UNIL | Université de Lausanne

Centre hospitalier universitaire vaudois

Mémoire de Maîtrise en médecine No 798

Malignant glioma after ependymoma : an unusual secondary malignancy

Etudiant
Delphine Tinguely

Tuteur
Dr. Maja Beck Popovic, PD & MER1
Unité d'hémato-oncologie pédiatrique,CHUV

Expert
Prof Philippe Maeder
Unité IRM, Neuroradiologie, CHUV

Lausanne, décembre 2012

Abstract :

Purpose : Secondary malignancies (SM) are a known long-term problem in children surviving brain tumors. We report on two unusual cases of SM observed after treatment of ependymoma. ***Case reports*** : 1. The first case is a female survivor of a low-grade ependymoma (Grade II). She had been treated at the age of 3 months with surgery and chemotherapy. A relapse of the primary tumor happened two years later, which was completely removed and treated with local radiotherapy to the posterior fossa. Fifteen years after the first cancer, she developed a pontine glioma near the location of the previous radiotherapy. 2. The second case is a femal survivor of an ependymoma (Grade III) which was removed and irradiated when she was 4 years old. The child developed a pontine glioma near the location of the previous radiotherapy ten years after the diagnosis of the first cancer. Further extension of the disease showed after biopsy PNET-like features. Both patients passed away.

Discussion and Conclusion : Second malignant neoplasia is a rare phenomenon and this risk should not overshadow the great success in treating cancer of childhood. Among the studied risk factors, young age and radiotherapy are well established. The reported patients were followed annually to ensure their remission and both developed symptoms and an unusual unreported secondary cancer a few months after the annual monitoring that was considered as normal. This issue highlights the complexity of monitoring cancer survivors and raises the question of the best way for their long-term follow-up.

Keyword : second cancer, ependymoma, CNS tumor

INTRODUCTION

Central nervous system (CNS) neoplasia is the second most frequent cancer in children between 1 year and 19 years old(1). In the United States, the estimated incidence of childhood CNS cancer is 4.5 cases per 100'000 person-years for children below 19 years old (2). In the last four decades, the survival rate for CNS malignancy has significantly improved with a global survival up to 74% at 5 years, due to the improved surgery, radiotherapy and chemotherapy(3).

All these treatments are associated with risks of long-term morbidity and late mortality, such as early death, organ dysfunction, reduced growth and development, decreased fertility, cognitive dysfunction or second malignancy. In the Childhood Cancer Survivor Study (CCSS) Cohort , the most frequent second malignancies after a primary CNS cancer are in order of frequency other CNS tumors, thyroid cancer and soft tissue sarcomas(4).

We report on two cases of female patients who developed a pontine glioma a few years after an intracranial ependymoma treated with surgery and irradiation. As far as we know, a similar case has not yet been described.

CASES REPORTS

Patient 1 :

A 10-week-old baby girl presented in November 1995 with respiratory distress, fever, feeding difficulties, vomiting and a six days history of right peripheral facial paresis. Physical examination demonstrated paralysis of the velum on the right side, explaining the difficulty in swallowing. The day of the admission, one episode of opisthotonos happened and she had to be intubated as a result of breathing difficulties. Cerebral CT showed a posterior fossa tumor with obstuctive hydrocephalus, bone deformation and a secondary compression of the brain-stem. MRI confirmed the findings suggesting an ependymoma. At surgery, the tumor was situated in the IVth ventricle with extension into the cisterna magna under the amygdalia and into the right cerebello pontine angle and could only be subtotally (90%) removed by an osteoplastic craniotomy of the posterior fossa. An otolaryngological examination showed a right vocal cord paresis. After the surgery, facial paresis and tongue sensibility disorder persisted. There weren't other neurological sequela. Neuropathological diagnosis was for low-grade ependymoma (WHO Grade II). The child entered the protocole Baby POG 92-33 and was treated with chemotherapy only (vincristine, cyclophosphamide, etoposide) from November 1995 to June 1997. In September 1997, at the age of 2 years and 3 months after end of treatment, the child presented a local relapse which could be removed completely. Histology was identical with the primary disease. She received then local radiatiotherapy to the posterior fossa with 180 cGy/day up to a total dose of 50.4 Gy. The child remained disease-free until September 2010. However, she presented numerous problems related to disease and treatment such as long-term feeding by percutaneous gastroenterotomy, neurocognitive difficulties needing special schooling, moderate hearing loss and precocious puberty at the age of 8.

