Review paper

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Metastatic tumours of the central nervous system – a pathological approach

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Abstract

Metastases are the most common tumours of the central nervous system. Histopathological diagnosis remains the most efficient and specific diagnostic procedure that provides the clinician with quick, specific and cost-effective information necessary for the optimal treatment of the patient. Therefore, the pathologist should be acquainted with the potential opportunities to determine the most precise diagnosis in case of metastatic deposits involving the central nervous system.

Key words: *central nervous system, metastasis, immunohistochemistry.*

Introduction

Metastatic tumours are the most common neuro-oncological lesions developing in the central nervous system (CNS). The metastatic tumours may herald the dissemination of the malignancy already being diagnosed or treated. In some cases (2-18% [3,22,32]), they may present as a cancer of unknown primary (CUP) and in these instances they require careful determination of the source of origin of the tumour. From the medical and economic points of view the histopathological determination of the phenotypic and genotypic profiles seems to be the most prudent. It enables an easy, relatively rapid and cheap method of tumour analysis [11]. Besides the detailed clinical evaluation of the patient, imaging (ultrasonography, endoscopy, computed tomography, positron emission tomography, magnetic resonance imaging, etc.) and laboratory procedures (serum tumour markers) are necessary to identify the primary tumour site. However, according to various reports, these analyses succeed in only approximately 20% of cases and their average cost is around $18,000 per patient. On the other hand, immunohistochemical profiling of the metastatic tumour requires an average of $2,000 per patient with a success rate of around 70% [11,33]. Therefore, cost-effectiveness analysis and enlarging specificity of immunohistochemical markers makes the pathological examination an important adjunct to the metastatic work-up.

The central nervous system is most frequently a target of metastatic dissemination from lung (18-60%) and breast carcinomas (5-21%), melanoma (4-16%), genitourinary (3-10%) and gastrointestinal (5-12%) malignancies [2,3,6,14]. Those cancers arise in the CNS following haematogenous dissemination in

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most cases, as the lymphatic vasculature in the brain is non-existent [23]. Brain or spinal cord may also be involved by contiguous infiltration of the malignant tumour from the surrounding tissues. This may occur in the vertebral metastases of the prostatic carcinomas that may invade the structure of the spinal meninges.

Depending on the site of origin and the biological properties of the malignant process, the involvement of the CNS may manifest either as a solid, well-circumscribed tumour(s) in the brain or spinal cord parenchyma, dura-based lesions or a not well localized process in the arachnoid space. Proper identification of the secondary involvement of the CNS is vital for the optimal treatment modalities in a patient, as some of the metastatic lesions may mimic primary brain neoplasms. Precise phenotyping and, in some cases, genotyping of the tumour are necessary to reach an unequivocal diagnosis and these issues are the main focus of the current review. In some cases, the identification of the histological diagnosis of the metastasis may provide the patient with beneficial systemic treatment, as occurs in cases of pulmonary small cell carcinoma or lymphomas.

Epidemiology

The true incidence of metastases to the CNS is unknown but it is believed to be underestimated [32]. Involvement of the CNS may occur as a solitary lesion or multiple metastases [29]. The anatomical location of metastatic tumours is dependent on the vascularization of the CNS, biological propensities of the metastatic deposits and, to a certain degree, the primary site of origin. As the prevailing pathway of spread is via the bloodstream, most of the metastases are located in the brain hemispheres (80%), especially in the parietal lobe, followed by the frontal and occipital lobes [3]. The cerebellum and the brainstem are affected less frequently, whereas leptomeningeal and dura-based metastases occur quite uncommonly [13,28]. Leptomeningeal involvement of the CNS usually occurs in patients with pulmonary and mammary carcinomas [28]. Dural metastases are the consequence of the direct spread of the tumour from the bone (skull, vertebra), with lung, prostate and breast carcinomas predominating [13,20].

Generally, metastases from the lung and breast carcinomas and melanoma most commonly present in the CNS; other malignancies (gastric, female reproductive tract, pancreatic, colorectal) are identified less frequently in the CNS and usually late in the course of the disease.

Histopathological identification of the original site of metastasis

Determination of the metastatic nature of the brain tumour relies on the typical morphological features of the lesion. In recent years, determination of the tumour immunophenotype has added much information in regard to the potential source of origin. As epithelial tumours make most of the secondary CNS deposits, cytokeratin profile is indispensable in determining the site of origin. Cytokeratin 7 (CK7) and cytokeratin 20 (CK20) are basic parameters in this regard. Additional information may be acquired with specific markers, e.g. thyroglobulin (thyroid follicular epithelium), calcitonin (thyroid C cells), prostate specific antigen – PSA (prostate gland), renal cell carcinoma marker – RCCMa (kidney), etc.

