6 (Table 4) was a endometroid type adenocarcinoma of endocervix. Neither granule nor vacuole was stained using PAS and Alcian blue. Only slight Alcian Blue and PAS-positive reaction in the luminal border of the endocervial neoplastic glands that was resembling with Fig 3.

DISCUSSION

Mucosa from the endocervix and the endometrium are histochemically different. Adenocarcinomas arising from these sites have also been studied and claimed that histochemical properties of these tumor cells are similar to that of the parental cells.[4] Histochemically, notably in the Alcian blue (PH = 2.5) and Periodic acid-Schiff (PAS) stainings, are considered to be a useful adjuvant in differentiating adenocarcimoma of cervix from metastatic adenocarcinoma of endometrial orgin. The mucin in the cytoplasm of normal enodocervical cells show an intensive diffuse PAS-positive reaction as a well as strong positive granules and vacuoles.[1-10] In our study, 10 normal endocervical specimens demonstrated strong positive staining of the cytoplasm with PAS and Alcian blue (pH = 2.5); meanwhile, the granules and vacuoles of the cytoplasm could also stained positive as strong as mucin.

Conversely, the normal mucosa cells of endometrium are rarely PAS positively stained in granule and vacuole. However, the cellular margin and the extracellular mucin can show a moderate positivity in PAS reaction.[1-10] In this article, 10 adenocarcinomas of endometrium and 10 mormal mucosa of endometrium all revealed faint or no granule and vacuole within the cytoplasm in PAS and Alcian blue staining (except the mucinous type endometrial adenocarcinoma in case 10), however, the cellular margin and extracellular mucin have a moderately positive reaction both in normal mucosa and in adenocarcinoma of endometrium. Notably, the normal mucosa of endometrium in secretory phase had stronger positive reaction than that in proliferating phase.

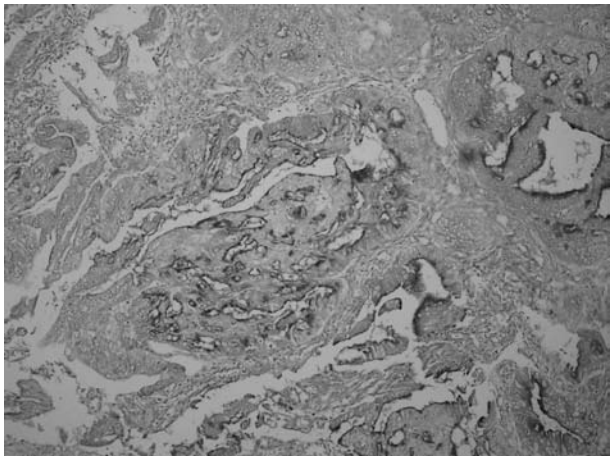

Fig. 4 In case 10, there was a moderate (grade 2) focal Alcian blue positive reaction in the luminal border and lumen of the mucinous type endometrial adenocarcinoma as well as focal positive granules and vacuoles of the cytoplasm (Alcain blue stain, 100X) [case10].

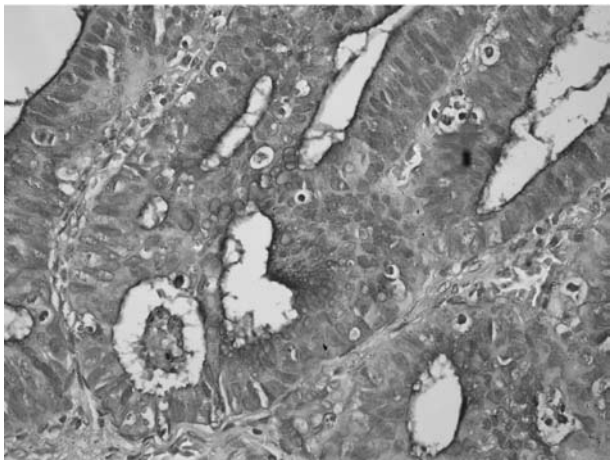

Fig. 5 Adenocarcinoma of endocervix. Moderate to marked staining of the cytoplasm as well as strong granules, vacuoles and the luminal border (Alcain blue stain, 200X)

Table 4. Staining in adenocarcinomas of endocervix

Cass No.	Reaction to stain									
	Alcian blue					Periodic acid-Schiff				
	Cells		Diff. reaction cytoplasm	Luminal border	Extra-cell mucin	Cells		Diff. reaction cytoplasm	Luminal border	Extra-cell mucin
	Granule	Vacuole				Granule	Vacuole			
1	3+	2+	+	2+	+	3+	2+	+	2+	+
2	2+	3+	2+	2+	2+	2+	2+	2+	2+	2+
3	+	3+	+	2+	2+	2+	2+	+	2+	+
4	3+	3+	± (focal)	2+	+	3+	2+	+	2+	+
5	0	+	+	2+	+	3+	3+	3+	3+	3+
6	0	0	0	2+	+	0	0	0	+	0
7	2+	2+	+	2+	+	2+	2+	+	2+	+
8	2+	2+	2+	2+	2+	3+	2+	2+	2+	+

Note:case 1~4:adenocarcinoma, mucinous type, case 5:clear cell type, case 6:endometroid type, case 7~8:adenocarcinoma in situ.

The cells of adenocarcinoma arising from endocervical mucosa can still retain many properties of the normal cells.[4] They produce and elaborate mucins that may have histochemical characteristics similar to those of the normal mucosa. The mucin and cytoplasm of these tumor cells had a strong positive reaction to the PAS and Alcian blue staining as a well as strong positvity of granules and vacuoles.[1-10], Alcian blue and PAS stain, however, are of no value in the diagnosis of diagnostic aid in endometroid type endocervical adenocarcinoma because mucinogenesis is generally minimal or absent in this kind of tumor, that is mimicking the endometroid adenocacinoma of the endometrium.[4]

In conclusion, the histochemical approach is presented here for the differential diagnosis of primary adenocarcinoma of the endometrium and the endocervix. The technigue is based on the differences in histochemical behavior of the mucins elaborated by the normal mucosa of endocervix and endometrium. The adenocarcinomas tends to reproduce in whole or in part the characteristic mucins of the respective normal mucosa. Alcian blue (pH =2.5), and Periodic acid-Schiff (PAS) are simple and orthodox histochemical methods which are effective for differential diagnosis the endometriod adenocarcinoma of the endometrium and convential adenocarcinoma of cervix. Finally, not with standing the histochemical approach is useful for differentiating the primary adenocarcinoma of endometrium from endocervix, yet it still cannot predict the prognosis only based on the sole parameter of the mucin distribution.

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正常子宮內膜及內頸與腺癌的黏液表現

曹唐義[1*]　劉錦成[2]　簡陳榮[2]

Alcian blue (pH=2.5) 染色及 PAS 染色可用來鑑別原發性子宮頸腺癌及轉移到子宮頸的子宮內膜腺癌，子宮頸腺癌含有大量的細胞內酸性黏液（Alcian blue 呈陽性）及中性黏液（PAS 呈陽性），這些黏液可以是瀰漫或是顆粒空泡狀呈現在細胞質內，而子宮內膜腺癌的細胞質內卻缺少這些黏液的呈現，它們只呈現在腺體管腔的頂部。本文利用此一化學染色特徵，將正常子宮內膜與內頸及子宮內膜腺癌與內頸腺癌的黏液做一比較分析。
（童綜合醫誌 2008; 2: 24-30）

關鍵詞：子宮頸腺癌、內膜腺癌、中性／酸性黏液、Alcian blue 及 PAS 染色。

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Obturator hernia: A report of three cases and review of the literature

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Obturator hernia is known to be a rare kind of hernia that often occurs in debilitated and/or aging women. High mortality rate has been reported to be due to delayed diagnosis and associated medical illness. Emerging evidence suggests that accurate preoperative diagnostic sensitivity can be obtained with abdominal computed tomography. Thus far, there is no consensus regarding the suitability of surgical repair for obturator hernia. Here we report three cases that have been diagnosed accurately with computed tomography. Among them, one has a history of therapeutic pelvic fracture. Thus we report here that pelvic injury may also constitute a risk factor for the occurrence of obturator hernia.
(Tungs' Med J 2008; 2: 31-36)

Key words: Obturator hernia, computed tomography, pelvic fracture

INTRODUCTION

Obturator hernia (OH) represents only a small proportion (0.073%) of all cases of hernia that has been reported elsewhere[1]. Generally, it presented in emaciated aging women with symptoms of intestinal obstruction, such as abdominal pain, fullness and vomiting[2,3]. This diagnosis of OH cannot be achieved merely by using nonspecific clinical manifestations and physical examinations. Most importantly, high mortality and morbidity rate of OH are often associated with delay in diagnosis and underlying disease[3,4]. Therefore, it is of importance to search for a rapid method for earlier diagnosis and treatment of OH. Although computed tomography (CT) scan has been advocated as an effective method for early diagnosis and treatment, yet the best approach and repair technique for OH are still unconclusive[5,6,7,8]. In this report, we present three cases of OH that are preoperatively diagnosed by CT scan and thus reaffirm its clinical utility in the diagnosis of OH.

CASE PRESENTATION

Case 1

An 88-year-old woman attended our emergent department with history of intermittent abdominal pain and vomiting for more than 10 times in two days. She was in bed-ridden and emaciated status (145 cm tall and weighed 35 kg). On physical examination, the abdomen was distended without muscle guarding. The leukocyte count was 5900/mm^3. The patient had received below knee amputation due to vascular gangrene of the left foot, but no history of abdominal surgery. (Fig. 1) The abdominal CT revealed diffuse distended small bowel and a segment of intestine was incarcerated between the right external obturator muscle and pectineus muscle. Through right inguinal approach, a 10 cm incarcerated small intestine with gangrenous change was found into the obturator hernia sac. Segmental resection with primary anastomosis was performed. The defect was approximated interruptedly with nonabsorbable sutures. The patient

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discharged 10 days after the surgery.

Case 2

The second patient, 74 year-old thin female (150cm, 33kg), presented to emergency department with intermittent right lower abdominal pain for several months. She had history of hypertension, cataract, brochiectasis and vascular headache, and had received herniorrhaphy for right inguinal and femoral hernia last year. The physical examination revealed a palpable tender mass over right inguinal region. Abdominal CT showed right sided OH with an incarcerated bowel segment (Fig.2). The leukocyte count was 11300/mm^3. C.R.P. was 2.7 mg/dl (the normal level: < 0.8 mg/dl). By lower midline laparotomy, the incarcerated segment of intestine was reduced without resection. The hernia defect was repaired with 5x5 cm polypropylene mesh, which fixed onto the pubic bone and peripheral obturator foramen by 2-0 Prolene suture preperitoneally. The peritoneum was closed over the mesh with 3-0 silk suture interruptedly. The patient was discharged without any complication on the 7th postoperative day.

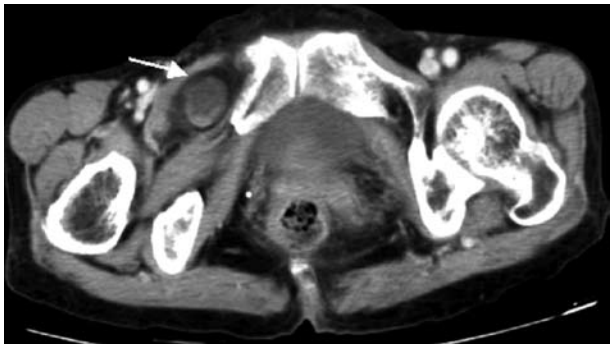

Fig. 1 Preoperative CT scan revealed bowel incarceration in the right-sided obturator hernia (arrow).

