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Review Article

Mini review: Breast cancer care in individuals with differences of sexual development

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A B S T R A C T

Disorders or differences of sexual development encompasses an important group of conditions that affects up to 1 in 5,000 live births. Many individuals living in the female gender includes Turner syndrome, congenital adrenal hyperplasia and conditions with 46XY karyotype such as gonadal dysgenesis (Swyer syndrome). Individuals are commenced on high dose oestrogen to initiate and maintain development of secondary sexual characteristics such as breasts which is paramount in them identifying in the female gender.

We highlight the first case of a patient with Swyer syndrome who was treated with long term oestrogen therapy and later developed breast cancer. In individuals with gonadal dysgenesis, testicular malignancy is a recognised risk and is screened for. Prolonged exposure to exogenous and endogenous hormones can increase the risk of breast cancer however how much this risk increases in those taking high dose hormones is not documented in the literature. We aim to highlight the importance of breast cancer treatment and surgical reconstruction in this group and whether they should be considered for early breast cancer screening.

Conclusion: It is imperative that triple assessment is undertaken in every patient with a breast lump, regardless of gender identification. Clinicians must not delay investigations in this patient group due to a misunderstanding of their condition. Those on long term hormone supplementation should be entered into the breast screening program at an earlier age with Magnetic Resonance Imaging surveillance. Careful consideration of post treatment endocrine therapy is required and under the care of the multi-disciplinary team.

1. Introduction

Disorders or differences of sexual development (DSD) replaces the outdated and confusing labels of intersex or hermaphroditism and encompasses an important group of conditions that result in atypical genital development both internally and externally. Causes include genetic variation in utero developmental programming and hormone regulation [1].

In this review we will focus on individuals with XY DSDs and whether their genetic condition and subsequent endocrine therapy places them at risk of breast cancer, the importance of screening for the disease and how surgical treatment should be addressed and whether neoadjuvant or adjuvant treatment (particularly hormone therapy) might affect these patient groups.

1.1. In-utero sexual determination

Sexual development is governed by factors which activate and suppress the Sex-determining region Y protein (SRY) gene on the Y chromosome. These factors create mutually antagonistic pathways regulating the expression of the SRY gene which lead to the production of external and internal genital structures that contribute to the gender determination of an individual [1].

DSD involves anomalies in the development of these genital structures and affect 1 in 4,500–5,000 live births [2] which is not an insignificant number. This group of conditions encompasses different chromosomal and hormonal abnormalities resulting in a variation of sexual development. People with DSD diagnoses living in the female gender includes Turner syndrome (45 XO and mosaic), congenital adrenal hyperplasia (46 XX and androgen excess) and multiple conditions with 46 XY karyotype e.g. androgen insensitivity syndrome (AIS) and gonadal dysgenesis (GD) [3].

1.2. Case report

In this review, we highlight the case of Patient C, a 58-year old female with a rare form of DSD known as Swyer syndrome that subsequently developed breast cancer.

Patient C was diagnosed with Swyer syndrome following investigations for primary amenorrhea aged 16. As part of her treatment she was commenced on high dose Premarin (conjugated oestrogen) and cyclical progesterone.

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As with most DSD patients, Patient C developed streak gonads which subsequently showed malignant changes which she had surgically removed aged 17. In her late 30s, she was treated with Oestradiol valerate and levonorgestrel (Nuvelle) Bayer PLC and more recently, Oestradiol/Norethisterone acetate (Kliofem, The Independent Pharmacy, UK). The patient reported that developing breasts was paramount in her identifying as a woman. She had engaged in the national breast screening program in the past and mammograms had showed indeterminate areas of microcalcification that were not suspicious. The patient presented to the two-week wait breast clinic with a three-week history of a hard pea sized mass in the lower central left breast. As part of the triple assessment in the one stop clinic an ultrasound of the targeted area revealed a 11 mm hypoechoic lesion. This lesion was mammographically occult. The mammogram only showed more prominent appearances of previously noted microcalcifications with no evidence of microcystic change. Core biopsy demonstrated an E-cadherin negative Grade 2 invasive lobular carcinoma, ER 8/8, PR 8/8 Ki67: 5% and HER 2 negative. A Magnetic Resonance Imaging (MRI) scan was undertaken as invasive lobular carcinomas can be mammographically occult in approximately 10% of patients and additional disease can present in the ipsilateral and contralateral breast. A unifocal tumour in the left breast was radiologically confirmed on the MRI (Figs. 1–4).