In September 2010, 12 years after end of treatment, the girl developed nausea, regurgitations with hiccup and reported a loss of weight with an unusual tiredness since July 2010. Her appetite decreased and odynodysphagia appeared with difficulty to swallow solid food and with frequent nasal discharge. Progressive balance disorders and dizziness were other complaints. Physical examination revealed discrete tremor and ataxia and an horizontal nystagmus. MRI showed an expansive process involving the ponto-bulbar region with compression of the fourth ventricle, suggestive of pontine

glioma (Figures 1.1, 1.2). As the tumor was unresectable, the girl was put on Temozolomide 90mg/m^2/d and radiotherapy (total dosis 40 Gy), followed by Temozolomide only (200mg/m^2/d 5 days per month). However, tumor progressed and the child passed away 4 months after diagnosis of the secondary cancer.

Figure 1.1 : expansive process involving the ponto-bulbar region with compression of the fourth ventricle, suggestive of pontine glioma (September 2010) *Transverse view*

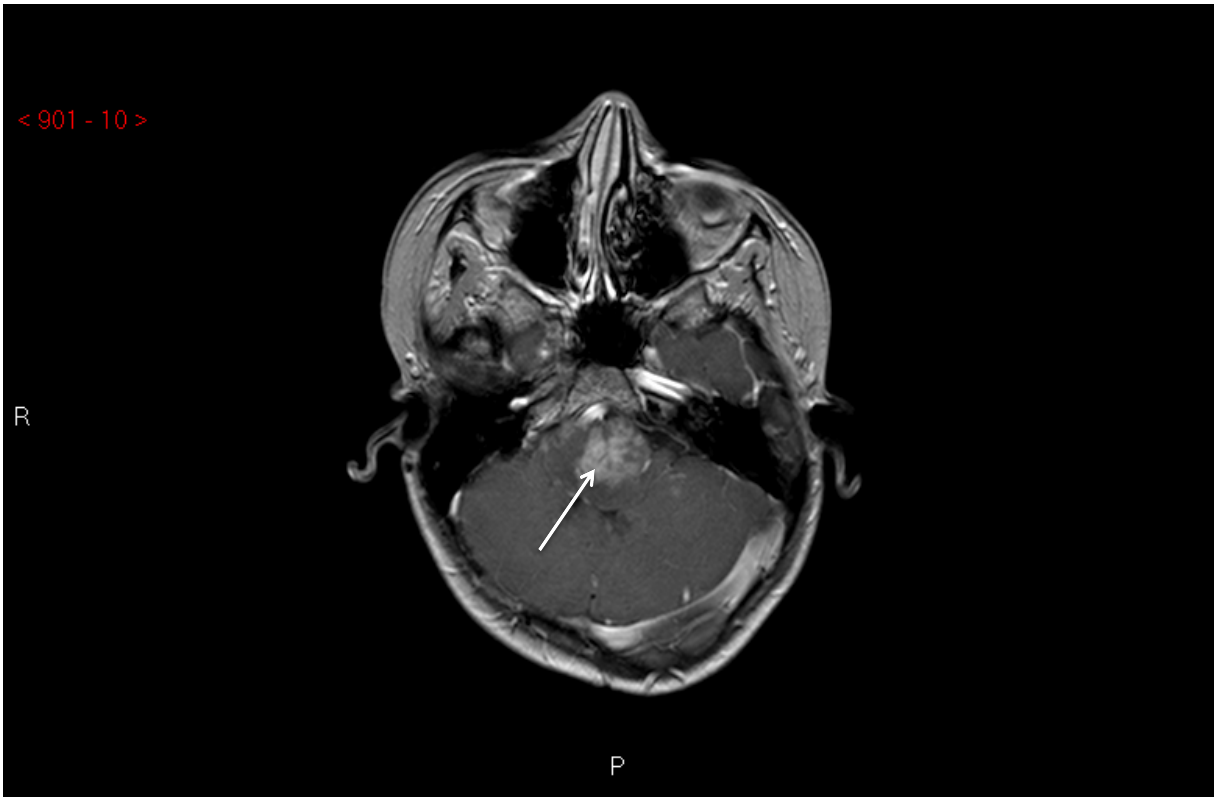
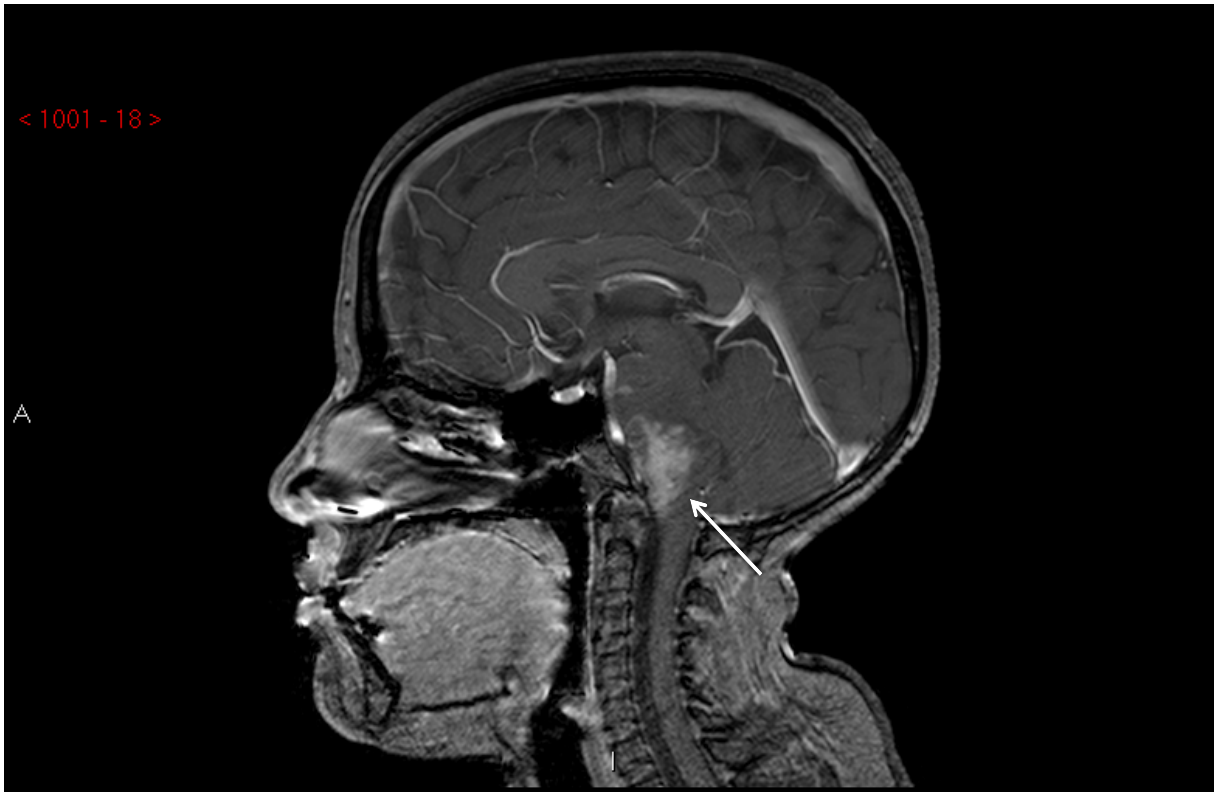


