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Thrombospondin 1 mediates transforming growth factor beta induced premature senescence in primary glioblastoma cells

R Kumar (Ottawa) I Lorimer (Ottawa)*

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Background: Glioblastoma is the most common primary malignant brain tumor. Primary Glioblastoma (PriGO) cells are key drivers of glioblastoma. Senescence is the irreversible growth arrest of cells with continued metabolic activity. Recently, I discovered PriGO cells undergo premature senescence in response to Fetal Bovine Serum (FBS). Determining the underlying molecular mechanisms may allow development of novel therapeutic strategies to decrease the malignant potential of glioblastoma. *Methods:* Global gene expression changes in PriGO cells treated with serum were analyzed and compared to untreated cells. Senescence was determined by the Senescence-Associated-Beta-Galactosidase (SA-B-Gal) assay. *Results:* PriGO cells treated with serum demonstrated increased expression of genes in the Transforming Growth Factor Beta (TGF-*B*) pathway, such as Thrombospondin 1 (TSP1), compared to untreated cells. TGF-*B* treatment of PriGO cells significantly increased senescence compared to untreated cells. Treatment of PriGO cells with serum and the TGF-*B* inhibitor SB431542 led to a decrease in senescence compared to serum only treated cells. Treatment of PriGO cells with serum and the TSP1 inhibitor LSKL led to a reduction in senescence compared to serum only treated cells. *Conclusions:* Our data identifies TGF-*B* as an important component of serum responsible for inducing senescence in PriGO cells. Furthermore, TGF-*B* induced senescence in PriGO cells is in part mediated by TSP1.

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Primary clear cell chondrosarcoma of the thoracic spine

S Mcgregor (London) M Kurdi (London) R Hammond (London) F Siddiqi (London) B Wehrli (London)*

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Background: Clear cell chondrosarcoma (CCC) is a rare, low-grade, subtype of chondrosarcoma. It arises most commonly in the epiphyses of the certain longbones. Spinal involvement is extremely rare, but when present it most frequently involves the thoracic spine. Complete surgical resection is the best curative treatment, with radiation therapy being a consideration for inoperable tumours. *Methods:* We report a case of a 70-year-old gentleman with CCC of the T7-8 thoracic spine. Gross en-bloc spondylectomy of the T6-8 vertebral bodies with expandable cage reconstruction and T3-11 instrumented fusion were performed. *Results:* Histological examination revealed a cellular neoplasm composed of well-defined, round to oval cells with abundant clear cytoplasm embedded in a loose cartilaginous matrix with large numbers of admixed osteoclast-type giant cells and scattered bone trabeculae between the lesional cells. The patient experienced significant improvement in neurological function and was discharged from hospital in stable condition seven days after surgery. *Conclusions:* CCC is a rare variant of chondrosarcoma that rarely involves the osseous spine. In this location, treatment may be challenging given the presence of spinal cord and nerve roots. Given the lack of effective chemotherapy and radiation therapy for CCC, en-bloc resection of CCC involving the spine should be considered.

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Diffuse large B-cell Lymphoma secondary to iatrogenic immunosuppression with unusual MRI findings and literature review

AH Naeem (London) MD Staudt (London) B Wang (London) D Lee (London) A Parrent (London)*

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Background: Immunosuppressive therapy is a risk factor for lymphoproliferative disorders. We present a case of primary CNS B-cell lymphoma in the setting of iatrogenic immunosuppression from azathioprine usage. A literature review is provided. *Methods:* Case report *Results:* 64-year-old male presents with several weeks of cognitive decline, impaired speech, and headache with a history of ulcerative colitis (on azathioprine and 5-ASA) with no radiological evidence of systemic malignancy. MR showed left frontal extra-axial mass (4.0 x 2.4 x 4.0 cm) with heterogeneous enhancement of a solid component with local dural thickening. The enhancing mass had solid and cystic components. Radiological differential included dural metastasis, atypical meningioma or unusual intra-axial mass including GBM with some dural involvement. He underwent surgical resection, which showed a primary CNS lymphoma, diffuse large B-cell, CD 20 + and EBV +. Post-operatively his cognition improved. Azathioprine was stopped and 5-ASA was increased. He proceeded with MPVC (methotrexate, procarbazine, vincristine, and cytarabine) chemotherapy. *Conclusions:* Our case shows isolated extra-nodal CNS manifestation of lymphoma in the context of immunosuppressive medications with strikingly atypical MR findings leading to a pre-operative diagnostic dilemma. Treatment is challenging and needs to be individually tailored due to a need for stopping immunosuppressive agents in conjunction with CNS lymphoma treatment.

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Increased survival when combining BRAF inhibitors and stereotactic radiosurgery in patients with melanoma brain metastases

A Wolf (London) A Pavlick (New York) M Wilson (New York) J Silverman (New York) D Kondziolka (New York)*

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Background: The purpose of the study was to evaluate the impact of BRAF inhibitors on survival outcomes in patients receiving stereotactic radiosurgery (SRS) for melanoma brain metastases. *Methods:* We prospectively collected treatment outcomes for 80 patients with melanoma brain metastases who underwent SRS. Thirty-five patients harbored the *BRAF* mutation (BRAF-M) and 45 patients did not (BRAF-WT). *Results:* The median overall survival from first SRS procedure was 11.2 months if treated with a BRAF inhibitor and 4.5 months for BRAF-WT. Actuarial survival rates for BRAF-M patients on an inhibitor were 54% and 41% at 6 and 12 months after radiosurgery, in contrast to 28% and 19% for BRAF-WT. Overall survival was extended for patients on a BRAF inhibitor if initiated at or after the first SRS. The local control rate did not differ based on BRAF status and was over 90%. Patients with higher KPS, fewer

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treated metastases, controlled systemic disease, RPA class 1 and BRAF-M patients had extended overall survival. *Conclusions:* Patients with BRAF-M treated with both SRS and BRAF inhibitors, at or after SRS, have increased overall survival. As patients live longer due to more effective systemic and local therapies, close surveillance and early management of intracranial disease with SRS will become increasingly important.

