ORIGINAL ARTICLE

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Eosinophil Infiltrates in Pilocytic Astrocytomas of Children and Young Adults

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ABSTRACT: ***Objective:*** Eosinophils may affect each stage of tumour development. Many studies have suggested that tumour-associated tissue eosinophilia (TATE) is associated with favourable prognosis in some malignant tumours. However, only a few studies exist on TATE in central nervous system (CNS) tumours. Our recent study exhibited eosinophils in atypical teratoid/rhabdoid tumours (AT/RTs), pediatric malignant CNS tumours with divergent differentiation. This study examines eosinophils in pilocytic astrocytomas (PAs). ***Methods:*** The study included 44 consecutive cases of patients with PAs and no concurrent CNS inflammatory disease. ***Results:*** We found eosinophils in 19 (43%) of 44 PAs (patient age range, 0.5-72 years). Eosinophils were intratumoural and clearly distinguishable. The density of eosinophils was rare to focally scattered. PAs containing eosinophils were located throughout the CNS. Furthermore, eosinophilic infiltration was identified in 18 (62%) of 29 pediatric (age range, 0.5-18 years) PAs but only 1 (7%) of 15 ($p < 0.001$, significantly less) adult (age range, 20-72 years) PAs. Eosinophilic infiltration showed no significant differences between PAs with and without MRI cystic formation, surgical procedures, or PAs with and without leptomeningeal infiltration. In comparison, eosinophils were absent in 10 pediatric (age range, 0.5-15 years) ependymomas (or anaplastic ependymomas). ***Conclusions:*** These results suggest that eosinophils are common in pediatric PAs but rare in adult PAs. This difference is probably related to the developing immune system and different tumour-specific antigens in children. TATE may play a functional role in the development of pediatric PAs, as well as some other pediatric CNS tumours such as AT/RTs.

RÉSUMÉ: **Infiltrats éosinophiles dans les astrocytomes pilocytiques de l'enfant et du jeune adulte.** ***Objectif:*** Les éosinophiles peuvent influencer chaque stade de l'évolution tumorale. Selon plusieurs études, l'éosinophilie tissulaire associée à certaines tumeurs malignes (ÉTAT) comporterait un pronostic favorable. Cependant, peu d'études sur l'ÉTAT de tumeurs du système nerveux central (SNC) ont été réalisées. Nous avons démontré récemment la présence d'éosinophiles dans des tumeurs tératoïdes/rhabdoïdes atypiques (TT/RA), des tumeurs malignes du SNC chez l'enfant avec différentiation divergente. Cette étude examine la présence d'éosinophiles dans les astrocytomes pilocytiques (APs). ***Méthode:*** Nous avons étudié 44 patients consécutifs atteints d'un AP, sans maladie inflammatoire concomitante du SNC. ***Résultats:*** Nous avons retrouvé des éosinophiles dans 19 (43%) des 44 AP. L'âge des patients atteints de ces tumeurs allait de 0,5 à 72 ans. Les éosinophiles étaient intratumoraux et clairement identifiables. Leur densité était variable, parfois rares ou en foyers dispersés. Les AP contenant des éosinophiles étaient localisés dans tout le SNC. De plus, une infiltration par des éosinophiles a été observée dans 18 (62%) des 29 AP chez les patients d'âge pédiatrique (écart de 0,5 à 18 ans), mais chez seulement 1 (7%) des 15 AP chez les adultes ($p<0,001$) dont l'âge variait de 20 à 72 ans. L'infiltration par des éosinophiles n'était pas significativement différente dans les AP avec ou sans formation kystique à l'IRM, selon l'intervention chirurgicale ou dans les AP avec ou sans infiltration des leptoméninges. Les éosinophiles étaient absents dans 10 épendymomes (ou anaplasiques) chez des enfants dont l'âge variait de 0,5 à 15 ans. ***Conclusions:*** Selon ces résultats, des éosinophiles sont souvent présents dans les AP de l'enfant, mais rarement dans les AP de l'adulte. Cette différence est probablement reliée au système immunitaire en développement chez l'enfant et à des antigènes spécifiques à la tumeur qui sont différents chez les enfants. L'ÉTAT pourrait jouer un rôle fonctionnel dans le développement des AP chez l'enfant ainsi que dans d'autres tumeurs du SNC telles les TT/RA.