Figure 1.2 : Sagittal view (September 2010)



Patient 2 :

A 4-year-old girl presented in April 1997 with a 2-months-history of biparietal headaches and a disorder of equilibrium with a lightheaded walking and falls for 2 weeks. A few episodes of vomiting were reported as well. The physical examination showed a bilateral papillary edema with a left horizontal and vertical nystagmus. There were neither signs of strabismus nor meningism and the audition was normal. She conserved strenght of the four limbs. An MRI made end of April 1997 showed an obstructive hydrocephalus with a voluminous tumor in the posterior fossa, with heterogeneous contrast enhancement. A subtotal resection because of proximity to the brainstem was performed a few days after the craniospinal imaging and introduction of a ventricular drain. The pathology showed an anaplastic ependymoma of the posterior fossa and the IVth ventricle, OMS grade III. After surgery the patient presented left central facial paresis, a bilateral oculomotor paresis (specially abduction to the right) with a bilateral limitation of horizontal movements and a transient mutism as postoperative complications. Another postoperative complication was transient cortical post ischemic blindness due to the blood loss during surgery with rapid

recovery within a few days. Left facial paresis, vertical right sided nystagmus and cerebellar ataxia persisted but were less important than before. Postoperative CT-scan didn't show a tumor residue. One month later, the patient showed still slight central left facial paresis, discrete ataxia and horizontal limitation of ocular movements and a new slight right convergent strabismus , whereas she had recovered from mutism. Treatment was completed by local radiotherapy at a total dose of 54 Gy by isocentric technique at first. The region of the tumor including a safety margin (2cm) was treated by four oblique beams with a 1.8 Gy per fractionated sessions, 5 sessions per week for a total dose of 50.4 Gy, and a boost at the residual tumor made by two opposed lateral beams for a total dose of 54 Gy. Whereas oculomotor disturbances and cerebellar syndrome persisted, however improving, the child remained in complete remission of disease until April 2007. Follow-up was marked by a strabismus operation, learning and concentration difficulties needing a special schooling and hormone deficiencies which led to a growth hormone treatment started in 2004.

