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Appendix **APP 1 (1-10)**

XIII Memorial Gaetano Barresi – Syllabus

Abstracts of Oral Communications presented at the Memorial by representatives of Italian Postgraduate Schools in Morbid Anatomy

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Introducing Member and Guest Editor: Giovanni Tuccari
Associate Guest Editors: Antonio Ieni, Guido Fadda

Introduction

On Friday 14th February 2025, a scientific meeting has been realized to celebrate the memory and academic activity of prof. Gaetano Barresi, a well-distinguished full professor of Pathology at the University of Messina, suddenly died in 2012. After the institutional greetings performed by prof.ssa Giovanna Spatari, Magnificent Chancellor of the University of Messina, some additional messages have been done by Coordinators of different Medical Courses.

The workshop was introduced by prof. Francesco Trimarchi, director of II^ Class (Medical-biological Sciences) of the Accademia Peloritana dei Pericolanti and by prof. Giovanni Tuccari, doyen of the National College of Pathology Professors. Three sessions have been scheduled.

The first concerning "La Scuola Messinese di Anatomia Patologica" has been perfomed by prof. Cosimo Inferrera, already full professor of Pathology, which illustrated the historical profile of Pathological Anatomy in Messina University. In its speech, all previous scientific actors, starting from prof. Filippo Battaglia, have been recorded, also stressing the main fields of diagnostic applications, teaching and scientific developments. Therefore, academic activity of proff. Antonino Ferrara, Paolo Barone, Dario Batolo, Pasquale Calapso, Giuseppe Carrozza, Vittorio Cavallari, Piero Antonio Nicotina, Salvatore Galatioto, Maddalena Grosso, Rosario Alberto Caruso, Giuseppe Speciale, Giuseppe Sippelli has been mentioned and commented.

In the second session, proff. Giuseppe Giuffrè, Antonio Ieni, Maria Lentini and Giovanni Tuccari, all components of the Scuola Messinese di Anatomia Patologica during the last three decades, have upgraded and summarized the actual lines of research as well as the modern technology acquired. Finally, prof. Guido Fadda, Dean of the post-graduated Specialty School of Pathological Anatomy reported the more significant financial grants obtained by PNRR program, in order to develop new scientific projects.

In the third session, the significance of professional progression in Pathology has been largely documented by a series of scientific reports presented by young researchers coming from the University of Naples, Rome, Palermo, Catania, Salerno, Campobasso and Messina. Under the chair of Dr. Vincenzo Fiorentino and Valeria Zuccalà, seven presentations have been performed and discussed, concerning fine needle cytology in lymph nodes as well as biomarkers evaluation in cytological samples, impact of artificial intelligence for HER2 detection in breast cancer as well as the application of Oncotype in breast clinical practice, morphological, immunohistochemical and neuroradiological characteristics of primitive B large cell diffuse lymphoma occurring in brain as well as the homozygous deletion of CDKN2A/B in gliomas; finally, some reports have been related to the occurrence of rare tumors in Lynch Syndrome.

Abstract #1

Interobserver agreement in PDL1 evaluation on cytological samples: a multi-institutional international study

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Objectives

The aim of this study is to assess interobserver agreement for PD-L1 scoring of non-small cell lung cancer (NSCLC) on cytological samples by using the cell block-derived tissue microarray (cbTMA) approach through a multicenter study.

Methods

65 cell blocks (CB) of NSCLC (n= 36 FNAs lung tumors and n= 29 pleural effusions) were retrospectively collected for the cbTMAs preparation. Hematoxylin&Eosin and PD-L1 stained slides were digitalized and uploaded on a free web sharing platform (PathPresenter). Participants provided PD-L1 scoring by using the clinically relevant cutoff of Tumor Proportion Score (TPS) (<1%; 1-49%; >50%). Overall and for each cutoff agreements were calculated using Fleiss's kappa for multiple raters.

Results

A total number of 54 CB were used for the preparation of 4 TMAs; 11 were deemed not suitable; 31 cytopathologists from 21 different institutions in 9 countries independently scored all the cores: a total of 1674 evaluations were provided. Statistical analysis showed moderate overall agreement (k = 0.49). The highest agreement was achieved in TPS>50% category (k = 0.57); a moderate

agreement was observed in TPS<1% category (k =0.51). The lowest kappa value was obtained for TPS <1-49% category (k = 0.32).

