Histograph

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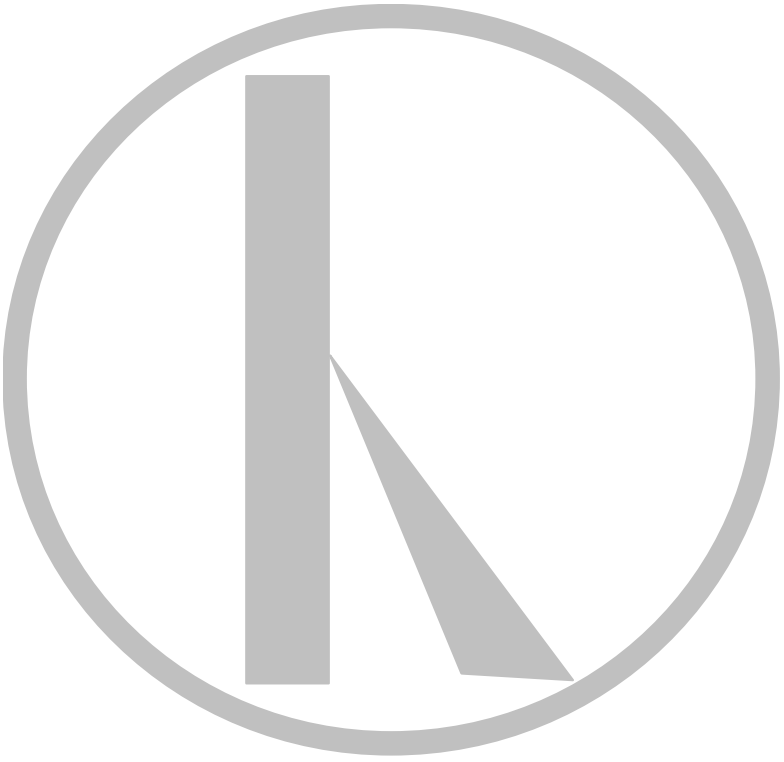

Contents

Editorial

This issue of Histograph is full of interesting stuff!! (Well I hope it is). We have part 1 of a review on the immunohistochemistry of mesotheliomas by Chow Heok P'Ng from Westmead as well as a review on mast cells and their role in tumours.

There are also two notices of meetings, the first An Update in Genetic Medicine at The Children's Hospital at Westmead (16-17th March) and the second our own State Conference at Mudgee (17-19th March). One conference after another!!

Please feel free to send me anything of interest for inclusion in Histograph. Our fellow members would very much appreciate it.

Hope to see you in Mudgee

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A Review of the Immunohistochemistry of Mesothelioma- Part 1

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Registrar in Histopathology
Institute of Clinical Pathology and Medical Research, Westmead and
The Children's Hospital at Westmead.

Editor's note: This timely review presents an update on the Immunohistochemistry of mesothelioma. Part 1 concentrates on the putative positive markers and part 2 describes the negative and other markers used to aid in the diagnosis of this difficult tumour.

Overall, three basic tenets in the immunodiagnosis of mesothelioma should be remembered. First, no single immunohistochemical marker is both entirely specific and sensitive for mesothelioma. Second, monoclonal antibodies generally offer higher specificity over polyclonal markers, although this can sometimes be accompanied by a higher percentage of false negative results. Third, the diversity of mesothelium has precluded the finding of a suitable single epitope and consequent efforts to produce a specific and sensitive mesothelial monoclonal antibody marker (1).

A panel of immunohistochemical markers can facilitate the distinction between epithelioid pleural mesotheliomas and pulmonary peripheral adenocarcinomas (2,3,4,8,9,16). Ordonez (2) advocated that a panel of four markers (two positive and two negative for mesotheliomas) enabled a correct diagnosis in nearly all cases. An extensive and detailed review of the literature follows.

Markers positive for mesothelioma

CK5/6

CK5/6 shows high specificity and sensitivity in detecting mesothelioma, but this marker can be expressed in a minority of adenocarcinomas, as well as in squamous cell carcinomas. Ordonez (3) reported all 60 (100%) mesotheliomas exhibited CK5/6 expression. In most cases, the staining was strong and diffuse and throughout the cytoplasm. Only 1 of 50 (2%) adenocarcinomas showed focal staining, with the reactivity in about 5% of the tumour cells. Carella et al (4) observed diffuse cytoplasmic staining for CK5/6 in 40 of 46 (87%) malignant mesotheliomas, whilst all 20 lung adenocarcinomas (100%) were completely negative. Similar results were also noted in another series by Ordonez (14) who reported CK5/6 reactivity in all 40 mesotheliomas, but none in any of the 30 pulmonary adenocarcinomas. Based on the data, cytokeratin 5/6 appears to be one of the most sensitive and specific markers for the diagnosis of mesothelioma (14).