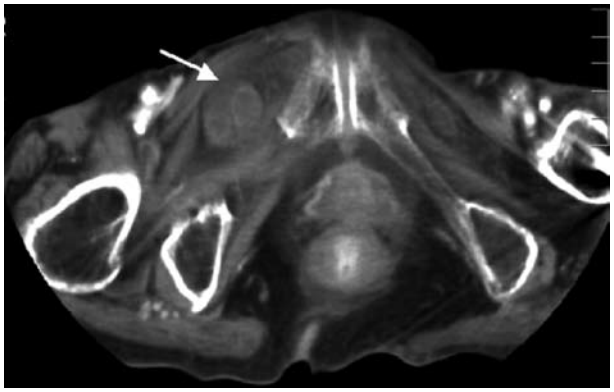

Fig. 2 The CT scan of patient 2 showed incarcerated bowel in the right obturator hernia (arrow)

Case 3

The third case is a 68-year-old female attended our emergency department with complaint of abdominal pain and vomiting intermittently for 2 days. She sustained traumatic right sided pelvic and tibiofibular open fracture in a motor vehicle accident 3 years ago. She is limping due to the event. On physical examination, the abdomen was distended without tenderness or rebounding pain. She is multiparous (four sons) and BMI is 21.875 (160 cm, 56 kg). A 5-cm mass was palpated at right uppermedial thigh just inferior to the inguinal fold. The mass is soft and irreducible without tenderness. The patient claimed that the mass had been recognized after the traffic accident. The leukocyte count was 8900/mm^3. C.R.P. was 5.6 mg/dl (the normal level: < 0.8 mg/dl). Distended bowel loops and a right incarcerated OH appeared on the abdominal and pelvic CT scan. (Fig.3) The old pelvic bone fracture and deformed right hip joint also has degenerative change were noted. On laparotomy, right femoral and obturator hernia were found. A piece of omentum was plugged into the femoral canal, but the obturator hernia sac contained a 15-cm gangrenous segment of ileum with perforation. The involved bowel segment was resected with anastomosis subse-

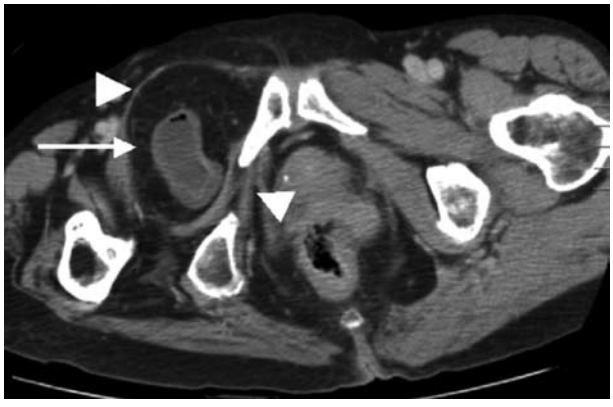

Fig. 3 The preoperative CT scan image of patient 3 revealed right obturator hernia containing an incarcerated segment of intestine (arrow), tear of the external and internal obturator muscle and pectineus muscle on the right side (arrow head), as compared with intact ones on the left side.

quently. The obturator canal was enlarged to 1.5cm in diameter. The orifice was closed with two layers of adjacent peritoneum by interrupted silk sutures. The patient discharged on the 14th postoperative day. The follow-up CT seven months later revealed only fatty tissue and granulation formation in the obturator region (Fig.4). Deformed obturator foramen with degenerative change of previous fracture was apparent (Fig.5). No recurrence was observed for ten months.

DISCUSSION

The obturator foramen is the largest foramen in the body and is formed by rami of the ischium and pubis, which is closed by obturator membrane encased by external and internal obturator muscle on both sides[8,9]. The obturator canal starts at the defect in the obturator membrane and pass obliquely downward outside the pelvis into the medial aspect of the thigh. The plausible mechanism of the formation of obturator hernia was hypothesized by Skandalakis et al.[9] The first stage is the entrance of preperitoneal connective tissue and fat into the pelvic orifice of the obturator canal. The peritoneal dimpling and invagination into the canal happened in the second stage.

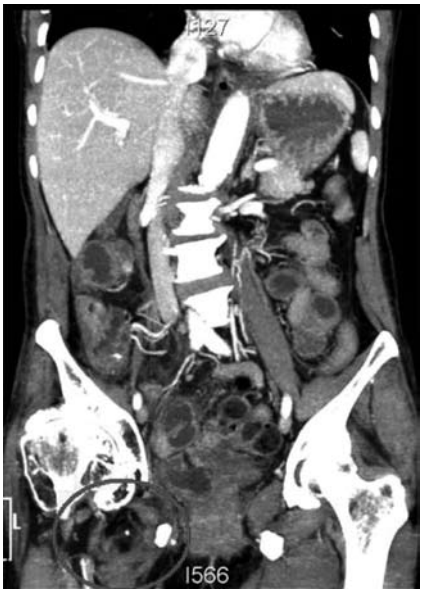

Fig. 4 The coronal view of multi-slice CT of patient 3 showed granulation tissue and fatty tissue in the right obturator region (circle) seven months after the operation.

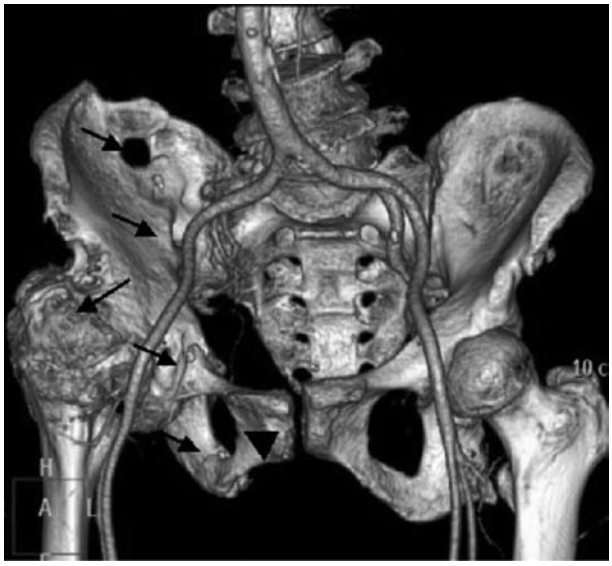

Fig. 5 The three-dimensional reconstruction bony structure from multi-slice CT of patient 3 showed degenerative change of right femoral joint with internal rotation, displacement of the right ileum, pubis and ischium (arrow) with deformed and enlarged obturator foramen (arrow head).

In the third stage, entrance of the bowel loop or other organ into the sac leads to the clinical symptoms of incarcerated hernia.

The majority of patients are between 70 and 90 years old at presentation. Women are six times more common than men[3], possibly because of the broader female pelvis, and more triangular canal opening and greater transverse diameter. In reported series, cases are weighed around 30-50 kgs with BMI≦18.5 [3,4,5,7]. Some authors considered that severe loss of body weight might contribute to the loss of fat in the obturator canal and reduce the protective effect of herniation of the peritoneal protrusion. The increase of intra-abdominal pressure also contributes to the protrusion of abdominal content into the sac, such as chronic pulmonary diseases, ascites, multiparity, chronic constipation and kyphoscoliosis[1,2,3,4].

There are four classic features of OH: intestinal obstruction, previous attacks of bowel obstruction, the Howship Romberg Sign (HRS), and palpable groin mass[10]. Most patients present symptoms of intestinal obstruction like abdominal pain, nausea and vomiting off and on[2,20]. A palpable mass on groin or proximal medial aspect is not common owing to the hernia lo-

cated deeply between the pectineus and external obturator muscle. Sometimes the protruded mass is mistaken as an incarcerated inguinal or femoral hernia due to adjacent anatomic structure. According to previous studies, obturator hernia occupies only 0.2~1.6% of all intestinal obstruction. Identifying the mass by digital vaginal or rectal examination should raise the suspicion of diagnosis of incarcerated OH[5,7,8]. In fact, most clinicians had little experience in the diagnosis of OH by digital exams. Positive HRS means the pain in the medial aspect of the thigh and knee when extending down the inner surface of the thigh to the knee, which is caused by the irritation of the anterior division of the obturator nerve induced by hernia. It is reported that the accuracy for diagnosis is around 25-50%[7]. The Hannington-Kiff sign refers to loss of adductor reflex in the thigh owing to the compression of the obturator nerve. It is more specific but less data published[5]. In addition, HRS is often misinterpreted because the elderly patients often have degenerative joint diseases[1,3,10]. Together, the physical examination results cannot provide sufficient evidence for the diagnosis of OH.

The image studies are required for the confirmation of diagnosis. CT, ultrasonography (US) and magnetic resonance imaging are reported to help make the correct diagnosis. US had been proposed for the accurate diagnosis of OH[7]. Despite being fast and widely accessible, US still have some difficulties in diagnosis of OH because of deeply embedded hernia sac, poor visuality of bowel condition and limited clinical experiences. The CT scan is considered as the standard modality owing to the rapidity, noninvasiveness, availability and the specificity. By CT scan, the low density between the external obturator and pecteneus muscles, especially different from the contralateral side, is thus considered to be a favorable method for the diagnosis of OH[11,12,13,14]. With the CT scan, the sensitivity for the correct preoperative diagnosis can reach 80%[7]. Our cases are all diagnosed accurately by preoperative CT scan. Yokohama et al., however, considered that the correct preoperative diagnosis of OH by CT has no impact on patient outcome[13].

Our first two cases have typical clinical picture, like chronically illness, bed rest, old and skinny female. However, in case three, the patient had average stature and dealt with daily life herself. The pelvic injury involved the right iliac ala, superior pubic ramus, ischial ramus, femoral head and acetabulum. It belongs to type B by the Tile classification and leads to the medical rotation of the right half of pelvis and disruption of the obturator foramen. The adjacent muscle, including the obturator muscle and pectineus muscle, revealed atrophic change or tear. The degenerative change of deformed pelvis and right hip joint were obvious (Fig.3).

The deformed obturator foramen may lead to the increase of the width of obturator canal, combined with the tear of the external obturator muscle and pectineus muscle, predisposed to the formation of the obturator hernia due to loss of the cushing effect for protrusion of the hernia sac. Limping gait rightward also promotes the increased intra-abdominal pressure to the pelvic cavity. The pelvic injury may be the etiological cause of OH previously[19], which has never been reported.

The mortality rate from OH has been reported as high as 30%[1]. The major cause is the delay in diagnosis and the associated diseases. In addition, the patients are always under medical treatment for the intestinal obstruction. The suspected cases should receive immediate abdominal CT scan. Chang et al. proposed the diagnostic algorithm for its diagnosis and treatment[6]. In patients with peritoneal signs or complete bowel obstruction, laparotomy should be performed. As for the patients who present partial obstructive symptoms and controversial physical findings, the emergent CT scan should firstly be taken into consideration, especially for those with predisposing factors of OH. Once the diagnosis was confirmed, surgical intervention should be undertaken.

Among those surgical approaches, laparotomy is the most adoptive method for uncertain diagnosis or existence of peritoneal sign. The advantages include the good exposure of the obturator ring, evaluation of the contralateral ring, avoidance of injury to the obturator vessels and nerve and performance of intestinal resection and anastomosis easily[4]. Inguinal approach, retropubic approach, total extraperitoneal and abdominal preperitoneal approach were reported[8,10,15,16]. Laparoscopic approach reduces postoperative pain and provides the definite diagnosis. However, bowel resection and anastomosis need minilaparotomy. Preperitoneal approach is considered to avoid the risk of intra-abdominal adhesions and entered the abdomen

easily if the bowel resection is needed[17]. There is so far no consensus regarding the repair methods for OH. Simple closure of the hernial defect with non-absorbable interrupted sutures was suggested by Yip et al.[3] for its rare recurrent rate (<10%) and those patients who are usually critically ill. However, it is not easy to approximate the larger defect due to bony border of the canal opening and the tough obturator membrane. Losanoff et al. summarized the reported repair methods other than simple apposition, such as fascial flap, uterine fundus, urinary bladder, and round ligament[8]. Prosthetic mesh for patching the defect used by laparoscopic or open method has been advocated for years, but it is not appropriate in the presence of gangrenous or perforated bowel[3,5,18]. No sufficient data of long-term results for various methods of repair had been reported.

OH is difficult to diagnose clinically. In addition to physical findings and history, early CT scan for suspected cases may provide an earlier diagnosis. Finally, we found that the pelvic fracture may be one of the contributing factors for the occurrence of OH. Surgical intervention should be performed as soon as possible in order to lower the necessity of bowel resection and reduce the mortality rate.

