

European Association of NeuroOncology Magazine

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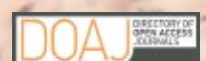
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The EUROPEAN ASSOCIATION of NEUROONCOLOGY



11th MEETING

2014

October 9-12

Turin, Italy

Lingotto Convention & Exhibition Centre

Abstract Deadline: March 23, 2014

Early Registration: June 15, 2014

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Editorial

Dear EANO members, dear colleagues,

I would like to open the editorial by announcing that the updated bylaws of the association were approved by an electronic extraordinary general assembly at the end of March and are now available on the website. Two new points are worth mentioning: first, we have inserted, as one of the main objectives of EANO, the development of guidelines or recommendations by “ad hoc” task forces; second, a committee of chairs of the National Multidisciplinary Groups of Neuro-Oncology has been set up to strengthen the position of EANO as an umbrella organisation within Europe in terms of organisational and regulatory issues, technology assessment initiatives, education tasks, etc.

There are ongoing discussions within ECCO, the European Cancer Association, in order to move toward a more efficient and powerful organisation, especially with regard to the relationships with the European Union authorities (so-called oncopolicy). EANO is one of the ECCO associations deeply involved in this project.

We are increasing the cooperation with other scientific societies, such as the European Association of Nuclear Medicine, the European Society of Neuroradiology, the European Society of Pediatric Oncology, and the International Brain Tumor Epidemiology Consortium in order to set up common workshops at the reciprocal congresses and/or guidelines on topics of common interest.

A call for fellowships and grant visits for 2015 has been generated on the website with a deadline of July 1, 2014.

At the EANO meeting in Torino from October 9–12, 2014, both the Executive Board and the Scientific Committee will be partially renewed: the calls for the different positions can be found on the website.

Last but not least, the EANO meeting in Torino has reached an advanced phase of organisation: the final educational and scientific programmes are on the website, and we have received 437 abstracts for oral and poster presentations, which represents the highest number in the history of EANO. As usual, travel grants for young investigators are available.

See you in Torino!

Best regards

Riccardo Soffiatti
EANO President 2012–2014



Riccardo Soffiatti, MD



Nerve Infiltration: Where, When, and How? An Introduction

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■ Introduction

This issue of *EANO Magazine* takes up the very important, albeit neglected topic of neoplastic nerve infiltration in neuro-oncology. It is important in regard to affected structures such as cranial nerves (CN), nerve roots, and nerve plexuses which are more frequently involved than individual peripheral nerves.

It seems that different tumours have different propensities when it comes to affecting cranial and peripheral nerves. Tumour spread via cranial nerves is quite uncommon in brain tumours, whereas ear, nose, and throat tumours, tumours of glands (eg, parotid), and also squamous cell carcinomas of the skin [1] seem to have a greater likelihood to propagate via peripheral nerves. It has turned out that in general pathology the spread of cancer cells along nerves within tumours is considered a negative prognostic factor [2], and studies have also shown that sometimes metastatic growth is associated with growth of small-nerve fibres [3].

The mechanisms of neoplastic damage of cranial or peripheral nerves implicate more beyond compression and local invasion. Furthermore, there are different mechanisms, which include antero- and retrograde spreading and the use of anastomoses to spread between different nerve territories.

■ Leptomeningeal Space

Infiltration of cranial nerves and nerve roots occurs during dissemination of tumours in the CSF, which is commonly termed leptomeningeal carcinomatosis (LC), in lymphoma also a primary leptomeningeal lymphoma has been described [4]. This type of spread affects CNs and nerve roots either isolated or

in multiple other ways. Pathological tumour spread is caused either by invasion, sometimes by local compression, or circular compression termed “cuffing”. In addition, nodular tumour growth exceeding the leptomeningeal spread occurs as well (Figure 1). Nodular dissemination in the CSF space may not only have mechanical local impact but also – contrary to leptomeningeal seeding tumour nodules – have its own vascularization and thus may not respond to local intrathecal therapy.

Tumour spread in LC is usually limited to within the CSF space and does not spread along CNs or nerve roots into the periphery, suggesting that a growth barrier between CNs or nerve roots in the CSF space and peripheral nerves exists. Conversely, retrograde spread from skin tumours as dissemination of malignant cells into the CSF seems to occur [5] whereas in neurolymphomatosis, where the peripheral nerves can be involved by lymphoma, the CSF space can remain tumour-free [6].

■ Base of the Skull, Dura, and Other Sites of Metastases

Metastases to the base of the skull have been well-characterised and 5 typical syndromes have been described by Greenberg and Vikram [7]. Metastases to the base of the skull are often combined with local pain syndromes. Osseous metastases without meningeal involvement can compress cranial nerves. The dura is rarely the site of metastases and directly or indirectly compresses cranial nerves. Imaging has shown that dural growth can invade the CNS parenchyma [8]. Malignant effusions occur, which may be mistaken for subdural haematomas. A localisation for both lymphomas and plasmocytomas are the orbits, where local mass lesions can mimic CN dysfunction.

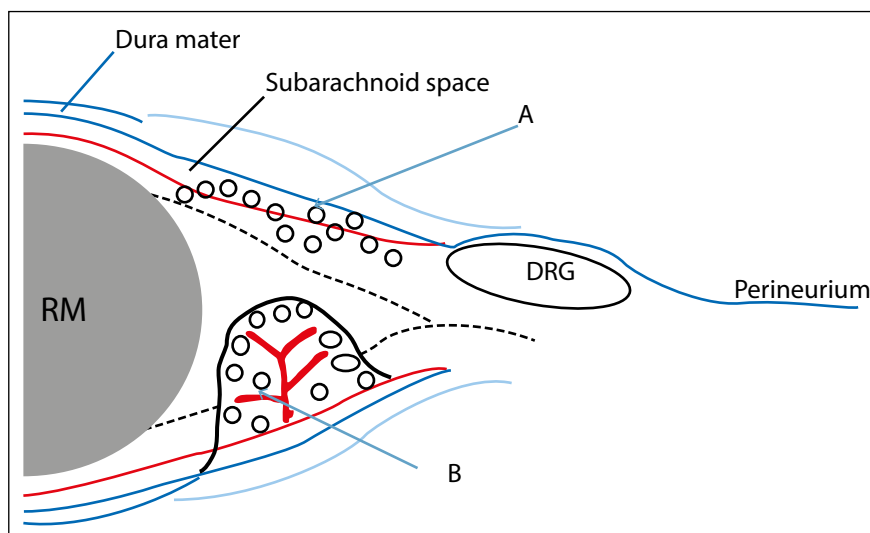
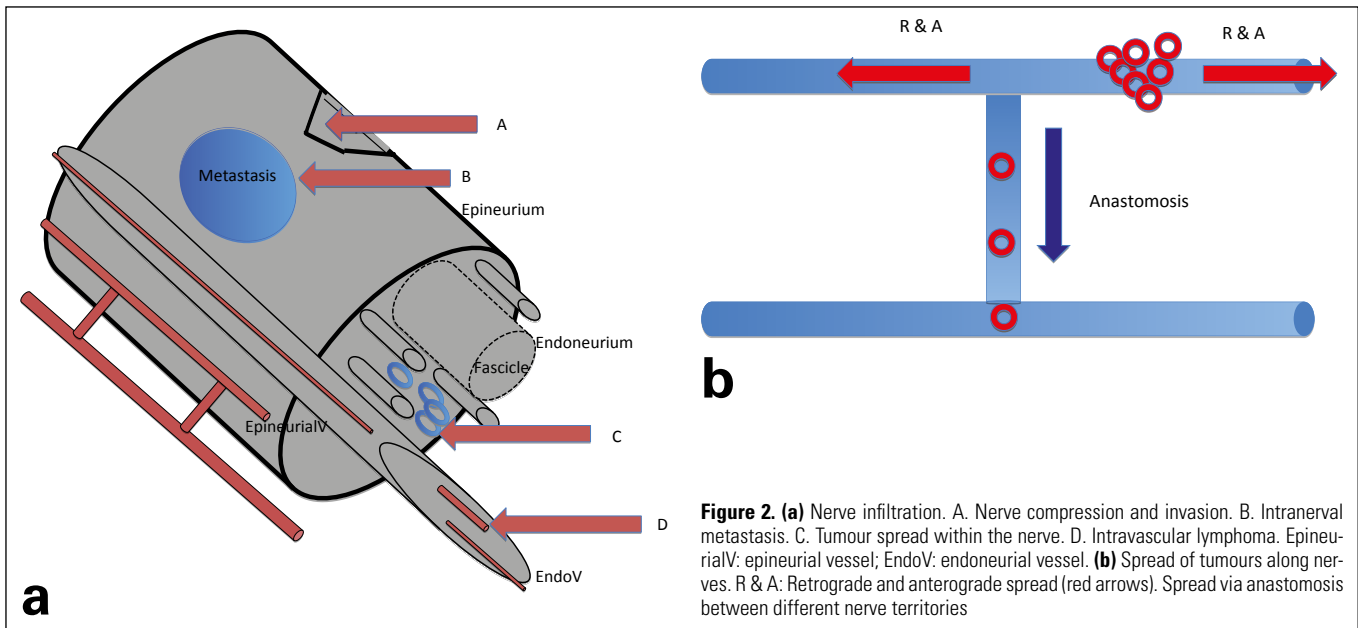


Figure 1. Meningeal infiltration. The dura mater continues as the perineurium. In general the tumor cells do not spread beyond this boundary centrifugally. **(A)** tumour spread in the subarachnoid space. **(B)** Lumps and nodules consist of tumour cells and have their own vascularisation. RM: spinal cord; DRG: dorsal root ganglion



In lymphoma, in addition to LC and focal growth, 2 other types of nerve involvement have been observed. One is neurolymphomatosis, the other intravascular or angiotropic lymphoma. Both are characterized by their peculiar spread and can affect both CNs and peripheral nerves [9, 10].

■ Cranial Nerves, Nerve Roots, and Other Types of Involvement

Cranial nerves have intraparenchymal, intracranial, and extracranial parts. In this context, 'extracranial' means 'outside of the bony skull'. The zone of transition of cranial nerves from the cavity of the skull is usually a defined passage through the bony skull and can be damaged by focal compression often caused by metastases. Cranial nerves can also be a trajectory for tumours, either in an antero- or retrograde direction, and this may also enable tumour spread from tumours outside of the skull into the skull and vice versa. Another interesting spread is the spread of tumours along nerve anastomoses. This has been observed in the auriculotemporal and the maxillary nerves and also from the cervical plexus into other CNs and into the skull [11, 12].

Damage of CNs outside the skull occurs either by direct involvement but retrograde spread from skin tumours into the brain has been observed as well. Even more unconventional is tumour spread in a centrifugal pattern as observed in zosteriform metastases. Although this might be a rare occurrence, this could be an interesting model of tumour spread within a dermatome [13].

■ Mechanisms

The mechanisms of nerve invasion comprise several types of mechanisms [14–16].

Mechanical injury causing compression, 'pushing' and stretching or 'engulfing' are most commonly assumed types. In addition to these mechanical concepts, the vicinity of tumours to the nervous structure proposes local infiltration or in-

vasion, which seems less clear in regard to the barriers of the peripheral nerve. Possible mechanisms are peripheral or endoneurial propagation of tumours and also rarely endovascular spread in lymphoma is reported. The spread within nerves seems to follow the intraneural vessels, however, the definite role of the connective tissue between the fascicles is not yet clear (Figure 2).

In addition to local invasion, tumours may spread along nerves, using peripheral nerve tissue as a scaffold. This propagation has been observed in CNs and may cross territories from different nerves and even between different structures such as CN and the cervical plexus. The present anatomical concept of vessels – nerve trunks resulting in dermatomas and myotomas – is useful but may have to be reconsidered in the face of the angiosoma concept [17, 18], which could be potentially useful to explain the distribution of metastases in the head and skull, and the sclerotoma [19] innervation of the osseous skull. Isolated metastases into peripheral nerves occur but are very rare [20].

These anatomy-based concepts neglect biological factors promoting and inhibiting nerve growth, such as NGF, NCAM, or p75 which have been recognized as important factors in nerve growth and regeneration and will have to be elucidated for future research [21].

■ Predilection Sites

The predilection sites are of particular importance, where CNs and peripheral nerves can be affected by tumours. In the CSF space, CNs and nerve roots can be compromised by leptomeningeal spread. Cranial nerves can be damaged at the base of the skull and in several extracranial sites such as skin, the cavities of the skull (in particular the orbit) and the tissues of the head and neck.

In other parts of the body, spinal nerve roots can be damaged by focal metastases and subsequent infiltration although the pathophysiologic pattern is not as clear as one would assume

due to the frequency of occurrence [22]. The nerve plexuses are also often the site of neoplastic involvement, either in the cervical plexus due to local tumours or lymph nodes or the brachial plexus, either by vicinity of the lung, or the lymph nodes which drain the tissue around the breasts.

The lumbar plexus is well-protected and remote from lymph nodes or potential tumours, whereas the sacral plexus is more often exposed to local tumours and to lymph nodes.

Neither are individual peripheral nerves affected by cancer nor is symmetric or asymmetric peripheral nerve involvement observed following the pattern of polyneuropathies. An exception are haematological malignancies which can have both a spread within the meningeal space and also a diffuse spread in peripheral nerves (neurolymphomatosis) [23] or in vessels (angiotropic lymphoma) causing peripheral nerve damage. The spread of leukaemic cells, termed neuroleukemiosis, has been described as well [24].

■ Mimicks

The neoplastic involvement of CNs, nerve roots, and peripheral nerves should be certain to avoid ineffective and potentially dangerous therapies. Mimicks resembling neoplastic disease can be infections, hypertrophic neuritis, local autoimmune disease like IgG4-related disorders, and unrelated events such as lipomatosis or perineuroma and need to be identified prior to treatment because they affect, to some extent, therapies such as local radiation or toxicity from chemotherapy.

The contributions to this topic may help to understand this important interaction between cancer and the nervous system better, and could, due to their diverse mechanisms, shed light on diagnostic aspects of cancer spread as well on new therapies.

■ Conflict of Interest

None.

■ Declaration

WG acts as managing editor of *EANO Magazine*.

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Lymphoma Nerve Infiltration

Joachim M Baehring

Abstract: Neurolymphomatosis (NL) denotes the invasion of cranial nerves, nerve roots, plexus, or nerves by Non-Hodgkin lymphoma (NHL) or leukaemia. This occurs in the absence (primary NL) or presence (primary NL) of systemic NHL. Clinical patterns include a painful polyneuropathy or polyradiculopathy, cranial neuropathy, painless polyneuropathy, and peripheral mononeuropathy.

Integration of clinical information, imaging findings, as well as histopathologic examination of involved nerves or non-neural tissue, and cerebrospinal fluid analysis are needed to establish the diagnosis. Timely recognition of the disease and its exact neuroanatomical extent is the basis for successful therapy using systemic chemotherapy and localized irradiation of bulky disease

sites. More complex regimens are required when cerebrospinal fluid and systemic disease sites are affected. **Eur Assoc NeuroOncol Mag 2014; 4 (2): 61–4.**

Key words: neurolymphomatosis, NHL, lymphoma, leukaemia

■ Introduction

Neurolymphomatosis (NL) is defined as invasion of cranial nerves, nerve roots, plexus, or nerves by Non-Hodgkin lymphoma (NHL). Most commonly, NL occurs as a result of dissemination from systemic disease sites, brain or cerebrospinal fluid (secondary NL). NL in the absence of systemic NHL (primary NL) is exceedingly rare. NL has to be distinguished from the much more common chemotherapy-induced, inflammatory, or paraneoplastic neuropathies.

In this review, the clinical manifestations of NL are described. Current knowledge of the mechanisms of NHL dissemination into nerves is summarised and diagnostic procedures as well as treatment options are outlined.

■ Epidemiology

NL appears to be the least common direct neurologic manifestation of NHL. The disease is slightly more common in men and manifests itself over a wide age range. However, population-based incidence data are not available. Relative frequencies ranging from < 1 % to 40 % have been reported in case series [1, 2]. The wide range is explained by varying definitions, variable inclusion of leukaemia cases, and differences in diagnostic material available for diagnosis (biopsy, autopsy, imaging only). In a small case series, the relative incidence of NL was estimated to be 3 % in patients with newly diagnosed intermediate or high-grade NHL patients annually [3]. The cumulative incidence of central nervous system (CNS) invasion by NHL ranges from 2.2–6.9 % (excluding Burkitt's lymphoma in which it is substantially higher) and by acute leukaemia from 9–10 % [4, 5]. NHL dissemination into the peripheral as well as central nervous systems most commonly occurs with aggressive subtypes such as diffuse large B-cell lymphoma (DLBCL) or lymphoblastic histologies. Based on reported population-based incidence data (approximately 70,000 cases

of NHL and 20,000 cases of acute leukaemia per year in the US [6]), it is estimated that there are < 2000 cases of NL per year in the US. Less than 10 % of these cases are primary NL.

■ Pathogenesis

NL patients, similar to patients with primary CNS lymphoma, have a history of idiopathic diseases of possible autoimmune aetiology (recurrent chorioretinitis, celiac disease, hypothyroidism, Bell's palsy, Sjögren's syndrome, systemic lupus erythematosus, erythema nodosum, erythema multiforme, allergic purpura) at a greater-than-expected rate [7–10]. Selected case reports with neuropathic symptoms for months to years preceding the diagnosis of NL suggest that lymphoma may arise in a subset of patients by malignant degeneration of an autoreactive B-cell clone targeting peripheral neural structures [7, 11–13]. We have observed several cases in which NL was preceded by lymphomatous invasion of cerebrospinal fluid. Clinical and radiographic signs of NL soon followed the initially successful eradication of tumour cells from CSF, suggesting that the intrathecally administered drug sufficiently eliminated freely floating tumour cells but failed to address tumour cell infiltration into proximal nerve roots and their intraneural spread.

The vast majority of NL cases consist of B-cell NHL [7, 14]. Based on autopsy data, systemic involvement by lymphoma is found in the majority of patients with NL. However, only 20 % are known to have systemic lymphoma at the time NL is diagnosed and in another 10 % systemic and peripheral nervous system involvement is found coincidentally although these numbers may represent a selection bias [7]. Given the morphologic similarities, it is likely that tumour cells in NL share molecular features with CNS lymphoma, for example, derivation from germinal centre or post-germinal centre B-cells [15]. Studies on molecular pathogenesis, the role of transforming viral pathogens, and chronic antigenic stimulation have not been performed in NL.

