[3]千葉大学大学院　医学研究院感染分子生物学・炎症制御学
[4]宮崎大学医学部　生殖発達医学講座小児科学分野・小児科学

1-6 Combined treatment with EPA and aspirin for ANCA vasculitis.
Junichi Hirahashi
Department of Nephrology and Endocrinology, Tokyo University Graduate School of Medicine
ANCA 血管炎に対する EPA とアスピリンの併用療法-基礎と臨床-
平橋淳一　(東京大学医学部附属病院腎臓内分泌内科)

10:45-11:00　Break

11:00-12:00

Chair: Kei Takahashi, Toho University Ohashi Medical Center
Junichi Hirahashi, Tokyo University Graduate School of Medicine

2-1 Comparison of Type I IFN systems amongst healthy subjects, MPO-ANCA nephritis patients, and IgA nephritis patients
[1]Kazuko Uno, [2]Eri Muso, [2, 3]Toshiko Ito-Ihara, [4]Kazuko Suzuki
[1]Louis Pasteur Center for Medical Research, [2]Div. Nephrology Kitano Hospital, The Tazuke Kofukai Medical Research Institute, [3]Dept. Clinical Innovative Med., Translational Research Ctr, Kyoto University Hospital, 4Dept Immunology, Inflammation Program, Chiba University Graduate School ofMedicine
MPO-ANCA 腎炎患者のインターフェロンシステム：　健常人、IgA 腎症との比較から
宇野賀津子[1]、武曾恵理[2]、猪原登志子[2,3]、鈴木和男[4]
[1]ルイ・パストゥール医学研究センター、[2]財）田附興風会医学研究所北野病院・腎臓内科、
[3]京大病院、探索医療センター、[4]千葉大学院医学研究院、免疫発生学・炎症制御学

2-2 Free heme markedly induces proinflammatory protein via resident macrophage in heart.
Haruo Hanawa,[1] Ken Toba,[1] Kazuhisa Hao,[1] Limin. Ding,[1] Kaori Yoshida,[1] Makoto Kodama,[1] Yoshimi Ota,[2] Yoshifusa. Aizawa[1]
[1]Division of Cardiology, Niigata University Graduate School of Medical and Dental Sciences,
[2]Department of medical technology,School of Health Sciences, Faculty of Medicine, Niigata University
フリーのヘムは心臓の在住マクロファージを介して炎症誘発性蛋白を誘導する
塙晴雄[1],鳥羽健[1],羽尾和久[1],丁立民[1],吉田香織[1],小玉誠[1],太田好美[2],相澤義房[1]
[1]新潟大学大学院医歯学総合研究科　循環器学分野,[2]新潟大学医学部保健学科

2-3 Deposition of Mannan-Binding Proteins in Coronary Artery during the Onset of the CAWS-induced Arteritis, a Murine Model of Kawasaki Disease
Kazuhide Uemura[1], Yusuke Oka[1], Noriko Miura[2], Naohito Ohno[2], Kazuo Suzuki[3] Tatsuya Morimoto[1], Takahiko Ono[1,4]
[1]School of Pharmaceutical Sciences, University of Shizuoka,　[2]School of Pharmacy, Tokyo University of Pharmacy and Life Science, [3]Dept Immunology, Inflammation Program, Chiba University Graduate School of Medicine, [4]Dept Nephrology, Shimada Municipal Hospital,
川崎病モデル CAWS 投与マウス血管炎形成過程におけるマンナン結合タンパク質の血管壁への沈着
上村 和秀[1]、岡 祐介[1]、三浦 典子[2]、大野 尚仁[2]、鈴木 和男[3]、森本 達也[1]、小野 孝彦[1,4]
[1)] 静岡県立大学薬学部、[2)] 東京薬科大学薬学部、[3)]千葉大学院　免疫発生学・炎症制御学、
[4)]島田市民病院　腎内

2-4 Analysis of cytokine production from PBMC by stimulation with intravenous immunoglobulin
Noriko N. Miura, Naohito Ohno (Tokyo Univ. Pharm. & Life Sci.)
免疫グロブリン製剤によるヒト白血球 PBMC のサイトカイン産生への影響
三浦典子，大野尚仁（東京薬科大学）

12:00-12:30　Lunch

12:30-13:00
Chair: Naohito Ohno Tokyo Univ. Pharm. & Life Sci.

2-5 Lung inflammation induced by zymosan, LPS, and CAWS in mice deficient in phagocyte NADPH-oxidase
Yasuaki Aratani, Yokohama City University
菌体成分誘発性肺炎における食細胞機能異常の影響
荒谷康昭(横浜市立大学大学院生命ナノシステム科学研究科)

2-6 Evaluation of variety of mono-valent VH-CH1-h artificial poly-clonal gamma globulin
Yosuke Kameoka, National Institute of Biomedical Innovation
モノバレント HV-CH1-h 型人工ガンマグロブリンの多様性と結合性の検討
亀岡洋祐

13:00-13:40
Special Lecture
Chair: Kazuo Suzuki, Chiba University Graduate School of Medicine

Strategy of anti-IL-6 receptor antibody therapy for autoimmune diseases
Norihito Nishimoto, Wakayama Medical College, Wakayama

13:40-14:00

Closing Remark Shiro Naoe, Toin University of Yokohama

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Shoji Kawachi, San Thi Luong, Mika Shigematsu, Hiroyuki Furuya, Thuy Thi Bich Phung, Phuc Huu Phan, Hiroyuki Nunoi, Liem Thanh Nguyen, Kazuo Suzuki.	Risk parameters of fulminant acute respiratory distress syndrome followed by avian influenza (H5N1) infection in Vietnamese children.	J. Infectious Dis.	200	510-515	2009
Yasuda H, Suzuki K.	Measures against transmission of pandemic H1N1 influenza in Japan in 2009: simulation model.	Euro Surveill.	14	14	2009
Masumitsu Hatta, Natsuo Yamamoto, Akiko Miyazato, Kiwamu Nakamura, Ken Inden, Tetsuji Aoyagi, Kazuo Suzuki, Mitsuo Kaku, Kazuyoshi Kawakami	Early production of tumor necrosis factor-α by Gr-1+CD11b+ mononuclear cells and its role in the host defense to pneumococcal infection in lungs	FEMS Immunol Med Microbiol	in press		2009
Chiaki Kaga, Shigeyuki Nomura, Mina Okochi, Tomoko Nozu, Tomokazu Nagao, Atsushi Nagai, Toshinori Nakayama, Kazuo Suzuki, Hiroyuki Honda.	Screening of epithelial cell-adhesive peptides from fibronectin loop region and its cell specificity.	J Chem. Engineering Japan	4	298-302	2009
Miura NN, Komai M, Adachi Y, Osada N, Kameoka Y, Suzuki K, Ohno N.	IL-10 is a negative regulatory factor of CAWS-vasculitis in CBA/J mice as assessed by comparison with Bruton's tyrosine kinase-deficient CBA/N mice.	J Immunol.	183(5)	3417-24	2009
Yuka Osaki, Yasuhiro Maehara, Masaki Sato, Akiyoshi Hoshino, Kenji Yamamoto, Tomokazu Nagao, Kazuo Suzuki, Shoji Kawachi.	Analysis of cytokines in broncho-alveolar lavage fluids of patients with ARDS: Increase of IL-6, G-CSF, MCP-1, MIP-1β.	JJSICM(Journal of Japanese Society of Intensive Care	in press		2009
Akihiro Hasegawa, Katsuhiro Hayashi, Hiroyuki Kishimoto, Meng Yang, Soichi Tofukuji, Kazuo Suzuki, Hiroshi Nakajima, Robert Hoffman, Mutsunori Shirai, Toshinori Nakayama	Color-coded real-time cellular imaging of T lymphocyte accumulation and focus formation in mouse asthma model	Journal of Allergy and Clinical Immunology	125	461-8	2010
Kei Takahashi, Toshiaki Oharaseki, Noriko Nagi-Miura, Naohito Ohno, Akiko Ishida-Okawara, Hitomi Yamada, Yoshiaki Kaneshiro, Shiro Naoe, Kazuo Suzuki	Administration of human immunoglobulin inhibited development of vasculitis in a murine model of vasculitis induced with CAWS, Candida albicans water soluble fraction.	Modern Reumatol	in press		2009
Tomoko Nozu, Mitsuko Kondo, Kazuo Suzuki, Jun Tamaoki, Atsushi Nagai.	A Comparison of the Clinical Features of ANCA-Positive and ANCA-Negative Idiopathic Pulmonary Fibrosis Patients.	Respiration	77	407-415	2009
橋本博史、小林茂人、藤元昭一、湯村和子、高橋啓、猪原登志子、平橋淳一、鈴木和男	血管炎の新分類基準、新治療や発症機構研究の世界的動向(前編)	日本医事新報	4470	43-51	2009

