

Fertility and pregnancy issues in a 46, XY (Swyer syndrome) patient in the face of ovarian cancer

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Research

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Abstract

Background

In this paper we focus on 46, XY pure gonadal dysgenesis-Swyer syndrome.

Methods

We present the case of a 33-year old patient and the medical procedures enabling to achieve a pregnancy in the couple struggling with infertility.

We analyzed patient's medical history, scheduled further diagnostic and therapeutic procedures that included genetic tests and consultations, MRI (magnetic resonance imaging), laparoscopy, oncological risk assesment and possibilities of pregnancy.

Results

Patients medical history revealed her last menstrual period dated one year before she started searching for medical help. Due to a low AMH (anti-Muellerian hormone) level, genetic consultation and genetic tests were recommended. The patient was diagnosed with Swyer syndrome. She underwent laparoscopy to search for gonadal tissue. Histopathology of removed streak tissues revealed dysgerminoma. No metastases were found in a follow up MRI. The patient decided to participate in an egg donation program.

Conclusions

The diagnosis of karyotype containing Y chromosome in a phenotypical adult female patient raised as female demands optimal managing. It has to cover not only psychological and fertility aspects, but also the risk of development of gonadal tumors.

Background

In 46,XY patients, depending on the severity of the defect, different phenotypes are possible. In severe forms of gonadal dysgenesis the patient's phenotype is female. The desire of pregnancy in Swyer syndrome patients may be fulfilled only by an oocyte donor procedure. The incidence of pure gonadal dysgenesis is around 1/80 000 to 1/20 000 (National Organization for Rare Disorders). The exact incidence is unknown. Swyer syndrome was first described by Dr. Swyer in 1955. A diagnosis is based on a clinical evaluation and the patients' medical history as many do not experience any symptoms until the age of expected first menstruation (primary amenorrhea) [1]. In addition to delayed puberty, usually weak breast development and subnormal pubic and axillary hair are observed. The adrenal gland is not affected and can produce androgens, so weak breast development is possible because of peripheral aromatization of androgens [2].

Usually, these are tall patients (as chromosome Y has loci that affect height) with extended arm distance and eunuchoid posture [1]. In patients with suspected 46 XY complete gonadal dysgenesis except for hormonal tests (FSH, LH, AMH, testosterone, hCG stimulation test), a pelvic ultrasound or MRI, and also chromosomal analysis is necessary in making a diagnosis [3]. Additional genetic testing confirms disorders of sexual development. There are plenty of possible genetic disorders causing gonadal dysgenesis, It is estimated that 15% of pure gonadal dysgenesis are due to SRY point mutations, another 15% are due to SRY deletions. So far 50 SRY mutations have been reported (sporadic, but familial cases are also known) [4]. Mutations in SRY and SOX9 account for approximately 20% of 46,XY complete gonadal dysgenesis patients. Genes such as CBX, DHH, WNT4, WT1, MAP3K1, NR5A1, NR0B1, FGFR2, DMRT, DHH are crucial in the stages of normal gonadal differentiation [5,6,7,8,9]. Mutations affecting DAX1 (NR0B1), SF1 (NR5A1), WNT4, DHH, and MAP3K1 are responsible for not more than 30% of cases. Still, little is known about the underlying genetic reasons for the remaining 50% up to 70% of patients. Also, rearrangements of non-coding sequences that disturb gene regulation may account for significant proportion in cases of disorders of sexual development [5].

Complete gonadal dysgenesis which is synonymous with pure gonadal dysgenesis can occur as the result of a new gene mutation or can be inherited in an autosomal dominant, autosomal recessive, X-linked or Y-linked manner [10,11]. Mutations in genes involved in testicular development cause Wolffian ducts to be underdeveloped or regressed which results in feminisation of urogenital sinus and external genitalia. With a lack of AMH (anti Mullerian hormone) the Mullerian ducts develop into fallopian tubes, a uterus, and upper vagina [12].