Site-specificity of NL in NHL reflects conserved physiological behaviour of the originating tumour cell. It is based on expression of a stimulating endogenous or exogenous antigen within the target organ and mediated through adhesion receptors [16]. Selectins (mediating tethering), integrins, and chemokines (mediating adhesion and migration) have been implicated in CNS dissemination of NHL [17–20], for example neural cell adhesion molecule (NCAM) expression (CD56) in peripheral

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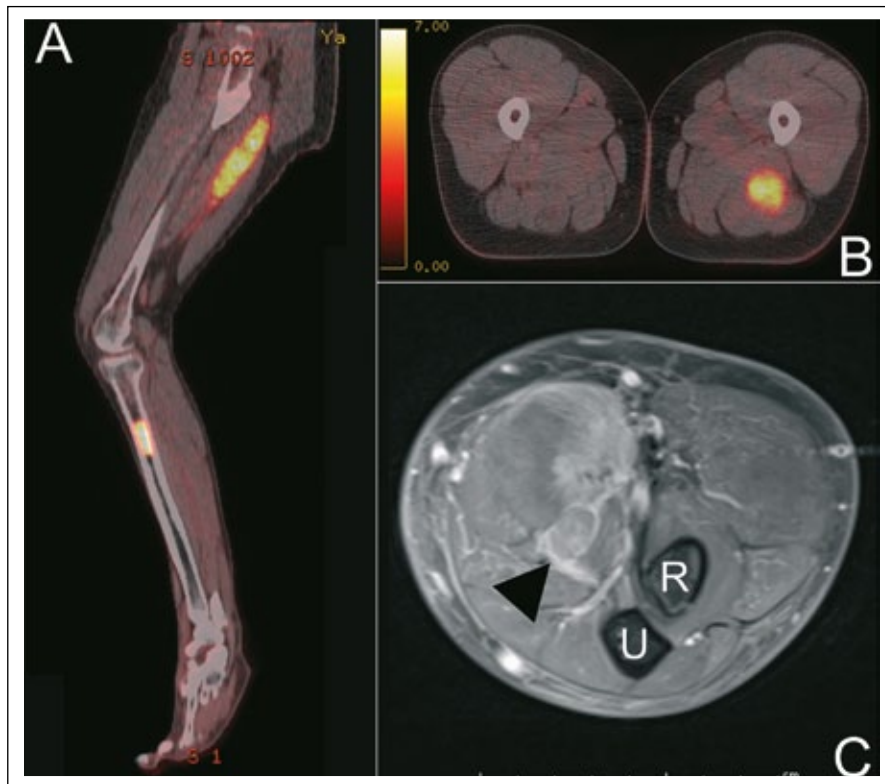


Figure 1. A 54-year-old man with a history of mantle cell lymphoma presented with tingling along the palmar surface of his left thumb. Then the left thumb, first and second digit started feeling “inflamed, swollen, about to explode”. The pain awakened him at night. At the same time, he felt a burning pain along the heel, lateral and anterior plantar surface of the right foot. Work-up revealed neurolymphomatosis. Multiple mass lesions were identified within the peripheral nervous system including the left sciatic nerve [**a**, **b**] 18-FDG-PET, the left median nerve (arrow head in [**c**]; axial T1-weighted MRI of the left forearm; note infiltration of the flexor musculature by tumour), right brachial plexus, right sciatic nerve, and left tibial nerve (not shown). Biopsy of the soft tissue mass in the right forearm revealed a mantle cell lymphoma.
R: radius; U: ulna

T-cell lymphoma [21]. Yet a role of CD56 in the targeting of peripheral neural structures could not be confirmed [22]. Specific adhesion molecules as the basis for target organ selection in NL have yet to be identified.

Clinical Presentation

NL presents most commonly as a painful polyneuropathy or polyradiculopathy, followed by cranial neuropathy, painless polyneuropathy, and peripheral mononeuropathy. Nervous-system involvement progresses over weeks to several months. A relapsing-remitting pattern of progression may be seen when the disease temporarily responds to empiric therapies for clinical diagnoses such as chronic inflammatory demyelinating polyneuropathy. At advanced disease stages, there is diffuse infiltration of peripheral neural structures as well as CSF and the substance of brain and spinal cord [7, 14].

In patients presenting with painful polyneuropathy or polyradiculopathy, lumbosacral roots or nerves are more often afflicted than cervical or thoracic ones. Neuropathic pain is followed by an ascending sensorimotor polyradiculoneuropathy resulting in more or less symmetric paraparesis or quadriplegia. Other patterns of progression such as mononeuropathy multiplex or isolated plexopathies have been observed. The disease usually evolves over weeks to months but hyperacute variants reminiscent of Guillain-Barré syndrome have been described [11].

NL presenting as painless peripheral neuropathy is characterised by paresthesias, numbness, and loss of deep-tendon stretch reflexes followed by weakness. Asymmetric or patchy onset or early proximal limb weakness reflecting plexus invasion are rare.

In about 20 % of patients with NL, the early disease course is characterised by isolated cranial neuropathy [7]. Peripheral facial nerve weakness, sometimes bilateral or recurrent, abducens, oculomotor, trigeminal neuropathy (including *tic doloreux*), hearing loss, and preauricular pain as well as vocal cord paralysis have been described.

Various mononeuropathies secondary to lymphomatous infiltration have been reported: sciatic, median, radial, and intercostal. Patients present with motor or sensory deficits, often in the absence of pain [7]. The mononeuropathy can remain isolated for months to years but the majority of patients develop more widespread lymphoma or have a history of prior systemic lymphoma.

Diagnosis

The diagnostic gold standard for NL is histopathologic examination of an involved nerve biopsy. NL is characterised by tumour cell infiltration of endo- and perineurium. Tumour cells display B-cell-associated surface antigens (CD19, CD20) and a high proliferative index. However, the decision to biopsy a nerve or root does not come easily and the procedure is performed in less than half of patients. Thus, diagnosis often relies on integration of clinical information, imaging findings, CSF analysis, and biopsy of non-neural tissue (for an example see Figure 1). The diagnosis is often delayed, especially in the absence of systemic lymphoma. Not uncommonly, it is the response to empiric treatment (steroid therapy, intravenous immunoglobulin, plasmapheresis) – or lack thereof – that may lead the clinician to the correct diagnosis. The diagnosis remains elusive until autopsy in almost half the reported cases [7].

Magnetic resonance imaging is the most sensitive and specific non-invasive diagnostic tool. Nerves, roots, or plexus infiltrated by NHL are enlarged and enhance after gadolinium administration (Figure 2A) [7, 14]. The radiographic differential diagnosis includes acute or chronic inflammatory radiculoneuropathies and tumours of the peripheral nerve sheath.

18-fluorodeoxyglucose positron emission tomography is a useful adjunct to the diagnosis of NL and identification of possible biopsy sites (Figure 2B) [3, 23–32].

CSF cytopathologic evaluation may be a useful diagnostic tool when NL is accompanied by meningeal dissemination (20–

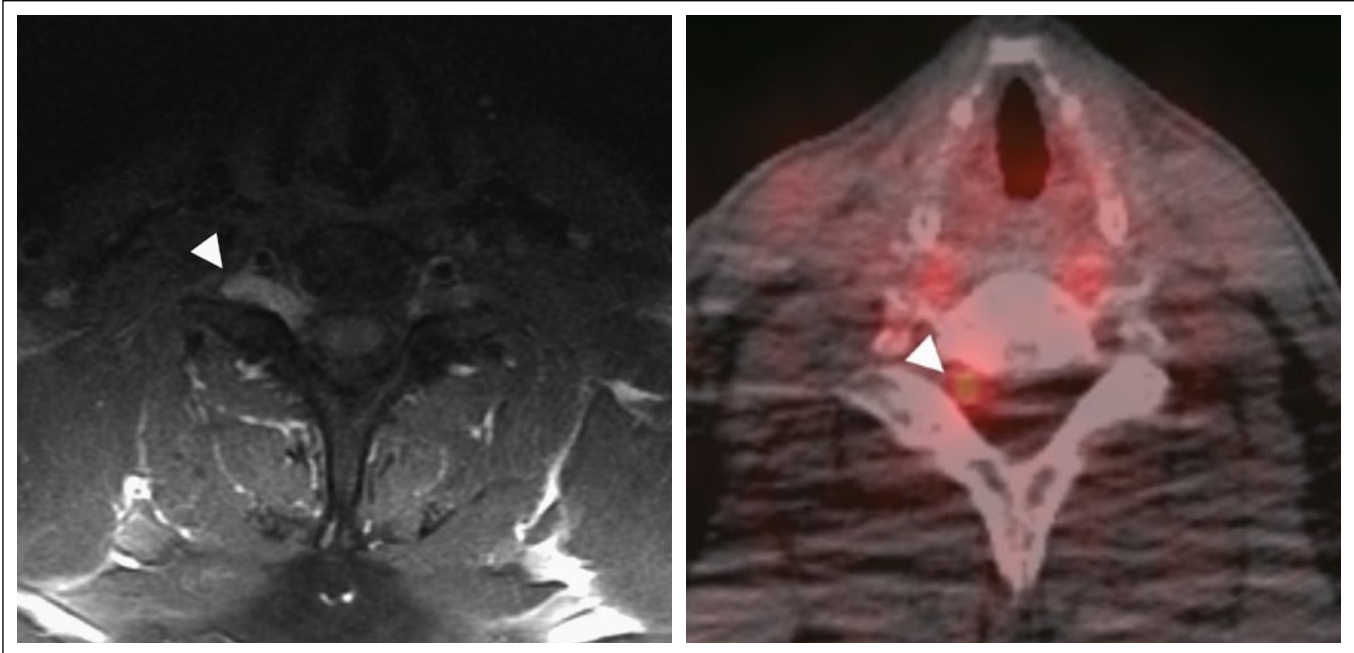


Figure 2. Magnetic resonance imaging shows a thickened and enhancing lower cervical nerve root in a patient with primary neurolymphomatosis (**[a]** T1-weighted sequence after administration of gadolinium). 18-Fluorodeoxyglucose positron emission tomography reveals increased tracer uptake within the affected nerve root (**[b]** arrow head).

40 % of patients) [7, 14]. The use of automated cell sorting and lymphocytic surface receptor gene rearrangement (immunoglobulin heavy chain gene, T-cell receptor gamma subunit gene rearrangement analysis) for clonality assessment increases the diagnostic sensitivity and specificity [14].

■ Treatment

The majority of patients with NL are treated with systemic chemotherapy alone or combined with intrathecal chemotherapy or external beam radiotherapy [7, 14]. Therapy must address both symptomatic and asymptomatic root and nerve involvements, as well as the coexistent dissemination into brain parenchyma, CSF, and systemic sites. The biggest challenge is the distinction between NL and meningeal lymphomatosis or the recognition of their coexistence as neurologic syndromes largely overlap. Accurate staging is of utmost importance and the guidelines established for PCNSL should be followed (slit lamp examination of the eyes, contrast-enhanced MR images of brain and spine, CT scans of chest, abdomen, and pelvis, bone marrow aspiration and biopsy) [33].

Systemic chemotherapy is the most promising approach to NL as it is best suited to address the multiple sites of involvement [7, 14]. Intravenous methotrexate in doses exceeding 3.5 g/m², either alone or in combination with other drugs, is provided as first-line treatment for cases with isolated nervous-system involvement. Polychemotherapy regimens such as CHOP, MCHOD (methotrexate, cyclophosphamide, doxorubicin, vincristine, dexamethasone), hyperCVAD (cyclophosphamide, doxorubicin, vincristine, dexamethasone alternating with methotrexate and cytarabine), VAC (vincristine, doxorubicin, cyclophosphamide), ProMACE (procarbazine, methotrexate, doxorubicin, cyclophosphamide, etoposide)/Cytabom (cytarabine, bleomycin, vincristine, methotrexate), and others are used for patients with concomitant systemic lympho-

ma. In the absence of systemic lymphoma, it is unclear whether polychemotherapy confers any survival benefit to patients with NL compared to methotrexate monotherapy as has been demonstrated in cerebral parenchymal disease. It remains to be shown if the addition of rituximab improves treatment outcomes in NL [3]. Intrathecal chemotherapy (methotrexate, cytarabine, rituximab) is used to eradicate leptomeningeal involvement by lymphoma but it cannot sufficiently treat nodular root infiltration. Its impact on treatment outcome is difficult to ascertain. It may be dispensable in patients receiving high-dose methotrexate or cytarabine-based regimens. Myeloablative chemotherapy with autologous stem cell transplantation is feasible and can be considered for consolidation in NL patients in complete remission after conventional chemotherapy.

Radiation therapy is provided either with curative intent or for palliation. As in systemic lymphoma, adjuvant radiotherapy may be particularly useful as localised consolidation of bulky disease.

Corticosteroids should be avoided prior to the diagnosis of NL since the lymphotoxic effects of these drugs may obscure the histopathologic findings. Moreover, clinical benefit from corticosteroid monotherapy is short-lived and disease progression is the rule, in spite of continuation of therapy or upon tapering.

Retrospective case series suggest response rates exceeding 50 %, disease stabilisation in 25 %, and disease progression with initial therapy in the remainder [7, 8]. Given the selection bias in reporting single cases and lack of uniform response criteria, the accuracy of these estimates is unclear.

Median overall survival of NL is 10 months from initial diagnosis. Patients with primary NL may have a more favourable outcome [7].

Conclusion

Dissemination into the peripheral nervous system is an uncommon complication of NHL and acute leukaemia. Timely diagnosis, preferably based on biopsy or CSF analysis, and sufficiently thorough staging are prerequisites for successful therapy. Characteristic neuroimaging findings may be sufficient for diagnosis in secondary NL and for patients in whom tissue acquisition is not deemed possible. Treatment needs to address the often widespread dissemination of the disease. Most neuro-oncologists use intravenous chemotherapy regimens including high-dose methotrexate or cytarabine. Patients with CSF involvement may benefit from the addition of intrathecal chemotherapy. Adjuvant radiation is used for consolidation of bulky disease. Primary NL carries a worse prognosis than cerebral parenchymal lymphoma, likely a function of diagnostic delay and suboptimal drug penetrance through the blood-nerve barrier. There remains a need for improvement of diagnostic tools and novel therapeutic strategies.

Conflict of Interest

None.

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Peripheral Nerve Dysfunction Secondary to Lymphomatous Infiltration of the Nervous System by Non-Hodgkin's Lymphoma

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Abstract: Lymphomatous meningitis (metastasis of lymphoma cells into the cerebrospinal-fluid spaces [CSF]) and neurolymphomatosis (lymphomatous infiltration of a peripheral nerve or root) are neurologic complications of non-Hodgkin's lymphoma (NHL) that frequently result in significant neurologic dysfunction. Leptomeningeal metastases most commonly present as cerebral dysfunction (hydrocephalus causing headache or apraxia of gait, encephalopathy, or seizures), cranial neuropathy (diplopia, facial weakness, vertigo, hearing loss, and tongue weakness), and spinal-nerve root dysfunction (incomplete cauda equina syndrome – asymmetric lower-extremity weakness, sensory loss, or incontinence). Diagnosis is made by finding leptomeningeal enhance-

ment on magnetic resonance imaging (MRI) of the brain or spine or demonstration of lymphomatous cells by CSF cytology or flow cytometry. Treatment consists of focal radiotherapy for areas of bulky disease followed by intra-CSF chemotherapy or systemic chemotherapy. Neurolymphomatosis typically presents as a painful, sensorimotor peripheral neuropathy affecting multiple limbs in an asymmetric fashion with rapid evolution although variability in presentation can occur. Diagnosis is made by demonstration of enhancement of nerve roots on MRI of the brachial or lumbosacral plexus or peripheral nerves or by increased hyper-metabolic activity following the course of affected nerves on fluorodeoxyglucose positron emission tomography (FDG-PET). Treat-

ment of neurolymphomatosis consists of focal radiotherapy (if significant neurologic dysfunction is present) and high-dose intravenous methotrexate therapy. Standard systemic chemotherapy agents are not effective since they do not penetrate the physiologic "nerve-blood barrier". Other disorders that must be differentiated from these entities include peripheral-nerve or nerve root compression and paraneoplastic neuropathy. **Eur Assoc NeuroOncol Mag 2014; 4 (2): 65–70.**

Key words: lymphoma, neurolymphomatosis, lymphomatous meningitis, leptomeningeal lymphoma, intravascular lymphomatosis

■ Introduction

Patients with systemic NHL may experience dysfunction of the peripheral nervous system by a variety of mechanisms including leptomeningeal metastases, nerve root or peripheral-nerve invasion (neurolymphomatosis), nerve root and peripheral-nerve compression, and as a complication of paraneoplastic peripheral neuropathies or intravascular lymphomatosis. This review primarily focuses on lymphomatous meningitis and neurolymphomatosis; metastatic complications that result from direct lymphomatous infiltration of the nervous system.

■ Lymphomatous Meningitis

Lymphoma cells that spread to the subarachnoid space (CSF space) and leptomeninges (pia and arachnoid membranes) are referred to as leptomeningeal metastases or lymphomatous meningitis (LM). The CSF space is the most common site of central nervous system (CNS) metastasis of systemic lymphoma with a clinical incidence of 6 % [1, 2]. Histology is the most important risk factor for metastasis of lymphoma to the CSF. The incidence of LM is greatest in Burkitt's lymphoma (BL) and lymphoblastic/acute lymphoblastic lymphoma (ALL) and, to a lesser extent, in diffuse large B cell lymphoma [3]. LM is rare in indolent lymphomas such as follicular or marginal zone lymphoma. Other risk factors include high serum lactate dehydrogenase (LDH), younger age, ≥ 2

extranodal sites, B symptoms, low albumin concentration, and specific sites of extranodal disease such as bone marrow, skin, testis, epidural space, retroperitoneum, orbit, paranasal sinus, and lung. Patients with BL, ALL, and diffuse B-cell lymphoma with multiple risk factors (particularly high LDH, ≥ 2 extranodal sites, and disease in bone marrow, testis, epidural space, orbits, palate, paranasal sinuses, or bone marrow) are often treated with prophylactic intra-CSF chemotherapy [4].

LM presents with a variety of symptoms and signs (Table 1). The anatomic regions affected by LM can be separated into (1) brain, (2) cranial nerves, (3) spinal cord and nerve roots.

Brain Dysfunction

LM may cause brain dysfunction by several mechanisms including increased intracranial pressure (ICP), superficial invasion and neuronal injury, mass effect, and ischaemia by

Table 1. Common presenting symptoms and signs of leptomeningeal metastases

New-onset seizures
Unexplained encephalopathy
Headache
Gait unsteadiness (apraxic or "magnetic" gait)
Blurred vision (optic neuropathy)
Diplopia
Face numbness ("numb chin")
Face weakness – "bells palsy" (unilateral or bilateral)
Vertigo
Hearing loss
Radicular pain
Back pain
Foot drop
Leg weakness
Bowel or bladder incontinence

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small-vessel occlusion. LM may also cause impaired flow and outflow obstruction of CSF at any site within the CSF compartment (most commonly at the level of the ventricles, basal cisterns, spinal subarachnoid space, and superior sagittal sinus), resulting in hydrocephalus and increased ICP. It is important to recognise that CSF flow disruption and associated ICP may be present, even in patients without evidence of hydrocephalus by CT or MRI neuroimaging. CSF flow disruption is best assessed by radioisotope CSF flow studies in patients with LM being considered for intra-CSF chemotherapy. LM by invading superficial brain may result in an encephalopathy manifesting as confusion or focal hemispheric deficits. Either subarachnoid or ventricular nodules can be of sufficient size to result in mass effect and corresponding topographic specific focal deficits. Small-vessel occlusion by LM is a consequence of invasion by a tumour of the vasa nervorum, small vessels that perfuse nerves, resulting in infarction.

