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Skin metastases of glioblastoma in the absence of intracranial progression are associated with a shift towards a mesenchymal immunophenotype: report of two cases

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Glioblastoma multiforme (GBM) is the most malignant astrocytic tumour. Extra-neural spread is exceedingly rare, and usually develops at the time of intracranial progression following a surgical procedure (2-4). Less frequently, metastases are a consequence of spontaneous tumour trans-dural extension or haematogenous spread. Here, we describe two unusual cases of GBM in which scalp metastases appeared in the absence of intracranial disease progression.

Case 1. A 48-year-old woman who presented with headache, speech disturbances and left facio-brachial paresis underwent magnetic resonance images (MRI), which revealed a large right fronto-parietal mass with a peripheral enhancement (Fig. 1a). The patient underwent gross total removal of the tumour, and a histopathological diagnosis of GBM was made. Using immunohistochemistry, the tumour cells were shown to co-express GFAP (intensely) and vimentin (less extensively). EGFR was positive in all tumour cells and YKL-40 showed a faint cytoplasm positivity in about 30% of cells (Fig 3). Conformal radiotherapy and adjuvant Temozolomide (TMZ) followed surgery. After 12 cycles, and in the absence of intracranial disease recurrence, the patient presented with a 2 cm scalp metastasis, close to but not contiguous with the surgical scar (Fig. 1b). A complete removal was performed and the diagnosis of GBM was confirmed. Histologically, the metastasis showed an infiltrating growth pattern dispersed into fibrotic tissue and consisted of a neoplastic population of large pleomorphic cells with a high mitotic index and strong positivity for vimentin, while the GFAP staining was less diffuse than in the intracranial tumour. Moreover, when compared with the primary lesion, EGFR was negative in the neoplastic cells, whereas a diffuse, intense YKL-40 immunoreactivity was found (Fig. 3). The patient underwent focal radiotherapy; four months later, an MRI revealed distant intracranial progression in the right temporal lobe. The patient received second-line chemotherapy but soon the progressive intracranial disease led to the patient's death.

Case 2. A 53-year-old woman presented with a one-month history of speech disturbances and facio-brachio-crural right motor deficit and underwent MRI, which showed a left frontal mass with contrast enhancement (Fig. 2a). She underwent craniotomy with partial resection of the mass,

and a diagnosis of GBM was made. Immunohistochemistry showed a diffuse and intense GFAP reactivity with vimentin co-expression in a few GFAP positive areas; EGFR positivity was diffuse, whereas YKL-40 showed weak and focal expression (Fig. 3). The patient underwent radiotherapy and standard TMZ treatment, and a partial response with a 90% reduction of the enhancing area was observed at MRI. Unexpectedly, the reduction of the intracranial disease was accompanied by the appearance of a mass in the scalp of the left parietal area, 2 cm away from the surgical scar (Fig. 2b). A biopsy was performed and the histology was consistent with a recurrent GBM. The skin metastasis was mainly composed of small cells, all intensely vimentin positive, with only few neoplastic elements still immunoreactive to GFAP; EGFR was completely negative, whereas an intense YKL-40 staining was evident in the cytoplasm of the majority of neoplastic cells (Fig. 3). The patient received local radiotherapy and TMZ, but 3 months later three new cutaneous satellite lesions developed, despite the absence of any intracranial progression. Four months later, a new MRI demonstrated intracranial progression, and the patient died after 2 months.

In both patients, the cutaneous metastases occurred close to the surgical scar, indicating the possibility of tumour spill during surgery and/or tumour trans-dural extension facilitated by the surgery. In contrast with the cases reported in literature, in which scalp metastases developed synchronously with intracranial progression, the metastases in the two cases reported here occurred in presence of a (radiologically) stable disease which may be attributed to radiotherapy and/or TMZ treatment. The acquisition of a divergent phenotype by the metastatic lesions could account for such differing responses to treatment. In fact, the immunophenotypical profile of the primary and cutaneous tumours showed two distinct patterns: in skin relapses, we observed dramatically reduced GFAP and EGFR staining paralleled by increased vimentin and YKL-40 expression. Although the “mesenchymal” markers vimentin and YKL-40 can be expressed in glioblastomas, the decrease of a very specific glial marker, such as GFAP, concomitant to the increase in vimentin/YKL40 expression suggests at least a partial loss of the glial phenotype. In both cases, the primary tumours displayed only very few areas of neoplastic cells with the same immuno-profile of skin metastases.

