Case report

Bilateral Ovarian Germ Cell Tumor in a 46,XX Female with Nijmegen Breakage Syndrome and hypergonadotropic hypogonadism

Short title: Bilateral Ovarian Germ Cell Tumor in NBS Patient

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Abstract
Nijmegen Breakage Syndrome (NBS) is a rare autosomal recessive disease, affecting mainly patients of Slavic origin. It is caused by a defect in *NBN* gene, resulting in defective nibrin protein formation. This leads to chromosomal instability, which predisposes to cancer, with lymphoid malignancies predominating. Nibrin is also involved in gonadal development and its disfunction in females with NBS frequently results in a pure gonadal dysgenesis (PGD) causing hypergonadotropic hypogonadism. However, only a few ovarian tumors in NBS patients have been reported to date. We describe the first case of a girl with NBS with PGD, who developed metachronous bilateral ovarian germ cell tumors (dysgerminoma and gonadoblastoma). Pathogenesis of PGD, neoplastic transformation and therapeutic approach in females with NBS are discussed.
Keywords: Pure gonadal dysgenesis, solid tumor, gonadoblastoma, dysgerminoma, children, cancer predisposition

What is already known on this topic?
• Nijmegen Breakage Syndrome (NBS) is an autosomal recessive disease characterized by chromosomal instability and increased risk of various malignancies, including solid tumors.
• Pure gonadal dysgenesis (PGD) resulting in hypergonadotropic hypogonadism is frequently encountered in females with NBS.
• Disorders of sex development, including PGD, are associated with an increased risk of germ cell tumors.
• The risk of ovarian germ cell tumors seems not to be significantly increased in NBS females with PGD therefore a routine prophylactic oophorectomy is not recommended in these patients.

What this study adds?
• In 46,XX NBS females diagnosed with ovarian germ cell tumor, an early prophylactic oophorectomy of the remaining nonfunctional streak ovary should be considered to exclude or avoid second germ cell tumor.
• Early detection and complete resection of ovarian malignancy in female NBS patients may enable successful treatment without the need of adjuvant chemotherapy, which should be avoided in patients with NBS as it significantly increases the risk of development of subsequent cancers.

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Introduction

Nijmegen Breakage Syndrome (NBS; OMIM#251260, ORPHA:647) is a rare autosomal recessive disease characterized by chromosomal instability similar to that of ataxia-telangiectasia, with preferential involvement of chromosomes 7 and/or 14 in a variable proportion of analyzed metaphases. The majority of patients are of Slavic origin with founder effect for the most common pathogenic variant, namely NM_002485.5(*NBN*):c.657_661delACAAA (p.Lys219Asnfs*16; rs587776650) (previously referred to as c.657_661del5) in exon 6 of the *NBN* gene. *NBN* gene encodes nibrin, the crucial component of the of the Mre11/Rad50/*NBN* (MRN) complex, responsible for repair of DNA-double-strand breaks. A genetic defect in this gene causes a defective nibrin protein formation, which in turn impairs G2/M checkpoint control during the cell cycle. This results in spontaneous chromosomal instability and hypersensitivity to ionizing radiation (1,2).

The hallmark features of NBS patients include microcephaly, distinct dysmorphic facial features (sloping forehead, prominent midface and receding mandible), growth retardation in first years of life, *café au lait* spots and some minor developmental defects (3). While microcephaly is a dominating feature, mental capabilities of NBS patients may not be affected in infancy and early childhood, however, cognitive functions usually worsen with age (1). Combined immunodeficiency of both the cellular and humoral types is an essential feature of NBS (4) and increased susceptibility to severe infections (particularly of the respiratory tract) is commonly observed (5).

Malignancies are the most frequent cause of mortality of NBS patients (6). The risk of malignancy is approximately 50-fold higher with risk for lymphomas 250-fold higher than in general population (5,7,8). In NBS, lymphoid malignancies occur also significantly more frequent than in other chromosome-breakage disorders, such as: ataxia-telangiectasia, Bloom syndrome, and Fanconi Anemia (5–7). Malignant solid tumors are uncommon, constituting less than 10% of cases. Among them, medulloblastoma and perianal rhabdomyosarcoma predominate (6,9,10), while breast cancer, prostate cancer, thyroid cancer, neuroblastoma and melanoma have been reported occasionally (6,11).