研究成果の刊行に関する一覧賞

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
橋本博史、小林茂人、藤元昭一、湯村和子、高橋啓、猪原登志子、平橋淳一、鈴木和男	血管炎の新分類基準、新治療や発症機構研究の世界的動向(後編)	日本医事新報	4472	46-52	2010
R. Tada, Y. Adachi, K. Ishibashi, N. Ohno	An unambiguous structural elucidation of a 1,3-beta-D-glucan obtained from liquid-cultured Grifola frondosa by solution NMR experiments	Carbohydr Res.	344(3)	400-404	2009
A. Miyazato, K. Nakamura, N. Yamamoto, H. M. Mora-Montes, M. Tanaka, Y. Abe, D. Tanno, K. Inden, X. Gang, K. Ishii, K. Takeda, S. Akira, S. Saijo, Y. Iwakura, Y. Adachi, N. Ohno, K. Mitsutake, N. A. Gow, M. Kaku, K. Kawakami	Toll-like receptor 9-dependent activation of myeloid dendritic cells by Deoxynucleic acids from Candida albicans	Infect Immun.	77(7)	3056-3064	2009
T. H-Hida, K. Ishibashi, N. N-Miura , Y. Adachi, Y. Shirasu, N. Ohno	Cytokine induction by a linear 1,3-glucan, curdlan-oligo, in mouse leukocytes in vitro	Inflamm Res.	58(1)	9-14	2009
T. H-Hida, H. Kawaminami, K. Ishibashi, N. N-Miura, Y. Adachi, T. Yadomae, N. Ohno	Effect of GM-CSF on cytokine induction by soluble beta-glucan SCG in vitro in beta-glucan-treated mice	Microbiol Immunol.	53(7)	391-402	2009
K. Inoue, H. Takano, E Koike, R. Yanagisawa, T. Oda, H. Tamura, Y. Adachi, K. Ishibashi, N. Ohno	Candida soluble cell wall beta-glucan facilitates ovalbumin-induced allergic airway inflammation in mice: Possible role of antigen-presenting cells	Respir Res.	10	68-79	2009
K. Uno, E Muso, T. Ito-Ihara, K.Yagi, S. Fujita, and K.Suzuki	Comparison of plasma cytokine/chemokine levels and IFN-alpha production capacity amongst healthy subjects, MPO-ANCA-positive MPA patients, IgA nephritis	APMIS	117	136	2009
T. Ito-Ihara, E. Muso, S. Kobayashi, K.Uno, N. Tamura, Y.Yamanishi, A.Fukatsu, R. A. Watts, D.G.I. Scott, D.R.W. Jayne, K.Suzuki, and H.Hashimoto.	A comparative study of the diagnostic accuracy of ELISA systems for the detection of anti-neutrophil cytoplasm antibodies available in Japan and Europe	APMIS	117	136	2009
Uno, K, Okuno K, Yagi K, Hamuro J	Prediction of overall survival through pre-operative blood plasma of colorectal cancer patients.	Cytokine	48	52	2009
Tominaga M, Uno K, Yagi K, Fukui M, Hasegawa G, Yoshikawa T, Nakamura N	Association between capacity of interferon-α production and metabolic parameters.	J IFN cyokine Res			in press
宇野賀津子	サイトカインハンティング:先頭を駆け抜けた日本人研究者達	細胞工学	Vol.28 No.11	1113-1115	2009

研究成果の刊行に関する一覧賞

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Iio K, Nagasawa Y, Iwatani H, Yamamoto R, Horii A, Okuzaki D, Furumatsu Y, Inohara H, Nojima H, Imai E, Isaka Y, Rakugi H.	Microarray analysis of tonsils in Immunoglobulin A nephropathy patients.	Biochem Biophys Res Commun.	in press	in press	2010
Nishioka, N., Inoue, K., Adachi, K., Kiyonari, H., Ota, M., Ralston, A., Yabuta, N., Hirahara, S., Stephenson., R. O., Ogonuki, N., Makita, R., Kurihara, H., Morin-Kensicki, E. M., Nojima, H., Rossant, J., Nakao, K., Niwa, H., and *Sasaki, H.	The Hippo signaling pathway components Lats and Yap pattern Tead4 activity to distinguish mouse trophectoderm from inner cell mass.	Dev Cell.	3	398-410	2009 Mar
Sato, J., Shimizu, H., Kasama, T., Yabuta, N. and Nojima, H.	GAK, a regulator of clathrin-mediated membrane trafficking, localizes not only in the cytoplasm but also in the nucleus.	Genes Cells	14	627-641	2009
Shimizu, H., Nagamori, I., Yabuta, N., and Nojima, H.	GAK, a regulator of clathrin-mediated membrane traffic, also controls centrosome integrity and chromosome congression.	J Cell Sci.	122 (Pt 17)	3145-52	2009 Sep 1
高橋啓, 大原関利章, 横内幸	急性期冠状動脈炎とその後の遠隔期硬化性病変のへの移行－成人期動脈硬化症との違い－を考察する	Jounal of Vascular Medicine	6	22-26	2010
Takahashi K, Oharaseki T, Yokouchi Y, Miura NN, Ohno N, Okawara AI, Murata H, Naoe S, Suzuki K.	Administration of human immunoglobulin suppresses development of murine systemic vasculitis induced with Candida albicans water-soluble fraction: an animal model of Kawasaki disease.	Mod Rheumatol	Epub 2009. Nov 27		2009
Yokouchi Y, Oharaseki T, Ihara F, Naoe S, Sugawara S, Takahashi K	Repeated stent thrombosis after DES implantation and localized hypersensitivity to a stent implanted in the distal portion of a coronary aneurysm thought to be a sequela of Kawasaki Disease: an autopsy report	Pathology International	60	112-118	2010
Ding L, Hanawa H, Ota Y, Hasegawa G, Hao K, Asami F, Watanabe R, Yoshida T, Toba K, Yoshida K, Ogura M, Kodama M, Aizawa Y.	Lipocalin-2/neutrophil gelatinase-B associated lipocalin is strongly induced in hearts of rats with autoimmune myocarditis and in human myocarditis.	Circ J.			in press
Isoda M, Hanawa H, Watanabe R, Yoshida T, Toba K, Yoshida K, Kojima M, Otaki K, Hao K, Ding L, Tanaka K, Takayama T, Kato K, Okura O, Kodama M, Ota Y, Hayashi J, Aizawa Y.	Expression of the peptide hormone hepcidin increases in cardiomyocytes under myocarditis and myocardial infarction.	J Nutr Biochem.			in press
Tanaka M, Yamada S, Iwasaki Y, Sugishita T, Yonemoto S, Tsukamoto T, Fukui S, Takasu K, Muso E	Impact of Obesity on IgA Nephropathy: Comparative Ultrastructural Study between Obese and Non-Obese Patients	Nephron Clin Pract	112	c71-c78	2009

