NEWSLETTER OF THE HONG KONG COLLEGE OF PATHOLOGISTS PARTIE OF THE HONG KONG COLLEGE OF PATHOLOGISTS

The Hong Kong College of Pathologists, Incorporated in Hong Kong with Limited Liability

Message from the President

Pathology is an important element in medicine. Such importance has been increasingly acknowledged in professional and general community. Our College has been active in several professional activities to maximize our impact to improve the community health.

A Working Group on Genetic and Genomics has been set up by the Hong Kong Academy of Medicine in 2014 to coordinate the training in this field with college representatives from Community Medicine, Obstetricians and Gynaecologists, Paediatricians, Pathologists and Physicians. Professor Rossa Chiu and I are representatives of our College in this group. Our College has also correspondingly set up a Task Force on Training for Genetics and Genomics, including Specialty Board Chairmen and Chief Examiners of various specialties to prepare syllabus and training options.

Locally, several Fellows and I have been involved as members in the Task Force of the Colorectal Cancer Screening Pilot Programme, expressing our opinions to ensure quality of pathology service in the programme. I have also been invited to join in the Cancer Expert Working Group on Cancer Prevention and Screening as our College representative. Such representation reflects that the contribution of pathology is increasingly recognized.



▲ The President (front row, 4th from left) attending the International Liaison of Pathology Presidents (ILPP) meeting in Chicago in November 2014.

Our College will continue to participate in media programmes coordinated by the Academy to explain our work and the contribution of our specialty to patients. In liaison with the international pathology community, activities related to the International Pathology Day are being planned to be conducted in the later part of 2015. The aim is to let the public understand our work better.

Internationally, we shall continue the collaboration with sister organizations in various countries both individually and collectively through associations such as International Liaison Pathology Presidents (ILPP) and World Association of Societies of Pathology & Laboratory Medicine (WASPaLM).

I believe that the future of pathology profession is challenging but promising. Fellows are most welcome to share opinions with the College so that our work can continue to be improved.

Prof CHEUNG Nga Yin Annie







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Dr. WONG Lap Gate, Michael

The 23rd Annual General Meeting 2014 and T.B. Teoh Foundation Lecture

The 23rd Annual General Meeting (AGM) was held after the 10th Trainee Presentation Session on 29th November, 2014. Dr SHUM Shui Fung Bobby was elected as Vice-President, succeeding Dr MA Shiu Kwan Edmond. Dr WONG Lap Gate Michael was elected as Honorary Treasurer to fill the vacancy left behind by Dr CHAN Kui Fat. Dr CHAN Kui Fat, Dr IP Pun Ching Philip, Dr LAI Sai Chak and Dr LO Yee Chi Janice were elected as Council Members. We would like to take this opportunity to thank immediate past Vice President Dr MA Shiu Kwan Edmond and immediate past Council Member Dr TSANG Ngai Chong Dominic for their contribution to the College.

(Left to right) Dr LUKWei Kwang, Dr LI Kwok Tung Donald (President of HKAM), Prof CHEUNG Nga Yin Annie, Prof HO Pak Leung, Dr KO Wing Man (Secretary for Food and Health) and Dr LEE Kam Cheong at the AGM reception.





The Council (2014-2015).



▲ Group photo of Guests, Council Members, new Fellows and new Members.



In the Conferment Ceremony, 9 Fellows and 6 Members were admitted to the College. The honourable guests included Dr LI Kwok Tung Donald (President of the Hong Kong Academy of Medicine) and Dr Hon LEUNG Ka Lau (Member of the Legislative Council of Hong Kong, Medical Functional Constituency). College President Prof CHEUNG Nga Yin Annie shared with the audience the opportunities and threats the College is facing.

Officers of the Council reporting at the AGM.



New Fellows admitted by the President.





The 23rd T.B. Teoh Foundation Lecture was delivered by Prof CHAN Kay Sheung Paul, Chairman, Department of Microbiology, The Chinese University of Hong Kong. In the lecture titled "The Multiple Faces of Papillomavirus", Prof Chan enlightened the audience on the various aspects of papillomavirus. Guests and members of the college enjoyed the subsequent Chinese banquet dinner.

We would like to thank Dr Regina LO for being the Mistress of Ceremonies in the AGM. We thank Ms CHONG Lai Shan and Mr WONG Hon Chiu for taking photos during the Trainee Presentation Session, AGM, Conferment Ceremony, T.B. Teoh Foundation Lecture and the dinner. We would also like to express our gratitude towards our College Secretary, Ms Adrienne YUNG, as well as Ms Maizie CHAN and Ms Heidi CHU, for their continuous support in organizing the AGM.

Looking forward to seeing you all in the coming AGM.



▲ Dr Hon LEUNG Ka Lau (left) enjoying the company of pathologists at the banquet.



▲ Prof CHAN Kay Sheung Paul delivers the 23rd T.B. Teoh Foundation Lecture.



A/Prof Peter STEWART President of RCPA, speaks at the Conferment Ceremony.



The 10th Trainee Presentation Session

The 10th Trainee Presentation Session was successfully held in the afternoon on 29 November 2014. Five senior fellows in different disciplines kindly agreed to be judges: Prof Allen K.C. CHAN (Chemical Pathology, Prince of Wales Hospital), Dr Janette S.Y. KWOK (Immunology, Queen Mary Hospital), Prof Margaret H.L. NG (Haematology, Prince of Wales Hospital), Prof K.F. TO (Anatomical Pathology, Prince of Wales Hospital) and Dr Dominic N.C. TSANG (Clinical Microbiology & Infection, Queen Elizabeth Hospital).



▲ Winner of the session Dr Alvin Ho Wan IP receiving the prize from Dr Liz YUEN Chairman of Education Committee.