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閉孔疝氣：三個病例報告及文獻回顧

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閉孔疝氣是一種發生在羸弱老年婦女的罕見疝氣，其高死亡率主因於延遲診斷及病人潛在疾病。近來研究顯示，對於有懷疑的病人實施電腦斷層檢查可以提高術前診斷率。至今對於手術修補此類疝氣仍未有共識。我們報告三個藉由電腦斷層檢查獲得術前診斷的病例。在其中，有一位患者曾有外傷性骨盆腔骨折造成閉孔變形的病史，也應作為危險因子的考量。

（童綜合醫誌 2008; 2: 31-36）

關鍵詞：閉孔疝氣 , 電腦斷層 , 骨盆腔骨折

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發展新進護理人員壓力感受量表之前驅研究

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背景及目的：新進護理人員因壓力大導致高離職率備受重視。本研究目的為發展一個簡單且具有信效度之量表，以評估新進護理人員壓力感受。

方法： 本研究分為三階段進行：第一階段為實地觀察及訪談新進護理人員，收集相關資料。第二階段為進行兩次焦點團體，分析其內容後，形成護理人員壓力感受量表。壓力項目涵蓋個人能力、工作量、人際溝通、工作環境、專業角色等五個層面計 16 題，以及單一整體性壓力 1 題，做為評估效標關聯效度的指標，共計 17 題。使用視覺類比量尺（visual analog scale）進行測量。第三階段進行量表信效度檢定，採立意取樣方式，以某區域教學醫院 45 名新進護理人員為研究對象。

結果： 研究結果顯示量表內部一致性信度係數 Cronbach's Alpha 為 .94，效標關聯效度為 .83，顯示量表具有良好之信效度。護理人員之整體壓力程度平均為 63.84 ± 19.91。

討論： 本壓力感受量表共 17 題，涵蓋五個層面，相較於國內外之護理人員壓力量表更為精簡，為一簡單且具信效度之量表。未來研究將以本前驅研究為基礎，進行因素分析，以檢定其建構效度及因素結構，並測量再測信度，以確定量表之穩定性。

（童綜合醫誌 2008; 2: 37-41）

關鍵詞：壓力感受量表、視覺類比量尺、焦點團體

前　言

護理人員離職率偏高，尤其以到職三個月內離職問題更為嚴重，中華民國護理師護士公會全國聯合會（2005）調查發現：新進護理人員離職原因有 51.4% 係因壓力大與適應不良[1]，台北市護理師護士公會於 2004 年 11 月調查發現：到職三個月內之新進護理人員離職率高達 32.1%，到職一年內之護理人員離職率為 57.7%，即每兩位新進護理人員，就有一位在一年內離開現任護理工作[2]。本院 2005 年到職三個月內之新進護理人員離職率高達 43.1%，404 位新進人員中 174 位於到職三個月內離職（174 ÷ 404 = 43.1%），高於往年。護理人員的高離職率造成護理人力安排的困難，影響病人的安全，如何降低護理人員的高離職率為目前重要議題。

護理一直被視為是一個高壓力的工作，壓力會影響其工作滿意度，能直接影響其離職意願[3,4]，護理人員感受到的壓力是一項值得重視的議題，「工作壓力感受」係指隨著個人對工作環境或事件導致個體緊張的主觀判斷。壓力乃是個體感受來自內外在環境平衡狀態遭受威脅的一種狀態。壓力是一種主觀性、個別性的感受，取決於個體如何去詮釋其與環境間的關係，當內外在環境要求高於能力所及時，壓力因而產生[5]。護理人員壓力來源有：行政管理、病患照護、人際關係、工作環境及行政回饋等六大類。造成壓力的原因包括：本身的自我期望、缺乏知識和技術、角色衝突和角色混淆、單位常規、人員調動及排班、行政管理工作、工作環境、工作量、價值觀的衝突，及缺乏支持等、病患及家屬的身心需求、與行政體系間的溝通、與同僚之間的配合、噪音干擾及物理傷害等[6-13]。

目前國內有關護理人員壓力的相關量表，所包含

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的題數相當多，例如：吳（1993）臨床護士的工作壓力頻率與感受量表有 157 題[14]，蔡、陳 (1996) 台灣護理人員壓力量表有 43 題[5]，且均以 Likert's 量尺進行測量[5,14]。Likert's 量尺是將同意度分成若干類，從非常同意到非常不同意，中間爲中性類，要求受試者表明對某一表述是否同意，由於類型增多，要考慮受試者之辨識力，容易造成受試者之心理負擔。採用 Likert's 量表時，填答者因受限於只能在數個回答項中勾選出一個答案，容易迫使填答者調整自己的感受配合選項來回答[15-17]。柯氏在測量運動治青少女痛經之成效時曾使用到自覺壓力指數量表（the perceived stress scale, PSS）及視覺類比量尺（the visual analog scale, VAS）來反映個體內在的心理感受[18]。視覺類比量尺可以將個人的心理感受轉化成物理量化的數值，透過這樣的轉化可以直接反映出個體的內在感受程度。

建構量表時，內容效度是一個重要的考量，題目是否能夠涵蓋到所有預測的內涵，是工具品質的重要標準。關於壓力評估，壓力量表的題項是否能夠涵蓋目標族群的壓力內涵會是一個重要的考量。透過與目標族群（target population）訪談是增加內容效度的方法[19]。焦點團體訪談法可用來發展研究工具的概念架構及量表，焦點團體係指符合特定條件的成員組成團體，針對某一主題進行訪談，經由主持人的引導及團體的互動，成員表達對特定主題的想法、意見、知覺、經驗、態度與信念[20]。焦點團體因同質性成員一起討論，促使成員引發豐富的反應，在短時間內收集多人資料，比個別訪談的資料來的豐碩且充足，是經濟且有效率的方法[19]。此種自發性的訪談方式，可獲得受訪者較眞實的意見及反應，訪談所獲得的資料具有較良好的表面效度[20]。Gibbons（2007）也採用焦點團體的方式來探索護理系學生的壓力狀態[21]，本研究也將採焦點團體的模式來探討護理人員的壓力內涵。

在臨床實務中，量表的長短會影響到實際的施測狀態，過長的量表會導致受訪者的疲勞效應與反感，所以，如何發展一套「小而美」的臨床評估工具，對於臨床實務的評估具有相當的意義。本研究目的旨在發展一個簡單及具有信效度之新進護理人員壓力感受量表，以評估新進護理人員壓力源及壓力感受程度。

材料與方法

一、研究工具發展：

本研究工具之發展分爲三階段進行，包括實地觀察及訪談、焦點團體、量表信效度分析，分述如下：第一階段進行實地觀察及訪談：由一位資深臨床心理師及九位資深護理人員，每兩人一組，計五組，分別至不同病房實地觀察新進護理人員的工作情形，並進行個別訪談，徵求受訪者同意後，個別訪談時進行錄音，收集護理人員的壓力內涵，共觀察及訪談十位護理人員。第二階段進行焦點團體：由資深臨床心理師擔任主持人，主持人具有豐富的團體動力和訪談能力，引導九位資深護理人員進行焦點團體。主持者是焦點團體訪談成功的重要關鍵[19,20]，主持者應於團體動力及訪談技能方面受過專業訓練，藉由營造輕鬆安全的訪談氣氛，引導受訪者自由的表達想法，催化討論，增加討論內容的豐富度[20]。依據所彙集的訪談資料，進行兩次焦點團體討論，並將討論內容以現場紀錄及事後內容分析的方式形成量表題項。第三階段進行量表信效度分析：採立意取樣方式，以某區域教學醫院 45 名新進護理人員爲研究對象，使用視覺類比量尺（visual analog scale）進行測量。在信度方面採用內部一致性信度分析。在效度方面，採用 Pearson 相關係數，進行效標關聯效度檢定。

二、研究對象：

本研究爲前驅性研究，該院 2006 年新進三個月內的護理人員爲研究母群體 252 人，採立意取樣方式，由研究者說明研究目的後，再請研究對象填寫問卷，發出問卷 54 份，回收 45 份，回收率達 83.3%。研究對象均爲女性（100%），平均年齡 21.7 歲（標準差＝ 2.2），研究對象工作單位包括內、外、婦、兒、開刀房、加護病房及心身科病房。

三、研究工具：

護理人員壓力感受量表（perceived pressure scale, PPS）採用視覺類比量尺（visual analog scale）0-10 分進行測量，以評估研究對象之壓力。壓力感受量表的壓力項目涵蓋個人能力、工作量、人際溝通、工作環境、專業角色等五個層面，計 16 題。第 17 題爲單一整體性壓力，做爲評估效標關聯效度的指標。

四、資料收集與資料分析：

資料收集期間爲 2006 年 8 月 1 日至 10 月 31 日，資料收集完成後，先進行譯碼建檔，再以 SPSS 10.0 套裝軟體進行統計分析，描述性統計方面採平均值及標準差。在信度方面採用內部一致性信度分析。在效度方面，採用 Pearson 相關係數，進行效標關聯效度檢定。

結　果

一、描述性統計：

護理人員整體壓力程度平均爲63.84（SD = 19.91），護理人員壓力感受量表各項壓力程度如表一。

二、量表信效度：

本問卷採用內部一致性信度係數進行信度分析，結果顯示 Cronbach's Alpha 爲 .94，內部一致性信度佳。內容效度方面：本研究採用焦點團體法形成題目，題目涵蓋範圍與 McGrath, Reid, Boore（2005）所彙整的護理人員職業壓力及滿意度吻合[21]，顯現本量表具有內容效度。效標關聯效度方面 : 本研究採用整體壓力評估作爲效標，結果顯示壓力量表總分與整體壓力之相關爲 .83，顯現壓力量表總分與整體壓力爲顯著正相關，具有良好之效標關聯效度。

表 1　護理人員壓力感受量表各項得分及排序（N = 45）

項　　目	平均值 ± 標準差	排序
經驗不足	77.22 ± 17.97	1
執行自己不熟悉之業務	73.40 ± 19.34	2
上級交代工作無法勝任	66.84 ± 19.65	3
時間緊迫性	66.00 ± 20.41	4
工作無力感	65.49 ± 23.52	5
病人狀況無法掌握	64.64 ± 20.66	6
與其他醫療人員溝通	64.58 ± 21.08	7
工作量大	64.58 ± 22.76	7
薪資收入	62.49 ± 25.14	9
護理人員角色	57.76 ± 23.39	10
工作環境不適應	55.27 ± 23.93	11
制度規章	53.91 ± 24.93	12
同事間的人際互動	51.93 ± 26.79	13
與家屬溝通	49.76 ± 23.77	14
資源不足	49.56 ± 22.08	15
與病人溝通	49.08 ± 22.20	16
整體而言，你在本院工作時的壓力程度	63.48 ± 19.91	

討論與結論

本量表評估新進護理人員對於工作之壓力感受程度，內在一致性信度係數（Alpha = .94），顯現本量表具有良好之信度。壓力程度與整體壓力感受程度爲顯著正相關，顯現本量表具有良好之效標關聯效度。本量表係藉由訪談新進護理人員及應用焦點團體而形成，且內容涵蓋範圍與 McGrath, Reid, Boore（2005）所彙整的護理人員職業壓力及滿意度吻合[22]，顯現本量表具有內容效度。

目前國內有關護理人員壓力的相關量表有限，其中吳（1993）編修之「臨床護士的工作壓力頻率與感受量表」內容包含行政管理、病人護理、人際關係、工作認同及常規工作等六類，共 157 項壓力事件，量表之 Cronbach's Alpha 爲 .85-.95；蔡及陳（1996）之「護理人員壓力量表」爲由專家翻譯成中文，量表之 Cronbach's Alpha 爲 .93，內容包含個人反應、工作關注、勝任以及無法完成私人工作等六類，共 43 項壓力事件；此兩份量表均以 Likert's 量尺進行測量[5,14]。由於 Likert's 量尺的選項類型較多，測量較爲耗時。本研究所發展之量表僅 17 題，內容涵蓋個人能力、工作量、人際溝通、工作環境、專業角色及單一整體性壓力，本量表使用視覺類比量尺進行測量，在施測的過程中，可發現受試者可以很快速地回答所有的題項，並且可提供受試者對於目前壓力狀態立即的反思。

壓力是一種主觀性、個別性的感受[5]，視覺類比量尺是護理人員評估個案主觀感受時最常用的一種方法[23]。評估病人主觀感受時，疼痛指數視覺類比量尺是護理人員常用且熟悉的，本量表採用護理人員熟悉的視覺類比量尺進行測量，以增加量表之可用性，且透過主觀壓力感受程度評估，更能自然呈現壓力狀態。視覺類比量尺是以一條 10 公分的直線來評估個案主觀感受，較一般量表常使用 Likert's scale 簡單、易懂、省時。且視覺類比量尺可用在測量某事件介入措施發生前後所產生的差異現象，研究者想檢視同一個案隨著時間的變化，此量尺的敏感度會較具有優勢[22]，故欲持續觀察護理人員之工作壓力的變化時，使用視覺類比量尺更能眞實呈現理人員之壓力變化。

焦點團體可提升量表的內容效度[19]，以焦點團體來發展護理人員壓力量表在國內及國外文獻甚爲缺乏。本量表的發展係經由觀察及訪談新進護理人員，參考受訪者的經驗及想法，藉由焦點團體形成量表，研究工具之發展應諮詢其目標族群，其資料內容即具有內容效度，本研究與 Vogt 的研究一致[19]。

本前驅研究僅適用於臨床工作未滿三個月之新進護理人員，應用於其他年資之護理人員則需進一步的驗證。未來研究將進一步進行因素分析，以檢定其建構效

度及因素結構，並作再測信度之測量，以確定量表之穩定性，使本量表成爲精確，且臨床方便持續使用的評估工具。

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The Development of a Perceived Pressure Scale for New Nursing Staff: A Pilot Study

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Background and Purpose: It is well recognized that "stress pressure" is the chief contributing factor associated with the high turnover rate for the new nursing staffs in the hospital. The specific aim of this pilot study is to establish a simple and can be deleted reliable instrument to assess the stress perception for the new nursing staffs.