研究成果の刊行に関する一覧賞

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Koyama A, Yamagata K, Makino H, Arimura Y, Wada T, Nitta K, Nihei H, Muso E, Taguma Y, Shigematsu H, Sakai H, Tomino Y, Matsuo S, Japan RPGN Registry Group.	A nationwide survey of rapidly progressive glomerulonephritis in Japan: etiology, prognosis and treatment diversity.	Clin Exp Nephrol	Dec;13(6)	633-50	2009
Shimosawa M, Sakamoto K, Tomari Y, Kamikado K, Otsuka H, Liu N, Kitamura H, Uemura K, Nogaki F, Mori N, Muso E, Yoshida H, Ono T	Lipopolysaccharide-Triggered Acute Aggravation of Mesangioproliferative Glomerulonephritis through Activation of Coagulation in a High IgA Strain of ddY Mice	Nephron Exp Nephrol.	112(4):	e81-e91	2009
Muro T, Maruyama Y, Onishi K, Saze M, Okada E, Matsuura H, Saji T	Mimicking Kawasaki disease in bur	Burns	35	594-599	2009
Takatsuki S, Ito Y, Takeuchi D, Hoshida H, Nakayama T, Matsuura H, Saji T	IVIG Reduced Vascular Oxidative Stress in Patients With Kawasaki Disease.	Circ J	73(7)	1315-8	2009
Hirono K, Kemmotsu Y, Wittkowski H, Foell D, Saito K, Ibuki K, Watanakbe K, Watanabe S, Uese K, Kanegane H, Origasa H, Ichida F, Roth J, Miyawaki T, Saji T	Infliximab reduces cytokine-mediated inflammation but does not suppress cellular infiltration of the vessel wall in refractory Kawasaki disease	Pediatr Res	65 (6)	696-701,	2009
Kobayashi T, Inoue Y, Otani T, Morikawa A, Kobayashi T, Takeuchi K, Saji T, Sonobe T, Ogawa S, Miura M, Arakawa H	Risk stratification in the decision to include prednisolone with intranvenous immunoglobulin in primary therapy of Kawasaki disease.	Pediatr Infect Dis J	28(6)	498-502	2009
佐地勉、鈴木啓之、市田蕗子、小林徹	川崎病急性期治療の最前線 冠動脈瘤を作らないための治療オプション	Pharma Medica	27 (3)	167-175	2009
荻野廣太郎、佐地勉、濱岡建城、薗部友良	特集 川崎病 －第33回禁忌川崎病研究会－ 我が国における難治性急性期川崎病に対するinfliximab療法の現状－３回の使用実態調査結果から－	Progress in Medicine	29	1722-1727	2009
佐地勉	特集にあたって （特集 成人期における川崎病安城動脈瘤を考える）	Vascular Medicine	6 (1)	1	2010
Seta N, Kobayashi S, Hashimoto H, Kuwana M	Characterization of autoreactive T-cell clones to myeloperoxidase in patients with microscopic polyangiitis and healthy individuals	Clin Exp Rheumatol.	27	826-9	2009

研究成果の刊行に関する一覧賞

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Suzuki Y, Takeda Y, Sato D, Kanaguchi Y, Tanaka Y, Kobayashi S, Suzuki K, Hashimoto H, Ozaki S, Horikoshi S, Tomino Y	Clinicoepidemiological manifestations of RPGN and ANCA-associated vasculitides: an 11-year retrospective hospital-based study in Japan	Mod Rheumatol.	Oct 10. [Epub ahead of print]		2009
小林茂人	リウマチをもっと知ろう,リウマチとうつについて	流	264	34-37	2009
Akao M, Uchida K, Kikuchi K, Yumura W, Nitta K	Short-Term Effects of Apheresis on Renal function and Proteinuria in the Treatment of Rapidly Progressive Glomerulonephritis	J TWMU	79		2009
武田真一, 湯村和子	腎炎、腎症の免疫抑制療法 ミゾリビン(プレディニン)	腎と透析	66	941-945	2009
湯村和子	臨床医学の展望2009 腎臓病学 ループス腎炎	日本医事新報	4430	69-71	2009
加藤真紀, 中澤英子, 秋元哲, 井上 真, 金敷絵里子, 目黒大志, 戸澤亮子, 武藤重明, 湯村和子, 草野英二	両側水腎症を伴ったループス腎炎、ループス腸炎の1例	日本腎臓学会誌	51	569-575	2009
湯村和子, 伊藤千春	ANCA関連血管炎の活動性と臓器傷害の評価	脈管学会誌	49	63-74	2009
Wang Y, Ito S, Chino Y, Goto D, Matsumoto I, Murata H, Tsutsumi A, Hayashi T, Uchida K, Usui J, Yamagata K, Sumida T	Laser microdissection-based analysis of cytokine balance in the kidneys of patients with lupus nephritis	Clin Exp Immunol	159	40188	2009
Koyama A, Yamagata K, Makino H, Arimura Y, Wada T, Nitta K, Nihei H, Muso E, Taguma Y, Shigematsu H, Sakai H, Tomino Y, Matsuo S	Japan RPGN Registry Group. A nationwide survey of rapidly progressive glomerulonephritis in Japan: etiology, prognosis and treatment diversity	Clin Exp Nephrol	13	633-650	2009
Hirayama K, Ishizu T, Shimohata H, Miyamoto Y, Kakita T, Nagai M, Ogawa Y, Fujita S, Hirayama A, Yamagata K, Kobayashi M, Koyama A	Analysis of T-cell receptor usage in myeloperoxidase-antineutrophil cytoplasmic antibody-associated renal vasculitis	Clin Exp Nephrol			in press
平山浩一, 小林正貴, 山縣邦弘, 小山哲夫	RPGNの治療	日本腎臓学会誌	51	107-113	2009
臼井丈一, 山縣邦弘	わが国のRPGNの現状と将来の展望	日本腎臓学会誌	51	71-83	2009
有村義宏	見逃しやすい臨床症候群—急速進行性腎炎症候群—	三鷹医人往来		15-19,	2009
Nakabayashi K, Sumiishi A, Sano K, Fujioka Y, Yamada A, Karube M, Koji H, Arimura Y, Nagasawa T.	Tubulointerstitial nephritis without glomerular lesions in three patients with myeloperoxidase-ANCA-associated vasculitis.	Clin Exp Nephrol.	13	605-613	2009
Nakabayashi K, Arimura Y, Yoshihara K, Fukuoka T, Karube M, Yamato T, Koji H, Ikegaya N, Ohtuka T, Kawashima S, Sudo M, Yamada A.	Classification of clinical subtypes, patient survival, kidney prognosis, and relapse in patients with MPO-ANCA-associated vasculitis: a single-center experience.	Mod Rheumatol.	19(4)	420-6	2009

研究成果の刊行に関する一覧賞

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
吉原堅,有村義宏	血液・膠原病　抗好中球細胞質抗体－ANCA.	診断と治療	97(9)	1911-1915	2009
有村義宏	免疫抑制療法と免疫療法—薬の上手な使い方—　腎炎,腎症の免疫抑制療法.	腎と透析	66	927-930	2009
有村義宏	腎症の免疫抑制療法　総論ミゾリビン(ブレディニン).	腎と透析	66(6)	927-945	2009
岩澤彰子,池谷紀子,齋藤督芸,要伸也,有村義宏,山田明,小川勝	症例報告　維持透析導入後も18年間MPO-ANCA高値が維持し、肺胞出血で再燃した顕微鏡的多発血管炎の１例.	透析会誌	42(10)	777-783	2009
有村義宏,川嶋聡子,吉原堅	急速進行性糸球体腎炎　ANCA関連血管炎とRPGN.	日本腎臓学会誌	51(2)	88-93	2009
藤元昭一	RPGN, ANCA関連血管炎の疫学。	日腎会誌	51	84-87	2009
川嶋聡子, 有村義宏, 中林公正, 山田　明	MPO-ANCA関連血管炎における糸球体内MPO陽性細胞および細胞外MPOについての腎病理組織学的検討.	日腎会誌	51	56-67	2009
Marumo T, Hishikawa K, Yoshikawa M, Hirahashi J, Kawachi S, Fujita T.	Histone deacetylase modulates the proinflammatory and -fibrotic changes in tubulointerstitial injury.	Am J Physiol Renal Physiol	298	F133-F141	2010
Hirahashi j, Hishikawa K, Kaname S, Tsuboi N, Wang Y, Simon DI, Stavrakis G, Shimoswa T, Xiao L, Nagahama Y, Suzuki K, Fujita T, Mayadas TN.	Mac-1(CD11b/CD18) links inflammation and thrombosis after glomerular injury	Circulation	120	1255-1265	2009
平橋淳一	ANCA関連血管炎と好中球	腎と透析	68	84-88	2010