The Trainee Presentation Session provides a good opportunity for our trainees to undertake research study and sharpen presentation skills. The number of participants broke our record this year: a total of 16 trainees across different subspecialties participated in the Trainee Presentation Session. This overwhelming response of participation was not only promising but also challenging to the Education Committee. The duration of the Trainee Presentation Session was limited by the availability of venue and judges. In order to provide optimal time for presentation and discussion, only 10 participants were selected to have on-stage oral presentation. The poster presentation was for the first time introduced this year to overcome the time constraint of the Trainee Presentation Session given the large number of participants. Both oral and poster presentations are recognized education activities that fulfil the training requirement of our College. All participants of oral and poster presentations received a certificate of participation but the best presentation was selected from the oral presentations only. The format of poster presentation will be reviewed by the Education Committee.

The best presentation was awarded to Dr H.W. IP (Haematology, Queen Mary Hospital). The topic was "Chronic lymphocytic leukaemia with chromosomal translocation involving chromosome 13q and submicroscopic deletion of 13q14.3".



Judges, organisers and participants of the 10th Trainee Presentation Session.

Experience sharing by the winner

Attending the 10th Trainee Presentation Session was a pleasant experience to learn about all the excellent work in translational research carried out by trainees from various disciplines of pathology. This important sharing platform organised by The Hong Kong College of Pathologists has cultivated and advanced the research and presentation skills of trainees, both of which are invaluable to our career and practice. It is my great honour to be awarded the Best Presentation Prize in the session this year. I would like to take this opportunity to express my heartfelt gratitude to my mentors, Dr Clarence LAM and Dr Jason SO, who have taught me everything about haematology throughout these years and have offered valuable guidance to my presentation. The honour belongs also to Dr K.F. WONG and Dr Lisa SIU from Queen Elizabeth Hospital, who have pioneered this study and granted me the opportunity to further their work.

In this study, we investigated a subset of chronic lymphocytic leukaemia (CLL) with chromosomal translocation involving 13q14 region. We utilised interphase fluorescence in-situ hybridisation (FISH) and multicolour banding (mBAND) FISH techniques to demonstrate the presence of submicroscopic deletion of 13q14 and characterise its minimal region of deletion. A hitherto unreported translocation in CLL, t(7;13)(p15;q14), was observed in 2 of our 10 patients. The minimal region of deletion was determined to be at 13q14.3 by mBAND analysis. We also attempted to compare the clinical outcome between the group with 13q14 translocation and the group with isolated 13q14 deletion. We observed no significant difference in time-to-first-treatment and overall survival between the two groups.

The discipline of cytogenetics concerns itself, in its own sophisticated yet impressionistic manner, with the investigation of the whole genome. In this era of robust molecular testing and next-generation sequencing, it is always pleasing for one to go back and admire the "whole picture" of the karyotype and the brightly (pseudo-)coloured rainbow-like mBAND diagrams. It is my great pleasure to share with my seniors and colleagues such colourful and interesting aspect of cytogenetics in that pleasant afternoon.



Ho-Wan IP Division of Haematology Department of Pathology and Clinical Biochemistry Queen Mary Hospital

Normal mBAND diagram of chromosomes 13 (left) and the mBAND ideogram (right).

THE HONG KONG COLLEGE OF PATHOLOGISTS:



Volume 10, Issue 1 January 2015

The Hong Kong College of Pathologists, Incorporated in Hong Kong with Limited Liability **Editorial note:** Non-alcoholic fatty liver disease (NAFLD) is the commonest metabolic liver disease worldwide and affects a quarter of general population in Hong Kong. Histological evaluation remains the gold standard for diagnosing NAFLD. This Topical Update reviews pathological features of NAFLD and highlights some practical points for our daily diagnostic work. We welcome any feedback or suggestions. Please direct them to Dr. Anthony CHAN (e-mail: awh_chan@cuhk.edu.hk) of Education Committee, The Hong Kong College of Pathologists. Opinions expressed are those of the authors or named individuals, and are not necessarily those of The Hong Kong College of Pathologists

Pathology of Non-Alcoholic Fatty Liver Disease



Dr. Anthony W.H. CHAN Associate Professor Department of Anatomical and Cellular Pathology, Prince of Wales Hospital, The Chinese University of Hong Kong

Introduction

Non-alcoholic fatty liver disease (NAFLD) is a serious global health problem and associated with overnutrition and its related metabolic risk factors including central obesity, glucose intolerance, dyslipidaemia and hypertension. It is the most common metabolic liver disease worldwide and its prevalence in most Asian countries is similar to that in the States, Europe and Australia. About 10-45% of Asian population have NAFLD.¹ With "westernized" sedentary lifestyle, the prevalence of NAFLD in general urban population in the mainland China is about 15%.2 NAFLD is even more prevalent in Hong Kong. Our recent study demonstrated that NAFLD is found in 27.3% of Hong Kong Chinese adults by using proton-magnetic resonance spectroscopy.³ We further realized that 13.5% of Hong Kong Chinese adults newly developed NAFLD in 3-5 years.⁴ Both prevalence and incidence of NAFLD in Hong Kong are alarmingly high. Accurate diagnosis of NAFLD is crucial to allow prompt management of patients to reduce morbidity and mortality. NAFLD is composed of a full spectrum of conditions from steatosis to steatohepatitis (NASH) and cirrhosis. Various non-invasive tests, based on clinical, laboratory and radiological tests, have been developed to assess the degree of steatosis and fibrosis in NAFLD.^{5, 6} However, liver biopsy remains the gold standard for characterizing liver histology in patients with NAFLD, and is recommended in patients with NAFLD at high-risk of steatohepatitis and advanced fibrosis (bridging fibrosis and cirrhosis), and concurrent chronic liver disease of other aetiology.⁷ This article reviews pathological features of NAFLD and highlights some practical points for our daily diagnostic work.

NADFLD is the most common metabolic liver disease worldwide. Our recent study demonstrated that NADFLD is found in 27.3% of Hong Kong Chinese adults by using proton-magnetic resonance spectroscopy.

Pathological patterns of NAFLD

Non-Alcoholic Steatohepatitis Clinical Research Network (NASH-CRN) has provided numerous important data on the natural history, clinical features, management and pathology of NAFLD. Different pathological patterns of NAFLD described by NASH-CRN have been widely adopted in clinical practice and research studies.