An evidence of hypergonadotropic hypogonadism affecting females with NBS has been reported, based on a longitudinal observation of a large cohort of Polish patients and anecdotal case-reports (12,13). Interestingly, homozygous and compound heterozygous pathogenic variants in *NBN* gene have been also found in patients with isolated infertility, lacking other typical NBS features. The infertility was caused either by premature ovarian insufficiency (14–16) or by oligo-terato-asthenozoospermia (15). These reports may suggest that nibrin play a role in normal development and function of gonads, and explain the cause and patomechanism of gonadal insufficiency in NBS patients lacking function of this protein (12).

Various specific forms of disorders of sex development (DSD), in which pure gonadal dysgenesis (PGD) is one of examples, are prone for development of germ-cell tumors. In NBS only one case of ovarian gonadoblastoma and one of dysgerminoma have been mentioned in the literature (6,11). However, heterozygous carriers of c.657_661del5 variant have been shown to be at increased risk of developing rare types of ovarian cancers and other malignancies (17–19).

In this report, we document the girl with NBS who developed bilateral ovarian germ cell tumor. The first clinically appeared dysgerminoma and, two years after, gonadoblastoma was detected contralaterally in the prophylactic ovariectomy.

Case Report

A 13-year-old girl with NBS was admitted to the Department of Pediatrics, Hematology and Oncology of the Medical University of Gdansk, Poland in 2007 due to the asymptomatic tumor of the left ovary, detected in a screening ultrasonography (US) imaging. At the age of 8 years, the patient was diagnosed with NBS, based on typical clinical features, including: microcephaly, typical facial features, growth retardation, immunodeficiency, and recurrent respiratory tract infections. The diagnosis of NBS was confirmed by molecular testing detecting a homozygous 5 base-pair deletion NM_002485.5(*NBN*):c.657_661delACAAA in exon 6. The family history of the patient was remarkable: among 5 siblings she had an older sister with very similar clinical features suggestive for NBS, but never confirmed molecularly. In 1999, at the age of 17 years, her sister died of rapidly progressing abdominal diffuse large B-cell lymphoma (DLBCL). Parents are both Polish and not related.

On admission, our patient was in a good condition, assessed as Tanner stage I. Her height was 146cm, weight 35kg, head circumference 49cm and chest circumference 60cm – all measurements were below the 3rd percentiles. US examination showed a solid and well demarcated tumor of the left ovary, measuring 35x30x26mm. There was an abundant pathological vasculature invading from the periphery of the lesion and a very low resistivity index of 0,51. The presence of a localized ovarian tumor was confirmed in magnetic resonance imaging (MRI) (Fig. 1a). No lymph nodes and distant metastases were detected. The serum levels of lactate dehydrogenase, uric acid, C-reactive protein, beta-chorionic gonadotropin, alpha-fetoprotein and carcinoembryonic antigen were within normal ranges for age. The suspicion of ovarian non-Hodgkin lymphoma (NHL) was raised, and a laparoscopic left oophorectomy was performed at the Department of Pediatric Surgery, Gdansk. Histopathology revealed total ovarian involvement by

dysgerminoma with a typical immunophenotype. The ovarian capsule was not infiltrated and no angioinvasion was detected (Fig 2a). The right ovary was found normal at the intraoperative macroscopic evaluation. According to the International Federation of Gynecologists and Obstetricians (FIGO) the tumor was classified as stage 1A, which did not require adjuvant oncologic therapy.

After the surgery, the patient remained under regular control of a pediatric oncologist with screening US of the abdomen and pelvis performed every 3 months and MRI every 6 months. No recurrence of the left ovarian tumor was found. However, both a small uterus and a streaked hypoplastic right ovary were recorded in subsequent examinations (Fig. 1bc). Finally, at the age of 15, primary amenorrhea with no secondary signs of puberty was diagnosed in the girl. Based on serum hormones levels [follicle-stimulating hormone (FSH) - 131.32 mlU/l, luteinizing hormone (LH) - 35.86 U/l, estradiol <37 pmol/l)], a hypergonadotropic hypogonadism was diagnosed and right ovary dysplasia was suspected. Cytogenetic studies revealed female karyotype with a number of distinct, nonclonal aberrations involving chromosome 7 and 14 in a significant proportion (13%) of the cells analyzed. A paracentric inversion of chromosome 14 was also present in all metaphases studied. No *SRY* signal was detected by FISH.

