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ICPALM 2023: International speakers

1. Anatomical Pathology

Molecular classification of gastric carcinoma
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Poundbury Cancer Institute.

During the past two decades there has been significant improvement of cancer outcomes due, at least in part, to increasing use of biological therapies. This requires the identification of specific subgroup of patients that may benefit from particular targeted treatment. The classical morphological classification of tumours is inadequate to support this transformation of treatment modalities. New molecular classifications have emerged for a number of cancer sites, based on comprehensive analyses of large number of parameters ("multi-omics"). In order to make it accessible to all patients, multi-omics classifications have been implemented into the histopathology diagnostic routine using a handful of on-slide tests.

Such implementation has yet to happen in gastric cancer (GC) and patients access to effective targeted treatment remains limited. We present an overview of the current molecular classification for gastric cancer and a study to assesses the feasibility of implementing a molecular classification based on 4 groups of on-slide tests. These are ISH for EBER (for the identification of GC EBV+), IHC for MLH1 and MSH2 (for the identification of GC MMR-deficient), IHC for E-cadhering and β-catenin (for the identification of GC EMT or epithelial-mesenchymal transformation) and IHC for p53 (for the identification of p53 mutated and p53 wild type GC). The prognostic and predictive implications for GC patients will be discussed.

Rewriting the Her2 testing handbook
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Histopathologists have been providing Her-2 status for breast cancer (BC) patients for over 4 decades. Testing aimed at identifying a small (12-15%) proportion of BC patients that have Her2 gene amplification as a main oncogenic driver in their cancer. Direct blocking of the Her2 receptor with mAb-based therapy is an effective treatment only in patients with Her2 over-expression or amplification.

Recently, targeting Her2 with specific antibodies that deliver cytotoxic payloads inside the tumour cells (ADC or antibody-drug conjugates) has shown effectiveness also in BC that has low level expression of Her2 but lacks amplification. Regulatory approval of this treatment means de facto that the traditional binary classification (positive/negative) has to be replaced with a new ternary classification (high/low/zero) and that the interpretation of the IHC staining needs to be re-focused to recognise the new thresholds.

We developed focused algorithms and training programmes for the interpretation of Her2 IHC in the new diagnostic landscape. We will be discussing the re-evaluation of the scope and parameters for Her2 testing in BC with particular focus on the analytical performance of current tests, the identification of various staining patterns and their significance, the interpretative algorithm and the new (2023) release of the ASCO-CAP and RCPath guidelines.

Surgical pathology of low-grade epilepsy-associated neuroepithelial tumors (LEAT): role of molecular genetic testing and surrogate immunohistochemical markers
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Low-grade epilepsy-associated neuroepithelial tumors (LEAT) is a generic term for CNS WHO grade 1 to 2 or equivalent tumors, with epileptic seizures as the main symptom developing mostly by the age of 15 years, and 88% of patients show a favorable postoperative seizure outcome, representing a clinicopathological concept distinct from the WHO classification of brain tumors. A past survey reported that the majority of LEAT consisted histopathologically of neuronal and mixed neuronal-glial tumors frequently localized in the temporal lobe, with ganglioglioma (GG) and dysembryoplastic neuroepithelial tumor (DNT) being the most common histopathological diagnoses comprising 60 to 90 % of cases. However, disagreement between experts on diagnosing GG and DNT was not uncommon, particularly when specific histological features were not

MM26: *Salmonella enterica* serotype Agona in infant with meningitis and cerebral abscess

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Introduction: Salmonella meningitis is an uncommon form of intracranial infection, particularly in infants. It remains a threat with severe complications. *Case report:* A 6-month-old girl presented with fever, vomiting and seizure. Due to impending status epilepticus, she was intubated and empirically treated for meningoencephalitis. The patient had no sick contact but started consuming formula milk in addition to breastfeeding before the onset of symptoms. Neurological examination revealed hypertonia of all four limbs and the contrast CT brain reported as asymmetrical bilateral thalamic changes, white matter lesion and cerebral oedema. Her blood and cerebrospinal fluid cultures yielded gram negative rod, non-fermenter organism with abundant hydrogen sulphide, positive for O and H antigen but negative for Vi antigen. Vitek 2.0 (BioMérieux, USA) named the organism as *Salmonella spp*. The serotyping test (Bio-Rad, USA) revealed *Salmonella enterica* serotype Agona. The organism was resistant to ampicillin, susceptible to amoxicillin-clavulanate, ceftriaxone and ciprofloxacin. Despite seven days on intravenous ceftriaxone, the patient had persistent temperature and MRI brain showed bilateral deep grey and white matter abscess and frontotemporal empyema. The patient's condition was improved after 4 weeks of intravenous ceftriaxone and 3 weeks of intravenous ciprofloxacin before being transferred to another hospital. The antimicrobial was continued for another 3 weeks before being discharged home. *Discussion: Salmonella spp*. infection has been linked to contaminated breast milk. *Salmonella* Agona can survive powdered milk products up to 180 days. Multiple outbreaks of *Salmonella* Agona in infant milk products had been reported in France. The knowledge on proper milk storage and handling can reduce risk of infection.

