Take-home messages

- TTF-1 may be expressed in prostatic ductal adenocarcinoma.
- On core biopsies, PSA and PSAP may not always decorate malignant cells of prostatic ductal adenocarcinoma.
- The coexistence of acinar adenocarcinoma favours a papilloglandular malignancy observed in the prostate to be of likely prostatic origin.
- The SPT24 antibody appears to possess greater affinity for TTF-1 protein that can potentially lead to a positive reaction in a small proportion of colorectal adenocarcinomas.

expensive and futile hunt. Cytoplasmic TTF-1 reactivity is sometimes found in tumours, especially non-neoplastic liver tissue, but is considered to be a non-specific finding.¹⁶

The underlying mechanism of TTF-1 expression in prostatic ductal adenocarcinoma is unclear. TTF-1 is a 38 kDa homeodomain-containing nuclear protein belonging to the Nkx2 gene family which is involved in activating transcription during embryogenesis. It is possible that molecular pathways to prostate carcinogenesis along ductal adenocarcinoma lines may involve dedifferentiation or transdifferentiation.²⁰ More such cases need to be studied to determine whether there is consistent TTF-1 expression in these tumours and its significance.

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Multiple congenital infantile hemangiomas of the lung in partial trisomy D

The postmortem examination of a multiformed infant with trisomy D revealed 33 capillary hemangiomas in both lungs, with the microscopic features of the common cutaneous GLUT-1 infantile hemangioma. The

finding further expands the spectrum of sites where this type of capillary hemangioma can be found, as it has been reported in the placenta, liver, salivary gland and mammary gland. Its association with the genetic condition trisomy D, already known to occasionally present cutaneous and hepatic hemangiomas, could be a clue to its pathogenesis.

Hemangiomas in children are most commonly recognised in the skin and liver. They are infrequent in the respiratory tract, presenting predominantly in the subglottic region, and extremely rare in the lung. Pulmonary hemangiomas include endobronchial and parenchymatous types. In accordance to its structure, they are classified as capillary and cavernous histological types.¹

Among the angiomatous lesions of childhood, the so-called infantile hemangioma (IH) shows a peculiar characteristic: its endothelial cells express the antigen GLUT-1^{2–4}. This feature allows differential diagnosis with other types of vascular tumours and malformations found at this age.

We are reporting the case of an infant with partial trisomy D presenting with a series of malformations already reported in this condition combined with the unique finding of multiple IH in both lungs.

Case report

This female newborn was referred from another medical centre 15 h after birth under assisted ventilation, with the tentative diagnosis of genetic syndrome and cyanotic congenital heart disease. She was born through caesarean section at 38 weeks gestational age. Birth weight was 2500 g and the Apgar was 4/7. The mother was 30 years old and presented with hypertension. After admission, an echocardiography demonstrated right ventricle with double outlet, pulmonary valve atresia, patent small ductus, subaortic ventricular septal defect with overriding aorta, dilated right atria and ventricle, dilated coronary sinus and patent foramen ovale. Karyotype was 46, XX, der (13;13) (q10;q10), +13, consistent with trisomy 13. The newborn was maintained in assisted ventilation with parenteral nutrition, developed jaundice and died at age 42 days in an episode of extreme bradycardia.

Postmortem examination showed peculiar facies with narrow forehead, small eyes, small eyelids fissures, wide nasal bridge with a cleft in the border of the nostrils, long philtrum, arched palate and low-set ears. The hands were dorsiflexed and prone, and both presented incomplete simian crease.

The internal examination showed a complex malformation of the heart, which included the referred echocardiographic findings and persistent left superior venacava. The ductus was closed. The lungs demonstrated irregularly distributed, 0.3–0.5 cm deeply red, subpleural patches reaching a total number of 18 in the right and 15 in the left. The brain presented microcephaly, hypoplasia of the optic chiasm and hypoplasia of the anterior cerebellar vermis. Other findings included spleen–pancreatic fusion, corticomedullary renal cysts involving the parenchyma of both kidneys only focally, and Meckel's diverticulum.

On microscopic study, the most peculiar finding resulted from the lung lesions that proved to represent supleural capillary proliferations constituted by tightly arranged units containing small vessels with patent lumen and prominent endothelial cells. These

histological features are very similar, if not identical, to that observed in cases of IH (fig 1A). Immunostaining for GLUT-1 proved to be positive in the endothelial cells (fig 1B), completing the identity with IH. Cytokeratin immunostaining with the cocktail of antibodies AE1/AE3 highlighted the differences between the endothelium-lined small vessels and the cytokeratin-positive cells of the alveolar epithelium (fig 1C).