After 10 years of disease-free follow-up, in April 2007, the girl presented new neurological symptoms such as language disorder, new balance disorder with falls and headache. At clinical examination, she presented ataxia, dysarthria and pronounced left facial paresis. MRI showed a new pontine mass (Figure 2), predominant on the right side with peripheral contrast enhancement suggesting a glial tumor rather than a relapse of the first ependymoma. (1.5x6 mm) As the tumor was inoperable, and with regard to previous radiotherapy, it was decided to administer VP-16 and temozolomide without proceeding to a biopsy because of high risk of local complications. After initial improvement during four months, neurological symptoms worsened due to tumor progression on MRI with appearance of 2 new tumor nodules in the left frontal region and right internal capsule. (Figure 3.1, 3.2) As clinical symptoms increased with left hemiparesis, facial paresis of the left side marked with dysarthria, important balance disorder with frequent falls and aggressiveness, it was decided to perform a PET-CT confirming malignant activity in the several locations. Considering this unusual evolution, a stereotactic biopsy was performed. Pathological report of the biopsy noted the presence of malignant tumor with neuroglial components, criteria for PNET were partially fulfilled by the high clinical aggressiveness, the immunohistochemical constellation and cell proliferation extreme (Mib> 70%) Brain tissue was largely infiltrated by highly atypical tumor cell proliferation with multinucleated giant cells,

many images of pycnoses and mitoses, and some atypical mitoses. There was no active vascularisation in the tumor or visualized necrosis. The clinical context continued to worsen with a left hemisyndrome, a massive dysarthia with difficulty to swallow and weakness on the contralateral side. MRI confirmed a massive growth of the entire tumor disease, invading the cerebellar peduncles on both sides, medulla, midbrain and diencephalon greater right than the left. We could note an intraventricular fluid dissemination by appearance of a new nodule of the right frontal horn and a new rupture of the blood-brain barrier at known tumor infiltration next to the left frontal horn. After the stereotactic biopsy, mutism, aphasia, incontinence and difficulty in swallowing appeared as consequences of the tumor progression. Because of the poor prognosis, it was decided to accompany the child with palliative care. She passed away in November 2007.

Figure 2.1 : new pontine mass, predominant on the right side with peripheral contrast enhancement suggesting a glial tumor (April 2007)

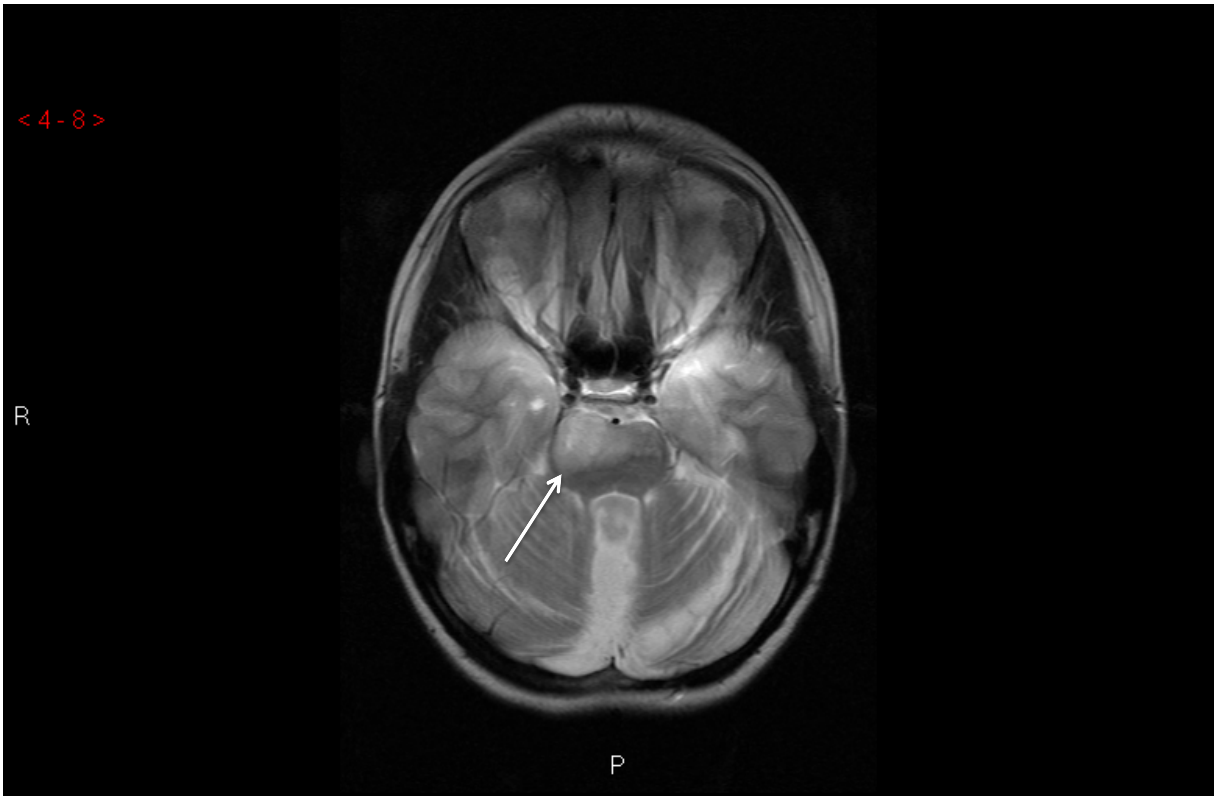


Figure 3.1 : new tumor nodules in the left frontal region (October 2007)

