Session 1: Tumour Neuropathology

Abstract 1

Pathological features determining recurrence and radioresistance in cerebral atypical meningioma

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We examined recurrence after gross total resection (GTR) or subtotal resection (STR) at St. Michael's Hospital, Toronto, of 181 cases of atypical meningioma (WHO grade II). In the entire group, Kaplan-Meier survival curves showed that combined necrosis and brain invasion was the feature associated with the worst outcome, followed in order by necrosis, histological variants (clear cell, rhabdoid, and chordoid), high mitotic count, and brain invasion. The highly significant difference between necrosis and brain invasion and necrosis was seen only in patients receiving GTR, and lost in those treated with STR. Adjuvant radiotherapy was associated with worse outcome, more so in patients receiving GTR. In the presence of high mitotic count (defined as >4/10HPF) radiation did not affect recurrence, but necrosis and specially combined necrosis and brain invasion magnified the apparent deleterious effect of adjuvant radiotherapy. In the presence of brain invasion, radiotherapy's small effect did not reach significance. Since patients were not randomized to adjuvant radiotherapy, these results should not be construed as indicating that this treatment is injurious. It can be stated that in the presence of necrosis and particularly necrosis and brain invasion, but not brain invasion alone, or high mitotic count, atypical meningiomas are more resistant to any possible beneficial effect of radiation in delaying recurrence.

LEARNING OBJECTIVES

This presentation will enable the learner to:

1. Describe histological and treatment factors determining recurrence in atypical meningioma.
2. List histological factors associated with radioresistance in atypical meningioma.

Abstract 2

A Machine Learning Analysis of TCGA Expression Data to Finding Signatures for "Normal-Like" IDH-WT Diffuse Gliomas with a Longer Survival

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Classification of primary CNS tumours is currently achieved by complementing histologic analysis with molecular information, in accordance with the WHO guidelines, and aims at providing accurate prognosis and optimal patient management. cIMPACT-NOW update 3 now recommends grading diffuse IDH-wild type astrocytomas as grade IV glioblastomas if they bear one or more of the following molecular alterations: EGFR amplification, TERT promoter mutation, and whole-chromosome 7 gain combined with chromosome 10 loss. In this reanalysis of the Cancer Genome Atlas (TCGA) glioma expression datasets, we identified 14 IDH-wt infiltrating astrocytic gliomas displaying a "normal-like (NL)" transcriptomic profile associated with a longer survival rate. Some of these tumours would be considered as GBM-equivalents with the current diagnostic algorithm. A k-nearest neighbors model was used to identify 3-gene signatures able to identify NL IDH-WT gliomas. Genes such as C5AR1 (complement receptor) SLC32A1 (vesicular gamma-aminobutyric acid transporter), and SMIM10L2A (long non-coding RNA) were overrepresented in these signatures which were validated further using the Chinese Glioma Genome and Ivy Glioblastoma Atlases. They showed high discriminative power and correlation with survival. This finding could lead to the validation of an immunohistochemical or PCR test which would facilitate classification of IDH-WT astrocytomas with unclear histological grading. Furthermore, associated signaling pathways might represent novel treatment targets for aggressive tumours.

LEARNING OBJECTIVES

This presentation will enable the learner to:

1. Reconsider recent updates in the WHO classification of infiltrating gliomas.
2. Discuss advanced bioinformatics profiling of the brain cancer transcriptome.

Abstract 3

Cerebrospinal fluid flow cytometry: utility in central nervous system lymphoma diagnosis

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Flow cytometry of the cerebrospinal fluid (CSF) is used in isolation or as an adjunct to cytology to increase the sensitivity of detecting primary central nervous system (CNS) lymphoma. We aim to evaluate the sensitivity of CSF flow cytometry as a diagnostic tool for primary CNS lymphoma in patients presenting with undifferentiated neurologic symptoms. We retrospectively reviewed all CSF samples received by the Calgary Laboratory Services Flow Cytometry Laboratory from 2012- 2015. Clinical data, laboratory investigations, radiologic imaging studies, and pathological data were analyzed. Clinical review extended to 2 years post CSF flow cytometric testing. The number of samples of CSF flow cytometry that were positive for a hematological malignancy was 43/763 (5.6%). The overall sensitivity of the test was 69.4%. A positive result was more likely to occur in patients with a prior history of a hematological malignancy or abnormal enhancement on MRI ($p<0.0001$). CSF flow cytometry was negative in all patients who did not have a previous hematological malignancy or abnormal enhancement on MRI ($n = 247$). CSF flow cytometry has a limited role in screening for primary CNS lymphoma, unless a strictly endorsed testing algorithm is applied. It is, however, an invaluable tool in evaluating CNS involvement in patients with a previous diagnosis of hematolymphoid malignancy or abnormal enhancement on MRI.

