

A synchronous occurrence of bifocal intracranial germinoma and bilateral testicular epidermoid cyst in an adolescent patient with Klinefelter's syndrome

Derya Özyörük¹, Ayça Kocayozgat¹, İnci Yaman-Bajin¹, Faik Çetindağ², Ayşe Selcen Oğuz-Erdoğan³, Altan Güneş⁴

Divisions of ¹Pediatric Oncology, ³Pathology and ⁴Radiology, Ankara Children's Hematology and Oncology Education and Research Hospital; ²Division of Radiation Oncology, Abdurrahman Yurtaslan Oncology Education and Research Hospital, Ankara, Turkey. E-mail: dozyoruk@yahoo.com

Received: 9th January 2019, Revised: 18th February 2019, Accepted: 4th March 2019

SUMMARY: Özyörük D, Kocayozgat A, Yaman-Bajin İ, Çetindağ F, Oğuz-Erdoğan AS, Güneş A. A synchronous occurrence of bifocal intracranial germinoma and bilateral testicular epidermoid cyst in an adolescent patient with Klinefelter's syndrome. Turk J Pediatr 2019; 61: 456-459.

Klinefelter syndrome (KS) is characterized by an additional X chromosome in males leading to a karyotype of 47,XXY. It is associated with an increased risk of certain malignancies, including leukemia, breast cancer and extragonadal germ cell tumor such as mediastinal germ cell tumors and rarely intracranial germ cell tumors. It is possible that the increased risk of developing certain cancers can be attributed to a direct effect of the chromosomal abnormality or the combined action of the abnormal chromosomes and hormonal imbalances. Here we describe a synchronous occurrence of bifocal intracranial germinoma and bilateral testicular epidermoid cyst in an adolescent patient with Klinefelter's syndrome. The synchronous occurrence of the dual tumors in this patient with Klinefelter's syndrome might be resulted from the migration defect during embryogenesis due to underlying genetic disease or it is a coincidental condition, yet there has been no case reported in the literature, so far.

Key words: Klinefelter's syndrome, germinoma, bilateral testicular epidermoid cyst.

In children, central nervous system (CNS) germ cell tumors (GCTs) represent approximately 3% of primary pediatric brain tumors and encompass a wide pathologic spectrum. They are most commonly located in the pineal and suprasellar regions of the brain and can be divided into major groups including germinomas and nongerminomatous GCTs (NGGCTs).¹⁻³ Epidermoid cyst of the testis is very rare in childhood and account for approximately 1% of all testicular tumors. According to a widely accepted theory, it represents monodermal or unilateral development of a teratoma.^{4,5} Shah et al.⁴ suggested that the epidermoid cyst is a subtype in the category of germ cell tumors of the testis. Here we describe a synchronous occurrence of bifocal intracranial germinoma and bilateral

testicular epidermoid cyst in an adolescent patient with Klinefelter's syndrome.

Case Report

A 17-year-old boy was admitted to our clinic after the resection of a pineal mass and diagnosed with germinoma. On his past history, he had febrile convulsion at 2 years of age. The family history was unremarkable except his grandfather who had been diagnosed with colorectal cancer and prostate cancer. The physical examination revealed atypical face, low-set ears, longer arms and legs, right scrotal mass with diameters of 1.5x1.5 cm. Laboratory tests were within normal limits. The serum and cerebrospinal fluid alpha-fetoprotein (AFP) and human

chorionic gonadotropin beta-subunit levels (β -hCG) were also within normal limits. The plasma luteinizing hormone and follicle-stimulating hormone levels were 11.5 mIU/mL and 8.8 mIU/mL, respectively. The plasma testosterone was low (1.93 ng/mL). The levels of other anterior pituitary hormones were normal. The visual field test was normal. The pre-operative magnetic resonance imaging (MRI) of the brain showed a mass in the pineal region with 29x25 mm diameters and thickened pituitary stalk measuring 7x6 mm with nodular enhancement together with significant post-contrast enhancement in tuber cinerium associated with Rathke cleft cyst (Fig. 1 A). After three weeks of near total excision of pineal mass, post-operative MRI showed no residue in pineal region but other lesions were remained the same (Fig. 1,B). The spinal MRI showed no metastases. The cerebrospinal fluid (CSF) cytology was found normal. The paraffin blocks were re-evaluated and histopathologic

investigation revealed pure germinoma (Fig. 2 A,B). A computed tomography (CT) scan of the chest and abdomen were found to be normal. An ultrasound examination of scrotum demonstrated bilateral heterogeneous avascular testicular masses. The right testicular mass measured as 1.6 cm \times 1.1 cm and demonstrated a somewhat concentric, lamellated appearance with alternate hypoechoic and echogenic layers. The left testicular mass was hypodense and measured 1.1cm in diameter. MRI of bilateral testicular lesions showed nodular pattern with low-signal intensity on the T1-weighted image and of high-signal intensity on the T2-weighted image (Fig. 1C). Chromosome analysis revealed a 47 XXY karyotype, and non-mosaic Klinefelter's syndrome was diagnosed. Semen analysis showed azoospermia. Testis-sparing surgery with enucleation of the tumor was performed to preserve fertility and avoid testosterone deficiency, with concomitant