Keywords: Tumour-associated tissue eosinophilia, eosinophils, pilocytic astrocytomas, pediatric patients, adult patients, immune cells

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Introduction

Tumour-associated tissue eosinophilia (TATE) has been increasingly reported, but the exact role of eosinophils in tumours is not yet defined. Many studies have suggested that TATE is associated with favourable prognosis for a variety of carcinomas,[1-6] whereas a few other studies have noted that TATE may have a tumour-promoting role[7] and association with tumoural invasion of

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the oral squamous cell carcinomas.[8,9] Eosinophils have been found in several malignant and benign tumours, including oral squamous cell carcinomas, breast carcinomas, gastric cancers, uterine cervix carcinomas, penile cancers, hematologic malignancies, and colonic adenomas.[1-12] However, few studies have described TATE in central nervous system (CNS) tumours.[12] Two studies from the same group revealed intracavitary eosinophils in malignant astrocytomas of patients who had received an infusion of interleukin 2 (IL-2) combined with ex vivo activated autologous killer cells into the surgical resection cavity. Eosinophils had been absent in the primary operative specimens of those patients, suggesting immunotherapy-induced esoinophila.[13,14] Our recent study showed the infiltration of eosinophils in all four cases of atypical teratoid/rhabdoid tumours (AT/RTs), but not in a small group of glioblastomas.[15]

Pilocytic astrocytoma (PA) is a slow-growing, often cystic astrocytic tumour that occurs predominantly in children.[16] It is the most common pediatric glial tumour. Pediatric patients with PAs survive longer than adult patients, according to the Central Brain Tumour Registry.[17,18] The discrepancy in outcome between two age groups is attributed to both genetic and nongenetic differences. For example, the glioma-associated antigen precursor protein profile displays the different types between pediatric and adult patients.[17] In addition, children's immune system undergo development that peaks at puberty, which may also help explain why pediatric patients with PAs survive longer.[18] Reports have inversely associated glioma risk with atopic diseases.[19-21] Eosinophils are established effector cells in atopic diseases[22,23] and therefore may be partially responsible for the reported inverse association with atopic diseases and the risk of gliomas.[12] In accordance with our observation of eosinophils in the tissues of AR/RTs,[15] we sought to examine the frequency of eosinophil infiltrates in PAs and determine its clinical-pathological correlation.

Materials and Methods

Patients and Study Design

We received ethics approval from the local institutional Committee on Human Research to complete this study. The study included 44 consecutive cases of patients with PAs diagnosed between 2007 and May 2013. For comparison, we also examined 10 consecutive cases of patients with ependymomas or anaplastic ependymomas diagnosed between 2008 and 2013. Table 1 shows patient characteristics. All patients had undergone surgical procedures at the University of Alberta Hospital. No evidence of concurrent primary infectious/inflammatory disease was present in these cases. Surgical specimens were sent to the pathology department for pathological examination. Tumours were diagnosed and classified according to international guidelines as published in the 2007 World Health Organization's *Classification of Tumours of the Central Nervous System*.[16] We excluded cases with controversial diagnosis.

Histopathology and Immunohistochemistry

Surgical specimens were formalin-fixed, routinely processed, paraffin-embedded, sectioned at 5 µm, and stained with hematoxylin and eosin and immunohistochemical methods. We examined stained slides for morphological features. To obtain further adjuvant diagnostic information, we performed immunohistochemical analysis on tissue sections by using the EnVision FLEX Mini kit, high pH (Autostainer/Autostainer Plus; Dako, Carpinteria, CA, USA) detection system after the tissue was deparaffinised and rehydrated according to standard protocol. We used the antibodies, including at least glial fibrillary acidic protein 6F2 and MIB-1 (both from Dako), to immunohistochemically confirm glial cell origin and further characterize the tumours.

Two authors (JQL and OR) assessed morphological features of each case or slide with consensus. Eosinophils were identified with their characteristic morphology (Figure 1). Frequency of eosinophils was then assessed semiquantitatively. The number of eosinophils in ten consecutive high-power microscopic fields (HPFs; each original magnification ×400, 0.16 mm^2) was scored using the following scheme: − (0 per 10 HPFs), + (1-3 per 10 HPFs), ++ (4-15 per 10 HPFs), and +++ (16 or more per 10 HPFs). This assessment excluded intravascular eosinophils.