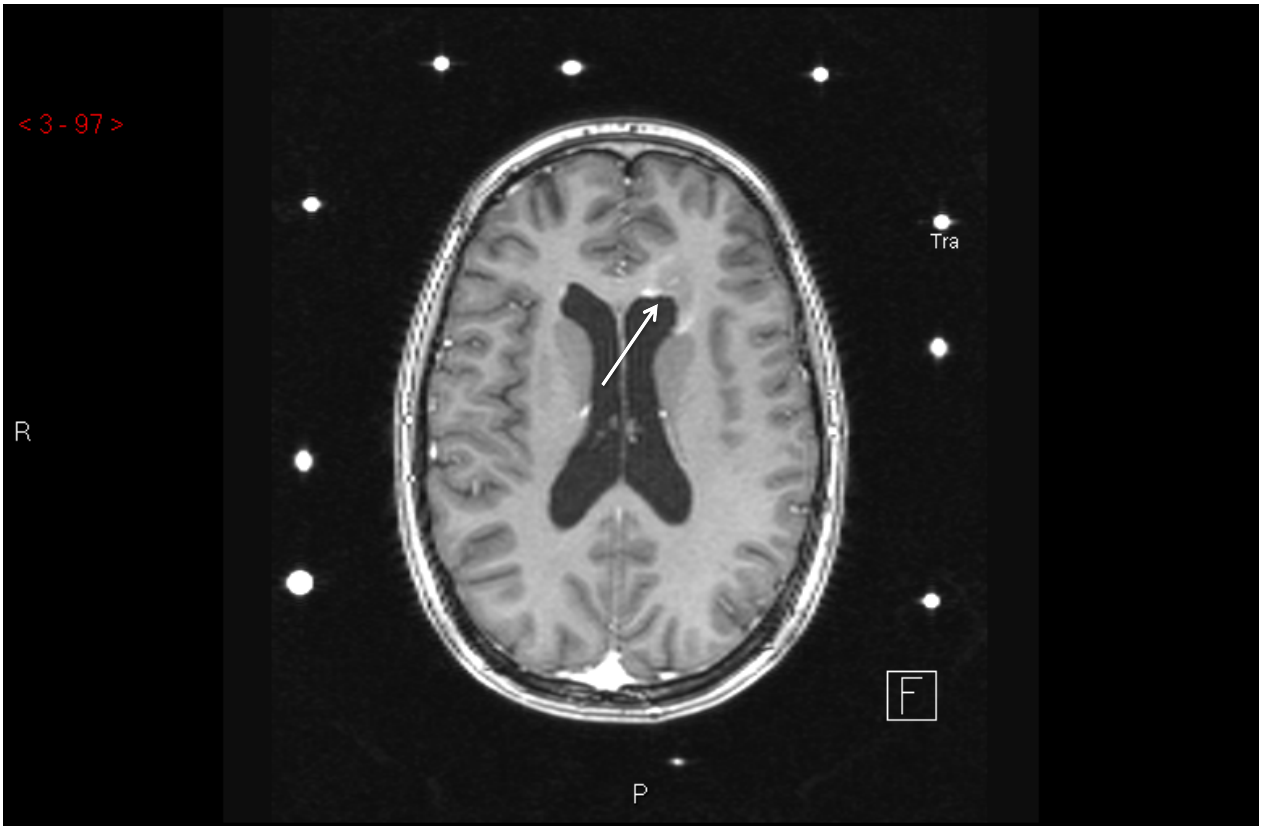
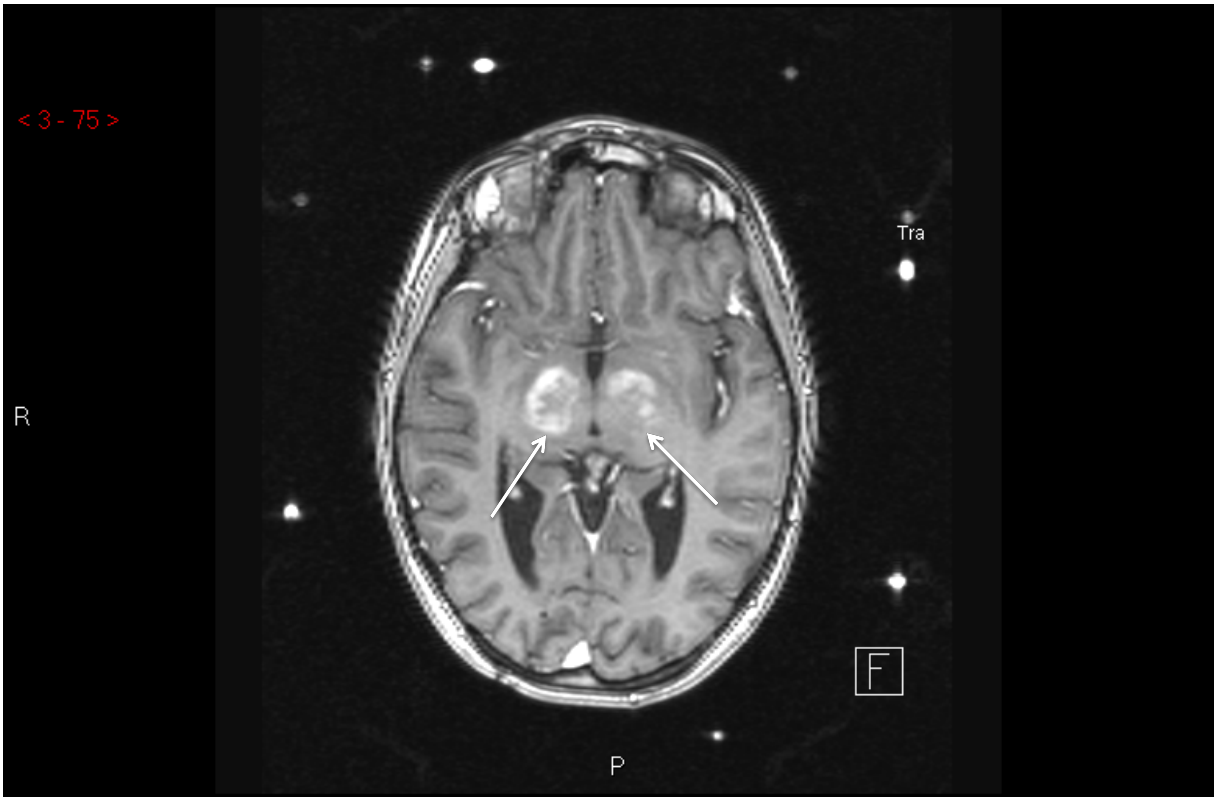