Brain-Associated Clinical Symptoms

Headache

Headache is a common complaint in patients with LM. It is usually non-specific and diffuse and may be associated with nausea, vomiting, or lightheadedness. The severity of headaches varies from severe and quality-of-life-interfering to low-grade and noxious.

Gait Dysfunction

Patients with LM often have a gait disturbance which may reflect either hemispheric disturbance or spinal-cord dysfunction. Some patients may develop the “apraxia of gait” or “magnetic gait” that is seen in patients with normal-pressure hydrocephalus; urinary incontinence is a frequent associated feature.

Encephalopathy

Patients may experience diffuse cognitive dysfunction which resembles delirium or a confusional state. LM must be considered in lymphoma patients with altered mental status particularly if no other cause is demonstrable, ie electrolyte disturbance or medication effect.

Episodic Loss of Consciousness

Seizures are the most common cause of loss of consciousness in patients with LM. Both non-convulsive focal and generalised seizures may occur. Episodic, transient increases in intracranial pressure secondary to CSF flow obstruction may result in the phenomena of “plateau waves”. Transient impairment of consciousness is a common sign from plateau waves.

Cranial-Nerve (CN) Dysfunction

The cranial nerves travel through the subarachnoid space before exiting the CNS and innervating peripheral targets. LM may infiltrate or cause ischaemia in an exiting cranial nerve, causing symptoms.

Any cranial nerve may be affected by LM. Common complaints include blurred vision (CN II) binocular diplopia (CN III, IV, or VI), face numbness (CN V), facial weakness (CN VII), vertigo or hearing loss (CN VIII), and tongue weakness (CN XII).

Spinal Nerve Root Dysfunction

Any spinal root can be affected by LM, although the involvement of the cauda equina is most common. Patients often present with asymmetric lower-extremity weakness and dermatomal sensory disturbance that ultimately evolves into a complete cauda equina syndrome (paraparesis, sensory loss, and incontinence). Subtle lower-extremity weakness is often the only evidence of LM affecting the spine. LM may infiltrate exiting nerve roots causing radicular pain, ie a radiculopathy. Nuchal rigidity, common in infectious meningitis, is rarely present in LM despite the presence of inflammation in the subarachnoid space.

Diagnosis

Neurologic Exam

The hallmark of LM is dysfunction of the nervous system separated in space; patients suspected of harbouring LM should be examined carefully for neurologic abnormalities that may not be associated with symptoms. A classic example is the finding of a lower-extremity monoparesis (early cauda equina syndrome) or in a patient complaining of diplopia and manifesting as an abducens (cranial nerve VI) cranial-nerve palsy.

Neurological-examination findings suggestive of LM include cranial neuropathies such as extra-ocular muscle dysfunction (cranial nerve VI > III > IV), facial sensory loss, facial weakness, hearing loss, alteration of gag reflex, tongue deviation, extremity weakness (in a lower-motor neuron nerve pattern), confusion, and gait disorder. The finding of a cranial neuropathy in patients with NHL is most suggestive of LM. Similarly, finding communicating hydrocephalus without an obstructing mass suggests the diagnosis of LM. As mentioned above, signs or symptoms of cauda equina dysfunction are characteristic of LM when there is no evidence of epidural spinal cord compression.

Imaging

Patients suspected of harbouring LM should undergo MRI of the brain and complete spinal axis (cervical, thoracic, and lumbar) if being considered for treatment. In the appropriate clinical setting, abnormal leptomeningeal enhancement is consistent with a diagnosis of LM. Classic MRI brain findings include cortical leptomeningeal enhancement (often focal), cerebellar folia enhancement, ventricular enhancement, enhancement of the brainstem surface, and nodular enhancement of cranial nerves. Subtle hydrocephalus may be present (< 10 %) and may only be appreciated if a prior imaging study is available for comparison. Computerised tomography (CT) of the head may show similar findings, although it is less sensitive than MRI.

The classic finding on spine MR is nodular contrast enhancement of the cauda equina nerve roots. Patients may also have clumping of nerve roots or enhancement of the spinal cord surface.

CSF Analysis

CSF examination should be performed in all patients suspected of having LM. CSF assessment should include measurement of opening pressure, cytology (to determine if pathologically malignant lymphoma cells are present), flow cytome-

try (more sensitive and less volume-dependent than cytology), cell count, protein, glucose, and Epstein Barr Virus polymerase chain reaction (in those with lymphoma secondary to immune-compromise).

Opening Pressure

Opening pressure measurement should be obtained with the patient in the lateral decubitus position. Measurements obtained in the sitting or prone (eg procedures under fluoroscopic guidance) position may under- or over-estimate ICP. Elevated CSF pressure measured by lumbar puncture is defined as > 20 cm H₂O (normal is approximately 12 cm H₂O).

Protein

Elevated protein is the most common CSF abnormality found in patients with LM. The finding is non-specific and not required for diagnosis. Normal CSF protein in the lumbar space and ventricle is < 45 mg/dl and < 25 mg/dl, respectively.

Pleocytosis

Patients with LM often have an increased CSF white count with lymphocyte predominance. CSF leukocytosis is defined as $> 4/\text{mm}^3$. The number of CSF white blood cells in patients with LM is usually between 5–50 cells/mm³. A higher number of leukocytes or neutrophil predominance should raise the possibility of infectious meningitis.

Glucose

Low CSF glucose (hypoglucorachia) is a common finding in patients with LM. Glucorachia is defined as CSF glucose $< \frac{2}{3}$ of serum glucose. Because patients may have rapidly fluctuating serum glucose and it takes several hours for serum glucose to equilibrate with CSF glucose, an absolute value < 40 mg/dl is considered low in patients without diabetes mellitus.

Cytology and Flow Cytometry

The demonstration of malignant lymphoma cells in the CSF is pathologically diagnostic of LM. Differentiating between a reactive versus malignant lymphocyte can be difficult on histological analysis. Flow cytometry is an analysis of cell surface markers by fluorescent probes to identify a monoclonal population of tumour cells. It is more sensitive than CSF cytology in patients with lymphoma [5]. The identification of a monoclonal population of lymphocytes in a CSF sample (predominantly B-cells) distinguishes neoplastic from reactive cells (overwhelmingly T-cells). A negative cytology does not rule out the diagnosis because of a high false negative rate (40 %). The poor sensitivity results from a combination of sampling error and difficulty with specimen processing. Sampling error occurs because of a small number of cancer cells circulating in CSF and the random event of capturing suspended tumour cells in a comparatively large fluid volume. LM cells adhere at various locations in the CSF compartment, diminishing the number of suspended cells available for analysis. The yield of cytology is improved by sending a large volume of CSF for analysis, ideally > 10 millilitres. The entire CSF cytology sample is centrifuged to concentrate the available cells for analysis. The CSF collected should be processed immediately or mixed with a preservative to prevent cell lysis. In some cases, a cervical puncture may improve yield (especially in patients where the LM are predominantly located along the

brainstem). In a patient with an intraventricular device (ie an Ommaya reservoir), a sample can be obtained from the ventricle as well. Even with correct specimen processing, the false negative rate is still high; up to 50 % of patients with eventual positive CSF cytology have a negative initial examination. Minimal benefit is obtained from a third CSF specimen if the first 2 CSF samples are negative for malignant cells. Importantly, nearly half of all patients with LM have persistently negative CSF cytology, suggesting positive CSF cytology is not the only parameter that defines LM. Neuroimaging (nearly 50 % of all studies are negative for LM) and clinical examination often provide the only evidence for LM.

Treatment

A physiologic blood-CSF barrier (analogous to the blood-brain barrier) excludes water-soluble substances, such as most systemic chemotherapy agents, from entering the CSF. Chemotherapy can be administered directly into the CSF space or systemically at high doses (methotrexate [MTX] 3–8 g/m² or cytarabine > 2 –3 g/m²). The intra-CSF chemotherapy agents most commonly used for LM are MTX, thio-TEPA, cytarabine (including liposomal cytarabine), and corticosteroids. The doses and schedules of these drugs are displayed in Table 2. Patients are typically treated with single-agent MTX or liposomal cytarabine, MTX alternating with cytarabine, or triple therapy with MTX, cytarabine, and corticosteroids. The optimal agent, dose, frequency or whether combination therapy is advantageous has never been established in prospective clinical trials. A small randomised trial suggested that liposomal cytarabine is more effective than free cytarabine when administered intra-CSF in patients with NHL and LM [6]. There is limited data to suggest intra-CSF rituximab (a monoclonal antibody directed at malignant CD20-expressing B-lymphocytes) either alone or combined with liposomal cytarabine may be safe and effective for lymphomatous meningitis [7, 8]. Intra-CSF chemotherapy may be administered either intralumbar, ie intrathecal therapy or by intraventricular injection through a ventricular access device, eg an Ommaya or Rickham reservoir and intraventricular catheter. There is a sin-

Table 2. Frequently used drugs for intrathecal instillation

Drug	Dose	Schedule
Methotrexate	12 mg	MTX/cytarabine twice weekly for 3 weeks, then alternate once a week until cytologic response, then alternate monthly
Cytarabine	30–60 mg	MTX/cytarabine twice weekly for 3 weeks, then alternate once a week until cytologic response, then alternate monthly
DepoCyt (liposomal cytarabine)	50 mg	Every 2 weeks
Methotrexate/cytarabine	12 mg/50 mg	MTX/cytarabine every 2 weeks, then alternate once a week until cytologic response, then monthly
Thiotepa	10–15 mg	Twice weekly for 3 weeks, then weekly for 4 weeks, then monthly

gle study that suggests intraventricular intra-CSF chemotherapy administration is superior to intralumbar intra-CSF chemotherapy administration, however, this was based upon a *post-hoc* analysis of a prospective trial [9].

The advantage of intra-CSF treatment is that tumourocidal CSF drug concentrations can be achieved at doses that do not usually cause systemic toxicity. The predominant toxicity of intra-CSF chemotherapy is the induction of transient chemical aseptic meningitis manifested by headache, nausea, vomiting, CSF pleocytosis, and occasionally confusion. It can usually be differentiated from infection without obtaining CSF cultures as the symptoms of aseptic meningitis occur within hours after injection, too soon for an iatrogenic bacterial infection. Aseptic meningitis usually resolves within 1–5 days and can be treated with oral antipyretics, antiemetics, and corticosteroids. Rare side effects of intra-CSF chemotherapy include acute encephalopathy, myelopathy, and subacute encephalopathy (reversible stroke-like syndrome). Prolonged survivors of LM may be at risk for developing a late leukoencephalopathy (dementia, urinary incontinence, and gait apraxia), especially if they are treated with concurrent MTX and whole-brain radiotherapy or receive MTX following whole-brain radiotherapy. Similar delayed late neurotoxicity may be seen with the use of intra-CSF liposomal cytarabine.

Although intra-CSF chemotherapy is the mainstay treatment for LM, there are several limitations. First, intra-CSF chemotherapy should not be administered to patients with CSF obstruction or impaired flow dynamics as demonstrated on a radionuclide ventriculography study. Impaired CSF flow dynamics is more common in leptomeningeal metastases from solid tumours although it is seen in nearly 15 % of patients with LM and is more common when bulky subarachnoid disease is present [10, 11]. Impairment of the normal CSF circulation leads to stasis of fluid in the ventricles and other regions. Chemotherapy injected into a blocked CSF compartment does not circulate and consequently does not treat the entire CSF space. Furthermore, the administered intra-CSF drug is effectively concentrated in the blocked compartment resulting in increased drug exposure and potentially enhanced neurotoxicity. Involved field radiotherapy to the site of CSF flow obstruction/bulky disease may alleviate obstruction and permit safe intra-CSF drug administration.

In addition, administration of intra-CSF chemotherapy is not always straightforward. Intra-CSF chemotherapy can be delivered into the lumbar space by repeated lumbar punctures (intrathecal therapy) or into the ventricle via an Ommaya reservoir (an intraventricular catheter attached to a subgaleal reservoir) as mentioned above. Both routes of intra-CSF drug delivery have limitations. Chemotherapy delivered via lumbar puncture is limited by patient discomfort, time required to perform the procedure, thrombocytopenia (platelets > 50,000 are required to reduce the risk of an iatrogenic epidural haematoma), and coagulopathy. In addition, the drug is often (approximately 15 %) injected into the subdural or epidural space so intrathecal therapy is not administered. Finally, even with successful intrathecal injection, therapeutic drug concentrations in the ventricular space may not be reliably achieved in nearly 1/3 of patients.

Because an Ommaya reservoir avoids these issues, it is employed in the majority of patients that are treated with intra-CSF chemotherapy in the United States. Treatment with a ventricular access device is not without complications; the device is subject to infection (nearly 10 %) and may occasionally be misplaced at the time of surgical implantation. Finally, placement of a ventricular access device requires a surgical procedure that is associated with risks of any neurosurgery procedure.

Summary

LM commonly presents with signs or symptoms of peripheral nerve dysfunction that may include cranial neuropathies, radiculopathy, and cauda equina dysfunction. As a consequence, any patient with NHL and manifesting these symptoms should be considered as having LM and if otherwise considered for treatment, undergo a diagnostic evaluation as summarised above. Involved-field radiotherapy (to sites of symptomatic disease, bulky disease as defined radiographically, and sites of CSF flow obstruction) and either high-dose systemic or intra-CSF chemotherapy are the main treatment modalities for patients with NHL and LM.

■ Neurolymphomatosis

Lymphomatous infiltration of a nerve root, peripheral nerve, cranial nerve, or multiple peripheral/cranial nerves is known as neurolymphomatosis (NL). NL is a rare neurologic complication of systemic lymphoma that is poorly recognised by oncologists and neurologists.

The predominant malignant cell type is diffuse large B-cell, although rare cases secondary to follicular lymphoma, peripheral T-cell lymphoma, and mantle cell lymphoma have been reported [12].

Clinical Presentation

NL classically presents as a painful, sensorimotor peripheral neuropathy affecting multiple limbs in an asymmetric manner with relatively rapid evolution [12]. Other patterns of presentation include cranial neuropathy with or without pain, painless involvement of peripheral nerves, and painless or painful involvement of a single peripheral nerve [12, 13].

This neurologic complication typically presents several months after successful treatment of systemic lymphoma. Another classic presentation is a patient successfully treated with intra-CSF chemotherapy for leptomeningeal lymphoma that develops a painful polyneuropathy. Rarely, the disorder presents prior to a diagnosis of lymphoma or is the sole manifestation of lymphoma. NL is frequently misdiagnosed as a paraneoplastic/inflammatory neuropathy, particularly if there is an initial response to steroids. Other misdiagnoses include LM, peripheral nerve compression, and chemotherapy-induced peripheral neuropathy.

Imaging

Brain or spine MRI or CT imaging often fails to show nerve root or peripheral nerve abnormalities in patients with NL, further potentiating the difficulty in making the diagnosis. Contrast-enhanced MRI of the brachial plexus, lumbosacral

plexus, or limb may show contrast enhancement of peripheral nerves with associated enlargement and nodularity [14, 15]. Infiltrated nerves may appear hyperintense on STIR and T2-weighted images reflecting lymphoma and peritumoural oedema. Caution must be made in interpreting the MRI as radiation plexopathy and other non-metastatic lesions may have a similar appearance. In addition, cases of biopsy-proven NL exist in which MR images displayed no abnormality [12, 14, 15]. Hypermetabolic activity along the course of a nerve root or peripheral nerve on FDG-PET supports a diagnosis of NL in patients with the appropriate clinical history with or without an abnormal MR imaging [12, 14–16]. Figure 1 displays typical MR and FDG-PET imaging for a patient with NL.

The only certain diagnostic test is biopsy, although patients with the classic clinical history of NL and abnormal PET imaging are usually treated empirically given the difficulty in making a histological diagnosis. The yield of a positive biopsy is dependent upon sampling a clinically or radiographically involved nerve. Because NL may not involve the entire peripheral nerve, blind nerve biopsies of affected nerves and non-involved sural nerve biopsies (the common site for a peripheral nerve biopsy) are frequently negative for lymphomatous infiltration [17]. In addition, treatment with steroids may result in a false-negative biopsy given their lytic effect on lymphoma. FDG-PET/CT may assist in identifying a target for biopsy in a patient in which a biopsy is necessary, such as those without a history of lymphoma.

Electrophysiological Studies

Nerve conduction studies reveal some degree of reduced compound muscle and sensory action potentials and demyelinating features may be present [18]. Patients with NL may meet the electrodiagnostic criteria of definite chronic inflammatory demyelinating polyneuropathy (CIDP), so caution must be taken to avoid misdiagnosis of an immune-mediated neuropathy [18].

Staging Work-Up

After establishing a diagnosis of NL, patients should undergo a staging work-up that includes a contrast-enhanced MRI of the brain (to evaluate for leptomeningeal or parenchymal involvement), CSF analysis (flow cytometry to evaluate for leptomeningeal involvement), and CT of the chest, abdomen, and pelvis with contrast (to evaluate for systemic lymphoma).