After the multidisciplinary consultation, it was decided to remove the remaining non-functioning ovary and to start the patient on hormone replacement therapy. The right small (1,5x1cm) gonad was resected by laparoscopy, showing histologically gonadal dysgenesis with gonadoblastoma. The gonad contained fibrous, focally evident ovarian type stroma with scattered granulosa cell groups and dispersed microcalcifications. Moreover, Sertoli cell nodules, as well as germ cells accompanied by Sertoli/granulosa cells in cord–like structures were present. Neither primordial follicles nor seminiferous tubules were present. Coexisting gonadoblastoma nests presented typical immunophenotype with Oct3/4, placental alkaline phosphatase (PLAP), CD117, and inhibin positivity (Fig 2bcdef). The patient was introduced with hormonal replacement therapy, and in 3 months she developed secondary sexual characteristics (breast Tanner stage 3 and growth gain of 5cm). On follow-up US examinations, an enlargement of the uterus from 11x5,7x22 mm to 31x14x55 mm and prominent endometrium were detected within the next few months. Currently, this 27-year-old patient is alive and free of any symptoms of cancer recurrence. She is under the care of a hematologist and on continuous immunoglobulin supplementation. However, after she turned 18 and was discharged from pediatric care, she discontinued hormonal replacement therapy. In the recently performed US examination, her uterus size was 24,5x11,6x30,5 mm, with no visible endometrium. An informed consent from the patient and her parents to publish this case-report has been obtained.

Discussion

NBS is a rare and possibly still underdiagnosed disease. It has been estimated that approximately 20-30% of patients are diagnosed with neoplasms prior to the diagnosis of this syndrome. Our patient was diagnosed with NBS soon after her sister's death of cancer, based on their specific phenotypic similarity. This led to discontinuation of repeated diagnostic x-rays of chest and paranasal sinuses during girl's recurrent infections. These procedures are now highly contraindicated in NBS patients, due to their hypersensitivity to ionizing radiation and high risk of malignancy induction (20). Since then, our patient underwent regular prophylactic US examinations, leading to the discovery of an asymptomatic left ovarian dysgerminoma at an early stage.

Gonadal dysgenesis is defined as an incomplete or defective formation of gonads, resulting from a disturbed process of migration of the germ cells and the organization of the primitive gonads. It is caused by aberrations of sex chromosomes or defects in genes involved in the formation of urogenital ridge and sex determination of the primarily bipotential gonad (21). Gonadal dysgenesis predisposes to the development of gonadoblastoma and dysgerminoma, particularly in patients with 46, XY karyotype (22). However, rare cases of these tumors in patients with female 46, XX karyotypes have been reported (23,24). Capito et al. suggested that highly elevated FSH serum level might be indirect marker of suspected ovarian tumor in patients with PGD (25). Gonadal dysgenesis resulting from defective nibrin function is a typical feature of females with NBS.

Dysgerminomas can be associated with many genetic syndromes, such as: Frasier, ataxia-telangiectasia, WAGR and Apert syndromes (26–29). However, to our best knowledge, only one case of dysgerminoma in a patient with NBS has been reported so far (6). In our patient, the 46,XX karyotype was confirmed; however, numerous abnormalities involving chromosomes 7 and 14 were detected in a significant percentage of cells. These aberrations are characteristic for NBS patients reflecting the flag mark of the disorder – the chromosomes instability. In our patient, along with the typical abnormalities of chromosomes 7 and 14 in 13% of cases, all metaphases revealed presence of pericentric inversion of chromosome 14. It is generally acknowledged that aberrations involving chromosomes 7 and 14 are present in 10-50% of the cells (30). To certain extent, the high rate observed in our patient might be age-related, resulting from mere accumulation of individual aberrations throughout the time. The girl was cytogenetically evaluated at the age of 20 years, while most of the published NBS patients had karyotype performed in early

childhood. We cannot exclude however, the parental origin of the chromosome 14 inversion, because the parents were unavailable for genetic testing at that time.