This observation suggests the selection of an aggressive therapy-resistant sub-population of neoplastic cells in the metastatic sites, induced either by treatment (autopsy studies have previously reported on radiotherapy-induced morphological changes) (1) or determined by tumour environment, such as in transdifferentiation of glioma cells through a “mesenchymal drift” (5).

References

1. Burger PC, Mahley MS Jr, Dudka L, Vogel FS (1979) The morphologic effects of radiation administered therapeutically for intracranial gliomas. A post-mortem study of 25 cases. Cancer 44:1256-1272

2. Figueroa P, Lupton JR, Remington T et al (2002) Cutaneous metastasis from an intracranial glioblastoma multiforme. J Am Acad Dermatol 46:297-300

3. Jain N, Mirakhur M, Flynn P, Choudhari A (2005) Cutaneous metastasis from glioblastoma. Br J Neurosurg 19:65-68

4. Mentrikoski M, Johnson MD, Korones DN, Scott GA. (2008) Glioblastoma multiforme in skin: a report of 2 cases and review of the literature. Am J Dermatopathol. 30:381-384

5. Paulus W, Huettner C, Tonn JC (1994) Collagens, integrins and the mesenchymal drift in glioblastomas: a comparison of biopsy specimens, spheroid and early monolayer cultures. Int J Cancer 15;58:841-846

Legends

Figure 1: *Case 1*: a: MRI demonstrating a large right fronto-parietal mass. b: MRI demonstrating the subcutaneous swelling without any visible recurrence of the intracranial disease (on T1-weighted MR images after contrast) fourteen months after surgery.

Figure 2. *Case 2*: a: MRI demonstrating a left frontal mass. b: MRI demonstrating the scalp metastasis, nine months after surgery, without any intracranial progression.

Figure 3: Histological and immunophenotypical patterns of the two cases studied.

Case 1. The *primary tumour* was characterized by pseudo-palisading necrosis and vascular proliferation with endothelial hyperplasia with pleomorphic cells with oval-to-elongated nuclei (a). The GFAP reactivity was strongly and diffusely present (b) whereas the vimentin immunoreaction was less extensive (c). YKL-40 staining showed a focal, faint cytoplasmic positivity (d) and EGFR was diffusely positive in neoplastic cells (e). The *metastatic tumour* exhibited areas of necrosis and vascular proliferation with a population constituted by pleomorphic cells (f) mainly immunoreactive to vimentin (h). The GFAP stain was less diffuse than in the primary lesion (g) whereas the YKL-40 immunoreactivity was increased (i) and EGFR was negative (j).

Case 2. The *primary tumour* showed a marked hypercellularity with pseudo-palisading necrosis, glomeruloid vascular proliferation (k) and an intense GFAP reactivity and a minor vimentin expression (l, m). YKL-40 showed focal expression (n) and EGFR immunoreactivity was diffusely present (o). The *metastatic tumour* was extensively necrotic and mainly composed of neoplastic cells with a small and hyperchromic nuclei (p); only a few neoplastic elements were immunoreactive to GFAP (q), whereas the majority of tumour cells were intensely vimentin positive (r). YKL-40 staining was diffuse in the cytoplasm of tumour cells (s) whereas the EGFR immunoreaction was negative (t).