Figure 3.2 : new tumor nodules in the internal capsule (October 2007)



DISCUSSION

Our two patients were diagnosed for ependymoma of the posterior fossa in childhood, that were mainly treated with surgery and radiotherapy. The youngest patient benefited from chemotherapy to delayed radiotherapy. After a decade of remission, both developped a secondary malignancy, radiologically diagnosed as pontine glioma. . Whereas in the the first patient the tumor behaved as such, the second patient developped in addition to the pontine tumor other tumors that could be biopsied and showed features of a PNET.

Second cancer is one of the highest impacts on morbidity and mortality in children who had a neoplasia in the past. With higher cure rates, increasing cumulative incidence of second malignant neoplasia is observed with 3.2% at 20 years in 2001(9) and 9.3% 30-year cumulative incidence in 2007 (4). In the Nordic population-based case control study, the relative risk for patients to develop a second cancer was 3.6-fold compared to the general population (10) and 5-fold relative risk of second maligancies among survivors in British Columbia study(11). Furthermore CNS tumors suvivors are at highest risk of death compared to other childhood cancer with a cumulative mortality rate of 16.8% at 20 years.(12). In the CCSS, 0.05% of children with primary cancer presented a second malignancy. (N=14'358). Among the CNS tumors (N=1877), 0.036% presented a second cancer, 0.26% of whom were a second CNS tumors.(4) In the 5 Nordic Countries study, 0.011 % of survivors developed a second cancer. (N=25'120)(10). Meningiomas are the most frequent second neoplasms observed survivors of primary CNS neoplasms(13). We didn't find any case report in the literature that matched with our two patients. So these two cases are interesting by their unusual location of second neoplasia in the pons. Literature about second malignancies reported various clues as possible risk factors and we are reporting some elements that seem interesting to us.

