

ANIRIDIA, GONADOBLASTOMA, WILMS' TUMOR AND DELETION 11p13

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Summary: An incidence of bilateral gonadoblastoma in a 23-month old, mentally retarded boy with congenital sporadic aniridia, undescended dysgenetic testes, deletion of a chromosome (11) (p1302p14.2) and a later occurring unilateral Wilms' tumor is reported. The patient was treated by bilateral gonadectomy, nephrectomy, and chemotherapy, and is alive and well five years later. Another three aniridia/gonadoblastoma observations from the literature are discussed, two of them without and one in combination with Wilms' tumor. Diagnosis of gonadoblastoma remained unsuspected in two cases until autopsy and in another two cases it was done at surgery. A comparison of four cases reveals common findings - aniridia, dysgenetic gonads, genital abnormalities, mental retardation, deletion of 11p13, early occurrence and bilaterality of gonadoblastoma.

Key words: Aniridia; Gonadoblastoma; Wilms' tumor; Deletion 11p13

Introduction

The association of AGR triad (aniridia, ambiguous genitalia and mental retardation) and Wilms' tumor with chromosome 11 short arm deletion, is a well known syndrome. The aniridia /Wilms' tumor association was first described in 1953 by Brusa and Torricelli (2). Miller et al. (8), in an epidemiologic study of 440 cases of Wilms' tumor, found six cases with congenital sporadic aniridia, i.e. an incidence of 1/73 and in association with mental retardation, anomalies of the pinna and hypospadias with cryptorchidism in males. In 1978, Riccardi et al. (11) described the association of aniridia with 11p interstitial deletion in three unrelated patients including one with a Wilms' tumor. Genital anomalies associated with the aniridia/Wilms' tumor syndrome were reported by DiGeorge and Harley, who found in these four male patients bilaterally undescended testes and in one of these a gonadoblastoma (5).

In the present paper we report a 23-month old male patient with mental retardation and the incidence of sporadic aniridia, deletion of a small chromosome segment (11) (p1302p14.2), associated with bilateral gonadoblastoma and later with a unilateral Wilms' tumor.

Case Report

The patient T.J., a boy, was born on May 5, 1990. His mother was healthy and 21 years old. The 27 years old father was

operated upon at the age of 18 years for a cerebral tumor. A healthy proband's brother was born one year later (1991).

The pregnancy and birth of the patient were normal. His birth weight was 3470 g and he measured 49 cm. Complete bilateral aniridia, congenital posterior cortical cataract in the left eye and undulating nystagmus were diagnosed in early infancy.

There was a striking hypogenitalism with bilateral cryptorchidism. The hypospadiac phallus was abnormally small with a length 12 mm on the dorsal side, and with moderate chordee on the ventral side. The scrotum was flat, empty and no gonade could be palpated.

Karyotype analysis was requested because of aniridia and this sexual anomaly. Chromosomal studies in the patient revealed the karyotype 46,XY,del (11) (p1302p14.2). Both parents and the proband's brother had normal karyotypes, i.e. the patient's chromosomal anomaly was considered to be a new mutation.

The discovery of an interstitial deletion of 11p, associated with aniridia, required further investigation in order to detect a latent Wilms' tumor. Routine ultrasound scan revealed the normal sized kidneys.

At the age of 23 months the patient was transferred for surgical bilateral cryptorchidism therapy. At that time an intravenous pyelogram showed normal morphology and function of the kidneys and excretory cavities. The operation was carried out by making horizontal inguinal incision on the left side. A bilobated pink-yellow coloured and fine-

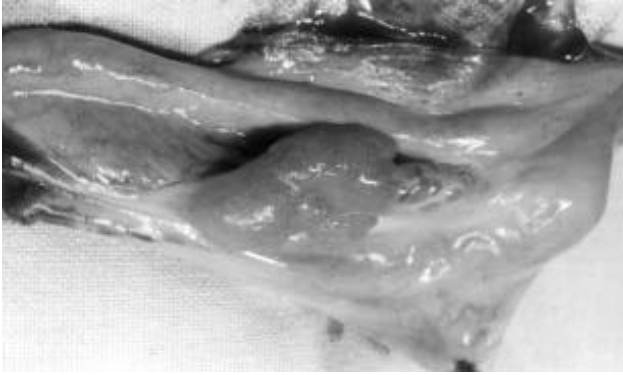


Fig. 1a: Finely granulated tumor 3 to 1.5 cm in left processus vaginalis peritonei in place of testis.

