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PRECISION ONCOLOGY IN CANCER SURVIVORSHIP: UNRAVELING THE FUTURE OF AFTERCARE : A CASE REPORT

Oncology

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ABSTRACT

This case report explores the role of precision oncology in the survivorship care of a 15-year-old female treated for stage IA ovarian mixed germ cell tumor. The patient presented with primary amenorrhea and was diagnosed with hypergonadotrophic hypogonadism. Next-generation sequencing (NGS) identified a heterozygous variant of uncertain significance (VUS) in the DIAPH2 gene, associated with premature ovarian failure. This genetic insight facilitated the development of a personalized survivorship plan, including hormone replacement therapy and fertility counseling. The case highlights how precision medicine extends beyond cancer treatment, optimizing long-term quality of life and addressing the unique needs of adolescent and young adult (AYA) cancer survivors.

KEYWORDS

Precision Oncology, Adolescent and Young Adult Oncology, Next-Generation Sequencing, Variant of Uncertain Significance, DIAPH2 Gene, Cancer Survivorship, Premature Ovarian Failure

INTRODUCTION

The landscape of oncology is undergoing a remarkable transformation. With survival rates for many cancers reaching unprecedented high levels, clinical focus is increasingly shifting towards quality of life in the post-cancer phase [1] . Cancer survivorship, defined as the health and well-being of individuals from the time of diagnosis throughout the remainder of their life, has become a critical area of clinical concern [2]

The adolescent and young adult (AYA) population, representing approximately 10% of all cancer survivors, faces unique and multifaceted challenges [3] . Among AYA survivors, females comprise 66% of this cohort, and a substantial proportion express significant concerns regarding fertility preservation, sexual health, and psychosocial adaptation [4] . These young survivors navigate developmental transitions while managing the physical and psychological consequences of cancer diagnosis and treatment.

Malignant germ cell tumors of the ovary, though rare and accounting for only 5% of all ovarian malignancies [5] , predominantly affect the AYA demographic, with a median age of presentation between 19 and 21 years . Despite their aggressive nature, the prognosis for these tumors is remarkably favorable, with survival rates exceeding 90% [6] . Many survivors can reasonably expect the restoration of normal menstrual function and successful pregnancies following treatment completion [6] .

This case report demonstrates how precision oncology, specifically next-generation sequencing (NGS), is extending its vital applications beyond the realms of cancer diagnosis and treatment into the domain of personalized, long-term cancer survivorship care [7] , [8]. Precision medicine increasingly recognizes that optimal survivorship outcomes require a comprehensive understanding not only of cancer-related sequelae but also of underlying host factors that influence long-term health and well-being .

Case Presentation

Clinical Background And Initial Presentation

A 15-year-old female had developed torsion of the right ovarian cyst. Emergency exploratory laparotomy with right oophorectomy was done. The HPE was reported as Germ Cell Tumour. Following the surgical procedure, she was referred to our institution for further oncological evaluation and management.

Clinical And Pathological Findings

Relevant History: She was born to consanguineous parents. She had not attained menarche.

Clinical Examination: She was of short stature with absent secondary sexual characteristics, with Tanner staging I for breast development.

Surgical Findings: Intraoperative findings by the surgical team revealed a rudimentary uterus and a streak left ovary, findings consistent with primary ovarian insufficiency.

Histopathological Analysis: Histopathological examination of the resected ovarian specimen revealed a mixed germ cell tumor composed of 70% embryonal carcinoma and 30% yolk sac tumor components. Mixed germ cell tumors of the ovary represent a distinct histologic category requiring multimodal treatment approaches [5] [6].

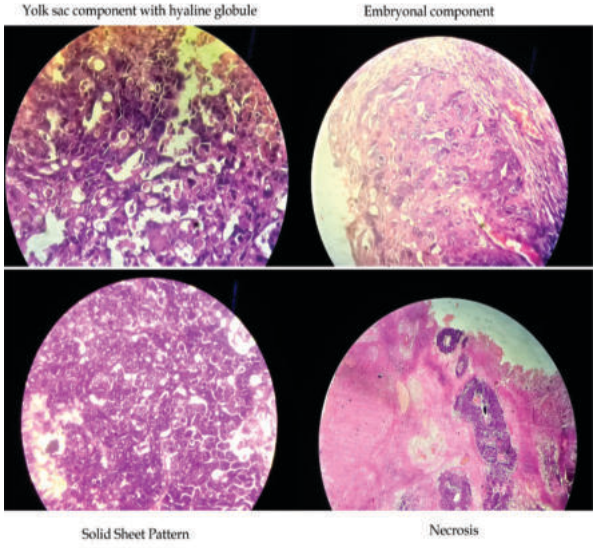

Image 1: Histopathological Examination

Tumor Markers And Staging:

Postoperative tumor marker evaluation demonstrated elevated levels: alpha-fetoprotein (AFP) 1000 ng/mL, beta-human chorionic gonadotropin (β-HCG) 3.2 mIU/mL, and lactate dehydrogenase (LDH) 406 IU/L. Comprehensive imaging studies confirmed stage IA disease according to the International Federation of Gynecology and Obstetrics (FIGO) staging classification.