Materials And Methods

We present a case report of a 33-year old patient who sought medical attention because of amenorrhoea and unsuccessful attempts to become pregnant. She dated her last bleeding to be in July 2017. She had had no prior surgery. Due to hypothyroidism she took 50 mcg of Levothyroxine once daily. A gynecological examination revealed normal female development of external genitalia. The vagina and cervix were normal and an internal examination found no pathological pelvic masses. A transvaginal ultrasound showed a uterus sized 31.7 mm (long) x 30.0 mm (wide) x 20.3 mm (deep). The endometrial thickness was 1.9 mm. No ovaries were visible. Comparing hormonal results presented by the patient during gynecological consultations (results from July 2016 and January 2018) a decrease of estradiol (43.82 pg/ml vs. < 5 pg/ml) and an increase of FSH (20.17 U/l vs 111.7 U/l) were noted. Her last LH level was 64.9 mIU/ml, testosterone 0.29 ng/ml, SHBG 71.42 nmol/ml, and DHEAS 104.7 mcg/dl, prolactin 377.1 mIU/l. AMH was below 0.01 ng/ml. The patient was referred to a genetic consultation and magnetic resonance imaging of the pelvis and abdomen. The first revealed male karyotype 46 XY with SRY mutation. Imaging examination (May 2018) showed a uterus sized 35x36 mm with 18 mm of cervix, and endometrium only partially seen, with a thickness not exceeding 1 mm. Neither ovaries nor testes were found. Lymph nodes were not enlarged and no pathological tissues suspected of metastases were observed. The patient was then evaluated for oncological risk and a decision to perform a laparoscopy was made. In the laparoscopy streak gonads' tissues were removed and no other abnormalities were

found. The postoperative period was free of any complications. Histopathology results showed dysgerminoma: PLAP (+), WT 1 (-), CD 10 (-/+), CK 20 (-), EMA (-). At the next oncological consultation the patient was diagnosed with ovarian cancer IA. Another histopathology examination reaffirmed previous findings. The MRI performed six months later (November 2018) revealed no metastases.

Figures 1-5. On gross examination of the post-operative specimen the left ovary was not found. The right ovary was occupied by a greyish-white, firm tumour measuring 1,3x0,6x0,5 cm.

On microscopic assessment the tumour was composed of sheets and nests of monotonous cells with clear to lightly eosinophilic cytoplasm and distinct cell membranes, separated by fibrous septae containing lymphocytes that were „spilling out” in between the tumour cells. There were multiple calcifications. Immunohistochemistry confirmed dysgerminoma (positive for: SALL4, OCT3/4, D2-40, CD117, PLAP) and excluded gonadoblastoma.

All results and diagnoses were carefully discussed with the patient. She refused additional psychological care. As the diagnostic process lasted for over six months, the patient and her husband have had time to gradually familiarize themselves with Swyer syndrome diagnosis and make an informed decision about the possibilities of parenthood. In December 2018 the patient decided to participate in an egg donation program. Her husband's sperm analysis was normal according to WHO 2010 ranges of sperm parameters. She was prescribed estradiol (Progynova 2 mg) pretreatment to observe the endometrium reaction. In March 2019 she started Estrofem treatment (4 mg from 2nd to 6th day, 6 mg from 7th to 13th) with System 50 patches (from day 10th). As the endometrium reached 9.6 mm the donor's oocytes were fertilized and vaginal progesteron treatment was administered (600 mg per day). Three consecutive embryo transfers did not result in pregnancy and the patient decided to discard plans related to artificial reproduction techniques.

Discussion

Oncological risk

The presence of the Y chromosome entails the risk of malignancy in dysgenetic gonad. In dysgenetic gonad the risk of gonadoblastoma development is around 30%. Gonadoblastoma is one of the most frequent neoplasms found in streak gonads (over 50%). Dysgerminomas and gonadoblastoma with dysgerminoma presence, concern about 20% and 17% hystopathological types, respectively [13]. In patients with pure gonadal dysgenesis seminomas and choriocarcinomas are also found [14]. Some histopathological examinations also report teratoma and embryonic carcinoma [15].