Steatosis with or without inflammation

Hepatic steatosis (fatty change) is the accumulation of fat droplets, primarily triglyceride, in the cytoplasm of hepatocytes. The cutoff between physiologic and pathologic steatosis is 5% of affected hepatocytes, which is based on studies by lipid content measurement and imaging.⁸ There are two morphological forms of steatosis: macrovesicular and microvesicular. Macrovesicular steatosis is typically featured by a hepatocyte containing a single large fat droplet displacing the nucleus to the periphery (Figure 1). However, hepatocytes containing multiple small to medium-sized fat droplets (Figure 2) in fatty liver disease are not uncommonly found adjacent to those hepatocytes with a single large fat droplet. It has been demonstrated that a single large fat droplet is resulted from fusion of these small to medium-sized fat droplets. We should not hesitate to apply the term macrovesicular steatosis to those hepatocytes with small to medium-sized fat droplets. Some experts may prefer to use "mediovesicular" steatosis to describe them. In contrast, "genuine" microvesicular steatosis is characterized by the accumulation of much smaller uniform minute fat droplets dispersed throughout the hepatocytes, and sometimes requires special stain (e.g. oil red O) for better visualization. Diffuse microvesicular steatosis is typically found in conditions with serious mitochondrial dysfunction and fatty acid oxidation defect (e.g. Reye syndrome, acute fatty liver of pregnancy, acute alcoholic foamy degeneration). However, focal microvesicular steatosis is recognized in up to 10% of liver biopsies in patients with NAFLD and is associated with higher grades of steatosis, ballooning degeneration, inflammation and advanced fibrosis.⁹

In a liver biopsy of patients with NAFLD, the degree and distribution of steatosis should be evaluated at low magnification (at most 10x and usually 4x). Assessment at higher magnification may overestimate the severity of steatosis. The degree of steatosis is semi-quantitatively categorized as mild (5 to 33%), moderate (>33 to 66%) and marked (>66%).¹⁰The severity of steatosis is associated with lobular inflammation and perivenular fibrosis but there is no significant correlation with ballooning degeneration, Mallory-Denk bodies or portal/ advanced fibrosis.¹¹ Predominant zonal distribution of steatosis should also be recorded unless steatosis is very mild or the biopsy is fragmented or inadequate. It is categorized into four patterns: zone 3 (perivenular), zone 1 (periportal), panacinar and azonal. Steatosis in NAFLD is usually present in zone 3 and panacinar distribution. Predominant zone I distribution is rare in adult (1%) but more commonly found in children and teenagers (12%).¹⁰ Steatosis in an azonal distribution is more likely to be associated with ballooning degeneration, Mallory-Denk bodies and advanced fibrosis.¹¹

When steatosis is accompanied by lobular and/or portal inflammation, a diagnosis of steatosis with inflammation is made. Inflammatory infiltrates are mainly lymphocytes, mononuclear cells and occasional eosinophils. Neutrophils are rarely seen in NAFLD, in contrast to alcoholic liver disease (ALD). Lobular inflammation can be present in the form of small aggregates of macrophages (microgranuloma) or lymphocytes, similar to spotty necrosis in chronic viral hepatitis. Mild lobular inflammation (<2 foci/20x) is often found in about



Figure 1: Macrovesicular steatosis.



Figure 2: Macrovesicular steatosis with small to mediumsized fat droplets.

80% of NAFLD with simple steatosis.⁹ Portal inflammation is usually absent or mild (76% and 77% in adults and children, respectively).¹² There is no correlation between the severity of portal inflammation and lobular inflammation. "More than mild" portal inflammation is defined when at least one portal area shows a moderate to marked density of inflammation and/or the presence of lymphoid aggregates. Its presence is associated with steatohepatitis and advanced fibrosis,¹² but should also raise the suspicion for other chronic hepatitis, particularly viral hepatitis C. Predominant portal inflammation exceeding lobular inflammation is more common in paediatric patients.¹³

Steatosis with or without inflammation is also known as simple steatosis and has been considered benign and non-progressive. However, our group demonstrated that 58% and 28% of patients with simple steatosis had increased disease activity and fibrosis progression in a 3-year interval, respectively.¹⁴ Moreover, the accumulation of fat droplets is one the mechanisms leading to ballooning degeneration, the hallmark of steatohepatitis, through oxidative fat injury, endoplasmic reticulum dysfunction and abnormalities of the cytoskeleton.¹⁵ Simple steatosis is not always quiescent and may mislead people on underestimation of the risk of disease progression.

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<u>Steatohepatitis</u>

Steatohepatitis does not simply mean steatosis with inflammation but is a distinctive pathological pattern characterized by steatosis more than 5%, inflammation and ballooning degeneration. Ballooning degeneration is the key lesion to differentiate steatohepatitis from steatosis with inflammation. It is the hallmark of hepatocellular injury in steatohepatitis and is characterized by cellular swelling, rarefaction of the hepatocytic cytoplasm and clumped strands of intermediate filaments (Figure 3). It is associated with substantial accumulation of fat droplets as well as dilatation of the endoplasmic reticulum and cytoskeletal injury.¹⁵ Ballooned hepatocytes are initially most frequently in the perivenular region in early stage of disease. This zonal distribution is lost



Figure 3: Ballooned hepatocytes with Mallory-Denk bodies.



▲ Figure 4: Ballooned hepatocytes are characterized by loss of cytoplasmic expression of CK8/18, whereas residual immunoreactivity is confined to their Mallory-Denk bodies. (Immunohistochemistry of CK8/18).

when disease progresses or in very active disease. Ballooned hepatocytes often but not necessarily contain Mallory-Denk body. Mallory-Denk body, which is also known as Mallory body and Mallory hyaline, is a deeply eosinophilic, ropey intracytoplasmic inclusion (Figure 3), and an aggregate of misfolded intermediate filaments with other different classes of proteins, including p62 and ubiquitin. The identification of ballooned hepatocytes may not be always straightforward and the immunohistochemical stain (cytokeratin 8/18 [CK8/18]) is helpful in such situations. Ballooned hepatocytes are characterized by loss of cytoplasmic expression of CK8/18, whereas residual immunoreactivity is confined to their Mallory-Denk bodies if present (Figure 4).¹⁶