Method: The research was conducted in three stages: Firstly, information were collected through direct on-site observations on the job performance and followed by interviewing with the designated studying subjects. Secondly, focus group were processed twice to analyze data and the instrument of new nursing staff stress was established based these data. The strength item contain includes personal ability, workload, relationship, work environment, and professional role totally includes sixteen items in five-part item. The seventeenth item was whole stress. Lastly, 45 participants from a local teaching hospital were sampled and asked to fill out the questionnaire using a visual analog scale. The information gathered will then be analyzed in order to test the reliability of this proposed stress-based questionnaire.

Result: Our data indicate that internal consistency reliability coefficient (Cronbach's α) and criterion validity coefficient were 0.94 and 0.83, respectively. These data suggest that our proposed instrument for "stress" is acceptable.

Conclusion: Our proposed measuring questionnaire for stress evaluation for new-coming nurses is useful, and reliable. However, it is recommend that further studies be made in order to improve the stability of instrument.

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Key words: Perceived Pressure Scale , Visual analog scale, Focus group

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Peritonitis and Empyema due to *Pasteurella multocida*: A Case Report

Chih-Ming Chen[1], Yuan-Chuan Kao[2]

Pasteurella multocida is a rare cause of peritonitis and empyema. We report here a case of peritonitis concomitant with empyema due to *P. multocida*. This 68-year-old male farmer and pet-dog owner with a history of liver cirrhosis and chronic obstructive pulmonary disease was admitted to the hospital due to bilateral legs edema for 3 months and decreased urine output for 7 days. Sepsis and acute respiratory failure developed during hospitalization. *P. multocida* was isolated from the cultures of ascites and pleural effusion. He was then discharged uneventfully after antibiotic treatment with imipenem/cilastatin, amoxicillin/clavulanate and close thoracentesis.
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Key words: *Pasteurella multocida*, Peritonitis, Empyema

INTRODUCTION

P. multocida is an aerobic Gram-negative coccobacilli, which usually inhabits in the oral cavity and respiratory tract of domestic animals, particularly cats, dogs, and pigs[1]. It can cause a variety of infectious diseases, including cellulitis, arthritis, pneumonia, meningitis, and bacteremia[1]. The skin and soft tissue are the most common sites of infection. The major routes of infection are scratch by the patients or bite by the animals. Peritonitis and empyema are rarely caused by *P. multocida*.

CASE HISTORY

A 68-year-old male farmer and pet-dog owner with a history of alcoholic liver cirrhosis, and chronic obstructive pulmonary disease was admitted to the hospital due to worsening bilateral leg edema for 3 months and decreased urine output for 1 week. He denied that he was being bitten or scratched by his domestic dog over the prior months. In addition, he denied for having fever, chills, productive cough, nausea, vomiting, diarrhea or abdominal pain recently.

During hospitalization, his physical examination showed that he was oriented and afebrile; his blood pressure was 120/70mm Hg; pulse, 90/min; respiratory rate, 22/min. Crackles over bilateral lung fields and pitting edema over bilateral legs were noted. The abdomen was soft, distended, and without tenderness. The sonography of abdomen showed massive ascites and moderate bilateral pleural effusion. The result of his initial laboratory data were as follows: peripheral blood hemoglobin, 17.5gm/dl; platelet, 66000/μl; white blood cell count, 5920/μl with 82.7% neutrophil, and 11.8% lymphocyte. The serum level of BUN was 31mg/dl; creatinine, 0.9mg/dl; SGOT, 41 IU/L; and SGPT, 48 IU/L. Diuretic was given initially.

Sudden onset of apnea happened on seventh day of hospitalization. Endotracheal tube was intubated

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and he was transferred to intensive care unit. The peripheral blood WBC count was 2960/μl with 95% neutrophil; hemoglobin, 15.9gm/dl; and platelet count, 24200/μl. The serum laboratory data included: BUN, 105mg/dl; creatinine, 1.5mg/dl; SGOT, 59 IU/L; SGPT, 36 IU/L; total bilirubin, 7.53mg/dl; direct bilirubin, 4.08mg/dl; Na, 135meq/L; and K, 5.5meq/L; and C-reactive protein, 13.09mg/dl. The left hemithorax of chest film became opaque. Paracentesis of the abdomen yielded cloudy, and yellowish fluid with 186/μl of white blood cell (10% polymorphonuclear leukocytes); negative Gram stain and acid fast stain; and albumin, 1.0gm/dl. Thoracocenetsis yielded cloudy and orange fluid with 3930/μl of white blood cell (75% polymorphonuclear leukocytes); negative Gram stain and AFS; LDH, 324 U/L; and total protein, 2.6g/dl. He was treated with intravenous imipenem/cilastatin 500mg every 6 h empirically under the suspicion of nosocomial pneumonia. Pigtail drainage of thoracic empyema was also performed on the same day. Bronchoscopy revealed sputum impaction on the left segmental of bronchus. On the tenth day, both cultures of ascitic fluid and pleural effusion were positive for *P. multocida* and viridans streptococci. The two isolates of *P. multocida* are susceptible to all testing antibiotics by disk diffusion, including ampicillin, piperacillin, ceftriaxone, cefepime, flomocef, imipenem, gentamicin, amikacin, ciprofloxacin, trimethoprim-sulfamethazole, and chloramphenicol. The blood culture was negative for growth. The culture of bronchoalveolar lavage yielded *Pseudomonas aeruginosa* and *Klebsiella pneumoniae*. The peritoneal-pleural communication scan showed no evidence of pleural-peritoneal communication. He was then successful extubated after 14 days of imipenem/cilastatin treatment and closed-tube drainage. Subsequent 2 weeks of successive intravenous treatments with amoxicillin-clavulanic acid (1.2 gm IV every 8 hr for 2 weeks) was given. He was then discharged uneventfully on the thirty-nine days after hospitalization.

DISCUSSION

P. multocida is a nonmotile, Gram-negative, aerobic or facultative anaerobic coccobacillus mainly inhabits the oral cavity and gastrointestinal tract of many domestic animals, particularly cats (70-90%), dogs (66%), and pigs (51%)[1]. On gram-stained smear the organisms generally present with single bacilli with biploar staining. It can grow well at 37°C on chocolate, sheep blood, and form smooth, gray colonies that are 0.5 to 2.0mm after 24 hours of incubation in CO_2. It is oxidase-positive, catalase-positive, urease-negative and strongly indole-positive. It can produce acid, but no gases from glucose, sucrose and mannitol can be detected[2].

Animal exposure is considered as the main risk factor of *P. multocida* infection. Beales et al. reported that 2 of 19 SBP patients due to *P. multocida* had not animal exposure history[3]. Oral cavity and respiratory tract colonization, particularly the tonsils, are often found in patients with upper or lower respiratory tract disease, or occasionally in apparently healthy humans with animal exposure history[4]. It can be asymptomatic during *P. multocida* colonization because of their low virulence. Transient bacteremia can be developed after microinjury by endoscopy, or gastrointestinal bleeding, and the colonization can become invasive disease. The belief of hematogenous infection is supported by reports of concurrent bacteremia and peritonitis in 85% (11/13) patients[5]. In contrast, only 20% (1/5) patients with *P. multocida* thoracic empyema had bacteremia[6]. In Weber et al. reported that 40% (six) thoracic empyema cases were associated with pneumonia[1].

Most humans acquire *P. multocida* infections from direct inoculation via bite or scratch. Non-traumatic exposure cases had ever been reported[5, 7-8]. Infections following animal exposure in the absence of bites or scratches probably result from contact with secretions of the animal[1]. Due to most case of respiratory tract infection has the animal contact history, investigators also hypothesize the transmission can occur via inhalation of infectious droplets aerosolized from the oropharynx of animals[6]. In rare report, *P. multocida* was isolated from stool or peritoneum after visceral perforation, so the translocation across the gastrointestinal wall maybe also has been the source of infection[1]. Our patient did not receive any procedure including nasogastric tube insertion or panendoscopy before the onset of *P. multocida* infection. Both the ascites and the pleural effusion cultures yielded viridans streptococci and *P. multocida*, suggesting bacterial translocation from the gastrointestinal tract was probably considered to be the main pathogenesis of our patient's *P. multocida* infection.

The skin was the most common site of infection (48.4%). *P. multocida* is the rare cause of empyema

(3.4%) and peritonitis (1.6%)[1]. To our knowledge, only two cases that combined *P. multocida* empyema and peritonitis were reported[7, 9]. Both cases had liver cirrhosis history and *P. multocida* bacteremia. One acquired *P. multocida* infection from cat scratches. Another one had non-traumatic animal exposure history[7, 9]. The *P. multocida* thoracic empyema usually develops in patients with underlying pulmonary disease, such as bronchitis, bronchiectasis, bronchial obstruction, and pulmonary lymphangiectasis[1, 6]. Peritonitis usually occurs in liver cirrhosis patients with a history of gastrointestinal bleeding or endoscopy[1]. Clinical characteristic and laboratory data of *P. multocida* peritonitis and empyema are similar to those caused by other organisms[5, 6]. Similar to previous reports, our patient had the history of chronic obstructive pulmonary disease and alcoholic liver cirrhosis. *P. multocida* infection occurred following non-traumatic exposure to his pet-dogs.

Penicillin is the drug of choice for the treatment of all forms of *P. multocida* infection. Ampicillin, amoxicillin-clavulanic acid, tetracycline, minocycline, chloramphenicol, trimethroprim-sulfamethoxazole, and cefuroxime were also active to *P. multocida*. Anti-staphylococcal penicillins such as oxacillin or cloxacillin, erythromycin, clindamycin, cephalexin, cefaclor, and aminoglycosides are not active and are not recommended for treatment of *P. multocida* infection[10, 11]. Later-generation cephalosporins, such as oral cefuroxime or parenteral ceftriaxone, have better in vitro activity and probably good substitutes for penicillin[12, 13]. Carbapenems are also active to *P. multocida*[14]. If the culture only grows *P. multocida* or the infection is not the result of an animal bite, crystal penicillin G should be the drug of choice. The duration of antibiotic treatment depends on the site of infection. Four to six weeks' treatment is thought necessary to bone and joint infection[15]. Because of the organism's propensity to produce tissue necrosis and abscess formation, higher doses for longer periods of time have been suggested in case of pneumonia[6]. Penicillin was actively against the *P. multocida* isolates of our patient, but was inactively against the other etiology of viridans streptococci. Due to suspicious of nosocomial pneumonia by *P. aeruginosa* and *K. pneumoniae*, imipenem/cilastatin and subsequent amoxicillin-clavulanic acid were prescribed.

The mortality rate associated with peritonitis in patients with cirrhosis with ascites is about 30-40%[16]. The mortality associated with *P. multocida* empyema is about 50%[6]. Due to the high mortality rate of *P. multocida* empyema and peritonitis, prophylactic treatment should be considered in cirrhotic patients or in patients with underlying pulmonary disease who are about to undergo bronchoscopy or who have sustained an animal bite or scratch. The role of prophylactic antibiotics in animal bite wound is still undetermined. The previous randomized studies showed insignificant difference between the placebo-treated and antibiotic-treated groups[1].