書籍

著者氏名	論文タイトル名	書籍全体の編集者名	書籍名	出版社名	出版地	出版年	ページ
長尾朋和、鈴木和男	ANCA関連血管炎とNeutrophil Extracelular Traps(NETs、好中球細胞外補足構造)		リウマチ科	科学評論社	東京都	in press	
長尾朋和、鈴木和男	MPO-ANCA関連血管炎と血管内皮細胞		腎臓と透析	東京都医学社	東京都	in press	
鈴木和男	ANCA関連血管炎モデルマウスの新知見		脈管学	メディカルトリビューン社	東京都	in press	
鈴木和男	ナノ粒子の知恵の塊-ドラッグデリバリーシステムのイメージング		光る生き物―ここまで進んだバイオイメージング技術	技術評論社	東京都	2009	140-153
長尾朋和、鈴木和男	好中球機能異常による血管炎・腎炎		細胞	ニューサイエンス社	東京都	2009	41(2)、pp. 60-63
長尾朋和、鈴木和男	ANCA関連血管炎		ANCA関連血管炎―発症機構解析・モデルマウス・新たな治療法―炎症と免疫	先端医学社	東京都	2009	17巻(6)11月 707-713
小林茂人	アレルギー性肉芽腫性血管炎(Churg-Strauss症候群)	山口　徹、北原光夫、福井次矢	今日の治療指針　私はこう治療している	医学書院	東京都	2010	695
武曾惠理	単状糸球体硬化症.　III.治療方針・治療法.　A.一次性糸球体疾患.腎疾患・透析	飯野靖彦、槇野博史、秋澤忠男　編集	最新の治療2008-2010年度版	南江堂	東京都	2009	109-113
武曾惠理	急速進行性糸球体腎炎、ANCA関連腎炎において血漿交換療法、大量γグロブリン療法は有効なのでしょうか？　C急速性糸球体腎炎、ANCA関連腎炎	富野康日巳　監修、柏原直樹　南学正臣編集	EBM腎臓病の治療　2008-2009	中外医学社	東京都	2008	69-73
佐地勉	急性期治療　ウリナスタチン療法.		小児科臨床ピクシス9　川崎病のすべて	中山書店	東京都	2009	106-108
山縣邦弘	急速進行性糸球体腎炎：管外性増殖性糸球体腎炎	下条文武	専門医のための腎臓病学第2版	医学書院	東京都	2009	275-282

著者氏名	論文タイトル名	書籍全体の編集者名	書籍名	出版社名	出版地	出版年	ページ
臼井丈一，山縣邦弘	急速進行性糸球体腎炎：抗糸球体基底膜抗体型急速進行性糸球体腎炎とGoodpasture症候群	下条文武	専門医のための腎臓病学第2版	医学書院	東京都	2009	282-291
山縣邦弘，臼井丈一	急速進行性糸球体腎炎：A. Goodpasture症候群	富野康日己	エキスパートのための腎臓内科学初版	中外医学社	東京都	2009	125-134
山縣邦弘，臼井丈一	急速進行性糸球体腎炎：B. ANCA関連腎炎	富野康日己	エキスパートのための腎臓内科学初版	中外医学社	東京都	2009	135-145
山縣邦弘，臼井丈一	急速進行性糸球体腎炎：C. MRSA関連腎炎	富野康日己	エキスパートのための腎臓内科学初版	中外医学社	東京都	2009	146-150
山縣邦弘	急速進行性腎炎症候群	山口徹，北原光夫，福井次矢	今日の治療指針2009	医学書院	東京都	2009	438-440
山縣邦弘，臼井丈一	急速進行性糸球体腎炎は，どういう疾患ですか？	富野康日己	かかりつけ医と腎臓専門医のためのCKD診療ガイド初版	中外医学社	東京都	2009	93-98
山縣邦弘，臼井丈一	急速進行性糸球体腎炎の食事療法と薬物療法は，どうするのですか？	富野康日己	かかりつけ医と腎臓専門医のためのCKD診療ガイド初版	中外医学社	東京都	2009	151-153
湯村和子	慢性腎臓病と高齢者の腎障害.	日本老年医学学会雑誌編集委員会	老年医学update2009-10	メジカルビュー社	東京都	2009	60-68
湯村和子	Immunotactoid glomerulopathy / Fibrillary glomerulonephritis	監修：下条文武　編集：内山　聖、富野康日己	専門医のための腎臓病学第２版	医学書院	東京都	2009	462-468
湯村和子，鈴木康夫，山田秀裕，吉田俊治，磯部光章	血管炎症候群	福井次矢、黒川　清	ハリソン内科学第3版	メディカル・サイエンス・インターナショナル	東京都	2009	2189-2202

The Asia Pacific Meeting of Vasculitis and ANCA Workshop 2012

Date: March 28 (Wed) - 31(Sat), 2012
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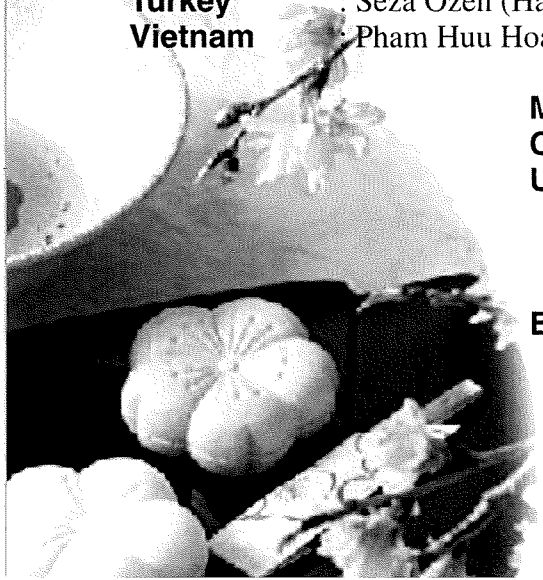

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Risk Parameters of Fulminant Acute Respiratory Distress Syndrome and Avian Influenza (H5N1) Infection in Vietnamese Children

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A clinical picture of patients with acute respiratory distress syndrome (ARDS) induced by highly pathogenic avian influenza A (H5N1) has been reported. We reviewed 37 sets of clinical data for pediatric patients with ARDS at the National Hospital of Pediatrics (Hanoi, Vietnam); 12 patients with H5N1-positive and 25 with H5N1-negative ARDS were enrolled. The H5N1-negative patients had a clinical picture and mortality rate similar to that for the pediatric ARDS patients. However, the H5N1-positive patients had ARDS with normal ventilation capacity at the time of hospital admission, then rapidly proceeded to severe respiratory failure. The survival probability and days until final outcome in groups of H5N1-positive ($n = 12$) vs. H5N1-negative ($n = 25$) patients were 17% versus 52% and 12.3 ± 5.7 days (median, 11 days) versus 21.5 ± 13.8 days (median, 22 days), respectively. Our observations clarified the clinical picture of H5N1-induced fulminant ARDS and also confirmed that relatively older age (~6 years of age), high fever at onset, and leukopenia and/or thrombocytopenia at the time of hospital admission are risk parameters for H5N1-induced fulminant ARDS.