Patient C underwent a left nipple sparing mastectomy and sentinel node biopsy with immediate implant and acellular dermal matrix-based breast reconstruction. Her resection margins and lymph nodes were clear of further disease. Her active oestrogen supplementation for her DSD was stopped. After multi-disciplinary team (MDT) discussion due to the genetic make-up of her cancer it was advised she start on Tamoxifen to prevent recurrence. Under the management of her endocrinologist she was commenced on topical oestrogen to support the vaginal epithelium and treat vaginitis, after careful deliberation she was also commenced on testosterone gel to help boost libido.

Her continued management involved; symmetrisation implant-based surgery for the contralateral breast, annual reviews with the breast surgical team and regular consultations with her endocrinologist and general practitioner.

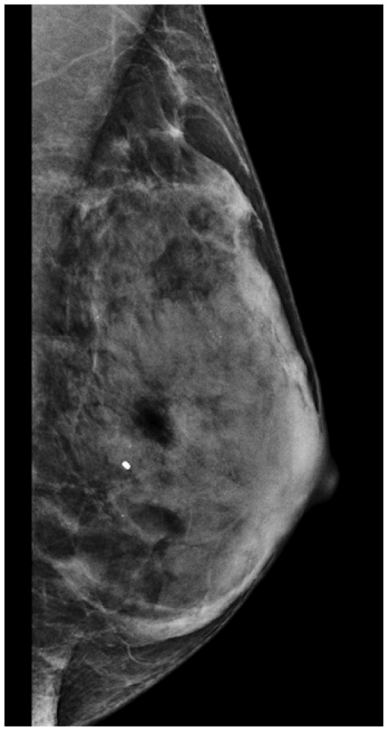

Fig. 1. Mammogram left mediolateral oblique (MLO) view.

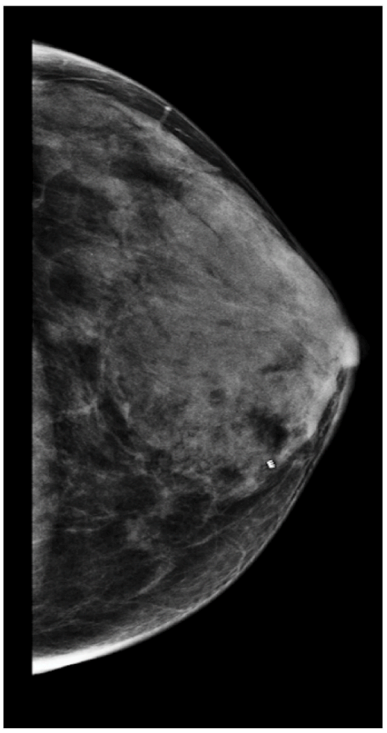

Fig. 2. Mammogram left cranial caudal (CC) view. Biopsy clip visible from previous unrelated biopsy site. Dual report describes focal cluster of microcalcification spanning 10 mm in the left upper outer quadrant. Reported as classification M3.

1.3. Swyer syndrome and other XY DSDs

Swyer syndrome, 46 XY, pure gonadal dysgenesis (PGD) is a rare form of DSD, the cause of which is thought to be deletion of the short arm of Y chromosome involving the sex determining region of the Y gene (SRY).