Ependymomas develop from primitive glia. They are mostly located in the brain, typically in posterior fossa or in the fourth ventricle, but can also present as spinal cord tumors .(5) Their incidence of 0.23 per 100'000 person-years represent only 10% of CNS tumors in children. (6) Males and females are equally concerned by this neoplasia and the median age at diagnosis is 5 years. The World Health Organization (WHO) classification of CNS tumors divides ependymal tumors into four subtypes :

subependymoma (WHO grade I), myxopapillary ependymoma (WHO grade I), ependymoma (WHO grade II) and finally anaplastic ependymoma (WHO grade III).(7)

The initial treatment for children with ependymoma consists of surgery followed by adjuvant radiotherapy. Chemotherapy does not have an important place in the treatment of this cancer but may play a role in young children to delay the radiotherapy.(5) Ependymoma, high grade glioma and medulloblastoma correlate with worse survival, compared with astrocytomas and low grade glioma.(8) When in remission, CNS cancer survivors have a higher risk of long-term morbidity and late mortality compared with the general population, such as early death, organ dysfunction, impaired growth and development, decreased fertility, cognitive dysfunction or second malignancy, most of them correlated with the treatments(8)

Second malignancies are caused by different factors, such as genetic predisposition, chemotherapy and radiotherapy. Moreover they are related as well to the age of patient at time of diagnosis and the histology of the tumor.

The CCSS demonstrated a significant linear dose-response relationship between radiotherapy dose and development of second CNS cancer such as gliomas (OR=6.78) and meningiomas (OR=0.94). They estimated the dose of irradiation of each child and matched it with control subjects on age, sex, and time since original cancer diagnosis.(13) They identified that children who survived of CNS neoplasms who were cured with CNS-direct radiation >50 Gy had a cumulative incidence of a second CNS cancer of 7.1 % (95% CI=4.5% to 9.6%) at 25 years compared to 1.0% (95% CI=0% to 2.3%) among children who haven't been treated with radiation.(14) The relative risks for doses above 30 Gy were RR=20 for glioma and RR=50-100 for meningioma.(13) The 5 Nordic Countries study found an increased risk for children who received radiotherapy more than five years before the second cancer. There was a relative risk of 1.8 already from 1 Gy and increased up to 18.3 for doses above 30 Gy. In this study, the interval between the first and the second CNS cancer diagnose was 8.8 years. (15) It has to be underlined that patient 1 received a total dosis of 50.4 Gy et and patient 2 received 54 Gy.

The main period to develop SM after radiotherapy is the interval of 5-9 years from the diagnosis of the primary cancer (SMR :17.2, 95% CI :14.7-31.8)(8). The risk remains always higher than in the control population. Our two cases developed their second cancer 15 and 10 years after the primary diagnosis.

Among risk factors studied, no significant association between chemotherapy exposure and CNS second cancer was found(13,16). However, combined with radiotherapy, chemotherapy could potentially contribute. . According to Svahn-Tapper et al, the relative risk increased from 2.3 (95% CI 1.4-3.7) for radiotherapy only to 4.3 (95% CI 2.6-7.0) when radiotherapy was combined to chemotherapy(15). Although exposure to high doses of alkylating agents is associated with occurrence of second malignant neoplasia, this seems not to be the main factor for secondary CNS cancer.(4) . It is important to mention that it is very rare to cure CNS tumors with chemotherapy alone, without radiotherapy.

The role of histology as risk factor for secondary cancer in long-term survivors was studied by some investigators. They observed a statistically significant difference (P<.001) in mortality according to initial tumor histology, high-grade glioma (estimated probability of death at 10 year 32.6+-10.7) and ependymoma (14.4+-5.7) having the worse survival compared to other CNS tumors.(17) However, for the CCSS study and the 5 Nordic Countries Study, original CNS neoplasia diagnosis had no relation with the independant risk to develop a SMN when adjusted to the radiation dose. (10,13)

Other risk factors are age under 6 years at irradiation because of the time of greatest brain tissue growth. (4)(10) Gender was another risk factors according to Svahn-Tapper et al with significantly higher r risk of secondary cancer in female patients (RR =3.4, 95% CI 1.7-6.8) compared to male patients. (1.3, 95% CI 0.7-2.5)(15), which is difficult to explain.

The carcinogenic effect of ionizing radiotherapy is well known, but its effect on the induced neoplasm is more difficult to establish and to quantify. The major problem of the studies is the lack of a sufficiently large patient group and the heterogeneity in order to match the patients with the controls. Furthermore, the quantification of the dose of radiotherapy is often hard to establish as treatment details are not always available. Moreover it is not mentioned in the studies in which context the second malignancies were diagnosed, whether the patients presented symptoms or the discovery was made during a planned clinical control.

CONCLUSION

In the CCSS cohort, about 1.88 additional cancer have been diagnosed for each 1000 children by years of follow-up.(N =13'581)(9) Therefore, the second malignant neoplasia is a very rare phenomenon and that risk should not overshadow the great success in treating cancer of childhood. However, patients and health-care providers must be aware of the risk of SMNs and must have a longterm surveillance, even more if they are concerned by established risk factors, such as radiotherapy.

During the past 35 years, pediatric cancer treatment protocols have been changed to a better balance between toxicity and efficacy with the idea to minimize the use of radiation in children, as long as the treatment results are not compromised. Better technique will always emerge due to the technologic research to treat children with less negative effects on healthy tissues, as the available imaging techniques of radiotherapy for a precise definition of the target volume.