Other findings included an extensive necrotising tracheobronchitis with necrotic debris filling the cavities of the bronchi and bronchioles. The pancreas presented an excess of small ducts, focal dilatation of some ducts and spleen-pancreatic fusion. The kidneys contained glomerular cysts, cortical and medullary tubular cysts, and medullary fibrosis. The brain showed immaturity of layers and neurones. The cerebellum exhibited foliar and vermis hypoplasia, as well as blastic and neuronal heterotopias in the folia and near the dentate nucleus.

Additional findings included extensive lobular and portal cholestasis, with portal areas presenting an excess of biliary ducts, cholemic nephrosis and bacterial emboli in the spleen and kidneys.

In summary, this 42-day-old infant with trisomy D presented with multiple malformations related to the cytogenetic disorder, and

died due to the structural heart disease and acute bacterial sepsis. The cholestasis seems to be related to total parenteral nutrition. Overall, the most striking finding in this case was the presence of multiple pulmonary IHs.

Discussion

Cutaneous and, less frequently, liver hemangiomas are within the spectrum of lesions described in cases of trisomy D.⁴ However, to the best of our knowledge, lung hemangiomas have never been reported in this condition.

When dealing with this group of lesions in the lungs, they are further analysed as related to the extension of the vascular proliferation, hence the localised and the diffuse (hemangiomatosis) forms. Clinically, the diffuse hemangiomatosis type may present with pulmonary hypertension (pulmonary capillary hemangiomatosis) or as haemoptysis associated with signs and symptoms of interstitial disease (the so-called pulmonary hemangiomatosis). The latter is usually combined with pleural effusion, and involvement of the mediastinum and pericardium.¹

Abrahams *et al.*,⁵ while studying two cases of pulmonary hemangiomas in infancy, reviewed the literature on the subject. They were able to identify and summarise seven examples. Three resulted from isolated lesions involving bronchi and four were localised to the distal lung. Of these cases, three presented as isolated lesions in the lower lobe of the right lung and the remaining one as multiple lesions in the right lung. The age of the patients was, 1 year, 10 weeks, 8 weeks and 9 years (the latter one showing the multifocal unilateral lesion). No sex predominance could be seen (2 female; 2 male). The three patients with localised lesions were submitted to lobectomy (n = 2) or wedge resection (n = 1). There were no evidences of reappearance of the lesions. The patient having the multiple lesions died postoperatively due to hemoptysis. Histological diagnosis of these cases was capillary hemangioma in three (localised in two and multifocal in one) and cavernous hemangioma in one.

Within the differential diagnosis of pulmonary angiomatous lesions in infancy, there are some other conditions to be considered. These include: pulmonary capillary hemangiomatosis, diffuse neonatal hemangiomatosis (DNH), arteriovenous malformation, which in approximately 50% of the cases is associated with hereditary haemorrhagic telangiectasia, lymphangiectasias, lymphangioma and lymphangiomatosis.

Since in our patient the lesions were multifocal, the differential diagnosis would include pulmonary capillary hemangiomatosis and DNH. The first is an angiomatous proliferation presenting as pulmonary hypertension in older children (not during the first year of life).¹ 5-7 DNH is frequently a fatal condition characterised by the presence of diffusely distributed capillary hemangiomas in the skin and internal organs.¹ The present case does not seem to fit in any of those conditions.

Jun *et al.*³ recently recognised that the hepatic infantile hemangioendothelioma shares biological features with skin IH, sometimes presenting simultaneously. From that study, the resulting GLUT-1-positive cases were categorised as hepatic infantile hemangioma (HIH), whereas the remaining were categorised as hepatic vascular malformations with capillary proliferation (HVMCP). The difference has clinical implications since incidence of

HIH is common during the first months of life and, in contrast to HVMCP, does not present cardiomegaly, anaemia, Kasabach-Merritt syndrome, hydrops fetalis or heart failure. The lesions representing HIH appear as small, multiple nodules, which mostly regress spontaneously after months or years. The fact that these lesions responded to the treatment with steroid or interferon was also noticeable. The HVMCP frequently requires surgical treatment. The authors concluded that the HIH represents the liver counterpart of the IH, the expression of the GLUT-1 marker by this lesion differentiating it from other vascular conditions of that organ.

