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Androgen insensitivity (testicular feminization) syndrome and XY gonadal dysgenesis (Swyer syndrome)

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Case 1: *Clinical History* -The patient was an 18-year-old woman with a history of primary amenorrhea. The physical examination revealed normal female external genitalia, moderate breast development, scarce pubic hair, and scant axillary hair. Pelvic examination revealed an absence of a uterus. The vagina ended in a blind pouch and measured 6cm in length. An abdominal ultrasonogram showed solid bilateral gonadal structures measuring 31x15mm right, and 30x 6mm left in the pelvic cavity without any evidence of a uterus. These findings were confirmed by MRI scan. Serum levels of estradiol and testosterone were 45.7pg/mL and 7.5nmol/L, respectively. FSH and LH levels were 8.46mlU/ml and 20.2mlU/ml. Cytogenetic analysis of peripheral blood lymphocytes revealed a 46,XY karyotype, with translocation t(13,14) inherited from her father. The molecular investigation confirmed active SRY with amplification of 6 non-polymorphic loci on AZFa, AZFb, and AZFc regions on Y chromosome. Three months after her first referral the patient underwent bilateral prophylactic laparoscopic gonadectomy. The patient is being followed up regularly and she has no complaints after five years. Pathological Findings- Grossly, the right gonad was 4.3x1.8x1.8cm and the left gonad was 4.5x2.0x1.7cm. The right fallopian tube was 3.8cm long and 0.2cm in diameter, while the left one was 1.5cm long and 0.2cm in diameter. In addition, 4 cysts measuring 0.3-1cm in diameter were found in the fat tissue on the surface of the left fallopian tube. The cut surface of the right gonad resembled testicular tissue showing two discrete, firm, well-demarcated, slightly bulging, homogenous, light grey-tan colored nodules, measuring 0.1 and 0.9cm in maximal dimension. Three similarly looking nodules were present in the left gonad measuring 0.4-0.5cm in diameter. In addition, a white whorled, firm, smooth muscle body fused to one pole of the gonad was found bilaterally measuring 1.2cm right, and 1.3cm left. Microscopically, both gonads were composed of varying proportions of small and solid, or less frequently larger, with early lumen formation seminiferous tubules lined by immature Sertoli cells, surrounded with fibrous, focally edematous stroma in which prominent Leydig cells were present. Rare tubules contained Sertoli cells with abundant cytoplasm filled with coarse, eosinophilic granules. The nodules were composed of solid immature tubules lined by cylindrical immature Sertoli cells separated by fibrous stroma containing fewer Leydig cells. Fallopian tubes were hypoplasic, while the cysts were lined by a single layer of cuboidal to columnar cells some of which had cilia. Thus, the clinical, laboratory, imaging, genetic and histological findings confirmed the diagnosis of complete androgen insensitivity syndrome with bilateral testicular hamartomas.Discussion Androgen insensitivity syndrome (AIS) is a disorder where there is resistance to androgen actions influencing both the morphogenesis and differentiation of androgen-responsive body structures. It is the most common type of male pseudohermaphroditism, characterized by an absence of androgen receptor activity due to a mutation at Xq11–q12 localization on the androgen receptor gene. the. In the largest series of 43 patients with the AIS published by Rutgers and Scully hamartomas were present in 63% of the cases, while Sertoli cell adenomas were reported in 23% and malignant tumors including two seminomas, one intratubular germ cell neoplasm with early stromal invasion and a malignant sex cord tumor in 9% of the cases.

Case 2: *Clinical History*- The patient was a 17-year-old girl with primary amenorrhea. On external examination, she had an unambiguous female phenotype albeit with poor breast development. Her external genitalia had a normal appearance but internal examination showed a hypoplastic uterus. Ultrasonography failed to show follicular activity in the gonads. Her gonadotropins were high (FSH, 55.6mU/ml; LH, 18.3mU/ml) and estradiol was low (20.0pg/ml). Nonmosaic 46,XY karyotype was detected in patient's leukocytes by cytogenetic analysis. Under the tentative clinical diagnosis of pure gonadal dysgenesis, a prophylactic bilateral laparoscopic gonadectomy with bilateral salpingectomy was performed. A biopsy specimens from the gonads were sent for cytogenetic analysis. The sequencing of the SRY gene of the proband revealed a C/G substitution at the first nucleotide of codon 133, leading to Arg/Gly replacement in the SRY protein. The mutation was also present in patient's father, who is a phenotypically normal male.

