Quiz

Correct answer to the quiz. Check your diagnosis

Case report

Malignant brain tumour with challenging intraoperative findings

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This case report describes a rare and challenging glioblastoma variant with a biphasic morphology comprising both giant cell and primitive neuronal components. The tumour exhibited aggressive features and was difficult to diagnose during the intraoperative evaluation due to the predominance of small blue cell morphology, which complicated differentiation from haematological and metastatic lesions. Immunohistochemistry and molecular profiling confirmed a glioblastoma, IDH-wildtype, with combined giant cell and primitive neuronal features, and the p53 mutation in both components is a novel finding with potential implications for diagnosis and treatment. This report emphasises the importance of recognising morphological diversity in glioblastoma to avoid misdiagnosis and enable appropriate clinical management.

Key words: glioblastoma, giant cell, primitive neuronal tumour, IDH wildtype.

Introduction

Glioblastoma (GB) is a glial neoplasm of the central nervous system that originates from astrocytic cells. GB exhibits aggressive biological behaviour, with a 5-year survival rate of only 6.8–10%. Microscopically, GB may present with more common cytological and histological features, typically showing some recognisable neoplastic cells with astrocytic differentiation, at least focally. However, it can present with a wide variety of morphological patterns [1], which is why it has historically been referred to as "multiform". Some of the rarer aspects cause serious interpretation difficulties, especially on intraoperative examination, opening differential diagnosis.

Case report

A 77-year-old male presented with headache and underwent magnetic resonance imaging, which revealed a large mass in the left parieto-temporal

region with an axial diameter of 41 mm (Fig. 1), with an irregular morphology, a necrotic central portion, and margins with intense contrast enhancement, surrounded by an area of hyperintense signal in long repetition time sequences. The patient underwent neurosurgery, and intraoperative evaluation was decided. Intraoperative touch imprint cytology showed a neoplasm composed of medium/small, hyperchromic, lymphoblast-like cells with many mitoses and some "cannibalistic" cells (Fig. 2); the cytology specimen also contained elements that could not be well evaluated, probably due to fixation. A malignant neoplasm, not otherwise specified, was diagnosed intraoperatively without excluding a haemato-lymphoid nature. Histology revealed a biphasic lesion with two distinct cellular components: one consisted of round, hyperchromic, medium/small cells with scant cytoplasm and a high mitotic rate (blue cell component), and the other consisted of pleomorphic, occasionally multinucleated giant