In conclusion, we report a case of peritonitis concomitant with empyema caused by *P. multocida* in a patient with liver cirrhosis and chronic obstructive pulmonary disease following non-traumatic exposure to dogs. This rare entity expanded the clinical spectrum of *P. multocida* infection.

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Pasteurella multocida 引起之腹膜炎及膿胸：病例報告

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由 *Pasteurella multocida* 引起的腹膜炎及膿胸都是很罕見的。我們報告一個由 *P. multocida* 所引起腹膜炎合併膿胸的個案。這位 68 歲的男性農夫，飼養一隻狗。先前有肝硬化及慢性阻塞性肺疾病的病史。因為兩個小腿腫脹及尿量減少而住院，住院中發生敗血症及呼吸衰竭。從病人的腹水及肋膜積水中分離出 *P. multocida*. 經過 imipenem/cilastatin，amoxicillin/clavulanate 的抗生素治療及胸管引流後病人順利出院。
（童綜合醫誌 2008; 2: 42-46）

關鍵詞：*Pasteurella multocida*、腹膜炎、膿胸

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Melanotic Oncocytic Metaplasia of the Nasopharynx: A Case Report

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The combination of oncocytic metaplasia and melanin pigmentation of the nasopharynx is an extremely rare condition and thus far only a few papers have been reported in the literatures. Herein, we report a case of such combination in a patient presenting with symptoms such as cough and globus sensation in the throat. Nasopharyngoscopic examination revealed multiple, blackish lesions and several of them appeared around bilateral Eustachian tube openings, especially accumulated at the torus tubarius. Three nodules were submitted for pathological examination. Microscopic and immunohistochemical studies confirmed the diagnosis of melanotic oncocytic metaplasia.
(Tungs' Med J 2008; 2: 47-51)

Key words: oncocytic metaplasia, melanin, nasopharynx.

INTRODUCTION

Melanotic oncocytic metaplasia of the nasopharynx is an extremely rare disorder which occurs predominantly in Asian men. Thus far, only 12 cases were reported in the literature. These tumors are most often discovered accidentally in the evaluation for other conditions. The mean age at the onset was 68 years (range: 56 – 80 years), and the male-to-female ratio was 11:1. The accompany symptoms of the reported cases are otitis media, tinnitus, discomfort of the throat, and hoarseness. Oncocytes are found in various locations, and they are very common to find oncocytes in the seromucinous glands of the elderly. Two hypothetical mechanisms have been proposed for the oncocytic change: a cell redifferentiation process involving malignant transformation and a cellular functional depletion as a means of compensatory process. Melanocytes derived from the neural crest migrated to and localized in other epithelia as well as that of the nasopharynx. Melanin is synthesized by melanocytes, but not by oncocytes, and melanin pigmentation of the oncocytes is thought to be transferred from the adjacent melanocytes. All of the reported cases showed a benign clinical outcome. Misdiagnosis as melanoma and even malignancy is uncommonly encountered and simple excison is sufficient.

CASE REPORT

A 63-year-old man visited the Outpatient Clinic of the Department of Otolaryngology presenting with a history of cough for more than one month and globus sensation in his throat for one day. He was a habitual smoker for forty years (1.5 packs of cigarettes daily) and was also a nut chewer for thirty years (10 areca nuts/day). Besides having DM and hypertension, he was otherwise healthy. Nasopharyngoscopic examination revealed multiple, well-defined, blackish, smooth-surfaced oval lesions ranging from 1- to 3-mm, with the mean diameter of 2 mm (Fig. 1). Several of these lesions appeared around bilateral Eustachian tube openings, concentrated especially at

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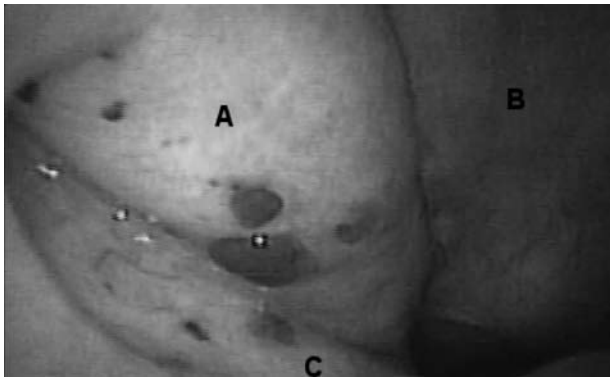

Fig. 1 Nasopharynx viewed by endonasoscopy, right side. Multiple melanotic oncocytic lesions scattered the nasopharynx, especially at the torus tubarius (A). Regional representations of the right side nasopharynx are: A = lateral wall, B = posterior wall, and C = anterior wall.

the torus tubarius (the base of the cartilaginous portion of the Eustachian tube). In addition, three smaller lesions at the posterior end of the right nasal floor, and two at the bilateral nasal septum. There was no obstruction to the Eustachian tube openings, and the typmpanic membranes and external auditory canals were normal. Under the impressions of hemangioma and/or melanoma of the nasopharynx, we therefore submitted three nodules for pathological examination. A 3-mm whitish patch situated at the anterior approximately one-third of the left vocal cord was also excised for the possible clinical diagnosis of leukoplakia.

GROSS PATHOLOGY

The specimen consisted of three pieces of gray-white, soft tissue measuring 3 mm in maximum dimension.

HISTOLOGICAL FEATURES

The lining cells revealed an upper respiratory type epithelium consisted of a pseudo-stratified ciliated columnar epithelium having numerous goblet cells between the ciliated cells. Beneath there were well-circumscribed clusters of mucous glands with oncocytic metaplasia situated in the submucosa (Fig. 2). These glands, which were tubular, slit-liked and microcystic in appearance of various sizes and shapes, composed of high-columnar pseudo-stratified ciliated epithelium. Eosinophilic mucoid fluid, some were more condensed, filled most of the lumina or openings. The cytoplasm was abundant, intensively oncocytic, and finely granular. The nuclei were small, round to oval, with inconspicuous nucleoli.

Patches of dark brown, granular, melanin pigments were predominantly presented in the cytoplasm of the oncocytic cells and much lesser degree in the

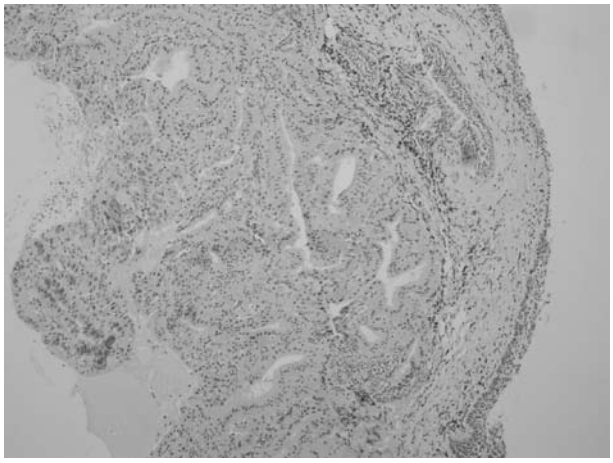

Fig. 2 Beneath the respiratory epithelium, there is a cluster of mucous glands with oncocytic metaplasia. These glands are tubular, slit-liked and microscystic in appearances. Patches of dark brown, granular, melanin pigments are seen in the left half of the picture. H & E, x100.

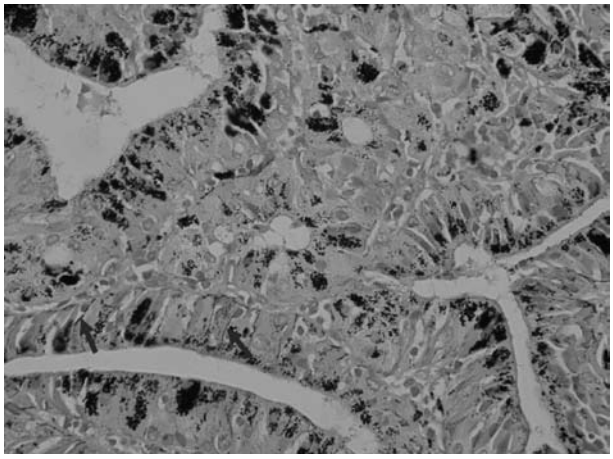

Fig. 3 Numerous melanocytes are demonstrated by Fontana-Masson staining. Note especially the dendritic processes which extended between oncocytic cells. Fontana-Masson staining (arrows), x400.

basal layer of the normal lining respiratory epithelium. These melanin pigments were confirmed by Fontana-Masson staining (Fig. 3). Immunohistochemical staining of melanoma (gp100) AB-1 was negative; however, the dendritic cells were positive for S-100 staining (Fig. 4).

The tunica propria, which composed of collagineous fibres, numerous blood vessels and lymphatic vessels, aggregates of lymphoid tissue and lymphocytes, are normal.

DISCUSSION

Melanotic oncocytic metaplasia of the nasopharynx is an extremely rare disorder occurs predominantly in Asian men. A MEDLINE search of the literature from 1966 to July 2007 using the key words of "melanotic oncocytic metaplasia" retracted four published studies in which only 12 cases were reported. The first reported case in the literature was published in 1995 by Shek et al.[1], and the largest series have been reported by Sakaki et al in 2004.[2] These tumors are most often discovered accidentally during the evaluation for other conditions, such as in this case which presented with a lump sensation in his throat. In the case series of Sakaki et al. the mean age at the onset of melanotic oncocytic metaplasia was 68 years (range:56 – 80 years), and the male-to-female ratio was 11:1.[2] The accompanying symptoms of these reported cases are otitis media, tinnitus, discomfort of the throat, and hoarseness, and all of the cases showed a benign clinical outcome.

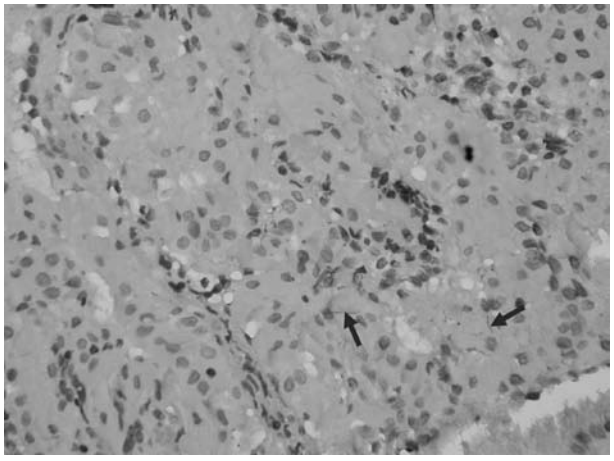

Fig. 4 Immunohistochemical staining of S-100 protein reviewed the expression of the dendritic processes. The section was bleached before rendering the S-100 staining. S-100, x400.

Oncocytes are found in various locations, including breast, pancreas, pituitary, testicle, fallopian tube, liver, stomach, larynx, respiratory tract, parathyroid, thyroid and salivary glands. It is very common to find oncocytes in the seromucinous glands of elderly,[4,5,6] but not in the patients younger than the age of 18.[5]

Oncocytic change, oncocytosis or oncocytic metaplasia, has been widely studied in various tissues including normal and abnormal conditions. Although many facets of oncocytosis have not yet been clearly defined, yet two possible mechanisms have been proposed. First of all, oncocytosis is considered to be a cell redifferentiation process involving malignant transformation. Second, oncocytosis may be a result of cellular functional depletion as a mean of compensatory process.[3]

Histochemically, high activity of mitochondrial respiratory enzymes and closely packed abnormal mitochondria with few remaining space for endoplasmic reticulum in the cytoplasm, are considered to be the features of aging or degeneration relevant to the oncocytic change.[4]

It has been well established that ethnic background and smoking babit are the predisposing factors relevant to the occurrence of oncocytic metaplasia of the nasopharynx.[2] However, a possibility existed that betel nut chewing may be another causative factor involved in the pathogenesis of this clinical condition. This possibility warrants further clarification.

On physical examination, the lesions are usually small, measuring up to a few millimeters in size, occasionally elevated, frequently bilateral involved, and nearly half of the cases are multiple.[2] In most of the cases, the lesions are noted close to the Eustachian tube opening.