Treatment

Given the rarity of the disease, prospective clinical trials evaluating potential treatments are lacking. Treatment is challenging as a physiologic “nerve-blood barrier,” analogous to the “blood-brain barrier,” excludes water-soluble chemotherapeutic agents from entering the nerves. Treatment with corticosteroids may initially result in a radiographic response and improve symptoms, although NL typically recurs or progresses as the malignancy develops resistance. As with central nervous system lymphoma, high-dose methotrexate chemotherapy achieves cytotoxic concentrations in the peripheral nerve and is the treatment of choice for most patients either alone or in combination with involved-field radiotherapy. Radiotherapy is particularly useful in patients with significant neurologic dysfunction since it may rapidly improve or stabilise symp-

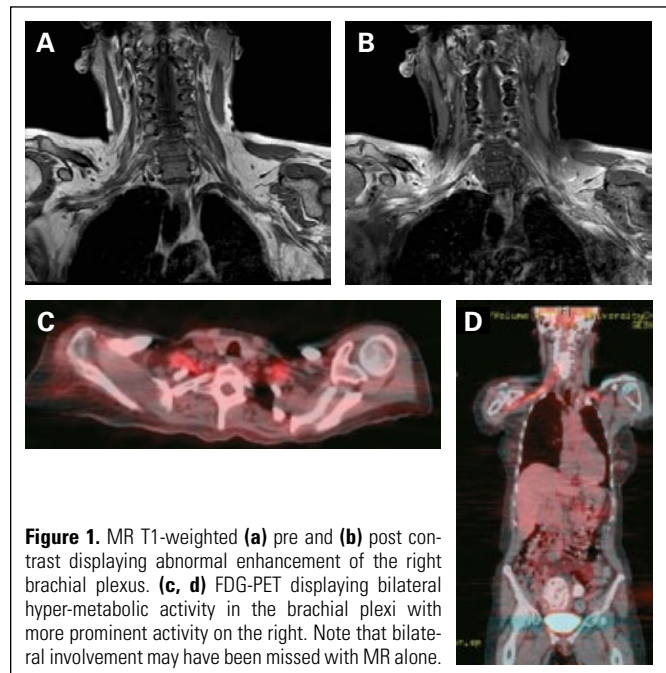


Figure 1. MR T1-weighted (a) pre and (b) post contrast displaying abnormal enhancement of the right brachial plexus. (c, d) FDG-PET displaying bilateral hyper-metabolic activity in the brachial plexi with more prominent activity on the right. Note that bilateral involvement may have been missed with MR alone.

oms. Given the rarity of the disease, prognosis is not well-established, although limited reports suggest a poor outcome. A retrospective study of 50 patients with NL reported a median survival of 10 months with 12-month and 36-month survival proportions of 46 % and 24 %, respectively [12]. The poor outcome is partially related to the frequent difficulty and delay in making the diagnosis. Limited reports suggest that consolidation with autologous stem cell transplantation following response to high-dose methotrexate may be an effective option [19].

Summary

Neurolymphomatosis classically presents as a painful, sensorimotor peripheral neuropathy affecting multiple limbs in an asymmetric manner several months after successful treatment of systemic lymphoma. This neurologic complication is poorly recognised by neurologists and oncologists and frequently misdiagnosed as a chemotherapy-induced or paraneoplastic/inflammatory neuropathy. Contrast-enhanced MRI of the brachial plexus, lumbosacral plexus, or limb may show contrast enhancement of peripheral nerves with associated enlargement and nodularity, or may be unremarkable. FDG-PET is useful in supporting the diagnosis in patients with the appropriate clinical history and normal MRI, to localise an appropriate nerve to biopsy, and to monitor response to therapy. High-dose systemic methotrexate alone or in combination with focal radiotherapy (in those with significant neurologic dysfunction) is the most common treatment. Although limited data regarding prognosis is available in the literature, there is a consensus that it is typically poor.

■ Unusual Causes of Peripheral Nerve Dysfunction

Epidural spinal cord metastases (ESCM) usually arise from the vertebral body or, less commonly, the vertebral lamina, pedicle, or spinous process. Epidural lymphoma causes neurologic dysfunction via spinal-cord, cauda equina, or nerve root

compression. Pain is the earliest and most common symptom of epidural metastases. Other symptoms include sensory loss or muscle weakness in a dermatomal or myotomal pattern. Treatment typically consists of focal radiotherapy or systemic chemotherapy. ESCM is a risk factor for the development of LM so appropriate patients should be screened.

Presumed paraneoplastic neuropathies that have been reported in patients with NHL include demyelinating neuropathy (resembling CIPD), sensory ganglionopathy, and vasculitic neuropathy [18, 20, 21]. The CIPD-type neuropathy typically presents subacutely as a painless, symmetric sensorimotor polyneuropathy. Electrophysiological studies display prolongation of distal latency and reduction of the conduction velocity. Sural nerve biopsy may show segmental demyelination without lymphomatous involvement. Patients with sensory ganglionopathy typically present with ataxia in the extremities from loss of proprioceptive sense. Electrophysiological studies reveal reduction of sensory nerve action potentials. A sural nerve biopsy reveals predominant large-fibre loss. Autopsy studies reveal loss of neurons in the dorsal-root ganglia with the preservation of motor neurons in the spinal cord and absence of lymphomatous infiltration. Vasculitic paraneoplastic neuronopathy presents clinically as mononeuritis multiplex, not as a diffuse symmetrical nerve dysfunction typical of peripheral neuropathies [20]. Electrophysiological studies reveal asymmetric axonal neuropathy. Nerve biopsy, which reveals occlusion of small vessels in the epineurium with inflammatory cellular infiltration without an atypical cellular appearance, is necessary to prove the diagnosis [18]. Intravenous immunoglobulin, plasma exchange, and rituximab may be an effective treatment in some patients, particularly those with CIPD-type or vasculitic-type paraneoplastic neuropathies. Other immunosuppressants such as steroids, mycophenolate, cyclophosphamide, and azathioprine may also be effective.

Intravascular lymphoma (IL), also known as angiotropic large-cell lymphoma or malignant angioendotheliomatosis, is a rare subtype of extranodal, diffuse large B-cell lymphoma characterised by occlusion of small vessels by malignant lymphomatous cells [22]. 75–85 % of IL patients present with neurologic symptoms [23]. The 4 most common neurologic presentations include multi-focal cerebrovascular events, spinal-cord and nerve-root vascular syndromes, subacute encephalopathy, and cranial-nerve or peripheral neuropathies [22]. The primary mechanism of nerve injury in the neuropathic presentation is ischaemic infarction caused by the proliferation of neoplastic lymphoid cells and immune-complex deposition within the walls of the vasa nervosum, leading to vessel occlusion. Ischaemic lesions accumulate randomly along the course of peripheral nerves, typically causing a painful, predominantly distal, asymmetric neuropathy. Long myelinated fibres are most susceptible, however, with disease progression, the pattern of damage becomes more diffuse with smaller unmyelinated fibres also being affected. With multiple-nerve or nerve-root involvement, mononeuropathy multiplex [24, 25] or lumbosacral polyradiculopathy (cauda equina syndrome) [26] may be the presenting syndrome. In those with peripheral nervous system manifestations, diagnosis can be made by biopsy of an affected nerve or nerve root. The highly varied presentation frequently results in diagnostic confusion, high-

lighted by the fact that the diagnosis is established at autopsy in most published cases.

■ Conclusions

LM and NL are 2 neurologic complications of NHL that are associated with significant neurological disability. Other neurologic complications of NHL affecting the peripheral nervous system include epidural spinal cord metastasis with nerve-root compression (after the nerves have exited from the subarachnoid space), compression of a peripheral nerve by a focal tumour, and paraneoplastic neuropathies.

■ Conflict of Interest

The authors report no conflicts of interest in relation to the subject matter of this review.

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Metastatic Skull Tumours: Diagnosis and Management

Koichi Mitsuya, Yoko Nakasu

Abstract: Metastases of the skull are classified into 2 anatomical groups, presenting distinct clinical features. One is calvarial metastasis, which is usually asymptomatic but may cause dural invasion, dural sinus occlusion, or cosmetic problems. The other is skull-base metastasis, which presents with cranial-nerve involvement leading to devastating symptoms. A high index of suspicion based on new-onset cranial nerve deficits or craniofacial pain in a cancer patient is important for early diagnosis and prompt management.

Magnetic resonance imaging is the primary diagnostic tool. Skull metastasis is a focal lesion with a low-intensity signal on T1-weighted images. Enhanced T1-weighted images with fat-suppression show tumour, dural infiltration, and cranial nerve involvements. Irradiation is the effective and first-line therapy for most skull metastases. Chemotherapy or hormonal therapy is applied depending on tumour sensitivity. Bone resorption inhibitory drugs are used as a part of systemic therapy, and are to be studied for prevention of symptomatic

skull metastasis. Surgery is indicated in selected patients with good performance status who need immediate decompression, cosmetic recovery, or histological diagnosis. **Eur Assoc NeuroOncol Mag 2014; 4 (2): 71–4.**

Key words: calvarium, cranial nerves, metastatic cancer, occipital condyle syndrome, radiation therapy, base of the skull

■ Introduction

Advances in oncology have extended survival for cancer patients, leading to a larger population at risk for complication of metastases. Skull metastases have rarely been clinically diagnosed, but are frequently found in autopsy and in head magnetic resonance (MR) imaging for staging in cancer patients [1, 2]. Skull metastasis has received limited neuro-oncological attention. Clinical studies for comparative treatment options or evidence-based practice guidelines are not available. The aim of this review is to present clinical features of and treatment strategies for patients with haematogenous skull metastases located at either the calvarium or the skull base.

■ Epidemiology

At *post mortem* examination, up to 70 % of patients dying of prostate or breast cancer have skeletal metastases. In patients with prostate cancer, 10 % have bone metastases at presentation [1]. Carcinomas of the thyroid, kidney, and lung also commonly give rise to bone metastases, with an incidence at *post mortem* examination of 30–40 % [1].

The true incidence of skull metastasis is not known. Reports have described skull metastases from all types of primary cancers, most commonly from breast, lung, prostate, and thyroid cancers [2, 3]. As for skull-base metastases, Laigle-Donadey reported that the most frequent primary neoplasms were prostate cancer (38 %) and breast cancer (20.5 %) in 279 patients in the literature [4]. Many other neoplasms affected the skull base: lung, colon, renal, thyroid cancers, lymphoma, melanoma, multiple myeloma, and neuroblastoma. Metastatic skull tumours are a late event in the course of cancer at a stage in which many patients already have disseminated disease, particularly other bone metastases [5]. However, skull-base involvement constituted the first sign of malignant tumours in 28 % of 279 patients [4].

■ Pathophysiology

Haematogenous spread to the skull or the meninges is the most frequent cause, particularly from a lung metastasis from a primary tumour. A postulated possible mechanism might be retrograde seeding through the Batson's valveless venous plexus from pelvic structures to the basilar plexus of veins without transiting through the lungs [6]. Direct extension or migration along the cranial nerves or perivascular structures from contiguous head and neck tumours are less common [7].

■ Clinical Presentation

Skull metastasis is basically in the class of systemic bone metastases, but it never causes pathologic fracture which is prominent in skeletal metastasis morbidity. Calvarial metastases are mostly asymptomatic, until they invade into dura mater, compress dural sinuses, or form a mass sufficient to cause cosmetic problems [3]. On the other hand, skull-base metastases frequently cause progressive ipsilateral involve-

Table 1. Tumour location and clinical syndromes in skull-base metastases. From [5].

Location and syndrome	Cranial nerves	Manifestations
Orbital	II, III, IV, V, VI	Supraorbital pain Diplopia Exophthalmos
Parasellar	III, IV, V, VI	Frontal headache Diplopia
Middle fossa (Gasserian ganglion)	V, VI, VII, VIII	Facial numbness Atypical facial pain Abducens palsy Hearing loss Facial paresis
Jugular foramen	IX, X, XI, XII	Occipital pain Dysphagia Hoarseness
Occipital condyle	XII	Occipital pain (severe) Neck stiffness Dysarthria Dysphagia

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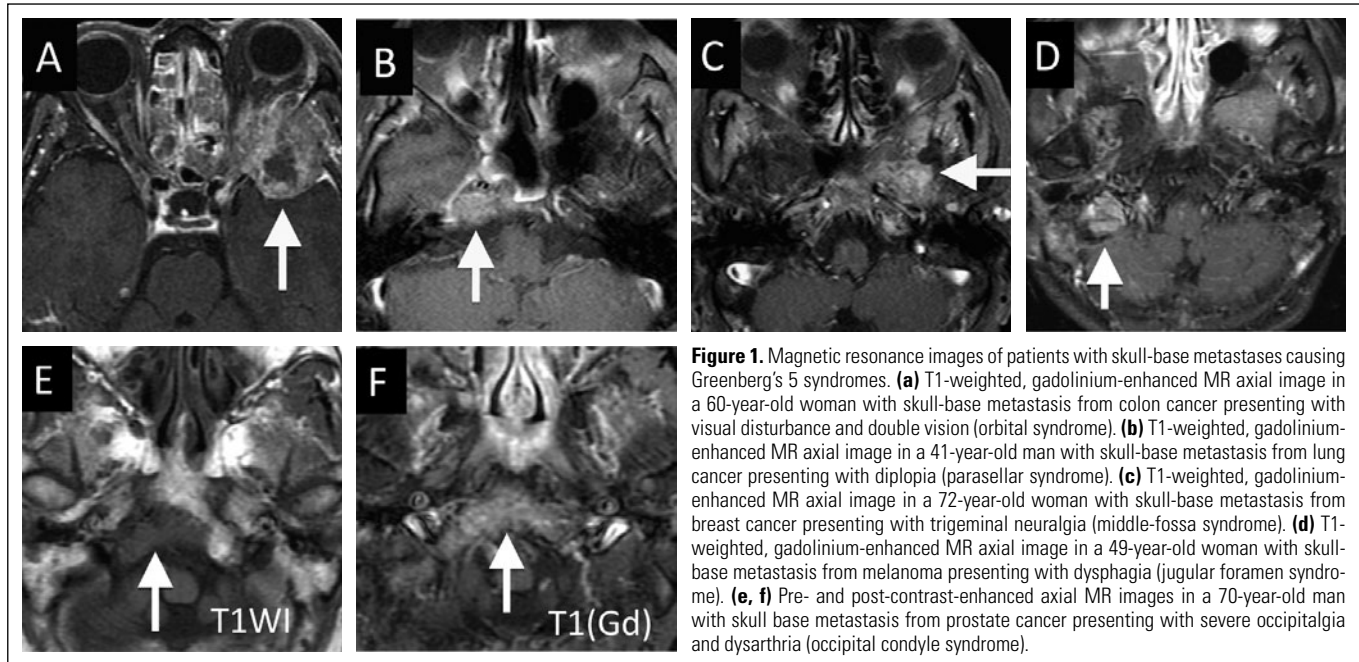


Figure 1. Magnetic resonance images of patients with skull-base metastases causing Greenberg's 5 syndromes. **(a)** T1-weighted, gadolinium-enhanced MR axial image in a 60-year-old woman with skull-base metastasis from colon cancer presenting with visual disturbance and double vision (orbital syndrome). **(b)** T1-weighted, gadolinium-enhanced MR axial image in a 41-year-old man with skull-base metastasis from lung cancer presenting with diplopia (parasellar syndrome). **(c)** T1-weighted, gadolinium-enhanced MR axial image in a 72-year-old woman with skull-base metastasis from breast cancer presenting with trigeminal neuralgia (middle-fossa syndrome). **(d)** T1-weighted, gadolinium-enhanced MR axial image in a 49-year-old woman with skull-base metastasis from melanoma presenting with dysphagia (jugular foramen syndrome). **(e, f)** Pre- and post-contrast-enhanced axial MR images in a 70-year-old man with skull base metastasis from prostate cancer presenting with severe occipitalgia and dysarthria (occipital condyle syndrome).

ment of cranial nerves, pain, or increased intracranial pressure resulting in poor quality of life (QoL). Especially dysphagia, diplopia, trigeminal and occipital neuralgia are seriously disabling symptoms and are alarming signs of skull-base involvement in cancer patients. For a high index of suspicion and for prompt diagnosis to lead to personalized treatment of the patients, 5 significant syndromes have been identified according to the metastatic site: the orbital, para-

seller, middle-fossa, jugular foramen, and occipital condyle syndromes (Table 1) [5]. Cases representative of the 5 syndromes are shown in Figure 1.

The overall prognosis is poor, with a median survival of about 2.5 years in 279 patients between 1963 and 2003 [4]. Survival time after diagnosis of skull metastases mainly depends on the prognosis of the primary cancers [4, 8].

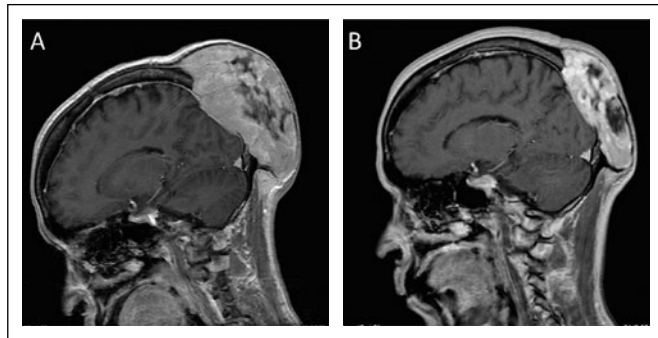


Figure 2. T1-weighted, gadolinium-enhanced sagittal MR images of a 57-year-old woman with calvarial metastasis from thyroid cancer. **(a)** Pre- and **(b)** 3 months post-irradiation 40 Gy per 20 fractions.

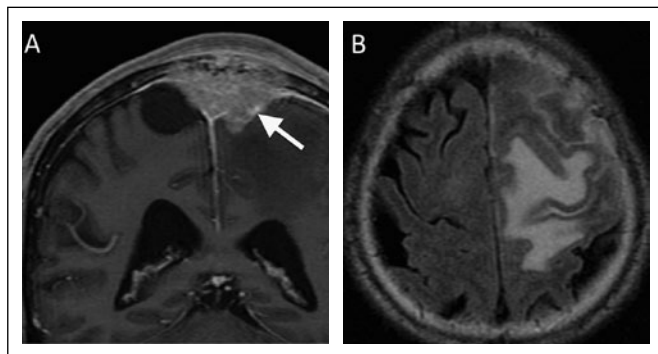


Figure 3. MR images of a 72-year-old man with calvarial metastasis from cholangiocarcinoma presenting with hemiparesis and partial seizures. **(a)** Coronal, T1-weighted, gadolinium-enhanced MR image demonstrating dural invasion and occlusion of the superior sagittal sinus (white arrow). **(b)** Axial FLAIR image demonstrating diffuse brain oedema in the left hemisphere.

■ Diagnosis

MR imaging is the best method to detect skull metastases [4], which appear as focal lesions of low-intensity signal on pre-contrast T1-weighted MR images. Contrast-enhanced fat-saturated sequence is important to demarcate the lesions in bone marrow fat [2]. MR imaging demonstrates tumour invasion into the dura mater, brain surface, or cranial nerves better than any other imaging modality. On X-ray film and CT scan, calvarial metastases are focal osteolytic or osteoblastic lesions of both the inner and the outer table. Radionuclide bone studies are still valuable screening tests to detect bone metastases [7].

Metastasis to the calvarium is easy to detect, but skull-base metastases that involve the ethmoid and sphenoid bones, clivus, and pyramids remain underestimated because their clinical expression is inconstant and because these regions are difficult to explore, even at autopsy [4]. When a cancer patient presents with headache, pain, or cranial nerve signs, a skull-base metastasis must be included in the differential diagnosis process. Prompt diagnosis is crucial for appropriate management to relieve symptoms of skull-base metastases.

Differential diagnosis consists of haemangioma, epidermoid cyst, meningioma, fibrous dysplasia, histiocytosis, neuroblastoma, primary sarcomas, haematologic malignancies, and others. In a surgical case series of osteolytic calvarial lesions, Hong reported that the most common pathological diagnosis was metastatic tumour in 25 % of 36 patients [9].

