

Anaplastic oligoastrocytoma: previous treatment as a possible cause in a child with acute lymphoblastic leukemia

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Abstract

Introduction The authors present a 14-year-old patient who developed an anaplastic oligoastrocytoma of the left parietal lobe 9 years after a successful treatment of acute lymphoblastic leukemia (ALL). He had a history of induction chemotherapy, intrathecal methotrexate and prophylactic whole brain irradiation (1,800 cGy in 10 fractions over 2 weeks).

Discussion Radiation-induced neoplasia is suggested to be the late complication of ALL treatment, and evaluation of large clinical series revealed a relationship between young age at ALL diagnosis (<6 years) and increased high-grade glioma occurrence risk.

Conclusion The authors have reviewed previously reported cases of secondary central nervous system malignancies focusing on age at ALL diagnosis, and they think that synergistic action of therapeutic modalities could have played a role in the oncogenetic process. Detailed systematic radiological follow-up should be done in these patients especially if a personal history of cranial irradiation is present.

Keywords Acute lymphoblastic leukemia · Anaplastic oligoastrocytoma · Methotrexate · Radiation · Secondary neoplasm

Introduction

Since the introduction of the routine use of central nervous system (CNS) prophylaxis for children with acute lymphoblastic leukemia (ALL), the cure rates have been markedly improved [20]. With the prolongation of the survival time, undesirable results of these protocols, such as secondary malignancies, have been identified. In this report, we describe a rare case of a child who developed an anaplastic oligoastrocytoma of the left parietal lobe 9 years after the successful treatment of ALL.

Case report

A 14-year-old male patient admitted to our neurosurgery clinic with a history of a single episode of generalized tonic-clonic seizure, which occurred 3 weeks ago. Neurological examination revealed nothing abnormal. He had a history of ALL treated 9 years ago with induction chemotherapy, intrathecal (IT) methotrexate (Mtx) and prophylactic whole brain irradiation (1,800 cGy in 10 fractions over 2 weeks). The magnetic resonance imaging (MRI) that was performed 2 weeks before his admission revealed two well-demarcated lesions localized in the left posterior parietal and right frontal regions (Fig. 1a–c). The patient was hospitalized for further investigation. He was consulted with pediatric hematology and oncology. The bone marrow and peripheral blood examinations showed no evidence of ALL recurrence. Cerebrospinal fluid studies

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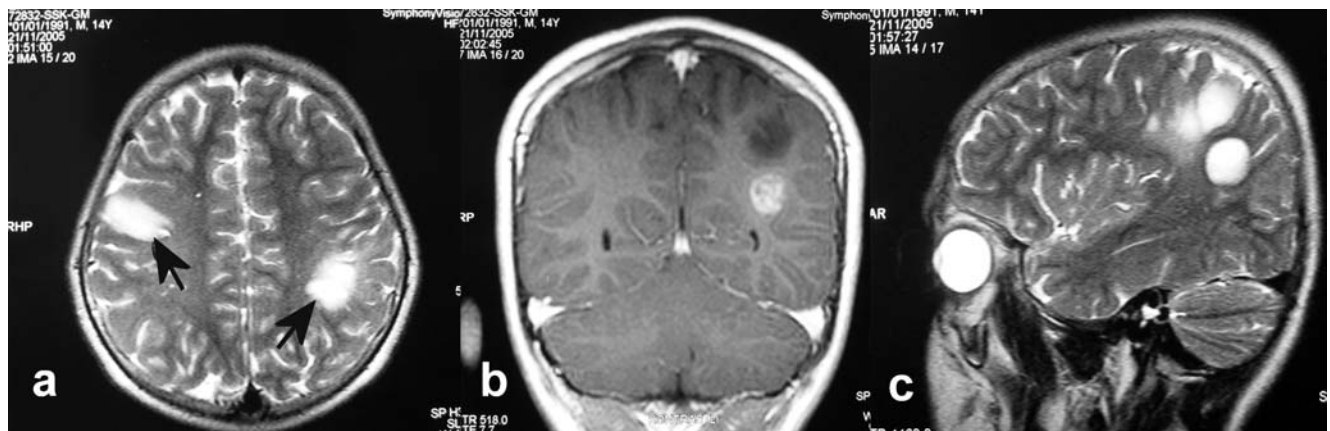


Fig. 1 **a** T2-weighted axial MRI scan demonstrates two well-demarcated lesions (*arrows*) localized in the left posterior parietal and right frontal regions. **b** T1-weighted contrast-enhanced coronal and **c** T2-weighted sagittal MRI images