Microscopically, oncocytes are cells with plenty eosinophilic cytoplasm, with a deeply staining, round, small nuclei. Electron microscopic examination of the oncocytes demonstrated a characteristic feature of mitochondrial hyperplasia. Oncocytic metaplasia is characterized by replacing the normal ducts and acini of seromucinous glands by these bright red cells. Oncocytic metaplasia can be observed in various kinds of organs, but seldom encountered in nasopharynx. Melanotic oncocytic metaplasia, which is characterized by the simultaneous presence of melanin pig-

mentation and oncocytic metaplasia, is even more rarely reported.[1,2,7,8,9]

Melanocytes are cells originated from the precursor melanoblasts[10], characteristic by the presence of long dendritic processes, which are derived from the neural crest and migrated to and localized in other epithelia functioning as normal pigment production and secretion of biopolymer melanin, such as in the skin, the leptomeninges, the mucosa of larynx, nasal cavity and paranasal sinus. Although melanin-associated lesions in nasopharynx are rarely reported, migration of melanin to the nasopharynx does sometimes occur.

Melanin is synthesized by melanocytes, but not oncocytes, and melanin pigmentation observed of the oncocytes is thought to be transferred from the adjacent melanocytes. This interchanging reaction of melanin pigments between the melanocytes and the surrounding cells may be carried out by transferring the melanosome directly or by functional regulators production and secretion.[11]

Since the gross appearance of the lesions is well-circumscribed and benign-looking at physical examination, misdiagnoses as melanoma[1,7,8] and even malignancy should be infrequently encountered. For this reason, a simple excision should be considered to be sufficient for the patient presenting with this clinical condition.

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鼻咽黑色素性嗜酸瘤細胞化生：病例報告

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鼻咽粘膜的嗜酸細胞化生（oncocytic metaplasia）和黑色素沉著（melanin pigmentation）兩者之結合是極其罕見的。到目前為止只有幾篇報告發表於文獻中。在此報告此一組合的個案。病人主訴咳嗽和喉嚨異物感。鼻鏡檢查發現很多黑色的病變，其中幾顆位於兩側的耳咽管（Eustachian tube）的開口處，尤其是堆積在咽鼓管圓枕（torus tubarius）。取樣三個病變做病理診斷。鏡檢及組織免疫化學確認此等組合 ---- 黑色素性嗜酸細胞化生（melanotic oncocytic metaplasia）。
（童綜合醫誌 2008; 2: 47-51）

關鍵詞：嗜酸細胞化生，黑色素，鼻咽。

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Hypercalcemia with Acute Renal Failure in Sarcoidosis – A case report

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Sarcoidosis is a systemic granulomatous disease that primarily affects the lung and lymphatic systems of the body; however, significanet renal involvement is rare.

We report herein a 58-year-old man who admitted to our hospital complaining of chest tightness and weight loss about 3 kg in one month. On laboratory evaluation, Chest X-ray film showed bilateral hilum node enlargement. Severe hypercalcemia, with serum level of calcium 11.2 mg/dl was noted. Renal failure was noted with serum creatinine of 5.1 mg/dl. Sarcoidosis with renal involvement was confirmed by typical chest radiography findings, and mediastinoscope biopsy of the mediastinal lymphadenopathy. Oral prednisolone , 0.5 mg/kg/day, resulted in the improvement of laboratory results.
(Tungs' Med J 2008; 2: 52-56)

Key words: Sarcoidosis, Acute renal failure , hypercalcemia

INTRODUCTION

Sarcoidosis is a multisystem disorder of unknown cause(s). It commonly affects young and middle-aged adults and frequently presents with bilateral hilar lymphadenopathy, pulmonary infiltration, and ocular and skin lesions. The liver, spleen, lymph nodes, salivary glands, heart, nervous system, muscles, bones, and other organs may also be involved[1]. Rarely, sarcoidosis may present with both renal failure and hypercalcemia[3]. Hypercalcemia results from increased calcium absorption secondary to 1,25-dihydroxyvitamin D production by sarcoid granulomas. If left untreated, hypercalcemia can result in renal calculi, nephroalcinosis and renal failure.

The diagnosis of sarcoidosis needs a compatible clinical picture, histological demonstration of noncaseating granulomas, and exclusion of other diseases capable of producing a similar histological or clinical picture. The diagnostic work-up for patients with sarcoidosis should attempt to accomplish four goals[4]: 1) provide histological confirmation of the disease; 2) assess the extent and severity of organ involvement; 3) assess whether the disease is stable or is likely to progress; and 4) determine whether therapy will benefit the patient. In patients with systemic, symptomatic disease, oral corticosteroids are often employed.

CASE REPORT

A 58-year-old man admitted to our hospital complaining of chest tightness and weight loss about 3 kg in one month. The clinical picture began two months ago with dyspnea on exertion but the patient overlooked it. Severe weakness, nausea and vomiting, dehydration and sudden weight loss during the previous month were noted. Chest tightness, dry cough and general malaise was also noted for the past 3 days. Subsequently, the patient was admitted to our hospital for help.

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On examination, the hemodynamic and respiratory parameters were all in the normal range, with normal heart and lung auscultation. Body temperature was normal. There was no focal sign of acute neurological disease.

On laboratory evaluation, Chest X-ray (Figure 1) showed bilateral hilar node enlargement. Severe hypercalcemia with serum calcium concentration of 11.2 mg/dl was noted. He had renal failure with serum creatinine of 5.1 mg/dl and blood urea nitrogen of 45.1 mg/dl. Computed tomography of the chest showed multiple enlarged mediastinal and bilateral pulmonary hilar lymph node(Figure 2). Mediastinoscope biopsy reported noncasseous granulomatous inflammation favor the diagnosis sarcoidosis(Figure 3). The serum concentration of angiotensin-converting enzyme was 42.1 IU (reference ranges 8.3-21.4 IU). Abdominal ultrasound showed chronic renal parenchymal disease with bilateral renal stones. Hormonal assessment (normal parathyroid and thyroid function) and respiratory function test (normal) were completed.

The first-line treatment consisted of isotonic hyperhydration, diuretics to obtain a high rate of diuresis and to improve calcluim renal excretion, and prednisolone at a daily dose of about 30 mg. The patient was discharged after 9 days with normal blood calcium level and serum creatinine of 4.2 mg/dl. After 2 months of prednisolone treatment, his serum creatinine was finally decreased to the elvel of 1.9 mg/dl.

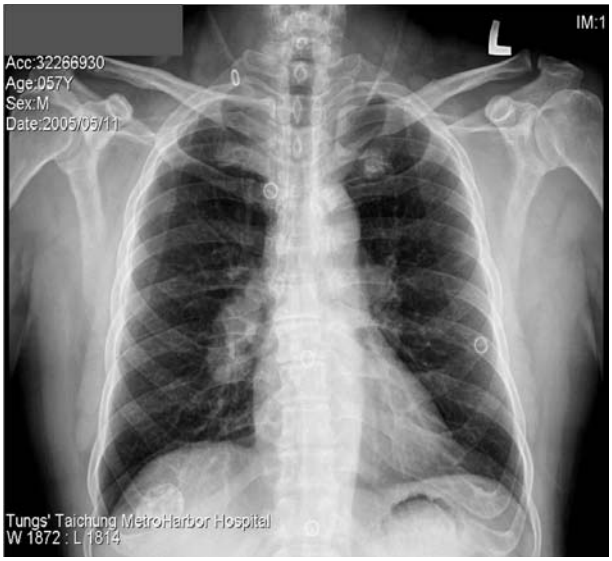

Fig. 1 CXR showed bilateral hilar node enlargement

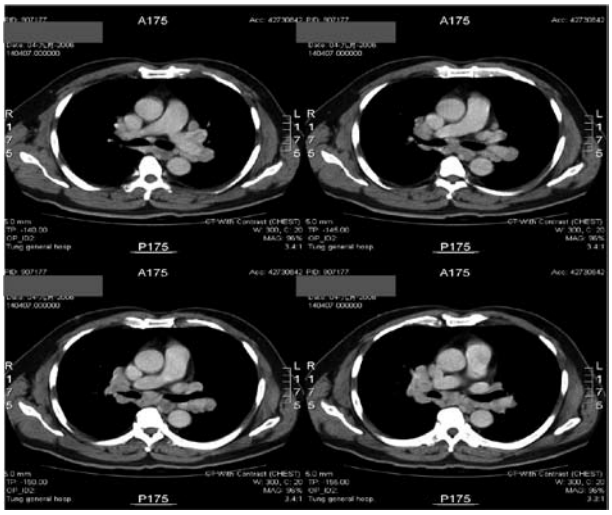

Fig. 2 Computed tomography of the chest showed multiple enlarged mediastinal and bilateral pulmonary hilar lymph node

DISCUSSION

Sarcoidosis is an immunomediated disease of unkown cause, characterized by an increased cellular immune response to an unknown antigen and the formation of noncaseating granulomas in affected tissues. Although the lungs and lymph nodes are the predominant sites affected (75–90%), other organs such as the bone marrow, eyes, heart, kidneys, liver, and spleen may also be involved[3]. Cases of extrapulmonary sarcoidosis affecting the kidneys are rare. The incidence of renal involvement ranges from 3-23% with a wide spectrum of abnormalities[5]. In acute renal failure (ARF), patients are frequently hypocalcemic. Usually, the presence of hypercalcemia associated with ARF is indicative of the presence of comorbidity, including sarcoidosis, multiple myeloma, cancer, hyperparathyroidism, vitamin D intoxication, or leprosy[6]. Sarcoidosis should be considered an important differential diagnosis in cases of hypercalcemia and renal failure.

Sarcoidosis with renal involvement may present as granulomatous infiltration of the renal parenchyma, glomerulonephritis, and nephrocalcinosis or renal stones. Rarely, the granulomatous process may

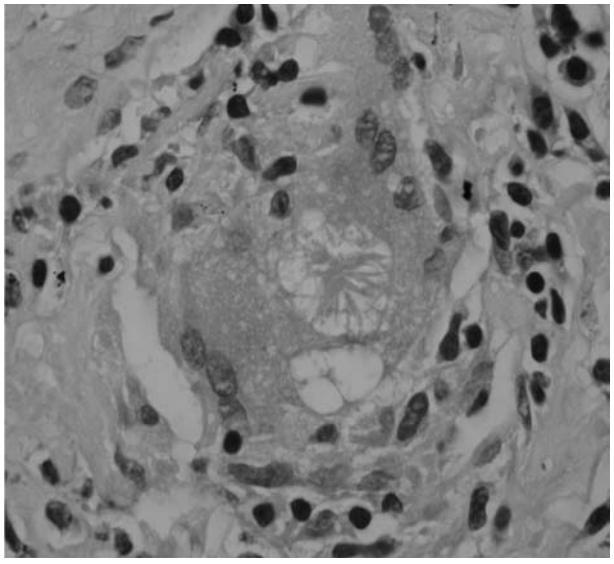

Fig. 3 Histopathology showed granuloma with Asteroid Body, multinucleated giant cell and surrounding epitheloid Histiocytes and lymphocytes (H&E stain, x 1000 oil)

produce interstitial nephritis by directly involving the kidneys. Nephrocalcinosis or renal stones are due to abnormalities of calcium metabolism[2]. Sarcoidosis causes renal dysfunction mainly through altered calcium metabolism[7]. Hypercalcemia in sarcoidosis is uncommon, accounting for approximately 10% of the cases[8]. It is usually caused by an endogenous overproduction of 1,25-dihydroxyvitamin D [1,25-(OH (2))-D] by granulomatous tissue and activated macrophages results in an increase of intestinal absorption of calcium[9].

Oral corticosteroids remain the first-line thaerapy in most cases. The need for treatment must be balanced against the overall excellent prognosis for most patients with sarcoidosis. This is particularly true for patients with stage I disease, for whom systemic therapy is rarely required[1]. Perisitently, symptomatic or progressive pulmonary disease is generally accepted to be an indication for a course of systemic therapy. Such indications include eye disease, cardiac involvement, neurologic involvement, hypercalcemia, hypercalciuria with associated renal insufficiency or recurrent nephrolithiasis, severe disfiguring skin lesions, progressive heart failure, severe incapacitating osseous or muscle involvement, and severe pulmonary involvement that is significantly impairing gas exchange. Treatment with corticosteroids is successful in improving renal function, but relapse is common on steroid withdrawal and prolonged treatment is necessary for disease control.