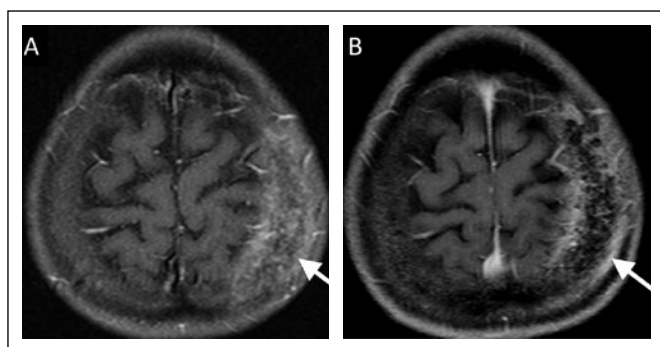


Figure 4. (a) T1-weighted, gadolinium-enhanced MR axial images of a 58-year-old woman with calvarial metastasis from breast cancer presenting with headache. (b) The tumour became less enhanced 3 years after 40 Gy per 20 fractions radiation therapy.

■ Treatment

Radiation Therapy

For patients with painful bone metastases, palliative radiotherapy gave an overall response rate for pain at 60 % in 5000 patients in a total of 16 randomized trials [10].

For patients with symptomatic skull-base metastases, Vikram et al reported that local radiotherapy relieved symptoms in 78 % of 46 patients, with improvement lasting until death in 81 % of the responders [8]. One must note that the likelihood of response dropped sharply if treatment was delayed. Improvement was observed in 87 % of patients with symptoms lasting < 1 month, while in only 25 % of patients with symptoms > 3 months. Therefore, they insisted that radiation therapy should not be withheld for patients with suspected skull-base metastases even if radiographic investigation is negative [8].

Figure 2 shows MR images of a patient with a huge calvarial metastasis from thyroid cancer with good response to radiation therapy. Radiation therapy is indicated even for asymptomatic skull metastases when they pose impending risks of dural sinus occlusion or mass effect with rapid growth (Figure 3).

Stereotactic radiosurgery (SRS) is a minimally invasive palliative option for primary management as well as for treatment of postsurgical or post-radiotherapeutic residual or recurrent skull-base metastases [11]. Response rates vary between 65 % and 90 % [11]. The main limitation of SRS is related to the size of the lesions. Patients with larger lesions near sensitive structures or in previously irradiated fields might benefit from fractionated stereotactic radiation techniques [12].

Chemotherapy

Patients with both skull and systemic bone metastases or with symptomatic skull metastases may undergo chemotherapy and hormonal therapy based on specific tumour types in addition to radiotherapy (Figure 4).

Much progress has been accomplished for the treatment of bone metastasis with bone resorption-inhibitory drugs. A human monoclonal antibody-inhibiting RANK ligand, denosumab, proved superior to bisphosphonate zoledronic acid in preventing skeletal-related events in patients with breast and prostate cancers, or achieved non-inferior effects in patients

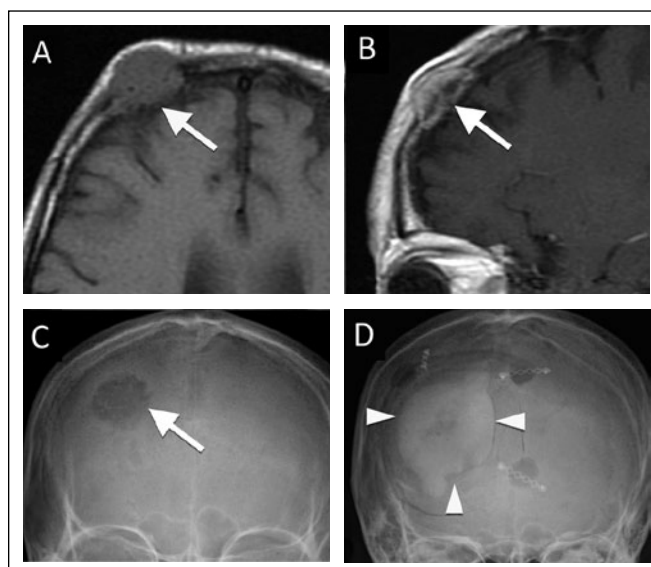


Figure 5. A 70-year-old woman with calvarial metastasis from lung cancer presenting with cosmetic problem in the forehead. (a) Pre-enhanced axial and (b) post-enhanced sagittal MR images demonstrating a mass lesion with focal invasion into the skin and dura mater. (c) Skull X-rays showing an osteolytic lesion (white arrow), and (d) surgical results of resection with a wide margin and reconstruction in the frontal bone (arrow heads).

with other solid tumours in phase-III trials [13]. Osteonecrosis of the jaw is the most important side effect of both compounds [14]. Potential major roles for antiresorptive agents are the prevention of bone metastases and improvement in survival in specific cancers. The contribution of these agents for patients with skull metastasis alone is to be examined.

Surgery

The goal of surgery for skull metastases is to provide rapid symptom relief and to preserve function with low morbidity. Surgery should be considered for the sake of histological diagnosis or for palliative decompression of radiotherapy-resistant tumours with worsening neurological deficits. Patients should be critically selected based on their clinical and functional status and also on supposed surgical morbidity. Michael et al reported that only 27 of 900 patients with calvarial metastases underwent surgery between 1993 and 1999 [3], and Chamoun reported that another 27 patients with skull-base metastases underwent surgery between 1996 and 2009 [15] at the MD Anderson Cancer Centre.

To achieve total removal, a wide resection of the lesion should be performed with removal of marginal bone tissue as well as resection of any infiltrated dura mater or skin [9] (Figure 5). Median survival times after cranial surgery have been reported as 8–11.4 months [3, 15, 16].

■ Conclusion

Patients with skull-base metastases present with syndromes of cranial neuropathies and headache or pain, and patients with calvarial metastases may have dural sinus occlusion or cosmetic problems. Patients can benefit from early diagnosis of the tumour and surrounding neurovascular structures on MR imaging and radiation therapy.

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Conflict of Interest

None.

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Glycosaminoglycans and Glioma Invasion

Soumi Kundu, Karin Forsberg-Nilsson

Abstract: There is a great need for novel therapies to target malignant glioma, a disease with an often dismal prognosis. One of the hallmarks of malignant glioma is its efficient invasion of the healthy brain parenchyma, which leads to rapidly recurrent disease upon surgical removal of the original tumour. To be able to establish new tumours at a distance from the original neoplasm, glioma cells must detach, migrate through the microenvironment, settle, and proliferate in their new location. This includes changing adhesive characteristics, breaking down extracellular matrix molecules (ECM), and perturbed growth factor signalling. Investigations of the glioma-specific ECM composition may therefore provide new

insights into glioma infiltration. In this review, we focus on glycosaminoglycans, important components of the ECM that are long unbranched polysaccharides composed of repeating disaccharide units. We discuss the roles for hyaluronan, one of the major brain ECM molecules, and that of the proteoglycans, heparan sulphate proteoglycans (HSPG) and chondroitin sulphate proteoglycans (CSPG), in glioma biology. Heparan sulphate (HS) and chondroitin sulphate (CS) chains act together with a wide variety of bioactive molecules, and these interactions depend on the HS and CS sulphation patterns. HS and CS chain modifications are implicated not only in normal development and homeostasis but they also play important

roles in pathological conditions including cancer. Dysregulated glycosaminoglycans, their biosynthetic and degradation enzymes as well as the proteoglycan core proteins are known to affect several stages of tumour progression, angiogenesis, and metastasis. Finding the specific characteristics of tumour cells that confer this infiltrative capacity of glioma may offer new avenues for drug development. **Eur Assoc NeuroOncol Mag 2014; 4 (2): 75–80.**

Key words: heparan sulphate, chondroitin sulphate, extracellular matrix, tumour invasion

■ Glioblastoma

Gliomas are classified according to WHO criteria in grades I–IV where glioblastoma is the most aggressive and also the most common malignant primary brain tumour among adults. Every year, approximately 3 per 100,000 individuals are diagnosed with glioblastoma [1] for which the standard treatment is surgery followed by radiation and chemotherapy. Even though the introduction of temozolomide has somewhat prolonged life expectancy, the outcome is still poor with a median survival of only ~15 months [2].

In addition to the classical WHO classification, glioblastoma can be further divided into subtypes, using a molecular-based taxonomy. This aims at better describing the heterogeneous nature of these tumours. The term glioblastoma multiforme (GBM) is used synonymously with glioblastoma to emphasize the intra-tumour and inter-tumour diversities. By means of a combination of mutational and expression profiling data several molecular subgroups have been described [3–5]. From the Cancer Genome Atlas (TCGA) data collection [5], GBM was divided into the following subtypes: (1) proneural, (2) neural, (3) classical, and (4) mesenchymal. An even more recent classification by Sturm et al [6] added the methylation patterns in the subtype analysis, and also included paediatric GBM. In addition, a description of the landscape of somatic mutations in GBM [7] provides further information on subtypes, survival, and increased understanding of the disease at the molecular level. Taken together, a solid base for patient stratification is becoming possible due to the increased availability of mutational analysis and expression data for GBM.

■ Glioblastoma Invasion Is a Major Clinical Problem

A typical feature of GBM is the extensive infiltration of tumour cells into the healthy parenchyma that makes complete resection impossible. This feature is common for all diffuse astrocytic tumours, but it is a particular problem in GBM [8]. After surgical removal, tumour recurrence within a distance of several centimetres from the original tumour site often occurs [9]. The high motility of glioma cells is underscored by their ability to spread even to the contralateral hemisphere via the corpus callosum. However, in contrast to its efficient invasion within the brain, GBM rarely metastasizes via the cerebrospinal fluid [10].

Therapies to target GBM invasion are highly warranted because of its efficient migration, eg, along white-matter tracts [11]. For a tumour to spread away from the original neoplasm, cancer cells have to detach and migrate through the parenchyma, which includes breakdown of several extracellular matrix molecules. It is well-known that glioma cells express cell adhesion molecules that facilitate the invasion process [12]. Tumour cell migration needs to be accompanied by matrix degradation, which is carried out by a variety of enzymatic processes [13]. This leads to ECM remodelling since the migrating tumour cells lay down *de novo* ECM of their own, composed primarily of ECM molecules supporting migration [14].

As of today, novel therapeutic approaches mainly target the cancer cells *per se* and focus less on the surrounding, non-tumour environment. In fact, most clinical trials have been directed against the bulk of cancer cells and few drugs have been tested that target the invasive mechanisms. Attempts at reducing matrix metalloproteinase (MMP) levels in glioma with marimastat were not successful since the combination of marimastat and temozolomide was approximately equivalent to temozolomide alone and also caused toxic effects [15, 16]. Another example are clinical trials with cilengitide, an inhibitor of integrin $\alpha\beta3$ and integrin $\alpha\beta5$ [17] that may affect both growth and spread of tumour cells as well as angiogenesis.

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However, in February 2013, it was announced that the phase-III clinical trial of cilengitide did not increase overall survival over standard treatment comprising radiation and temozolomide. In light of these failures, more targets specific for tumour cell invasion are needed, based on mechanisms responsible for tumour cell infiltration. In this review, we focus on the role of glycosaminoglycans because they are major components of the extracellular matrix and important players in the invasive processes.

■ The Extracellular Matrix of the Healthy and Malignant Brain

Several aspects of ECM biology are different between the brain and non-CNS tissues. Collagen-containing basement membranes that are typical for the extra-CNS tissue are only present in the meninges and around blood vessels in the normal brain. Basal lamina extensions from the vessels in the subventricular zone form structures called fractones [18] that have been suggested to enrich growth factors and other HS-binding signalling molecules in the neurovascular niche, where adult neural stem cells reside. Cancer stem cells (CSC) in glioblastoma share many properties with normal neural stem cells, such as their ability for self-renewal, and they are highly motile [19]. The perivascular niche in glioma is believed to harbour CSCs that are supported by trophic factors from the vasculature [20]. Sequestration of growth factors by HSPG in the tumourigenic niche could thus maintain cancer stem cells in a tumourigenic niche with similarities to the normal neurogenic niche (reviewed in [21]). In contrast to the normal brain glioblastoma has greatly increased levels of collagen [22] and the importance of the collagen structure for glioblastoma neovascularization and tumour growth has recently been reported [23].

In the adult brain, the extracellular matrix regulates structural and functional plasticity, partly through the brain-specific dense ECM structures called perineuronal nets. These were first described by Golgi (reviewed in [24]) and are composed mainly of chondroitin sulphate proteoglycans, hyaluronan, Tenascin-R, and Sema3A [26]. The perineuronal nets restrict reorganization of process formation mainly through inhibitory CSPG and Sema3A. CSPGs are highly up-regulated in glioma [27] but their role in glioma invasiveness is not fully elucidated [28, 29], as will be discussed below.

■ Glycosaminoglycans Are Major Components of the Brain ECM

Glycosaminoglycan (GAG) is the common term for linear polysaccharides that are composed of repetitively appearing disaccharides consisting of an N-acetylated or N-sulphated hexosamine together with either uronic acid (glucuronic acid or iduronic acid) or galactose. These molecules are highly conserved during evolution, which points at their ubiquitous functions in many biological processes [30]. Hyaluronan, a major constituent of the extracellular matrix (ECM), is a large, unbranched glycosaminoglycan that lacks sulphate groups. The glycosaminoglycans heparan sulphate (HS), chondroitin

sulphate (CS), dermatan sulphate (DS), and keratan sulphate (KS) make up the proteoglycans, consisting of core proteins covalently linked to one or more glycosaminoglycan chains. The glucosaminoglycan components of proteoglycans are sulphated in various positions, with a differing disaccharide composition. Dermatan sulphates (DS) have iduronic acid, while chondroitin sulphates (CS) lack these residues. Keratan sulphates (KS) have no uronic acid and are instead made up by N-acetylglucosamine and galactose units. Proteoglycans are either attached to the plasma membrane, found in vesicles inside cells, or exported to the extracellular space [31]. Because of the high abundance of hyaluronan, heparan sulphate, and chondroitin sulphate in the brain, relative to dermatan sulphate and keratan sulphates, this review will focus on the first 3 types of molecules.

Hyaluronan

Hyaluronan (HA) is the principal component of the brain ECM with a unique composition, and it does not undergo sulphation and epimerization [32, 33]. HA content is elevated in primary brain tumours [34]. In contrast to other GAGs, HA is not synthesized in the Golgi apparatus. Hyaluronan synthase is the primary biosynthetic enzyme in mammals, which occurs in 3 isoforms synthesizing HA polymers of different lengths. The enzyme is located in the plasma membrane and catalyzes polymerization as well as translocation of HA out of the cell [35, 36]. In most tissues, HA is rapidly degraded by hyaluronidase (Hyal). Mammalian Hyal has overlapping substrate specificity and is known to degrade HA and CS and, to some extent, DS. Hyaluronidase acts in concert with 2 other exoglycosidases (removing sugars from the non-reducing end [37]). Human glioblastoma expressed levels of hyaluronan synthases above that of normal cells [38, 39] and over-expression of hyaluronan synthase-2 reduced growth of murine glioma, but only if hyaluronidase was concomitantly present [38]. Furthermore, hyaluronan synthase has been associated with increased receptor tyrosine kinase activity [40] and hyaluronan synthase-2 mRNA levels were higher in GBM than in normal brain [41]. This implies an important balance between synthesis and breakdown of HA in brain tumour biology.

HA can reach high molecular mass, consisting of 25,000–30,000 disaccharide repeats under normal conditions, and it attains complex secondary and tertiary structures regulating physiological processes. As a major element of the brain ECM, HA is abundant in white-matter tracts [42]. These are the preferred migration routes for neural stem cells, eg, after transplantation into the injured rodent brain [43–45], and similarly these tracts constitute dissemination paths for tumour cells in glioma [11, 14, 46]. HA is also present in the neurogenic niche and important for stem cell maintenance [47]. Under pathological conditions, such as injury, inflammation, and repair, it undergoes regulations. The HA polymer becomes degraded by a series of enzyme reactions, thus generating HA with a range of molecular weights that are involved in various biological functions [37]. Low and intermediate molecular-weight HA has distinct biological functions as compared to native high molecular-weight HA, for example stimulating gene expression in macrophages, endothelial cells, and certain epithelial cells as well as scar formation [48]. In glioma, low molecular-weight HS oligomers have been shown to act

as an inhibitor of hyaluronan-dependent release of putative effector molecules from tumour cells [49].

HA interacts with several receptors [50] out of which CD44 and RAHM (receptor for hyaluronic acid-mediated motility) affect cell growth and motility, and thereby has the ability to mediate primary tumour cell invasion and migration [51, 52]. CD44 is the principal cell surface receptor for HA, and HA-CD44 interactions play a crucial role in eg development and inflammation, tumour growth, and metastasis [53, 54]. Signalling through the intracellular part of CD44 was shown to affect cell adhesion and motility through interactions with cytoskeletal proteins [55, 56]. In addition, CD44 interacts with a large number of signalling molecules that promotes matrix degradation and the spread of tumour cells (reviewed in [57]). HA-independent roles for CD44 have also been proposed in cell adhesion/migration because CD44 can act as a cell-surface anchor for the ECM-degrading enzyme MMP-9 [58].

Heparan Sulphate

Heparan sulphate proteoglycans (HSPG) are found either at the cell surface (syndecans and glypicans) or secreted (eg, perlecan and agrin) [59]. HSPGs are main components of the ECM where they interact with a large number of physiologically important macromolecules, thereby influencing biological processes [60]. HSPGs modulate growth factor activities, regulating interactions between ligand and receptor [61], and during CNS development, morphogen gradients can be maintained by HSPGs [62] (Figure 1). Its unique molecular design is composed of clusters of N- and O-sulphated sugar residues, separated by regions of low sulphation, which determines specific protein-binding properties [59]. In the adult brain, HS is associated with neural stem cell niches [63], where it may be involved in regulating neural stem cell maintenance. Recently, levels of 6O-sulphation of HS have also been linked to injury response as increased sulphation promoted glial scarring [64].

Mouse gene knockout experiments have shown the vital role of HSPGs in development and homeostasis [65]. Studies on neural differentiation have, to a large extent, been performed on *in vitro* differentiated ES cells to neural progenitors due to early embryonic lethal phenotypes of mice with deletions in crucial HS chain modification enzymes [66]. Our recent publication showed that N-sulphation enzymes in HS biosynthesis are indispensable for neural differentiation and that the ratio between HS and FGF was the crucial factor determining neural differentiation [67].

