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CASE REPORT

Atypical teratoid/rhabdoid tumor in an infant conceived by in vitro fertilization

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Abstract
Background Atypical teratoid/rhabdoid tumor (ATsRT) is a rare tumor and extremely aggressive embryonal neoplasm of the central nervous system. Brain tumors in infant are suggestive of some oncogenic prenatal factors.
Case presentation We report on a case of ATRT in a 4-month-old infant conceived by in vitro fertilization (IVF). Some previous reports have raised a question about the possible relation between IVF and childhood cancer, particularly embryonal tumors.
Conclusion Report of such cases may provide some evidence to identify if there is a real association between congenital tumors and IVF.

Keywords Atypical teratoid/rhabdoid tumor · In vitro fertilization · Infant · Brain tumors

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Background

Utilization of assisted reproductive technologies which include in vitro fertilization (IVF) has rapidly become an established method in the treatment of couples with infertility problems. Short-term outcomes of these techniques including complicated multiple pregnancies, preterm birth, small babies for gestational age, and a slightly higher rate of congenital malformations such as neural tube defect have been well documented [10, 29]. Besides, some authors have speculated a possible relation between IVF and childhood cancer, especially embryonal tumors [15, 30, 33]. Whether these tumors are causally related to IVF or not still remain unknown. Brain tumors in infants consist of a variety of histological types, nevertheless, one tumor type relatively specific to the infant population is the atypical teratoid/rhabdoid tumor (ATRT), which is rare and an extremely aggressive embryonal neoplasm of early childhood. Most patients are younger than 2 years [24, 26, 28]. We report here a case of ATRT of the central nervous system in the setting of IVF to highlight a possible increased risk of tumorigenesis in the setting of IVF.

Case report

A 4-month-old girl, co-twin of an IVF pregnancy, born at full-term with a birth weight of 2,300 g was referred to the emergency department because of vomiting for 15 days, weight loss, downward gaze, and nystagmus. On the initial physical examination, lethargy and irritability, macrocephaly (head circumference >90th percentile) with bulging of the anterior fontanel, and a downward gaze ("setting-sun" sign) was noticed. Neurological examination demonstrated bilateral