Fibrosis is an indicator of chronicity and disease progression. Although it is not necessary to establish a diagnosis of steatohepatitis, it is commonly found in adult (84%) and paediatric patients (87%) with NASH.¹⁰ Its presence helps



Figure 5: Perivenular and pericellular fibrosis. (Sirius red stain)

us to more confidently make a diagnosis of steatohepatitis in equivocal cases. Perivenular and pericellular/perisinusoidal fibrosis (Figure 5) is the distinctive pattern of fibrosis in fatty liver disease and not typically encountered in chronic viral hepatitis, autoimmune hepatitis and chronic cholestatic disease. It represents deposition of fibrous tissue in the space of Disse and is related to activation of stellate cells. It is typical in early stage of fibrosis in adult NAFLD/NASH, similar to that in ALD. However, the fibres tend to be thinner and less marked in NAFLD/NASH. As the disease progresses, periportal fibrosis will develop with fibrous strands entrapping periportal hepatocytes. Later, bridging fibrosis may occur between central regions (central-central fibrous bridging), between portal tracts (portal-portal bridging) or between central and portal regions (central-portal bridging). Cirrhosis is eventually established after progressive fibrosis, parenchymal extinction and hepatocellular regeneration. Two practical issues concerning pathological assessment of fibrosis are highlighted here. Firstly, a good quality connective tissue stain is crucial to highlight the earliest delicate fibrosis. Masson trichrome, Gordon-Sweets reticulin and Sirius red stains are common connective tissue stains widely used in hepatopathology. A good trichrome stain requires an adequate step of differentiation, usually by phosphomolybdic acid. Inadequate or excessive differentiation leads to over- or understaining, which may lead to over- or underestimation of the degree of fibrosis. Sirius red stain is recommended for morphometric quantitation of fibrosis because it provides highly detailed and contrasted staining and is more sensitive in identifying mild pericellular fibrosis.¹⁷ Secondly, aberrant arteries and microvessels in the perivenular region are commonly found in about 40% of patients with NASH, especially in those with advanced fibrosis (62%). Ductular reaction is present in 55% of arterialized scarred perivenular region.¹⁸ The presence of aberrant artery and ductular reaction may cause misidentification of a perivenular

region as a portal tract. Such misidentification could lead to erroneous interpretation of a portal-based process, potentially resulting in a missed NAFLD/NASH diagnosis and inaccurate assessment of fibrosis. To avoid this misidentification, proper appreciation of normal liver histology is necessary. In a normal portal tract, a hepatic artery is usually (>90%) accompanied by a nearby (within a distance two to three times that of its diameter) interlobular bile duct of similar diameter. They are embedded within the fibrous stroma of the portal tract and separated from periportal hepatocytes by a limiting plate. However, in arterialized scarred perivenular region of NAFLD/ NASH patients, aberrant artery and ductule may lie too far apart without an accompanied portal vein, or lie adjacent to or among hepatocytes without separation from the limiting plate in a portal tract.

Steatohepatitis does not simply mean steatosis with inflammation but is a distinctive pathological pattern characterized by steatosis more than 5%, inflammation and ballooning degeneration. Ballooning degeneration is the key lesion to differentiate steatohepatitis from steatosis with inflammation.

Borderline steatohepatitis

Steatohepatitis may be further classified as definite or borderline. Definite steatohepatitis is applied for cases fulfilling all three diagnostic features of steatohepatitis (steatosis more than 5%, inflammation and ballooning degeneration), typically with a predominantly perivenular distribution. Borderline steatohepatitis is designated for those cases falling in the grey zone between steatosis with/ without inflammation and definite steatohepatitis. Two forms of borderline steatohepatitis have been described by NAFLD-CRN. Zone 3 borderline steatohepatitis is applied for those do not have full-blown unequivocal histological features of definite steatohepatitis. It may include those cases with characteristic perivenular/pericellular fibrosis in absence of ballooning degeneration, and those cases with equivocal ballooning degeneration. However, this practice is controversial and not yet accepted universally. Some pathologists prefer to describe those cases with perivenular/ pericellular fibrosis in absence of ballooning degeneration as steatosis with fibrosis or steatofibrosis in such cases. Zone I borderline steatohepatitis is characterized by portal-based injury (periportal steatosis, predominantly portal inflammation and portal fibrosis).¹⁰ Ballooning

degeneration is usually absent. This distinctive form of borderline steatohepatitis is a unique histological pattern that appears to predominantly affect paediatric patients with NASH (75%) and also known as type 2 (compared to usual "type I" NASH in adult) or paediatric NASH in the literature. It more frequently affects boys, younger children, and Asian and Hispanic ethnicity.¹³

Zone 1 borderline steatohepatitis is a unique histological pattern that appears to predominantly affect paediatric patients with NASH (75%) and also known as type 2 (compared to usual "type 1" NASH in adult) or paediatric NASH in the literature. It more frequently affects boys, younger children, and Asian and Hispanic ethnicity.

Cryptogenic cirrhosis

A diagnosis of cryptogenic cirrhosis is designated for those cases with minimal recognizable diagnostic features after exclusion of viral hepatitis, metabolic, autoimmune and cholestatic liver diseases. Cryptogenic cirrhosis accounts for 8-9% of liver transplantation in the States and NAFLD has been recognized as a common cause of cryptogenic cirrhosis.¹⁹

In patients with cryptogenic cirrhosis, the prevalence of diabetes mellitus and obesity is comparable to that of patients with NAFLD and far exceeds that of patients with cirrhosis associated with chronic viral hepatitis and autoimmune liver disease.²⁰ Typical histological features of steatosis and/or necroinflammatory activity in patients with NAFLD/NASH may resolve as disease progresses to advanced fibrosis. Recognition of residual ballooning degeneration, Mallory-Denk bodies and pericellular fibrosis, together with clinical evidence of metabolic risk factors, helps us to reach a diagnosis of "burnt-out" NAFLD cirrhosis.