Metastatic pulmonary carcinoma

Among non-small lung carcinomas, adenocarcinoma is most commonly identified in the CNS metastases. These lesions usually are CK7+/CK20- and may present expression of low molecular cytokeratins (CAM5.2) [3]. In addition, thyroid transcription factor (TTF-1) is frequently identified in the tumour nuclei of pulmonary adenocarcinomas (Fig. 1A) [34]. This marker is a member of the Nkx homeodomain-containing transcription factor family and is expressed during embryogenesis of the thyroid gland, lungs and forebrain [21]. Apart from adenocarcinomas, pulmonary large cell carcinomas, small cell carcinomas and neuroendocrine carcinomas may also show TTF-1 positivity [21,26]. On the other hand, squamous cell carcinomas of the lung usually do not show expression of that marker [26]. Small cell carcinomas (SCCs) of the lung, as belonging to the spectrum of neuroendocrine cell tumours, may show expression of neuroendocrine markers (chromogranin A, synaptophysin, neural cell adhesion molecule – NCAM / CD56, etc.) in addition to the CK7-/CK20- profile [3]. As small cell neuroendocrine carcinomas usually are morphologically indistinguishable, it is prudent to distinguish pulmonary SCC from others, and CK20 and TTF-1 expression may be a helpful panel in this regard as it discriminates cutaneous neuroendocrine carcinoma (Merkel cell carcinoma) from its pulmonary counterpart [9].

Metastatic mammary carcinoma

Breast carcinoma metastasizing to the CNS may be of any histological type but usually it is positive with CK7 and negative with CK20 [3]. Oestrogen (Fig. 1B) and progesterone receptors are often positive [3], although their expression is not restricted to that site of origin. There are also pulmonary carcinomas and other less commonly metastasizing carcinomas involving CNS that may present these two steroid receptors (endometrial, ovarian, etc.) [18]. Gross cystic disease fluid protein-15 (GCDFP-15) is also commonly expressed in mammary carcinomas but not unequivocally specific [19]. In contrast to pulmonary adenocarcinomas, TTF-1 is not typical for breast-derived metastases [3].

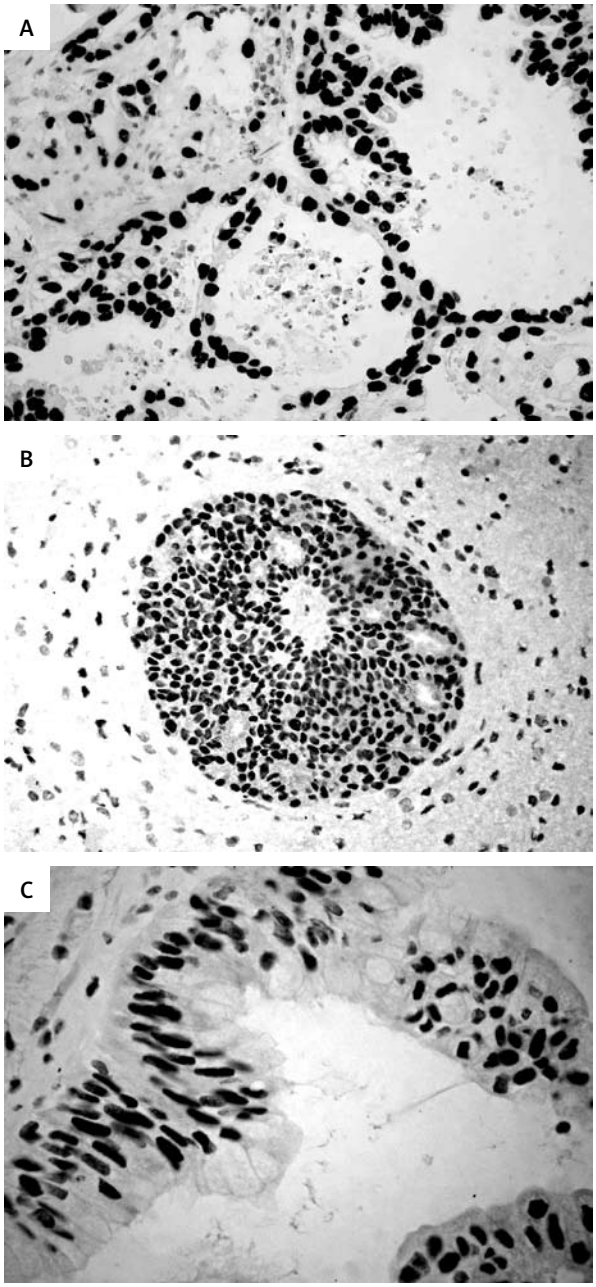

Fig. 1A-C. A. Nuclear expression of TTF1 confirms pulmonary origin of the brain metastatic deposit. **B.** Metastatic breast carcinoma shows nuclear expression of oestrogen receptor. **C.** CDX2 antigen in brain metastasis of colorectal carcinoma with typical nuclear localization.