Highly pathogenic avian influenza A (H5N1) came to the attention of the international scientific community for the first time in 1997 [1, 2]. The current global spread of human infection by this subtype started in 2003 in Hong Kong [2, 3], during the global outbreak of severe acute respiratory syndrome [4, 5]. Vietnam reported the first human case of H5N1 infection in January 2004 [6] and a suspected human-to-human transmission family cluster in the following months [7]. Since then, many clinical case reports have been reported from several countries, such as Thailand, Indonesia, and Vietnam [8–14]. However, it is still difficult to detect most infection at first examination without a clear history of patient contact with sick poultry.

The fatality rate associated with pediatric acute respiratory distress syndrome (ARDS) has decreased during recent decades because of advances in medical treatment, especially respiratory management as a lung-protective therapy [15]. However, the majority of patients with H5N1 subtype influenza virus infection experienced or presented ARDS during their clinical courses, often followed by a serious outcome. The histopathology of these cases demonstrated diffuse alveolar damage in the lung, which also suggests ARDS as a clinical condition of the respiratory system [16–18]. Because of the significant possibility that H5N1 subtype influenza will the source of the next pandemic influenza strain [19, 20], the pathophysiology of the clinical course of H5N1

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Table 1. Clinical Features of H5N1-Positive and H5N1-Negative Patients

Feature	H5N1-positive patients (n = 12)		H5N1-negative patients (n = 25)		P
	Mean value ± SD	Median value	Mean value ± SD	Median value	
Age, year	6.7 ± 3.9	6	1.2 ± 2.9	0.3	<.001
pH	7.46 ± 0.07	7.49	7.29 ± 0.17	7.32	<.001
PaO_2, mmHg	61.4 ± 59.3	41.9	58.9 ± 23.8	58.6	.253
$PaCO_2$, mmHg	33.2 ± 12.4	32.5	47.5 ± 18.1	41.3	.009
FiO_2	0.81 ± 0.28	1	0.82 ± 0.27	1	.987
Body temperature at onset, °C	39.1 ± 0.4	39	37.7 ± 1	37.8	<.001
WBC count, cells/mm^3[a]	2863.6 ± 1545	2300	13,376 ± 9478	11,000	<.001
Platelet count × 10^3, cells/mm^3[a]	123.5 ± 52.3	125	366 ± 179.5	374	<.001
AST level, IU/L[a]	1723 ± 2784	724	259 ± 653	105	<.001
ALT level, IU/L[a]	628 ± 1042	248	221 ± 845	40	<.001

Variable	H5N1-positive patients, no. (%) of patients (n = 12)	H5N1-negative patients, no. (%) of patients (n = 25)	P
Prognosis			
Alive	2 (16.7)	13 (52.0)	.091
Dead	10 (83.3)	12 (48.0)	
Sex			
Male	8 (66.7)	8 (32.0)	.046
Female	4 (33.3)	17 (68.0)	
Multiple organ failure			
Yes	1 (8.3)	18 (72.0)	<.001
No	11 (91.7)	7 (28.0)	

NOTE. P values <.05 indicate statistically significant differences between H5N1-positive and H5N1-negative groups. ALT, alanine aminotransferase; AST, aspartate aminotransferase; SD, standard deviation; WBC, white blood cell.

[a] WBC and platelet counts were available for only 11 H5N1-positive patients, and AST and ALT levels were available for only 7 H5N1-positive patients and 23 H5N1-negative patients.

influenza virus infection and the identification of the key objective clinical data are crucial pieces of information that will help physicians provide timely and adequate treatment.

In the present study, we reviewed the clinical data from pediatric ARDS cases to identify distinctive findings of cases of H5N1 subtype influenza virus infection among Vietnamese children. This work was performed in close collaboration with the National Hospital of Pediatrics (NHP) in Hanoi and was supported by the Ministry of Health, Labour, and Welfare in Japan and the Ministry of Health in Vietnam.

MATERIALS AND METHODS

Data source. Clinical and laboratory data for pediatric patients (aged >1 month) with severe illness examined at the NHP from December 2003 through June 2008 were analyzed. Patients examined prior to 2007 were enrolled in the study retrospectively by hospital record review and were followed prospectively after hospital admission. The diagnosis of ARDS was made according to international standards [21], which involve acute onset; PaO_2/FiO_2 ratio (P/F ratio) <200, independent of controlled mechanical ventilation; and bilateral infiltration observed on chest radiography without left heart failure or with pulmonary artery wedge pressure <18 mmHg. We enrolled patients with severe ARDS whose P/F ratios were <100 during their clinical courses. H5N1 infection was confirmed with throat and/or nasal swabs tested by reverse-transcriptase polymerase chain reaction at the hospital laboratory or at the National Institute of Hygiene Epidemiology (Hanoi). The study was reviewed by the ethical committee of the International Medical Center Japan in 2007, and the design was approved on 28 September 2007.

Statistical methods. Fisher's exact test was employed for bivariate analysis of categorical data. The nonparametric Mann-Whitney test was used for 2-group comparisons of continuous data. Survival curves and rates were calculated by the Kaplan-Meier method. The log-rank (Mantel-Cox) test was used for the comparison of 2 survival curves. All statistical analyses were performed with SPSS, version 14.0 (SPSS).

RESULTS

Thirty-nine patients with ARDS who met the inclusion criteria visited the hospital during the study period, but 2 were excluded