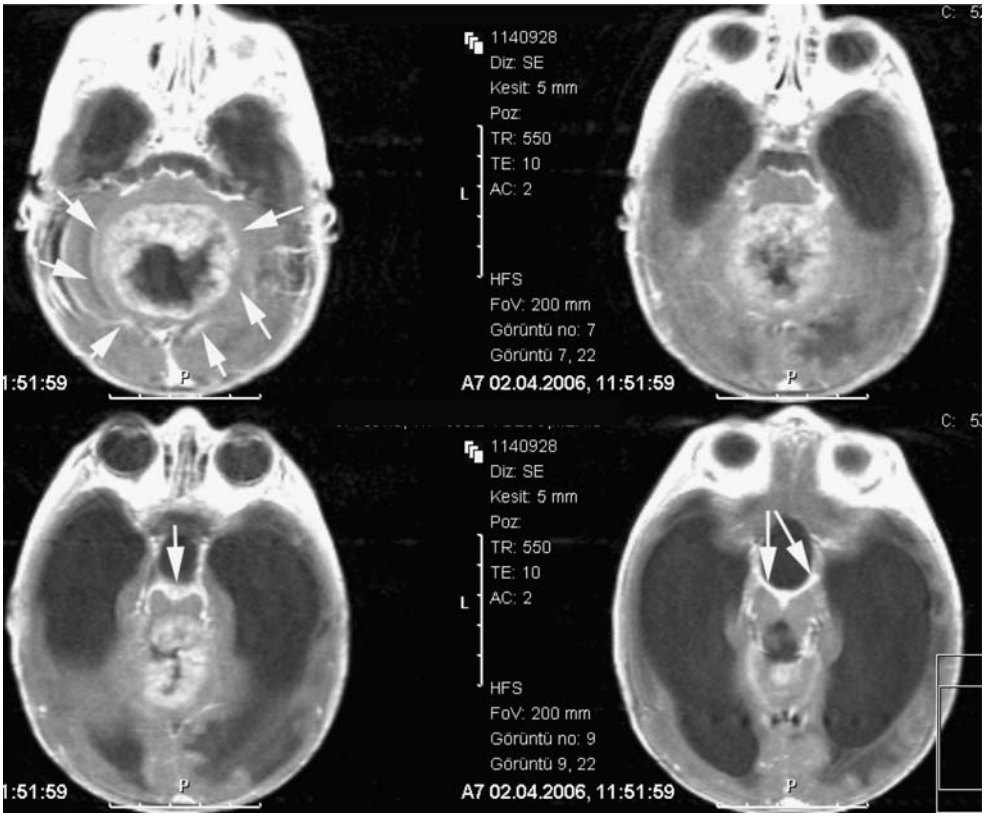

Fig. 1 After contrast injection axial T1-weighted MRI **a**, **b** shows large tumor within and expanding fourth ventricle with prominent cystic/necrotic components. **c**, **d** The tumor invading the brain stem and level of prepontin systern shows leptomeningeal metastasis

papiloedema. A cranial ultrasonography and computed tomography (CT) depicted an intracranial mass of the posterior fossa and hydrocephalus. Subsequent MRI demonstrated a large mass occupying the fourth ventricle and compressing the brain stem with leptomeningeal metastasis and hydrocephalus (Fig. 1). The presumptive diagnosis was medulloblastoma. She was put on corticosteroids. The patient was operated on by median suboccipal approach on prone position. On operation, firstly external ventricular drainage system was applied. Then, tumor was tried for excision. Profuse bleeding from the lesion did not allow us to perform total removal. She did not tolerate surgery and died during the surgical intervention. The resected tumor was sent for histological examination. Histopathological examination revealed a diagnosis of ATRT (Fig. 2).

Discussion

The relationship between ATRT and cancer risk has already been well highlighted in the first half of this decade. There are several studies reporting the incidence of childhood cancer in cohorts of children conceived by IVF and/or following other ATRT [1–3, 7, 14, 17]. None of these studies reported an increase in the incidence of cancers in children born after ATRT. But the authors of some concede that their cohorts are not large enough to detect an increase incidence. Many of the studies done in the area have been retrospective and thus subject to selection and/or reporting bias. They are subject to a short follow-up and lack adequate and matched control groups. In a study of 16,000 children born after IVF in Sweden, no significantly increased risk of childhood tumors was seen (29 cases againts the expected 21), but there was an apparent excess

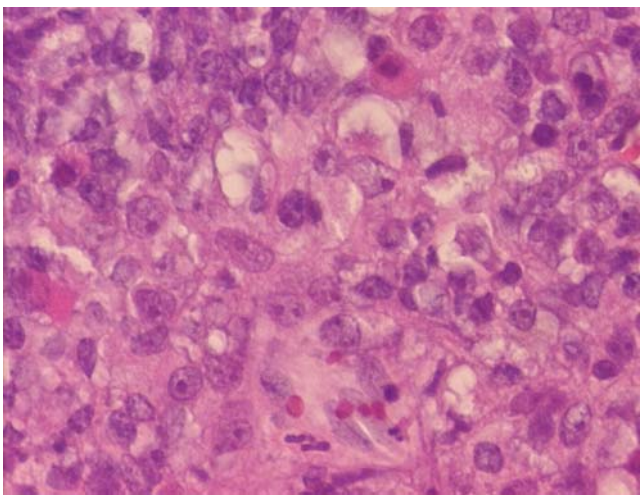

Fig. 2 Histology of the tumor. Hypercellular with primitive-appearing, neoplastic cells admixed with intermediate-sized, rhabdoid cells with prominent nucleoli in varying proportions. Hematoxylen-eosin staining, ×400 original magnification

of children with histiocytosis (five cases againts the expected 0.9). Eight (eight cases againts the expected 4.2) of these 29 children had central nervous system (CNS) tumors including four pilocytic astrocytomas, two medulloblastomas, one brainstem tumor, and one spinal ependymoma [12]. Raimondi et al. [25] did a meta-analysis on 11 studies and concluded that the data on ATRT and cancer is still limited after evaluating the results of their meta-analysis. Development of malignancy in children who were born after ovulation induction treatment and/or IVF has been described either as sporadic case reports or case-control studies. These reports have highlighted a possible relation between IVF and specific subsets of tumors including leukemia, lymphoma, neuroblastoma, hepatoblastoma, retinoblastoma, and clear cell sarcoma in addition to CNS tumors [15, 16, 19–21, 30, 33]. Five case reports have been published so far on development of congenital brain tumor in children who were born by assisted reproductive technologies. The definition of congenital is at best diagnosis within 2 months of birth [4, 11, 32]. Morof et al. [23] report of a congenital glioblastoma multiforme in the setting of IVF. Rizk et al. [27] described an infant who developed a CNS gliosarcoma. Cohen et al. [5] reported prenatal sonographic diagnosis of a lateral ventricle choroid plexus papilloma in an IVF-induced pregnancy. Another reported case was a neonate with congenital anaplastic astrocytoma [6]. Recently, Kim et al. [13] described a case of ATRT of the brain and acute myeloid leukemia (AML) as a secondary malignancy in a 3-year-old boy conceived via IVF. In addition, Moore et al. [22] wrote a comment in 2007 and shared a personal unpublished observation of a large fetal intracranial teratoma discovered at an autopsy of a 33-week-old male fetus whose mother was treated with ovulation-stimulating drugs.

