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Title

Secondary anaplastic astrocytoma developing in a young adult with autoimmune
lymphoproliferative syndrome (ALPS)

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Autoimmune lymphoproliferative syndrome (ALPS; OMIM#601859) is a rare apoptotic disorder attributable to a failure in FAS-mediated apoptosis signaling [1, 2] that leads to lymphadenopathy, hypersplenism, and autoimmune cytopenia with childhood onset. The major determinants of morbidity and mortality in ALPS are the severity of the autoimmune disease; about 10% of patients develop malignant lymphoma [3-5]. We encountered a 23-year-old male with ALPS type 1A who developed a secondary anaplastic astrocytoma. This is the first reported case of its kind.

Malignant astrocytoma is now known to develop via 2 different pathways [6]. Low-grade diffuse astrocytomas, commonly accompanied by *IDH1* (> 80%) and *TP53* (> 60%) mutations, eventually progress to a more malignant form of anaplastic astrocytoma followed by secondary glioblastoma [7, 8]. We present an extremely rare case of secondary anaplastic astrocytoma in an ALPS patient and document genetic alterations in the course of tumour progression, i.e. germline *FAS* mutation without *IDH* mutation.

The patient was a 23-year-old male with ALPS type 1A manifesting a germline *FAS* mutation that resulted in the failure of FAS-mediated apoptosis signal transduction [9]. His sister had non-Hodgkin's lymphoma, his mother was asymptomatic. His maternal grandmother had died at the age of 70 of secondary glioblastoma without signs of immunodeficiency. On his father's side there was no family history of immunodeficiency

diseases or brain tumours (Fig. 1). At the age of 9 years the patient manifested precocious puberty and was treated with anti-FSH therapy. Brain MRI scans obtained at that time revealed a diffuse T2 hyperintensity lesion in the right temporo-occipital lobe that was suspected to be a low-grade glioma (Fig. 2A, B). The lesion was followed by annual MRI study and remained unchanged until he was 22 years old. At the age of 23 he suffered severe headache lasting for one month. Gd-enhanced T1-weighted MRI revealed a huge ring-enhanced mass in the right temporal lobe adjacent to the previously-recognised diffuse lesion (Fig. 2C, D). He underwent surgical resection of the enhanced mass and biopsy of the adjacent diffuse lesion. The resected mass was diagnosed as malignant glioma and he received radiochemotherapy (local irradiation with 50 Gy and oral temozolomide). At present, 24 months after the operation, he remains free of tumour recurrence.

Paraffin-embedded tissues obtained at surgery were stained with hematoxylin and eosin and then stained for immunohistochemical study using antibodies for GFAP (monoclonal, 1:300, Dako Co., Carpinteria, CA, USA), S100 (monoclonal, 1:500, Dako), synaptophysin (monoclonal, 1:20; SY-38, Chemicon International, Temecula, CA, USA), MIB-1 (monoclonal, 1:200, Funakoshi, Tokyo, Japan), and TP53 (mouse monoclonal, 1:20; DO-7, Dako). The histological diagnosis was made independently by 2 pathologists.

DNA was extracted from snap-frozen tissues with TissueGen (Nippongene, Toyama, Japan) according to the manufacturer's instructions. Direct sequencing of exons 5-8 of the

TP53 gene and of the junction between exon 7 and intron 7 of the *FAS* gene was with the Big-Dye DNA sequencing system (Applied Biosystems, Branchburg, NJ, USA) as described elsewhere [10-12].

Frozen tissue was subjected to dual-colour FISH at SRL Co. (Tokyo, Japan). Paired FISH probes for 1p36/1q25, 19p13/19q13, and CEP7/EGFR (Vysis, Downers Grove, IL) were used for detecting loss of heterozygosity (LOH) at 1p and 19q [13] and for amplification of the *EGFR* gene [14], respectively. To detect duplications at chromosome band 7q34 containing a *BRAF-KIAA1549* gene fusion, a FITC-labeled locus-specific probe (RP11-355D18 corresponding to *KIAA1549*) and a digoxigenin-labeled locus-specific probe (726N20 corresponding to *BRAF*) were used [15].