LEARNING OBJECTIVES

This presentation will enable the learner to:
Discuss the costs and benefits of using CSF flow cytometry to diagnose CNS lymphoma

1. Identify appropriate clinical indications for using CSF flow cytometry as a first-line test
2. Apply a testing algorithm to increase the diagnostic yield of CSF flow cytometry

Session 2: Tumour Neuropathology

Abstract 4

Diagnostic and pathogenic features of calcifying pseudoneoplasm of the neuraxis

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Calcifying pseudoneoplasm of the neuraxis (CAPNON) is a rare tumefactive lesion with unclear pathogenesis. It is diagnosed by pathological findings of the typical histological features that include granular amorphous cores with palisading spindle to epithelioid cells, variable fibrous stroma, foreign-body reaction with giant cells, and calcification/ossification occasionally with psammoma bodies. However, its histopathology may be variable and currently immunohistochemistry plays a limited role in its diagnosis and understanding the pathogenesis. In this study, we examined 6 cases of CAPNONs including 3 intracranial and 3 spinal epidural lesions (age range: 59–69 years; 3 males and 3 females). Immunohistochemistry revealed that all CAPNON cores contain abundant positive deposits of neurofilament protein (NFP), which was supported by electron microscopy finding of filaments (8–13 nm in diameter). In comparison, no NFP positivity was found in 5 psammomatous/metaplastic meningiomas or 7 intervertebral tissue lesions with calcification/ossification. In addition, CAPNON cellular areas showed variable numbers of CD8+ cytotoxic T-cells with less CD4+ T-cells and a decreased ratio of CD4/CD8+ cells, versus the intervertebral tissue lesions without CD8+ or CD4+ cells. Our findings suggest that NFP may be a principal constituent of CAPNONs, and thus involved in the pathogenesis of CAPNON. Given the decreased CD4/CD8 ratio, the pathogenic process of CAPNON is possibly immune- mediated.

LEARNING OBJECTIVES

The presentation will enable the learner to:

1. Discuss histopathological features of calcifying pseudoneoplasm of the neuraxis (CAPNON) with variation of non-core components.
2. Explore diagnostic and pathogenic roles of immunohistochemical markers including neurofilament protein and CD4/CD8 in CAPNON.

Abstract 5

Synthesis of glioma histopathology images using generative adversarial networks

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Deep learning, a subset of artificial intelligence, has shown great potential in several recent applications to pathology. These have mainly involved the use of classifiers to diagnose disease, while generative modelling techniques have been less frequently used. Generative adversarial networks (GANs) are a type of deep learning model that has been used to synthesize realistic images in a range of domains, both general purpose and medical. In the GAN framework, a generator network is trained to synthesize fake images, while a dueling discriminator network aims to distinguish between the fake images and a set of real training images. As GAN training progresses, the generator network ideally learns the important features of a dataset, allowing it to create images that the discriminator cannot distinguish from the real ones. We report on our use of GANs to synthesize high resolution, realistic histopathology images of gliomas. The well- known Progressive GAN framework was trained on a set of image patches extracted from digital slides in the Cancer Genome Atlas repository, and was able to generate fake images that were visually indistinguishable from the real training images. Generative modelling in pathology has numerous potential applications, including dataset augmentation for training deep learning classifiers, image processing, and expanding educational material.

LEARNING OBJECTIVES

This presentation will enable the learner to:

1. Explain basic principles of generative modelling in deep learning.
2. Discuss applications of deep learning to neuropathology image synthesis.

Session 3: Pediatric, Neuromuscular, Infectious/Immune Mediated Neuropathology

Abstract 6

Familial juvenile onset Alexander Disease demonstrating germline mosaicism and presenting with a tumor-like mass of the medulla

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Alexander Disease (AD) is a rare and ultimately lethal leukodystrophy, typically presenting in infants who exhibit developmental delay, macrocephaly, seizures, spasticity and quadriparesis. Classic *infantile* forms are generally due to sporadic mutations in *GFAP* that result in the massive deposition of intra-astrocytic Rosenthal fibres, particularly in the frontal white