The incidence of Swyer syndrome is 1:80,000 in genetic males [4]. While male genitalia is expected with the XY karyotype, those with Swyer syndrome present with female external genitalia and hypoplastic to normal female internal genitalia along with minimal breast development. Instead of ovaries, they present with streak gonads which have the potential to turn malignant. The absence of ovaries or testicles suggests no heavy influence of testosterone or oestradiol, therefore leading to the absence of breast formation and amenorrhea unless treated with hormone replacement [4].

The medical management for this patient group includes monitoring the streak gonads for malignant change i. e gonadoblastoma or dysgerminoma and subsequent surgical removal when identified. Additionally, hormone supplementation (replacement therapy) remains the mainstay treatment to help them develop secondary sexual characteristics [5]. There is currently no early screening pathway for breast cancer in this patient group.

1.4. Androgen insentivity syndrome (AIS)

AIS is a more commonly diagnosed XY DSD with an estimated prevalence of 2–5 in 100,000. The cause of the pathology is a mutation in the androgen receptor gene that relates to a partial or complete inability of the cell to respond to androgens, leading to errors in development of primary and secondary sexual characteristics [6]. The presence of the Y chromosome suggests normal expression of the SRY gene [7]. The testes develops during gestation which then produces anti-mullerian hormone and testosterone, however as cells fail to respond to testosterone it leads to a formation of female secondary

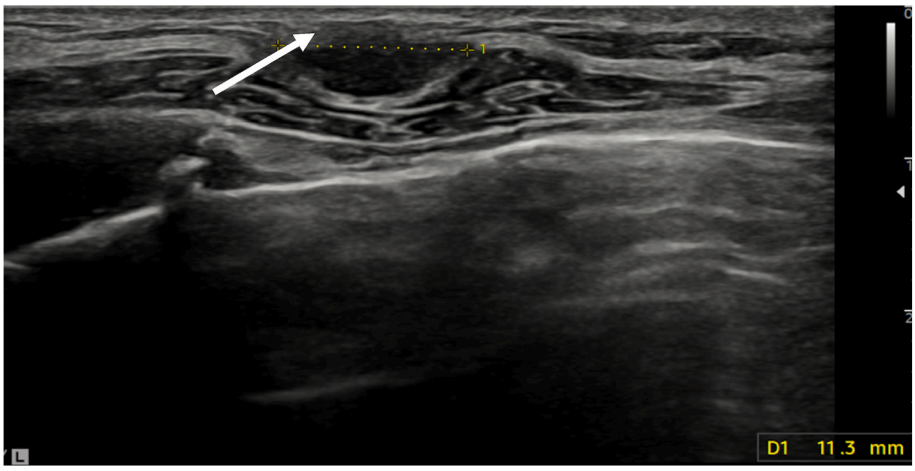

Fig. 3. Ultrasound of left breast. 11 mm hypoechoic mass (marked with arrow). Reported as classification U3/4.

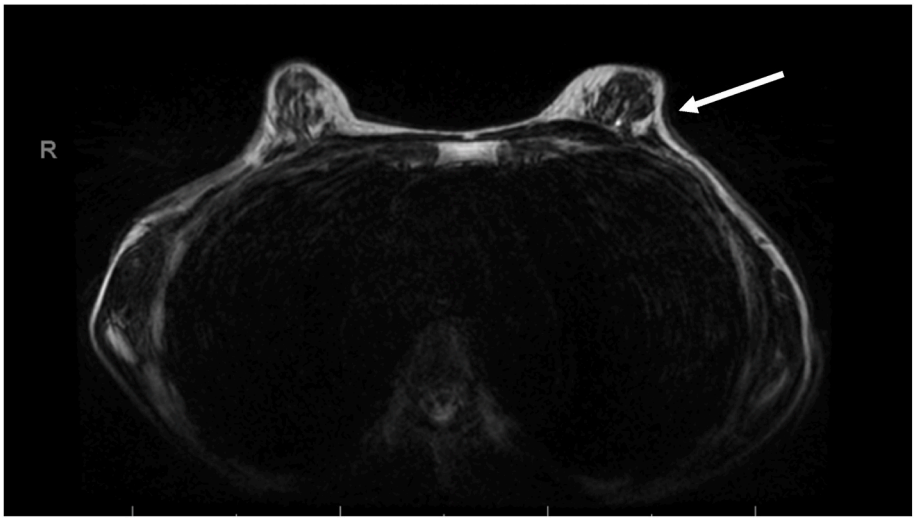

Fig. 4. MRI of both breasts. Malignant lesion in left breast marked with an arrow.

sexual characteristics.