Our patients suffered from renal failure and hyeprcalcemia, instead of hypocalcemia which is usually seen in patients with acute renal failure. His chest radiography disclosed bilateral hilar lymp node enlargement. Sarcoidosis with renal involvement was highly suspected. Mediastinal lymphadenopathy biopsy confirmed the diagnosis of sarcoidosis. In addition to fluid supplement for hydration, oral prednisolone was prescribed. Both of them resulted in a gradual recovery of renal function. We are not able to distinguish whether the renal failure in our case was due to a renal involvement by sarcoidosis or a calcemic nephropathy[10], because our patient did not undergo a biopsy. The rapid improvement allowed the exclusion of such an invasive procedure.

In conclusion, renal failure with hemodialysis is a costly therapy. Surgical intervention for stone extraction is unnecessary for sarcoidosis with renal involvement. Detail history taking, physical examination and laboratory evaluation can prevnet a patient being from inappropriately treated.

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類肉瘤病以高血鈣症併急性腎衰竭來表現—病例分析

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類肉瘤病乃一全身性發炎的疾病，其原因至今仍然不明，可以侵犯任何器官，包括肺臟、週邊淋巴結、眼睛、肝臟、脾臟、骨髓、腎臟。其中肺部大約佔了 75-90%，但侵犯到腎臟卻是相當罕見。文獻上，侵犯到腎臟的病例中，以腎石症來表現為主。高血鈣症併急性腎衰竭來表現非常稀少。

我們報告了一名 58 歲男性，因胸悶及體重一個月減輕三公斤來本院求診。實驗室檢查發現血鈣和肌酸酐升高。經由胸部 X 光片，電腦斷層和縱膈腔鏡淋林巴結切片確定病人罹患類肉瘤病。病人在接受類固醇治療後，腎功能及血鈣皆逐漸獲得改善。

（童綜合醫誌 2008; 2: 52-56）

關鍵詞：類肉瘤病，急性腎衰竭，高血鈣

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頸部淋巴節之濾泡樹突狀細胞肉瘤：病例報告

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濾泡樹突狀細胞肉瘤（Follicular dentritic cell sarcoma）為一罕見之惡性腫瘤，自 Monda 氏於 1986 年提出首例後，至目前為止文獻上約有 70 餘例病例報告。好發部位以頸部淋巴結為主，但淋巴結外組織亦可發生。本病例為 17 歲男性病患、主訴發現右側頸部無痛性腫塊約 2 個月，並曾有輕微感冒症狀。理學檢查為可動性無痛性右頸部腫塊，約 4 cm 大小。頸部電腦斷層掃瞄下所見，除右頸腫塊，並無其他部位病灶。病患接受腫瘤切除式手術後，根據其臨床表現、組織學形態、免疫組織化學染色結果，診斷為濾泡樹突狀細胞肉瘤。濾泡樹突狀細胞肉瘤為一中度惡性腫瘤，治療以廣泛性手術切除為主，術後輔助性放射線及化學治療有助於腫瘤的控制。
（童綜合醫誌 2008; 2: 57-61）

關鍵詞：follicular dendritic cell sarcoma, neck malignancy, immunohistochemistry, CD21, CD35

引　言

濾泡樹突狀細胞肉瘤（Follicular dentritic cell sarcoma）爲一罕見之惡性腫瘤，自 Monda 於 1986 年提出首例後，至今約有 70 餘例病例報告[1]。好發部位以頸部淋巴結爲主，但也可發生於淋巴結外組織，如頭頸部的扁桃體、軟顎、咽側壁、甲狀腺，或胸腹部的縱隔腔、乳房、肝、脾、大腸等[2]。其臨床表現爲慢性無痛性、局部性腫塊，確診後檢查，常有遠處轉移。若發生於胸腹部時，因發現較晚，預後較差[3]。治療方式以廣泛性手術切除爲主，術後輔以放射線或化學治療增進腫瘤的局部控制及防止遠處轉移。此病在世界衛生組織腫瘤分類歸類爲組織細胞、樹突狀細胞腫瘤，一般視爲中低度惡性腫瘤。本科於於 2005 年 8 月經歷 1 例濾泡樹突狀細胞肉瘤病患。由於此病例罕見，在臨床上易與惡性淋巴瘤混淆，且病理學上有其特殊性，故特提出報告。

病例報告

病患爲 17 歲年輕男性，於 2005 年 8 月由外院轉介至本院耳鼻喉科就診。主訴右側頸部無痛性腫塊約 2 個月餘，除兩個月前曾有感冒症狀外，無發燒等其他不適症狀。病人無吸煙、喝酒、嚼檳榔等不良史或癌症家族史。理學檢查爲一無痛性右頸部腫塊，約 4 × 5 cm 大小。血液、生化檢查除中性粒细胞減低（37%）及淋巴球细胞增加外（50%），無其他異常。電腦斷層掃瞄檢查可見一腫塊直徑約爲 4 cm 位於右側頸前三角上區（圖 1）。由於臨床表徵及發生位置與頸部淋巴腺病和淋巴瘤十分相似，且病患無其他口腔、口咽、鼻咽等耳鼻喉科範圍異常，故進行腫瘤切除式切片手術。病理切片在光學顯微鏡下可見淋巴結已被片狀或束狀排列的腫瘤細胞所取代，其細胞呈卵圓形或紡錘形（圖 2A, 2B）。腫瘤細胞呈現細胞異化現象，且內含豐富的細胞質和濾泡性細胞核及顯著的核仁，並出現頻繁的細胞分裂現象。經免疫組織化學染色，腫瘤細胞呈廣泛性 CD21，CD35，vimentin 及 EMA（Epithelial Membrane Antigen）陽性反應（圖 2C, 2D）；至於 cytokeratin、desmin、smooth muscle actin、chromogranin、S-100、CD30、ALK（Anaplastic lymphoma kinase）、HMB-45、T-cell、B-cell 等染色則呈陰性反應。綜合組織學形態及免疫組織化學染色結果，

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診斷爲濾泡樹突狀細胞肉瘤。病患術後傷口復原良好無任何併發症，並於手術後 1 個月接受放射治療，追蹤至今已 20 個月，情況良好，無任何復發及遠處轉移跡象。

討　論

濾泡樹突狀細胞主要位於淋巴結的初級淋巴濾泡生發中心，其主要功能是由濾泡樹突狀細胞胞膜表面吸附抗原抗體複合物，並長期保留抗原，及產生免疫調節因子，調節 B、T 淋巴細胞等免疫功能。不同於其他抗原呈現細胞，濾泡樹突狀細胞並不經由細胞內處理抗原，而是在細胞表面傳遞抗原抗體複合物整體給予淋巴細胞。濾泡樹突狀細胞因參與免疫功能，故與一些淋巴、免疫疾病有關，如Ｂ細胞淋巴瘤、後天免疫缺失症候群（AIDS）和自體免疫疾病等。其致病機轉可能是：1. 在後天免疫缺失症候群病人，濾泡樹突狀細胞捕捉大量人類免疫缺損病毒（HIV），長期持續儲藏病毒和做爲病原體的儲藏所，導致病毒不易從體內清除。2. 淋巴濾泡生發中心的Ｂ細胞需要與抗原抗體複合物結合才能存活，並分化爲Ｂ記憶細胞及漿細胞。在Ｂ細胞淋巴瘤病人中，濾泡樹突狀細胞除了供給Ｂ細胞抗原抗體複合物外，還產生 8D6 和 interleukin-15（IL-15）等因子刺激 B 淋巴細胞增生，及產生 B-cell-activating factor of the tumor necrosis factor family（BAFF/BLys）等因子抑制Ｂ淋巴細胞死亡 [4]，進而導致淋巴瘤細胞大量增生。

濾泡樹突狀細胞肉瘤爲一罕見疾病，源自濾泡樹突狀細胞。此病好發於青年及中年，無顯著性別差異。此病與 hyaline-vascular Castleman's disease 和 EB 病毒感染有關聯 [1]。臨床上常表現為頸部無痛性，生長緩慢腫塊。此病因其病理、臨床表現與淋巴組織有密切關係，易與反應性濾泡增生症（reactive follicular hyperplasia）、炎性假瘤（Inflammatory pseudotumor）、被套細胞淋巴瘤（Mantle Cell Lymphoma）、Hodgkin 氏淋巴瘤等混淆 [2]。

病理診斷方面除鏡檢外，還需依賴多種免疫組織化學方法。在組織學方面，腫瘤細胞多呈卵圓形、梭形，片狀及束狀排列，細胞分界不清，呈融合現象。細胞質呈微嗜酸性，顯著的核仁併細胞分裂現象。在免疫組織化學染色方面，因濾泡樹突狀細胞與抗原抗體複合物是由其表面 Fc 接受器，（如 CD32、CD23），或由補體接受器，（如 CD21、CD35），所結合。若是細胞呈現 CD21，CD35 陽性反應，且 LYS）Lysozyme）、CD1 爲陰性反應即可與其他網狀組織細胞腫瘤區分 [6,8]（表一）。P53 變性蛋白質亦可見於該腫瘤，表示濾泡樹突狀細胞肉瘤也有 p53 基因突變 [5]。電腦斷層掃瞄、核磁共振影像則可幫助術前腫瘤分期及預後評估。

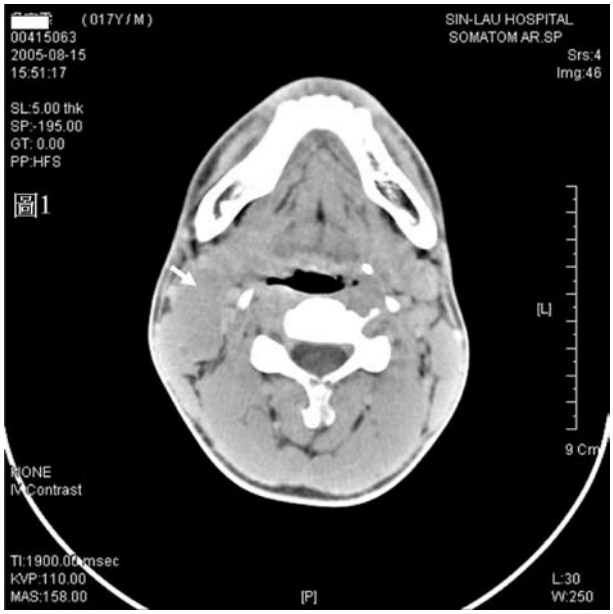

圖 1　電腦斷層橫切面加顯影劑顯示一右頸部腫瘤（箭頭）。

根據 Vargas[7] 等人在 2002 年發表 34 例回顧性頭頸部濾泡樹突狀細胞肉瘤病例，此腫瘤有高度術後復發率及遠端轉移性，應視爲中高度惡性腫瘤。但據 Pileri[8] 等人報告 13 例濾泡樹突狀細胞肉瘤病例，其存活率高達 91%，可視其爲中低度惡性腫瘤。Chan[3] 等人則提出若腫瘤發生於腹腔、腫瘤組織若併有凝血性壞死、細胞異化、頻繁細胞分裂等因子，則預後不良。濾泡樹突狀細胞肉瘤因病例稀少，現無標準建議治療方法。但根據文獻上記載，治療以手術廣泛性切除爲主，若併有不良預後因子，則需再進行術後放射線或化學治療 [6]。台灣曾於 2001 年報導一例大腸濾泡樹突狀細胞肉瘤，術後給予化療 [9]。Chan[3] 等人報導經治療後復發率爲 43%、遠端轉移 24%。Vargas[7] 等人則建議手術切除後，合併放射線治療。若有轉移時則需加做化學治療。本病例因手術切除腫瘤，術後放射線治療，經 20 個月追蹤後，腫瘤尚無任何復發或遠端轉移跡象，故沒有接受化學治療。

濾泡樹突狀細胞肉瘤爲罕見網狀組織細胞腫瘤。近年來由於對免疫系統細胞大幅的認識及免疫組織化學染色診斷技術的進步，使得此疾病診斷病例近 2 年來得以快速增加。臨床上若有無痛性頸部腫塊，淋巴結有卵圓形、梭型腫瘤細胞，則須排除此病。本病例因併有 2 個預後不良因子（細胞異化、頻繁細胞分裂），術後需輔以