(biochemistry, cytology, oligoclonal IgG) and blood biochemistry were in normal ranges. Acute disseminated encephalomyelitis or malignancy was suspected in the differential diagnosis. The second cranial MRI scan, which was performed approximately 4 weeks after the first, revealed a rapid progression of both lesions (Fig. 2a–c). He then underwent a left frontoparietal craniotomy, and the lesion located at the left parietal lobe was totally removed (Fig. 3). The postoperative period was uneventful, and the patient was discharged on the sixth postoperative day. The pathological diagnosis was anaplastic oligoastrocytoma grade III (Fig. 4). He was referred to pediatric hematology–oncology department for further treatment.

Discussion

Central nervous system (CNS) prophylaxis is an essential component of the management of ALL in children. The treatment modalities to prevent CNS leukemia include cranial irradiation, IT chemotherapy, and high-dose systemic chemo-

therapy. With the use of these protocols, the cumulative incidence of CNS leukemia has been reduced from 30–50% to less than 10% [4, 20]. Among these treatment modalities, cranial irradiation has been shown to have serious complications both in short term and in long term. These side effects, such as white matter destruction, vascular damage leading to calcifications, and enlargement of ventricles and/or sulci secondary to cortical atrophy, have all been identified in radiologic examinations [22]. Clinically, post-radiation damage represents a broad spectrum of signs and symptoms such as intellectual dysfunction, learning disabilities, growth retardation, neurological sequelae, seizures, and secondary neoplasia [4, 22]. Due to these effects, recent CNS prophylaxis regimens have shifted from cranial irradiation to IT plus high-dose systemic chemotherapy.

Radiation-induced neoplasia is a well-recognized condition, in which the meningiomas and sarcomas predominate among other tumor types [12, 23]. In 1950s, a retrospective survey of 11,000 children irradiated for tinea capitis revealed a significantly higher risk of both benign and malignant head and neck tumors [12]. In the majority of

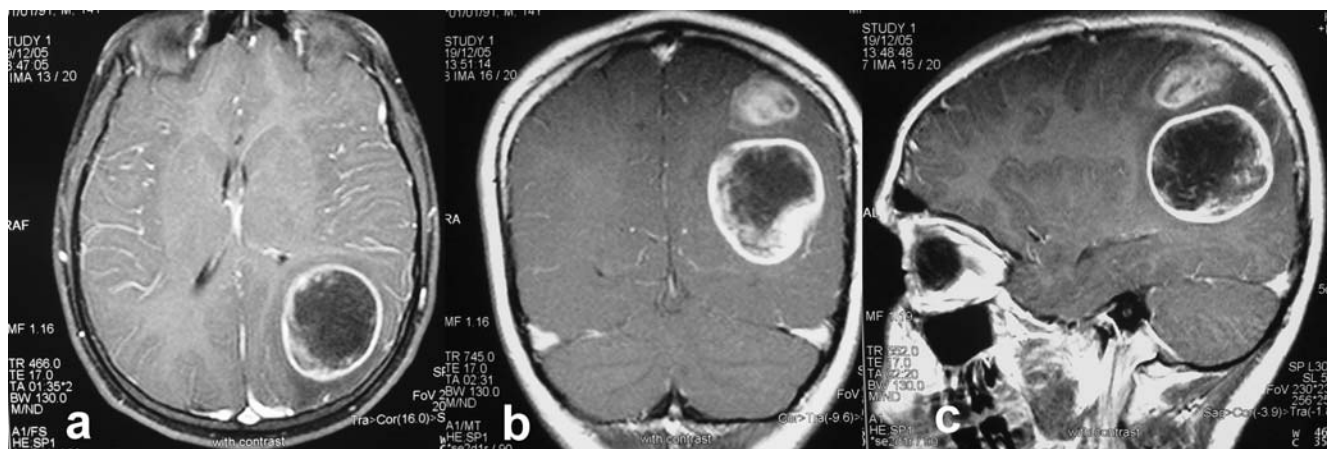


Fig. 2 T1-weighted contrast-enhanced MRI scans **a** axial, **b** coronal, and **c** sagittal sections clearly reveals rapid progression



Fig. 3 Postoperative cranial CT shows total resection of the tumor

these cases, the interval between radiation and tumor diagnosis was more than 9 years. Possible radiation-induced gliomas following ALL treatment have also been reported in the literature, and this concomitant presentation has been investigated [1, 3, 6–8, 10, 13, 15, 18, 24–26].