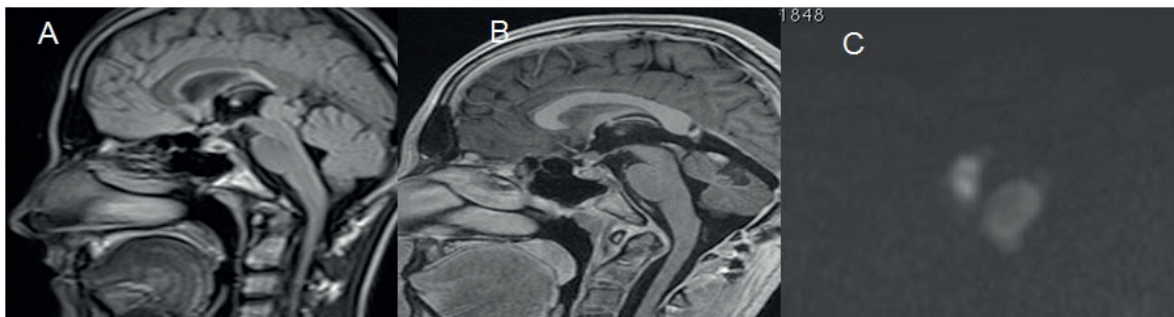


Fig. 1. **A.** The pre operative magnetic resonance imaging(MRI) of brain showed pineal region mass in 29x25 mm diameters and thickened pituitary stalk measuring 7x6 mm with nodular enhancement together with significant post-contrast enhancement in tuber cinerium associated with Rathke cleft cyst. **B.** The post operative MRI of brain showed no residue in pineal region but the other suprasellar lesion was remained the same. **C.** MRI of bilateral testicular lesions showed nodular lesions of low-signal intensity on the T1-weighted image and of high-signal intensity on the T2-weighted image.

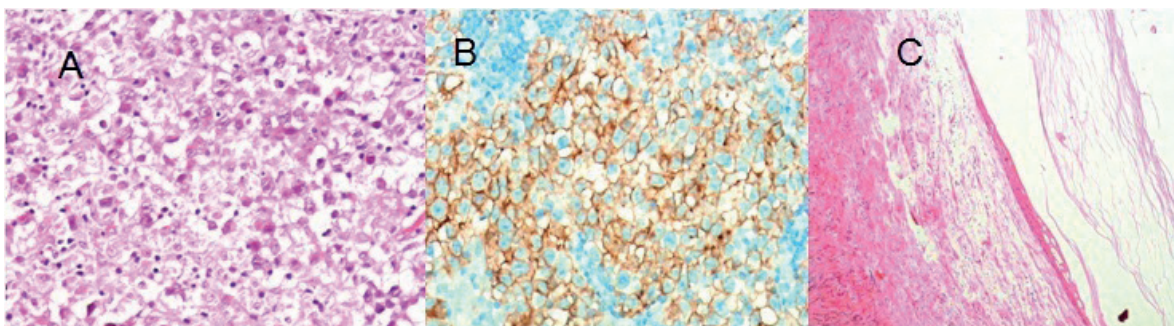


Fig. 2. **A.** Hematoxylin and eosin stain of tissue (70 \times magnification) obtained from a pineal tumor of a patient presenting with synchronous bifocal masses, which displays a germinoma **B.** Immunoperoxidase stain for CD 117 and PLAP reveals the positive staining of cells in the germinoma **C.** The histological examination revealed an epidermoid cyst of the bilateral testis.

use of intraoperative frozen section histologic analysis, to rule out occult malignancy within the tumor. Also, multiple biopsies were performed to rule out the case of intratubular germ cell neoplasia (ITGCN) presence. The histological examination revealed an epidermoid cyst of the bilateral testis (Fig. 2C). The patient with Klinefelter's syndrome was diagnosed with bifocal intracranial germinoma together with bilateral testicular epidermoid cyst. According to modified Chang staging system, the patient was staged as T1M0. He received 4 cycles of carboplatine and etoposide at 3-week intervals. Each cycle of chemotherapy consisted of carboplatin 300mg/m² on days 1 and 2 along with etoposide 150mg/m² on days 1,2 and 3. After 3-week of chemotherapy, the whole ventricular system with a 0,7-1 cm margin received 23,4 Gy in 13 fractions of 1,8 Gy followed by sequential boost to the primary tumor with a 1,5 cm margin of 8 Gy in 4 fractions of 2Gy, for a total dose of 31,4 Gy using intensity-modulated radiation therapy (IMRT) beam.^{2,6} He has been following up on remission for 6 months. Informed consent was received from the family.