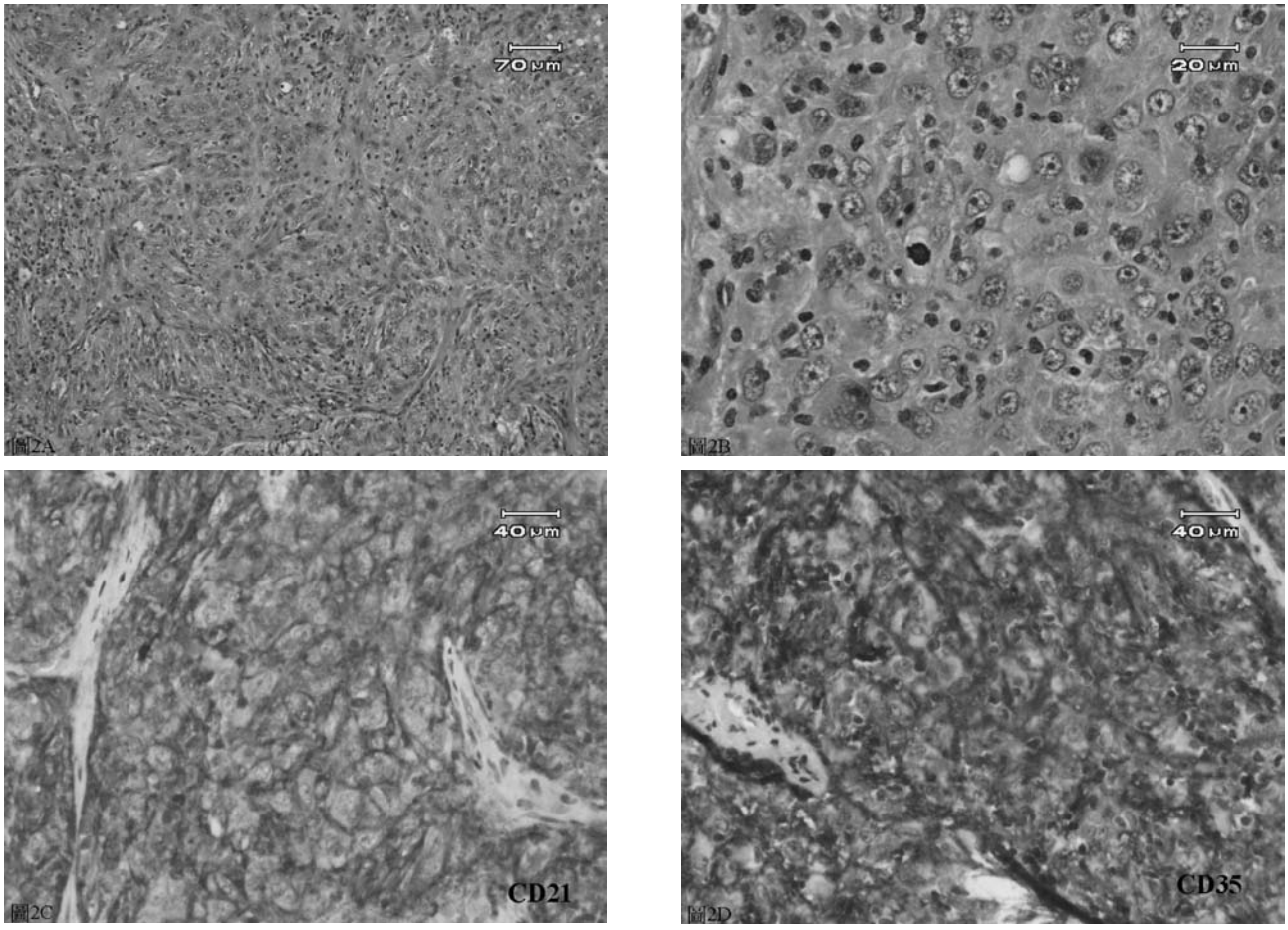

圖 2　(A) 病理切片可見片狀或束狀排列腫瘤細胞（H&E; ×100）。(B) 病理切片可見卵圓形或紡錘型腫瘤細胞（H&E; ×400）。(C) CD21 免疫組織化學染色呈陽性反應（×200）。(D) CD35 免疫組織化學染色呈陽性反應（×200）。

表 1　濾泡樹突狀細胞肉瘤與其他腫瘤免疫組織化學染色。

Disease/Marker	CD68	LYS	CD1a	S100	CD21	CD35
Histiocytic sarcoma	+	+	–	+/–	–	–
Langerhans cell tumor sarcoma	+	+/–	+	+	–	–
Interdigitating cell tumor sarcoma	+/–	–	–	+	–	–
Follicular dendritic cell tumor sarcoma	+/–	–	–	+/–	+	+

Adapted from Pileri SA, Grogan TM, Harris NL, etal. Histopathology 2002; 41: 1-29.

放射線或化學治療，並長期定期追蹤。

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Follicular Dendritic Cell Sarcoma of Cervical LN: case report

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Follicular dendritic cell sarcoma (FDCS), first described in 1986 by Monda, is a rare type of malignancy and thus far, more then 70 cases have been documented in the literature. FDCS is frequently occurred at cervical lymph node, but other extra-nodal locations can also be seen. Here, we report a case of cervical FDCS. This patient, a 17-years old adolescent, was originally presented with a painless nodule at the right neck for 2 months. He underwent surgical excision and based on microscopic findings and immunohistochemistry results, he was diagnosed to be a case of FDCS with two poor prognostic factors. The patient was subsequently received adjuvant radiotherapy. During the follow-up period of 20 months, there have been no signs of recurrence. Together, we suggest that the proper treatment for a moderately aggressive FDCS should include wide excision and post-operative adjuvant chemotherapy or radiotherapy.
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Key words: follicular dendritic cell sarcoma, neck malignancy, immunohistochemistry, CD21, CD35

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童綜合醫學雜誌投稿相關規則

本雜誌刊載與醫學有關之論述，包括原著論文、臨床病理討論、病例報告等論述及特別約稿之綜論（review article）、special article、Editorial（編著的話）等。惠稿請送 43503 台中縣梧棲鎮中棲路一段 699 號童綜合醫學雜誌編審委員會。

壹、投稿前注意事項

1. 投稿時，需附原稿三份（一份原稿和兩份複印稿，但圖片應用三份原圖）並以電腦打字（請以 MS WORD 文書處理格式，中文字型以標楷體，英文字型以 Time New Roman 12 號字大小，稿紙之左右緣爲 2.54 公分，上下緣爲 3.17 公分），請勿裝訂，同時須提供最後版本之電子檔一份，若圖片或照片有電子檔提供者，請以附檔 jpg 的形式提供。
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5. 凡刊載於本雜誌之著作，若涉及「研究用人體檢體採集」及「人體試驗」等情事，應遵守該注意事項，以落實保障受檢人權益。詳文請參考須附上相關審議認可之文件。
6. 論文中如涉及使用脊椎動物進行科學應用計畫者，應檢附該計畫業經所屬機構動物實驗管理小組審議認可之文件，以落實實驗動物之人道管理。

貳、寫作原則

1. 原著論文按下列順序撰寫：摘要、前言、材料與方法、結果、討論與結論、誌謝、參考文獻、附表、圖片說明、圖片（含照片）。
2. 病例報告按下列順序撰寫：摘要、前言、病例、討論、參考文獻、附表、圖片說明、附圖、照片。
3. 病例報告，每篇以五頁以內爲限（即約 9,000 字），依題目、所屬機構、作者姓名（作者以 5 人爲限）、病例之病史經過及重要之診療資料、主要之臨床問題、討論或分析、結論、推薦讀物等順序繕寫。凡病患顏面部位之相片必須遮去眼睛部位，表示尊重隱私。診療資料或臨床經過之圖表，原則上均限六個月以內。
4. 綜說不必按原著論文格式撰寫，但必須列出參考文獻。
5. 其他類文章連圖表，以不超過四頁（每頁約 2,000 字）爲原則，但特約稿例外。學術文章，題目、姓名均須以中文書寫。
6. 其他細節，請參閱國際指導委員會（International Steering Committee）發表之生物醫學雜誌稿件統一規格（Uniform Requirements for Manuscripts Submitted to Biomedical Journals，見 The New England Journal of Medicine 336: 309-315, 1997）。

參、投稿須知

一、稿件須符合「生物醫學雜誌投稿之統一規定」[1]，請以電腦隔行 double space 書寫並編頁碼。

二、第一頁爲標題頁，須列出中文及英文之論文題目、簡題（running title）、中英文作者姓名、所屬機構及單位之中英文稱號（分屬不同單位，請以阿拉伯數字標出作者與單位）、聯絡人姓名、電話及中英文通訊錄。

三、第二、三頁爲中文及英文之摘要及關鍵詞 (請提供 3 至 5 個關鍵詞或簡短片語)，中英文摘要須完全相同，英文摘要不超過 250 字，中文摘要不超過 500 字，摘要分段撰寫，依序爲背景及目的（Background and purpose）、方法（Methods）、結果（Results）及討論（Discussion）。

四、請附三份原稿（一份原稿和兩份複印稿，但圖片應使用原圖），包括附表、附圖及照片。圖表應專業製作，一張紙僅一個附圖或附表，依引用順序以阿拉伯數字標出排列。附表須有標題及說明。照片須 5 × 7 吋光面黑白，背面以鉛筆編號，附圖須有簡單說明（Legend），並另頁撰寫。光學或電子顯微鏡照片，請註明擴大倍率或比例。

註：[1] 根據「生物醫學雜誌投稿之統一規定」第五版，刊載於 Annals of Internal Medicine 1997; 126(1): 36-47.

肆、參考文獻

未經發表之論文或摘要不得列爲參考文獻，但可於本文中說明並註明「未發表」（unpublished observations）。博碩士論文可引用。已被任何雜誌接受刊發但仍未發表之著作，請列出雜誌名稱及年份，並註明「in press」。

原著論文、臨床病理討論、病例報告等論述及特別約稿之綜論（review article）按下列格式撰寫：

一、雜誌名稱之簡稱須按照 Index Medicus 型式，作者人數小於 6 位時，詳列所有作者姓名，超過 6 位時，只須列出前 6 位，其它以「等」（et al）代替。

例：Bhasin S, Storer TW, Berman N, Callegari C, Clecenger B, Phillips J, et all. The effects of supraphysiologic doses of testosterone on muscle size and strength in normal men. N Engl J Med 1996; 335: 1-7.

二、本文內引用時，若兩名以下作者請列出姓氏。兩名以上則列出第一名之姓氏，其他以「等」（et al）代替，並以阿拉伯數字方括弧表示於引用之後。

例：One of the first well documented reports of ECH poisoning with fatality in young children was reported by Miller et al. in 1970[2].

例：Boulet 等人 [3] 報告氣喘患者接受衛教後的知識改變量不受個人因素影響。

三、參考範例

A. 期刊：[作者姓名：題目。雜誌簡稱　年代；卷數（期數）：起迄頁數]

1. 許吟姿、楊光道、張恆鴻：結締組織疾病併發間質性肺病變患者 99mTc-DTPA 肺廓清率之臨床研究。內科學誌 1992;3:79-83.
2. Yang KTA, Chen HD: A semi-automated method for edge detection in the evaluation of left ventricular function using ECG-gated single-photon emission tomography. Eur J Nucl Med 1994; 21: 1206-11.

B. 單行本：[作者姓名：書名，版數（卷數）。發行地；出版公司，年代：引用部份頁數]。

1. 楊志良：生物統計學新論，一版。台北；巨流圖書公司，1984：33-8.
2. Plum F, Posner JB: Diagnosis of Stupor and Coma. 3rd ed. Philadelphia: Davis, 1980:132-3.

C. 多重作者之單行本：[有關文章作者姓名：書名，版數（卷數）。發行地；出版公司，年代：引用部份頁數]。

1. 蔣欣欣：護理與健康，編輯：顧乃平：護理專業導論，一版。台北；匯華出版公司，1991：83-121。
2. Levinsky NG: Fluid and electrolytes. In: Thorn GW, Adams RD, Braunwald E, lsselbacher K, Petersdprf RG eds. Harrison's Principles of Internal Medicine, 8th ed. New York: Mcgraw-Hill, 1977:364-75.

伍、著作權

若著作人投稿於本刊經收錄後，版權即歸本院所有，除本院同意外不得轉載。若爲摘譯、譯稿或改寫稿，需附原作者之正本同意書，並附原文影本一份；來稿如涉及版權，概由作者自負文責。

童綜合醫學雜誌

原　著

病例報告