Statistical Analysis

We used Fisher's exact test to evaluate the association between categorical variables. A two-tailed p value of less than 0.05 was considered significant.

Results

Pilocytic Astrocytomas

PAs exhibited characteristic morphologic features, including a biphasic pattern with various proportions of densely fibrillary and microcytic areas (Figure 1a-c), various numbers of Rosenthal fibres (Figure 1b), and eosinophilic granular bodies (Figure 1c). We noted leptomeningeal infiltration in 14 (32%) of 44 PAs. Only three PAs (cases 3, 10, and 41 [Table 1]) exhibited marked perivascular cuffing of lymphoid cells. The frequency and degree of perivascular lymphoid infiltrates in PAs seen here are similar to those of previously published series.[24,25] While glomeruloid vasculature was often noted in PAs,[16] a few PAs contained microfoci of extravasated erythrocytes or microhaemorrhages with occasional hemosiderin deposition.[26]

Tumour-Infiltrating Eosinophils

We found eosinophils in tumour tissue of 19 (43%) of 44 (cases 1-19 [Table 1]) PAs. Density of intratumoural infiltrating eosinophils was rare to focally scattered (Figure 1a). Eosinophils were morphologically distinguishable from Rosenthal fibres (Figure 1b) and eosinophilic granular bodies (Figure 1c). Sites of PAs containing eosinophils were present throughout the brain (Table 1). Two resections of spinal cord PAs showed no eosinophils. We noted the presence of eosinophils in seven biopsy samples and 12 resections of PA tissues (not statistically significant between two surgical procedures; $p = 0.16$). Eosinophils were present in only 3 of 8 secondary operations for residual/recurrent PAs, compared with those in 16 of 36 original operations of PAs (not statistically different; $p = 1.00$). We found eosinophils in 6 PAs with leptomeningeal infiltration but not in the other 8 PAs with leptomeningeal infiltration (not statistically significant, compared with PAs without leptomeningeal infiltration; $p = 1.00$). No difference ($p = 0.36$) was evident in finding eosinophils between PAs with and without MRI cystic formation. We occasionally identified eosinophils in the perivascular spaces

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Table 1: Patient clinical and pathological features

Case	Sex	Age (y)	Tumor location	MRI cystic formation	OR	Eosinophils	Leptomeningeal infiltration	FU
1	M	5	Cerebellar vermis	+	Re	+++	–	Stable at 18 mo
2	M	3	Medulla, exophyatic	–	Re	++	–	Stable at 40 mo
3	F	5	Suprasellar region	+	Re	++	–	Stable at 51 mo
4	F	9	Left thalamus	–	Bx	++	–	Stable at 12 mo
5	F	10	Midline posterior fossa	–	Re	++	–	Stable at 10 mo
6	M	12	Left temporal lobe	+	Re*	++	–	Stable at 6 mo; previously resected 11 yr ago
7	M	17	Tectum, exophyatic	–	Bx	++	–	Stable at 10 mo
8	M	20	Third ventricle	+	Bx	++	–	Followed by resection at 8 days, then stable at 53 mo
9	M	1	Optic chiasm	–	Bx	+	+	Stable at 42 mo
10	F	4	Cerebellar vermis	–	Re	+	+	Stable at 12 mo
11	F	5	Suprasellar region	+	Bx	+	–	Followed by resection at 1 mo, then stable at 51 mo
12	M	5	Suprasellar region, third ventricle, with leptomeningeal deposits over the cerebellum and spinal cord	+	Bx	+	+	Followed by chemotherapy, stable at 58 mo, with decreased size of deposits
13	F	7	left pons, middle cerebellar peduncle	+	Re	+	+	Stable at 23 mo
14	F	9	Medulla, exophyatic	–	Re	+	–	Statble at 9 mo
15	M	11	Left thalamus and temporal lobe	+	Re	+	–	Stable at 33 mo
16	F	14	Right occipital lobe	–	Re	+	–	Stable at 24 mo
17	F	15	Left cerebellum	+	Re*	+	+	Stable at 18 mo; previously resected 78 mo ago
18	M	15	Left temporal lobe, with ventricular deposits	–	Bx	+	+	Progressive increase in intraventricular and leptomeningeal seeding for 47 mo
19	F	18	Optic chiasm	+	Re*	+	–	Stable at 62 mo; previously resected 5 yr ago
20	M	0.5	Spinal cord C3-T5	–	Re	–	–	Stable at 7 mo
21	M	1	Spinal cord C2-4	–	Re*	–	–	Stabel at 35 mo
22	M	2	Right cerebellum	+	Re	–	+	Stable for 24 mo
23	F	3	Left thalamus and tectum	+	Bx	–	+	Stable for 36 mo; increased size of enhancement at 49 mo
24	M	4	Midline cerebellum with leptomeningeal deposits over the brainstem and spincal cord	+	Re	–	+	Stable at 58 mo; no RT or chemotherapy
25	F	6	Fourth ventricle	+	Re	–	–	Stable at 33 mo
26	M	9	Left temporal lobe	+	Re	–	–	Stable at 36 mo
27	F	13	Left cerebellum	+	Re	–	–	Stable at 23 mo
28	M	15	Right thalamus	+	Bx	–	–	Stable at 36 mo
29	F	18	Cerebellar vermis	–	Re	–	–	Stable at 24 mo
30	F	18	Left frontal lobe	+	Re	–	+	Stable at 18 mo
31	M	18	Right thalamus	+	Re	–	–	Stable at 46 mo
32	M	20	Third ventricle	+	Re*	–	–	Stable at 53 mo; previously biopsied 8 days ago
33	F	21	Midline cerebellum	+	Re	–	–	Stable at 42 mo
34	F	22	Midline posterior fossa	+	Re	–	–	Stable at 35 mo
35	M	22	Midline cerebellum	+	Re	–	+	Stable at 49 mo
36	M	26	Left posterior fossa	+	Re	–	–	Stable at 6 mo