WT1

Recent studies have suggested that the Wilms' tumour suppressor gene (WT1) located on chromosome 11p13 plays an important role in the development of the mesothelium, as well as the pathogenesis of mesothelioma. According to Ordonez (3), WT1 reactivity

was seen in 56 of 60 (93%) mesotheliomas. In most cases, the staining was strong and diffuse, and was confined to the nuclei. All 50 adenocarcinomas were negative for this marker. Oates and Edwards (9) noted that WTI was unequivocally positive in 38% of mesotheliomas. It was noted, however, that there was no reaction in any of the 17 autopsy cases, and if these were excluded, the proportion of positives rose to 64%. Among the adenocarcinomas, 20% gave a positive or equivocal nuclear reaction. Based on the results, it appears that WT1 could be useful in distinguishing between epithelioid mesotheliomas and lung adenocarcinomas; however it cannot be used on autopsy material, thus rendering its use in the present case study unhelpful. The lack of staining in autopsy material may be related to delayed fixation.

Thrombomodulin

Thrombomodulin (CD141) is a 75-KDA glycoprotein with anticoagulant properties. It is shared by mesothelia, endothelia, and certain epithelia, especially squamous type. Thrombomodulin produces predominantly membrane staining in normal endothelial and mesothelial cells, and in the epithelial component of malignant mesothelioma (11). Anti-thrombomodulin was initially reported to be a highly sensitive (all of 31 mesotheliomas) and specific (94%; 1 of 48 pulmonary adenocarcinomas) marker for mesothelioma (5). Subsequent studies have not replicated this, and found lower sensitivities and specificities for mesothelioma (3,7,10). According to the literature, the percentage of epithelial mesotheliomas that express thrombomodulin have ranged from 27.7% to 80% in different series (3,4,7, 8,10, 15) while positivity for adenocarcinomas have ranged from 5% to 15% (3,4,6,7,8,15). Ordonez (3) reported 46 of 60 (77%) mesotheliomas showing reactivity for thrombomodulin while 7 of 50 (14%) lung adenocarcinomas were also positive. In recent years, several other markers which are more sensitive and specific have been introduced, thus relegating thrombomodulin to a secondary role in the diagnosis of mesothelioma.

Calretinin

Calretinin is cytoplasmic and nuclear calcium-binding protein and is abundantly expressed in central and peripheral neural tissues, especially in the retina and sensory neurones. Calretinin is involved in the homeostasis of intracellular calcium ions and probably plays a key role in somatosensory transduction (16). The reported sensitivity for mesotheliomas have ranged from 40% to 100% (3,4,7,8,9,10) and from 6% to 22.5% (3,4,8,9,10) for adenocarcinomas. The series by Ordonez (3) reported all 60 (100%) mesotheliomas were positive for calretinin. In most cases, the staining was strong and diffuse and was present in both the cytoplasm and nucleus. Only 4 of 50 (8%) lung adenocarcinomas in that series exhibited focal positivity for calretinin. Although this antibody has relatively low specificity and sensitivity, its use may be helpful by providing additional evidence supporting the diagnosis of mesothelioma.

HBME-1

The antibody HBME-1 is believed to react with an antigen present on the microvillus surface of mesothelial cells, producing thick circumferential membranous staining. Adenocarcinomas show either cytoplasmic or brush-border staining. Roberts et al (7) reported positive staining in 25 of 82 (30%) epithelioid mesotheliomas and 2 of 18 (11%) adenocarcinomas. The series

by Bateman et al (13) reported that HBME-1 labelled mesothelioma cells in all 17 cases (100%) and 10 of 13 (71%) cases of adenocarcinoma cells. Ordonez (3) reported that 51 of 60 (85%) cases of mesotheliomas and 34 of 50 (68%) adenocarcinomas reacted with HBME-1 antibody. These results showed that HBME-1 does not label mesothelial cells with sufficient specificity to be useful for differentiating malignant mesothelioma from adenocarcinoma. However, negative staining with HBME-1 makes a diagnosis of malignant mesothelioma unlikely.

Mesothelin

Mesothelin is a cell surface antigen of unknown function that is strongly expressed in mesothelial cells. To determine whether mesothelin can assist in discriminating epithelioid mesotheliomas from lung adenocarcinomas or from other carcinomas metastatic to the serosal membranes, 55 mesotheliomas and 86 non-pulmonary adenocarcinomas were investigated for mesothelin expression in a study by Ordonez (12). Reactivity was obtained in all of the mesotheliomas, 39% of the lung adenocarcinomas, and 49% of non-pulmonary adenocarcinomas. In the same series, 18% percent of the squamous carcinomas of the lung, but none of the sarcomatoid mesotheliomas exhibited positivity for this marker. It has low specificity, being positive in epithelioid mesotheliomas and pulmonary adenocarcinomas, thus limiting the practical use of this marker. Although mesothelin is not recommended for inclusion in the standard immunohistochemical pattern used to assist in distinguishing between these malignancies, it may have some utility in those cases in which the results are equivocal. Because of the common and strong mesothelin expression in epithelioid mesotheliomas, a negative staining for this marker can be regarded as a strong indication against such a diagnosis.