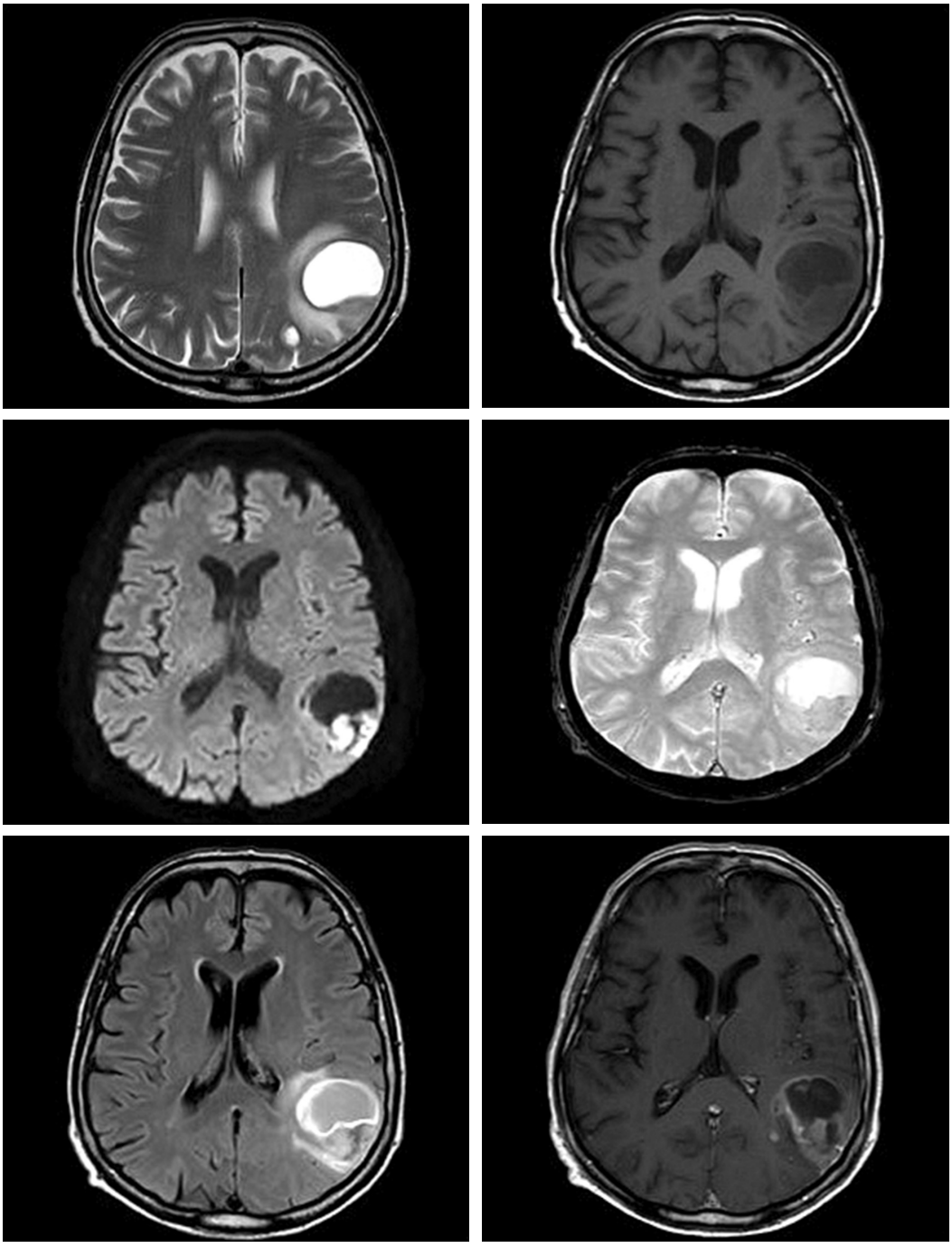

Fig. 1. Magnetic resonance showing the lesion in the left parieto-temporal region surrounded by an area of hyperintense signal in long repetition time sequences