Conclusions

As far as we know, the present study is the largest interobserver concordance study in PD-L1 assessment on cytological samples. We assume that the high volume of PD-L1 assessments and the multicentricity of our study reflect more accurately the heterogeneity of real-life clinical practice, thus explaining the lower kappa values observed compared to literature data. The overall moderate agreement highlights that improvement is still needed in inter-pathologist agreement for PD-L1 evaluation on cytological samples. Sample preparation standardization, focused training in PD-L1 evaluation on cytological material, its inclusion in External Quality Assessment and machine learning-derived image analysis tools could improve interobserver agreement.

The Authors declare no conflict of interest

Abstract #2

Morphologic, immunophenotypic and neuroradiological characteristics of primitive B – large cells diffuse lymphoma occurring in the central nervous system: a retrospective cohort analysis

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Objectives

Diffuse Large B Cell Lymphoma (DLBCL) accounts for 2-3% of all Central Nervous System (CNS) tumours, most of which involves supratentorial sites of adult patients1. We have analysed the immunohistochemical profile in a cohort of CNS DLBCLs to verify if this expression may reveal a correlation with clinicopathological and neuroradiologic parameters of the patients.

Materials and Methods: 23 cases of CNS DLBCLs were neurosurgically obtained (8 M, 15 F). For all cases, clinicopathological features, such as age, gender and location of the tumours were collected. Immunohistochemical analysis with B-cells markers (CD20, CD79a, PAX5), BCL2, CD10, BCL6, MUM1 and c-Myc was performed, as well as the assessment of Ki67 labelling index. Hans algorithm has been applied to subtype DLCBLs in Germinal type (GC) and Not Germinal

type (Activated B-Cell Lymphoma, ABCL)2. MRI images were collected in T1, T2, post-contrast, and diffusion-weighted imaging (DWI), considering the Enhancement value as an expression of the blood-brain barrier (BBB) alteration3. A univariate statistical analysis was performed using Fisher's exact test and the MedCalc software to identify statistically significant associations between the clinicopathological, immunohistochemical, and radiological variables. A multivariate analysis was then conducted to assess the independent effects of these variables on overall survival (OS).

Results

The most frequent location of DLBCLs was confirmed in supratentorial sites, with invasion of midline structures; 7 cases presented as a single lesion, while 11 were multifocal disease. All cases showed a positive expression of CD20, PAX5 and CD79a; 21 cases showed a positive expression of BCL2. Ki67 labelling index mean value was 80%. 17 cases were classified as ABCL and 6 as GC. A statistically significant association between site of disease and number of lesions (p=0,04), site of disease and subtype (p=0,03), IHC subtype and mean Enhancement value was documented (p = 0.008).

Conclusions

This study confirms that DLBCLs with non-GC immunohistochemical profile include mostly patients with unfavourable prognostic factors, such as age > 60 years and high Ki67 labelling index, and poor prognosis, compared with DLBCLs with GC profile. A statistically significant association was found between disease location and the number of lesions (p = 0.04), between disease location and IHC subtype (p = 0.03), and between IHC subtype and the mean Enhancement value (p = 0.008), which may serve as a predictor for the IHC subtype, but it doesn’t reach prognostic significance. Multivariate analysis and Kaplan-Meier curves revealed that only the IHC subtype was an independent prognostic factor, with GC cases showing longer overall survival and a better prognosis compared to ABCL cases (p=0,0158).

The Authors declare no conflict of interest

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Abstract #3

Oncotype DX in clinical practice: impact on treatment decision and cost-effectiveness

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Objectives

Genomic evaluation of early breast cancer is part of current clinical practice (1). The aim of this study is to estimate the impact of Oncotype DX genomic test on both treatment decisions and economic burden in Italian institution experience.

Materials and Methods

Data were retrospectively collected from Fondazione Policlinico Universitario Campus Bio-Medico of Rome. Oncotype DX was performed on 313 female patients with HR-positive and HER2-negative breast cancer between August 2020 and January 2024. Clinical and pathological data were collected. To presume the oncological prescription on the basis of clinicopathological variables, we used PREDICT 2.2 algorithm. From Oncotype DX reports, Recurrence Score, Recurrence Risk and chemotherapy benefit were collected.