On pathological examination, tissue from the newly-developed tumour exhibited a biphasic pattern comprised primarily of piloid cells without an angiocentric pattern on a myxoid background (Fig. 2E). High-cellular regions contained compact cells with mitoses (Fig. 2F); the maximum MIB-1 labeling index was 34.3% (Fig. 2G). Immunohistochemically, the tumour cells were positive for TP53 (Fig. 2H), GFAP, and S100 but negative for synaptophysin. They tended to infiltrate perivascular spaces (Fig. 2I). Rosenthal fibers and eosinophilic granular bodies were absent, a finding essential for a diagnosis of pilocytic astrocytoma. The tumour tissue exhibited no necroses or microvascular proliferation, a finding incompatible with a diagnosis of glioblastoma. The final histological diagnosis was

anaplastic astrocytoma WHO grade III rather than pilocytic astrocytoma or glioblastoma.

Considering radiological-, immunohistochemical-, and genetic findings, the anomalous T2 hyperintensity on MRI, positivity for GFAP, and the presence of a *TP53* mutation (Fig. 3B), the long-standing diffuse lesion was diagnosed as a diffuse astrocytoma WHO grade II (Fig 2J).

Direct sequencing of the *TP53* gene through exons 5-8 [10] revealed a missense mutation in exon 8 c.830G>T (p.Cys277Phe) in both the new- and the long-standing tumour; the mutation of the old tumour was homozygous and that of the new tumour was heterozygous (Fig. 3A, B). DNA obtained from the patient's blood did not manifest the *TP53* mutation, indicating that it was somatic (Fig. 3C). Direct sequencing of the *FAS* gene in both tumour- and blood cells identified a heterozygous *FAS* mutation at the splicing site of intron 7 that is known to produce a dominant-negative form of FAS [9] (Fig. 3D). Direct sequencing of exon 4 of the *IDH1* and the *IDH2* gene [16, 17] did not reveal mutations in either tumour. FISH study of both tumours yielded no evidence of *EGFR* gene amplification [14], LOH in chromosome 1p/19q [13], or *BRAF* gene rearrangement [15], findings that are often returned in glioblastoma, oligodendroglioma, and pilocytic astrocytoma, respectively.

To our knowledge, among 200 reported ALPS patients, ours is the first patient with malignant glioma [3]. Approximately 10% of ALPS patients manifested malignant

lymphoma [3,4], suggesting that the *FAS* mutation *per se* is carcinogenic. In addition, the mutation may play a role in tumourigenesis in other types of malignancies including basal- [18] and squamous cell carcinoma [19], malignant melanoma [20], and non-small cell lung cancer [21-23]. In our patient the possible association between the development of anaplastic astrocytoma and the *FAS* mutation is unclear because the mutation has not been reported in gliomas. The coexistence of *FAS*- and *TP53* mutations is strongly carcinogenic in some types of tumour [18, 22]. Interestingly, our patient with a family history of ALPS developed 2 astrocytic tumours, suggesting that the *FAS* mutation may play an important role in some types of astrocytic tumour as it does in other types of malignancies, especially in the presence of a *TP53* mutation.

Our patient's newly-developed tumour was positive for TP53, probably due to a missense *TP53* mutation in exon 8 c.830G>T (p.Cys277Phe). The pre-existence of a low-grade lesion with the identical heterozygous *TP53* mutation and the absence of *EGFR* amplification suggests that the development of his anaplastic astrocytoma followed the “classical” pathway for secondary glioblastoma development characterised by the presence of a less malignant precursor lesion and a high incidence (> 60%) of *TP53* mutations without *EGFR* amplification [24-26]. The heterogeneous *TP53* status of the long-standing- (Fig. 3B) and the absence of the normal *TP53* allele in the newly-developed tumour (Fig. 3A)

suggest that the eventual loss of the normal *TP53* allele is associated with malignant transformation.

The pathological features of his newly-developed tumour included the presence of a portion that resembled pilocytic astrocytoma; it consisted of piloid cells with a myxoid background and small cells with high cellularity. The absence of Rosenthal fibers and eosinophilic granular bodies, and the lack in his newly-developed tumour of *BRAF* rearrangement, a hallmark of pilocytic astrocytoma (~70%) [27-29], argued against a diagnosis of pilocytic astrocytoma. We based our histological diagnosis of anaplastic astrocytoma WHO grade III on the absence of definite necrosis and microvascular proliferation.