MM27: A rare case of infective endocarditis caused by *cfiA*-positive *Bacteroides fragilis*

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Introduction: Bacteroides fragilis is an anaerobic gram-negative bacillus that is part of the normal flora in the human gastrointestinal tract. Anaerobic bacteria are an uncommon but important cause of infective endocarditis, which accounts for 2–16% of all cases. We report here a case of infective endocarditis caused by a rare multidrug-resistant strain of *Bacteroides fragilis*. *Case report:* A 58-year-old lady with underlying end-stage renal failure presented with a sudden onset of left-sided body weakness, facial asymmetry, and slurred speech. Plain CT-brain showed multifocal acute infarcts and subsequently, a transthoracic echocardiogram revealed vegetation measuring 0.95cm by 0.52 cm over the lateral tricuspid annular. She was empirically started on intravenous cefazolin and ampicillin-sulbactam. However, no growth was obtained from the three sets of blood cultures taken upon admission. A fourth set of blood cultures was taken as her condition was not improving. The anaerobe blood culture was positive for gram-negative bacilli. The isolate was identified by MALDI-TOF MS as *cfiA*-positive *Bacteroides fragilis*. Antibiotic susceptibility testing using E-test showed resistance to amoxicillin-clavulanic acid (>256 µg/ml), ceftriaxone (>256µg/ml), imipenem (>32 µg/ml), piperacillin-tazobactam (>256 µg/ml) and meropenem (>32 µg/ml). Her condition deteriorated and she passed away due to infective endocarditis with cerebral infarction. *Discussion:* A higher mortality rate among patients with anaerobic infective endocarditis can be due to the delay in diagnosis. In addition, the absence of effective antibiotic in this patient further contributed to poor prognosis. Utilisation of MALDI-TOF MS in rapid identification of cfiA-positive strain is useful in directing patients management to reduce morbidity and mortality.

MM28: Fatal disseminated melioidosis in an unlucky middle-aged lady due to delay in diagnosis

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Introduction: In Malaysia, Melioidosis is not a notifiable disease but has a very high mortality rate, especially in diabetic patients. The disseminated case is potentially fatal. About 16–37% of cases, present with indefinite presentation, and some with clinical signs of abscess formation in multiple organs with or without bacteraemia. We report a fatal case of disseminated melioidosis in diabetic patients due to a delay in diagnosis. *Case report:* 49 years old lady with underlying diabetes mellitus with diabetic foot ulcer presented with a disseminated melioidosis clinical manifestation with the initial presentation was a history of dyspnoea later on, developed abdominal pain and persistent fever, and subsequently went into septicaemia. She was initially misdiagnosed as NSTEMI, chest x-ray showed a fluid overload picture and due to the low septic parameter, no antibiotic was prescribed. Later on, she was empirically covered with intravenous ceftriaxone and intravenous metronidazole for almost 5 days for acalculous cholecystitis based on ultrasound abdomen and Contrast Enhanced CT scan (CECT) results at that time. However, no sonographic evidence of gallbladder empyema. Diagnosis of septic shock secondary to disseminated melioidosis was only made later after observation of laboratory findings and her condition deteriorated further on day 10 of admission developing septic shock, acute kidney injury, coagulopathy, and transaminitis and required intubation. Repeated Chest x-ray shows worsening pulmonary infiltrate. The treatment was upgraded to intravenous meropenem. However, the patient succumbed after 16th day of hospitalization. *Discussion:* Diagnostic challenge in this patient was that there is no pathognomonic presentation in Melioidosis. The diagnosis of Melioidosis was not apparent in this patient until the blood culture and sensitivity show a Gram-negative rod and the final results show *B.pseudomallei*. She has very vague symptoms that initially were misdiagnosed with the addition of the initial culture being negative which further caused delays in diagnosis.