In a recent paper from our laboratory,⁴ we studied the expression of GLUT-1 antigen in eight paediatric skin IH and five extracutaneous hemangiomas, which included chorangioma (n = 2), liver (n = 1), salivary gland (n = 1) and mammary gland (n = 1). The extracutaneous hemangiomas presented the same histological features as IH of the skin. In all the cases, the endothelial cells proved to be GLUT-1-positive. Notably, the two chorangiomas, one associated to liver hemangiomas, presented in patients with Beckwith-Wiedemann syndrome (BWS). Based on the BWS association, the hypothesis was raised that the chromosomal alteration found in that syndrome involving chromosome 11p15 might be the clue to the development of these hemangiomas, because the insulin growth factor 2 gene is also localised at the same locus and is related to the overgrowth which develops in the BWS. In favour of this hypothesis is the finding of Ritter *et al.*⁸ who reported an increased expression of insulin growth factor 2 mRNA and its protein in the growth phase of IH.

Relevant to this discussion about congenital hemangiomas is Berenguer *et al.*'s⁹ report on skin congenital hemangiomas. They were able to recognise one category, which they called rapidly involuting congenital hemangioma. This type is completely developed at birth and does not show a growing phase in the postnatal period. Clinically the tumour presents as a protuberant, lilaceous mass with a central depression, scar or ulcer, which regresses by the age of 1 year. The above features permit its separation from a related lesion, the so-called non-involuting congenital hemangioma and the common IH. However, the authors recognised that these three conditions share some clinical and histological features. Notably, only the endothelial cells of the IH were positive for the GLUT-1 marker.

So, the peculiar histological and IHC findings of the pulmonary lesions of the present case seem to represent a previously unrecognised type of multicentric congenital hemangioma of the lung exhibiting the features of the common skin IH, including GLUT-1 positivity, further expanding the spectrum of extracutaneous vascular lesions with these characteristics. The presentation in a patient with trisomy D, a condition already known to be associated with hemangiomas, could provide clues to genes involved in the development of these lesions.

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SHORT REPORTS

Unrepresentative astrocytoma biopsy sampling is partly overcome by assessment of the MIB-1-labelled growth fraction

Representative sampling of gliomas at biopsy is essential for correct assignment of histological grade and subsequent patient management. If sampling is unrepresentative, tissue devoid of mitoses or necrosis may be obtained and result in a falsely low glioma grade. The objective of the present study was to assess whether the MIB-1 labelling index of glioma tissue cores specifically constructed so as to replicate ‘unrepresentative’ astrocytoma biopsies would predict the real or actual glioma grade. Tissue microarrays were prepared from 134 samples of low-grade astrocytoma (LGA; WHO grade II), anaplastic astrocytoma (AA) and glioblastoma multiforme (GBM). Donor blocks were sampled in such a way as to avoid mitoses, necrosis and endothelial hyperplasia. Immunohistochemistry was performed using the Ki-67 (MIB-1) proliferation marker, and the percentage of MIB-1-positive cells per core was calculated. Mean MIB-1% values for LGA (n = 47), AA (n = 38) and GBM (n = 46) were mean (SD) 0.54 (0.82), 5.68 (6.69) and 7.21 (7.98); ranges 0–3.07, 0–30.08 and 0–29.08, respectively. An MIB-1% count of >3.07 excludes LGA, but an MIB-1% count of <3.07

does not exclude GBM or AA. It is concluded that in unrepresentative glioma biopsy material, MIB-1 labelling may be used to exclude LGA, but cannot be used to distinguish between GBM and AA.

Astrocytomas in adults demonstrate considerable cellular heterogeneity, and pathological grading is the most significant predictor of clinical outcome.¹ While grading may be suggested radiologically, it is recommended that all astrocytomas be biopsied to establish a correct diagnosis and grade. The presence of mitoses and necrosis is a key adjunct in the grading of astrocytomas. Mitoses are a feature of high-grade gliomas, including anaplastic astrocytomas (AAs), and would not generally be seen on a biopsy of a low-grade astrocytoma (LGA). Moreover, the presence of palisaded necrosis in an astrocytoma distinguishes GBM from AA.

Inadequate or unrepresentative tissue sampling at biopsy may lead to erroneous diagnosis of an astrocytoma having a lower grade than is actually the case, with adverse consequences in terms of failure to administer supplementary treatments including radiotherapy. If sampling is inaccurate, glioblastoma multiforme (GBM) may be devoid of mitoses and necrosis, and AAs may be devoid of mitoses.