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Table 1: *(Continued)*

Case	Sex	Age (y)	Tumor location	MRI cystic formation	OR	Eosinophils	Leptomeningeal infiltration	FU
37	M	28	Tectum, exophytic?	+	Re*	–	–	Stable at 19 mo; previously biopsied 44 mo ago
38	M	32	Right cerebral peduncle	–	Re	–	–	Stable 31 mo
39	M	42	Left cerebellum	–	Re	–	+	Stable at 9 mo
40	M	47	Midline cerebellum	+	Re*	–	–	Stable at 69 mo
41	F	53	Cerebellar vermis	–	Bx	–	+	Stable at 23 mo
42	F	56	Cerebellar vermis	–	Re*	–	+	Stable at 6 mo; previously biopsied 16 mo ago
43	M	62	Right frontal lobe	+	Re	–	–	Stable at 6 mo
44	F	72	Fourth and third ventricles	–	Bx	–	–	Stable at 12 mo
C1	M	0.5	Posterior fossa	–	Re			
C2	M	4	Posterior fossa	–	Re*			
C3	F	6	Left lateral ventricle	–	Re*#			
C4	F	7	Posterior fossa	–	Re*#			
C5	M	7	Right frontal lobe	–	Re*			
C6	M	11	Right frontal lobe	–	Re			
C7	M	13	Left frontal lobe	–	Re*			
C8	F	14	Occipital lobe	–	Re			
C9	M	14	Left frontal lobe	–	Re*			
C10	F	15	Left frontal lobe	–	Re*			

Abbreviations: mo = months; yr = years; M = male; F = female; FU = follow-up by neuroimaging; RT = radiotherapy.; Bx = biopsy; OR = operation; Re = resection.

Eosinophils: – (0 per 10 high-power fields [HPFs]), + (1-~3 per 10 HPFs), ++ (4-15 per 10 HPFs), and +++ (≥16 per 10 HPFs).

*, resection for residual/recurret tumors.

C1–10: control cases of ependyomomas, recurrent ependymomas*, and anaplastic ependymomas#.

(Figure 1c) and associated with extravasated erythrocytes or microhaemorrhages (Figure 1d).

Further analysis revealed that eosinophils were identified in 18 (62%) of 29 PAs in pediatric patents (age range, 0.5-18 years) but only in 1 (7%) of 15 (significantly less than that of pediatric patients; $p = 0.0004$) PAs in adult patients (age range, 20-72 years). The adult patient with a PA containing eosinophils was 20 years old (case 8 [Table 1]).

In comparison, eosinophils were absent in all ten ependymomas (including recurrences) or anaplastic ependymomas in pediatric patients (age range, 0.5-15 years; case C1-10 [Table 1]).