References

1. Attanoss RL, Gibbs AR. Pathology of malignant mesothelioma. Histopathology 1997;30(5):403-418.
2. Ordonez NG. Immunohistochemical diagnosis of epithelioid mesothelioma: a critical review of old markers, new markers. Human Pathology 2002;33(10):953-967.
3. Ordonez N. The immunohistochemical diagnosis of mesothelioma: a comparative study of epithelioid mesothelioma and lung adenocarcinoma. Am J Surg Pathol 2003;27(8):1031-1051.
4. Carella R, Deleonardi G, D'Errico A, Salerno A, Egarter-Vigl E, Seebacher C, Donazzan G, Grigioni W. Immunohistochemical panels for differentiating epithelial malignant mesothelioma from lung adenocarcinoma: a study with logistic regression analysis. Am J Surg Pathol 2001;25(1):43-50.
5. Collins C, Ordonez NG, Schaefer R, et al. Thrombomodulin expression in malignant pleural mesothelioma and pulmonary adenocarcinomas. Am J Pathol 1992;141:927-933.
6. Wick M, Moran C, Mills S, Suster S. Immunohistochemical differential diagnosis of pleural effusion, with emphasis on malignant mesotheliomas. Curr Opin Pulm Med 2001;7(4):187-192.

7. Roberts F, Harper CM, Downie I, Burnett RA. Immunohistochemical analysis still has a limited role in diagnosis of malignant mesothelioma. A study of thirteen antibodies. Am J Clin Pathol 2001;116(2):253-62.
8. Riera J, Astengo-Osuan C, Longmate J, Battifora H. The immunohistochemical diagnostic panel for epithelial mesothelioma: re-evaluation after heat-induced epitope retrieval. Am J Surg Pathol 1997; 21(12):1409-1419.
9. Oates J, Edwards C. HBME-1, MOC-31, WT1 and calretinin: an assessment of recently described markers for mesothelioma and adenocarcinoma. Histopathology 2000;36(4):341-347.
10. Ataanoos RL, Webb R, Dojcinov S, Gibbs AR. Malignant epithelioid mesothelioma: anti-mesothelial marker expression correlates with histological pattern. Histopathology 2001;39(6): 584-588.
11. Miettinen M, Salomo-Rikala M. Expression of calretinin, thrombomodulin, keratin 5, and mesothelin in lung carcinomas of different types: an immunohistochemical analysis of 596 tumours in comparison with epithelioid mesothelioma of the pleura. Am J Surg Pathol 2003; 27(2):150-158.
12. Ordonez N. Value of mesothelin immunostaining in the diagnosis of mesothelioma. Mod Pathol 2003; 16(3):192-197.
13. Bateman AC, al-Talib RK, Newman T, Williams JH, Herbert A. Immunohistochemical phenotype of malignant mesothelioma: predictive value of CA125 and HBME-1 expression. Histopathology1997;30:49-56.
14. Ordonez NG. Value of cytokeratin 5/6 immunoassaying in distinguishing epithelial mesothelioma from lung adenocarcinoma. Am J Surg Pathol 1998;22(10):1215-1221.
15. Ordonez NG. Role of immunohistochemistry in differentiating epithelial mesothelioma from adenocarcinoma. Review and update. Am J Clin Pathol 1999;112(1):75-89.
16. Ordonez NG. The immunohistochemical diagnosis of epithelial mesothelioma. Hum Pathol 1999; 30(3):313-323.

Sam, get me a PAS on this - STAT!

Now and then, I switch the TV onto CSI or one of the other Forensic-type shows, and comment on the accuracy/stupidity of what I am watching much to my children's exasperation. The above quote came from one of my favourite shows, *Quincy*. Others on Histonet have made similar observations:

Paul Monfils:
But CSI, which I also watch frequently, really is a mix of science and science fiction. I wish we did have machines that could do everything their machines do. Some of them are really way out there. Like the episode where two people had a conversation near a pottery wheel, and the clay picked up the vibrations of their conversation, which were subsequently scanned by a laser and turned back into audible voices.

I even noticed a technical error related to my vocation - malacology. In one episode a dealer in illegally harvested abalone (a type of shellfish) is shot. The medical examiner says "serves him right for selling an endangered bivalve". As you may remember from your invertebrate zoology class, abalone are gastropods, not bivalves.

Pam Marcum:
Heck, I thought Quincy and now CSI were sitcoms at first as it was so far from what we were doing and really funny for mistakes. All my first boss in histology (and also a city/county coroner) wanted for several years was a Sam like Qunicy had with all the equipment of course. He figured he could rid of at least 5 people in the lab with one Sam.