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Large partially thrombosed posterior circulation aneurysms: A treacherous masquerader of benign brain tumors

N Alizadeh Vakili (Toronto) A Chiu (Toronto) B Drake (Toronto) W Montanera (Toronto) A Bharatha (Toronto) T Marotta (Toronto) D Sarma (Toronto) J Spears (Toronto)*

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Background: On imaging, thrombosed aneurysms can be mistaken for tumor with potentially disastrous consequences. *Methods:* We present two cases of aneurysms mimicking tumor. *Results:* Patient 1 (6 months of left-sided facial weakness): MRI demonstrated a 3.3cm, T1-isotense, T2-hypertense heterogeneous enhancing mass favored to represent a CPA schwannoma. Biopsy revealed a thrombosed aneurysm. DSA subsequently revealed an area of contrast penetration, treated by parent artery (AICA) obliteration. Two-year follow-up revealed stable occlusion with reduced mass effect. *Patient 2* (1 year of headaches): Imaging demonstrated an extra-axial T1-mixed, T2-hyperintense heterogeneously enhancing mass in the left CPA adjacent to the vertebral artery, enlarging from 1.7cm to 3.2cm over 2 years. DSA revealed slow, crescentic filling with suggestion of arborisation distally. Patient deteriorated due to mass effect requiring a VP shunt and passed away from SAH 3 months later. Imaging review revealed crescentic filling of the remnant lumen on CE-MRA and signal voids on T2 in both cases, which may suggest the aneurysm diagnosis. However our cases did not have other features such as lamellated thrombus or pulsation artifact. *Conclusions:* Central contrast enhancement does not necessarily preclude the diagnosis of thrombosed aneurysm. The possibility of revascularization or penetration of contrast through the thrombus in giant aneurysms needs to be considered.

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Mechanical properties of fusiform aneurysms in a rabbit model

M Altamimi (Calgary) C Meek (Calgary) E Di Martino (Calgary) A Mitha (Calgary)*

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Background: Animal models of human cerebral aneurysms have been a vital part of the development of endovascular treatments for decades. Rabbit models have been successfully used to simulate the morphology and hemodynamics of human intracranial aneurysms. However, the lack of mechanical testing of human intracranial aneurysm tissue limits our understanding of the mechanisms of aneurysm rupture. The goal of this project is to develop techniques for the mechanical testing of fusiform aneurysms in a rabbit model. *Methods:* Fusiform aneurysms were created using the right carotid artery using an elastase-based method. Thirty fusiform aneurysms and healthy rabbit carotid artery samples were then collected from our lab and tested with a uniaxial and biaxial loading system. Rectangular strips of aneurysm and healthy tissue were obtained in the axial and circumferential direction with a micro-cutting instrument. The test samples were gripped by a custom-designed micro-clamp and placed in a bath of phosphate-buffered saline at 37˚C temperature. *Results:* Maximum stress of healthy and aneurysm arteries are 50 Kpa and 0.6 Kpa *Conclusions:* The strength of healthy tissue was significantly higher than tissue from the fusiform aneurysm. These techniques will provide us with strategies for the eventual testing of human intracranial tissue and may help us to understand mechanisms of aneurysm rupture.

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Validation and standardization of cerebral vasospasm grading on CT angiography

D Ben-Israel (Calgary) E Caverzasi (Toronto) A Bharatha (Toronto)*

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Background: The diagnosis of cerebral vasospasm, either by digital subtraction angiography (DSA), or now more commonly by computerized tomographic angiography (CTA) occurs in up to 70% of patients with aneurysmal subarachnoid hemorrhage (aSAH). The lack of standardization among vasospasm grading has made its clinical correlation with delayed cerebral ischemia challenging *Methods:* 36 of the 764 aSAH patients found on the St. Michael's Hospital RIS database had both DSA and CTA performed, at time of admission and again between day 2 and 14 following SAH. Two blinded neuroradiologists graded all vessels for vasospasm on two separate scales, by consensus for DSA and independently for CTA *Results:* Comparing CTA and DSA, Grading Scale (GS)1 had the highest Spearman Correlation Coefficient (SCC): 0.691 ($P<0.001$) for Rater (R)1, and 0.687 ($P<0.001$) for R2. SCC was higher when only considering proximal vessels. Cohen's Kappa (CK) measuring inter-rater reliability was 0.695 ($P<0.001$) for GS2 and 0.681 ($P<0.001$) for GS1. CK was higher in anterior circulation vessels, and tended to decrease with increasing vasospasm grade. *Conclusions:* Although either scale will provide the benefits of standardization to clinical practice and research, GS1 is recommended as it is more intuitive and provides higher SCCs, with only slightly lower CKs.

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