It has long been known that HSPGs are involved in the progression of various cancers [68] including glioma, where the levels of HSPGs are higher than in the normal brain [69]. Syn-

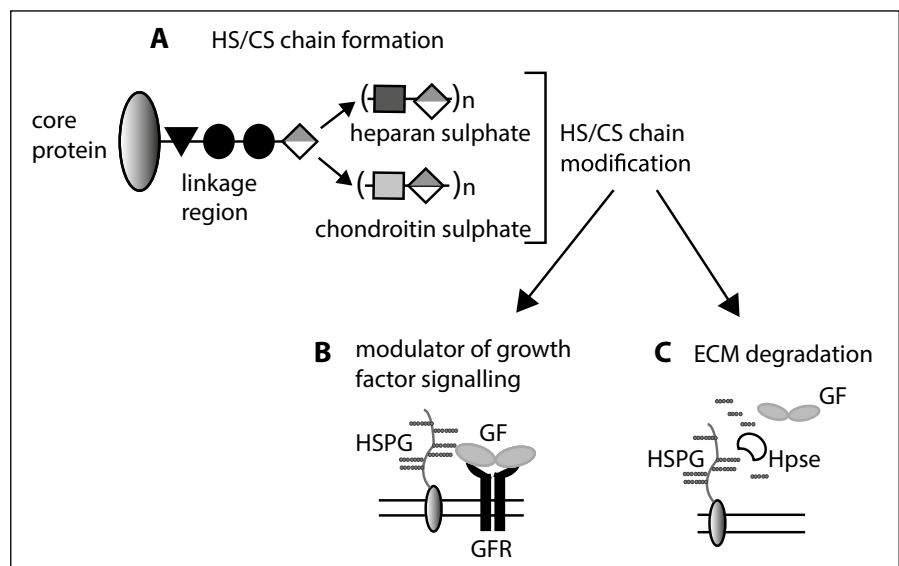


Figure 1. (A) Schematic representation of heparan sulphate (HS) proteoglycan and chondroitin sulphate (CS) proteoglycan biosynthesis and chain modifications. (B) Heparan sulphate proteoglycans (HSPG) act as co-receptors for growth factor (GF) signalling via growth factor receptors (GFR), thereby promoting cell proliferation, angiogenesis, and migration. (C) Degradation of HSPG by heparanase (Hpse) contributes to ECM degradation and release of HS-bound growth factors.

decan-1 [70] and glypican-1 [71] are examples of HSPG core proteins with increased expression in glioma cells compared to non-neoplastic cells. Su et al [71] found that glioma cell-associated HSPG was more capable of stimulating FGF-2 signalling than HSPG from normal cells, further supporting the role for HS-mediated growth factor signalling in glioma. There are several receptor tyrosine kinase pathways that can be modulated by altered HS amounts and composition. The extracellular sulphatase Sulf-2, which controls 6O-sulphation, thereby regulating HSPG interactions with eg PDGF receptors, has recently been shown to be highly expressed in glioblastoma and demonstrated to increase tumour size [72]. Increased Sulf-2 expression was most prominent in the proneural subclass that is associated with increased PDGF receptor activity, and the PDGF alpha receptor pathway was particularly influenced by altered Sulf-2 levels although IGF1 receptor and EPHA2 stimulation were affected as well.

A systematic analysis of proteoglycan expression of glioblastomas included in The Cancer Genome Atlas [73] showed that several of the proteoglycans as well as their biosynthetic and degradation enzymes were differently regulated in GBM compared with the normal brain [41]. The authors found by means of database mining that biosynthetic enzymes were mostly down-regulated, except for HS3ST3a1, as previously reported [71]. Sulphation of HS is critical for its function as a co-receptor for various growth factor receptors, and therefore the increase in 3O-sulphation (by HS3ST3a1) and decreased 6O-sulphation (by increased Sulf2 [72]) may be specific for GBM [41].

Heparanase, the major HS-degrading enzyme, was found to be up-regulated in TCGA GBM patients [41]. There are some reports implicating heparanase in glioma. In a study using human glioma cell line U87, heparanase over-expression led to increased motility and invasion. Larger tumours were found after xenografting of glioma cells with elevated heparanase, whereas at further increased levels, tumour growth was inhib-

ited [74]. Another study reports that heparanase was not expressed in human GBM and that U87 glioma cells lost their heparanase expression upon intracranial grafting to form tumours [75]. In contrast, Hong et al [76] found that mRNA levels of heparanase were elevated in glioma of various WHO grades relative to normal human brain, and that heparanase-expressing tumour cells *in vivo* had elevated proliferation. Similarly, U251 glioma cells over-expressing heparanase have increased proliferation, migration, and colony formation, accompanied by increased AKT phosphorylation [77]. Recently, heparanase has been shown to be a target gene for TGL1 [78], an alternatively spliced form of the GLI1 transcription factor, which causes migration and invasion of glioblastoma [79].

Chondroitin Sulphate

Chondroitin sulphate occurs as sulphated GAGs covalently attached to a core protein on cell surfaces and within extra-/pericellular matrices [80]. The synthesis of CSPG starts in a similar way as the HSPGs, in the endoplasmic reticulum/Golgi compartment with the synthesis of the GAG-protein linkage region. Like the HS, CS moieties vary considerably in their size and number of chains per protein core and in the position and degree of sulphation. A wide variety of biological functions have been attributed to CSPGs including cytokinesis, morphogenesis, and neuronal plasticity. It is also described to play an important role in pathological processes like brain injury, infections, and cancer metastasis [27].

As is the case with HSPGs, CSPGs show high expression in neurogenic niches of the brain, where they play important roles in regulating growth factor signalling [81]. Furthermore, the presence of CSPGs on neural progenitors is correlated to their ability to respond to FGF-supported proliferation and EGF-induced migration [82]. Neuronal migration and formation of neurites are believed to depend on over-sulphated CS [83]. Studies of knockout mice deficient in CS sulphotransferases confirmed that these enzymes are needed for radial migration of cortical neurons [84].

It has long been known that CSPG4, also referred to as NG2, is a marker of oligodendrocyte progenitor cells (OPC) [85], and that it promotes proliferation and migration by functioning as a co-receptor for growth factor signalling. Both PDGF-AA and FGF2 bind NG2 core protein [86], and a large number of studies have delineated the role for these interactions in oligodendrocyte biology [87]. Moreover, NG2 was also found to regulate EGFR signalling in OPCs and to contribute to their polarity [88]. Apart from OPCs, NG2 is also expressed on pericytes in the brain, and thereby involved in maintaining the integrity of the blood-brain barrier [89]. After injury of the CNS, CSPGs are the main inhibitory molecules of the glial scar [90], thereby creating barriers to prevent injury/inflammation to spread. In doing so, CSPGs also block axonal re-growth into the injured area, thereby counteracting regenerative processes. CSPGs thus make up important molecular boundaries in the brain, preventing cell movement.

A role for CSPGs in malignant progression of glioma was suggested several years ago [91] and followed by many other studies [92]. In many cancers, the expression of versican is

increased [93]. Furthermore, NG2 knockout mice exhibit reduced tumour angiogenesis [94] and CSPG levels also regulate immune cell infiltration in tumours [95]. In an experimental model of glioblastoma, GBM over-expressing NG2 gave rise to larger, more vascularised tumours as compared to tumours from NG2-negative cells [96]. Patients with high NG2 levels had a shorter survival time, suggesting NG2 as a prognostic predictor. These authors showed that elevated NG2 expression was correlated to increased resistance to radiation, and an induction of scavenging enzymes was proposed as one of the mechanisms behind this observation [97]. Furthermore, human GBM-derived NG2-positive tumour cells generated more aggressive tumours than the NG2-negative population [98]. An oncolytic virus was reported to be more efficient when CS was enzymatically removed and the tumours became smaller, without signs of increased tumour spread [99]. In addition, expression of the core proteins and the biosynthetic enzymes for CSPGs were found to be predominantly over-expressed in human glioblastoma based on the analysis of the TCGA database [41]. Taken together, these studies suggest CSPGs as targets in glioblastoma therapy.

The notion that CSPGs promote invasiveness of brain tumours despite their function to form barriers in the normal and injured brain may seem somewhat contradictory. For example, the lectican family of CSPGs is the most abundant CSPG in the adult brain where it provides a structural and functional link from the cell into the matrix, which is mainly composed of HA [100]. Lectican deposition has thus been shown to be the major inhibitory molecules for axonal outgrowth both *in vitro* and *in vivo* [27]. Nonetheless, the lectican family core proteins are highly up-regulated in GBM with the exception of neurocan [41]. This potential inconsistency was recently discussed by Silver et al [29]. In their study, the authors showed that CSPG borders were associated with contained, non-invasive tumours, and that glycosylated CSPGs were absent from diffusely infiltrating GBM. They propose that the degree of glycosylation of CSPGs is inversely correlated to the invasiveness of glioblastoma. This notion is supported by a previous study in which a less glycosylated form of the CSPG brevican was associated with human glioma [101]. Thus, the side chain modifications of CS would be of importance, not only the expression levels of the CSPG core protein.

Concluding Remarks

In conclusion, we have discussed the effector roles for glycosaminoglycans, including hyaluronan and the proteoglycans HSPG and CSPG in glioblastoma growth and invasion. These molecules and the enzymes regulating their synthesis and degradation are abundant and differently regulated in glioblastoma compared to the normal brain. They may therefore constitute new therapeutic opportunities for targeting malignant glioma, a disease characterised by diffuse infiltration and local invasion.

Conflict of Interest

The authors declare that they have no conflicts of interest.

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Intravascular Large B-Cell Lymphoma of the Brain

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■ Case Report

A 61-year-old man with a history of hypertension, dyslipidaemia, and monoclonal gammopathy of undetermined significance was admitted for recurrent strokes.

15 months earlier the patient had presented a sudden left hemiparesis. Brain magnetic resonance imaging (MRI) revealed subacute ischemia in the right corpus callosum. Transthoracic echocardiography, cervical Doppler sonography, electrocardiographic Holter, transoesophageal echocardiography (TOE), immunological tests, and microbiological tests (including tests for syphilis and human immunodeficiency virus) were performed. All of these examinations were normal. He was therefore started on aspirin.

Six months later, the patient presented a recurrence of the left hemiparesis. A new MRI showed new, multifocal, acute infarcts. Compared to the first MRI, the current MRI (Figure 1) showed multiple, hyperintense, multifocal, cortical, or subcortical lesions with hyperintensity on fluid-attenuated inversion recovery (FLAIR).

Due to the possibility of a prothrombotic state anticoagulant treatment was started. Cerebral angiography showed segmentary stenoses of small and medium vessels.

Despite normal inflammatory markers, a possible underlying inflammatory disease (brain vasculitis) as a cause of ischemic damage was considered. The patient was admitted to neurosurgery for cerebrospinal biopsy.

Histopathological examination revealed intravascular proliferation of large atypical lymphoid cells with pleomorphic nuclei and prominent nucleoli (Figure 2a), in the leptomeningeal and cortical vessels (Figure 2b), producing luminal obstruction.

On immunohistochemistry, the neoplastic cells were positive for CD 20 (Figure 2c). The T-lymphocyte marker CD3 showed reactive perivascular T-lymphocytes. The MIB-1 labelling index was > 95 %.

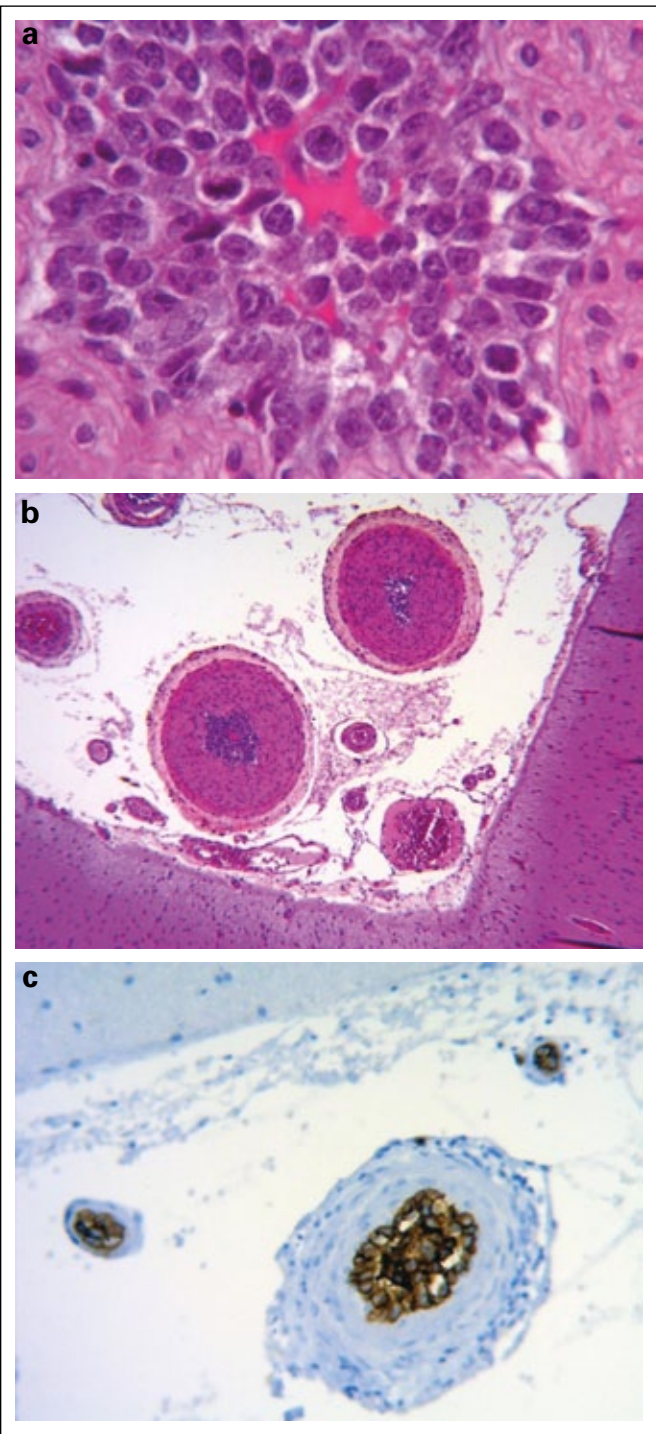


Figure 2. Histopathological and immunohistochemical findings of cerebrospinal biopsy ([a] HES × 400; [b] HES × 50; [c] CD 20 × 100).

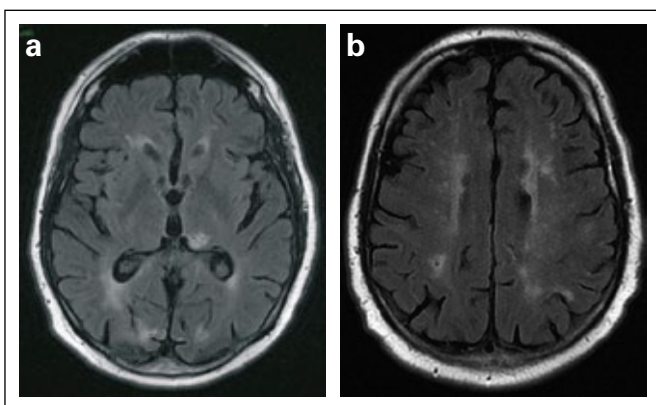


Figure 1. FLAIR MRI depicting the status during the current hospitalisation.

■ Comments

Intravascular large B-cell lymphoma is an uncommon subtype of large-cell lymphoma that is characterised by proliferation of lymphoid cells within the lumina of small and medium blood vessels. The current literature shows that it tends to affect the elderly in their 6th to 7th decades of life. Presentation is varied, manifesting as rapidly progressive encephalopathy, subacute neurological defects (due to brain infarcts), or headaches.

MRI is the best imaging tool for intravascular lymphoma, revealing abnormalities such as multiple, hyperintense, multifocal, cortical, or subcortical lesions with hyperintensity on T2-weighted and fluid-attenuated inversion recovery (FLAIR) imaging, suggesting small-vessel ischemia. The main differential diagnosis is central nervous system vasculitis.

Conventional cerebral angiography is normal > 50 % of cases but can show multiple segmentary stenoses and dilatations. But it lacks the specificity to differentiate intravascular large B-cell lymphoma from cerebral vasculitis.

Brain biopsy is the diagnostic key of diagnosis if it is large enough, lesions being focal. It shows neoplastic cells with irregular nuclei and prominent nucleoli. Immunohistochemistry shows a CD 20 expression of tumoural cells that are localised in the blood vessels of the leptomeninges, cerebral cortex, and white matter with multifocal vessel occlusion.

The outcome of intravascular lymphoma is very poor with a 1-year mortality rate approximating 80 % from the time of diagnosis. So far, no curative treatment exists.

This case report intends to highlight the key role of histopathology since non-invasive examination did not lead to correct diagnosis.

Further Reading:

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Ethical Decision-Making in Glioma Patients

Hanneke Zwinkels

■ Introduction

Caring for patients with brain tumours often includes considering ethical issues and dilemmas. With respect for autonomy of the patient and with respect for relatives, health care professionals try to provide care with the interest of the patient in mind.

Patients with intracranial tumours are asked to make important decisions about their treatment. It is increasingly well-documented that people with intracranial tumours suffer from cognitive impairment. However, should we or do we take this into account when providing information about and seeking consent to treatment?

A study by Kerrigan et al [1], assessing the mental capacity of 100 people with radiologically suspected intracranial tumours to consent to neurosurgery using the MacArthur Competence Assessment Tool for Treatment showed that 25/100 patients with radiologically suspected intracranial tumours did not have the requisite mental capacity to consent to neurosurgery. Neurosurgeons identified incapacity in 13/25 (52 %) people. The authors did not find a relation between symptoms of anxiety or depression and capacity. The conclusion of the study was that mental incapacity is common in people with intracranial tumours and is under-recognised by clinicians seeking informed consent for neuro-oncological treatment. Decisions about treatment are often made in the absence of any objective evidence of cognitive function. They recommended that clinicians should do more to help people understand the nature of their disease and the risks/benefits of treatment and should adopt a more structured approach to confirm understanding.

■ Case

This case report outlines how the incapacity of the patient to judge and to comprehend her situation as well as the fact that she was at home and at a certain point was denied care by her sisters and home care nurses posed the nurse practitioner neuro-oncology (NP) in an unpleasant position. It was difficult to intervene, working at the outpatient clinic and being the contact person for care in the hospital. Besides, the husband – who was her legal representative – never asked the NP for help. Knowledge of the severe situation from information provided by the patient's sisters, who came to the outpatient clinic for help, led to an ethical dilemma for the NP.

A 42-year-old Dutch woman presented with episodes of flashes in her right visual field of both eyes, accompanied with speech disturbances, confusion, headache, and nausea. She had unintentionally lost a lot of weight (20 kilos) over the past 6 months. She was married to a man from Morocco and had 3 children (20, 11, and 9 years old). Brain imaging showed a left-temporal lesion, mainly in the hippocampus and spleni-

um of the corpus callosum. She was prescribed levetiracetam (500 mg BID) and underwent biopsy to determine the pathology of the lesion.