Within the AIS family, the expression of varying degrees of AR gene mutation allows us to divide patients into those with Complete AIS (CAIS) and Partial AIS. Similar to Swyer's syndrome, patients with CAIS present with female external genitalia and have retained testes, with a diagnosis usually made with presentation of primary amenorrhea [6]. Those undergoing pre-pubertal gonadectomy will require again require oestrogen replacement to continue the development of secondary sexual characteristics [6] (Table 1).

2. Discussion

In a recent review, it is suggested [9] that in the absence of oestradiol, breast development does not occur and therefore breast cancer has not been reported in individuals with PGD [10]. To our knowledge, we have identified the first case of a patient with Swyer's syndrome who was treated with long term oestrogen therapy and subsequently developed breast cancer.

2.1. Long term oestrogen therapy association of breast cancer and subsequent endocrine therapy

We know that risk factors for breast cancer include increasing age, genetic mutations for example the Breast Cancer gene 1 and 2 (BRCA1 and 2), family history of breast cancer and previous radiotherapy exposure, many of these patients are entered into early screening programs for breast cancer. Reproductive history in cases of early menstruation and late menopause which result in a prolonged endogenous hormonal exposure can also be a risk factor for the disease.

The Lancet meta-analysis shows that consumption of exogenous hormones such as hormone replacement therapy (HRT) taken during the menopause over a five-year period including both oestrogen and progesterone and certain oral contraceptive tablets can raise breast cancer risk. In the UK, approximately one million women use HRT [10].

Table 1
Prevalence of DSD and their and association with breast cancer [8].

Pathology	Prevalence	Genotype	Phenotype	Breast Development	Breast Cancer Risk
Swyer Syndrome	1:100,000	XY	Male	No	Very Low
CAIS	1:90,000	XY	Female	Yes	1:1000

These are all extremely well documented in the scientific community and breast cancer charities. Yet early treatment with exogenous oestrogen in individuals with DSD and its associated risks of development of breast cancer goes undocumented in the literature.

Low oestrogen production is synonymous with reduced breast development, and this appears to be the case with women with DSD [8]. Early start of HRT/oestrogen therapy helps support the development of bone mass, psycho-social and psycho-sexual maturation along with development of secondary sexual characteristics, particularly breast development which is paramount for these individuals to identify with the female gender [8] especially as many of their female peers have already undergone such developmental changes. It is a necessary and important treatment plan to offer at the crucial stages of adolescent development however we have no data to reflect the true increased risk ratios for breast cancer development.

In people with DSD we know that testicular malignancy is a recognised risk and early gonadectomy is advocated [2], early screening for this is well implemented. We also know from various studies that individuals with Kleinfelters syndrome (47,XXY) are at an increased risk of developing male breast cancer, data seems to support that this risk may be around 20-30-fold higher than expected, however the exact nature of why this occurs is unknown [11]. Yet there is no literature identifying the risk of breast cancer in patients with 46 XY DSD and little is known about the consequences of prolonged hormonal treatment of these individuals. This raises the question on how thoroughly endocrinologists can counsel these individuals of the risks of breast cancer in the absence of any data especially when essentially committing them to taking HRT from such a young age.

2.2. Triple assessment, imaging modality and screening in increased risk groups

Triple assessment of a lump in the breast is crucial when trying to establish a diagnosis of breast cancer. Triple assessment consists of physical examination, breast imaging (mammogram and ultrasound scan) and biopsy (fine-needle aspiration cytology or core) and this combination of breast cancer assessment has proved to be more accurate than any single modality alone [12].