The prognosis and treatment of dysgerminomas depend on their pathological and clinical stage. Patients with disease limited to one ovary may be treated by unilateral oophorectomy alone, especially when fertility is to be maintained. However, in patients with PGD, early bilateral gonadectomy is recommended to avoid neoplasms' development. In our patient, no secondary signs of puberty with primary amenorrhea were observed at the age of 15. In US and MRI performed repeatedly after left ovariectomy the hypoplastic uterus and right ovary were described. With very low estradiol levels and significantly elevated FSH concentrations, the hypergonadotropic hypogonadism was diagnosed and the right ovarian dysplasia was suspected. Because of a history of dysgerminoma in the left ovary, a decision to perform prophylactic right oophorectomy was made, following the rules established for PGD XY females (Swyer syndrome) (25). Histopathological examination of the resected right ovary confirmed its dysgenetic features and revealed gonadoblastoma areas. The surgery was complete so the patient did not require adjuvant oncological therapy and remains cancer-free. Hormonal replacement therapy produced satisfactory clinical effect with induction of the secondary sexual characteristics.

Our patient is the first case with metachronous ovarian gonadoblastoma and dysgerminoma developing within the dysgenetic ovaries, occurring in the patient with NBS and 46,XX karyotype. Although it seems that nibrin may play a role in normal development and function of the ovary, only one case of gonadoblastoma and one of dysgerminoma in NBS patient have been mentioned in the literature to date (6,11).

The optimal management of NBS females with hypergonadotropic hypogonadism suggesting PGD is controversial. In 2010 Chrzanowska et al. have published results of a longitudinal study showing that primary ovarian insufficiency with the associated hypergonadotropic hypogonadism are common and typical features in females with NBS (12). The authors suggested that careful, but minimally invasive diagnostics, including auxiological follow-up, US examinations and basic hormonal assays are sufficient in these patients. Accordingly, Huang et al demonstrated within the group of 33 patients with XX PGD, that the risk of malignant transformation in case of absence of the Y chromosome is low. Therefore, in XX PGD patients the prophylactic gonadectomy is not recommended and only careful follow-up should be provided (24). However, in patients, in whom ovarian germ cell tumor has been already diagnosed within one gonad, we advocate for early prophylactic oophorectomy of the remaining nonfunctional streak ovary to exclude or avoid second germ cell tumor. This recommendation is particularly meaningful for XX, PGD females with NBS because early detection and complete resection of malignancy in these patients gives a chance for successful outcome without need of adjuvant chemotherapy, which is extremely risky in terms of development of subsequent cancers. Such strategy of management was adopted in our patient, resulting in a long-lasting clinical remission of metachronous bilateral ovarian germ cell tumors.

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Fig. 1a: Axial T2-weighted MR scan shows well demarcated hyperintense pathological mass in the left ovary, which doesn't infiltrate ovarian capsule. Tumor is oval and homogenic.
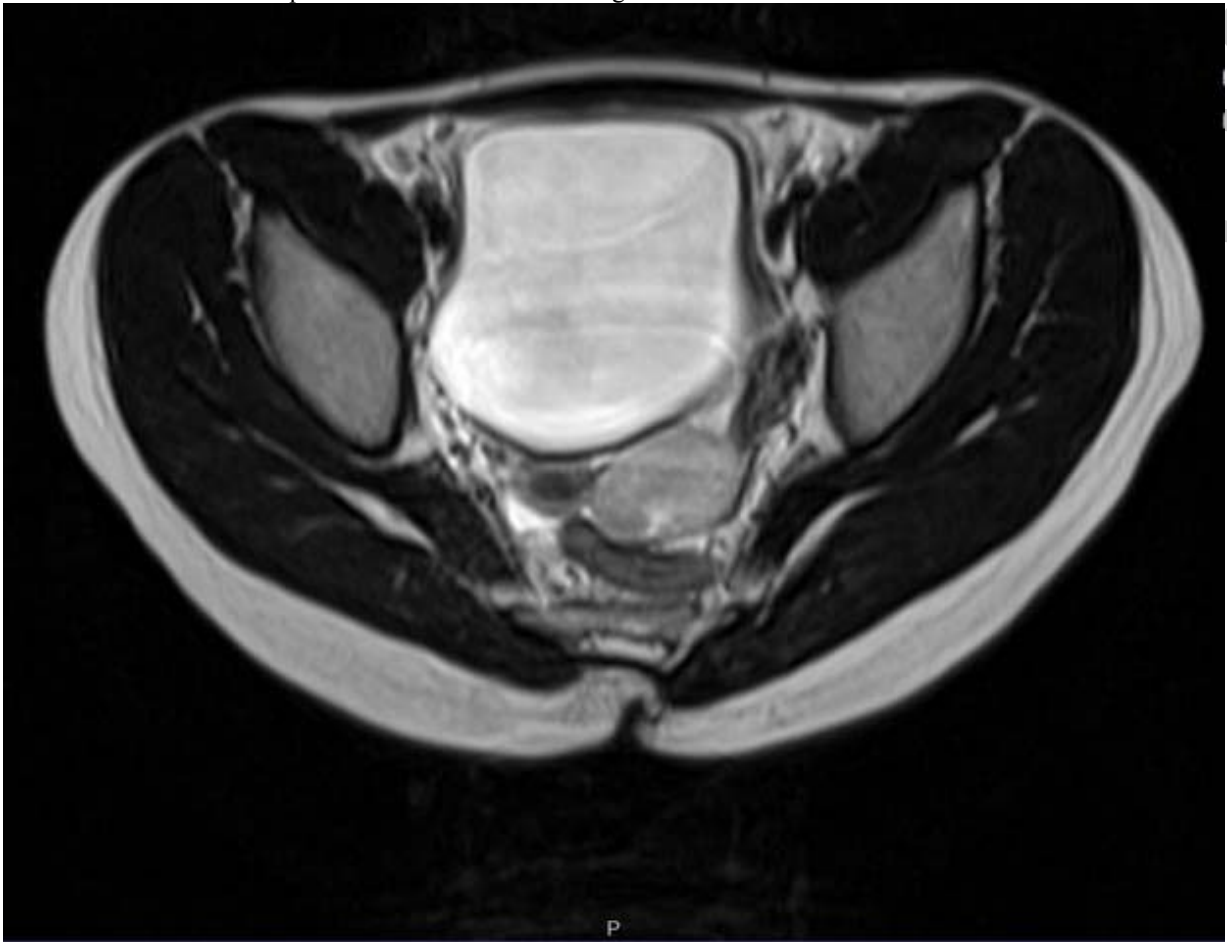