Brain tumors in infants and children differ in terms of biological behavior, anatomic distribution, prognosis, and outcomes from those in later childhood and adults. The role of exposures to exogenous agents or genetic predisposition in tumorogenesis are limited in infant cases and established data suggest a more rapidly evolving malignant transformation that occurs either prenatally or perinatally [9].

Various infertility treatments including ovulation induction may have different potential effects on gametes and embryos [14]. It is possible that the drugs and procedures involved in assisted reproductive technologies may lead to epigenetical changes of DNA and alter imprinted gene expression, potentially resulting in the development of cancer in the offspring. Alternatively, infertile couples treated with these technologies may already have an increased number of epigenetic defects in their gametes [18]. In addition, a high frequency of cytogenetic abnormalities and errors in cell-cycle regulation are reported in the oocytes generated by IVF or intracytoplasmic sperm injection. Some of these aberrations, especially in regulatory genes, may lead to the development of cancer in some children born by IVF [8, 31]. Since our patient has a twin without a malignancy, further discussion would be provided on the incidence of congenital malignancies in natural conception twins and IVF twins. But we have not found any data in the English literature regarding this issue. If the co-twin of another had been affected, it was strongly suggest that IVF is a accountable factor.

In conclusion, although the available data showed no evidence for an overall increased risk of cancer in the offspring conceived by assisted reproduction, there may be an increased risk for some specific tumor subtypes such as embryonal brain tumors. Accumulation of data on such cases may help to clarify if there is an association between these tumors and assisted reproductive technologies. Alternatively, the risk of genetic abnormality among infertile couples may predispose their offspring to develop malignant embryonal tumors. Molecular studies in both parents and the child, as well as in these embryonal tumors may provide important clues to this speculation.

References

1. Bergh T, Ericson A, Hillensjo T, Nygren KG, Wennerholm UB (1999) Deliveries and children born after in-vitro fertilisation in Sweden 1982–95: a retrospective cohort study. Lancet 354:1578–1585
2. Brinton LA, Kruger Kjaer S, Thomsen BL, Sharif HF, Graubard BI, Olsen JH, Bock JE (2004) Childhood tumor risk after treatment with ovulationstimulating drugs. Fertil Steril 81:1083–1091
3. Bruinsma F, Venn A, Lancaster P, Speirs A, Healy D (2000) Incidence of cancer in children born after in vitro fertilization. Hum Reprod 15:604–607
4. Buetow PC, Smirniotopoulos JG, Done S (1990) Congenital brain tumors: a review of 45 cases. AJR Am J Roentgenol 155:587–593
5. Cohen ZR, Achiron R, Feldman Z (2002) Prenatal sonographic diagnosis of lateral ventricle choroid plexus papilloma in an in vitro fertilization-induced pregnancy. Pediatr Neurosurg 37:267–270
6. Das A, Simmons C, Danielpour M (2005) A congenital brain tumor associated with assisted in vitro fertilization. J Neurosurg 103:451–453
7. Doyle P, Bunch KJ, Beral V, Draper GJ (1998) Cancer incidence in children conceived with assisted reproduction technology. Lancet 352:452–453
8. Edirisinghe W, Murch A, Junk S, Yovich J (1997) Cytogenetic abnormalities of unfertilized oocytes generated from in-vitro fertilization and intracytoplasmic sperm injection: a double-blind study. Hum Reprod 12:2784–2791
9. Giuffre R (1989) Biological aspects of brain tumors in infancy and childhood. Childs Nerv Syst 5:55–59
10. Hansen M, Bower C, Milne E, de Klerk N, Kurinczuk JJ (2005) Assisted reproductive technologies and the risk of birth defects-a systematic review. Hum Reprod 20:328–338
11. Jellinger K, Sunder-Plassmann M (1973) Connatal intracranial tumours. Neuropadiatrie 4:46–63
12. Kallen B, Finnstrom O, Nygren KG, Olausson PO (2005) In vitro fertilization in Sweden: child morbidity including cancer risk. Fertil Steril 84:605–610