Table 2. Summary of All Clinical Data

Patient	Sex	Age, years	Duration,[a] days	Prognosis		BT at onset, °C	Blood pH	Respiratory parameters				Liver function levels, IU/L		Blood counts[b]			Cause of ARDS
				Death	MOF			PaO_2, mmHg	$PaCO_2$, mmHg	P/F	Lowest P/F	AST	ALT	WBC	RBC	PLT	
H5N1 positive (n = 12)																	
1	F	12	7	Yes	Yes	39.5	7.48	29.1	30.7	29	29	NT	NT	2100	4510	45	Pneumonia (H5N1)
2	M	5	16	Yes	No	39.0	7.49	70.3	35.0	70	35	NT	NT	3400	4380	174	Pneumonia (H5N1)
3	M	10	11	Yes	No	39.5	7.51	33.5	28.1	84	24	NT	NT	2800	3750	143	Pneumonia (H5N1)
4	F	5	7	Yes	No	39.5	7.34	29.1	54.1	29	29	NT	NT	1100	3980	91	Pneumonia (H5N1)
5	M	4	15	Yes	No	39.5	7.5	40.9	26.1	41	36	NT	NT	2300	4190	150	Pneumonia (H5N1)
6	F	1	6	Yes	No	38.5	7.41	76.1	26.2	190	34	1121	484	NT	NT	NT	Pneumonia (H5N1)
7	M	1.3	9	Yes	No	39.0	7.52	243.0	9.3	607	65	8010	2972	1400	2190	31	Pneumonia (H5N1)
8	M	11	11	Yes	No	39.0	7.54	34.0	22.0	34	34	801	217	4800	4500	125	Pneumonia (H5N1)
9	F	9	26	No	No	39.5	7.47	42.8	34.2	43	43	312	248	6300	3970	122	Pneumonia (H5N1)
10	M	4	12	Yes	No	38.5	7.44	31.4	43.1	31	18	583	89	2300	4220	154	Pneumonia (H5N1)
11	M	7	18	No	No	38.5	7.49	58.0	41.0	116	97	511	105	3300	398	116	Pneumonia (H5N1)
12	M	11	10	No	No	39.5	7.55	52.0	29.6	52	49	724	282	1700	4530	207	Pneumonia (H5N1)
H5N1 negative (n = 25)																	
13	F	4	2	Yes	Yes	38.8	7.33	58.6	32.4	59	52	77	49.5	9300	2990	83	Pneumonia
14	M	0.2	23	No	Yes	34.3	7.35	34.5	41.3	35	31	142	67	3250	4030	57	Pneumonia
15	M	0.2	53	No	No	37.4	7.37	74.5	29.6	186	50	NT	NT	29200	4250	547	Unknown
16	F	3	29	No	Yes	38.5	7.19	25.0	50.0	25	25	55	36	4000	3030	37	Pneumonia
17	F	3	19	Yes	Yes	39.0	7.31	34.5	40.5	35	35	284	55	1600	3910	352	Pneumonia
18	M	0.4	2	Yes	Yes	38.5	7.32	108.0	28.2	108	47	120	31	4200	NT	332	Pneumonia
19	F	0.33	8	Yes	Yes	38.5	7.30	108.4	31.4	108	38	126	31	9500	3680	374	Pneumonia
20	F	0.18	10	Yes	Yes	37.2	7.29	67.0	43.0	67	31	105	37	19100	3690	448	Pneumonia (rhinovirus)
21	F	0.18	13	No	Yes	38.5	7.37	63.0	56.0	63	33	79	16	4200	3910	403	Pneumonia (rhinovirus)
22	F	0.18	6	Yes	Yes	37.5	7.31	24.0	56.5	24	24	77	44	23900	3640	534	Pneumonia (adenovirus)
23	F	0.25	8	Yes	Yes	38.0	7.23	42.7	75.7	43	26	287	51	16900	3450	176	Pneumonia (rhinovirus)
24	F	0.18	22	Yes	Yes	36.0	7.15	25.7	55.1	26	26	219	69	11000	3980	442	Pneumonia (rhinovirus)
25	F	0.25	5	Yes	Yes	37.8	6.61	75.6	113.6	76	76	196	40	14800	4010	590	Pneumonia
26	M	0.25	38	No	Yes	38.5	7.32	48.4	37.0	121	21	78	36	19000	4660	430	Pneumonia (bacterial)
27	F	14	12	No	Yes	37.5	7.45	95.1	37.0	95	95	3235	4097	28000	3510	278	Pneumonia
28	M	0.33	19	No	No	37.2	7.19	43.0	59.0	43	43	246	50	8600	3360	342	Pneumonia
29	M	0.25	36	No	Yes	36.9	7.32	39.0	40.0	98	49	83	25	1950	3200	497	Unknown
30	F	0.2	14	No	No	37.5	7.39	88.6	38.0	89	89	36	108	5300	5180	322	Pneumonia (bacterial)
31	F	0.12	35	No	Yes	37.2	7.41	61.0	41.0	153	55	118	52	13700	8480	592	Pneumonia
32	F	0.33	44	No	No	37.5	7.15	48.0	45.0	48	30	NT	NT	8800	4480	58	Pneumonia
33	F	0.2	35	No	Yes	38.5	7.30	70.0	31.0	175	49	99	38	28400	4290	532	Pneumonia
34	F	0.2	35	No	No	36.5	7.22	61.0	38.4	153	66	71	59	11400	3680	330	Pneumonia
35	M	0.25	22	Yes	Yes	38.0	7.47	58.0	63.0	73	22	46	14.6	10800	4140	508	Pneumonia (adenovirus)
36	F	0.2	23	Yes	No	38.6	7.36	65.0	50.0	65	27	111	27	12000	3440	233	Pneumonia
37	M	0.2	24	No	No	38.5	7.42	55.0	54.0	138	47	65	38	35500	3540	654	Unknown

NOTE. ALT, alanine aminotransferase; ARDS, acute respiratory distress syndrome; AST, aspartate aminotransferase; BT, body temperature; MOF, multiple organ failure; NT, not tested; P/F PaO_2/FiO_2 ratio; PLT, platelet; RBC, red blood cell; WBC, white blood cell.

[a] The duration represents the time from onset of illness to death or hospital discharge.

[b] WBC and RBC counts are cells/mm^3; PLT counts are 10^3 cells/mm^3.

because of insufficient medical data. Twelve of 37 patients were shown to be positive for H5N1 influenza by polymerase chain reaction performed in the laboratory of the NHP (table 1).

Most patients in the H5N1-positive group experienced rapid deterioration of ARDS and died of respiratory failure even with proper medical care. Although 3 patients had thrombocytopenia (patients 1, 4, and 7) and 7 (patients 6–12) had increased serum aminotransferase levels (table 2), multiple organ failure was not followed by pathological investigation for H5N1-positive patients (data not shown).

The P/F ratio of all patients enrolled in this study was <100 during their clinical courses. However, $PaCO_2$ level at hospital admission was lower among H5N1-positive than among the H5N1-negative patients, illustrating that ventilation capacity was higher in the H5N1-positive group, compared with the H5N1-negative group. These clinical features of ARDS in the H5N1-negative group made us wonder why ARDS in the H5N1-positive group was not more severe than that in the H5N1-negative group on hospital admission. The survival probability and days until final outcome (± standard deviation) among H5N1-positive ($n = 12$) and H5N1-negative ($n = 25$) patients were 17% and 52% and 12.3 ± 5.7 days (median, 11 days) and 21.5 ± 13.8 days (median, 22 days), respectively, demonstrating that the survival probability in the H5N1-positive group was significantly lower than that in the H5N1-negative group ($P = .022$, by log-rank test; $P = .038$, by Tarone-Ware test) (figure 1). These observations are the first step toward examining the clinical data for the H5N1-positive patients, which we designated as having fulminant ARDS.

As summarized in table 1, leukopenia and thrombocytopenia were observed in the H5N1-positive group, but leukophilia and normal-range thrombocyte levels were observed in the H5N1-negative group. Serum aspartate aminotransferase and alanine aminotransferase levels were also increased in the H5N1-positive but not the H5N1-negative group. Clinically, body temperature at illness onset in the H5N1-positive group was significantly higher than that in the negative group. We observed differences in clinical features between the H5N1-positive and H5N1-negative groups; we also analyzed differences with regard to sex, age distribution, and prognosis between these groups. The number of male patients in the H5N1-positive group was significantly higher than that in the H5N1-negative group, and H5N1-positive patients were significantly older than those in the H5N1-negative group. The mean time from illness onset until death (± standard deviation) was 10.4 ± 3.3 days (median, 10.5 days) in H5N1-positive group ($n = 10$) and 11.7 ± 3.3 days (median, 9 days) in H5N1-negative group ($n = 12$), and the mean time until hospital discharge (recovery) was 26 ± 18 days (median, 22 days) in the H5N1-positive group ($n = 2$) and 30.5 ± 11.8 days (median, 35 days) in the H5N1-negative group ($n = 13$). No significant differences were observed between groups with regard to time from illness onset to death.

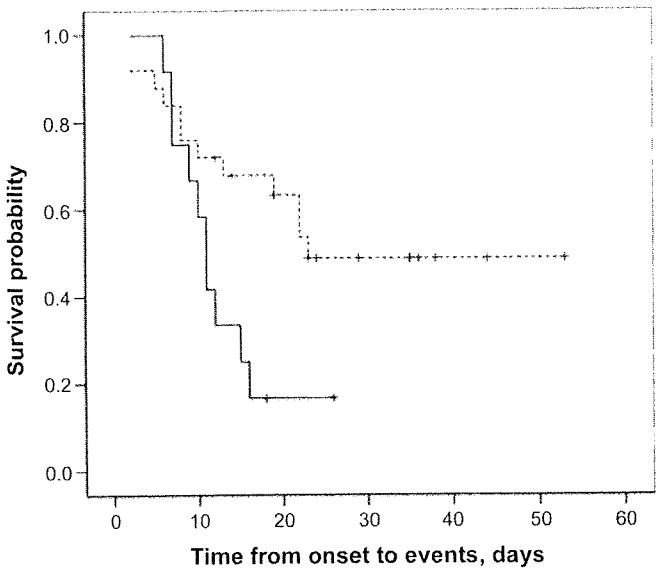

Figure 1. Survival probability for H5N1-positive (*solid line*) and H5N1-negative (*dashed line*) patients. For differences between 2 groups, $P = .022$ (by log-rank test) and $P = .038$ (Tarone-Ware test). The duration (± standard deviation) with disease until final outcome was 12.3 ± 5.7 days (median,. 11 days) for the H5N1-positive group and 21.5 ± 13.8 days (median, 22 days) for the H5N1-negative group.