Metastatic colorectal carcinoma

Most metastatic tumours are adenocarcinomas and they usually retain morphological features of the primary lesion. In favour of colorectal derivation, the presence of 'dirty' necrosis and 'garland-like' growth pattern are frequently identified [18]. In addition, CK7-/CK20+ cytokeratin profile, expression of carcinoembryonic antigen (CEA) and an intestine-specific homeodomain transcription factor CDX2 (Fig. 1C) help in confirming this anatomical derivation of the tumour [3].

Metastatic ovarian carcinoma

Rarely, ovarian cancer may involve the CNS. The most common ovarian primary is serous carcinoma, which morphologically may mimic primary papillary tumours of the brain, e.g. choroid plexus carcinoma. While showing expression of CK7+/CK20- phenotype, serous carcinoma frequently strongly expresses WT-1, which enables differential diagnosis [18]. Additionally, BerEP4 expression may be a useful adjunct to the diagnosis as it is usually present in ovarian carcinomas [1], while only rarely being identified in choroid plexus tumours [12].

Metastatic gastric carcinoma

Metastases of gastric carcinoma may occur in the CNS. They present with CK7+/CK20- profile and in addition may show expression of CEA [3]. As this phenotype (CK7+/CK20-/CEA+) is also shared by some other carcinomas (pancreatic, colon, lung) close morphological and clinical correlations are inevitable.

Metastatic renal carcinoma

Most primary renal cancers present as the clear cell carcinoma subtype. Due to the specific mor-

phology it may closely mimic some of the CNS primary tumours, e.g. haemangioblastoma. This is sometimes an important issue clinically, especially in patients with von Hippel-Lindau syndrome. This familial tumour syndrome dependent on germline (inborn) mutations of the VHL gene [15,27] may present both with haemangioblastoma (sometimes multicentric) and renal cell carcinoma [30]. Morphologically, haemangioblastoma is composed of stromal and vascular cells. The former are arranged in alveolar structures and have abundant clear cytoplasm, which closely mimic the structure of clear cell carcinoma of the kidney. Nuclear pleomorphism of the stromal cells present in some cases may additionally confer atypical features to these cells, making problematic an unequivocal differentiation between the two on morphological grounds alone. Haemangioblastoma is a tumour of uncertain histogenesis, but it quite constantly shows expression of NCAM (CD56) and S100 protein, and lack of EMA and cytokeratins. In contrast, renal cell carcinoma shows expression of RCCMa, EMA and CD10, while being CK7-negative [7].

Metastatic melanoma

Known for its enormous morphological plasticity, malignant melanoma always needs to be taken into account in the histopathological differentiation of tumours metastasizing to the CNS. It may show epithelioid, spindle and small cell anaplastic morphology, but phenotypically may be discriminated by expression of melanosome-bound proteins. Most commonly used are HMB45, Melan-A (MART-1) and, although less specific but more sensitive, especially in spindle cell melanomas, S100 protein. This in combination with lack of cytokeratin expression may allow proper diagnosis. Malignant melanoma of the CNS is usually a metastasis from extraneural sites (skin, anus, eye bulb, etc.) but it should be remembered that it may also develop as a primary CNS lesion. Most commonly such tumours arise as meningeal-based lesions [5].

Lymphomas

These tumours may affect the CNS as a single tumour or multifocal lesions usually in supratentorial location. Bilateral symmetrical subependymal lesions are highly suggestive of CNS lymphoma. Sometimes, these lesions may be discreet in imaging procedures and may mimic small infarctions (intravascular large B-cell lymphoma). The lymphoma infiltrates of the CNS are sensitive to steroids and may vanish within hours after such treatment [16].

The abundance of nosological entities among lymphoid neoplasms makes a brief review of their histological differentiation difficult. However, in the CNS there is a predominance of a certain set of lymphomas that preferentially affect this system. Most commonly, high-grade B-cell lymphomas involve the brain and the spinal cord, with diffuse large B-cell lymphoma being the most frequent one [16,24]. The common leukocyte antigen CD45 (LCA) is shared by most lymphomas. Pan-B (CD20, CD79a) or pan-T (CD3, CD4, CD8, CD2) markers are usually helpful in determination of the exact lineage of the proliferation, and in combination with the morphology of the tumour provides a strong basis for precise classification. Extremely differentiated plasma cells lack expression of pan-B markers and show presence of other specific antigens, i.e., CD138, VS38c (Fig. 2B). In some cases, use of steroids decreasing intracranial pressure in the period preceding diagnostic biopsy may alter the structure of the tumour [25]. Increase in apoptotic bodies, macrophages and necrosis are typical manifestations of such treatment.