Is there a misconception that if a DSD patient does not have breast tissue, then they do not develop breast cancer? If this is the case both clinicians in the primary care setting who refer to urgent breast clinics and those with DSD may delay in referral or presentation which could be detrimental to outlook if the pathology is malignant [9].

Women with dense breasts have a higher risk of developing breast cancer and mammography performs lower in its ability to detect breast cancer within more glandular and fibrous tissue [13]. Dense breast tissue has generally been associated with younger age and premenopausal status, which is why screening in high-risk patients tends to be with MRI.

Patient C's tumour was mammographically occult and was subsequently identified on ultrasound. For mammographically occult tumours MRIs are required to investigate for further disease in the ipsilateral and contralateral breast. It raises the question whether the mammogram offered as part of the assessment in DSD individuals is sufficient? [13] The national breast screening program in the United Kingdom is for women between the ages of 50 and 70, it is also for some trans or non-binary people. The National Institute for Health and Care Excellence (NICE) and National Health Service (NHS) England outlines very clear guidance on screening protocols for the surveillance of women at higher risk of developing breast cancer. These patient groups include those who are carriers of the BRCA1 and BRCA 2 genetic mutations as well as others such as Partner and localizer of BRCA2 (PALB2) or Li Fraumeni syndrome in addition to those who have undergone radiotherapy to the chest wall in the past [14,15]) (Table 2). However, there is no mention of patients who have had prolonged exposure to high levels of exogenous oestrogen or progesterone. Should we therefore be classifying patients with DSD who have taken prolonged hormone supplementation in this group also?

Table 2
NICE guidance of early screening tests and frequency for very high risk breast cancer women (i.irradiated between ages of 10–19, ii. Irradiated between ages of 20–35) [14].

Risk factors of very high-risk women	Age of screening	Test	Frequency
BRCA1 carriers, BRCA2 carriers, mutations in PALB2, PTEN, STK11, CDH1 (E-Cadherin)	25–29	MRI	Annual
	30–39	MRI	
	40–50	MRI and mammography	
	51–71	Mammography ±MRI	
TP53 (Li-Fraumeni)	20–71	MRI (no mammography)	Annual
A-T homozygotes	25–71	MRI (no mammography)	Annual
Radiotherapy to breast tissue	25–29	MRI	Annual
	30–39	MRI	Annual
	40–50	MRI and mammography	Annual
	51-71(i)	Mammography ±MRI	Annual
	30–39	MRI	Annual
	40–50	MRI and mammography	Annual
	51-71 (ii)	Mammography ±MRI	Annual

The American Cancer Society recommends dynamic contrast-enhanced MRI in addition to standard mammography in high-risk individuals [13]. Would there be a need to perhaps change our current practice and offer not only early screening but specifically MRI as a supplemental screening tool for such DSD individuals. A bilateral ultrasound may also be useful in detecting small occult cancers [16] however we know that diffusion weighted imaging may detect more occult tumours than ultrasound which may be limited in detecting non-mass enhancements [13]. MRI, however, is not without its own risks. These studies require the use of intravenous gadolinium and this increases the risks of allergy and renal impairment, it is an expensive test that takes longer to perform than mammography or ultrasound scan and claustrophobia can also be an issue. All these factors would need to be taken into account when consenting the individual for enhanced screening.

2.3. Breast cancer management and endocrine therapy

The following questions still go unanswered in the literature; when individuals with DSD use high levels of exogenous hormone supplementation such as oestrogen and progesterone for a prolonged period of time, does this put them at a significantly increased risk of breast cancer? Would it be length of treatment or dose related? If so by what factor does the risk increase by? The answers to these questions are paramount if we are to advise and counsel patients on uses of these high dose hormone treatments. This further raises the question on how individuals undergoing gender affirming hormone therapy are also at risk? Which even though a different gender minority group to the one this paper discusses, it is still very much a translatable topic and raises the way we approach exogenous hormone therapy, gender affirming treatment and screening for breast cancer.