Other pathological lesions in NAFLD

Some pathological changes may be found in NAFLD but have not been used to classify the pattern of the disease. Lipogranuloma is characterized by a loose aggregate of lymphocytes and macrophages surrounding a central fat globule (Figure 6). It can be found in NAFLD as well as ALD and ingestion of mineral oil in food and medication. It should be distinguished from fibrin ring granuloma, which has a characteristic fibrin ring highlighted by phosphotungstic acidhaematoxylin stain o immunostaining for fibrin. Glycogenated nuclei are featured by nuclear clear vacuolation due to the



Figure 6: Lipogranuloma.



Figure 7: Glycogenated nuclei.



Figure 8: A giant mitochondrion.



Figure 9: Hepatocellular carcinoma with steatohepatitic features.

accumulation of glycogen (Figure 7). They are found much more commonly in NAFLD than ALD. They may be considered evidence of impaired glucose tolerance or insulin resistance. However, they may occur physiologically in children and young adults (11% and 4% in the 20s and early 30s, respectively),²¹ and pathologically in glycogen storage disease, Wilson disease, and other copper overload disorders. Giant mitochondria, also called megamitochondria, are eosinophilic oval or needleshaped intracytoplasmic inclusions (Figure 8). Although they typically are found in alcoholic and non-alcoholic fatty liver diseases, they may be associated with a wide variety of physiologic and pathologic conditions, such as aging, acute fatty liver of pregnancy, glycogen storage disease and urea cycle defects. Glycogenic hepatocyte distension is characterized by marked enlargement of hepatocytes with cytoplasmic clearing by excessive accumulation of cytoplasmic glycogen. It occurs in glycogenic hepatopathy in poorly controlled diabetes, glycogen storage disease and urea cycle defects.

Metabolic syndrome is a significant risk factor for hepatocellular carcinoma (HCC; odds ratio 2.13) and intrahepatic cholangiocarcinoma (odds ratio 1.56).²² Salomao et al. recently described a distinctive histological variant of HCC, steatohepatitic HCC. It is characterized by HCC with features resembling steatohepatitis (steatosis in more than 5% of tumour cells, ballooning degeneration, Mallory-Denk bodies, intratumoral inflammatory infiltrate and pericellular fibrosis) (Figure 9). It is associated with underlying NAFLD and metabolic risk factors but does not carry any prognostic significance.^{23,24}

		NAFLD Activity Score					
Score	Steatosis	Lobular inflammation	Ballooning degeneration				
0	<5%	None	None				
I	5-33%	<2 foci/20x field	Few				
2	>33-66%	2-4 foci/20x field	Many				
3	>60%	>4 foci/20x field					
Fibrosis Score							
Stage	Histological findings						
la	Mild pericellular fibrosis (only seen on connective tissue stain)						
lb	Moderate pericellular fibrosis (readily seen on H&E)						
lc	Portal/periportal fibrosis without pericellular fibrosis						
2	Pericellular and portal/periportal fibrosis						
3	Bridging fibrosis						
4	Cirrhosis						

▲ Table 1: NAFLD Activity Score (NAS) and fibrosis stage by NASH-CRN.¹⁰

Grading, Staging and Scoring Systems

To assess the severity of NAFLD in a liver biopsy, both activity (grade) and chronicity (stage) should be evaluated. Semi-quantification or scoring of the grade and stage are welcomed by some clinicians and pathologists to guide clinical management, standardize pathology reporting and facilitate research studies. In 1999, Brunt et al. proposed the first semi-quantitative grading and staging system based on liver biopsies from 5 I patients with NAFLD. The disease activity grade was based by a combination of parameters including steatosis, lobular and portal inflammation, and ballooning degeneration. The fibrosis stage was assigned on fibrosis patterns of adult NAFLD from perivenular/ pericellular to periportal, bridging and cirrhosis.²⁵

SAF (steatosis, activity, fibrosis) Score								
Steatosis		Steatosis						
SO		<5%						
SI		5-33%						
S2		>33-66%						
\$3		>60%						
Activity Sco	ore	Lob	ular inflammation (LI)	Ballooning degene	eration (BD)			
A0-4 (LI+BD)		0	None No	ne				
		1	≤2 foci/20x field	Hepatocytes with	a rounded shape and pale			
				cytoplasm usually r	reticulated. Size is quite			
				similar to that of n	ormal hepatocytes			
		2	>2 foci/20x field	Hepatocytes with	a rounded shape and pale			
				cytoplasm usually i	reticulated. Some cells are			
				twice of the size o	f normal hepatocytes			
Fibrosis	Fibrosis Histological findings							
Fla		Mild pericellular fibrosis (only seen on connective tissue stain)						
FIb		Moderate pericellular fibrosis (readily seen on H&E)						
Flc		Portal/periportal fibrosis without pericellular fibrosis						
F2		Pericellular and portal/periportal fibrosis						
F3		Bridging fibrosis						
F4		Cirrhosis						
FLIP Algorithm								
Steatosis	Bal	looni	ng degeneration Lo	obular inflammation	Diagnosis			
0		0, 1	or 2	0, 1 or 2	Not NAFLD			
I, 2 or 3		0		0, 1 or 2	NAFLD			
I, 2 or 3		l or	2	0	NAFLD			
I, 2 or 3		l or	2	l or 2	NASH			

Table2: SAF (steatosis, activity, fibrosis) score and FLIP algorithm.²⁹

In 2005, a revised Brunt's system by NASH-CRN was published (Table 1).¹⁰ The disease activity grade, wellknown as "NAFLD Activity Score (NAS), is the unweighted sum of scores for steatosis, ballooning degeneration, and lobular inflammation. In the fibrosis staging, early disease (stage I) was subclassified into Ia (mild pericellular fibrosis), Ib (moderate pericellular fibrosis) and Ic (portal/ periportal fibrosis only). The Asian-Pacific Working Party for NAFLD encouraged using this system for routine reports and research studies.²⁶ In a validation study of the NASH-CRN system in 976 patients, cases with NAS of 0 to 2 were largely considered not diagnostic of definite steatohepatitis (99%: simple steatosis 75% and borderline steatohepatitis 24%); on the other hand, most cases with scores of 5 or more were diagnosed as definite steatohepatitis (86%).27 Cases with NAS of 3 and 4 were distributed almost evenly between all three patterns: steatosis (27%), borderline steatohepatitis (32%) and definite steatohepatitis (41%). It has been repeatedly emphasized that NASH-CRN system should not be used as the diagnostic criteria for steatohepatitis (i.e., diagnosis of steatohepatitis only if NAS is 5 or more), although clinical trials have often selected patients with steatohepatitis based on an NAS value of 5 or more. 10, 27