Evaluation of proliferative activity using the Ki-67 (MIB-1) antibody has been used as an adjunct in the assessment of tumour grade in human astrocytomas,^{2,3} and its prognostic value in distinguishing subtypes is recognised.^{4,5} We sought to evaluate the ability of this marker to predict the underlying histological grade of gliomas using tissue microarray (TMA) technology to simulate inadequately sampled biopsy specimens. TMA methodology is now widely used in cancer research⁶ and is a validated method for tumour immunoprofiling.⁷ More recently, it has been used in the study of non-neoplastic disease of the central nervous system.⁸ In this study, we hypothesised that the MIB-1 labelling index in tissue cores designed to replicate unrepresentative astrocytoma biopsies would predict the histological grade in three astrocytoma subtypes.

Patients and methods

Subject material

Adult astrocytomas were selected from the neuropathology tissue archives in Beaumont Hospital, Dublin, Ireland. The material that was chosen consisted of surgically resected formalin-fixed paraffin-embedded tumour tissue. Astrocytomas were graded according to the WHO International Classification of brain tumours.¹ Forty-eight were classified as LGA (WHO grade II); 39 as AA (WHO grade III); and 47 as GBM (WHO grade IV), yielding 134 cores. WHO grade I or pilocytic astrocytomas, glioneuronal tumours and mixed oligoastrocytomas were specifically excluded.

Tissue microarray construction

TMAs were constructed by extracting ‘core biopsies’ from a precise morphologically

representative area of the original paraffin ‘donor’ block, with subsequent re-embedding of carefully selected cores into a ‘recipient’ microarray paraffin block. This was done using a precision instrument (Beecher Instruments, Silver Spring, MD, USA), employing separate core needles for punching donor and recipient blocks. Glioma TMAs were prepared using cores designed to replicate intraoperative inadequate astrocytoma sampling. Cores (0.6 mm diameter) were prepared from resected LGA, AA and GBM. During core sampling, tissue areas were targeted to avoid mitoses, necrosis and endothelial hyperplasia. Specifically, two experienced neuropathologists examined haematoxylin and eosin-stained sections of the original tumour resection, and astrocytoma grade was agreed. Core biopsies were not used as they did not provide sufficient tissue for sampling nor could we have been certain that such true in vivo biopsies accurately reflected correct tumour grade. Areas of highest cell density but without mitoses were marked with a Nikon optical circular marker having a diameter of 1 mm. With grade II astrocytomas, which by definition are devoid of mitoses, we sought to sample the most cellular areas. The donor block was overlaid with the marked slide; cores were obtained from within the marked circle and subsequently arranged in the recipient tissue block together with location and immunocytochemical controls. Later, all cores in the recipient block were again examined to ensure that mitoses were not inadvertently included.

Immunohistochemistry

TMAs were immunostained with the Ki-67 (MIB-1) antibody (DakoCytomation, Glostrup, Denmark) using a standard avidin–biotin peroxidase technique with the Vectastain® Elite ABC kit (Vector Labs, Burlingame, CA, USA) with diaminobenzidine as the chromogenic substrate. The sections were counterstained with haematoxylin.

Scoring of MIB-1 immunostaining

The tissue arrays were labelled so that the investigator (K.M.S.) was blinded as to the origin of the individual cores. Using image analysis (Olympus DP-soft version 3) with a grid overlay, the individual cores were evaluated for total cell count and total number of MIB-1-positive cells. The results were then expressed as the percentage of MIB-1-positive tumour cells per core. MIB-1 positivity was defined as definitive brown nuclear staining. The mean number of cells per core analysed was 516, 504 and 942 for LGA, AA and GBM, respectively. Statistical analysis was performed using a t test. A p value of <0.05 was considered statistically significant.

Results

LGA tumours had significantly lower MIB-1% positivity in comparison with GBM (T = –5.7; p<0.0001) and AA (T = –4.6; p<0.0001)

Table 1 Mean MIB-1% labelling indices in each of the glioma subtypes

	GBM (n = 46)	AA (n = 38)	LGA (n = 47)
Mean	7.21	5.68	0.54
SD	7.9	6.69	0.82
Range	0–29.08	0–27.16	0–3.07

GBM, glioblastoma multiforme; AA, anaplastic astrocytoma; LGA, low-grade astrocytoma