Ford M. Royer:
I always got a kick out of Quincy when he would get personally involved with a victim's family... even to the extent of going to their homes and sitting down with them in their family room. Great stuff, and very touching, but I just could not see any of our pathologists doing this. Not that they might not have wanted to at times, they were a great bunch of guys & gals... but a "house call" by the chief pathologist? I don't THINK so...

Diane C. Gladney:
I, too, was a fan of Quincy and now am a fan of CSI. But the episode of CSI where I saw the pathologist cutting a block on the microtome and turning the fly wheel backwards sent me screaming at the TV...."Are you trying to strip every gear in that microtome!!!" I absolutely cringed when I saw that. But the biggest laugh that I got out of the episode was seeing a pathologist cutting blocks. Not to put down pathologists but it is very rare to see one cutting blocks in a clinical environment. The CSI consultants also need to get with the latest technology in histology and not have someone drying slides over an open flame. If anyone saw this episode, you know what I mean. Hollywood, you gotta love them; they hire consultants then refuse to listen to them. I still am a huge fan of CSI and the program has sparked an interest in the medical laboratory field including histology. Hey, we need as much exposure as possible. Histology is the greatest of laboratory professions. I have no regrets of working for more than 30 years in this profession and look forward to working many more.

Histotechnology Group of NSW (25 years)

State Conference 17 - 19 March, 2006

The Conference

ACCOMMODATION

The conference will be held at the Country Comfort Parklands Resort, Cassilis Road, Mudgee. 6372 4500.
Rooms have been reserved at the Motel but must be booked individually by 17 February. Mention the Histotechnology Group to receive the following rates:

$159 Single room
$175 Double room

MUDGEE

Mudgee is located in the Cudgegong Valley in the Central West of New South Wales, 282 km NW of Sydney.
The town has many sites classified by the National Trust and is famous for its honey and wine.

COMPETITIONS AND PRIZES

The Committee anticipates holding competitions such as "Longest Ribbon" and "Best H & E" in the Exhibition Area.
In keeping with the Irish theme for St Patrick's Day the famous "Hat Prize" will be awarded for the best outfit on Saturday night. A lucky door prize is also up for grabs.
A special, unique award will be given to the winner of the conference QUIZ.

SOCIAL FUNCTION

Saturday evening will be a celebration of St Patrick's Day with all things Irish, including a band and dinner. So dress appropriately!

REGISTRATION

All prices quoted in this brochure are GST inclusive.

Registration – includes breakfast, lunch, morning and afternoon teas.

Name:

_____

Address: (H or W?):

_____

_____

Institution:

_____

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Email:

_____

Tel (H):

_____

Tel (B):

_____

Please note the following

- Unexpected day registrations cannot be accepted due to catering requirements.
- Unused meal tickets cannot be redeemed on another day unless it has been arranged with the secretary 1 week prior to the conference.

WORKSHOP REGISTRATION

- IHC workshop ($75.00)
- Museum workshop ($50.00)
- Full weekend registration member ($250.00)
- Full registration non member ($320.00. Includes membership for 1 year)
- Day registration member - specify day ($175.00)
- Day registration non member – specify day ($220.00. Includes membership for 1 year)

SUBTOTAL $ _____

Saturday evening dinner

- People at $67.00 per person

TOTAL PAYABLE:

$_____

MISCELLANEOUS

Do you or any of your party have special dietary requirements? Please advise the Motel at the time of booking your accommodation.

:

Provisional Programme

DAY	TIME	TITLE	SPEAKER
Friday	10.00	Museum workshop	Andrew and Frank
		Morning tea	
	13.00	IHC antigen retrieval workshop	Penny Marr
		Afternoon tea	
	18.00	Wine tasting	
Saturday	8.30	Registration	Kathy D +
	9.00	Opening	Simon
	9.15	FISH, CISH and Her2	Belinda Leahy
	9.55	Veterinary pathology	Ross Matthews
	10.35	Trade	
	10.40	Trade	
	10.45	Morning tea	
	11.15	Forensic DNA	Michelle Franco
	11.55	Breast Cancer and viruses	Prof. Jim Lawson
	12.35	Trade	
	12.40	Trade	
	12.45	Lunch	
	13.45	Trade	
	13.50	Trade	
	13.55	Haematoxylin	Dr Phil Baird
	14.35	Melanoma	Ruma Dutta
	15.15	Afternoon tea	
	15.45	Trade	
	15.50	Trade	
	15.55	Posters	
	16.15	Quiz	
	17.30	Happy Hour	
	19.00	St Pat's dinner	
Sunday	9.30	Body Identification in Kosovo	Dianne Little
	10.10	Flow cytometry	Mary Sartor
	10.50	Trade	
	10.55	Trade	
	11.00	Morning tea	
	11.30	Trade	
	11.35	Trade	
	11.40	Cut up for technicians	Tony Woods
	12.20	Posters	
	12.40	Renal EM	Paul Kirwan
	13.30	Lunch	

Abstracts from the Literature

Mechanisms of Heat-induced Antigen Retrieval: Does pH or Ionic Strength of the Solution Play a Role for Refolding Antigens?