In 2012, Bedossa et al. proposed an algorithm and a scoring system based on a cohort of 679 obese patients underwent bariatric surgery (Table 2).²⁸ The FLIP (fatty liver inhibition of progression) algorithm is proposed for segregating lesions into normal liver, NAFLD or NASH by semiquantitative evaluation of steatosis, ballooning degeneration, and lobular inflammation. The SAF (steatosis, activity, fibrosis) score is the combination of scores of steatosis, activity (ballooning degeneration and lobular inflammation) and fibrosis. It integrates both grade and stage together. Compared to the NASH-CRN system, steatosis is excluded from the activity score because there is no significant difference in transaminase levels between patients with normal liver and simple steatosis. A recent validation study involving 6 expert liver pathologists and 10 general pathologists showed that the FLIP algorithm significantly improve interobserver variations among pathologists at different levels of hepatopathology expertise.29

Differentiation between NAFLD and alcoholic liver disease

One may be asked by clinicians for the underlying aetiology of steatosis/steatohepatitis in a liver biopsy from a patient with concurrent drinking history and metabolic risk factors. Can pathological examination confidently differentiate between NAFLD and ALD? In most occasions, there is a considerable overlap between NAFLD and ALD at both the morphologic and clinical levels. Although ALD tends to have more Mallory-Denk bodies, satellitosis (hepatocyte with Mallory-Denk body surrounded by neutrophils) and less glycogenated nuclei, these changes are not unique to ALD. Few pathological lesions specific to ALD include acute foamy degeneration, sclerosing hyaline necrosis, acute/chronic cholestasis and venoocclusive disease but they are present in a small portion of patients with ALD. The key distinguishing feature is in fact the amount of alcohol consumption obtained from clinical history. Low level of alcohol intake is beneficial to patients with NAFLD by reducing risk of developing steatohepatitis and fibrosis. I Intake levels of two standard drinks (20 g ethanol daily/140 g weekly) for men and one standard drink daily (70 g weekly) for women are endorsed as the acceptable threshold to define non-alcoholic.²⁶

Can pathological examination confidently differentiate between NAFLD and ALD? The key distinguishing feature is in fact the amount of alcohol consumption obtained from clinical history.

Conclusion

Histological evaluation remains the gold standard for diagnosing NAFLD. Understanding different pathological patterns of NAFLD is important to establish an accurate diagnosis. Grading and staging systems are valuable tools to providing a standard reference in pathology reporting, monitoring disease progression and therapeutic response in patient management and clinical trials. We should be reminded that the pathological diagnosis of NAFLD/NASH should be relied on interpreting a constellation of histological findings and patterns, and could not be simply replaced by numeric scores. Last but not latest, steatosis and even steatohepatitis are not only exceptional to NAFLD and ALD but also found in viral hepatitis C, drug-induced liver injury (e.g. methotrexate, tamoxifen, corticosteroid), Wilson disease and various metabolic liver diseases. Careful pathological examination, as well as good communication with clinicians, and proper correlation with clinical and laboratory parameters are essential for correct diagnosis of NAFLD and all other medical liver diseases.

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Prof KHOO Ui Soon and Prof WOO Chiu Yat Patrick receive Croucher Senior Medical Research Fellowships 2015

The Senior Medical Research Fellowship is awarded to local academics who have excelled in scientific research work as judged by leading international scientists invited to provide confidential reviews of candidates nominated in a competitive exercise. Funds are awarded to the universities of the fellowship recipients, enabling the university to recruit replacement teachers to take over the award winner's duties for the period of the fellowship. This enables the awardees to devote more time and effort to research work.

This year, two Fellows of the College, Prof KHOO Ui-Soon and Prof WOO Chiu Yat Patrick received Croucher Senior Medical Research Fellowships in April 2015.

Prof Khoo, Clinical Professor at the Department of Pathology, The University of Hong Kong, is known for her expertise and research in breast cancer, particularly in molecular genetics and pathobiology. She pioneered the study of breast cancer susceptibility genes, *BRCA1* and *BRCA2* in Chinese breast and ovarian cancer patients. Among her achievements has been the identification of a novel alternatively spliced variant BQ to the *NCOR2* gene which is associated with development of tamoxifen resistance. Her current research encompasses the development and characterisation of a monoclonal antibody to this novel BQ variant which will be used for in vitro and in vivo studies to confirm the role of BQ in the development of tamoxifen resistance, the elucidation of the underlying mechanisms and its application as a biomarker for tamoxifen resistance prediction.

Professor Woo is Head and Clinical Professor at the Department of Microbiology, The University of Hong Kong. Professor Woo has established himself as one of the leaders in the field of emerging infectious diseases, novel microbe discovery and microbial genomics. In the past 15 years, Professor Woo's team has discovered more than 100 novel viruses, bacteria and fungi, most of which were named after Hong Kong or HKU. Some of the most well-known examples include *Laribacter hongkongensis*, human coronavirus HKU1, and the recently discovered dromedary camel coronavirus UAE-HKU23 from the Middle East. His group has discovered the largest number of coronaviruses in the world and has also sequenced the first bacterial and fungal genomes in Hong Kong. These have laid down the foundation of microbial genomics studies in Hong Kong.



Prof Patrick WOO (left) and Prof KHOO Ui Soon (right) receiving the award from Mr John TSANG, Financial Secretary.