Pathology showed a glioblastoma multiforme without methylation of the MGMT-promotor. It was decided that the patient should start with temozolomide combined with radiation followed by 6 adjuvant cycles of temozolomide. At the end of chemoradiation, the patient came – accompanied by her 2 sisters – to the outpatient clinic to speak with the NP. She was complaining about fatigue and because of that, difficulties in managing her household. The NP contacted the general practitioner (GP) to organise home care and help for guidance for the 2 young children.

Four weeks later, the patient and her husband (who was frequently away from home and not able to participate in the care for either the children or the household) came to the NP for the initiation of adjuvant treatment. They communicated that they had decided against starting home care because they felt that home care would disturb their privacy. The eldest daughter – who had only recently given birth to a boy – came to live with her parents and the patient's sisters helped her with her household, partly because of apraxia and fatigue.

In June 2013, shortly before the start of the fourth adjuvant cycle, the patient was admitted to hospital because of a secondary generalised seizure. Post-ictally, she suffered from confusion, inertia, and speech disturbances. The MRI made to evaluate the first 3 cycles showed a substantial increase of the tumour growing to the right temporal lobe and a satellite lesion in the left semiovale centre. The patient was not able to function adequately, muscle strength in both sides was normal but there was a subjective hypaesthesia in the right arm and leg.

Participation in a clinical research trial was suggested to the patient but she wanted to consider this and went to another centre for a second opinion, which caused some delay. Ultimately, she decided to undergo a new tumour treatment, which existed at that time – because the trial was permanently closed – of procarbazine, lomustine, and vincristine (PCV) chemotherapy.

At that time, the patient suffered from fatigue, inertia, worsened appetite, and memory problems. The NP spoke with her and her sisters about psychosocial help for the home situation by the home care oncology nurse. Besides, she was referred to the psychology outpatient clinic with her consent.

After the first cycle of PCV, the patient visited the emergency room together with her husband after a seizure: she had speech arrest, was confused, suffered from hemianopia, and lab results showed pancytopenia. We wanted to admit the patient to the hospital ward but her husband wanted to take her home. PCV was put on hold because of her pancytopenia. A

brain CT showed an increase in the lesions as compared to the latest MRI but no acute problems (eg, herniation, hydrocephalus, haemorrhage), anti-epileptic drugs were increased and the patient went home.

The NP was contacted by the patient's sister who stated that the patient was doing worse: the patient was bedridden with more severe headache, more memory problems, and more fatigue. Besides, her husband had made her convert to the Muslim faith, while a few weeks earlier the patient had spoken of a Catholic funeral and discussed her last wishes with her sisters. Home care was still deterred and the specialised oncology nurse had made several attempts at speaking with both the patient as well as her husband, but appointments were subsequently cancelled by him. The NP contacted the GP who visited the patient and prescribed pain medication.

The patient was deteriorating rapidly and her sister contacted the NP again with the consent of the patient, and all appointments in the hospital were cancelled. The GP then was responsible for care and prescribed dexamethasone and pain medication, the family was aware of the fact that the end of life was near. The patient was alone most of the time without being taken care of, not able to go to the toilet or eat or drink. Because the patient's sisters were having problems with the lack of care from the husband, they withdrew their help and support to press him to allow home care to come. They asked the NP to intervene and arrange for hospice care, but shortly thereafter they withdrew this question because they were afraid of the husband and his anger about their involvement.

The NP discussed this problem with the neurologist, who suggested to call the GP to arrange admission to the hospital ward and during admission, we would try to guide the patient and her family to transfer to a hospice. A social worker as well as an imam would try to speak with the couple. The spouse approved of this, he also would like to have an MRI made and his wife to start PCV again. During admittance the patient became more clear and adequate after tapering pain medication, the responsible physician noted neglect at home and a husband who refused delivered care. MRI showed progressive disease and leptomeningeal dissemination.

Patient, spouse, sisters, and the involved health care professionals came to an agreement on going home on the condition that care was accepted and that they would contact the hospital when the situation was deteriorating again, in which the GP played an important role during the end-of-life phase.

Reference:

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Banned!

Kathy Oliver

Overzealous, overprotective, and anachronistic legislation forbids patient advocates access to information and networking at one of the world's major cancer conferences.

Cancer patient advocacy – including important work by advocates in the brain tumour community – is now a well-established, respected movement in Europe.

After years of dedicated, determined work, patient advocates are finally becoming accepted as equal stakeholders in the multidisciplinary cancer setting. In the brain tumour world, this is vital as there is so much which needs to be done to serve our patients well during their journeys.

Patient advocates participate as advisors to pan-European academic institutions and global pharmaceutical companies. They are members of important committees at august medical societies. They contribute wise insights to regulatory, pricing, and approval bodies.

Patient advocates share the plenary podium at international conferences with the best clinicians and researchers in the world and deliver high-quality presentations to auditoriums packed with medical professionals, journalists, key opinion leaders, and politicians. They often work exhausting hours, travel tirelessly from country to country raising awareness of cancer, master complex scientific theories, lend their expertise in various fora, and frequently do all of this on a purely voluntary basis.

Importantly, patient advocates also serve as delegates at many medical conferences. In busy exhibition halls, they meet with the pharmaceutical industry to discuss the latest promising cancer therapies and to learn what is in the companies' pipelines that might be relevant to their disease-specific populations.

One of the crucial aspects of medical congresses is the free flow of information between patient representatives and the pharmaceutical industry.

■ Patient Advocates Refused Entry

But one autumn day in September 2013, patient advocates found themselves relegated to the outside of the barriers that wound their way around the vast exhibition hall at the European Cancer Congress (ECC) in Amsterdam, forbidden to enter this area and stymied in their efforts to access information hitherto always available to them at these types of events¹.

¹The European Cancer Congress (ECC) is organised by the European CanCER Organisation (ECCO), European Society for Medical Oncology (ESMO), and European Society for Radiotherapy and Oncology (ESTRO) in partnership with the European Society of Surgical Oncology (ESSO), European Association for Cancer Research (EACR), European Oncology Nursing Society (EONS), and the European Society for Paediatric Oncology (SIOPE). See <http://www.ecco-org.eu/>



Cancer patient advocates mounted a dramatic but dignified protest at the ECC and signed a petition stating their strong objections to anachronistic and unnecessary regulation. Photo courtesy of Jan Geissler, ECCO Patient Advisory Committee.

There was suddenly – after years of unfettered access to conference exhibition halls – no chance to interact personally with companies, no on-the-spot exposure to new pharmaceutical information about promising therapies. It was a real blow, a retrograde step back to the days when the patient community was seen, but never heard.

■ Why the Discrimination?

Article 86 of the 2001 EU Directive 2001/83/EC prohibits advertising and promotion of prescription-only drugs to the general public. The article requires that promotion of drugs must only be to those who are qualified to prescribe and supply medicinal products [1].

The Dutch Medicines Act (DMA) incorporates this Directive within its country's law and the Dutch Healthcare Inspectorate – which is responsible for overseeing compliance with the DMA – recently extended the enforcement of the DMA to international medical congresses. However, for some reason neither Dutch conference venues nor conference organisers were made aware of this fact [2].

Once the European CanCER Organisation (who were running the ECC) heard about the legislation, they were stuck between a rock and a hard place. With their congress occurring in September (some few months after hearing the news) there was not enough time for industry to change their booth set-ups to accommodate different types of visitors (for example setting aside a private part of the booth for prescribers only). Nor was there sufficient time to redesign the whole exhibition layout.

The only feasible solution, the organisers felt, was to badge participants as either “prescribers” or “non-prescribers” which is what happened.

■ Other Professionals Left Out

Not only patient advocates but also non-accredited journalists, professional medical society staff, and others were also banned from the exhibition hall because they were non-prescribers.

What is more, a major exhibition such as the European Cancer Congress includes not only pharmaceutical companies but the booths of medical publishers, professional societies, pre-clinical and research groups, nursing organisations and a range of other non-pharma stakeholders. Access to these displays – because they were in the exhibition hall – was also banned to non-prescribers.

As Jan Geissler, one of Europe's leading cancer patient advocates said: *"Exhibitions like these have been a key meeting point for all stakeholders for many years, across many countries. Patient advocates attend in their capacity as experts; most of them are members of government committees, regulatory authorities, research groups, and healthcare advisory boards. They are not just participants informing themselves about drugs, but they provide a platform for discussing all kinds of services for their constituents. Patient advocates must be entitled to access all information as equal stakeholders in healthcare."*

■ Patient Advocates Are the Crucial Link

Patient advocates occupy a privileged position. They are the vital conduits between patients in the general public and drug developers and other parties. Congresses like the ECC are not attended by members of the general public but rather by groups of professionals – be they medical experts, allied healthcare workers, researchers, or indeed patient advocates. All of these groups need the information available from the exhibition hall.

Davi Kaur, Head of Congress Unit at the European Cancer Organisation in Brussels who helped organise the European Cancer Congress in Amsterdam, points out: *"Our philosophy for the congress has always been that it is open to professionals only who have an interest in cancer. It is a closed and regulated environment, which ensures that there is always a fair exchange of dialogue between all stakeholders ... [so] to impose restrictions in a closed environment makes no sense"* [3].

■ Advocates Protest

Patient advocates are neither shy nor retiring, nor ever at a loss for making a strong point.

So in response to the ban at Amsterdam, cancer patient advocates mounted a dramatic but dignified protest at the ECC and signed a petition stating their strong objections to what was seen as anachronistic, outdated, insulting, and unnecessary regulation.

Imposing EU Directive 2001/83/EC in the manner seen in Amsterdam is a dangerously retrograde step which stifles communication and flings professional advocates back to a time when patients were only considered subjects of care, rather than active and well-informed partners in their own disease journeys.

Ironically, some of the information which would have been available to patient advocates in the exhibition hall at the ECC was already freely available on the internet.

■ Future Worries

What happened in Amsterdam may only be the beginning of this very worrying trend in discrimination within the closed environment of medical conferences.

Organisers of major international medical congresses in Europe are at this very moment reviewing their plans for future events and will undoubtedly become far more selective in their choice of country and venue.

As Davi Kaur says: *"This would mean that local and national doctors, nurses, and researchers would miss out on the opportunity to be educated by high-level global experts at low cost."* Additionally, she notes: *"The economic value in bringing a congress to a city and country is high"* [3].

As for patient advocates?

Never a group of campaigners to tolerate inequity, they are fervently urging all stakeholders in the cancer journey to impress upon their governments their objections to the unacceptable face of discrimination and exclusion which existed at the ECC.

There is also the fear that being banned from exhibition halls at scientific conferences today could result in far-reaching consequences tomorrow. We may find that further legislation building on that which exists already will see patient advocates forbidden to contribute to medical journals, denied access to crucial information on the internet, banned from academic and industry advisory boards, and barred from a range of other important activities, all of which they do altruistically.

Shunting patient advocates off to a peripheral corridor and shutting the exhibition doors against them denies access to a crucial stakeholder.

After all – whether patients, patient advocates, medical professionals, or industry, we are all waging the same battle against cancer. We must do this together, not apart.

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1. Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use. http://ec.europa.eu/health/documents/eudralex/vol-1/index_en.htm [accessed April 3, 2014].
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Calendar of Events

2014

June 12–13	Advances in Biology and Treatment of Malignant Brain Gliomas	Rome, Italy	http://www.atenaonlus.com/2_internationalcongress.php
June 12–14	16 th Biennial Canadian Neuro-Oncology Meeting	Halifax, Canada	http://www.cnomeeting.ca/
June 26–28	Oncologic Imaging Course	Dubrovnik, Croatia	http://www.oncoic.org/
June 28–July 2	International Symposium on Pediatric Neuro-Oncology (ISPNO) 2014	Singapore	http://www.ispno2014.com/
July 3–6	20. Jahrestagung der Deutschen Gesellschaft für Radioonkologie	Düsseldorf, Germany	http://congress.cpb.de/2/Grusswort.degro-201200.0.html
July 9–11	BNOS 2014: Contemporary Approaches to Paediatric and Adult Brain Tumours	Liverpool, UK	http://www.bnos.org.uk/conference.html
July 26–30	5 th World Congress – IFHNOS and Annual Meeting AHNS	New York, USA	http://www.ahns2014.org/
September 7–11	18 th International Conference on Cancer Nursing (ICCN)	Panama City, Panama	http://www.isncc.org/?page=18th_ICCN
September 26–30	39 th ESMO Congress	Madrid, Spain	http://www.esmo.org/events/madrid-2014-esmo-congress.html
October 9–10	50. Jahrestagung der Österreichischen Gesellschaft für Neurochirurgie	Vienna, Austria	http://www.oegnc-jahrestagung.at/
October 9–12	11 th EANO Congress	Turin, Italy	www.eano.eu
October 13–17	EANS 2014	Prague, Czech Republic	http://www.eans2014.com/
October 22–25	46 th Congress of the International Society of Paediatric Oncology	Toronto, Canada	http://siop.kenes.com/
October 24–25	ASCO's Palliative Care in Oncology Symposium	Boston, USA	http://www.asco.org/meetings/ascos-palliative-care-oncology-symposium
November 1–2	ASCO Quality Care Symposium	San Diego, USA	http://quality.asco.org/
November 12–13	CNS Anticancer Drug Discovery/Development Conference	Miami, FL, USA	http://www.soc-neuro-onc.org/en/cev/140
November 12–14	Neuro-Oncology Review Course	Miami, FL, USA	http://www.soc-neuro-onc.org/en/cev/138
November 13–16	Society for Neuro-Oncology Meeting	Miami, FL, USA	http://www.soc-neuro-onc.org/2014-annual-meeting/
November 18–21	EORTC – NCI – AACR International Symposium on Molecular Targets and Cancer Therapeutics	Barcelona, Spain	http://www.aacr.org/home/scientists/meetings--workshops/molecular-targets-and-cancer-therapeutics.aspx

2015

April 18–22	American Association for Cancer Research Annual Meeting	Philadelphia, USA	http://www.aacr.org/
May 29–June 2	2015 ASCO Annual Meeting	Chicago, IL, USA	http://www.asco.org

2016

April 16–20	American Association for Cancer Research Annual Meeting	New Orleans, USA	http://www.aacr.org/
June 3–7	2016 ASCO Annual Meeting	Chicago, IL, USA	http://www.asco.org
October 13–16	12 th EANO Congress	Heidelberg, Germany	www.eano.eu

2017

June 2–6	2017 ASCO Annual Meeting	Chicago, IL, USA	http://www.asco.org
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2018

June 1–5	2018 ASCO Annual Meeting	Chicago, IL, USA	http://www.asco.org
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2019

May 31–June 4	2019 ASCO Annual Meeting	Chicago, IL, USA	http://www.asco.org
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Call for Applications – SNO Travel Scholarships

The International Outreach Committee of the Society for Neuro-Oncology is pleased to offer travel scholarships to colleagues in developing regions of the world to attend the 19th Annual SNO Scientific Meeting and Education Day, November 13–16, 2014, in Miami, Florida.

Scholarship applications are now being accepted.

Deadline for applications: July 1, 2014.

A total of seven \$ 1500.00 scholarships* will be awarded at the discretion of the International Outreach Committee for each of the following geographical regions (one per region):

- South America/Central America & the Caribbean
- Central and Southern Africa
- China & Associated Countries
- Eastern Europe
- Far East and Australasia
- Indian Sub-Continent
- North Africa & the Middle East

To download the application, click the link below:

<http://www.soc-neuro-onc.org/attachments/wysiwyg/7/2014%20SNO%20Meeting%20Travel%20Scholarship%20Application.doc>

Award Criteria

In order to be considered for one of the travel scholarships, the applicant must meet the following guidelines:

1. Work and live outside the United States or Canada
2. Be a medical professional with a focus in neuro-oncology
3. Could otherwise not attend without the benefit of a travel scholarship
4. Is not the presenting author of a poster or giving an oral presentation at the SNO meeting
5. Have no visa issues entering the United States (SNO cannot provide visa assistance other than providing a letter of invitation)
6. Complete accompanying application and return by July 1, 2014

Applicants will be notified via email by August 1, 2014, if their application is accepted for a scholarship.

SNO will arrange and provide hotel accommodations and complimentary registration to the entire meeting. The award winner will be responsible for arranging his or her own air transportation to and from the meeting.

*The award, in the amount of 1500.00 USD, will be presented to the winning applicants on-site at the meeting in Miami.



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November 13-16, 2014

EANS Tumor Section

Zvi Ram

Department of Neurosurgery, Tel-Aviv Sourasky Medical Center, Tel Aviv, Israel

The Tumor Section of the European Association of Neurosurgical Societies (EANS) was founded in 2010. The Section has replaced the Neuro-oncology Committee of the EANS as the professional organisation in charge of research, education, and neurosurgical aspects of the clinical management of patients with brain tumours.

As a major branch of the EANS, the Tumor Section's charter encompasses the vibrant and heterogeneous medical environments of all individual neurosurgical societies across Europe.

The Tumor Section serves as the main consulting body on neuro-oncological issues to the EANS and its members. Members of the section are neurosurgeons who have demonstrated significant interest, input, and achievement in the field of neuro-oncology and serve for a period of 4 years.

From a clinical research standpoint, the Tumor Section acts to identify major European neurosurgical centres and enrol them in a neuro-oncology network. This network creates a major platform to perform high-quality clinical trials, to advise pharmaceutical and biotechnology companies of various sizes on designing clinical studies, and help with the execution of such studies. Section members serve on the steering committees and advisory boards of many such companies and strengthen the collaboration and interaction between the medical world and the industry.

The Tumor Section is also in charge of dissemination of education and guidelines regarding therapy of malignant CNS pathologies. This is done via dedicated workshops, courses, and symposia as well as through contribution to the scientific programmes of EANS meetings. The section is particularly keen to facilitate international exchange between young and experienced neurosurgeons and between units. Recommendations and information regarding fellowship opportunities in neurosurgical oncology are also provided. Special competitive education grants are also provided to young European neurosurgeons each year for an exchange programme to neurosurgical oncology centres in the USA. This is reciprocated by a similar mechanism from the AANS/CNS Section on Tumors for American neurosurgeons.

The Tumor Section fosters collaboration with other international societies and maintains a close relation with the AANS/CNS Section on Tumors, participation and liaison with the Committee for Neuro-Oncology of the WFNS, SNO, EANO, ASNO and various research groups, such as the EORTC and NCRI where several members of the section are active participants.

The Tumor Section is proud to include the largest number of individual members from the EANS who may benefit from the various functions of the section. Membership in the EANS Tumor Section is possible for a nominal fee through the EANS main office (susie.eans@gmail.com).

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Interview with Florian Boele, MSc, and Martin Klein, MD, VU University Medical Center, Amsterdam, about the Randomised Trial on Internet-Based Treatment of Depressive Symptoms in Glioma Patients

Ufuk Abacioglu

From the Department of Radiation Oncology, Neolife Medical Center, Istanbul, Turkey

Q: Dear Florian Boele, can you tell us about the ongoing randomised trial on internet-based treatment of depressive symptoms in glioma patients? What are the rationale and background for this trial?