General health issues, fertility, and pregnancy

In gonadal dysgenesis the fibrous tissue lacks follicles which leads to a hypoestrogenic state [16]. It contributes towards many possible complications later in life of the patient. In younger patients, with early diagnosis, hormone replacement therapy is used for the development of secondary sex

characteristics. Hormone replacement therapy may help to avoid proceeding and rapid reduction in bone density. Estrogen therapy also mitigates virilization in these patients [1]. Finally, estrogens are essential for cycle regulation as a uterus is present in Swyer syndrome and spontaneous menstruations were also observed [17]. Estrogen insufficiency in menopausal women may affect many aspects of life and also health. Hypertrophic cardiomyopathy and idiopathic hypertension were reported in patients with complete gonadal dysgenesis [18,19]. It is still unclear whether a relationship exists between Swyer syndrome and connective tissue anomalies [20].

The reproductive implications of Swyer syndrome require multidisciplinary management. As the Müllerian structures are preserved, successful pregnancies have been reported in egg donation programs [21]. Nevertheless, the oncological aspects may strongly influence procreative plans. Especially, when surgery treatment requires chemotherapy or radiotherapy. The presence of chromosome Y does not seem to seriously influence uterine and endometrial response to hormone therapy. However, in many cases of Swyer syndrome, ultrasonography examination or laparoscopy diagnostics reveal uterines smaller than normal. In patients with late diagnosis and prior pregnancy, hormone replacement therapy is necessary to increase the size of the uterus. A small number of successful pregnancies in pure 46,XY gonadal dysgenesis patients have been reported [22]. The definite period of a hormonal replacement therapy cycle has not been established for Swyer syndrome patients. An endometrial thickness of 11 mm on day 14 in a study presented by Gao et al. was sufficient for successful embryo implantation [23]. In a paper by Tulic et al. recipient treatment consisted of stimulation of GnRH and estrogen [1]. Mutinger et al. reported a pregnancy in an oocyte donation program for a patient with a trilaminar structure of endometrium and a thickness of 5.57 mm (oestradiol valerate of 6 mg/day orally and progesterone in oil of 100 mg/day IM starting 5 days prior blastocyst transfer) [24].

Assisted reproduction techniques and oocyte donation allow for the achievement of pregnancy in Swyer syndrome patients although little is known about the nature and underlying causes of this disorder. Thus the answer to the question about possible pregnancy complications is still not provided. Some reported complications: gestational hypertension, preeclampsia, and reduced amniotic fluid as well as fetal intrauterine growth restriction [1, 19, 22, 25]. In most cases of pure gonadal dysgenesis, a caesarian section has been the method of delivery, however vaginal labour has also been reported [26]. That would mean the possibility of myometrial receptors to respond on oxytocin and prostaglandin induction [24].

In addition to oocyte donation, Swyer syndrome patients may consider adoption as an option to become a parent, although related procedures may be very complicated. In cases of early diagnosis in childhood or young adulthood appropriate information about fertility aspects should be discussed with the patient and parents [27].

Conclusion

We still need more data on pregnancy and its outcome in Swyer syndrome patients, but also long life follow up in cancer survivors. Optimal health care managing should be planned to cover short and long

term health goals.

Abbreviations

DSD disorders of sexual development

AMH anti Mullerian hormone

MRI magnetic resonance imaging

FSH follicle stimulating hormone

LH luteinizing hormone

SHBG sex hormone binding globuline

SRY sex determining regionY

PLAP placental alkaline phosphatase

WT1 Wilms tumor 1 proteine

CK20 keratin 20

EMA epithelial membrane antigene

hCG human chorionic gonadotrophin

SOX9 SRY-box transcription factor 9

CBX chromobox

DHH Desert Hedgehog

WNT Wnt Family Member 4

MAP3K1 Mitogen Activated Protein 3 Kinase 1

NR5A1 (SF1) Nuclear Receptor subfamily 5 groupA Member 1

NR0B1 (DAX) Nuclear Receptor subfamily 0 group B Member 1

FGFR2 Fibroblast Growth Factor Receptor 2

DMRT Doublesex and Mab3 Related Transcription Factor

SALL4 sol-like protein 4

OCT 3/4 octamer binding transcription factor 3/4

D2-40 podoplanin

Declarations

Ethics approval

According to decision of Bioethics Comitee of Silesian Medical University data presented in the manuscript is not a medical experiment and ethics approval is not applicable.

Consent to participate and consent for publication

Patient gave her consent to use her medical results in publication.

Availability of data and materials

The data analysed in this publication is available from the corresponding author upon reasonable request and with the permission of the patient.