Discussion

This study has shown TATE in pediatric PAs. We have also found that, in contrast, TATE has been rare in adult PAs and absent in pediatric ependymomas. In combination with previous studies showing TATE in AT/RTs[15] and in malignant astrocytomas,[13,14] these findings suggest that TATE in CNS tumours may be cell origin dependent and age dependent.

The CNS has generally been considered a relatively immunologically privileged organ because of the blood–brain barrier. When CNS injury occurs, antigen-specific cells can traffic to relevant sites in the CNS. With the anatomic complexity of the CNS, researchers have proposed three routes by which immune cells may enter the CNS: from blood to the cerebrospinal fluid via the choroid plexus, from blood to the subarachnoid space, and from blood to the parenchyma.[27,28] The mechanism of eosinophil entry into the CNS remains unclear. The trafficking route from blood to CSF via the choroid plexus may be disfavoured in PAs, on the basis of our study revealing the absence of eosinophils in ependymomas and many PAs involving the choroid plexus. Eosinophilic infiltrates have been present in various CNS disorders,[12] including eosinophilic meningoencephalitis,[29] Langerhans cell histiocytosis,[30] and chronic subdural hematomas,[31] which mostly involve the leptomeninges. The location of those disorders containing eosinophil infiltrates appears to favour eosinophils trafficking into the CNS from blood to the subarachnoid space. Although mast cells have been identified in the dura, leptomeninges, choroid plexus, and brain parenchyma,[32] the presence of eosinophils in the noninfectious process may be attributed to their bidirectional interactions with mast cells.[23,31,32] In our study, however, we found no difference in eosinophil infiltrates between PAs with and without leptomeningeal infiltration. Instead, we often observed eosinophils along with extravasated erythrocytes in the perivascular spaces of PAs. This observation suggests that eosinophils are more likely trafficking from blood directly into the CNS tumours, after the vascular structures of "brain–tumour barrier" have been substantially altered in gliomas.[28]

Eosinophils are pleiotropic multifunctional leukocytes involved in the initiation and propagation of diverse inflammatory responses. They are important modulators of innate and adaptive immunity.[23] In

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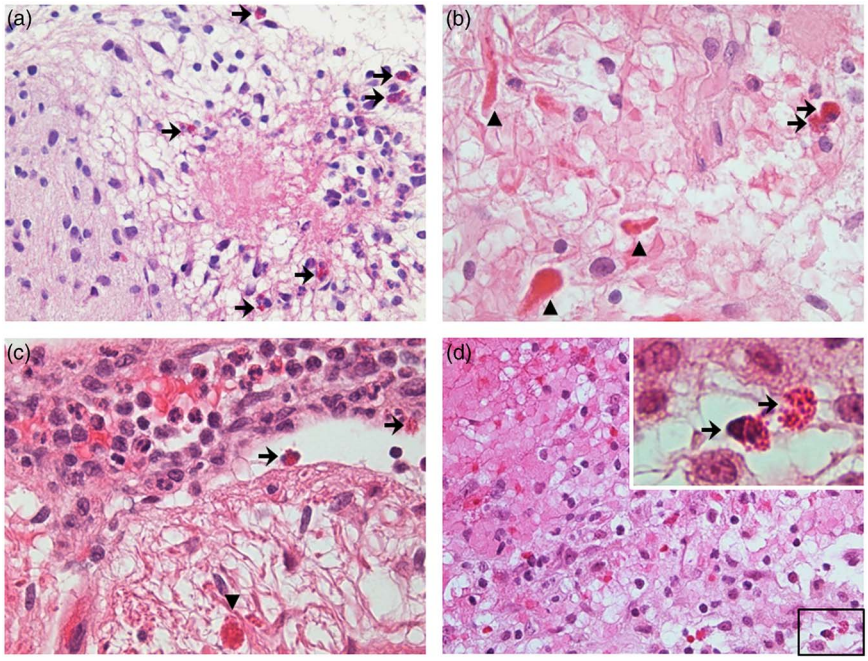