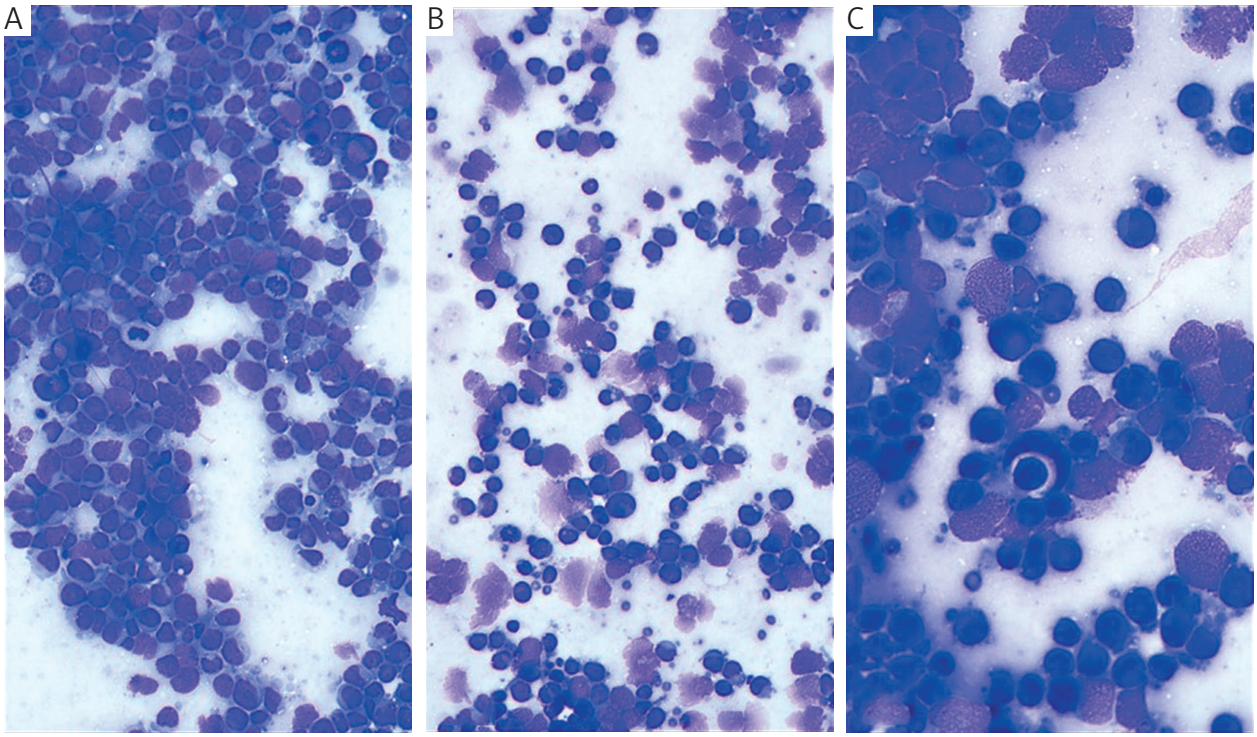

Fig. 2. Cytological specimen (intraoperative touch imprint) showing in: **A)** numerous mitotically active cells (May-Grünwald-Giemsa stain, ×40); **B)** numerous medium/small, hyperchromic, lymphoblast-like cells (May-Grünwald-Giemsa stain, ×20); **C)** small aggressive cells exhibiting "cannibalism" (May-Grünwald-Giemsa stain, ×40)