Anaplastic tumours

Poorly differentiated tumours may involve the CNS as one of the potential targets in their dissemination throughout the body. They require differentiation from primary anaplastic tumours of the CNS, e.g. PNET, glioblastoma, germ cell tumours, etc. Thorough clinical metastatic work-up and immunohistochemical analysis (sometimes molecular genetics) can resolve this issue in most cases. Poorly differentiated sarcomas should be taken into account. Ewing sarcoma presents typical translocation t(11;22) that may be identified by molecular techniques (PCR, FISH). This tumour usually expresses CD99 (MIC-2), which is quite typical for this lesion, although it may also be shared by T-cell lymphoblastic lymphomas and poorly differentiated synovial sarcoma [10]. The latter may be differentiated by coexpression of epithelial markers (epithelial membrane antigen, EMA and cytokeratins) and non-random translocation t(X;18), which may also be identified by molecular techniques. Another small round blue cell tumour that sho-

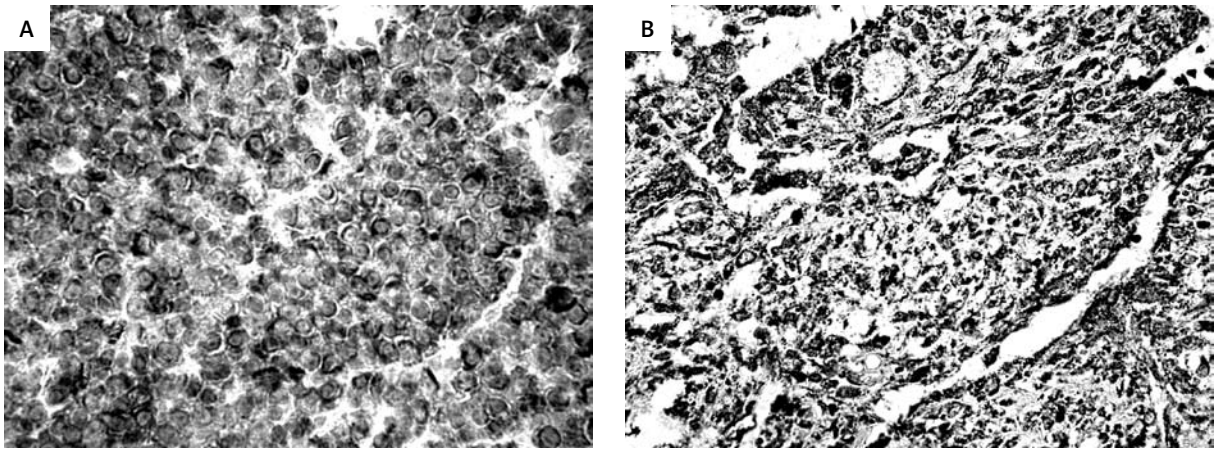

Fig. 2A-B. A. Plasmacytoma infiltrating the meninges shows cytoplasmic expression of VS38c. B. Dura-based metastasis of gastrointestinal stromal tumour (GIST) has expression of CD117 (c-kit) antigen.

uld be taken into account is rhabdomyosarcoma. Its anaplastic cells extensively present vimentin, and only differentiating rhabdomyoblasts may show expression of desmin and actin. Very specific for rhabdomyosarcomas are myoD1 and myogenin (myf-4) [8]; however, only nuclear reactivity should be regarded as a true marker of myogenic differentiation [31].

The CNS is frequently affected by metastases of choriocarcinoma; these are usually haemorrhagic tumours presenting with an apoplectic onset of disease. In the blood clots, one can identify typical morphological structure of syncytiotrophoblasts and cytotrophoblasts. The former expresses beta-chorionic gonadotrophin (ß-hCG) that may be identified in the tissue or, alternatively, in the blood. Rarely, other malignancies may spread into the CNS, e.g. sarcomas (malignant peripheral nerve sheath tumour, gastrointestinal stromal tumour [Fig. 2B]), carcinoid tumours, etc. [4;17].

Summary

Metastatic lesions in the CNS are very frequently identified in everyday neurosurgical and neuropathological practice. Therefore, acquaintance with and use of the immunohistochemical markers are essential for the correct histopathological diagnosis and the optimal treatment of patients with CNS malignancies.

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