Competing interests

Authors declare no competing interests.

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Authors contribution

K.OW- patient management, literature searching, manuscript writing; AT- manuscript writing, A.WS- histopathological analyses, A.O- patient management, edited the manuscript and approved the final version.

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Figures

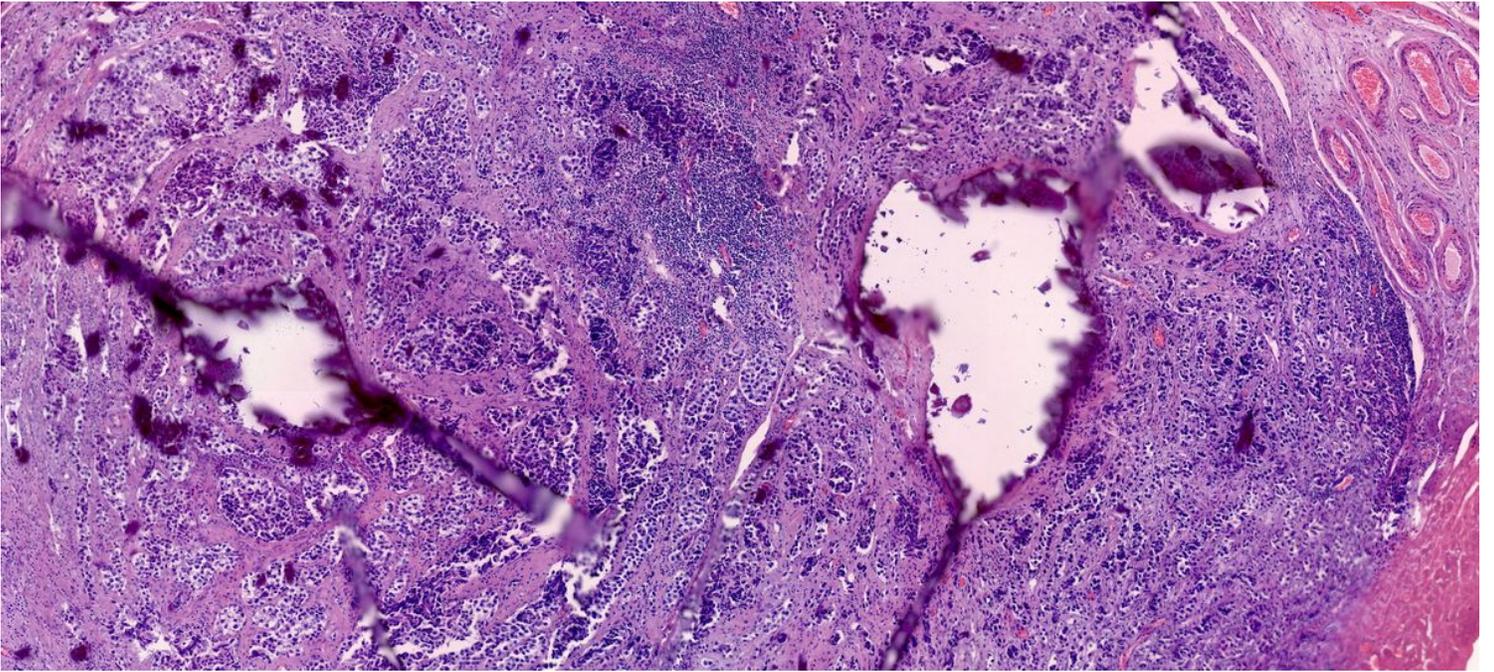


Figure 1

Haematoksylin-eosine staining

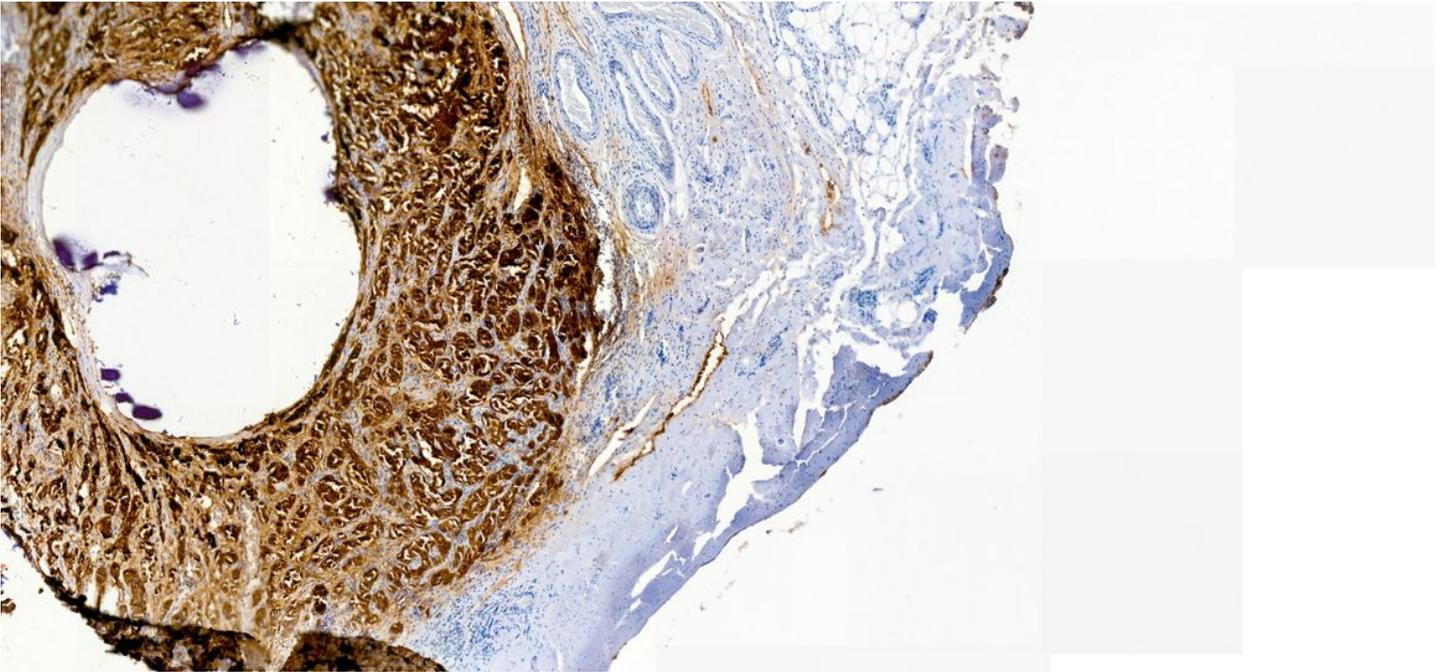


Figure 2

D2-40 immunohistochemical staining

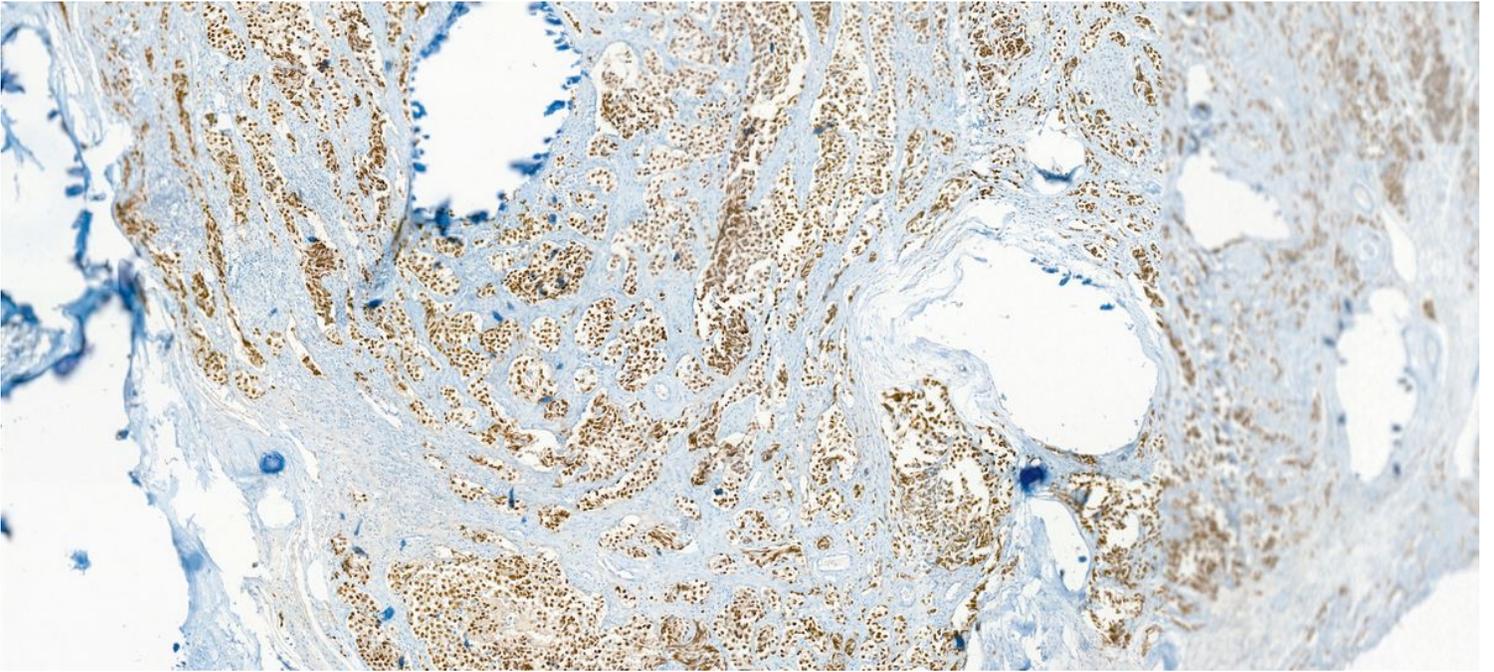


Figure 3