Katsura Emoto, Shuji Yamashita and Yasunori Okada

J Histochem Cytochem 53:1311–1321, 2005.

We investigated the effects of pH and ionic strength of solutions used for antigen retrieval to elucidate the mechanism of heat-induced antigen retrieval (HIAR) in immunohistochemistry. The immunostaining intensity of nuclear, cytoplasmic, cell membrane, and extracellular matrix antigens with 17 different antibodies was evaluated in formaldehyde-fixed and paraffin-embedded mouse and human tissues. Deparaffinized sections were autoclaved for 10 min in buffers with different pH values ranging from 3.0 to 10.5. To test the influence of ionic strength on immunoreactions, the sections were autoclaved for 10 min in 20 mM Tris-HCl buffers (TB) at pH 9.0 and 10.5 with or without 25, 50, and 100 mM NaCl. There were two immunostaining patterns for pH dependency of HIAR. First, the majority of antibodies recovered their antigenicity when heated in the buffers with both acidic pH (pH 3.0) and basic pH (pH 9.0 and 10.5). Second, some antibodies showed strong immunostaining only at basic pH values (pH 9.0 and 10.5). When the sections were autoclaved in TB at pH 9.0, immunostaining of all eight antibodies examined decreased as the NaCl concentration increased. On the other hand, when the sections were treated with TB at pH 10.5, all antibodies yielded stronger reactions in the buffer containing NaCl than in the buffer without NaCl; five antibodies exhibited the strongest immunoreaction at concentrations from 25 to 50 mM. These results suggest that the extended polypeptides by heating are charged negatively or positively at basic or acidic pH, and that an electrostatic repulsion force acts to prevent random entangling of polypeptides caused by hydrophobic attractive force and to expose antigenic determinants, during cooling process of HIAR solution.

Discrepancies between clinical and autopsy diagnosis and the value of post mortem histology; a meta-analysis and review.

Roulson J, Benbow E W & Hasleton P S
Histopathology 47: 551–559, 2005

The autopsy is in decline, despite the fact that accurate mortality statistics remain essential for public health and health service planning. The falling autopsy rate combined with the Coroners Review and Human Tissue Act have contributed to this decline, and to a falling use of autopsy histology, with potential impact on clinical audit and mortality statistics. At a time when the need for reform and improvement in the death certification process is so prominent, we felt it important to assess the value of the autopsy and autopsy histology. We carried out a meta-analysis of discrepancies between clinical and autopsy diagnoses and the contribution of autopsy histology. There has been little improvement in the overall rate of discrepancies between the 1960s and the present. At least a third of death certificates are likely to be incorrect and 50% of autopsies produce findings unsuspected before death. In addition, the cases which give rise to discrepancies cannot be identified prior to autopsy. Over 20% of clinically unexpected autopsy findings, including 5% of major findings can be correctly diagnosed only by histological examination. Although the autopsy and particularly autopsy histology are being undermined, they are still the most accurate method of determining the cause of death and auditing accuracy of clinical diagnosis, diagnostic tests and death certification.

Histopathology and Immunohistochemistry in the Diagnosis of Bioterrorism Agents

Jeannette Guarner and Sherif R. Zaki

J Histochem Cytochem
54:–, 2006
From October to November 2001, the inhalational and cutaneous anthrax cases that occurred in the U.S. underscored the importance of recognizing the clinical and pathological features of infectious agents that can be used in acts of terrorism. Early confirmation of bioterrorist acts can only be performed by making organism-specific diagnosis of cases with clinical and pathologic syndromes that could be caused by possible bioterrorism weapons. Recognition and diagnosis of these cases is central to establish adequate responses. This review will examine the events that occurred during the anthrax bioterrorist attack with specific emphasis on the role of pathology and immunohistochemistry and will describe the histopathologic features of category A bioterrorism agents (anthrax, plague, tularemia, botulism, smallpox, and viral hemorrhagic fevers).