13. Kim YD, Kim KJ, Hy L (2008) Secondary leukemia in a child conceived using in vitro fertilization. Pediatr Int 50:831–832
14. Klip H, Burger CW, de Kraker J, van Leeuwen FE (2001) Risk of cancer in the offspring of women who underwent ovarian stimulation for IVF. Hum Reprod 16:2451–2458
15. Kobayashi N, Matsui I, Tanimura M, Nagahara N, Akatsuka J, Hirayama T, Sato K (1991) Childhood neuroectodermal tumours and malignant lymphoma after maternal ovulation induction. Lancet 338:955
16. Kramer S, Ward E, Meadows AT, Malone KE (1987) Medical and drug risk factors associated with neuroblastoma: a case control study. J Natl Cancer Inst 78:797–804
17. Lerner-Geva L, Toren A, Chetrit A, Moden B, Mandel M, Rechavi G, Dor J (2000) The risk for cancer among children of women who underwent in vitro fertilization. Cancer 88:2845–2847
18. Lightfoot T, Bunch K, Ansell P, Murphy M (2005) Ovulation induction, assisted conception and childhood cancer. Eur J Cancer 41:715–724
19. Mandel M, Toren A, Rechavi G, Dor J, Ben-Bassat I, Neumann Y (1994) Hormonal treatment in pregnancy: a possible risk factor for neuroblastoma. Med Pediatr Oncol 23:133–135
20. Melamed I, Bujanover Y, Hammer J, Spirer Z (1982) Hepatoblastoma in an infant born to a mother after hormonal treatment for sterility. N Engl J Med 307:820
21. Michalek AM, Buck GM, Nasca PC, Freedman AN, Baptiste MS, Mahoney MC (1996) Gravid health status, medication use, and risk of neuroblastoma. Am J Epidemiol 143:996–1001
22. Moore SW, Sasco AJ, Dechelotte P, Satgé D (2007) In vitro fertilization and brain tumors. J Neurosurg 106:418
23. Morof DF, Levine D, Stringer KF, Grable I, Folkerth R (2001) Congenital glioblastoma multiforme: prenatal diagnosis on the basis of sonography and magnetic resonance imaging. J Ultrasund Med 20:1375–1396
24. Plon S, Malkin D (2006) Childhood cancer and heredity. In: Pizzo P, Poplack D (eds) Principles and practice of pediatric oncology, 5th edn. Lippincott Williams & Wilkins, Philadelphia, p 23
25. Raimondi S, Pedotti P, Taioli E (2005) Meta-analysis of cancer incidance in children born after asisted reproductive tecnologies. Br J Cancer 93:1053–1056
26. Raisanen J, Hatanpaa KJ, Mickey BE, White CL 3rd (2004) Atypical teratoid/rhabdoid tumor: cytology and differential diagnosis in adults. Diagn Cytopathol 31:60–63
27. Rizk T, Nabbout R, Koussa S, Akatcherian C (2000) Congenital brain tumor in a neonate conceived by in vitro fertilization. Childs Nerv Syst 16:501–502
28. Rorke LB, Packer RJ, Biegel JA (1996) Central nervous system atypical teratoid/rhabdoid tumors of infancy and childhood: definition of an entity. J Neurosurg 85:56–65
29. Schieve LA, Rasmussen SA, Buck GM, Schendel DE, Reynolds MA, Wright VC (2004) Are children born after assisted reproductive technology at increased risk for adverse health outcomes? Obstet Gynecol 103:1154–1163
30. Toren A, Sharon N, Mandel M, Neumann Y, Kenet G, Kaplinsky C, Dor J, Rechavi G (1995) Two embryonal cancers after in vitro fertilization. Cancer 76:2372–2374
31. Voullaire L, Wilton L, McBain J, Callaghan T, Williamson R (2002) Chromosome abnormalities identified by comparative genomic hybridization in embryos from women with repeated implantation failure. Mol Hum Reprod 8:1035–1041
32. Wakai S, Arai T, Nagai M (1984) Congenital brain tumors. Surg Neurol 21:597–609
33. White L, Giri N, Vowels MR, Lancaster PA (1990) Neuroectodermal tumours in children born after assisted conception. Lancet 336:1577