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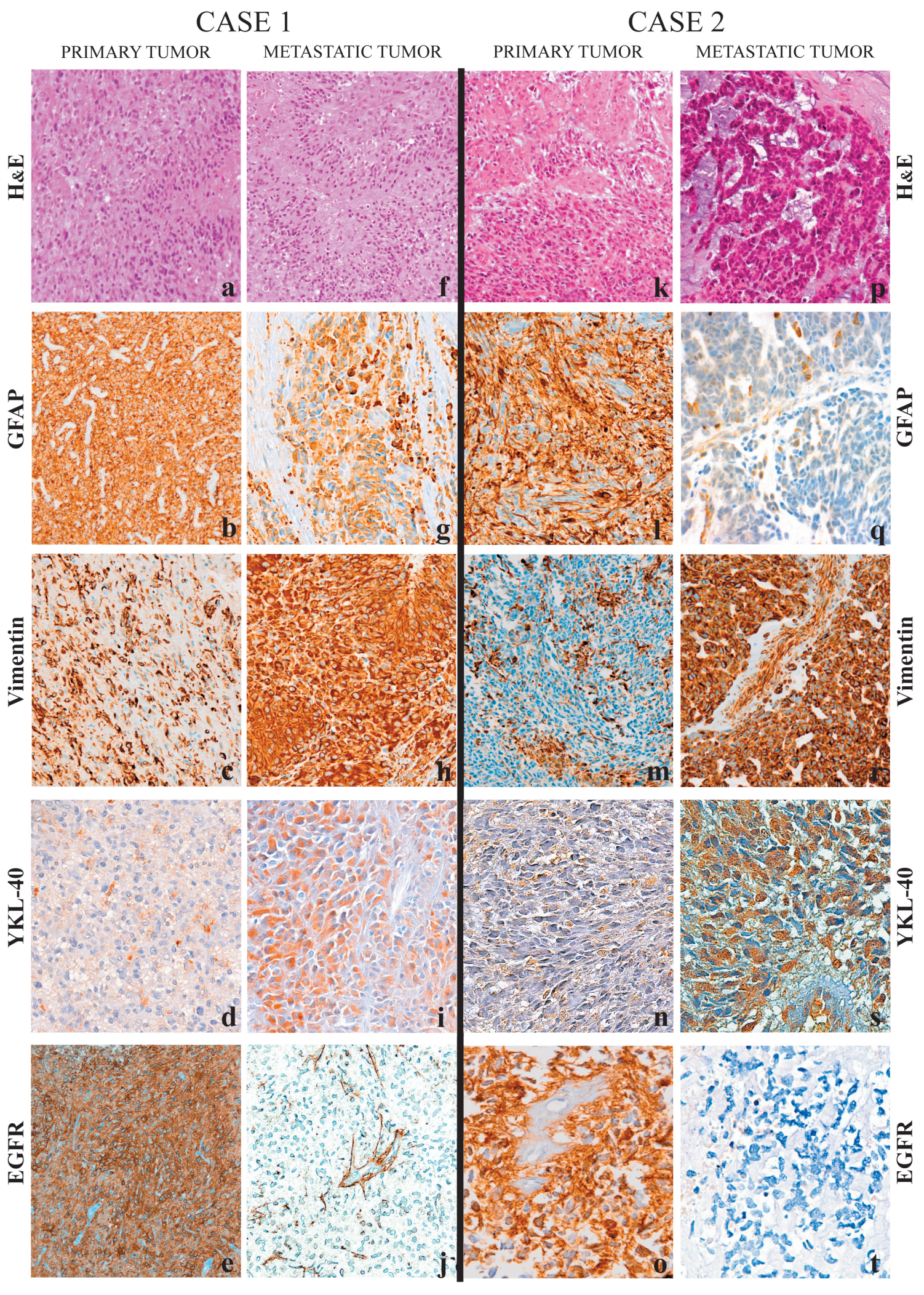
CASE 1
CASE 2
PRIMARY TUMOR
METASTATIC TUMOR
PRIMARY TUMOR
METASTATIC TUMOR
H&E
GFAP
Vimentin
YKL-40
EGFR
a
b
c
d
e
f
g
h
i
j
k
l
m
n
o
p
q
r
s
t