Application of Heat-induced Antigen Retrieval to Aldehyde-fixed Fresh Frozen Sections

Shuji Yamashita and Yasunori Okada

J Histochem Cytochem 53:1421–1432, 2005

We applied the heat-induced antigen retrieval (HIAR) to aldehyde-fixed fresh frozen sections based on a new approach (i.e., a rapid and complete immobilization of antigen followed by heating). Frozen sections were fixed with 10% formalin in 0.1 M cacodylate buffer (pH 7.4) containing 25 mM CaCl2 for 30 min, or with 0.5% glutaraldehyde in 0.1 M phosphate buffer (pH 7.4) for 1 min at room temperature, and then autoclaved in 20 mM Tris-HCl buffer (pH 9.0) for 10 min at 120C. Both fixatives yielded good tissue structure after autoclaving. In the sections fixed with formalin containing CaCl2, 20 of 22 antigens located in the nucleus, cytoplasm, membranes, and extracellular matrix greatly recovered their antigenicity after autoclaving; only two antigens exhibited stronger immunoreaction in acetone-fixed fresh frozen sections than these sections. Heating also retrieved the immunoreactivity of at least 14 antigens in the sections fixed with glutaraldehyde. We used the similar procedures to localize ligand-free estrogen receptor (ER) and glucocorticoid receptors (GR). Mouse uterine cells exhibited almost the same nuclear ER immunostaining regardless of the hormonal status in glutaraldehyde-fixed fresh frozen sections and unliganded GR was localized mainly in the nucleus of mouse hepatocytes in fresh frozen sections fixed with 20% formalin containing 50 or 75 mM CaCl2 at 40C, after autoclaving. These results demonstrate that HIAR is useful for the immunohistochemistry of many antigens in aldehyde-fixed fresh frozen sections.

Immunohistochemistry in bone marrow pathology: a useful adjunct for morphologic diagnosis

Marcus Kremer, Leticia Quintanilla-Martínez, Jörg Nährig, Christoph von Schilling and Falko Fend

Virchows Archiv Volume 447 Number 6 Pages: 920 - 937

Pathomorphological examination of trephine biopsies of the bone marrow (BM) represents a standard method for the diagnosis and staging of hematologic neoplasms and other disorders involving the BM. The increasing knowledge about the genetic basis and biology of hematologic neoplasms, as well as the recently proposed WHO classification system, provide the framework for an accurate diagnosis. Although conventional morphology remains the gold standard for paraffin-embedded BM trephines, immunohistochemical stainings have become an integral part of the diagnostic workup. Antibodies suitable for paraffin sections are generally applicable to BM trephines, but modifications of staining protocols may be necessary due to the alternative fixatives and decalcification procedures used for BM biopsies. The indications for immunostainings range from confirmation and classification of lymphoma involvement, subclassification of acute leukemias, and estimating blast counts in myelodysplastic and myeloproliferative syndromes to characterization of BM involvement in nonhematologic neoplasms. Although subtyping of NHL in the BM is more difficult from the point of morphology, classification of the entities that frequently involve the BM, especially the small B-cell lymphomas, can easily be achieved with the help of immunohistochemistry. In this review, we try to summarize the current state of the art in BM immunohistochemistry for the diagnosis of hematologic disorders. Moreover, diagnostic algorithms and useful antibody panels are proposed for a rational and cost-effective approach.

Update on Mast Cells

Editor's note: This a summary of a review article that appeared in volume 19 of Modern Pathology, written by New Zealand researchers Sydney Ch'ng, Richard Wallis, Lan Yuan, Paul Davis and Swee Tan.

Mast cells originate from the bone marrow and the immature progenitor cells migrate to peripheral tissues and mature in situ. Mast cells are not identified in the circulation.

Mast cells possess many properties that enable them to participate in a diverse range of biological activities. They phagocytose, process antigens, produce cytokines and release a variety of preformed (eg, histamine, proteoglycans and proteases) and newly formed (eg, leukotrienes and prostaglandins) physiological mediators. Mast cells carry an array of adhesion molecules, immune response receptors and other surface molecules which permit them to react to multiple specific and nonspecific stimuli. These wide-ranging biological characteristics, their ubiquitous distribution and strategic locations near blood vessels, nerves, inflamed tissues and neoplastic foci enable them to play a central role in a multitude of physiologic, immunologic and pathologic processes.

Studies have shown that mast cells accumulate around the margin of many cutaneous malignancies. There is compelling evidence that mast cell accumulation among the peritumoral inflammatory infiltrates contributes to a permissive microenvironment for carcinogenesis and metastasis.

The increased density of mast cells around many types of tumours is independent of the presence of an inflammatory infiltrate. It has been found that the degree of peribasal cell carcinoma inflammation does not correlate with the relative density of mast cells. This suggests that mast cells are preferentially recruited to the vicinity of basal cell carcinoma.

Histopathology studies on human basal cell carcinoma and squamous cell carcinoma have shown that mast cell density is especially high in the more aggressive variants. As well, the density of mast cell and microvessels is increased in melanoma compared to benign naevus and melanoma in situ.

Mast cells stimulate neovascularization at the tumour-host interface. The growth and metastasis of a tumour depends on its ability to elicit new blood supply. Acquisition of the angiogenic phenotype, which enables the tumour to establish its independent blood supply, represents an increase in malignancy potential.