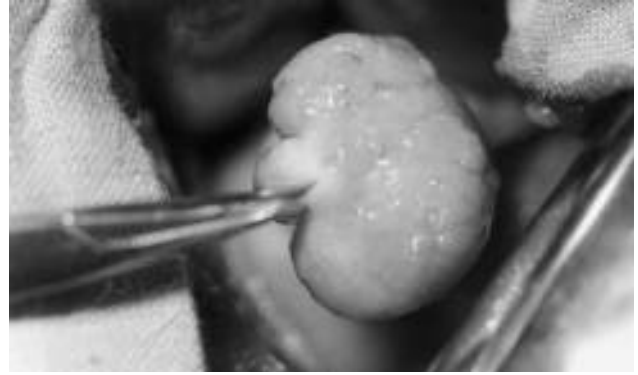


Fig. 1b: Pink-yellow coloured and granulated tumor 3.5 cm in diameter connected with vas deferens was revealed in right peritoneal cavity.

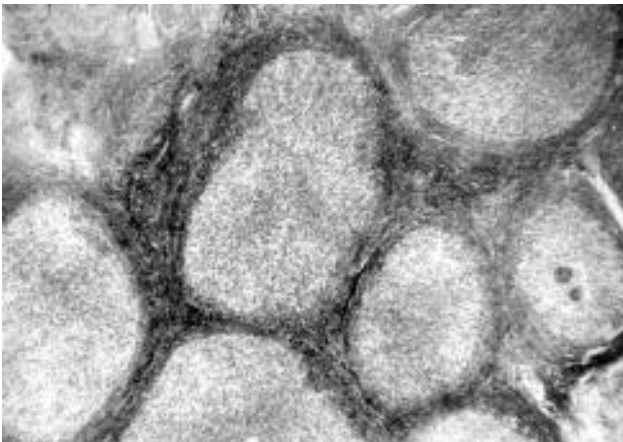


Fig. 2: Gonadoblastoma nests occupying a peripheral part of the abdominal dysgenetic testis is demarcated by connective tissue stroma. Mag. x 63.

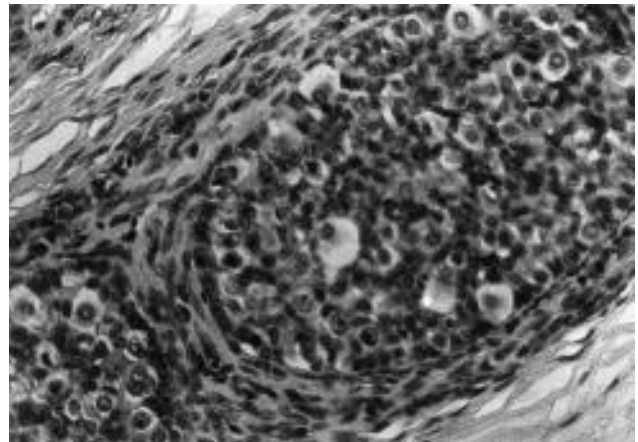


Fig. 3: Detail view of the gonadoblastoma nest showing large germinal cells admixed and surrounded by smaller primitive sex cord derivatives (immature Sertoli cells). Mag. x 160.

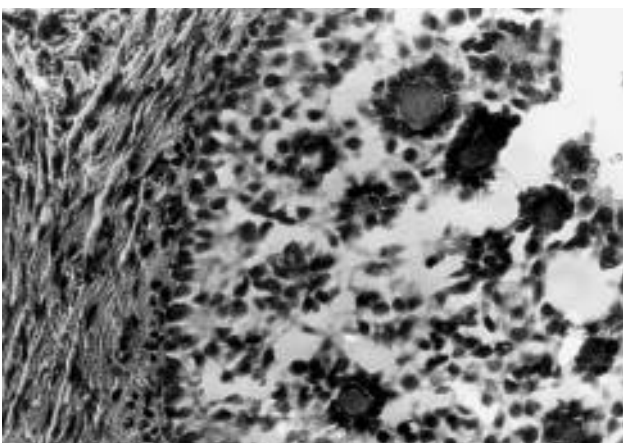


Fig. 4: The gonadoblastoma nest with focal hyalinizations. The surrounding cells are arranged in rosette-like mode (resembles the Call-Exner bodies). Mag. x 160.