Dr LEE Kam Cheong receives wider recognition for his contribution to patient safety

In 2010, Dr LEE Kam Cheong and his team at Princess Margaret Hospital introduced a novel approach to identify and track pathology samples, which not only improves workflow efficiency, but more importantly, enhances patient safety. In association with this project, Dr Lee and his team have won:

- The Hospital Authority 2013 Best Oral Presentation in Quality and Safety
- The Hospital Authority 2014 Best Paper in the New Advances in Care Delivery
- The Hospital Authority 2014 Outstanding Team Award

More recently, on 19 December 2014, at the Academy Conferment Ceremony, Dr Lee received the MPS–HKAM Excellence in Patient Safety Award. This award is jointly organised by the Medical Protection Society (MPS) and the Hong Kong Academy of Medicine (HKAM). The Award aims to encourage medical professionals to promote on the subjects of patient safety, risk management, medical ethics and quality and professional standards.

Outside the medical circle, Dr Lee and his team further received the Hong Kong ICT Awards 2015 (Bronze) in "Best Smart Hong Kong" category for his innovative use of technology to enhance patient safety.

In this issue we have invited Dr Lee to explain the rationale and significance of this new approach in the "Featured Article" section.



Dr Lee receives the MPS-HKAM Excellence in Patient Safety Award.

An innovative approach in using barcode tracking to improve patient safety and workflow efficiency in anatomical pathology laboratory

Dr LEE Kam Cheong

Identification error is the leading cause of patient safety incidents in pathology and laboratory. Correct specimen identification is especially crucial in pathological examination of tissue and cells as the results obtained often have a high impact in patient management. It is difficult to determine the true incidence of errors in an anatomical pathology laboratory, as there is no widely accepted definition for an "error", and there are many different error detection methods. In a large study involving 136 institutions, an overall error rate of 0.11% was found due to misidentification.¹ Despite recent advances in laboratory science and technology, however, processing of such specimens is still largely manual, requiring multistep transfer of specimens, and every step adds to the cumulative risk of error.

In clinical laboratories, automation in specimen processing is instrumental in reducing identification errors. In anatomical pathology analysis, however, the complexity, variability, and unpredictability of processing workflow are some major barriers to prevent encapsulating procedural steps into automatic analysers. The introduction of barcode technology in laboratory thus appears to be especially promising to ensure patient safety in assisting or replacing some visual checking steps, so as to minimize the inevitable human errors associated with fatigue, lack of concentration and heavy workload of manual processing.

With advances in technology and materials in generating high-fidelity barcode labels on tissue cassettes and slide, successful experiences have been reported to allow designing and implementing end-to-end, barcode-based solutions suitable for anatomical pathology laboratory workflow. The ability of barcode systems in real-time detecting and correcting errors represent a big leap in quality improvement in processing tissue and cytology specimens. The systems reported are designed on the basis of on-demand approach, so that cassettes and slides are being printed one-at-atime and just-in-time, at the moment of sample transfer during processing.²⁻⁴

However, such case-by-case ondemand barcode printing requires substantial workflow changes in order to accommodate the additional on-site scan-and-print routine. Moreover, by design the approach precludes batch pre-printing of barcode identifiers to cassettes and slides, so that processing time could be affected by the relatively slow printing process. The need to provide printing facilities at every spot of specimen and sample transfer also means that the implementation would come with a significant cost that may be unattainable by the most laboratories.⁵ Furthermore, in a crowded working environment commonly found in local laboratories in Hong Kong, bench space for placing an additional printer in every workstation could be lacking.

The barcode system therefore needs to be redesigned to make it more cost-effective and more adaptable if wider implementation for quality improvement is to be considered. One of our design targets is to provide the efficiency of batch printing, while at the same time to ensure correct identification by processing only one case at a time. The core of the present novel design is to make use of the tree-like, one-to-many relationship between a specimen and the subsequent samples derived, including tissue blocks and histology slides, to generate a virtual relational map in computer, one for each specimen accessioned. Instead of case-by-case printing, it employs case-by-case coupling of preprinted barcodes that are associated with each other in a relational map, whereby samples are being checked against the corresponding tree branches and nodes to ensure their correct identities. Through referencing to the specific relational map, there is no physical need of presenting a sample as would be required in on-demand printing; the design thus effectively eliminates a rigid requirement in the workflow - somewhat analogous to moving to credit card transactions from cash payments.

The unbundling of "printing" and "caseby-case", the latter is still a prudent step in carrying out identification still required in the relational-coupling approach, has thus rendered the workflow more flexible and scalable. As the relational map mirrors the connection and relatedness between a specimen and all subsequent samples derived, the design therefore could capture the complexity and variation of business logics specific to tissue and cytology processing, and thus open up opportunities for developing further applications. A pathologist can order special staining and ancillary studies of a case, for example, from a remote workstation in reporting room, while at the same time unique barcodes of the relevant slides as ordered can

be generated and ready for printing in the laboratory. Furthermore, with no limitation in the number of coupling workstations, the design allows laboratories of different sizes and specimen-mix to easily customize their own workflows according to needs.

Remarkably, with over five years' experience since our system has been implemented in 2010, with hundreds of thousands of tissue and cytology specimens processed, we have encountered no mix-up error. The relational-coupling approach thus has been demonstrated to be very effective in ensuring correct specimen identification and patient safety. All potential mismatch errors, mostly due to a lapse in sustained vigilance, were successfully signaled to the operator for immediate rectification. With the ability of batch pre-printing, the overall increase in processing times associated with relational-coupling has been found to be marginal, and we have not experienced significant delay in slide delivery. The technical staff have very positively accepted the new working procedure, as it is less prone to fatigue comparing to the previous manual visual checking.

Another important advantage of the new design is the real-time case traceability throughout the entire processing procedure. The knowledge of when, where and why misidentification errors occur, which is a fundamental prerequisite for their successful reduction, has been documented automatically.



With the capability in seamlessly capturing every relevant processing step, valuable information unavailable previously by manual means is readily available to laboratory staff for continuous quality improvement.

Because the flexibility and adaptability of the novel approach, the system has been adopted by the Hong Kong Hospital Authority for large-scale implementation, rolling out to every public hospital laboratory that processes surgical and cytology specimens in 2015.

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An Novel (Relational Coupling) Design



ANNOUNCIEMIENT FIBOM THE TRAINING AND EXAMINATIONS COMMITTEE

1. Examination Date

College Written Examination for all disciplines will be held on 6 July 2015 (Monday).