IDH1/2 mutations are commonly detected in low-grade astrocytomas and oligodendrogliomas, and in the course of progression from low-grade astrocytoma, secondary glioblastomas tend to manifest *IDH1/2* mutations [7, 30]. However, neither his long-standing- nor his newly-developed tumour manifested *IDH1/2* mutations, suggesting that in our patient the path of tumour progression was different from the ordinary pathway to secondary glioblastoma.

This is the first report describing the development of glioma in an ALPS patient. We posit that germline *FAS*- and somatic *TP53* mutations were associated with the development of his secondary anaplastic astrocytoma from his pre-existing less malignant diffuse

astrocytoma. Furthermore, the absence of *IDH1/2* mutations suggests an uncommon pathway in his astrocytic tumour progression.

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Figure Legends

Fig. 1.

The pedigree of the patient's family. Two secondarily-developed gliomas and a non-Hodgkin's lymphoma were part of the family history.

Fig. 2

(A-D) MRI images showing Gd-enhanced T1- and T2-weighted MR images acquired in 1993 when the patient was 9 years old (A, B) and in 2008 when he was 23 years old (C,D). Note the ring-enhanced tumour with peritumoural edema and the midline shift adjacent to the diffuse long-standing lesion.

(E-J) Pathological features of the newly-developed tumour (E-H), adjacent brain tissue (I), and the long-standing lesion (J). Hematoxylin and eosin staining of tissue from the newly-developed tumour shows that the tumour tissues consist of piloid tumour cells on a myxoid background (E) and high-cellular regions (F). There are no Rosenthal fibers, eosinophilic granular bodies, microvascular proliferation, or necrosis evident in the tumour tissues. (G) MIB-1 staining revealed a highly cellular region with high proliferative activity (labeling index >30%). (H) The tumour cells were positive for TP53 antibody staining. (I) The cells infiltrated into surrounding brain

tissue via perivascular spaces. (J) Tissue from the long-standing lesion showed the diffuse distribution of well-differentiated fibrillary cells.

Fig. 3

- (A-C) Direct sequencing of the *TP53* gene. A missense mutation in exon 8 c.830G>T (p.Cys277Phe) was observed in both the new (homozygous) (A) and long-standing (heterozygous) (B) tumour.
- (C) DNA from the patient's blood did not manifest the *TP53* mutation.
- (D) Direct sequencing of the *FAS* gene revealed a heterozygous *FAS* mutation at the splicing site of intron 7 (T/T -> C/T).