Discussion

It is suggested that the patients presenting with synchronous bifocal intracranial tumors (masses in the pineal and neurohypophyseal region), detectable β -hCG levels (5-100 mIU/mL) and normal AFP levels (\leq 10 ng/mL) are usually diagnosed with pure germinoma without any pathologic confirmation.¹⁻⁵ On the other hand, Aizer et al.¹ suggested that clinicians should strongly consider a biopsy in patients presenting with bifocal masses and normal or modestly elevated biomarkers, because misclassification of such cases as germinomas could result in under treatment and a possible increased risk for recurrence according to their study. Our case had been operated when he referred to our pediatric oncology clinic and the histopathologic investigation of resected pineal mass revealed pure germinoma.

Although, craniospinal radiotherapy has traditionally been considered the gold standard treatment for intracranial germinoma, its late neurologic detrimental effects led to

physicians omitting spinal irradiation and reducing the radiation field as much as possible in limited disease.⁷ In recent years, it has been reported that patients with localized intracranial germinoma treated with four cycles of carboplatin and etoposide noted an excellent response rate of 95% with 100% OS at 3 years following reduced radiotherapy.³ Similar to that, our patient has been treated with the same chemotherapy followed by whole ventricular and local boost irradiation.

Klinefelter syndrome is a common genetic disorder characterized by an additional X chromosome in males leading to a karyotype of 47,XXY. The clinical syndrome was first described nearly 75 years ago in several males with small testes, tall stature, gynecomastia, and azoospermia.⁸⁻¹⁰ Klinefelter's syndrome is associated with an increased risk of certain malignancies, including leukemia, breast cancer and extragonadal germ cell tumor such as mediastinal germ cell tumors and rarely intracranial germ cell tumors. It has been suggested that stimulation of gonadotropin and estrogen sensitive tissues might predispose patients with Klinefelter syndrome to the development of malignancies.¹¹⁻¹⁴

The first case of Klinefelter's syndrome associated with intracranial germ cell tumor with the high plasma AFP and β -hCG concentrations of patient were 868 ng/ml and 68.6 IU/ml respectively was reported in 1987. He died because of talamic bleeding after radiotherapy.¹² Prall et al.¹³ reported a case of intracranial mixed malignant germ cell tumor (GCT) together with Klinefelter syndrome in 1995. According to their report, their case represents the sixth reported case of intracranial GCT with Klinefelter syndrome but the first to be histologically confirmed to have mixed malignant germ cell elements in English literature. Therefore, they strongly emphasized the need for a histopathological diagnosis prior to initiation of therapy. In addition, Ahagon et al.¹⁵ reported a Klinefelter syndrome associated with suprasellar germinoma case which is scarcely found in the literature. So far, only one case of bilateral epidermoid testicular cyst associated with Klinefelter's syndrome was reported.¹⁶ The treatment of testicular epidermoid cysts has varied. The preferable treatment, whether

radical orchiectomy or testis-sparing surgery, remains controversial. Although, in terms of psychological implications and preservation of fertility, testis-sparing surgery is desirable.^{4,5,17}

It is well known that the primordial germ cells appear in the yolk sac wall in the third gestational week and migrate via the dorsal mesentery of the hindgut into the genital ridge at the 6th gestational week. If primordial germ cells are disturbed and some cells stray into other places, extragonadal GCT develops later in retroperitoneum, mediastinum or diencephalons, during the migration. The dual occurrence of 2 primary germ cell tumors in one patient result from a mutation in the germ cell line or oncogenic factors simultaneously affect the gonadal and the extragonadal germ cell.¹⁸ Unfortunately, we could not explained if the synchronous occurrence of a bifocal secretory intracranial germinoma and bilateral testicular epidermoid cyst in our patient with Klinefelter's syndrome was resulted from the migration defect during embryogenesis due to the underlying genetic disease or only a coincidental condition.

In conclusion, the synchronous occurrence of the dual tumors in this patient with Klinefelter's syndrome might be resulted from the migration defect during embryogenesis due to the underlying genetic disease or maybe a coincidental condition, yet there has been no case reported in the literature, so far.

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