Results

According to Oncotype DX results, chemotherapy treatment was not recommended in 223/313 (71,2%) patients, whereas in PREDICT 2.2 scenario 147/313 (47%) patients were not recommended chemotherapy. Taken together, genomic test led to a general decrease of 24,2% in chemotherapy prescription if compared to traditional clinicopathological approach. Moreover, we tracked one-year follow-up hospital costs for 63 patients of our cohort. Patients receiving chemotherapy and endocrine therapy (15/63) had a median reimbursement of €11.746 (IQR: €10.485,5 - €14.124,5); whereas patients receiving endocrine therapy only (48/63) had a median reimbursement of €8.935 (IQR: €6.402,75 - €10.683,5).

Conclusions

Our study shows that Oncotype DX performance results in lower rates of chemotherapy prescription and in possible healthcare system cost savings. Further research is needed to expand genomic tests applicability in real practice to personalize treatment options.

The Authors declare no conflict of interest

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Abstract #4

Rare tumors in Lynch syndrome: two case reports

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Introduction

Lynch syndrome (LS) is a hereditary disorder caused by variants in DNA mismatch repair (MMR) genes, resulting in increased mutation rates and promoting many epithelial cancers (gastric, intestinal, endometrial, bilio-pancreatic)[1]. We discuss two cases rarely reported as related to LS cases: a case of Undifferentiated Pleomorphic Sarcoma (UPS) and a case of sarcomatoid Hepatocarcinoma (HCC).

Clinical cases

Case 1: 65-year-old woman with a dorsal subcutaneous lesion, previously diagnosed for LS, developing several tumors (colon, endometrial, urothelial) over her lifetime.

Case 2: 77-year-old woman with a hypoechogenic liver nodule. Her family history includes uterine carcinoma

(mother), colon carcinoma (brother and nephew) and a son died from colon cancer at age 20.

Materials and Methods

In both cases Fine Needle Biopsies (FNB) were stained with hematoxylin & eosin (H&E) and immunohistochemistry (IHC).

IHC panel for case 1: vimentin, desmin, myogenin, caldesmon, MDM2; for case 2: panCK, vimentin, glutamine synthetase (GS), HepPAR1, Glypican 3, CK7, CK19. Based on clinical history, microsatellite instability (MSI) was also evaluated in both cases (MLH1, PMS2, MSH6, MSH2).

Results

Case 1: H&E and IHC staining showed a poorly differentiated mesenchymal neoplasm with spindle cells positive for vimentin, desmin and focally myogenin, leading to a diagnosis of UPS with rhabdomyoblastic differentiation. MDM2 FISH indicated Chr12 polysomy.

Case 2: H&E and IHC staining showed a poorly differentiated neoplasia with spindle cells and necrosis, positive for panCK, vimentin, GS and negative for HepPar1, Glypican3, CK7, and CK19, leading to a diagnosis of HCC – sarcomatoid variant.

In both cases, the nuclear expression for MSH2 and MSH6 was absent.

Conclusions

The absence of MSH2 and MSH6 suggests MMR deficiency and MSI in both tumors, linking UPS and HCC– sarcomatoid variants to LS rather than sporadic neoplasms. In case 1 immunotherapy was administered with reduction of the mass. This highlights the importance of considering LS diagnosis also in unusual LS- correlated neoplasias and detecting MMR proteins to assess immunotherapy suitability.

The Authors declare no conflict of interest

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Abstract #5

Development of an AI model for HER2 detection in BC: an added value in interpreting HER2-low cases.

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Objectives

The aim of this study was to create an Artificial Intelligence (AI) model to improve the diagnostic accuracy and standardization of HER2 expression assessment in Breast Cancer (BC), reducing inter-observer variability, and identifying patients who fall into the HER2-low category (and HER2-ultra low in a prospective manner).

Materials and Methods

119 BC slides immunostained for HER2 were selected from the archive of the Surgical Pathology Section of the University of Naples "Federico II". We manually annotated the Whole Slide Images (WSI) using the QuPath platform, distinguishing six classes: HER2 negative, 1+, 2+, 3+ tumor areas, stroma, and background tiling the annotated ROIs to build the training/validation dataset. We built a classification model based on a pre-trained ResNet-50; finally, we validated the model

on a different pool of WSIs, taking advantage of the WSInfer framework and a dedicated QuPath extension.

Results

In both annotated and non-annotated regions, our model identifies clusters of cancer cells and classifies them into the appropriate categories. It can distinguish varying levels of HER2 expression within the same sample, which is crucial in cases with heterogeneous expression. Furthermore, in instances where the overall HER2 score is considered ultralow and designated as negative, the model primarily classifies cancer cells as HER2 negative, while also identifying a subset as HER2 1+.