2. Revision of College Examination Fees

With effect from 21 April 2015, the College examination fees (and examination exemption fee) have been revised as follows:

Type of Examination	Examination / Exemption Fee		
Fellowship Assessment	\$20,000		
Membership Examination	\$15,000		
Membership Examination Exemption	\$15,000		
Supplementary Examination	\$15,000		

UPCOMING AGNI

The 24th AGM 2015 will be held on 28 November 2015 (Saturday).

Mark your diaries!

CORRECTION

On P.4 of the last issue of Patholgue (Vol 23, Issue 2. Nov 2014) Dr CHOI Wai Lap's affiliation was erroneously quoted as the "Department of Chemical Pathology, Tuen Mun Hospital". It should be the "Department of Clinical Pathology, Tuen Mun Hospital". We apologise to Dr Choi for the inconvenience caused.

NEW E-MAIL ADDRESS OF COLLEGE SECRETARY

Please note that with immediate effect, the e-mail address of our College Secretary has been changed to:

hkcpath@hkcpath.org

Out of the Whitecoat:

Half a Century of Affectionate Poetry 半世紀的詩情話意

by Janice LO

Friends and colleagues of Dr. MAK Wai Ping, President of the Hong Kong College of Pathologists from 1995 to 1999, would know that he has a passion for writing poems. Dr. Mak's poems have some unique features: each poem is mostly written for one individual or an event; the first word of each line of many of the Chinese poems, when read in sequence, would become the name of an individual or event; the poem would be vividly descriptive of the subject.

Dr. Mak's passion for writing poems has developed since young. Over the years, he has written poems for his family members, friends, colleagues, and for different special occasions, including weddings, anniversaries, retirement, etc. Recently, Dr. Mak took the effort to compile all his poems spanning over half a century into a booklet, which was



Cover of booklet.

published in December 2014. Dr. Mak prefaced the booklet with a brief autobiography, followed by different sections with collections of poems dedicated to the following: (1) Youthful passions (少年情); (2) Love and romance (愛·浪漫); (3) Heartfelt affections (一點心意一點情); (4) Family ties (親情); (5) Friendship (友情); and (6) Serendipity (惜緣).

During a recent conversation, Dr. Mak explained to the author about his works. In the collection, his beloved wife Mrs. Mak was featured most often. She is affectionately nicknamed T.T. ($\pm \pm$). Poems dedicated for Mrs. Mak amply illustrated the loving relationship of the couple, ever since courtship, through the many milestones after marriage, birthdays, anniversaries, Valentine's Days, up till the very present. Dr. Mak also treasures family ties, showering his creative ingenuity to many extended family members. As for friends, university classmates and work colleagues provided Dr. Mak with abundant occasions for expressing his literary skills. One of Dr. Mak's friends in his youth is former Director of the Hong Kong Observatory, Mr. LAM Chiu Ying. Dr. Mak and Mr. Lam attended King's College together, and joined the same youth group to help with road works in Ma Wan.



Dr Mak for his "TT" on her birthday.



On the 15th anniversary of the College.



▲ Poem for Mr. LAM Chiu Ying, former Director of the Hong Kong Observatory and Dr. Mak's secondary school friend.

20. 萬能神探 病因鑽研尋根究底 理據論證員本追終 Pathology underpinning Medicine. 26. 幕後英雄 幕前協力情珍貴、 後台化驗顯光輝, 英氟充盈聖誕夜, 雄心常在可恭维。 Heroes behind the scene Before the screen our concerted effort is valuable. Behind the scene our laboratory testing will glow. Our high spirits fill this Christmas night. Our heroic hearts deserve others to cite. Pathologists as heroes behind the scene. 香港醫學博物館 30.

運動與健康展覽 運籌帷幄好才智, 動力中國顯英姿, 健兒齋撐與運會, 康樂港人傳愛意。 香港醫學博物館 神奇疫苗展覽開幕 2011 年

Support for the Hong Kong Museum of Medical Sciences.

Dr. Mak, as most acquaintances would know, is still very active both physically and intellectually. His retirement from the civil service in 2005 opened a new chapter of his life, with dedication to pathology service provision in the private sector. Dr. Mak is also passionate about volunteering his services for the Hong Kong Museum of Medical Sciences, a not-for-profit organization receiving little financial assistance from the government. Dr. Mak is continually supportive of various functions of The Hong Kong College of Pathologists. We will certainly continue to be graced by Dr. Mak contributions both to the field of pathology and to poetry with a human touch.



College Activities: "International Pathology Day" Exhibition

Our College organised the "International Pathology Day" Exhibition – The Science Behind Medicine from 5 November 2014 to 11 November 2014 at the Hong Kong Museum of Medical Sciences. The building of the museum used to be a pathology institute, and it has served Hong Kong for more than a century and has played an active role in the research of plague.

The Opening Ceremony of the exhibition on 5 November 2014 was well attended by practicing and retired pathologists, President of the Hong Kong Academy of Medicine, Presidents of sister Colleges, event sponsors, volunteer exhibition tour guides, high school students and general public. Our College President and officiating guest Under Secretary for Food and Health of the Hong Kong Government welcomed and addressed the guests, and guided tours began immediately afterwards. Visitors curiously looked through microscopes, displaying before them various normal and diseased tissues, blood cells, and microorganisms. Students handled the multichannel pipettes, agar plates and electrophoresis gel with interest. Some chemistry teachers and students were attracted by a simulated liquid chromatography and mass spectroscopy programme, and CSI fans were captured by the forensic pathology slide show. The event has been covered by various local media.

Facebook link: https://www.facebook.com/HKIPD2014



▲ (Left to right) Dr LI Kwok Tung Donald (President of the Hong Kong Academy of Medicine), Prof Sophia CHAN (Under Secretary for Food and Health), Prof Annie CHEUNG College President and Dr Edmond MA, then College Vice-President at the Exhibition.



▲ Organiser Dr Michael WONG Lap Gate (left) doubles as exhibition tour guide for visiting Past Presidents, Prof Faith HO (centre) and Dr MAK Wai Ping (right).



Group photo taken on the opening day of the Exhibition.