A: Certainly! This project, funded by the Dutch Cancer Society, aims at the development of an internet-based intervention for glioma patients with mild-to-moderate depression. Glioma patients are at an increased risk for depression compared with both the general population and other oncological populations. This may affect brain tumour patients negatively, as in this population, depression has been associated with increased morbidity, poorer survival, and poorer health-related quality of life.

While depression is potentially treatable, depressive symptoms are often overlooked in clinical practice and subsequently undertreated. In addition, standard treatment of depression (antidepressants and/or cognitive behavioural therapy) may encounter specific problems in glioma patients. Glioma patients often take many medications concurrently, which increases the risk for drug interactions. Moreover, psychotherapy usually requires good cognitive functioning in order for the patient to benefit most, while many glioma patients experience cognitive deficits. Therefore, it remains to be determined if either antidepressants or psychotherapy are as effective in glioma patients as they are in the general population and other oncological populations. We want to make an effort in filling this gap in the literature by evaluating the effectiveness of a short, online problem-solving therapy – a form of cognitive behavioural therapy.

This type of intervention has already been proven effective in treating symptoms of depression in the general population. We believe that a problem-solving therapy may be particularly suitable for glioma patients as it is a brief (5 weeks) and practical approach. Moreover, because patients can access the intervention through the internet at any place and at any time, the threshold for participation is low.

Q: What are the objectives of this interesting trial?

A: Our primary goal evidently is to decrease depressive symptoms. Secondary outcome measures include health-related quality of life, fatigue, and patient satisfaction with the intervention offered. We also enquire after health care utilisation and loss of productivity to make an estimation of the cost-effectiveness of the intervention in economical terms.

Q: What is the study population and which patient groups are in the 3 arms?

A: We include adult glioma patients (WHO grade II, III, or IV) with an estimated life expectancy > 3 months who have mild-to-moderate depressive symptoms. Patients are excluded if they have suicidal intent, if they have insufficient mastery of the Dutch language, and if they do not have access to the internet and an e-mail address.

We hope to include 126 glioma patients in total. 63 patients will be randomly assigned to the intervention group – they can start the online therapy straight away. Another 63 will be randomly assigned to a waiting-list control group – they can start online therapy after a waiting period of 3 months. In this way, we can evaluate the effectiveness of the intervention compared with standard care.

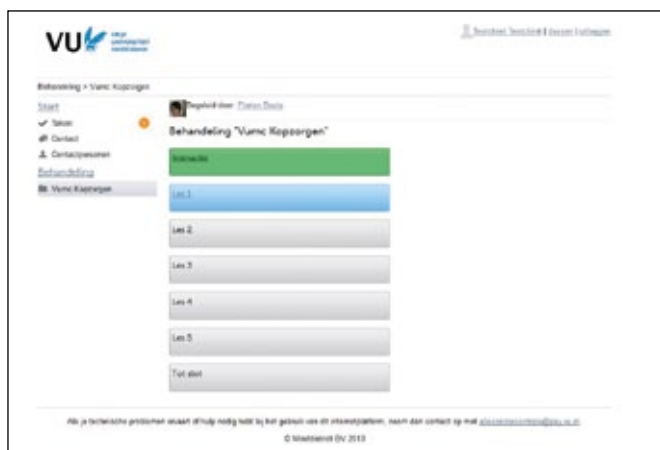
In addition, we hope to include 63 patients with haematological malignancies not involving the central nervous system who are also mildly-to-moderately depressed. They can participate in the intervention straight away. This extra control group will enable us to investigate whether the intervention is equally effective in patients with central nervous system disease and those with other malignancies and a comparable prognosis.

Q: Which scales do you use to assess the patients' psychological status?

A: The Center for Epidemiological Studies Depression Scale (CES-D) will be used to assess depressive symptoms. During our screening process, we also evaluate suicidal ideation with the Beck Scale for Suicide Ideation (BSS) and we exclude patients who may have suicidal intent. They are subsequently referred to their general physicians.

Q: What types of interventions are performed when a patient is diagnosed as having depressive symptoms in the trial?

A: The intervention is an adapted version of “Everything Under Control”, which has been shown effective in improving depression, anxiety, and stress/burnout in the general population [1]. The original intervention has been adapted to suit patients with brain tumours: additional information about the disease and treatment and its psychological impact on daily life has been included, and examples of the assignments have been made disease-specific. The highly structured intervention protocol includes 5 modules with texts and exercises. During the online course, patients define what is important in their lives. They also make a list of their problems and concerns, and they identify whether or not these are related to what they feel is truly important. Problems are then divided into 3 distinct categories: unim-



An overview of the online course as a participant will see it. Completed modules will turn green, active modules are blue. With kind permission from Minddistrict BV.

portant problems, problems that are important, but solvable, and problems that are important, but unsolvable. For each of these problems, patients make a plan on how to cope with them, guided by methods explained in the modules. During the intervention, a personal coach provides feedback on the completed assignments. The coach (either myself or trained and supervised Master students) only supports the patient in working through the intervention, but does not provide additional therapy.

Q: *Is this a nationwide study in the Netherlands? Which groups and how many centres participate in the trial?*

A: Yes, I am happy to say it is. The Dutch Society for Neuro-Oncology supports our trial, as do various patient organisations and 17 hospitals throughout the Netherlands. We are very grateful for their support and their efforts in informing patients about our trial.

Q: *What is the extent of burden and risks associated with participation?*

A: During the intervention, the participants are to spend about 3 hours a week on the assignments. This means a total of 15 hours for the entire intervention. Additionally, 4 extra hours will be reserved for completing the questionnaires during the pre- and post-assessments. The risks of participation in this study are negligible. The control group of glioma patients who do not receive the intervention immediately might be made more aware of their depressive symptoms because of the questionnaires they are asked to complete. However, we keep track of their CES-D and BSS scores. This way, we can monitor whether or not their depressive symptoms worsen, in which case we will contact their respective physicians.

Q: *How is the recruitment and when do you expect to reach the accrual goal? When can we get the first results?*

A: As in most randomised controlled trials on treating psychological symptoms, accrual is progressing slowly. So far, we have received 188 completed depression screening questionnaires, which equals an estimated 5–10 % of the patients who received our information brochure. So far, we have included 77 glioma patients and 18 patients with a haematological malignancy. Efforts to improve accrual are still ongoing, and we



The research team: Martin Klein (left) and Jaap Reijneveld (right) standing in the back, Florian Boele (left) and Irma Verdonck-de Leeuw (right).

will continue to include patients until May 2015. Our data collection will subsequently be completed in August 2016, but we hope to report on the short-term effects of the intervention around December 2015. In the meantime, we would be more than happy to share our knowledge and experience with those who are interested in initiating comparable studies in this exciting field of research.

Thank you very much!

Reference:

1. van Straten A, Cuijpers P, Smits N. Effectiveness of a web-based self-help intervention for symptoms of depression, anxiety, and stress: randomized controlled trial. *J Med Internet Res* 2008; 10: e7.

Florien Boele, MSc, is the study coordinator and Dr Martin Klein is the principal investigator of the trial with the working title "Internet-based treatment of depressive symptoms in patients with tumours inside or outside of the central nervous system".

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Hotspots in Neuro-Oncology

Riccardo Soffietti

From the Department of Neuro-Oncology, University Hospital Turin, Italy

■ IDH-1 Mutant Malignant Astrocytomas Are More Amenable to Surgical Resection and Have a Survival Benefit Associated with Maximal Surgical Resection

Beiko J, et al. Neuro-Oncology 2014; 16: 81–91.

Large retrospective series on malignant gliomas have provided compelling evidence that more extensive resections are associated with better outcomes. So far, no data have been available on the relationship between the impact of surgery and molecular alterations. In the January issue, Beiko et al analysed in a retrospective cohort of 335 malignant astrocytomas (WHO grade III or IV) the correlations between the extent of surgery (based on tumour volumetry) and IDH-1 status (based on immunohistochemistry and sequencing). Interestingly, they found that IDH-1 mutation was an independent predictor of the success of obtaining complete resection of the enhancing tumour. Moreover, patients with IDH-1 wild-type tumours derived a benefit from complete resection of the enhancing tumour, but no further benefit from the resection of the non-enhancing one. Conversely, patients with IDH-1-mutant tumours derived maximum benefit when both enhancing and non-enhancing tumours were completely removed. To date, the most important implication of this study, whose results need to be further confirmed, is that future prospective studies on the impact of the extent of surgery on survival will need to include the IDH-1 status as a covariate.

■ Investigation of the Diffusion Abnormality Index as a New Imaging Biomarker for Early Assessment of Brain Tumor Response to Radiation Therapy

Farjam R, et al. Neuro-Oncology 2014; 16: 131–9.

Diffusion-weighted (DW) MRI has the potential to be a biomarker for early assessment of tumour response to therapies, but can be confounded by oedema and necrosis in or near brain tumours. In the present study, Farjam et al have developed a new diffusion abnormality index (DAI) based upon diffusion-weighted MRI: specifically, the DAI weighs the abnormal ADC contributions from high cellularity and oedema differently for prediction of tumour response. The authors evaluated the performance of DAI in patients with brain metastases who received WBRT, alone or associated with bortezomib as a radiosensitizer. Compared to other ADC metrics published previously and conventional metrics, the DAI showed a greater potential to predict the volumetric response of brain metastases to radiotherapy. Moreover, diffusion-related physiological changes in the tumour tended to occur earlier than morphological changes. These results need to be validated using independent datasets. In the future, it would be interesting to

investigate the DAI in malignant gliomas for an early response assessment to radiotherapy or other experimental drugs (ie, antiangiogenic agents, etc).

■ Phase II Study of Everolimus in Children and Adults with Neurofibromatosis Type 2 and Progressive Vestibular Schwannomas

Karajannis MA, et al. Neuro-Oncology 2014; 16: 292–7.

Preclinical studies have suggested that the activation of the mammalian target of rapamycin (mTOR) signalling pathway could be a key driver of tumour growth in Merlin- (NF2-) deficient tumours, being a potential target for therapy. In the February issue, Karajannis et al conducted a single-institution pivotal phase-II trial to evaluate the response rate to everolimus, a rapamycin analogue, in neurofibromatosis type 2 (NF2) patients with progressive vestibular schwannomas (VS). Unfortunately, none of the 9 evaluable patients experienced a $\geq 15\%$ decrease in VS volume (primary endpoint) or had significant hearing improvement (secondary endpoint). Interestingly, the largest volumetric decrease (14 %) was observed in a cervical nerve root tumour, raising the possibility that everolimus might be more effective in treating non-VS tumours in NF2 patients. Two phase-II studies of everolimus for NF2 patients with a very similar trial design are ongoing in the US and will better define the role of this drug. So far, bevacizumab and lapatinib remain the sole compounds that have been demonstrated to lead to significant MRI and hearing improvements in VS of NF2.

■ Targeting Wee1 for the Treatment of Pediatric High Grade Gliomas

Mueller J, et al. Neuro-Oncology 2014; 16: 352–60.

Despite surgery, radiotherapy, and chemotherapy, paediatric high-grade gliomas (HGG) have a dismal prognosis with the vast majority of patients dying within 5 years. Wee1 is a potential specific molecular target for therapy: in fact, when activated, it causes inhibitory phosphorylation of Cdc2, preventing G2-M cell cycle progression. In this preclinical study, Mueller et al investigated the expression of Wee1 in a series of 38 paediatric gliomas and evaluated the efficacy of MK-1775, a selective Wee1 kinase inhibitor, in potentiating radiation effectiveness. The authors showed that Wee1 is over-expressed in paediatric HGGs with increasing expression positively correlated with grade of malignancy, and the expression is markedly high in DIPGs (diffuse intrinsic pontine gliomas). Furthermore, combination treatment of MK-1775 and radiation reduced clonogenic survival to a greater extent than achieved

by radiation. Finally, combined MK-1775 and radiation conferred greater survival benefit to mice bearing engrafted, orthotopic HGG and DIPG tumours compared with radiation alone. In conclusion, this preclinical study provides a strong rationale for future clinical trials exploring the combination of MK-1775 with radiotherapy in children with newly diagnosed HGGs, in particular DLPG.

■ Clinical Value of Chromosome Arms 19q and 11p Losses in Low Grade Gliomas

Alentorn A, et al. Neuro-Oncology 2014; 16: 400–8.

Low-grade gliomas (LGG) are a complex subgroup of glial tumours with a heterogeneous prognosis. 1p/19q co-deletion, which is associated with IDH-1 mutation, is associated with a favourable prognosis, while non-co-deleted tumours display a worse outcome. In this study, Alentorn et al focused on the latter subgroup to better characterise the driving molecular alterations. They showed in a retrospective series of 126 LGGs that non-1p/19q-co-deleted tumours can be divided into 5 main

genomic subgroups: 11p loss, 19q loss, 7 gain, 19 gain, and unclassified. Interestingly, 11p loss was associated with astrocytoma phenotype and had an independent negative prognostic value, and 19q loss diminished the favourable prognostic value of IDH-1 mutation. All these findings were validated in an independent cohort of 98 LGGs. This study demonstrates that genomic changes commonly associated with the pathogenesis of LGGs may help to stratify these tumours regarding prognosis and, in the future, may facilitate the individualisation of treatment. Prospective studies are needed to confirm these findings.

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Annual Neuro-Tumor Club Dinner Meeting Recap

J Charles Haynes

Society for Neuro-Oncology, Bellaire, TX, USA

The 20th Annual Neuro-Tumor Club Dinner Meeting took place on April 7, 2014, in San Diego, California. This meeting, for brain tumour researchers attending the AACR Annual Meeting, was organised by the Society for Neuro-Oncology with the support of Genentech, Novocure, and the National Brain Tumor Society. Frank Furnari of the Ludwig Institute for Cancer Research, University of California, San Diego, and Shi-Yuan Cheng of Northwestern University, served as co-chairs for the dinner.

The event drew approximately 150 investigators from diverse disciplines relevant to brain tumour research, and was very successful in strengthening existing personal research connections and collaborations, generating new associations and presenting the group with updates in topics important to brain tumour research.

40 abstracts were received of uniformly high quality. Submissions came from 8 countries and were reflective of cutting-edge, thought-provoking basic and translational research in the field of neuro-oncology. Trying to reduce this to 14 talks was difficult given the standard of the submissions. The talks were arranged in 4 consecutive sessions that encompassed the following topic areas:

- Genomic Phenotyping and Personalized/Combinatorial Therapy
- Tumour Microenvironment, Signalling, and Cancer Stem Cells
- Novel Agents, Markers, and Immunotherapy
- Animal Models and CNS Metastases

Each topic area was excellently framed by overviews from authority figures in those areas including: Dr Richard Gilbertson, St. Jude Children's Research Hospital; Albert Wong, Stanford University; Isabella Taylor, Johns Hopkins University; and Carol Kruse, University of California, Los Angeles.

The dinner took place at the Hotel Solamar, a boutique property located near the 2014 Annual AACR Meeting venue. Attendees' registration continued right up to the dinner and in the end there were over 150 researchers present. The 14 speakers were scheduled over 3 hours, requiring a tight time-line, which was kept judiciously by all presenters. All speakers managed to finish on time and yet conveyed an astonishing amount of background information and experimental data. The talks were followed by lively discussions. There were many excellent presentations during the night. In the first session, Richard Gilbertson presented data derived from whole-genome and RNA sequencing of supratentorial ependymomas showing a highly recurrent oncogenic fusion occurring between RELA and an uncharacterised gene, C11orf95, in 70 % of these tumours. Expression of the C11orf95-RELA fusion protein in neural stem cells drove their transformation in conjunction with an oncogenic NF- κ B transcription signature, raising the possibility of new avenues for therapeutic intervention.

In the next session, Albert Wong showed that the mutant EGF receptor, EGFRvIII, is frequently co-expressed with the stem cell marker, CD133, and that EGFRvIII⁺/CD133⁺ tumour cells were highly aggressive. Targeting these double positive cells with a bi-specific monoclonal antibody greatly enhanced survival of tumour-bearing mice. Also in this session, Terry Johns showed that extracellular domain mutants of EGFR found in glioma are more sensitive to the pan-ErbB inhibitor, dacomitinib, when compared to the wild-type receptor, and that Ras mutations cause up-front resistance to EGFR-based therapy. In session 3, Chien-Tsun Kuan provided updates on the development of recombinant immunotoxins (RIT) that target wild-type EGFR and EGFRvIII on the surface of glioma cells and a new surface marker for gliomas, glycoprotein NMB. He also described new approaches of reducing immunogenicity of these RITs in humans and the next generation of RITs. Elizabeth Maher reported detection of 2HG by MR spectroscopy, which proved to be a robust clinical biomarker in low-grade gliomas. The initial success of using 2HG levels to guide therapies for gliomas, especially for these low-grade gliomas, was highly encouraging. The final session had 4 excellent presentations that described studies using various animal models of brain tumours to demonstrate the role of ATRX in glioma progression and response to DNA damage, initial characterisation of a new *de novo* animal model of leptomeningeal metastasis, combination of cellular and gene therapies to treat breast cancer patients with brain metastases, and deciphering circulating tumour cells from patients with breast cancer metastatic to the brain. The evening concluded with many of the attendees remaining to engage in informal conversation prompted by the presented topics.

The Society thanks Drs Furnari and Cheng for organising a stimulating and enjoyable evening. The next Neuro-Tumor Club Dinner is scheduled to take place on Monday, April 20, 2015, in Philadelphia, PA.

Members of EANO are encouraged to save the date for the 19th Annual Scientific Meeting and Education Day of the Society for Neuro-Oncology, to be held November 13–16, 2014, at the Loews Hotel South Beach in Miami. Following the format of past SNO meetings, the main conference will be abstract-driven, with a pre-conference Education Day entitled "Metastasis Biology and Treatment" along with concurrent quality-of-life sessions entitled "Neurologic Rehabilitation, Pediatric Survivorship and Caregivers".

The abstract deadline for submitting an abstract to the SNO meeting is June 9, 2014. Details can be found on the SNO website, www.soc-neuro-onc.org.

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EANO Neuro-Oncology Online Magazine

Instructions for Authors

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Dedicated to providing superior and rapid publication of information in all areas of neuro-oncology, this education-oriented journal contains peer-reviewed articles and reviews, case reports, congress reports, letters, society news, and announcements from around the world with a special focus on Europe and EANO member states.

The goal of the EANO Magazine is to provide the European neuro-oncology community, in particular of EANO member states, with high-quality rapid publication of information in all fields of neuro-oncology via open online access.

Areas covered include, but are not limited to, neurology, neurosurgery, medical oncology, radiotherapy, paediatric neuro-oncology, neuropathology, neuroradiology, neuroimaging, nursing, and patient issues.

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