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ICPALM 2023: International speakers

1. Anatomical Pathology

Molecular classification of gastric carcinoma
Corrado DÁrrigo
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

CP15: Under-five mortality due to inborn errors of metabolism in Malaysia

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Introduction: A fatal severe enzyme deficiency or a co-factor in a metabolic pathway may result in early childhood mortality. The aim of this study was to review the mortality rate of children less than five years old in Malaysia with a diagnosis of inborn errors of metabolism (IEM). *Materials & Methods:* Secondary data were obtained from Malaysian children aged five years old or less who were diagnosed and died with IEM. 36,467 patients' samples underwent selective screening between January 2015 to December 2021. *Results:* Forty-two cases of under-five mortalities were found. 69% aged one month; 31% aged between one month to three years old. 57% were male. Ethnic distribution: Malays (80%), Sabah and Sarawak (7%), Indian (5%) and Chinese (5%). Fatty acid oxidation disorder contributed the most common diagnoses (50%) compared to organic aciduria (21%), urea cycle defect (19%), and congenital lactic acidosis (10%). The 7-year average mortality rate related to IEM in children < five years old per 10,000 population at risk in Malaysia was 1.6 with a range of 0 to 3.8. *Discussion:* There is a variable mortality rate between states in Malaysia. Apart from traditional values of health beliefs and socioeconomic factors, the availability of genetic services may play a major role in detecting IEM as the cause of death in these children. As expanded newborn screening is shown to prevent early mortality, it is only appropriate for all sectors including public, private and non-governmental organisations to contribute more towards preventive healthcare in children.

CP16: Do we need daily analysis of beta-human choriogonadotropin?

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Introduction: Beta-human choriogonadotropin (β-HCG) analysis is useful for screening, diagnosis and monitoring of many reproductive-related diseases. β-HCG analysis is currently offered on every other day in our laboratory, the Chemical Pathology unit, at the state hospital. However, requests have been made by our clinical colleagues to offer β-HCG analysis daily to assist their clinical management. *Material & Methods:* We conducted a 10-week audit in our Chemical Pathology unit, at the state hospital, to determine the cost-effectiveness of daily β-HCG analysis based on our laboratory workload. *Results:* A total of 521 β-HCG tests were requested during the 10 weeks audit period and none of these requests were made as urgent test requests. 123 tests were for pregnancy of unknown location, 110 were for malignancy cases and the remaining were for ectopic pregnancies, molar pregnancies, miscarriages, and gestational trophoblastic disorders. 265 tests were registered on the analysis day and 256 on non-analysis day. Based on the calculation of reagent and quality control material costs, the total weekly cost for daily and every other day analyses of β-HCG were RM296.60 and RM186.30, respectively. This cost difference can cover approximately 500 additional tests per year. *Discussion:* Testing is considered as not cost-effective if daily analysis is less than 30 tests. Clinically, β-HCG is not a diagnostic marker for molar pregnancies, ectopic or pregnancies of unknown location. We recommend that every other day analysis of β-HCG is still cost-effective without affecting the clinical outcomes.

CP17: Rare among the ultra-rare: Report of the first confirmed case of N-acetylglutamate synthase (NAGS) deficiency in Hospital Tunku Azizah

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Introduction: N-acetylglutamate synthase (NAGS) deficiency is the rarest of the urea cycle disorders that, if left untreated, results in hyperammonaemia and significant morbidity and mortality. *Case Report:* A boy was born at term via caesarean section to non-consanguineous parents with birth weight of 3.1kg and good Apgar scores, following an uneventful pregnancy. He was the second child with a healthy sibling. He presented at 59 hours of life with grunting and respiratory distress requiring ventilatory support. He suffered from hypotonia, poor feeding, lethargy, seizures with progressive encephalopathy and EEG showed a burst suppression pattern. Hyperammonaemia was detected at day 6 of life, and he received acute management including peritoneal dialysis, protein restriction, ammonia scavengers and carbamylglutamate, which successfully treated the hyperammonaemia. *Disucssion:* Initial laboratory investigations showed profound hyperammonaemia (>750 mmol/L), with elevated lactate (6.4 mmol/L) and transient impaired renal profile. Plasma aminoacidogram showed significant raised levels of glutamine, glycine, alanine and lysine with mild increased of glutamate and proline along with undetected citrulline and normal arginine. Similar findings were observed from dried blood spot analysis with marked elevation of alanine, proline and glutamate with low citrulline and low normal arginine. Urinary organic acids showed severe lactic aciduria with the absence of orotate. A proximal urea cycle defect was highly suspected and molecular genetic studies confirmed the diagnosis of NAGS deficiency with the identification of two *compound heterozygous* pathogenic variants in the *NAGS* gene (NM_153006.2) with *c.846dupC* inherited from his father and *c.854_858delins GACGCA* inherited from his mother. Genetic counselling was given. This case illustrates the importance of early detection of neonatal encephalopathy due to hyperammonaemia and the