A relationship between young age at ALL diagnosis and increased occurrence of high-grade gliomas has been proposed in large clinical studies [9, 24]. Walter et al. [24], in their series of 1,612 patients consecutively treated for childhood ALL with a median follow-up of 15.9 years, evaluated the incidence and potential risk factors for secondary malignant neoplasms of the brain. The cumula-

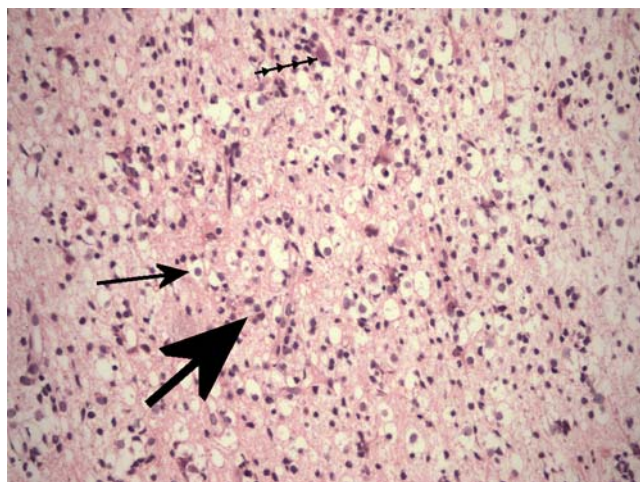


Fig. 4 Photomicrograph (original magnification $\times 200$ hematoxylin-eosin). Highly cellular tumor with both oligodendroglial (~35%) and astrocytic (~65%) components. Typical neoplastic oligodendrocyte with a round nucleus and a perinuclear halo (*thin arrow*); a neoplastic astrocyte with pleomorphic, hyperchromatic nuclei (*thick arrow*); pleomorphism (*repeating short arrows*). No necrosis or microvascular proliferation was identified. These features are consistent with an anaplastic oligoastrocytoma (WHO grade III)

tive incidence of brain tumors among these patients was reported to be 1.39% at 20 years. Of the 21 patients with 22 brain tumors, 10 were high-grade gliomas, 1 was a low-grade glioma, and 11 were meningiomas. Gliomas occurred at a median latency of 9.1 years in contrast to longer latency of meningiomas (19 years). The risk factors for developing any secondary brain tumor included presence of CNS leukemia at diagnosis and increased cranial irradiation dose. Young age at ALL diagnosis (<6 years) was found to have an association with an increased risk of developing a high-grade glioma. Nine out of 10 patients with high-grade gliomas in this study were younger than 6 years old at the time of ALL diagnosis [24]. In a multicenter study enrolling 5,006 children treated for ALL, 13 secondary CNS neoplasms were detected [9]. Likewise, tumors of the CNS were most commonly found to occur among children below the age of 7 at the time of ALL diagnosis. The cumulative probability that a CNS tumor would develop in these patients was 1.5% after 15 years, significantly higher compared with the risk of 0.1% in patients 7 years of age or older [9]. Our patient was 5 years old at the time of ALL diagnosis, and this may have played an important role in the oncogenic process. Previously reported, fully documented cases of secondary glioma following ALL treatment in patients who were less than 6 years old at the time of ALL diagnosis are summarized in Table 1.

We believe that relative immaturity of the brain at the time of radiation therapy in ALL patients can be a predisposing factor for secondary CNS neoplasia. Traditionally, CNS has been described as relatively resistant to radiation-induced changes. However, in young children, the turnover of glial cells, especially in the early postnatal period, is more intense, making them potential targets for oncogenesis. This was stressed by Palma et al. [13] who speculated that the child's brain is susceptible to the mutagenic effects of ionizing radiation particularly during myelinogenesis.

Several criteria must be fulfilled in order to accept radiation as a possible etiological factor for neoplasia [2, 19]. These are as follows: (1) the tumor must occur in the irradiated area, (2) the tumor must not be present prior to radiation, (3) a sufficient latency period must elapse between irradiation and the occurrence of the tumor, (4) the radiation-induced tumor should differ histopathologically from the original lesion, and this must be proven. Even though our case fulfils all of the above-mentioned criteria, the definite factors participating in the development of secondary neoplasia remain to be speculative. The evaluation of the second cranial MRI, which was performed approximately 4 weeks after the first investigation, demonstrated the aggressiveness of the tumor, and the factor triggering this rapid progression also remains to be unknown.