DISCUSSION

H5N1-infected patients were significantly older than patients in the comparator group. To our knowledge, the mortality rate by age has not been discussed precisely for pediatric patients with ARDS; Flori et al [22] collectively discussed age and mortality in their analysis of 328 patients with ARDS who were aged between 36 weeks (corrected gestational age) and 18 years, and the mortality rate among patients with a P/F ratio <100 was ~35%. The observed significant difference in mortality rate by age could prove that relatively older age (6.7 ± 3.9 vs 1.2 ± 2.9 years) is one of the risk factors for H5N1 infection.

ARDS frequently results in a lethal outcome attributable not only to respiratory failure but also to multiple organ failure [15, 23, 24]. Our study confirmed that survival of patients with ARDS aged <16 years is drastically improved by medical care, but that these patients die of respiratory failure and multiple organ failure [14]. On the other hand, most patients in the H5N1-positive group still showed rapid progress and deterioration of ARDS and died of respiratory failure, even with proper medical care followed by pathological investigation. Although aspartate aminotransferase and alanine aminotransferase levels were higher in the H5N1-positive but not the H5N1-negative group, the elevation of serum aminotransferase levels is a relatively common feature in H5N1 patients [6, 9, 25]. A

review of 2 groups of patients in large case studies has shown that elevated aminotransferase levels are not thought to be specific in H5N1 patients [26, 27]. These observations strongly suggest that H5N1-infected patients die because of rapidly progressive respiratory failure before revealing typical multiple organ failure status accompanied by failure of multiple organs such as liver, heart, and kidney.

Physiologically, we further analyzed data regarding the P/F ratio, which is a good parameter of oxygenation capacity for respiratory function. P/F ratios were <100 in both H5N1-positive and -negative patients, which means that the oxygenation capacity in both groups was severely damaged. Surprisingly, $PaCO_2$ levels revealed that ventilation capacity was normal in H5N1-positive patients but was severely damaged in H5N1-negative patients with ARDS; that is, H5N1-negative patients experienced more severe respiratory failure than did H5N1-positive patients on hospital admission. The log-rank test and the more severely conditioned Tarone-Ware test also showed a significant difference in survival probability between the H5N1-positive and H5N1-negative groups. H5N1-positive patients started with normal ventilation capacity on hospital admission, then rapidly proceeded to severe respiratory failure and death. Patients in the H5N1-positive group demonstrated a shorter duration until final outcome than patients in the H5N1-negative group; therefore, we designated these as fulminant ARDS patients. The initial check of blood gas levels may be an early diagnostic indicator of H5N1 infection. There may also be some mechanisms that influence cell activity during H5N1 infection and accelerate alveolar damage, resulting in death [28, 29]. Pathology and immunomodulator activity in H5N1 infection have been discussed elsewhere [30], but precise mechanisms have not been clarified yet [31].

Body temperature was significantly higher in H5N1-positive patients at the onset of disease, compared with H5N1-negative patients. This seasonal influenza-like symptom appears early in the course of the disease, with a body temperature >38°C in almost all infected patients [26]. Significant leukopenia and thrombocytopenia were observed in the H5N1-positive group ($P < .001$). Leukopenia and thrombocytopenia are observed in the majority of patients with H5N1 [26, 27]. There has been some discussion of the possibility that lymphopenia and increased levels of lactate dehydrogenase at presentation are associated with a poor prognosis [27]. Further investigation into lymphopenia and liver function in H5N1 patients is necessary for clarification.

We have demonstrated here that H5N1 infection with ARDS starts with high fever but relatively mild respiratory symptoms, then proceeds to serious respiratory failure with lower survival probability and shorter periods of illness (fulminant ARDS), compared with ARDS without H5N1 infection. Leukopenia, thrombocytopenia, and liver function on hospital admission might be risk parameters and early indicators of patients with H5N1 influenza virus infection.

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References

1. Shortridge KF, Zhou NN, Guan Y, et al. Characterization of avian H5N1 influenza viruses from poultry in Hong Kong. Virology **1998**; 252:331–42.
2. Bridges CB, Katz JM, Seto WH, et al. Risk of influenza A (H5N1) infection among health care workers exposed to patients with influenza A (H5N1), Hong Kong. J Infect Dis **2000**; 181:344–8.
3. Peiris JSM, Yu WC, Leung CW, et al. Re-emergence of fatal human influenza A subtype H5N1 disease. Lancet **2004**; 363:617–9.
4. WHO guidelines for the global surveillance of severe acute respiratory syndrome (SARS). Updated recommendations, October **2004**.
5. Peiris JS, Lai ST, Poon LL, et al; SARS study group. Coronavirus as a possible cause of severe acute respiratory syndrome. Lancet **2003**; 361: 1319–25.
6. Hien TT, Liem NT, Dung NT, et al; for the World Health Organization International Avian Influenza Investigative Team, Farraret J. Avian influenza A (H5N1) in 10 patients in Vietnam. N Engl J Med **2004**; 350: 1179–88.
7. Ungchusak K, Auewarakul P, Dowell SF, et al. Probable person-to-person transmission of avian influenza A (H5N1). N Engl J Med **2005**; 352: 333–40.
8. Apisarnthanarak A, Kitphati R, Thongphubeth K, et al. Atypical avian influenza (H5N1). Emerg Infect Dis **2004**; 10:1321–4.
9. Chotpitayasunondh T, Ungchusak K, Hanshaoworakul W, et al. Human disease from influeanza A (H5N1), Thailand, 2004. Emerg Infect Dis **2005**; 11:201–9.
10. Uiprasertkul M, Puthavathana P, Sangsiriwut K, et al. Influenza H5N1 replication sites in humans. Emerg Infect Dis **2005**; 11:1036–41.
11. Oner AF, Bay A, Arslan S, et al. Avian influenza A (H5N1) infection in eastern Turkey in 2006. N Engl J Med **2006**; 355:2179–85.
12. Kandun N, Wibisono H, Sedyaningsih ER, et al. N Engl J Med **2006**;355: 2186–94.
13. Sedyaningsih ER, Isfandari S, Setiawaty V, et al. Epidemiology of cases of H5N1 virus infection in Indonesia, July 2005-June 2006. J Infect Dis **2007**; 196:522–7.
14. Kandun N, Tresnaningsih E, Purba WH, et al. Factors associated with case fatality of human H5N1 virus infections in Indonesia: a case series. Lancet **2008**; 372:744–9.
15. Anderson MR. Update on pediatric acute respiratory distress syndrome. Respir Care **2003**; 48:261–78.
16. The Writing Committee of the World Health Organization Consultation (WHO) on Human Influenza A/H5. Avian influenza A (H5N1) infection in humans. N Engl J Med **2005**; 353:1374–85.
17. Liem NT, Nakajima N, Phat lP, et al. H5N1-Infected cells in lung with diffuse alveolar damage in exudative phase from a fatal case in Vietnam. Jpn J Infect Dis **2008**; 61:157–60.
18. Korteweg C, Gu J. Pathology, molecular biology, and pathogenesis of avian influenza A (H5N1) infection in humans. Am J Pathol **2008**; 172:1155–70.
19. Marmel LA. Pandemic avian influenza. Lancet Infect Dis **2005**; 5:666–7.
20. McFee, RB. Avian influenza: the next pandemic? Dis Mon **2007**; 53: 348–7.
21. Bernard GR, Artigas A, Brigham KL, et al. The American-European