Fig. 1

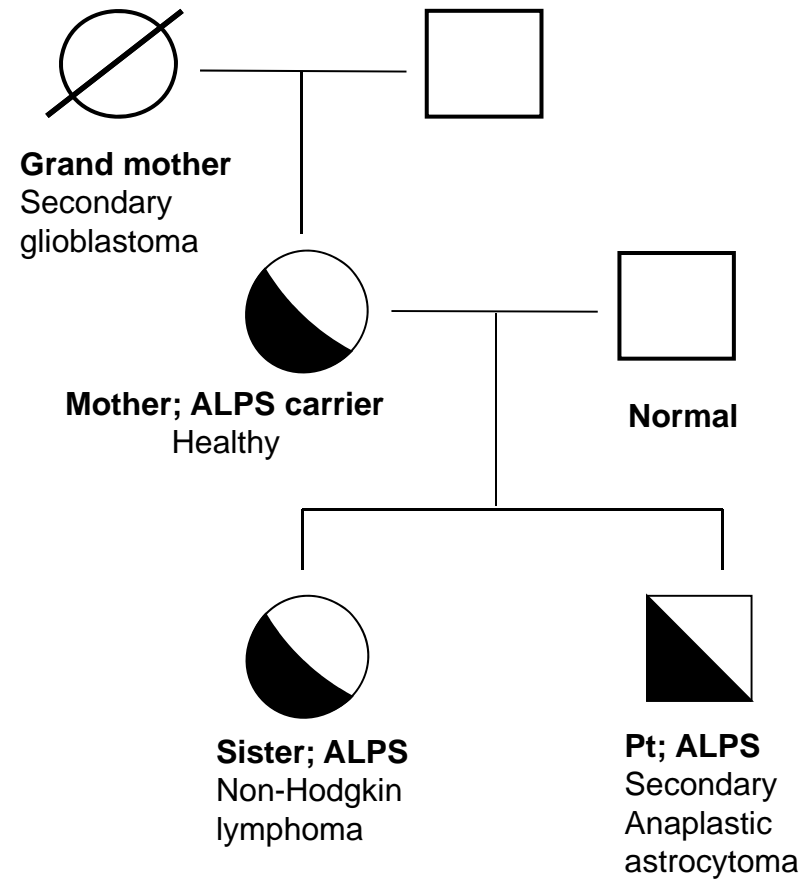


Fig. 2

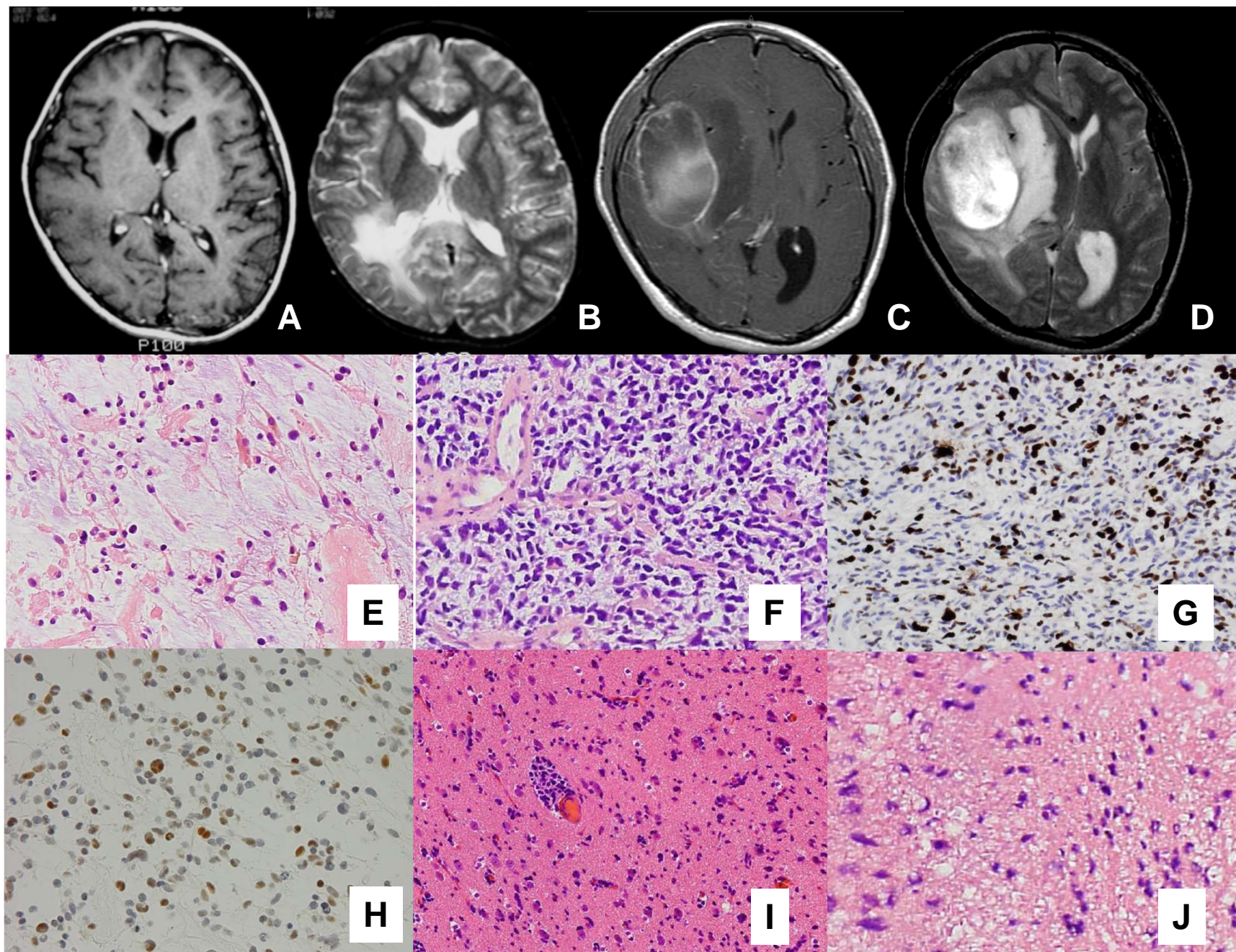


Fig. 3