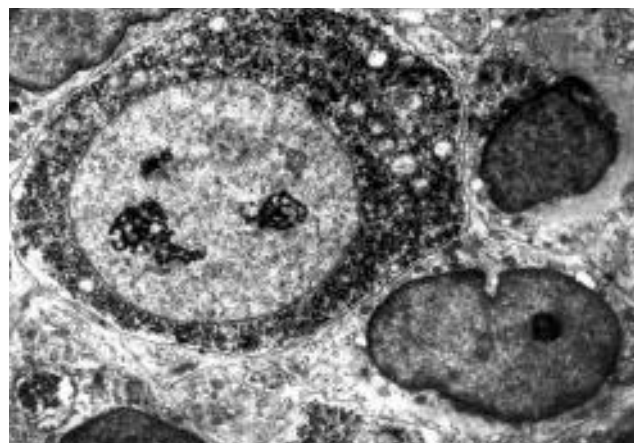


Fig. 5: Ultrastructurally the cell is characterized by a large oval nucleus with prominent nucleoli. The cytoplasm contains considerable numbers of glycogen granules. Mag. x 10 400.

ly granulated tumor, 3 to 1.5 cm, was found in the processus vaginalis peritonei short of the inguinal canal. Distal to the tumor was a cluster of small cysts in place of epididymis (Fig. 1a). Left-sided total gonadectomy was carried out.

During the laparotomy on the right side a finely granulated spherical tumor, 3.5 cm in diameter and of the same color as on the left side, was discovered in the peritoneal cavity (Fig. 1b). A gonadectomy was performed. No Müllerian structures were detected, bilaterally there was vas deferens with an evident connection to the gonads.

A histopathological examination in both dysgenetic gonads disclosed typical gonadoblastoma. Large germ cells were arranged in alveolar clusters separated by a sex cord/gonadal stromal component that exhibited differentiation towards the Sertoli cells (Fig. 2, 3, 4, 5,).

Six months later, fever and hematuria developed and a tumor in the left kidney was suspected after an ultrasound scan. During surgery the Wilms' tumor (stage I) was found in the left kidney and treated by nephroureterectomy followed by chemotherapy. The right kidney was normal. At 5 years postoperatively this patient is alive and asymptomatic with no evidence of tumor.

Discussion

The first report of gonadoblastoma in association with aniridia/Wilms' tumor and genital abnormalities was published by DiGeorge and Harley (5). It documented the case of a 3-year old boy D.W. with cryptorchidism, mental retardation, bilateral congenital aniridia, cataracts and with Wilms' tumor which had been removed when the patient was 29 months of age. Pulmonary metastases developed and the patient underwent pneumonectomy. He died suddenly of unexplained causes 5 months later. During the autopsy, a small residual tumor in the right upper lobe of the remaining lung, Wolffian duct and ovarian remnants plus testicular tissue intraabdominally were found. There was bilateral gonadoblastoma (9). According to the first report of this case a gonadoblastoma was found in one of the testes only (5). The patient's karyotype was not reported (Table 1).

A clinicopathological report of gonadoblastoma with the syndrome of aniridia, cataract in a mentally retarded girl P.R. with deletion of chromosome 11 was presented by Andersen et al. (1). The patient was a 21-month old girl with karyotype 46,XX,del (11) (pter → p13:: p11 → qter). She died of bronchopneumonia following measles and at autopsy the ovaries were macroscopically undetectable. Microscopy disclosed bilateral typical gonadoblastoma in discrete gonadal streaks. Studies of the kidneys demonstrated no signs of Wilms' tumor or presence of abnormal embryonal structures. The authors believed it was very unlikely that a Wilms' tumor would have occurred later in life had the child lived longer.

In the case of Turleau et al. (16) a 20-month old male patient was referred because of severe growth and mental retardation, bilateral aniridia, glaucoma, penile hypospadias, and bilateral cryptorchidism. Karyotyping revealed a de novo complex three-chromosome rearrangement as well as deletion of band 11p13:46,XY,t (4,7,15) (q21.2; p14; q26), del (11) (p13p14). A deficiency in catalase activity allowed the regional assignment of catalase gene to band 11p13. Catalase levels allow for differentiation of either isolated aniridia or isolated Wilms' tumor from the syndrome, particularly since the syndrome is variably expressed. The operation and histologic examination discovered and confirmed the presence of vagina, uterus, two Fallopian tubes and a vas deferens on the right side. Both streak gonads contained seminiferous tubules which appeared dysgenetic and contained areas of gonadoblastoma. Wilms' tumor was not detected.

Aniridia may serve as a marker for tumor diathesis, but not for the tumor itself (11). The present study stresses the importance in such cases of systematically searching not only for Wilms' tumor but also for gonadoblastoma. The complex of aniridia/gonadoblastoma and Wilms' tumor occurred only in the first observation (5,9) and in the present case report. Another two observations of the association between aniridia/gonadoblastoma were reported without or instead of Wilms' tumor (1,16). In patients who exhibit sporadic aniridia, the risk of tumorigenesis appears to be considerably greater (18).