Conclusions

Our AI model has demonstrated exceptional performance in identifying BC and interpreting HER2 expression. In clinical settings, it has the potential to significantly enhance diagnostic accuracy, particularly in differentiating between HER2-negative and HER2 1+ cases. Additionally, the model excels at identifying cases with HER2 heterogeneity or exhibiting an ultralow HER2 score, accurately characterizing these instances as a mixture of predominantly negative areas with a smaller proportion of 1+ regions.

The Authors declare no conflict of interest

Abstract #6

Homozygous deletion of CDKN2A/B in gliomas: comparison of immunohistochemistry for MTAP, FISH and NGS

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Objectives

Homozygous deletion (HD) of CDKN2A/B is commonly found in pleomorphic xanthoastrocytomas (PXA). This deletion can be predicted by the loss of immunohistochemical methylthioadenosine phosphorylase (MTAP) [1], encoded by a gene on chromosome 9p21. MTAP immunostaining as a predictive tool may reduce diagnosis time and cost compared to FISH and/or next-generation sequencing (NGS) [2].

Materials and Methods

We assessed the accuracy of MTAP immunostaining in 7 PXA cases. Samples were analyzed for copy number variations and mutations across 409 genes using NGS and for CDKN2A/B HD using FISH.

Results

Two PXAs exhibited MTAP loss and CDKN2A/B HD in both FISH and NGS. Five cases retained MTAP: three had disomic CDKN2A/B in FISH and NGS, while two were disomic in FISH but showed CDKN2A or CDKN2A/B HD in NGS. MTAP loss predicted CDKN2A/B HD by FISH with 100% sensitivity and specificity but 50% sensitivity by NGS.

Conclusion:

The discrepancy between FISH and NGS results may stem from FISH's inability to detect microdeletions in the 9p21.3 region, which includes CDKN2A, CDKN2B, and MTAP. This suggests that the reliability of FISH in detecting isolated CDKN2A/B deletions should be further studied for diagnostic purposes.

The Authors declare no conflict of interest

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Abstract #7

From smear to diagnosis: the role of ancillary techniques in lymph node fine-needle cytology

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Objectives: Diagnostic accuracy of lymph node fine-needle aspiration cytology (LN-FNAC) relies on proper management of diagnostic material and ancillary techniques (AT). Immunocytochemistry (ICC), flow cytometry (FC), and fluorescence in situ hybridization (FISH) play a crucial role in diagnosing LN-FNAC in reactive processes, Hodgkin lymphoma (HL), non-Hodgkin lymphoma (NHL), and metastases. While the role of AT in LN-FNAC has been extensively highlighted, their actual impact on diagnostic accuracy remains underexplored in the literature. This study aims to analyze the impact of AT on the diagnostic accuracy of LN-FNAC.

Materials and methods: A retrospective analysis was conducted on 452 LN-FNAC samples, retrieved from the database of the Pathology, Cytopathology, and Molecular Department at the University Hospital of Salerno (Italy), performed between 2021 and 2024. AT were applied in 187 cases based on clinical indications and/or rapid on-site evaluation (ROSE). All these cases were reclassified according to the Sydney System, initially without AT and subsequently with AT information. The impact of AT on the final diagnoses was categorized as follows: "non-contributory", for cases where AT yielded inadequate results; "confirmed", when AT confirmed the initial diagnosis; "improved", when AT further refined the diagnosis, and "allowed", when AT enabled a diagnosis that could not have been reached without AT.

Results: A comparison of diagnostic categories before and after applying AT revealed a significant impact on the final diagnosis. The analysis showed the following results: AT confirmed the FNAC diagnosis in 19.79% of cases (n = 37/187); AT improved the FNAC diagnosis in 36.36% of cases (n = 68/187); AT allowed a diagnosis that otherwise could not have been made in 37.97% of cases (n = 71/187); and AT was non-contributory in 5.88% of cases (n = 11/187).

Conclusions: This analysis shows that AT significantly refined diagnoses in a significant proportion of cases, with nearly 95% of cases showing either improvement, confirmation, or completely new diagnosis made possible by AT. These findings highlight the importance of utilizing and incorporating AT in the LN-FNAC to achieve more precise and reliable diagnoses, ultimately enhancing patient management and outcomes.

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