consensus conference on ARDS: definitions, mechanisms, relevant outcomes, and clinical trial coordination. Am J Respir Crit Care Med **1994**; 149:818–24.
22. Flori HR, Glidden DV, Rutherford GW, Matthay MA. Pediatric acute lung injury: prospective evaluation of risk factors associated with mortality. Am J Respir Crit Care Med **2005**; 171:995–1001.
23. Ware LB, Matthay MA. The acute respiratory distress syndrome. N Engl J Med **2000**; 342:1334–49.
24. Bernard G. Acute respiratory distress syndrome: a historical perspective. Am J Respir Crit Care Med **2005**; 172:798–806.
25. Yu H, Shu Y, Hu S, et al. The first confirmed human case of avian influenza A (H5N1) in mainland China. Lancet **2006**; 367:84.
26. Arabi Y, Gomersall CD, Ahmed QA, Boynton BR, Memish ZA. The critically ill avian influenza A (H5N1) patient. Crit Care Med **2007**; 35:1397–403.
27. Writing Committee of the Second World Health Organization Consultation on Clinical Aspects of Human Infection with Avian Influenza A (H5N1) Virus. Update on avian influenza A (H5N1) virus infection in humans. N Engl J Med **2008**; 358:261–73.
28. Daidoji T, Koma T, Du A, et al. H5N1 avian influenza virus induces apoptotic cell death in mammalian airway epithelial cells. J Virol **2008**; 82:11294–307.
29. Imai Y, Kuba K, Neely GG, et al. Identification of oxidative stress and toll-like receptor 4 signaling as a key pathway of acute lung injury. Cell **2008**; 133:235–49.
30. Gu J, Xie Z, Gao Z, et al. H5N1 infection of the respiratory tract and beyond: a molecular pathology study. Lancet **2007**; 370:1137–45.
31. Korteweg C, Gu J. Pathology, molecular biology, and pathogenesis of avian influenza A (H5N1) infection in humans. Am J Pathol **2008**; 172:1155–70.

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Screening of Epithelial Cell-Adhesive Peptides from Fibronectin Loop Region and Its Cell Specificity

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Using a peptide array-based cell system, screening of cell adhesive peptides has been investigated against two epithelial-type cells, such as mouse lung epithelial cell (mLEC) and mouse glomerular epithelial cell (mGEC), and one endothelial cell such as human umbilical vein endothelial cell (HUVEC). When 63 pentamer peptide sequences of human fibronectin type III domain were synthesized on the cellulose membrane assayed, GSKST (No. 124) and GLKPG (No. 126) showed high adhesion activity against all three type cells. The adhesion pattern of mGEC using the library was different from mLEC. Eight adhesive peptides were found for mGEC as peptides with higher adhesion activity compared with HUVEC. It was found that the adhesion pattern of mLEC was similar to that of human mesenchymal stem cell (MSC), not HUVEC. The results suggest that a tissue specific adhesion peptides can be designed, which has the potential for the development of a tissue specific molecular tag.

Introduction

Peptides are signal molecules for mammalian cells, which can promote cell proliferation, cell differentiation, and cell death by way of signaling pathway. We have recently developed a peptide array-based cell assay system that allows for screening of bioactive peptides. Peptide arrays, developed as the SPOT method by Frank (2002), are a designable peptide library that is covalently synthesized on a cellulose-support and have been applied to various interaction assays (Kumer and Schneider-Mergener, 1998; Frank, 2002). By the cell assay system, we have screened cell adhesion peptides (Kato *et al.*, 2006) and cell death inducible peptides (Okochi *et al.*, 2006; Kaga *et al.*, 2008). For screening of cell adhesion peptides, we constructed oligopeptide array covering peptide sequences from fibronectin (Kato *et al.*, 2006) or laminin (Nomura *et al.*, 2008), which is well known as an adhesive protein and exists in tissues as an extracellular matrix. Each cell such as fibroblast and keratinocyte was seeded on the peptide library and some adhesive peptides were successfully found, which were RYYR, YIIR, RITY, and GSKS for fibrobrast and DWKLVR and GLRLLI for keratinocyte, respectively. This system has high potential ability for adhesive peptide screening. In other previous studies using fibronectin library, ALNGR was also found as an adhesive peptide for human mesenchymal stem cell, which is multipotent cell resident in the bone marrow (Okochi *et al.*, 2008). In other previous studies, when randomized peptide library was fabricated, adhesive peptides for fibroblast were screened and combined with computational analysis (Kaga *et al.*, 2008). Sixty newly designed adhesive peptides were obtained and especially GKFQ showed 3.3 times higher adhesive

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Table 1 Medium composition for mLEC and mGEC

Components	Suppliers	Amount	
mLEC medium			
DMEM	SIGMA		
L-Glutamine	GIBCO	2	mM
Sodium pyruvate	GIBCO	1	mM
2-Mercaptoethanol	GIBCO	50	μM
Non-essential amino acid	GIBCO	1	%
Endothelial cell growth supplement	Upstate	150	μg/mL
Penicillin/Streptomycin	GIBCO	1	%
FBS	SIGMA	20	%
Hepalin solution	Shimizu Pharmaceutical Co.	12	U/mL
mGEC medium			
RPMI-1640	SIGMA		
VEGF	PeproTech	0.1	ng/mL
EGF	SIGMA	2	ng/mL
bFGF	SIGMA	2	ng/mL
Hepalin solution	Shimizu Pharmaceutical Co.	4	unit/mL
FBS	SIGMA	20	%
Penicillin/Streptomycin	GIBCO	1	%
Hydrocortisone	SIGMA	1	μg/mL

activity compared with that of RGDS, which is the integrin-binding ligand from fibronectin.

In the present study, screening of adhesive peptides for epithelial cells (ECs) is demonstrated by a peptide array-based cell assay system. Two ECs such as mouse lung epithelial cell (mLEC) and mouse glomerular epithelial cell (mGEC) were assayed on peptide library spotting 64 peptides from a fibronectin outer loop. A specific adhesive peptide sequence for each cell was selected, and the possibility of a tissue specific targeting molecule was suggested compared with human umbilical vein endothelial cell (HUVEC).

1. Experimental

Mouse lung epithelial cell (mLEC) and mouse glomerular epithelial cell (mGEC) were isolated from a C57 BL6 mouse 9 weeks old as a primary cell, according to the guidelines approved by the National Institute of Infectious Diseases Animal Care and Use Committee (Nagao *et al.*, 2007). The medium listed in **Table 1** was used for cell cultivation.

Peptides partly covering the human fibronectin type-III domain (Swiss-Prot No. P02751) were selected and constructed on a cellulose membrane. A peptide array was prepared by Fmoc chemistry using the SPOT-synthesis method employing a peptide auto-spotter (ASP222, INTAVIS Bioanalytical Instruments AG) as described previously (Kumer and Schneider-Mergener, 1998; Frank, 2002). Sixty-three pentamer peptide sequences, which were shifted by one amino acid, were constructed. Fmoc amino acid of 0.5 mM was spotted on an activated cellulose membrane, and consequently the synthesized peptide spot of 6 mm diameter was constructed. According to this method, the C-terminal end of the peptide was anchored on the surface of the cellulose membrane. Positive and negative control sequences were RGDS and AAAAA, respectively. Each spot was punched out by a cork borer with a 6 mm diameter to put into the 96-well plate after the protective group-degraded, washed, and the completely dried. A fresh serum-free medium listed in Table 1 was added in each well to embed a peptide disk, and EC cells (5,000 cells/well) were directly incubated for 5 h at 37°C under 5% CO_2. After washing the non-adhered cells with phosphate-buffered saline (PBS), a calcein AM solution (Invitrogen Co.) was added to each well for a final concentration of 20 μg/mL, and the fluorescent intensity (FI) was measured using a fluorescence plate reader (Fluoroskan Ascent, Labsystems Co.) after 1 h. The relative cell adhesion ratio was defined by the following equation as the ratio of the number of viable cells remaining on the peptide disk as compared with both that with no peptide and that with RGDS peptide. The relative cell adhesion ratio from cells remaining on RGDS peptide was calculated to be 1.0 and that on no peptide to be zero.

$$\text{Relative adhesion ratio} = \frac{(\text{FI on peptide of interest} - \text{FI on no peptide})}{(\text{FI on RGDS peptide} - \text{FI on no peptide})}$$

The adhesion ratio for human umbilical vein endothelial cell (HUVEC) was also investigated to compare with that of ECs.