Ch'ng et al (2006) in their review suggest that mast cells contribute to the tumourigenesis of cutaneous malignancies through four mechanisms:

(1) Immunosuppression: Ultraviolet-B radiation, the most important initiator of cutaneous malignancies, activates mast cells. Upon irradiation of the skin, trans-urocanic acid in the epidermis isomerizes to cis-urocanic acid, which stimulates neuropeptide release

from neural c-fibres. These neuropeptides in turn trigger histamine secretion from mast cells, leading to suppression of the cellular immune system.

(2) Angiogenesis: Mast cells are the major source of vascular endothelial growth factor in basal cell carcinoma and malignant melanoma. Vascular endothelial growth factor is one of the most potent angiogenic factors, which also induces leakage of other angiogenic factors across the endothelial cell wall into the matrix. Mast cell proteases reorganize the stroma to facilitate endothelial cell migration. As well, heparin, the dominant mast cell proteoglycan, assists in blood-borne metastasis.

(3) Degradation of extracellular matrix: Through its own proteases, and indirectly via interaction with other cells, mast cells participate in degradation of the matrix, which is required for tumour spread.

(4) Mitogenesis: Mast cell mediators including fibroblast growth factor-2 and interleukin-8 are mitogenic to melanoma cells..

The body of evidence presented thus far supports a tumorigenic role for mast cells in the development and progression of cutaneous malignancies but Ch'ng et al question whether this could be an incomplete portrayal of the mast cells. Could mast cells in fact fulfil opposing roles depending on the microenvironment in which they reside, playing the Jekyll and Hyde of tumour growth?

This dual role for mast cells certainly seems probable. Firstly, mast cells have a vast array of mediators, some of which have promoting, and others, inhibitory effects on malignancies. Secondly, the phenotypic expression of mast cell is not static and its secretory pattern alters according to the microenvironment. Mast cells have the ability to secrete individual granules (in contrast to indiscriminate degranulation in an anaphylactic reaction) or distinct mediators selectively. For instance, acidity inhibits allergic degranulation but promotes IL-4 production. IL-6 can be secreted without histamine in vitro; and murine mast cells can secrete VEGF without parallel release of serotonin.

Mast cell attracts as much interest as controversy today in a variety of physiological and pathological processes, including cutaneous malignancies. The divergence in opinion on the functional role of mast cell in these tumours is not surprising given its versatility and the plethora of mediators it secretes, which have wide-ranging and sometimes opposing effects. However, the great majority of studies to date support an accessory role for mast cells in the development and progression of cutaneous malignancies.

Reference:

Ch'ng et al (2006) Modern Pathology 19, 149-159

Chief’s Job at St Vincent’s

St Vincent's Pathology, SYDPATH
Senior Operations Manager, Anatomical Pathology

Applications are invited from suitably qualified and experienced Hospital Scientists (or equivalent) for the position of Senior Operations Manager, Anatomical Pathology.

The position involves overall supervision and management of the operations of the SydPath Histology and Cytology Laboratories (staff 23 FTEs). Responsibilities include the financial managament of budgets, maintaining asset registers, ensuring the maintenance of laboratory manuals and document control, stock management/ordering and peronnel managment and training.

Experience at a senior level in Histopathology/Cytology laboratory is essential, as are the management, communication and organiszational skills necessary to lead a team dedicated to the provision of high quality and timely tissue pathology results. Familiarity with NATA accrediation procedures, OH&S legislation, business case development and prior experience with personnel and budget management are highly desirable.

Enquiries may be directed to Dr A Morey, Director, Anatomical Pathology, St Vincent's Hospital, (02) 8382 9210.

Applications including the names of 3 referees should be addressed to: David Hodgson, General Manager, SydPath, Level 6 Xavier Building, St Vincents Hospital, Victoria St. Darlinghurst NSW 2010.

Closing date: 2nd March 2006.

The Children's Hospital at Westmead

and

The University of Sydney

UPDATE IN GENETIC MEDICINE 2006

16th – 17th March 2006

genzyme

SPEAKERS

Dr. Deya Corzo, M.D.
Medical Director
Genzyme Corporation, Cambridge

Dr. Jack Goldblatt
Department of Genetics
Princess Margaret Hospital for Children
The University of Western Australia

Dr. Peter Meikle
Head of National Referral Laboratory
Department of Chemical Pathology
Women's & Children's Hospital Adelaide

Dr. Liza Thomas
Consultant Cardiologist
Westmead Private Hospital
Lecturer
Faculty of Medicine, University of Sydney

Prof. Kathy North
Department Head
Neurogenetic Research, CHW
Associate Dean, CHW Clinical School
The University of Sydney

Dr. Ian Alexander
Department Head
Gene Therapy Research Unit, CHW

Dr. Bruce Bennetts
Department Head
Molecular Genetics, CHW

Dr. Greg Peters
Department Head
Cytogenetics, CHW

Prof. David Sillence
Department Head
Academic Department of Medical Genetics, CHW

Dr. Bridget Wilcken
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Department Head
Biochemical Genetics, CHW

Dr. Veronica Wiley
Department Head
Newborn Screening, CHW

Dr. Meredith Wilson
Department Head
Clinical Genetics, CHW

TRAVEL INFORMATION

The Children's Hospital at Westmead is located on the corner of Hawkesbury Road and Hainsworth Street, Westmead. Parking is available at the visitor parking station located on Hainsworth Street (near the roundabout) at a flat rate of $12 per day.