Table 1: Relevant data from three aniridia/gonadoblastoma patients reported in the literature and in the present case.

Nr. Patient	Eyes	Age at diagnosis of gonadoblastoma	Age at diagnosis of Wilms' tumor	Genital abnormalities	Chromosomal rearrangement	References
1 D.W.	Aniridia, cataracts	36 months at autopsy	29 months	Cryptorchidism dysgenetic testes	Not determined	DiGeorge and Harley (5) Pilling IV (9)
2 P.R.	Aniridia, glaucoma, cataracts, nystagmus	21 months at autopsy	-	Female external and internal genitalia Small gonadal streaks	46, XX del (11) (p13p11) Both parents normal	Andersen et al (1)
3 -	Aniridia, glaucoma, corneal clouding	23 months at surgery	-	Hypospadias, cryptorchidism, dysgenetic gonads, Müllerian and Wolffian derivatives	46, XY t(4;7;15) (q21.2;p14;q26) del(11) (p13p14) Both parents normal	Turleau et al (16)
4 T.J.	Aniridia, glaucoma, cataract oculi sin., nystagmus	23 months at surgery	30 months	Hypospadias, cryptorchidism, dysgenetic testes	46, XY del(11) (p1302p14.2) Both parents normal	Stefan and Semecký

Gonadoblastoma is a neoplasm composed of germ cells, sex cord structures and stromal elements that occur mainly in dysgenetic, and streak gonads of intersex patients who have a Y chromosome (12,15). The short arm of this Y chromosome carries a locus GBY, the presence of which causes gonadoblastoma in such cases. The gonadoblastoma gene can be localized to a discontinuous region in proximal Yp/Ycen (19).

Gonadoblastoma constitutes about 0.5 per cent of all testicular neoplasms and occurs in all age groups, although most have been observed in persons under thirty years of age (4). Comparison of data for these four gonadoblastoma cases reveals that they have an early average age at diagnosis, i.e. between 21 and 36 months. Bilateral gonadoblastomas occur in approximately a third of cases (12) and they were found in all four patients. Due to a high rate of bilaterality of this tumor, removal of the contralateral gonad has been recommended, especially when gonadal dysgenesis is present (4). If the germ cell element is nonmalignant, the prognosis is excellent (4). Since the malignant change in gonadoblastoma, usually in the form of germinoma, may appear in the first decade, and since the neoplasm arises in an expendable gonad, radical gonadectomy should be done as soon as its presence has been detected (12).

In Pilling's series, 7 of 20 patients with sporadic aniridia developed Wilms' tumor, one with gonadoblastoma (9). The aniridia/Wilms' tumor association has been shown to be linked to deletion of the short arm of chromosome 11del(11)(p13) (11). Knudson and Strong (6) have proposed the „two-events“ embryonal tumorigenesis, that two mutations are necessary for the development of Wilms' tumor. It has been suggested that 11p deletion may be one of the events (14).

Only 50% of AGR patients actually develop Wilms' tumor, indicating incomplete penetrance of predisposing mutation (3). The tumor does not appear to be grossly or microscopically different from neoplasms in the general Wilms' tumor population. But there is a difference in male preponderance 2.7:1 and an extremely high incidence of bilateral tumor (36%) (13). This contrasts strikingly with an incidence of 2-4.4% of bilateral Wilms' tumor in children without aniridia. Also, the mean age at diagnosis is different, in 11 Wilms' tumor/aniridia patients it was 2.8 years (range 2 days - 8.5 years) (13).

Genital anomalies in aniridia/del 11p complex are practically constant in XY patients: 20 out of 25 had cryptorchidism, associated in 12 with hypospadias, five of them had more ambiguity (17). Male pseudohermaphroditism in this complex was reported by more authors (5,7,9,16).

There are many variations of the chromosome rearrangement of aniridia/gonadoblastoma and/or Wilms' tumor patients in the nature and in the size of deletion, but chromosome band 11p13 is invariably involved. This indicates that this part of the chromosome is of importance to the normal development of the iris and of the primordial structures of the kidney and /or the primitive gonads

(1). Cowell et al. (3) 1989 reported an overlapping deletion with breakpoints in chromosome region 11p13, associated with a Wilms' tumor, aniridia, genital anomalies and mental retardation. They have been able to identify a small region in 11p13 which contains the aniridia/Wilms' loci. The aniridia gene lies distal to the Wilms' tumor in this region, but other abnormal phenotypes, such as mental retardation and gonadal dysplasia, gonadoblastoma, and possibly the Drash syndrome, have not been precisely mapped (3).

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Submitted January 1998.

Accepted January 1998.

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