Figure 1: *Eosinophil infiltrates in a suprasellar pilocytic astrocytoma (case 3 in Table 1). The tumour shows a biphasic pattern with densely fibrillary and microcytic areas, as well as scattered eosinophils (a, arrows) that are morphologically distinguishable from Rosenthal fibres (b, arrowheads; arrows point to eosinophils) and eosinophilic granular body (c, arrowhead; arrows point to eosinophils). Eosinophils are occasionally identified in the perivascular spaces (c, arrows) and associated with associated with extravasated erythrocytes (d, arrows point to eosinophils; rectangle indicates area of the inset with higher magnification). Original magnifications: ×400 (a and d); ×630 (b and c).*

response to various stimuli, the eosinophils can produce cytotoxic granules, neuromediators, and proinflammatory cytokines, as well as growth factors and profibrotic and angiogenic factors, which are involved in pathogen clearance and tissue remodeling and repair.[12] However, once eosinophils have selectively infiltrated inflamed tissues, they release various toxic proteins, including major basic protein, eosinophil cationic protein, eosinophil peroxidase, and eosinophil neurotoxin, which contribute to tissue damage.[33] The role of eosinophils in CNS tumours is therefore complex and probably dual, since eosinophils can induce neurotoxicity to adjacent brain tissue and/or apoptosis of tumour cells.[15] Increasing evidence has suggested that eosinophils may affect each stage of tumour development; for example, cytokines and chemokines produced by tumour cells have been indicated to alter the tumour-suppressive functions of innate immune cells, creating a microenvironment conducive to tumour development. Also, some cytokines have been suggested to induce recruitment and activation of immune cells (including eosinophils) in association with the tumour rejection and enhanced host survival.[12] Nevertheless, the exact role of infiltrating eosinophils in glial tumours deserves further investigation.

Immune cell infiltrates in tumours often vary with tumour type and size.[34,35] TATE is common and occurs in several non-CNS tumour types, particularly tumours of epithelial origin in the colon and breast.[1,10,36] Autologous neuroblastoma cells modified to secrete IL-2 and given to pediatric patients with advanced neuroblastoma generated local and systemic antitumour immune responses, including infiltration of eosinophils, as well as dendritic cells, $CD4^+$, and $CD8^+$ lymphocytes.[37] In two studies, after the original operation of malignant astrocytomas, intracavitary injection of IL-2 plus ex vivo activated autologous killer cells induced eosinophilia in the intracavitary fluid, tissue, and CSF.[13,14] This eosinophilia appeared to correlate with enhanced patient survival. However, both studies found no eosinophils in the original operative specimens of patients before the IL-2–killer cell immunotherapy, suggesting that eosinophilia is immunotherapy induced in malignant astrocytomas. We recently showed infiltration of eosinophils in all four resections of AT/RTs that are malignant embryonic tumours with divergent differentiation, but absence in four original resections of glioblastomas.[15] The present study revealed the presence of eosinophils in PAs but not in ependymomas. On the basis of these observations, eosinophil infiltrates are probably limited to some CNS tumours with certain cell origins, particularly in astrocytomas or tumours containing an astrocytic component/differentiation. Although the pathogenesis of cell origin-dependent TATE is unclear, it may be at least partially attributed to different types of tumour-specific antigens present in those CNS tumours.[17,18,28,38] With the presence of this cell origin-dependent TATE and its dissociation from other peripheral blood elements, the infiltration of eosinophils in astrocytomas seems to be actively involved in their pathogenesis other than a passive reactive process.[12,25]

The major finding of our study is that eosinophils are commonly present in pediatric PAs but rarely (only one 20-year-old patient) in adult PAs. This age-dependent finding is consistent with that of our other study showing eosinophils in AT/RTs of all

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four patients younger than 2 years.[15] Two possibilities exist to interpret this age-dependent CNS TATE in pediatric tumours: One is the developing immune system in children, since their immunity peaks around puberty. The other is the difference in tumour-specific antigens between pediatric and adult gliomas.[17,18] The exact mechanisms of the age-dependent TATE require further study.

Conclusion

Our results suggest that the presence of eosinophils is a common feature of pediatric PAs but not of adult PAs. This finding may be at least partially attributed to developing immune system and different tumour-specific antigens in children. Since increasing evidence has suggested that TATE is associated with favourable prognosis in a few tumours, including malignant astrocytomas,[1-6,13,14] the presence of infiltrating eosinophils in PAs might be related to the much longer survival of pediatric PA patients than that of adults. The infiltration of eosinophils may play a functional role in the development of pediatric PAs, as well as some other pediatric CNS tumours such as AT/RTs.

Disclosures

The authors report no conflicts of interest.

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