The patient is alive and well 12 years after the operation without any evidence of disease. Pathological Findings- Macroscopically, both fallopian tubes were 4cm long and 0.4cm in diameter, while the gonads were measuring 3x2.2x1.2cm the right, and 2.2x0.8x1cm the left. Upon dissection, both gonadal streaks had a similar, variegated appearance with multiple areas of microcalcification. The histological evaluation of the gonads confirmed a gonadoblastoma of 3cm in diameter in the right gonad and a predominantly "burnt-out" gonadoblastoma of 2.2cm in the left gonad with only a microscopic focus of recognizable gonadoblastoma less than 1mm in diameter. The tumors were composed of primordial germ cells intimately admixed with sex cord elements, which surrounded round spaces filled with eosinophilic basement membrane-like material. The atypical germ cells had abundant clear or pale, slightly granular cytoplasm and round vesicular nuclei with prominent nucleoli. The small, often fusiform sex cord element cells had uniform round or oval nuclei with indiscernible nucleoli and scant cytoplasm. The uninvolved gonadal tissue bilaterally had the morphology of a streak gonad composed largely of ovarian-type stroma, with extended calcification and small germinal inclusion cysts present, without any follicles. The fallopian tubes were infantile. Therefore, the histopathological findings confirmed the diagnosis of bilateral gonadoblastoma in streak gonads, FIGO Stage IB, in a patient with a XY gonadal dysgenesis (Swyer syndrome). Discussion: XY gonadal dysgenesis (GD) is a result of abnormal testis development in utero. Pure 46,XY GD should be considered when an adolescent presents as a phenotypic female with delayed puberty and primary amenorrhea. Rarely, they may present with a detectable abdominal or pelvic gonadoblastoma mass. When the presumptive diagnosis suggests GD, further criteria may strengthen the diagnosis, while ultimately, the most definitive diagnosis is through biopsy of the gonads. Bilateral streak gonads are seen in pure XY GD. The risk of otherwise undetected gonadoblastoma in XY GD patients is high, and prophylactic or therapeutic gonadectomy is therefore often indicated when XY GD is diagnosed.

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Sarkomatoidna diferencijacija u karcinomima bubrega

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Sarkomatoidna diferencijacija u karcinomu bubrega (sarkomatoidni karcinom bubrega - sRCC) predstavlja dediferentovanu neoplazmu bubrega visokog gradusa koja sadrži karcinomsku i sarkomsku komponentu. sRCC su relativno retki tumori sa incidencom od 5-8% u karcinomu bubrega. Sarkomatoidna diferencijacija je rezultat divergentne diferencijacije malignih epitelnih ćelija. U ovom procesu tumorske ćelije gube fenotipske karakteristike epitelnih, a zadobijaju mezenhimske karakteristike, što im obezbeđuje veću sposobnost za migraciju i metastaziranje. Ovaj fenotip se može javiti u svim podtipovima RCC, uključujući svetloćelijski, papilarni, hromofobni RCC i karcinom sabirnih kanalića. Sarkomatoidna komponenta može pokazivati sliku fibrosarcoma ili ne diferentovanog pleomorfnog sarkoma. Ređe je prisutna heterologna diferencijacija, sa slikom koja podseća na rhabdomyosarcom, chondrosarcom, ili osteosarcom. Rabdoidni fenotip predstavljaju agresivnu formu divergentne diferencijacije koja je opisana u clear cell RCC, papilarnom RCC, kao i hromofobnom RCC (CRRCC). CRRCC se javlja u oko 6% svih RCC i ima bolju prognozu u odnosu na ostale podtipove RCC. Sarkomatoidna diferencijacija u CRRCC se sreće u oko 8% ovih tumora i indikator je loše prognoze, kao i u ostalim RCC. Sarkomatoidna komponenta može da predstavlja terminalno dediferentovan klon koji se može razviti iz bilo kog podtipa RCC ili se može razviti iz posebnog klona. Iako se sRCC najčešće vidi u high grade tumorima, pojava sarkomatoidne diferencijacije u RCC, Fuhrman ½, što je detektovano u >30%, osporava tvrdnju da je sarkomatidna diferencijacija