For more information please visit
http://www.chw.edu.au/about/location/

ACCOMMODATION

Can be booked through Crowne Plaza Parramatta on 61+2+9689 3333, or Wesley Lodge Westmead on 61+2+96351233. Please advise that you are attending a seminar at the Children's Hospital. Accommodation for out of town speakers has already been booked.

REGISTRATION DETAILS:
(PLEASE USE CAPITALS)

Preferred Name for badge _____ Title _____

First Name _____ Last Name _____

Position _____ Department _____

Organisation _____

Street Address _____

Suburb or City _____ State _____

Postcode _____ Country _____

Telephone (Work) _____ Fax (Work) _____

E-mail _____

ATTENDANCE: (Please select)

☐ 16/03/2006 (Thursday) ☐ 17/03/2006 (Friday)

SPECIAL DIETARY REQUIREMENTS:

✂

Please forward completed registration form

By mail ✉: Short course
Academic Department of Medical Genetics
The Children's Hospital at Westmead
Locked Bag 4001
Westmead NSW 2145
Australia

By fax 🖷: + 61 2 9845 0684

By E-mail 🖱: KancyH@chw.edu.au

For more details please contact: Dr. Angela Beaton AngelaB4@chw.edu.au

To avoid disappointment and to assist with catering numbers please register by **Friday 3rd March 2006.**

This course is funded by an unrestricted educational grant from Genzyme, Australasia. No fee is payable by registrants.

UPDATE IN GENETIC MEDICINE 2006

Thursday 16th – Friday 17th March 2006
Lorimer Dods Lecture Theatre, Level 4
The Children's Hospital at Westmead

PROGRAM DESCRIPTION AND OBJECTIVES

- To provide an update of trends in genetic medicine
- To address emerging therapies for genetic metabolic disorders in adult medicine with an emphasis on neuromuscular disorders and cardiomyopathies

PROVISIONAL PROGRAM

Thursday, 16 March 2006

12:30 – 1:00	Registration
1:00 – 2:00	Children's Hospital at Westmead Weekly Grand Rounds
2:00 – 2:15	Welcome and Introduction
2:15 – 3:00	Glycogen Storage Diseases type II (Pompe disease) and its treatment in childhood
3:00 – 3:30	Afternoon Tea
3:30 – 4:00	Enzyme Replacement Therapy Past, Present and Future
4:00 – 4:40	Prospects for treatment of muscle diseases in children due to defects in Structural Proteins
4:40 – 5:20	Gene Therapy
5:20 – 6:00	Drinks will be available following the final talk of the day

Friday, 17 March 2006

Genetic Therapies 2006

8:45 – 9:30	Gaucher Disease in Children – Future prospects
9:30 – 10:15	Pompe Disease
10:15 – 10:45	Morning Tea

Diagnosis and Investigation in Genetic Medicine

10:45 – 11:25	Update in Cytogenetics
11:25 – 12:05	Update in Molecular Genetics
12:05 – 1:30	Lunch

Newborn Screening

1:30 – 2:00	International Perspective on Screening and Testing for IBE's
2:00 – 2:30	Newborn Screening by Tandem Mass Spectrometry
2:30 – 3:00	Newborn Screening for LSDs
3:00 – 3:30	Afternoon Tea

Fabry Disease and Cardiomyopathies

3:30 – 4:00	Fabry Disease
4:00 – 4:30	Heritable Cardiomyopathies

REGISTRATION INCLUSIONS:

- Morning Tea, Lunch, Afternoon Tea
- Certificate of Attendance
- Symposium Materials

2005 - 2006

I wish to become a member of the Histotechnology Group of N.S.W. and enclose

PLEASE TICK

- ☐ $38.50 for annual subscription of $35.00 and $3.50 GST.
- ☐ $16.50 for student subscription of $15.00 and $1.50 GST
  (Full-time or working toward first qualification)
- ☐ $82.50 for company subscription of $75.00 and $7.50 GST
  (2 representatives, one of whom must be a NSW representative)
- ☐ RENEWALS ☐ ANY CHANGES TO PREVIOUS DETAILS.

PLEASE PRINT ALL INFORMATION.

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TITLE: MR, MRS, MS, DR, MISS. (Circle one)

OCCUPATION_____POSITION_____

INSTITUTION_____DEPARTMENT_____

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2ND COMPANY CONTACT

SURNAME_____ GIVEN NAME_____

TITLE: MR, MRS, MS, DR, MISS. (Circle one)

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