Fig. 1b: Sagittal T2-weighted MR image shows a small hypoplastic uterine remnant in the anatomic location of the uterus.
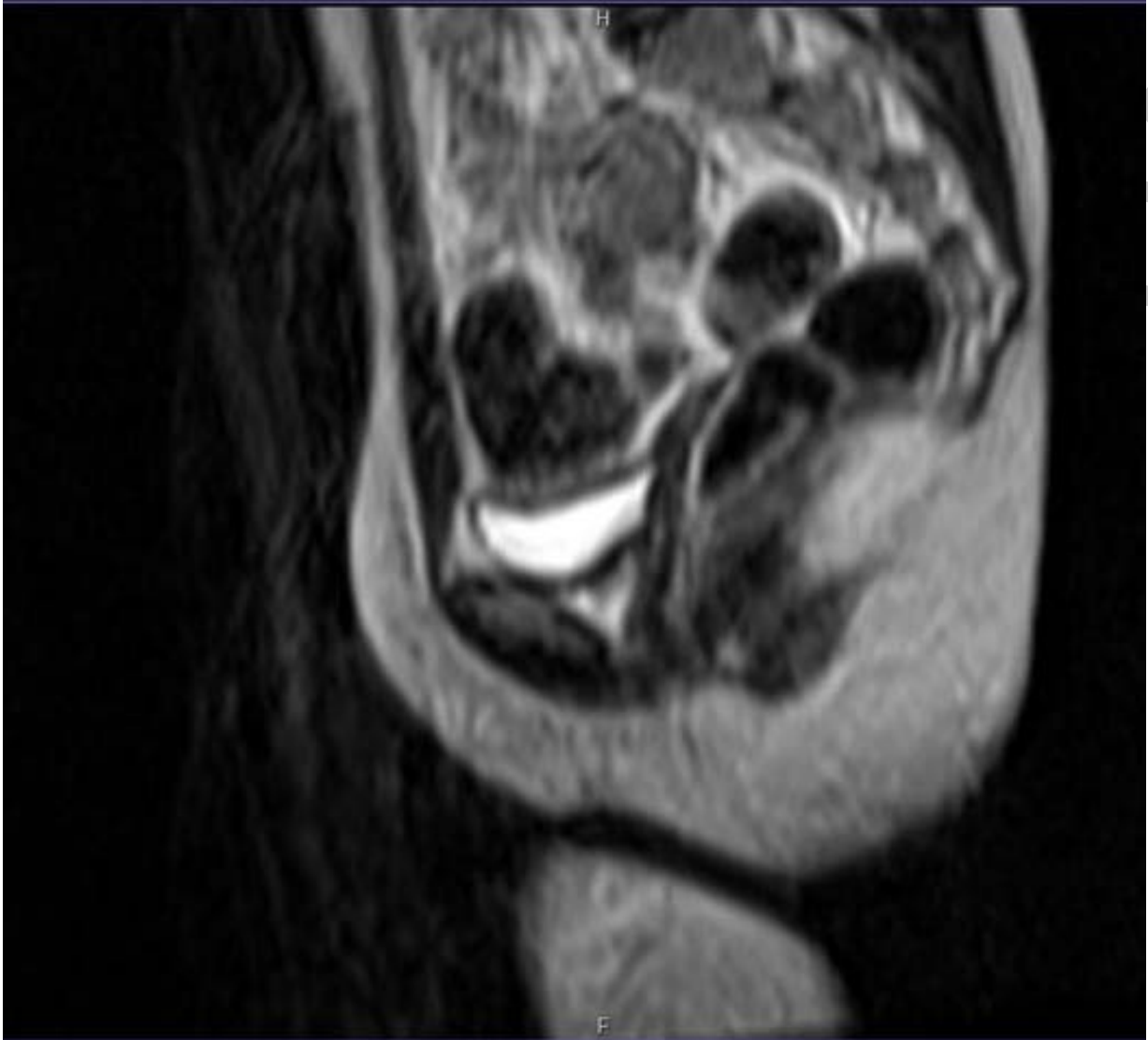
Fig. 1c: Axial T2-weighted MR image shows a hypoplastic ovary on the right side (the longest diameter of the ovary is 13 mm). The morphology of the right ovary is normal without any visible pathological structure inside.
