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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 mimick CN dysfunction.

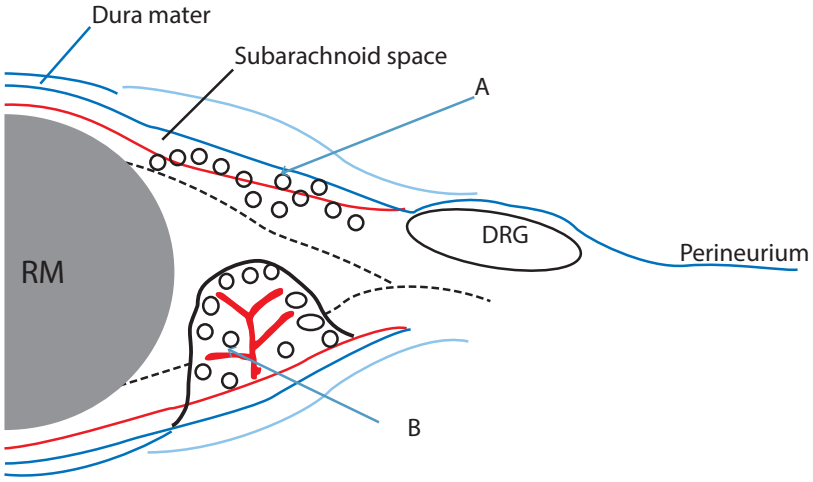

Figure 1. Meningeal infiltration. The dura mater continues as the perineurium. In general the tumor cells do not spread beyond this boundary centrifugally. **(A)** tumour spread in the subarachnoid space. **(B)** Lumps and nodules consist of tumour cells and have their own vascularisation. RM: spinal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

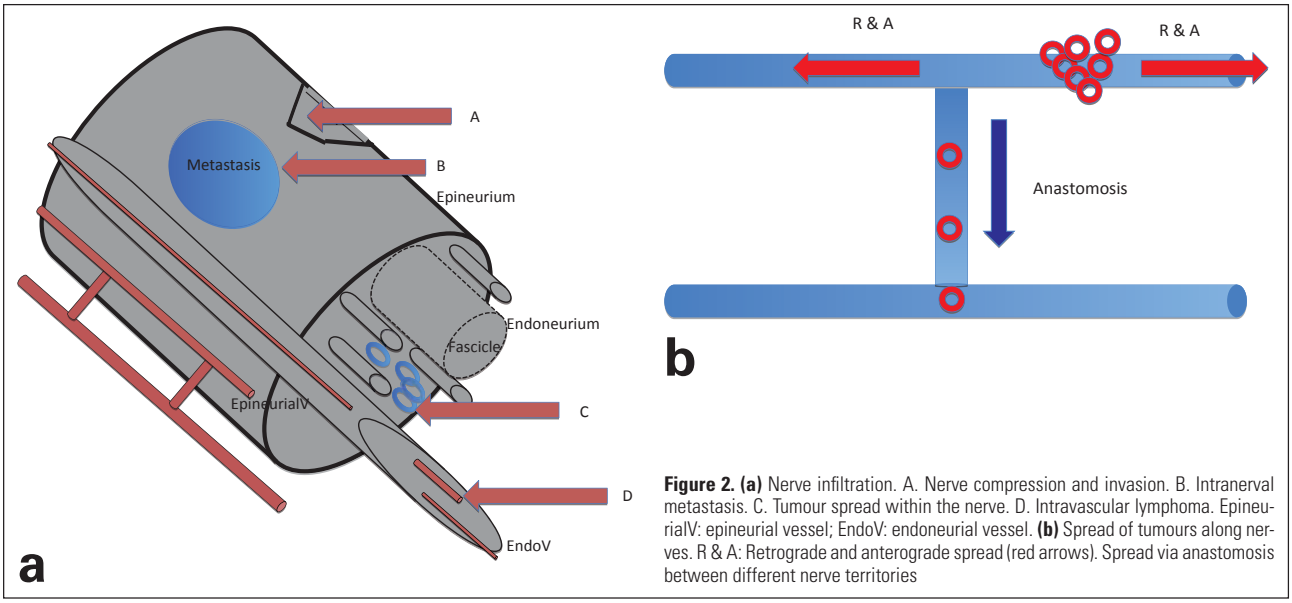

Figure 2. (a) Nerve infiltration. A. Nerve compression and invasion. B. Intranerval metastasis. C. Tumour spread within the nerve. D. Intravascular lymphoma. EpineurialV: epineurial vessel; EndoV: endoneurial vessel. **(b)** Spread of tumours along nerves. R & A: Retrograde and anterograde spread (red arrows). Spread via anastomosis between different nerve territories

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 invasion, which seems less clear in regard to the barriers of the peripheral nerve. Possible mechanisms are peripheral or endoneural 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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