Table 1 : Tumour Markers			
Parameter	**Value in Patient**	**Normal Value**	**Remarks**
AFP (Alpha Feto Protein)	1000 ng/mL	< 10 ng/ml	Elevated
bHCG (Beta HCG)	3.2 mIU/mL	< 5 mIU/ml	Normal
LDH	406 IU/L	< 280 IU/L	Elevated

Cancer Treatment And Treatment Response

Following multidisciplinary tumor board discussion, the patient was prescribed four cycles of BEP (bleomycin, etoposide, and cisplatin) chemotherapy [3] , [9]. BEP represents the standard chemotherapy regimen for malignant ovarian germ cell tumors in the pediatric and adolescent population. She demonstrated excellent treatment response, with serial tumor marker estimations normalizing and remaining within reference ranges throughout the treatment course and subsequent follow-up period.

Investigation Of Underlying Endocrine Pathology

The patient's history of primary amenorrhea prompted a comprehensive endocrinological investigation. Consultation with an endocrinologist established a diagnosis of hypergonadotrophic hypogonadism, indicative of primary ovarian insufficiency [10]. Standard karyotyping revealed a normal 46,XX genotype. 30 cell karyotype was done to rule out mosaic turner syndrome. To elucidate the underlying genetic etiology, the patient was referred for advanced genetic testing.

Precision Medicine Approach: Genetic Investigation

To identify the molecular basis for primary ovarian insufficiency, next-generation sequencing (NGS) was performed on whole blood DNA (EDTA anticoagulant). NGS has emerged as a powerful diagnostic tool for identifying genetic causes of diverse clinical phenotypes, including reproductive disorders [7] , [8].

Sequencing Parameters: -
Sample Type: Whole blood (EDTA) -

Methodology: Next-Generation Sequencing (targeted gene panel) -

Test Material: Genomic DNA

Genetic Findings:

NGS analysis identified a heterozygous variant of uncertain significance (VUS) in the DIAPH2 gene. The specific variant details are as follows:

Table 2 : Specific Variant Details	
Parameter	Details
Gene	DIAPH2 (NM_006729.5)
Exon	Exon 21
Variant Nomenclature	c.2550T>G; p.Asn850Lys
Variant Depth	57X/125X (100% coverage)
Genomic Nomenclature	chrX:g.96369925T>G
Zygosity	Heterozygous
Classification	Uncertain Significance
Associated Phenotype (OMIM)	Premature Ovarian Failure 2A (POF2A)
Inheritance Pattern	X-linked Dominant
Variant Details	
Type of variant	missense_variant
gnomAD frequency	Absent
Computational evidences	REVEL: 0.237 CADD Phred: 23.3
Amino acids conserved by	GERP++ PhyloP
LOF disease mechanism of action	NA
Downstream LOF	NA
Previously reported [reported zygosity]	No
Variant references	NA

Interpretation: Although a definitive pathogenic mutation was not identified, the discovery of a VUS in the DIAPH2 gene carried significant clinical relevance. The DIAPH2 gene encodes diaphanous related formin 2, a protein involved in the regulation of the actin cytoskeleton and plays a critical role in ovarian development and function. Mutations in DIAPH2 [11] have been definitively linked to Premature Ovarian Failure 2A (POF2A) [12] , an X-linked dominant disorder. This genetic finding provided a plausible molecular explanation for the patient's primary amenorrhea and streak ovary findings [13] [14], which appeared to exist independently of her cancer diagnosis.

Personalized Survivorship Care Plan

Integrating clinical, pathological, and genetic information, a comprehensive and individualized long-term survivorship plan was developed and implemented.

Hormone Replacement Therapy (HRT):

The patient was initiated on hormone replacement therapy [15] with dual therapeutic objectives to induce the development of pubertal characteristics and secondary sexual development and to promote long-term bone health and prevent osteoporosis.

Fertility Counseling And Reproductive Guidance: The patient and her family received comprehensive counseling regarding her reproductive prognosis and fertility options. She has been counseled on the future use of assisted reproductive technology (ART) and gestational surrogacy when she elects to pursue pregnancy [15] .

Long-Term Surveillance Strategy: The patient was enrolled in a dual surveillance pathway in accordance with contemporary survivorship guidelines [1]:
Oncology Surveillance: Regular imaging studies and tumor marker evaluations to monitor for cancer recurrence.

Endocrinology Surveillance: Ongoing hormonal assessment and management of endocrine replacement therapy.

Clinical Outcome

At one-year follow-up, the patient is clinically thriving well. She has demonstrated a growth spurt and shows encouraging development of secondary sexual characteristics consistent with appropriate pubertal progression. She remains disease-free with persistently normal tumor markers and unremarkable imaging studies.