Many patients with hormone receptor positive cancers are commenced on drugs such as tamoxifen, an oestrogen inhibitor [17,18] or letrozole, an aromatase inhibitor to help or eliminate the effects of oestrogen which can drive breast cancer recurrence [18]. In the case of our patient and women with breast cancer who are on systemic hormone replacement therapy for the menopause, it is a difficult but a necessary

decision to stop the treatment in both hormone receptive positive and negative breast cancers to prevent recurrence of the disease [19] and if appropriate to commence such drugs like tamoxifen or letrozole which in some cases can exacerbate the symptoms of the menopause.

In reference to patients with DSD who have stopped exogenous hormone supplementation once diagnosed with breast cancer, restoration of general wellbeing and sexual function is vital and quality of life is an important focus post treatment. Solutions include treatment with low dose topical oestrogen and testosterone. There is a theoretical risk of aromatisation of the latter to oestradiol, but at the dose it should be used this will be minimal. There is to the best of our knowledge no direct effect on breast cancer prognosis however this should always be under the careful advice of the MDT and specialised care of an endocrinologist who will monitor blood tests and symptom management.

It is extremely important that when discussing surgical treatment plans with DSD patients all reconstructive breast surgical options are explored which there are many (autologous flap, implant based). This should be in the presence of the surgeon and the specialist breast cancer care nurse. Individuals with some of the DSDs discussed have strong body image associations with breast formation, restorative breast surgery may be central to their identification as a woman.

2.4. Which team takes responsibility?

Long term follow-up with annual reviews are recommended for patients under the care of a specialist for their DSD however there is very little evidence to suggest that this is being carried out [20]. In the 2017 study, patients with Klinefelters and 46XY DSD groups were dissatisfied about the information given about their level and standard of care and up to 38% of patients 46 XY DSD individuals remained dissatisfied about the risks and side effects associated with HRT(20).

Understanding one's treatment plan is essential in motivating patients to care for themselves. Hormone therapy needs to be tailored to different phases of life. A well-regulated follow up plan is essential for individuals with DSD as they are perhaps the only group that requires long term HRT which is initiated from the second decade of life and for many decades afterwards in order to preserve their physical appearance as well as holistic wellbeing. Clearly the mainstay of care should be led by the Endocrinologist with a special interest in DSD as this will likely be the initial clinician the patient encounters during their adolescent years and one that will monitor their care for many years after. The patient's General Practitioner is an important central pillar of support and care, it is vital that they are actively included and educated on the matter as treatment plans may be continued by them. Integration of specialists such as urologists for monitoring of testicular neoplasia and breast clinicians for breast cancer should be considered when it is appropriate and if early screening were to be offered to patients, they should be inducted into the national screening program at this stage. This does not take into consideration the rest of the MDT including psychologists, plastic surgeons, specialist nurses and geneticists.

3. Conclusion

It is imperative that triple assessment is undertaken in every patient with a breast lump, regardless of gender or how they identify. Clinicians must not delay referral to a specialist and for relevant investigations in patients with DSD due to any misunderstanding of the individual's condition or genetics.

It may be worth considering whether women with DSD on long term HRT should be monitored for breast cancer, before the normal screening age. However, this would require additional funding and resources such as MRI surveillance.

CRediT authorship contribution statement

B.N. Ertansel: Conceptualization, Study concepts, Study design, Funding acquisition, Manuscript preparation. **S. Rajagopal:** Conceptualization, Study concepts, Study design, Manuscript preparation. **S. Lodhia:** Conceptualization, Study concepts, Study design, Manuscript preparation, Manuscript editing, Writing – review & editing. **G. Boutsikos:** Conceptualization, Study concepts, Study design, Funding acquisition, Manuscript review, Writing – review & editing. **D. Banerjee:** Conceptualization, Study concepts, Study design, Manuscript review, Writing – review & editing.

Declaration of competing interest

I confirm there are no conflicts of interest in producing this paper.

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