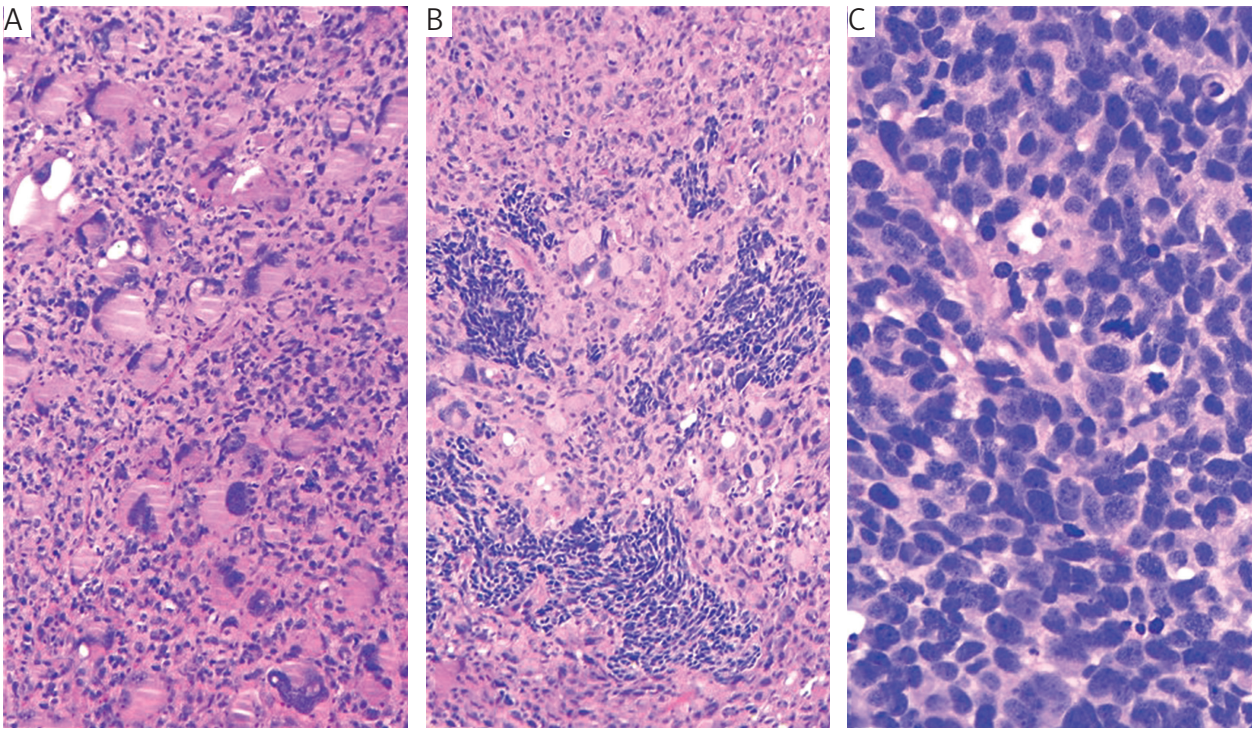

Fig. 3. Histological photomicrograph showing in: **A)** numerous large cells (HE, ×40); **B)** a mixed pattern, with large cells and foci of small blue cells (HE, ×20); **C)** small aggressive cells displaying numerous mitotic figures (HE, ×40)

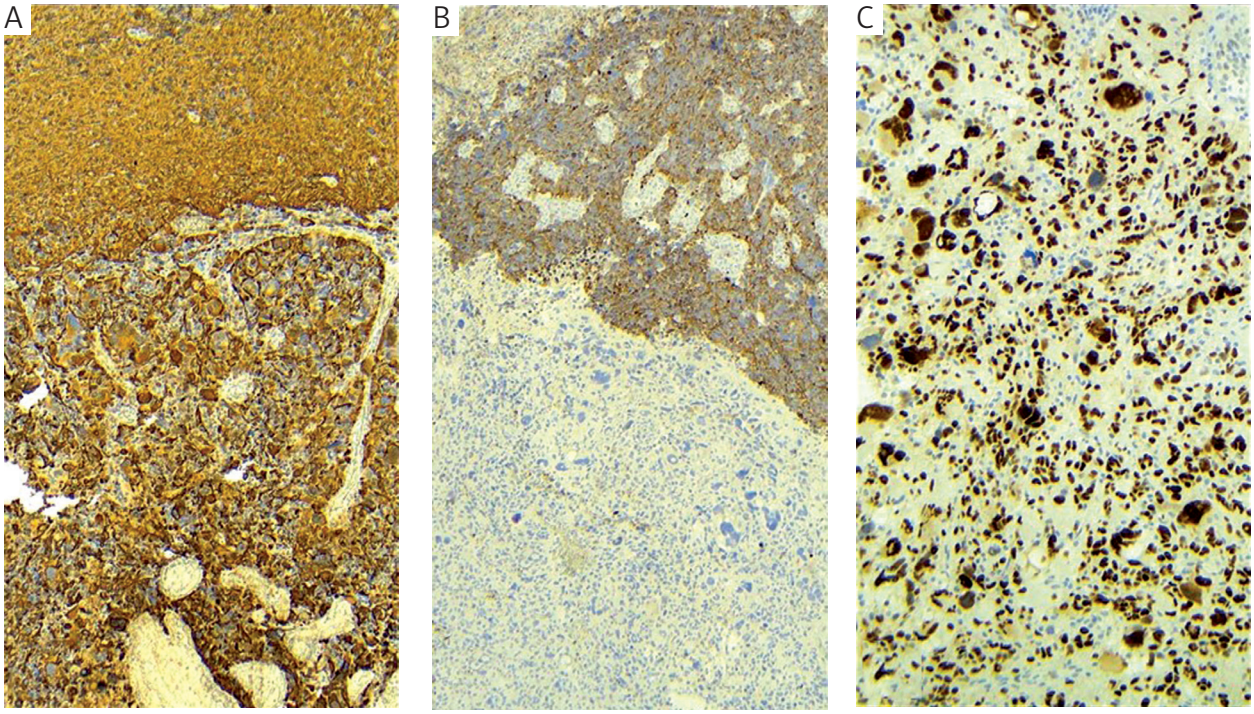

Fig. 4. Histological photomicrograph showing immunohistochemistry positivity for: **A)** GFAP, intensely and diffusely positive in both large cells (bottom) and small cells (top); **B)** synaptophysin, expressed only in small cells; **C)** p53, widely expressed in all components (×20)