Although radiotherapy is clearly a strong risk factor, the occurrence of glioma in ALL patients who have not received

Table 1 Previously reported, fully documented cases of CNS glioma following ALL treatment, with focus on age at first ALL diagnosis (<6 years old)

Reference	Age at ALL diagnosis/sex	Rad. dose (Gy)	IT Mtx	Latency (years)	Histopathology
Walters [25]	3/F	26.2	+	6	Astrocytoma
Chung et al. [3]	2/M	24	+	5.2	GBM
Sanders et al. [18]	4/F	24	+	4.8	GBM
Anderson and Treip [1]	3/F	24	+	6.1	Astrocytoma
Judge et al. [7]	3/F	24	+	9.2	Astrocytoma
Fontana et al. [6]	3/M	24	+	10	GBM
Palma et al. [13]	3/M	24	+	11	Oligoastrocytoma
Kaschten et al. [8]	1.5/M	24	+	12	Gliosarcoma
Walter et al. [24]	2.1/F	24	+	9.8	Malignant glioma
	2.7/M	24	+	7.6	GBM
	2.3/F	24	+	13.2	Anaplastic astrocytoma
	3.8/M	24	+	7.6	Malignant glioma
	2/M	18	+	11	GBM
	2.9/M	40	+	10.5	Malignant glioma
	2.2/M	18	+	14.1	Anaplastic oligodendroglioma
Present case	5/M	18	+	9	Anaplastic oligoastrocytoma

such treatment [16, 21] prompted the evaluation of other factors. Genetic susceptibility and linkage between brain tumors and hematologic malignancies has been proposed [9–11]. Meadows et al. [11], in their clinical study of 102 children, each harboring more than one malignant neoplasm, reported that there was a notable association of glioma with leukemia or lymphoma. The authors suggested that this finding may be associated with “a new cancer syndrome,” and certain patients with ALL might be genetically susceptible to the development of gliomas [11]. Although lacking definitive proof, increased incidence of CNS tumors among the first-degree relatives of patients suffering from leukemia supports this hypothesis [5, 8]. Systemic chemotherapy agents, such as thiopurines and antifolates, have also been suggested to participate in the oncogenetic processes [17], and IT Mtx has been accused for increasing the risk of glioma development [6, 17]. Mtx, when administered in combination with 200 cGy or more cranial irradiation, has been shown to cause multiple necrotic areas and leukoencephalopathy [14]. However, there is no single evidence both in man and experimental animals to indicate that Mtx alone is carcinogenic or that it enhances the carcinogenic effect of radiation. Moreover, the use of intrathecal chemotherapy was not found to increase the risk of developing secondary brain tumor in a clinical study [24]. Depending on the pertaining literature, we think that the oncogenic process of secondary CNS malignancy in ALL patients is multifactorial, and synergistic action of the previous treatment modalities plays a major role.

In conclusion, children suffering from ALL and treated by prophylactic CNS irradiation and IT Mtx can present with intracranial tumors even long after the completion of the initial treatment. Although the tumor would most likely

to be a high-grade glioma in these cases, the possibility of an oligo component should not be ignored. Since early detection of the intracranial lesions may permit a safe surgical removal, regular follow-up with radiological investigations should be performed systematically, especially if a personal history of cranial radiotherapy is present.

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References

- Anderson JR, Treip CS (1984) Radiation-induced intracranial neoplasms: a report of three possible cases. *Cancer* 53:426–429
- Cahan WG, Woodard HQ, Higinbotham NL, Stewart FW, Coley BL (1948) Sarcoma arising in irradiated bone: report of eleven cases. *Cancer* 1:3–29
- Chung CK, Stryker JA, Cruse R, Vannuci R, Towfighi J (1981) Glioblastoma multiforme following prophylactic cranial irradiation and intrathecal methotrexate in a child with a lymphocytic leukemia. *Cancer* 47:2563–2566
- Cortes J (2001) Central nervous system involvement in adult acute lymphocytic leukemia. *Hematol Oncol Clin North Am* 15(1):145–162
- Farwell J, Flannery JT (1984) Cancer in relatives of children with central-nervous-system neoplasms. *N Engl J Med* 311(12):749–753 (September 20)
- Fontana M, Stanton C, Pompili A, Amadori S, Mandelli F, Meloni G, Riccio A, Rubinstein LJ (1987) Late multifocal gliomas in adolescents previously treated for acute lymphoblastic leukemia. *Cancer* 60:1510–1518
- Judge MR, Eden OB, O’Neill P (1984) Cerebral glioma after cranial prophylaxis for acute lymphoblastic leukemia. *Br Med J* 289:1038–1039
- Kaschten B, Flandroy P, Reznik M, Hainaut H, Stevenaert A (1995) Radiation-induced gliosarcoma. Case report and review of the literature. *J Neurosurg* 83(1):154–162