OCT 3/4 immunohistochemical staining

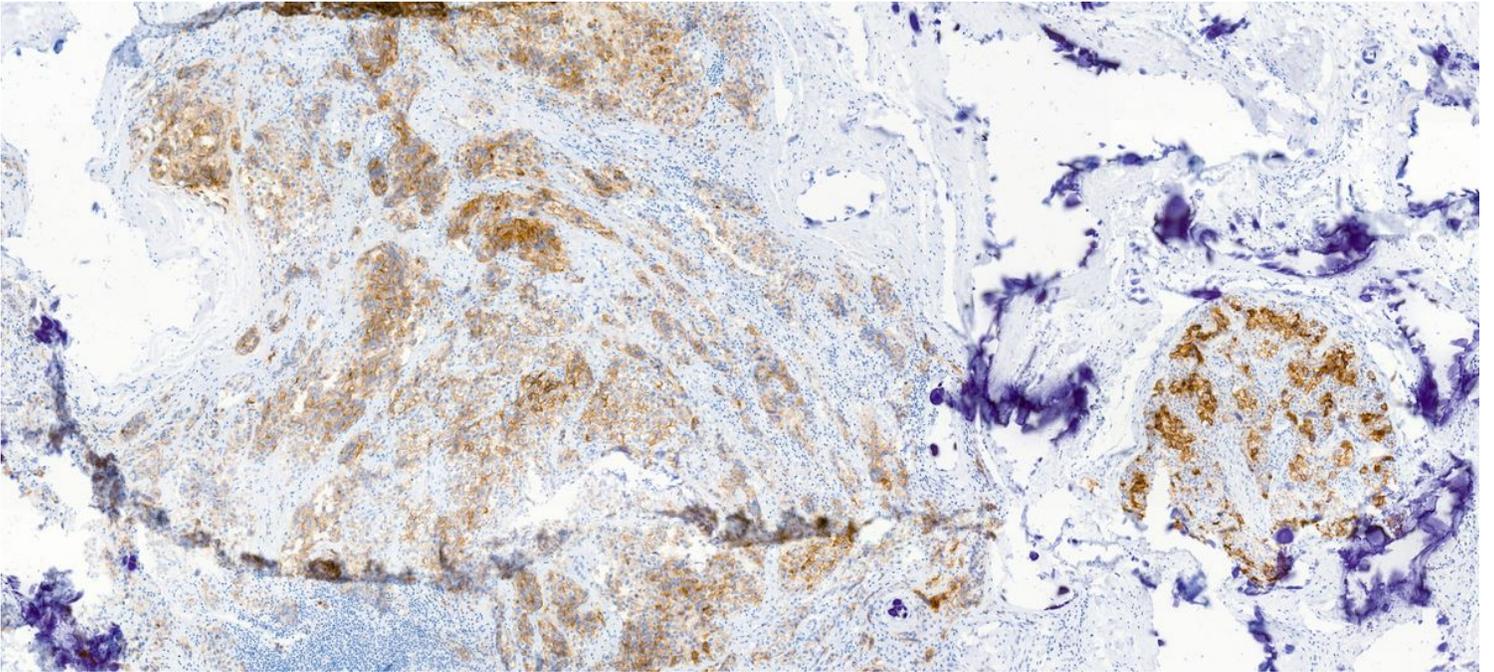


Figure 4

PLAP immunohistochemical staining

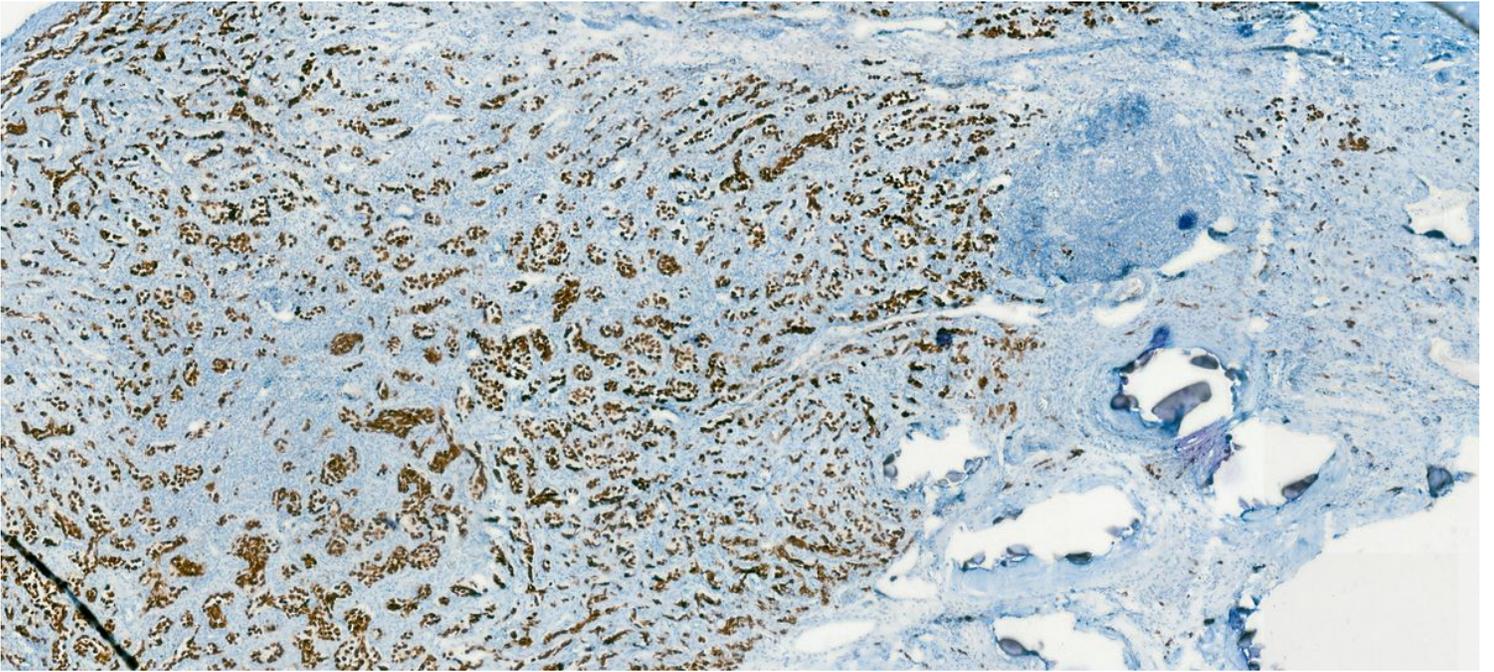


Figure 5

SALL4 immunohistochemical staining