cells, absent on intraoperative examination (Fig. 3). Immunohistochemistry showed GFAP positivity (Fig. 4A), IDH1-R132 negativity (molecularly corresponding to an IDH-wildtype profile) and strong/diffuse nuclear positivity for p53 in both components (Fig. 4C). Of note was the zonal positivity for synaptophysin, which was expressed only in the blue cell component (Fig. 4B). In addition, foci of necrosis (non-palisading) and vascular endothelial proliferation were present.

Discussion

The lesion displayed both a giant cell component and a primitive neuronal component, which made it difficult to categorise according to the criteria of the World Health Organization Classification of Central Nervous System Tumours of 2021 (WHO-CNS 2021).

It was situated between the categories of giant cell glioblastoma and glioblastoma with a primitive neuronal component. It was therefore decided that the diagnosis should be "adult-type diffuse glioma, consistent with GB IDH-wildtype (grade 4), with giant cell aspects and primitive neuronal component".

GB is the most common malignant brain tumour in adults, accounting for 45–50% of primary malignant brain tumours. WHO-CNS 2021 assigns it an exclusively IDH-wildtype profile and classifies it as a distinct entity included in the group of adult-type diffuse gliomas (group that also includes astrocytoma IDH mutant and oligodendroglioma IDH mutant and 1p/19q-codeleted) [1].

GB used to be called "multiform": this outdated term suggests the multiple morphologies in which this neoplasm can appear microscopically.

However, there are some much rarer cytotypes, including:

- oligodendrocyte-like cells, which places GB in the differential diagnosis with anaplastic oligodendroglioma [2];
- with giant pleomorphic cells, which places GB in the differential diagnosis of gliosarcoma and anaplastic pleomorphic xanthoastrocytoma;
- with primitive neuronal component (previously defined as: "with neuroectodermal differentiation"), which, with its small blue-cell aspects, places it in the differential diagnosis of embryonal tumours, germ cell tumours, supratentorial primitive neuroectodermal tumour, lymphomas or metastases.

These microscopic forms, unusual in themselves, are even rarer in combination.

Despite the high diagnostic accuracy of intraoperative cytology of CNS tumours observed in both adult and paediatric series [3, 4], the mixed giant cell/small neuroectodermal cell case presented here represents a significant microscopic challenge due to its rarity as a "collision" finding [5]. This challenge is particularly highlighted in our case where only the

small cell component was identified intraoperatively. The cyto-histological aspects of this tumour must be borne in mind in order to avoid pitfalls in differential diagnosis that could lead to incorrect management of the patient, both intraoperatively with surgery and postoperatively with pharmacological and/or radiotherapy.

Another crucial factor to take into account is the risk of misdiagnosing the primitive neuronal component as metastatic lung cancer: indeed, the lesion was found to be TTF1 positive (finding histologically not displayed), which was also consistent with the diagnosis of metastatic lung cancer. However, the observed positivity for glial markers ruled out the possibility of extra-CNS primitivity.

Finally, a molecular consideration regarding the detected immunohistochemical positivity for p53 (Fig. 4C), both in the giant cell component and in the neuroectodermal component, indicating a p53-mutated profile of the entire neoplasm: in the recent GB literature, this aspect is known to be particularly associated with neuroectodermal differentiation of GBs [6], however, to the best of our knowledge, there are no histologically described cases of neuroectodermal differentiating giant cell GBs co-expressing this mutation in both components.

Disclosures

1. Institutional review board statement: Not applicable.
2. Assistance with the article: None.
3. Financial support and sponsorship: None.
4. Conflicts of interest: None.

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