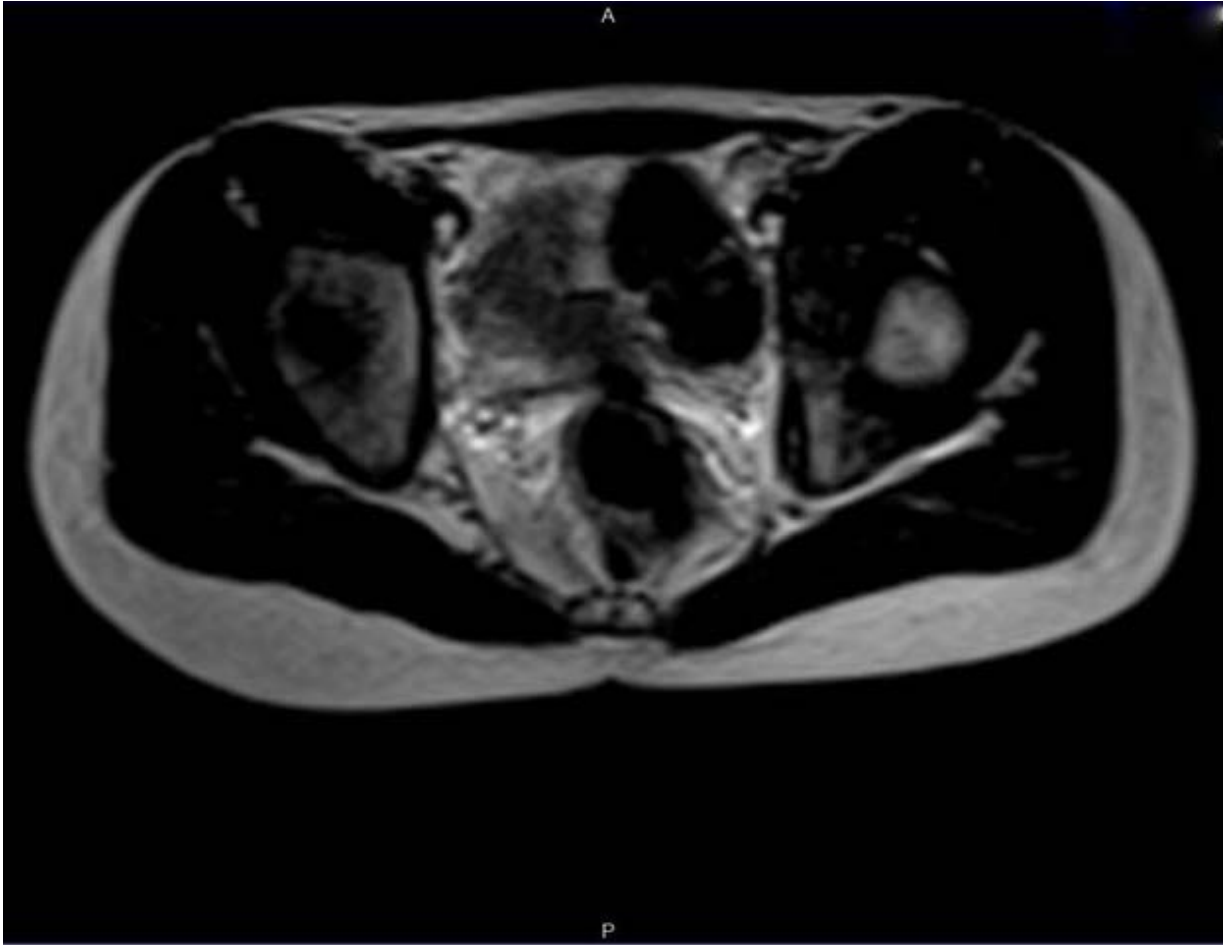
Fig. 2a: Histology of the dysgerminoma from the left ovary (HE 200x)
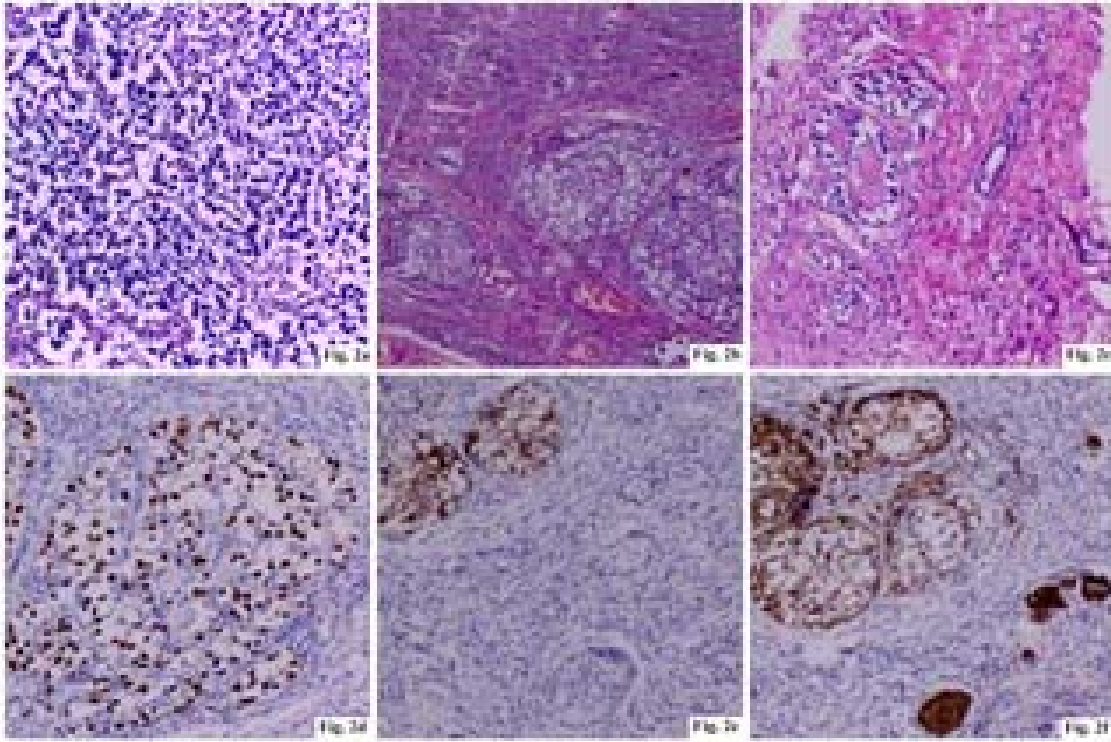
2b: Dysgenetic gonad containing gonadoblastoma foci within the ovarian type stroma (HE 100x)

2c: A small group of tubular structures of sex cord cells arranged around the hyalinic cores, scattered in the stroma of dysgenetic gonad (HE 400x)

2d: Oct 3- positive germ cells within gonadoblastoma structures (Oct 3, 400X)

2e: CD117 expression within the germ cell component of gonadoblastoma, and immunonegative sex cord elements within the surrounding gonad (CD117, 200X)

2f: inhibin alpha staining present within the sex cord element of gonadoblastoma and stromal sex cord structures (inhibin, 200x)