9. Loning L, Zimmermann M, Reiter A, Kaatsch P, Henze G, Riehm H, Schrappe M (2000) Secondary neoplasms subsequent to Berlin–Frankfurt–Munster therapy of acute lymphoblastic leukemia in childhood: significantly lower risk without cranial radiotherapy. *Blood* 95(9):2770–2775 (May 1)
10. Malone M, Lumkey H, Erdohazi M (1986) Astrocytoma as a second malignancy in patient with acute lymphoblastic leukemia. *Cancer* 57:1979–1985
11. Meadows AT, D’Angio GJ, Mike V, Banfi A, Harris C, Jenkin RD, Schwartz A (1977) Patterns of second malignant neoplasms in children. *Cancer* 40(4 Suppl):1903–1911
12. Modan B, Mart H, Braidtz D, Sternit ZR, Levin SG (1974) Radiation-induced head and neck tumours. *Lancet* 1:277–279
13. Palma L, Vagnozzi R, Annino L, Ciapetta P, Maleci A, Cantore G (1988) Post-radiation glioma in a child. Case report and review of the literature. *Child’s Nerv Syst* 4(5):296–301
14. Peylan RN, Poplack DG, Pizzo PA, Adornato BT, Dichiro G (1978) Abnormal CT scans of the brain in asymptomatic children with acute lymphoblastic leukemia after prophylactic treatment of central nervous system with radiation and intrathecal chemotherapy. *N Engl J Med* 298:815–818
15. Raffel C, Edwards MSB, Davis RL, Ablin AR (1985) Postirradiation cerebellar glioma: case report. *J Neurosurg* 62:300–303
16. Regelson W, Bross ID, Hananian J, Nigogoyan G (1965) Incidence of second primary tumors in children with cancer and leukemia. *Cancer* 18:58–72
17. Relling MV, Rubnitz JE, Rivera GK, Boyett JM, Hancock ML, Felix CA, Kun LE, Walter AW, Evans WE, Pui CH (1999) High incidence of secondary brain tumours after radiotherapy and antimetabolites. *Lancet* 354(9172):34–39 (July 3)
18. Sanders J, Sale GE, Ramberg R, Clift R, Buckner CD, Thomas ED (1982) Glioblastoma multiforme in a patient with acute lymphoblastic leukemia who received a marrow transplant. *Transplant Proc* 14(4):770–774
19. Schrantz JL, Araoz CA (1972) Radiation induced meningeal fibrosarcoma. *Arch Pathol* 93(1):26–31
20. Surapaneni UR, Cortes JE, Thomas D, O’Brien S, Giles FJ, Koller C, Faderl S, Kantarjian H (2002) Central nervous system relapse in adults with acute lymphoblastic leukemia. *Cancer* 94(3):773–779 (February 1)
21. Tefft M, Vawter GF, Mitus A (1968) Second primary neoplasms in children. *Am J Roentgenol* 103(4):800–822
22. Waber DP, Silverman LB, Catania L, Mautz W, Rue M, Gelber RD, Levy DE, Goldwasser MA, Adams H, Dufresne A, Metzger V, Romero I, Tarbell NJ, Dalton VK, Sallan SE (2004) Outcomes of a randomized trial of hyperfractionated cranial radiation therapy for treatment of high-risk acute lymphoblastic leukemia: therapeutic efficacy and neurotoxicity. *J Clin Oncol* 22:2701–2707
23. Waga S, Handa H (1976) Radiation induced meningioma: with review of literature. *Surg Neurol* 5:215–219
24. Walter AW, Hancock ML, Pui CH, Hudson MM, Ochs JS, Rivera GK, Pratt CB, Boyett JM, Kun LE (1998) Secondary brain tumors in children treated for acute lymphoblastic leukemia at St Jude Children’s Research Hospital. *J Clin Oncol* 16(12):3761–3767
25. Walters TR (1979) Childhood acute lymphocytic leukemia with a second primary neoplasm. *Am J Pediatr Hematol Oncol* 1:285–287
26. Wojcik D, Dyrda T, Pietras W (1998) Astrocytoma in a 6-year old girl after the treatment for acute lymphoblastic leukemia. *Wiad Lek* 51(Suppl 4):318–321