These two patients were followed up annually to ensure their remission. Nevertheless both patients developed symptoms of the second cancer a few months after the annual monitoring that was considered as normal. This issue highlights the complexity of monitoring cancer survivors and rises the question of the best way to follow long-term survivors.

REFERENCES

1. Linabery AM, Ross JA. Trends in childhood cancer incidence in the U.S. (1992-2004). Cancer. 2008 janv 15;112(2):416–32.
2. Central Brain Tumor Registry of the United States statistical report, 2000-2004,CBTRUS - Reports and Tables [Internet]. [cité 2011 sept 22]. Available de: http://www.cbtrus.org/reports/reports.html
3. Ries LAG, Melbert D, Krapcho M, et al. SEER cancer statistics review [Internet]. National Cancer Institute. 1975. Available de: http://seer.cancer.gov/csr/1975_2004/
4. Meadows AT, Friedman DL, Neglia JP, Mertens AC, Donaldson SS, Stovall M, et al. Second neoplasms in survivors of childhood cancer: findings from the Childhood Cancer Survivor Study cohort. J. Clin. Oncol. 2009 mai 10;27(14):2356–62.
5. Grill J, Pascal C, Chantal K. Childhood ependymoma: a systematic review of treatment options and strategies. Paediatr Drugs. 2003;5(8):533–43.
6. Allen JC, Siffert J, Hukin J. Clinical manifestations of childhood ependymoma: a multitude of syndromes. Pediatr Neurosurg. 1998 janv;28(1):49–55.
7. Louis DN, Ohgaki H, Wiestler OD, Cavenee WK, Burger PC, Jouvet A, et al. The 2007 WHO classification of tumours of the central nervous system. Acta Neuropathol. 2007 août;114(2):97–109.
8. Armstrong GT. Long-term survivors of childhood central nervous system malignancies: the experience of the Childhood Cancer Survivor Study. Eur. J. Paediatr. Neurol. 2010 juill;14(4):298–303.
9. Neglia JP, Friedman DL, Yasui Y, Mertens AC, Hammond S, Stovall M, et al. Second malignant neoplasms in five-year survivors of childhood cancer: childhood cancer survivor study. J. Natl. Cancer Inst. 2001 avr 18;93(8):618–29.
10. Garwicz S, Anderson H, Olsen JH, Døllner H, Hertz H, Jonmundsson G, et al. Second malignant neoplasms after cancer in childhood and adolescence: a population-based case-control study in the 5 Nordic countries. The Nordic Society for Pediatric Hematology and Oncology. The Association of the Nordic Cancer Registries. Int. J. Cancer. 2000 nov 15;88(4):672–8.
11. MacArthur AC, Spinelli JJ, Rogers PC, Goddard KJ, Phillips N, McBride ML. Risk of a second malignant neoplasm among 5-year survivors of cancer in childhood and adolescence in British Columbia, Canada. Pediatr Blood Cancer. 2007 avr;48(4):453–9.
12. Mertens AC, Yasui Y, Neglia JP, Potter JD, Nesbit ME Jr, Ruccione K, et al. Late mortality experience in five-year survivors of childhood and adolescent cancer: the Childhood Cancer Survivor Study. J. Clin. Oncol. 2001 juill 1;19(13):3163–72.
13. Neglia JP, Robison LL, Stovall M, Liu Y, Packer RJ, Hammond S, et al. New Primary Neoplasms of the Central Nervous System in Survivors of Childhood Cancer: a Report From the Childhood Cancer Survivor Study. Journal of the National Cancer Institute. 2006 nov 1;98(21):1528 –1537.
14. Armstrong GT, Liu Q, Yasui Y, et al. Long-term outcommes among adult survivors of childhood central nervous system malignancies in the Childhood Cancer Survivor Study. J Natl Cancer Inst. 2009;946–58.
15. Svahn-Tapper G, Garwicz S, Anderson H, Shamsaldin A, De Vathaire F, Olsen JH, et al. Radiation dose and relapse are predictors for development of second malignant solid tumors after cancer in childhood and adolescence: a population-based case-control study in the five Nordic countries. Acta Oncol. 2006;45(4):438–48.

16. Little MP, de Vathaire F, Shamsaldin A, Oberlin O, Campbell S, Grimaud E, et al. Risks of brain tumour following treatment for cancer in childhood: modification by genetic factors, radiotherapy and chemotherapy. Int. J. Cancer. 1998 oct 29;78(3):269–75.
17. Morris EB, Gajjar A, Okuma JO, Yasui Y, Wallace D, Kun LE, et al. Survival and late mortality in long-term survivors of pediatric CNS tumors. J. Clin. Oncol. 2007 avr 20;25(12):1532–8.