DISCUSSION

The DIAPH2 Gene and Premature Ovarian Failure

The diaphanous related formin 2 (DIAPH2) protein, encoded by the DIAPH2 gene [11] located at chromosome Xq13.3-q21.1 [13] , is a member of the formin homology protein family involved in regulating the cytoskeleton [17] . This protein plays an essential role in the normal development and function of the ovaries [17]. The protein is particularly involved in the regulation of endosome dynamics and the organization of epithelial structures through interactions with the actin cytoskeleton. [17]

Defects in the DIAPH2 gene have been definitively associated with Premature Ovarian Failure 2A (POF2A), characterized by cessation of ovarian function before age 40 years. The inheritance pattern is X-linked dominant, explaining the predominance of the condition in females. Premature ovarian insufficiency (POI) encompasses a spectrum of ovarian dysfunction resulting from early depletion of ovarian follicles, manifesting clinically as primary amenorrhea or premature menopause depending on age of onset [10]. The genetic basis of POI is heterogeneous, with multiple genes implicated beyond DIAPH2, including FMR1, POF1B, FOXL2, BMP15, NOBOX, FIGLA, and NR5A1.

Variants Of Uncertain Significance In Clinical Practice

This case underscores a fundamental principle in modern genomic medicine. A variant of uncertain significance (VUS) [16] must be carefully correlated with the patient's clinical phenotype. A VUS does not constitute a definitive genetic diagnosis; rather, it represents a clue that, when integrated with clinical findings, can guide clinical judgment and direct management decisions. As genomic sequencing becomes increasingly prevalent in clinical oncology, clinicians must develop proficiency in interpreting VUS findings within their clinical context. In this patient, the identification of a heterozygous DIAPH2 VUS, in a clinical context of hypergonadotrophic hypogonadism and streak ovary, provided compelling circumstantial evidence for a genetic contribution to her ovarian insufficiency.

The Expanding Scope Of Cancer Survivorship

Cancer survivorship encompasses the entire lifespan of individuals following a cancer diagnosis [1] , [2]. Survivors require comprehensive care addressing not only potential cancer recurrence

but also the acute and late effects of cancer treatment, psychosocial needs and management of any underlying predisposing conditions [1]. Current estimates project that cancer survivors represent a significant and growing population, with survivorship care emerging as a critical public health priority [2] , [4]. Host factors, including hereditary cancer syndromes and genetic risks for therapy-associated toxicity, significantly influence long-term survivorship outcomes [6].

While all Adolescent and Young Adult survivors face challenges, female AYA survivors, in particular, require specialized attention to reproductive health, fertility preservation counseling, and long-term hormonal management [2], [4].

Role Of Precision Oncology Beyond Cancer Treatment

Precision medicine has traditionally been conceptualized as the science of selecting targeted cancer therapeutics based on individual tumor genomics. This case demonstrates the expanding scope of precision oncology into the domain of survivorship care. Precision medicine now encompasses the identification of genetic risk factors for late treatment effects, the discovery of underlying host factors affecting long-term health, and the crafting of individualized survivorship plans tailored to each patient's specific molecular and clinical profile. By integrating genomic information with clinical data, precision oncology moves beyond a one-size-fits-all model of survivorship toward a truly personalized, individual-centric approach to long-term care.

Clinical Implications And Best Practices

This case highlights several important clinical lessons for oncologists and survivorship specialists. First, primary amenorrhea in a cancer survivor, particularly one with ovarian pathology, warrants thorough endocrinological investigation [1]. Second, advanced genetic testing using NGS may provide valuable insights into underlying reproductive pathophysiology [8]. Third, identification of genetic factors influencing survivorship should drive personalized therapeutic interventions, including hormone replacement and fertility counseling [1]. Finally, optimal cancer survivorship care requires multidisciplinary collaboration among oncologists, endocrinologists, genetic counselors, and reproductive specialists to address the complex and multifactorial needs of survivors [1]

CONCLUSION

The dramatic improvements in cancer survival rates over recent decades represent one of medicine's greatest achievements. However, survival alone is insufficient; quality of life, reproductive health, and long-term well-being constitute equally important outcomes for cancer survivors, particularly in the AYA population. This case exemplifies how precision oncology is fundamentally transforming the approach to cancer survivorship, evolving from a traditional model focused primarily on cancer recurrence surveillance to a comprehensive, individualized strategy addressing the totality of survivorship needs.

By integrating molecular diagnostics such as NGS with clinical acumen, we can uncover underlying genetic factors that influence survivorship outcomes These insights enable the development of personalized interventions-whether hormonal, reproductive, or psychosocial-that optimize long-term health and quality of life. Continued research initiatives, enhanced investment in survivorship science, and multidisciplinary collaboration remain essential for advancing the field. The future of cancer care depends not only on achieving cure but on ensuring that survivors thrive in all dimensions of health and well-being. Precision oncology, with its capacity to tailor care to individual molecular and clinical profiles, offers tremendous promise in achieving this vision.

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